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# Proton Transfer, Acid-Base Catalysis, and Enzymatic Hydrolysis

## PART 1: ELEMENTARY PROCESSES [*]

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*Dedicated to Dr. W. Foerst on the occasion of his 65th birthday*

*The proton occupies a special position as a promoter and mediator in chemical reactions occurring in solution. Many reactions in organic chemistry are catalysed by acids or bases; likewise, most enzymes contain active groups which promote acid-base catalysis. To understand the reaction mechanisms involved, it is necessary to identify the elementary steps as well as their course in time. Systematic investigation of these elementary steps has become possible only with the development of new methods for studying very fast reactions. The present paper reviews the information obtained in this type of investigation. The result is a relatively complete picture of the elementary proton transfer mechanisms and a comprehensive description of the modes and laws of acid-base and enzymatic catalysis.*

### 1. Structural Prerequisites for Proton Transport in Aqueous Media

The state of the (solvated) proton in aqueous media may be described in terms of four structural species:

the elementary proton, $H^+$

the hydronium ion, $H_3O^+$ (primary hydration)

the complex ion $H_9O_4^+$, (secondary hydration), and a tertiary hydration at the periphery of the complex.

Figure 1 shows the model of such a hydrate complex which has been described in detail in previous papers [1–3].

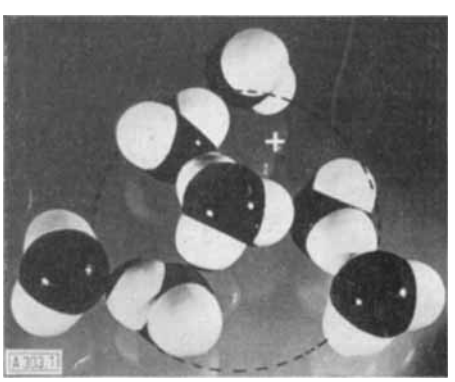


Fig. 1. Model of a $H^+$ hydrate complex containing the structural units $H_3O^+$ (center), $H_9O_4^+$ (within the circle) and with tertiary hydration (outside the circle). The pyramidal arrangement fits into the structure of hexagonal ice. Additional H-bridging between the secondary $H_2O$ molecules [4] would be possible only by outward displacement of bridge protons from the O–O bond direction.

The different structural species can be identified experimentally (literature see Table 1).

[*] Part II (Catalytic Mechanisms) will appear shortly in this journal.

[1] *E. Wicke, M. Eigen*, and *Th. Ackermann*, Z. physik. Chem. (N. F.) *1*, 340 (1954).

[2] *M. Eigen* and *L. de Maeyer*, Proc. Roy. Soc. (London), Ser. A *247*, 505 (1958).

[3] *M. Eigen* and *L. de Maeyer in*: The Structure of Electrolytic Solutions. Wiley, New York 1959, p. 64 et seq.

[4] *W. v. E. Doering*, personal communication.

Table 1. Detection of the hydronium ion [a] and of the $H_9O_4^+$ complex [b].

| Method | Medium | Reference $H_3O^+$ | Reference $H_9O_4^+$ |
|---|---|---|---|
| Mass spectroscopy | water vapor | [9] | |
| a) Field emission | water vapor | [5] | [5] |
| b) Glow discharge | water vapor | [7] | [7] |
| X-ray analysis | acid monohydrate | [10] | |
| Infrared spectroscopy | acid monohydrate | [11, 12] | |
| | solution | [13, 14] [c] | |
| Raman spectroscopy | acid monohydrate | [15] | |
| | aqueous solution | [16] [c] | |
| Nuclear magnetic resonance | acid monohydrate | [6, 17, 18] | |
| Molar refraction | aqueous solution | [19] | |
| Conductivity | $H_2O$ in abs. $H_2SO_4$ | [20] | |
| Calorimetry | | | |
| a) Cryoscopy | $H_2O$ in various solvents | [20] | |
| b) Heats of hydration | aqueous solution | [21] | |
| c) Temperature dependence of specific heats | aqueous solution | | [1] |
| Solvent extraction | Solvent mixtures | | [23—25] |
| Kinetic studies | | | |
| Acid-base catalysis | $H_2O$ in various solvents | [22] | |
| Effective cross-section of protolytic reactions | aqueous solution | | [2, 3] |
| Theoretical | | [26—29] | [30] |

[a] First mention of $H_3O^+$ by *Collie* and *Tickle* [31].

[b] For additional literature references see *R. P. Bell*, The Proton in Chemistry, Cornell University Press, 1959. $H_3O^+$: pp. 19—23; $H_9O_4^+$: pp. 81—83.

[c] Assignment to $H_3O^+$ is doubtful, since the same band appears in concentrated base solutions.


[5] *H. D. Beckey*, Z. Naturforsch. *14a*, 712 (1959); *15a*, 822 (1960).

[6] *R. E. Richards* and *J. A. S. Smith*, Trans. Faraday Soc. *47*, 1261 (1951).

[7] *P. F. Knewstubb* and *A. W. Tickner*, paper presented at the Meeting on Mass Spectrometry, A.S.T.M. Atlantic City 1960 (experimental data: personal communication).

[8] *Th. Ackermann*, Discuss. Faraday Soc. *24*, 180 (1957).

[9] *M. M. Mann*, *A. Hustrulid*, and *J. T. Tate*, Physic. Rev. *58*, 340 (1940).

[10] *M. Volmer*, Liebigs Ann. Chem. *440*, 200 (1924).

[11] *D. E. Bethel* and *N. Sheppard*, J. chem. Physics *21*, 1421 (1953).

[12] *C. C. Ferriso* and *D. F. Hornig*, J. Amer. chem. Soc. *75*, 4113 (1953).

[13] *M. Falk* and *P. A. Giguère*, Canad. J. Chem. *35*, 1195 (1957).

[14] *Th. Ackermann*, Z. physik. Chem. (N. F.) *27*, 253 (1961).

[15] *J. T. Mullhaupt* and *D. F. Hornig*, J. chem. Physics *24*, 169 (1956).

[16] *W. R. Busing* and *D. F. Hornig*, J. physic. Chem. *65*, 284 (1961).

[17] *J. A. S. Smith*, Quart. Revs. (Chem. Soc., London) *7*, 279 (1953).

[18] *Y. Kakiuchi*, *H. Shono*, *H. Kamatsu*, and *K. Kigoshi*, J. chem. Physics *19*, 1069 (1951).

[19] *K. Fajans* and *G. Joos*, Z. Physik *23*, 1 (1924).

[20] *A. Hantzsch*, Z. physik. Chem. *61*, 257 (1908).

[21] *K. Fajans*, Naturwissenschaften *9*, 729 (1921).

[22] *H. Goldschmidt* and *O. Udby*, Z. physik. Chem. *60*, 728 (1907).

[23] *D. G. Tuck* and *R. M. Diamond*, Proc. chem. Soc. (London) *1938*, 236.

[24] *A. H. Laurene*, *D. E. Campbell*, *S. E. Wiberey*, and *H. M. Clark*, J. physic. Chem. *60*, 901 (1956).

[25] *R. P. Bell* and *K. N. Bascombe*, Discuss. Faraday Soc. *34*, 158 (1957).

[26] *F. Hund*, Z. Physik *31*, 81 (1925); *32*, 1 (1925).

[27] *F. O. Rice* and *E. Teller*: The Structure of Matter. Wiley, New York 1940, p. 94, 113.

[28] *Y. K. Syrkin* and *M. E. Dyatkina*: Structure of Molecules and the Chemical Bonds. Butterworth, London 1949, p. 111.

[29] *R. Grahn*, Arkiv Fysik *19*, 147 (1961); *21*, 1 (1962).

[30] *R. Grahn*, Arkiv Fysik *21*, 13 (1962).

[31] *J. N. Collie* and *Th. Tickle*, J. chem. Soc. (London) *75*, 710 (1899).


The proton, being an elementary particle, differs from all other ions that are stable in aqueous solutions in that it lacks an electron shell. Its conduction properties (*e.g.* in ice crystals, see below), in particular, are in many respects similar to those of the electron. It differs from the latter, however, by its substantially greater mass, which has a decisive effect on its wave character (tunnel effect in proton transfer). Table 2 gives a comparison of the most important basic characteristics of the proton, the electron, and the $Li^+$ ion.

Table 2. Basic properties of the electron, proton and $Li^+$ ion

| | Radius [cm] | Mass number $[m/m_p]$ | De Broglie wavelength [cm] [a] |
|---|---|---|---|
| Electron | $1.42\times10^{-13}$ [b] | 1/1836 | $6.2\times10^{-7}$ |
| Proton | $\sim2\times10^{-13}$ | 1 | $1.5\times10^{-8}$ |
| $Li^+$ ion | $7.8\times10^{-9}$ | 7 | $5.5\times10^{-9}$ |

[a] $\lambda = \frac{h}{\sqrt{2mE}}$; refers to a particle kinetic energy of 3/2 kT (T = 300 °K) in a potential free space.

[b] "Classical" electron radius: $e^2/2\,m_e c^2$.

## $H_3O^+$ (Hydronium Ion)

Because of its small radius, the proton can come into close contact with polar molecules and also exert a strong polarizing effect. Thus, in water, it does not exist as an isolated elementary particle, but adds onto a molecule of $H_2O$, forming a covalent bond.

The existence of the molecule-ion $H_3O^+$ in ionized water vapor can be demonstrated by mass spectrometry. Thus, using a field emission ion source, *Beckey* [5] was able to show that the mass spectrum of an $H_2O$–$D_2O$ mixture exhibits four peaks, one mass unit apart from each other. These peaks can be assigned to the ions $H_3O^+$, $H_2DO^+$, $HD_2O^+$, and $D_3O^+$ (Figure 2). The symmetrical structure of the $H_3O^+$ ion is reflected in the nuclear magnetic resonance spectrum shown in Figure 3.

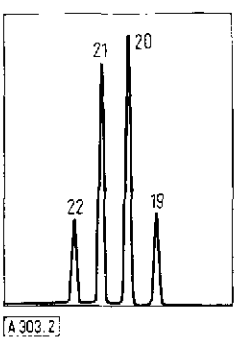



Fig. 2. Field emission mass spectrum of a mixture of $H_2O$ and $D_2O$ recorded by *Beckey* [5]. The appearance of four peaks proves the existence of $H_3O^+$. If $H_2O^+$ were the ionization product, then only 3 peaks would be observed. In this experiment, proof of the existence of $H_3O^+$ is given without absolute calibration of the mass scale.

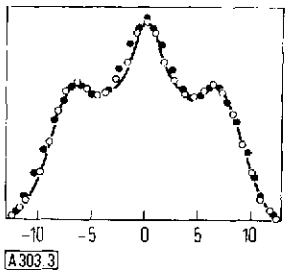



Fig. 3. Nuclear magnetic resonance spectrum of $H_3O^+$ in crystals of $HNO_3$ monohydrate at 90 °K (*Richards* and *Smith* [6]). The full line was calculated for distribution of a proton over the apices of an equilateral triangle (side length = 1.72 Å).

Abscissa: Magnetic field strength [gauss].

## $H_9O_4^+$ (Secondary Hydration)

The symmetrical distribution of the excess positive charge among the three protons in the hydronium ion allows formation of very stable hydrogen bridges to the neighboring $H_2O$ molecules. The proton possesses a very high mobility within this molecular complex. Thus, its localization in the central $H_3O^+$ portion simply expresses a maximum in its probability of position.

The existence of the $H_9O_4^+$ complex and its remarkable stability compared to the other complexes can also be demonstrated directly by mass spectrometry [5]. Thus, *Knewstubb* and *Tickner* [7] were able to show that a pronounced $H_9O_4^+$ frequency maximum occurs in the equilibrated ionization products formed in a glow discharge (Figure 4).

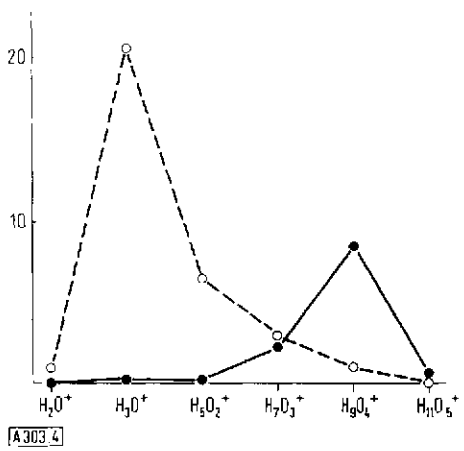



Fig. 4. Mass spectrometric frequency distribution of $H^+$ hydrate complexes in a glow discharge according to *Knewstubb* and *Tickner* [7].

○ - - - ○ Cathode distance: 1.5 cm; ●—● cathode distance: 6 cm. In the vicinity of the cathode, the equilibrium is markedly disturbed. Significant amounts of $H_3O^+$ (and small amounts of $H_2O^+$) are found only in this zone. Under normal conditions (greater cathode distance), $H_9O_4^+$ exhibits the greatest stability.

Ordinate: relative frequency [arbitrary units].

## Tertiary Hydration

Additional (relatively labile) hydrogen bridges, similar to those between $H_2O$ molecules in the liquid phase, are formed at the periphery of the $H_9O_4^+$ complex. The directed formation and breaking of these bonds results in "structural diffusion" of the entire hydrate complex. This diffusion is the rate-limiting step in the drift mobility of the proton in aqueous solution. The tertiary hydration shows strong dependence on temperature between 0 °C and 150 °C. Thus, it becomes particularly evident in the temperature dependence of the apparent molar heats of strong acids [1].

Similar structural relationships exist for the defect proton [8]; here, the hydroxyl ion $HO^-$ corresponds to the hydronium ion, and the (probably less stable) structural species $H_7O_4^-$ to the secondary hydrate complex $H_9O_4^+$.

## Mechanism of Proton Transport

The conductance in liquid $H_2O$ due to excess protons and defect protons may be explained by two possible mechanisms: a) The rate-determining step involves proton transfer from $H_3O^+$ to an $H_2O$ molecule of the secondary hydrate structure. Then the transformation within the tertiary structure (transition to the secondary and formation of a new tertiary hydrate structure) is complete before the proton jumps back into its previous central position.

b) Structural rearrangement (structural diffusion) presents the rate-limiting step. In this case, the proton will frequently oscillate between the primary and the secondary structure before the center of the complex is shifted by the length of one hydrogen bridge.

Direct decision as to which of the two mechanisms is dominant can be obtained by comparing the drift mobility of the proton in water and ice. Mechanism a) predominates in ice, at least for small proton concentrations, when the disorientation of the lattice caused by proton jumps can be neglected; in this case, the perfect tetrahedral hydrogen bridge structure is ideal for proton transfer.

Proton mobility in ice crystals has been determined directly by methods based on reaction kinetics [3, 32], and found to exceed the mobility in the liquid phase by one to two orders of magnitude. It then follows directly that mechanism b) predominates in water. The time required by the proton to travel a given distance (*e.g.* the length of a hydrogen bridge) can be calculated from the rate of drift by applying the Nernst-Einstein relationships. Measurements on ice crystals give values of $0.8\times10^{-13}$ to $1\times10^{-13}$ sec for the lifetime of an $H_3O^+$ ion, while the lifetime of $D_3O^+$ is larger by a factor of 6–8 [33]. On the other hand, the time constant for the liquid phase has a value of about $3\times10^{-12}$ sec, with a "normal" isotope effect ($\tau_{D_2O}/\tau_{H_2O}$) of $\sqrt{2}$. This time constant can, however, be interpreted only as the mean residence time of a proton in a given central position of the hydrate complex. Its order of magnitude is in agreement with the time constant for the structural rearrangement of water, which can be determined directly from ultrasonic absorption measurements [34].

The time constant for the defect proton, which can be derived from the drift mobility in the liquid phase, exceeds that for the excess proton by a factor of 1.75. In ice crystals this difference is probably somewhat great-

[32] *M. Eigen* and *L. de Maeyer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *60*, 1037 (1956).

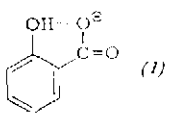
[33] *H. Ch. Spatz*, Diploma Thesis, Universität Göttingen, 1962.

[34] *L. Hall*, Physic. Rev. (2) *73*, 775 (1948).

er; the exact numerical value has not yet been determined in this case.

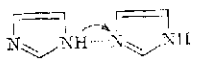
The short lifetime of the "individual" $H_3O^+$ ion should cause the corresponding vibration bands in the infrared and Raman spectra to appear diffuse. In aqueous solution, the $H_3O^+$ bands produced by crystalline monohydrates of strong acids are in fact not very sharp. A band with a very large half-width between 3 and 6 $\mu$ was recently identified in both the infrared [13, 14] and Raman spectra [15]; this corresponds to the continuous increase in absorption in the 2–3 $\mu$ region found previously [35]. However, this band cannot be assigned directly to the $H_3O^+$ ion, since it appears with nearly identical shape in the spectra of concentrated base solutions. Its half-width ($\Delta\lambda \approx 3\ \mu$) corresponds to a lifetime of about $10^{-13}$ seconds (see above [35a]), but it has not yet been shown unequivocally to which normal vibration it should be assigned. Since the lifetime involved here refers to an excited vibrational state, this lifetime can only indirectly be related to that obtained from kinetic measurements.

The high proton mobility in ice crystals – it differs from that of conduction band electrons in metals by only about 2 orders of magnitude, cf. $\sqrt{m_{H^+}/m_{e^-}}$ – and in particular the relatively large isotope effect point to a nonclassical behavior of the proton while overcoming the potential barrier. In the classical sense, the high transfer rate would correspond to practically unlimited mobility of the proton. Similar observations can be made for other hydrogen bridged systems. For example, *Weller* [36] observed a fluorescence transformation [36a] of salicylic acid anions *(1)* which occurs even at the



*(1)*

temperature of liquid hydrogen and which can be attributed to proton transfer between the hydroxyl and carboxyl groups. The time constant involved is $\tau \ll 10^{-8}$ sec. For imidazole crystals, *Zimmermann* [37] observed term splitting which he attributes to delocalization of the protons attached to the ring nitrogen ("protomerism") *(2)*. This delocalization is favored by the resonance of the ionic limiting structures.



*(2)*

## 2. The Kinetics of Recombination and Charge Transfer

The following structural and transport properties of hydrated protons are of particular importance for the kinetics of protolytic reactions:

1. Superposition of the potentials in hydrogen bridges permits practically unhindered proton transfer from the donor to the acceptor, provided the difference [37a] is

$$pK_{acceptor} - pK_{donor}$$

positive. The existence of a hydrogen bridge between the donor and acceptor is a basic prerequisite for this interaction.

2. The rate of proton transfer is determined by the frequency of encounters resulting from molecular thermal motion. We refer to such reactions as diffusion-controlled.

3. Owing to the fact that the proton jumps back and forth between the different $H_2O$ molecules of the complex at a very high rate, the effective cross-section for reactions involving $H_{aq}^+$ is determined by the extent of the entire hydrate complex.

In any mathematical treatment of such processes, it is advantageous (and completely correct in the formal sense) to consider the encounter and its reversal, the diffusion controlled separation of the reactants, as a step preliminary to the actual reaction [38]:

$$\underset{(a)}{H_{aq}^+ + X^{\ominus}} \rightleftharpoons \underset{(b)}{H_{aq}^+ \ldots X^{\ominus}} \rightleftharpoons \underset{(c)}{{}^{\oplus}HX} \qquad (1)$$

$$HO_{aq} + {}^{\oplus}HX \rightleftharpoons HO_{aq} \ldots {}^{\oplus}HX \rightleftharpoons H_2O + X^{\ominus} \qquad (2)$$

Under normal circumstances, the stationary concentration of the encounter complex (b) is invariably very small [compared to (a) and (c)]; on this assumption, the overall rate constants can be expressed as follows:

$$\vec{k} = \frac{k_{ab} \cdot k_{bc}}{k_{ba} + k_{bc}}\ ; \quad \overleftarrow{k} = \frac{k_{cb} \cdot k_{ba}}{k_{ba} + k_{bc}} \qquad (3)$$

The reaction is diffusion-controlled when $k_{bc} \gg k_{ba}$,

$$\vec{k} = k_{ab} \text{ and } \overleftarrow{k} = k_{ba}\frac{k_{cb}}{k_{bc}} \qquad (4)$$

In this case, proton transfer between two systems, HX and HY, can be treated analogously:

$$\underset{(a)}{HX + Y} \rightleftharpoons \underset{(b)}{XH \ldots Y} \rightleftharpoons \underset{(b')}{X \ldots HY} \rightleftharpoons \underset{(a')}{X + HY} \qquad (5)$$

[35] *R. Suhrmann* and *F. Breyer*, Z. physik. Chem. Abt. B *23*, 193 (1933).

[35a] The lifetime of a central $H_3O^+$ in the $H_9O_4^+$ complex should be somewhat greater and that of a peripheral $H_3O^+$ somewhat less than that in ice crystals because of the electrostatic effect of the secondary and tertiary $H_2O$ molecules which are oriented towards the center.

[36] *A. Weller*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *60*, 1144 (1956), recent data: personal communication.

[36a] Fluorescence transformation is the prototropic or protolytic transformation of a molecule due to a pK change upon excitation. According to *Th. Förster* (Fluoreszenz organischer Verbindungen. Vandenhoeck & Ruprecht, Göttingen 1951) this change can amount to about 5 to 7 pK units. It appears as a pH shift of the point where the fluorescence spectrum changes (from the spectrum of the acid towards the spectrum of the base) relative to the corresponding point where the absorption spectrum changes. The effect is only observable if the reaction takes place within the lifetime of the excited state ($\approx 10^{-8}$ sec).

[37] *H. Zimmermann*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *65*, 821 (1961).

[37a] pK = the negative logarithm of the acid dissociation constant.

[38] *M. Eigen*, Z. physik. Chem. (N.F.) *1*, 176 (1954).

(Proton transfer in the encounter complex can also take place via water molecules). In this case, the overall rate constants are

$$\vec{k} = \frac{k_{ab}\, k_{bb'}\, k_{b'a'}}{N} \quad \text{and} \quad \overleftarrow{k} = \frac{k_{a'b'}\, k_{b'b}\, k_{ba}}{N} \tag{6}$$

where

$$N = (k_{ba} + k_{bb'})\, k_{b'a'} + k_{ba}\, k_{b'b} = (k_{b'a'} + k_{b'b})\, k_{ba} + k_{b'a'}\, k_{bb'} \tag{7}$$

Here, the intermediate stages b and b′ are again assumed to be in a steady state. Diffusion-controlled reactions result when at least one of the conditions

$$k_{ba} \ll k_{bb'} \qquad k_{b'a'} \ll k_{b'b} \tag{8}$$

is fulfilled. Then, we have

$$\vec{k} = \frac{k_{ab}}{1 + K_b \cdot k_{ba}/k_{b'a'}} \quad \text{and} \quad \overleftarrow{k} = \frac{k_{a'b'}}{1 + k_{b'a'}/(k_{ba} K_b)} \tag{9}$$

The ratio of the rate constants for the two separation processes ($k_{ba}/k_{b'a'}$) for reactants of similar nature equals approximately unity. The factor $K_b$ is the equilibrium constant for proton exchange in the encounter complex. For $k_{ba} \approx k_{b'a'}$, $\log K_b$ is essentially equal to the pK difference of the two acids (HX and HY).

In protolytic reactions, the condition $k_{bc} \gg k_{ba}$ is identical with the assumption that proton transfer takes place immediately after formation of a hydrogen bridge between the reactants (encounter complex), before they again separate as a result of thermal motion. It is of no significance here that this rapid reaction step is followed by another step, *viz.* the breaking of the hydrogen bridge framework of the hydrate complex. This bond-breaking is a multimolecular process involving relatively large entropy and energy increments which partially cancel each other out. This breakdown of the complex structure can take place within $10^{-11}$ sec. For the reverse reaction, this event must be reflected in the equilibrium constants of the partial reaction c $\rightleftharpoons$ b [Equations (1) and (2)] or a′ $\rightleftharpoons$ b′ $\rightleftharpoons$ b [Equation (5)].

The constants $k_{ab}$ and $k_{ba}$ can be calculated from the equations of motion of the reactants (taking electrostatic interactions into account). According to *Debye* [39], one obtains for diffusion-controlled encounters:

$$k_{ab} = 4\pi N_L R_{ij} (D_i + D_j) \frac{\varphi_{ij}}{\exp(\varphi_{ij}) - 1} \tag{10}$$

and for the reverse reaction, *i.e.*, diffusion-controlled separation of the reactants [38]:

$$k_{ba} = (3/R_{ij}^2) \cdot (D_i + D_j) \frac{\varphi_{ij}}{1 - \exp(-\varphi_{ij})} \tag{11}$$

(where $N_L$ = Avogadro's number; $R_{ij}$ = reaction distance; $D_i$ and $D_j$ = diffusion coefficients of the reactants; $\varphi_{ij}$ = ratio of the potential energy of electrostatic interaction and the thermal energy kT).

[39] *P. Debye*, Trans. electrochem. Soc. *82*, 265 (1942).

For dilute solutions, the electrostatic interaction can be represented by a simple coulombic term:

$$\frac{z_i z_j e_o^2}{\varepsilon R_{ij}}$$

(where z = valence; $e_o$ = elementary charge, and ε = effective dielectric constant).

Equation (10) applies to reactants with spherical symmetry. Deviations from this structure must be accounted for by suitable correction factors. (If all quantities are expressed in c.g.s. units, then $k_{ab}$ must be divided by $10^3$ in order to arrive at the usual $M^{-1}$ $sec^{-1}$ dimensions. The quantity $k_{ba}$, being a rate constant of a first-order reaction, has the dimension $sec^{-1}$).

For protolytic reactions, the order of magnitude of $k_{ab}$ is generally $10^{10}$ to $10^{11}$ $M^{-1}$ $sec^{-1}$ (see below); the value of $k_{ba}$ is then between $10^{10}$ and $10^{11}$ $sec^{-1}$. Both constants are essential for the description of the reaction mechanism: $k_{ab}$ represents the maximum value of the overall rate constant for recombination; however, the value of $k_{ba}$ (in relation to $k_{bc}$) determines how closely the actual rate constant can approach this maximum value. For protolytic reactions, $k_{bc}$ is generally of the same order of magnitude as the reciprocal of the lifetime of $H_3O^+$ or $HO^-$ ($>10^{12}$ $sec^{-1}$) so that here the condition $k_{bc} \gg k_{ba}$ is satisfactorily fulfilled, and $k_{ab}$ represents the overall recombination rate constant $k_{H^+}$ or $k_{HO^-}$. The chemical effects, which are reflected in the acidity or basicity of the compound, are then essentially accounted for in the overall rate constant for the dissociation $HX \rightarrow X^\ominus + H^+$ or for the hydrolysis $X^- + H_2O \rightarrow HX + OH^\ominus$ [see Equation (4)]. However, there may be other effects in addition to the individual factors ($D_i + D_j$), $z_i z_j$ and $R_{ij}$ that also influence $k_{ab}$; these will be discussed in greater detail in Section 3.

Experimental study of the kinetics of acid-base reactions was made possible by the development of modern techniques. In

Table 3. Methods for studying fast reactions in solutions.

| Method | Time range [sec] | Method of recording |
|---|---|---|
| Relaxation [40] | | |
| Temperature jump | 1 $10^{-6}$ | Spectrophotometric, polarimetric, fluorimetric, conductometric |
| Pressure jump | $10-5\times10^{-5}$ | Conductimetric |
| Electric field pulse | $10^{-4}-10^{-8}$ | Conductimetric (spectrophotometric) |
| Electric traveling waves | $\approx 10^{-9}$ | impedance measurement |
| Dielectric absorption | $10^{-6}$ $10^{-9}$ | resonance line width (in superimposed, strong d. c. fields) |
| Sound absorption and dispersion [41] | $10^{-5}-5\cdot10^{-10}$ | resonance and reverberation light diffraction (Debye-Sears effect) impulse echo |
| Proton magnetic resonance [42] | $1-10^{-3}$ | line broadening (spin-echo) |
| Fluorescence transformation [43] | $\approx 10^{-8}$ | quantum yield, decay time |

[40] *M. Eigen* and *L. de Maeyer* in *A. Weissberger:* Technique of Organic Chemistry. Wiley, New York 1963, Vol. VIIIb, p. 895.

[41] *K. Tamm* in: Handbuch der Physik. Springer, Heidelberg 1961, Vol. XI/1, p. 202.

[42] *H. Strehlow* in *A. Weissberger:* Technique of Organic Chemistry. Wiley, New York 1963, Vol. VIIIb, p. 799.

[43] *R. M. Noyes* and *A. Weller* in *A. Weissberger:* Technique of Organic Chemistry. Wiley, New York 1963, Vol. VIIIb, p. 845.

general, the half-lives for attainment of equilibrium are substantially less than one second. For the normal acid and base species defined below, they are even less than 30 μsec. Most of the half-lives reported here were obtained from relaxation spectrometric studies in the time range of $10-10^{-9}$ sec. Some data obtained from nuclear magnetic resonance [44, 45] and of fluorescence transformation [43] studies were also used. Table 3 gives a list of the methods of measurement and their range of application. A detailed description can be found elsewhere [40–43].

## 3. Protolysis and Hydrolysis

### a) Reaction Mechanism

A simple acid-base equilibrium in aqueous solution can be represented by the general reaction diagram shown in Figure 5.

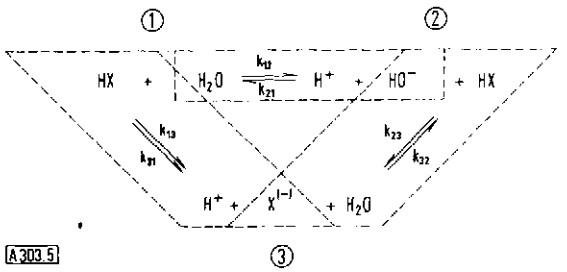



Fig. 5. Reaction scheme for an acid-base equilibrium in aqueous solution.

This diagram shows that the pH value of a solution can be established by means of two mutually indepent processes. We refer to these as protolysis and hydrolysis. In the case of protolysis ($1 \rightleftharpoons 3$), an excess proton ($H^+ \cdot nH_2O$) arises from dissociation of an acid molecule HX or disappears by direct recombination with the base molecule $X^\ominus$. In the case of hydrolysis ($3 \rightleftharpoons 2$), a defect proton ($HO^- \cdot H_2O$) is formed by reaction of the base $X^\ominus$ with an $H_2O$ molecule. The reverse reaction consists of direct recombination of $HO^-$ with the acid HX. The connection between the two reaction paths is brought about by the neutralization ($1 \rightleftharpoons 2$) and its reverse reaction, the dissociation of $H_2O$.

The rate of neutralization can be determined independently of other protolytic and hydrolytic processes only in pure water. Such measurements have been carried out [46] using various relaxation methods (high electric field pulse, temperature jump [47]). The values for the rate constant at 25 °C as determined by the various methods are in good agreement (cf. Table 4a).

Recombination of $H^+$ with $HO^-$ is one of the fastest reactions known. Its rate exceeds that of any other reaction of the same charge type in aqueous solution. Even the reaction of an excess proton with a solvated electron (polaron) in aqueous solution is slower [48] (cf. Table 4a).

In a molecular-kinetic sense, the high rate of reaction of the excess and defect proton is attributable to the special transport mechanism in hydrogen-bridged systems (see above). The orientation of the $H_2O$ molecules during an encounter by structural diffusion favors formation of hydrogen bridges between the two hydrate complexes and thus permits fast proton transfer. The effective reaction distance according to Equation (10) is therefore relatively large. It corresponds to the projection of three to four hydrogen bridges (assuming a bond angle of about 110 °). Both the activation energy [48] and the isotope effect (see Table 4a) are in accordance with the assumption of a diffusion-controlled reaction. The ratio of the recombination rate constants in water and in ice [33] also clearly reflects the influence of the mobilities (see Table 4a). In the hydrogen-bridged lattice of ice crystals, the rate of proton transfer is not restricted by structural diffusion (see above); recombination can therefore occur faster than in the liquid state [2].

### b) Relaxation Spectrum [40]

The kinetics for the establishment of equilibrium can generally be described by two coupled differential equations. By selecting as the variable $x_i(t)$ the deviations of the concentration of the two reactants from their equilibrium values (according to temperature and pressure), *e.g.*, $\delta c_{HX} \equiv x_1$ and $\delta c_{H^+} \equiv x_2$, then the remaining concentration variables are fixed by the secondary conditions:

$$\begin{aligned} \delta c_{X^-} &= -\delta c_{HX} &&= -x_1 \\ \delta c_{H_2O} &= -\delta c_{HX} - \delta c_{H^+} &&= -(x_1 + x_2) \\ \delta c_{HO^-} &= -\delta c_{H_2O} &&= x_1 + x_2 \end{aligned} \qquad (12)$$

At equilibrium ($x_i = 0$), gross change disappears. Hence, for conditions near equilibrium ($x_i \ll c_i$), the rate equations may be linearized. From the original relations ($\dot{x} \equiv dx/dt$), we obtain

$$\begin{aligned} \dot{x}_1 &= a_{11}x_1 + a_{12}x_2 \\ \dot{x}_2 &= a_{21}x_1 + a_{22}x_2 \end{aligned} \qquad (13)$$

where

$$\begin{aligned} a_{11} &= -[k_{13} + k_{31}\, c_{H^+} + k_{32} + k_{23}(c_{HO^-} + c_{HX})] \\ a_{12} &= k_{31}\, c_X - k_{23} c_{HX} \\ a_{21} &= k_{13} + k_{31}\, c_{H^+} - k_{12} - k_{21} c_{H^+} \\ a_{22} &= -[k_{12} + k_{21}\,(c_{H^+} + c_{HO^-}) + k_{31}\, c_X] \end{aligned} \qquad (14)$$

[44] *E. Grunwald, A. Loewenstein*, and *S. Meiboom*, J. chem. Physics *27*, 630, 1067 (1957); *S. Meiboom, A. Loewenstein*, and *S. Alexander*, ibid. *29*, 969 (1958); *A. Berger, A. Loewenstein*, and *S. Meiboom*, J. Amer. chem. Soc. *81*, 62 (1959).

[45] *E. Grunwald, P. J. Karabatsos, R. A. Kromhout*, and *E. L. Purlee*, J. chem. Physics *33*, 556 (1960).

[46] *M. Eigen* and *L. de Maeyer*, Z. Elektrochem. *59*, 986 (1955).

[47] *G. Ertl, H. Gerischer* and Z. Elektrochem. *65*, 629 (1961).

[48] *E. A. Taub* and *L. M. Dorfman*, Abstract, 144th National ACS Meeting, Los Angeles, March 1963; *E. J. Hart* and *J. W. Boag*, J. Amer. chem. Soc. *84*, 4090 (1963). See also *G. Czapski* and *H. Schwarz*, J. physic. Chem. *66*, 471 (1962); *E. Collinson, F. Dainton, D. Smith*, and *S. Tazaki*, Proc. chem. Soc. (London) *1962*, 140.

The (reciprocal) time constants $\tau_I$ and $\tau_{II}$, which are characteristic for the kinetics of equilibration, are the roots of the "characteristic equation"

$$\begin{vmatrix} \left(a_{11} + \frac{1}{\tau}\right) & a_{12} \\ a_{21} & \left(a_{22} + \frac{1}{\tau}\right) \end{vmatrix} = 0 \qquad (15)$$

and have the values

$$1/\tau_{I,\,II} = -\frac{S}{2}\left(1 \pm \sqrt{1-4P/S^2}\right) \qquad (16)$$

where

$$S = a_{11} + a_{22} \text{ and } P = a_{11}\,a_{22} - a_{12}\,a_{21} \qquad (17)$$

The coupling of protolysis and hydrolysis becomes evident primarily under neutral conditions. Here, the relaxation times can no longer be ascribed to a single reaction step.

An entirely analogous behavior is observed for coupled vibrations. Here, too, resonance measurements yield only the "normal frequencies," and not the eigenfrequencies of the isolated oscillators. In the case of chemical relaxation, the "normal coordinates" are given by a linear combination of the concentration variables $x_i$. The (reciprocal) relaxation times are assigned, as the negative eigenvalues of the matrix of the rate coefficients $a_{ik}$, to these normal coordinates.

The expression for the relaxation times $\tau_I$ and $\tau_{II}$ describes a relatively simple physical situation: the quantity $(-S)$ contains the sum of all the rate terms, and hence the sum of the reciprocal relaxation times for the three partial equilibria (neutralization, protolysis, and hydrolysis).

$$-S = [k_{12} + k_{21}(\bar{c}_{H^+} + \bar{c}_{HO^-})] + [k_{13} + k_{31}(\bar{c}_{H^+} + \bar{c}_X)]$$
$$+ [k_{32} + k_{23}(\bar{c}_{HO^-} + \bar{c}_{HX})] = 1/\tau_{12} + 1/\tau_{13} + 1/\tau_{23} \qquad (18)$$

Since the square-root term in Equation (16) can only assume values from 0 to 1, $(-S)^{-1}$ determines the order of magnitude of the shortest time constant. Hence, $\tau_I$ is always fixed by the highest rate in the over-all reaction system. Whenever $4P \ll S^2$ (see below), we have

$$\tau_I = -(S^{-1}). \qquad (19)$$

The term P is rather complicated. Using the relaxation times for individual systems defined above ($\tau_{ik}$), it can be represented as follows:

$$P = (1/\tau_{12})(1/\tau_{13}) + (1/\tau_{12})(1/\tau_{23}) + (1/\tau_{13})(1/\tau_{23}) - R \qquad (20)$$

with the remainder (negligible in many cases):

$$R = k_{31}\bar{c}_X k_{21}\bar{c}_{HO^-} + k_{23}\bar{c}_{HX}(k_{12} + k_{21}\bar{c}_{H^+})$$
$$+ (k_{23}\bar{c}_{HO^-} + k_{32})(k_{13} + k_{31}\bar{c}_{H^+}) \qquad (21)$$

Under the above condition, *i.e.*, $4P \ll S^2$, we have

$$\tau_{II} = -(S/P). \qquad (22)$$

It can be shown that this condition applies only if one of the relaxation times $\tau_{ik}$ becomes substantially shorter than the other two, *i.e.* $\tau_{ik} \ll \tau_{il} \lesssim \tau_{kl}$. $\tau_I$ is then given by this shortest relaxation time $\tau_{ik}$, whereas $\tau_{II}$ becomes greater than $\tau_{il}$ but less than $\tau_{kl}$. Whether the value of $\tau_{II}$ is closer to $\tau_{il}$ or to $\tau_{kl}$ depends on the special conditions that determine the magnitude of the remainder in Equation (20). If this term is negligible, we have

$$\tau_{II} \approx \frac{\tau_{il}\,\tau_{kl}}{\tau_{il} + \tau_{kl}} \qquad (23)$$

As an example of the situation described by Equations (19) and (22), let us consider a simple acidic or basic solution of finite concentration. In 0.1 M acetic acid, $c_{HX} \gg \bar{c}_X \approx c_{H^+} \gg \bar{c}_{HO^-}$; in a corresponding ammonia solution $c_X \gg c_{HX} \approx c_{HO^-} \gg \bar{c}_{H^+}$. These conditions are valid as long as the pH is either large or small compared to the pK of the acid, and the degree of dissociation is very much smaller than unity. In such systems, however, only one, *viz.* the longer, relaxation time can be measured. For acetic acid, this is the simple relaxation time $\tau_{13}$ for protolysis, for ammonia, it is that for hydrolysis ($\tau_{23}$). The shorter time constant $\tau_I$, determined by the terms $k_{23}\bar{c}_{HX}$ (acetic acid) and $k_{31}\bar{c}_X$ (ammonia) is not observable. This is because the concentration change (normal variable) associated with this constant, is immeasurably small owing to the extreme differences betwen $c_{HX}$ and $\bar{c}_{HO^-}$ and between $\bar{c}_X$ and $\bar{c}_{H^+}$, respectively. The terms arising from $\tau_{12}$ are also missing; they are cancelled out by the remainder in $\tau_{II}$. In general, two relaxation times can be measured only near neutrality (pH 5–9). The degeneration of the two relaxation times into one time constant in this case is of particular interest. This degeneration occurs when the relaxation times for protolysis ($\tau_{13}$) and hydrolysis ($\tau_{23}$) become equal and large, compared to the relaxation time for neutralization ($\tau_{12}$). In addition, $\bar{c}_{HX}$ and $c_X$ must become large compared to $\bar{c}_{H^+}$ and $\bar{c}_{HO^-}$. For acid-base systems with a pK of about 7, this condition is readily fulfilled in the neutral region. If the recombination of $H^+$ and $HO^-$ is sufficiently fast, then $\frac{1}{\tau_{12}} \ll \frac{1}{\tau_{13}}, \frac{1}{\tau_{23}}$, where $\frac{1}{\tau_{13}} = k_{31}c_X$ and $\frac{1}{\tau_{23}} = k_{23}c_{HX}$. In this case, there is a pH value (close to the pK value) at which $\tau_{13}$ and $\tau_{23}$ become equal

$$k_{31}\bar{c}_X = k_{23}\bar{c}_{HX} \qquad (24)$$

This means that $4P = S^2$, and the square-root term in Equation (16) disappears. Only one time constant is then obtained:

$$\tau = -(S^{-1}) \approx 2[k_{23}\bar{c}_{HX} + k_{31}\bar{c}_X]^{-1} \qquad (25)$$

This case is of particular importance in buffering and in acid-base catalysis.

Let us consider imidazole (pK = 6.95) as an example. The rate constants $k_{31}$ and $k_{23}$ are both of the same (maximum) order of magnitude (see Table 4g). Condition (24) is fulfilled at pH 7.2 ($\tau \approx 10^{-10}/C_0$ sec, where $C_0$ = total molar concentration of imidazole). Attainment of the overall equilibrium, which is characterized by a single relaxation time, is fastest at this pH. At pH above or below about 7, one of the relaxation times (the more important one) becomes longer. Correspondingly, under comparable concentration conditions, acid-base systems with pK values $\neq 7$ should also possess larger time constants in the neutral region (pH $\approx$ pK). Hence it

Table 4. Rate constants for the recombination of bases with $H^+$($k_{H^+}$) and of acids with $HO^-$($k_{HO^-}$).

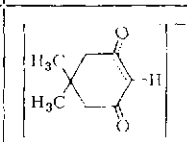
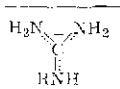
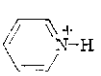
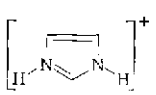
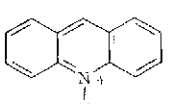
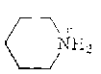
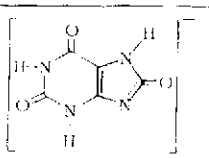
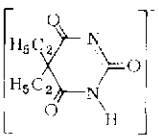
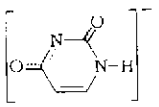
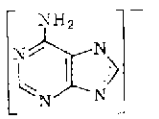
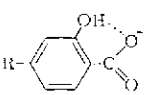
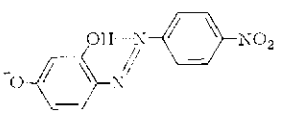
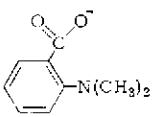
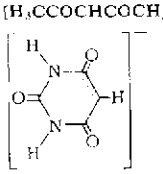
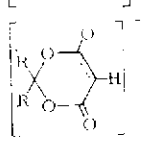
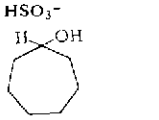
| Acid | Conjugate base | pK | $k_{H^+}$ [$M^{-1}$ sec$^{-1}$] | $k_{HO^-}$ | Ionic strength [mole/liter] | Temp. [°K] | Ref. |
|---|---|---|---|---|---|---|---|
| a) *Elementary ions* | | | | | | | |
| $H_2O$ | $HO^-$ | 15.75 | $1.4\times10^{11}$ | | 0 | 298 | [46] |
| $H_2O$ (ice) | $HO^-$ | 21.4 | $8.6\times10^{12}$ | | 0 | 263 | [2, 33] |
| $D_2O$ | $DO^-$ | 16.5 | $8.4\times10^{10}$ | | 0 | 298 | [49] |
| H | $e^-_{aq}$ | ≈12 | $2.3\times10^{10}$ | | 0 | 298 | [48] |
| HF | $F^-$ | 3.15 | $1.0\times10^{11}$ | | 0 | 298 | [50] |
| $H_2S$ | $HS^-$ | 7.24 | $7.5\times10^{10}$ | | 0 | 298 | [50] |
| $NH_4^+$ | $NH_3$ | 9.25 | $4.3\times10^{10}$ | | >0.1 | 298 | [45] |
| b) *Inorganic oxy-acids* | | | | | | | |
| $HSO_4^-$ | sulfate | 2 | $\approx1\times10^{11}$ | | 0.1 | 293 | [51] |
| $H_2CO_3$ | hydrogen carbonate | 3.77 | $4.7\times10^{10}$ | | 0 | 298 | [52] |
| $HCO_3^-$ | carbonate | 10.3 | | $\approx6\times10^9$ | 1 | 293 | [53] |
| $HPO_4^{2-}$ | ortho-phosphate | 11.71 | | $\approx2\times10^9$ | 0.1 | 298 | [54] |
| $HP_2O_7^{3-}$ | pyrophosphate | 8.45 | | $4.7\times10^8$ | 0.1 | 285 | [54] |
| $HP_3O_{10}^{4-}$ | tripolyphosphate | 7.87 | | $2.1\times10^8$ | 0.1 | 285 | [54] |
| $HATP^{3-}$ [a] | adenosine triphosphate | 6.50 | $>10^{10}$ | $1.2\times10^9$ | 0.1 | 285 | [54] |
| c) *Metal complexes* | | | | | | | |
| Pentaquocopper(II) ion | $[HOCu(H_2O)_5]^+$ | ≈7 | $\approx10^{10}$ | | <0.1 | 293 | [54] |
| Monoaquopentamminocobalt(III) ion | $[HOCo(NH_3)_5]^{2+}$ | 5.13 | $5\times10^9$ | | 0.1 | 283 | [54] |
| Triethylenediamminoplatinum(IV) ion | $[HNR\text{-}Pt(en)_2]^{3+}$ [b] | 5.30 | $1.9\times10^9$ | | 0.1 | 283 | [54] |
| d) *Aliphatic and aromatic hydroxy and carboxyl compounds* | | | | | | | |
| Benzoic acid | $H_5C_6{-}COO^-$ | 4.20 | $3.5\times10^{10}$ | | 0 | 298 | [55] |
| Acetic acid | $CH_3COO^-$ | 4.74 | $4.5\times10^{10}$ | | 0 | 298 | [56] |
| β-Naphthol [c] | $H_7C_{10}{-}O$ | 3.09[c] | $5.1\times10^{10}$ | | 0 | 298 | [57] |
| *p*-Nitrophenol | $p\text{-}O_2N{-}H_4C_6{-}O$ | 7.14 | $3.6\times10^{10}$ | | 0 | 298 | [50] |
| Phenol | $H_5C_6{-}O$ | 9.98 | | $\approx1.4\cdot10^{10}$ | 0 | 298 | [58] |
| Dimedone (enol) |  | 5.23 | $3.0\times10^{10}$ | | 0 | 298 | [59] |
| Acetylacetone (enol) | $[H_3C{-}CO{-}CH{-}CO{-}CH_3]$ | 8.24 | $3.10\times10^{10}$ | $1.9\times10^7$ | 0 | 298 | [60] |
| | | | | | 0.1 | 283 | |
| Glucose | $C_6H_{11}O_6^-$ | 12.3 | | $>10^{10}$ | 0 | 298 | [58] |
| e) *Sulfhydryl compounds* | | | | | | | |
| Hydrogen sulfide | $HS^-$ | 7.24 | $7.5\times10^{10}$ | | 0 | 298 | [50] |
| Thioglycol | $HO{-}(CH_2)_2{-}S^-$ | 9.5 | | $\approx10^9$ | 0 | 298 | [58] |
| f) *Aliphatic and aromatic amines* | | | | | | | |
| $NH_4^+$ | ammonia | 9.25 | $4.3\times10^{10}$ | $3.4\times10^{10}$ | 0 | 293 | [38, 45, 56] |
| $(CH_3)_3NH^+$ | trimethylamine | 9.79 | $2.5\times10^{10}$ | $2.1\times10^{10}$ | 0 | 293 | [45, 61] |
| $^-OOC{-}CH_2{-}NH_3^+$ | glycine | 9.78 | | $1.4\times10^{10}$ | 0 | 293 | [61] |
| $H_5C_6{-}NH_3^+$ | aniline | 4.58 | $>10^{10}$ | | 0 | 293 | [58] |
|  | guanidine (arginine) | ≈12.5 | | $>10^{10}$ | 0 | 298 | [58] |
| g) *Heterocyclic nitrogenous bases* | | | | | | | |
|  | pyridine | 5.18 | $>10^{10}$ | | 0 | 293 | [58] |
|  | imidazole | 6.95 | $1.5\times10^{10}$ | $2.5\times10^{10}$ | 0 | 298 | [62] |
|  | acridine [c] | 10.65[c] | | $1.9\times10^{10}$ | 0 | 298 | [63] |
|  | piperidine | 11.13 | | $2.2\times10^{10}$ | 0 | 298 | [58] |
| Uric acid |  | 5.7 | $8.5\times10^9$ | | 0 | 298 | [59] |

Table 4 (Continued)

| Acid | Conjugate base | pK | $k_{H^+}$ [$M^{-1}$ $sec^{-1}$] | $k_{HO^-}$ | Ionic strength [mole/liter] | Temp. [°K] | Ref. |
|---|---|---|---|---|---|---|---|
| 5,5-Diethylbarbituric acid |  | 7.98 | $1.1\times10^{10}$ | | 0 | 298 | [59] |
| Uracil |  | 9.45 | | $9.8\times10^{9}$ | 0 | 298 | [58] |
| Adenine |  | 9.80 | | $1.0\times10^{10}$ | 0 | 298 | [58] |
| h) *Phosphines* | | | | | | | |
| $(CH_3)_3PH^+$ | trimethylphosphine | 8.8 | $5\times10^{9}$ | $4.6\times10^{7}$ | ≈1 | 295 | [64] |
| i) *Amino-polycarboxylic acids* | | | | | | | |
| Nitrilotriacetic acid | $N(CH_2COO^-)_3$ | 9.73 | | $1.4\times10^{7}$ | 0.1 | 285 | [54] |
| Ethylenediaminetetraacetic acid | $(CH_2)_2[N(CH_2COO^-)_2]_2$ | 10.26 | | $3.75\times10^{7}$ | 0.1 | 285 | [54] |
| k) *Hydrogen, bond chelates* | | | | | | | |
|  | Alizarine S (anion) (salicylate) | 11.05 | | $1.4\times10^{7}$ | 0.1 | 285 | [54] |
|  | 2,4-dihydroxy-4'-nitroazobenzene (anion) | 11.90 | | $4.75\times10^{5}$ | 0.1 | 285 | [54] |
| Di-(n-propyl)malonic acid | $(C_3H_7)_2C(COO^-)_2$ | 7.41 | | $5.3\times10^{7}$ | 0.1 | 285 | [54] |
| *N,N*-Dimethylanthranilic acid |  | 8.42 | | $1.1\times10^{7}$ | 0.1 | 285 | [54,55] |
| l) *CH-Acids* | | | | | | | |
| HCN | $CN^-$ | 9.1 | | $3.7\times10^{9}$ | ≈0 | 298 | [65] |
| Acetone | $[H_3CCOCH_2]^-$ | ≈20 | $\approx5\times10^{10}$ | $2.7\times10^{-1}$ | 0 | 298 | [66] |
| Acetoacetic ester | $[H_3CCOCHCOOR]^-$ | 10.68 | $5.8\times10^{7}$ | | 0 | 298 | [66] |
| Acetylacetone | $[H_3CCOCHCOCH_3]^-$ | 9.0 | $1.2\times10^{7}$ | $4\times10^{4}$ | 0.1 | 285 | [60] |
| Barbituric acid |  | 4.0 | $1.0\times10^{5}$ | | 0.1 | 285 | [67] |
| Meldrum's acid |  | 5.3 | $4.8\times10^{5}$ | | 0.1 | 285 | [67] |
| m) *Anhydro acids* | | | | | | | |
| $CO_2(+H_2O)$ | $HCO_3^-$ | 6.35 | $5.6\times10^{4}$ | $1\times10^{4}$ | 0 | 298 | [68,69] |
| $SO_2(+H_2O)$ | $HSO_3^-$ | 1.8 | $2\times10^{8}$ | | 0 | 298 | [70] |
| Tropylium ion $(+H_2O)$ |  | 4.75 | $6.6\times10^{4}$ | | 0.1 | 285 | [71] |
| $I_2(+H_2O)$ | $I_2OH^-$ (→ IOH + $I^-$) | 9.82[d] | $1.6\times10^{10}$ | $>10^{9}$ | 0.1 | 293 | [72] |

[a] ATP = adenosine triphosphate. [b] $H_3NR^+$ = en = $H_2N-(CH_2)_2-NH_2$. [c] In an excited state. [d] Referred to $I_2OH^-$ as conjugate base.


[49] *G. Ertl* and *H. Gerischer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 560 (1962).

[50] *M. Eigen* and *K. Kustin*, J. Amer. chem. Soc. *82*, 5952 (1960).

[51] *M. Eigen*, *G. Kurze*, and *K. Tamm*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *57*, 103 (1963).

[52] *M. Eigen*, *K. Kustin*, and *R. Munson*, Z. physik. Chem. (N. F.), in the press.

[53] *M. Eigen*, *G. Maass*, and *G. Schwarz*, Z. physik. Chem. (N. F.), in the press.

[54] *M. Eigen* and *W. Kruse*, Z. Naturforsch. *17b* (1963), in the press.

[55] *M. Eigen* and *E. M. Eyring*, J. Amer. chem. Soc. *84*, 3254 (1962).

[56] *M. Eigen* and *J. Schoen*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 483 (1955).

follows that, from a kinetic standpoint, imidazole is an optimum buffer (and catalyst, see below). The same is true for any other acid-base system with a pK near 7 and with a maximum recombination-rate constant in the neutral region. The condition that pH $\approx$ pK for optimum buffering is already known from equilibrium theory. However, it holds in kinetics only if the recombination rate constants $k_{31}$ and $k_{23}$ (and hence, if pK $\approx$ 7, also the dissociation rate constants $k_{13}$ and $k_{23}$) are of the same order of magnitude. For some acids and bases, this is not so (see below). Since at least one of the rate constants is not at a maximum value corresponding to diffusion-controlled reactions, less advantageous kinetic conditions are obtained for buffering and catalysis. This is also true when several acid-base systems are present together and when in addition to the protolysis and hydrolysis reactions under discussion direct proton transfer between the various systems takes place (see Section 4).

### c) Rate Constants

Table 4 gives a list of the rate constants for the most important types of inorganic and organic acids and bases. Only the rate constants for recombination of the base with $H^+$ ($k_{H^+} = k_{31}$) and of the acid with $HO^-$ ($k_{HO^-} = k_{23}$) are given. In the pK range 5–9, both constants are generally important for the process of equilibration. The rate constants for the reverse reactions (acid dissociation and hydrolysis) can be calculated from $k_{31}$ or $k_{23}$ using the pK values:

$$k_{13} = k_{31} \times 10^{-pK}\ sec^{-1}$$

$$k_{32} = k_{23} \times 10^{-(14-pK)}\ sec^{-1}.$$

It should be kept in mind, however, that the pK values cited are referred to zero ionic strength. For the rate constants in Table 4 that are given for finite ionic strengths, the pK values as well as the ion product of water must therefore be corrected, using the (known) activity coefficients, in order to correspond to these ionic strengths before they can be used to compute $k_{13}$ and $k_{23}$.

Apart from a few well-understood exceptions, the order of magnitude of the recombination constants is between $10^9$ and $10^{11}$ liter/mole·sec for all the acids of the OH-, SH- (partly), NH- and $NH^+$-types whose pK values lie in the range −1 to +15. These values are consistent with the expectations discussed in Sections 1 and 2. As will be shown below, the absolute values of the rate constants corresponding to these "normal" acids and bases can be expressed quantitatively. This offers the possibility of evaluating the kinetic constants of all "normal" acid-base systems (including those that have not yet been investigated). This is important for enzyme kinetics, since the exact pK values of acid and basic groups occurring in proteins are not always known. Nearly all the groups that occur in natural amino acids fall into the category of "normal" acids and bases. These groups are (in addition to the carboxyl and α-amino groups) the second carboxyl in aspartic and glutamic acids, the phenolic hydroxyl in tyrosine, the aliphatic hydroxyls in serine and threonine, the sulfhydryl group in cysteine, the ε-amino group in lysine, the imidazole residue in histidine, and the guanidyl group in arginine. Nucleic acid constituents, which are important as substrates, such as phosphate, sugars, and purine and pyrimidine bases (cyclic NH, amino, and enolic hydroxyl groups) also belong in this category. The CH-acids (see below), which are also important as substrates, and some "normal" acids in which special structural relationships (internal hydrogen bridging, *etc.*) prevail form exceptions.

Let us now examine in detail the factors which determine the absolute values of rate constants.

On the basis of the considerations discussed in Section 2, the encounter frequency depends on mobility, reaction distance, possible steric effects, and charge of the two reactants. For the type of reaction under discussion here, the first two quantities do not vary greatly. They depend essentially on the properties of the excess and defect proton discussed above. In agreement with this, all $k_{H^+}$ rate constants generally exceed the $k_{HO^-}$ constants by a factor of 2–3, provided the reactions are diffusion-controlled. The frequency of encounter is rate-determining only if recombination to the acid or base is sufficiently fast, *i.e.*, is complete before the reactants again separate as a result of thermal motion. This requires complete superposition of their potentials and hence a negligibly small activation energy. This requirement is met only if the excess or defect proton has free access to the reaction site via hydrogen bridging (lone electron pair of the base or proton in the acid molecule) and if the reactants are already in a configuration suitable for reaction. Hence, in discussing $k_{H^+}$ and $k_{HO^-}$, we must consider essentially the following four effects:

1. Spatial symmetry and steric factors
2. Electrostatic interactions
3. Hydrogen bond structure
4. Electron distribution (resonance, tautomerism), and molecular structure.


[57] *A. Weller*, Z. physik. Chem. (N.F.) *17*, 224 (1958).

[58] *G. Maass*, unpublished work.

[59] *M. Eigen, E. M. Eyring*, and *G. Ilgenfritz*, unpublished work.

[60] *M. Eigen* and *W. Kruse*, unpublished work.

[61] *M. Eigen, G. Maass*, and *G. Schwarz*, unpublished work.

[62] *M. Eigen, G. G. Hammes*, and *K. Kustin*, J. Amer. chem. Soc. *82*, 3482 (1960).

[63] *A. Weller*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 956 (1957).

[64] *B. Silver* and *Z. Luz*, J. Amer. chem. Soc. *83*, 786 (1961).

[65] *J. Stuehr, E. Yeager, Th. Sachs*, and *F. Hovorka*, J. chem. Physics *38*, 587 (1963).

[66] *R. P. Bell* in: The Proton in Chemistry. Cornell University Press, Ithaca 1959, p. 161.

[67] *G. Ilgenfritz*, Diploma Thesis, Universität Göttingen, 1963.

[68] *F. J. W. Roughton*, J. Amer. chem. Soc. *63*, 2930 (1941).

[69] *S. Ljunggren* and *O. Lamm*, Acta chem. scand. *12*, 1834 (1958); *J. Meir* and *G. Schwarzenbach*, Helv. chim. Acta *40*, 907 (1957).

[70] *M. Eigen, K. Kustin*, and *G. Maass*, Z. physik. Chem. (N.F.) *30*, 130 (1961).

[71] *W. Kruse*, unpublished work.

[72] *M. Eigen* and *K. Kustin*, J. Amer. chem. Soc. *84*, 1355 (1962).

The absolute strength of the acid or base (or the electrophilicity or nucleophilicity) affects the recombination rate only if condition 4 is controlling. In diffusion-controlled reactions, acidity and basicity (depending on pK) are reflected only in the rate constants for acid dissociation ($k_{13}$) or hydrolysis ($k_{32}$).

These effects are evident in the examples given in Table 4 (for more detailed information see [73]).

*1.* The reduced symmetry of $HS^-$ (3 electron pairs) compared to $F^-$ (4 electron pairs) causes a decrease in $k_{H^+}$ by a factor of 0.75. $HO^-$ differs from $HS^-$ in its mechanism of motion (structural diffusion) which in the case of $HO^-$ promotes orientation of the hydrate regions on encounter, so that reaction is favored. For carboxylates, the proton cannot penetrate beyond a hemisphere (factor: 0.5). The symmetry factor, however, is not always as evident as in this case. In the recombination of $HO^-$ with substituted amines, one would expect a decrease in the rate constant relative to the value for $NH_4^+$. Instead, a rate increase is first observed for methylamine followed by a (relatively slight) decrease towards trimethylamine. Here the influence of symmetry is evidently cancelled out by another effect. In water, the hydrophobic methyl groups effect structural aggregation and thus increase the reaction distance (which in reactions between $H^+$ and $HO^-$ is determined by the extension of the hydrogen bridge structure in the vicinity of the reactants). Thus, for example, the rate constant for ethanolamine is less than that for ethylamine or even propylamine [61]. This effect manifests itself particularly in the apparent molar heats of these compounds; it also causes anomalies in acid-base catalysis [74,75].

*2.* Simple electrostatic interactions also have only a relatively small effect on the recombination rates. This is because $H^+$ always adds onto a lone electron pair (*i.e.* to a negative site of the base molecule), whereas $HO^-$ always undergoes recombination with a positively charged reactant, *i.e.* the proton of the acid. Repulsion effects due to excess charge of the same sign are therefore always attributable to more distant groups. As shown by examples b) and c) of Table 4, the rate constant decreases by a factor of 2–3 (for an ionic strength of 0.1) for each charge of equal sign on the other reactant. This applies only to charge centers which are sterically near to each other. More distant groups eventually tend to exert only a very slight effect, *e.g.* heptaphosphate is only negligibly different from triphosphate [54]).

*3.* The effect of the hydrogen bridge structure has already been pointed out in the discussion of amines; it is much more evident from examples i) and k) of Table 4. Here, recombination of $HO^-$ with the acid proton is hindered by disturbance or blockage of the hydrogen bonds between the reactants. In the case of amino polycarboxylic acids, such disturbance is caused by the presence of negatively charged carboxyl groups. These groups disturb the orientation of $H_2O$ molecules in the vicinity of the ammonium proton, thus hindering proton transfer to the hydrated $HO^-$. In hydrogen-bridged chelates of the salicylic acid type or in *o*-hydroxyazo compounds (Table 4 k), approach to the proton is completely blocked. Only after the intramolecular hydrogen bridge is broken (*i.e.* when the molecule rearranges to an isomeric structure by rotation of a group participating in a hydrogen bridge) can a hydrogen bridge arise between the acid proton and the hydrated $HO^-$. Hence, the constant $k_{HO^-}$ is reduced by the value of the stability constant for the internal hydrogen bridge (in $H_2O$ as solvent) compared to the $k_{HO^-}$ values for diffusion-controlled reactions [54]. Whereas the $k_{HO^-}$ values for diffusion-controlled reactions are entirely independent of the basicity of the compound, in the case of hydrogen-bridged chelates the value of the rate constant of recombination reflects the amount of internal hydrogen bridging. The stability of the hydrogen bond depends on the electronegativity of the proton-acceptor group, on any excess charges present, on steric and resonance stabilization of the chelate ring (six-membered rings possess maximum stability), and on other factors.

The chelate effect is of practical interest in relaxation measurements carried out with indicators above pH 11. Many such indicators are of the hydrogen-bridge chelate type mentioned (*e.g.* Tropeolin O, Alizarin Yellow S, *etc.*) and hence are not suitable for use in very fast reactions.

It should be stressed that it is not only the high mobility of the proton as an elementary particle, but primarily the existence of hydrogen bridges that accounts for the high rates of protolytic and hydrolytic reactions relative to electron transfer reactions. Thus, for example, the reaction of the proton with $HO^-_{aq}$ is nearly one order of magnitude faster than the reaction of the proton with a solvated electron (polaron) (Table 4a; the rate of this reaction has been determined only recently with the aid of a pulse radiolysis method [48].) In the case of the neutralization reaction, the proton is led through hydrogen bridges to the electron localized in $HO^-$. On the other hand, the solvated electron (polaron) is delocalized and less likely to undergo recombination. The corresponding hydrolytic reactions of $e^-_{aq}$ are relatively slow, although in aqueous solution, the hydrogen atom is a relatively strong acid. The rate constant for the reaction

$$e^-_{aq} + H_2O \rightarrow HO^- + H$$

lies between $10^3$ $sec^{-1}$ (extrapolated as a lower limit) from measurements on dilute solutions of $H_2O$ in ethylenediamine [76]) and $4\times10^4$ $sec^{-1}$ (obtained as upper limit from pulse radiolysis measurements [48]). The rate constant for the reverse reaction was estimated by *Jortner* and *Rabani* [77] to be $6\times10^5$ $sec^{-1}$. Although the error in these (experimental) values may still be relatively large, it is clear that lack of a hydrogen bridge structure leads to reaction rates which are substantially lower than those of "normal" acids and bases. This is true even for small, highly mobile reactants. As shown by the data under i and k in Table 4, any disturbance of the hydrogen bridge structure in the vicinity of the proton donor and acceptor has a greater effect than simple electrostatic repulsion or steric hindrance.

*4.* If the acid and its conjugate base differ in their electron distribution and molecular structure, *i.e.* if the recombination with $H^+$ or $HO^-$ is associated with a resonance or tautomeric transformation, then the reaction rates may be relatively low, as indicated by the examples under l and m in Table 4. Compounds of the CH- and carbonium type belong to this category.

In general, C–H compounds, *e.g.* simple hydrocarbons, are much too weak acids to be of interest in our considerations. However their acidity can be markedly increased by introducing suitable substituents (*e.g.* halogen). The conjugate base of the CH-acid is a carbanion-type compound. It can be stabilized by delocalization of the negative charge, as in the case of nitroparaffins or the ketones listed in Table 4l. Here, resonance exists between the enolate and carbanion structure of the conjugate base.

Let us consider acetylacetone as an example. The reaction of the negative ion with $H^+$ to give the enol (Table 4d) constitutes a "normal" diffusion-controlled recombination. The reaction with $HO^-$ (Table 4d) is somewhat slower, because the enol is stabilized by an internal hydrogen bridge. The corresponding rate constants for the ketone (Table 4l), on the other hand, are several orders of magnitude smaller. This is due to two interrelated factors:

a) the CH or the $C^-$ group do not readily form hydrogen bridges;

[73] *M. Eigen, W. Kruse, G. Maass,* and *L. de Maeyer* in: Progress in Reaction Kinetics. Pergamon Press, London 1963, Vol. II.

[74] *R. P. Bell* in: The Proton in Chemistry. Cornell University Press, Ithaca 1959.

[75] *A. A. Frost* and *R. G. Pearson:* Kinetics and Mechanism. 2nd Edit., Wiley, New York 1961.

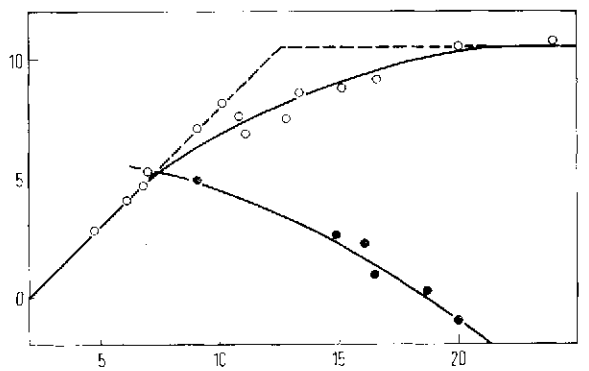
[76] *R. Dewald, J. L. Dye, M. Eigen,* and *L. de Maeyer,* unpublished work.

[77] *J. Jortner* and *J. Rabani,* J. physic. Chem. *66,* 2081 (1962).

b) the recombination is associated with a charge displacement and structural modification.

The second factor similarly manifests itself also in the reaction of $CO_2$ with $HO^-$ or of $HCO_3$ with $H^+$ (to give $CO_2 + H_2O$) or in corresponding reactions of carbonium-type compounds.

The widely varying values listed in Table 4 l and m show no obvious general regularities. For example, in the case of acetone, recombination with $H^+$ is practically diffusion-controlled, whereas that with $HO^-$ is very slow. The reaction of $HCO_3^-$ with $H^+$ to give $CO_2$ (linear complex) is slow compared to the analogous formation of $SO_2$ (bent molecule), even though the latter reaction is not diffusion-controlled either. However, regularities do exist within individual groups of compounds; these will become clear from the discussion presented in the following section. The rate of recombination with $H^+$ and $HO^-$ for compounds of this class is associated with the pK difference of the proton donor and acceptor. This is clearly indicated by a plot of log $k_{H^+}$ and log $k_{HO^-}$ *vs.* pK for a few ketones (Fig. 6). In the case of chloroacetone (pK = 16.5), the pK difference with respect to




A 303.6

Fig. 6. Dependence of the recombination rate constants $k_{H^+}$ (○—○) and $k_{HO^-}$ (●—●) on their pK in the protolysis of ketonic compounds. Experimental data are from [60, 78, 79]. The broken line denotes the linear extrapolation.

Ordinate: log $k_{H^+}$ and log $k_{OH^-}$.
Abscissa: pK.

the hydrated proton is very large ($\approx 18$) so that recombination of the anion with $H^-$ is very fast. Conversely, the difference with respect to $H_2O$ is small (−0.8): recombination of the ketone with $HO^-$ is therefore slow. In the case of the relatively "strong" barbituric acid (ketone), $k_{H^+}$ is relatively small. It also becomes clear now why the resonance stabilization difference between the acidic and basic forms of the carboxylic acids, phenols, aromatic amines, and other compounds listed under b–g in Table 4 is not reflected in the rates of recombination. As will be shown in the following section, this effect applies to $k_{H^-}$ and $k_{HO^-}$ only when the pK differences between the proton donor and acceptor are relatively small. Qualitatively, however, the behavior is not much different from that of the compounds listed under l and m in Table 4. This problem will be discussed further in the following section, in connection with the question of the definition of "pseudo acids."

Processes of the type just described are decisive for many important reactions of organic chemistry such as the keto-enol rearrangement, halogenation of organic molecules, aldol condensation, *etc.* The fast elementary stages of these reactions can be identified separately using relaxation methods. For example, it is possible to determine separately the rates of protolytic reactions of the keto and enol forms of heterocyclic ring compounds such as barbituric acid, Meldrum's acid [67], *etc.*, even if one of these forms is present in concentrations of $< 0.1$ % of the other. In the relaxation spectrum, the reactions of the keto and enol forms appear in the millisecond and microsecond range, respectively. Until now, relatively little was known about the position of the keto-enol equilibrium for these compounds.

Another class of "anhydro acids" is represented in Table 4 m by $I_2$. Here, the equilibrium is attained relatively slowly, because it is coupled with a further transformation:

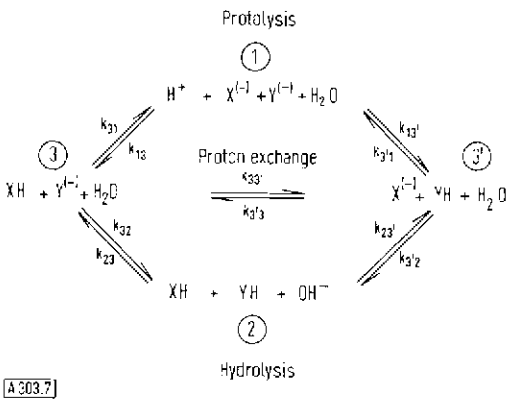
$$X_2 + H_2O \rightleftharpoons X_2OH^- + H^+ + XOH \rightleftharpoons X^- + H^+$$

The relaxation times for $Cl_2$, $Br_2$, and $I_2$ are in the millisecond range; equilibration occurs most rapidly for $Br_2$ (see [72]). The first step in this scheme, however, consists of a normal protolytic reaction with $k_{H^+}$ values of the order of $10^{10}$ $M^{-1}$ $sec^{-1}$.

## 4. Proton Transfer between Different Acid-Base Systems

### a) Reaction Mechanism

In the protolysis and hydrolysis treated in Section 3, proton transfer takes place between the conjugated acid-base pair and the solvent. Let us now consider the more general case of proton transfer between two different acid-base pairs in the presence of water as solvent. The general reaction scheme is shown in Figure 7 [*]. Here, the $H_2O$ molecules (present in large




A 303.7

Fig. 7. Reaction scheme for proton transfer between two different acid-base pairs in the presence of water.

excess as the solvent) are not explicitly shown. However, they participate as reactants in the hydrolytic reactions (3 → 2) and (3′ → 2); hence, their dissociation equilibrium $H_2O \rightleftharpoons H^- + HO^-$ must also be considered.

A diagram of this kind describes both the reaction behavior of an acid-base system in the presence of a buffer and the process of pH indication. In these reactions, maintenance of a constant pH value requires the presence of excess buffer, while the indicator, on the other hand, must be present in minute concentration so as not to mask the behavior of the system. In simple cases, the mechanism of acid-base catalysis and of analogous enzymatic processes (to be described in more detail in the second part) can also be represented by such a reaction scheme.

[78] *R. P. Bell* [74], p. 163 et seq.

[79] *R. G. Pearson* and *R. L. Dillon*, J. Amer. chem. Soc. *75*, 2439 (1953).

[*] Owing to the notation chosen to represent this reaction diagram, certain reaction rates are necessarily denoted by symbols different from those used in the protolysis-hydrolysis scheme (Fig. 5). $k_{13}$ and $k_{31}$ have a different meaning: $k_{13}$ in this case refers to the recombination with $H^-$, $k_{31}$ to dissociation of the acid.

b) Relaxation Times

Protolysis-hydrolysis of an acid-base pair in aqueous solution can be completely described by two relaxation times [cf. Equation (16)]. The presence of a second acid-base pair results in a number of additional reactions (protolysis and hydrolysis in the system $HY/Y^{\ominus}$, direct proton exchange with $HX/X^{\ominus}$), but only in one additional normal coordinate. The concentration change for HY always equals that for $Y^{\ominus}$. The reaction diagram (Figure 7) is thus completely described by three relaxation times. Since simultaneous occurrence of three relaxation times is extremely rare, discussion of the complete expression – the solution involves the roots of a cubic equation – can be omitted. Instead, let us consider the following simpler cases.

1. pH $\approx$ 7. The reactants, HX, $X^{\ominus}$, HY, and $Y^{\ominus}$ are all present in finite condentration ($\gg 10^{-7}$ M). The essential transformation consists of a direct proton transfer, described by reaction (3 $\rightleftharpoons$ 3') in Figure 7. This direct transfer is generally so fast that the transformation via states (1) and (2) may be neglected (otherwise cf. case 2). The reciprocal relaxation time for this process is then:

$$\frac{1}{\tau} = k_{33'}(\bar{c}_{HX} + \bar{c}_{Y}) + k_{3'3}(\bar{c}_{X} + \bar{c}_{HY}). \qquad (26)$$

If the systems $HX/X^{\ominus}$ and $HY/Y^{\ominus}$ are present in equimolar amounts, then $1/\tau$ is a linear function of the total (weighed in) concentration in contrast to the $1/\tau$ obtained from Equation (16).

2. pH $\approx$ 4 to 10. The concentrations of HX, $X^{\ominus}$, HY, and $Y^{\ominus}$ are still large compared to $c_{H^+}$ and $c_{HO^-}$; the reactions taking place via the intermediate states (1) and (2), which can be considered to be in a steady state must, however, no longer be neglected. Hence, $k_{33'}$ and $k_{3'3}$ in Equation (26) must be replaced by the following expressions:

$$k^{*}_{33'} = k_{33'} + \frac{k_{31}k_{13'}}{k_{13}\bar{c}_{X} + k_{13'}\bar{c}_{Y}} + \frac{k_{32}k_{23'}}{k_{23}\bar{c}_{HY} + k_{23'}\bar{c}_{HX}}$$
$$k^{*}_{3'3} = k_{3'3} + \frac{k_{3'1}k_{13}}{k_{13}\bar{c}_{X} + k_{13'}\bar{c}_{Y}} + \frac{k_{3'2}k_{23}}{k_{23}\bar{c}_{HY} + k_{23'}\bar{c}_{HX}} \qquad (27)$$

In general, of course, only one of the additional terms appears at a time; for pH $<$ 7, it is the first term (with (1) as intermediate stage), and for pH $>$ 7 the second (with (2) as intermediate stage).

3. The concentration of $H^+$ (pH $\ll$ 7) or $HO^-$ (pH $\gg$ 7) can no longer be neglected compared to the concentration of the two acid-base pairs. In this case, either only the upper (pH $\ll$ 7) or only the lower (pH $\gg$ 7) half of the reaction diagram (Fig. 7), is valid. In either case, two relaxation times are obtained; they can be expressed by relations similar to Equation (16). However, here the coefficients $a_{ik}$ are:

$$a_{11} = [k_{33'}(\bar{c}_{HX} + \bar{c}_{Y}) + k_{3'3}(\bar{c}_{X} + \bar{c}_{HY}) + k_{31} + k_{13}c_{H^+}] \qquad (28)$$

or

$$= -[k_{33'}(\bar{c}_{HX} + \bar{c}_{Y}) + k_{3'3}(\bar{c}_{X} + \bar{c}_{HY}) + k_{32} + k_{23}c_{HO^-}]$$

$$a_{22} = -[k_{13}c_{X} + k_{3'1} + k_{13'}(\bar{c}_{H^+} + \bar{c}_{Y})]$$

or

$$= -[k_{23}\bar{c}_{HY} + k_{3'2} + k_{23'}(\bar{c}_{HO^-} + \bar{c}_{HX})]$$

$$a_{12} = -[k_{33'}\bar{c}_{HX} + k_{3'3}\bar{c}_{X} + k_{13}c_{X}$$

or

$$= -[k_{33'}\bar{c}_{Y} + k_{3'3}\bar{c}_{HY} + k_{23}\bar{c}_{HY}]$$

$$a_{21} = -[k_{3'1} + k_{13'}\bar{c}_{H^+} + k_{31} + k_{13}\bar{c}_{H^+}]$$

or

$$= -[k_{3'2} + k_{23'}\bar{c}_{HO^-} + k_{32} + k_{23}\bar{c}_{HO^-}]$$

The shorter relaxation time is again determined primarily by the sum of all reaction terms, *i.e.*, by the fastest reaction in the overall system.

This section deals primarily with the rate constants for direct proton transfer, $k_{33'}$, and $k_{3'3}$. In determining these constants, conditions should be chosen so that $1/\tau$ is measured directly according to Equation (26) [for pK $\gg$ 7 or $\ll$ 7 according to Equation (27)]; the remaining constants can be determined separately for the isolated systems $HX/X^{\ominus}$ or $HY/Y^{\ominus}$. Such relaxation studies have been carried out on a great number of systems [60,80]. In the following we shall consider again only a selection of typical cases.

c) Rate Constants

As indicated in Section 3, there is a relationship between the rate constant for proton transfer and the pK difference of the donor (*e.g.* HX or HY) and acceptor ($X^{\ominus}$ or $Y^{\ominus}$).

Which behavior may then be expected from the above considerations?

We already know that most of the so-called "normal" bases or acids undergo a diffusion-controlled reaction with the excess or defect proton. The fastest proton transfer, at least at large pK differences, then occurs in the direction of the stronger acceptor ($k_{33'}$, when $pK_{HY}$

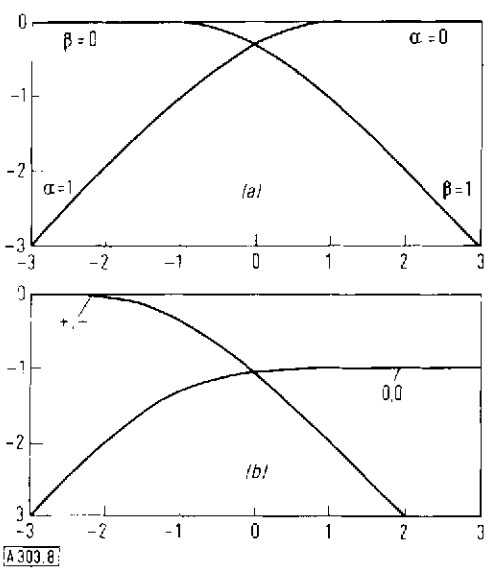



Fig. 8. Idealized log k *vs.* ΔpK dependence for proton transfer in "normal" acid-base systems: (a) for the symmetrical charge type, (b) for charge neutralization.
Ordinate: $\log k/k_{max}$.
Abscissa: $pK_{acceptor} - pK_{donor}$.

[80] *M. Eigen* and *G. Maass*, unpublished work.

$> pK_{HX}$), the rate will be independent of the difference in pK. Correspondingly, the logarithm of the rate constant for the reverse reaction ($k_{3'3}$) must be a linear function of the pK difference, since then

$$\log k_{33'} - \log k_{3'3} = pK_{HY} - pK_{HX} = \Delta pK$$
$$\text{or} \qquad \log k_{3'3} = \log k_{3'3} - \Delta pK \tag{29}$$

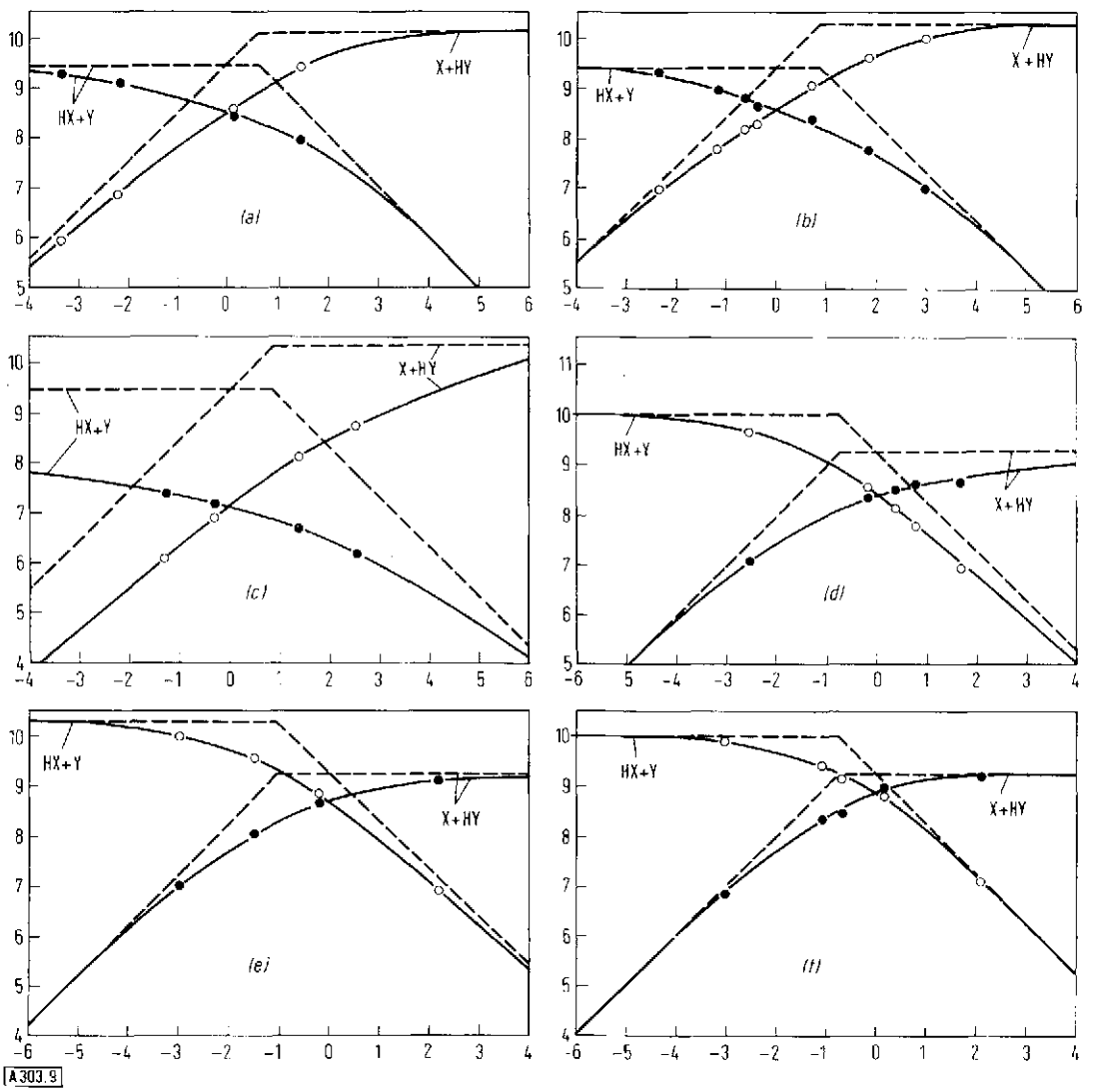
Moreover, from the considerations presented in Section 1 we know that proton transfer can be very fast even in a symmetrical hydrogen bond (*e.g.* during excess and defect proton conduction in ice, $\Delta pK = 0$), *i.e.* it can take place without any hindrance. In such an "ideal" case, one should expect behavior such as that depicted in Figure 8a. The rate of proton transfer should be independent of the pK difference (diffusion-controlled) as long as the pK value of the acceptor is greater than that of the donor. In the vicinity of $\Delta pK \approx 0$, there is a relatively sharp transition to a linear dependence of log k on $\Delta pK$, since now the reverse reaction becomes diffusion-controlled. For $pK_{HX} = pK_{HY}$, a 50 % probability exists for both directions: $k_{33'}$, ($= k_{3'3}$) is therefore half as large as the maximum value. If we denote the slope d(log k)/d($\Delta pK$) of the curve by $\alpha$ (and that for the reverse reaction by $\beta$), we have

$$\begin{aligned} &\alpha = 0\ (\beta = 1) \text{ for } pK_{HY} \gg pK_{HX} \\ &\alpha = 1\ (\beta = 0) \text{ for } pK_{HY} \ll pK_{HX} \end{aligned} \tag{30}$$

with a relatively sharp transition of $\alpha$ and $\beta$ between 0 and 1 in the vicinity of $pK_{HY} = pK_{HX}$.

Many of the transfer reactions to which these considerations apply present an asymmetry of charge, for example

$$HX + Y \rightleftharpoons X^- + YH^+. \tag{31}$$




A 303.9

Fig. 9. log k *vs.* $\Delta pK$-Dependence for proton transfer reactions. Experimental points [80] refer to the following donors or acceptors in the order from left (negative $\Delta pK$) to right (positive $\Delta pK$):

(a) Donor (HX): acetic acid; acceptors (Y): hydrazine, imidazole, aniline, *m*-chloroaniline.

(b) Donor (HX): phenol; acceptors (Y): phosphate ($PO_4^{3-}$), piperidine, propylamine, carbonate, ammonia, hydrazine, imidazole.

(c) Donor (HX): thioglycol; acceptors (Y): dimethylamine, trimethylamine, hydrazine, imidazole.

(d) Acceptor (X): aniline; donors (HY): *p*-nitrophenol, acetic acid, benzoic acid, formic acid, chloroacetic acid.

(e) Acceptor (X): imidazole; donors (HY): phenol, $HP_2O_7^{3-}$, *p*-nitrophenol, acetic acid.

(f) Acceptor (X): ammonia; donors (HY): glucose, $HCO_3^-$, phenol, boric acid, *p*-nitrophenol.

The broken lines denote the extrapolated curves with $\alpha$ or $\beta = 0$ or 1 according to Fig. 8.

Ordinates: log k. Abscissae: $pK_{HX} - pK_{HY}$.

In this case, the limiting values for the diffusion-controlled reactions are different for the two directions [$k_3'_3 > k_{33}'$, see Equation (10)], hence, the symmetric behavior with respect to $\Delta pK = 0$ represented in Figure 8a is valid only for reactions of the charge type

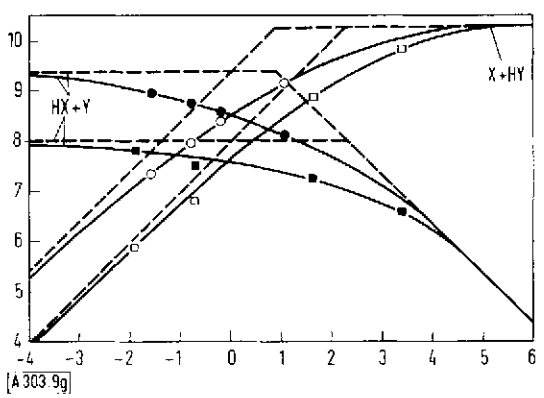
$$\begin{aligned} &XH^+ + Y \rightleftharpoons X + YH^+ \\ \text{and}\quad &HX + Y^- \rightleftharpoons X^- + HY \end{aligned} \qquad (32)$$

For the asymmetric charge type described above, one would also expect that the $\alpha$ and $\beta$ curves will become asymmetric with respect to $\Delta pK = 0$ (Fig. 8b). Similarly, any other factor which hinders the reaction and which does not affect $k_{33}'$, and $k_3'_3$ in the same manner (*e.g.*, internal hydrogen bridging) will result in a modification of symmetry.

Figures 9a-f show a few (experimental) curves of this type (additional examples are given in [80,81], some values have also been reported by *Weller* [82] and by *Meiboom*, *Grunwald* et al. [44]). It can readily be seen that the acids and bases referred to as "normal" in the preceding section closely approach the ideal behavior illustrated in Figure 8a. However, greater individual deviations are observed in this case than in simple protolytic and hydrolytic reactions. Thus, all the factors discussed in detail in the preceeding section clearly come into play in this case.

As an example Figure 9g shows the different behavior of two geometric isomers, *viz.* fumaric acid and maleic acid. In the case of maleic acid, proton transfer from the mono-protonated form is strongly retarded because this proton is not free to form a hydrogen bridge with the acceptor. The retardation is equivalent to the existence of a pre-equilibrium for forming a hydrogen bond with the acceptor. On the other hand, as an acceptor, maleate ion resembles the fumarate ion and the other carboxylates.

In addition to these effects, which already manifest themselves in simple protolytic and hydrolytic reactions and which primarily affect the limiting values of k (for $\alpha = 0$ and 1), there are deviations from ideal behavior that are restricted to the range in which $pK_{HX} \approx pK_{HY}$ and thus affect only the shape of the $\alpha$- and $\beta$-curves.



[A 303.9g]

Fig. 9g. See legend for Fig. 9a—f.

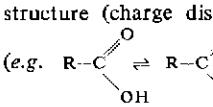
○—○ and ●—●: Donor (HX): fumaric acid; acceptors (Y): α-picoline, pyridine, aniline, *m*-chloroaniline.

□—□ and ■—■: Donor (HX): maleic acid; acceptors (Y): hydrazine, imidazole, aniline, *m*-chloroaniline.

The log k-$\Delta pK$ relation approximates the ideal behavior depicted in Figure 8 most closely when

a) both the donor and acceptor group belong to the classical hydrogen bond formers (O- or N-type), and b) the electronic and spatial configurations of the acids and their conjugate bases are identical.

With regard to a), Figure 9c (thioglycol) shows that proton transfer in the configuration SH·····N is no longer unhindered when $pK_{HX} \approx pK_{HY}$. Proton transfer between phosphonium ion and phosphines is even slower ($k \approx 10^2$ $M^{-1}$ $sec^{-1}$ [64]). However, the inhibition is greatly reduced at sufficiently large pK differences. Furthermore, as shown in the case of 5,5-diethylbarbituric acid, proton transfer does not occur as readily in hydrogen bridges of the NH···N type as in OH···O-, OH···N-, $O^-$···HN-, or $NH^+$···O-bridge bonds.

With regard to b): Most organic acids differ in electronic structure (charge distribution) from their conjugate bases (*e.g.*  , phenol, aniline, *etc*). At $\Delta pK = 0$, proton transfer can be retarded by the fact that at the instant of transition, the donor and (or) acceptor are not in their final configuration. Hence systems containing conjugated double bonds, such as acetate, phenoxide, aniline, and others, show a less sharp transition from $\alpha = 0$ to $\alpha = 1$ than systems containing only simple bonds [*e.g.*, $NH_3$ in Figure 9f]. A very sharp transition exists also for $H_3O^+$ and $H_2O$ because of their very high transport rates, as reflected in the excess and defect proton conductance in ice. Deviations from the limiting curves shown in Figures 8a and b are restricted to a relatively narrow $\Delta pK$ range for resonance-stabilized OH- and NH-compounds. According to the Franck-Condon principle, as long as protonation is not associated with a marked alteration of the steric structure (bond lengths, bond angle), changes in electron distribution should not significantly affect the reaction rates (cf. the coupling of "protomerism" and "mesomerism" in imidazole [37] described above and acetylacetone [54]). When pK differences between donor and acceptor are large, then proton transfer is associated with an energy gain even for unfavorable limiting structures.

The category of acids and bases, designated as "normal" in Section 3 could thus be subdivided [*]. Systems with conjugated double bonds and resonating structures that are not identical in the protonated and deprotonated state differ in their proton transfer characteristics at $\Delta pK \approx 0$ from simple systems such as $H_2O$, $NH_3$, aliphatic hydroxy compounds, oximes, *etc.*

Phenomena of this kind also determine the kinetic behavior of the ketonic substances listed in Table 4l. Figure 10 shows the log k *vs.* $\Delta pK$ relationship for proton transfer between acetylacetone (keto form) and a few bases, and between its negative ion and conjugate acids [60]. As can be seen, the process is qualitatively the same as that for the other "normal" acids and bases, except that here the transition from $\alpha = 0$ to $\alpha = 1$ occurs over a substantially wider pK range. Also, the individual differences of various acids and bases are more pronounced (see Section 5). However, compounds of a given class have curves of identical shape. For example,

[81] *G. Maass*, Dissertation, Universität Göttingen, 1962.

[82] *A. Weller*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 55 (1960).

[*] This subdivision corresponds to the differentiation between "hard" and "soft" acids which *R. G. Pearson* (personal communication) proposed in a somewhat different connection.

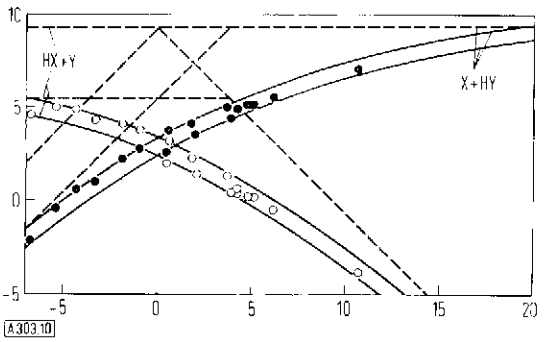



Fig. 10. log k *vs.* ΔpK Dependence for proton transfer between acetylacetone (HX) or its enolate (X) and a series of bases (Y) or acids (HY) [60]. Acetylacetone reacts in its keto form. The acceptors (Y) are (from left to right): $HO^-$, glycerol (anion), mannose (anion), glucose (anion), trimethylphenoxide, phenoxide, pyrophosphate, chlorophenoxide, *p*-nitrophenoxide, $HS^-$, dimedone (enolate), pyridine, acetate, benzoate, hydroxyacetate, chloroacetate, $H_2O$.

all aliphatic and aromatic OH compounds and carboxylic acids fit one curve. Deviations observed for individual compounds can be explained quantitatively, as was shown elsewhere [60].

*Examples:*

Acetylacetone-dimedone: The pK difference can be attributed to the existence of an intramolecular hydrogen bond in acetylacetone. This fraction is kinetically inactive.

Barbituric acid and Meldrum's acid: The activity of CH-acids is very low; only the stronger acidic enol forms are active.

Primary, secondary, and tertiary amines: Like the pK anomalies, these anomalies are associated with the effect of the solvent structure discussed above.

Similar log k *vs.* ΔpK interdependences exist for other CH-acids. Substances of similar molecular structure show almost identical behavior in this respect. This is particularly true for compounds whose protolytic reactions can be represented by a monotonic log k *vs.* $pK_{substrate}$ relation (see Fig. 6). *Bell* [74] has already called attention to a similar relationship between the rate of protolytic reactions and the Brönsted coefficient for acid-base catalysis (see below).

Most of the ketonic compounds cited above are more stable than their enolic tautomers. This shows that the ketone is a weaker acid than the enol: $pK_{ketone} > pK_{enol}$. In spite of this, reaction of the mesomeric anion with proton donors generally yields the enol first; the latter then rearranges to the more stable ketone. This effect can be observed in many systems and led to the formulation of the following rule [83,84]:

When a proton is supplied by acids to the mesomeric anion of weakly ionizing tautomers of markedly unequal stability, then the tautomer which is most quickly formed is the thermodynamically least stable: it is also the tautomer from which the proton is lost most quickly to bases.

However, it follows from the above considerations that this rule cannot have general validity. The reason for the lower rate of reaction of the keto form is not its higher thermodynamic stability, since this would only favor protonation of the anion (and possibly retard deprotonation), but simply the cited structural difference between the CH- and OH-forms. In general, the OH-form is formed faster, especially if it is more stable than the CH-form (cf. dimedone, Table 4d).

[83] *A. G. Catchpole, E. D. Hughes,* and *C. K. Ingold,* J. chem. Soc. (London) *1948*, 11.

[84] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Cornell University Press, Ithaca 1953.

### d) Relationships

The nature of the log k *vs.* ΔpK relationship can be characterized empirically by a few parameters. These are:

a) The limiting values of the rate constants (in both directions) at $\alpha$ and $\beta = 0$;

b) The slope of the curves, *i.e.*, the absolute values of $\alpha$ and $\beta$ at $\Delta pK = 0$;

c) The absolute values of the rate-constants at $\Delta pK = 0$ ($k_{33'} = k_{3'3}$).

The factors a) and b) determine the symmetry of the curves with respect to $\Delta pK = 0$. Factor c) characterizes the breadth of the ΔpK range within which the coefficients $\alpha$ and $\beta$ change from 0 to 1 (and from 1 to 0).

If the limiting values of k (at $\alpha$ or $\beta = 0$) are identical, *i.e.*, when the extrapolated straight lines $\alpha = 1$ and $\beta = 1$ intersect at $\Delta pK = 0$, then the slope of the log k curves at $\Delta pK = 0$ is often close to 0.5. However, it is not necessarily equal to 0.5; on the contrary, certain deviations from symmetry with respect to $\Delta pK = 0$ are highly probable for acceptors and donors of different acid or base types (see below). If, however, the limiting values of k differ, then the center of symmetry, defined by the point of intersection of the straight lines $\alpha = 0$ and $\alpha = 1$ (or $\beta = 1$ and $\beta = 0$), is displaced along the ΔpK axis by the difference of the logarithms of these limiting values of k, although the log k curves still intersect at $\Delta pK = 0$, of course (see Fig. 10). If the absolute value of k is much smaller in this ΔpK range than its limiting value, then the transition of the coefficient $\alpha$ from 1 to 0 also extends over a relatively wide ΔpK range. This means that over a narrow interval, the value of $\alpha$ may be approximated by a constant (Brönsted relationship, see below). The closer k is to the limiting value, the narrower is the range over which the approximations can be applied.

From a molecular-kinetic standpoint, the behavior observed can be interpreted as follows.

According to the reaction diagram [Equation (5) of Section 2], one must differentiate between the encounter and separation of the reactants ($k_{ab}$, $k_{a'b'}$, $k_{ba}$, $k_{b'a'}$) on the one hand and proton transfer in the reaction complex ($k_{bb}$, $k_{b'b}$) on the other. The reaction complex is completely defined when a hydrogen bond is formed between the donor proton and the lone electron pair of the acceptor, possibly also with inclusion of an $H_2O$ molecule; otherwise one must assume the existence of a simple encounter complex with a lifetime of 1/k, according to Equation (11). Furthermore, it is thus possible that additional reaction steps occur in the reaction scheme, *e.g.* breaking or formation of an internal hydrogen bond, following the a -> b process or preced-

ing the b′ → a′ step. Evidently, only the rate constants for proton transfer depend on ΔpK, so that, from Equation (6), one obtains:

$$\alpha \equiv \frac{d \log k}{d\,\Delta pK} = \frac{k_{ba}\,k_{b'a'}}{N} \cdot \alpha' + \frac{k_{ba}\,k_{b'b}}{N} \qquad (33)$$

where N is defined as in Equation (7), and

$$\alpha' \equiv \frac{d \log k_{bb'}}{d\,\Delta pK}\;;\left[\frac{d \log k_{b'b}}{d\,\Delta pK} = -(1-\alpha') \cdots -\beta'\right] \qquad (34)$$

If an acid or base molecule exhibits multiple donor or acceptor properties, then the usual statistical corrections [85] must be applied. This relationship fulfills all the requirements arising from the experimental evidence discussed above. Thus:

for $k_{ba} \ll k_{bb'}; k_{bb'} \gg k_{b'b}$ (diffusion-controlled in the forward direction)
$\alpha \to 0$,

for $k_{b'a'} \ll k_{b'b}; k_{b'b} \gg k_{bb'}$ (diffusion-controlled in the reverse direction)
$\alpha \to 1$

and for $k_{ba} \gg k_{bb'}; k_{b'a'} \gg k_{b'b}$ (proton transfer is rate-determining in both directions)
$\alpha \to \alpha'$ $(0 < \alpha' < 1$: transition range).

The ΔpK dependence of α and α′ in the transition range is of particular interest. This is determined by superposition of the potentials of the interaction of the donor and acceptor with the proton in the reaction complex. This superposition is expressed directly neither by the difference of the free reaction energies (≈ΔpK) with their various ΔH and TΔS contributions nor by the enthalpy difference ΔH alone. Thus it is not to be expected theoretically that a given ΔpK dependence will apply to all types of compounds equally well. Nevertheless, the relative pK change should parallel the change in potential for compounds of the same type. A close relation to the electrophilic behavior of the proton donor and the nucleophilic behavior of the proton acceptor should exist (cf. below [91]). Individual deviations from a given log k ΔpK interdependence as shown in Figure 10 thus become understandable.

In the transition region, the coefficient α′ depends on the following properties of the interaction potentials:

1. If the potential curves for donor and acceptor are of the same type, then the variation of α′ will be symmetrical with respect to the state of equal depth of the potential-well characterized (in the simplest case) by $k_{bb'} = k_{b'b}$. This kind of symmetry is not to be expected when the donor and acceptor belong to different categories of acids and bases. On the other hand, the "normal" acids of the OH- and NH-type, which are known to form hydrogen bridges readily, exhibit this symmetry (Fig. 9a-g), although the superposition of potentials is generally so complete here that the α′ transition range becomes very narrow.

2. α′ can be expressed by a constant, if both overlapping branches of the potential function (Figure 11) can be approximated by straight lines. The magnitude of α is determined only by the slope of the straight lines, and not by the distance between the potential minima nor by any deviation from linearity outside the area of intersection.

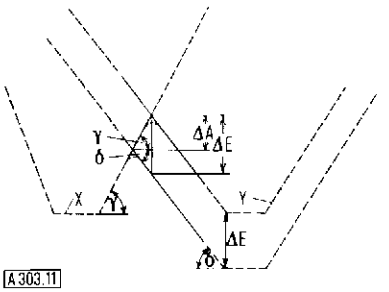



Fig. 11. Geometric illustration of the coefficient α′. The branches of the two potential curves X and Y intersect in a linear range. Displacement of one curve by ΔE causes a shift in the height of the point of intersection by $\Delta A = \frac{1}{1+(\mathrm{tg}\,\delta/\mathrm{tg}\,\gamma)} \cdot \Delta E = \alpha'' \cdot \Delta E$ $(0 < \alpha'' < 1)$. The magnitude of the coefficient α″ (or α′, see below) depends only on the ratio of the slopes of the two branches. On the other hand, the displacement is independent of the distance between the potential minima and of the curvature of the potential functions outside the linear range of intersection. The relationship between ΔA and ΔE therefore also applies to potential curves of realistic (*e.g.* parabolic) shape, provided that in the intersection range they can be approximated by straight lines. For similar compounds, the potential shift ΔE can be assumed to be proportional to ΔpK; the shift in the point of intersection ΔA corresponds to a change in activation energies ($\sim \Delta \log k_{bb'}$). This two-dimensional representation corresponds to a section of the energy surface with three distance coordinates XH, HY, and XY. An explanation of the simple geometric significance of the reaction coordinate as a line connecting the centers X and Y (movement of the "light" proton between the fixed "heavy" donor and acceptor atoms) was given by *Bell* [74].

3. In general, however, the branches of the potential function still possess finite curvature thereby causing continuous variation of α with ΔpK. This variation is particularly pronounced when overlapping is considerable (in the neighborhood of the "bottom of the valley"). This occurs, for example, for all "normal" types of acids and bases (narrow transition range) and generally also in the vicinity of the limiting values $\alpha = 0$ and $\alpha = 1$. On the other hand, linearity is closely approximated [constant $\alpha = 0$ or 1] in the middle of a very wide transition range (small values of k). It should be noted, in particular, that such "linear free-energy relationships" are only approximate relationships derived by expansion of the real function in a Taylor or MacLaurin series:

$$\log k - f(\Delta pK) \approx f(\Delta pK = 0) + \alpha\,\Delta pK + \ldots \qquad (35)$$

### e) Some Remarks on the Characterization of "Pseudo Acids"

The results discussed above also permit an approach to the question of the definition of a "pseudo acid". *Hantzsch* [86] based the differentiation between the "aci" and "pseudo" forms on the difference in their rates of reaction. The disadvantages of such a classification are obvious, even where differentiation between "fast" and "slow" establishment of equilibrium no longer depends on experimental potentialities. The absolute value of the rate constant alone cannot form the basis for a definition

[85] *R. P. Bell:* Acid Base Catalysis. University Press, Oxford 1941.

[86] *A. Hantzsch*, Ber. dtsch. chem. Ges. *32*, 575, 3066 (1899).

(otherwise, according to Table 4l, acetone and acetylacetone, for example, would belong to different categories). The concept of "pseudo"- and "aci"-forms should either be abandoned altogether or used only to characterize limiting structures. One may speak of an "aci"-form when the condition $\alpha$ or $\beta = 0$ in the log k *vs.* $\Delta$pK relation is associated with a diffusion-controlled proton exchange. If, on the other hand, one of the coefficients equals zero, whereas the limiting value is not attained, then a real equilibrium precedes proton exchange. The acid or base is then in a "pseudo"-form. From this it follows that the order of magnitude of the rate constants in the transition range ($\Delta pK \approx 0$) is not sufficient for identification of the limiting forms. In this respect, resonance-stabilized compounds, for example, do not show a well-defined behavior. Most CH-acids are intermediate forms. Thus, at large pK differences, the rate constants for recombination of the carbanion with $H^+$ reach values of the order of $10^{10}$ liter/mole·sec (acetone), whereas the constants for recombination of the CH-acid with $HO^-$ tend to level off already at substantially lower values (Fig. 10 and Fig. 5). The lack of polarity and the small ability to form hydrogen bonds of the CH group account for this effect. If the above classification is used, then even a hydrogen-bridged chelate has the properties of a pseudo-form. Here, rearrangement to an isomer (where the hydrogen bridge is opened) is required before the proton can be released. It is essential for this classification that the preceding reaction step (*e.g.* H-bond opening) be independent of the strength of the acceoptor.

## 5. Remarks Concerning Acid-Base Catalysis

The preceding considerations dealt primarily with the elementary processes of proton transfer in simple acid-base reactions such as protolysis, hydrolysis, pH-indication, and buffering. In the second part of this article [*], the manner in which these elementary processes determine the mechanisms of more complicated reactions catalyzed by (Brönsted) acids or bases will be discussed.

In the simplest case, proton transfer from the catalyst to the substrate is the rate-determining step of the reaction (examples: halogenation of ketones [87], keto-enol rearrangements [88], certain condensation reactions [89]); a more detailed list of prototypes of acid-base catalysis will be given in Part II [*]. Thus, the rules established in Section 4 should also apply to catalysis. Numerous studies of such reactions have been made using classical methods of measurement (for literature see [74,85]). The correlation between the rate constant for the catalysed reaction and the dissociation constant of the catalytically active acid or base was generally established (more or less accurately) using an expression first formulated by *Brönsted* [90]. In its simplest form (statistical corrections are neglected), this equation can be written as:

$$k = G_S \cdot K_S^{\alpha} \quad \text{or} \quad k = G_B \cdot K_B^{\beta} \tag{36}$$

(cf. also Hammett's $\sigma\rho$ relationship [91]).

Here, the coefficients $\alpha$ and $\beta$ are independent of the acid dissociation constant $K_S$ of the catalyst. However, on the basis of considerations presented in Section 4, it can be shown that this (integrated) form of the equation is only an approximation. *Brönsted* and *Pedersen* realized this and expressed it clearly in their fundamental paper on acid-base catalysis [90] (cf. Fig. 3 in [90]). However, the general constancy of $\alpha$ and $\beta$ observed later (disregarding scatter due to individual deviations) explains why relationships of this type have found their way into the literature as "laws of catalysis". The reason for the fact that deviations from constancy of the coefficients $\alpha$ and $\beta$ have been observed in only few cases lies in the relatively limited time range used in classical kinetic experiments. The only reactions studied were those with rate constants sufficiently smaller than the limiting values ($10^9$ to $10^{10}$ liter/mole/sec). The applicability of linear approximations ($\alpha$ or $\beta$ = constant) in this case extends over a relatively wide pK range.

Thus, for example, in the base-catalyzed halogenation of acetylacetone, *Bell* [74,87] found a linear log k – pK relationship with $\alpha = 0.48$ that holds over the limited range accessible by classical methods. Here the rate-determining step is deprotonation of the substrate. His absolute values of the rate constants are in quantitative agreement with the rate constants of proton transfer obtained directly from relaxation measurements (Fig. 10). These measurements show that in a wider pK range $\alpha$ is not a constant. Furthermore, the same catalysts gave other values of $\alpha$ for other ketones, in accordance with the shift in the $\Delta$pK scale. For example, for acetone, pK = 20.0, $\alpha = 0.88$; for bromoacetylacetone, pK = 8.3, $\alpha = 0.42$ [92]. All the curves can be constructed on the basis of the generalized relationship [Equation (33)].

Even the classical example of acid-base catalysis studied by *Brönsted* and *Pedersen* [90], *viz.* the decomposition of nitramide:

$$H_2N{-}NO_2 \rightarrow N_2O + H_2O$$

shows a continuous variation of the coefficient $\alpha$ (Figure 12). On extrapolation of the curve to $\alpha = 0$, it has a limiting value for log k that is about 3 units less than the limiting value for the diffusion-controlled reactions. However, this difference is consistent with the constant (log K) determined by *Brönsted* and *Peder-*

[*] To appear shortly in this journal.

[87] Literature review [74], p. 144 et seq.

[88] Literature review [74], [75] and [84].

[89] Discussion in [75], p. 335 et seq.

[90] *J. N. Brönsted* and *K. Pedersen*, Z. physik. Chem. *108*, 185 (1923).

[91] *L. P. Hammett*, Chem. Revs. *17*, 125 (1935); Physical Organic Chemistry. McGraw Hill, New York 1940, chapter VII; *R. J. C. Lewis* and *W. Taft*, J. Amer. chem. Soc. *80*, 2436 (1958). See also *C. G. Swain* and *C. B. Scott*, J. Amer. chem. Soc. *75*, 141 (1953).

[92] *R. P. Bell* [74], p. 172.

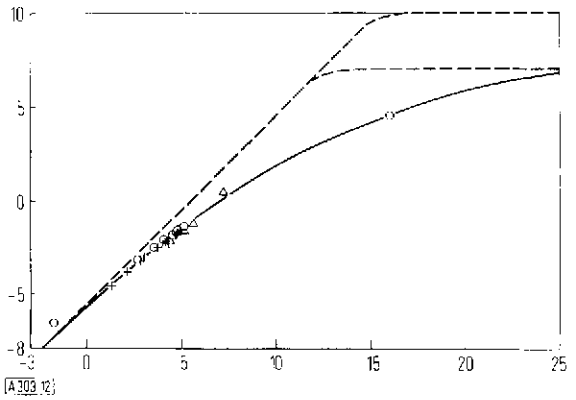
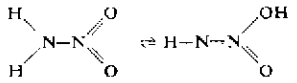



Fig. 12. log k vs. Δ pK Dependence for base-catalysed decomposition of nitramide at 15 °C (*Brönsted* and *Pedersen* [90].

Catalytically active base = Y (conjugate acid HY).
The broken lines denote the extrapolated curves with α and β = 0 ar 1.
Upper curve: diffusion-controlled limiting value.

Ordinate: log k.
Abscissa: $pK_{HY}$.

*sen* for the tautomerization equilibrium of nitramide which precedes decomposition. If the rate constant is based on the concentration of the reactive form, then extrapolation to $\alpha - 0$ affords exactly the limiting value for diffusion-controlled reactions.



In other systems, such as mutarotation of glucose [93], dehydration of acetaldehyde hydrate [94], constancy of the values of α is observed over a relatively wide pK range. As expected in these cases, k is relatively small over the entire range. Here, the rate-determining step is not a simple proton transfer but the coupling of several intermediate steps. Such events are particularly important with regard to enzymic processes. They will be the main subject of the discussion presented in Part II.

*The present article summarizes results which have been obtained in collaboration with many coworkers. The author wishes to express his sincere thanks to all who have contributed to these results (cf. bibliography), especially to Dr. L. de Maeyer, Dr. W. Kruse, and Dr. G. Maass.*

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# The Course of the Willgerodt-Kindler Reaction of Alkyl Aryl Ketones [*]

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*Respectfully dedicated to Prof. Dr. Karl Ziegler on the occasion of his 65th birthday*

*Ketones react with sulfur and $NH_3$ or amines at room temperature to produce $\Delta^3$-thiazolines, 5-alkylidene-$\Delta^3$-thiazolines, $\Delta^3$-imidazoline-5-thiones, hexathiacycloheptane derivatives, α,α'-dioxodisulfides, bis-(1-aralk-1-yl) disulfides, or thiocarboxamides, depending on the coreactant and on the reaction conditions. It was recognized that the formation of all of these numerous types of compounds can be explained basically by primary thiolations and geminal dithiolations, which in conjunction with their reverse reaction (desulfurization) and the assumption of a thioreductone equilibrium permit a new interpretation of the course of the Willgerodt-Kindler reaction of alkyl aryl ketones.*

## Introduction

The Willgerodt reaction [3–9] proper is the reaction of alkyl aryl ketones with aqueous ammonium polysulfide at 200 °C in a sealed tube. It affords ω-carboxamides and ω-carboxylic acids of the same chain-length without skeletal rearrangement, *i.e.* it involves the reduction of the oxo group to a methylene group, in combination

[*] A review article (a continuation of [1]) is being prepared in which the new compounds discussed in the present paper are treated in greater detail. A paper recently published [2] prompted us to make our concept of the course of the Willgerodt-Kindler reaction known.

[1] *F. Asinger* and *M. Thiel*, Angew. Chem. *70*, 667 (1958).

[2] *K. F. Funk* and *R. Mayer*, J. prakt. Chem., 4. Reihe, *21* (293), 65 (1963).

[3] *C. Willgerodt*, Ber. dtsch. chem. Ges. *20*, 2467 (1887).

[4] *C. Willgerodt*, Ber. dtsch. chem. Ges. *21*, 534 (1888).

[5] *C. Willgerodt*, J. prakt. Chem. *80*, (2) 183 (1909).

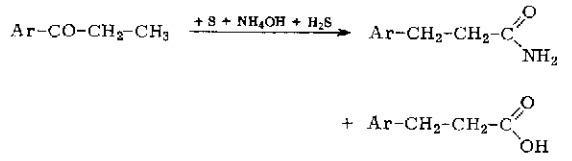
[6] *C. Willgerodt* and *F. H. Merk*, J. prakt. Chem. *80*, (2) 192 (1909).

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with an oxidative modification of the end of the alkyl chain (redox amidation) [10]:



Sulfur acts as the oxidizing agent; the reducing action of $H_2S$ in the reaction was first recognized by *Willgerodt*.

The most important preparative modification of the Willgerodt reaction was introduced by *Kindler* in 1923 [11]. Since then, the Willgerodt-Kindler reaction denotes the reaction of alkyl aryl ketones with sulfur and primary or secondary amines at elevated temperatures. *Fieser* and *Kilmer* [12] were able to reduce the temperature of the Willgerodt reaction to 160 °C by adding dioxan. When morpholine is employed, the Willgerodt-Kindler reaction can be carried out at 130 °C in an open vessel [13].

To date, this reaction has attracted considerable scientific interest; 250 publications have appeared on this subject; nearly 700 compounds have been reacted under Willgerodt and Willgerodt-Kindler conditions. However, the reaction mechanism has not yet been definitely clarified. A comprehensive review of prior work is not indicated here, since several good reviews exist [14–19].

Previous publications concerning the course of the reaction have dealt with the primary attack (at the carbonyl group [20–24] or at the α-position relative to the carbonyl group [16, 25–30]), with the problem of the migration of functional groups along the carbon chain [20–28, 30], and with the irreversible oxidation at the end of the chain [31]. Most frequently, attempts were made to convert hypothetical intermediates into ω-aralkylcarboxylic acids or their derivatives or to throw light on the intermediates of the reaction by using special ketones [3, 22, 25, 27, 32–38].

In 1956, we reported for the first time [39] that the combined action of sulfur and $NH_3$ upon ketones such as cyclohexanone or diethyl ketone, leads to $\Delta^3$-thiazolines [1]. The reaction occurs even at room temperature and often gives excellent yields. Since then, thorough studies have been made of the scope, mechanism, and dependence on the conditions, *etc.* of this reaction and have led to the discovery of several new heterocycles.

With regard to the starting materials (ketone, S, $NH_3$ or amine, possibly $H_2S$), this reaction does not differ from the Willgerodt-Kindler reaction, but the temperature at which it occurs is different. It was to be expected that the reactions would show similarities under these circumstances; hence, a substantial part of our investigations was directed toward uncovering such analogies. The temperatures used were intentionally different from those of the Willgerodt-Kindler reaction. We felt that conducting the reaction at room temperature offered the possibility of obtaining reactive intermediates whose isolation at higher temperature would be impossible. Moreover, we avoided the difficulty of exactly reproducing the Willgerodt-Kindler reaction medium, an aspect that has so far been neglected in reactions where suspected intermediates are used as reactants.

In the primary step of the $\Delta^3$-thiazoline synthesis, α-mercaptoketones (α-mercaptoketimines) are formed [40] [*] in very small concentrations as a result of ketone thiolation. However, these are irreversibly eliminated from the mixture by further reaction with unreacted ketone and $NH_3$ to give $\Delta^3$-thiazolines almost immediately. This technique of capturing reactive intermediates in the form of stable secondary products by systematically varying the reaction conditions and the reactants proved to be very fruitful. The present paper is an attempt to interpret the mechanism of the Willgerodt-Kindler reaction on the basis of results so obtained.


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[13] *E. Schwenk* and *E. Bloch*, J. Amer. chem. Soc. *64*, 3051 (1942).

[14] *W. A. Pryor:* Mechanisms of Sulfur Reactions. McGraw-Hill, New York 1962, pp. 127, 162, 172.

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[*] For clarity, the intermediates in Scheme 1 are shown exclusively as ketimines.

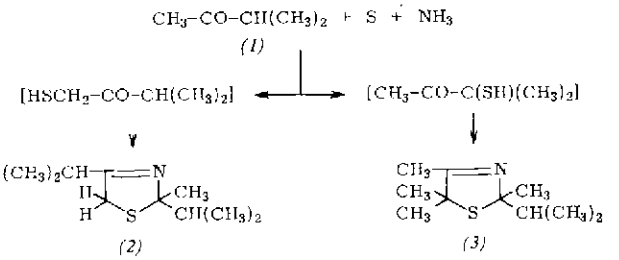
For chemical reasons, the subject matter is arranged into three main sections dealing with the products of the reaction of ketones and S with $NH_3$, or primary, or secondary amines, respectively. These correspond to the reaction sequences A, B, and C shown in Scheme 1, where the isolated intermediates and end-products are boxed in.

## 1. The Reaction of Ketones with S and $NH_3$ (Reaction Sequence A)

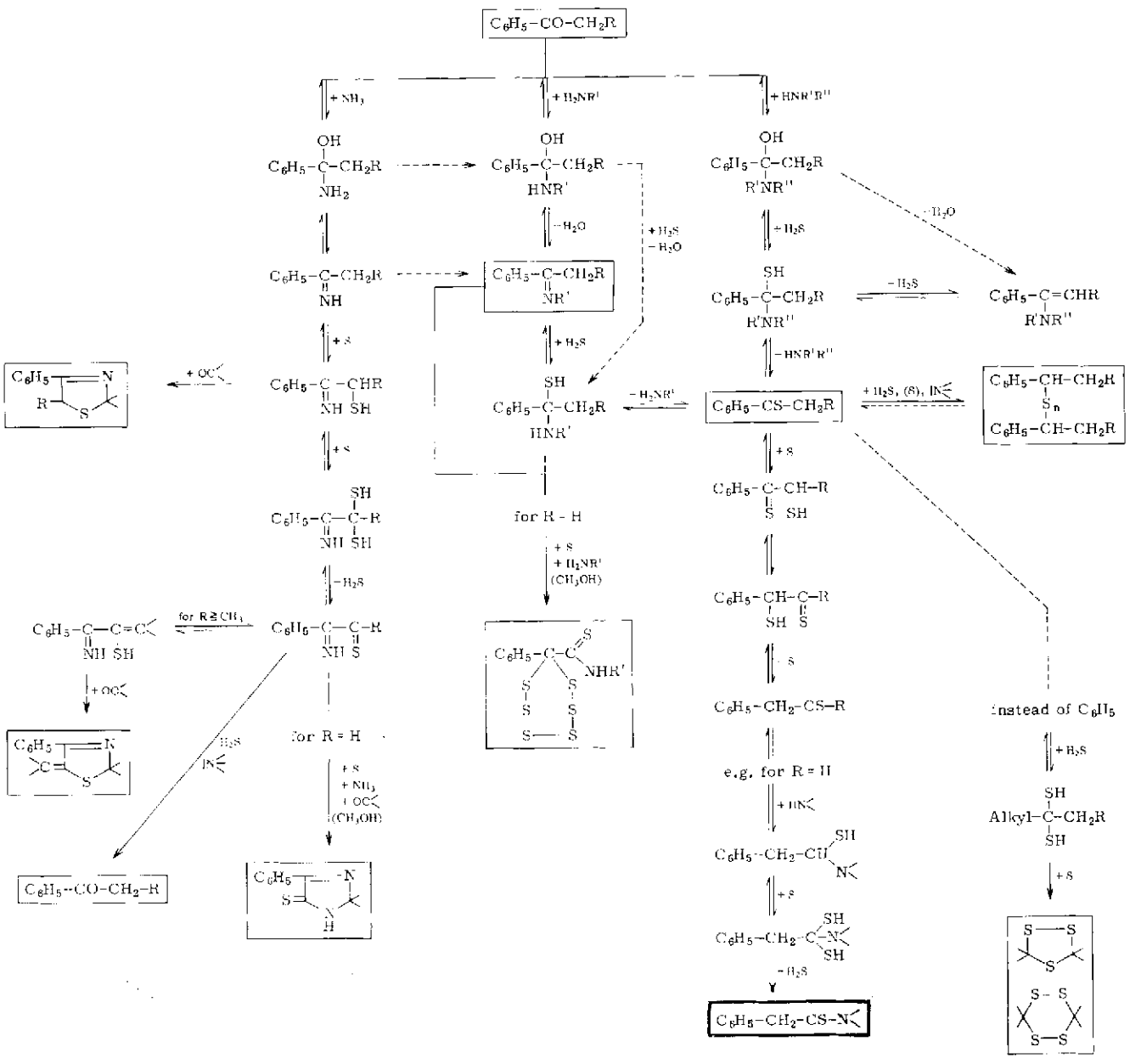
### a) α-Thiolation of Ketones; $\Delta^3$-Thiazolines

The intermediate α-thiolation of the ketone during $\Delta^3$-thiazoline formation is an amine-catalysed ionic reaction. It can take place only if at least one of the carbon atoms next to the carbonyl group bears at least one hydrogen atom capable of undergoing substitution (thiolation).

Unsymmetric ketones are particularly interesting. They produce as intermediates usually two positionally isomeric α-mercaptoketones or α-mercaptoketimines and hence two $\Delta^3$-thiazolines that are structurally isomeric




with respect to the 4- and 5-positions. For example, isopropyl methyl ketone *(1)* affords the $\Delta^3$-thiazolines *(2)* and *(3)*.




Scheme 1. Review of the reactions carried out to elucidate the mechanism of the Willgerodt-Kindler reaction.

The proportions in which the two $\Delta^3$-thiazolines are formed give some indication of the relative extent of the competing thiolations and permit comparisons of the reactivities of all possible pairs of $CH_3$, $CH_2$, and CH groups. The reactivity generally decreases in the order $CH_2 \gg CH > CH_3$ [41,42]. The isomer ratio remains practically unaltered during the reaction and is unaffected by the overall conversion. In general, the direction of the thiolation can best be influenced by temperature changes. Table 1 shows that thiolation of the $CH_3$ group is always relatively greater at higher temperatures, particularly when a $CH_3$ group is in competition with a CH group.

Solvents and organic bases also affect the isomer ratio, but their effect is generally small. Alcohols tend primarily to increase conversion.

Table 1. Effect of the reaction temperature on the α-thiolation of unsymmetrical ketones with S and $NH_3$.

| Ketone | Thiolated groups | Thiolation [%] at 20 °C | Thiolation [%] at 80 °C |
|---|---|---|---|
| Butanone | $CH_3$ | 3 | 10 |
| | $CH_2$ | 97 | 90 |
| 2-Pentanone | $CH_3$ | 5 | 23 |
| | $CH_2$ | 95 | 77 |
| Methyl isobutyl ketone | $CH_3$ | 20 | 31 |
| | $CH_2$ | 80 | 69 |
| Methyl isopropyl ketone | $CH_3$ | 6 | 72 |
| | CH | 94 | 28 |
| Methyl s-butyl ketone | $CH_3$ | 19 | 87 |
| | CH | 81 | 13 |
| Ethyl isopropyl ketone | $CH_2$ | 94 | 96 |
| | CH | 6 | 4 |

As the first step of the thiolation one might discuss the removal of a proton from the position *alpha* to the carbonyl group. This presupposes that the α-hydrogens are sufficiently acidic to be removed in a nucleophilic reaction with $NH_3$ or an amine. The activity of the α-hydrogens is appreciably increased if the imine is first formed from the ketone.

According to *Haury* [43,44], Schiff bases of acetophenone can be acetylated at the methyl group with ketene. *Moszew* et al. [45] were able to react acetophenone anilide twice with phenyl isocyanate at the methyl group. Neither reaction occurs with acetophenone itself. The *N*-n-butylimine of acetophenone (*N*-butyl-α-phenethylideneimine) is readily thiolated with sulfur in methanol [46, 47]; this will be discussed later. Other, as yet incomplete, experiments [48] show that *N*-substituted ketimines and aldimines undergo thiolation with sulfur, sometimes under very mild conditions. Experiments of this kind have been carried out before, but at markedly higher temperatures [11,16,49–51].

The reverse of thiolation is the desulfurization of α-mercaptoketones to ketones. The latter reaction can generally by accomplished with amines [1] and in certain cases also with $NH_3$ [52]. Secondary amines are less suitable, and tertiary amines are practically unsuitable for this purpose.

The sulfur in polysulfides acts as a thiolating agent; the presence of small amounts of $H_2S$ has a favorable effect on thiolation. Amine/sulfur mixtures (with the exception of pyridine/sulfur) can also give rise to $H_2S$ [53]. This explains the induction period observed in the reaction of S and $NH_3$ with ketones to give $\Delta^3$-thiazolines. This induction period is eliminated when traces of $H_2S$ are added to the system in advance. This is in agreement with the fact that the addition of amines onto ketones or aldehydes is acid-catalysed [54]; $H_2S$ could possibly assume this catalytic role. Naturally, polysulfide formation could also be formulated with carbanions of the system to be thiolated or with free electrons of another catalyst system.

Following the successful extension of the $\Delta^3$-thiazoline synthesis [41,52,55–63] to numerous (including functionally substituted) aliphatic, cycloaliphatic, and heterocyclic ketones, we studied acetophenone, propiophenone, and n-butyrophenone. In these cases, too, the expected $\Delta^3$-thiazolines were formed, but the yields were lower and the products less uniform. Since alkyl aryl ketones are very suitable starting materials for the Willgerodt-Kindler synthesis, we concentrated our attention particularly on the by-products. Thus, we discovered two hitherto unknown types of compounds, *viz.* $\Delta^3$-imidazoline-5-thiones and 5-alkenyl-$\Delta^3$-thiazolines.


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[58] *M. Thiel, F. Asinger,* and *G. Reckling,* Liebigs Ann. Chem. *611,* 131 (1958).

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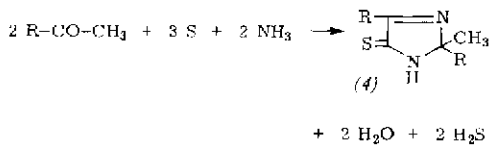
[61] *F. Asinger, M. Thiel, H. Sedlak, O. Hampel,* and *R. Sowada,* Liebigs Ann. Chem. *615,* 84 (1958).

[62] *F. Asinger, W. Schäfer, M. Baumann,* and *H. Römgens,* Liebigs Ann. Chem., in the press.

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b) $\Delta^3$-Imidazoline-5-thiones

Acetophenone or its ring-substituted derivatives afford yellow, crystalline $\Delta^3$-imidazoline-5-thiones, usually in very good yields, when one mole of the ketone is mixed with 8 gram-atoms of sulfur (theoretically, only 1.5

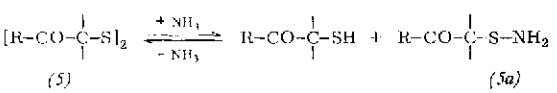


*(4)*

gram-atoms are required) in 250 ml of methanol, and the mixture is treated with $NH_3$ for 24 hours at 20 °C and normal pressure [64, 65]. The structure of these compounds has been unequivocally established [66, 67] and will not be discussed here.

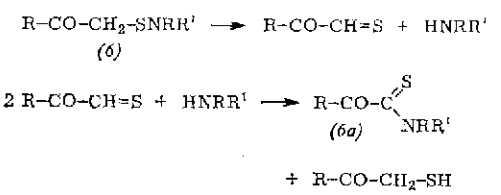
*Course of Reaction*

α-Mercaptoketones react with sulfur in the presence of catalytic amounts of amine or $NH_3$ to produce α,α'-dioxodisulfides. This reaction is more vigorous than the analogous reaction with simple thiols discovered by *McMillan* and *King* [31]. Hence, one would expect the reaction of S and $NH_3$ with ketones to yield α,α'-dioxodisulfides rather than $\Delta^3$-thiazolines. This is not the case, however, because the disulfide formation is an equilibrium reaction [68]. It is therefore possible that α,α'-dioxodisulfides are intermediates in the formation of both $\Delta^3$-thiazolines and $\Delta^3$-imidazoline-5-thiones and that ammonolytic (hydrolytic) cleavage of the dioxodisulfides *(5)* and the reverse reaction also take place [69, 70]. β-Oxosulfenamides *(5a)* are prepared



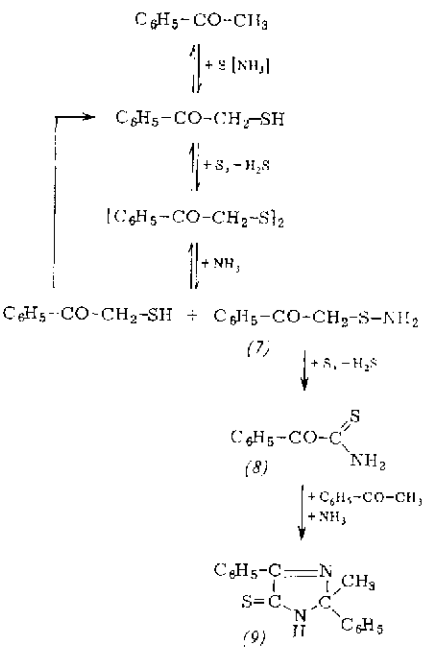
*(5)* *(5a)*

by treating the β-oxosulfenyl chlorides obtained by chlorolytic cleavage of α,α'-dioxodisulfides with $NH_3$ or primary or secondary amines at −70 °C. The compounds are stable at higher temperatures only in exceptional cases [69]. Phenacylsulfenylmorpholide *(6)*, the primary product of the reaction between phenacylsulfenyl chloride and morpholine, undergoes rearrangement to phenylthioglyoxylmorpholide *(6a)* on heating to room temperature [71]. This novel rearrangement occurs with dehydrogenation and can be formulated as follows [2, 46]:



*(6)* *(6a)*

Addition of sulfur to the mixture before it is heated to room temperature results in appreciably increased yields of the thiomorpholide *(6a)* [72]. Other β-oxosulfenamides also undergo this rearrangement in 20 to 60 % yields [64], but well-defined products are obtained only from *N*-disubstituted sulfenamides [64]. Nevertheless, we wanted to see whether 2-methyl-2,4-diphenyl-$\Delta^3$-imidazoline-5-thione *(9)* could be produced by condensation with acetophenone and $NH_3$ of the phenylthioglyoxylamide *(8)* formed by rearrangement of the unstable phenacylsulfenamide *(7)*.



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

We were able to establish that the increase in yield expected on the basis of this scheme from an increase in the amount of sulfur used actually did materialize. We also proved that phenylthioglyoxylamide *(8)* occupies a central position in the reaction scheme. Compound *(9)* is also produced on treating phenylglyoxylonitrile with acetophenone, $NH_3$, and $H_2S$ in a reaction in which phenylthioglyoxylamide is an intermediate [66]. Phenylthioglyoxylamide can be prepared smoothly and in good yields by treating phenylglyoxylonitrile with $H_2S$ in the presence of a tertiary amine and in the absence of solvents having acidic hydrogen [46, 73]; it can be condensed with acetophenone and $NH_3$ to give *(9)* [46].

New informations were gained from the reaction of phenacylsulfenylmorpholide *(10)* with radioactive sulfur [46]. In the resulting mixture of phenylthioglyoxyl-

[64] *F. Asinger, W. Schäfer, G. Baumgarte*, and *P. F. Müting*, Liebigs Ann. Chem. *661*, 95 (1963).

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[68] *F. Asinger, M. Thiel*, and *H. G. Hauthal*, Liebigs Ann. Chem. *615*, 70 (1958).

[69] *F. Asinger, M. Thiel*, and *W. Schäfer*, Liebigs Ann. Chem. *637*, 146 (1960).

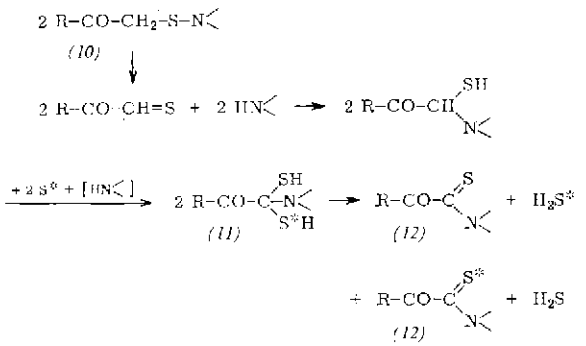
[70] *M. Thiel, F. Asinger, W. Schäfer*, and *H. G. Hauthal*, Liebigs Ann. Chem. *638*, 174 (1960).

[71] *W. Schäfer*, Ph. D. Thesis, Universität Halle, 1959.

[72] *P. Püchel*, Ph. D. Thesis, Universität Halle, 1959.

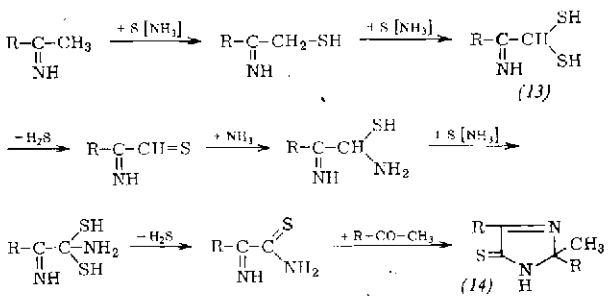
[73] *F. Asinger* and *F. Gentz*, Angew. Chem. *75*, 577 (1963); Angew. Chem. internat. Edit. *2*, 397 (1963).

morpholide *(12)* and $H_2S$, the radioactivity was equally divided between these two products. This distribution of the activity exists right from the very beginning of the reaction and remains constant as the reaction proceeds. The possibility of sulfur exchange is thus eliminated. This result can be explained only by postulating the formation of the intermediate *(11)* containing two equally bound sulfur atoms [46].



The sulfenamide *(10)* is cleaved to a thioaldehyde and amine, which immediately react to give the α-amino-α-mercaptoketone. The latter is thiolated further at the methine group whose hydrogen is highly activated by the -I effect of the thiol and amino group. The α-amino-α,α-dimercaptoketone *(11)* becomes stabilized by elimination of $H_2S$ and formation of the α-oxothioamide *(12)*. The probability of elimination is the same for both mercapto groups, and this would account for the observed distribution of radioactivity.

On the basis of these results, the formation of $\Delta^3$-imidazoline-5-thiones can be explained simply and in accordance with all experimental observations by a mechanism involving dithiolation at the same carbon atom, promoted by excess sulfur (Scheme 2).

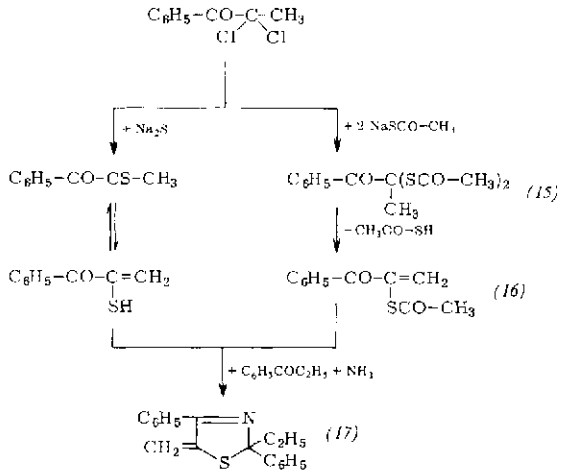


Scheme 2. Formation of $\Delta^3$-imidazoline-5-thiones *(14)*.

To check this hypothesis, ω,ω-dimercaptoacetophenone (synthetized from the corresponding dichloride and NaSH) was treated with morpholine in the presence of excess sulfur to produce phenylthioglyoxylmorpholide. In the absence of sulfur, lower yields were obtained. The reaction of the ω,ω-dithiol *(13)* with acetophenone and $NH_3$ in the presence of S gave an 84 % yield of *(14)* in a very short time [46]. Without sulfur, lower yields were obtained or the $\Delta^3$-thiazoline was produced [46].

### c) 5-Alkylidene-$\Delta^3$-thiazolines

5-Alkylidene-$\Delta^3$-thiazolines are produced when higher homologues of acetophenone are used, particularly in the presence of excess sulfur. These compounds are also a result of α-dithiolation. For example, treatment of propiophenone or n-butyrophenone with S and $NH_3$ at room temperature affords predominantly the corresponding $\Delta^3$-thiazolines; oils of nearly identical elemental composition are also obtained. The oily fractions were identified as 5-alkylidene-$\Delta^3$-thiazolines *(17)*. The reaction sequence of Scheme 3, which is illustrated with the propiophenone derivatives [74], gives a clue to the structure of these oxidation-sensitive compounds.



Scheme 3. Proof of the structure of the 5-alkylidene-$\Delta^3$-thiazolines *(15)*.

The reaction of α,α-dichloroketones with *S*-sodium thioacetate leads to the unstable diacetylated dithiols *(15)*. These compounds begin to lose thioacetic acid already during their preparation, hence the resulting reaction mixture contains predominantly the α-acetylthio-α-methyleneketone *(16)*. These results agree with those obtained by *Campaigne* and *Edwards* [75] in the acetylation of 1,3-diphenyl-2,2-dimercaptopropane with acetic anhydride.

Our own studies [76] have shown that the condensation of α-acetylthioketones with a variety of oxo derivatives and $NH_3$ generally leads smoothly to $\Delta^3$-thiazolines, sometimes even more readily than that of the α-mercaptoketones themselves. As illustrated in Scheme 3, 1-phenyl-2-acetylthio-2-propene-1-one *(16)* also reacts readily with numerous ketones or aldehydes and $NH_3$ to give 4-phenyl-5-methylene-$\Delta^3$-thiazolines *(17)* [74].

5-Alkylidene-$\Delta^3$-thiazolines are produced by the following reactions (cf. Scheme 1, reaction sequence A). Dithiolation of the carbon atom *alpha* to the oxo (or imino) group produces an α-thioxoketone or an α-thioxoketimine which in its tautomeric α-oxo- (or α-imino) enethiol form, *i.e.* as an α-alkylidene-α-mercaptoketone, undergoes the known condensation with unreacted ketone and $NH_3$ to give the $\Delta^3$-thiazoline. Increasing the amount of sulfur should favor the formation of 5-alkylidene-$\Delta^3$-thiazoline over that of the normal $\Delta^3$-thiazoline. This has been confirmed experimentally [74].

### d) Desulfurization of α-Thioxoketones

The desulfurization of α-thioxoketones with $H_2S$ in the presence of amines, with conversion of the –CO–CS– grouping into $-CO-CH_2-$ [74] (cf. Table 2) is an essential step in the Willgerodt-Kindler reaction.

[74] *F. Asinger, W. Schäfer,* and *H. Triem,* unpublished and partly incomplete work.

[75] *E. Campaigne* and *B. Edwards,* J. org. Chemistry *27*, 4488 (1962).

[76] *F. Asinger, W. Schäfer,* and *N. B. Desai,* unpublished work.

Since α-thioxoketones are very unstable compounds, we used geminal α-oxodichlorides (α,α-dichloroketones) instead. On treatment with $H_2S$ and amine, these undergo desulfurization to the ketone by way of α,α-dimercapto- or α-thioxoketones. Some indication of the course of the reaction is given by the pyridine-catalysed desulfurization with $H_2S$. By this method, α-thioxopropiophenone affords bis-(1-phenylpropane-1-on-2-yl) trisulfide.

Thiones are known to undergo analogous reactions. For example, dichlorodiphenylmethane reacts with NaSH in saturated alcoholic $H_2S$ to produce bis(diphenylmethyl) disulfide [77], from which *Bergmann* et al. [78] obtained disulfides of benzophenone using alcoholic ammonium sulfide.

The exothermic desulfurization of α-thioxoketones discovered by us takes place even at room temperature and can be formulated as the reverse of thiolation:

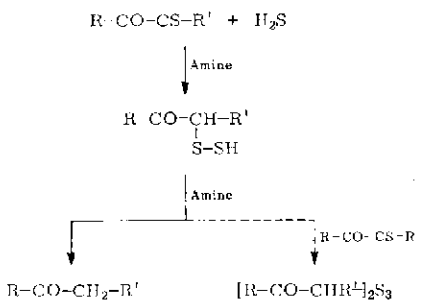



Table 2. Desulfurization of α-thioxoketones with $H_2S$ in the presence of amines in aqueous methanol at room temperature.

| Starting ketone $C_6H_5$–CO R, R = | Amine | S [%] | Ketone [%] [a] | α-Oxopolysulfide [%] |
|---|---|---|---|---|
| $-CHCl_2$ | $C_4H_9NH_2$ | 84 | 45 Ac | – |
| $-CHCl_2$ | $(C_2H_5)_2NH$ | 75 | 36 Ac | – |
| $-CHCl_2$ | $(C_2H_5)_3N$ | 90 | 65 Ac | – |
| $-CHCl_2$ | $C_5H_5N$ | 59 | traces Ac | 93 Di-Ac |
| $-CS-CH_3$ | $(C_2H_5)_3N$ | 79 | 75 Pro | – |
| $-C(SOCH_3)=CH_2$ | $C_4H_9NH_2$ | 65 | 62 Pro | – |
| $-C(SOCH_3)=CH_2$ | $(C_2H_5)_2NH$ | 67 | 79 Pro | – |
| $-C(SOCH_3)=CH_2$ | $(C_2H_5)_3N$ | 75 | 84 Pro | – |
| $-C(SOCH_3)=CH_2$ | $C_5H_5N$ | – | | 49 Di- + Tri-Pro |
| $-CS-CH_2-CH_3$ | $C_5H_5N$ | 25 | traces But | 67 Tri-But |
| $-CCl_2-CH_2-CH_3$ | $C_4H_9NH_2$ | 75 | 80 But | – |
| $-CCl_2-CH_2-CH_3$ | $(C_2H_5)_2NH$ | 81 | 76 But | – |
| $-CCl_2-CH_2-CH_3$ | $(C_2H_5)_3N$ | 84 | 83 But | – |

[a] Ac = acetophenone; Pro = propiophenone; But = n-butyrophenone.

## 2. Acetophenone, Sulfur, and Primary Amines (Reaction Sequence B)

Other important indications of the mechanism of the Willgerodt-Kindler reaction are obtained from the reaction of acetophenone [*] with butylamine and sulfur.

[77] *L. Gattermann* and *H. Schulz*, Ber. dtsch. chem. Ges. *29*, 2944 (1896).

[78] *E. Bergmann*, *M. Magat*, and *D. Wagenberg*, Ber. dtsch. chem. Ges. *63B*, 2576 (1930).

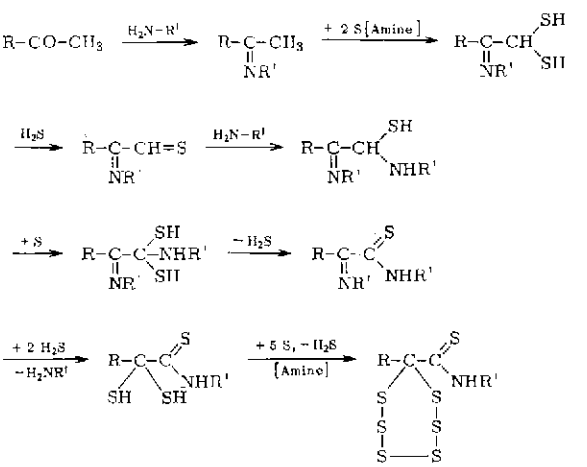
[*] A study of higher alkyl aryl ketones is in progress [47,48].

### a) 1-Phenyl-2,3,4,5,6,7-hexathiacycloheptane-1-thiocarboxamide

For all practical purposes, acetophenone and propiophenone do not react with n-butylamine at 20 °C. In the presence of sulfur at room temperature, however, the *N*-n-butylimines of these ketones are obtained in approximately 40 % yields [15]. Thus, for the first time, we succeeded in isolating an intermediate that was formed under mild conditions from the Willgerodt-Kindler reaction mixture (ketone, S, and amine). It was already suspected by *Kindler* [11] and others [49, 79] that ketimines occurred as intermediates.

1-Phenyl-*N*-n-butyliminoethane may be obtained in about 50 % yield by treating butylamine with acetophenone for 20 hours in methanol in the absence of sulfur [46]. Reaction of the ketimine with sulfur and morpholine in methanol for 20 h at 20 °C affords phenylthioacetomorpholide in 65 % yield [46]. To our knowledge, this is the lowest temperature at which a Willgerodt-Kindler reaction has ever been carried out. On treating the ketimine with sulfur and butylamine instead of morpholine at 20 °C, unexpectedly a 40 % yield of 1-phenyl-2,3,4,5,6,7-hexathiacycloheptane-1-n-butylthiocarboxamide was obtained. With acetophenone as starting material, the yields are somewhat lower.

The structure of the compound can be considered as established, although our studies on the mode of formation, the degradation reactions, *etc.* are not yet complete [80]. Preliminary results obtained to date indicate that this reaction can also be used to prepare other hexathiacycloheptanes and that it, too, involves dithiolation at the methyl group with formation of 2 moles of $H_2S$. In analogy to the formation of geminal dithiols from the Schiff bases of some aliphatic ketones observed by *Magnusson* [81,82], $H_2S$ adds onto the azomethine linkage. The resulting dithiol undergoes an intramolecular McMillan-King reaction leading to the formation of the hexathiacycloheptane ring (Scheme 4).




| R | R' | M.p. [°C] |
|---|---|---|
| $C_6H_5$ | n-$C_3H_7$ | 139 |
| $C_6H_5$ | $CH(CH_3)_2$ | 138 |
| $C_6H_5$ | n-$C_4H_9$ | 109 |

Scheme 4. Hexathiacycloheptane formation.

[79] *R. Boudet*, Ann. Chimie *10*, 178 (1955).

[80] *F. Asinger*, *W. Schäfer*, and *H.-W. Becker*, unpublished work.

[81] *B. Magnusson*, Acta chem. scand. *16*, 1536 (1962).

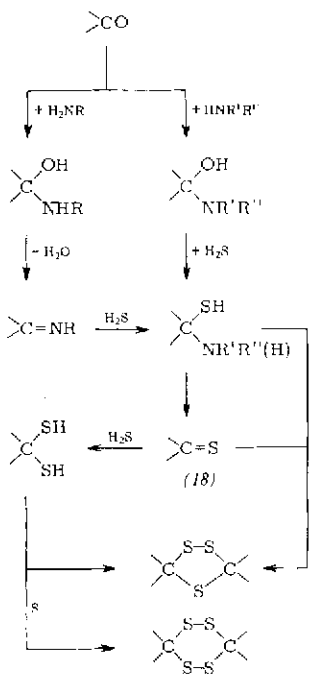
[82] *B. Magnusson*, Acta chem. scand. *17*, 273 (1963).

### 3. Reaction of Alkyl Aryl Ketones with Sulfur and Secondary Amines (Reaction Sequence C)

#### a) Di-(α-aralkyl) Polysulfides

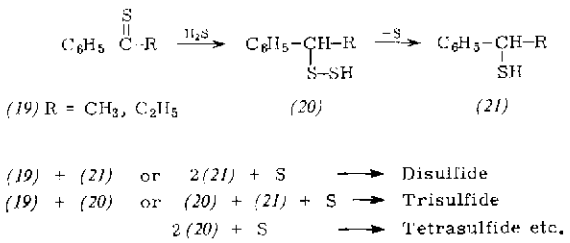
The formation of hexathiacycloheptane derivatives from α-phenethylideneimines in the presence of excess sulfur poses the question whether the reaction mechanism in addition can be altered by an excess of $H_2S$. This was found to be the case.

This study was based on the observation that $\Delta^3$-thiazoline formation can be inhibited by introducing excess $H_2S$ during the reaction (cf. [1]). While studying this phenomenon, we found a new synthesis for 1,2,4-trithiolanes and 1,2,4,5-tetrathianes [83,84]. It involves treatment of $H_2S$ and S with ketones (aldehydes are less suitable) in the presence of $NH_3$ or primary or secondary amines at 0 °C. In the absence of S, geminal dithiols are obtained [85]. Since these dithiols can also be synthetized from ketimines (aldimines are less suitable) and $H_2S$ [81,82], the reaction mechanism represented in Scheme 5 is probably correct.



Scheme 5. Formation of 1,2,4-trithiolanes and 1,2,4,5-tetrathianes.

The central intermediate is the thione *(18)*. Its formation is readily explained when either primary or secondary amines (or $NH_3$) are used, and no differentiation between the amines is necessary for the following discussion. It is significant that especially the alkyl aryl ketones which are predestinated for the Willgerodt-Kindler reaction, when treated with $H_2S$ and amine, do not afford trithiolanes or tetrathianes, and that the reaction of the corresponding ketimines with $H_2S$ does not give dithiols [83,87]. Instead, open-chain di-(α-aralkyl) di- and polysulfides are obtained [86]:



Because of the proximity of the phenyl group, the addition of $H_2S$ onto the thione *(19)*, leads to the monoarylalkylsulfane *(20)* rather than to the geminal dithiol. In the presence of amine or $NH_3$, the sulfane undergoes partial desulfurization to the thiol *(21)* [87,88]. Further desulfurization is precluded by the lack of activating groups in the α-position.

Combinations between *(19)*, *(20)*, or *(21)* lead to polysulfides, and McMillan-King reactions are rendered possible by the presence of sulfur (from the partial desulfurization). It is known that disulfides can be produced in the reaction of thiones or thioaldehydes with thiols containing an adjacent phenyl group [22,23,34,87–92]; sulfurization of disulfides in the presence of base is also known [93]. Di-(α-phenethyl) disulfide was first obtained, along with an unidentified oil, by *Baumann* and *Fromm* on treating acetophenone with $NH_4SH$ for 7 days in methanol [94]. The oily product was identified as a mixture of di-(α-phenethyl) di- and polysulfide [86]. Under identical conditions, propiophenone gives analogous products [86].

On passing $H_2S$ into the *N*-n-butylimine of acetophenone or propiophenone a deep dark-blue solution (thioacetophenone formation) is first obtained, followed by polysulfide formation, which is indicated by brightening of the solution [86]. Secondary amines form the geminal aminohydroxy compound first. On treatment with $H_2S$, the latter undergoes replacement of a hydroxyl by a mercapto group to give the geminal aminomercapto compound, which is then converted into the thione by elimination of amine. Enamine formation by dehydration of the geminal aminohydroxy compound is less probable in view of the mild reaction conditions.

Thus, di-(α-aralkyl) polysulfides are not the real intermediates in the Willgerodt-Kindler reaction. Although they undergo conversion into ω-aralkylcarboxylic acids under Willgerodt-Kindler conditions, the yields are markedly lower than those obtained when, for example, acetophenone or propiophenone are treated directly with amine and sulfur under identical conditions [86]. Moreover, these polysulfides are not formed to an appreciable extent in the Willgerodt-Kindler reaction


[83] *F. Asinger, M. Thiel, G. Lipfert, R. E. Pleßmann,* and *J. Mennig,* Angew. Chem. *70*, 372 (1958).

[84] *F. Asinger, M. Thiel,* and *G. Lipfert,* Liebigs Ann. Chem. *627*, 195 (1959).

[85] *J. Jentzsch, J. Fabian,* and *R. Mayer,* Chem. Ber. *95*, 1764 (1962).

[86] *F. Asinger* and *K. Halcour,* Mh. Chem., in the press.

[87] *V. O. Lukashevich* and *M. M. Sergeyero,* Dokl. Akad. Nauk SSSR *67*, 1041(1949); Chem. Abstr. *44*, 1921 (1950).

[88] *A. J. Parker* and *N. Kharasch,* Chem. Reviews *59*, 583 (1959).

[89] *H. Staudinger* and *H. Freudenberger,* Ber. dtsch. chem. Ges. *61*, 1576 (1928).

[90] *G. F. Bloomfield,* J. chem. Soc. Ind. *67*, 14 (1948).

[91] *Y. Minoura,* Rubber Chem. and Technol. *31*, 615 (1958); Chem. Zbl. *1960*, 7871.

[92] *H. E. Johnson* and *D. G. Crosby,* J. org. Chemistry *27*, 3692 (1962).

[93] *Y. N. Guryanova, Ya. K. Ssyrkin,* and *L. Ss. Kusina,* Dokl. Akad. Nauk SSSR *86*, 107 (1952); Chem. Zbl. *1953*, 2420.

[94] *E. Baumann* and *E. Fromm,* Ber. dtsch. chem. Ges. *28*, 907 (1895).

of alkyl aryl ketones, probably because of their low reactivity. *Naylor* [24] suggested that the di- and polysulfides are intermediates.

However, the study of these compounds has produced further support for the contention that ketimines and thiones are the intermediates in the Willgerodt-Kindler reaction and that they enter into the "polysulfide side-branch" only in the presence of excess $H_2S$. Moreover, regardless of whether the reaction is carried out in the presence of $NH_3$ or a primary or secondary amine, their existence indicates that geminal aminohydroxy compounds, imines and thiones are central intermediates that do not depend on the type of amine used. Intermediates containing thioxo groups have also been suggested by other workers [21,25,34,35].

### b) Migration of Functional Groups along the Alkyl Chain

So far, this discussion has dealt with reactions which, on the basis of our current knowledge, could take place at room temperature, depending on the combination and concentration of the reactants, *i.e.* ketone, S, $NH_3$ or a primary or secondary amine, and $H_2S$, and might be important for the Willgerodt-Kindler reaction. The problem of the migration of any particular functional group along the hydrocarbon chain was not considered. The assumption that the thiolation and desulfurization reactions are associated with a thioreductone equilibrium [*] [95], seems to us at present to offer the best possibility of bringing this phenomenon into harmony with the established facts (see Scheme 1, reaction sequence C). Thus, the Willgerodt-Kindler reaction involves the following steps:

$\alpha$) *Oxidation Steps.* Methylene and, at slower rates, methine and methyl groups undergo thiolation to give $\alpha$-mercaptoketones, whereas $CH_2$ and $CH_3$ groups are also dithiolated to give $\alpha$-thioxoketones when the $\alpha$-position is occupied by unsaturated groups ($\rangle C{=}N$ ; $\rangle C{-}S$; $\rangle C{-}O$) which can be modified (*e.g.* $\rangle N\text{-}C\text{-}OH$, OR, SH, SR) tending to increase the mobility of the hydrogen atoms [**].

$\beta$) *Reduction Steps.* In the presence of amine alone or amine + $H_2S$, reversal of the formation of mercapto and thioxo compounds according to $\alpha$) leads to desulfurization.

$\gamma$) *Migration and Capture Steps.* The oxidations (thiolations) and reductions (desulfurizations) as reversible reactions proceed in both directions along the carbon chain, with migration of the – possibly modified – functional groups, until the irreversible oxidation (thiocarboxamide formation) of the thiolatable chain ends occurs. The resulting increase in the amount of $H_2S$ formed ensures continuation of the reaction (ketimine → thione).

The fact that primary amines are less suitable for the Willgerodt-Kindler reaction than secondary amines is probably due to the higher desulfurization activity of the former. If the chain contains a quaternary carbon atom, then only reduction of the carbonyl to the methylene group takes place [21]; when a tertiary carbon atom is present, the Willgerodt reaction still takes place, but the yields are only 0.5–3 % [5,7,8,21,31, 96–98]; higher yields were obtained only in a few cases (maximum: 19 %) [6,20,21]. Since, in the case of branched chains, the thioreductone phase of the reaction is not so easy to interpret, we see in these results a confirmation of our proposed mechanism. In agreement with this concept, the Willgerodt-Kindler reaction of unbranched alkyl aryl ketones gives far higher yields.

The use of $C_6H_5COCH_2CD_2CH_2CH_3$ in the Willgerodt reaction leads to 95 % loss of $D_2$ [99]; this is readily explained by intermediate formation of C=S.

The fact that migration does not proceed via acetylenic and olefinic bonds (cf. [20,21]) is supported by the results of *Nightingale* et al. [100]. On using $C_6H_5\text{-}C{\equiv}CCOCH_3$ and $C_6H_5{-}CH{=}CHCOCH_3$ in the Willgerodt-Kindler reaction, these workers obtained the corresponding unsaturated carboxylic acids containing the triple and double bond in their original positions [101].

The migration of a thioxo group is supported not only by the increased yield resulting when trithioacetophenone is used in place of acetophenone (72 → 83 %) [102], but also by the results of a Willgerodt reaction with compounds that already contain a carbonyl group at the end of the side chain. In this case, the migrating thioxo group eventually reaches the carboxyl group, *i.e.* a configuration favorable for $NH_3$- or amine-catalysed decarboxylation is attained. In fact, aralkylcarboxylic acids with one less carbon atom and with a terminal carboxyl group are obtained [23,38,103,104].

Additional interpretations of special cases (retention of the oxo group, reaction of compounds such as cyclohexanone or tetralone) are now also possible; however, because of lack of space, these cases will not be considered here.

[*] The possibility that thioreductones play an important role in the Willgerodt-Kindler reaction was first suspected by my (F. A.) former close collaborator Dr. *Max Thiel*. On the basis of our findings concerning $\alpha$-thiolation, *Berchtold* [25] considered thioreductone reactions as one of three possible explanations for functional group migrations.

[95] For information concerning thioreductones, see *H. v. Euler* and *B. Eistert:* Chemie und Biochemie der Reduktone und Reduktonate. Enke, Stuttgart 1957.

[**] For clarity, only $\rangle N\text{-}C\text{-}OH$ and $\rangle C{=}N$ are shown in Scheme 1.


[96] *A. Claus*, J. prakt. Chem. *46* (2), 474 (1892).

[97] *W. E. Bachmann*, and *M. Carmack* J. Amer. chem. Soc. *63*, 2494 (1941).

[98] *M. Carmack*, Ph. D. Thesis, University of Michigan, 1940.

[99] *E. Cerwonka, R. C. Anderson*, and *E. V. Brown*, J. Amer. chem. Soc. *75*, 30 (1953).

[100] *D. Nightingale* and *R. A. Carpenter*, J. Amer. chem. Soc. *71*, 3560 (1949).

[101] Cf. also *G. A. R. Kon*, J. chem. Soc. (London) *1948*, 224.

[102] *E. Campaigne* and *P. V. Rutan*, J. Amer. chem. Soc. *69*, 1211 (1947).

[103] *C. H. Davis* and *M. Carmack*, J. org. Chemistry *12*, 76 (1947).

[104] *H. Feichtinger*, Chem. Ber. *95*, 2238 (1962); Brit. Pat. 709573, Chem. Abstr. *49*, 11003 (1955); German Patent 877605; Chem. Zbl. *1953*, 8991.

## 4. Future Prospects

Because of the large number of steps which can occur in the Willgerodt-Kindler reaction, especially when one considers in a broader sense the different classes of compounds that have already been reacted with sulfur and amine, no single reaction mechanism can possibly account for all the observed facts. It is possible, however, that a thione is a central intermediate in any case. We believe that the Willgerodt-Kindler reaction also takes place with starting materials other than ketones, for example, in the presence of suitable solvents, at markedly lower temperatures than those used previously. This gives us a chance to extend our knowledge of the Willgerodt-Kindler reaction with new viewpoints and possibly provides a means for reducing the number of reactions and side reactions.

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# Recent Developments in the Study of Lysozymes [*]

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*Lysozymes are widely distributed enzymes. They split the chemical skeleton of bacterial cell walls by hydrolysing the β(1 → 4) linkages between N-acetylmuramic acid and N-acetylglucosamine. The amino acid sequence of lysozyme from hen's egg-white is known (129 amino acid residues). Lysozymes of different origins frequently differ in their primary structures although they exhibit qualitatively the same biological activity. The results obtained from investigations with lysozymes allow conclusions to be drawn regarding the chemical structure of the "backbone" of bacterial cell walls.*

## Introduction

The name of *Fleming* is not only associated with the discovery of penicillin but also with that of an enzyme which was called lysozyme and which has "the power of rapidly dissolving certain bacteria, which is possessed by many animal and vegetable tissues and secretions, and to a very marked degree by egg-white" [1]. About the same time, *Fleming* also discovered a coccus which was very sensitive to the action of lysozyme, *viz. Micrococcus lysodeikticus*. His first observations were rapidly confirmed by many research workers. Lysozymes were found in a great number of human organs, tissues, and secretions (spleen, kidney, tears, saliva, etc.). Similar lytic enzymes were characterized in organs and secretions of many vertebrates; invertebrates, bacteria, and even plants (*e.g. Papaya* latex) also contain lysozymes, which therefore appear to be widely distributed substances [2]. The most important source for lysozyme is the white from the eggs of different birds, especially hens. For this reason, the knowledge of egg-white lysozyme is the most extensive.

This paper will deal in a first section with recent results concerning the physico-chemical properties, the structure, and the relationship between the biological activity and structure of hen's egg-white lysozyme. In the second part, a short comparative study is given of lysozymes of various origins recently obtained chromatographically pure. Finally, some recent experiments concerning the lysozyme substrate and some aspects of the action of lysozyme on the latter will be discussed. However, first the definition of a lysozyme and a quantitative assay method will be given.

### a) Definition of a Lysozyme [3,4]

A lytic enzyme can becalled a lysozyme when it possesses the following properties: it must be a basic protein of low molecular weight (near 15000), which is stable at acidic pH (even at 100 °C and pH 4.5 for 1–2 minutes) without significant loss of activity and unstable at alkaline pH; it must be active against suspensions of *Micrococcus lysodeikticus* and liberate by its action on an appropriate substrate compounds which can be detected by reagents for reducing sugars and for *N*-acetylhexosamines and which are derived from glucosamine and muramic acid. For this reason, lysozyme is also called β-glucosaminidase or muramidase or *N*-acetylmuramide glycanohydrolase.

[*] The survey of literature pertaining to this review was completed on January 28th, 1963.

[1] *A. Fleming*, Proc. Roy. Soc. (London), Ser. B. *93*, 306 (1922).

[2] Lysozyme, A Review. Armour and Co., Chicago 1952.

[3] *C. Fromageot* and *P. Jollès*, Experientia Suppl. II, 181 (1955).

[4] *M. R. J. Salton*, Biochim. biophysica Acta *22*, 495 (1956).

b) Determination of Lytic Activity

The lytic activity of a preparation containing a lysozyme is usually determined by observing spectrophotometrically the extent of lysis of a suspension of dead cells of *M. lysodeikticus*. Beside the classical methods of *Smolelis* and *Hartsell* [5] and *Fraenkel-Conrat* [6], some recent modifications introduced by *Shahani* [7] and *Léonis* [8] are worthy of mention.

## II. Hen's Egg-White Lysozyme

### 1. Purification

Lysozyme can be crystallized directly from hen's egg-white as described by *Alderton* and *Fevold* [9]. The method was modified by *Sophianopoulos* et al. [10] by introducing fractionation with ammonium sulfate as a final step in order to obtain chromatographically pure lysozyme. Purification of crystallized or commercial preparations can be achieved by chromatography on carboxymethylcellulose or Amberlite CG-50 [11]. Beside the principal peak (90 + 10 %), it is possible to detect two other fractions. However, since the amounts of these fractions vary with the method of preparation and the time of storage, their slightly different chromatographic behavior may reflect only different contents of amide groups: this point of view seems to be confirmed by quantitative amino-acid analyses.

### 2. Physico-Chemical Studies

Physical data on lysozyme are surprisingly scant, especially in comparison with the progress made in elucidating its sequence of amino acids. In addition, many of the physical measurements were made before the advent of purification by ion-exchange and cellulose chromatography, which have shown, as noted above, that the enzyme can contain varying amounts of minor components.

Its isoelectric point lies between 10.5 and 11.

The molecular weight obtained for lysozyme by different physical methods have recently be reviewed by *Jollès* [12]. The value nearest to that based on analytical data is 14500 ± 200. Some recent experiments by *Sophianopoulos* et al. [10] on chromatographically pure lysozyme indicate a molecular weight of 14400 ± 100 at pH 5.4. These authors re-determined the sedimentation coefficient; after extrapolation to infinite dilution, $S_{20w} = 1.91\times10^{-13}$ sec (previous values: $1.8\times10^{-13}$ $1.87\times10^{-13}$, $1.9\times10^{-13}$, and $2.11\times10^{-13}$ sec); they also gave an average value for the partial specific volume of 0.703 ml/g at 20 °C which is lower than values quoted by *Charlwood* [13] (0.714 at 15 °C) and *McMeekin* et al. [14] (0.722 at 20 °C) but higher than that given by *Colvin* [15] (0.688 at 25 °C).

Recently published values for the optical rotation and optical rotatory dispersion of lysozyme are given in Table 1 [16–18]. These values are important as the partial helical content of lysozyme has been estimated from optical rotatory dispersion and its degree of folding from the change in optical rotation with denaturation [22]. These results suggest that the peptide chain of lysozyme contains about 35 % of its residues in a helical conformation [16, 23].

Table 1. Optical rotation $[\alpha]_D$ and optical rotatory dispersion constant $\lambda_c$ of hen's egg-white lysozyme.

| Solvent | $[\alpha]_D$ | $\lambda_c$ [mμ] | Ref. |
|---|---|---|---|
| 2 M NaCl | −47.1 | 254 | [19] |
| $H_2O$ | −44 | | [16] |
| 8 M urea | −85 | | [16] |
| 0.25 M NaBr, pH 5.6 | −47 | 254 | [17] |
| 4 M guanidine thiocyanate | −83 | 215 | [20] |
| 0.1 M NaCl, pH 3.1 | −51.3 | | [21] |
| 1.9 % aqueous solution, pH 5.5 | | 251 | [18] |

Hydrogen-deuterium exchange was used by *Blout* [24] as an index of the partial helical content in native lysozyme; he found that only 45 % of the amide hydrogen was readily exchanged. *Kanarek* et al. [25] stated that this exchange is a function of pH and is high in acidic solutions. The minimum helical content calculated here is again 35 %.


[5] *A. N. Smolelis* and *S. E. Hartsell*, J. Bacteriol. *58*, 731 (1949).

[6] *H. Fraenkel-Conrat*, Arch. Biochem. Biophysics *27*, 109 (1950).

[7] *K. M. Shahani, R. C. Chandan, P. L. Kelly*, and *E. L. MacQuiddy* in: *XVI th* International Dairy Congress, Copenhagen 1962. Andelsbogtrykkeriet, Odense 1962.

[8] *P. Godfrine* and *J. Léonis* [8a], Vol. *1*, p. 115.

[8a] Atti del II° Symposium internationale sul lisozima di Fleming, Milano 1961. Boscome, Milan 1961.

[9] *H. L. Fevold* and *G. Alderton* in *H. E. Carter*: Biochemical Preparations. Wiley, New York 1949, Vol. 1, p. 67.

[10] *A. J. Sophianopoulos, C. K. Rhodes, D. N. Holcomb*, and *K. E. van Holde*, J. biol. Chemistry *237*, 1107 (1962).

[11] *H. H. Tallan* and *W. H. Stein*, J. biol. Chemistry *200*, 507 (1953).

[12] *P. Jollès* in *P. D. Boyer, H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd Edit., Academic Press, New York 1960, Vol. IV, Chap. 25.

[13] *P. A. Charlwood*, J. Amer. chem. Soc. *79*, 776 (1957).

[14] *T. L. McMeekin* and *K. Marshall*, Science (Washington) *116*, 142 (1952).

[15] *J. R. Colvin*, Canad. J. Chem. *30*, 831 (1960).

[16] *P. Doty*, Collection czechoslov. chem. Commun. *22*, 5 (1957).

[17] *B. Jirgensons*, Arch. Biochem. Biophysics *93*, 172 (1961).

[18] *J. W. Donovan, M. Laskowski*, and *H. A. Scheraga*, J. Amer. chem. Soc. *82*, 2154 (1960).

[19] *J. T. Young* and *P. Doty*, J. Amer. chem. Soc. *79*, 761 (1957).

[20] *B Jirgensons*, Tetrahedron *13*, 166 (1961).

[21] *L. Josefsson* in: First Symposium on Lysozyme, Milan 1959. Istituto italiano d'arti grafiche, Bergamo 1959, p. 131.

[22] *C. Schellmann* and *J. A. Schellman*, C. R. Trav. Lab. Carlsberg, Sér. chim. *30*, 463 (1958).

[23] *P. Urnes* and *P. Doty*, Advances Protein Chem. *16*, 401 (1961).

[24] *E. R. Blout, C. de Lozé*, and *A. Asadourian*, J. Amer. chem. Soc. *83*, 1895 (1961).

[25] *L. Kanareck, A. Hvidt, J. Léonis*, and *M. Ottesen* [8a], Vol. 1, p. 111.

The intrinsic viscosity and sedimentation coefficient are consistent with either a nearly spherical molecule with a hydration of 0.6 g of water per g of protein or an oblate ellipsoid of lower hydration [10]. *Donovan* et al. [18] used titration curves and ultraviolet difference spectra to obtain information about interactions which make some of the carboxyl groups of lysozyme behave abnormally.

Crystallographic investigations by *Alderton* [26], *Corey* [27], *Steinrauf* [28], and *King* [29] showed that lysozyme can be crystallized in several crystal forms as salts of mineral acids.

Crystals of lysozyme chloride grown at pH 4.7 [26] are tetragonal; each unit contains eight lysozyme molecules [28] together with 1 M NaCl solution (the buffer used contained $Na^+$-ions) which is occluded and contributes about 33.5 % of the weight of the crystal.

Recently a detailed X-ray crystallographic investigation was begun by *Blake* et al. [30], which ought to lead to a knowledge of the molecular configuration. Their first result was a three-dimensional electron-density map at 6 Å resolution of lysozyme in the tetragonal crystal form. Three heavy-atom derivatives have been used, containing mercuric iodide, hexachloropalladate(IV) and 2-hydroxymercury(II)-toluene-4-sulfonic acid. Similar studies are being made by *Stanford* et al. [31] using tetragonal lysozyme chloride crystals containing complex ions of niobium and tantalum and by *Dickerson* et al. [32] with triclinic lysozyme nitrate.

## 3. Chemical Structure

### a) Analysis

Hen's egg-white lysozyme contains 129 amino acid residues (molecular weight: 14388): $Gly_{12}$, $Ala_{12}$, $Ser_{10}$, $(Cys)_8$, $Met_2$, $Thr_7$, $Pro_2$, $Val_6$, $Leu_8$, $Ileu_6$, $Phe_3$, $Tyr_3$, $Try_6$, $Asp_{21}$, $Glu_5$, $Lys_6$, $Arg_{11}$, $His_1$, $(NH_2-)_{18}$. It is the first protein containing all the common amino acids, especially Met, Try, and Cys together, whose chemical structure has been determined [12].

### b) Primary Structure

*Jollès* and *Jollès* [33] determined the chemical structure of egg-white lysozyme in 1961. The protein consists of a single polypeptide chain folded by the four –S–S– bridges of the cystine residues. Cleavage of the –S–S- bridges does not split the molecule into several polypeptide chains.

Table 2. Separation of the products of digestion with trypsin of hen's egg-white lysozyme by ion-exchange column chromatography. Behavior of the amino acids tryptophan (Try), cystine (Cys), and methionine (Met) [34].

| Resin | Lysozyme | Try | Cys | Met | Observations |
|---|---|---|---|---|---|
| | | appears in eluate as | | | |
| Dowex 50X2 | Native | Try | Cys | Met | Very slight digestion by trypsin |
| | Heat-denatured | Try | Cys | Met | Cys-containing peptides remain adsorbed |
| | Oxidized | Kynurenine | Cysteic acid | Methionine-sulfone | Try-containing peptides remain adsorbed |
| | Reduced and treated with $ICH_2COOH$ | Try | *S*-Carboxy-methyl-cysteine | Homoserine | Peptides with high content of aromatic amino acids remain adsorbed |
| Dowex 1X2 | Reduced and treated with $ICH_2COOH$ | Try | *S*-Carboxy-methyl-cysteine | Homoserine | Separation of all the products |

To establish the primary structure, the lysozyme was denatured (heat, oxidation, reduction) and digested with trypsin; the native enzyme cannot be split by trypsin. The products of this hydrolysis were separated by chromatography on Dowex 50X2 or Dowex 1X2 columns. Table 2 points out the differences encountered in this study [34]. It was possible to join the units from the digestion with trypsin together in the right order after hydrolysis with chymotrypsin yielded units containing basic amino acids which gave information about the sequence of the tryptic cleavage products. Figure 1 indicates the primary structure [33–35].

### c) Secondary and Tertiary Structure; Disposition of the –S–S-Bridges

Some results concerning the secondary and tertiary structure have already been mentioned in the part devoted to the physico-chemical properties. *Léonis* [36] investigated the secondary structure, *i.e.* the hydrogen-bonds between the peptide groups, by dissolving the enzyme in urea and by measuring the absorption spectrum in the far ultraviolet and the variations of the optical rotatory dispersion.

The tertiary structure (arrangement of the side chains, etc.) was also studied by *Léonis* [36]. The results of his experiments suggest the importance of the hydrophobic linkage in the stability of the molecular configuration of lysozyme. The configuration of native lysozyme is not necessarily the most organized structure. Following treatment of lysozyme with urea, column chromatography on Amberlite CG-50 yielded a whole family of

[26] *G. Alderton* and *J. Fevold*, J. biol. Chemistry *164*, 1 (1946).

[27] *R. B. Corey*, *J. Donohue*, *K. N. Trueblood*, and *K. J. Palmer*, Acta crystallogr. *5* 701 (1952).

[28] *L. K. Steinrauf* Acta crystallogr. *12* 77 (1959).

[29] *G. S. D. King* Acta crystallogr. *12*, 216 (1959).

[30] *C. C. F. Blake*, *R. H. Fenn*, *A. C. T. North*, *D. C. Phillips*, and *R. J. Poljak*, Nature (London) *196*, 1173 (1962).

[31] *R. H. Stanford*, *R. E. Marsh*, and *R. B. Corey*, Nature (London) *196*, 1176 (1962).

[32] *R. E. Dickerson*, *J. M. Reddy*, *M. Pinkerton*, and *L. K. Steinrauf*, Nature (London) *196*, 1178 (1962).

[33] *J. Jollès* and *P. Jollès*, C. R. hebd. Séances Acad. Sci. *253*, 2773 (1961).

[34] *J. Jollès*, *J. Jauregui-Adell*, *I. Bernier*, and *P. Jollès*, Biochim. biophysica Acta, in the press.

[35] *J. Jollès* and *P. Jollès*, Biochim. biophysica Acta *45*, 407 (1960).

[36] *J. Léonis* [8a], Vol. 1, p. 125.

very closely related lysozymes which seem to differ mainly by their tertiary structure [8]. *Jauregui* and *Jollès* [37] also obtained similar results after treatment of lysozyme with iodoacetic acid at pH 5.5.

peptide was then oxidized with performic acid with a view to determining which of the half-cystine residues were joined together in native lysozyme. Figure 1 indicates a first disulfide bond characterized in this way.

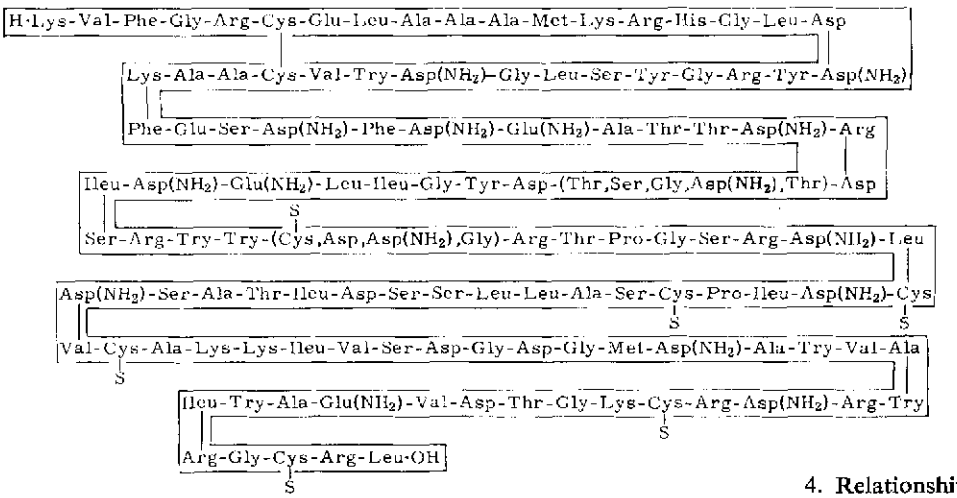



Fig. 1. The chemical structure of hen's egg-white lysozyme.

## 4. Relationships between Structure and Biological Activity

In order to identify the positions of the disulfide bonds, *Jollès* et al. [38] digested the native enzyme with pepsin and chymotrypsin and were then able to isolate the peptides containing cystine by chromatography on Dowex 50X2 (Figure 2). Each peak containing a cystine

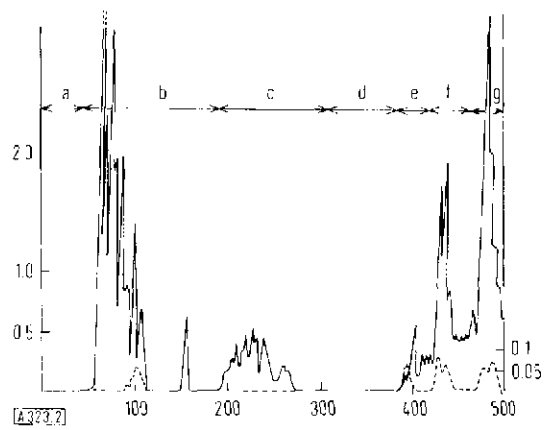



Fig. 2. Chromatogram of the peptides obtained by hydrolysis of hen's egg-white lysozyme with pepsin and chymotrypsin on a Dowex 50 X 2 column (length: 100 cm, diameter: 2 cm) [38]. Eluting buffer:

(a) 0.2 M sodium citrate, pH 3.1
(b) 0.2 M sodium citrate, pH 3.1 → 1.0 M sodium citrate, pH 5.1
(c) 1.0 M sodium citrate, pH 5.1 → 2.0 M sodium citrate, pH 5.1
(d) 2.0 M sodium acetate, pH 6.4
(e) 0.5 M sodium phosphate, pH 7.2
(f) 0.75 M sodium borate, pH 9.5
(g) 0.5 M sodium borate, pH 12.3.

Volume of the mixing chamber for (b) and (c): 500 ml.
Volume of fractions: 10 ml.

Ordinate on the left and full curve: Intensity of the ninhydrin reaction after alkaline hydrolysis (leucine equivalents [mmole/l]).

Ordinate on the right and dashed curve: Peptides containing cystine; intensity of the coloration with phosphotungstic acid (absorption at 700 mμ).

Abscissa: Number of fractions.

The biological activity of lysozyme cannot, of course, be related to any single amino acid, but the maintainance of different groups of amino-acid residues seems necessary for the enzymatic properties; these include:

a) the tryptophan residues; the activity is lost if these residues are altered by treatment with *N*-bromosuccinimide [39];

b) the cystine residues; maintainance of at least two –S–S– bridges appears to be necessary for the biological activity, judging from partial reduction experiments by *Jollès* et al. [34]. *Churchich* [40] observed that oxidation in air of the partially reduced lysozyme resulted in 80% recovery of the protein, yielding a water-soluble compound with 60% of the specific activity of the native enzyme. Lysozyme oxidized with performic acid is inactive;

c) the single histidine residue; it is inaccessible to iodoacetic acid at pH 5.5; if the native enzyme is treated with iodoacetic acid for 20 minutes, a group of active lysozymes can be separated by column chromatography, which seem to be very closely related substances (Figure 3) [37]. They all contain histidine and probably differ slightly in their tertiary structure.

The C-terminal Arg-Leu sequence of the protein can be split off without loss of activity; however, it has not yet been possible to isolate a short active sequence from lysozyme.

The relationships between treatment with various reagents and the biological activity of lysozyme are indicated in Table 3. The following points are noteworthy:

a) Radioactive lysozyme remains active up to a specific activity of 0.20 mC/mmole [41].


[37] *J. Jauregui-Adell* and *P. Jollès*, unpublished results.

[38] *J. Jollès, J. Jauregui-Adell*, and *P. Jollès*, Biochim. biophysica Acta *71*, 488 (1963).

[39] *I. Bernier* and *P. Jollès*, C. R. hebd. Séances Acad. Sci. *253*, 745 (1961).

[40] *J. E. Churchich*, Biochim. biophysica Acta *65*, 349 (1962).

[41] *A. G. Schnek, L. Ledoux*, and *J. Léonis* [8a], Vol. 1, p. 103.

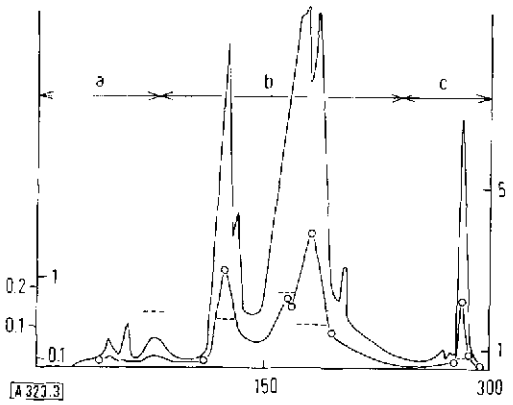



Fig. 3. Products obtained after treating hen's egg-white lysozyme with iodoacetic acid for 20 min at pH 5.5 [37] by chromatography on Amberlite CG-50. Eluting buffer:

(a) 0.15 M sodium phosphate, pH 7.18
(b) 0.2 M sodium phosphate pH 7.18
(c) 0.8 M sodium phosphate, pH 7.18.

Volume of fractions: 3 ml.

Ordinate on the outer left and curve o—o: Intensity of the coloration with Folin reagent [μmoles of lysozyme per l].
Ordinate on the inner left and dashed lines: Specific activity relative to *M. lysodeikticus* (Hen's egg-white lysozyme = 1).
Ordinate on the right and curve – : Intensity of the ninhydrin reaction after alkaline hydrolysis [μmoles of amino nitrogen/l].

Abscissa: Number of fractions.

Table 3. Enzymatic activity of hen's egg-white lysozyme after various treatments

| Treatment | Amino acids or groups altered by treatment | Activity | Ref. |
|---|---|---|---|
| Oxidation | Cys [*], Met, Try | Inactivation | [6] |
| Photooxidation | His, aromatic amino acids | Reduced activity | [44] |
| Reduction | Cys | Reversible inactivation | [40,44a] |
| Anhydrous formic acid | $N \rightarrow O$-Acyl shift; hydroxyamino acids | Reversible inactivation | [45] |
| Esterification | Free COOH groups | Depends on the reagent | [6] |
| Acetylation | Free $NH_2$ groups | Progressive inactivation | [6,42] |
| Guanidination | Lys | Active | [42] |
| Xanthination | Try | Inactivation | [43] |
| Iodination | His, aromatic amino acids | Inactivation; reactivation possible | [6] |
| Iodoacetic acid (pH 5.5) | Partially Met, Lys | Formation of active closely related substances | [37] |
| Urea | | Formation of active closely related substances | [8] |
| *N*-Bromo-succinimide | Mainly Try | Progressive inactivation | [39] |
| Incorporation of radioisotopes | | Active up to 20 mC/mmole | [41] |

[*] Cys = cystine.

[42] *I. I. Gerschwind* and *C. H. Li*, Biochim. biophysica Acta *25*, 171 (1957).

[43] *S. R. Dickman, R. B. Kropf*, and *C. M. Proctor*, J. biol. Chemistry *210*, 491 (1954).

b) Urea has two modes of action: an instantaneous but completely reversible inhibition, and a slow but irreversible action, whereby native lysozyme is transformed into closely related active substances [8].

c) Any treatment of the enzyme which increases its (relative) content of acidic groups (acetylation) inactivates it, any treatment increasing its basicity (guanidination) leaves the protein active [42].

It will be interesting to search for the structural basis of the bacteriolytic activity at the level of the tertiary structure, especially in the stabilizing action of the hydrophobic linkages, as it is possible to obtain inactive fractions without modification of the secondary structure [36].

## III. Lysozymes of Different Origins

The purification and analysis of different lysozymes has been undertaken in the author's laboratory with a view to comparing the enzymes and establishing whether the same qualitative biological activity can be related to some common points.

### 1. Choice of the Lysozymes

Two groups of lysozymes were investigated: 1. Lysozymes extracted from the same organ of two different animal species (hen's and duck's egg-white [46], rabbit [47] and dog spleen [48]). 2. Lysozymes extracted from different organs or body fluids of the same animal (hen's egg-white and lung [49]; dog spleen [48] and kidney; human milk [50], placenta [51], saliva [51a], leucocytes [52], and spleen). All these lysozymes have been obtained in a chromatographically pure state by the procedure described below.

### 2. Purification Procedure

The purification procedure described by *Jollès* et al. [53] includes five main steps:

1. Heating of the ground organ or fluid at 100 °C for 1–2 minutes at pH 4–4.5.

[44] *L. Weil, A. R. Buchart*, and *J. Maher*, Arch. Biochem. Biophysics *40*, 245 (1952).

[44a] *K. Imai, T. Takagi*, and *T. Isemura*, J. Biochemistry (Tokyo) *53*, 1 (1963).

[45] *L. Josefsson*, Biochim. biophysica Acta *59*, 128 (1962).

[46] *P. Jollès, G. Spotorno*, and *J. Jollès*, unpublished results.

[47] *G. Jollès* and *C. Fromageot*, Biochim. biophysica Acta *11*, 95 (1953); *14*, 219 (1954).

[48] *P. Jollès* and *C. Fromageot*, Biochim. biophysica Acta *19*, 91 (1956).

[49] *P. Jollès* and *S. Zuili*, Biochim. biophysica Acta *39*, 212 (1960).

[50] *P. Jollès* and *J. Jollès*, Nature (London) *192*, 1187 (1961).

[51] *J. F. Petit, M. Panigel*, and *P. Jollès*, Bull. Soc. Chim. biol. *45*, 211 (1963).

[51a] *J. F. Petit* and *P. Jollès*, Nature (London) *200*, 168 (1963).

[52] *P. Jollès* and *D. Charlemagne*, unpublished results.

[53] *P. Jollès, H. Zowall, J. Jauregui-Adell*, and *J. Jollès*, J. Chromatogr. *8*, 363 (1962).

2. Adsorption on Amberlite CG-50 and elution of basic substances.

3. Chromatography on carboxymethylcellulose.

4. Desalting on Sephadex G-25 or G-50.

5. Ion-exchange chromatography on Amberlite CG-50 columns, without change of the temperature, the pH, and the molarity of the buffer. The enzyme obtained is chromatographically pure. Table 4 indicates the pH at which the various lysozymes were chromatographed.

Table 4. Optimum conditions for quantitative elution of lysozymes of various origins from ion-exchange chromatography columns; 1 mg of enzyme on Amberlite CG-50 columns (length: 20 cm, diameter: 1 cm) with a phosphate buffer at 20 °C [12,46–52].

| Lysozyme | pH (± 0.02) | Molarity of buffer | Volume of eluate [ml] |
|---|---|---|---|
| Hen's egg-white | 7.18 | 0.2 | 90 |
| Hen lung I | 6.40 | 0.325 | 70 |
| Hen lung II | 6.40 | 0.412 | 70 |
| Duck egg-white I | 7.58 | 0.2 | 20 |
| Dog spleen | 6.50 | 0.2 | 120 |
| Dog kidney | 6.40 | 0.2 | 20 |
| Rabbit spleen I | 6.55 | 0.2 | 20 |
| Rabbit spleen II | 6.55 | 0.2 | 60 |
| Human milk I | 6.82 | 0.2 | 40 |
| Human milk II | 6.98 | 0.2 | 70 |
| Human saliva | 6.98 | 0.2 | 30 |
| Human leucocytes | 6.98 | 0.2 | 40 |
| Human placenta | 6.98 | 0.2 | 30 |
| *Nephthys hombergi* (annelid) | 6.60 | 0.2 | 1000 |

All the lytic enzymes studied except for the lysozymes from human saliva and human placenta have different chromatographic behaviors.

### 3. Analysis and Molecular Weight

The various lysozymes summarized in Table 4 have been analyzed. With the exception of the two enzymes isolated from rabbit spleen [47], which differ only in the number of their amide groups [12] and the lysozymes from human saliva and placenta, all the lysozymes studied have different amino-acid compositions [12]. These differences affect mainly the Glu, Pro, and Arg residues and the aromatic amino acids (Table 5). The molecular weight of all these enzymes is approximately 15000, judging from estimations with calibrated cellophane membranes.

Table 5. Main differences in the amino-acid compositions of some lysozymes [12,46–49,51,54,56].

| Lysozyme | Residues/molecule | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cys [a] | Glu | Pro | Tyr | Phe | Try | His | Arg |
| Hen's egg white | 4 | 5 | 2 | 3 | 3 | 6 | 1 | 11 |
| Hen lung I | | 9–10 | 8 | 3 | 3 | | 3 | 6 |
| Dog spleen | 4 | 10±1 | 8 | 3 | 3 | 6 | 1 | 8 |
| Dog kidney I | | 6±1 | 7±1 | 3 | 3 | | 1 | 11±1 |
| Rabbit spleen I [b] | 4–5 | 11 | 5 | 3 | 3 | 2 | 1 | 6 |
| Rabbit spleen II [b] | 4–5 | 11 | 5 | 3 | 3 | 2 | 1 | 6 |
| Human placenta [c] | 3 | 9±1 | 3 | 5 | 2 | 3±1 | 1 | 11±1 |
| Human saliva [c] | 3 | 9±1 | 3 | 5 | 2 | 3±1 | 1 | 11±1 |
| Human milk I | | | 5–6 | 3 | 3 | | | 11±1 |
| Human milk II | | | 3 | 5 | 2 | | | 11±1 |
| *Nephthys hombergi* | | 8–9 | 12 | 3 | 3 | 1–2 | | 7 |
| *Papaya* latex | 8 | 11 | 18 | 13 | 12 | 7 | 3 | 13 |

[a] Cys = cystine.
[b] Differ in their amide-group content.
[c] Do not differ even in the content of other amino acids.

### 4. Biological Activity

The lysozymes listed in Table 4 have qualitatively the same biological activity toward the same bacteria. Under the same conditions of assay at the optimum pH, hen's egg-white lysozyme is as active as rabbit spleen lysozyme [47] or hen lung lysozyme [49], but only one-half to one-third as active as dog spleen lysozyme [48], human placenta lysozyme [51], or *Nephthys hombergi* (annelid) lysozyme [49]. Lysozymes from *Papaya* latex [54] and from *B. subtilis* [55] are only one-fifth as active as egg-white lysozyme.

### 5. Comparison of the Structures and Activities of Different Lysozymes (Heteroenzymes)

Lysozymes isolated from different animal species (even from the same organ) have different chromatographic behaviors, and different amino-acid compositions. The units from digestion with trypsin of oxidized dog spleen lysozyme have been isolated, analyzed, and compared with those of hen's egg-white lysozyme [57]; it was not possible to find any common sequences between the two, the primary structures of these two enzymes must therefore be different. The same applies to human milk lysozyme I and hen's egg-white lysozyme [56]. On partial reduction, dog spleen lysozyme loses its activity but can be reactivated.

If two lysozymes extracted from the same organ exhibit different chromatographic behaviors, this may be due to differences in the number of their amide groups (*e.g.* with rabbit spleen lysozymes I and II) or amino-acid residues (*e.g.* with human milk lysozymes I and II).

Lysozymes from different organs or fluids of the same animal may have the same chromatographic behavior and the same amino-acid composition (*e.g.* human placenta and human saliva lysozymes) [51]; it is rea-

[54] *E. L. Smith, J. R. Kimmel, D. M. Brown,* and *E. O. P. Thompson,* J. biol. Chemistry *215,* 67 (1955).

[55] *Y. Satomura, S. Okada,* and *J. Fukumoto,* J. agric. chem. Soc. Japan *31,* 281 (1957).

[56] *P. Jollès* and *J. Jollès,* unpublished results.

[57] *P. Jollès* and *M. Ledieu,* Biochim. biophysica Acta *36,* 284 (1959).

sonable to consider that they then have the same structure. However, such lysozymes can also be quite different chromatographically and in composition; this applies, for example, to human placenta (or human saliva) lysozyme [51] and human milk lysozyme I [56]. A first comparison of the products of hydrolysis with trypsin by paper chromatography and electrophoresis indicated that the structures of these lysozymes seem to be different. Another example is the lysozymes from dog spleen and kidney, the first instance of the occurrence of heteroenzymes [*] in different organs of the same animal [3, 48].

It is actually possible to relate the common biological activity of lysozymes to their basicity and to some common aspects of their tertiary structure (some hydrogen and hydrophobic bonds, and presence of at least two –S–S– bonds). The single histidine residue contained in a great number of these enzymes and some aromatic amino acids may be of importance. Sequences that are common to two or more lysozymes with different amino-acid contents have not been isolated until now. In one case, such sequences were definitely excluded [57].

### 6. Lysozymes from Plants and Bacteria

Beside the lysozymes described above, only few others have been obtained in sufficient purity. The only pure lysozyme obtained from plants until now is the enzyme from *Papaya* latex [54] (molecular weight: 25000).

Lysozymes from bacteria include those from strains of *B. subtilis* studied by *Richmond* [59] and *Satomura* [55]. One of the enzymes from *Streptomyces* studied by *Ghuysen* [60] is essentially an *N*-acetylhexosaminidase and therefore similar to egg-white lysozyme.

*Koch* and *Dreyer* characterized an enzyme of phage $T_2$ as a lysozyme [61]. $T_2$-infected cells of *Escherichia coli* B synthetize an enzyme which lyses the cell from within: it is also a lysozyme with a molecular weight of 15000 and was studied by *Weidel* et al. [62]. A particle-bound $T_2$-phage lysozyme which appears to have a higher molecular weight (21000) was isolated by the same authors [63].

## IV. The Substrate and Enzymatic Action of Lysozyme

As already mentioned, *Fleming* discovered simultaneously lysozyme and a Gram-positive coccus which he named *Micrococcus lysodeikticus* because of its great susceptibility to the enzyme. The first substrate of lysozyme used was a suspension of *Micrococcus lysodeikticus*. After various attempts to isolate the substrate directly from whole cells, *Salton* [64] reported that the substrate occurred entirely in the cell wall, and thanks to his efforts, purified cell wall preparations were then obtained [65]. *Salton* and *Pavlik* [66] observed that the isolated walls of 23 different Gram-positive bacteria investigated showed some degree of susceptibility to digestion with lysozyme; the percentage reduction in turbidity varied from 9 % for *Staphylococcus aureus* walls to 98 % for the walls of *M. lysodeikticus*. Although all of the cell walls contained muramic acid and glucosamine, the sensitivity to lysozyme could not be correlated to the total amino sugar content.

Over the past few years, attempts to isolate the bacterial substrate from *M. lysodeikticus* have been made by *Schütte* and *Krisch* [67]. Their substrate was highly purified, entirely soluble in water, but not homogeneous. *Colobert* et al. [68] purified a similar preparation by chromatography on DEAE-cellulose. It appeared to be a mucopeptide. *Jollès* [69] has shown that after chromatography on DEAE-cellulose it was possible to obtain two different soluble substrates containing equal quantities of glucosamine and muramic acid, glucose, and a peptide consisting of Gly, Ala, Glu, and Lys. Lysozymes from hen's egg-white, duck's egg-white (I) and human milk (II) hydrolyse these substrates. This fact seems to confirm that the three lysozymes which are analogous but not identical substances are β-glucosaminidases. However, the kinetics of their action are different. At pH 5.8, duck's egg-white lysozyme is the most basic and is also the most active (Figure 4).

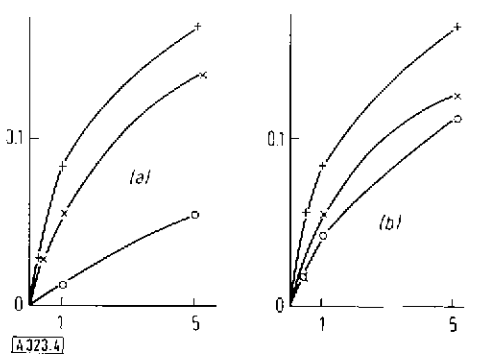



Fig. 4. Kinetics of the hydrolysis of two substrates by three lysozymes at pH 5.8 [69].

(a) Substrate: eluted from DEAE-cellulose at pH 7.2 [69]
(b) Substrate: eluted from DEAE-cellulose at pH 2.8 [69]
+–+–+ Lysozyme I from duck's egg-white
x–x–x Lysozyme from hen's egg-white
o–o–o Lysozyme II from human milk.
Ordinate: Released sugar (as galactose [μmole]).
Abscissa: Time [min].

[*] *i.e.* proteins of different origins that differ in their physical, chemical and biological properties but have the same biological action [58].

[58] *T. Wieland* and *G. Pfleiderer*, Angew. Chem. *74*, 261 (1962); Angew. Chem. internat. Edit. *1*, 169 (1962).

[59] *M. H. Richmond*, Biochim. biophysica Acta *33*, 78 (1959).

[60] *J. M. Ghuysen*, Arch. internat. Physiol. Biochim. *65*, 173 (1957).

[61] *G. Koch* and *W. J. Dreyer*, Virology *6*, 291 (1958).

[62] *W. Weidel* and *W. Katz*, Z. Naturforsch. *16b*, 156. (1961).

[63] *W. Katz* and *W. Weidel*, Z. Naturforsch. *16b*, 363 (1961).

[64] *M. R. J. Salton*, Nature (London) *170*, 746 (1952).

[65] *M. R. J. Salton* and *R. W. Horne*, Biochim. biophysica Acta *7*, 177 (1951).

[66] *M. R. J. Salton* and *J. G. Pavlik*, Biochim. biophysica Acta *39*, 398 (1960).

[67] *E. Schütte* and *K. Krisch*, Hoppe-Seylers Z. physiol. Chem. *311*, 121 (1958).

[68] *L. Colobert* and *G. Dirheimer*, C. R. hebd. Séances Acad. Sci. *250*, 423 (1960).

[69] *P. Jollès*, Biochim. biophysica Acta *69*, 505 (1963).

The substrate of hen's egg-white lysozyme is now known to be distributed not only in Gram-positive but also in Gram-negative bacteria following investigations of *Weidel* et al. [70,71] on the occurrence of both diaminopimelic acid and muramic acid in the walls of *Escherichia coli* and of *Salton* [72,73] on a variety of Gram-negative bacteria. *Mandelstam* [74] also noted that the cell walls of the Gram-negative *E. coli* contain lysozyme-sensitive mucopeptides made up of muramic acid, glucosamine, Gly, Glu, Ala, diaminopimelic acid and Lys. *Martin* and *Franck* [75] recently identified a rigid layer in the cell wall of *E. coli* B which contains a mucopolymer and which can be digested by lysozyme. *Colobert* et al. [76] succeeded in obtaining another highly purified substrate from the Gram-negative organism *Salmonella typhosa*. It is interesting that blue-green algae contain a mucopolymer cell-wall component closely resembling that found in the cell walls of bacteria [77].

Although it was known that lysozyme splits glycosidic bonds with liberation of *N*-acetylamino sugars, direct evidence establishing the nature of the linkages broken became available only when isolated cell walls were used as a substrate. This question has been discussed recently by *Salton* [78]. He observed that enzymatic lysis of cell walls from *M. lysodeikticus*, *Bacillus megatherium*, and *Sarcina lutea* resulted in dialysable and non-dialysable products; the former consisted in part of a disaccharide of *N*-acetylglucosamine and *N*-acetylmuramic acid and the latter of compounds with molecular weights of 10000 to 20000 [79]. The structure of the disaccharide was determined by *Salton* and *Ghuysen* [80]: it is an *N*-acetylglucosaminyl-$\beta(1 \rightarrow 6)$-*N*-acetylmuramic acid. Quite recently, *Jeanloz* et al. [80a] proposed a different structure with a $\beta(1 \rightarrow 4)$ linkage instead of *Salton*'s $\beta(1 \rightarrow 6)$ linkage. In addition to the disaccharide, a tetrasaccharide was detected [80] which is a dimer of the disaccharide joined by a $\beta(1 \rightarrow 4)$ linkage. This tetrasaccharide (Figure 5) is split by egg-white lysozyme which possesses $\beta(1 \rightarrow 4)$-*N*-acetylglucosaminidase or $\beta(1 \rightarrow 4)$-muramidase action, and may be considered to be a characteristic substrate of lysozyme.

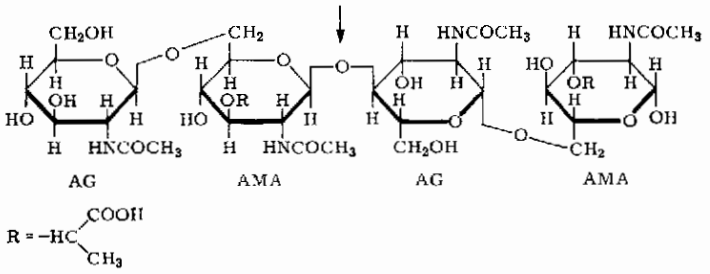



Fig. 5. Tetrasaccharide released by lysozyme from the cell walls of *M. lysodeikticus* and used as a lysozyme substrate [80].
AG = acetylglucosamine; AMA = acetylmuramic acid; the arrow indicates the bond split by lysozyme.

These studies confirm and extend the observations of *Berger* and *Weiser* [81] and of *Perkins* [82]. *Jollès* [83] detected the same disaccharide not only when egg-white lysozyme but also when lysozymes from dog spleen and *Nephthys hombergi* degraded the cell walls of *M. lysodeikticus*. *Ghuysen* found that an enzyme secreted by a *Streptomyces* has the same effect [60].

From these results it was possible to obtain an idea of the structure of the cell-wall mucopeptide. The wall probably has a basic skeleton [84] of alternating *N*-acetylmuramic acid (AMA) and *N*-acetylglucosamine

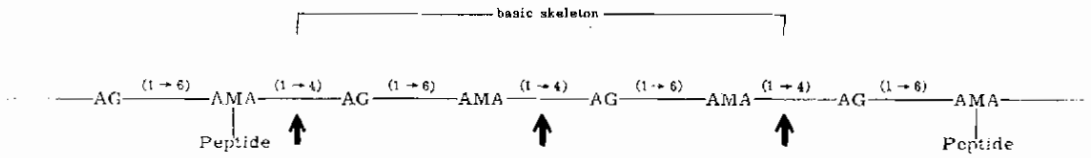



Fig. 6. Schematic representation of the structure proposed for the basic skeleton of the cell walls of *M. lysodeikticus* [80].
AG = acetylglucosamine; AMA = acetylmuramic acid; the bonds marked with arrows are split by lysozyme.

(AG) residues with alternating $\beta(1 \rightarrow 4)$ and $\beta(1 \rightarrow 6)$ linkages. Some of the muramic acid residues have peptide substituents: AMA-Ala-($Glu_1$, $Gly_1$, $Lys_1$, $Ala_1$) [85]. Figure 6 shows the structure proposed by *Salton* for the skeleton of *Micrococcus lysodeikticus* walls.

It is now possible to understand the manner in which lysozyme degrades bacterial walls but many problems concerning lysozyme sensitivity remain to be solved. Lysozyme can act on a naturally resistant cell wall if the substrate is present and exposed by the synergistic action of certain agents, *e.g.* trypsin [86], antibiotica, solvents, or metal complexing reagents [87]. The development of resistance to lysozyme by *M. lysodeikticus*

[70] *W. Weidel* and *J. Primosigh*, Z. Naturforsch. *12b*, 421 (1957).
[71] *W. Weidel* and *J. Primosigh*, J. gen. Microbiol. *18*, 513 (1958).
[72] *M. R. J. Salton*, Biochim. biophysica Acta *10*, 512 (1953).
[73] *M. R. J. Salton*, Nature (London) *180*, 338 (1957).
[74] *J. Mandelstam*, Nature (London) *189*, 855 (1961).
[75] *H. H. Martin* and *H. Frank*, Z. Naturforsch. *17b*, 190 (1962).
[76] *L. Colobert* and *O. Creach*, Biochim. biophysica Acta *40*, 167 (1960).
[77] *H. Frank*, *M. Lefort*, and *H. H. Martin*, Z. Naturforsch. *17b*, 262 (1962).
[78] *M. R. J. Salton:* Microbial Cell Walls. Wiley, New York 1960, p. 59.
[79] *M. R. J. Salton*, Biochim. biophysica Acta *22*, 495 (1956).
[80] *M. R. J. Salton* and *J. M. Ghuysen*, Biochim. biophysica Acta *36*, 552 (1959); *45*, 355 (1960).
[80a] *R. W. Jeanloz*, *N. Sharon*, and *H. M. Flowers*, Biochem. biophys. Res. Commun. *13*, 20 (1963).
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[83] *S. Zuili* and *P. Jollès*, C. R. hebd. Séances Acad. Sci. *250*, 3521 (1960).
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[85] *J. M. Ghuysen*, Biochim. biophysica Acta *47*, 561 (1961).
[86] *M. E. Becker* and *S. E. Hartsell*, Arch. Biochem. Biophysics *55*, 257 (1955).
[87] *R. Repaske*, Biochim. biophysica Acta *30*, 225 (1958).

was described by *Brumfitt* [88,89], who associated this phenomenon with an increase in the content of *O*-acetyl groups in the cell wall, and by *Litwack* [90–92], who reported that resistant cells were white in color and devoid of carotenoids. *Salton* and *Pavlik* [66] established that only walls of *M. lysodeikticus* and *Lactobacillus arabinosus* were more sensitive to lysozyme after removal of *O*-ester groups or teichoic acid. Other explanations of differences in sensitivity to lysozyme include the possibility of different linkages between the amino sugars of the skeleton, differences in the ratios of amino sugars, relatively few disaccharide units, branching points, single amino-acid substituents attached to muramic acid, and a high frequency of cross-linked peptides between muramic acid residues [66].

Finally it is of interest to note that a lysozyme can carry out a transglycosylation reaction: *Salton* [93] observed that on incubation of *Papaya* latex-lysozyme with the disaccharide AG–AMA an appreciable amount of tetrasaccharide is formed.

[88] *W. Brumfitt, A. C. Wardlaw,* and *J. T. Park,* Nature (London) *181,* 1783 (1958).

[89] *W. Brumfitt,* Brit. J. exp. Pathol. *40,* 441 (1959).

[90] *G. Litwack,* Nature (London) *181,* 1348 (1958).

[91] *A. L. N. Prasad* and *G. Litwack,* Biochim. biophysica Acta *46,* 452 (1961).

[92] *G. Litwack* and *A. L. N. Prasad,* Nature (London) *196,* 543 (1962).

[93] *M. R. J. Salton* [8a], Vol. 12, p. 1.

## V. Conclusion

Thanks to their stability, the lysozymes of different origins are excellent for comparative studies of structure, enzymatic action, speed of action, and specificity. These enzymes also helped to increase our knowledge of the structure of the cell walls of Gram-positive and Gram-negative bacteria. The fact that numerous species of both groups contain a lysozyme substrate lends new interest to *Fleming*'s original hypothesis that lysozyme plays a part in the body's fight against infection. Antibiotic action is certainly one of the functions of the enzyme and will find practical applications; hen's egg-white lysozyme is already used together with other antibiotics. However, distinction must be made between enzymatic and non-enzymatic activity of lysozymes [94]: *e.g.* the role of lysozyme in blood coagulation is due to its basicity; however, when added to cow's milk for feeding sucklings, its action seems to be an enzymatic one. *Runti* [95] has recently published a review on the pharmacological applications of lysozyme. Finally, the production of lysozyme-like substances by a broad variety of living systems seems to indicate a fundamental metabolic role for these enzymes.

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[94] *L. Colobert,* Path. Biol. *8,* 1023 (1960).

[95] *C. Runti* [8a], Vol. 1, p. 35.

# Theories of the Glass Electrode

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*A review of the various theories of potential formation on the glass-electrode is followed by a discussion of the deviations from the ideal hydrogen (H) electrode function in the acidic and alkaline ranges from the viewpoint of the phase-boundary-potential theory. The effect of the composition and solubility of the glasses on the electromotive behavior is interpreted as a "medium effect" in the gel layer.*

## I. Introduction

Glass electrodes are used today not only in almost every laboratory and in the most diverse industrial undertakings for measuring and regulating pH [1,2], they are also finding increasing use in the determination of alkali ion content [3]. Although the formation of potentials on glass membranes has been studied for some sixty years, theoretical treatment of the phenomenon is difficult and has only in recent years yielded a certain modicum of clarity. It is thus understandable that numerous attempts have been made at interpretation of the electromotive behavior of glass electrodes, starting from a variety of points of view.

The *adsorption-potential theory* starts from the concept that an adsorbed layer of cations, especially $H^+$-ions, exists at the glass surface in equilibrium with the corresponding ions in solution. A potential drop occurs at the adsorption layer/solution boundary and corresponds to the chemical potential difference between adsorbed and free ions.

[1] *R. G. Bates:* Electrometric pH-Determinations. Wiley, New York 1954.

[2] *K. Schwabe:* Fortschritte der pH-Meßtechnik. Verlag Technik, Berlin 1958.

[3] *H. D. Suschke* and *J. Lüdenbach,* Z. Chem., in the press.

The *membrane-potential theory* considers the glass membrane to be permeable to cations, in particular to $H^+$-ions, and regards the potential drop as a diffusion potential caused by the difference in mobility of the cations and anions in the glass.

The *statistical-mechanical theory* attempts to interpret the behavior of the glass-electrode by considering the bond relations between the cations, especially $Na^+$- and $H^+$-ions, in the glass and in the solution. The passage of the $H^+$- and $Na^+$-ions from one phase into the other is computed statistically. The potential difference arises from the difference in the chemical potentials of the ions, which tend to attain an exchange equilibrium.

The *phase-boundary-potential theory* also traces the cause of the glass-electrode potential to the formation of a thermodynamic equilibrium between the glass phase and the electrolyte solution. Because the ions participating in the establishment of the equilibrium, especially the $H^+$-ions, must be present in both phases (hence also in the glass phase), and furthermore because the establishment of the potential at the glass electrode occurs much faster than would be expected from a true phase equilibrium, it is assumed that only the gel layer of the glass participates directly in the establishment of equilibrium. According to recent measurements [4], it is even certain that only that part of the gel layer which is directly adjacent to the solution is responsible for the establishment of the potential, whereas the deeper regions of the gel layer have essentially no effect upon potential formation. The external part of the gel layer exchanges ions with both the glass phase and the solution and acts as an intermediary in the establishment of equilibrium between the deeper regions of the gel layer and the electrolyte solution.

The preceding classification is actually more or less arbitrary, because the views of the various authors approach and overlap one another in many respects. In the following, a review is presented of the development and status of the theory of the glass electrode.

## I. Adsorption-Potential Theory

During investigations of the electromotive behavior of quartz membranes, *von Lengyel* alone and in collaboration with *Matrai* [5] found that even though the potential of quartz glass electrodes depends on the pH of the solution, it does not obey the Nernst relationship. Since quartz is a nearly ideal dielectric, it prevents establishment of the electrical equilibrium in the solid phase which is necessary for the existence of a quartz-solution phase-boundary potential. Thus the electrical behavior of the quartz membrane is attributed to an adsorption potential, *i.e.* the potential drop is caused by a difference in the concentration of charge carriers in the adsorption layer relative to that in the solution. Although these considerations cannot be applied without reservation to electrode glasses, which have relatively high electrical conductivity and current carrying capacity, *Yevstrop'yev* and *Suikovskaya* [6] also assumed such an adsorption mechanism for glass electrodes. Assuming that the Freundlich adsorption relationship also holds for $H^+$-ions on glass, they found that

$$\frac{\Delta E}{\Delta \ln c_{H^+}} = \left(1 - \frac{1}{n}\right) \frac{RT}{F} \qquad (1)$$

where E = electrode potential; R = gas constant; $c_{H^+}$ = proton concentration in solution; T = absolute temperature; n = constant in the Freundlich equation; F = Faraday constant

A linear dependence of the electrode potential on the hydrogen ion concentration in the electrolyte is thus obtained, although the slope is smaller than that for the hydrogen electrode.

Moreover, the behavior of the glass electrode in acidic and alkaline ranges cannot be interpreted by means of this theory.

## II. Membrane-Potential Theory

### 1. The Glass Foil as a Membrane

*Cremer* [7] and *Michaelis* [8] investigated electrical phenomena at membranes and observed characteristics similar to those shown by the glass electrode, and thus arrived at a basically different concept. They therefore interpreted the electromotive behavior of the glass electrode in terms of the specific permeability characteristics of the glass. *Michaelis* observed that the ratios of anion to cation mobility in various membranes are much lower in the membrane than in the solution. He therefore assumed by analogy that only $H^+$-ions can pass through the glass membrane in the acidic and neutral range.

The glass-electrode potential can then be computed from the Donnan equations for semipermeable membranes or from diffusion potentials, setting the anion mobility at zero. On this assumption, *Cremer* derived a hydrogen-electrode function [$E = f(H^+)$] for the potential at the glass membrane:

$$E = \frac{l_K - l_A}{l_K + l_A} \cdot \frac{RT}{F} \ln \frac{a_{H^+(b)}}{a'_{H^+}} + \frac{l_K - l_A}{l_K + l_A} \cdot \frac{RT}{F} \ln \frac{a'_{H^+}}{a_{H^+(a)}} \qquad (2)$$

where $l_K$ = mobility of the cation; $l_A$ = mobility of the anion; $a'_{H^+}$ = $H^+$-activity in the glass; $a_{H^+}$ (a) and $a_{H^+}$ (b) = $H^+$ activity on sides (a) and (b) of the glass electrode, respectively

[4] *K. Schwabe* and *H. Dahms*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 518 (1961).

[5] *B. v. Lengyel*, Z. physik. Chem., Abt. A *153*, 425 (1931); *159*, 145 (1932); *159*, 393 (1932).

[6] *Yu. Yevstrop'yev* and *Suikovskaya*, cited in *B. P. Nikolskiy*, Zh. Fiz. Khim. *10*, 495 (1937).

[7] *M. Cremer*, Beitr. Physiol. *2*, 229 (1924); in *A. Bethe* and *G. Bergmann:* Handbuch der normalen und pathologischen Physiologie. Springer, Berlin, Vol. 8, p. 999.

[8] *L. Michaelis*, Naturwissenschaften *14*, 33 (1926).

Assuming that the hydrogen-ion activity in the glass $a'_{H^+}$ is constant and setting $l_A = 0$ (*i.e.* the anion makes no contribution to the diffusion potential since it does not cross the phase boundary), Equation (2) becomes:

$$E_H = \frac{RT}{F} \ln \frac{a_{H^+(b)}}{a_{H^+(a)}} \tag{3}$$

This equation is still valid even when the solution contains other ions, provided their mobilities in the glass membrane are negligible compared to that of the $H^+$-ions.

To interpret the deviations of the glass electrode from the function given in (3), *Michaelis* assumed that other ions, especially alkali metal ions, can also diffuse through the glass at higher pH values, but he gave no quantitative relationships.

### 2. Comparison of the Glass-Electrode Potential to a Liquid Potential

A quantitative explanation of the electrode error was first given by *Dole*, who rejected the view of the glass membrane as a semipermeable membrane but retained the concept of the glass-electrode potential as a liquid potential.

a) *Acid Error*

*Dole* [9] regarded the altered activity of the water in the solution under examination as the source of the acid error in the glass electrode. By assuming that $H_2O$ is transferred concurrently with the $H^+$-ion, he determined the acid error quantitatively as

$$\Delta E_{acid} = \frac{RT}{F} \ln a_{H_2O(b)} \tag{4}$$

b) *Alkali Error*

To interpret the alkali error, *Dole* also took the activity of the $Na^+$-ion in the solution and in the glass into account and considered the cell:

$$\begin{array}{c|c|c} \text{Reference Solution (a)} & \text{Glass} & \text{Test Solution (b)} \\ a_{H^+(a)} & a'_{H^+};\ a'_{Na^+} & a_{H^+(b)};\ a_{Na^+(b)} \end{array} \tag{5}$$

which yields an electromotive force

$$E_g = \varepsilon_a + \varepsilon_b = \frac{RT}{F} \ln \frac{l_{H^+}\, a_{H^+(b)} + l_{Na^+}\, a_{Na^+(b)}}{l_{H^+}\, a_{H^+(a)}} \tag{6}$$

$$= \frac{RT}{F} \ln \frac{a_{H^+(b)} + a_{Na^+(b)}\, l_{Na^+}/l_{H^+}}{a_{H^+(a)}}$$

(where $\varepsilon_a$ and $\varepsilon_b$ = phase-boundary potentials)

under conditions at which the Planck-Henderson relationsbip is valid (*i.e.* at constant mobility of the ions in both phases) and hence the mobility of the anions in the glass can be taken as zero.

Since Equation (3) is valid for ideal behavior, the alkali error of the glass electrode becomes

$$\Delta E_{alkali} = E_g - E_H = \frac{RT}{F} \ln \frac{a_{H^+(b)} + a_{Na^+(b)}\, l_{Na^+}/l_{H^+}}{a_{H^+(b)}}$$

$$= \frac{RT}{F} \ln \left[ 1 + \frac{l_{Na^+}}{l_{H^+}} \cdot \frac{a_{Na^+(b)}}{a_{H^+(b)}} \right] \tag{7}$$

This relation predicts an increasing alkali error with decreasing hydrogen-ion activity and with increasing $Na^+$-activity. It shows furthermore that for low $H^+$-activity, as long as $l_{Na^+} \ll l_{H^+}$, the error increases with $\ln a_{Na^+(b)}$ and that thus the glass electrode functions as a sodium electrode.

Because the ratio $l_{Na^+}/l_{H^+}$ is itself found to be dependent on the pH, *Dole* provides the $a_{H^+(b)}$ term with an exponent $n < 1$ to effect agreement with the experimental values:

$$\Delta E_{alkali} = \frac{RT}{F} \ln \left[ 1 + \frac{B}{\left(a_{H^+}\right)^n_{(b)}} \right] \tag{8}$$

$$B = \frac{l_{Na^+}}{l_{H^+}} \cdot a_{Na^+(b)}$$

The constant B must be determined here for every ion which disturbs the H function (hydrogen-electrode function) and for every activity.

According to electrolytic experiments by *Haugaard* [10], the glass electrode cannot be regarded as a selectively permeable ion sieve in the sense of *Michaelis*. *Haugaard* established that only $Na^+$-ions can pass through the glass membrane. However, since his measurements were rendered inaccurate by the release of alkali from the glass and by the small amount of material involved in the reactions, they were repeated by *Schwabe* and *Dahms* [11], who were able to show by using tritium as a tracer that the glass electrode does not act as a membrane providing direct passage of $H^+$-ions.

## III. The Statistical-Mechanical Theory

Equation (7) agrees quantitatively with the experimental results only if it is assumed that the mobility of the $H^+$-ion exceeds that of the $Na^+$-ion by a factor of approximately $10^{11}$. *Dole* [12] was able to explain the value $l_{Na^+}/l_{H^+} = 10^{-11}$ by means of a statistical-mechanical interpretation. Starting from the theory of *Gurney* [13], he assumes that the positive ions assume equilibrium positions and that the distribution of the ions among diffe-

[9] *M. Dole*, J. Amer. chem. Soc. *54*, 2120, 3095 (1932).

[10] *G. Haugaard*, C. R. Trav. Lab. Carlsberg, Sér. chim. *22*, 199 (1938).

[11] *K. Schwabe* and *H. Dahms*, Mber. dtsch. Akad. Wiss. Berlin *1*, 279 [1959].

[12] *M. Dole*, J. chem. Physics *2*, 862 (1934).

[13] *R. W. Gurney*, Proc. Roy. Soc. (London), Ser. A *136*, 378 (1932).

rent energy levels obeys Boltzmann statistics. The H function for the potential of the glass electrode is then attributed to the ability of $H^+$-ions to pass from their equilibrium state close to a water molecule in solution to an equilibrium state at the glass surface.

By computing the number of s- and d-states, *i.e.* the number of ions with sufficient energy to pass from the glass into the solution (s) and from the solution to the glass surface (d), he arrives at the relationship:

$$\Delta E_{alkali} = E_g - E_H \qquad (9)$$

$$= \frac{RT}{F} \ln \left[ 1 + \frac{\beta_{Na^+}}{\beta_{H^+}} \cdot \exp \left( \frac{Q_{Na^+} - Q_{H^+}}{RT} \right) \cdot \frac{a_{Na^+(b)}}{a_{H^+(b)}} \right]$$

where $Q_{Na^+}$ = difference in the bonding energy of the cation $_{Na}{}^+$ in solution and at the glass surface and $\beta$ is the quotient of the probabilities of d and s transitions for any ion.

When the ratio $\beta_{Na^+}/\beta_{H^+}$ is set equal to 1 and $Q_{H^+}$ is larger than $Q_{Na^+}$ by about 15 kcal/mole, one obtains

$$\frac{\beta_{Na^+}}{\beta_{H^+}} \exp \left( \frac{Q_{Na^+} - Q_{H^+}}{RT} \right) = 10^{-11}.$$

## IV. Phase-Boundary-Potential Theory

### 1. Development of the Phase-Boundary-Potential Theory

*Nernst* [14] already predicted the existence of potential differences at solid electrolyte/liquid electrolyte phase boundaries when both phases contain the same ions. Even though it would then be expected that soda glass would show sodium-dependent behavior, *Cremer* [15] established that the potential at the glass/electrolyte phase boundary depends on the acidity of the solution. However, previous work by *Schott* [16] and *Förster* [17] had shown that the glass surface is able to take up water. *Haber* and *Klemensiewicz* [18] considered this hydrated glass as an "electrolytically conductive water phase", in which both the $H^+$ and $OH^-$ activities are constant. They subjected the system

| $H_2O$ | $H_2O$ | $H_2O$ | (10) |
|---|---|---|---|
| I(a) | II | I(b) | |
| $a_{H^+} \cdot a_{OH^-} = \text{const.}$ | $a_{H^+} = \text{const.}$ $a_{OH^-} = \text{const.}$ | $a_{H^+} \cdot a_{OH^-} = \text{const.}$ | |

in which the "solid" water phase II is surrounded on both sides by an aqueous phase I, to a thorough thermodynamic analysis, and obtained for the electromotive force

$$E = \frac{RT}{F} \ln \frac{a_{H^+(b)}}{a_{H^+(a)}} \qquad (11)$$

This relation is used to compute the unknown $H^+$-activity $a_{H^+(b)}$ in practical pH measurements when $a_{H^+(a)}$ is known and kept constant.

However, according to *von Lengyel* and *Blum* [19], this relation is only valid in the pH range from 2 to 9, when a MacInnes glass (72 % $SiO_2$, 22 % $Na_2O$, 6 % CaO) is used. The limited validity of Equation (11) must have remained unknown to *Haber* and *Klemensiewicz*, since they used the glass electrode only for potentiometric titrations. Thus, they neglected to apply their equation to the computation of pH values in the strongly alkaline or strongly acidic regions.

The "solid" water phase with constant $H^+$-activity assumed by *Haber* and *Klemensiewicz* was interpreted by *Watson* [20] in terms of a buffer action exerted on silicic acid by the sodium and calcium silicates present in the glass. With this concept, *Hughes* [21] was able to interpret qualitatively the disturbance of the hydrogen electrode function of the glass electrode in the alkaline region. In the pH region from 2 to 9, the buffer action prevents the ion exchange at the glass/electrolyte boundary – which determines the phase-boundary potential – from altering the $H^+$-activity in the glass phase. However, at pH > 9, the buffer action of sodium silicate is no longer sufficient to stop the decrease of the $H^+$-activity in the glass phase resulting from an exchange with alkali metal ions.

*Hughes* professed to see a confirmation of his theory in the facts that the deviations from the hydrogen-electrode function start at an $H^+$-activity in the solution of $10^{-9}$ and that the first dissociation constant of silicic acid is approximately $10^{-9}$.

However, it is known from studies by *Gardiner* and *Sanders* [22] and by *Powney* and *Jordan* [23] that the higher the $Na^+$-ion concentration in the solution, the higher is the $H^+$-activity at which the glass electrode begins to deviate from the hydrogen-electrode function. This phenomenon and its dependence on the nature of the cation could not be explained by *Hughes*' theory.

*Gross* and *Halpern* [24] interpreted that the deviations in the behavior of the glass electrode at extreme pH values result from the appearance of mixed potentials but were also unable to provide quantitative relationships. They considered not only the solubility of water in the glass phase but also that of the glass in water. An electrolyte $M^+A^-$ dissolved in the aqueous phase should also tend towards an equilibrium distribution between both phases. This assumption leads to a phase-boundary potential:

$$\varepsilon = \frac{RT}{F} \ln \frac{a'_{M^+}}{a_{M^+}} \qquad (12)$$

where $a'_{M^+}$ = the activity of the metal ion in the solid phase
$a_{M^+}$ = the activity of the metalion in the solution


[14] *W. Nernst*, J. physic. Chem. *9*, 137 (1892).
[15] *M. Cremer*, Z. Biol. *47*, 562 (1906).
[16] *O. Schott*, Z. Instrumentenkunde *9*, 86 (1889).
[17] *F. Förster*, Ber. dtsch. chem. Ges. *25*, 2494 (1892); *26*, 2915 (1893).
[18] *F. Haber* and *Z. Klemensiewicz*, Z. physik. Chem. *67*, 385 (1909).
[19] *B. v. Lengyel* and *E. Blum*, Trans. Faraday Soc. *30*, 461 (1934).
[20] *F. J. Watson*, Chem. Engng. Mining Rev. *20*, 59 (1927).
[21] *W. S. Hughes*, J. chem. Soc. (London) *1928*, 491.
[22] *W. C. Gardiner* and *H. L. Sanders*, Ind. Engng. Chem., analyt. Edit. *9*, 274 (1937).
[23] *J. Powney* and *D. O. Jordan*, J. Soc. chem. Ind., Chem. and Ind. *56*, 133 (1937).
[24] *P. Gross* and *O. Halpern*, Z. physik. Chem. *115*, 54 (1925).

The dissociation constants of $M^+ A^-$ in both phases and the distribution coefficient are all involved in this relationship.

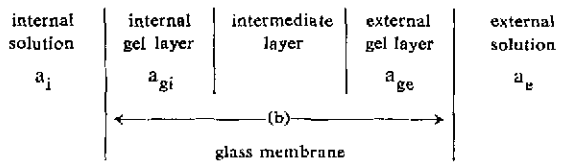
If it is assumed that the activity of $M^+$ in the solid phase is negligible in comparison with the $H^+$-activity $a'_{H^+}$ and that (except for the solid electrolyte anion) only $H^+$- or $OH^-$-ions occur in the solid phase, then the ratio $a'_{M^+}/a_{M^+}$ becomes proportional to the $H^+$-activity of the solution.

On the other hand, when there are practically no $H^+$- or $OH^-$-ions present in the glass, and the ionic content of the solid phase is thus determined solely by the ions of the glass itself, then the potential becomes a function of the activity of the $M^+$-ion in the solution. Such an electrode then behaves like a metal electrode and its potential varies according to the Nernst equation.

However, because of numerous simplifying assumptions, some of which appear to be poorly founded, this theory does not lead to quantitative predictions.

## 2. Status of the Phase-Boundary-Potential Theory

The fact that a new glass electrode gives up $Na^+$-ions to the solution and takes up $H^+$-ions in return with formation of a hydrated silica-gel layer led *Haugaard* [25] to the concept of a three-layer membrane in which an intermediate conductor consisting of unaltered glass is covered on both sides with a layer which strongly protects the glass from further attack (Scheme 1).




Scheme 1. Glass-electrode layers according to the phase-boundary-potential theory

This view led to the assumption that a thermodynamic equilibrium is established only between gel layer and solution without direct participation of the intermediate conductor.

*Schwabe* and *Glöckner* [26] thus subjected the transport of electrical charges by $H^+$-ions across the a/b and b/c phase boundaries to thermodynamic analysis. The change in chemical potential on passage of one mole of $H^+$-ions from the internal solution into the internal gel layer is

$$\Delta\mu_{(b)/(a)} = \mu_{gi} - \mu_i \qquad (13)$$
$$= \left(\mu^\circ_{gi} - \mu^\circ_i\right) + RT \ln \frac{a_{gi}}{a_i} = + F \cdot \varepsilon_{(a)/(b)}$$

Similarly, for the passage of $H^+$-ions from the external solution into the external gel layer:

$$\Delta\mu_{(b)/(c)} = \left(\mu^\circ_{ge} - \mu^\circ_e\right) + RT \ln \frac{a_{ge}}{a_e} = + F \cdot \varepsilon_{(c)/(b)} \qquad (14)$$

If the same reference state is always choosen for the chemical potential of the $H^+$-ions in the gel layer, then $\mu^\circ_{ge} - \mu^\circ_{gi}$. Since $\mu^\circ_e$ also equals $\mu^\circ_i$, the potential difference between the internal and external solutions is:

$$E_{(a(/(c)} = \varepsilon_{(a)/(b)} + \varepsilon_{(b)/(c)} = \frac{RT}{F} \ln \frac{a_e}{a_i} + \frac{RT}{F} \ln \frac{a_{gi}}{a_{ge}} \qquad (15)$$

When the $H^+$-activity is the same in both gel layers, the electromotive force of the glass cell becomes

$$E = \frac{RT}{F} \ln \frac{a_e}{a_i} . \qquad (16)$$

The deviation from ideal behavior is then given by

$$\Delta E = \frac{RT}{F} \ln \frac{a_{gi}}{a_{ge}} . \qquad (17)$$

Consequently, the phase-boundary-potential theory is able to explain both the acid and alkali errors by changes in the $H^+$-activity in the gel layer. However, supplementary assumptions are necessary to account for the mechanism of this activity change.

### a) *Interpretation of the Acid Error*

Some time ago, *MacInnes* and *Belcher* [27] discovered that the glass electrode shows deviations from the H function in the strongly acidic range. They attributed these poorly reproducible potential shifts to the effect of anions in the solution. *Dole* [9] did not accept this view, since he was unable to observe any effect of the anion species in solution in the neutral range even at high electrolyte concentrations; this was confirmed by *Schwabe* [28] in a series of careful measurements. *Dole* saw the cause of the acid error in the altered activity of the water in the test solution and determined the acid error from Equation (4). However, *Hubbard*, *Hamilton*, and *Finn* [29] discovered that the behavior of the electrode glass differed in strong HCl and in $H_2SO_4$. The acid error of a MacInnes-glass electrode in 5 N HCl observed by *Sinclair* and *Martell* [30] exceeded the error computed by *Dole*, whereas measurements in 5 N and 10 N $H_2SO_4$, even on prolonged exposure, yielded smaller errors than would be expected from *Dole*'s relationship. On the other hand, *Ismailov* and *Aleksandrova* [31] were able to demonstrate a pure anion function with certain electrode glasses in strongly acidic solutions. *Ismailov* and *Vassil'yev* [32] sought the cause

[25] *G. Haugaard*, Nature (London) *140*, 66 (1937); J. physic. Chem. *45*, 148 (1941).

[26] *K. Schwabe* and *G. Glöckner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 504 (1955).

[27] *MacInnes* and *D. Belcher*, J. Amer. chem. Soc. *53*, 3315 (1931).

[28] *K. Schwabe*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *42*, 874 (1937).

[29] *D. Hubbard*, *E. H. Hamilton*, and *A. N. Finn*, J. Res. nat. Bur. Standards *22*, 339 (1939).

[30] *E. Sinclair* and *A. E. Martell*, J. chem. Physics *18*, 992 (1950).

[31] *N. A. Izmailov* and *A. M. Aleksandrova*, Doklady Akad. Nauk SSSR *71*, 311 (1950).

[32] *N. A. Izmailov* and *A. G. Vassil'yev*, Doklady Akad. Nauk SSSR *95*, 579 (1954).

of this phenomenon in the replacement of the hydroxyl group in the Si–OH of the gel layer by an anion from the acid. Finally, *Beck* and *Wynne-Jones* [33] ascribe the deviation of the glass electrode in the acid range solely to a change of the asymmetry potential.

*Schwabe* and *Glöckner* [26] also investigated the behavior of the glass electrode in HCl, $H_2SO_4$, and $H_3PO_4$. For the acid-error range, they assumed a rise in $H^+$-activity in the external gel layer, leading to a negative value of $\Delta E$ [see Equation (17)] in agreement with experiment. Furthermore, since the electroneutrality of the gel layer must be preserved, the following processes are conceivable:

α) The transfer of $H^+$-ions from the solution to the gel layer is associated with a simultaneous transfer of anions.

β) In accordance with the ion-exchange equilibrium

$$Na^+_{glass} + H^+_{soln} \rightleftharpoons Na^+_{soln} + H^+_{glass}$$

a $Na^+$-ion is given up to the solution for each $H^+$-ion penetrating into the gel layer.

γ) Although their volumetric concentration remains constant, the activity of the $H^+$-ions can be increased by dehydration of the gel layer.

The change in the acid error of a MacInnes-glass electrode with time can be described by the relation

$$-\Delta E_{acid} = A + B \log (C + t) \qquad (18)$$

Since at time $t = 0$, the acid error is zero, one obtains

$$q = 10^{-\Delta E_{acid}/B} = \frac{C + t}{C} \qquad (19)$$

A similar relationship is obtained when $a_{gi}$ in Equation (17) is made equal to C and the increment of the $H^+$-activity in the outer gel layer caused by the acid is denoted by x

$$-\Delta E_{acid} = \frac{RT}{F} \ln \frac{C + x}{C} \qquad (20)$$

$$q = 10^{-\Delta E_{acid} \cdot F/2.303 \cdot RT} = \frac{C + x}{C}$$

The increment x of the $H^+$-activity in the external gel layer can thus be deduced from the variation of q with time.

When $\frac{dq}{dt} = \frac{t}{C}\left(\frac{dx}{dt}\right)$ is constant – as is the case with HCl – then the acid uptake is uniform. Case α) can then be assumed to apply, for the rate of penetration of the acid will be proportional to its concentration, which is not appreciably decreased.

On the other hand, the reverse reaction will set in to a noticeable extent in cases β) and γ), after a unidirectional process has gone on for a time. Thus, a constant value for dq/dt cannot be expected. This is in fact observed with $H_2SO_4$ and $H_3PO_4$.

These results were checked and confirmed by *Schwabe*, *Dahms*, *Nguyen*, and *Hoffmann* [34] by means of radioactive tracer experiments. It turned out that the uptake of acid by the gel layer, u, was about an order of magnitude higher in 4 N HCl than in equal concentrations of HBr or HI, the immersion times being equal in all cases. Since the acid error q exhibits the same behavior and the ratio u/q for these acids has practically the same value for any given time, the acid error can be unequivocally attributed in these cases to the uptake of acid by the gel layer.

The variation with time of the acid error $dq/dt = \dot{q}$ varies with the acid concentration and also assumes consistently much higher values for HCl than for HBr or HI.

If it is assumed that only ion pairs penetrate into the gel layer, it would be expected that the acid error would increase with activity, *i.e.* with the vapor pressure of the acid over the solution. However, at equal acid concentrations, the vapor pressures of hydrogen halides decrease rapidly in the sequence $HCl \gg HBr \gg HI$; it is thus understandable that the acid error also decreases in the same order.

However, $\dot{q}$ will also increase with the vapor pressure of the acid. *Boksay*, *Csákvári*, and *von Lengyel* [35] had already found that for HCl, the variation of the acid error with time can be expressed by the relationship

$$\log \dot{q} = K_1 \log p_{HCl} + K_2 \qquad (21)$$

The fact that the quotients

$$\frac{\log \dot{q}_{HCl}/\dot{q}_{HBr}}{\log p_{HCl}/p_{HBr}}, \quad \frac{\log \dot{q}_{HCl}/\dot{q}_{HI}}{\log p_{HCl}/p_{HI}} \quad \text{and} \quad \frac{\log \dot{q}_{HBr}/\dot{q}_{HI}}{\log p_{HBr}/p_{HI}}$$

yield similar values confirms the hypothesis that the abilities of the halogen acids to penetrate into the glass depends significantly on their fugacities.

In contrast there was no observable uptake of sulfate or phosphate ions by the gel layer. The acid error can be ascribed here to the reduced activity of the water in these acids. The acid error calculated from Equation (4) is in satisfactory agreement with the values obtained experimentally for $H_2SO_4$ and $H_3PO_4$.

While the acid error can thus be explained successfully by assuming that the acid molecules migrate into the gel layer (case α) or that the activity of water in the gel layer is altered (case γ), the alkali error can be derived quantitatively by assumption of ion exchange at the glass surface (case β).

### b) *Interpretation of the Alkali Error*

In his treatment of the alkali error of the glass electrode, *Nikolskiy* [36,37] considered the ion exchange that occurs at the glass surface and linked it with certain ideas of *Horovitz* [38], who had previously assumed that

[33] *W. H. Beck* and *W. F. K. Wynne-Jones*, J. Chim. physique *49*, 97 (1953).

[34] *K. Schwabe*, *H. Dahms*, *O. Nguyen*, and *G. Hoffmann*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 304 (1962).

[35] *Z. Boksay*, *B. Csákvári*, and *B. v. Lengyel*, Z. physik. Chem. *207*, 223 (1957).

[36] *B. P. Nikolskiy*, Zh. Fiz. Khim. SSSR *10*, 495 (1937).

[37] *B. P. Nikolskiy* and *T. A. Tolmatsheva*, Zh. Fiz. Khim. SSSR *10*, 513 (1937).

[38] *K. Horovitz*, Z. Physik *15*, 369 (1923).

cations in the glass can be replaced by cations from the solution via an "exchange" adsorption (he later corrected this to "ion exchange" [39]). According to his view, in acid solutions, $H^+$-ions are taken up and impart a $H^+$-solution pressure to the glass electrode. According to this concept, the glass electrode can take up other positive ions in neutral and alkaline solution in lieu of $H^+$ and can then act as an Na, K, or Li electrode, depending on the cation in the solution.

According to this picture, $Na^+$- and $H^+$-ions are exchanged between the glass and the solution until an equilibrium is established between the nascent gel layer Q and the solution:

$$H^+_{soln} + Na^+_Q \rightleftharpoons H^+_Q + Na^+_{soln} \qquad (22)$$

The position of this equilibrium depends on the activity of the ions in the solution and on their bonding strength in the gel layer and in the solution.

Using the equilibrium constant for this ion exchange

$$K = \frac{a_{H^+} \cdot N_{Na^+} \cdot f'_{Na^+}}{a_{Na^+} \cdot N_{H^+} \cdot f'_{H^+}}, \qquad (23)$$

where $f'_{Na^+}$ and $f'_{H^+}$ = the activity coefficients in the gel layer, and $N_{Na^+}$ and $N_{H^+}$ = the mole fractions of the ions in the gel layer,

and from thermodynamic considerations, *Nikolskiy* arrived at the relationship

$$E_G = E^\circ + \frac{RT}{F} \ln \frac{a_{H^+} \cdot (f'_{Na^+}/f'_{H^+}) + K \cdot a_{Na^+}}{f'_{Na^+}}, \qquad (24)$$

where $N_{Na^+} + N_{H^+} = N_0$ is assumed to be constant.

*Nikolskiy* first assumed that the interaction of the $H^+$- and $Na^+$-ions with the neighboring positive and negative ions is constant for a given glass and is independent of the degree to which the $Na^+$-ions have been replaced by $H^+$-ions. He considered these interactions to be weak because of the relatively large distances between the ions and because the intervening medium (silicic acid) has a relatively high dielectric constant (5–7). He therefore assumed $f'_{Na^+} = f'_{H^+} = 1$ and obtained from (24):

$$E_G = E^\circ + \frac{RT}{F} \ln (a_{H^+} + K \cdot a_{Na^+}). \qquad (25)$$

The alkali error $\Delta E_{alkali}$ then becomes

$$\Delta E_{alkali} = E_G - E_H = -\frac{RT}{F} \ln \left(1 + K \frac{a_{Na^+}}{a_{H^+}}\right) \qquad (26)$$

which is identical with the relationship derived by *Dole* by statistical analysis.

The exchange constant K can be determined by measurement of the electromotive force of the glass cell at varying $Na^+$-activities and constant pH values [39]. Thus, at 20 °C one obtains from Equation (25)

$$\left(\frac{\partial E}{\partial \log a_{Na^+}}\right)_{pH} = \alpha = 58 \frac{K \cdot a_{Na^+}}{a_{H^+} + K \cdot a_{Na^+}} \qquad (27)$$

or

$$K = \frac{\alpha \cdot a_{H^+}}{(58 - \alpha) \cdot a_{Na^+}}. \qquad (28)$$

[39] *K. Horovitz*, Z. physik. Chem. *115*, 424 (1925).

However, the value of K can also be computed from measurements of the EMF of the glass cell at constant $Na^+$-activity and variable pH when $E^\circ$ is known from measurements within the range of applicability of the hydrogen-electrode function. In the high pH range, where the glass electrode behaves like a sodium electrode, one obtains:

$$E_{Na} = E^\circ + \frac{RT}{F} \ln K + \frac{RT}{F} \ln a_{Na^+} \qquad (29)$$

$$\text{or} \quad -\log K = \frac{E^\circ - E_{Na}}{58} + \log a_{Na^+}. \qquad (30)$$

However, later investigations showed that even though Equation (25) holds well in the region of applicability of the pure hydrogen-electrode function ($a_{H^+} \gg K a_{Na^+}$) and of the pure sodium-electrode function ($a_{H^+} \ll K a_{Na^+}$), it shows large deviations (up to 20 mv) from data obtained experimentally in the transition region.

In a generalized theory, *Nikolskiy* [40] accounts for this phenomenon by assuming that because of the differences in composition, structure, and relative arrangement of the anions, the $H^+$-ions may form z species of bonds with the anions in the gel layer. Thus the activity coefficients of the $H^+$-ions remain constant, independent of their concentration in the gel layer, but vary for the various anion species. Furthermore, the $Na^+$-activity in the gel layer is assumed to be equal to the $Na^+$-concentration regardless of which sites the $Na^+$-ions occupy. *Nikolskiy* thus arrived at the relationship.

$$E = E^\circ - \frac{RT}{F} \ln \sum_{i=1}^{z} \frac{\alpha_i \cdot \beta_i}{a_{H^+} + \alpha_i \cdot K \cdot a_{Na^+}}. \qquad (31)$$

It is assumed that the stability of a bond between an $H^+$-ion and an anion species $A_1^-$, $A_2^-$, ····· $A_z^-$ in the glass phase increases from 1 to z. Furthermore, an equilibrium is assumed to be set up in the gel layer between free $H^+$- and $Na^+$-ions and the $H^+$- and $Na^+$-ions bound to anions of species i ($A_i^-$)

$$H^+A_i^- + Na^+_{free} \rightleftharpoons Na^+A_i^- + H^+_{free} \qquad (32)$$

The equilibrium constant for this reaction is $\alpha_i$. Its value decreases as the strength of the bonds between the $H^+$-ions and the $A_i^-$-anions increases.

Let us denote the number of anion sites per unit volume of the glass at which $H^+$-ions can form the bond i by $N_i^\circ$; $N_i^\circ$ then consists of sites occupied by $H^+$-ions ($N_i$) and sites occupied by $Na^+$-ions ($N_i^\circ - N_i$). We thus obtain

$$\alpha_i = \frac{N_i^\circ - N_i}{N_i} \cdot \frac{a''_{H^+}}{a''_{Na^+}}. \qquad (33)$$

where a'' = the activity of the "free" ions in the glass phase.

Assuming the activity coefficient of the $Na^+$-ions to be constant ($f_{Na^+} = 1$) and considering all the bonds of the $H^+$-ions from 1 to z, it follows that

$$a''_{H^+} = \sum_{i=1}^{z} \alpha_i \cdot N_i. \qquad (34)$$

[40] *B. P. Nikolskiy*, Zh. Fiz. Khim. *27*, 724 (1953).

Hence, the $H^+$-activity in the glass phase is seen to be the sum of partial activities, each representing the product of the individual equilibrium constant $\alpha_i$ and the concentration of the $HA_i$ molecules. Thus, $\alpha_i$ can be regarded formally as the activity coefficient of the $H^+$-ions that enter into bonds of type i. The state of the $H^+$-ions that form the weakest type of bond, *i.e.* bonds of type 1 representing the state of the $H^+$-ions in $HA_1$ molecules, is taken as the standard state with $\alpha_1 = 1$. We can then designate $\beta_i = N_i^0/N_1^0$ as the ratio of sites with bonds of type i to those with bonds of the weakest type 1 ($\beta_1 = 1$).

1. In the case of the same kind of bonding of all the $H^+$-ions in the gel layer ($\beta_2 = \beta_3 = 0; \alpha_1 = 1$), Equation (31) reverts to the relationship obtained from the simple ion-exchange theory

$$E = E^0 + \frac{RT}{F} \ln \left(a_{H^+} + K \cdot a_{Na^+}\right). \tag{35}$$

2. Limiting Cases

*a)* $a_{H^+} \gg K \cdot a_{Na^+}$

$$E = E^0 - \frac{RT}{F} \ln \sum_{i=1}^{z} \frac{\alpha_i \beta_i}{a_{H^+}} \tag{36}$$

$$= E^0 - \frac{RT}{F} \ln \sum_{i=1}^{z} \alpha_i \beta_i + \frac{RT}{F} \ln a_{H^+},$$

$$= E^{0'} + \frac{RT}{F} \ln a_{H^+}.$$

The glass electrode behaves like a hydrogen electrode.

*b)* $a_{H^+} \ll K \cdot a_{Na^+}$

$$E = E^0 - \frac{RT}{F} \ln \sum_{i=1}^{z} \frac{\beta_i}{K \cdot a_{Na^+}} \tag{37}$$

$$= E^0 + \frac{RT}{F} \ln K - \frac{RT}{F} \ln \sum_{i=1}^{z} \beta_i + \frac{RT}{F} \ln a_{Na^+},$$

$$= E^{0''} + \frac{RT}{F} \ln a_{Na^+}.$$

The glass electrode behaves like a sodium electrode.

By assuming three types of bonds (z = 3), it is generally possible to choose such values of the constants $\alpha_i$ and $\beta_i$ that their substitution in Equation (31) will give good agreement with experiments.

Whereas Equation (31) is based on the assumption that the activity coefficient of the $Na^+$-ions in the gel layer is constant and that only $f'_{H^+}$ can assume a range of values, exactly the opposite conclusion was reached by *von Lengyel, Czákvári,* and *Boksay* [41]. They assumed that the $H^+$-ions in the gel layer are predominantly bound to $H_2O$ molecules, so that deep penetration of the protons into the electron cloud of the oxygens in the silicate framework can hardly be expected; however, their polarizing action via hydrogen bridges remains more strongly marked than that of the metal cations.

[41] *B. v. Lengyel, B. Csákvári,* and *Z. Boksay,* Acta chim. Acad. Sci. hung. *25*, 225 (1960).

Incorporation of an $H^+$-ion in the gel layer shifts the distribution of the electrons surrounding the oxygen atom in such a way that the bonding between the oxygen and the more distant ions is weakened. Thus, the activity coefficient of the $H^+$-ions should be regarded as constant, while $f'_{Na^+}$ should vary with the composition of the gel layer. On the basis of this picture, an equation describing the alkali error is developed which contains three empirical constants.

These assumptions of *Nikolskiy* and *von Lengyel* serve only to simplify the process of the computation. However, radioactive tracer measurements of the concentration of ions in the gel layer, combined with simultaneous observation of the electromotive forces [4], gave some information concerning the variation of the activity of $H^+$- and $Na^+$-ions with their concentration in the gel layer. Since the activity $a'_{H^+}$ of the $H^+$-ions in the gel layer may be considered constant in the range of the H function of the glass electrode, and the same is true for $a'_{Na^+}$ in the range of pure Na function, it is advantageous to define these activities as reference states with $a'_{H^+} = 1$ for the H function and $a'_{Na^+} = 1$ for the Na function, respectively.

With this assumption it is easy to determine the activity of the $H^+$-ions in the gel layer in the range of the alkali error of the glass electrode by means of the cell

$$(Pt)H_2/a_{H^+(b)}, a_{Na^+}/glass/a_{H^+(a)}, KCl, Hg_2Cl_2/Hg \tag{38}$$

In the range of pure H function of the glass electrode and with a constant internal content, this cell has a constant EMF at varying $a_{H^+(b)}$. The deviations $\Delta E$ in the alkali-error range can then be attributed solely to a change in the $H^+$-activity in the gel layer:

$$\Delta E_{alkali} = -\frac{RT}{F} \ln a'_{H^+} \tag{39}$$

or, when the EMF is expressed in pH units:

$$\Delta pH = -\log a'_{H^+} \tag{40}$$

The concentration of $H^+$ in the gel layer, corresponding to the activity $a'_{H^+}$ computed from Equation (40), is obtained from measurements of the uptake of $Na^+$ by the gel layer.

If the total number $N_0$ of exchangeable sites per unit area of the gel layer is divided among the $H^+$- and $Na^+$-ions, then the share x falling to each of these ions is

$$x_{Na^+} = \frac{N_{Na^+}}{N_0} \quad \text{and} \quad x_{H^+} = 1 - x_{Na^+}. \tag{41}$$

$N_0$ can be determined radiochemically with $^{24}Na$, from the saturation value for uptake of $Na^+$ by the gel layer from a solution of low $H^+$- and high $Na^+$-activity. The number $N_{Na^+}$ of $Na^+$-ions exchanged per $cm^2$ may also be obtained from radiochemical measurements.

Employing the equilibrium constant for the ion exchange, which can be obtained from a single EMF measurement in the range of the Na function of the glass electrode,

$$K = \frac{10^{-pH}}{10^{-\Delta pH} \cdot a_{Na^+}} = \frac{a_{H^+} \cdot a'_{Na^+}}{a'_{H^+} \cdot a_{Na^+}} \quad (42)$$

$a'_{Na^+}$, the activity of the $Na^+$ in the gel layer can then be calculated. This value corresponds to that of $a'_{H^+}$ in Equation (40).

Figure 1 shows a plot of the $H^+$-activity obtained from Equation (40) *vs.* the mole fraction $x_{H^+}$ derived from (41), and of $a'_{Na^+}$ computed from (40) and (42) *vs.* $x_{Na^+}$. It is seen that both $f'_{Na^+}$ and $f'_{H^+}$ vary with the composition of the gel layer.

A simple relationship exists between the activities of the $H^+$- and $Na^+$-ions in the gel layer:

$$a'_{Na^+} = \left(1 - a'_{H^+}\right)^n \quad (43)$$

With the aid of Equations (40), (42), and (43), it is possible to set up a simple function describing the dependence of the alkali error of the glass electrode on the activities of the $H^+$- and $Na^+$-ions in the solution.

$$\Delta pH + n \log \left(1 - 10^{-\Delta pH}\right) = pH + \log a_{Na^+} + \log K . \quad (44)$$

The factor n can be found from a single EMF measurement in the region of transition from the H to the Na function.

*Nikolskiy* tested his theory primarily on glasses containing $Al_2O_3$ and $B_2O_3$, which were already known from *Hughes*' experiments to show deviations from hydrogen-electrode function even in the neutral range.

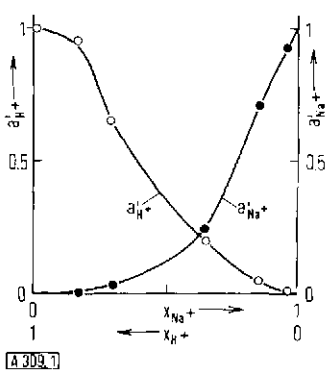



Fig. 1. Relationship between the activity (a') and the mole fraction (x) of the $H^+$- and $Na^+$-ions in the gel layer of a titanium glass.

The replacement of $H^+$ in the gel layer by $Na^+$ from the solution occurs readily in these glasses because borates and aluminosilicates bind $Na^+$-ions more firmly than silicates. It can also be assumed that the gel layer contains complex silicic acids, in which the proton bond to the anion is weakened.

The stronger the bonding of the alkali metal ions to the glass and the weaker the corresponding $H^+$-ion bonding, the more readily the electrode function changes. While MacInnes glass (exchange constant $K = 2 \times 10^{-12}$) shows pure hydrogen-electrode function up to pH 11 in solutions of low $Na^+$ content, marked deviations from ideal behavior can be observed in sodium glass containing approximately 9 % $B_2O_3$ even at pH 7 ($K = 6 \times 10^{-9}$). In sodium glasses containing approximately 7 % $Al_2O_3$ ($K = 2 \times 10^{-6}$), these disturbances of the H function start already in the strongly acid region [36, 37]. Furthermore, the pH values at which the deviations of the glass electrode from the H function start decrease with increasing $Na^+$ concentration in the solution.

However, it is not only transitions from H to Na function that are obtained with glass electrodes, transitions from one metal-electrode function to another are also observed. *Nikolskiy* et al. [42] made a quantitative study of the effect of various ions on the Na function of a sodium glass by comparing the cell without transport

$$Ag/AgCl,NaCl(a)/glass/NaCl(a'),AgCl/Ag \quad (45)$$

which has the equilibrium EMF

$$E_{eq} = \frac{RT}{F} \ln \frac{a_{NaCl}}{a'_{NaCl}} + \varepsilon_{As} \quad (46)$$

where $\varepsilon_{As}$ is the asymmetry potential, with the hypothetical Helmholtz double cell

$$Ag/AgCl,NaCl(a')/Na/NaCl(a''),AgCl/Ag , \quad (47)$$

which has a theoretical EMF

$$E = \frac{2\,RT}{F} \ln \frac{m'_{NaCl} \cdot f'_{\pm NaCl}}{m''_{NaCl} \cdot f''_{\pm NaCl}} \quad (48)$$

When the glass electrode in cell (45) behaves like an ideal Na electrode and the EMF of this cell is measured with a constant internal content using both an NaCl solution of activity $a'_{NaCl}$ ($E'_{eq}$) and an NaCl solution of activity $a''_{NaCl}$ ($E''_{eq}$), then the EMF must be:

$$\Delta E_{eq} = E'_{eq} - E''_{eq} = E$$

If another chloride (MCl), whose concentration is kept constant during a test series, is then added to the NaCl solution then the EMF of cell (47) will be

$$E = \frac{RT}{F} \ln \frac{m'_{NaCl}\,(m'_{NaCl} + m_{MCl})}{m''_{NaCl}\,(m''_{NaCl} + m_{MCl})} + 2\frac{RT}{F} \ln \frac{f'_{\pm NaCl(MCl)}}{f''_{\pm NaCl(MCl)}} \quad (49)$$

where m = concentration in moles/kg of solvent.

As long as the $M^+$-ion added does not affect the Na function of the glass electrode, the relationship $\Delta E_{eq} = E$ still holds.

Mixtures of NaCl with HCl, LiCl, KCl, RbCl, $NH_4Cl$, $MgCl_2$, and $CaCl_2$ were studied in this way at 20, 35, 60, and 65 °C. The MCl concentration was constant and the NaCl concentration ranged from $10^{-3}$ to 2 M.

The effect of cations on the Na function of a soda-glass (71 % $SiO_2$, 3 % $Al_2O_3$, 11 % $B_2O_3$, 15 % $Na_2O$) electrode decreases in the order $H^+ > K^+ > Li^+ > Rb^+ > NH_4^+ > Mg^{++} > Ca^{++}$.

The effect of these cations on the K function of an electrode of potassium glass (71 % $SiO_2$, 3 % $Al_2O_3$, 11 % $B_2O_3$, 15 % $K_2O$) decreases in the order $H^+ > Na^+ > Li^+ > Ba^{++} > Mg^{++} > Ca^{++}$.

[42] *B. P. Nikolskiy, M. M. Schulz,* and *N. V. Peschechonova*, Zh. Fiz. Khim. SSSR *32*, 19 (1958).

The $Li^+$-ion has a relatively small effect on the Na or K function of a glass electrode.

Potassium glasses do not appear suitable for practical application, since they have high melting points and narrow transformation ranges [*] – serious disadvantages in the preparation of glass electrodes. Furthermore, potassium-glass electrodes have very high resistance and display high and variable asymmetry potentials.

However, a K function can be induced to a marked extent in Na glass electrodes by subjecting the latter to prolonged electrolysis in a solution of a potassium salt [43].

In order to test whether the simple ion-exchange theory can give a quantitative explanation of the transition of boron aluminosilicate glasses from the Na function to H, K, and Li functions, *Nikolskiy* et al. [44] considered the cell

$$Ag/AgCl,NaCl(a)/glass/NaCl(a') + MCl,AgCl/Ag \qquad (50)$$

Using a soda glass and applying the ion-exchange theory, they calculated the equilibrium EMF of the cell to be

$$E_{eq} = \frac{RT}{F} \ln \frac{K \cdot a_{NaCl}}{a'_{MCl} + K\, a'_{NaCl}} - + \varepsilon_{As} . \qquad (51)$$

The difference in EMF of two mixed solutions with MCl and NaCl activities a′ and a″, respectively, is:

$$\Delta E_{eq} = \frac{RT}{F} \ln \frac{a'_{MCl} + K\, a'_{NaCl}}{a''_{MCl} + K\, a''_{NaCl}} . \qquad (52)$$

From this, the change in EMF to be expected theoretically can be computed if the exchange constant and the average activity coefficients of MCl in the presence of NaCl ($f_{\pm\,MCl(NaCl)}$) and of NaCl in the presence of MCl ($f_{\pm\,NaCl(MCl)}$) are known for the given case. A comparison can then be made with the experimental values determined with cell (50). Every deviation from the simple ion-exchange theory must then show up as a difference between the calculated and observed values. It was thus established at room temperature that there are deviations in the region of transition from the Na- to the H-electrode function which can only be explained with the aid of the generalized theory. Since these deviations do not occur at higher temperature (65 °C), it can be assumed that the exchange constants of the variously bonded $H^+$-ions become identical at higher temperatures. On the other hand, since the transition of the glass electrode from the Na function to the K or Li function also follows the "simple" ion-exchange theory in the transition region, all the bonds of the $Na^+$-, $K^+$-, or $Li^+$-ions to the silicate anion in the gel layer can be regarded as being energetically equivalent.

When small amounts of $Al_2O_3$ and $B_2O_3$ are added to the glass, the behavior of the glass electrode can be described by Curve I (Fig. 2) and can be explained by the generalized theory; however, higher concentrations (3–9 %) of $Al_2O_3$, $B_2O_3$, $Fe_2O_3$, or $ZrO_2$ (Curve II) cause the disappearance of the second region (d-e) of the hydrogen-electrode function [45].

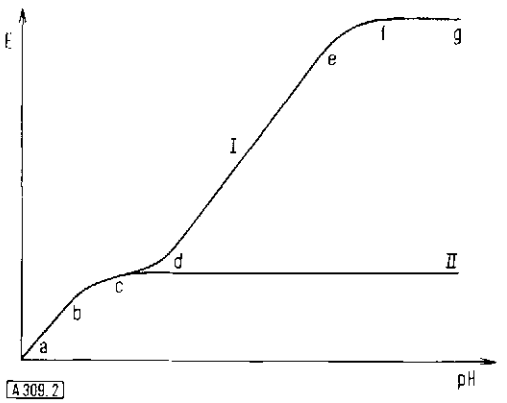



Fig. 2. Dependence on pH of the glass-electrode potential E for various glass compositions.
Curve I: Low $Al_2O_3$ and $B_2O_3$ content.
Curve II: A total content of 3–9 % $Al_2O_3$, $B_2O_3$, $Fe_2O_3$, $ZrO_2$.

The region a-b corresponds to the pure H function; b-c-d is the region of transition from the H to the metal function. This region corresponds to the replacement of the $H^+$-ions which are weakly bound to the anions of the gel layer by alkali metal ions from the solution. In the segment d-e, the electrode has a partial H function owing to firmly bonded $H^+$-ions in the gel layer. These are also displaced from the gel layer at high pH values so that the pure metal function (f-g) results after a new transition region e-f. Curve I is gradually transformed into curve II with increasing content of $B_2O_3$ or $Al_2O_3$; thus, addition of sufficient amounts of these oxides can produce glass electrodes which display pure metal functions over wide ranges of pH [19,46].

Although interpretation of the electromotive behavior of the glass membrane in terms of adsorption potentials does not lead to quantitative relationships, it is possible to give a satisfactory explanation of the behavior of the glass electrode not only in the neutral region but also in alkaline and acid media by means of either the membrane theory or diffusion potentials. However, since it has been definitely established that the glass electrode is not a semipermeable membrane, preference must be given to the phase-boundary-potential theory. With its help, the behavior of the glass electrode in both the acid and alkaline regions can be explained, but only after the determination of two or three empirical constants.

### c) *Interdependence of Electrode Function and Glass Composition*

The relationship between the composition of the electrode glass and the electromotive behavior can also be interpreted, in principle, on the basis of the phase-boundary-potential theory. The first empirical attempt to explain the differing electromotive behavior of glasses of different composition was undertaken by *Horovitz*

[*] Transformation range denotes the range of temperature, where the glass is plastic.

[43] *B. P. Nikolskiy*, Zh. Fiz. Khim. SSSR *10*, 504 (1937).

[44] *B. P. Nikolskiy, M. M. Schulz*, and *N. W. Peschechonowa*, Zh. Fiz. Khim. SSSR *33*, 1922 (1959).

[45] *B. P. Nikolskiy, M. M. Schulz, N. W. Peschechonova*, and *A. A. Belyustin*, Doklady Akad. Nauk SSSR *14*, 641 (1961).

[46] *G. Eisenman, D. O. Rudin*, and *J. U. Casby*, Science (Washington) *126*, 831 (1957).

[38,39]. According to his studies, the H function of a glass is related to its solubility. He established nearly pure H functions for easily attacked glasses but found a sodium functional behavior in glasses that were resistant to attack. *Horovitz* hypothesized that the adsorption of $H^+$-ions reaches a saturation value relatively fast with readily attacked glasses, whereas with resistant glasses this state occurs only at very high $H^+$-activities in the solution, so that a hydrogen function can be expected here only in the acid region.

*Hubbard, Hamilton,* and *Finn* [29] also found a relationship between the H function and the solubility of the glass. Systematic investigations [47] of Na and K glasses of various compositions revealed that glasses of very high chemical stability and low water uptake and glasses with high solubility and high water uptake yield H functions that do not obey the Nernst relationship: $\Delta E/\Delta pH = 58$ mv at 20 °C (cf. Fig. 3). Optimum electrode behavior is shown by glasses of intermediate solubility, containing 84–86 % $SiO_2$ and 14–16 % $Na_2O$.

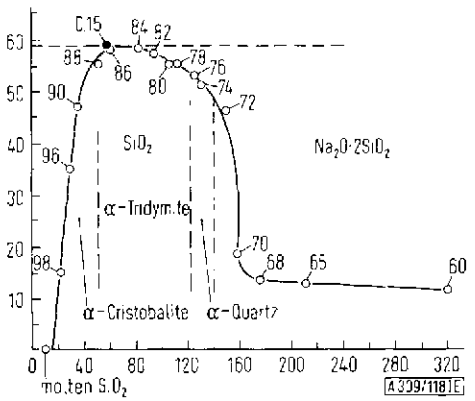



Fig. 3. Average $\Delta E/\Delta pH$ values for various $Na_2O$–$SiO_2$ glasses and for Corning-0.15-glass as a function of their hygroscopicity.

(The numbers at the plotted points give the percentage of $SiO_2$ in the glass.)

Ordinate: $\Delta E/\Delta pH$ [mv].

Abscissa: Water uptake at saturation [mg/ml].

As emphasized by *Nikolskiy* [36,37,40,42–45], the difference in bonding energies of the $H^+$- and $Na^+$-ions in the glass phase and those in the solution plays a decisive role in the formation of the gel layer. These factors determine the magnitude of the exchange constant K, which evidently assumes higher values for Na-functional electrode glasses, because the bond energy of the $H^+$-ions in the glass phase of these glasses is of the same order of magnitude as that of the $Na^+$-ions. However, high solubility of the glass implies high hydration energy of the ions in the glass, since otherwise the bond energies in the solid could not be overcome. Dissolution of the glass is thus preceded by solvation of the ions, leading to the water uptake observed. However, the more the solid swells, the more waterlike the solid phase becomes. This is associated with weakening of the bond between the $H^+$-ions and the anions in the glass; the standard state of the $H^+$-ions in the glass phase thus approaches that of the $H^+$-ions in the aqueous solution. The phase-boundary potential must then decrease, since it depends on the existence of two different phases with different standard states of the same ion.

When the pure H function is chosen as the reference state for the $H^+$-ions in the gel layer, and the chemical potential of the $H^+$-ions in the gel layer is written as

$$\mu = \mu^0 + RT \ln a'_{H^+} \qquad (53)$$

then, for a pure H function, $\mu^0$ refers to the $H^+$-activity ($a'_{H^+} = 1$) in the gel layer. It also seems appropriate to assume a "medium effect" in the glass phase, analogous to the change in $H^+$-activity observed at constant $H^+$-concentration in aqueous solutions upon addition of organic solutes, *i.e.* a decisive effect on the form of the electrode function can be ascribed to the water content of the gel layer. Thus, in the formation of an ideal H function, the equilibrium constant for the exchange between $H^+$-ions and the cations of the glass is not the only important factor, since the water content of the gel layer is also of great significance.

It is only when this content is low compared with that in the solution, *i.e.* when there is a sharp phase boundary, that there can be a phase-boundary potential that rigorously satisfies the Nernst equation in the form of Equation (25). It also follows from studies of the kinetics of the variation of the potential and of the rate of uptake of labelled cations by the gel layer [4] that the condition of the phase boundary does in fact determine the potential. In practice, the very slow uptake of alkali metal ions by the interior of the gel layer ceases to influence the potential. On the other hand, in the acid region, where the $K \cdot a_{Na^+}$ term of Equation (35) is negligible, MacInnes glasses show as exact a dependence on the $H^+$-activity, *i.e.* on the average activity of the acid, as the hydrogen electrode does (deviations $\leqq 10$ μv) [48]. From this it may be concluded that a genuine thermodynamic equilibrium is the sole factor determining the potential under these conditions. According to the present state of our knowledge, an ion-exchange equilibrium is involved here at the glass/solution phase boundary. This equilibrium cannot be formed when the glass phase is either a waterlike gel or is only capable of adsorbing ions without formation of an ion-exchanging solid phase (quartz).

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[47] *D. Hubbard, M. Black, S. Holley,* and *G. Rynders,* J. Res. nat. Bur. Standards *46,* 168 (1951).

[48] *A. K. Covington,* J. chem. Soc. (London) *1960,* 4441.

# The Reaction of Oxides with Water at High Pressures and Temperatures

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*Dedicated to Prof. Dr. H. Brockmann on the occasion of his 60th birthday*

*The reactions of the oxides $SiO_2$, $MoO_3$, and $WO_3$ with steam at temperatures between 400 and 700 °C and pressures of 5 to 500 atm were studied by means of the transfer method. The results were evaluated by a new method. In the system $SiO_2/H_2O$, the formation of gaseous $Si(OH)_4$, $Si_2O(OH)_6$, and $[SiO(OH)_2]_\lambda$ was found to occur in three different water-density ranges. In the systems $MoO_3/H_2O$ and $WO_3/H_2O$, the gaseous compounds $MoO_2(OH)_2$ and $WO_2(OH)_2$, which were already known, exist up to densities of approximately 0.05 g/cm³. At higher densities, at which the supercritical phase begins to show the properties of a liquid to an ever increasing extent, isopolymolybdic or isopolytungstic acids appear.*

## 1. Introduction

When various oxides are treated with steam at elevated temperatures and at pressures of up to 1 atm, gaseous hydroxides are formed [1]. Gaseous hydroxides are also formed by evaporation or sublimation of solid and liquid hydroxides. Thus, there are two classes of gaseous hydroxides, which are distinguished by their formation equilibria, as follows:

(1) Evaporation or sublimation equilibrium:
$\text{Hydroxide}_{(\text{solid, liquid})} \rightleftharpoons \text{Hydroxide}_{(\text{gas})}$

(2) Reaction equilibrium:
$\text{Oxide}_{(\text{solid, liquid})} + \text{H}_2\text{O}_{(\text{gas})} \rightleftharpoons \text{Hydroxide}_{(\text{gas})}$

Most of the hydroxides formed according to Equation (2) are stable only at elevated temperatures and in the gaseous state; at lower temperatures, they redecompose into the oxide and water. Several suboxides and subhalides, *e.g.* SiO, AlCl, behave in a similar manner. This reversibility of the equilibrium (2) permits transport of the oxides via the gas phase. Since reactions of this type may also occur in nature, their study can provide the mineralogist and the petrologist with a better understanding of geological transport phenomena which lead to the formation of mineral deposits.

The existence of gaseous hydroxides is also of technical interest. For example, beryllium oxide may be purified by its reaction with steam, *i.e.* via the gaseous beryllium hydroxide [2]. Corrosion phenomena in iron and alloy steel can be better understood; thus the scaling of certain alloy steels takes place more rapidly in the presence of steam, because the alloying elements vanadium, chromium, molybdenum, and tungsten form gaseous hydroxides [1]. Indeed, even the well-known reaction between steam and iron proceeds above 1300 °C according to:

(3) $\text{Fe}_{(\text{solid})} + 2\,\text{H}_2\text{O}_{(\text{gas})} \rightleftharpoons \text{Fe(OH)}_{2(\text{gas})} + \text{H}_{2(\text{gas})}$

*i.e.* via the formation of gaseous $Fe(OH)_2$ [3].

However, neither in nature nor in technical applications are the reactions of oxides with steam limited to pressures below 1 atm. Therefore, it was the purpose of the present investigations to study oxide reactions with steam at pressures ranging from 1 atm to supercritical pressures [4]. It might be pointed out already now that, at low steam pressures, the reactions can be described to a good approximation by assuming ideal behavior in the gas phase. However, at higher pressures or densities a range is attained in which the supercritical phase gradually acquires the properties of a liquid. Thus, the gas phase changes into a system in which, as *Franck* [5] has shown, solvation and electrolytic dissociation can occur in the same fashion as in liquid water.

The question is whether definite compounds can be expected under such conditions. Several authors [6] answer in the affirmative as far as the reaction of $SiO_2$ with water is concerned; however, they differ greatly in their opinions as to what possible compounds actually do exist.

In the following, the reactions of $SiO_2$, $MoO_3$, and $WO_3$ with water at elevated temperatures and pressures will be discussed.

## II. Experimental Technique

### 1. General Description of the Apparatus and Method

Equilibrium reactions between an oxide and steam can be investigated by the transfer method. In this process, steam (diluted, if necessary, with an inert gas) is passed through the reaction zone in such a way that it is satu-

[1] *O. Glemser*, Österr. Chemiker-Ztg., in the press; *O. Glemser* and *H. G. Wendlandt*, Advances inorg. Chem. Radiochem. *5* (1963); *O. Glemser*, Angew. Chem. *73*, 785 (1961).

[2] U.S. Pat. 2531143 (Nov. 21st, 1950), inventors: *J. G. Malm* and *Cl. A. Hutchison*.

[3] *G. R. Belton* and *F. D. Richardson*, Trans. Faraday Soc. *85*, 1562 (1962).

[4] The term "supercritical water" or "supercritical phase" was applied by *E. U. Franck* [5] to water at supercritical temperatures with densities $\geq$ 0.2–0.3 g/cc.

[5] *E. U. Franck*, Angew. Chem. *73*, 309 (1961).

[6] Literature references see Section IV. 1 (The System $SiO_2/H_2O$).

rated with the reaction products under equilibrium conditions. The reaction products are carried along by the gas stream and are condensed in the receiver as oxides which are then determined quantitatively.

The apparatus for measurements at pressures below 1 atm is shown schematically in Figure 1. Its basic features have been

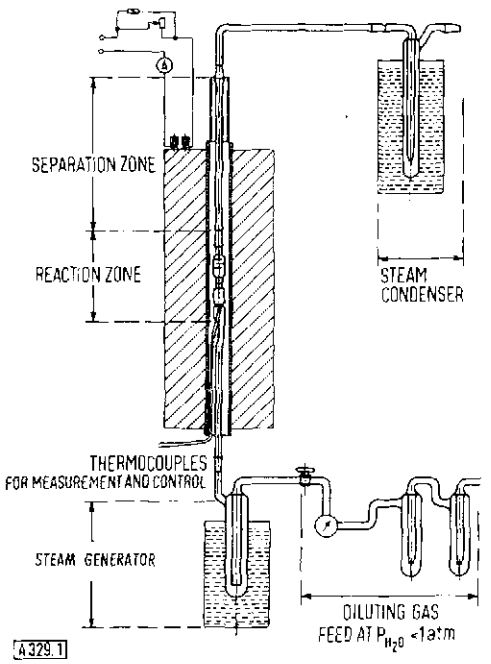



Fig. 1. Diagram of a transfer-method apparatus for pressures of up to 1 atm.
A = ammeter.

adapted for application to the high-pressure equipment (Fig. 2). In the latter, water from the feed vessel W is passed at a given temperature over the oxide contained in the reaction cell R. Below the critical point, the total pressure in the reaction cell is given by the pressure of the saturated water vapor. Above the critical point, the pressure is determined by the total volume of the apparatus and by the quantity of

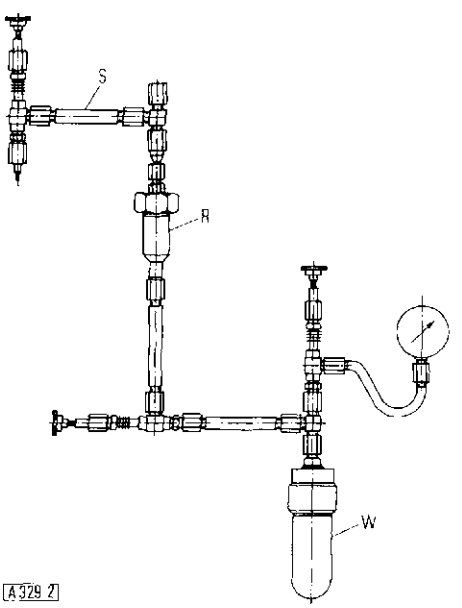



Fig. 2. Diagram of a transfer method apparatus for measuring reactions at higher pressures.
S = separator
R = reaction cell (cf. Fig. 3)
W = water reservoir.

water present in it at that time. The steam containing the dissolved reaction products is cooled in the separator S to a temperature of 60–70 °C. It is then discharged from the apparatus through a pressure relief valve attached to S. The transported sample, which is mostly dissolved in the liquid water, is determined by analysis of the water collected. When the substance has no solubility in water at the separation temperature, the separator S is unscrewed after the end of the experiment, and the substance precipitated on the walls of this receiver is removed with solvents and analysed.

## 2. Structural Elements of the Apparatus

The various parts of the apparatus [7] are designed to withstand a maximum temperature of 700 °C and pressures of up to 500 atm in the reaction cell. All internal parts of the apparatus are protected by a noble metal lining; the reaction cell (including the feed and drain pipes) is lined with gold foil and the other parts of the apparatus with silver foil.

The water feed vessel W has a volume of approximately 220 $cm^3$ and is provided with a Bridgman seal [8]. The two holes in its cover carry, respectively, a thermowell and a screw fitting. The latter carries adapters for the removal of the water and for attaching the armatures of the pressure gauges.

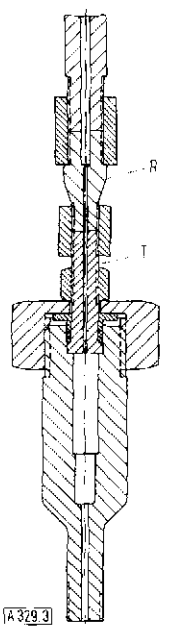



Fig. 3. Reaction cell.
T = transition adapter.
R = reducing adapter.

The reaction cell (Fig. 3) has a volume of approximately 15 $cm^3$ and is sealed with a Bridgman-type seal. The transition adapter T has an axial 1 mm⌀ capillary boring. It is connected to a $^3/_8 \times {}^1/_2$ inch reducing adapter R, which in turn is coupled to the outlet pipe. The 1 mm internal diameter helps to reduce diffusion effects. The total volume of the cell is available for the test material. A platinum wool plug is inserted into the bottom feed pipe to support the test substance. The test substance in the cell is loosely packed to allow good exchange with the passing gas. The topmost layer of the test

[7] Constructed with Remanit 1880 SST, Product No. 4571, from Deutsche Edelstahlwerke. The reaction vessel was made of Thermax 1636, Product No. 6864, from Deutsche Edelstahlwerke.

[8] *P. W. Bridgeman:* The Physics of High Pressure. McMillan, New York 1950.

substance is compressed and sintered, in order to prevent elutriation of fine particles. Depending on the nature of the test material, 20–40 g of it can be placed in the reactor.

The reactor cell and the feed vessel are connected by means of pipes with 22 mm outer diameter and 6 mm internal diameter. The separator is of the same dimensions as the connecting pipes. Self-sealing flanges without gaskets are used throughout. The flange bolts carry double locking nuts. The 4 mm internal diameter valves [9] serve both for cutoff of the flow and for regulation of the flow rate.

The water feed vessel and the reaction cell are heated by resistance furnaces. Each of these furnaces has two coils, which can be controlled separately. In addition, each furnace has an auxiliary heating coil, so that better control over the preset temperature gradients can be achieved. The exposed parts of the apparatus and the ends of the furnaces are insulated with asbestos wool in order to minimize heat losses. The separation zone S is wound with a lead coil through which cold water flows.

The temperature over the entire length of the reaction cell is measured by means of miniature-thermocouples (Chromel-Alumel), which are placed in thermowells. The e.m.f. produced is measured in a potentiometer circuit. Compensating wires lead from the thermocouples to a constant-temperature junction. Several calibrated platinum/platinum-rhodium thermocouples are used as controls.

Two resistance thermometers with appropriate controllers are available for regulating the temperature of the reactor furnace. All other controllers are activated by means of thermocouples. The water temperature in the feed vessel is controlled by means of a thermocouple placed in a thermowell immersed in the water. This thermocouple activates a controller connected to an auxiliary resistance heater, wrapped around the feed vessel. The feed vessel is placed in a furnace the temperature of which is kept 5 °C below the desired water temperature. When working in the supercritical range, the temperature of the water is controlled manually from the manometer readings, using the auxiliary heating coil.

Pressure measurements are made with a Class 1.0 set of manometers, which were checked against PTB-calibrated [*] manometers. In the subcritical range good agreement is reached between the manometer pressure and the saturated-steam temperature and pressure as given by the steam tables of the Verein Deutscher Ingenieure [10]. The density of the supercritical phase was calculated from the data of *Holser* and *Kennedy* [11].

## 3. Evaluation of Results

Let us consider the general reaction equation

(4) $r\,(\mathrm{Oxide})_{solid} + m\,(H_2O)_{gas} \rightleftharpoons [(\mathrm{Oxide})_r \cdot m\,(H_2O)]_{gas}$

Experimentally, the moles of oxide $n^*_{ox}$ dissolved per mole of $H_2O$ ($n_{H_2O}$) at equilibrium are determined. However, $n_{H_2O} \gg n^*_{ox}$ and $P_{total} \approx P_{H_2O}$. Therefore, the mole fraction $X^*_{ox}$ of the transported oxide is

$$X^*_{ox} = n^*_{ox}/n_{H_2O}$$

Since the effect of the saturated oxide vapor pressure can be disregarded, it follows that $X_{hyd} = n_{hyd}/n_{H_2O}$, where $n_{hyd}$ = the number of moles of hydroxide formed in the reaction and $X_{hyd}$ = the mole fraction of the hydroxide with the empirical formula $[(\mathrm{Oxide})_r \cdot m\,H_2O]$ formed in the reaction.

In order to clarify the stoichiometry of Equation (4), the coefficient m, which we designate as the association number, is determined first. To do this, $X_{hyd}$ has to be expressed as a function of the concentration of the water in the gas-filled space. In this way, we account for the real behavior of the gas or supercritical phase, as well as for the pressure dependence of the chemical potential of the solid phase. Thus the measurements are described as a function of the pressure-volume-temperature data of water, known experimentally and represented by the density. It will be assumed that interactions between the molecules of the nascent compound, as well as interactions between these molecules and those of the water, have no perceptible influence. The equilibrium constant of Equation (4) is:

$$K_c = C_{hyd}/(C_{H_2O})^m \qquad (5)$$

where $C_{hyd} = C_{[(\mathrm{Oxide}) \cdot m\,H_2O]}$

Moreover, $C_{hyd} = n_{hyd}/V$ and $C_{H_2O} = n_{H_2O}/V$.

$V \approx V_{H_2O} = n_{H_2O}/\rho_{H_2O}$; $V_{hyd} \ll V_{H_2O}$; $\rho_{H_2O}$ = density of the water; V = total volume.

Using Equation (5), one obtains

$$(6)\quad K_c = \frac{n_{hyd}}{n_{H_2O}} \cdot \frac{\rho_{H_2O}}{(\rho_{H_2O})^m} = X_{hyd}\,\frac{1}{(\rho_{H_2O})^{m-1}}$$

The pressure dependence of the chemical potential $\mu_{oxide}$ of the solid phase may be expressed as

$$\left(\frac{\delta \mu_{oxide}}{\delta p}\right)_T = V_{oxide}$$

where $V_{oxide}$ = molar volume of the oxide.

By integrating the pressure from $p^1 = 1$ atm to the reaction pressure P and by assuming pressure independence of the molar volume we obtain

$$\mu^P_{Oxide} - \mu^o_{Oxide} = P \cdot V_{Oxide}$$

and, therefore,

$$(6a)\quad \log a = \frac{V_{Oxide} \cdot P}{4{,}574 \cdot T}$$

where a = activity of the solid phase. Accordingly, the experimental data can be represented by the equation

$$(7)\quad K^a_c = \frac{X_{hyd}}{(\alpha_{Oxide})^r \cdot (\rho_{H_2O})^{m-1}}$$

where $K^a_c$ = equilibrium constant

or

$$(8)\quad \log [X_{hyd}/(a_{Oxide})^r] = (m-1) \log \rho_{H_2O} + \log K^a_c$$

Equation (8) can be evaluated, if the reaction follows Equation (4). However, since the present investigation covers a wide range of densities, *viz.* from 0.003 to 0.8 g/cm³, the possibility of the occurrence of several reactions must be considered. Certain density ranges might be reserved to a certain kind of molecules, others might be transition ranges, in which more than one species may occur. On the basis of these assumptions, Equation (8) becomes the equation of the tangent of the curve that limits the range of existence of the i-th species. It therefore permits determination of the i-th association number and the i-th equilibrium constant. If the experimental conditions are favorable, then the curves for the range of existence can be approximated with straight lines.

[9] Supplied by: A. Hofer, Hochdruckapparatebau GmbH, Mülheim/Ruhr (Germany).

[*] PTB = Physikalisch-Technische Bundesanstalt (The German Bureau of Standards).

[10] *E. Schmidt:* VDI-Wasserdampftafeln. Springer, Heidelberg 1956.

[11] *W. T. Holser* and *G. C. Kennedy*, Amer. J. Sci. *256*, 744 (1958); *257*, 71 (1959).

The evaluation is first carried out with an estimated value of r. The determination of the association number m is not adversely affected by this, but the value of the equilibrium constant becomes uncertain by a factor of r. This first evaluation yields an indication whether several species, *i.e.* several reactions, occur in the density range considered. If this is the case, the evaluation is repeated with the most probable r values.

## III. Experimental Procedure

The powdered sample is made into a paste using a small amount of water and then dried at 300 °C. The resulting hard material is crushed into particles of 2–3 mm diameter. The reaction cell is filled with the sample. Material of a somewhat larger particle size (5–6 mm diameter) is placed at the bottom of the cell. A total of 20–40 g of substance is normally needed. The cell is then closed and connected to the apparatus. Screw joints, which will be subjected to high temperatures, are lightly greased with molybdenum disulfide paste. At this stage the movable furnace attached to a mounting frame is still in its upper position to allow free access to the cell and the thermocouples. The auxiliary heaters are installed. The furnace is then lowered and turned on. The preselected temperature program is regulated by means of a controller and checked on recorder charts. While the furnace is heating up, the feed vessel W is filled with doubly distilled water, and also heated to the temperature required for the desired pressure.

The actual experiment starts after the preselected temperatures have become stabilized. The pressure relief valve is then opened and adjusted to a flow rate of 10–20 g of water/hour. It has been ascertained by preliminary tests that, other conditions being equal, the quantity $A_{(Oxide)}$ of substance transported is independent of the rate of flow in this flow range.

The condensed water, in which the entrained substance is dissolved, is removed through the pressure relief valve. A graduated tube, provided with Schellbach strips, serves as receiver; using this tube and a stop watch, the flow rate can be rapidly checked and regulated as necessary. Five to 10 ml of water are collected for one determination. Since the apparatus has a dead volume [12] of approximately 5 ml (based on a water density of 1.0), each run was preceded by a forerun in which 5–10 ml of condensate was removed and discarded. In this way, the effect of the dead volume is eliminated; in addition, the forerun also allowed careful adjustment of the flow rate. Below the critical point, the pressure in the entire apparatus is, of course, a well-defined function of the water temperature in the feed tank. In the supercritical range, the total pressure can be kept constant to a good approximation by increasing the temperature of the water in the feed vessel.

### Error Analysis

Assuming that the solid phase is well defined and remains unaltered during the measurement, systematic errors can occur owing to supersaturation or incomplete saturation in the reaction cell. Supersaturation can occur as a result of diffusion. Incomplete saturation is caused by too high a flow rate, which would exceed the reaction rate [13]. Both errors can be reduced by taking suitable precautions in the construction of the apparatus. When proper experimental conditions are selected, such errors can be eliminated for all practical purposes. The analytical methods used for determining the transferred substance were checked with standard solutions. The accuracy of the temperature and pressure measurements was tested by control runs and was checked against calibrated thermocouples and gauges. They were thus eliminated as a source of systematic errors. The individual measurements may vary within the following limits:

| | |
|---|---|
| Reaction temperature: | ± 2 °C |
| Pressure: | ± 3 atm (for pressures below 100 atm ± 2 atm) |
| The quantity of entrained substance: | ± 3 % |

## IV. Examples

### 1. The System $SiO_2/H_2O$

Data on the reaction between $SiO_2$ and water can be obtained from the solubility of the oxide, determined at various pressures and temperatures. The experimental breakthrough goes back to the work of *Morey* and *Hesselgesser* [14] and *Kennedy* [15]. These authors found that the solubility of $SiO_2$ in steam increases with pressure. According to *Jasmund* [16] and *Mosebach* [17], the data obtained by the above authors can be correlated by the empirical equation [18, 19],

$$\log L = (m \cdot \log D) + b$$

which led to the conclusion that the association number is m = 2, hence the reaction was formualted as $SiO_2 + 2\,H_2O = Si(OH)_4$. In agreement with this finding, *Franck* [20] and *Wasserburg* [21] have also adopted the association number of m = 2 for the entire pressure range up to 2000 bars. *Wood* [22] believes that m = 2

[12] The dead space is the volume between the reaction cell and the pressure release valve.

[13] *H. K. Hofmeister, R. von Haeseler,* and *O. Glemser,* Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64,* 513 (1960).

[14] *G. W. Morey* and *J. M. Hesselgesser,* Trans. Amer. Soc. mech. Engrs. (ASME) *1951,* 865; Econ. Geol. *46,* 821 (1951).

[15] *G. C. Kennedy,* Econ. Geol. *45,* 629 (1950).

[16] *K. Jasmund,* Heidelberger Beitr. Mineralog. Petrogr. *3,* 380 (1952).

[17] *R. Mosebach,* Neues Jb. Mineralog. Mh. *87,* 351 (1955); J. Geology *65,* 347 (1957).

[18] L = the solubility of $SiO_2$ in water [g of $SiO_2$ per kg of water]; D = density of the vapor phase; m = association number; b = a constant dependent upon the temperature.

[19] This empirical relationship can be derived from an expression given by *Franck* [20]. For the limiting case of high densities and strong interaction *Franck* obtains the formula

$$\ln \frac{X_2}{x_2^0} = \frac{V_{2f} \cdot P}{RT} + m \ln \frac{K_m}{V}$$

where $X_2$ = the mole fraction of solute, $x_2^0$ = the mole fraction of oxide dissolved under its own vapor pressure, $V_{2f}$ = the molar volume of the solid, P = total pressure, m = association number, 1/V = overall density, and $K_m$ = constant.

[20] *E. U. Franck,* Z. physik. Chem. N. F. *6,* 345 (1956); Angew. Chem. *73,* 309 (1961).

[21] *G. J. Wasserburg,* J. Geology *66,* 559 (1958).

[22] *J. A. Wood,* Amer. J. Sci. *256,* 40 (1958); see, however, *G. J. Wasserburg* and *J. A. Wood,* Amer. J. Sci. *256,* 438 (1958).

probably holds to a pressure of 500 bars; he assumes that the association numbers are greater at higher pressures. On the other hand, *Brady* [23] believes that m = 3 holds for lower pressures and m = 2 for higher pressures.

We have studied the effect of water on $SiO_2$ (quartz) [24] at 400 and 500 °C, between 10 and 500 atm. The quantity of $SiO_2$ transported was determined as silicomolybdenum blue by photometric analysis of the silicic acid dissolved in the condensed water [25,26]. Concentrations of as low as 0.001 mg of $SiO_2$ per g of water could be detected by this method.

*Results*

The results of measurements made at 400 and 500 °C are plotted in Figure 4 in the form $\log X_{hyd} = f(\log \rho_{H_2O})$, corresponding to Equation (6). For orientation purposes, the pressures (in atm) corresponding to the various temperatures are printed above the abscissa for several density values. The figure also shows the experimental data of *Morey* and *Hesselgesser* and of *Kennedy*. The agreement of our values with those given by

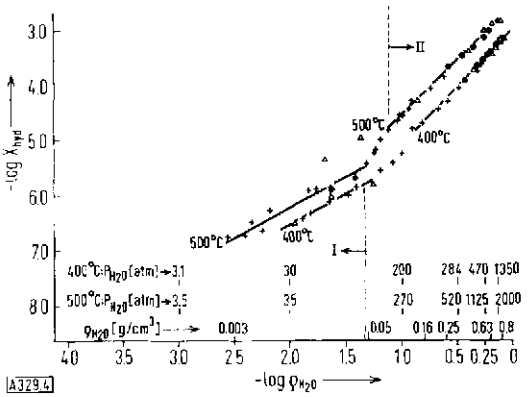



Fig. 4. Solubility of $SiO_2$ (quartz) in $H_2O_{(gas/liquid)}$ at 400 and 500 °C in relation to the density of the water.

Δ Values of *Morey* and *Hesselgesser*

● Values of *Kennedy*

+ Our values.

these authors is good, so that all the experimental data can be discussed together. Two density ranges (I, II) appear. To a good approximation the points in each range fall on a straight line (isotherm). In range II, the increase in the solubility with the density is greater, but it is assumed that this is not caused by changes in the solid phase.

For higher pressures the pressure dependence of the chemical potential of the solid phase has to be taken into account, according to Equation (4). The recalculated data are given in Figure 5. Let us assume r = 1 for the density range I and r = 2 for range II. Up to pressures of approximately 350 atm, the curves in Figure 5 are in practically complete agreement with those in Figure 4. With in-

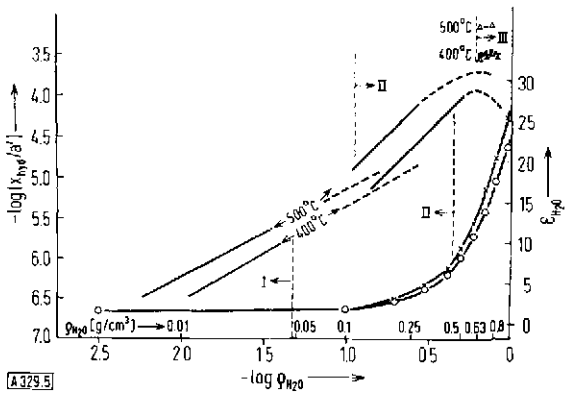



Fig. 5. Solubility of $SiO_2$ (quartz) in $H_2O_{(gas/liquid)}$ at 400 and 500 °C in relation to the density of the water. The values measured were evaluated with due consideration of the pressure dependence of the chemical potential and on the assumption of different possible reactions.

Δ Values of *Morey* and *Hesselgesser*.

● Values of *Kennedy*

+ Dielectric constant $\varepsilon_{H_2O}$ at 400 °C

o Dielectric constant $\varepsilon_{H_2O}$ at 500 °C.

creasing pressure, however, a sharp curvature becomes apparent. From this, one would infer a negative solubility gradient, which seems impossible. The downward curvature actually results from the fact that the assumption of r = 2 does not hold any more at high pressures. Thus, a transition region appears between the density range II and another range III. Assuming that r = 1, we find that, within the limits of error, the isotherms in range III run parallel to the abscissa. In order to get a first orientation the limits of the various density ranges might be drawn, irrespective of different temperatures, as follows:

| | |
|---|---|
| Density range I | up to approximately 0.05 g/cm³ |
| Density range II | from 0.1 to 0.45 g/cm³ |
| Density range III | from 0.65 g/cm³ upwards |

The transition region between I and II coincides with the sharp increase of the dielectric constant (DC) with density, as is clearly evident from the shape of the curve in Figure 5 [27]. The increase in solubility observed in range II might be correlated with this increase of the DC. It is important to note that the solubility starts increasing below a density of 0.2–0.3 g/cm³, which served as a basis for the definition of the "supercritical water" [4].

The values of aggregation number r have been surmised. Their postulation can be reconciled with the following considerations. *Morey* et al. [28] have shown that in the range 65–300 °C and at 1000 atm, the heat of solution of quartz is 5.4 kcal/mole. From the temperature function of the isotherms of density range II, we found a heat of solution of quartz of 10.6 kcal per unit formula. This estimate was made with only two $K_c$ values, but the result is representative since each $K_c$ value is based on approximately 20 determinations.

By this, one avoids the use of the term kcal/mole, since it is not known from our experiments how many moles of the solid phase participate in the reaction. This limitation also

[23] *E. L. Brady*, J. physic. Chem. *57*, 706 (1953).

[24] *E. Merck*, Darmstadt, analytical grade, washed and ignited.

[25] *O. Glemser:* Photometrische Bestimmungsmethoden; No. 1: Wasseranalysen. E. Leitz, Wetzlar 1951.

[26] *J. Bochem*, Mitt. Vereinig. Großkesselbesitzer *27*, 150 (1952).

[27] The dielectric constants are taken from a publication by *Franck* [20].

[28] *G. W. Morey, R. O. Fournier*, and *J. J. Rowe*, Geochim. cosmochim. Acta *26*, 1029 (1962).

holds for the value given by *Morey* et al. It can be seen that the values are related by a ratio of approximately 1:2. The conditions of *Morey*'s experiment correspond roughly, as far as the density and the pressure are concerned, to those of our density range III. Assuming that the heat of solution of quartz in kcal/mole has the same value in ranges II and III, and that one mole of $SiO_2$ per unit formula enters into the reaction in range III, it follows that in range II 2 moles of $SiO_2$ per unit formula are dissolved. Accordingly, if $r_{III} = 1$, we would have to assume that $r_{II} = 2$. With these values for r we have plotted log $(X_{hyd}/a^r)$ versus log $\rho_{H_2O}$ (Fig. 5); $X_{hyd}$ is the mole fraction that was determined with the given value of r; $r_I$ was likewise made equal to 1.

In Figure 5, there are three prominent density ranges, I, II, and III, with the corresponding association numbers $m \approx 2$, $m \approx 3$, and $m \approx 1$ [29]. Using the tentative aggregation numbers $r_I \approx 1$, $r_{II} \approx 2$, $r_{III} \approx 1$, the experimental results can be represented by the following equations:

| | | Density range |
|---|---|---|
| (9) | $SiO_{2(quartz)} + 2\,H_2O_{(gas)} \rightleftharpoons Si(OH)_{4(gas)}$ | I |
| (10) | $2\,SiO_{2(quartz)} + 3\,H_2O_{(gas)} \rightleftharpoons Si_2O(OH)_{6(gas)}$ | II |
| (11) | $SiO_{2(quartz)} + H_2O_{(gas)} \rightleftharpoons SiO(OH)_{2(gas)}$ | III |

$Si(OH)_{4(gas)}$ appears under reaction conditions which correspond approximately to ideal behavior in the gas phase. The other compounds are present as solutes in the supercritical phase only. Their designation by the subscript (gas) holds true only when the supercritical phase is defined as a gaseous phase. This, however, is not quite justified, since in range III (Equation 11) the density approaches a value of 0.6 g/cm³. Therefore, this reaction should be regarded as a reaction in solution. Furthermore, the nascent "$SiO(OH)_{2(gas)}$" will possibly polymerize yielding oligosilicic acids [30] of the type $(H_2SiO_3)_x$, with x = 5 or 6 [31].

## 2. The System $MoO_3/H_2O$

The reaction of $MoO_{3(solid)}$ with $H_2O_{(gas)}$ has been investigated at steam pressures below 1 atm and temperatures of 400–630 °C [32, 33]. Gaseous molybdenum hydroxide is formed according to the equation:

$$MoO_{3(solid)} + H_2O_{(gas)} \rightleftharpoons MoO_2(OH)_{2(gas)}$$

The effect of $H_2O$ on $MoO_3$ at higher pressures had not yet been studied systematically. The first paper about this problem was published by *van Nieuwenberg* and *Blumendal* [34]. *Elliott* [35] later attempted to determine what association number should be assigned to the reaction of steam with $MoO_3$ at higher pressures. He gives an association number of m = 1, but does not specify to what pressure this number applies. Scrutiny of his experimental results does not allow any conclusions on this matter either.

We studied the action of water on $MoO_3$ between 380 and 500 °C in the pressure range 10–500 atm. As solid phase, we used chemically pure, analytical grade $MoO_3$ from E. Merck, Darmstadt. The amount of $MoO_3$ transported was determined by two analytical methods. In the first, the molybdenum compound is titrated with a 0.005 M lead nitrate solution, which gives lead molybdate [36]. Pyridyl-2-azoresorcinol is used as an indicator. The other method uses the fact that molybdenum(VI) solutions form a yellow complex with thioglycolic acid in weakly acidic solutions (pH 3.5 to 4.5). This complex is well suited to the photometric determination of molybdenum. The extinction is measured at 365 mμ [37]. The titrimetric method allows determination of concentrations of 0.2 mg of $MoO_3$ per g of water, provided a lead nitrate solution of known concentration is added prior to titration. With the photometric method, as little as 0.01 mg of $MoO_3$ per g of water can be determined.

### *Results*

Figure 6 shows the results of the measurements at 500 °C. From a density of 0.05 g/cm³ onwards, the solubility starts to increase. After a transition interval, the solubility curve assumes a constant slope. This curve of

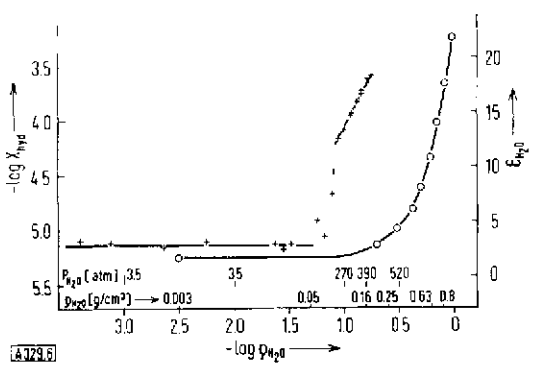



Fig. 6. Solubility of $MoO_{3(solid)}$ in $H_2O_{(gas/liquid)}$ at 500 °C in relation to the density of the water.
o Dielectric constant $\varepsilon_{H_2O}$.

constant slope starts at a density of approximately 0.08 g/cm³ which corresponds to the relationships observed in the case of $SiO_2$. Again there is a possible correlation between the solubility and the rise in the DC with density. Another isotherm was determined at 440 °C. Its slope corresponds to that of the isotherm shown in Figure 6.

Appraisal of Figure 6 yields the association number $m \approx 1$ for densities up to 0.05 g/cm³, and $m \approx 3$ for densities of the order of 0.1 g/cm³. These relationships may be described by the following equations:

(12) $MoO_{3(solid)} + H_2O_{(gas)} \rightleftharpoons MoO_2(OH)_{2(gas)}$

(13) $7\,MoO_{3(solid)} + 3\,H_2O_{(gas)} \rightleftharpoons Mo_7O_{18}(OH)_{6(gas)}$, *i.e.* $H_6Mo_7O_{24}$

[29] Like *Franck* [20], we also select whole numbers for our association numbers.

[30] *R. Schwarz* and *K. G. Knauff*, Z. anorg. allg. Chem. *275*, 190 (1954).

[31] An example of a derivative of cyclic hexasilicic acid $(H_2SiO_3)_6$ or $H_{16}(Si_6O_{18})$ is the mineral beryl $Be_3Al_2(Si_6O_{18})$.

[32] *O. Glemser* and *R. von Haeseler*, Z. anorg. allg. Chem. *316*, 168 (1962).

[33] *A. Müller*, Diploma Thesis, Universität Göttingen, 1962.

[34] *C. J. Van Nieuwenberg* and *H. B. Blumendal*, Rec. Trav. chim. Pays-Bas *53*, 989 (1931).

[35] *G. R. B. Elliott*, Ph. D. Thesis, University of California, 1952.

[36] *E. Lassner* and *R. Scherf*, Z. analyt. Chem. *167*, 114, 429 (1959).

[37] *F. Will* and *J. H. Yoe*, Analytic. Chem. *25*, 1363 (1953).

Since mass-spectrometric studies on the system $WO_3/H_2O$ gave the aggregation number r = 1 and hence the formula $WO_2(OH)_2$ for gaseous tungsten hydroxide [32], a similar formula is very probable for the corresponding compound in the system $MoO_3/H_2O$. However, this formula holds only for the low-density range. The aggregation number r = 7 selected for the higher density range is stoichiometrically plausible, since it explains the increase in solubility observed for the compound with the experimental association number m = 3, in contrast to the reaction with the association number m = 1. Using the aggregation number r = 7, we can formulate the reaction product. The resulting formula is analogous to that of the isopolymolybdates $[Mo_7O_{24}]^{6-}$, which are formed by acidification of molybdate solutions. The ultraviolet absorption curves of our aqueous solutions, obtained by quenching the reaction products, do in fact show a displacement of the absorption peaks toward longer wavelengths as compared to a monomolybdate solution. This can be taken as an indication that heptamolybdate ions are present [38].

However, it should be noted that the experimental results are also compatible with values of r = 6 or r = 8. Moreover, even though heptamolybdate seems to occur in the quenched reaction solution, it still remains to be proved that this ion is present during the actual high-temperature reaction. Definite proof of this can only be obtained from experiments in which the activity of the solid phase is varied. Studies along this line are in progress.

### 3. The System $WO_3/H_2O$ [39]

The reaction of $WO_3$ with $H_2O_{(gas)}$ had previously been studied between 400 and 1100 °C at steam pressures below 1 atm [32,40]. Gaseous $WO_2(OH)_2$ is formed according to the equation:

(14) $WO_{3(solid)} + H_2O_{(gas)} \rightleftarrows WO_2(OH)_{2(gas)}$

As mentioned above, the aggregation number r = 1 was demonstrated by mass spectrometric experiments.

The starting material for our pressure experiments was $WO_3$ obtained from E. Merck, Darmstadt. The quantity of $WO_3$ transported can be determined photometrically with sodium alizarin-3-sulfonate [41]. It can also be determined titrimetrically in a procedure similar to that used for $MoO_3$ [42].

The experimental data obtained at 500 °C and in the pressure range 40–400 atm are plotted in Figure 7. Two density ranges can be distinguished. The upper limit of range I, with m = 1 and r = 1, has been found by extrapolation at a density of 0.01 g/cm³. Range II gives m = 3. This system also shows some correlation between the solubility and the increase in the DC with the

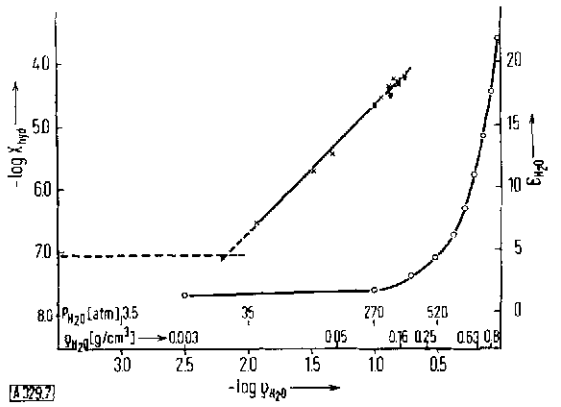



Fig. 7. Solubility of $WO_{3(solid)}$ in $H_2O_{(gas/liquid)}$ at 500 °C in relation to the density of the water.
o Dielectric constant $\varepsilon_{H_2O}$.

density. To account for the greatly increased solubility in range II, we selected the value r = 6 and formulated the reaction as

(15) $6\ WO_{3(solid)} + 3\ H_2O_{(gas)} \rightleftarrows W_6O_{15}(OH)_{6(gas)}$, *i.e.* $H_6W_6O_{21}$

The aggregation number r = 6 indicates a relationship between the product of the vapor reaction and the ion $[HW_6O_{21}]^{5-}$, which is produced on acidification of tungstate solutions [43,44]. As we know [45], this ion polymerizes relatively rapidly to a dodecatungstate ion, thus a polymerization can follow the primary reaction, as was assumed above for "$SiO(OH)_2$".

The experimental results are also compatible with a value of r = 4 yielding the equation:

(16) $4\ WO_{3(solid)} + 3\ H_2O_{(gas)} \rightleftarrows W_4O_9(OH)_{6(gas)}$, *i.e.* $H_6W_4O_{15}$

On acidifying tungstate solutions, *Schwarzenbach* et al. [46] found an initial short-lived intermediate product which proved to be a tetratungstate ion $[H_5W_4O_{16}]^{3-}$ with a degree of acidity of Z = 1.25 [47]. It converts further into $[HW_6O_{21}]^{5-}$ via an as yet unexplained sequence of reactions. However, instead of an $[H_5W_4O_{16}]^{3-}$ ion, the above value of Z also permits a formulation such as

$$4\ WO_4^{2-} + 5\ H^+ \rightleftarrows H_3W_4O_{15}^{3-} + H_2O$$

which bears a relationship to Equation (16). The question remains whether it is Equation (15) or Equation (16) which is correct. An answer will be given by experiments that will yield some information on the aggregation number r. In both cases, the primary reaction is expected to be followed by condensation or polymerization reactions.

## V. Concluding Remarks

The experiments have shown that the action of water on $SiO_2$, $MoO_3$, and $WO_3$ at high temperatures results in different reactions, depending on the density of the gas

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or the supercritical phase. It has been shown that the quantity of oxide transported per unit volume of the transport medium is more than two orders of magnitude greater at high densities of the transport media than at low densities. This finding is pertinent to the study of the corrosion of industrial materials. It also helps to explain transport phenomena in nature, which are of great importance, for example, in the formation of mineral deposits. Last but not least, it also opens up new preparative possibilities.

The present results are in good agreement with the recently developed concept regarding the supercritical water as an electrolytic solvent. The magnitude of the effects observed is certainly a function of the specific interaction between the appropriate oxide and water. However, the prerequisite for a solubility effect is polarity of the water molecules in the supercritical state. With increasing density, the electrolytic properties of this supercritical phase will become similar to those of a liquid. This might explain why, at higher pressures, the concentration of the solute tends towards a limit. It might also explain the fact that at high temperatures and pressures compounds will appear in the supercritical phase which are already known from aqueous solutions. It might in future be possible to use pressure methods for the study of polyanions. By the determination of the heat of reaction one has the possibility to determine the enthalpies of formation of these compounds. It will be necessary to clarify whether, under the prevailing reaction conditions, these compounds exist as hydrated undissociated molecules or whether they dissociate into ions. Conductivity measurements might offer further insight into this problem.

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# Reversibility of Energy Transformations in the Respiratory Chain [*]

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*Dedicated to Otto Warburg on the occasion of his 80th birthday*

*In oxidative phosphorylation, the energy from the combustion of substrate hydrogen can be reversibly transformed into phosphate-bond energy. This is the reason that oxidation-reduction reactions in the respiratory chain can take place against the redox potential gradient if energy is supplied. The latter can come from ATP or directly from energy-rich intermediates arising in the course of oxidative phosphorylation. – At the center of the present considerations is the postulate that there is an equilibrium prevailing in the respiratory chain that results from the reversibility of the reactions. At the same time this postulate provides a unifying approach to various phenomena related to the process of oxidative phosphorylation. Such an equilibrium may involve several components of the respiratory chain. Respiration thus corresponds to a dynamic equilibrium in the respiratory chain which deviates increasingly from the static equilibrium the greater the rate of respiration. Consequently, respiration can be considered as being regulated by the phosphorylation potential. – The stationary redox state of the components of the respiratory chain can be viewed as a simultaneous function of the phosphorylation potential and of the redox potential that effects both ends of the respiratory chain. The latter reacts to either extreme, i.e. to minimum or maximum differences in the redox potential, by forming characteristic patterns of the state of reduction of its components. Differences in redox potential amounting to as much as 280 mV can be overcome by the phosphorylation potential for a single phosphorylative step. – The conditions for an equilibrium in the respiratory chain are also fulfilled from a kinetic viewpoint as the rates of the reverse reactions involving either electron or proton transfer are of the same order of magnitude as those of the forward reactions.*

## 1. Introduction

The combination of hydrogen from an appropriate substrate with oxygen via the respiratory chain – reactions studied many years ago by *Otto Warburg* – is the reaction sequence in animal metabolism with the highest energy gradient. It is not surprising therefore that it has generally been considered to be irreversible. This view presumably rested on the analogy of the overall process of cellular "combustion" to that of the combustion of hydrogen with oxygen. Because the energy of oxidation in the respiratory chain is transformed into the energy of the phosphoric anhydride

[*] Based on lectures given in April, 1962 at the Enzyme Research Institute, University of Wisconsin, Madison, and the Johnson Foundation, University of Pennsylvania, Pa. (U.S.A.).

bond of adenosine triphosphate (ATP) [*], it must be possible in principle to reverse the substrate-combustion reaction, provided the energy supply is also reversed. Such an eventuality presupposes a firm coupling between the oxidation-reduction reactions and those involving the transfer of energy to ATP. On the basis of this prerequisit it has in fact proved possible to demonstrate the reversibility of the major portion of the respiratory chain.

The reversibility of oxidative phosphorylation should not be considered simply as an extreme reversal of physiological events, possible only *in vitro*. Rather, it makes possible a static equilibrium within the respiratory chain with important consequences for energy transfer *in vivo*. The most important application is probably the regulation of respiration. Here the static equilibrium represents the limiting situation from which the actual dynamic equilibrium deviates increasingly as the rate of respiration increases. In this review, we shall lay particular emphasis on the aspect of the energy-dependent redox equilibrium in the respiratory chain as we interpret the various phenomena of reversibility.

## 2. Survey

In principle, the reverse reaction of oxidative phosphorylation consists of an ATP-dependent oxidation-reduction reaction between two components $C_1$ and $C_2$ of the respiratory chain:

$$C_{2\,red} + C_{1\,ox} + ATP \rightleftharpoons C_{2\,ox} + C_{1\,red} + ADP + P \qquad (1)$$

Here it is assumed that the ATP-consuming reaction corresponds inversely to the pathway of ATP synthesis during the course of oxidative phosphorylation. Reaction (1) can be written in two steps, one involving energy transfer, *i.e.*

$$X + ATP \rightleftharpoons {\sim}X + ADP + P \qquad (2)$$

and the oxidation-reduction reaction that is coupled to the energy transfer:

$$C_{2\,red} + {\sim}X + C_{1\,ox} \rightleftharpoons C_{2\,ox} + C_{1\,red} + X \qquad (3)$$

In the above notation, $\sim$X designates the chemical bond energy which may occur in an as yet unknown form lying between the redox energy and that of phosphate bonds. It may be localized either in the components of the respiratory chain or in another unknown compound. This intermediate form of energy does not contain phosphate; its existence is a necessary postulate as a result of investigations on the reversibility of oxidative phosphorylation.

The reversibility of the phosphorylation reaction (2) has long been known from the exchange between $^{32}PO_4^{3-}$ and ATP, that is catalysed by mitochondria, and the exchange among $H_2{}^{18}O$, ATP, and $PO_4^{3-}$ [1–5]. Doubts have been repeatedly expressed concerning the significance of this reaction for oxidative phosphorylation, in spite of strong arguments in its favor. It appears that this reaction is involved in only one of the three phosphorylation steps of the respiratory chain, *i.e.* in the step concerned with flavin. The reversibility of Reaction (3) was also discovered before the reversibility of Reaction (1) was known: mitochondrial DPN is reduced in respiring mitochondria by substrates which are dehydrogenated primarily by flavoproteins [6–9].

However, today a large amount of experimental evidence is available to demonstrate the reversibility of oxidative phosphorylation. The intimate coupling required between the oxidation and the energy transfer is accomplished in physiologically intact preparations of the respiratory chain, *viz.* in mitochondria, which consequently have become the favorite preparation for these investigations. The short list that follows includes only completely reversible reaction sequences, *i.e.* those that were achieved with ATP. Figure 1 shows a diagram that illustrates the interrelationships.

1. Control of respiration by ATP [10, 11].

2. Influence of ATP on the pattern of stationary oxidation-reduction reactions in the respiratory chain and reversal of the transfer of electrons and protons by ATP:

a) in respiring mitrochondria [10–12].

b) in mitochondria with inhibited respiration [13–16].

[*] The following abbreviations will be used:
ADP = adenosine diphosphate
ATP = adenosine triphosphate
Cyt = cytochrome
DPN = diphosphopyridine nucleotide
DPNH = reduced DPN
EDTA = ethylenediaminetetraacetic acid
KG = ketoglutarate
OxAc = oxaloacetate
P = phosphate
TPN = triphosphopyridine nucleotide
TPNH = reduced TPN
UbiQ = ubiquinone


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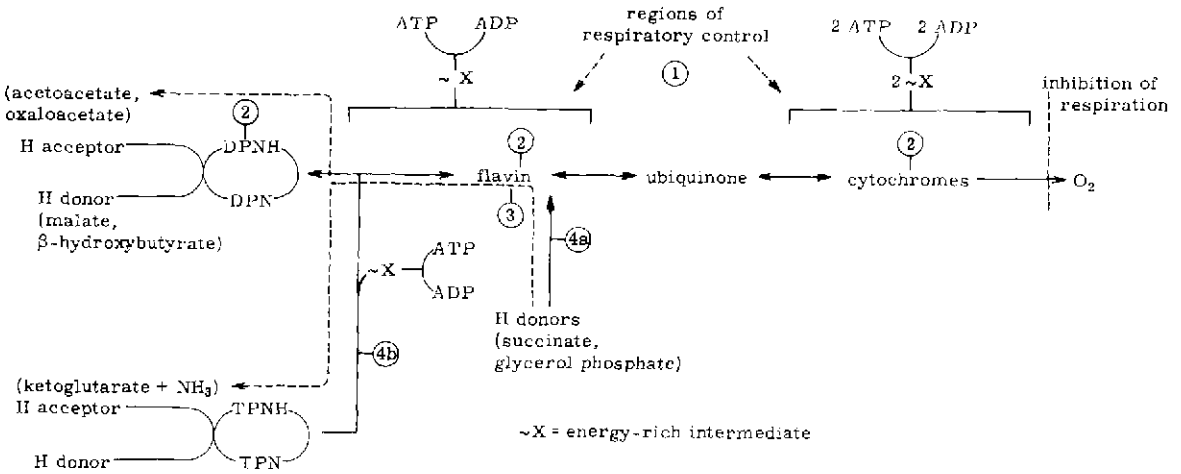



Fig. 1. Scheme of reactions showing various phenomena associated with the reversibility of oxidative phosphorylation. The numbers in circles refer to the list in the text.

3. ATP-induced transfer of hydrogen between exogenous hydrogen donors and acceptors [11, 17–26].

4. ATP-dependent redox reactions occurring outside the respiratory chain:

a) stimulation of succinate oxidation [27–29].

b) hydrogen transfer between the DPN and TPN system in mitochondria [30, 31].

c) energy-dependent hydrogen transfer between substrates which are dehydrogenated primarily by pyridine nucleotides [21, 32, 33].

The reversal of electron or hydrogen transport processes within the respiratory chain was first observed in respiring mitochondria to which no ATP had been added. Here the chemical bond energy produced in the course of respiration is apparently in an intermediate form, *i.e.* it does not first form ATP, and is used up in the reverse reaction of hydrogen transfer. The effectiveness of this intermediate form of energy becomes particularly clear when respiring mitochondria are allowed to pump fairly large quantities of hydrogen from one substrate to the other against a redox potential [19, 20]. An example of such a situation is the transfer of hydrogen from succinate (standard potential $E'_0$ = + 50 mV at pH 7) to acetoacetate (standard potential $E'_0$ = −260 mV at pH 7).

### 3. Energy-Dependent Oxidation-Reduction Equilibrium

To understand these phenomena the occurrence of an energy-dependent redox equilibrium in the respiratory chain has been postulated [16, 34, 35]. The components of the respiratory chain may be involved in an oxidation-reduction equilibrium provided that the redox potential of one of the components has been shifted so far, *e.g.* towards negative values, owing to the formation of an energy-rich intermediate, that it equals the potential of its neighbor (Fig. 2). This intermediate would then be involved in a phosphorylation equilibrium with the ATP/ADP system. These alternating redox and phosphorylation equilibria constitute a system of equilibria throughout the entire respiratory chain. This aspect proved to be particularly fruitful for analysis of the effects of ATP in the case of total reversal of oxidative phosphorylation. It permits both a qualitative and a quantitative interpretation of these effects [36].

At equilibrium, the redox state of the respiratory-chain components involved in oxidative phosphorylation is a function of the phosphorylation potential of ATP, *i.e.* of the quotient (ATP)/(ADP)·(P). Moreover, the reversibility of oxidative phosphorylation should always be a function of this ratio. The assumption of an energy-dependent redox equilibrium also has kinetic implications.

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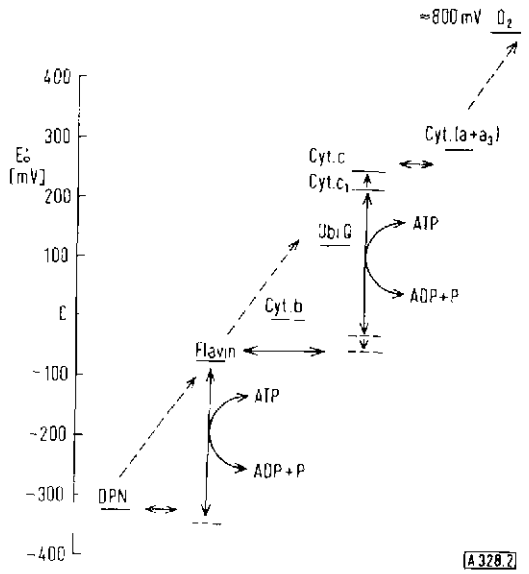



Fig. 2. The equilibrium in the respiratory chain. The components of the chain have been arranged in the order of their standard potentials at pH 7. Their redox potentials are shifted in a negative direction by virtue of the formation of an energy-rich intermediate in the phosphorylation equilibrium involving ATP. The shift of 280 mV indicated was observed under anaerobic conditions [36]. Solid arrows indicate equilibria, broken arrows states of nonequilibrium. The overall equilibrium in the respiratory chain results from the alternating sequence of redox(↔) and phosphorylation (↕) equilibria.

Ordinate: Standard potential $E'_0$ at pH 7 [mV].

For example, it implies that, close to equilibrium, the rate of the reverse reaction involving electron transport is of the same order of magnitude as the forward reaction, *i.e.* respiration. Thus, in the case of respiration coupled to oxidative phosphorylation, a dynamic equilibrium develops which must be considered to lie in general close to the static equilibrium. Consequently, it becomes possible to analyse dynamic equilibria in the respiratory chain with the relatively simple methods which have been developed for the analysis of relaxation spectra of chemical reactions [37] and which have also been applied to the analysis of reactions with isolated enzymes [38, 39].

## 4. Respiration

In physiologically intact preparations, the rates of respiration and phosphorylation are interdependent. The rate of respiration can be limited by the rate of phosphorylation. If the latter is inhibited by the lack of suitable substrates (ADP or phosphate) respiration is also inhibited. Both *Lardy* [40] and *Chance* [41, 42] have designated the lack of ADP or of phosphate as the controlling factor in their analysis of the regulation of respiration which they have termed "respiratory control". In this connection an effect of ATP opposite to that of ADP or phosphate has not been reported. Therefore, an ADP-trigger mechanism for the regulation of respiration was postulated [43]. Since this hypothesis of the regulation of respiration is considered to involve inhibition and activation, it implies a kinetic control mechanism.

The mechanism of the control of respiration based on the phosphorylation equlibrium differs in principle from the preceding hypothesis. Here respiration is thought to be controlled by the concentration of phosphate and ADP on the one hand, and by ATP on the other. This constitutes a thermodynamic mechanism for respiration control.

The first piece of evidence for the existence of this thermodynamic mechanism came from observations on mitochondria from skeletal muscles, whose respiration was inhibited by the addition of ATP [10, 11]. In subsequent studies, it proved possible to demonstrate that the respiration of liver mitochondria was dependent on the ratio of the concentrations of ADP and ATP [44]. Figure 3 illustrates by means of a simultaneous recording of respiratory activity and pyridine nucleotide absorption that the addition of ATP can partially inhibit respiration that has been fully stimulated by prior addition of ADP. At the same time, the pyridine nucleotides

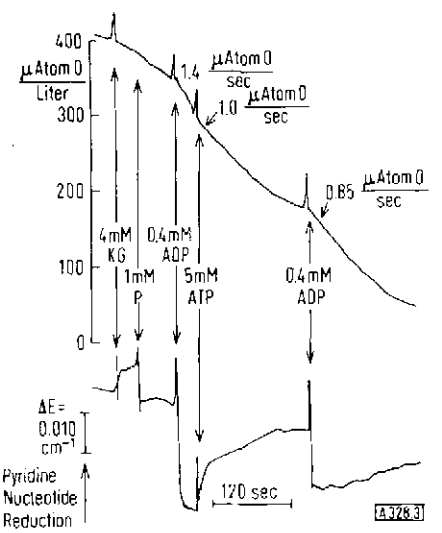



Fig. 3. The opposing influence of ADP and ATP on the respiratory activity and the redox state of the pyridine nucleotides in mitochondria. Simultaneous recording of respiration and absorption of pyridine nucleotides in a suspension of liver mitochondria: 2 mg of protein in 0.5 ml of sucrose-EDTA medium at pH 7 and 25 °C.

The respiration with α-ketoglutarate (KG) as substrate was speeded up by the addition of ADP and slowed down by the addition of ATP before all of the ADP had been used up. The pyridine nucleotides were oxidized by the addition of ADP and reduced even more strongly after the addition of ATP. After the first addition of ADP had been used up, new DAP was added, but the respiration was then stimulated less and the pyridine nucleotides were oxidized less than they were before the addition of ATP.

Spectrophotometrically the difference between absorption at 340 mμ (the maximum of the DPNH band) and at 405 mμ (reference wavelength) was measured.

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change to a more reduced state. This reduction of the pyridine nucleotides, which occurs parallel with the inhibition of respiration, shows that ATP, by reversing oxidative phosphorylation, exerts an effect that opposes that of ADP. In this ATP-induced state of the respiratory chain, the pyridine nucleotides attain a situation similar to that which occurs during ADP deficiency (the "controlled state"), for they are more reduced than they are when there is a sufficient supply of ADP (the "active state") [*].

It can thus be seen that the activity of respiration depends on the ratio (ATP)/(ADP) (cf. Fig. 4). In the absence of ATP, respiration is approximately at half of its maximum if approximately 0.05 mM ADP is present. This is in agreement with the data of *Chance* and *Williams* [42]. However, in the presence of ATP, appreciably higher concentrations of ADP are required for respiration to attain the half-maximum value, *e.g.* 0.1 mM ADP for 2.5 mM ATP, and 0.25 mM ADP for 5 mM ATP. If 5 mM ATP has been added, maximum respiration requires 1 mM ADP instead of the 0.1 mM ADP needed in the absence of ATP. The correlation between respiratory activity and the ratio (ATP)/(ADP) is in accord with the suggestion that respiration is controlled by an equilibrium between the ATP/ADP system and the respiratory chain. Hence, control of respiration is a function of the reversibility of oxidative phosphorylation.

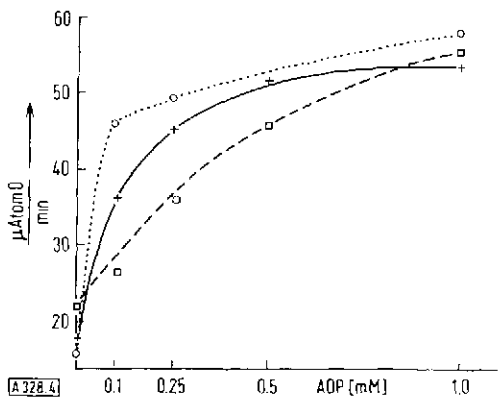



Fig. 4. Respiratory activity of mitochondria shown as a function of the phosphorylation potential, which was varied by changing the ratio (ATP)/(ADP). Liver mitochondria were incubated in sucrose-EDTA media at pH 7 and 25 °C.

o = no ATP; + = 2.5 mM ATP; □ = 5 mM ATP.

The above relationships observed in isolated mitochondria are of special significance for the physiological control of respiration, because ATP occurs in most cells *in vivo* in relatively large concentrations. The respiratory activity of a cell can therefore be supposed to show a dependence on the (ATP)/(ADP) ratio similar to that depicted in Figure 4. This implies that respiration would increase only relatively sluggishly with an increase in the concentration of ADP, and would be fully activated only at a relatively high ADP level. It can therefore be regulated over a fairly wide range by changes in the ADP level and is hence a subtle function of the differential utilization of ATP by the organism. In contrast, the "kinetic mechanism" would provide a more abrupt regulation of respiration because of its narrower range of regulation. The new theory demands reinterpretation of a variety of experiments which were previously interpreted along the lines of the kinetic theory of respiratory control; an example is the question of the amount of ADP liberated in a single contraction when a muscle performs work [45,46].

[*] The terms "controlled" and "active" state refer to the respiratory and oxidative phosphorylation activities of mitochondria and constitute extreme cases. The "controlled" state exists when phosphorylation and the respiration coupled to it are inhibited owing to lack of substrates of the oxidative phosphorylation, *e.g.* inorganic phosphate or ADP, but not of oxidizable substrates. In the "active" state both oxidative phosphorylation and, hence, respiration are fully activated, as phosphate and ADP are in sufficient supply.

## 5. The Redox Patterns of the Respiratory Chain

The first indications of the reversibility of oxidative phosphorylation were provided by changes in the redox state of respiratory-chain components. These observations implied a reversal of the direction of flow of protons and electrons. After the observation in isolated instances of the reduction of pyridine nucleotides in mitochondria [6,9], the general significance of this phenomenon for mitochondria of varying origin was recognized [7]. In addition, the reduction of the iron-flavoprotein complex in the respiratory chain was shown to be energy-dependent [35]. Until then, reversibility had been demonstrated only for the phosphorylation step in the DPN-flavin region of the respiratory chain. By changing the experimental conditions, it then also proved possible to demonstrate the reversibility of the electron transport in the cytochrome region [13–16].

For better comprehension, it may be best at first to neglect the reverse transport of hydrogen and electrons and instead to concentrate on the static picture of the redox pattern, on the basis of which the redox state of the components can be compared in a variety of functional states of the repiration chain. The concept of an energy-dependent equilibrium appears to be particularly fruitful in this connection.

Frequently the redox patterns can be arranged according to a surprisingly simple scheme. The influence of the respiratory control on the redox pattern – which we had demonstrated previously on mitochondria from insect flight muscle [46a] – may be shown here again on another example (liver mitochondria) in Fig. 5a. In the presence of phosphate (controlled state) and of succinate as substrate, the percentage degree of reduction of the components of the respiratory chain decreases progressively from the substrate side, *i.e.* from DPN, towards cytochrome a. However, in the presence of ADP, the degree of reduction is more balanced. This behavior was already observed in principle by *Chance* and *Williams*

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[46a] See Figures 18 and 19 in [6].

[47] in their fundamental studies of the redox states of the respiratory chain. In the presence of ATP, the drop in the degree of reduction is preserved even upon addition of ADP (Fig. 5b). The relatively small shifts ob-

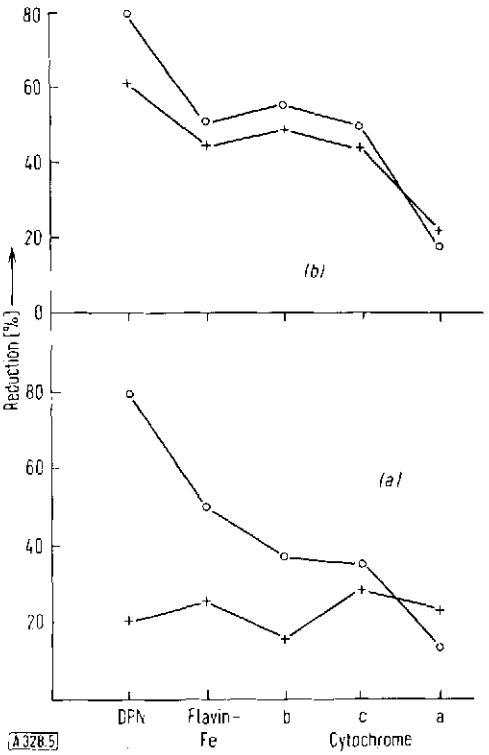



Fig. 5. Redox patterns of the respiratory chain of respiring mitochondria. Stationary redox states before (o—o) and after (+ +) addition of 0.25 mM ADP. Liver mitochondria were incubated in air-saturated sucrose-EDTA media at pH 7.2 and 25 °C; 4 mM succinate; 1 mM $PO_4^{3-}$.

a) Mitochondria without ATP b) Mitochondria with 5 mM ATP.

served upon addition of ADP reflect the partial transition of the controlled to the active state. As shown above, in this case, respiration is also only partially activated (cf. Fig. 2). The redox patterns of the respiratory chain are therefore subject to the opposing in-

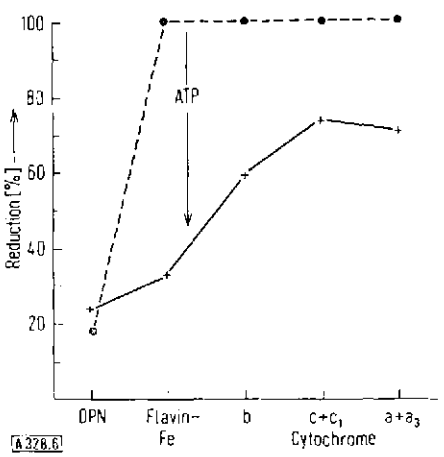



Fig. 6. Redox patterns of the respiratory chain of mitochondria with inhibited respiration. State of the respiratory-chain components before and after addition of 1 mM ATP. 1 mM KCN served as respiration inhibitor and 1 mM oxaloacetate as hydrogen acceptor on the DPN side.

[47] *B. Chance* and *G. R. Williams*, J. biol. Chemistry *217*, 409 (1955).

fluences of ADP and ATP between the extremes of the "active" and "controlled" states.

If respiration and hence the electron flux in the respiratory chain are prevented either by elimination of oxygen or by inhibition with cyanide, the resulting redox patterns are of a different type (Fig. 6). In the absence of ATP, the components of the respiratory chain are then either totally or largely reduced and become partially reoxidized only on addition of ATP. This occurs because the reduction equivalents of the cytochromes and flavoproteins are shifted towards the substrate side by reversal of the electron flux. There they can be taken up by mitochondrial DPN and by DPNH-oxidizing substrates. These experiments thus demonstrate the reversal of electron transport in the cytochrome region, including cytochrome a [13–16].

Under these conditions, the stationary redox patterns may exhibit a rise in the degree of reduction from the substrate side in the direction towards the oxygen. This rise is particularly noticeable in the presence of small concentrations of ATP and of substrates that oxidize DPNH (cf. Fig. 6). The rise can be explained by an energy-dependent redox equilibrium in the following manner. On the substrate side, the redox potentials are relatively positive in the presence of an excess of hydrogen acceptor, whereas they are relatively negative on the side of cytochrome oxidase without oxygen. In the case of the effect of ATP on respiring mitochondria, as shown in Figure 4, the supply of the respiratory chain is exactly the reverse: there is an excess of reducing substrate and of oxygen, with the result that the difference between the redox potential at the two ends of the chain is relatively small [30]. Hence, the state of reduction of the respiratory-chain components can be under the control of the terminal redox potentials as the equilibrium embraces the entire respiratory chain.

## 6. Kinetics

Any shift in the respiratory chain from nonequilibrium to equilibrium can lead to a net forward or backward flux of reduction equivalents. It is to be assumed that the rate of the reverse reaction near the equilibrium equals that of the forward reaction. Two methods are available to measure the forward and reverse reactions of electron transport, *viz.* either measurement of the changes in the redox state of the respiratory-chain components themselves, or measurement of the entire electron transport in the reaction substrate → oxygen (respiration) and in the reaction substrate → substrate, where turnover is higher by several orders of magnitude, because here the components of the respiratory chain act as catalysts for the overall reaction.

The rate of the reverse reaction in electron transport can be determined for the ATP-dependent oxidation of cytochromes in mitochondria with inhibited respiration [44]. In order to do this it is necessary to ensure that the rate is in fact limited by electron transport and not, for example, by limited permeability of ATP into the mitochondria. As shown in Figure 7a, the oxidation of

cytochrome c initiated by ATP proceeds relatively slowly. The reverse reaction assumes a much higher rate if ATP in the presence of excess Mg, *i.e.* in the form of an ATP-Mg complex, is first allowed to act on the mitochondria for a few seconds (Fig. 7b). ATP-Mg has a lower phosphorylation potential than free ATP. On

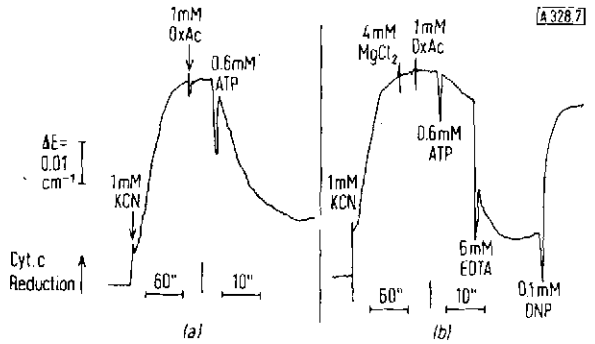



Fig. 7. Kinetics of the reversed electron transport: ATP-induced oxidation of cytochrome c in mitochondria with inhibited respiration. A double-beam spectrophotometer was used to record the absorption of a suspension of liver mitochondria (2 mg of protein in sucrose-EDTA medium at 9.5 °C). Following the addition of KCN, cytochrome c was first reduced by endogenous proton donors of the mitochondria.

(a) On addition of ATP, the cytochrome c became oxidized, oxaloacetate having been added as hydrogen acceptor for the hydrogen from DPNH. The rate of oxidation was relatively small.

(b) After prior addition of $Mg^{2+}$, the rate of oxidation of cytochrome c was still smaller than in case (a). When EDTA was added 10 sec after the addition of ATP, cytochrome c was oxidized quite rapidly. Subsequent addition of an agent such as dinitrophenol (DNP) that uncouples oxidative phosphorylation induces a rapid reduction. The spectrophotometric measurements were made of the difference in absorption at 550 mμ, the maximum of the α-band of cytochrome c, and at 540 mμ, the reference wavelength.

addition of EDTA, cytochrome c undergoes oxidation more rapidly than can be measured with the apparatus used. It can be assumed that ATP can diffuse into the mitochondria in the form of a relatively inactive ATP-Mg complex and then be released at the site of reaction by the action of EDTA. This may be the reason that the rates, which may conceivably be the true rates of the reverse reaction of electron transport, are much higher than those observed at the start of ATP addition.

It is also possible to measure the rate of the reverse reaction with the aid of the energy-dependent hydrogen transport between two substrates; this transport is catalysed by mitochondria and hence by enzymes of the respiratory chain. In practice, succinate is used as the reducing and either acetoacetate or ketoglutarate + $NH_3$ as the oxidizing substrate [11, 17–21]. The reverse reaction then occurs only in the DPN-flavin region of the respiratory chain. The kinetics of this reaction can be followed by determining the substrate disappearing and the substrate being formed. These "overall" experiments involve minutes rather than the seconds required for the study of cytochrome oxidation.

Table 1 gives a comparison of both methods based upon the cytochrome-c-content as a common reference point for the concentration of the respiratory chain components. The rates of the ATP-induced cytochrome-c-oxidation can only be estimated approximately from the recordings. The values should be multiplied by a factor of 5 if they are to be compared with the data of the substrate reaction, in order to compensate for the temperature difference of 18 °C between the two experiments. This shows that the rate of electron transport in the reaction cytochrome → substrate, given here as cytochrome-turnover rate (approx. 100 $min^{-1}$), is approximately equal to the rate of hydrogen transport in the reaction succinate → acetoacetate; consequently it is also approximately equal to the reverse reaction in the DPN-flavin region. The value is also equal to the rate of the forward reaction which can be determined from the activity of respiration: the cytochrome-c-turnover rate for oxidation of hydroxybutyrate is 110 $min^{-1}$, and that of succinate is 440 $min^{-1}$.

Table 1. Rates of the reverse reaction in the electron transport of the respiratory chain. Liver mitochondria in sucrose-EDTA medium.

| Conditions | Temp. [°C] | Rate expressed as cytochrome-c-turnover rate [$min^{-1}$] |
|---|---|---|
| Cytochrome c | | |
| ↓ | | |
| Oxaloacetate | | |
| Inhibited with KCN | 9,5 | |
| + ATP | | 4 |
| + ATP + $Mg^{2+}$ | | 0,8 |
| + ATP + $Mg^{2+}$ + EDTA | | 20 |
| Succinate | | |
| ↓ | | |
| Acetoacetate | | |
| aerobic | 28 | 110 |
| anaerobic ($N_2$) | | 70 |

The preceding considerations show that the kinetic requirements for the existence of an energy-dependent redox equilibrium in the repiratory chain have been met. On the basis of experiments with ATP-induced oxidation of cytochrome c, *Chance* and *Hagihara* [48] reported a ratio of 25:1 for the rates of the forward and reverse reactions. They had previously interpreted the reverse reaction as excluding an energy-dependent redox equilibrium in the respiratory chain [49]. In the light of the experiments described above, the low rate of the reverse reaction reported by *Chance* and *Hagihara* can probably be attributed to inhibition of the diffusion of the ATP to the respiratory chain.

## 7. Thermodynamic Considerations

Thermodynamic considerations provide the framework for an energy-dependent oxidation-reduction equilibrium: The free energy of the ATP-ADP system must be equivalent to the free energy resulting from the difference in redox potentials of components $C_2$ and $C_1$ [Equation (1)]. Quantitative studies of mitochondria with inhibited respiration did in fact result in the ex-

[48] *B. Chance* and *B. Hagihara:* Proceedings of the Fifth International Congress of Biochemistry, Moscow 1961. Pergamon Press, Oxford 1963, Vol. 5, p. 3.

[49] *B. Chance*, J. biol. Chemistry *236*, 1577 (1961).

pected relationship between the redox ratio of cytochrome c ($c_{red}/c_{ox}$) and the phosphorylation potential, (ATP)/(ADP) · (P) [36]. For a ratio of $c_{red}/c_{ox} = 1$, a "normal" phosphorylation potential of $\Delta F = -12.8$ kcal/mole was found. This corresponds to a difference in redox potential of $\Delta E = 260$ mV. Consequently, it appears possible to overcome the potential difference between cytochrome c and DPN ($\Delta E = 520$ mV) by means of two successive phosphorylation steps.

Respiring mitochondria apparently require a higher phosphorylation potential for equilibrium to occur. On the basis of the relationship between respiratory activity and the ratio (ATP)/(ADP) (see Fig. 3), it can be estimated that the normal phosphorylation potential (ATP)/(ADP)·(P) is 15 l/mmole at half-maximum respiration. This would correspond to $\Delta F = -14.5$ kcal/mole and to a redox potential of $\Delta E = 320$ mV.

The differences in phosphorylation potential observed under aerobic and anaerobic conditions can be explained by differences in the terminal redox potentials in the respiratory chain. Thus, in respiring mitochondria, the redox potentials of the two ends of the respiratory chain appear to differ fairly widely, as discussed above. Hence a higher phosphorylation potential is also required in order to overcome this relatively large potential difference. In mitochondria with inhibited respiration on the other hand, the redox potentials approach one another in value, owing to the exclusion of oxygen and the excess of oxidizing substrates, with the result that the entire respiratory chain can be bridged with a smaller potential.

### 8. Conclusions

In principle, the efficiency of oxidative phosphorylation can approach 100 % on the basis of reversibility. From the present state of our knowledge, this applies only to the potential difference between the substrate and cytochrome c; this difference amounts to between 520 and 600 mV and can thus theoretically be overcome by two successive phosphorylation steps. The reversibility of the third step of phosphorylation, which is presumed to involve the activation of oxygen by cytochrome oxidase, has not yet been demonstrated. It is conceivable that this step is not reversible even with an extremely large phosphorylation potential, as there are particularly large redox-potential differences to be overcome ($\Delta E \approx 420$–$520$ mV). If this is true, then the effects of the reversibility of oxidative phosphorylation, *e.g.* the regulation of respiration, involve only the first two phosphorylation steps.

This reversibility has significance not only for cellular function and the energy yield of oxidative phosphorylation. Its study also provides a new approach for the exploration of the mechanism of energy transfer and the associated oxidation-reduction reactions in the respiratory chain. The as yet unidentified energy intermediate which is bound to be involved in the transformation of redox energy into phosphate-bond energy can be generated from ATP rather than from electron transport. Moreover, a study of the reversibility will lead to knowledge of the conditions under which this intermediate is likely to accumulate. Hence, such a study can also serve as a means – which has already found frequent application – for elucidating the mechanism of oxidative phosphorylation.

The reversibility of these reactions may also have significance for a phenomenon that has not been discussed here in detail, *viz.* "active" transport; the latter may well be driven with the aid of "redox pumps" which in turn generate a cyclic, ATP-dependent electron transport, as a result of which charge displacement effecting "active" transport may occur [50]. The reversibility of oxygen uptake may also be of significance in photosynthetic oxygen formation [51].

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German version: Angew. Chem. *75*, 900 (1963)

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## COMMUNICATIONS

### Preparation of Pure Disulfur Monoxide

By Prof. Dr. P. W. Schenk and Dipl.-Chem. R. Steudel

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Disulfur monoxide is formed by disproportionation of sulfur monoxide, which is stable only at high temperatures.

$$3\,SO = S_2O + SO_2$$

The mixture has hitherto not been separated. Up to 85 % $S_2O$ is also obtained [1] when SO is prepared by a glow discharge and allowed to react with sulfur vapor.

$$2\,SO + S_2 = 2\,S_2O$$

By modification of a procedure for the preparation of sulfur monoxide by the reaction of thionyl chloride vapor and dehalogenating reagents, *e.g.* Ag or Sn [2],

$$SOCl_2 + 2\,M = 2\,MCl + SO$$

we have prepared disulfur monoxide directly by using metal sulfides, *e.g.* CuS, PbS, $Sb_2S_3$, CdS, or $Ag_2S$, in place of the metals. For $Ag_2S$, the reaction with thionyl chloride

$$SOCl_2 + Ag_2S = S_2O + 2\,AgCl$$

proceeds quantitatively at 160 °C and 0.5 mm Hg, $S_2O$ resulting in over 96 % purity, accompanied by some $SO_2$. The purity depends largely on the experimental conditions. Elevated temperatures promote $Ag_2S$-catalysed decomposition [3] of the $S_2O$ into sulfur and sulfur dioxide.

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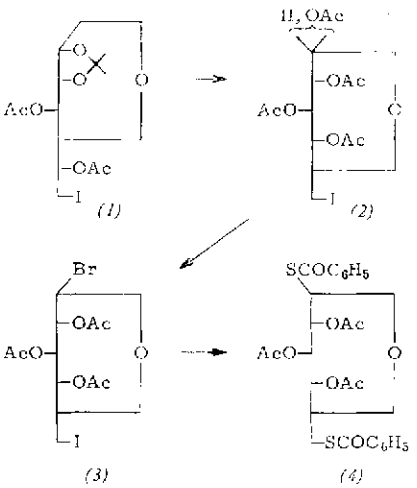
[1] *P. W. Schenk* and *W. Holst*, Z. anorg. allg. Chem. *319*, 337 (1963).
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## Preparation of 1,6-Dithio-D-glucose

By Dr. J. Kocourek, Dipl.-Chem. Marie Tichá, and Dr. V. Jiráček

Biochemistry Department, Faculty of Science, University of Prague (Czechoslovakia)

We have found that the sequence of reactions given in Scheme 1 is especially favorable for the preparation of 1,6-dithio-D-glucose [1].



(1) (2) (3) (4)

1,2-Isopropylidene-3,5-di-*O*-acetyl-6-deoxy-6-iodo-α-D-glucofuranose *(1)* [2] was subjected to acidic hydrolysis in acetone plus aqueous $H_2SO_4$ and subsequent acetylation with sodium acetate and acetic anhydride to give a mixture of the α- and β-anomers of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-D-glucopyranose *(2)* [3] in 56 % yield. Acetobromination of the latter yielded 84 % of compound *(3)* [4]. This derivative, which can also be obtained in lower yields by direct acetobromination of the hydrolysate obtained from *(1)* after removal of the water, is readily converted with potassium thiobenzoate [5] in dimethylformamide at room temperature into *(4)*, m.p. 130–131 °C, $[\alpha]_D^{20} = -9.0°$ (c = 4 in $CHCl_3$), in 65 % yield. Compound *(4)* can easily be converted into the free sugar (61 %) by the usual methods.

Received, October 17th, 1963 [Z 616/444 IE]
German version: Angew. Chem. 76, 50 (1964)

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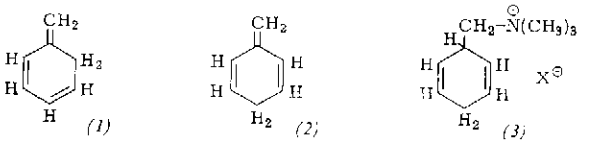
## 1-Methylene-2,5-cyclohexadiene

By Prof. Dr. H. Plieninger and Dipl.-Chem. W. Maier-Borst

Organisch-Chemisches Institut der Universität Heidelberg (Germany)

The existence of the two toluene isomers *(1)* and *(2)* has long seemed to be unlikely [1]. Recently, however, 5-methylene-1,3-cyclohexadiene *(1)* was identified by *Bailey* and *Baylouny* [2] as a chemical entity which is quite stable at low temperature in dilute solution.

We have now managed to prepare 1-methylene-2,5-cyclohexadiene *(2)* from 1,4-dihydrobenzoic acid by conversion via the acid chloride to the dimethylamide, reduction of the latter to *N*-dimethyl-1,4-dihydrobenzylamine, and methylation of the amine to give the quaternary salt *(3)*; the latter is heated with powdered KOH and the resultant vapors are passed into cooled ether.



(1) (2) (3)

An ether solution is obtained which has an ultraviolet absorption maximum at 242 mμ with a shoulder at 247 mμ, log ε = 4.4 (concentration determined by rearrangement to toluene); toluene is also produced. Traces of mineral acid destroy the absorption at 242 mμ and increase the yield of toluene. Sufficient *(2)* was obtained by preparative gas chromatography to enable its NMR spectrum to be determined. The required proton ratio of 4:2:2 is observed. The four vinyl protons attached to the ring give signals between 3.7 and 4.5 τ; the *exo*-methylene-group protons resonate at 5.35 τ and the protons on the saturated carbon atom at 7.06 τ. Confusion with *(1)* is not possible as the latter exhibits an absorption maximum at 303 mμ.

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German version: Angew. Chem. 75, 1177 (1963)

[1] *E. C. Horning,* Chem. Reviews *33,* 89 (1943).

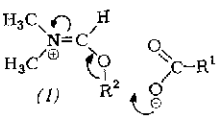
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## N,N-Dimethylformamide Dineopentylacetal: a Reagent for Esterifying Carboxylic Acids with Benzyl Alcohols

By H. Büchi, Katharina Steen, and Prof. Dr. A. Eschenmoser

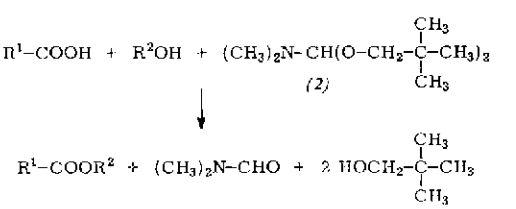
Organisch-chemisches Laboratorium der Eidgenössischen Technischen Hochschule Zürich (Switzerland)

The results of stereochemical [1] and kinetic [2] investigations support the view that the rate-determining step of the esterification [1,3] of carboxylic acids with *Meerwein*'s acetals of dimethylformamide [4] is the alkylation of the carboxylate anion with an alkoxyimmonium ion of type *(1)* [5]; both of these ions and the alcohol $R^2OH$ are in eqilibrium with the reagents.



(1)

This reaction scheme predicts that, because of the low reactivity of the immonium ion *(1)*, $R^2$ = neopentyl] in the $S_N2$ alkylation step, dimethylformamide dineopentylacetal *(2)* will mediate esterification according to Scheme 1 of carboxylic acids with alcohols the alkoxyimmonium ions *(1)* of which are highly reactive. We have tested this hypothesis with a number of amino-acid derivatives using *p*-dodecylbenzyl alcohol *(3)* and *p*-methoxybenzyl alcohol *(4)*; the results are given in Table 1.



Scheme 1

Table 1. Esterification of carboxylic acids with 1.1 equivalents of *(3)* or *(4)* using 1.3 equivalents of *(2)* at room temperature.

| $R^1$ COOH [mole/l] | $R^2OH$ | Solvent | Time [h] | $R^1$-COOR$^2$ M.p. [°C] | $[\alpha]_D$ [°] | Yield [a] [%] |
|---|---|---|---|---|---|---|
| *N*-DoBC-Phe [b] [0.16] | *(3)* | $CH_2Cl_2$ | 46 | 91 | + 4.2 ($CHCl_3$) | 90 |
| *N*-DoBC-Ala [0.15] | *(3)* | $CH_2Cl_2$ | 43 | 70 | − 1 ($CHCl_3$) | 83 |
| *N*-DoBC-Gly [0.15] | *(3)* | $CH_2Cl_2$ | 47 | 76 | | 86 |
| *N*-DoBC-Gly-Gly [0.15] | *(3)* | $CH_2Cl_2$ | 144 | 118 | | 72 |
| *N*-DoBC-Gly-Gly-Gly [0.10] | *(3)* | Benzene | [c] | 160 | | 75 |
| *N*-DoBC-Phe-Ala [0.22] | *(3)* | $CH_2Cl_2$ | 53 | 108 | + 3.0 ($CHCl_3$) | 78 |
| *N*-DoBC-Phe [0.12] | *(4)* | $CH_2Cl_2$ | 41 | 61 | − 7.6 ($C_2H_5OH$) | 80 |
| *N*-DoBC-Val [0.24] | *(4)* | $CH_2Cl_2$ | 47 | 42 | − 14.3 ($C_2H_5OH$) | 73 |
| *N*-DoBC-Gly [0.24] | *(4)* | $CH_2Cl_2$ | 47 | 69 | | 75 |
| *N*-Cbo-Gly [b] [0.26] | *(4)* | $CHCl_3$ | 47 | 61 | | 74 |
| $C_6H_5COOH$ [0.19] | — | $CH_2Cl_2$ | 46 | | | 96 [d] |

[a] Recrystallized, thin-layer-chromatographically homogeneous material.

[b] DoBC = $CH_3-(CH_2)_9-O-C_6H_4-CH_2-O-CO-$; Cbo = $C_6H_5-CH_2-O-CO-$.

[c] Because of low solubility, reacted for 48 h at 80 °C and subsequently for 72 h at room temperature.

[d] Unchanged benzoic acid.

The advantages of this procedure over the use of the dimethylformamide acetals derived from *(3)* and *(4)* are that only one equivalent of the alcohol is required and that, in the optimum case, only volatile by-products are formed.

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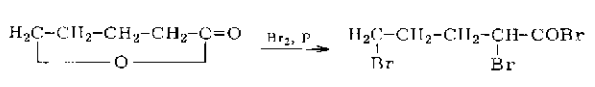
## α,δ-Dibromovaleryl Bromide and Methyl α,δ-Dibromovalerate

By Prof. Dr. N. Isenberg, I. Barkocy, and S. R. Parker [*]

Chemistry Department, Skidmore College, Saratoga Springs, N.Y. (U.S.A.)

Acyl halides are useful intermediates in the synthesis of peptides. We wish to report a convenient synthesis of α,δ-dibromovaleryl bromide *(2)* which gives reasonably good yields; *(2)* has not been described in the literature before.

1,5-Pentanediol was converted into δ-valerolactone *(1)* with copper chromite in 61 % yield [1]. The lactone (22.6 g) was mixed with 2.64 g of red phosphorus, and 43.51 g of bromine were added with cooling and stirring at 20–30 °C [2]. The mixture was heated to 70 °C, and additional 43.5 g of bromine were added. The mixture was allowed to stand for 3 hours at 70 °C and was then distilled to yield 62.8 g (86 %) of α,δ-dibromovaleryl bromide *(2)*, b.p. 106°/1.6 mm, $n_D^{25} = 1.5604$. The position of the carbonyl absorption peak in the infrared spectrum was 1770 cm$^{-1}$.



*(1)* *(2)*

Methyl alcohol (0.5 ml) was added dropwise with stirring to 4.0 g of *(2)* to yield 2.5 g (73 %) of methyl α,δ-dibromovalerate, b.p. 93–95 °C/1.5 mm, $n_D^{25} = 1.5099$. The position of its carbonyl absorption peak in the infrared spectrum was 1725 cm$^{-1}$.

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German version: Angew. Chem. *75*, 1205 (1963)

[*] We are indebted to the National Science Foundation for financial support under grant NSF-G12705 (Undergraduate Science Education Program).

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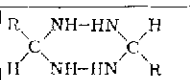
## Dimeric Aldehyde Hydrazones

By Doz. Dr. Th. Kauffmann, cand. chem. G. Ruckelshauss, and Jutta Schulz

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der Technischen Hochschule Darmstadt (Germany)

The apparently unknown oily hydrazones (Table 1) of acetaldehyde, propionaldehyde, butyraldehyde, valeraldehyde, and capronaldehyde, which are produced by cleavage of the corresponding styrene derivatives with sodium hydrazide [1] or, more simply, by reaction of the aldehydes with hydrazine hydrate below 5 °C [2] and distillation of the reaction products extracted with ether, dimerize at room temperature to give the crystalline 3,6-dialkylhexahydro-*s*-tetrazines *(1)–(5)* [3].

Table 1. Monomeric and dimeric aldehyde hydrazones.

| R | $R-CH=N-NH_2$ B.p. [°C/mm] | Yield [%] |  M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| $H_3C$ | 100–102/755 | 68 | *(1)* 163–164 | 45 |
| $H_3C-CH_2$ | 108–110/755 | 60 | *(2)* 193–194 | 52 |
| $H_3C-(CH_2)_2$ | 149–151/750 | 51 | *(3)* 153–154 | 44 |
| $H_3C-(CH_2)_3$ | 65–66/20 | 50 | *(4)* 168–170 | 46 |
| $H_3C-(CH_2)_4$ | 83–85/15 | 46 | *(5)* 150–152 | 43 |
| $H_3C-(CH_2)_5$ | | | *(6)* 154–155 | 52 |
| $H_3C-(CH_2)_6$ | | | *(7)* 147–149 | 71 |
| $H_3C-(CH_2)_8$ | | | *(8)* 143–144 | 75 |

The dimers *(1)–(5)* and their higher homologues *(6)–(8)* [4] are formed directly by addition of the aldehyde to hydrazine hydrate below 5 °C; the solution is allowed to stand for several days in a refrigerator and the hydrated crystals which separate out are dried and recrystallized from absolute ethanol.

At 20 °C in 0.05 M aqueous solution, *(3)* is 77 % dissociated, as is indicated by cryoscopic molecular-weight determinations on a solution that was rapidly chilled after attainment of equilibrium; at 60 °C, *(3)* is almost completely dissociated. The dry solid also dissociates into the monomer when heated above its melting point. Like the other dimeric hydrazones described in Table 1, it is stable when kept in a sealed tube at 20 °C.

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German version: Angew. Chem. 75, 1204 (1963)

[1] Cf. *Th. Kauffmann* et al., Angew. Chem. *74*, 650 (1962); Angew. Chem. internat. Edit. *1*, 456 (1962).

[2] The following statement in *C. C. Clark:* Hydrazine, Mathieson Chemical Corporation, Baltimore 1953, p. 38, is misleading: "Most aldehydes condense very readily with hydrazine in the cold. The aldehydrazone first formed reacts with aldehydes with greater speed than does hydrazine itself so that the azine is the normal end-product".

[3] Hexahydro-*s*-tetrazines with substituents on the nitrogen atoms are known: cf. *E. Schmitz* and *R. Ohme*, Liebigs Ann. Chem. *635*, 82 (1960).

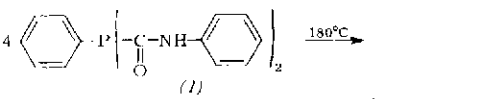
[4] The compounds alleged to be enanthaldehyde hydrazone described by *A. Darapsky*, J. prakt. Chem. [2] *97*, 214 (1918), and by *W. Seibert*, Chem. Ber. *80*, 499 (1947), melting at respectively 132 °C and 148–155 °C were probably incompletely dried samples of the base *(6)*.

## A New Method for the Formation of P-P Bonds

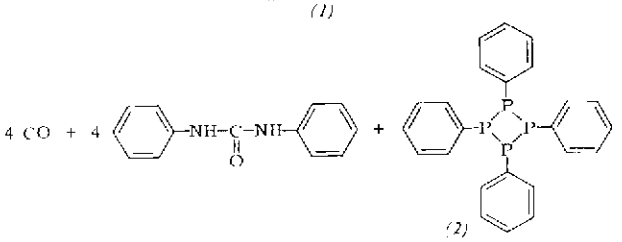
By Dr. H. Fritzsche, Dr. U. Hasserodt, and Prof. Dr. F. Korte

Shell Grundlagenforschung-GmbH.,
Schloß Birlinghoven (Germany)

When phenylbis(phenylcarbamoyl)phosphine *(1)* was heated for 2 hours at 180 °C under nitrogen, it gave tetraphenylcyclotetraphosphine *(2)* in 40 % yield, together with CO and diphenylurea.

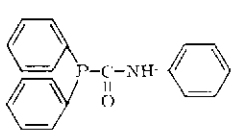


*(1)*

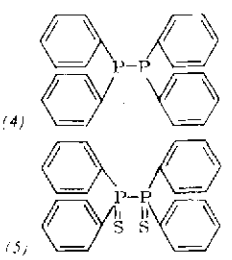


*(2)*

Under the same conditions, diphenylphenylcarbamoylphosphine *(3)* gave tetraphenyldiphosphine *(4)*, CO, and diphenyl urea; *(4)* was characterized by its reaction with sulfur to give a 32 % yield of tetraphenyldiphosphine-*P*,*P'*-disulfide *(5)*.

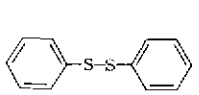


*(3)*

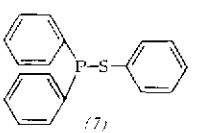


*(4)* *(5)*

As diphenylphosphorus radicals [1] were thought to be formed during the decomposition of *(3)* at elevated temperatures, we tried to trap them with phenylsulfur radicals [2].



*(6)*



*(7)*

The mixed dimer, *viz.* phenyl diphenylthiophosphinate *(7)*, m. p. 46–48 °C, was successfully isolated in 80 % yield from the decomposition under nitrogen of a mixture of *(3)* and *(6)*.

Received, October 29th, 1963 [Z 609/436 IE]
German version: Angew. Chem. 75, 1205 (1963)

[1] *U. Schmidt* et al., Angew. Chem. *75*, 640 (1963); Angew. Chem. internat. Edit. *2*, 400 (1963).

[2] *U. Schmidt* and *A. Müller*, Angew. Chem. *75*, 299 (1963); Angew. Chem. internat. Edit. *2*, 216 (1963).

## Dimerization during the Cyclization of Proline Peptides [1]

By Priv.-Doz. Dr. M. Rothe, cand. chem. K.-D. Steffen, and Dr. I. Rothe

Organisch-Chemisches Institut
der Universität Mainz (Germany)

For steric and energetic reasons, cyclohexapeptides arise on cyclization of tripeptides, rather than the expected 9-membered rings of cyclotripeptides [2]. Tripeptides of proline seemed to form an exception [2a].

Our experiments on the cyclization of varying concentrations of tripeptides containing different sequences of L-proline and glycine always yielded the crystalline 18-membered cyclohexapeptide c-diglycyl-L-prolyl-diglycyl-L-prolyl as sole product [m.p. > 350 °C (decomp.); $[\alpha]_D^{25}$ – + 48.3 ° (c = 0.6 in $H_2O$)] contrary to results described in the literature [2a]. Ring closure was effected with the *p*-nitrophenyl ester of glycyl-L-prolyl-glycine (yield: 88 %) and the 2,4-dinitrophenyl ester of diglycyl-L-proline (73 %) in dimethylformamide at 100 °C and 50 °C, respectively, and also with the two linear free tripeptides by the phosphite method [3] in diethyl phosphite at 100 °C (55 % and 48 % yield, respectively), making use of the dilution principle. The identity of all these cyclic peptides with the product obtained from glycyl-L-prolyl-glycine ethyl ester and tert. amine according to [2a.] was shown by infrared spectroscopy and by paper and thin-layer chromatography in four different solvent systems [4]. The ring size was elucidated by molecular-weight determinations in the vapor pressure osmometer, by cryoscopy according to *Rast* in the lactam of 4-aminocyclohexane-1-carboxylic acid (found 430), and by partial hydrolysis with 0.1 N $Ba(OH)_2$ followed by thin-layer chromatographic identification of the resulting linear peptides. Further indications are provided by the infrared spectrum; the appearance of the amide II band at 1535 $cm^{-1}$ indicates the *trans*-amide bonds of the 18-membered ring [4a]. Our results show that the association brought about by hydrogen bonding of two peptide molecules that are lying antiparallel to each other cannot be the deciding factor in the cyclodimerization.

The chlorination method using t-butyl hypochlorite [5] is particularly suitable for rendering the cyclopeptides (and *N*-masked peptides) visible on thin-layer chromatograms.

Received, October 29th, 1963 [Z 611/438 IE]
German version: Angew. Chem. 75, 1206 (1963)

[1] Cyclic Peptides, Part X; Part IX: *M. Rothe* et al. Makromolekulare Chem., in the press; Part VIII: *M. Rothe* and *R. Timler*, Chem. Ber. *95*, 783 (1962).

[2] *R. Schwyzer* and *P. Sieber*, Helv. chim. Acta *41*, 2186, 2190, 2199 (1958).

[2a] *P. W. G. Smith*, J. chem. Soc. (London) *1957*, 3985; *R. Schwyzer* et al. Angew. Chem. *72*, 270 (1960).

[3] *M. Rothe* et al., Angew. Chem. *71*, 700 (1959); *M. Rothe*, Habilitation Thesis, Universität Halle, 1960.

[4] $R_F$-Values on Merck Silica Gel G: 0.38 in n-butanol/acetone/glacial acetic acid/ammonia/water (4.5:1.5:1:1:2), 0.32 in n-butanol/glacial acetic acid/ammonia (5.5:3:1.5), and 0.12 in n-butanol/glacial acetic acid/ammonia (6:1:1:2), *E. Ehrhardt* and *F. Cramer*, J. Chromatogr. *7*, 405 (1962); on Schleicher-Schüll paper 2043b: 0.58 in n-butanol/glacial acetic acid/water (4:1:5), upper phase.

[4a] The same results have been obtained by *R. Schwyzer* and by *J. Rudinger* (personal communication).

[5] *R. H. Mazur* et al., J. biol. Chemistry *237*, 1619 (1963).

## Explosion of a Mixture of Triethylaluminum and Carbon Tetrachloride

By Dr. H. Reinheckel

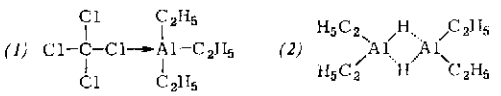
Institut für Fettchemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

References to the action of halogenated hydrocarbons on aluminum alkyls [1] are sparse and occasionally contradictory. In the course of our investigations into the suitability of the lower halogenated hydrocarbons as solvents for reactions involving organoaluminum compounds, a violent explosion occurred with a mixture of triethylaluminum and $CCl_4$.

When mixtures of $Al_2Cl_3(C_2H_5)_3$ with $CCl_4$ that had been prepared with ice-cooling reached room temperature, they first darkened, then exploded violently. No reaction was evident when a mixture of triethylaluminum and $CCl_4$ in a molar ratio of 1:3 was kept cold in ice, and unchanged $CCl_4$ was recovered after working up.

When the experiment was repeated with a mixture of identical composition, and the ice was then removed, the violent explosion occured even before the mixture reached room temperature, and without previous darkening. The hood was destroyed; the reaction flask and stirrer were so completely shattered that it was impossible to find a single splinter.

The explosion must be due to the formation of an adduct *(1)*.



*(1)* *(2)*

Diethylaluminum hydride *(2)*, which does not form adducts of the type *(1)* owing to its tendency to associate, has a weakly dehalogenating action on $CCl_4$; exothermic reaction only occurs after long boiling under reflux (molecular ratio 1:3 or more concentrated) and without damage to the apparatus.

Received, October 30th, 1963 [Z 614/441 IE]
German version: Angew. Chem. *75*, 1205 (1963)

[1] *W. Dahlig* and *S. Pasynkiewicz*, Roczniki Chem. *34*, 1197 (1960); *S. Pasynkiewicz*, *W. Dahlig*, and *M. Cieślak*, ibid. *35*, 1283 (1961); *K. Jenkner*, Chemiker-Ztg./Chem. Apparatur *86*, 527, 563 (1963); *J. E. Knap*, *R. E. Leech*, *A. J. Reid*, and *W. S. Tamplin*, Ind. Engng. Chem. *49*, 874 (1957); *E. R. B. Baker*, Ph. D. Thesis, Ohio State University, 1953.

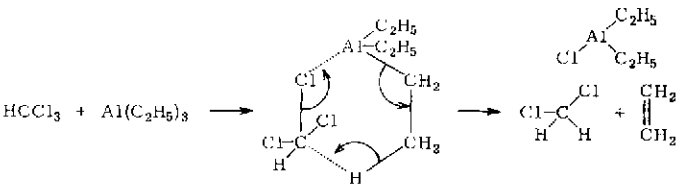
## The Reducing Action of Triethylaluminum

By Dr. H. Reinheckel

Institut für Fettchemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

The action of triethylaluminum on halogenated hydrocarbons is not substitutive, as might be expected, but reductive. $CH_2Cl_2$ is converted into $CH_3Cl$, $CHCl_3$ into $CH_2Cl_2$ plus $CH_3Cl$, and $CCl_4$ under suitable conditions (*e.g.* high dilution to avoid explosions [1]) into the three lower halogenated methanes. This is not due to initial dissociation of the triethylaluminum into ethylene and diethylaluminum hydride, with the latter as the actual reducing agent. Indeed, the above halogenomethanes react differently with pure diethylaluminum hydride: $CH_2Cl_2$ is not dehalogenated, $CHCl_3$ only very slightly, and $CCl_4$ only reacts on refluxing. Reaction of $CCl_4$ evidently proceeds differently, as is shown, for example, by the formation of ethyl chloride.

We attribute the reducing action to the formation of a cyclic transition complex *(1)* from the initial adduct. Because of its marked tendency towards association [1], the pure hydride does not form any such adducts.



*(1)*

The ethylene cannot be isolated. It apparently adds onto Al-ethyl bonds, as in the *Ziegler* synthesis, to give butyl and hexyl residues, since these can be detected as butane and hexane after hydrolysis.

Received, October 30th, 1963 [Z 615/442 IE]
German version: Angew. Chem. *75*, 1206 (1963)

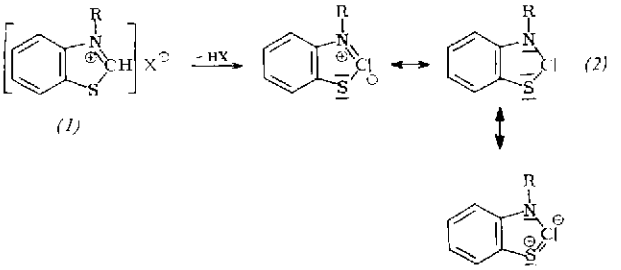
[1] *H. Reinheckel*, Angew. Chem. *75*, 1205 (1963); Angew. Chem. internat. Edit. *3*, 65 (1964).

## Low-Energy "Carbenes" [1]

By Prof. Dr. H.-W. Wanzlick and Dr. H.-J. Kleiner

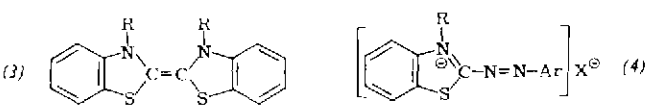
Organisch-Chemisches Institut der Technischen Universität Berlin (Germany)

Some initial results have been obtained in our search for "carbenes possessing quasi-aromatic resonance stabilization" [2]. *N*-Alkylbenzthiazolium halides *(1)* lose hydrogen halide even on mild treatment with certain tertiary amines, *e.g.* triethylamine. Yellow crystalline products are formed which behave chemically like the resonance hybrids *(2)*.



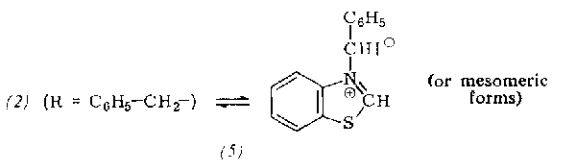
*(1)* *(2)*

Dimerization occurs more or less readily, according to the nature of R, to yield colorless, sometimes stereoisomeric ethylene derivatives *(3)*. However, before dimerization occurs, some typical reactions can be carried out. The salts *(1)* are reformed on reaction with acids, *N*-alkyl-2-thionobenzthiazolines are formed with sulfur, and azo dyes *(4)* are formed with diazonium salts.



*(3)* *(4)*

The new compounds possess intact alkyl groups (NMR spectra). The benzyl derivative, on the other hand, shows indications of tautomerism, cf. *(5)*.



*(2)* (R = $C_6H_5$–$CH_2$–) *(5)* (for mesomeric forms)

Received, November 8th, 1963 [Z 613/443 IE]
German version: Angew. Chem. *75*, 1204 (1963)

[1] Nucleophilic Carbene Chemistry, Part V. Part IV: *H.-W. Wanzlick* and *H.-J. Kleiner*, Chem. Ber. *96*, 3024 (1963).

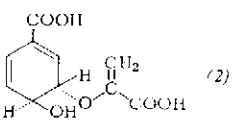
[2] *H.-W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1962).

## Detection of a Nitrogen-Free Precursor of Anthranilic Acid in the Biosynthesis of Tryptophan by Saccharomyces cerevisiae

By Doz. Dr. F. Lingens and Dipl.-Chem. W. Lück

Chemisches Institut der Universität Tübingen, Biochemische Abteilung (Germany)

The biosynthesis of tryptophan in microorganisms has been well worked out from the stage of anthranilic acid *(1)* onward. Precursors of *(1)* in tryptophan-deficient mutants have not yet been described. Recently we succeeded in obtaining proof of the accumulation of a nitrogenous product in the medium of a tryptophan-deficient mutant of *S. cerevisiae* with a genetic block before the stage of *(1)* [1]. A second labile, crystalline accumulation product, m.p. 178–182 °C (decomp.) has now been isolated from the medium of another mutant, which also grows selectively with tryptophan, indole, or *(1)*. Its properties are in accordance with the structure of a 3-enolpyruvic acid ether of *trans*-3,4-dihydroprotocatechuic acid *(2)*. Ether *(2)* has maxima in the ultraviolet at $\lambda = 274$ and 224 mμ in water, reacts in the cold with alkaline triphenyltetrazolium chloride, and gives no reaction with 2,6-dichloroindophenol. On heating *in vacuo*, *(2)* yields pyruvic acid *(3)* and phenol. Disproportionation of neutralized *(2)* with Pd/C gives an aromatic compound, which on ether cleavage yields



*(2)*

*(3)* and protocatechuic acid; identical treatment of unneutralized material leads to preferential production of *p*-hydroxybenzoic acid and *(3)*. Compound *(2)* can be split with periodate. In addition to the 2,4-dinitrophenylhydrazone of *(3)*, a second acidic 2,4-dinitrophenylhydrazone *(4)* is also obtained. The ultraviolet spectrum of *(4)* is in agreement with that of the 2,4-dinitrophenylhydrazone of mucondialdehyde. A crystalline compound is obtained by hydrogenation of *(4)* with $Pt/H_2$. On ether cleavage under mild conditions [2], this yields lactic acid and a substance which behaves on paper chromatograms like *trans*-3,4-dihydroxycyclohexane-1-carboxylic acid [3]. Compound *(2)* can be converted into *(1)* enzymatically [4]. *Gibson* has demonstrated that *(2)* occurs as a by-product of aromatic biosynthesis in bacteria [4]. His proof of the constitution of *(2)*, which was isolated as the labile Ba salt, was derived from ultraviolet, infrared, and NMR spectroscopic data.

Received, November 15th, 1963 [Z 619/448 IE]
German version: Angew. Chem. 76, 51 (1964)

[1] *F. Lingens, W. Lück,* and *W. Goebel, Z.* Naturforsch. *18b*, 851 (1963).

[2] *R. D. Youssefyeh* and *Y. Mazur,* Tetrahedron Letters *26*, 1287 (1962).

[3] *R. Grewe, A. Heinke,* and *C. Sommer,* Chem. Ber. *89*, 1978 (1956).

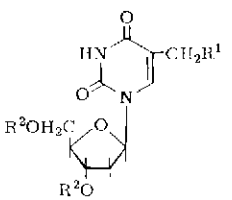
[4] *F. Gibson* and *L. M. Jackman,* Nature (London) *198*, 388 (1963).

## A Simple Synthesis of Natural and Artificial 5-Hydroxymethyluracil Nucleosides

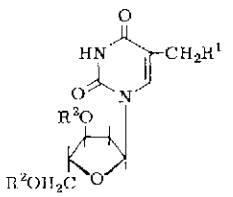
By Dr. R. Brossmer and E. Röhm

Max-Planck-Institut für Medizinische Forschung, Institut für Chemie, Heidelberg (Germany)

We have managed [1] to synthetize 5-hydroxymethyl-2′-deoxyuridine *(1)* in good yield. The 5′-phosphate of *(1)* is known to replace the entire thymidylic acid in the DNA of the *Bacillus subtilis* phage SP 8. Benzylation of 5-hydroxymethyluracil with benzyl alcohol and hydrochloric acid gives a 91 % yield of 5-benzyloxymethyluracil *(2)*, m.p. 202–203 °C [2], which is especially suitable for nucleoside syntheses. Compound *(2)* reacts either via its 1-acetyl derivative *(3)*, m.p. 131–132 °C, 80–90 %, or more simply directly with mercuric acetate to yield a mercury salt *(4)*. The latter condenses almost quantitively with 3,5-di-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride in toluene to give a mixture of the anomers of the nucleoside: β-anomer *(5)*, m.p. 141–142 °C, $[\alpha]_D^{20} = -60°$ in chloroform, 49 %; α-anomer *(6)*, m.p. 99–101 °C, $[\alpha]_D^{19} = +10°$ in chloroform, 25–35 %. Proof of the constitution of *(5)* is afforded by its conversion into β-thymidine.

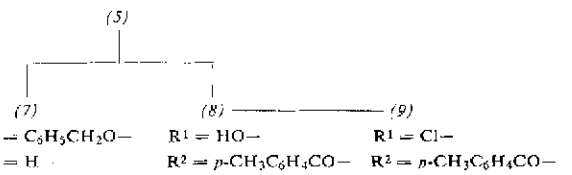


*(5)* $R^1$ = O-Benzyl, $R^2$ = p-Toluyl



*(6)* $R^1$ = O-Benzyl, $R^2$ = p-Toluyl

Selective removal of the protective groups yields partially substituted nucleosides. For example, 90 % *(7)*, m.p. 117 to 118 °C, arises on alkaline treatment of *(5)*, while catalytic hydrogenation of *(5)* yields 98 % *(8)*, m.p. 167–169 °C. The allylic hydroxyl group of *(8)* is readily etherified, *e.g.* to the butyl ether, m.p. 162–163 °C. The reaction of *(8)* with thionyl chloride gives a quantitative yield of *(9)*, m.p. 201–203 °C, and alkaline hydrolysis of the acyl groups produces 90 % free *(1)*, m.p. 180–182 °C, $[\alpha]_D^{20} = +19°$ in water [3].



*(7)* $R^1 = C_6H_5CH_2O-$, $R^2 = H$ — *(8)* $R^1 = HO-$, $R^2 = p\text{-}CH_3C_6H_4CO-$ — *(9)* $R^1 = Cl-$, $R^2 = p\text{-}CH_3C_6H_4CO-$

The previously unknown compounds of the α-series, including the free α-nucleoside, m.p. 169–170 °C, $[\alpha]_D^{20} = 0°$ in water, are derived analogously from *(6)*.

The chloride *(9)* reacts with nucleophilic substances to give biologically interesting compounds. Condensation of *(4)* with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide affords the protected β-nucleoside *(10)*, m.p. 124–126 °C in 80 % yield. A 61 % yield of the free *N*-glucosidic analogue of *(1)*, m.p. 230–231 °C, $[\alpha]_D^{21} = +15°$ in $H_2O$, is obtained from *(10)* via the 5-hydroxymethyl compound, but it is not as yet known to occur naturally.

Received, November 15th, 1963 [Z 618/447 IE]
German version: Angew. Chem. 76, 50 (1964)

[1] See also *R. Brossmer* and *E. Röhm,* Angew. Chem. *75*, 1105 (1963); Angew. Chem. internat. Edit. *2*, 742 (1963).

[2] *J. Farkuš* and *F. Šorm,* Collect. czechoslov. chem. Commun. *28*, 1620 (1963), recently described *(2)* and *(3)* independently.

[3] Free *(1)* is obtained in low yield by direct hydroxymethylation of 2′-deoxyuridine: *R. E. Cline, R. M. Fink,* and *K. Fink,* J. Amer. chem. Soc. *81*, 2521 (1959).

## A New Method for Preparing Trialkylarsines and Trialkylstibines

By Dr. W. Stamm and A. Breindel, M.S.

Research Center, Stauffer Chemical Company, Chauncey, N.Y. (U.S.A.)

Alkylations of arsenic and antimony halides with Grignard reagents, zinc alkyls [1], or aluminum alkyls [2] are known methods for the preparation of trialkylarsines and -stibines. We have succeeded in alkylating the oxides $As_2O_3$ and $Sb_2O_3$

with aluminum alkyls to form $AsR_3$ and $SbR_3$, respectively, in acceptable yields [3].

Finely powdered $As_2O_3$ (or $Sb_2O_3$) is dispersed in hexane, and the trialkylaluminum is added slowly, the mixture then being kept at 60 °C for 1–2 h. The trialkylarsines (or trialkylstibines) formed are then removed from the equilibrium mixture at highly reduced pressure:

$$2\ AlR_3 + M_2O_3 \rightleftharpoons (R_2M)_2O + 2\ RAlO \xleftarrow{AlR_3} 2\ MR_3 + 3\ RAlO$$

In order to obtain fully alkylated arsines and stibines in satisfactory yields, excess trialkylaluminum has to be employed. The yields of $MR_3$ decrease in the following order:

$M = Sb > As > Bi$ and

$R = C_2H_5- > n\text{-}C_4H_9- > i\text{-}C_4H_9- > i\text{-}C_6H_{13}-$

as can be seen from the following examples, where a molar ratio $AlR_3 : M_2O_3 = 3:1$ was employed:

$(C_2H_5)_3Sb$ — 89 %; $(n\text{-}C_4H_9)_3Sb$ — 87 %; $(i\text{-}C_4H_9)_3Sb$ — 71 %; $(i\text{-}C_6H_{13})_3Sb$ — 62 %; $(C_2H_5)_3As$ — 72 %; $(i\text{-}C_4H_9)_3As$ — 32 %, and $(n\text{-}C_4H_9)_3Bi$ — 6 %.

Alkylation of $As_2O_3$ with higher aluminum alkyls ($R \geq C_4$) resulted mainly in dialkylarsine oxides. Some of these were hitherto unknown, *e.g.* $[(i\text{-}C_4H_9)_2As]_2O$ (62 %, b.p. 68 to 70 °C/0.05 mm).

Diisobutylarsine oxide was oxidized to the new compound diisobutylarsinic acid $(i\text{-}C_4H_9)_2AsOOH$, m.p. 135 °C.

Received, November 18th, 1963 [Z 626/451 IE]
German version: Angew. Chem. 76, 99 (1964)

[1] *E. Krause* and *A. v. Grosse:* Die Chemie der metallorganischen Verbindungen. W. de Gruyter, Berlin 1937.

[2] German Patent Application K 20071 IVb/120 (April 5th, 1956), Kali-Chemie inventor: *H. Jenkner.*

[3] German Patent Application (November 16th, 1961), Stauffer Chem. Co., inventors: *W. Stamm* and *A. Breindel.*

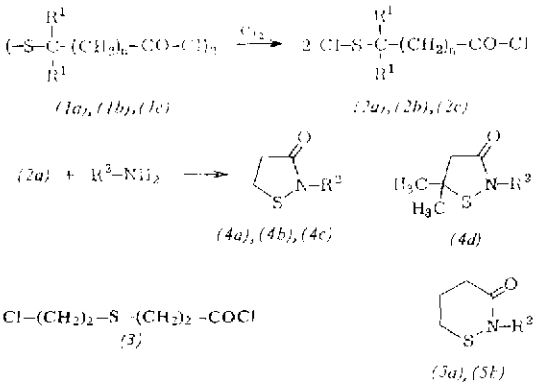
## ω-Chlorosulfenylalkylcarbonyl Chlorides

By Prof. Dr. A. Lüttringhaus and Dr. Rupert Schneider

Chemisches Laboratorium der Universität Freiburg/Breisgau (Germany)

We were able to convert dithiaalkane-α,ω-dicarboxylic acids into the corresponding α,ω-dicarbonyl chlorides *(1a)*, *(1b)*, and *(1c)* by treatment with thionyl chloride [1]. Chlorolysis of these at −25 °C in $CCl_4$ according to the method of *Brintzinger* [2] produced the ω-chlorosulfenylalkylcarbonyl chlorides *(2a)*, *(2b)*, and *(2c)* [3]. The yields were so good (up to 90 %) that the $CCl_4$ solutions could be used directly for further reactions, *e.g.* for the addition onto olefins to give β-chloroalkyl thioethers which serve as evidence for the structures of *(2)*. Thus, *(2a)* and ethylene formed 4-thia-6-chlorocaproyl chloride *(3)*, b.p. 80–81 °C/0.1 mm. Reaction of *(2a)* in $CCl_4$ with primary amines in the presence of pyridine and with strict exclusion of moisture gave rise to the new *N*-alkylisothiazolidin-3-ones *(4a)*, *(4b)*, and *(4c)*. Correspondingly, *(2b)* formed *(4d)*, and *(2c)* gave the new *N*-alkyltetrahydro-1,2-thiazin-3-ones *(5a)* and *(5b)*.

The heterocyclic compounds *(4a)*, *(4b)*, *(4c)*, *(5a)*, and *(5b)* are colorless oils which decompose fairly rapidly on exposure to moist air. Aqueous bases and acids hydrolyse the S–N bond almost instantaneously. They presumably [4] give rise to intermediate carboxamides with an ω-sulfenic acid group, for we always found disulfide-type products of disproportionation of the latter, namely the diamides corresponding to *(1)*, among the subsequent products. Compound *(4d)*, which is also a colorless oil, has its sulfur atom bonded to a tertiary carbon atom and is thus considerably more stable.



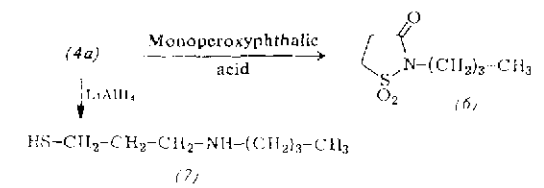




| | R¹ | n | b.p. [°C/mm] | | R² | b.p. [°C/mm] |
|---|---|---|---|---|---|---|
| *(1a)* | H | 1 | 130–150/$10^{-3}$ [a] | *(4a)* | $C_4H_9$ | 62–62/0.05 |
| *(1b)* | $CH_3$ | 1 | 120–130/$10^{-3}$ [a] | *(4b)* | $CH_3$ | 46–47/0.05 |
| *(1c)* | H | 2 | 150–$10^{-3}$ [a,b] | *(4c)* | $C_6H_5$ | [c] |
| *(2a)* | H | 1 | | *(4d)* | $C_4H_9$ | 55/0.01 |
| *(2b)* | $CH_3$ | 1 | | *(5a)* | $C_4H_9$ | 62–63/0.01 |
| *(2c)* | H | 2 | | *(5b)* | $CH_3$ | 46/0.4 |

[a] Oil-bath temperature.
[b] Unstable.
[c] Decomposes on distillation.

Oxidation with excess monoperoxyphthalic acid in ether/chloroform converts *(4a)* into *N*-butylpropanesultam-3-one *(6)* [5], whereas reduction with lithium aluminohydride in ether causes ring fissure to give 3-(butylamino)propane-1-thiol *(7)*, b.p. 82–84 °C/0.2 mm.




Received, November 22nd, 1963 [Z 620/449 IE]
German version: Angew. Chem. 76, 51 (1964)

[1] *R. Schneider*, Ph. D. Thesis, Universität Freiburg, 1963.

[2] *H. Brintzinger, K. Pfannenstiel, H. Koddebusch,* and *K. F. Kling*, Chem. Ber. *83*, 87 (1950).

[3] *N. Kharrasch* and *B. Langford*, J. org. Chemistry *28*, 1901 (1963), recently achieved the synthesis of 4-chlorothiobutyroyl chloride *(2c)* by a different route.

[4] *N. Kharasch:* Organic Sulfur Compounds. Pergamon Press, Oxford 1961, Vol. 1, p. 351.

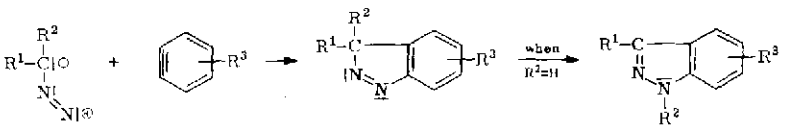
[5] The name propanesultam-3-one was proposed by *H. Baganz* and *G. Dransch*, Chem. Ber. *93*, 784 (1960).

## Capture of Benzynes by Acyldiazoalkanes

By Prof. Dr. W. Ried and Dipl.-Chem. M. Schön

Institut für Organische Chemie der Universität Frankfurt am Main (Germany)

Benzynes (dehydrobenzenes) are readily accessible [1], and are trapped in the presence of acyldiazoalkanes to give substituted indazoles as their conversion products. The reaction is essentially a 1,3-dipolar addition [2]. A solution of anthranilic




$R^1$ = acyl
$R^2$ = H or $C_6H_5$

Scheme 1.

acid in acetone was added dropwise to a boiling solution in methylene chloride of a mixture of the diazo compound and isoamyl nitrite. The indazoles thus prepared are listed in Table 1.

Table 1. Indazoles obtained according to Scheme 1.

| Diazo compound | Dehydrobenzene | Reaction product | M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| Benzoyldiazomethane | $C_6H_4$ | 3-benzoylindazole [3] | 189 | 88 |
| *m*-Methylbenzoyldiazomethane | $C_6H_4$ | 3-(*m*-methylbenzoyl)-indazole | 157 | 81 |
| *p*-Chlorobenzoyldiazomethane | $C_6H_4$ | 3-(*p*-chlorobenzoyl)-indazole | 202 | 79 |
| β-Naphthoyldiazomethane | $C_6H_4$ | 3-(β-naphthoyl)-indazole | 208 | 82 |
| Benzoyldiazomethane | $C_6H_3Br$ | 3-benzoyl-5(6)-bromoindazole | 258–259 | 71 |

The structure of the new indazoles follows from their analyses, infrared spectra, and derivatives (*e.g.* 2,4-dinitrophenylhydrazones). Furthermore, some of the reaction products have already been prepared by another route [3]. These experiments, which have so far produced yields of over 70 %, are being continued.

Received, November 8th, 1963 [Z 624/454 IE]
German version: Angew. Chem. *76*, 98 (1964)

[1] *L. Friedman* and *F. M. Logullo*, J. Amer. chem. Soc. *85*, 1548 (1963); see also *M. Stiles* and *R. G. Miller*, ibid. *82*, 3802 (1960); *M. Stiles, R. G. Miller*, and *U. Burkhardt*, ibid. *85*, 1792 (1963); *G. Wittig* and *R. W. Hoffmann*, Angew. Chem. *73*, 435 (1961).

[2] *R. Huisgen* and *R. Knorr*, Naturwissenschaften *48*, 716 (1962).

[3] *J. Meisenheimer* and *A. Diedrich*, Chem. Ber. *57*, 1715 (1924).

# CONFERENCE REPORTS

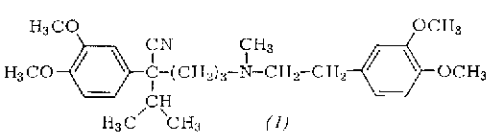
## Therapy Congress and Pharmaceutical Exhibition

### Karlsruhe (Germany), August 31st to September 7th, 1963

Nearly 8000 physicians, pharmacologists, and representatives of the pharmaceutical chemical industry from Germany and elsewhere assembled at the 15th German Therapy Week in Karlsruhe. The program of lectures dealt with treatment of the peripheral circulation and disturbances of the blood supply to organs, with the therapy of bronchitis, bronchial asthma, and emphysema of the lungs, with the early detection and treatment of malignant tumors, with the clinical use of steroids, with the therapeutic problems of geriatry, with the importance in therapy of the water-electrolyte balance, and with the treatment of diseases of the abdomen and the maxillary sinus, *etc.* In his plenary lecture on "Scientifically Based Therapy", Prof. Dr. *H. Schäfer*, Heidelberg (Germany), pointed out *inter alia* that although the pathogenesis of diseases was often known nowadays, the etiology, *i.e.* the actual cause of illness, was usually still unknown, especially in the case of internal disorders. Therapy of such diseases must, therefore, still be confined largely to the treatment of the symptoms.

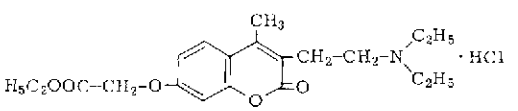
Almost 250 firms took part in the exhibition of pharmaceuticals. Of the many new preparations on show, only those in which new chemical compounds are being put on the market receive mention below. No reference is made to new presentations that are merely mixtures of known substances.

Knoll AG., Ludwigshafen (Germany), exhibited a new coronary dilator, Isoptin®. This greatly increases the supply of blood to the coronary vessels for a long time, and in particular ensures increased oxygenation of the heart muscle without greater effort from the heart. Therapeutic doses of Isoptin do not influence any other blood vessels. The active compound is 2-(3,4-dimethoxyphenyl)-5-(*N*-homoveratryl-*N*-methylamino)-2-isopropylvaleronitrile *(1)*, mol. wt. 454.62, a pale yellow oil of b.p. 243–246 °C/0.01 mm, $n_D^{25} = 1.5448$. It is used in the form of its hydrochloride, a white crystalline powder, m.p. 138.5–140.5 °C (corr.), which is sparingly soluble in chloroform, readily soluble in methanol and dimethylformamide, soluble in ethanol, isopropanol, acetone, ethyl acetate, *etc.*, and 7.2 % soluble in water at 21 °C.



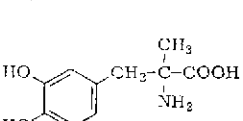
*(1)*

Another preparation for increasing coronary circulation is Intensain®, introduced by Cassella-Riedel Pharma GmbH. Intensain is 3-(β-diethylaminoethyl)-7-ethoxycarbonylmethoxy-4-methyl-2-oxo-1,2-chromene hydrochloride *(2)*, mol. wt. 397.66, a white crystalline powder, m.p. 159–160 °C, with a slightly bitter taste. It is readily soluble in water, alcohol, methylene dichloride, and chloroform. The free base is insoluble in water. Oral or parenteral administration of Intensain gives a degree of dilation of the coronary heart vessels not previously attained, and this is maintained for some hours. It has no effect on the blood pressure and causes no vasodilation in the peripheral circulation.



*(2)*

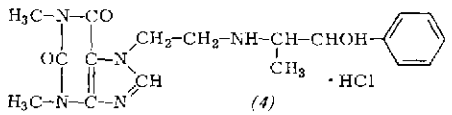
Presinol® from Farbenfabriken Bayer is a new hypotensive agent with the structure of (−)-3-(3,4-dihydroxyphenyl)-2-methylalanine *(3)*, (generic name: α-methyldopa). It melts at 292–293 °C and is soluble in water and in aqueous acids and alkalis. Although Presinol causes a large drop in the blood pressure, it ensures sufficient circulation in the peripheral system and vital organs. It is well tolerated and can be used for extended treatments. α-Methyldopa is a structural analogue of the natural amino acid dihydroxyphenylalanine (dopa), a precursor in the biosynthesis of noradrenaline. Administration of α-methyldopa probably blocks the synthesis of noradrenaline by inhibiting dopa decarboxylase.



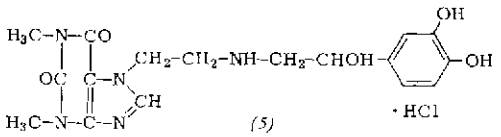
*(3)*

Chemiewerk Homburg have brought out a circulation analeptic, Akrinor®, containing two new derivatives of theophylline, *viz.* (−)-7-[2-(β-hydroxy-α-methyl-β-phenethylamino)ethyl]-theophylline hydrochloride *(4)*, mol. wt. 393.9, m.p. 244 to 246 °C, and 7-{2-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]ethyl}theophylline hydrochloride *(5)*, mol. wt. 411.9,

m.p. 186–188 °C; both are white crystalline powders. Akrinor is indicated in all cases of circulatory failure or poor circulation, of hypertonia, and of defective orthostatic regulation of the circulation.

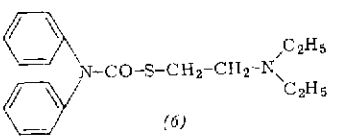


(4)



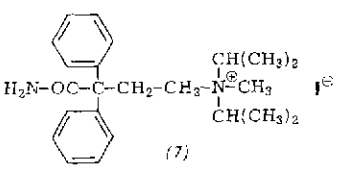
(5)

Farbenfabriken Bayer introduced a newly developed spasmolytic for use in parturition, Escorpal®. This reduces the abdominal tension of the natal canal, dilates the external orifice of the uterus, and thus shortens and eases childbirth. Escorpal is diethylaminoethyl diphenylthiocarbamate *(6)*, (generic name: phencarbamide), a white crystalline material, mol. wt. 328.5, m.p. 48–49 °C; it is very readily soluble in methanol, ether, and chloroform, readily soluble in light petroleum, and practically insoluble in water. It is administered either as the free base in suppositories, or intramuscularly or intravenously as a solution of the hydrochloride, mol. wt. 364.9, m.p. 180–182 °C.



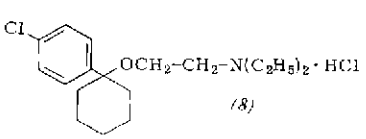
(6)

Stelabid®, an anticholinergic and neuroleptic from Röhm and Haas, Darmstadt (Germany), contains the known neuroleptic phenothiazine derivative Jatroneural® (generic name: trifluoperazine) together with the anticholinergic Tyrimide®, 4-(*N*,*N*-diisopropyl-*N*-methylammonium)-2,2-diphenylbutyramide iodide *(7)*, (generic name: isopropamide), which has been known for some time in the U.S.A. but which is new to the German market. Isopropamide is a crystalline compound, m.p. 198–201 °C (decomp.); the free base melts at 84–86 °C. Stelabid is suitable for stress-conditioned disorders of the digestive tract; it prevents hypermotility and spasm, reduces gastric secretion, and protects against nausea and vomiting.



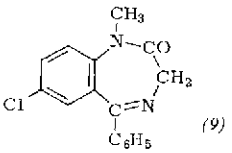
(7)

Tonoquil®, from C. H. Boehringer & Co., Mannheim (Germany), is a psychotherapeutic combination of a new parasympatholytic drug, Chlorphencyclan, with the known phenothiazine derivative thiopropazate. Chlorphencyclan is 1-*p*-chlorophenyl-1-(β-diethylaminoethoxy)cyclohexane hydrochloride *(8)*, m.p. 143–145 °C, and has predominantly central with a little peripheral sympatholytic activity, combined with an antidepressant and stimulant action. Thiopropazate mainly suppresses the sympathetic system and thus relieves anxiety and emotional tension.



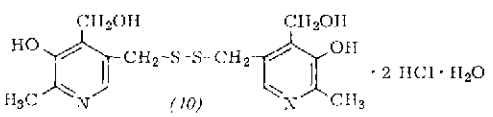
(8)

A new tranquillizer, Valium®, was introduced by Hoffmann-La Roche. The active constituent is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one *(9)*, which is closely related structurally to the known tranquillizer Librium®. Valium has marked relaxant, sedative, hypnotic, and muscle relaxant properties. It is usually well tolerated; serious side-effects are not encountered at therapeutic doses.



(9)

Encephabol® is a new dynamizing neurotrophic agent produced by E. Merck, Darmstadt (Germany). It contains Pyrithioxin® (generic name: pyritinol), bis-(3-hydroxy-4-hydroxymethyl-2-methylpyrid-5-ylmethyl) disulfide dihydrochloride monohydrate *(10)*, which is a crystalline solid that is readily soluble in water. Encephabol increases vigilance tone and thus relieves many clinical symptoms associated with cerebral insufficiency. It is indicated, for example, in organic psychosyndromes resulting from damage to cerebral blood vessels, nervous exhaustion and failure in senile involution, in secondary conditions arising from skull and brain traumas, intoxications, apoplectic attacks, encephalitis, *etc.* In spite of its structural resemblance to pyridoxin, Pyrithioxin has no vitamin $B_6$ activity.

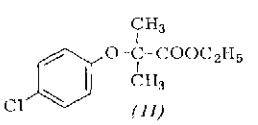


(10)

Pergalen®, a new and completely synthetic anticoagulent, produced by Farbwerke Hoechst, is presented in the form of an ointment that causes thrombolysis and resorption. The active substance is the sodium salt of a polyethylenesulfonic acid with a mean molecular weight of 7000, is highly effective, and has low toxicity. It is a white, non-crystalline powder which is stable at room temperature and readily soluble in water. Pergalen can be used for treating thrombosis, thrombophlebitis, ulcus cruris, hematomas, and contusions and for the dispersal of scar tissue, *etc.*

Epsilon-aminocaproic acid "Behringwerke" is a new blood-clotting agent marketed by Farbwerke Hoechst. It is suitable for stopping haemorrhages caused by excessive fibrinolysis and fibrinogenolysis, and can be used to prevent bleeding in gynecology, surgery, and especially in cases of overdosing with streptase or other fibrinolytic agents. Epsilon-aminocaproic acid blocks the activation of the proactivator-plasminogen complex leading to plasmin, and large doses will inhibit active plasmin itself. The drug is supplied as ampoules of sterile pyrogen-free solution, containing 10 g of the amino acid per 100 ml.

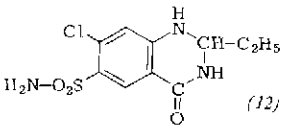
Atromid is an orally administered drug for arteriosclerosis and diseases of the blood vessels that was developed by I.C.I. and is marketed in Germany by Rhein-Pharma GmbH., Heidelberg. It is a mixture of androsterone and ethyl α-(*p*-chlorophenoxy)isobutyrate *(11)*, (generic name: clofibrate), a colorless liquid with a faint odor, $d_{20}$ = 1.140, b.p. 158–160 °C/25 mm, that is soluble in the usual solvents but not in water. Atromid causes rapid lowering of the serum triglyceride and cholesterol levels. It also reduces the uric acid level when this is raised by disease of the coronary arteries.



(11)

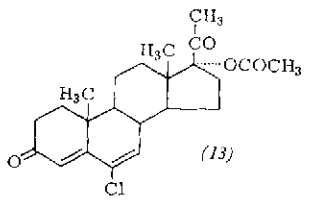
7-Chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide, *(12)*, (generic name: quinethazone), is a new mercury-free diuretic that was introduced in the U.S.A. a few

months ago by Lederle under the name Hydromox and is now marketed in Germany as Aquamox. It may be classified as a saluretic, since it promotes excretion of sodium chloride by inhibition of resorption in the renal tubules. Aquamox lowers pathologically high blood pressures without affecting the normal blood pressure. It differs from the benzothiadiazine dioxide series of sulfonamide diuretics by the formal replacement of the $SO_2$ group with a CO group.



*(12)*

E. Merck, Darmstadt (Germany), have marketed a new, highly active, and well tolerated oral progesterone derivative, *viz.* Gestafortin®, 17α-acetoxy-6-chloro-6-dehydroprogesterone *(13)* (generic name: chloromadinone acetate), m.p. 212–214 °C. The indications for Gestafortin are in general the same as for other gestagens. It causes a secretory change of the mucous membrane of the uterus producing a transformation of the endometrium that is histologically almost identical with that of a normal secretory change.



*(13)*

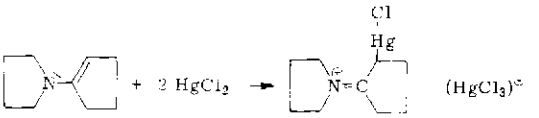
[VB 748/104 IE]

German version: Angew. Chem. *76*, 55 (1964)

## Recent Investigations on the Structure of Heavy Metal Compounds

*K. Brodersen*, Aachen (Germany)

The reaction between mercuric chloride or bromide and tertiary enamines (*e.g.* 1-pyrrolidino-1-cyclohexene, 1-pyrrolidino-1-cyclooctene, 1-pyrrolidinoisobutene, 1-morpholino-1-cycloheptene, and α-morpholinostyrene) in ether gives *N*-mercurated α,β-unsaturated ammonium salts. 1-Pyrrolidino-1-cyclopentene and $HgCl_2$ or $HgBr_2$ react in ether, however, to yield *C*-mercurated immonium salts.



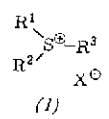
Reduction at −70 °C with lithium aluminohydride or metallic sodium or potassium formate in the presence of potassium t-butoxide as proton acceptor at room temperature gives the saturated tertiary amine (pyrrolidinocyclopentane), metallic mercury, and the halides from the *C*-mercurated immonium salts. When the *N*-mercurated enammonium salts are reduced, the enamines are recovered, and their hydrolysis products can be characterized. The conversion of enamines into *N*-mercurated enammonium salts is accompanied by a bathochromic shift whereas conversion into *C*-mercurated immonium salts results in a hypsochromic shift of the double-bond band in the infrared spectrum.

[GDCh-Ortsverband Erlangen (Germany), November 22nd, 1963] [VB 758/107 IE]

German version: Angew. Chem. *76* (1964), in the press.

# SELECTED ABSTRACTS

**Sulfonium salts with alkyl and β-halogenoethyl ligands** have been prepared by *A. Lüttringhaus* and *A. Machatzke*. Their cytostatic activity was examined. These compounds are analogous to the previously known tri-(β-halogenoethyl)- and di-(β-halogenoethyl)vinylsulfonium salts *(1a)* and *(1b)*. The di-(β-chloroethyl)alkylsulfonium salts *(1c)* could be prepared by careful treatment of the β-hydroxyethylsulfonium compounds with thionyl chloride, but not by direct alkylation of mustard gas. The mono-(β-halogenoethyl)dialkylsulfonium



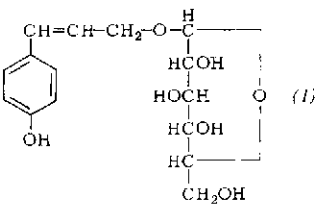
*(1)*

*(1a)* $R^1 = R^2 = R^3 = -CH_2CH_2Cl$
*(1b)* $R^1 = R^2 = -CH_2CH_2Cl$; $R^3 = -CH{=}CH_2$
*(1c)* $R^1 = R^2 = -CH_2CH_2Cl$; $R^3$ = alkyl
*(1d)* $R^1 = -CH_2CH_2Cl$; $R^2 = R^3$ = alkyl

salts *(1d)* could be prepared both by direct alkylation of hemi-mustard compounds [mono-(β-chloroethyl)mustards] and by chlorination of the β-hydroxyethylsulfonium salts with thionyl chloride. The sulfonium salts *(1c)* had a good cytostatic effect on tumors in experimental animals. On account of their improved effect on the Ehrlich carcinoma and of the possibility of varying the alkyl ligands, these compounds were found to be superior to the tri-(β-chloroethyl)sulfonium salts. The salts *(1d)* have no cytostatic activity. / Arzneimittel-Forsch. *13*, 366 (1963) / –R. [Rd 684/188 IE]

**The electron configuration of tetravalent and trivalent uranium** was examined by *B. Jezowska-Trzebiatowska*. It has so far not been possible to ascertain whether the elements with atomic numbers over 89 incorporate their additional electrons as d- or as f-electrons. The spectra of uranium(III) and uranium(IV) compounds can be interpreted by the ligand field theory, on the basis of an electron configuration $5f^2$ for U(IV) and $5f^26d^1$ for U(III). This view gained support from the magnetic properties of U(IV). / J. Chimie Physique *60*, 843 (1963) / –Hz. [Rd 776/200 IE]

**Triandrin, a new phenolic glycoside,** was isolated by *H. Thieme* from the bark of the almond willow (*Salix triandra* L.) by means of polyamide chromatography and was shown to be 3-(*p*-hydroxyphenyl)-2-propen-1-yl-1-β-D-glucopyranoside. Triandrin *(1)*, $C_{15}H_{20}O_7$, forms colorless needles from ethyl acetate, m.p. 177–179 °C, $[\alpha]_D^{20} = -60.5°$ (water). Emulsin splits *(1)* into glucose and *p*-coumaryl alcohol, m.p. 115 to 117 °C. Treatment with acetic anhydride/pyridine converts *(1)* into the pentaacetyl derivative, m.p. 108 °C, $[\alpha]_D^{20} = -37.2°$.



*(1)*

Triandrin was also detected in several other species of willow. / Naturwissenschaften *50*, 571 (1963) / –De. [Rd 780/195 IE]

**A method for the micro-determination of $Mg^{2+}$ and $Ca^{2+}$ in tissues** has been developed by *M. Höfer*. Phosphates and heavy-metal ions, such as $Fe^{2+}$, $Zn^{2+}$, $Cu^{2+}$, and $Mn^{2+}$, do not interfere. The test solution is passed through an ion-exchange column (Dowex 50-X8, $H^+$ form) and $Mg^{2+}$ and heavy metals are eluted with 2 N HCl. The heavy metals are complexed with 8-hydroxyquinoline and extracted with chloroform. $Mg^{2+}$ is titrated with EDTA in the presence of Eriochrome Black T, the end-point being detected by extinction measurements at 650 mμ. $Ca^{2+}$ is eluted with 3 N HCl and determined photometrically at 390 mμ as calcium naphthylhydroxamate. Sensitivity limits for the simultaneous determinations are: 15 μg $Mg^{2+}$, 5 μg $Ca^{2+}$. / Experientia (Basel) *19*, 367 (1963) / –Re. [Rd 787/206 IE]

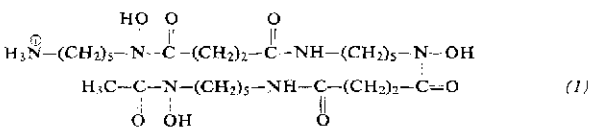
**Optically excited electron states of mono- and disubstituted benzene derivatives** (nitro- and nitrosobenzene, dimethyl- and *p*-nitrodimethylaniline, *p*-dimethylaminobenzaldehyde) were measured and calculated by *H. Labhart* and *G. Wagnière* with regard to the position and intensity of the bands, the charge distribution, and the magnitude and direction of transition moments. The experiments are based on measurements of the dipole moments of the excited singlet states according to three methods, *viz.* electrical fluorescent polarization, electrical dichroism, and the influence of solvents on the spectra. The calculation is carried out according to the Pariser-Parr and Pople method, the single electron functions being taken as self-consistent for the ground state. The $\pi-\pi^*$ transitions are calculated from the basic functions, the configurational interaction being taken into account. The free parameters are adjusted so that the $\pi$-dipole moments, $\pi-\pi^*$ transitions, and $\pi$-ionisation energies for simple molecular fragments agree as closely as possible with the experimental values. / Helv. chim. Acta *46*, 1314 (1963) / –Jg.

[Rd 694/192 IE]

**The stability constants of 1:1, 1:2 and 1:3 complexes of Fe(III) with hezhydroxamic acid and acethydroxamic acid (CHA)** were determined by *G. Schwarzenbach* et al. by combination of optical ($FeA^{2+}$), redox potentiometric ($Fe^{3+}$), and pH measurements, the acidity constant of free hydroxamic acid being known.

$$Fe^{3+} + HA \rightleftharpoons FeA^{2+} + H^+;\ \log K_I = 11.42$$
$$FeA^{2+} + HA \rightleftharpoons FeA_2^{+} + H^+;\ \log K_{II} = 9.68$$
$$FeA^{+} + HA \rightleftharpoons FeA_3 + H^+;\ \log K_{III} = 7.2$$

The equilibrium constants of the Fe(III) complexes of deferri-ferrioxamine B ($H_4$-DFO$^+$) *(1)* and similar polybasic hydroxamic acids can be obtained only by optical methods



*(1)*

(on account of their marked complex formation) from the equilibria with aminopolycarbonic acid (Trilon) complexes.

$$Fe^{3+} + H_2\text{–DFO}^- \rightleftharpoons Fe(H_2\text{–DO})^{2+};\ \log K_{II} = 21.7$$
$$Fe^{3+} + H\text{–DFO}^{2-} \rightleftharpoons Fe(H\text{–DFO})^{+};\ \log K_{III} = 30.5$$

Hydroxamic acid complexes are formed by many heavy metals as well as by $Ca^{2+}$, $Al^{3+}$, $Th^{3+}$, $La^{3+}$, and the rare earths. As these complexes are considerably less stable than those of Fe(III), the complex constants can be obtained from the NaOH titration curves of the free acids and the chelates. Hydroxamate (hydroxamic acid) complexes of Fe(III) occur in micro-organisms. / Helv. chim. Acta *46*, 1390, 1400, 1409 (1963) / –Jg. [Rd 693/191 IE]

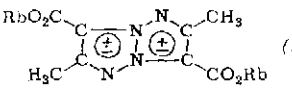
***S*-Phosphorylated thiols, a new class of energy-rich compounds,** can be obtained in high yield according to *S. Åkerfeldt* by a new synthetic pathway, *viz.* alkylation of the $SPO_3^{3-}$ ion by substituted alkyl halides. The *S*-phosphorylated thiols are obtained in up to 95 % yield and are separated as their Li or Li/Na salts; on hydrolysis, the S–P-bond is split only on warming in mineral acid (*e.g.* 1 N HCl at 100 °C) or enzymatically, *e.g.* by enzymes from human erythrocytes. For example, these split cysteamine-*S*-phosphate into cysteamine and orthophosphate. Some of the compounds synthetized, *viz.* *S*-(2-dimethylaminoisopropyl)-, *S*-(2-guanidinoethyl)-, and *S*-(3-guanidinopropyl)-phosphorothioxide possess radiation protective action. *S*-Phosphorylated thiols can serve as phosphorylating reagents as well as intermediate products for thiols (high yields); the compounds are of biochemical interest. / Svensk kem. Tidskr. *75*, 4 (1963) / –De.

[Rd 691/193 IE]

*ortho*-**Substituted phenols** were examined by *R. A. Nyquist*. They show an intense and remarkably wide infrared absorption band in the range 300–860 cm$^{-1}$, which can be ascribed to a non-planar deformation vibration of the hydroxyl group. The wide frequency range in which the band occurs is explained by the marked influence of intramolecular hydrogen bonds on this vibration. Relationships were found between the frequency of this vibration and both the valence frequency of the hydroxyl group and the Taft resonance parameters; accordingly, this vibration appears useful as a "characteristic" vibration. / Spectrochim. Acta *19*, 1655 (1963) / –Hz.

[Rd 774/198 IE]

**Identification of an aromatic non-benzenoid ring system by X-ray analysis** has been achieved by *M. Brufani*, *W. Fedeli*, *G. Giacomello* and *A. Vaciago*. The structure of derivatives of 1,3a,4,6a-tetra-azapentalene was elucidated by Patterson synthesis, with successive refinement by two-dimensional Fourier and Fourier-difference synthesis.

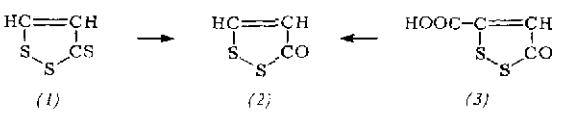


*(1)*

Derivatives of *(1)* are approximately planar; the stability of these compounds containing a ten-$\pi$-electron system confirms the "(4n + 2) rule". / Chem. Ber. *96*, 1840 (1963) / –Kr.

[Rd 777/194 IE]

**Dithione,** *i.e.* **1,2-dithiacyclopenten-3-one** *(2)*, has been synthetized for the first time by *R. Mayer* and *J. Faust*. Compound *(2)*, $C_3H_2OS_2$, m.p. 3 °C, b.p. 47 °C/0.1 mm, is obtained in 70 % yield by desulfurization of trithione *(1)* with mercurous acetate in chloroform/glacial acetic acid at room temperature. Decarboxylation of dithione-5-carboxylic acid



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

*(3)* by pyrolysis at 230–240 °C/10 mm affords 2–7 % *(2)*. Dithione is a colorless oily liquid, which is very stable, and is smoothly converted into *(1)* on treatment with $P_4S_{10}$ in $CS_2$. / Chem. Ber. *96*, 2702 (1963) / –Ma. [Rd 784/197 IE]

**Photocyanation of saturated ethers,** such as diethyl ether, glycol dimethyl ether, dioxan, tetrahydrofuran, and tetrahydropyran, gives yields of over 90 % according to *Eugen Müller* and *H. Huber*. Anhydrous ether/cyanogen chloride solutions (1:1) are irradiated with ultraviolet light from a high-pressure mercury lamp at 10–20 °C. Equivalent amounts of suspended $NaHCO_3$ absorb the HCl formed. Even small amounts of acetone increase the rate of photocyanation appreciably, probably by supplying additional radicals to initiate the reaction, which is thought to have a free radical mechanism. Open chain ethers are substituted exclusively in the $\alpha$-position, and cyclic ethers predominantly so. The amount of other isomers decreases with increasing distance from the oxygen atom. Saturated hydrocarbons can be cyanated in a similar manner. / Chem. Ber. *96*, 2319 (1963) / –Jg.

[Rd 782/196 IE]

**The mechanism of the protection by 1-hydrazinophthalazine against radiation** has been investigated by *S. Fallab* and *H. Erlenmeyer*. The reaction between *o*-phenylenediamine *(1)* and $H_2O_2$, which is catalysed by copper phthalocyaninetetrasulfonate, was taken as a model. In this reaction, H and OH radicals, which are produced in the material by hard radiation, are involved as well as $H^+$ and $OH^-$ ions. Oxidation of *(1)* with $H_2O_2$ was completely suppressed by stoichiometric quantities of 1-hydrazinophthalazine. It is concluded that oxidation-kinetic factors are decisive in the protective action observed *in vivo*. These experiments support the mechanism proposed for the protection by thiols. / Experientia (Basel) *19*, 374 (1963) / Re. [Rd 786/205 IE]

**Fresh Water from the Sea** (Dechema Monographs Nos. 781—834, Vol. 47) in two parts, 54 lectures presented at the European symposium "Fresh Water from the Sea" in Athens (Greece), May 28th to June 2nd, 1962. Verlag Chemie GmbH., Weinheim/Bergstr. 1962. 1st Edit., xii + 875 pp., numerous illustrations and tables. Clothbound, DM 100.– (about $25.00).

At the present time, it costs about $1 to produce 1000 gallons of fresh water from sea water; in favorable cases, this figure may be reduced to about $0.40 per 1000 gal. Of the most important methods, *viz.* evaporation, freezing, electrodialysis, hydrate formation, and ion-exchange techniques, the first two have the best prospects technically. In the distillation process, it is possible to conserve heat by evaporation in several successive stages and to prevent boiler scale formation by flash distillation; in the freezing process, the main difficulties are finding cheap methods of producing low temperatures and freeing the ice crystals from brine. The sharp increase in demand for domestic water supplies due to rises in population, industrial development, and the raising of the standard of living (present annual demand in the U.S.A. is 1000 $m^3$ per person; estimated demand for the year 2000 is 2000 $m^3$ per person) makes desalination of sea water one of the most important technical problems of our time.

The Greek Chemical Society and Greek Chamber of Technology invited specialists from all over the world to the 39th Congress of the European Federation of Chemical Engineering at Athens in order to discuss these problems. The 54 lectures of this symposium have now been printed in Dechema monographs in the lecturers' own languages (German, English, or French). Twenty-three articles deal with the evaporation process and 9 with the freezing process, while 20 contributions are devoted to the electrodialysis and related processes. Each paper has a summary in three languages, and each section is prefaced with an introductory article which indicates the present state of the appropriate technique and outlines its problems and possible developments.

Thus, this volume of Dechema monographs does not only give a comprehensive review of this technically and economically very important field, but also reveals the very special problems involved and makes it obvious that considerable development work will have to be undertaken before deserts can be irrigated and made useful. *D. Moegling* [NB 00685/62 IE]

**Analyse der Metalle** (Analysis of Metals), published by the Chemikerausschuß der Ges. Deutscher Metallhütten- und Bergleute (Chemical Committee of the German Society of Mining and Metallurgy), Vol. 2: Routine Analysis. 2nd Edit. Part 1. Aluminum-Sulfur, XVI + 726 pp., Part 2: Selenium-Zirconium, Physico-chemical Procedures, IV + 842 pp., Springer-Verlag, Berlin-Göttingen-Heidelberg, 1961, cloth. Price for both volumes: DM 158.-(about $40.-)

The fact that Vol. 2 of the "Analysis of Metals", covering "Routine Analysis", was sold out within six years of its first appearance indicates clearly the high regard and wide circulation that this detailed collection of analytical methods for routine work enjoys in the laboratories of the mining and metallurgical industries. The appearance of this second revised edition within eight years of the first publication is greatly to be welcomed. The established reliable arrangement of the extensive material has been retained unaltered. Some chapters are greatly extended, many old procedures have been discarded, others improved, and many new methods, particularly those employing complexometric titration and photometry, have been included. Chapters on conductometric and high-frequency titration have been added; the chapter on "Standard Samples" has been omitted and a chapter on "Buffer Solutions" is taken up, which contains an extensive collection of commonly used buffer solutions, with details of their pH values and adjustable pH ranges. The progress and development of analytical methods since the publication of the first edition has been taken into account in a pleasing and completely satisfactory manner. The size of the complete volume has only increased by about 10% despite these considerable additions and extensions. It is certain that this second edition will quickly gain the wide circulation it undoubtedly deserves and that its use will not be confined to the laboratories of the branches of industry that are immediately interested.

This positive overall evaluation, far from being undermined by some critical remarks, should be complemented by some suggestions for a new edition which is sure to be required before very long. It is noticeable that in only some of the chapters have the old methods for the determination of iron – titration with titanium(III) chloride, or colorimetric determination with potassium thiocyanate – given way to the new photometric methods of analysis. In various chapters different temperatures are recommended for the ignition of silicon dioxide (between 800 and 1200 °C) and of alumina and sesquioxides (between 900 and 1200 ± 50 °C). The reviewer is well aware of the time and trouble involved in securing the desirable improvements in the co-ordination of the chapters as mentioned in these examples. The terms "analytical moisture" and "analytically moist samples for analyses" (chapter on "Solid Fuels", p. 1144) are most unhappily chosen; they imply respectively the actual moisture content of the air-dried sample, and the air-dried sample in contrast to the sample dried to constant weight by heating (mostly at 110 °C).

The need for better accordance is also apparent in the chapters on "Physico-chemical Procedures". The principle adopted in the chapter on "Spectrophotometric Analysis" (see preamble, p. 1350) of extensively restricting the description of commercial instruments and of working out in exchange the user's requirements on these instruments to form a clear judgement ought to have been applied also in the following chapters, including the chapter on photometry. The user of the book is little served by mere enumeration of instrument types, some of which are already completely out-of-date and almost commercially unobtainable.

The chapter on "Potentiometry" should be expanded by inclusion of the techniques of amperometric and voltametric titrations and entitled "Analytical Measurements Employing Electrical End-Point Detection", as is fittingly required by the increasing use of these analytical methods derived from potentiometry.

The new chapter on "High-Frequency Titration" certainly gives an excellent survey of the literature of its applications, with 180 references, but it goes far beyond the strict field of metal analysis.

The reviewer, who is himself a long-standing user of the "Analysis of Metals" manuals, hopes that the defects pointed out can be rectified in the next edition and wishes the editor and authors all success. *K. E. Stumpf* [NB 72/60 IE]

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# Defensive Substances of the Arthropods, Their Isolation and Identification

BY PROF. DR. H. SCHILDKNECHT [*]
IN COLLABORATION WITH DR. K. HOLOUBEK, DR. K. H. WEIS, AND DIPL.-CHEM. H. KRÄMER
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*Numerous orders of arthropods have organs which produce and store defensive substances. The purpose of our studies was to learn more about the chemical composition of these defensive secretions. In this work, we had to forego a priori many of the possibilities of classical organic-chemical analysis, since some of the insects were difficult to obtain and operation with substantial amounts of material was precluded. However, the defensive substances of various families of Arthropoda were characterized by using modern chemical and physical analytical procedures and our own methods of separation, purification, and enrichment which we developed specifically for this purpose.*

## 1. Introduction

On a winter's afternoon, on January 10th, 1789, *Pierre Lyonet* died in the Hague (Holland). Like *Swamerdam* [1], as an ingenious master of the lens and with homemade microscopes, he had investigated the internal fine morphology of insects [2]. Less than a decade after his death, the entomologist *Wilhelm* demanded a "new Lyonet", from whom he hoped to obtain a "micrographia" of the *Brachynidae*, by which the riddle of the bombardier beetle was to be solved [3]; however, he did not live to see the most important anatomical studies on the abdominal organs of carabid beetles [4–8]. He would perhaps have been disappointed; for, after outstanding work on the pygidial bladders of the great water beetle [9], *Dierckx* came to the conclusion that only with a knowledge of the chemistry of these organs could their significance and function be explained. What was lacking, therefore, was a "chemical anatomy", *i.e.* the correlation of the substances contained in the secretions and the chemical mechanisms involved in their formation to the types of organ already defined anatomically.

*Lyonet* extended and deepened the knowledge of insect anatomy with new means; the insect chemistry desired as a parallel to it likewise needed new methods to help identify the secretions of the defense bladders (Figs. 1 and 2) of different beetle species.

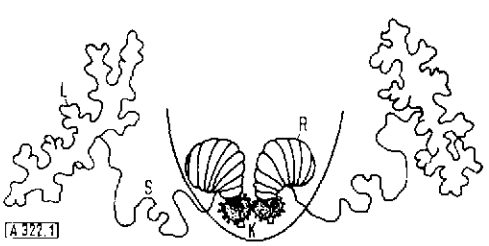



Fig. 1. Pygidial bladders of the bombardier beetle with reservoir R, explosion chamber K, lobes L, and collecting channel S (S and L have been drawn outside the abdomen). After [10].

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[1] *J. Swamerdam:* Bibel der Natur. Utrecht 1669.

[2] Cf. *W. H. Van Seters:* Pierre Lyonet, 1706–1789, Sa Vie – Ses Collections de Coquillages et de Tableaux – Ses Recherches Entomologiques. Martinus Nijhoff, The Hague 1962.

[3] Unterhaltungen aus der Naturgeschichte der Insecten, erster Theil. Mart-Engelbrechtische Buchhandlung, Augsburg 1796.

[4] *L. Dufour*, Ann. Sci. natur. *1826*, Pl. 19, 20.

[5] *H. Meckel*, Müllers Archiv *1846*, 1.

[6] *Fr. Stein:* Vergleichende Anatomie und Physiologie der Insekten. Duncker & Humboldt, Berlin 1847, p. 84.

[7] *H. Karsten*, Müllers Archiv *1848*, 367.

[8] *F. Leydig*, Müllers Archiv *1859*, 33.

[9] *Fr. Dierckx*, La Cellule *16*, 61 (1899).

[10] *K. Holoubek*, Ph. D. Thesis, Universität Erlangen, 1959.

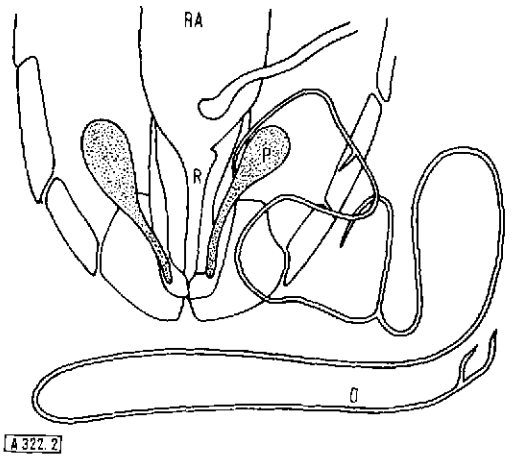



Fig. 2. Pygidial bladders P of the great water beetle, with rectal ampulla RA, rectum R, and a glandular tube D (D drawn outside the abdomen). After [10].

## 2. Methods

Because of the small size of the organs and the often very small number of experimental animals that are available, the classical methods for the enrichment, separation and identification of mixtures of substances usually have to be dispensed with and modern microprocedures applied or developed [11].

Gases can be identified [12] accurately and elegantly with the mass spectrometer, and volatile compounds may be isolated with the simple suction apparatus [13] illustrated in Fig. 3.

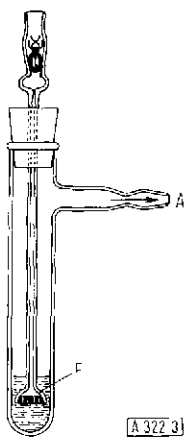



Fig. 3. Suction apparatus for isolating insects' defensive substances. F = porous glass plate.

If the beetle is irritated by pressing, pinching, or heat and air is slowly sucked past it and bubbled through a solvent in a trap, then only the substances discharged for defense are obtained. The beetle should remain alive so that, when it has regenerated its defensive material, it can be "milked" afresh. Naturally the extracts obtained in this way are still very dilute, so that the compounds sought can often not be determined unequivocally. The solutions, however, can be concentrated – without loss by decomposition and solvent volatility – by freezing out the solvent, *i. e.* by "normal freezing" [14, 15] and ice zone melting [16].

Using zone melting, traces of substances may also be isolated from solid solutions on a micropreparative scale [17], and mixtures of substances can even be separated, *e.g.* insect waxes [18] and fatty alcohols [19]. The most important supplement to these procedures for enrichment and separation are chromatographic methods, which also facilitate identification; however, successful identification usually requires spectroscopy.

We began our experiments in this way with carabid beetles, 6 to 8 mm in size, which possessed the best-developed defensive mechanism, *viz.* with the bombardier beetles [12, 20] (cf. Fig. 4).



Fig. 4. *Brachynus crepitans*, a carabid beetle 8 mm long with rust-red prothorax and blue-green elytra (wing cases); cf. [21]. Magnification: 2.5-times.

## 3. Bombardier Beetle (Brachynidae)

It was only many years after the old master of entomology, *De Geer* [22], had reported in his natural history of insects on the bombardier beetles that *Bergsträsser* [23] in 1778 ventured an explanation of the discharge, which he took to be a "Windschuss", *i.e.* an effect of compressed air. After this rather physical consideration, a doctor in the medical corps of the third French army corps of Napoleon gave the first details of the chemical nature of the substances expelled. During the Spanish campaign of 1808 in the Pyrenees, he had enough time to investigate the bombardier beetles *Brachinus* and *Aptinus* [4, 24, 25]. Inspired by the familiar chemistry of defense

[11] *H. Schildknecht* in: XIth International Congress for Entomology, Vienna *1960*, Proceedings. Istituto di Entomologia Agraria dell'Università die Pavia, 1960, Vol. III, p. 269.

[12] *H. Schildknecht*, Angew. Chem. *69*, 62 (1957).

[13] *H. Schildknecht*, Angew. Chem. *71*, 524 (1959).

[14] *H. Schildknecht*, *G. Rauch*, and *F. Schlegelmilch*, Chemiker-Ztg. *83*, 549 (1959).

[15] *H. Schildknecht* and *F. Schlegelmilch*, Chemie-Ing.-Techn. *35*, 637 (1963).

[16] *H. Schildknecht* and *A. Mannl*, Angew. Chem. *69*, 634 (1957).

[17] *H. Schildknecht*, Z. analyt. Chem. *181*, 254 (1961).

[18] *H. Schildknecht* and *H. Vetter*, Fette, Seifen, Anstrichmittel *65*, 551 (1963).

[19] *H. Schildknecht*, *G. Renner*, and *W. Keess*, Fette, Seifen, Anstrichmittel *64*, 493 (1962).

[20] *H. Schildknecht* and *K. Holoubek*, Angew. Chem. *73*, 1 (1961).

[21] *E. Reitter:* Fauna Germanica – Die Käfer des Deutschen Reiches. K. G. Lutz, Stuttgart 1908, Vol. I, p. 31.

[22] *C. de Geer:* Mémoirs pour Servir a l'Histoire des Insectes. Hosselberg, Stockholm 1752, Vol. 7.

[23] *J. A. B. Bergsträsser:* Nomenclatur I. Published by the author, Hanau (Germany) 1778.

[24] *L. Dufour*, Annales de Musée *18*, 70 (1811).

[25] *L. Dufour*, Nouveau Bulletin des Sciences, par la Société Philomatique, *1812*, Vol. III, n. 58.

of that time, he explained the red to brown spots on the skin caused by the discharge as being due to the action of nitric acid or of nitrous gases.

Without knowing of the results of this investigation, naturalists continued to interpret the bombardier beetle's discharge either from a physical or from a chemical point of view (Table 1). The final decision occurred only in 1957 when we were able to detect benzoquinone and toluquinone [12] in the "powder smoke" from living

Table 1. History of research on the bombardier beetle.

| Suggested bladder contents | Suggested expulsion mechanism | Year | Reference |
|---|---|---|---|
| Compressed air | "Windschuß" | 1778 | [23] |
| $HNO_3$ | Liquid spray | 1808 | [4, 24, 25] |
| Transparent liquid; reacts with $O_2$ of the air to give $HNO_2$ and $N_2O$ | Vapor spray | 1848 | [7] |
| Low boiling liquid | Vapor spray | 1860 | [27] |
| Compressed air (in the "condensateur") | "Air gun" with a "shot of an organic chemical nature" | 1884 | [28] |
| Iodine from an iodine-nitrogenous compound | Liquid spray | 1885 | [29] |
| Low boiling liquid with b.p. 8 and 15 °C | Vapor spray | 1899 | [9] |
| Nitrites, nitrous acid | Liquid spray | 1939 | [30] |

bombardier beetles by "bombardment" of chromatography paper impregnated with 2,4-dinitrophenylhydrazine (2,4-DNP) and by ultraviolet spectroscopy of the *Brachynus* extract together with 95–98 % oxygen, which was identified by mass spectroscopy and by micro gas analysis according to *Berg* [26]. However, in the storage bladders, which on the average weigh 0.8 mg, the appropriate "ammunition" must have occurred as a liquid or as a dissolved, colorless mixture of substances, for this is all that can be recognized by examination of the defense organs (Fig. 5).



Fig. 5. Bombardier beetle with pygidial bladders exposed.

However, if the secretion reservoir is pierced, its contents bubble out, and become colored more and more red-brown and finally violet (Fig. 6a–d).

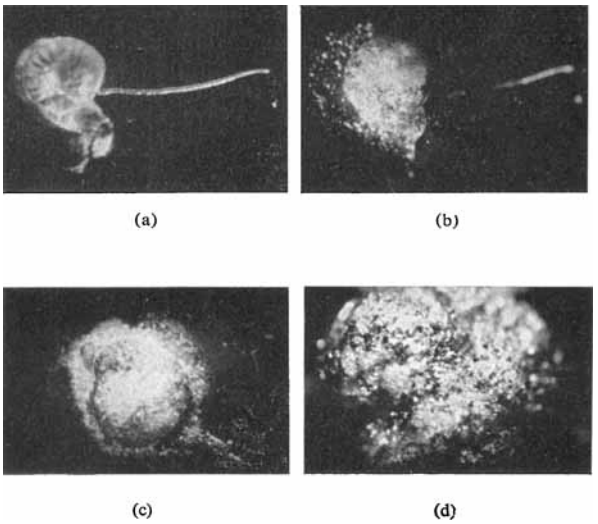


Fig. 6.
(a) An undamaged bladder from a bombardier beetle, entirely filled with a colorless liquid, dissected out with its collecting channel.
(b) Injured bladder. Start of the reaction: effervescence and bubble formation.
(c) End of the bladder reaction.
(d) The bladder reaction has stopped and crystalline quinhydrone (black dots) can be recognized.

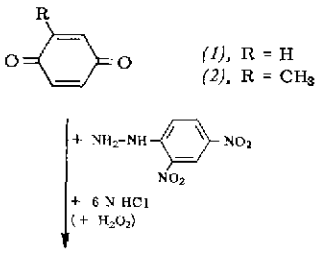
The air around the destroyed bladder has a pungent smell like that of the discharge of the beetle. The smell is caused by enzymatically catalysed development of quinones. The coloration is sometimes very intense blue to violet and can be understood as being due to quinhydrone formation. That was a first indication that the quinones arose from hydroquinones. These were in fact detected in the colorless bladder contents in substance, by paper chromatography, and also by ultraviolet and infrared spectroscopy. They occur in the bladder as an approximately 10 % solution in about 25 % hydrogen peroxide, which was identified both qualitatively and quantitatively.

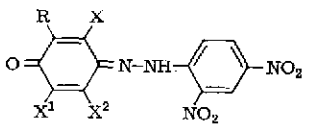
The hydrogen peroxide was detected in bladder extract obtained at −50 °C by oxidation of potassium iodide and reduction of potassium permanganate as well as colorimetrically with titaneous sulfate. The final decision as to whether $H_2O_2$ alone was really present was provided by paper chromatography with the solvent system ethyl acetate/dioxan/water (20:45:46) recommended by *Rieche* [31] for the separation of hydrogen peroxide and peroxides.

Also the 2,4-dinitrophenylhydrazones formed from the bladder substances indicated highly concentrated $H_2O_2$. As a study of the reaction of benzoquinones with 2,4-DNP showed, chlorinated hydroquinones are formed in presence of 6 N HCl before hydrazone formation occurs. These react either as such or after oxidation with still unreacted quinone to yield chlorinated 2,4-dinitrophenylhydrazones. In presence of $H_2O_2$, a further chlorobenzoquinone is generally formed. Thus, *p*-benzoquinone *(1)* reacts with 2,4-DNP in 6 N HCl to give the hydrazones of benzoquinone *(3)* and 3-chlorobenzoquinone *(4)*. In presence of $H_2O_2$, the 2,4-dinitrophenylhydrazone of 2,3-dichlorobenzoquinone

[26] *W. E. Berg*, Science (Washington) *104*, 575 (1946).
[27] *M. C. Dumeril*, Memoires de l'academie des Sciences de l'Institut Impérial de France *31* (1st part), 277 (1860).
[28] *Ph. de Rougemont*, Mitt. Schweiz. entom. Ges. *6*, 99 (1884).
[29] *C. Loman*, Tijdschrift der Nederlandsche Dierkundige Vereenigung *1886*, Deel I, Afte Vering 2, p. 106.
[30] *M. Vialli*, Riv. Biol. Coloniale *2*, 273 (1939).
[31] *A. Rieche*, Angew. Chem. *70*, 263 (1958).

*(5)* was also formed. Toluquinone, 2,4-DNP, and 6 N HCl yield the hydrazones of toluquinone *(6)* and




| | R | X | $X^1$ | $X^2$ |
|---|---|---|---|---|
| *(3)* | H | H | H | H |
| *(4)* | H | H | H | Cl |
| *(5)* | H | H | Cl | Cl |
| *(6)* | $CH_3$ | H | H | H |
| *(7)* | $CH_3$ | Cl | H | H |
| *(8)* | $CH_3$ | H | Cl | H |

6-chlorotoluquinone *(8)*; if $H_2O_2$ is present, the hydrazone of 3-chlorotoluquinone *(7)* is obtained as well. In contrast to all the other hydrazones investigated, the 2,4-dinitrophenylhydrazones of 3- and 6-chlorotoluquinone dissolve in ethanol with a blue-green to violet color. Table 2 shows the $R_F$-values of the hydrazones *(3)* to *(8)*.

Table 2. Paper chromatography (descending) of the 2,4-dinitrophenylhydrazones of benzoquinones. The colors appear usually only after gassing the chromatograms with ammonia or spraying with caustic alkali. They remain after the evaporation of the ammonia.

| Compound | $R_F$-value[a] in; Color after treatment with | | |
|---|---|---|---|
| | Benzene/$CHCl_3$ (1:1); $NH_3$ | Diisopropyl ether/cyclohexane (1:1); 0.1 N NaOH | Diisoamyl ether/cyclohexane (4:1); 0.1 N NaOH |
| *(3)* | 1.0; red-violet | 1.0; red-violet | 1.0; red-violet |
| *(4)* | 0.08; red-violet | 1.20; red-violet | 1.39; red-violet |
| *(5)* | 0.00 | 0.42; red-violet | 0.44; red-violet |
| *(6)* | eluted | 1.10; blue | 1.15; blue |
| *(7)* | 0.47; red-violet | 0.21; red-violet | 0.11; red-violet |
| *(8)* | 1.0; violet | 1; blue-violet | 1; blue-violet |

[a] Relative to $R_F$ of *(3)* = 1.0.

The change in color of the hydrazones mentioned with alkalies is of the greatest value, especially if it is measured spectrophotometrically, for the rapid and reliable characterization of very small amounts of quinones (Figs. 7–9).

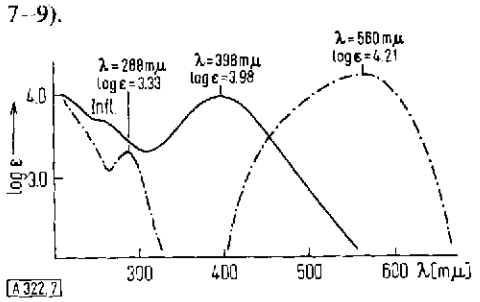



Fig. 7. Ultraviolet absorption curves of benzoquinone-2,4-dinitrophenylhydrazone *(3)*:
—— in 95 % ethanol; — · — · — in 0.1 N ethanolic NaOH.

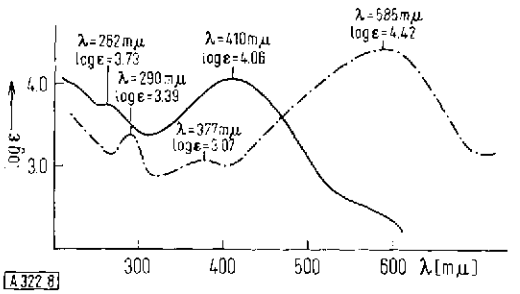



Fig. 8. Ultraviolet absorption curves of toluquinone-2,4-dinitrophenylhydrazone *(4)*:
—— in 95 % ethanol; — · — · — in ethanolic 0.1 N NaOH.

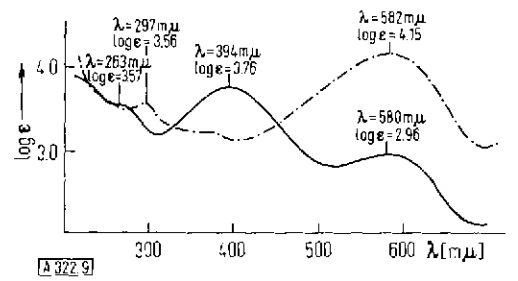
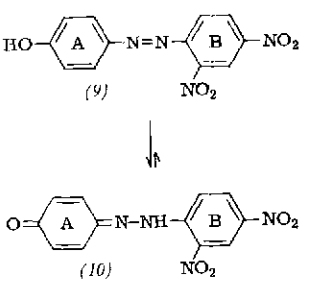



Fig. 9. Ultraviolet absorption curves of 6-chlorotoluquinone-2,4-dinitrophenylhydrazone *(8)*:
—— in 95 % ethanol; — · — · — in 0.1 N ethanolic NaOH.

This bathochromic shift is understandable when one realizes that 2,4-dinitro-4'-hydroxyazobenzene *(9)*, for example, exists entirely in the quinonoid form *(10)* [34] (in contrast to 4-hydroxyazobenzene [32, 33]).




In alcoholic solution, the 2,4-dinitrophenylhydrazones of quinones or even those of aldehydes and ketones [35–38] can therefore be regarded as weak acids, with the proton on the basic azo nitrogen [39]. The dissociation of these very weak acids is stronger if ring A is substituted with a methyl group. It is strenghtened even further by halogeno substituents.

The resonance-stabilized cation can be recognized in the ultraviolet absorption spectra by an inflexion of the absorption curve between 580 and 585 mμ for toluquinone-2,4-dinitrophenylhydrazone (Fig. 8, continuous curve) and by a maxi-


[32] *R. Kuhn* and *F. Bär*, Liebigs Ann. Chem. *516*, 143 (1935).

[33] *H. Shlingu*, Sci. Pap. Inst. Physic. Chem. Research (Tokio) *35*, 78 (1938).

[34] *W. Lauer* and *S. Miller*, J. Amer. chem. Soc. *57*, 520 (1935).

[35] *C. J. Timmons*, J. chem. Soc. (London) *1957*, 2613.

[36] *A. J. Sensabaugh, R. A. Cundiff*, and *P. C. Markunas*, Analytic. Chem. *30*, 1445 (1958).

[37] *R. S. Starns* and *G. W. Wheland*, J. Amer. chem. Soc. *69*, 2025 (1947).

[38] *R. Schaal* and *C. Gadet*, Bull. Soc. Chim. France *1961*, 2154.

[39] *L. Doub* and *J. M. Vandenbelt*, J. Amer. chem. Soc. *69*, 2714 (1947); *71*, 2414 (1949); *77*, 4535 (1955).

mum at 580 mμ for 6-chlorotoluquinone-2,4-dinitrophenylhydrazone (Fig. 9, continuous curve). It corresponds to the chief maximum of benzoquinone-2,4-dinitrophenylhydrazone in alkaline solution (Fig. 7, broken curve).

## 4. Darkling Ground Beetles (Tenebrionidae)

The members of this family of beetles are often termed "black beetles", although not all of them are black; a better designation would be "quinone beetles", for neither a study of the literature [40,41] nor our own investigations [13,42,43] have disclosed a tenebrionid without benzoquinone. Even 100 year old black beetles we obtained from museums contained quinones in the abdomen [43]. Since the tenebrionids do not always possess a well-filled storage organ for their defensive substances and as their defensive reaction often simply involves exposure of folds in the skin that contain glands [44], the secretion must be collected and concentrated by frequent "milking" of the beetles with the arrangement shown in Fig. 3. Frequently, however, when certain species – especially the death-watch beetle – are threatened, they give off a liquid, highly volatile yellow secretion from two cylindrical vessels [45], which can be analyzed without previous enrichment, *e.g.* by zone melting techniques.

In each case, the defensive fluid gave the typical ultraviolet absorption spectrum of *p*-benzoquinone, formed a quinhydrone, and gave a precipitate with 2,4-dinitrophenylhydrazine which was easy to purify by chromatography on a column of silica gel with chloroform as eluant. This enabled us to carry out a semiquantitative determination of the amounts of quinone stored by the beetles (Table 3).

Table 3. Amounts of quinone secreted by black beetles.

| Number of animals "milked" | Beetle species | Total amount of mono-hydrazones obtained [μg] | Calculated amount of quinone/beetle [μg] |
|---|---|---|---|
| 5 | *Blaps mortisaga* | 270 | 20 |
| 5 | *Bl. lethifera* | 360 | 27 |
| 10 | *Bl. mucronata* | 580 | 22 |
| 10 | *Bl. requienii* | 2430 | 91 |
| 20 | *Diaperis boleti* | 950 | 17 |
| 10 | *Helops quisquilius* | 160 | 6 |
| 5 | *Opatrum sabulosum* | 180 | 13 |
| 5 | *Scaurus uncinus* | 130 | 10 |

The monohydrazones of quinones may be identified rapidly and without much effort using our chromatographic procedure. When working with unknown mixtures, it is recommended to select the solvent after preliminary tests with a drop of secretion. As markers, the mono-2,4-dinitrophenylhydrazone of benzoquinone is used for the solvent mixture chloroform/benzene (2:1), that of 2-ethylquinone for cyclohexane/benzene (1:2), and that of 2-butylquinone for cyclohexane/benzene (2:1). The most suitable mixture for the 2,4-dinitrophenylhydrazones of the quinones from *Tenebrionidae* was chloroform/benzene (1:1). Fig. 10 shows a typical chromatogram.

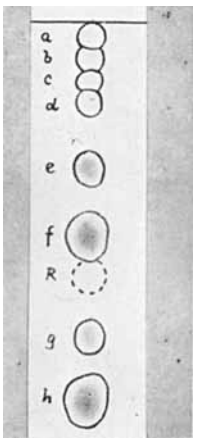



Fig. 10. Chromatogram of the bladders of different *Blaps* species, after treatment with 2,4-dinitrophenylhydrazine hydrochloride.

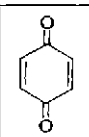
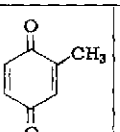
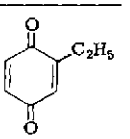
The red-violet spots a–d are the 2,4-dinitrophenylhydrazones of chlorinated quinones, which are formed in 6N HCl and facilitate interpretation of the chromatogram. The blue-violet spot f and the greyish, dark violet spot h are due to the 1-mono-2,4-dinitrophenylhydrazones of 2-methyl- and 2-ethyl-*p*-benzoquinone, respectively. The blue-violet spots e and g are derived from the 1-mono-2,4-dinitrophenylhydrazones of 3-methyl- and 3-ethyl-*p*-benzoquinone.

We have confirmed this allocation of the spots by paper chromatographic comparison with monohydrazones which we synthetized by coupling the corresponding phenols with 2,4-dinitroaniline according to the procedure of *Lauer* and *Miller* [34].

The secretions of all the black beetles investigated contain – with exception of the flour beetle *T. molitor* [13] – ethylbenzoquinone and toluquinone. In the case of two species of death-watch beetles and a *Scaurus* from Italy, benzoquinone is also found (Table 4).

In addition, the male of *Blaps requienii* possesses a brown bristly spot between the first and second ventral sternites that has been designated as its "Duftapparat"

Table 4. Substances contained in the pygidial bladders of 12 *Tenebrionidae* and one *Alleculidae* species.

| |  |  |  |
|---|---|---|---|
| *Tenebrionidae* | | | |
| *Blaps mortisaga* | – | + | + |
| *Bl. mucronata* [46] | – | + | + |
| *Bl. requienii* [46] | (+) | + | + |
| *Bl. lethifera* | + | + | + |
| *Bl. gigas* | + | + | + |
| *Scaurus uncinus* | + | + | + |
| *Diaperis boleti* [46] | – | + | + |
| *Helops quisquilius* | – | + | + |
| *Helops aeneus* | – | + | + |
| *Opatrum sabulosum* | – | + | + |
| *Opatroides punctulatus* | – | + | + |
| *Tenebrio molitor* | – | + | – |
| *Alleculidae* | | | |
| *Prionychus ater* Fabr. | – | + | + |

[40] *R. Trave, L. Garanti,* and *M. Pavan,* Chim. et Ind. *41,* 19 (1959).

[41] *L. M. Roth* and *T. Eisner,* Annu. Rev. Entom. 7, 107 (1962).

[42] *H. Schildknecht* and *K. H. Weis,* Z. Naturforsch. *15b,* 200 (1960).

[43] *H. Schildknecht* and *K. H. Weis,* Z. Naturforsch. *15b,* 757 (1960).

[44] *L. M. Roth,* Ann. entomol. Soc. America *38,* 77 (1945).

[45] *G. Gilson,* La Cellule *5,* 3 (1889).

[46] We thank Prof. Dr. *Pavan* (Pavia, Italy) for sending us this beetle.

or "perfume gland" [47]. In it we found a very small amount of *p*-benzoquinone, which is absent in the pygidial bladders of this species.

### 5. Earwigs (Forficulidae)

Our attempts to find secretions in the vast and multifarious insect family of the *Hymenoptera* had to be limited to earwigs, because our native grass-hopper species have no sign of the presence of defensive substances. There are five species of earwig in Germany, but we were only able to secure the common earwig *Forficula auricularia* (Fig. 11).

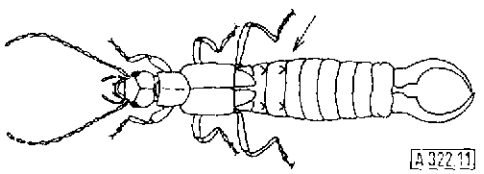


Fig. 11. *Forficula auricularia* Linn. (after [48]) with the 4 glandular orifices (arrow), from which the insects can spray their defensive substances distances of up to 10 cm.

Its stink bladders contain a yellow to brownish, often violet-tinged liquid, in which quinones can be detected even in preliminary tests, *e.g.* by its absorption at 246 mμ. The secretion was worked up micropreparatively as for the death-watch beetles, *viz.* by "milking" the secretion into a trap with 2,4-DNP solution, extraction of the hydrazones with chloroform and purification on a silica gel column. The hydrazones obtained were those of toluquinone and ethylbenzoquinone; one earwig even yielded 20 μg of the quinone mixture per ejaculation [49]. Besides the quinones, the defensive bladders contain the hydroquinones, as can be shown by thin-layer chromatography [50].

### 6. Millipedes (Diplopoda)

When attacked, millipedes at once roll themselves together (Fig. 12) and extrude a yellow liquid from nearly every segment of their extremely hard chitinous shell.

This appeared at first to have a composition similar to that of the secretion of the *Tenebrionidae* and *Forficulidae*, but there were in fact two distinct differences. The ultraviolet absorption curve showed maxima between 250 and 254 mμ and between 370 and 375 mμ, and a micropreparation of a quinone fraction, obtained by column chromatography, dissolved in alkali very slowly with decompositon. The position of the ultraviolet absorption maxima suggested a methoxyquinone

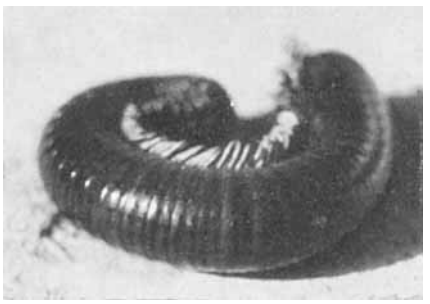
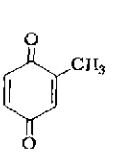
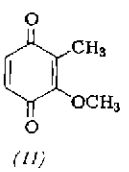


Fig. 12. Millipede (a *Spirostreptus* species from Peru) in alarmed condition [51].

[52], which, being a vinologous ester, ought to be saponifiable. We were able to characterize the quinone [54] as 2-methyl-3-methoxy-*p*-benzoquinone *(11)* in good agreement with the analytical results which *Pavan* [53] obtained with *Archiolus sabulosus*.

Table 5. Composition of the secretion of different diplopod species.

| Diplopod species | Relative amounts [%] of  |  *(11)* |
|---|---|---|
| Diplopod from Belgian Congo | 21 | 79 |
| Diplopod from New Guinea | 17 | 83 |
| Diplopod from Madagascar | 36 | 64 |
| *Rhinocricus* species from Peru | 48 | 52 |
| *Brachyiulus unilineatus* | 49 | 51 |
| *Cylindroiulus teutonicus* | 58 | 42 |

All six species of diplopods investigated secreted toluquinone and 3-methoxytoluquinone *(11)*, although the origins of the animals were quite different. Only the proportions vary. We isolated 0.5–1.5 mg of quinones per specimen in the form of their hydrazones from the indigenous species and more than 3.0 mg of quinones from the foreign species.

### 7. Bugs (Pentatomidae)

Very few readers will know the stink bladders of leaf beetle, but most may well have tasted their contents. From this detestable taste it may be concluded that the substances of the stink bladders of *Dolycoris baccarum*, for example, are not quinones but rather carbonyl compounds, as preliminary chemical and spectroscopical

[47] *G. Brandes*, Z. Naturwiss. *72*, No. 3 (1899).

[48] *T. Eisner*, Psyche *67*, 62 (1960).

[49] *H. Schildknecht* and *K. H. Weis*, Z. Naturforsch. *15b*, 755 (1960).

[50] *H. Schildknecht* and *H. Krämer*, Z. Naturforsch. *17b*, 701 (1962).

[51] We wish to thank Dr. *O. Kraus* (Senckenbergische Naturforschende Gesellschaft), Prof. Dr. *H. J. Stammer* and Priv.-Doz. Dr. *G. Osche* (Institut für Zoologie der Universität Erlangen) for supplying us with foreign millipedes.

[52] *W. Flaig* and *J. Ch. Salfeld*, Liebigs Ann. Chem. *618*, 117 (1958).

[53] *R. Trave*, *L. Garanti*, and *M. Pavan*, Chim. et Ind. *41*, 19 (1959).

[54] *H. Schildknecht* and *K. H. Weis*, Z. Naturforsch. *16b*, 810 (1961).

tests did in fact show. Hence in this case, too, a red precipitate is obtained with 2,4-DNP; this we investigated with reference to our work on the phytoncides of angiosperms [55]. After preliminary purification on a silica gel column, we separated the mixture of hydrazones by thin-layer chromatography on silica gel G and analysed the fractions by paper chromatography. Table 6 gives the melting points and absorption maxima of the 2,4-dinitrophenylhydrazones found and synthetized for comparison.

Table 6. Ultraviolet absorption maxima and melting points of the 2,4-dinitrophenylhydrazones of three α,β-unsaturated carbonyl compounds and of three substances (A, B, and C) isolated from bugs.

| Substance | M.p. [°C] | $\lambda_{max}$ in ethanol [mμ] | $\lambda_{max}$ in ethanol/ 0.25 % NaOH [mμ] |
|---|---|---|---|
| A | 142 | 374 | 455 |
| $\Delta^2$-n-Hexenal-DNPH | 144 | 374 | 455 |
| B | 126 | 374 | 460 |
| $\Delta^2$-n-Octenal-DNPH | 126 | 372 | 455 |
| C | 120 | 372 | 455 |
| $\Delta^2$-n-Decenal-DNPH | 124 | 374 | 455 |

In agreement with the findings of *Waterhouse* [56], who investigated Australian leaf beetles, all our analytical data pointed to the result that the bug species listed in Table 7 give off $\Delta^2$-n-hexenal *(12)*, $\Delta^2$-n-octenal *(13)*, $\Delta^2$-n-decenal *(14)*, and a still unknown carbonyl compound for their defense [57].

Table 7. Proportions of the contents of bug bladders.

$H_3C-(CH_2)_n-CH=CH-CHO$ *(12)*, n = 2; *(13)*, n = 4; *(18)*, n = 6

| Bug species | Relative proportions [%] of | | | |
|---|---|---|---|---|
| | *(12)* | *(13)* | *(14)* | unknown carbonyl compound |
| *Dolycoris baccarum* L. | 50 | 20 | 5 | 25 |
| *Eurogaster* species | 60 | 20 | 0 | 20 |
| *Palomena viridissima* P. | 30 | 5 | 25 | 40 |
| *Cimex lactularius* P. (bed bug) | 70 | 30 | 0 | 0 |

Since hexenal is not lacking in the stink bladders of the bed bug, this is a good indication that leaf bugs very probably also synthetize hexenal in their own metabolism and do not merely take it up with their food from leaves, in which unsaturated aldehydes invariably occur [55, 58, 59].

[55] *H. Schildknecht* and *G. Rauch*, Z. Naturforsch. *16b*, 422 (1961).

[56] *D. F. Waterhouse*, *D. A. Forss*, and *R. H. Hackmann*, J. Insect Physiol. *6*, 113 (1961).

[57] *H. Schildknecht* and *K. H. Weis*, Z. Naturforsch. *17b*, 350 (1962).

[58] *W. Karrer:* Konstitution und Vorkommen der organischen Pflanzenstoffe. Birkhäuser, Basel/Stuttgart 1958, p. 149.

[59] *R. T. Major*, *P. Marchini*, and *Th. Sproston*, J. biol. Chem. *235*, 3289 (1960).



*Scherny* reported the occurrence of about 20000 known carabid beetle species [60], of which about 900 are found in Germany. When excited, all of these beetles release colorless, liquid, highly volatile secretions from paired defense organs [61]. In this way, two groups of carabids can be distinguished simply by their smell.

One group, including all members of the subfamily *Carabinae*, but also some *Harpalinae*, secrete, as *Scherney* himself put it, "a sharp, peculiarly aromatic smelling liquid", which causes a transient but nonetheless painful burning sensation in the eye. *Horion* [62] speaks of an intense musky smell, that clings to the fingers.

The other group, exclusively beetles of the subfamily *Harpalinae*, also excrete a liquid secretion, but this has a pungent smell.

### a) The "Aromatic" Carabid Beetle Secretion

As early as more than a hundred years ago, a notable publication by *Pelouze* [63] appeared which has not been questioned till today. In his article "Sur la nature du liquide sécreté par la glande abdominale des insectes du genre Carabe" he advanced the view that the secretion of *Carabus niger* and of *C. auratus* consisted of mainly butyric acid. In our experience, butyric acid smells differently. In agreement with *Pelouze*, however, we found that the carabid beetle's secretion reacts acidic, corrodes the skin, and that its alkali salts are strongly surface active.

The observation that the secretion evaporated easily but often formed spontaneously a plastic film were hard to explain. The question of the state of aggregation of the acid we were seeking could not be elucidated at first by repeated observation of the crude secretion. The possibility of a gaseous or solid substance in solution existed just as much as that of a liquid compound. We were extremely fortunate, therefore, when a gold beetle *Carabus auratus* (Fig. 13) sprayed the lens of my companion's

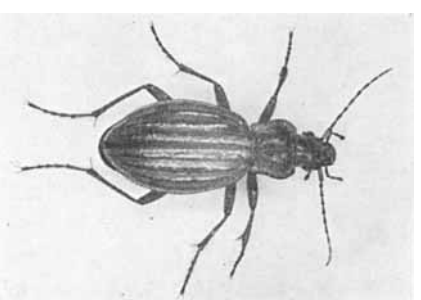


Fig. 13. *Carabus auratus* L., the gold beetle, a carabid beetle 20–27 mm long, with a metallic green colored prothorax and yellowish, gold-green elytra. Magnification ca. 1.1-times.

[60] *F. Scherny:* Die neue Brehm-Bücherei. Ziemsen, Wittenberg 1959, No. 245.

[61] *A. Berlese:* Gli Insetti. Milano 1909, Vol. I, p. 543.

[62] *A. Horion:* Käferkunde für Naturfreunde. Vittoria Klostermann, Frankfurt/M. 1949.

[63] *M. J. Peloaze*, C. r. hebd. Séances. Acad. Sci. *43*, 122 (1856).

spectacles and its defensive secretion immediately solidified, at least partially. From its melting point of 62 °C preliminary spectrophotometrical tests, preliminary chemical tests with $KMnO_4$, bromine water, and tetranitromethane, and by chromatographic comparison with different organic acids, we were also led to suspect a carboxylic acid of moderate molecular weight, but an unsaturated one.

Further characterization of the acid was only possible when we happened to observe how a beetle's discharge gave a persistent mist of an ammonium salt when held near to an open bottle filled with aqueous ammonia.

Afterwards by collecting the secretion spray on a microscope slide and treating it with ammonia gas, we succeeded in obtaining a colorless, crystalline, easily sublimable ammonium salt. This was particularly suitable for establishing a small store of secretion. Nevertheless, we had only a few milligrams from which to remove always only a minute fraction for infrared spectroscopical comparison with other branched and unsaturated carboxylic acids. We finally found the best agreement between the secretion and tiglic acid. In spite of the similarity of the infrared spectra of the ammonium salts of the two acids, two absorption bands that were especially characteristic for each of the spectra lay at different wave numbers. The spectrum of tiglic acid contains bands at 798 and 748 $cm^{-1}$, that of the beetle secretion at 924 and 823 $cm^{-1}$ (Fig. 14). From the differing positions of these skeletal vibrational bands, the spectroscopist can interpret differing chain lengths. Elementary analysis [64] and a quantitative microhydrogenation were also indicative of a shorter chain, thus suggesting methacrylic acid *(15)*. In addition, we examined the hydrogenation product by paper chromatography. Surprisingly, we established thereby that instead of the one acid expected, there were actually two, one of which, of course, greatly predominated. This not only showed the same $R_F$-value in the chromatogram as isobutyric acid, but also gave the same infrared spectrum. This was the second important indication of methacrylic acid in the beetle secretion; examination of the secretion in the crude state then gave the infrared spectrum of this acid (Fig. 15).

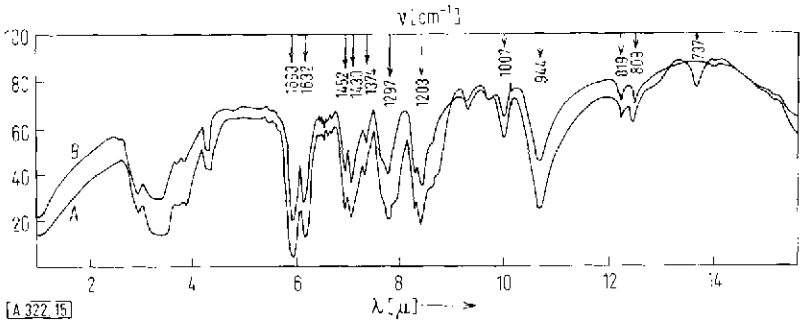



Fig. 15. Infrared spectra of the crude beetle secretion (A) and of methacrylic acid (B).
Ordinate: Transparency [%].

Here, a broadening of the band at 1297 $cm^{-1}$ and an only moderately pronounced band at 737 $cm^{-1}$ also indicate a second substance, which was later identified as tiglic acid. On comparing the spectra of the ammonium salts of the secretion, of methacrylic acid *(15)*, and of tiglic acid *(16)* (Fig. 14), the inflexion at 798 $cm^{-1}$ and the band at 748 $cm^{-1}$ may equally be ascribed to tiglic acid. Finally tiglic acid itself was successfully isolated in the crystalline state from the secretion and characterized [66] like the methacrylic acid by its infrared and mass spectra and as its tetraphenylstibonium salt [65].

The similar appearance of all the infrared absorption spectra of the crude ammonium salts served as particular evidence that methacrylic acid and tiglic acid also occur in the secretions of numerous other carabids. At the same time, the relative proportions of the acids may be determined from these spectra (Table 8).

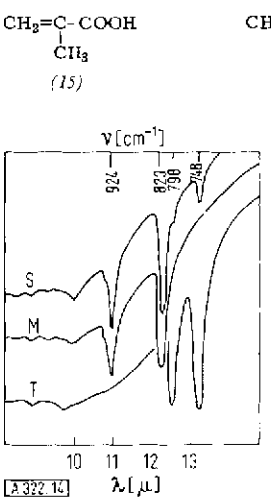



Fig. 14. Sections from the infrared spectra of the ammonium salts of carabid beetle secretion (S), methacrylic acid (M) *(15)*, and tiglic acid (T) *(16)*, superposed for comparison.

Table 8. Carabid beetles with methacrylic acid and tiglic acid as defensive substances.

| Beetle | Methacrylic acid [%] | Tiglic acid [%] |
|---|---|---|
| *Carabus granulatus* L. | 93.7 | 6.3 |
| *C. convexus* Fbr. | 90.4 | 9.6 |
| *C. auronitens* Fbr. | 88.9 | 11.1 |
| *C. auratus* L. | 87.0 | 13.0 |
| *C. cansellatus* Illig. | 86.8 | 13.2 |
| *Abax ovalis* Dftsch. | 89.8 | 10.2 |
| *Ab. ater* Villers | 91.4 | 8.5 |
| *Ab. parallelus* Dftsch. | 88.8 | 11.2 |
| *Pterostichus vulgaris* L. | 92.3 | 7.7 |
| *Pt. niger* Schall. | 91.3 | 8.7 |
| *Apotomopterus albr.* esakii | 91.2 | 8.8 |
| *Ap. insulicula* | 90.1 | 9.9 |

[64] We wish to thank Dr. *H. Gysel* (CIBA AG., Basel) for his great kindness in carrying out the relevant elementary analyses.

[65] *H.E. Affsprung* and *H.E. May*, Analytic. Chem. *32*, 1164 (1960).
[66] *H. Schildknecht* and *K. H. Weis*, Z. Naturforsch. *17b*, 439 (1962).

In the manner described, we have also found a methacrylic-tiglic acid mixture qualitatively in the following carabid beetles:

*Carabus coriaceus* L.
*C. cyaneus* F.
*C. violaceus* L.
*C. irregularis* Fbr.
*C. Ullrichi* Germ.
*Pterostichus metallicus* Fbr.

We found only methacrylic acid in the Japanese carabid beetles *C. procerulus*, *Damaster oxuroides*, and in the indigenous *Cychrus rostaratus*.

b) The "Pungent" Carabid Beetle Secretion

In contrast to the *Pterostichini* on the one hand and the *Brachynini* on the other, *Pseudophonus pubescens* and *Ps. griseus* excrete a quickly evaporating, sharp and pungent smelling liquid in self-defense. Its reaction with pH indicators, its ultraviolet spectrum, and its irritant properties suggest a strong acid. Chromatography according to *Long* [67] gave only one spot for the bladder contents of these three *Harpalinae* species. Paper chromatography was also the only method that could be used for investigating the secretion of *Harpalus dimidiatus* Rossi, since we had only two specimens of this species available. Chromatography afforded formic acid, which was also determined quantitatively by the method of *Frehden* and *Fürst* [68] and by titration. It was calculated that 1.5–2.0 mg of 75 % formic acid must be present in the beetle's bladder [69].

Using paper chromatography with the system ethanol/water/ammonia (80:16:4) (Schleicher and Schüll paper 2043b), we also detected formic acid ($R_F = 0.50$) as the defensive substance in members of the genera *Calathus*, *Acinopus*, and *Carterus* (Sicilian carabid beetles) which were not identified more closely.

## 9. Water Beetles (Dytiscidae)

The true water beetles became aquatic only late in the process of evolution. They have then very probably lost the ability of the carabid beetles of suddenly discharging the contents of the pygidial bladder. Thus one finds – especially with freshly caught water beetles – that the glistening yellow bladders are usually tightly filled. On extrusion into ethanol, one obtains a yellow solution and a colorless precipitate, which was at first recognized only as a glycoprotein by infrared spectroscopy and electrophoresis [70].

Chromatography on silica gel of the solution from one beetle yields about 3 mg of colorless crystals, which can be readily sublimed (m.p. 110 °C) [71]. These crystals have a low molecular weight *(115)*, but a very complex infrared absorption spectrum, and are not made up of a homogeneous substance. That was to be expected, for, in accordance with the thin-layer and paper chromatograms, which contain at least three spots, different types of gland cells can be clearly distinguished in the secretion-producing cell complexes [72].

Since we did not obtain a reliable analytical result simply by chromatography, and since the mixture of substances could be separated by micropreparative zone melting, we subjected the pygidial bladder secretion of the great water beetle to micro-zone melting [73]. After the passage of 20 zones through a micro-ingot [74], we obtained at first two fractions. A eutectic was separated from the low melting fraction by renewed zone melting [75] (Fig. 16).

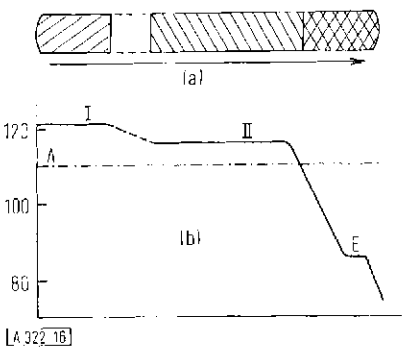



Fig. 16. Zone-melted ingot (a) and melt diagram (b) of the soluble portion from the crude secretion of *Dytiscus marginalis*. The data leading to characterization of the fractions I (m.p. 121 °C) and II (m.p. 116 °C) as well as one of the substances isolated from the eutectic E (m.p. 86 °C) are shown in Table 9.

A = Starting mixture (m.p. 110 °C).

The arrow under the ingot indicates the direction of movement of the zones.

Ordinate: Melting point [°C].

Table 9 shows how chemical characterization of the components of the secretion became possible by comprehensive analysis of the fractions obtained by zone melting. The eutectic mixture which was not further separable by fractional melting, was subjected to thin-layer chromatography and yielded a substance, which after repeated zone melting, was pure enough to be identified as methyl *p*-hydroxybenzoate. All the species of the genus *Dytiscus* investigated by us defend themselves – presumably only against attack by micro-organisms – with a mixture of benzoic acid *(17)*, methyl *p*-hydroxyhenzoate *(19)*, and *p*-hydroxybenzaldehyde *(18)* (Table 10); the first two compounds may also be used, according to German food laws, for stabilizing foodstuffs, especially canned fish. In

[67] *A. G. Long, J. R. Quayle,* and *R. J. Stedman,* J. chem. Soc. (London) *1951*, 2197.

[68] *O. Frehden* and *K. Fürst,* Mikrochemie *25*, 256 (1938).

[69] *H. Schildknecht* and *K. H. Weis,* Z. Naturforsch. *16b*, 361 (1961).

[70] We wish to thank Dr. *H. Determann* for his assistance in the elucidation of the structure of the protein.

[71] *H. Schildknecht, K. Holuobek,* and *M. Wolkenstörfer.* Z. Naturforsch. *17b*, 81 (1962).

[72] *E. Korschelt:* Der Gelbrand, *Dytiscus marginalis* L. Engelmann, Leipzig 1924, Vol. I.

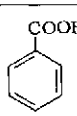
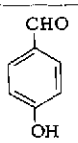
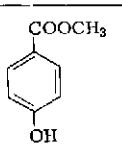
[73] *H. Schildknecht* and *H. Vetter,* Angew. Chem. *71*, 723 (1959).

[74] *H. Schildknecht* and *H. Vetter,* Angew. Chem. *73*, 240 (1961).

[75] *H. Schildknecht* and *K. H. Weis,* Z. Naturforsch. *17b*, 448 (1962).

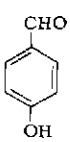
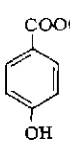
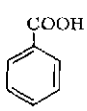
the genus *Cybister*, benzoic acid is replaced by a still unknown carboxylic acid. The nature of the yellow pigment that always occurs in the bladders is also not yet clear.

Table 9. Identification of Fractions I and II obtained by zone melting (Fig. 16) as well as of a substance separated from the eutectic E.

| | Fraction | | |
|---|---|---|---|
| | I | II | E |
| 2,4-Dinitrophenylhydrazone | | M.p. 279 °C | — |
| $R_F$-value [a] | 0.61 | 0.70 | — |
| Ultraviolet absorption maxima (log ε) | in water<br>227 mμ (4.1)<br>273 mμ (3) | in ethanol<br>221 mμ (4.22)<br>285 mμ (4.35) | |
| Infrared absorption band [76] for | | | |
| monosubst. benzene | $\gamma_{CH}$ 708 cm$^{-1}$ | — | — |
| arom. carboxylic acid | $\omega_{C=O}$ 1695 cm$^{-1}$<br>$\Gamma_{OH}$ 935 cm$^{-1}$ | – | — |
| *p*-subst. benzene | – | $\gamma_{CH}$ 832 cm$^{-1}$ | |
| phenol | – | $\nu_{OH}$ 3250 cm$^{-1}$ | |
| arom. aldehyde | – | $\omega_{C=O}$ 1675 cm$^{-1}$ | — |
| arom. ester | — | — | $\omega_{C-O}$ 1690 cm$^{-1}$<br>$\omega_{C-O}$ 1292 cm$^{-1}$<br>1119 cm$^{-1}$ |
| Elemental analysis | $C_7H_6O_2$ | $C_7H_6O_2$ | – |
| Result |  (17) |  (18) |  (19) |

[a] Paper chromatography with water saturated with $CO_2$ as eluant; paper: Schleicher and Schüll 2043b.

Table 10. Substances contained in the pygidial bladders of water beetles.

| Beetle species (size) |  (18) |  (19) |  (17) |
|---|---|---|---|
| *Dytiscus marginalis* (30–35 mm) | + | ± | ± |
| *D. lattissimus* (36–44 mm) | + | + | ± |
| *Cybister laterimarginalis* (30–35 mm) | ± | ± | – |
| *Hydroporus palustris* L. (3.5–4 mm) | + | – | – |

## 10. Summary

We have identified homologues of *p*-benzoquinone in all darkling ground beetles (*Tenebrionidae*). The quinones are sometimes stored in bladders and are always accompanied by the corresponding hydroquinones, which, in the bombardier beetles (*Brachynidae*), are present alone and undecomposed besides hydrogen peroxide. It was surprising that earwigs, too, which taxonomically belong to the *Hymenoptera*, squirt out toluquinone and ethylbenzoquinone for self-defense and even lower animals like the millipedes can give off toluquinone and methoxytoluquinone dropwise in the form of a yellow solution or suspension. The stink bladders of bugs contain α,β-unsaturated carbonyl compounds, too, *viz.* hexenal, octenal, and decenal.

The bladder contents of most carabid beetles (*Carabinae*, *Harpalinae*) are either nearly 75 % formic acid or a mixture of 95 % methacrylic acid and 5 % tiglic acid. Here, too, it is not yet explained how this mixture can be stored without decomposition and without attacking the very thin walls of the bladder. Although the water beetles (*Dytiscidae*) are closely related to the carabid beetles, their pygidial bladders contain only one carboxylic acid, *viz.* benzoic acid. The major amount of the contents is formed by *p*-hydroxybenzaldehyde, which is accompanied by methyl *p*-hydroxybenzoate.

Who ever watched one of the insects described aiming and shooting at an intruder, is convinced that they cannot only fight their like but also larger animals. The amounts of defensive substances are small, but so are most of the aggressors, who frequently can only rescue themselves by fleeing hastily from the biting and ill-smelling cloud of poison gas. An insect kept in a closed jar is perished by its own defensive substances. From the type of compounds found and particularly from the chemical composition of the bladder contents of water beetles it follows that the defensive substances produced can also be directed against micro-organisms. Hence these substances might also be termed antibiotics of the insect kingdom. They make it possible for the animals to live in most awful surroundings without being troubled by parasites.

*We are very grateful to the Deutsche Forschungsgemeinschaft and to the Fonds der Chemischen Industrie for supporting our work on insect compounds by financial and material aids. We also thank our colleagues who, with much idealism, helped us to catch and to determine the insects and millipedes.*

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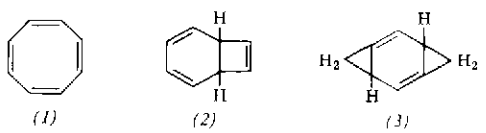
# The Valence Tautomerism of Cyclooctatetraene

BY PROF. DR. R. HUISGEN AND DIPL.-CHEM. F. MIETZSCH

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN (GERMANY)

*The Diels-Alder adducts of cyclooctatetraene and its derivatives are derived from the bicyclo[4,2,0]octane structure. A kinetic investigation shows that the Diels-Alder addition of dienophiles to cyclooctatetraene and phenylcyclooctatetraene is preceded by a valence tautomerism equilibrium with bicyclo[4,2,0]octa-2,4,7-triene or its 7-phenyl derivative.*

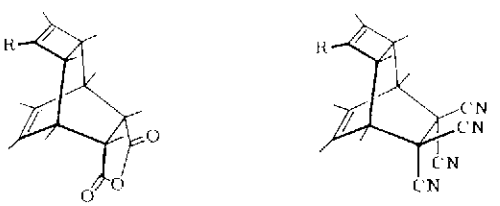
The reactions of cyclooctatetraene have repeatedly claimed the attention of theoretical chemists. *Willstätter* and *Waser* [1], whose outstanding work first made the tetra-unsaturated hydrocarbon available, expressed some disappointment at the establishment of its non-aromatic character. A thorough study of the chemistry of cyclooctatetraene was made possible by *Reppe*'s discovery of a convenient synthesis [1a] for this compound. The variety of its reactions required an interpretation which involved the structures *(1)* to *(3)* [2].



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

However, it was not known whether the eight-membered ring structure *(1)* first isomerized to form *(2)* or *(3)*, or whether rearrangement occurred in a collision complex formed with the reagent, thus giving products which are formal derivatives of *(2)* or *(3)*. Both the first [3] and the second [4,5] interpretation have been suggested. The following kinetic studies of the Diels-Alder reaction indicate a true valence tautomerism between cyclooctatetraene *(1)* and bicyclo[4,2,0]octa-2,4,7-triene *(2)*.

It has been firmly established [2,6] that the maleic anhydride adduct of cyclooctatetraene is represented by structure *(4)*. The analogous adduct *(5)* of phenylcyclooctatetraene [7], which was isolated in 92 % yield, exhibits the ultraviolet absorption characteristic of styrene derivatives. Addition of one mole equivalent of hydrogen to the cyclobutene ring changes the light absorption to that of an alkylbenzene, and indicates that the phenyl group is situated as shown in *(5)*. Nuclear magnetic resonance spectra confirm this constitution. The number of vinyl hydrogen atoms in the cyclobutene ring is shown to be two for *(4)* but only one for *(5)*. Sharp singlets occur at 4.03 $\tau$ for *(4)* and 3.80 $\tau$ [7a] for *(5)*. Formulae *(6)* and *(7)* for the Diels-Alder adducts of tetracyanoethylene with *(1)* [8] and *(8)* respectively, which we obtained in yields of 92 % and 96 %, are also supported by NMR spectra and hydrogenation. The adduct of fumaryl chloride with *(8)*, which was analyzed and investigated by NMR spectroscopy after methanolysis (two diastereoisomers), was shown to contain the same ring structure. These Diels-Alder adducts are therefore, at least formally, derived from the bicyclic structures *(2)* and *(9)*.



*(4)* R = H
*(5)* R = $C_6H_5$

*(6)* R = H
*(7)* R = $C_6H_5$

The boat conformation of cyclooctatetraene *(1)*, proven by physical methods, contains no 1,3-diene system providing the approximately planar configuration essential for a Diels-Alder reaction. On the other hand, the bicyclic structure *(2)* does offer a planar diene system, particularly since the incorporation of the cyclobutene ring causes further flattening of the 1,3-cyclohexadiene system. At 140 °C, 1,3-cyclohexadiene adds maleic anhydride [9] 120 times more rapidly than does *(1)*. This suggests that a moderate equilibrium concentration of *(2)*, rather than *(1)*, may enter into the Diels-Alder reaction. Neither 1,3-cyclooctadiene [3] nor 1,3,5-cyclooctatriene can take up maleic anhydride, but bicyclo-[4,2,0]octa-2,4-diene [10], which is also a derivative of cyclohexadiene, is able to do so. This behavior, like the configuration of the adducts, confirms the above hypothesis.

[1] *R. Willstätter* and *E. Waser*, Ber. dtsch. chem. Ges. *44*, 3442 (1911).

[1a] For mechanism, cf. *G. N. Schrauzer*, Angew. Chem. *76*, 28 (1964); Angew. Chem. internat. Edit. *3* (1964), in the press.

[2] *W. Reppe, O. Schlichting, K. Klager*, and *T. Toepel*, Liebigs Ann. Chem. *560*, 1, 11 (1948).

[3] *K. Ziegler* and *H. Wilms*, Liebigs Ann. Chem. *567*, 1, 26, 28 (1950).

[4] *S. L. Friess* and *V. Boekelheide*, J. Amer. chem. Soc. *71*, 4145 (1949).

[5] *L. E. Craig*, Chem. Reviews *49*, 103, 119 (1951).

[6] Configuration: *M. Avram, G. Mateescu*, and *C. D. Nenitzescu*, Liebigs Ann. Chem. *636*, 174 (1960).

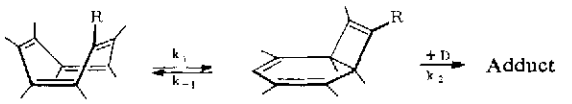
[7] *A. C. Cope* and *M. R. Kinter*, J. Amer. chem. Soc. *73*, 3424 (1951).

[7a] Values referred to tetramethylsilane as internal standard in deuterochloroform.

[8] *P. Scheiner* and *W. R. Vaughan*, J. org. Chemistry *26*, 1923 (1961).

[9] *J. Sauer*, Habilitation Thesis, Universität München, 1963.

[10] *A. C. Cope, A. C. Haven, F. L. Ramp*, and *E. R. Trumbull*, J. Amer. chem. Soc. *74*, 4867 (1952).




C B A

*(1)* R = H *(2)* R = H

*(8)* R = $C_6H_5$ *(9)* R = $C_6H_5$

The reaction of cyclooctatetraene *(1)* with an excess of dienophiles was followed dilatometrically [11] (any union of two molecules to form one molecule is accompanied by a contraction in volume) and the pseudo-first-order rate constants $k_d$ were determined.

$$\frac{d[A]}{dt} = k_d [C].$$

As long as the valence tautomerism is mobile and the rate is dependent only on the reaction of *(2)* with the dienophile D ($k_2 \ll k_1, k_{-1}$), the following relationship holds (with the symbols as above):

$$k_d = \frac{k_1}{k_{-1}} k_2 [D].$$

The required linear relationship between $k_d$ and [D] may be illustrated by the reaction of cyclooctatetraene with maleic anhydride in chlorobenzene at 140 °C (I in Fig. 1).

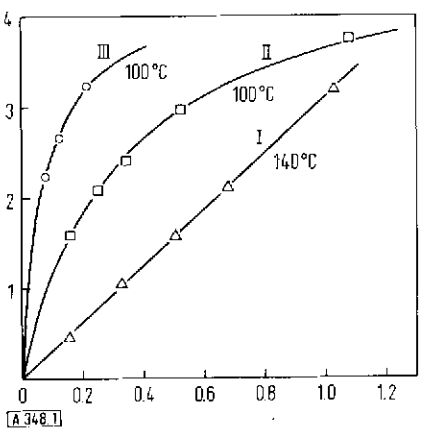



Fig. 1. Pseudo-first-order rate constants for the reactions of cyclooctatetraene with maleic anhydride in chlorobenzene (I), and with tetracyanoethylene (II), and dicyanomaleic imide (III) in dioxane.
Ordinate: $10^4 k_d$ [sec$^{-1}$].
Abscissa: dienophile concentration [mole/l].

The use of an extremely reactive dienophile which immediately traps every molecule of the bicyclic tautomer *(2)* formed from *(1)* (*i.e.* $k_2 \gg k_1, k_{-1}$), would give dilatometrically measured rate constants which are independent of the concentration of excess dienophile, *i.e.* $k_d = k_1$. We would then expect a straight line, parallel to the abscissa in Fig. 1.

Between these two extremes, *i.e.* where $k_2$ is of the same order of magnitude as $k_1$ and $k_{-1}$, a more complicated rate equation is obtained, which gives rise to a concave curve, bent towards the abscissa, when $k_d$ is plotted against increasing dienophile concentrations. Since the concentration of the intermediate *(2)* is small, the concentration change will also be small, and the Bodenstein theorem can be applied.

$$\frac{d[B]}{dt} = 0; \; k_1 [C] = k_{-1} [B] + k_2 [B] [D].$$

$$\frac{d[A]}{dt} = k_d [C] = \frac{k_1 k_2 [C] [D]}{k_{-1} + k_2 [D]}.$$

By a simple transformation one arrives at the equation for a straight line for the plot of $k_d$ against $k_d/[D]$.

$$k_d = k_1 - \frac{k_{-1}}{k_2} \frac{k_d}{[D]}.$$

At 20 °C, tetracyanoethylene adds onto 1,3-cyclohexadiene 1150 times more rapidly than does maleic anhydride [9]. The reaction of tetracyanoethylene with *(1)* can be followed at 100 °C in dioxane. The $k_d$ values measured for increasing concentrations of tetracyanoethylene indicate that the order of magnitude of $k_2$ becomes comparable to that of $k_{-1}$ (II in Fig. 1). The plot of $k_d$ against $k_d/[D]$ is indeed a straight line (I in Fig. 2) with $10^4 k_1 = 4.85$/sec and $k_{-1}/k_2 = 0.34$ mole/l.

The constant $k_1$ of the preliminary valence isomerization, measured via $k_d$, should be independent of the nature of the dienophile, provided that the latter is sufficiently active. In confirmation, dicyanomaleic imide, which adds to butadiene at 20 °C five times more rapidly than does tetracyanoethylene [9], gives the following values with cyclooctatetraene: $10^4 k_1 = 4.4$/sec and $k_{-1}/k_2 = 0.078$ mole/l (III in Fig. 1 and II in Fig. 2).

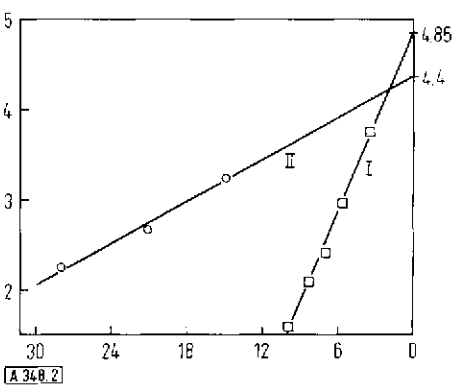



Fig. 2. Dilatometrically determined rate constants from Fig. 1, plotted against $k_d/[D]$ (dioxane, 100 °C).
I: Reaction with tetracyanoethylene
II: Reaction with dicyanomaleic imide
Ordinate: $10^4 k_d$ [sec$^{-1}$].
Abscissa: $10^4 k_d/[D]$ [l·mole$^{-1}$, sec$^{-1}$]

Surprisingly, it is found that the dilatometrically determined rate constants for the reaction of phenylcyclooctatetraene *(8)* with tetracyanoethylene at 70 °C and concentrations greater than 0.2 M depend only slightly on the excess concentration of the dienophile (I in Fig. 3). The small slope of the straight line I in Fig. 4 corresponds to $k_{-1}/k_2 = 0.022$ mole/l and shows that in this case the reverse reaction, *i.e.* *(9)* → *(8)*, has already been largely suppressed. Even more striking is the "plateau phenomenon" observed with dicyanomaleic imide (III in Fig. 3). The curved path followed by the $k_d$ values for the addition of fumaryl chloride to phenylcyclooctatetraene (II in Fig. 3) gives $k_{-1}/k_2 = 0.49$ mole/l,

[11] We thank Dr. *W. D. Wirth*, Universität München 1960, for the development of the dilatometric technique used in these experiments.

when plotted against $k_d/[D]$ in Fig. 4. Kinetic studies with the three dienophiles furnish the respective values of 2.28, 2.28 and 2.21 for $10^4 k_1$ [$sec^{-1}$], and confirm the required independence of the nature of the dienophile.

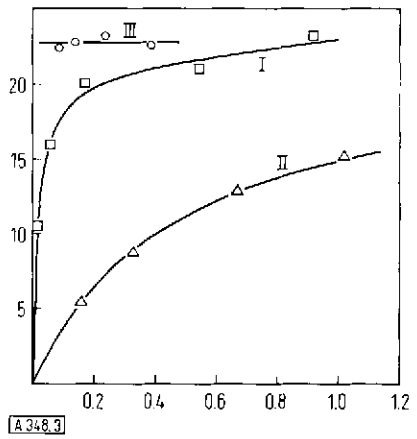



Fig. 3. Dilatometrically determined rate constants ($k_d$) for the reactions of phenylcyclooctatetraene *(8)* at 70 °C with tetracyanoethylene (I) and fumaryl chloride (II) in ethyl acetate, and with dicyanomaleic imide (III) in tetrahydrofuran.
Ordinate: $10^5 k_d$ [$sec^{-1}$].
Abscissa: Dienophile concentration [mole/l].

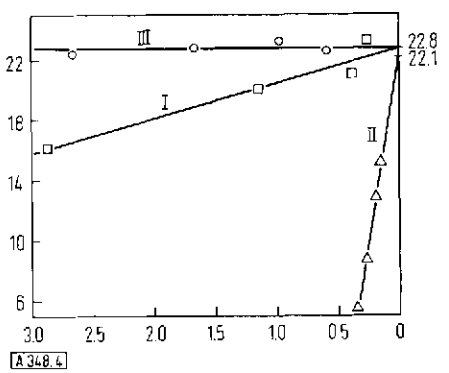
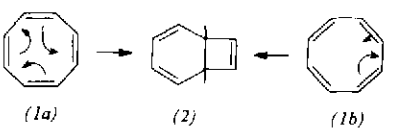



Fig. 4. Rate constants of the Diels-Alder reactions shown in Fig. 3, plotted against $k_d/[D]$.
I: Tetracyanoethylene
II: Fumaryl chloride
III: Dicyanomaleic imide
Ordinate: $10^5 k_d$ [$sec^{-1}$].
Abscissa: $10^5 k_d/[D]$ [$l \cdot mole^{-1} \cdot sec^{-1}$].

It appears almost certain that the equilibrium which consists of first-order forward and reverse reactions and precedes the Diels-Alder addition is the valence tautomerism *(1)* $\rightleftharpoons$ *(2)* or *(8)* $\rightleftharpoons$ *(9)*. An alternative explanation of the "plateau phenomenon" of Figures 1 and 3 (without valence tautomerism) which suggests a practically complete combination of diene and dienophile to form a charge-transfer complex has been refuted. At room temperature, the association constants of the charge-transfer complexes which are found in the systems studied kinetically are so small that they cannot be determined spectrophotometrically [12] ($K \leqslant 0.2$).

The activation parameters for the valence tautomerism of phenylcyclooctatetraene and *(9)* in ethyl acetate can be determined from the plateau values ($k_1$) at 60, 70, and 78 °C: $\Delta H^{\neq} = 25.0$ kcal/mole; $\Delta S^{\neq} = -3$ e.u.

The activation energy is therefore considerably higher than the value of 13.7 kcal/mole found for the isomerization of cyclooctatetraene, which involves the interchange of double and single bonds, probably through a strained planar configuration [13]. Of the two possible modes of electron displacement [14,15], *(1a)* (3 $\pi$-bonds $\rightarrow$ 2 $\pi$-bonds and 1 $\sigma$-bond) appears to be sterically more favorable than *(1b)* (2 $\pi$-bonds $\rightarrow$ 1 $\pi$- and 1 $\sigma$-bond).




The above data do not as yet give the thermal equilibrium concentration of *(2)* or *(9)*, which we are attempting to determine. An estimate can be made by equating the rate constants of the addition of tetracyanoethylene onto *(2)* with that onto bicyclo[4,2,0]octa-2,4-diene, the valence tautomer of 1,3,5-cyclooctatriene [10]. Preliminary measurements [16] give a value of $k_2 = 16$ $l \cdot mole^{-1} \cdot sec^{-1}$ in dioxane at 100 °C. Under these conditions, the equilibrium concentration of the bicylic tautomer *(2)* is found to be 0.01 %.

Compound *(2)* has recently been postulated as a product of the photorearrangement of *(1)* [17].

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[13] *F. A. L. Anet*, J. Amer. chem. Soc. *84*, 671 (1962).

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[16] Kinetic data: *G. Boche*, Universität München, 1963.

[17] *E. Migirdicyan* and *S. Leach*, Bull. Soc. chim. Belges *71*, 845 (1962); *G. J. Fonken*, Chem. and Ind. *1963*, 1625.

# Recent Developments in the Chemistry of Aminoboranes

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*The isosterism of BN and CC groupings invites comparisons. Recent investigations on substituted aminoboranes $R^1R^2N-BR^3R^4$ have been attempted in order to evaluate this concept of isosterism. Some of the latest results include evidence for geometric isomerism due to hindered rotation about the B–N bond, isolation of isomeric compounds which can be considered as formal analogues of cyclohexanes, and the incorporation of BN groups into aromatic systems.*

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B. The nature of the B–N bond in aminoboranes
C. Acyclic aminoboranes
  1. Monoaminoboranes
  2. Bis- and trisaminoboranes
  3. Bisborylamines
  4. Hydrazino- and azidoboranes
  5. Boron subcompounds with aminoborane-type linkages
D. Cyclic aminoboranes
E. Pseudo-aromatic compounds with aminoborane-type bonds
  1. Five-membered ring systems
  2. Six-membered BN-heteroaromatics

## A. Introduction

The chemistry of boron hydrides has had great appeal for some time in the search for high-energy solid propellants. As a result, other aspects of boron chemistry have been neglected. Within the last five to eight years, however, interest in the chemistry of boron-nitrogen compounds has been rejuvenated. This resulted primarily from the recognition of isosterism of the BN group with a CC grouping, a phenomenon which invited stimulating comparisons of both systems. Earlier basic investigations in this area, such as the work of *Wiberg* [1] from 1930 to 1940, were already founded on this concept. New interest in boron-nitrogen chemistry was also aroused by the synthesis of *B*-trichloroborazine [1a], which resulted in partial supplantation of high vacuum techniques, and by the utilization of spectroscopy as a tool for explaining both structures and mechanisms.

Some results of recent investigations in the field of aminoborane chemistry are reported in this article [*], the scope of which is necessarily rather limited [**]. Those compounds will be considered as aminoboranes which have a normal covalent bond between boron and nitrogen atoms and in which the free electron pair of the nitrogen can participate in the N–B bond [1b]. The chemistry of borazines (= borazoles) will not be discussed, as a detailed review can be found elsewhere [2].

Three major areas of research have developed in the chemistry of aminoboranes:

1. The investigation of open-chain aminoboranes, with special interest in the interpretation of BN bonding.
2. The chemistry of trimeric aminoboranes, which can be considered as formal analogues of cyclohexane.
3. The synthesis and characterization of heteroaromatic compounds, in which a CC group of an aromatic ring system has been substituted by an isosteric BN group.

## B. The Nature of the B-N Bond in Aminoboranes

*Wiberg* [1] already postulated a B–N double bond in aminoboranes due to participation of the free electron pair from the nitrogen atom in the linkage, possible because of the electron deficiency on the boron atom. The planarity of the three bonds of boron, which was demonstrated by *Goubeau* and *Becher* [3], is a prerequisite for this interaction ($sp^2$ hybridization). Calculation of the force constants [4a] indicated a bond order of 1.8 for the B–N bond of aminoboranes at room temperature.

[1] Cf. *E. Wiberg*, Naturwissenschaften *35*, 182, 212 (1948).

[1a] *C. A. Brown* and *A. W. Laubengayer*, J. Amer. chem. Soc. *77*, 3699 (1955).

[*] Nomenclature recommended by the Committee for Nomenclature on Boron Compounds of the American Chemical Society is used herein.

[**] Older literature is not included; references to publications that appeared before 1950 can be found in Gmelin's Handbuch der anorganischen Chemie. The reader is also referred to an article by *M. F. Lappert*, Chem. Reviews *56*, 959 (1956).

[1b] Attention is called to the distinction between aminoboranes $R_2N-BR_2$ and amine-boranes $R_3N\rightarrow BR_3$.

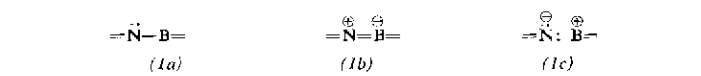
[2] *J. C. Sheldon* and *B. C. Smith*, Quart. Reviews (Chem. Soc., London) *1960*, 200.

[3] *J. Goubeau* and *H. J. Becher*, Z. anorg. allg. Chem. *268*, 133 (1952).

[4] Cf. Preprints of Papers, International Symposium on Boron-Nitrogen Chemistry, Durham, N.C. (U.S.A.), April 1963. A revised version of these preprints will be published by the "American Chemical Society" in the "Advances in Chemistry" Series, Vol. 42.

[4a] Cf. review article by *J. Goubeau* in [4].

The BN group is the only combination of boron with another element which can reach such a high bond order at room temperature. Dipole measurements by *Becher* [5] indicated, however, that three structures *(1a)–(1c)* are necessary to illustrate the BN bond according to *Pauling*'s electronic theory. Since the bond moments



*(1a)* *(1b)* *(1c)*

of some methylated aminoboranes have been found to be practically zero, it can be assumed that resonance between the forms *(1a)*, *(1b)*, and *(1c)* occurs. In agreement with this, calculations of the charge distribution between the boron and nitrogen by the LCAO-molecular orbital method [6] indicated that in simple aminoboranes, charge transfer occurs from the boron to the nitrogen; the nitrogen is the more negative partner of the bond by a value of about 0.28 electrons.

Another result of the molecular orbital calculations was that hindered rotation about the BN linkage of about 10 kcal/mole should exist. The possibility of hindered rotation, and thus of the occurrence of geometric isomers in the aminoborane system, was discussed in 1960 by *Niedenzu* and *Dawson* [7]. Nuclear magnetic resonance investigations later confirmed this concept [8]. Therefore the double bond character of the boron-nitrogen linkage in aminoboranes can be accepted.

The NMR investigations are based on the following considerations. In an unsymmetrically substituted aminoborane, *e.g.* of the type $Me_2B-NR'R''$ [8a], the two methyl groups are magnetically non-equivalent if hindered rotation about the BN linkage exists. The $^1H$ resonance spectrum will therefore indicate two methyl signals with different chemical shifts. At higher temperatures the rotation about the BN bond increases, so that the two groups will become magnetically equivalent, and their NMR signals will merge. The energy of activation of rotation can be calculated from the temperature dependence of the chemical shift. Thus far, experimental values in the order of 10–15 kcal/mole have been found; these are in good agreement with the theoretical value.

The B–N distance in aminoboranes has not been determined experimentally. However, an estimate of about 1.44 Å should be fairly close to the actual value. By the use of empirical formulae, such as *Gordy*'s rule [9], the BN bond order can then be calculated from the position of the BN absorption in the infrared and Raman spectrum of any aminoborane. Decreases in bond order are indicated by shifts of the asymmetrical BN stretching frequency to lower values. Generally this vibration has been found in the range 1500–1350 $cm^{-1}$ for aminoboranes. Detailed investigations resulted in the following picture. Substitution at the nitrogen by aryl groups causes a decrease in the BN bond order as compared with *N*-alkyl compounds, due to resonance of the free electron pair on the nitrogen with the aromatic ring. The N-$C_{aryl}$ bond assumes partial double-bond character, and the electron density at the boron atom is correspondingly decreased. Aryl groups at the boron show a lesser effect, although here too resonance of the π-electrons of the aromatic system with the electron deficiency of the boron is possible. Thus, the electron density of the boron is not diminished, although the BN bond order is.

The results of such a spectroscopic investigation [10] have been checked by LCAO-MO-calculation according to *Hückel* [11] and were completely confirmed. A detailed review of such a spectroscopic investigation is reported elsewhere [12].

## C. Acyclic Aminoboranes

### 1. Monoaminoboranes

The basic compound of this group, $H_2N-BH_2$, is not known in monomeric form (see below). Monoaminoboranes with the following substituents are known:

at the boron atom: hydrogen, deuterium, alkyl, aryl, silyl, halogen, alkoxyl, and aroxyl;

at the nitrogen atom: hydrogen, deuterium, alkyl, aryl, and silyl.

In addition, either the nitrogen or the boron can be incorporated in a ring system. Examples of relatively unusual compounds with aminoborane linkages include dimethylisocyanatoborane, $(CH_3)_2B-NCO$ [13], and the compounds $S_7N-BX_2$, where X = Cl or Br [14].

Aminoboranes $R_2N-BX_2$, that are halogenated at the boron atom, were obtained more than sixty years ago by *Michaelis* on interaction of boron halides and secondary amines [15]. *Wiberg* [1] reported a number of substituted aminoboranes in his investigations on the thermal decomposition of amineboranes (→ aminoboranes → borazines). *Schaeffer* and *Anderson* reported the preparation of aminoboranes by the reaction of metal borohydrides with amine salts [16]:

$$R_2NH_2Cl + LiBH_4 \rightarrow 2H_2 + LiCl + R_2N-BH_2$$

Some recent investigations [7, 17] dealt with the Grignard reaction of aminohalogenoboranes, which can readily be obtained from amine-halogenoboranes by dehydrohalogenation with tertiary amines [18]:

$$R_2NH\cdot BX_3 + NR'_3 \rightarrow R_2N-BX_2 + R'_3NHX$$
$$R_2N-BX_2 + 2\,R'MgX \rightarrow R_2N-BR'_2 + 2\,MgX_2$$

[5] *H. J. Becher*, Z. anorg. allg. Chem. *270*, 273 (1952).

[6] *R. Hoffman* in [4].

[7] *K. Niedenzu* and *J. W. Dawson*, J. Amer. chem. Soc. *82*, 4223 (1960).

[8] (a) *G. E. Ryschkewitsch*, *W. S. Brey*, and *A. Saji*, J. Amer. chem. Soc. *83*, 1010 (1961); (b) *P. A. Barfield*, *M. F. Lappert*, and *J. Lee*, Proc. chem. Soc. (London) *1961*, 421; (c) *K. Niedenzu* et al., unpublished work; (d) *W. S. Brey* et al., and *M. Kubo* et al. in [4].

[8a] The following abbreviations have been used in this article: Me = methyl, Et = ethyl, Ar = aryl, and R = alkyl.

[9] *W. Gordy*, J. chem. Physics *14*, 305 (1946).

[10] *G. M. Wyman*, *K. Niedenzu*, and *J. W. Dawson*, J. chem. Soc. (London) *1962*, 4068.

[11] *J. J. Kaufman* et al. in [4].

[12] *H. J. Becher* in [4].

[13] *J. Goubeau* and *H. Gräbner*, Chem. Ber. *93*, 1379 (1960).

[14] *H. G. Heal*, J. chem. Soc. (London) *1962*, 4442.

[15] *A. Michaelis* and *K. Luxemburg*, Ber. dtsch. chem. Ges. *29*, 710 (1896).

[16] *G. W. Schaeffer* and *E. R. Anderson*, J. Amer. chem. Soc. *71*, 2143 (1949).

[17] *K. Niedenzu* and *J. W. Dawson*, J. Amer. chem. Soc. *81*, 5553 (1959).

[18] *J. F. Brown*, J. Amer. chem. Soc. *74*, 1219 (1959).

Unsymmetrically substituted aminoboranes of the type $R^1R^2N{-}BR^3R^4$ have been obtained from the appropriate starting materials via the intermediates $R^1R^2N{-}BR^3X$ *(2)* [7]. Analogous compounds *(2)* are formed by dismutation of $R_2N{-}BX_2$ with $R_2N{-}BR_2$ [19].

*Nöth* described the reaction of bis(dialkylamino)boranes with HCl, which resulted in the formation of dialkylamine hydrochloride and (dialkylamino)chloroborane, $R_2N{-}BHCl$ [20]. *Comproportionation of trisdialkylaminoboranes* with trialkylboranes according to the

$$B(NR_2)_3 + 2\,BR'_3 \rightarrow 3\,R_2N{-}BR'_2$$

equation has also been investigated [21]. Transamination, however, seems to be especially important for preparative purposes. Within the last three years, the equilibrium reaction

$$R_2N{-}BR_2 + HNR'_2 \rightleftharpoons R'_2N{-}BR_2 + HNR_2$$

has been studied in various laboratories [22a-d]; its application to boron chemistry is based on work by *Gerrard* and co-workers [23]. The action of $Al(NMe_2)_3$ on various boron compounds (trialkylboranes, boroxines, *etc.*) has also been investigated [24] and found advantageous for the preparation of *N,N*-dimethylaminoboranes. Some typical aminoboranes which have become available in recent years are listed in Table 1:

Table 1. Aminoboranes $R^1R^2N{-}BR^3R^4$.

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Constants [°C] | Ref. |
|---|---|---|---|---|---|
| H | H | $C_6H_5$ | $C_6H_5$ | m.p. 129–130 | [25] |
| $CH_3$ | $C_{10}H_7$ | $CH_3$ | $CH_3$ | b.p. 89/3 mm | [17] |
| $C_2H_5$ | $C_6H_5$ | $CH_3$ | $CH_3$ | b.p. 51/4 mm | [17] |
| $C_6H_5CH_2$ | $CH_3$ | $C_6H_5CH$ | $C_6H_5$ | b.p. 170–180/3 mm | [21] |
| cyclo-$C_6H_{11}$ | $CH_3$ | n-$C_6H_{13}$ | $C_6H_5$ | b.p. 102–104/3 mm | [21] |
| $CH_3$ | $C_6H_5$ | $CH_3$ | $C_6H_5$ | b.p. 98/3 mm | [7] |
| $(-CH_2-)_5$ | | Cl | $C_6H_5$ | b.p. 82 | [7] |
| $C_6H_5CH_2$ | $CH_3$ | $C_6H_5$ | Cl | b.p. 123–127/3 mm | [21] |
| $(-CH_2-)_5$ | | Cl | Cl | b.p. 82–83/20 mm | [26] |
| $(-CH{=}CH-)_2$ | | $CH_3$ | $CH_3$ | b.p. 21/12 mm | [27] |
| n-$C_5H_{11}$ | n-$C_5H_{11}$ | Cl | Cl | b.p. 121/10 mm | [28] |
| i-$C_3H_7$ | i-$C_3H_7$ | $C_6H_5$ | Cl | b.p. 94/4 mm | [21] |
| $(-CH_2-)_4$ | | $CH_3$ | $CH_3$ | b.p. 38/3 mm | [21] |
| $CH_3$ | $CH_3$ | $-OCH_2CH_2CH_2O-$ | | b.p. 24/0,1 mm | [29] |
| H | $C_4H_9$ | $CH_3$ | $CH_3$ | b.p. 114/722 mm | [22c] |
| H | H | $C_4H_9$ | $C_4H_9$ | b.p. 64–66/17 mm | [30] |
| H | $(CH_3)_3Si$ | F | F | decomp. 260 | [31] |

Aminoboranes are usually monomeric. However, dimeric compounds and more highly aggregated species are known; association occurs most readily if one or more of the substituents is hydrogen or halogen. The monomeric aminoboranes are sensitive towards hydrolysis. Steric effects are important for the stability of these compounds; however, *N*-phenyl compounds are extraordinarily unstable and it is noteworthy that, in general, with decreasing double-bond character of the B–N linkage, the stability toward water, alcohols, *etc.*, decreases. Although no detailed investigations of this problem have been made, it can be assumed that by decreasing the BN bond order, the possibility for Lewis acid-Lewis base interaction is increased. It has been shown [32,33] that the addition of acceptor molecules is directly related to their strength as acceptors. Trimethylborane and dimethylfluoroborane do not react with aminoboranes at low temperatures. Trichloroborane, however, forms an addition compound, which decomposes near −60 °C.

$$Me_2N{-}BMe_2{\cdot}BCl_3 \rightarrow Me_2BCl + Me_2N{-}BCl_2$$

Trifluoroborane reacts analogously.

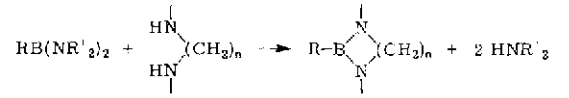
## 2. Bis- and Trisaminoboranes

Bisaminoboranes $R'B(NR_2)_2$ are readily obtained by aminolysis of organodichloroborane or by comproportionation of trisaminoboranes with triorganoboranes. *Mikhailov* [34] described the aminolysis of the S–B bond in alkylthioboranes, which can be utilized especially for the preparation of bisaminoboranes with $R' = H$.

$$(Et_2N)(RS)BH + Et_2NH \rightleftharpoons (Et_2N)_2BH + RSH$$

This latter type has also been obtained by hydrogenation of bisdialkylaminochloroboranes with lithium hydride in ether or by transamination of the readily available compound $HB(NMe_2)_2$ [20]. Pyrolysis of dialkylamine boranes, $R_2NH{\cdot}BH_3$, in the presence of dialkylamine has been investigated by *Burg* [35]. In the presence of catalytic amounts of $(R_2NH_2)^+$, the corresponding bis(dialkylamino)alkylboranes [36] are formed from dialkylamine and trimethylamine alkylborane at 100–150 °C. Analogous compounds have been obtained on interaction of boron compounds with $Al(NR_2)_3$ [24].

Transamination of bisaminoboranes with aliphatic diamines affords access to cyclic aminoboranes [22c,22d].



*(3)*

[19] *F. C. Gunderloy* and *C. E. Erickson*, Inorg. Chem. *1*, 349 (1962).

[20] *H. Nöth, W. A. Dorochov, P. Fritz*, and *F. Pfab*, Z. anorg. allg. Chem. *318*, 293 (1962).

[21] *K. Niedenzu, H. Beyer, J. W. Dawson*, and *H. Jenne*, Chem. Ber. *96*, 2653 (1963).

[22a] *W. D. English, A. L. McCloskey*, and *H. Steinberg*, J. Amer. chem. Soc. *83*, 2122 (1961).

[22b] *K. Niedenzu, D. H. Harrelson*, and *J. W. Dawson*, Chem. Ber. *94*, 671 (1961).

[22c] *H. Nöth*, Z. Naturforsch. *16b*, 470 (1961).

[22d] *K. Niedenzu, H. Beyer*, and *J. W. Dawson*, Inorg. Chem. *1*, 738 (1962).

[23] *W. Gerrard, M. F. Lappert*, and *C. R. Pearce*, J. chem. Soc. (London) *1957*, 381.

[24] *J. K. Ruff*, J. org. Chemistry *27*, 1020 (1962).

[25] *G. E. Coates* and *J. G. Livingstone*, J. chem. Soc. (London) *1961*, 1000.

[26] *O. C. Musgrave*, J. chem. Soc. (London) *1956*, 4305.

[27] *H. J. Becher*, Z. anorg. allg. Chem. *289*, 262 (1957).

[28] *K. Niedenzu, D. H. Harrelson, W. George*, and *J. W. Dawson*, J. org. Chemistry *26*, 3037 (1961).

[29] *H. Finch, P. J. Gardner, J. E. Lockhard*, and *E. J. Pearce*, J. chem. Soc. (London) *1962*, 1428.

[30] *B. M. Mikhailov* and *Y. N. Bubnov*, J. Gen. Chem. USSR (English translation) *31*, 531 (1961).

[31] *M. Becke-Goehring* and *H. Krill*, Chem. Ber. *94*, 1059 (1961).

[32] *A. B. Burg* and *J. Banus*, J. Amer. chem. Soc. *76*, 3903 (1954).

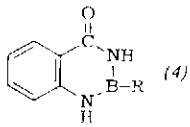
[33] *H. J. Becher*, Z. anorg. allg. Chem. *288*, 235 (1955).

[34] *B. M. Mikhailov* and *W. A. Durochov*, Zh. Obschei Khimii *31*, 750 (1961).

[35] *A. B. Burg* and *C. L. Randolph*, J. Amer. chem. Soc. *73*, 953 (1951).

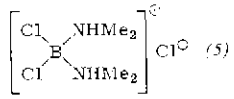
[36] *M. F. Hawthorne*, J. Amer. chem. Soc. *83*, 2671 (1961).

This reaction proceeds more smoothly than the thermal decomposition of the corresponding amine-$BR_3$ adducts [37]. This procedure offers future possibilities, since even more complicated compounds, for example *(4)*, are obtained via transaminations [38].



*(4)*

Bisaminoboranes do not dimerize. Correspondingly, the chemical shift of the $^{11}B$ resonance is found at about 20 ($\delta \times 10^{-6}$) [36,39]. They are readily hydrolysed, but the rate of hydrolysis decreases with increasing chain length of the alkyl substituents. An interesting salt-like compound *(5)* was obtained by *Nöth* [40] on treating HCl with $ClB(NMe_2)_2$.



*(5)*

Such compounds are encountered relatively seldom in boron chemistry [41].

The preparation of trisaminoboranes $B(NR_2)_3$ has been investigated in detail. In addition to aminolysis of boron trichloride, the reaction of boron trifluoride with primary or secondary amines in the presence of either a Grignard reagent [42] or metallic lithium [43] is suitable. Transamination also proceeds smoothly [22a,22c,44] and can also be utilized for the preparation of unsymmetrical trisaminoboranes [45].

Physicochemical investigations of trisaminoboranes are not as advanced. Studies of trisdimethylaminoborane [46] disclosed a valence force constant of the boron-nitrogen linkage of about $5.5 \times 10^5$ dyne/cm. This value is below those reported for borazines (6.3) and monoaminoboranes (7.0 7.5) but above the value calculated for amine boranes (ca. $3.5 \times 10^{-5}$ dyne/cm). The infrared spectra of various trisaminoboranes were recorded by *Lappert* [47]. A considerable double-bond character can be deduced for the BN linkage. The bond order, however, decreases in the series

$B(NHAr)_3 > B(NHR)_3 > B(NR_2)_3 > B(NRAr)_2$

The heat of formation of trisdimethylaminoborane was determined by *Skinner* and *Smith* [48] to be 77.1 kcal/mole, resulting in an energy of dissociation of the BN bond of 89.7 kcal/mole. This value is in the order of that of the BN bond in borazines.

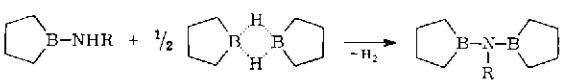
Hydrochlorides of the type $B(NR_2)_3 \cdot nHCl$ are not stable [40]. The action of HCl on trisaminoboranes causes them to rearrange to amine boranes.

### 3. Bisborylamines

Bisborylamines $(R_2B)_2NH$ in which two boron atoms are bonded to a central nitrogen atom were first mentioned by *Nöth* [49], who obtained such compounds by the reaction of dialkylchloroboranes with bistrimethylsilylamine.

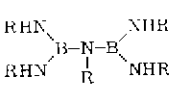
$$2\ R_2BCl + (Me_3Si)_2NH \rightarrow R_2B{-}NH{-}BR_2 + 2\ Me_3SiCl \qquad (6)$$

*Köster* [50] obtained analogous compounds with a B–N–B grouping in which the boron is incorporated in an aliphatic ring on thermal decomposition of bisborolanes *(7b)* with aminoborolanes *(7a)*.



*(7a)* *(7b)* *(8)*

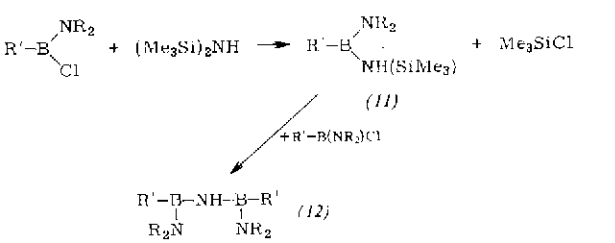
*Lappert* [51] reported the preparation of *(9)* by aminolysis of bis-t-butylaminochloroborane with t-butylamine.



*(9)*, R = t.Butyl

In the first step of the reaction of dialkylchloroborane with bistrimethylsilylamine, *Niedenzu* [52] obtained an *N*-silylated aminoborane *(10)*. With excess diorganochloroborane, the bisborylamine *(6)* is obtained with elimination of additional trimethylchlorosilane. In the corresponding reaction of aminochloroboranes, primar-

$$R_2BCl + (Me_3Si)_2NH \rightarrow R_2B{-}NH(SiMe_3) + Me_3SiCl \qquad (10)$$



*(11)* *(12)*

[37] *J. Goubeau* and *A. Zappel*, Z. anorg. allg. Chem. *279*, 38 (1955).

[38] *K. Niedenzu* et al., unpublished results.

[39] *W. D. Phillips*, *H. C. Miller*, and *E. L. Muetterties*, J. Amer. chem. Soc. *81*, 4496 (1959).

[40] *H. Nöth* and *S. Lukas*, Chem. Ber. *95*, 1505 (1962).

[41] *N. Wiberg* and *J. W. Buchler*, J. Amer. chem. Soc. *85*, 243 (1963).

[42] *A. Dornow* and *H. H. Gehrt*, Z. anorg. allg. Chem. *294*, 81 (1958).

[43] *C. A. Kraus* and *E. H. Brown*, J. Amer. chem. Soc. *52*, 4414 (1930).

[44] *D. W. Aubrey* and *M. F. Lappert*, Proc. chem. Soc. (London) *1960*, 148.

[45] *R. J. Brotherton* and *T. Buckman*, Inorg. Chem. *2*, 424 (1963).

[46] *H. J. Becher*, Z. anorg. allg. Chem. *287*, 285 (1956).

[47] *D. W. Aubrey*, *M. F. Lappert*, and *H. Pyszora*, J. chem. Soc. (London) *1960*, 5239.

[48] *H. A. Skinner* and *N. B. Smith*, J. chem. Soc. (London) *1953*, 4025.

[49] *H. Nöth*, Z. Naturforsch. *16b*, 618 (1961).

[50] *R. Köster* and *K. Iwasaki* in [4].

[51] *M. F. Lappert* and *M. K. Majumdar*, Proc. chem. Soc. (London) *1963*, 88.

[52] *K. Niedenzu*, Symposium on "Current Trends in Organometallic Chemistry" Cincinnati, Ohio (U.S.A.), June 1963; see also *H. Jenne* and *K. Niedenzu*, Inorg. Chem. *3*, 68 (1964).

ily a monosilylated bisaminoborane *(11)* is formed which reacts with excess aminochloroborane to yield the bisborylamine *(12)*.

Bisborylamines of type *(6)* are relatively unstable and decompose to form borazoles.

$$3\,(R_2B)_2NH \rightarrow 3\,BR_3 + (-BR-NH-)_3$$
*(6)*

This decomposition is catalysed by acids and also occurs during exchange reactions of *(8)*, *e.g.* during attempts to convert *(8)* into *(6)* with tetraalkyldiboranes.

Trisborylamines in which three boron atoms are bonded to a central nitrogen atom have not yet been recorded.

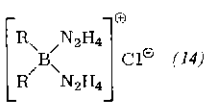
### 4. Hydrazino- and Azidoboranes

First attempts to prepare hydrazinoboranes date back to *Emeleus* [53] and *Schlesinger* [54], but it was not until 1961 that *N,N'*-diborylhydrazine $H_2B-NH-NH-BH_2$ was obtained; it was then made by pyrolysis of the adduct of diborane onto hydrazine [55]. Hydrazinoboranes substituted at the boron atom were obtained in good yield by the action of tetraalkyldiborane $(R_2BH)_2$ on hydrazine at 100–150 °C [56].

$$(R_2BH)_2 + N_2H_4 \rightarrow R_2B-NH-NH-BR_2 + 2\,H_2$$
*(13)*

Adducts of the amine-borane type $R_3B{\cdot}N_2H_4$ are primarily formed in an exothermic reaction on treating trialkylborane with hydrazine. They decompose above 170 °C. In the presence of excess $BR_3$, *N,N'*-diborylhydrazines of type *(13)* are formed.

Hydrazinolysis of diorganochloroboranes does not always proceed unequivocally. $R_2BCl$ and *N,N*-dimethylhydrazine form $R_2B-NH-NMe_2$ in a smooth reaction. With free hydrazine, however, mainly a salt-like compound *(14)* is formed.


*(14)*

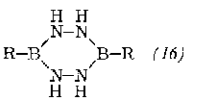
The best preparative results were obtained by hydrazinolysis of a BN bond.

$$R_2B-NR'_2 + N_2H_4 \rightarrow R_2B-NH-NH_2 + HNR'_2$$
*(15)*

The hydrazinoborane *(15)* decomposes in an equilibrium reaction.

$$2\,R_2B-NH-NH_2 \rightleftharpoons R_2B-NH-NH-BR_2 + N_2H_4$$
*(16)*

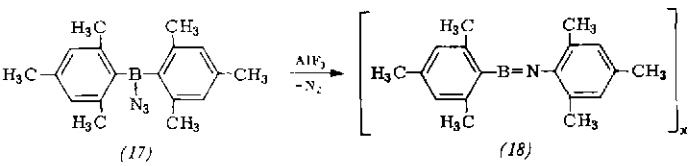
The formation of compounds of type *(15)* also occurs with substituted hydrazines, and trisaminoboranes, bisaminoboranes [22d], and mercaptoalkylboranes [57] can be utilized instead of the monoaminoborane. Although hydrazinolysis of bisaminoboranes with *N*-substituted hydrazines readily yields bishydrazinoboranes $RB(NH-NR'_2)_2$, a new ring system *(16)* is formed [22d] with free hydrazine.


*(16)*

Derivatives of *(16)* were recently obtained by reducing azobenzene with diborane [58] and by the reaction of dichlorophenylborane with symmetrical dilithium diphenylhydrazine [58] or with hydrazobenzene in the presence of triethylamine [59].

All the hydrazinoboranes investigated so far are monomeric. They are sensitive towards hydrolysis and oxidize readily. A detailed review of hydrazinoboranes has been compiled by *Nöth* [58].

Azidoboranes have not yet been characterized. However, a reaction of dimesitylfluoroborane with aluminum azide has been reported [60], which should result in the corresponding azidoborane. A strong absorption near 2100 cm$^{-1}$ was assigned to an asymmetrical vibration of an azido group bonded to boron. Thermal decomposition of *(17)* yields *(18)*.

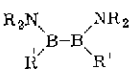

*(17)* *(18)*

### 5. Boron Subcompounds with Aminoborane-Type Linkages

Until recently, almost the only route leading to subcompounds of boron, *i.e.* compounds with B–B bonds, proceeded by way of diboron tetrachloride $B_2Cl_4$. Then a very simple preparation of amino derivatives of diboron by condensation of bisaminochloroboranes with metals was reported in two independent publications [61,62].

$$2\,(R_2N)_2BCl + 2\,Na \rightarrow (R_2N)_2B-B(NR_2)_2 + 2\,NaCl$$

Mixed substituted compounds of type *(19)* are also available by means of this method, and its preparative possibilities have been studied in detail [63–65]. Trans-


*(19)*

[53] *H. J. Emeleus* and *F. G. A. Stone*, J. chem. Soc. (London) *1951*, 840.

[54] *J. Steindler* and *H. I. Schlesinger*, J. Amer. chem. Soc. *75*, 756 (1953).

[55] *J. Goubeau* and *E. Ricker*, Z. anorg. allg. chem. *310*, 123 (1961).

[56] *H. Nöth*, Z. Naturforsch. *16b*, 471 (1961).

[57] *B. M. Mikhailov* and *Y. A. Bubnov*, Zh. Obschei Khimii *1960*, 368.

[58] *H. Nöth* and *W. Regnet* in [4].

[59] *M. F. Lappert* et al. in [4].

[60] *J. E. Leffler* and *L. J. Todd*, Chem. and Ind. *1961*, 512.

[61] *R. J. Brotherton, A. L. McCloskey, L. L. Petterson*, and *H. Steinberg*, J. Amer. chem. Soc. *82*, 6242 (1960).

[62] *H. Nöth* and *W. Meister*, Chem. Ber. *94*, 509 (1961).

[63] *H. Nöth* and *P. Fritz*, Angew. Chem. *73*, 408 (1961).

[64] *R. J. Brotherton, H. M. Manasevit*, and *A. L. McCloskey*, Inorg. Chem. *1*, 749 (1962).

[65] *M. P. Brown* and *H. B. Silver*, Chem. and Ind. *1963*, 85.

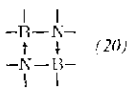
amination with primary or secondary amines [61,66] resulted in numerous new compounds, and alcoholysis yielded hypoborates $(RO)_2B-B(OR)_2$. Mixed amino-chloro compounds of diboron were obtained from tetrakisdimethylamino diboron and boron trichloride [65] and are also formed on treatment of tetrakisdimethylamino diboron with HCl [67].

The B- B bond in amino derivatives of diboron is pronouncedly more stable than that in other derivatives of diboron. This can be explained by back coordination of the free electron pair of the nitrogen to the boron, resulting in the formation of partial BN double-bond character. The vibration spectrum of tetrakisdimethylamino diboron was measured by *Becher* and co-workers [68]. Steric effects produce a structure in which the $N(CH_3)_2$ groups and both $BN_2$ groups are tilted against each other.

Trisaminoboranes and bisaminoboranes are formed on thermal decomposition of tetrakisamino diboron compounds; this has been investigated in detail with tetrakisdimethylamino diboron [69].

### D. Cyclic Aminoboranes

Dimeric aminohoranes were recognized by *Wiberg* [70], who proposed a cyclic structure *(20)*, which can be considered correct because the dimeric compounds are chemically not very reactive and the absorption of the BN bond in the infrared has been found at very low values (ca. 900 $cm^{-1}$). Thus, participation of the free electron pair of the nitrogen in a BN double bond can be excluded.



*(20)*

Dimeric aminoboranes are usually formed if one or more of the substituents is hydrogen or halogen. Aminodihalogenoboranes in particular dimerize very readily, apparently owing to steric factors [26]. The dimerization can be reversed by distillation [26] or sublimation [18]. Conventional molecular-weight determinations do not always give unequivocal results. $^{11}B$ nuclear magnetic resonance, however, permits elucidation of the degree of association [24,36,39]. Higher polymeric aminoboranes are also known, but have only recently been investigated [71]. They have no recognized technical importance.

Trimeric aminoboranes are of scientific interest because they can be considered as formal analogues of cyclohexane. The first trimeric compound was obtained in 1955 by *Bissot* and *Parry* [72] in small yield on pyrolysis of *O,N*-dimethylhydroxylamine-borane. Better yields are obtained on heating methylamine-borane to 100 °C.

$$3\ MeNH_2{\cdot}BH_3 \rightarrow 3\ H_2 + (MeHN{-}BH_2)_3$$

In 1957 a compound $(Me_2N)_3B_3H_4$ was described [73]. Two years later, however, a three-dimensional X-ray structural analysis [74] indicated that this compound is really trimeric dimethylaminoborane. The compound consists of alternating $BH_2$ and $NMe_2$ groups with a BN bond distance of 1.59 ± 0.02 Å [75]. An independent $^{11}B$ resonance investigation [76] indicated a 1:2:1 triplet signifying three equivalent $BH_2$ groups. It was also shown that the trimer is readily formed on heating dimeric dimethylaminoborane with higher boron hydrides to 100 -110 °C.

Recent investigations by *Schaeffer* [77] are based on the known property of borazine to add on HX. Compounds of the type $B_3H_3N_3H_3{\cdot}3HX$ are formed to which a cyclic structure had already been ascribed [1]. $B_3N_3H_6{\cdot}3HCl$ was reduced with sodium borohydride to $B_3N_3H_{12}$. Another possibility to obtain this compound was reported by *Shore* [71]. In liquid ammonia, the diammoniate of diborane reacts with strong bases such as sodium amide or sodium acetylide to yield crystalline compounds $(BH_2-NH_2)_x$, where $x = 2-10$, from which the trimer was isolated in 15 % yield. The structures of the higher members with $x > 3$ is still uncertain. Two steroisomeric compounds have been isolated from the trimeric methylaminoborane [77]. The equilibrium constant for their interconversion of 2.28 corresponds to a difference in free energy of - 0.51 kcal/mole. The symmetrical isomer with three methyl groups in the equatorial position is favored over the unsymmetrical one with one axial methyl group. These BN analogues of cyclohexane prefer the chair form, in contrast to cyclohexane derivatives.

### E. Pseudo-Aromatic Compounds with Aminoborane-Type Linkages

#### 1. Five-Membered Ring Systems

A new chapter in aminoborane chemistry has developed during the past five years. The preparation of numerous ring compounds in which an aromatic CC grouping is replaced by BN has been reported from various laboratories. The possibility of incorporating the BN group into carbon rings was recognized by *Goubeau* in 1955 [37], but was not investigated in detail. Only 2-methyl-

[66] *M. P. Brown, A. E. Dann, D. W. Hunt,* and *H. B. Silver,* J. chem. Soc. (London) *1962*, 4648.

[67] *H. Nöth* and *W. Meister,* Z. Naturforsch. *17b*, 714 (1962).

[68] *H. J. Becher, W. Sowodny, H. Nöth,* and *W. Meister,* Z. anorg. allg. Chem. *314*, 226 (1962).

[69] *J. L. Petterson* and *R. J. Brotherton,* Inorg. Chem. *2*, 423 (1963).

[70] *E. Wiberg* and *K. Schuster,* Z. anorg. allg. Chem. *213*, 77, 89 (1933).

[71] *S. G. Shore* et al. in [4].

[72] *T. C. Bissot* and *R. W. Parry,* J. Amer. chem. Soc. *77*, 3481 (1955).

[73] *A. B. Burg,* J. Amer. chem. Soc. *79*, 2129 (1957).

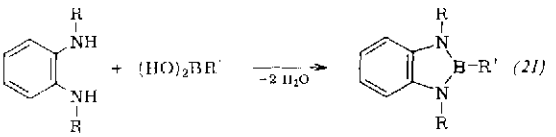
[74] *L. M. Trefonas* and *W. N. Lipscomb,* J. Amer. chem. Soc. *81*, 4435 (1959).

[75] *L. M. Trefonas, F. S. Mathews,* and *W. N. Lipscomb,* Acta crystallogr. *14*, 273 (1961).

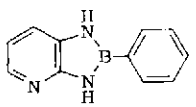
[76] *G. W. Campbell* and *L. Johnson,* J. Amer. chem. Soc. *81*, 3800 (1959).

[77] *G. H. Dahl* and *R. Schaeffer,* J. Amer. chem. Soc. *83*, 3032 (1961); refer also to [4].

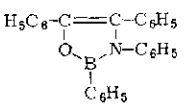
4,5-benzo-1,3,2-diazaboroline *(21)* was obtained [78] on reaction of *o*-phenylenediamine with trimethylborane. A general synthesis of this ring system by condensation of aromatic *o*-diamines with organoboric acids has been developed by *Letsinger* [79] and by *Soloway* [80].



*Hawthorne* [81] obtained analogous compounds from *o*-diamines and trialkylamine alkylboranes, and the preparation of *(21)* via transamination reactions has been reported [82,83]. Other systems in which one nitrogen is replaced by another hetero-atom, such as oxygen or sulfur, are known [84]. Functional aromatic nuclei [85,86] lead to structures such as *(22)*. Another interesting example *(23)* is obtained by condensation of phenyl-



*(22)*

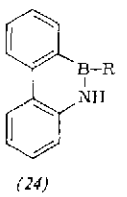


*(23)*

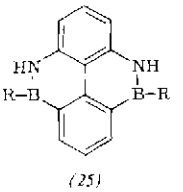
boric acid with an equimolar mixture of benzoin and aniline [87]. These few examples indicate the possibilities which still exist in this area for the synthetic chemist. Possible use of these boron-containing heterocycles in tumor therapy is being investigated at the Massachusetts General Hospital in Boston, Mass. (U.S.A.) [80].

## 2. Six-Membered BN Heteroaromatics

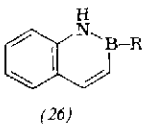
Six-membered BN heteroaromatic compounds have been investigated by *Dewar* and co-workers with great success. Within a few years, more than twenty new ring systems were obtained in which one or more CC groupings are replaced by the isosteric BN combination. Because a detailed survey of this area of chemistry cannot be made here, the interested reader is referred to two articles by *Dewar*, one reporting work up to about 1961 [88], and the other reviewing more recent results [89]. Some examples of the compounds obtained are indicated by formulae *(24)–(28)*.



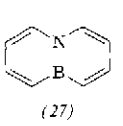
*(24)*



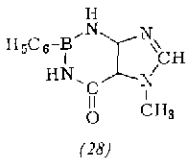
*(25)*



*(26)*



*(27)*



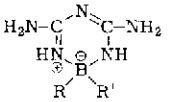
*(28)*

A general synthesis of the parent monocyclic 2,1-borazarene system *(28a)* has just been developed by dehydrogenation of the novel 1,2-azaboracyclohexanes [89a].



*(28a)*

Another interesting system of heteroaromatic boron compounds in which the boron is tetravalent should be mentioned. Such compounds, *e.g. (29)*, are obtained on treating biguanidine with aminoboranes or organoboric acids [90]. The high stability of heteroaromatic com-



*(29)*, R = $C_6H_5$, $C_4H_9$, $C_2H_5$, OH, $OCH_3$
R' = $C_6H_5$, OH, $OC_2H_5$, $OCH_3$

pounds containing boron and nitrogen compared with other organic boron-nitrogen compounds is most remarkable and indicates conjugation of the free electron pair of the nitrogen with the aromatic $\pi$-electrons.

Molecular-orbital calculations have been performed for a few samples. The Hückel method faces the known difficulties for calculations of compounds with hetero-atoms. The formal charges on boron and nitrogen have rather low values (< 0.2 electrons). Nevertheless, the resonance energies of the BN-containing ring systems cannot be neglected [89]. *Kaufman* [11] utilized Pariser-Parr and Pariser-Parr-Pople molecular orbital methods for analogous calculations. Various models based on possible resonance structures can be used as a basis for such calculations. Accurate conclusions cannot yet be made, owing to the lack of sufficient experimental data; these might be obtained, for instance, by NMR spectroscopy. However, calculations of the charge distributions seem to be relatively independent of the selection of the model, although calculations of the bond order indicate direct dependence on the model not only for BN, but also for CC.

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[78] *D. Ulmschneider* and *J. Goubeau*, Chem. Ber. *90*, 2733 (1957).
[79] *R. L. Letsinger* and *S. B. Hamilton*, J. Amer. chem. Soc. *80*, 5411 (1958).
[80] *E. Nyilas* and *A. H. Soloway*, J. Amer. chem. Soc. *81*, 2681 (1959).
[81] *M. F. Hawthorne*, J. Amer. chem. Soc. *81*, 5836 (1959).
[82] *R. J. Brotherton* and *H. Steinberg*, J. org. Chemistry *26*, 4632 (1961).
[83] *H. Beyer*, *K. Niedenzu*, and *J. W. Dawson*, J. org. Chemistry *27*, 4701 (1962).
[84] *M. J. S. Dewar*, *V. P. Kubba*, and *R. Pettit*, J. chem. Soc. (London) *1958*, 3076.
[85] *H. Zimmer*, *A. D. Sill*, and *E. R. Andrews*, Naturwissenschaften *16b*, 378 (1960).
[86] *M. Pailer* and *W. Fenzl*, Mh. Chem. *92*, 1294 (1961).
[87] *R. L. Letsinger* and *S. B. Hamilton*, J. org. Chemistry *25*, 592 (1960).
[88] *M. J. S. Dewar*: Recent Advances in Boron Chemistry. Pergamon Press, London, in the press.
[89] *M. J. S. Dewar*, in [4].
[89a] *D. G. White*, J. Amer. chem. Soc. *85*, 3634 (1963).
[90] *J. E. Milks*, *G. W. Kennerly*, and *J. H. Polevy*, J. Amer. chem. Soc. *84*, 2529 (1962).

# The Mechanism of the Action of Organometallic Catalysts

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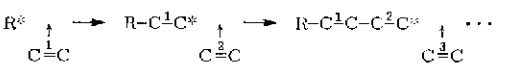
*Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday*

*Kinetic investigations of the polyreaction of isoprene with organolithium compounds as initiators in n-heptane as solvent indicate the following sequence of reactions: 1. formation of an adduct between a monomeric form of the organolithium compound and the isoprene and 2. reaction of this adduct with an associated form of the organolithium compound with insertion of the isoprene. The adduct formation is considered to be due to chemisorption, and proof of such chemisorption of a monomer (ethylene) is also demonstrated for a homogeneous Ziegler-type catalyst. All the reactions can be formulated in the form of cyclic structures with electron-deficient character. Postulation of such ring structures explains the surprising values obtained for the frequency factors and equilibrium constants.*

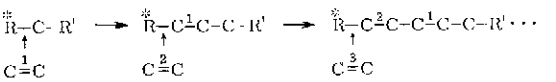
## 1. Introduction

The characteristics indicating relationships between liquids and solids should be determinable primarily by kinetic investigations in the liquid phase, since structural elements must play a more important part in kinetic measurements than in measurements of physical quantities, which can merely encompass such elements in an integral manner. Enzymatic reactions, too, indicate a dependence of the specificity and selectivity of the reaction on the structure of the catalyst, *viz.* the enzyme. From such considerations by one of us (F. P.) [1] we proposed a working hypothesis for the course of the low-pressure polymerization of ethylene with mixed Ziegler-type catalysts [2]. This hypothesis is shown in Scheme 1.

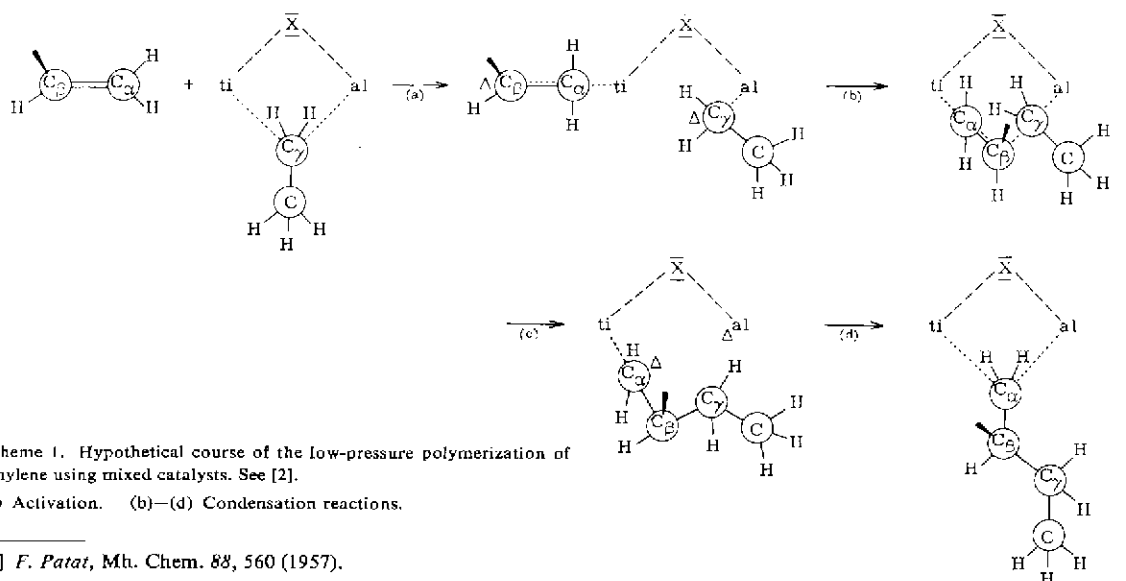
In contrast to the known polyreactions, such as polymerizations, polycondensations, and polyadditions [2a], where the monomer (which is at least bifunctional) is condensed within a growth cycle in a monofunctional manner (grain type reaction) [*],



in Scheme 1 the monomer combines bifunctionally within a growth cycle, *i.e.* it is inserted (insertion type reaction).



The activation step in Scheme 1 [Reaction (a)] is postulated to be chemisorption, for both heterogeneous and homogeneous systems (adduct formation by partial electron transfer).



Scheme 1. Hypothetical course of the low-pressure polymerization of ethylene using mixed catalysts. See [2].

(a) Activation. (b)—(d) Condensation reactions.

[1] *F. Patat*, Mh. Chem. *88*, 560 (1957).

[2] *F. Patat* and *H. Sinn*, Angew. Chem. *70*, 496 (1958).

[2a] This nomenclature is in accordance with the proposals presented in Makromolekulare Chem. *38*, 1 (1960).

[*] In this and the following equations, the asterisk designates the point of extension of the molecule.

It should also be pointed out that insertion of the monomer takes place only in organometallics which undergo association [*e.g.* 2 $AlR_3 \rightleftharpoons (AlR_3)_2$; 6 $LiR \rightleftharpoons (LiR)_6$]; insertion reactions of olefins do not take place with non-associating compounds such as $ZnR_2$, $BR_3$, or $Cl_3TiR$.

According to the kinetic investigation of the "Aufbau"-reaction

$$AlR_3 + H_2C{=}CH_2 \longrightarrow \begin{matrix} R \\ R \end{matrix}\!\!>\!Al{-}CH_2{-}CH_2{-}R$$

carried out by *Ziegler* [3] and to the studies of the insertion of isoprene into alkenyl-lithium compounds (polyisoprenyl-lithium) in hydrocarbons as solvent

$$Li(CH_2{-}CH{-}C(CH_3){-}CH_2)_n{-}R + H_2C{-}CH{-}C(CH_3){-}CH_2 \rightarrow Li(CH_2{-}CH{-}C(CH_3){-}CH_2)_{n+1}{-}R$$

carried out by our research group, for concentrations of organometallic of greater than 0.1 mole/l, the overall rate of reaction is

$$v_{tot} = k \cdot [M]\sqrt[n]{[(MO)_{titr}]} \qquad (1)$$

where k is the constant of proportionality, [M] the concentration of ethylene or isoprene, $[(MO)_{titr}]$ the total concentration of the organometallic compound as determined by titration, and n the degree of association (see below).

When the organometallic compound is triethylaluminum, which is almost completely dimeric in the concentration range investigated, then n in Equation (1) is equal to 2; if the organometallic compound is polyisoprenyl-lithium, which under these conditions is present substantially as the hexamer, then n is equal to 6.

In general,

$$[(MO)_{titr}] = \sum_n n[(MO)_n] \qquad (2)$$

where MO is the monomeric and $(MO)_n$ the associated form of the organometallic compound. The law of mass action can be applied to the equilibrium $nMO \rightleftharpoons (MO)_n$, so that

$$[MO]^n/[(MO)_n] = K_{ii} \qquad (3)$$

If almost exclusively associated forms are present (as is the case for aluminum and lithium alkyls at concentrations greater than 0.1 mole/l), then the following approximation may be considered:

$$n\,[(MO)_n] = [(MO)_{titr}] \qquad (4)$$

Combination of Equations (3) and (4) gives

$$[MO] = k'\sqrt[n]{[(MO)_{titr}]} \qquad (5)$$

Making use of Equation (5), the rate equation [Equation (1)] suggests that within the concentration range investigated (for which the approximation of Equation (4) is valid), it is the monomeric organometallics, and not the associated forms, which are either the sole or the rate-determining reaction promoters. Kinetic investigations alone cannot differentiate between these two alternatives, since in principle kinetic analysis cannot establish a fact but can merely concede its possibility. The postulate that the monomer forms are the sole reaction promoters is therefore correct until indications can be found that the rate-determining step of a reaction sequence has been measured. We have succeeded in finding such indications.

[3] *K. Ziegler*, Angew. Chem. *71*, 623 (1959); *K. Ziegler* and *H. Hoberg*, Chem. Ber. *93*, 2938 (1960).

## 2. Formation of Polyisoprene with the Aid of Organolithium Compounds

### a) Preliminary Remarks

Lithium alkyls are soluble in hydrocarbons, and the degree of association reaches values of up to 6 in these solvents; saltlike organic compounds of alkali metals are insoluble in hydrocarbons. Polyisoprenes with more than 90 % 1,4-*cis*-structures can be obtained in hydrocarbons with organolithium compounds under homogeneous conditions; the molecular weights of the products justify the assumption that one molecule of polymer is formed for each atom of lithium used. The ratio of the weight-average to the number-average molecular weight was 1.04 for some products prepared at 0 °C [4].

In polar solvents, the organic compounds of both lithium and the other alkali metals gave rise to polyisoprenes which contained little 1,4-*cis*- but predominantly the 1,2-, 3,4- and 1,4-*trans*-structures. A typical yellow color occurs when the polyreaction is carried out in ether; this color is ascribed to the polyisoprenyl anion, for its spectrum is almost, but not entirely, independent of the nature of the alkali metal. The reaction in polar solvents at least is normally described as "anionic". However, conductivity measurements did not give any support to this designation [4a].

### b) Kinetic Investigations

Particularly clear relationships are obtained when lithium polyisoprenyls or oligoisoprenyls are used to initiate the formation of polyisoprene. This initiator is obtained by treating an alkyl-lithium with isoprene:

$$Li{-}R + CH_2{=}CH{-}CCH_3{-}CH_2 \rightarrow Li(CH_2{-}CH{=}CCH_3\ CH_2)R \quad (e)$$

$$Li(CH_2{-}CH{=}CCH_3{-}CH_2)_n{-}R + CH_2{-}CH\ CCH_3{=}CH_2 \rightarrow Li(CH_2{-}CH{=}CCH_3{-}CH_2)_{n+1}{-}R \quad (f)$$

The isoprene molecule is thus inserted at the metal-carbon bond, with the formation of an alkenyl-lithium LiR′ from the alkyl-lithium LiR, *i.e.* with the formation of a polyisoprenyl-lithium. If further molecules of isoprene are interspersed between the alkenyl radical and the lithium atom, the alkenyl-lithium structure is still preserved, so that the nature of the surroundings of the Li atom and hence the reactivity of the Li–C bond remains unchanged. It was demonstrated separately that the reactivity of the polyisoprenyl-lithium compounds is independent of their molecular weight.

[4] *K. F. Elgert*, Ph. D. Thesis, Technische Hochschule München, 1963; *M. Hilal ab del Kader*, Ph. D. Thesis, Technische Hochschule München, 1963.

[4a] *S. Bywater*, Pure appl. Chem. *4*, 319 (1962).

Various authors [5] agree that the formation of polyisoprene is a first order reaction with respect to the concentration of isoprene. On the other hand, the order with respect to the concentration of initiator varies with the latter [6], which was measured over the range of six powers of ten [7]. The reaction rates found for an isoprene concentration of 2.57 moles/l (our normal initial concentration) are shown in Fig. 1, in relation to the titratable concentration of the organolithium compound [cf. Equation (2)].

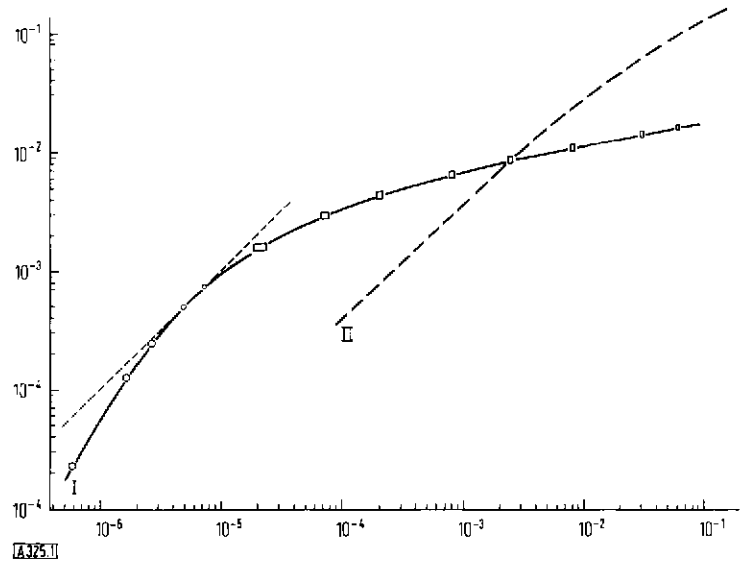



Fig. 1. The overall rate of the polyreaction of isoprene (ordinate) as a function of the initiator concentration (abscissa), at 20 °C. Alkenyllithium (polyisoprenyl-lithium) prepared according to reactions (e) and (f) was used as the initiator; the butyl-lithium content was < 1 %.

Curve I: in n-heptane
Curve II: in diethyl ether.

The broken-line plot represents the slope (order of reaction) which the curve would finally have to assume, or which it must not exceed, if the non-associated form (monomer) of the initiator is the sole reaction promoter.

Ordinate: $v_{tot}$ [moles/l/min]
Abscissa: Initiator concentration [moles/l].

The change in the order of the reaction with the initiator concentration (as shown by the slope of the curve in Fig. 1) is evidently related to the degree of association of the organolithium compound. The relationships in the upper region of concentration have already been discussed in the introduction. Complete dissociation of the associated lithium alkenyls takes place at sufficient dilution, and then the concentration of the monomeric form becomes identical with the titratable lithium concentration. In contrast to the approximation of Equation (4), the following relationship is now valid:

$$[MO] = [(MO)_{titr}] \qquad (6)$$

where [MO] = [alkenyl-lithium] = [LiR'].

This behavior is evidently the case for the concentration at which the slope of the curve in Figure 1 is equal to unity. The overall rate of reaction can thus be described by:

$$v_{tot} = k_w\,[\text{isoprene}]\,[LiR'] = k_w\,[\text{isoprene}]\,[(LiR')_{titr}] \qquad (7)$$

so that $k_w$ can be obtained from the corresponding point on the curve.

If the relationship

$$v_{tot} = k_w\,[\text{isoprene}]\,[LiR'] \qquad (8)$$

is considered to be valid for the entire curve above an alkenyllithium concentration of $10^{-5}$ mole/l, then, using Equation (8), any desired number of points taken from the curve at a known value of $k_w$ gives a corresponding number of pairs of values for [LiR'] and $[(LiR')_{titr}]$. Values of the equilibrium constant $K_n$ can then be found from these pairs using Equations (2) and (3). Surprisingly, it is found that only the monomeric, trimeric, and hexameric forms need to be considered for the calculation of the total concentration of the organolithium compounds; correspondingly, only three measurements are necessary for the determination of $k_w$, $K_3$, and $K_6$. With the aid of these three constants, the overall rate of reaction can then be calculated for any initiator concentration $[(LiR')_{titr}]$, and checked by means of the curve in Figure 1. The calculated and measured values agree within the thickness of the drawn line. Conversely, it is possible to determine experimentally the overall reaction rates corresponding to any desired values of $[(LiR')_{titr}]$, to calculate the LiR' concentration (in monomeric form) with the aid of $K_3$ and $K_6$, and to check the constancy (*i.e.* concentration independence) of $k_w$ using Equation (8). The results are shown in Table 1.

Table 1. The independence of the rate constant $k_w$ of the initiator concentration $[(LiR')_{titr}]$.

| $[(LiR')_{titr}]$ [mole/l] | $k_w\,[LiR']\cdot 10^3$ [l/min] | $[LiR']\cdot 10^5$ [mole/l] | $k_w$ [l/mole/min] |
|---|---|---|---|
| $6.0\times 10^{-2}$ | 6.72 | 17.0 | 39.6 |
| $1.5\times 10^{-2}$ | 5.22 | 13.0 | 40.0 |
| $2.4\times 10^{-3}$ | 3.50 | 9.0 | 39.0 |
| $8.0\times 10^{-4}$ | 2.77 | 7.0 | 39.6 |
| $4.0\times 10^{-4}$ | 2.20 | 5.6 | 39.4 |
| $2.0\times 10^{-4}$ | 1.70 | 4.3 | 39.5 |
| $7.0\times 10^{-5}$ | 1.14 | 2.9 | 39.4 |
| $2.0\times 10^{-5}$ | 0.7 | 1.8 | 39.0 |

$[(LiR')_{titr}]$ = titratable organolithium concentration.
$k_w[LiR']$ = the experimentally determined product of the rate constant and concentration of the monomeric form of the organolithium compound.
[LiR'] = concentration of the organolithium monomer, calculated from the equilibrium constants.
$k_w$ = rate constant (values in column 2 divided by values in column 3).


[5] *H. E. Diem, H. Tucker*, and *C. E. Gibbs*, 132nd ACS-Meeting, Abstracts of Papers U 9, 24 (1957); Reviews: *F. Dawans* and *G. Lefevre*, Rev. Inst. franç. Petrole Ann. Combustibles liquides *17*, 110 (1962); *L. Küchler*: Polymerisationskinetik. Springer, Heidelberg 1951.

[6] *H. Sinn* and *C. Lundborg*, Makromolekulare Chem. *47*, 86 (1961); *C. Lundborg* and *H. Sinn*, ibid. *41*, 242 (1960).

[7] *H. Sinn* and *O. T. Onsager*, Makromolekulare Chem. *55*, 167 (1962).

Below an initiator concentration of $10^{-5}$ mole/l, the organolithium compound is present almost exclusively as the monomer, so that, if Equation (7) is valid, a linear decrease in the overall rate of reaction with diminishing initiator concentration is to be expected. This, however, is not the case; instead, the order of the reaction with respect to $[(LiR')_{titr}]$ increases to values greater than unity.

The fact that minimum values are represented by the slope of the curve in Figure 1 when the initiator concentration is less than $10^{-4}$, *i.e.* that the values may only be greater but never smaller, was demonstrated by the following method.

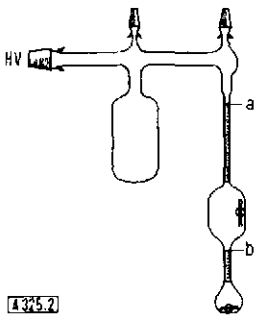
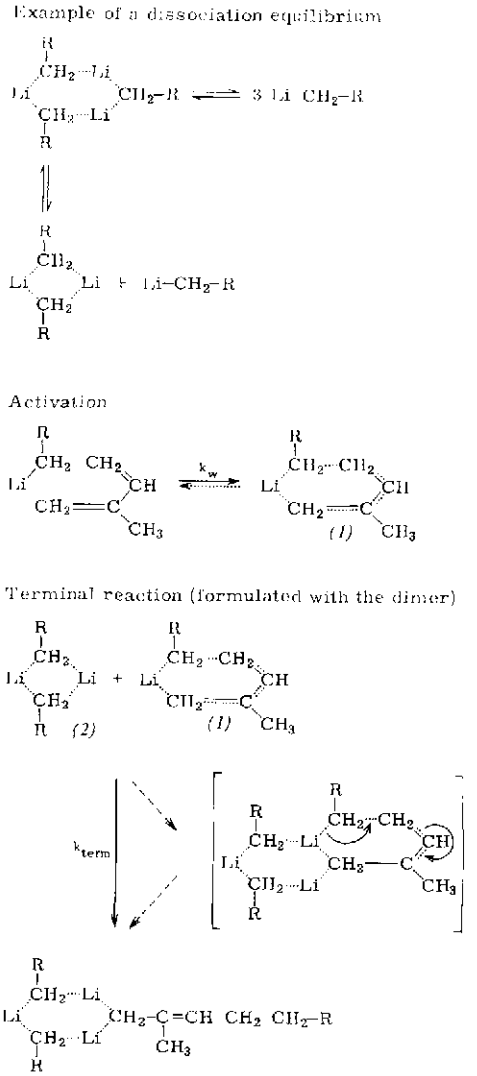



Fig. 2. Dilatometer for measuring the rate of polymerization at very low initiator concentrations.
a, b = filling marks.
HV = vacuum connection.

The dilatometer was filled up to the mark a *in vacuo* by a quantity of initiator x and isoprene. After determining the overall rate of reaction, $v_{tot}$ the isoprene was evaporated off until the dilatometer was filled only up to the mark b. The initiator concentration is thus increased, although the absolute amount of initiator is not, so that for an initiator amount x', after removal of some of the isoprene by condensation, the relationship $x' \leqslant x$ must apply. A value of $v'_{tot}$ was determined for x'. The original amount x was chosen so that this value of $v'_{tot}$ lies on a known part of the curve; x' was determined from the measured value of $v'_{tot}$ for a known dilatometer volume, and the initial value of $v_{tot}$ was related to x', making allowance for the concentration factor. A detailed discussion is given by *Sinn* and *Onsager* [7].

If an analogous study to that made in the introduction is carried out for initiator concentrations below $10^{-5}$ mole/l, where the reaction order based on the titratable initiator concentration is greater than 1, application of Equations (2), (3), and (6) leads to the conclusion that associated forms of the organolithium compounds are either the sole or the rate-determining reaction promoters. However, since the monomeric forms in the one instance and associated forms in the other cannot be the sole reaction promoters, it can be postulated that a sequence of reactions takes place, either the first or the second stage of this sequence being the rate-determining step, depending on the concentration. These relationships can be represented by Scheme 2.

The quantity $k_w$ is therefore the rate constant for the formation of an adduct between the monomeric alkenyl-lithium and isoprene. The adduct *(1)*, in which the isoprene necessarily has the 1,4-*cis*-structure, reacts with an associated form, *e.g.* with the dimer *(2)*. Insertion of the isoprene takes place in the course of this reaction. This second stage is designated as a terminal step, and is



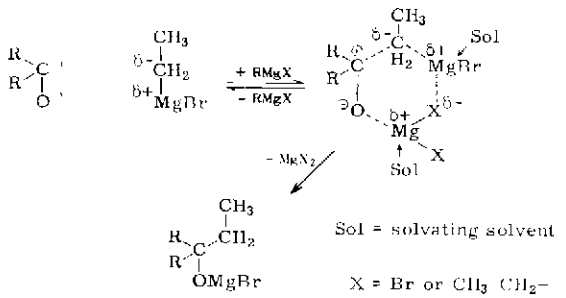

Scheme 2. Polyisoprene formation using alkenyl-lithium as initiator.

characterized by the rate constant $k_{term}$. Since $k_w$ is smaller than $k_{term}$, the activation reaction (adduct formation) is the rate-determining step in the normal concentration region ($> 10^{-5}$ mole/l); the overall rate of reaction is thus proportional to the concentration of the monomeric form of the organolithium compound. In the region of virtually complete dissociation, the associated form practically disappears from the solution, so that although $k_w < k_{term}$, $k_w [LiR']$ ultimately $> k_{term} [(LiR')_n]$, since $[LiR'] \gg [(LiR')_n]$. The terminal reaction with the participation of the associated form is therefore slower than the activation reaction, and is thus rate-determining.

At this point is should be mentioned that the participation of two molecules of an organometallic compound has also been observed [8] in the reaction (growth) cycle in Grignard addition reactions (Scheme 3).

If butyl-lithium is used as the initiator in place of separately prepared polyisoprenyl-lithium, then Reactions (e) and (f) take place side by side, (e) being termed the initial reaction. Since both reactions use up isoprene, the overall rate is obtained by summation of the ex-

[8] *C. G. Swain* and *H. B. Boyles*, J. Amer. chem. Soc. *73*, 870 (1951); cf. *P. Karrer:* Lehrbuch der organischen Chemie. Thieme, Stuttgart 1959, p. 101.




Scheme 3. Grignard addition reactions involving two molecules of the Grignard reagent [8].

pressions for the rates of the component reactions (e) and (f) [Equation (9)].

$$v_{tot} = k_i \cdot f \cdot [I]\,[(LiR)_{titr}] + k_w \cdot f \cdot [I]\,[(LiR')_{titr}] \qquad (9)$$

where $f = \frac{[LiR]}{[(LiR)_{titr}]} = \frac{[LiR']}{[(LiR')_{titr}]} = \frac{[Li]}{[(Li)_{titr}]}$,

$[LiR] + [LiR'] \equiv [Li]$,

$[(LiR)_{titr}] + [(LiR')_{titr}] \equiv [(Li)_{titr}]$,

and [I] = the concentration of isoprene.

The conversion of LiR into LiR′ according to Reaction (e) is given by the relationship

$$-\frac{d[(LiR)_{titr}]}{dt} = k_i \cdot f \cdot [I]\,[(LiR)_{titr}] \qquad (10)$$

Combination of Equations (9) and (10) and the assumption that equilibria between the monomeric and the associated forms of the organolithium compound are very quickly established permit predetermination and a complete description of the time-conversion curves determined experimentally.

The assumptions made in the calculation of f, *viz.* that LiR and LiR′ are associated in a similar manner and that all possible mixtures of associated structures between LiR and LiR′ are formed, have been confirmed by our kinetic measurements. Viscosity determinations have also shown that long polyisoprenyl chains do not (appreciably) alter the association of the organolithium compounds. Since small additions of tetrahydrofuran promote dissociation, the degree of association can be calculated from the viscometer efflux times before and after the addition of tetrahydrofuran. The degree of association found experimentally is in satisfactory agreement with that determined kinetically [9a].

Equation (10) was not merely found indirectly from the kinetics for the overall reaction, but was also obtained by an analytical study of the variation of the butyl-lithium content (chromatography of the gas produced by hydrolysis) with time in polyreactions initiated with pure butyl-lithium [9].

A list of all the constants which have so far been determined is given in Table 2. The rate constants are all given for a temperature of 20 °C with n-heptane as solvent.

In our opinion, the activation (adduct formation) is somehow related to the association – dissociation reaction of the organolithium compound, and the terminal reaction to the alkyl exchange reaction which proceeds at high rates in all organometallic systems capable of association. This relationship has already been indicated by the superposition of these reactions in Scheme 2. The validity of six-membered rings with electron-deficient bonding used throughout to describe the structures has not been proved, but it is a useful

[9] *H. Sinn* and *W. Hofmann*, Makromolekulare Chem. *56*, 243 (1962).

[9a] *H. Sinn, O. T. Onsager*, and *C. Landborg*, Makromolekulare Chem., in the press.

Table 2. Constants for the polyreaction of isoprene using an organolithium compound as initiator.

| | |
|---|---|
| Rate constants for the formation of the adduct from butyl-lithium and isoprene (initial reaction) | $k_i = 0.003$ l/mole/sec |
| Activation energy of the initial reaction | $E_i = 15$ kcal/mole |
| Frequency factor of the initial reaction | $A_i = 10^{8.3}$ |
| Rate constant for the formation of the adduct from polyisoprenyl-lithium and isoprene | $k_w = 0.65$ l/mole/sec |
| Activation energy | $E_w = 19.2$ kcal/mole |
| Frequency factor | $A_w = 10^{14.2}$ |
| Rate constants for the terminal reaction (adduct with associated species) | $k_{term} = 1 \quad 10$ l/mole/sec |
| Activation energy of the terminal reaction | $E_{term} = 10$ kcal/mole |
| Frequency factor of the terminal reaction | $A_{term} = 10^{7.5}$–$10^{8.5}$ |
| Equilibrium constant for the equilibrium 3 LiR′ ⇌ $(LiR')_3$ | $K_3 = 1.86 \times 10^{-9}$ mole$^2$/l$^2$ |
| Equilibrium constant for the equilibrium 6 LiR′ ⇌ $(LiR')_6$ | $K_6 = 2.8 \times 10^{-21}$ mole$^5$/l$^5$ |

method of formulation, supported by the fact that according to kinetic investigations the associated forms are present as trimers and hexamers.

Considering the frequency factors shown in Table 2, the large difference between $A_i$ and $A_w$ is surprising, since the same transition state, *i.e.* the adduct of a monomeric form of alkyl-lithium or alkenyl-lithium and isoprene, is assumed for the respective reactions. Figure 3 gives a comparison of butyl-lithium *(4)* and polyisoprenyl-lithium *(5)* with the six-membered ring *(6)* and the cage structure of the associated forms *(7)*. While there is no reason that the butyl-lithium chain in *(4)* should be fixed in position (decrease in entropy), the interaction between the 6,7-double bond and the Li-C

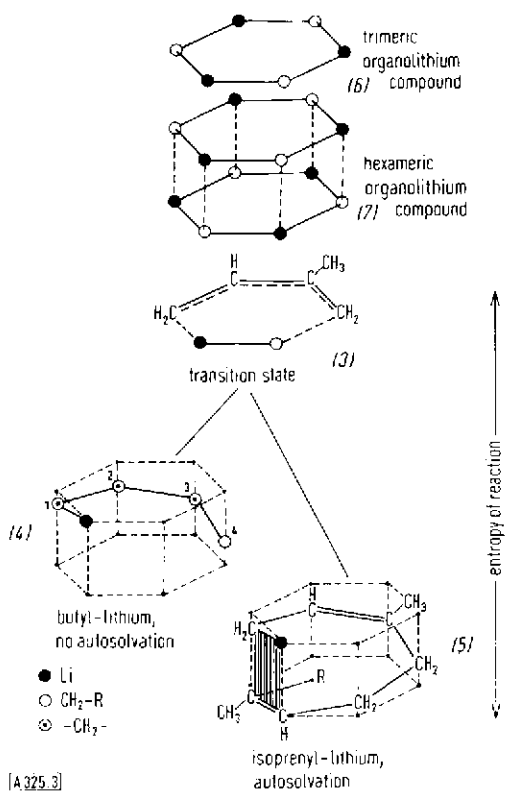



Fig. 3. Possible structures of associated organolithium compounds, the adduct of organolithium compounds and isoprene *(3)*, the monomeric form of butyl-lithium *(4)*, and the autosolvated monomeric form of polyisoprenyl-lithium *(5)*. See text for a discussion of the frequency factors.

bond in the polyisoprenyl-lithium *(5)* requires fixation of the carbon chain and thus a loss of degrees of freedom.

The authors were able to confirm such relationships kinetically, and even better by infrared analysis. Splitting of the C–C bands of cyclohexene when dissolved in butyl-lithium was observed by *Craubner* [10]. If adduct formation with isoprene occurs with such an "autosolvated" monomeric form of the polyisoprenyl-lithium to give the transition state *(3)*, then the fixation of the polyisoprenyl chain is eliminated, *i.e.* degrees of freedom are gained in contrast to the corresponding reaction with butyl-lithium. This fact explains the difference in the frequency factors, because these contain the difference in entropy of the fundamental and the transition states (cf. the first sentence of this paper).

In all the results hitherto described, n-heptane was used as the solvent for the polyreaction. It has already been mentioned in the preliminary part of this paper that polar substances, such as ether or tetrahydrofuran, prevent a stereoregular course of reaction [10a]. Our own kinetic measurements in diethyl ether are shown in Curve II of Figure 1. Since Curves I and II intersect, it follows that they represent entirely distinct reactions. The rate constant for the reaction in ether is substantially smaller than that for the reaction in n-heptane. The rate equation is

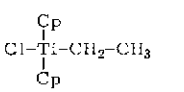
$$v_{t_{ot,\,ether}} = 0.03\ [(LiR)_{titr}]\ [isoprene] \qquad (11)$$

(Units in moles, litres, sec).

Structural considerations thus appear to play a far smaller role in the reaction in ether than in hydrocarbons.

## 3. The Mode of Reaction of Mixed Catalysts Based on Bis(cyclopentadienyl)titanium(IV) Compounds and Organoaluminum Compounds

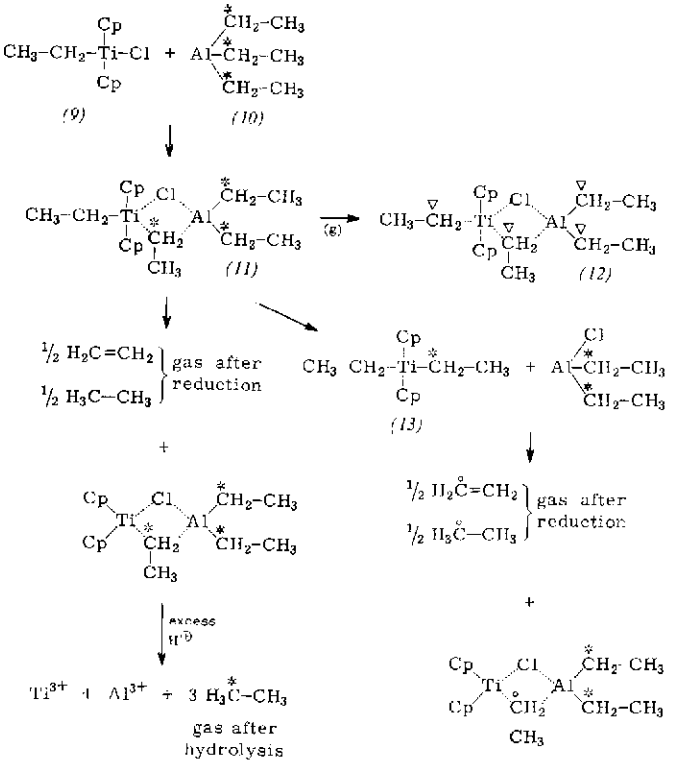
In contrast to most mixed catalysts for Ziegler-type olefin polyreactions, catalysts based on bis(cyclopentadienyl)titanium(IV) compounds plus organoaluminum compounds are homogeneous [11]. Cryoscopic and spectroanalytical studies have shown that complex formation takes place when these components are mixed (in as little as 0.01 sec), if a small excess of the aluminum compound is present, provided that at least one halogen atom is available in the system for each titanium atom. It is immaterial whether this halogen atom is introduced as aluminum or titanium halide. If at least one alkyl group (containing at least two carbon atoms) is present for each titanium atom, then Ti(IV) is reduced to Ti(III) after complex formation, the rate of reduction increasing with increasing values of the ratio alkyl groups: Ti. The necessity for preliminary complex formation for the reduction is clearly shown by the fact that compound *(8)* is practically stable at room temperature, is rapidly reduced on addition of triethyl aluminum, and more slowly reduced on addition of ethylaluminum dichloride. On reduction, one alkyl group per molecule is split off (presumably as an alkyl radical) to give some olefin and some alkane. *Breslow* [12] found that this system is an initiator for the polymerization of ethylene only if Ti(IV) is still present.



*(8)*, Cp = Cyclopentadienyl

It is certain that this complex formation is related to a very rapid ligand exchange (excluding the cyclopentadienyl groups). Attempts to elucidate the site of active growth of the polymer chain from the positions in the polymer of the groups which were originally attached to the aluminum or titanium were therefore unsuccessful. It was however demonstrated that ethylene is inserted.

We assume that the complex formed from the bis-(cyclopentadienyl)titanium(IV) and organoaluminum compounds contains a halogen bridge and a carbon bridge, *i.e.* that it is an electron-deficient compound (Scheme 4).



Scheme 4. Reactions occurring on mixing bis(cyclopentadienyl)-ethyltitanium(IV) chloride *(9)* with triethylaluminum *(10)*.
Cp = cyclopentadienyl.
*C = radioactive carbon atom.
▽C = radioactivity equal to 3/4 of that of *C.
°C = radioactivity equal to 1/2 that of *C.
(g) = uniform distribution of radioactivity owing to ligand exchange.

A structure of this type has meanwhile been demonstrated by *Natta* [13] for the corresponding complex with Ti(III). This formulation explains the rapid ligand exchange that is well-known in electron-deficient compounds [14].

[10] *I. Craubner*, Institut für Technische Chemie, Technische Hochschule München, unpublished work.

[10a] *H. Sinn* and *F. Bandermann*, Makromolekulare Chem. *62*, 134 (1963).

[11] *D. S. Breslow*, Belg. Pat. 551283 (1957).

[12] *W. P. Long* and *D. S. Breslow*, J. Amer. chem. Soc. *82*, 1953 (1960), where references to previous publications are given.

[13] *G. Natta* and *G. Mazzanti*, Tetrahedron *8*, 86 (1960).

[14] *N. Muller* and *D. E. Pritchard*, J. Amer. chem. Soc. *82*, 248 (1960).

The complex formation and reduction processes can be formulated as shown in Scheme 4.

During spectroanalytical investigations of the complex formation, we observed that the reduction is appreciably more dependent upon the temperature than the ligand exchange is. Investigations with radioactively labelled triethylaluminum and with unlabelled *(9)* on the gas obtained from the reduction and the hydrolysis (cf. Scheme 4) indicated the following: at −15 °C, ligand exchange (Reaction g) is practically complete before the reduction commences, whereas at + 40 °C, the reduction is completed before a uniform distribution of radioactivity has been attained (cf. Table 3).

Table 3. Radioactivity of the gases given off on reduction and hydrolysis at various temperatures. The activities are given in arbitrary but comparable units (counts per minute referred to the molecular weight per unit area of the gas chromatogram); the bracketed numbers underneath denote the number of determinations.

| | −15 °C | +40 °C |
|---|---|---|
| Specific activity of the ethane obtained on hydrolysis | 203 ± 4 (5) | 189 ± 10 (6) |
| Specific activity of the ethane obtained on reduction | 174 ± 1 (2) | 83 ± 1 (2) |
| Specific activity of the ethylene obtained on reduction | 175 + 9 (2) | 125 ± 1 (2) |
| Expected specific activity of the gases obtained on hydrolysis and reduction for equal distribution (calculated) [a] | 163 | 142 |

[a] In the calculation of the activity for equal distribution, an allowance was made at −15 °C for the excess of alkyl used, but not at + 40 °C.

The higher activity of the ethylene as compared with the ethane obtained will be discussed later. What is important here is that the specific activity of the reduced ethane in the experiment at 40 °C is less than half of the specific activity of the hydrolysed ethane. This means that the titanium atom [*e.g.* as in our formula *(11)*] must be linked to two unsymmetrical alkyl groups and that the reduction takes place not by decomposition of a preformed dialkyltitanium compound *(13)* but by elimination from *(11)* of the exocyclic ethyl group attached to the titanium.

These experiments therefore determine the location of the reduction and show that this technique is capable in general of differentiating between individual alkyl groups in the complex.

In an experiment at 20 °C, we succeeded in splitting the gas obtained on reduction – which is generated within 0.1 sec – into successive fractions. The results of chromatographic studies on the radioactive gas fractions are illustrated in Figures 4 and 5 and show that ethylene is given off more slowly and has a higher specific activity than ethane. Since both ethane and the ethylene must be formed simultaneously, as was shown by a reaction *in vacuo* using continuous pumping, the delayed liberation of ethylene can only be explained by assuming that the ethylene formed is initially chemisorbed on the tetravalent titanium that is still present (Scheme 5), and is only given up when this central atom is also reduced. The higher specific activity of the ethylene compared to that of the ethane is explained by a displacement reaction.

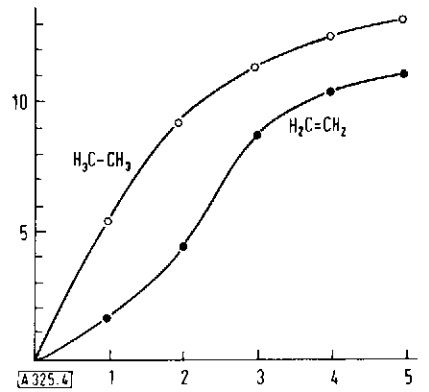



Fig. 4. Gas generated by reduction after mixing 1 mmole of bis(cyclopentadienyl)ethyltitanium(IV) chloride with 1.3 mmole of $^{14}C$ triethylaluminium *in vacuo*. The evolved gas was passed into evacuated vessels with a total volume of 5 litres, which were successively opened and closed. The divisions on the abscissa are not exactly linear for experimental reasons (from 0 5 = approx. 0.1 sec).

Ordinate: Volume [ml]
Abscissa: Time

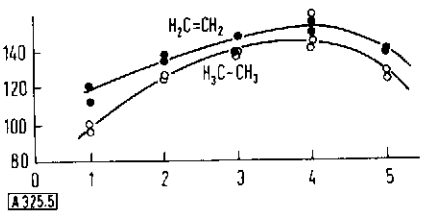
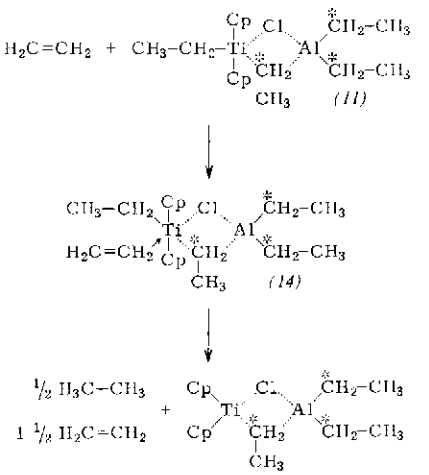


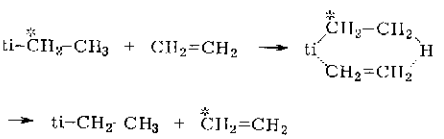

Fig. 5. Specific radioactivity of the fractions shown in Figure 4. The decrease of activity at abscissa values above 4 is caused by some undissolved crystals having zero-point conditions at their surfaces.

Ordinate: Specific radioactivity [arbitrary units, cf. Table 3].
Abscissa: Time [cf. Fig. 4].




Scheme 5. The delayed evolution of ethylene in the reduction according to Scheme 4.

If uniform distribution of activity [*(11)* ⇄ *(12)*] had occured before commencement of the reduction, then the activity of the ethylene would obviously be no greater than that of the ethane (cf. Table 3, experiment at −15 °C).




These results are clearly shown in Scheme 5. The titanium atom in complex *(11)* has a coordination number of 5, *i.e.* it is coordinately unsaturated. By chemisorp-

tion of a molecule of ethylene, it is transformed into the hexacoordinated, saturated state *(14)*. On reduction, the stable tetracoordinated state is formed, with simultaneous evolution of the chemisorbed ethylene. The chemisorptive nature of the link between the ethylene and the titanium atom follows from the aforementioned fact that in the experiment *in vacuo* with continuous pumping, no retardation in the liberation of ethylene could be observed.

The formation of compound *(14)* in Scheme 5 evidently corresponds to the activation stage in our hypothetical mechanism of the low pressure polyreaction of ethylene [cf. Reaction (a) in Scheme 1]. Consideration of the coordination gives a ready explanation of the results observed by *Breslow*, *i.e.* that tetravalent titanium [in the bis(cyclopentadienyl) compound] is essential for initiation. At any rate, these findings have confirmed that an activation step occurs in the mixed catalyst-ethylene system which is comparable with the adduct formation between alkenyl-lithium and isoprene.

Different groups of workers have proposed various mechanisms to explain the action of the mixed catalysts. These suggestions can be classified into two groups. One group postulates a specific mode of action of the complex catalyst [15], whilst the other ascribes a reactivity that is responsible for the polyreaction to the dissociation products of the complexes [16]. This last postulate evidently arose from the assumption that "simple organometallic addition" is a one-step reaction, but this cannot be taken as proven, considering the facts mentioned in the introduction and in the discussion of the alkenyl-lithium isoprene system. The products of dissociation of mixed catalysts, *e.g.* $Cl_3TiR$, $Cp_2TiClR$, or $Cp_2Ti(CH_3)_2$, which were eventually prepared in an indirect manner, were found to be catalytically inactive. The postulates of the first group (specific complex action) vary in their different emphasis of details. In this connection it is necessary to quote *Breslow*: "Actually, if the migration of the alkyl group and the formation of the new titanium-carbon bond is considered to be a concerted reaction, it is probably meaningless to postulate where the electrons come from." [17]

Now that the occurrence of an activation step associated with the complex has been demonstrated, it remains to clarify whether the insertion of the activated ethylene occurs into the same complex or into a second complex molecule, and to determine the identity of the bond at which this insertion takes place. Some indication has been obtained only with regard to the last point.

If this reaction is carried out not *in vacuo* but under an inert atmosphere, some of the ethylene added onto the titanium is inserted, so that butyl groups are formed from the ethyl groups. Butane is found in the reduced gas, as well as in the gas formed by the hydrolysis of the trivalent complex present after reduction, but the amount of butane in the hydrolysis gas exceeds that in the reduction gas by a factor of seven. Chromatographic investigations of the radioactive gas (shown in Table 4) suggest that the terminal reaction of the ethylene which is activated on the titanium atom does not occur at the exocyclic alkyl group linked to the titanium atom but either at the $CH_2$ group which forms the bridge between the titanium and the aluminum atoms or at the exocyclic alkyl group attached to the aluminum atom.

Table 4. Comparison of the activities of the gases liberated after the reduction by hydrolysis (ethane and butane) with the activities of the gases obtained on reduction. Data as in Table 3; here the activities are referred to one carbon atom of the stated compounds.

| | |
|---|---|
| Ethane from hydrolysis | $47 \pm 1$ (2) |
| Butane from hydrolysis | $40 \pm 3$ (4) |
| Ethane from reduction | $36 \pm 1$ (2) |
| Ethylene from reduction | $36 \pm 1$ (2) |

## 4. Summary

The successive stages of the activation and the subsequent terminal reaction have been demonstrated for both the alkenyl-lithium/isoprene and the homogeneous mixed catalyst/ethylene systems. For the alkenyl-lithium isoprene system, it has been established that after the induction period caused by the transformation of alkyl-lithium into alkenyl-lithium [Reaction (e)], a system with a constant number of active particles is present (particles with the Li–C bond). This fact distinguishes this system from polymerizations which are characterized by chain initiation, chain extension, and chain termination reactions, and also from polycondensation and polyaddition reactions, which are characterized by a decrease in the number of available functional groups at progressive degrees of conversion.

It seems noteworthy that in these organometallically initiated polyreactions it is not the actual monomer (isoprene or ethylene), but rather a monomer molecule that is modified by an adduct formation comparable to chemisorption, which undergoes combination. In consequence, copolymerization experiments give no indication of the relative reactivities of the free monomers but only differentiate the reactivities of the chemisorbed monomeric molecules. It may be assumed, and it is evident in the case of the isoprene/alkenyl-lithium adduct, that this adduct formation determines the configuration. If the combination reaction which follows such an activation corresponds to the insertion type of reaction (*i.e.* bifunctional combination) then the configuration obtained during the activation stage remains intact, *i.e.* stereospecific polymers are formed.

It must be stated that no evidence contradicting our initial postulate has been obtained [18]. Detailed aspects of this proposed mechanism, for example, the separate activation step, have been confirmed. It should be possible to locate the point of insertion with the mixed catalysts by further kinetic investigations. In conclusion, it must however again be stated that, in principle, kinetic studies cannot prove a fact but merely serve "not to exclude" it.

[15] *F. Basolo* and *R. G. Pearson:* Mechanism of Inorganic Reactions. Wiley, New York 1958; *C. H. Bawn*, Lecture at the 2nd International Symposium "Rubber and Plastics Age", London, October 1960; *G. Natta* and *I. Pasquon*, Advances Catalysis related Subjects *11*, 2 (1959); for further references, see [2] and [12].

[16] *K. Ziegler:* International Conference on Coordination Chemistry, 1959. Special Publication No. 13 of the Chemical Society (London).

[17] *D. S. Breslow* and *N. R. Newburg*, J. Amer. chem. Soc. *81*, 81 (1959).

[18] Cf. *B. Vollmert:* Grundriß der makromolekularen Chemie. Springer, Berlin 1962, p. 126, footnote.

*This paper is based, in part, on the habilitation thesis of H. Sinn, Technische Hochschule Munich 1963, on the Ph. D. thesis of O. T. Onsager, Technische Hochschule Munich 1962, and on the Ph. D. thesis of C. Lundborg, Technische Hochschule Munich 1961. These authors were supported in their work by grants from the Verband der Chemischen Industrie, the Norwegian Research Association, and the Royal Swedish Academy of Engineering Sciences. Materials were provided by the Deutsche Forschungsgemeinschaft, the Bundesatomministerium and the Bundesministerium für wissenschaftliche Forschung, the Badische Anilin- und Soda-Fabrik and, above all, by Farbwerke Hoechst. The authors wish to express their gratitude for this assistance.*

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# The Biochemistry of Yeast Threonine Deaminase

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*Dedicated to Prof. Dr. Otto Warburg on the occasion of his 80th birthday*

*An optical assay, according to Warburg, for measuring the activity of the enzyme threonine deaminase (threonine → α-ketobutyrate + $NH_4^+$) is described. Some of the properties of the enzyme from yeast have been studied using this assay. Pyridoxal phosphate and pyridoxamine phosphate stabilize the enzyme in the crude extract. Valine, leucine, and isoleucine, and to a lesser extent threonine, $NH_4^+$, and $K^+$ protect the enzyme from inactivation when diluted with buffer. The enzyme is inhibited by isoleucine. The extent of the inhibition is dependent on the pH. Thus, in yeast, just as described for Escherichia coli by Umbarger, isoleucine exerts a control on its biosynthesis from threonine by means of a feed-back mechanism, the extent of the control being related to the consumption of isoleucine in protein synthesis. $NH_4^+$ represses the biosynthesis of threonine deaminase. This mechanism regulates the threonine deaminase-catalysed formation of $NH_4^+$ from threonine in accordance with the $NH_4^+$-requirements of the growing cell.*

## 1. Introduction

*Otto Warburg* discovered and developed the most important methods for the isolation of enzymes and the measurement of their activity [1]. In the last three decades, many enzymes have been characterized, and the most important metabolic pathways have been elucidated with the aid of these methods.

In general, it is found that any enzyme has a constant activity in a given biological material. However, measurements of enzyme activity in microorganisms have demonstrated that characteristic alterations in enzyme activity can occur owing to adaptation to environmental changes. For example, increased β-galactosidase activity is found in yeast cells after the addition of lactose to the nutrient medium. This adaptive process enables the yeast cells to hydrolyse lactose to galactose and glucose and thus to exploit this substance as a substrate capable of yielding energy and building materials. In the analysis of such adaptive processes, activation or inhibition of existing enzymes, and acceleration or deceleration of enzyme syntheses have been observed. The effects on existing enzymes are said to be due to feed-back mechanisms and those on enzyme synthesis to induction or repression of synthesis (for a summary, see *e.g.* [2]). In the present communication, changes in activity of this nature are described for yeast threonine deaminase [**]. They assist in the regulation of $NH_4^+$ metabolism by adapting to changes in the composition of the nutrient medium.

## 2. Position of Threonine Deaminase in Metabolism

In the presence of pyridoxal phosphate, threonine deaminase catalyses the irreversible conversion of threonine into α-ketobutyrate and $NH_4^+$. As shown in Figure 1, this is the initial reaction in the biosynthesis of isoleucine from threonine. However, α-ketobutyrate is not only an intermediate in the synthesis of isoleucine, but can also be degraded oxidatively to yield energy.

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[1] *O. Warburg:* Wasserstoffübertragende Fermente. Verlag Dr. Werner Saenger GmbH., Berlin 1948.

[2] *H. Holzer*, Naturwissenschaften *50*, 260 (1963).

[**] In the "Report of the Commission on Enzymes of the International Union of Biochemistry 1961" the enzyme is designated under number 4.2.1.16, as "L-threonine hydro-lyase (deaminating)" with the trivial name "threonine dehydratase".

The first step of this latter path is oxidative decarboxylation to give propionyl-CoA [2a]. This substance is then broken down further in the citric acid cycle by way of succinyl-CoA. Not only α-ketobutyrate but also $NH_4^+$, the second product of the threonine deaminase reaction,

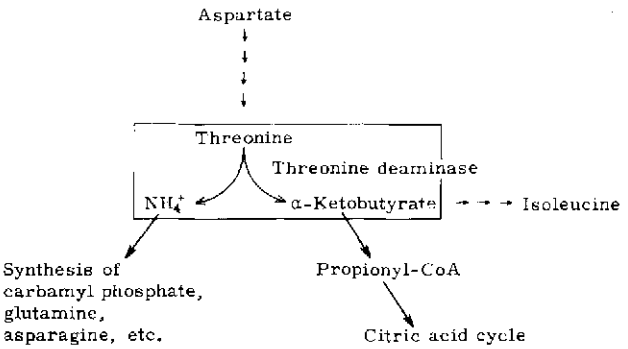



Fig. 1. Position of threonine deaminase in metabolism.

is employed as a building material in synthetic reactions. Together with ATP and $CO_2$, $NH_4^+$ gives rise to carbamyl phosphate, and with aspartic and glutamic acids, it yields asparagine and glutamine, respectively; it also brings about amidation of deamido-NAD to yield NAD. As shown in the present communication, the threonine deaminase-catalysed formation of $NH_4^+$ from threonine is always of particular importance when $NH_4^+$ is lacking in the nutrient medium and must therefore be provided from other nitrogenous sources. All the amino acids which yield aspartate by direct or indirect transamination with oxaloacetate can serve as the source of nitrogen for threonine and thus for $NH_4^+$. Since the carbon atoms of threonine can themselves be re-employed in the synthesis of aspartate, a cycle is obtained, as depicted in Figure 2. The conditions under which this "threonine cycle", which transforms amino-nitrogen into $NH_4^+$, is of biological importance have still to be determined.

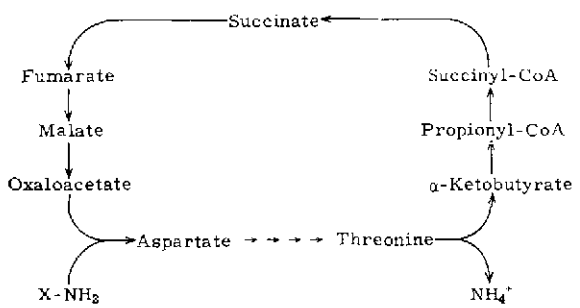



Fig. 2. Production of $NH_4^+$ from amino-nitrogen (X—$NH_2$) in the "threonine cycle".

The scheme reproduced in Figure 1 is valid for yeast, *Escherichia coli*, and many other microorganisms. In mammals, the transformation of aspartate into threonine and of α-ketobutyrate into isoleucine does not occur. For this reason, threonine and isoleucine are essential amino acids for mammals. However, threonine deaminase is probably of significance in mammals, too, since the decomposition of threonine by way of the citric acid cycle to yield energy and $NH_4^+$ are important processes. Evidence in support of this is provided by the characteristic changes in threonine deaminase activity which were measured in rat livers under varying dietary conditions (see *e.g.* [3]).

[2a] ATP = adenosine triphosphate; CoA = coenzyme A; EDTA = ethylenediamine tetraacetate; LDH = lactate dehydrogenase; NAD = nicotinamide adenine dinucleotide; NADH = reduced NAD; PALP = pyridoxal-5-phosphate; PAMP = pyridoxamine-5-phosphate.

## 3. Assay

The activity of threonine deaminase was hitherto determined by colorimetry of the 2,4-dinitrophenylhydrazone of α-ketobutyric acid. This assay does not allow the enzyme's activity to be followed continuously, since individual samples must be withdrawn and analyzed. We have employed the principle of the optical assay according to *Warburg* [4] for following the reaction. Since commercially available crystalline lactate dehydrogenase from rabbit muscle reduces α-ketobutyrate as well as pyruvate with NADH, the formation of α-ketobutyrate from threonine can be followed optically with the aid of this enzyme. The reactions forming the basis of this assay are:

(1) $CH_3-CHOH-CHNH_2-COOH$ (Threonine) $\rightarrow CH_3-CH_2-CO-COOH + NH_4^+$ (α-Ketobutyrate)

(2) $NADH + CH_3-CH_2-CO-COOH \rightarrow CH_3-CH_2-CHOH-COOH + NAD$ (α-Hydroxybutyrate)

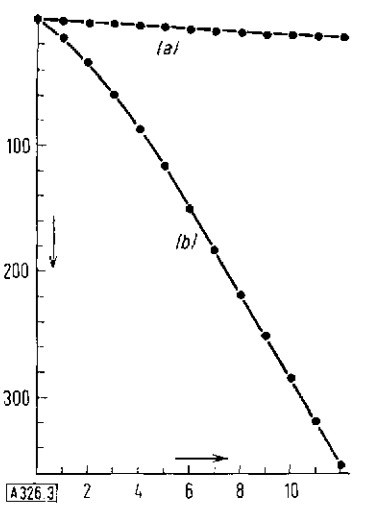



Fig. 3. Standard assay for threonine deaminase. Wavelength 366 mμ, light path 1 cm, total volume 3.00 ml, 22 °C. The following are pipetted *into the cuvette in the order given*: 2.74 *ml of* 0.1 *M triethanolamine*/HCl buffer (pH 7.9), 0.1 ml of 10 mg/ml NADH, 0.02 ml of a suspension of 5 mg of crystallized LDH in 1 ml of 2.2 M $(NH_4)_2SO_4$ (Boehringer), 0.02 ml of 0.01 M PALP, and 0.1 ml of 0.5 M L-threonine. After waiting at least 1 min until the change in extinction due to the formation of the Schiff base between threonine and PALP has gone to completion, the reaction is started with 0.02 ml of crude extract containing approx. 0.3 mg of protein. To prepare the crude extract, the yeast (*Saccharomyces cerevisiae* R 59 Ephrussi) was grown in a culture medium with DL-threonine as nitrogen source, centrifuged off, and washed; the cells were then ground with thrice their weight of aluminum oxide powder (AL-COA A 305), extracted with a threefold volume of 0.05 M phosphate buffer (pH 7.6; containing $10^{-3}$ M EDTA), and centrifuged for 1 hour at 34000 g (cf. [5]). Unless otherwise stated, a crude extract stabilized with $1\times10^{-3}$—$2\times10^{-3}$ M PALP was employed.
Curve (a): without threonine
Curve (b): with threonine
Ordinate: decrease in extinction at 366 mμ (= $\Delta E\times1000$)
Abscissa: time [min]

[3] *V. R. Potter* and *T. Ono*, Cold Spring Harbor Symp. quantitat. Biol. *26*, 355 (1961).
[4] *O. Warburg* and *W. Christian*, Biochem. Z. *287*, 291 (1936).

The kinetics of such an assay are reproduced in Figure 3. Only minute oxidation of NADH occurs when threonine deaminase, in the form of a crude extract from yeast, is added to the reaction mixture in the absence of threonine, whereas in the presence of threonine, the NADH is oxidized with increasing rapidity. The constant terminal velocity is reached after approximately 6 min. An "acceleration time" is required in order to reach the constant terminal velocity, which is limited by the activity of the threonine deaminase, because a certain quantity of α-ketobutyrate must first accumulate before the lactate dehydrogenase reaction can proceed with the necessary velocity. This "acceleration time" is relatively long, since lactate dehydrogenase has only a slight affinity for α-ketobutyrate. It can be shortened by increasing the amount of lactate dehydrogenase added (cf. Fig 4). Routinely, we use 0.1 mg (0.02 ml) of lactate

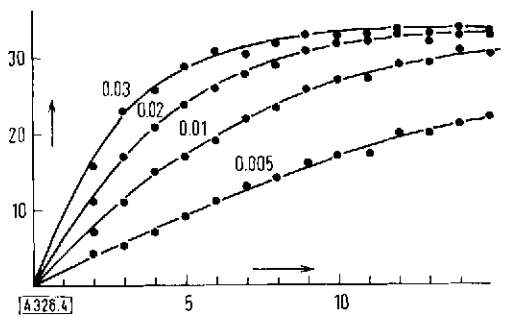



Fig. 4. Dependence of the rate of reaction on the concentration of lactate dehydrogenase. For details, see legend to Fig. 3.

The numbers on the curves indicate the volumes (in ml) of LDH-suspension added.

Ordinate: $\frac{\Delta E \times 1000}{\text{min} \times (0.02\text{ ml of crude extract})}$

Abscissa: Time [min]

dehydrogenase per assay, and take the activity of the threonine deaminase to be represented by the constant terminal velocity reached after approximately 10 min. Figure 5 shows that the terminal velocity is proportional to the amount of crude extract added.

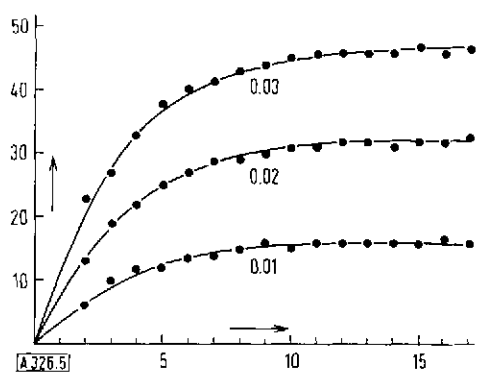



Fig. 5. Rate of reaction in the standard assay (cf. Fig. 3) on addition of various amounts of crude extract.

The numbers on the curves indicate the volumes (in ml) of crude extract.

Ordinate: (ΔE × 1000)/min

Abscissa: Time [min]

Figure 6 illustrates the dependence of the reaction velocity on the pH in various buffers. We usually work (cf. legend to Fig. 3) with triethanolamine/HCl buffer at pH 7.9.

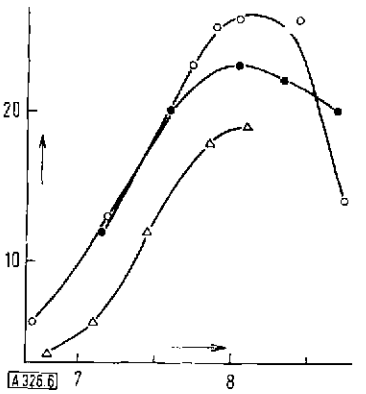



Fig. 6. Dependence of the reaction rate on pH.

○ = 0.1 M triethanolamine/HCl buffer.

● = 0.1 M tris(hydroxymethylamino)methane/HCl buffer.

Δ = 0.1 M phosphate buffer according to *Sorensen*.

Otherwise as in legend to Fig. 3.

Ordinate: $\frac{\Delta E \times 1000}{\text{min} \times (0.02\text{ ml of crude extract})}$

Abscissa: pH

## 4. Stabilization of the Enzyme in the Crude Extract

Curve 1 in Figure 7 shows that a crude extract from yeast loses approximately half of its threonine deaminase activity at 0 °C within 12 hours. The decrease in activity is prevented by the addition of pyridoxal phosphate (Curve 3). We found that after storage for 54 hours,

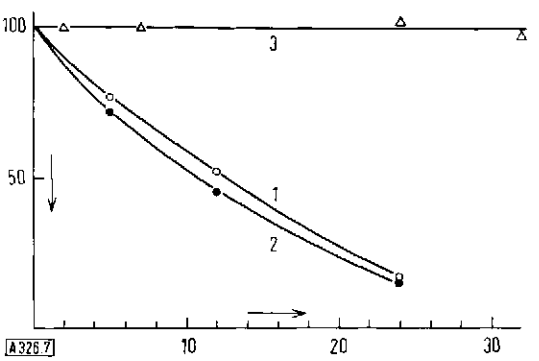



Fig. 7. Stabilization of the crude extract by PALP.

Enzyme assay: cf. Fig. 3.

Curve 1: no addition.

Curve 2: with $4.4 \times 10^{-2}$ M $(NH_4)_2SO_4$

Curve 3: with $10^{-3}$ M PALP

Ordinate: Activity [% of initial activity]

Abscissa: Duration of storage of crude extract at 0 °C [h]

crude extract with $10^{-3}$ M pyridoxal phosphate still contains 88 % of the activity of the fresh extract. Table 1 shows that even $10^{-5}$ M pyridoxal phosphate still has a definite stabilizing effect. Pyridoxamine phosphate also stabilizes the enzyme; unphosphorylated derivatives of vitamin $B_6$ are ineffective. L-Threonine, the substrate of the enzyme, as well as other amino acids, has no protective effect. Ammonium sulfate stabilizes only in unbiologically high concentrations (cf. Curve 2 in Fig.7). The decline in activity is irreversible: if pyridoxal phosphate or pyridoxamine phosphate is added to crude extract kept without stabilizer for 24 hours, no reactivation occurs. Approximately $10^{-5}$ mole of pyridoxal phosphate or pyridoxamine phosphate is

Table 1. Stabilization of the crude yeast extract by various additions. Activity assay: cf. Fig. 3.

| Substance added | Concentration [mole/l] | Activity after 22–24 h at 0 °C in percent of initial activity |
|---|---|---|
| – | – | 12 |
| PALP | $1\times10^{-3}$ | 100 |
| | $5\times10^{-4}$ | 92 |
| | $1\times10^{-4}$ | 80 |
| | $2\times10^{-5}$ | 55 |
| PAMP | $2\times10^{-3}$ | 72 |
| | $1\times10^{-4}$ | 48 |
| Pyridoxal | $2\times10^{-3}$ | 12 |
| Pyridoxol | $2\times10^{-3}$ | 20 |
| L-Threonine | $1\times10^{-1}$ | $<3$ |
| L-Valine | $2\times10^{-2}$ | $<3$ |
| $(NH_4)_2SO_4$ | $1\times10^{-1}$ | 16 |
| | 1 | 52 |

found in one litre of yeast [6,7]. It is possible, therefore, that the stabilization of the enzyme by pyridoxal phosphate and pyridoxamine phosphate observed in our experiments is also of importance for the living cell.

## 5. Inactivation of the Enzyme Following Dilution

If the concentrated crude extract obtained by grinding yeast cells with aluminum oxide powder is diluted with buffer solutions, a very rapid decrease in enzyme activity is observed. If, for example, 0.02 ml of crude extract is diluted to 3 ml with 0.1 M triethanolamine buffer (pH 7.9), as routinely done during performance of the optical assay, then the activity decreases from 33 to 2 units [*], that is to less than 10 %, if the reaction mixture is allowed to stand for 15 min at 22 °C (cf. Table 2).

Table 2. Protection of the enzyme from inactivation following dilution of the crude yeast extract. The crude extract was diluted 1:150 with 0.1 M triethanolamine/HCl-buffer (pH 7.9), containing the additions indicated, and incubated for 15 min at 22 °C. Subsequently, measurement of the activity (see legend to Fig. 3) was started by the addition of LDH (suspended in $(NH_4)_2SO_4$) NADH, PALP, and threonine.

| Addition before incubation | Activity [$\Delta E\times1000$/min/0.02 ml of crude extract] |
|---|---|
| – | 2 |
| PALP $3\times10^{-4}$ M | $<1$ |
| L-Threonine $1.7\times10^{-2}$ M | 28 |
| D-Threonine $1.7\times10^{-2}$ M | 2 |
| L-Valine $1.7\times10^{-2}$ M | 29 |
| L-Serine $1.7\times10^{-2}$ M | 2 |
| L-Glutamate $1.7\times10^{-2}$ M | 1 |
| $(NH_4)_2SO_4$ $1.47\times10^{-2}$ M | 25 |
| $NH_4Cl$ $2.94\times10^{-2}$ M | 23 |
| KCl $2.94\times10^{-2}$ M | 15 |
| NaCl $2.94\times10^{-2}$ M | 2 |
| without incubation | 33 |

[5] *H. Holzer* and *G. Hierholzer*, Biochim. biophysica Acta *77*, 329 (1963).

[6] *H. Holzer, U. Gerlach, G. Jacobi*, and *M. Gnoth*, Biochem. Z. *329*, 529 (1958).

[7] *G. Schreiber, M. Eckstein, A. Oeser*, and *H. Holzer*, unpublished results.

[*] The unit is defined as $\Delta E\times1000$/min/0.02 ml crude extract.

Although pyridoxal phosphate, as demonstrated in the previous section, protects the concentrated enzyme in the crude extract from inactivation, it has no influence on the fast inactivation of the diluted enzyme. L-Threonine, on the other hand, does have a protective effect. L-Isoleucine, L-valine, and L-leucine protect the enzyme in even lower concentrations. If rather high concentrations of isoleucine and leucine are employed, then the protective effect is superimposed by the inhibition of enzyme activity described in the following section (cf. Fig. 8). L-Serine, L-glutamate, and D-threonine are

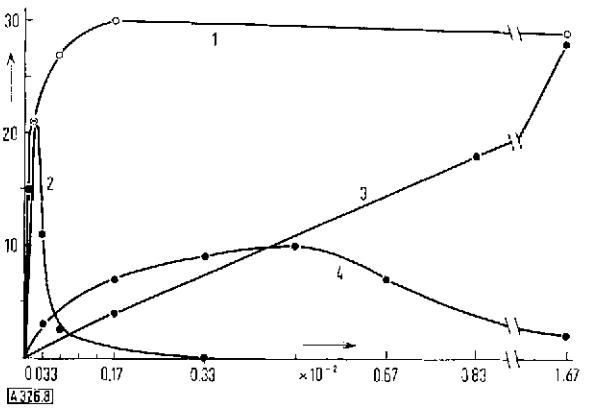



Fig. 8. Protection by various amino acids against inactivation of the enzyme following dilution of the crude yeast extract.

For details, see legend to Table 2.
Curve 1: Addition of L-valine
Curve 2: Addition of L-isoleucine
Curve 3: Addition of L-threonine
Curve 4: Addition of L-leucine

Ordinate: $\frac{\Delta E\times1000}{\text{min}\times(0.02\text{ ml of crude extract})}$

Abscissa: Final concentration of the amino acid added in the cuvette following dilution of the crude extract [mole/l]

ineffective (Table 2). On the other hand, inactivation can also be prevented by high concentrations of ammonium sulfate (cf. Fig. 9). The sulfate anion is not of importance here, since ammonium chloride has the same effect (Table 2). The effect is not specific, for ammonium chloride or potassium chloride also have a protective action. Sodium chloride is inactive.

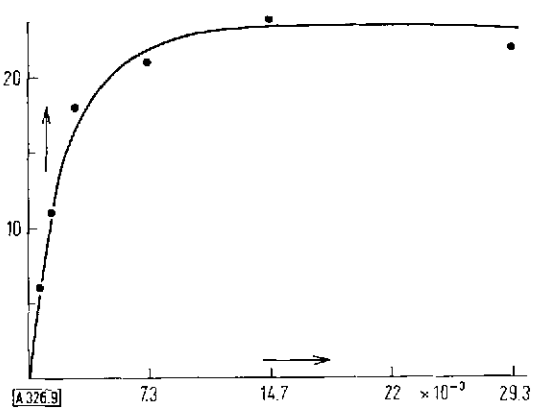



Fig. 9. Protection by $(NH_4)_2SO_4$ against inactivation of the enzyme following dilution. For details, see legend to Table 2.

Ordinate: $\frac{\Delta E\times1000}{\text{min}\times(0.02\text{ ml of crude extract})}$

Abscissa: Final concentration of $(NH_4)_2SO_4$ in the cuvette following dilution of the crude extract [mole/l]

The effects reproduced in Table 2 and Figures 8 and 9 probably have no significance in the living cell, since they only occur after the enzyme solution has been diluted. However, they are of interest in connection with the analysis of the mechanism of the action and, in particular, with the biosynthesis of the enzyme. In addition to stabilization by substrates and coenzymes – a phenomenon known to occur in many other instances – in our case, the enzyme is also stabilized by amino acids (L-valine, L-isoleucine, and L-leucine) which do not serve as substrates, but on the contrary inhibit the biosynthesis of the enzyme (in *Salmonella typhymurium* and *E. coli*) by multivalent repression [8]. As a general rule, it must be borne in mind that when enzymes are in high dilution, as they usually are during assay, they can exhibit a quite different behavior from that in concentrated solution, in which they are found in the living cell.

The precautions to protect the enzyme from inactivation described in this and in the preceding section have enabled us to achieve enrichment of the enzyme [9]. However, since characteristic properties of the enzyme are altered by fractionation procedures, only experiments with crude extracts will be reported in this communication, which is concerned with the importance of the enzyme for the intact cell. We are unable to say to what extent the properties of the enzyme are already altered during the preparation of the crude extract. There is much that indicates that the remark of *Racker* [10], "First purify, then think; don't waste pure thinking time on dirty enzymes", is not valid in all cases. A certain amount about the behavior of an enzyme in the living cell can certainly be learned from a study of the purified enzyme, but not everything.

## 6. Inhibition of the Enzymatic Activity by L-Isoleucine

In 1956, *Umbarger* [11] found that the threonine deaminase reaction in *E. coli* extracts is inhibited by low concentrations of isoleucine. This is a "useful" regulation mechanism for the economy of the cell, since isoleucine is the final product of a synthetic sequence starting from threonine (cf. Fig. 1). If there is sufficient isoleucine available to satisfy the requirements of protein synthesis, then the isoleucine supply by synthesis is inhibited at the threonine deaminase step. If the isoleucine concentration declines as a result of consumption in protein synthesis, then the inhibition of the enzyme chain which synthetizes isoleucine from threonine is decreased. The concentration of isoleucine, and consequently the degree of inhibition exerted, are interrelated in such a way that the supply of isoleucine corresponds to the consumption of this amino acid. A "feed-back" mechanism is in fact in operation which is in some ways analogous to that of amplifying electronic tubes.

[8] *M. Freundlich, R. O. Burns,* and *H. E. Umbarger,* Proc. nat. Acad. Sci. USA *48*, 1804 (1962).

[9] *C. Cennamo, M. Boll,* and *H. Holzer,* unpublished results.

[10] *E. Racker,* Nachr. Chem. Techn. *9*, 348 (1961).

[11] *H. E. Umbarger,* Science (Washington) *123*, 848 (1956).

Table 3. Inhibition of threonine deaminase activity by various amino acids. Activity assay: cf. Fig. 3.

| Amino acid added | Final concentration [mole/l] $\times 10^3$ | [$\Delta E \times 1000$/min /0.02 ml of crude extract] | Inhibition [%] |
|---|---|---|---|
| – | – | 14 | 0 |
| L-Isoleucine | 10 | 0 | 100 |
| | 1.7 | 0 | 100 |
| | 0.67 | 1.5 | 93 |
| | 0.3 | 7 | 50 |
| | 0.17 | 12 | 15 |
| | 0.03 | 14.5 | $<5$ |
| D-Isoleucine | 10 | 14 | $<5$ |
| L-Leucine | 10 | 4 | 71 |
| | 0.67 | 14 | $<5$ |
| L-Valine | 10 | 14 | $<5$ |
| L-Serine | 10 | 14.5 | $<5$ |
| L-Aspartate | 10 | 14 | $<5$ |

Table 3 shows that yeast threonine deaminase, too, is inhibited by low concentrations of isoleucine. The effect is rather specific: all other amino acids tested so far inhibit only slightly or are without effect. The inhibition of the enzymatic activity by L-isoleucine is strongly dependent on the pH (cf. Fig. 10). $3 \times 10^{-4}$ M isoleucine

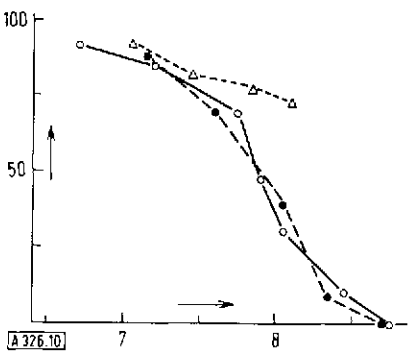



Fig. 10. Dependence on pH of the inhibition of activity by isoleucine: 15 min after starting the reaction with crude extract, 1 µmole of isoleucine was added per cuvette (final concentration $3.3 \times 10^{-4}$ M); after further 15 min, the constant terminal velocity was recorded.

○ = 0.1 M triethanolamine/HCl buffer
● = 0.1 M tris(hydroxymethylamino)methane buffer
Δ = 0.1 M phospbate buffer acc. to *Sørensen*

Ordinate: Inhibition of enzyme activity by L-isoleucin [%]
Abscissa: pH

inhibits completely at pH 7, only 50 % at pH 7.9, and not at all at pH 8.7. The pH-dependence of the isoleucine inhibition may possibly be of significance for metabolic regulation in the living cell [*].

## 7. Repression of the Synthesis of the Enzyme by $NH_4^+$

We tested whether $NH_4^+$, like isoleucine, inhibits the enzyme, but found that this is not the case [**]. However, the $NH_4^+$ concentration does exert an effect on the extent of the threonine deaminase reaction in the living

[*] Note added in proof: It also suggests that an "allosteric" proton dissociating group with pK 7.9 participates in the mechanism of inhibition.

[**] A report on the activation by $NH_4^+$ ("reaction product activation") will be published elsewhere.

cell. The control in this case is brought about by influencing the rate of the synthesis of the enzyme. Differing threonine deaminase activities are found in yeast cells cultured in nutrient media containing different nitrogen sources, as shown in Table 4. It can be seen

Table 4. Specific activity of threonine deaminase after growing the yeast on nutrient media with various nitrogen sources [12].

| Nitrogen source | Activity [ΔE × 1000/min/ml of crude extract] | mg of protein/ml of crude extract | Specific activity [ΔE × 1000/min/mg of protein] | Specific activity [% of the value with $NH_4^+$ as nitrogen source] |
|---|---|---|---|---|
| $NH_4^+$ | 170 | 6.4 | 26 | 100 |
| $NH_4^+$ + DL-Threonine | 130 | 5.4 | 24 | 92 |
| DL-Threonine | 400 | 5.5 | 73 | 280 |
| DL-Serine | 530 | 6.9 | 77 | 295 |
| DL-Isoleucine | 400 | 7.0 | 57 | 220 |

that when $NH_4^+$ is present in the nutrient medium, the specific activity of the enzyme (and therefore its concentration) is low. When amino acids are the only source of nitrogen, the concentration of the enzyme is high. As threonine deaminase liberates $NH_4^+$ from the amino-nitrogen of amino acids (cf. Fig. 2), this effect is of advantage to the cell in the exploitation of its nitrogen supply: if $NH_4^+$ is already present in the medium, then the enzyme is not required. If amino acids are the sole source of nitrogen, then the enzyme is synthetized to mediate the supply of $NH_4^+$, which is necessary in particular for the formation of carbamyl phosphate.

Experiments with bacteria, in particular with *E. coli*, have shown that such changes in enzyme activity which are determined by altered environmental conditions are brought about by "induction" or "repression" of enzyme synthesis. In the case of induction, synthesis is initiated by certain substances in the nutrient medium, in the case of repression, it is inhibited; for a summary, see [13, 14]. The data reproduced in Table 4 make it probable that the velocity of the synthesis of threonine deaminase in yeast is subject to such control. If it is assumed that $NH_4^+$ suppresses synthesis of the enzyme, it can be understood why the enzyme occurs only with low specific activity, *i.e.* in low concentration, when the cells have been cultured in a medium containing $NH_4^+$. Similarly, it is clear why the enzyme is found to be highly active after the cells have been grown in the presence of nitrogen sources other than $NH_4^+$. In this case, repression of the synthesis of the enzyme by $NH_4^+$ is lacking ("derepression" is said to occur). The experiment in which $NH_4^+$ and the amino acid threonine were present in the medium together (Table 4) is particularly informative. Since a threonine deaminase activity is found under these circumstances that is just as low as that in the presence of $NH_4^+$ alone, it is apparent that the synthesis of the enzyme is repressed by the $NH_4^+$, and that increased synthesis is not being induced by amino acids.

Deamination of threonine is necessary for providing not only $NH_4^+$, but also α-ketobutyrate for the synthesis of isoleucine. With this in mind, it becomes clear why the synthesis of the enzyme is not completely repressed by $NH_4^+$. After growing the yeast in a medium containing $NH_4^+$, the activity of the enzyme is only about one-third of that found after culture with amino acids as nitrogen source. Presumably, therefore, one third of the enzyme activity suffices to provide that amount of α-ketobutyrate from threonine which is necessary for the synthesis of isoleucine.

## 8. Discussion

Like threonine deaminase, the NAD-dependent glutamate dehydrogenase, previously demonstrated by us to be present in yeast [15], provides $NH_4^+$ from amino-nitrogen:

$$\text{Glutamic acid} + \text{NAD} \rightarrow \alpha\text{-ketoglutarate} + \text{NADH} + NH_4^+$$

We found that similar conditions prevailed in the control of the activity of this enzyme as occur with threonine deaminase: synthesis is repressed by $NH_4^+$ [5, 16]. The activity of NAD-glutamate dehydrogenase in yeast cells grown in the presence of $NH_4^+$ is less than 5 % of that observed when amino acids are the nitrogen source. From this it would seem highly probable that the main biological function of the NAD-dependent glutamate dehydrogenase from yeast is the supply of $NH_4^+$ from glutamic acid. If $NH_4^+$ is not required, then neither is the enzyme. Glutamic acid, like aspartate (and consequently threonine) can acquire its amino group by transamination from all other amino acids. Thus, the glutamate dehydrogenase reaction, like the threonine deaminase reaction, assists in supplying the growing cell with $NH_4^+$ at the expense of amino-nitrogen. In Figure 11, the position of $NH_4^+$ in metabolism is summarized. The $NH_4^+$ is supplied from the amino-nitrogen of aspartic and glutamic acids, or of the other

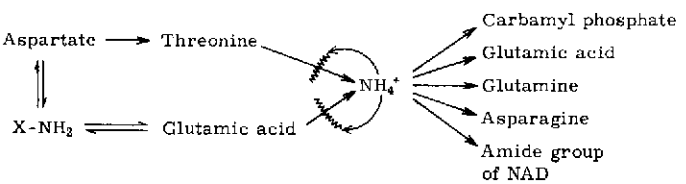



Fig. 11. Regulation of the $NH_4^+$ economy in yeast cells by repression of the synthesis of threonine deaminase and NAD-glutamate dehydrogenase.

amino acids which are in equilibrium with them by transamination, and is subsequently employed in the synthesis of carbamyl phosphate, glutamic acid, glutamine, and other cell constituents. The $NH_4^+$ requirements determine its production; increased $NH_4^+$ concentrations

[12] *H. Holzer, M. Boll*, and *C. Cennamo*, Lecture at the meeting of German, French and Swiss biochemists in Strasbourg (France), September 1963.

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

14] *H. J. Vogel*, Cold Spring Harbor Symp. quantitat. Biol. *26*, [63 (1961).

[15] *H. Holzer* and *S. Schneider*, Biochem. Z. *329*, 361 (1957).

[16] *G. Hierholzer* and *H. Holzer*, Biochem. Z., in the press.

cause the synthesis of the $NH_4^+$-supplying enzymes to be repressed.

Inhibition of threonine deaminase by isoleucine occurs rapidly. According to our observations, inhibition is complete in less than 1 min. In contrast, repression of the synthesis of the enzyme by $NH_4^+$ can only affect the enzyme content of the cells with that velocity with which dilution of the enzyme by cell multiplication, occurs. In the case of yeast, the time intervals are of the order of hours [16]. Since protein synthesis depends on maintenance of the level of L-isoleucine, it is clear that the synthesis of isoleucine must be regulated by a very rapid mechanism. Under natural conditions, changes in the $NH_4^+$ content of the nutrient medium will take place only gradually. It is sufficient then, if adaptation to a change in the $NH_4^+$ content of the nutrient medium occurs by a mechanism which comes into action only slowly *viz.* by control of the velocity of enzyme synthesis. Inhibition of activity by the feed-back mechanism is consequently a means of rapid "fine control" of metabolism; repression of enzyme synthesis, on the other hand, is a "rough control" whose effect develops over a long period [17].

*We wish to thank Prof. Dr. O. Wiss (Hoffman-La Roche, Basel) for supplying us with pyridoxal phosphate and pyridoxamine phosphate. We also wish to thank the Deutsche Forschungsgemeinschaft and the Bundesministerium für Wissenschaftliche Forschung for financial support.*

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German version: Angew. Chem. *75*, 894 (1963)

[17] *H. A. Krebs*, Meeting of the Nobel-Laureates at Lindau (Germany), July 1963; *J. M. Ashwort* and *H. L. Kornberg*, Biochim. biophysica Acta *73*, 519 (1963).

# Complex Formation with Organoaluminum Compounds

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*Dedicated to Prof. Dr. Karl Ziegler on the occasion of his 65th birthday*

*From theoretical considerations of the Lewis-acid character of the organoaluminum compounds $AlR_3$ and $AlEt_2X$ and of possible combinations of these acids with Lewis bases chiefly anions combined with alkali metal ions – by reactions analogous to neutralizations, as well as on the basis of experimental findings, the compounds $AlEt_2X$ and the alkali salts MY can be arranged in the order of their tendency to form complexes, in dependence on the nature of X and Y, respectively. Numerous displacement reactions, in which a stronger complexing group replaces a weaker one, confirm these series. These reactions have led to the formation of new complex compounds of alkylaluminum with the hitherto unknown alkyls of calcium, strontium, and barium, and also to the preparation of $[NEt_4][AlEt_4]$ and $[SbEt_4][AlEt_4]$. Displacement of ethylsodium from $NaAlEt_4$ with the aid of NaOR – which is readily complexed – in the presence of benzene provides a simple mode of conversion of alkylaluminum into phenylaluminum compounds:*

$$NaAlEt_4 + 4\ C_6H_6 \xrightarrow{NaOR} NaAlPh_4 + 4\ C_2H_6$$

## 1. Tendency towards Complex Formation

As compounds of trivalent aluminum, unassociated monomeric alkylaluminum compounds are Lewis acids and will therefore combine with Lewis bases to form molecular compounds or complex anions. For example, tertiary amines, ethers, or hydride, ethyl, and halogen anions can function as electron donors. Compounds containing four-coordinate aluminum are obtained. Higher coordination numbers for organoaluminum compounds are not yet known.

Monomeric alkylaluminum compounds are usually unobtainable as such since they associate on account of their electron-deficiency to form dimers or trimers. Complex formation must therefore always be preceded by dissociation of the alkylaluminum associates, or at least the equilibrium (1) must be set up [*].

$$(1)\quad (AlR_2X)_2 \rightleftharpoons 2\ AlR_2X$$

The tendency towards formation of a complex ion according to Equation (2) is greater, the stronger the Lewis acid, *i.e.* the monomeric alkylaluminum, and the Lewis base, *i.e.* the added anion, involved.

$$(2)\quad AlR_2X + Y^- \rightarrow [AlR_2XY]^-$$

[1] Presented in part at the Hauptversammlung of the Gesellschaft Deutscher Chemiker in Heidelberg (Germany), September 1963.

[*] In this paper, the following abbreviations will be used: Me = $CH_3$; Et = $C_2H_5$; Ph = $C_6H_5$; R = alkyl; M = metal; Hal = halogen; THF = tetrahydrofuran.

An exchange equilibrium [Reaction (3)] must also be considered simultaneously with the complex formation.

(3) $AlR_2X + Y^- \rightleftharpoons [AlR_2]^+ + X^- + Y^- \rightleftharpoons AlR_2Y + X^-$
Acid I Base I Acid II Base II

One component in this equilibrium is the hypothetical cation $[AlR_2]^+$, which attempts to capture the substituent which is the best electron donor. When this occurs, the accepting capacity of the resultant acid II is diminished. Only the weaker base II is then available for the formation of the complex ion. If the basic and acidic strengths are large enough to provide the energy in the reaction, analogous to neutralization, to separate the reactants from their possible partners (these energies are for $X^-$ the lattice energy of the salt MX, and for $AlR_2Y$ the energy of association), then a complex anion can result. Otherwise complex formation either does not occur, or – if the reaction of MY with $AlR_2X$ is attempted – only an exchange reaction [Equation (4)] occurs instead.

(4) $AlR_2X + MY \rightleftharpoons AlR_2Y + MX$

## 2. 1:1 Complexes with Trialkylaluminum

*K. Ziegler* and co-workers [1a] investigated complexes of alkali metal halides and hydrides with trialkylaluminum and found that the tendency towards complex formation increases as the ionic radius of the alkali metal cation increases, but decreases as the anionic radius and the length of the alkyl chain increase (Figs. 1 and 2).

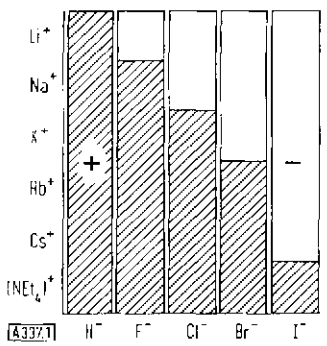



Fig. 1. Complexes of alkali metal hydrides and halides with triethylaluminum [1].

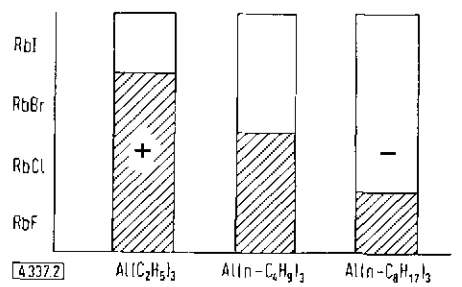



Fig. 2. Complexes of rubidium halides with trialkylaluminum [1].

Supporting these findings are the decrease in lattice energy from lithium halide to cesium halide in an alkali metal halide series with a given halide ion, and the decrease in the energy of reaction on addition of a halide ion to an alkylaluminum with increasing anionic radius (analogous to the energy of hydration of halide ions [2]) and with increasing length of the hydrocarbon chain.

The halides of the pseudo-alkali-metal cation $[NEt_4]^+$ are the salts with the largest "alkali metal" cation and thus display the greatest tendency towards complex formation. Tetraethylammonium iodide is the only "alkali metal" iodide to form a complex with triethylaluminum.

The capacity for complex formation of ethylaluminum chlorides increases as follows: $AlEt_3 < AlEt_2Cl < AlEtCl_2$ (Fig. 3). The adduct of KCl with $AlEt_3$ is only

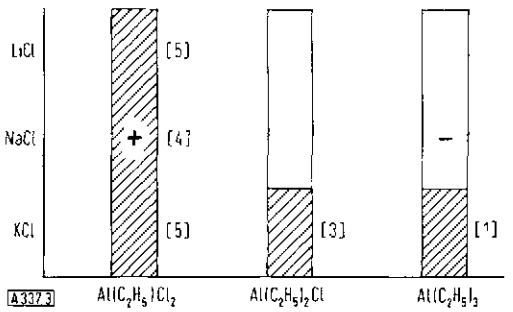



Fig. 3. Complexes of alkali metal chlorides with triethylaluminum and ethylaluminum chlorides.

slightly stable and dissociates into its components on heating *in vacuo* at 80–100 °C [1]. $K[AlEt_2Cl_2]$ is more stable and decomposes only above 150 °C, to a small extent into KCl and $AlEt_2Cl$ but mainly by disproportionation according to Equation (5) [3–5].

(5) $2\,K[AlEt_2Cl_2] \rightarrow KCl + KAlEtCl_3 + AlEt_3$

Since solutions and melts of alkali metal alkylaluminates are not completely dissociated into the ions (as indicated by their rather low electrical conductivity), complex formation is assisted by the interaction between the alkali metal ion and the anion, possibly with formation of electron-deficient bonds similar to those in associated alkylaluminum [6].

(6) $M^+ + [AlEt_4]^- \rightleftharpoons$ 


The change in free energy for the formation of $Na[AlEt_3F]$ and $K[AlEt_3F]$ can be calculated from the difference in lattice energies of NaF and KF [1] using the simplifying assumption that the melts of both compounds contain only ions and no undissociated molecules.

$1/2\,[AlEt_3]_2 \rightleftharpoons AlEt_3 + \Delta F_1$

$Na(K)F \rightarrow Na^+(K^+) + F^- + 218\ (195)$ kcal/mole

$F^- + AlEt_3 \rightarrow [AlEt_3F]^- + \Delta F_2$

(7) $NaF + 1/2\,(AlEt_3)_2 \rightarrow Na^+ + [AlEt_3F]^- + \Delta F_1 + \Delta F_2 + 218$ kcal/mole

(8) $KF + 1/2\,(AlEt_3)_2 \rightarrow K^+ + [AlEt_3F]^- + \Delta F_1 + \Delta F_2 + 195$ kcal/mole

By subtraction of Equation (8) from Equation (7), Equation (9) is obtained together with the difference in the energies of complex formation.

(9) $NaF + K[AlEt_3F] \rightleftharpoons KF + Na[AlEt_3F] + 23$ kcal/mole

This difference can be estimated independently by combination of thermodynamic values to give 8–10 kcal/


[1a] *K. Ziegler, R. Köster, H. Lehmkuhl,* and *K. Reinert,* Liebigs Ann. Chem. *629,* 33 (1960).

[2] *K. Fajans,* Verh. dtsch. physik. Ges. *21,* 549, 557 (1919).

[3] *R. Köster* and *W. R. Kroll,* Liebigs Ann. Chem. *629,* 50 (1960).

[4] *F. C. Hall* and *A. W. Nash,* J. Instn. Petroleum Technologists *23,* 679 (1937).

[5] *G. J. Sleddon,* Chem. and Ind. *1961,* 1492.

[6] *K. Ziegler* in *H. Zeiss:* Organometallic Chemistry. Reinhold Publishing Corp., New York 1960, p. 201.

mole [7] (cf. p. 112). In practice, the difference is thus substantially lower than 23 kcal owing to different interactions between the cation and anion in the two complexes; the energy of interaction for the sodium compound must be about 15 kcal greater than that for the potassium compound. This effect, which opposes electrolytic dissociation, also accounts for the fact that the specific conductivity of a $Na[AlEt_3F]$ melt is less by a factor of ten than that of a $K[AlEt_3F]$ melt.

### 3. 1:2 Complexes with Trialkylaluminum

The complexes $M[AlR_3X]$ of aluminum trialkyls with alkali metal halides and hydrides can often add on a further mole of trialkylaluminum to form compounds of the type $M[Al_2R_6X]$, where X = H, F, Cl, Br, or I (Fig. 4) [1]. Aluminum alkyls higher than tri-n-butylaluminum do not form stable 1:2 complexes with NaF. However, definite 1:2 complexes are obtained from KF, RbF, or CsF and aluminum trialkyls up to tri-n-octylaluminum.

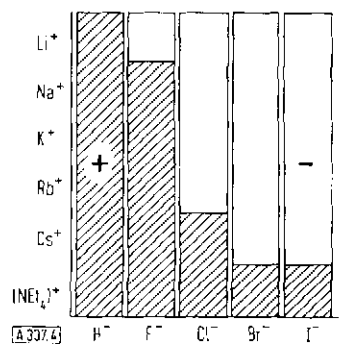



Fig. 4. 1:2 Complexes of alkali metal hydrides and halides with triethylaluminum [1].

Alkali metal cyanides [1] and azides [8] also form complexes with triethylaluminum, but here the 1:1 complexes do not appear to be stable. Interaction of equimolar quantities of $NaN_3$ with $AlEt_3$ yields a product having the approximate composition $NaN_3 \cdot 1.6AlEt_3$, together with undissolved $NaN_3$. The complex phase can be split into its components at 100 °C *in vacuo*. In the reaction of NaCN with $AlEt_3$ (molar ratio 1:1), a lot of NaCN also remains undissolved, but the supernatant liquid has approximately the composition of the 1:2 compound. In both cases, the 1:2 complexes seem to be more stable.

The structure proposed by *Ziegler* for the 1:2 complexes [9]

$$K^+[Et_3Al{:}\ddot{\underset{\cdot\cdot}{F}}{:}AlEt_3]$$

has meanwhile been confirmed by *Natta* [10] using X-ray structure analysis. According to this analysis, the coordination is tetrahedral about the aluminum with normal Al–C and C–C distances. The Al–F–Al bond is linear, and the interatomic distances correspond to those in $Na_3AlF_6$.

[7] *H. Lehmkuhl*, unpublished work.

[8] *E. Bonitz*, unpublished work; additional quantitative investigations from the author.

[9] *K. Ziegler*, International Conference on Coordination Chemistry, London, April 6th–11th, 1959.

[10] *G. Natta, G. Allegra, G. Perego* and *A. Zambelli*, J. Amer. chem. Soc. *83*, 5033 (1961).

There are no 1:2 complexes of alkali metal alkyls or alkoxides with trialkylaluminum; at 130 °C, molten sodium tetraethylaluminate dissolves only 0.28 mole of $AlEt_3$ per mole of complex. The partition coefficient of $AlEt_3$ between $NaAlEt_4$ and a high boiling, aliphatic hydrocarbon which is immiscible with the complex (*e.g.* liquid paraffin) is not constant but dependent on the concentration of $AlEt_3$ in $Na[AlEt_4]$ [7]. The system alkali metal fluoride (or hydride)/triethylaluminum/diethylaluminum hydride includes complexes with up to four moles of aluminum compound per mole of alkali metal salt [11].

### 4. Ethylaluminum Alkoxide Complexes

Diethylaluminum fluoride forms complexes more readily than triethylaluminum. Alkali metal alkoxides also have a greater tendency towards complex formation than alkali metal halides have. For example, lithium ethoxide reacts with triethylaluminum to give $Li[AlEt_3OEt]$, but lithium fluoride does not react [1]. It was to be expected that a sodium alkoxide would form a very stable complex with diethylaluminum fluoride – more stable than the known compounds $Na[AlEt_3F]$, $Na[AlEt_2F_2]$, or $Na[AlEt_3OEt]$. In fact, however, diethylaluminum alkoxide and sodium fluoride were obtained [12].

$$(10)\quad NaOR + AlEt_2F \rightleftharpoons NaF + AlEt_2OR$$

According to the postulated exchange equilibrium (3), $[AlEt_2]^+$ selects the more strongly basic alkoxide from the available anions $OR^-$ and $F^-$.

$$(11)\quad NaOR + AlEt_2F \rightleftharpoons [AlEt_2]^+ + Na^+ + F^- + OR^- \rightleftharpoons NaF + AlEt_2OR$$

In this manner, the electron density at the aluminum is increased and the acidic character of the aluminum compound is correspondingly weakened, so that the formation of a complex with sodium fluoride is no longer possible. The lattice energy of the sodium fluoride and the association energy of the $AlEt_2OR$ are greater than the gain in energy on complex formation. NaF does not react with diethylaluminum alkoxides, but KF and CsF do react since their lattice energies (NaF: 218, KF: 195, CsF: 185 kcal/mole) are smaller.

$$(12)\quad NaF + AlEt_2OR \not\longrightarrow$$

$$(13)\quad KF + AlEt_2OEt \rightarrow K[AlEt_2(OEt)F] \quad (m.p.\ 96–98\ ^\circ C)$$

$$(14)\quad CsF + AlEt_2OEt \rightarrow Cs[AlEt_2(OEt)F] \quad (m.p.\ \approx 40\ ^\circ C)\ [7]$$

The much decreased acidic character of diethylaluminum alkoxides is also shown in their reactions with sodium hydride, which is more readily complexed than sodium fluoride.

When diethylaluminum n-hexyloxide was heated with the equivalent amount of sodium hydride at 160–180 °C for 24 hours, 10–20 % (with the 2-ethylhexyloxide only about 2 %) of the NaH reacted according to Equation (15).

$$(15)\quad NaH + AlEt_2OR \rightarrow Na[AlEt_2(OR)H]$$

[11] *K. Ziegler, H. Lehmkuhl*, and *E. Lindner*, Chem. Ber. *92*, 2320, 2322 (1959).

[12] *R. Schäfer*, Ph.D. Thesis, Technische Hochschule Aachen, 1961.

Attempts to combine sodium alkoxide with diethylaluminum hydride resulted in conversion of 70–90 % of the sodium introduced into sodium hydride by the exchange equilibrium (3) [7].

(16) $NaOR + AlEt_2H \rightarrow Na[AlEt_2(OR)H] \rightleftharpoons 2\,NaH + 2\,AlEt_2OR$

The reaction of sodium diethyldihydroaluminate with sodium diethyldialkoxyaluminates, which should have resulted in the formation of $Na[AlEt_2(OR)H]$, yielded mixtures consisting mainly of sodium hydride and diethylaluminum alkoxide [Equation (17)] [7].

(17) $Na[AlEt_2H_2] + Na[AlEt_2(OR)_2] \rightarrow 2\,Na[AlEt_2(OR)H] \rightleftharpoons 2\,NaH + 2\,AlEt_2OR$

The lack of stability of $Na[AlEt_2(OR)H]$ was unexpected, since sodium hydride complexes of $AlR(OR)H$ and of triethoxyaluminum are known [14, 15]. According to *Schmitz-DuMont*, sodium hydride combines with α-$Al(OEt)_3$ only in the presence of ethers, but afterwards the ether-free compounds can be isolated. Sodium hydride also combines readily with diethylaluminum alkoxides in the presence of tetrahydrofuran (THF) [7]. During attempts to distil off the tetrahydrofuran, the stabilized tetrahydrofuranate complexes decompose again into solid sodium hydride and diethylaluminum alkoxide [Equation (18)].

(18) $NaH + AlEt_2OR + THF \longrightarrow Na[AlEt_2(OR)H] \cdot THF \xrightarrow{-THF} NaH + AlEt_2OR$

Suspensions of sodium hydride in diethylaluminum alkoxide in the presence of ethylene behave like stable complexes: sodium triethylalkoxyaluminate is obtained at about 140 °C with ethylene at several atmospheres pressure [13].

(19) $NaH + AlEt_2OR + C_2H_4 \rightarrow Na[AlEt_3OR]$

$Na[AlEt_3H]$ adds on ethylene under similar reaction conditions with comparable reaction rates [16].

On passing from diethylaluminum alkoxides to monoethylaluminum dialkoxides, $AlEt(OR)_2$, the tendency towards complex formation increases. $AlEt(OEt)_2$ reacts readily with NaH or KF (Fig. 5) to give $Na[AlEt(OEt)_2H]$, m.p. 160–162 °C, or $K[AlEt(OEt)_2F]$, m.p. 184 °C [7].

During the reaction of $K[AlEt_2(OEt)F]$ with $AlEt(OEt)_2$, the stronger complexing group displaces the weaker one [Equation (20)].

(20) $K[AlEt_2(OEt)F] + AlEt(OEt)_2 \rightarrow K[AlEt(OEt)_2F] + AlEt_2OEt$

Within the series $AlEt_3$, $AlEt_2OEt$, $AlEt(OEt)_2$, the minimum capacity for complex formation is observed at diethylaluminum ethoxide. A plausible explanation for this has not yet been put forward.

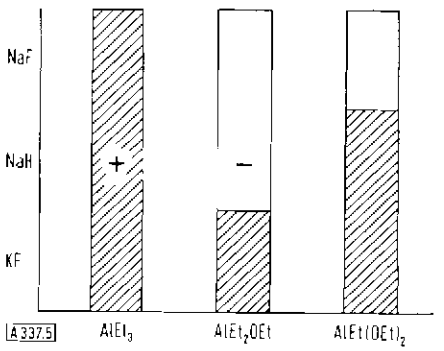



Fig. 5. Complexes of alkali metal hydrides and halides with triethylaluminum and ethylaluminum ethoxides.

## 5. Displacement of Weakly Complexed Organoaluminum Ligands

The displacement mentioned above of a complexed aluminum ligand by a more strongly complexing group (Equation 20) can be applied in general to organoaluminum compounds, *e.g.* as in Reaction (21), in which the stronger acid triethylaluminum displaces the weaker acid diethylaluminum alkoxide.

(21) $M[AlEt_3OR] + AlEt_3 \rightarrow M[AlEt_4] + AlEt_2OR$ (M = K or Na; [17, 18])

This reaction has been realized with all the alkoxides investigated, *viz.* ethoxide, n-butoxide, t-butoxide, n-hexyloxide, n-octyloxide, 2-ethylhexyloxide, and n-decyloxide; the reaction proceeded quantitatively in every case. The acidic properties of diethylaluminum phenoxide, $AlEt_2(OPh)$, and of diethylaluminum *N*-methylanilide, $AlEt_2N(CH_3)Ph$, are more pronounced than those of diethylaluminum alkoxides. As electron acceptors, both compounds resemble triethylaluminum.

Sodium tetraethylaluminate and sodium triethylphenoxyaluminate are sparingly soluble in cold benzene. On adding equivalent amounts of diethylaluminum phenoxide to the first and triethylaluminum to the second of these complexes, a clear solution in benzene results at room temperature, indicating the formation of a 1:2 complex of sodium phenoxide with two moles of triethylaluminum [12]:

(22) $Na[AlEt_4] + AlEt_2(OPh) \rightarrow Na[Al_2Et_6(OPh)]$

(23) $Na[AlEt_3(OPh)] + AlEt_3 \rightarrow Na[Al_2Et_6(OPh)]$

After removal of the solvent, one equivalent of triethylaluminum can be distilled off at 150 °C/$10^{-3}$ mm. The residue is sodium triethylphenoxyaluminate. This means that, with the phenoxy compound, Reaction (21) is reversed compared to that with diethylaluminum alkoxides. Probably an equilibrium is set up [Equation (24)] which can be shifted to the right by distilling off the triethylaluminum, which is more volatile than $AlEt_2(OPh)$.

(24) $Na[AlEt_4] + AlEt_2(OPh) \rightleftharpoons Na[AlEt_3(OPh)] + AlEt_3$

[13] Belg. Pat. 575595 (August 11th, 1959), inventors: *K. Ziegler* and *H. Lehmkuhl*; in addition unpublished work by *H. Dislich* and *H. Lehmkuhl*.

[14] German Published Patent Application 1122952 (Febr. 1st, 1962), inventors: *G. Hamprecht* and *M. Schwarzmann*.

[15] *O. Schmitz-DuMont* and *V. Habernickel*, Chem. Ber. *90*, 1054 (1957).

[16] German Pat. 917006 (June 4th, 1954), inventors: *K. Ziegler* and *H. G. Gellert*.

[17] *W. Eisenbach*, Ph. D. Thesis, Technische Hochschule Aachen 1961.

[18] Belg. Pat. 575641 (August 12th, 1959), inventors: *K. Ziegler* and *H. Lehmkuhl*.

Here the difference between diethylaluminum phenoxide and alkoxides is especially apparent. With the higher alkoxy compounds – *e.g.* $AlEt_2(OC_{10}H_{21})$, which is very difficult to volatilize – triethylaluminum cannot be distilled off.

An indication of the probable position of the equilibrium can be obtained when the 1:2 complex $Na[Al_2Et_6(OPh)]$ is washed for some time with hot hexane. After cooling, the residue consists of three components, *viz.* $Na[AlEt_4]$, $Na[AlEt_3(OPh)]$, and the unaltered 1:2 complex, in the molar ratio 1.2:1:1; thus, during the extraction with hexane, cleavage of the 1:2 complex occurs to almost equal extents according to Equations (25) and (26).

(25) $Na[Al_2Et_6(OPh)] \rightarrow Na[AlEt_4] + AlEt_2(OPh)$

(26) $Na[Al_2Et_6(OPh)] \rightarrow Na[AlEt_3(OPh)] + AlEt_3$

As these investigations show, the acidic character of diethylaluminum phenoxide is only slightly different from that of triethylaluminum (probably a little less marked). By complexing diethylaluminum phenoxide with NaEt in the presence of triethylaluminum, an exchange equilibrium reaction [Equation (27)] via the labile 1:2 complex is set up.

(27) $Na[AlEt_3(OPh)] + AlEt_3 \rightleftharpoons Na[Al_2Et_6(OPh)] \rightleftharpoons Na[AlEt_4] + AlEt_2(OPh)$

The 1.2:1 molar ratio favoring the tetraethyl complexes during extraction with hexane makes triethylaluminum appear to be a slightly stronger complex-forming acid than diethylaluminum phenoxide. Thus, for instance, diethylaluminum phenoxide dissolves both sodium fluoride and potassium fluoride to form complexes, but it does not react with potassium chloride [7]. Diethylaluminum *N*-methylanilide behaves in a similar manner to diethylaluminum phenoxide. All the triethylaluminum can be distilled off at 150 °C/$10^{-3}$ mm from a reaction mixture of triethylaluminum and $Na[AlEt_3N(CH_3)Ph]$ [7].

These results are in accordance with those considered earlier. As a consequence of the possibility of mesomerism in phenoxide and anilide ions, it was to be expected that the donor properties of both ions would be only weak. Thus, capture of a phenoxide (anilide) anion by the hypothetical $[AlEt_2]^{\oplus}$ cation ought to result in a stronger Lewis acid $AlEt_2Y$ than that obtained by capture of an alkoxide anion, which causes a greater electron density at the aluminum and hence weakens the acidic character of the $AlEt_2Y$. Aluminum compounds can be arranged in the order of decreasing tendency towards complex formation as follows:

(27a) $AlEt(Hal)_2 > AlEt_2(Hal) > AlEt_3 > AlEt_2(OPh) \approx AlEt_2N(CH_3)Ph > AlEt(OEt)_2 > AlEt_2(OR)$

## 6. Displacement of Complexed Bases

It is possible to replace a weaker electron donor $X^-$ in an organoaluminum complex by a stronger anion $Y^-$ by a process analogous to the displacement of a complexed Lewis acid by a stronger one.

(28) $[R_3Al \rightarrow X]^- + Y^- \rightleftharpoons [R_3Al \leftarrow Y]^- + X^-$

Examples are the cleavages of triethylaluminum etherates by sodium fluoride or potassium fluoride and of the aminates by potassium fluoride [1], the reaction of these aluminum compounds with sodium to split off the ether or the amine, and the displacement of sodium fluoride from complexes by sodium hydride [Equation (29)][19].

(29) $NaH + Na[AlEt_3F] \rightarrow NaF + Na[AlEt_3H]$

As a result of these and further investigations, a basicity series of some of the anions which function as Lewis bases can be drawn up; however, this series only applies to the behavior of the Lewis bases with organoaluminum compounds and not to the affinities of the members for protons.

(29a) $I^- < Br^- < Cl^- < F^- < H^- \leqslant Et^- \leqslant (OPh)^- < (OC_{2n+1})^-$

Moreover, the same Lewis base $Y^-$, which is an efficient donor and exhibits a strong tendency towards complex formation with organoaluminum compounds, may inhibit or even completely prevent complex formation if it occurs as a ligand of a dialkylaluminum compound whose acidic character is weakened. A base will displace from a complex any member standing on its left in the Series (29a). This applies, for example, in Reaction (30), in which the strongest base, a sodium alkoxide, displaces the more weakly complex-bound sodium hydride [7].

(30) $NaOC_{10}H_{21} + Na[AlEt_3H] \rightarrow NaH + Na[AlEt_3(OC_{10}H_{21})]$

Since sodium hydride and ethylsodium are almost equal in their complexing ability, sodium alkoxide would similarly be expected to displace ethylsodium from sodium tetraethylaluminate.

(31) $NaOR + Na[AlEt_4] \rightarrow NaEt + Na[AlEt_3(OR)]$

The ethylsodium liberated as in Equation (31) is not very stable thermally – it decomposes above 60 °C to give mainly sodium hydride and ethylene [20] – but it reacts with warm benzene to form phenylsodium [21]. Thus, the reaction of sodium alkoxide with sodium tetraethylaluminate in benzene should result in the production of a phenylmetal compound. First investigations indicate that, in accordance with Series (29a), the displacement of ethylsodium by sodium alkoxide does not proceed so readily as that of sodium hydride from sodium triethylaluminum hydride.

A suspension of sodium tetraethylaluminate and sodium 2-ethylhexyloxide in benzene does not yield ethylsodium spontaneously, as would be expected by analogy to the reaction with the production of sodium hydride, but ethane is only liberated at 80–90 °C [Equation (32)]. This ethane can be explained only in terms of the primary formation of ethylsodium according to Equation (31). The net reaction is shown in Equation (32).

(32) $Na[AlEt_4] + NaOR + C_6H_6 \rightarrow Na[AlEt_3(OR)] + NaPh + C_2H_6$

The reaction is not limited to the displacement of one ethyl group. All the available ethyl groups in the molecule can be replaced by phenyl groups, with a maximum yield of 75 % $Na[AlPh_4]$. Moreover, not only sodium

[19] Belg. Pat. 593386 (Jan. 25th, 1961), inventors: *K. Ziegler* and *H. Lehmkuhl*.

[20] *W. H. Carothers* and *D. D. Coffman*, J. Amer. chem. Soc. *51*, 588 (1929).

[21] *P. Schorigin*, Ber. dtsch. chem. Ges. *41*, 2723 (1908); *43*, 1938 (1910).

alkoxide, but also the phenylsodium formed in the reaction can displace ethylsodium from its complexes with alkylaluminum. This displacement reaction – catalysed by sodium alkoxide or phenylsodium – is a route [Equation (33)] leading to arylaluminum compounds via benzene and sodium tetraethylaluminate, which is readily obtainable by direct synthesis [12].

(33) $Na[AlEt_4] + 4\,C_6H_6 \xrightarrow{NaOR\ (NaPh)} Na[AlPh_4] + 4\,C_2H_6$

## 7. Cationic Exchange Reactions

Exchange reactions of cations by treatment of alkali metal alkylaluminum complexes with halides of other alkali metals were studied, mainly with the system $NaAlEt_4/KAlEt_4$.

Starting from sodium tetraethylaluminate and potassium chloride, a mixture of 80–90 mole-% $KAlEt_4$ and 20–10 mole-% $NaAlEt_4$ is obtained. In contrast, cation exchanges proceed practically to completion with pseudo-alkali-metal halides [7].

(34) $[NEt_4]I + Na[AlEt_4] \rightarrow [NEt_4][AlEt_4] + NaI$

(35) $[SbEt_4]I + Na[AlEt_4] \rightarrow [SbEt_4][AlEt_4] + NaI$

In our experience, the reaction of metallic potassium with organoaluminum compounds is a poor method for the preparation of potassium tetraethylaluminate. However, exchange reactions of sodium alkylaluminate complexes with potassium amalgam proceed readily according to Equation (36) [22].

(36) $Na[AlEt_4] + K(Hg)_x \rightarrow Na(Hg)_x + K[AlEt_4]$

The reaction proceeds almost quantitatively, although 0.6 % potassium amalgam at 90 °C has an energy of formation about 3.6 kcal higher than that of an equivalent sodium amalgam (0.35 %). In the exchange reaction with amalgam, the effect of the small ionization energy of potassium compared with that of sodium is predominant. The free energy of the exchange reaction [Equation (36)] has been determined ($\Delta F_{90\,°C} = -6.76$ kcal/mole) from the e.m.f. of appropriate galvanic cells [23]. From these data, the equilibrium constant

$$K_c = \frac{Na/Hg \cdot KAlEt_4}{K/Hg \cdot NaAlEt_4}$$

has been calculated to be $1.25 \times 10^4$. The experimental value found by mixing together equimolar quantities of sodium amalgam and potassium tetraethylaluminate is $K_c = 1.7 \times 10^4$ [17].

The transformation of $Na[Al_2Et_6F]$ into the potassium compound proceeds as readily as that of sodium tetraethylaluminate. The equilibrium constants of the reactions of $Na[AlEt_3F]$ or $Na[AlEt_3(OR)]$ with potassium amalgam are not as favorable towards the potassium complexes. The same is true for the addition of ethers [$(C_4H_9)_2O$ or THF] in the molar ratio 1:1 to $Na[AlEt_4]$; the equilibrium constants fall with increasing ether content to about $10^2$ (molar ratio 1:4). The effect is less marked for additions of triethylamine [7].

By calculating the free energies $\Delta F$ for the exchange from the equilibrium constants, eliminating the free energies for amalgam formation, and then substituting the ionization energies of the alkali metals, the free energy $\Delta F_2$ for Reaction (37) is obtained; it has positive values of 12–15 kcal/mole.

(37) $K^+_{gas} + Na[AlEt_3X] \rightleftharpoons Na^+_{gas} + K[AlEt_3X]$

Since Equation (37) can be expressed as the difference of Equations (37a) and (37b), which represent the interaction between the cation and the complex anion, the $\Delta F_2$ values signify that the equilibrium energy of reaction between the dissociated and undissociated forms is about 12–15 kcal greater for the sodium complexes.

(37a) $K^+_{gas} + [AlEt_3X]^- \rightleftharpoons K[AlEt_3X]$

(37b) $Na^+_{gas} + [AlEt_3X]^- \rightleftharpoons Na[AlEt_3X]$

## 8. Etherates of Alkali Metal Tetra-alkylaluminates

Although complexes of alkali metal halides with triethylaluminum are often split by ethers (*e.g.* $K[AlEt_3Cl]$ or $Rb[AlEt_3Br]$) or by triethylamine (*e.g.* $Na[AlEt_3F]$) [1], the alkali metal tetra-alkylaluminates dissolve readily in these solvents. When attempts were made to isolate the ether-free compounds from these solutions, it was found that the solvent was firmly bound in a molar ratio of 1:1. It was also observed that 1:1 molar mixtures of potassium tetraethylaluminate and diethyl ether are insoluble in pentane or hexane and two liquid phases result. The ether is not extracted by the hydrocarbon [23a].

This capacity for addition of electron donors onto alkali metal tetraethylaluminates is unexpected, since the four coordination sites of the aluminum in the complex anion are occupied, and since coordination numbers greater than four for organoaluminum compounds have not been observed hitherto.

Measurements of the transport number of the cation of potassium tetraethylaluminate in benzene solutions to which increasing amounts of dibutyl ether were added indicated that there is probably no coordinate linkage between the ether and the aluminum, but rather between the ether and the alkali metal cation, which can

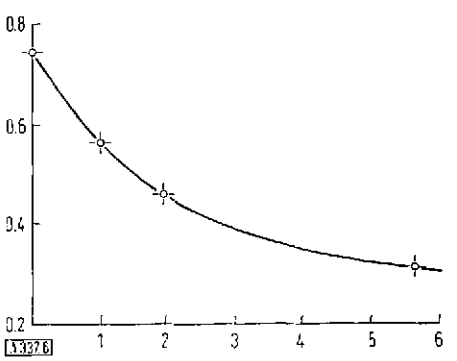



Fig. 6. Variation of the transport number $n_K$ of the cation in a 1 M solution of $K[Al(C_2H_5)_4]$ in benzene with the dibutyl ether content. Ordinate: Transport number $n_K$. Abscissa: Moles of dibutyl ether/mole of $K[Al(C_2H_5)_4]$

[22] *K. Ziegler* et al., Chemie-Ing.-Techn. *35*, 325, 328 (1963).

[23] *H. Lehmkuhl* and *W. Grimme*, Chemie-Ing.-Techn. *35*, 332 (1963).

[23a] *W. Eisenbach*, unpublished work.

also act as an electron acceptor. Whereas in a ca. 1 M solution of potassium tetraethylaluminate in benzene about 75 % of the electrical conductivity is due to the cation, the cation of $K[AlEt_4]\cdot 4Bu_2O$ in solution in benzene – which is much larger and therefore less mobile owing to solvation – transports only about 36 % of the current (Fig. 6) [7].

## 9. Alkaline Earth Tetra-alkylaluminates

In contrast to alkylmagnesium compounds, the organometallic compounds of calcium, strontium, and barium have only been investigated to a small extent. The diethyl metals are not known. Besides the preparation of a few compounds MRX [24], there is only one reference in the literature to crystalline products formed from alkaline earth metals with diethylzinc: their composition was given by *Gilman* as $Et_2M\cdot ZnEt_2$ [25]. *Ziegler* and *Holzkamp* [26] studied the reaction of dialkylmagnesium with trialkylaluminum or of ether-free Grignard compounds with trialkylaluminum and found two classes of complexes: $[RMg][AlR_4]$ and $MgR_2\cdot 2AlR_3$. In both classes, the bond between the trialkylaluminum and the dialkylmagnesium is weak. The compounds can be cleaved by distilling off the trialkylaluminum *in vacuo* at 100–115 °C, or by adding a powerful electron-donor, *e.g.* triethylamine, to the trialkylaluminum according to Equation (38) [27].

(38) $MgEt_2\cdot 2\,AlEt_3 + 2\,NEt_3 \rightarrow MgEt_2 + 2\,AlEt_3\cdot NEt_3$

On heating $[MeMg][AlMe_4]$ at 70–75 °C/$10^{-3}$ mm, the complex compound distills over. Some unsuccessful attempts were made to obtain calcium ethylaluminate compounds by treating calcium with triethylaluminum by analogy to the formation of sodium tetraethylaluminate [28, 29] from sodium and triethylaluminum. The discovery of the reaction of alkali metal alkoxides with triethylaluminum suggested that the synthesis of alkaline earth ethylaluminates using alkaline earth alkoxides may be possible. Various other methods of preparation of alkali metal tetra-alkylaluminates, *e.g.* the addition of alkali metal hydride onto triethylaluminum and subsequent reaction with an olefine according to Equation (39), had proved to be unsuitable for calcium compounds.

(39) $NaH + AlEt_3 \rightarrow Na[AlEt_3H] \xrightarrow{C_2H_4} Na[AlEt_4]$

Calcium hydride and calcium chloride and fluoride do not form complexes with triethylaluminum [7].

Like the alkali metal alkoxides, the alkoxides of calcium, strontium, and barium dissolve in warm triethylaluminum to form $M[AlEt_3(OR)]_2$ complexes. On treating the resultant viscous liquid compounds with further two moles of triethylaluminum per mole of complex, the triethylaluminum displaces the diethylaluminum alkoxide [30].

(40) $M[AlEt_3(OR)]_2 + 2\,AlEt_3 \rightarrow M[AlEt_4]_2 + 2\,AlEt_2(OR)$

After removal of the diethylaluminum alkoxide, which is no longer complexed, by distillation (a suitable lower alkoxide, *e.g.* $-OC_2H_5$, $-OC_3H_7$, $-O\text{-}n\text{-}C_4H_9$, will make the distillation easier) the analytically pure calcium and strontium compounds can be distilled off at reduced pressure ($10^{-3}$ mm).

$Ca[AlEt_4]_2$: m.p. 41 °C; b.p. 90–95 °C/$10^{-3}$ mm

$Sr[AlEt_4]_2$: m.p. 109 °C; b.p. 122–128 °C/$10^{-3}$ mm

$Ba[AlEt_4]_2$ decomposes on distillation; purification by recrystallization from hot benzene is preferable (m.p. 138 °C). All attempts to obtain pure, uncomplexed alkaline earth alkyls by thermal decomposition of the new complexes were unsuccessful, since together with triethylaluminum, ethylene was evolved, and alkaline earth hydrides were precipitated from the reaction mixture [7].

(41) $M[AlEt_4]_2 \xrightarrow[10\,mm]{130\,^\circ C} [MEt_2 + 2\,AlEt_3] \rightarrow MH_2 + 2\,C_2H_4 + 2\,AlEt_3$

Whether ethylene is split off and the unstable hydrocomplex $M[AlEt_3H]_2$ decomposes into $MH_2$ and $AlEt_3$ or whether an alkaline earth alkyl loses ethylene to leave the alkaline earth hydride cannot yet be established.

Calcium, strontium, and barium in contrast to magnesium [31] do not react perceptibly with diethylmercury to yield diethylmetals. However, the metals do react with a 1:2 mixture of diethylmercury and triethylaluminum [Equation (42)] to yield alkaline earth ethylaluminate complexes [7].

(42) $M + HgEt_2 + 2\,AlEt_3 \rightarrow M[AlEt_4]_2 + Hg$ [*]

Another route to alkaline earth alkylaluminate complexes involves the reaction of an alkaline earth chloride with sodium tetraethylaluminate.

(43) $MCl_2 + 2\,Na[AlEt_4] \rightleftharpoons M[AlEt_4]_2 + 2\,NaCl$

However, Reaction (43) is not quantitative; apparently an equilibrium is set up. In benzene, the forward reaction is about 70 % complete with calcium chloride, 30 % with strontium chloride, and 40 % with barium chloride. Nevertheless, this method is applicable to the preparation of the calcium and strontium compounds since separation is readily attained thanks to the good solubility of both complexes in cold benzene; unreacted sodium tetraethylaluminate is insoluble. Only in the case of barium is separation from the mixture difficult.

The distillability of the $M[AlEt_4]_2$ complexes of calcium and strontium and the volatility of the barium complex are unexpected, since these compounds are analogues of

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[25] *H. Gilman* and *L. A. Woods*, J. Amer. chem. Soc. *67*, 521 (1945).

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[29] *A. v. Grosse* and *J. M. Mavity*, J. org. Chemistry *5*, 111 (1940).

[30] *H. Lehmkuhl* and *W. Eisenbach*, Angew. Chem. *74*, 779 (1962); Angew. Chem. internat. Edit. *1*, 590 (1962).

[31] *Ph. Löhr*, Liebigs Ann. Chem. *261*, 48, 82 (1891).

[*] Calcium tetraethylborate $Ca[BEt_4]_2$ can be prepared similarly from a 1:2 mixture of diethylmercury and triethylboron with calcium [7].

sodium and potassium tetraethylaluminates and magnesium octaethyldialuminate $Mg[AlEt_4]_2$.

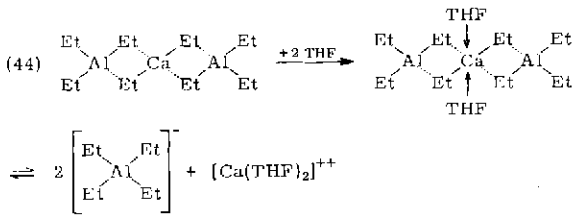
Sodium and potassium tetraethylaluminates are non-volatile salt-like compounds with high electrical conductivities (at 130 °C: $5.5\times10^{-2}$ and $13\times10^{-2}$ mho/cm). The magnesium compounds decomposed readily *in vacuo* to yield diethylmagnesium and triethylaluminum. Moreover, calcium octaethyldialuminate is soluble in aromatics and in polar solvents such as ethers, as well as in saturated hydrocarbons such as hexane or heptane (≈ 50 g/50 ml). Strontium octaethyldialuminate dissolves in hexane (≈ 0.8 g/50 ml); the barium compound is soluble on heating in aromatics but is insoluble in hexane. The salt-like character increases with atomic number as is clearly shown by comparing the specific conductivities.

$Ca[AlEt_4]_2$: $\varkappa < 10^{-7}$ mho/cm  $Sr[AlEt_4]_2$: $\varkappa = 3.7\times10^{-4}$ mho/cm
$Ba[AlEt_4]_2$: $\varkappa = 0.9\times10^{-2}$ mho/cm

The calcium and strontium compounds have little or no salt-like character; evidence for this is their volatility [**] and their solubility in non-polar solvents.

[**] The volatility of the Ca-Al complexes does not appear to be limited to these organometallic compounds. *Meerwein* [32] describes $Ca[Al(OEt)_4]_2$ as being distillable *in vacuo*.

Calcium octaethyldialuminate forms a stable crystalline addition compound $Ca[AlEt_4]_2\cdot2THF$ with tetrahydrofuran (m.p. 57–60 °C), the conductivity thereby increasing by more than a factor of 1000 [7]. After addition of the electron-donor THF, the electron density on the calcium is increased to such an extent – probably by solvation of the cation – that the electron-deficient bonds involved in the bridging ethyl groups between the calcium and the aluminum are broken and tetraethylaluminate ions are formed

(44) 


Received, September 17th, 1963 [A 337/136 IE]
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# Recent Developments in the Chemistry of Pteridines

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*The abundant experimental material available on the chemistry of the pteridines, as well as the reports given at the Third International Symposium on Pteridines have been reviewed and the most important results of the past ten years incorporated into the present article. Syntheses, reactions, and structural problems are reviewed and natural pteridines and their possible biochemical significance are discussed.*

Introduction

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VI. Biosynthesis of pteridines

VII. The biochemical role of unconjugated pteridines

## Introduction

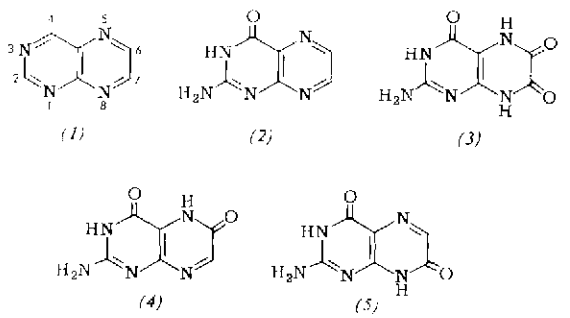
Pteridine chemistry actually began with the studies on the pigments of butterfly wings carried out by *Hopkins* [1] at the end of the last century. Almost thirty years later, in 1924, *Wieland* urged on by *Schöpf*, his assistant and student at that time, began systematic studies in the endeavor to elucidate the chemical structure of butterfly pigments.

Although they soon succeeded in isolating and purifying the yellow pigment [2] from the wings of the brimstone

[1] *F. G. Hopkins*, Nature (London) *40*, 335 (1889); Proc. chem. Soc. (London), Abstr. *5*, 117 (1889); Nature (London) *45*, 197 (1891); Proc. Roy. Soc. (London) Ser. B, *57*, 5 (1895); Philos. Trans. Roy. Soc. (London) Ser. B *186*, 661 (1895).

[2] *H. Wieland* and *Ch. Schöpf*, Ber. dtsch. chem. Ges. *58*, 2178 (1925).

butterfly, and the colorless pigments [3] of the cabbage butterfly, they met with unexpected difficulties when they attempted to determine the structures of these two natural products, which were designated as xanthopterin *(4)* [2] and leucopterin *(3)* [3]. Not before 1940, 15 years later, was *Purrmann* [4] able to show that leucopterin [4], xanthopterin [5], and isoxanthopterin *(5)* [7] which was first described in1933 [6],were aminohydroxy derivatives of a bicyclic nitrogenous ring system, *viz.* of pyrimido[4,5-*b*]pyrazine, which *Wieland* [8] designated in 1941 as pteridine *(1)*.

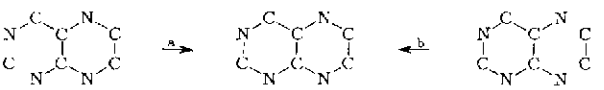


*(1)* *(2)* *(3)* *(4)* *(5)*

We now know the basic structure of the pteridine nucleus and recognize the fact that insect pigments also include purine derivatives, phenoxazine derivatives, *viz.* the ommochromes [9], as well as brown to black pigments of the melanin type; it thus seems appropriate to revise the use of the word "pterins" as a collective term for butterfly wing pigments [2] or even for insect pigments in general [10]. The fortunate circumstance that all the natural pteridines designated by trivial names "....pterin" have a similarly substituted pyrimidine ring suggests the possibility of restricting the term "pterins" so as to include only derivatives of 2-amino-4-pteridone, *i.e.* of pterin *(2)*, in a special group.

A number of reviewers [11] have attempted to keep pace with the fast developments in the field of pteridine chemistry since 1940. The most recent reviews are those by *Albert* in 1952 [12] and 1954 [13]. Since then, much progress has been made from the chemical, biochemical, and biological points of view. This paper will therefore deal with the most important results obtained in recent years, as well as with some of the most recent reports [14].

Examination of the pyrimido[4,5-*b*]pyrazine structure of pteridines reveals two possible pathways for the synthesis of this ring system, namely, fusion of a pyrimidine ring onto a pyrazine derivative (Pathway a), or addition of a pyrazine ring onto a pyrimidine derivative (Pathway b). Since pyrimidines are relatively



easily accessible, the Isay reaction [15], *i.e.* condensation of a 4,5-diaminopyrimidine with a 1,2-dicarbonyl compound, continues to be of major importance [16–29].

Syntheses proceeding from 4,5-diaminopyrimidines and unsymmetrical 1,2-diketones, α-keto aldehydes, or α-keto acids or their esters yield mixtures of substituted pteridines which are isomeric in positions 6 and 7. Since separation of such mixtures involves losses of time and yield and often is extremely difficult, syntheses are sought which selectively produce a single isomer.

### 1. pH-Dependent Condensation of 4,5-Diaminopyrimidines

The principle of pH-dependent condensation, first recognized by *Purrmann* [7] and later applied generally [30], can well be explained in the case of 4,5-diaminouracil *(6)*, 2,4,5-triamino-6-oxodihydropyrimidine, and correspondingly substituted 4,5-diamino-6-oxodihydropyrimidines. Because of their different positions with respect to the 6-oxo group and to the nitrogen atoms in the ring, the amino groups present at carbon atoms 4 and 5 possess very different nucleophilic potentials [33]. In reactions with α-keto acids in neutral or

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[19] *J. W. Daly* and *B. E. Christensen*, J. Amer. chem. Soc. *78*, 225 (1956).

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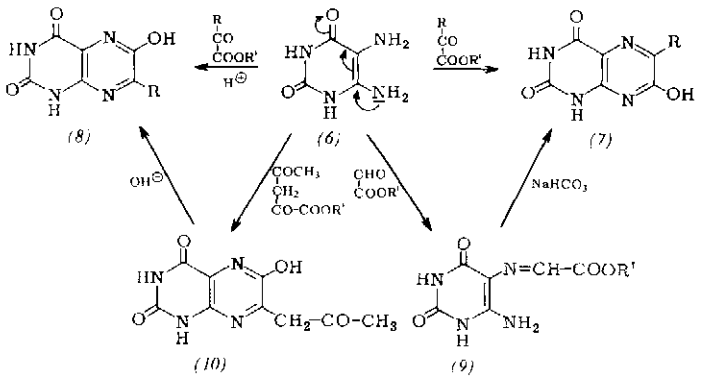
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weakly acidic media [31–38] or in organic solvents [39], the primary condensation between the 5-amino and the keto groups produces 7-hydroxypteridines *(7)*, whereas in a strongly acidic medium, protonation of the more strongly basic 5-amino group leads to the opposite orientation of the substituents in the molecules, *i.e.* to the formation of 6-hydroxypteridines *(8)* [40–42]. Condensations with glyoxylic ester proceed particularly smoothly and uniformly if the 5-azomethinecarboxylic ester *(9)* is synthetized first and if then this Schiff base is cyclized under mild conditions in bicarbonate solution [33,35,43].

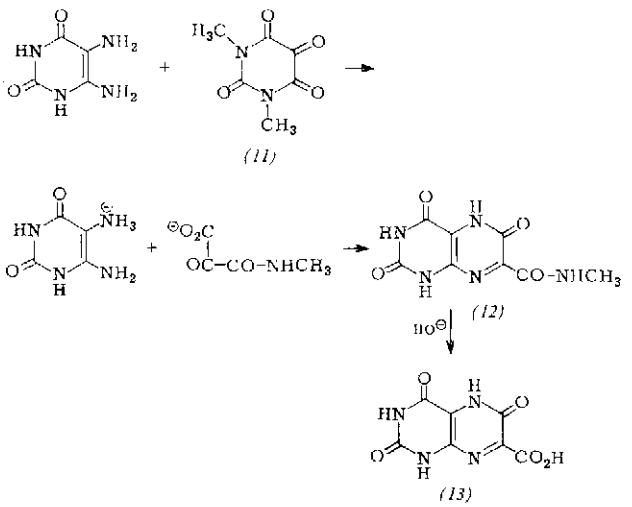
The easiest way to synthetize 2,4-disubstituted 6-hydroxy-7-methylpteridines [*(8)*, R = $CH_3$] is via 6-hydroxy-7-acetonylpteridines *(10)* which readily undergo acid hydrolysis in the presence of alkalis and which are obtained in pure form when 4,5-diaminopyrimidines are condensed with acetonyloxalic ester [42]. However, direct condensation with pyruvic acid always yields a mixture of isomers. Recent reports



indicate that 6-hydroxy-7-alkylpteridines can also be obtained from 2-trifluoromethyl-4-alkyl-5-oxazolones and 6-isopropoxy- or 6-oxodihydro-2,4,5-triaminopyrimidine [44].

7-Hydroxypteridine-6-carboxylic acids [*(7)*, R = COOH] can be synthetized in analogous manner using mesoxalic ester at a neutral pH [34,36,38,39,45] or alloxan in dilute aqueous alkali [46–48]. It is difficult to prepare the isomeric 6-hydroxypteridine-7-carboxylic acids [*(8)*, R = COOH] from the same starting materials, since changes in the pH merely shift the isomer ratio in the direction of the 6-hydroxy derivatives.

A novel synthetic possibility is presented by the reaction of 4,5-diaminopyrimidines with 1,3-dimethylalloxan *(11)* [49,50]. Dimethylalloxan is alkali-labile and is split by the heterocyclic base to yield the mono-N-



methylamide of mesoxalic acid which then forms a salt with the more strongly basic 5-amino group of the diamine, thereby assuming an orientation such that the formation of *N*-methylhydroxypteridine-7-carboxamide *(12)* is favored during the reaction leading to ring closure. The amides of type *(12)* can then be hydrolysed with alkali to form the acids *(13)*.

### 2. Syntheses Involving Nitrosopyrimidines

Pteridines can also be obtained via a method first developed by *Timmis* [51]. 4-Amino-5-nitrosopyrimidines such as *(14)* can be condensed not only with ketones [52–54,59] and aldehydes [54,59], but also with nitriles [55–61] and esters [59–61] that have an activated methylene group adjacent to the functional group.

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[44] *F. Weygand* [14].

[45] *G. B. Elion* and *G. H. Hitchings*, J. Amer. chem. Soc. *75*, 4311 (1953).

[46] *E. C. Taylor* and *H. M. Loux*, Chem. and Ind. *1954*, 4109.

[47] *E. C. Taylor* and *H. M. Loux*, J. Amer. chem. Soc. *81*, 2474 (1959).

[48] *W. Pfleiderer* and *E. C. Taylor*, J. Amer. chem. Soc. *82*, 3765 (1960).

[49] *W. Pfleiderer*, Chem. Ber. *90*, 2624 (1957).

[50] *W. Pfleiderer*, Chem. Ber. *95*, 749 (1962).

[51] *G. M. Timmis*, Nature (London) *164*, 139 (1949); U.S. Pat. 2581889 (1952), inventor: *G. M. Timmis*.

[52] *D. G. Felton* and *G. M. Timmis*, J. chem. Soc. (London) *1954*, 2881.

[53] *D. G. I. Felton, T. S. Osdene*, and *G. M. Timmis*, J. chem. Soc. (London) *1954*, 2895.

[54] *G. P. G. Dick, H. C. S. Wood*, and *W. R. Logan*, J. chem. Soc. (London) *1956*, 2131.

[55] *R. G. W. Spicknell* and *G. M. Timmis*, J. chem. Soc. (London) *1954*, 2887.

[56] *T. S. Osdene* and *G. M. Timmis*, J. chem. Soc. (London) *1955*, 2036.

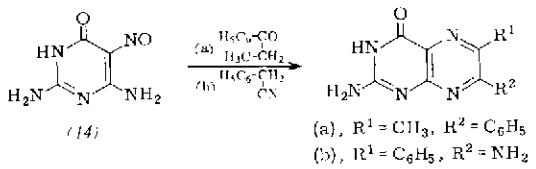
[57] U.S. Pat. 2975180 (1961), inventors: *T. S. Osdene* and *E. C. Taylor*.

[58] *J. Weinstock* [14].

[59] *I. J. Pachter* [14].

[60] *T. S. Osdene* [14].

[61] *T. S. Osdene* and *G. M. Timmis*, J. chem. Soc. (London) *1955*, 2038.



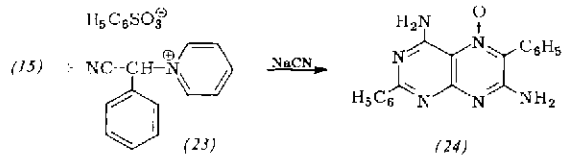
(14)

(a), $R^1 = CH_3$, $R^2 = C_6H_5$
(b), $R^1 = C_6H_5$, $R^2 = NH_2$

The recent work of *Pachter* has led to additional approaches to pteridine syntheses [59]. Reaction of 5-nitroso-4,6-diamino-2-phenylpyrimidine *(15)* with benzyl methyl ketone in the presence of potassium acetate gives 4-amino-7-methyl-2,6-diphenylpteridine *(16)*; however, if cyanide ions are present, 4,7-diamino-2,6-diphenylpteridine *(17)* is unexpectedly formed. Further examples of this reaction have shown that the cyanide ions, in analogy to earlier report [59], can displace the acyl groups in the ketone.

The preferential dehydrogenation of hydroxylamine derivatives of type *(18)* is not without parallel [62,63]. The occurrence of the intermediate *(20)* explains why compound *(17)* is so readily formed from *(15)* and α-phenyl-α-acetylacetonitrile in the presence of alkali. This reaction made it possible to prepare 6-alkyl-7-aminopteridines *(21)* from alkylacylacetonitriles, whereas insufficient activation prevented formation of this compound from 5-nitroso-4-aminopyrimidine and alkyl cyanides.

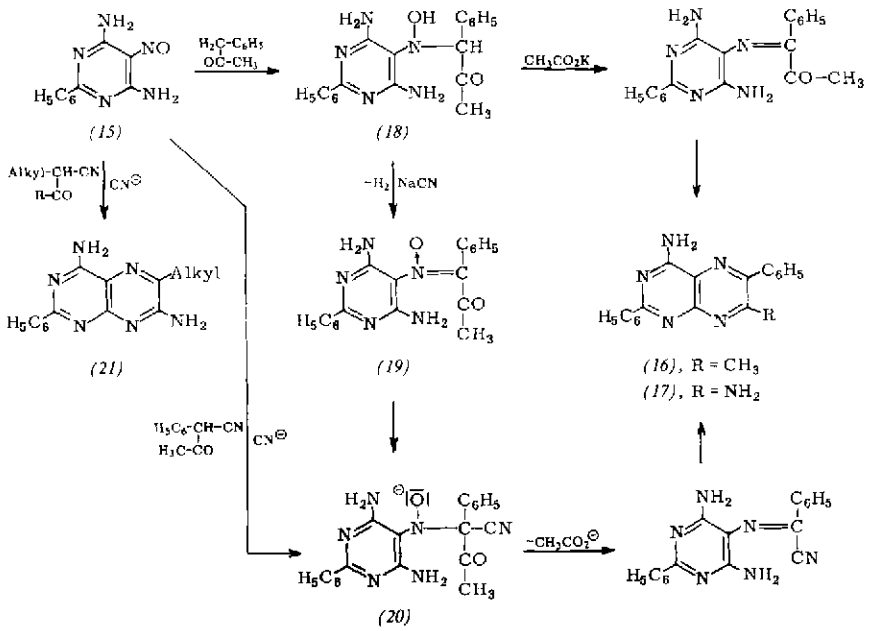
Both phenacylpyridinium and acetonylpyridinium salts are very suitable for the synthesis of 7-aminopteridyl ketones *(22)*, since in the presence of NaCN they behave like β-keto nitriles [64]. Pteridine-5-oxides *(24)* can be prepared in the same manner by reaction of the pyridinium salt *(23)* – resulting from α-cyanobenzyl benzenesulfonate and pyridine – with a 5-nitroso-4-aminopyrimidine.



(15) (23) (24)

### 3. Further Syntheses via *o*-Diaminopyrimidines

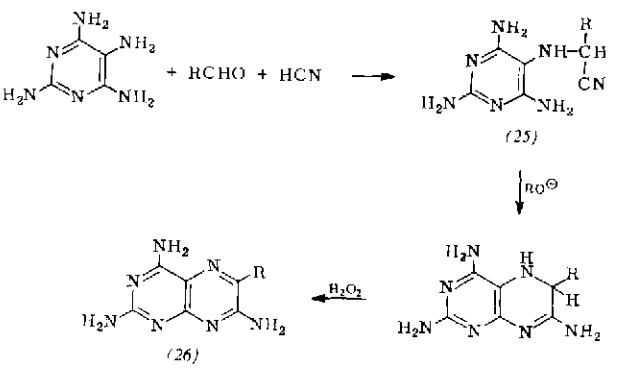
Another method of fusing the pyrazine ring onto a 4,5-diaminopyrimidine involves treatment of this *o*-diamine with aldehydes and HCN [59,65,66]. The first products are 4-amino-5-(α-cyanalkylamino)pyrimidines *(25)*.



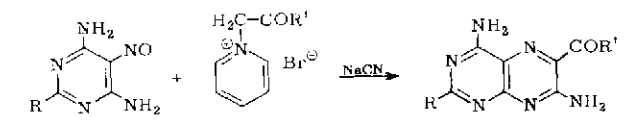
(15) (18) (21) (19) (20)

(16), R = $CH_3$
(17), R = $NH_2$

These are then isolated, cyclized in alkali, and oxidized to form 7-amino-6-alkylpteridines *(26)*.



(25) (26)



R = H, $C_6H_5$, $SCH_3$ ; R' = $CH_3$, $C_6H_5$ (22)

[62] *F. Kröhnke*, Chem. Ber. *80*, 298 (1947).

[63] *A. Schönberg* and *R. Michaelis*, J. chem. Soc. (London) *1937*, 627; *E. Bergmann*, J. chem. Soc. (London) *1937*, 1628; *F. Kröhnke*, Ber. dtsch. chem. Ges. *71*, 2583 (1938); *F. Barrow* and *F. J. Thorneycroft*, J. chem. Soc. (London) *1939*, 769; *H. L. de Waal* and *C. V. d. M. Brink*, Chem. Ber. *89*, 636 (1956); *D. C. Dittmer* and *J. M. Kolter*, J. org. Chemistry *27*, 56 (1962).

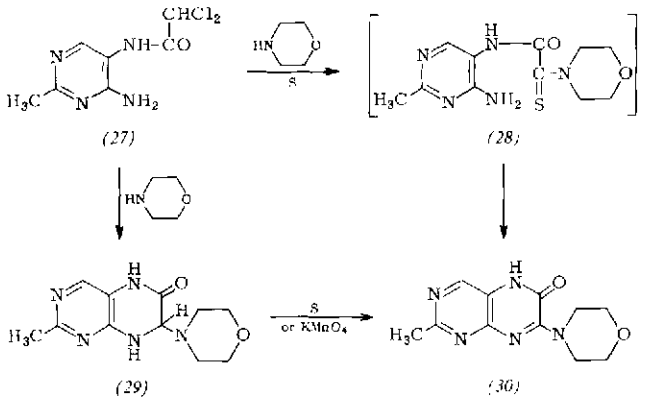
[64] *F. Kröhnke*, Angew. Chem. *65*, 605 (1953).

[65] *F. F. Blicke* and *H. C. Godt*, J. Amer. chem. Soc. *76*, 2798 (1954).

[66] *M. Polonovski* in: Ciba Foundation Symposium on Chemistry and Biology of Pteridines. Churchill, London 1954, p. 171.

[67] *P. Schmidt* [14].

A novel type of ring closure is the reaction of 5-dichloroacetylamino-4-aminopyrimidine *(27)* with sulfur/morpholine under the conditions of a Kindler reaction [67]. The resulting 6-hydroxy-7-aminopteridines *(30)* are formed either via the thio-oxamide derivatives *(28)*



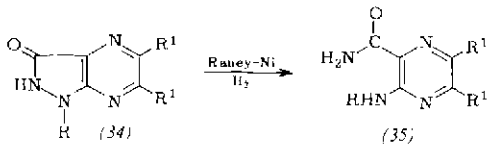
*(27)* *(28)* *(29)* *(30)*

– which cannot be isolated – or via the 7,8-dihydropteridines *(29)* which can be obtained with morpholine only.

### 4. Syntheses Starting from Pyrazine Derivatives

Pteridine syntheses based on pyrazine derivatives have been used only rarely because the latter are not easily accessible. The reaction of 2-chloropyrazine-3-carboxylic esters with guanidine salts [68] can be used for the preparation of pterins. Cyclization of 2-aminopyrazine-3-hydroxamic acid or 2-aminopyrazine-3-carbohydrazide gives 3-hydroxy- [69] or 3-amino-4-oxodihydropteridine, respectively [70, 71].

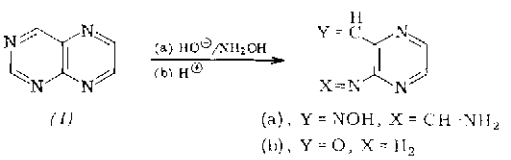
Aminolytic or hydrolytic ring cleavage of suitable pteridine derivatives *(31)* leads to 2-aminopyrazine-3-carboxamides *(32)*, which can be cyclized to result in new pteridines *(33)*. This procedure is quite general and can be varied in many ways [72, 73]. A quite peculiar synthesis [74] of 2-aminopyrazine-3-carboxamides *(35)* is based on reductive cleavage of the ring of 3-hydroxypyrazolo[*b*]pyrazines *(34)*, which are obtained from 4,5-diaminopyrazolones and 1,2-dicarbonyl compounds.



*(34)* *(35)*

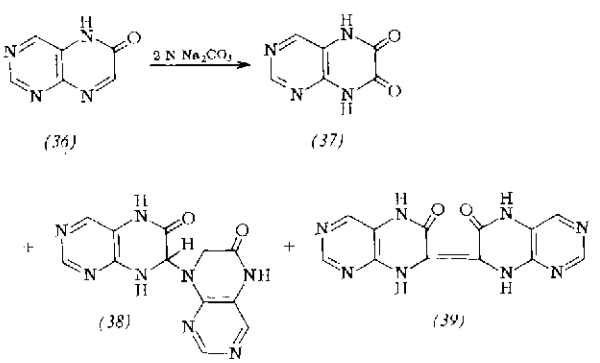
## II. Reactions

The reactions of the pteridines are determined by nature and number of their substituents. The basic nucleus, *viz.* pteridine *(1)*, is relatively unstable. The instability is caused by the accumulation of four nitrogen atoms in this ring system, by their special mutual spatial relationship, and by their interaction with the ten π-electrons, all resulting in a considerable reduction of the heteroaromatic character of this compound. Pteridine *(1)* can be degraded with ring opening by both acids and alkalis [75]; this tendency towards hydrolytic cleavage



*(1)* (a), Y = NOH, X = CH·NH$_2$ (b), Y = O, X = H$_2$

of the pyrimidine ring is confirmed by calculations based on its electron density distribution [76] which show that this diazine system has the greater polarity of the two rings. As the number of strong electron donor substituents (*e.g.* OH, $NH_2$, SH, $N(CH_3)_2$) increases, this electron deficiency becomes partially compensated, and the pteridine ring begins to assume the stability common for the natural pteridines [77]. The intermediate position of the monosubstituted pteridines is not just a matter of form, but also causes unexpected reactions, which



*(36)* *(37)* *(38)* *(39)*

[68] *G. P. G. Dick* and *H. C. S. Wood*, J. chem. Soc. (London) *1955*, 1379.

[69] *W. B. Wright* and *J. M. Smith*, J. Amer. chem. Soc. *77*, 3927 (1955).

[70] *E. C. Taylor*, *O. Vogl*, and *P. K. Loeffler*, J. Amer. chem. Soc. *81*, 2479 (1959).

[71] *F. Dalacker* and *G. Steiner*, Liebigs Ann. Chem. *660*, 98 (1962).

[72] *E. C. Taylor*, *J. A. Carbon*, and *D. R. Hoff*, J. Amer. chem. Soc. *75*, 1904 (1953).

[73] *E. C. Taylor*, *R. B. Garland*, and *C. F. Howell*, J. Amer. chem. Soc. *78*, 210 (1956).

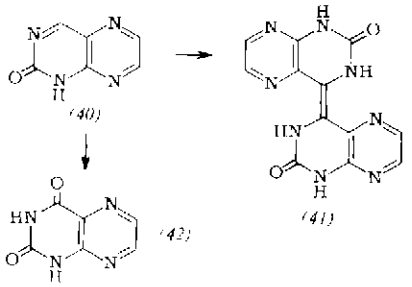
[74] *T. S. Osdene* and *E. C. Taylor*, J. Amer. chem. Soc. *78*, 5451 (1956); *E. C. Taylor*, *J. W. Barton*, and *T. S. Osdene*, J. Amer. chem. Soc. *80*, 421 (1958).

[75] *A. Albert*, *D. J. Brown*, and *H. C. S. Wood*, J. chem. Soc. (London) *1956*, 2066.

[76] *A. Albert*, Quart. Rev. *6*, 213 (1952).

[77] *A. Albert*, *D. J. Brown*, and *G. Cheeseman*, J. chem. Soc. (London) *1952*, 4219.

can be demonstrated, for example, with the monohydroxy derivatives. Thus, treatment of 6-hydroxypteridine *(36)* with boiling sodium carbonate leads to the formation of the three substances *(37)*, *(38)*, and *(39)* [78]. Treatment of the 2-hydroxy isomer *(40)* with boiling dilute alkali in an atmosphere of nitrogen leads to *(41)* [79]; treatment in air leads to lumazine *(42)*.



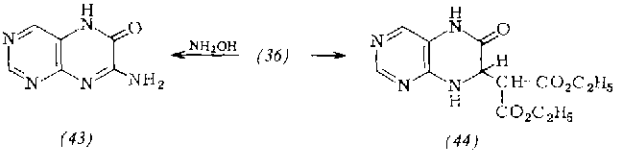
*(40)* *(41)* *(42)*

## 1. Nucleophilic Reactions

So far electrophilic substitutions at the ring carbon atoms, such as nitration, nitrosation, sulfonation, or halogenation, have not been reported in the pteridine series.

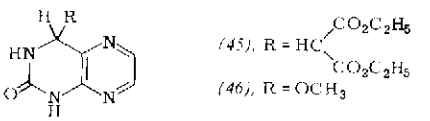
However, the nucleophilic displacement of chlorine atoms or of mercapto, alkylthio, amino, and substituted amino groups is one of the most common reactions of the pteridines. Chloropteridines, which can be prepared from hydroxypterines by treatment with either $PCl_5$/$POCl_3$ or $PCl_5$/$PCl_3$ [16,31,35,80–84], are very reactive because the chlorine atom is adjacent to the nitrogen atoms of the ring; hence, they react readily with ammonia [31,81,82], amines [16,31,80,84,85], alkoxides [16,31,35,82–84], and thiols [84]. The displacement of mercapto [80,86] and alkylthio groups [16,86] by amines is, in most cases, likely to involve a normal $S_N2$ reaction at the intact pteridine nucleus, even though there are reports suggesting the occurrence of intermediary cleavage of the ring by a process similar to that thought to occur in the conversion of amino into substituted amino groups [85].

Nucleophilic additions onto pteridines have also assumed significance, particularly because the pronouncedly polar character of the $\Delta^7$-double bond of 6-hydroxypteridines would seem to predestinate them for this reaction. Thus, 6-hydroxypteridine *(36)* not only adds on water, ammonia, hydroxylamine [to form *(43)*], a second molecule of 6-hydroxypteridine, or a molecule of 7,8-dihydro-6-hydroxypteridine [78], but in an alkaline medium it also adds on CH-acidic compounds [87] such as malonic ester [to form *(44)*], cyanoacetic ester, and acetone.



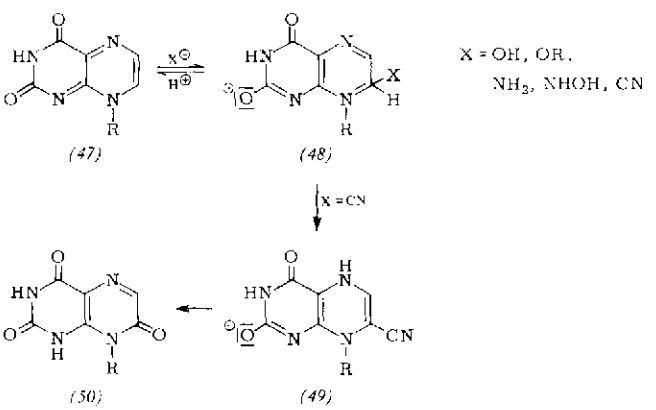
*(43)* *(36)* *(44)*

Under carefully controlled conditions, 2-hydroxypteridine *(40)* undergoes Michael additions [88] with acetylacetone or malonic, acetoacetic, or cyanoacetic ester, but not with acetone, to give, for example, compounds *(45)* and *(46)*.



*(45)*, R = $HC(CO_2C_2H_5)_2$
*(46)*, R = $OCH_3$

The resultant 7,8- and 3,4-dihydro derivatives do not undergo autoxidation. They thus differ from the corresponding addition compounds of multiply substituted 6-hydroxypteridines, *e.g.* xanthopterin *(4)* [89,90], whose dihydro compounds can usually not be isolated owing to their increased tendency to aromatize. 8-Alkyl-4-pteridones *(47)* also add on nucleophilic compounds in the 7-position [91,92]. Thus, *(47)* is transformed into the 7,8-dihydropteridine derivative



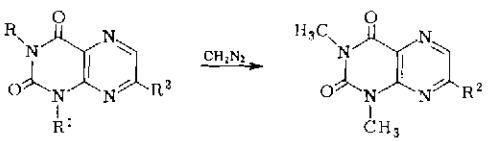

*(47)* *(48)* *(50)* *(49)*

*(48)* by loss of its quinonoid electron system. Such reactions are usually reversible in the absence of light. However, if substituents such as CN, which have a negative mesomeric effect, are introduced, a 7,5-prototropy occurs leading to the formation of a 5,8-dihydropteridine *(49)*. The latter then undergoes immediate autoxidation and is transformed into a 7-oxodihydropteridine *(50)*.

[78] *A. Albert*, J. chem. Soc. (London) *1955*, 2690.
[79] *A. Albert* and *F. Reich*, J. chem. Soc. (London) *1960*, 1370.
[80] *E. C. Taylor* and *C. K. Cain*, J. Amer. chem. Soc. *73*, 4384 (1951).
[81] *A. Albert*, *J. H. Lister*, and *C. Pedersen*, J. chem. Soc. (London) *1956*, 4621.
[82] *E. C. Taylor* and *W. R. Sherman*, J. Amer. chem. Soc. *81* 2464 (1959).
[83] *W. Pfleiderer* and *F. Reisser*, Chem. Ber. *95*, 1621 (1962).
[84] German Published Patent Application 1088969 (June 27th, 1957), Dr. Karl Thomae G.m.b.H., inventor: *I. Roch*.
[85] *E. C. Taylor*, J. Amer. chem. Soc. *74*, 1648 (1952).
[86] *E. C. Taylor* and *C. K. Cain*, J. Amer. chem. Soc. *74*, 1644 (1952).
[87] *A. Albert* and *F. Reich*, J. chem. Soc. (London) *1961*, 127.
[88] *A. Albert* and *C. F. Howell*, J. chem. Soc. (London) *1962*, 1591.
[89] *F. Korte* and *H. Bannuscher*, Liebigs Ann. Chem. *622*, 126 (1959).
[90] *M. Viscontini* and *M. Piraux*, Helv. chim. Acta *45*, 1000 (1962).
[91] *T. Rowan*, *H. C. S. Wood*, and *P. Hemmerich*, Proc. chem. Soc. (London) *1961*, 260.
[92] *P. Hemmerich* [14].

## 2. Alkylations

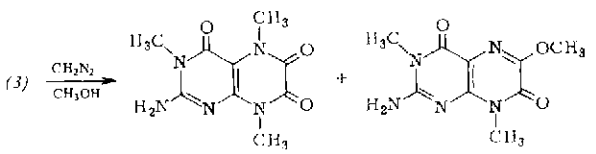
Alkylations, particularly those of the many hydroxypteridines, constitute a second major group of reactions. The arrangement of the nitrogen atoms in positions 1,3,5, and 8 of the pteridine ring leads to complications with the hydroxy derivatives, insofar as the proximity of the hydroxyl groups with at least one hetero-atom confers the ability to undergo lactam-iminol tautomerism. It is therefore to be expected that alkylation does not always lead to the same results, but may result in *O*- and/or *N*-substitutions, depending on the nature of the cyclic amide, the reaction conditions, and the compound used for the alkylation [93].



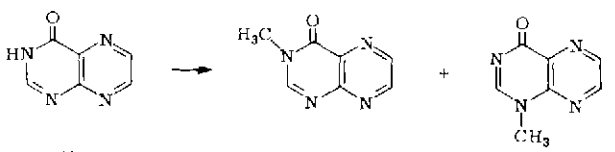
*(42)*, R = $R^1$ = $R^2$ = H
*(51)*, R = $R^1$ = $CH_3$, $R^2$ = OH

*(42a)*, $R^2$ = H
*(51a)*, $R^2$ = $OCH_3$

The result is least predictable in the case of methylation with diazomethane; exclusive *N*- [23,31,54] and exclusive *O*-methylations [32,34,42,94] have been reported, as exemplified, respectively, by lumazine *(42)* [23] and 1,3-dimethyl-7-hydroxylumazine *(51)* [34]. Mixtures of the possible *O*- and *N*-methyl derivatives have also been reported [75,95], *e.g.* with leucopterin *(3)*.

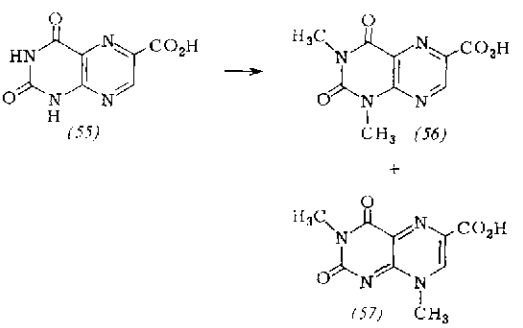


Methylations with dimethyl sulfate, carried out in dilute alkali [35,75,94,96–99] or in methanol in the presence of alkoxides [75], are much more predictable, since under these conditions, the mesomeric anions function as nucleophilic partners of the dimethyl sulfate. Because of the $S_N2$-character of this reaction, the anions react preferentially with the most nucleophilic centers, *viz.* the nitrogen atoms of the ring [93,100]. Because of the energy relationships in the system, *N*-methylation normally occurs on the nitrogen atom adjacent to the carbonyl group. However, because the nitrogen atoms in positions 1, 3, and 8 are capable of direct mutual interaction (since they are in *meta*-orientation to each other), it is not surprising that certain mesomeric anions of multivalent nature produce mixtures of *N*-methyl derivatives. The anion of 4-hydroxypteridine *(52)* [75], for example, yields both 3-methyl- *(53)* and 1-methyl-4-pteridone *(54)*.



*(52)* *(53)* *(54)*

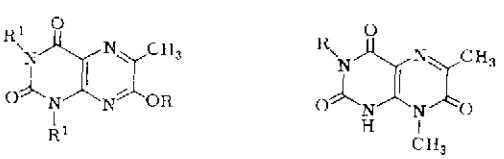
In the presence of excess dimethyl sulfate in alkali, lumazine-6-carboxylic acid *(44)* [97] produces a mixture consisting of 73 % of the 1,3- *(56)* and 16 % of the 3,8-dimethyl compound *(57)*.



*(55)* *(56)* *(57)*

Steric factors also influence the course of the reaction. For example, 7-hydroxy-6-methyllumazine *(58)* normally undergoes *N*-methylation. However, its 1,3-dimethyl derivative *(59)* [33] undergoes exclusively *O*-substitution, leading to the formation of 1,3,6-trimethyl-7-methoxylumazine *(60)*.

Partial methylations of polyhydroxypteridines have shown that steric factors can also induce deviations from the physico-chemically determined sequence of dissociation of the acidic hydrogen atoms. Thus, 6,8-dimethyl-2,4,7-pteridinetrione *(61)* [94] does not yield a 1,6,8-trimethyl derivative, as would be expected from the N-1 > N-3 dissociation sequence but rather the 3,6,8-trimethyl derivative *(62)*.



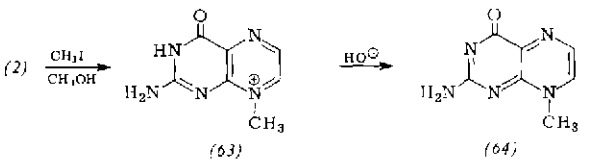
*(58)*, R = $R^1$ = H
*(59)*, R = H, $R^1$ = $CH_3$
*(60)*, R = $R^1$ = $CH_3$

*(61)*, R = H
*(62)*, R = $CH_3$

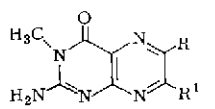
If alkylations are carried out under the conditions normally used for quaternization, *e.g.* with methyl iodide in methanol [101,102] or with dimethyl sulfate in dimethylformamide in the presence of acetic acid [97,99], then the tertiary nitrogen atoms would be expected to react. In the case of pterin *(2)*, transannular methylation occurs at the nitrogen atom in position 8 [101,102]. The methiodide *(63)* can be transformed

[93] *R. Gompper*, Chem. Ber. *93*, 187 (1960).
[94] *W. Pfleiderer*, Chem. Ber. *91*, 1671 (1958).
[95] *W. Pfleiderer* and *M. Rukwied*, Chem. Ber. *94*, 118 (1961).
[96] *R. B. Angier* and *W. V. Curran*, J. org. Chemistry *26*, 2129 (1961).
[97] *R. B. Angier* and *W. V. Curran*, J. org. Chemistry *27*, 892 (1962).
[98] *W. V. Curran* and *R. B. Angier*, J. org. Chemistry *27*, 1366 (1962).
[99] *R. B. Angier* [14].
[100] *N. Kornblum*, *R. A. Smiley*, *R. K. Blackwood*, and *D. C. Iffland*, J. Amer. chem. Soc. *77*, 6269 (1955).
[101] *D. J. Brown* and *N. W. Jacobsen*, Tetrahedron Letters *1960*, 17.
[102] *D. J. Brown* and *N. W. Jacobsen*, J. chem. Soc. (London) *1961*, 4413.

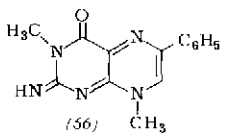
into the free quinonoid compound 8-methylpterin *(64)* by means of alkali. Steric hindrance due to adjacent



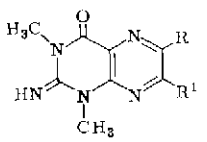
substituents was also observed in the quaternization of hydroxyaminopteridines. Treatment of 3-methyl-6-phenylpterin *(65)* with the system dimethyl sulfate/glacial acetic acid/dimethylformamide yields 63 % of the 3,8-dimethyl derivative *(66)* and only 13 % of the 1,3-dimethyl derivative *(67)*, whereas the same treatment of 3-methyl-7-phenylpterin *(68)* leads to exclusive formation of 1,3-dimethyl-7-phenyl-2-imino-4-oxotetrahydropterin *(69)* [99].



*(65)*, R = $C_6H_5$, $R^1$ = H
*(68)*, R = H, $R^1$ = $C_6H_5$



*(56)*

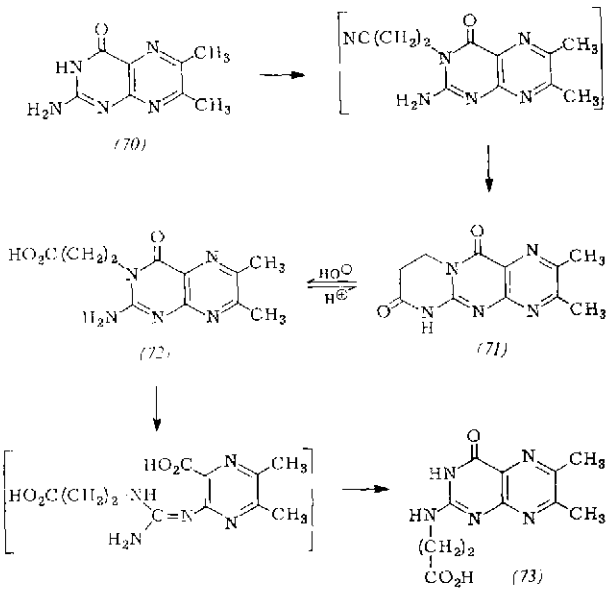


*(67)*, R = $C_6H_5$, $R^1$ = H
*(69)*, R = H, $R^1$ = $C_6H_5$

Alkylations of aminopteridines [102, 103] in the absence of bases lead to similar results, *i.e.* they are quaternized at the nitrogen atoms of the ring and are not substituted at the exocyclic amino groups.

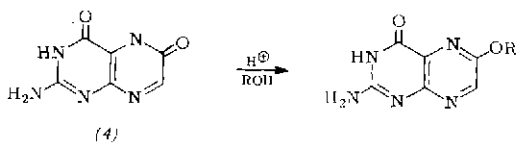
Cyanoethylation of hydroxypteridines with acrylonitrile in pyridine/water provides a parallel to the alkaline alkylations: substitution occurs at the nitrogen atoms of the lactam groups [98, 104]. Moreover, in the presence of suitable *ortho*-substituents, condensed ring systems of higher order may be produced. Thus, 6,7-dimethylpterin *(70)* may be converted into 2,3-dimethyl-7,11-dioxo-6,7,8,9,10,11-hexahydropyrimido[2,1-*b*] pteridine *(71)* [105].

Under mildly alkaline conditions, *(71)* is converted into 3-(β-carboxyethyl)-6,7-dimethylpterin *(72)*, which as an *N*-alkylpteridine can undergo a Dimroth rearrangement to 2-(β-carboxyethyl)amino-6,7-dimethylpterin *(73)*. The latter conversion occurs in hot 1 N sodium hydroxide and is analogous to the reactions of 3-methylpterin [28, 101] and of 3,6,7-trimethylpterin [25]. Dimroth rearrangements are not infrequent among heterocyclic nitrogen compounds [106–108].



*(70)* *(72)* *(71)* *(73)*

The transformation of 6-hydroxypterins such as *(4)*, which have two potentially tautomeric groups in the pyrimidine moiety of the molecule, into 6-alkoxy derivatives with alcohol/$H^+$ is a novel reaction of the pteridine system [109]. This is not an alkylation in the

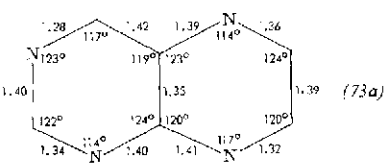


*(4)*

usual sense, but is probably an acid-catalysed addition of the alcohol onto the amide group with subsequent dehydration.

## III. Structural Considerations

Formally, pteridine *(1)* is a 1,3,5,8-tetraaza derivative of naphthalene. Chemically, however, the two compounds have nothing in common, as is readily seen from their greatly differing stabilities to external influences. Because of their electronegative nature, the nitrogen atoms of the ring compete with the π-electrons of the system and partially localize the latter. This interferes with the cyclic resonance and reduces the aromatic stabilization of the compound. X-ray analysis [110] indicated a planar arrangement of the atoms in pteridine. Bond-angle and bond-length measurements [110, 111] have shown that pteridine is not centrally symmetric *(73a)*.



*(73a)*

[103] *D. J. Brown* and *N. W. Jacobsen*, J. chem. Soc. (London) *1960*, 1978.

[104] *W. V. Curran* and *R. B. Angier*, J. org. Chemistry *26*, 2364 (1961).

[105] *R. B. Angier* and *W. V. Curran*, J. Amer. chem. Soc. *81*, 5650 (1959).

[106] *D. J. Brown* [14].

[107] *O. Dimroth*, Liebigs Ann. Chem. *364*, 183 (1909).

[108] *J. Goerdeler* and *W. Roth*, Chem. Ber. *96*, 534 (1963).

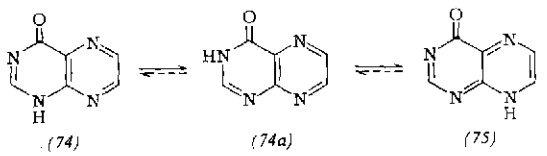
[109] *W. Pfleiderer*, *E. Liedek*, and *M. Rukwied*, Chem. Ber. *95*, 755 (1962).

[110] *T. A. Hamor* and *J. M. Robertson*, J. chem. Soc. (London) *1956*, 3586.

[111] *R. H. Goodwin* and *A. L. Porte*, J. chem. Soc. (London) *1956*, 3595.

## 1. Tautomerism

The possibilities of tautomerism in this series have given rise to structural problems. Detailed studies of the tautomeric relationships existing in the hydroxypteridines [23, 31, 34, 38, 42, 49, 94, 112–114], particularly as the result of ultraviolet spectrophotometric comparisons with the corresponding *O*- and *N*-methyl derivatives, have shown that with only a few exceptions [33, 34, 94], the form favored at equilibrium from an energy point of view is the lactam. This agrees with the situation in most α- and γ-hydroxy nitrogenous heteroaromatics [115]. Inasmuch as all four monohydroxypteridines exist in the form of true cyclic amides *(74a)* and do not have the vinylogous amide structure [*(74)*, *(75)*], as might be possible for valence reasons for the 2-, 4-, and 7-hydroxypteridines, it can be concluded that mesomeric stabilization is greatest in compound *(74a)*. The rare



*(74)* *(74a)* *(75)*

situation where an iminole form predominates in the tautomeric equilibrium is encountered with 1,3-disubstituted and 1-monosubstituted 7-hydroxy-2,4-pteridinediones [33, 94] (Fig. 1) and with 7-hydroxy-2,4-pteridinedione-6-carboxylic acids [34].

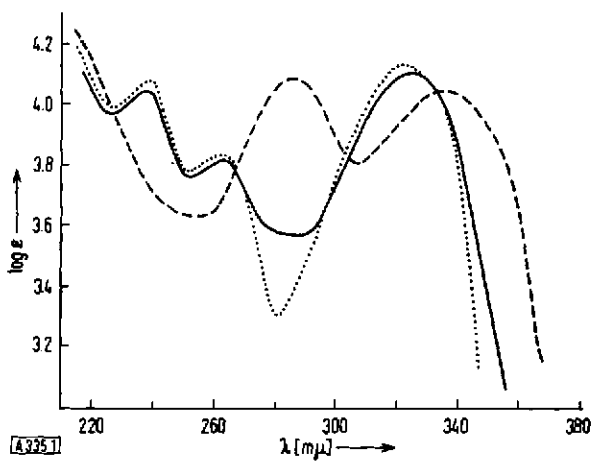



Fig. 1. Ultraviolet spectra of the neutral molecules of 1,3-dimethyl-7-hydroxy-2,4-pteridinedione at pH 1.0 (—), of 1,3-dimethyl-7-methoxy-2,4-pteridinedione at pH 5.0 (. . .) and of 1,3,8-trimethyl-2,4,7-pteridine trione at pH 6.0 (- - -).

The situation is less complicated with the aminopteridines [31, 77, 103]. So far no instance is known where the normal exocyclic amino configuration *(76)* [115] has been displaced by a tautomeric iminodihydro configuration *(77)*. Comparison of the $pK_a$ values is the best method of determining which tautomeric form predominates at equilibrium.



*(76)* *(77)*

Without exceptions, pteridine molecules that have both amino and hydroxy substituents also obey the general rule. Because of energy considerations, the mutual interaction of their potentially tautomeric groups permits the existence of only the amino and lactam configurations. It is these two structural elements which largely determine the physical properties of the natural pterins [28, 35–37, 95, 102].

## 2. Reversible Hydration

Knowledge of the tautomeric configuration does not, however, completely solve the structural problems inherent in some pteridines. Additional factors can complicate the situation, as is indicated, for example, by the C=N hydration [117] first observed with 6-oxodihydropteridine *(37)* [31, 116]. Thus, the curve obtained when compound *(37)* is titrated potentiometrically with alkali is very different from the curve obtained by back-titration with acid (Fig. 2).

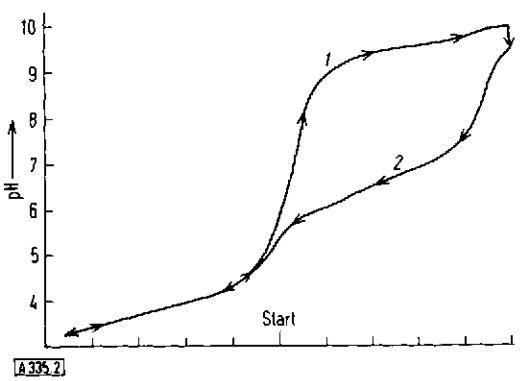
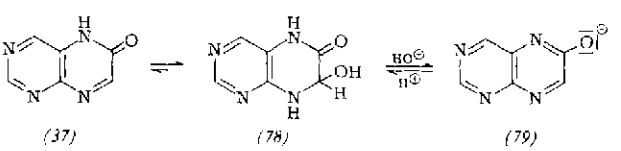



Fig. 2. Titration of 6-oxodihydropteridine with alkali (Curve 1) and back-titration with acid (Curve 2).

The $pK_a$ values of 9.7 and 6.7 derived from these two curves do not indicate cleavage of the ring nor tautomerism but rather that the neutral form of *(37)* is a hydrate *(78)* with covalently bound water, whereas the anionic form *(79)* tends to be anhydrous [78].



*(37)* *(78)* *(79)*

Ultraviolet and infrared spectroscopy and mild oxidation to 6,7-dioxotetrahydropteridine fixed the position of the water added [111]. Another means of determining the point at which the water is added is to carry out comparisons between the potentiometric and ultraviolet spectrophotometric meas-

[112] *D. J. Brown* and *S. F. Mason*, J. chem. Soc. (London) *1956*, 3443.

[113] *W. Pfleiderer*, Chem. Ber. *90*, 2631 (1957).

[114] *E. Lippert* and *H. Prigge*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 662 (1960).

[115] *A. Albert*, *R. Goldacre*, and *J. Phillips*, J. chem. Soc. (London) *1948*, 2240; *A. Albert* and *J. N. Phillips*, ibid. *1956*, 1294; *S. F. Mason*, ibid. *1957*, 4874, 5010; *1958*, 674; *A. Albert:* Heterocyclic Chemistry. The Athlone Press, London 1959, p. 52.

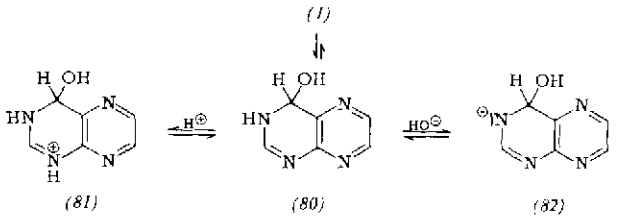
[116] *A. Albert* in: Ciba Foundation Symposium on Chemistry and Biology of Pteridines. Churchill, London 1954.

[117] *A. Albert* [14].

urements made on the basic compounds and on their corresponding C-methyl derivatives [88, 118]. For mainly steric reasons, the methyl groups in these compounds prevent hydration of the adjacent double bond. Considering that the covalent hydrates constitute dihydro derivatives of the anhydrous form, the differences in the ultraviolet absorption and in the acidic and basic strengths of the two series can be readily understood.

The reversible covalent hydration is not restricted to neutral molecules and to the 7,8-positions of 6-hydroxypteridines [119, 120]. It also occurs outside the pteridine series [116, 121–125], mostly with strongly polar, nonsubstituted C=N double bonds. Both the neutral molecule of 2-hydroxypteridine and the cation of 2-aminopteridine add on water in the 3,4-positions and thereby behave like pteridine *(1)* [126].

In aqueous solution, pteridine *(1)* is in equlibrium with its 4-hydroxy-3,4-dihydro form *(80)* which remains present in both acid and alkaline media as the anion *(81)* or cation *(82)*, respectively. This fact helps to explain the relatively high basic $pK_a$ value of pteridine and the existence of an anion.



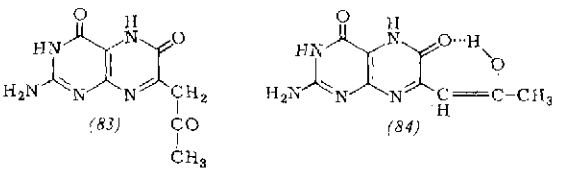
*(1)*

*(81)* *(80)* *(82)*

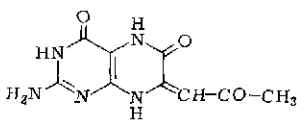
### 3. Results from Physicochemical Studies

Polarographic studies [127–133] have also yielded valuable information on the pteridines. Because two-electronic potential steps normally occur, it is possible to recognize corresponding configurational characteristics of different molecules by means of their half-wave potentials. The relationships between the half-wave potentials of reduction, the dissociation constants, and the wave number of the second $\pi \rightarrow \pi$-transition band of the ultraviolet absorption, in conjunction with the additivity of the polarographically obtained substituent-dependent structural increments, allow preliminary evaluation of the relationships between polarographic reducibility and structure [131].

Proton resonance spectroscopy is another method for clarifying structural questions [134]. The spectra are mostly simple and can be simplified even further by deuteration. Thus, it was found that only structure *(85)* can correctly describe 7-acetonylxanthopterin *(83)*. This compound cannot possess a $CH_2$ group and it cannot exist in a tautomeric enolic form *(84)*.



*(83)* *(84)*

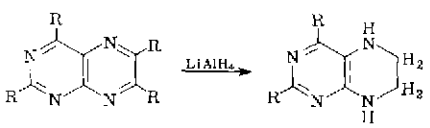


*(85)*

## IV. Hydrogenated Pteridines

### 1. 5,6,7,8-Tetrahydro Derivatives

Only very recently, after the discovery of naturally occurring dihydro- and tetrahydropteridines, have hydrogenated pteridines assumed the importance that should be their due. The chemical and physical properties of these compounds can best be understood by considering 5,6,7,8-tetrahydropteridine *(86)*. The fact



*(1)*, R = H
*(87)*, R = Cl

*(86)*, R = H
*(88)*, R = Cl

that *(86)* can be produced either by reduction of *(1)* with $LiAlH_4$ or by stepwise reductive dehalogenation of 2,4,6,7-tetrachloropteridine *(87)* via 2,4-dichloro-5,6,7,8-tetrahydropteridine *(88)* [82] is in accordance with the behavior of the two diazines which make up the pteridine system, for pyrazines are reduced relatively easily [135], whereas pyrimidines are very difficult to hydrogenate, particularly in an alkaline medium [136, 137].

In contrast to pteridine *(1)*, which is unstable, the tetrahydro compound *(86)* is quite stable to boiling

[118] *A. Albert, C. F. Howell,* and *E. Spinner,* J. chem. Soc. (London) *1962*, 2595.

[119] *D. D. Perrin* and *Y. Inoue,* Proc. chem. Soc. (London) *1960*, 342.

[120] *Y. Inoue* and *D. D. Perrin,* J. chem. Soc. (London) *1962*, 2600.

[121] *A. Albert, W. L. F. Armarego,* and *E. Spinner,* J. chem. Soc. (London) *1961*, 2689.

[122] *A. Albert, W. L. F. Armarego,* and *E. Spinner,* J. chem. Soc. (London) *1961*, 5267.

[123] *W. L. F. Armarego,* J. chem. Soc. (London) *1962*, 561.

[124] *W. L. F. Armarego,* J. chem. Soc. (London) *1962*, 4094.

[125] *W. L. F. Armarego,* J. chem. Soc. (London) *1962*, 5030.

[126] *D. D. Perrin,* J. chem. Soc. (London) *1962*, 645.

[127] *Y. Ashahi,* J. pharmac. Soc. Japan *79*, 1548, 1554, 1559, 1565, 1570, 1574 (1959).

[128] *J. Komenda,* Collect. czechoslov. chem. Commun. *24*, 903 (1959).

[129] *J. Komenda, L. Kisova,* and *J. Koudelka,* Collect. czechoslov. chem. Commun. *25*, 1020 (1960).

[130] *J. Komenda* and *D. Laskafeld,* Collect. czechoslov. chem. Commun. *27*, 199 (1962).

[131] *J. Komenda,* Collect. czechoslov. chem. Commun. *27*, 212 (1962).

[132] *J. Komenda* [14].

[133] *H. Rembold* [14].

[134] *W. v. Philipsborn* [14].

[135] *I. J. Krems* and *P. E. Spoerri,* Chem. Reviews *40*, 279 (1947).

[136] *B. Lythgoe* and *L. S. Rayner,* J. chem. Soc. (London) *1951*, 2323.

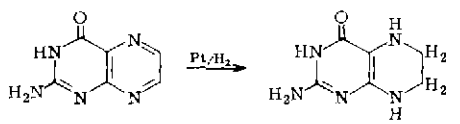
[137] *E. B. Brown* and *T. B. Johnson,* J. Amer. chem. Soc. *45*, 2702 (1923).

1 N HCl or 1 N NaOH; it also appears to be stable to light. So far, all attempts to reoxidize *(86)* to *(1)* have failed. The transition of the pteridine system to the 4,5-disubstituted pyrimidine derivative which occurs on reduction of the pyrazine ring must therefore effect an increase in heteroaromaticity - with the result that reoxidation of compound *(86)* to *(1)* can be achieved only under drastic conditions. These would lead in turn to further conversions of the oxidation product, so that *(1)* cannot be isolated.

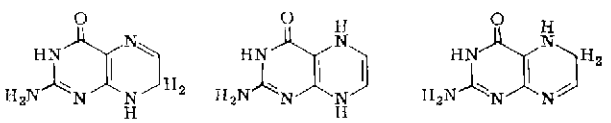
If first-order substitutents are introduced in sequence into the 2- and 4-positions of dihydro- and tetrahydropteridines, the extreme stability of compound *(86)* gives way to sensitivity to oxidation which increase with any increase in the electron donor properties of the substituents.

Although the alkyl derivatives of 5,6,7,8-tetrahydropteridine are stable [138–141] and the 2- or 4-monosubstituted hydroxy and amino derivatives of dihydro- and tetrahydropteridines can be isolated [138, 139, 142, 143] and are stable as solids, 2,4-disubstituted 5,6,7,8-tetrahydropteridines [82, 143, 144, 145] undergo rapid autoxidation because of their potentially tautomeric groups.

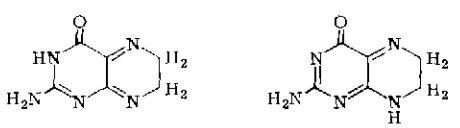
If 5,6,7,8-tetrahydropterin *(89)*, which is obtained from *(2)* by catalytic reduction, is oxidized by air, three of the five theoretically possible dihydropterins *(90)–(94)* seem to be formed; however, so far only the structures of 7,8-dihydropterin *(90)* [146] and its 6-methyl derivative [147, 148] have been established.




*(2)* *(89)*



*(90)* *(91)* *(92)*



*(93)* *(94)*

[138] *J. H. Lister* and *G. R. Ramage*, J. chem. Soc. (London) *1953*, 2234.

[139] *J. H. Lister*, *G. R. Ramage*, and *F. Coates*, J. chem. Soc. (London) *1954*, 4109.

[140] *P. R. Brook* and *G. R. Ramage*, J. chem. Soc. (London) *1955*, 896.

[141] *P. R. Brook* and *G. R. Ramage*, J. chem. Soc. (London) *1957*, 1.

[142] *A. Albert* and *S. Matsuura*, J. chem. Soc. (London) *1961*, 5131.

[143] *A. Albert* and *S. Matsuura*, J. chem. Soc. (London) *1962*, 2162.

[144] *M. Visconti* and *H. R. Weilenmann*, Helv. chim. Acta *41*, 2170 (1958).

[145] *M. Visconti* and *H. R. Weilenmann*, Helv. chim. Acta *42*, 1854 (1959).

[146] *H. C. S. Wood* [14].

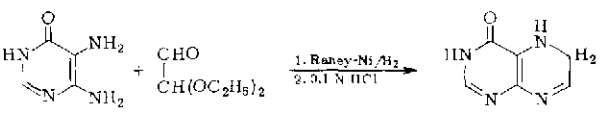
[147] *W. R. Boon* and *T. Leigh*, J. chem. Soc. (London) *1951*, 1497.

[148] *W. Pfleiderer* and *H. Zondler*, unpublished work.

*Important contributions to the unsolved problems of the* hydrogenated pteridines are provided by systematic investigations of the reduction of mono- and polyhydroxypteridines [142] with potassium borohydride, sodium dithionate, potassium or sodium amalgam, or with hydrogen and Pt, Pd, or Raney-nickel catalysts.

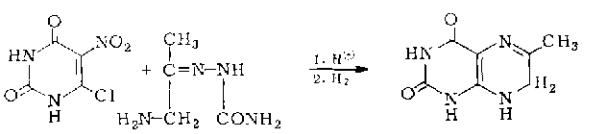
## 2. Direct Synthesis of Hydrogenated Pteridines

The first direct synthesis of 5,6-dihydropteridines *(95)* was accomplished by reductive condensation of glyoxal monoacetal with 4,5-diaminopyrimidine [142]. The 7,8-dihydropteridine *(96)* can be obtained most readily via




*(95)*

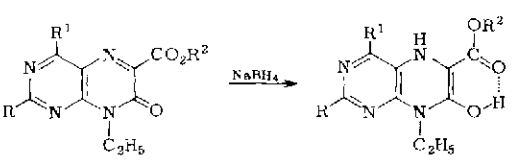
the Boon synthesis [20, 142, 146, 147, 149–151], applied to either 4-chloro-5-nitropyrimidines or 4-chloro-5-benzazopyrimidines and α-amino esters, α-amino ketones, or α-amino aldehydes.




*(96)*

## 3. Reduction with Boron Hydrides

Reduction of 8-substituted 7-pteridone-6-carboxylic acid derivatives with sodium borohydride [48, 152] led to a surprising result: when position 4 is either free or bears an alkyl substituent, stable dihydropteridines result, whose ultraviolet absorption bands in the long-wave region exhibit a pronounced bathochromic shift. Since 5,6-dihydro- and 5,6,7,8-tetrahydropteridines behave spectroscopically in the same way as the corresponding 4,5-diaminopyrimidine derivatives, it was apparent that a novel chromophoric pteridine system had been obtained. A 5,8-dihydro structure *(97)* was proposed for this compound and was found to conform with all the pertinent chemical and physical findings.




R = OH, $NH_2$, $NHC_2H_5$, $N(CH_3)_2$
$R^1$ = H, $CH_3$
$R^2$ = H, $CH_3$, $C_2H_5$

*(97)*

[149] Brit. Pat. 677342 (1952), inventors: *W. R. Boon* and *T. Leigh*.

[150] *W. R. Boon* and *W. G. Janes*, J. chem. Soc. (London) *1951*, 591.

[151] *T. Neilson* and *H. C. S. Wood*, J. chem. Soc. (London) *1962*, 44.

[152] *E. C. Taylor* [14].

Both the formation and stability of compound *(97)* can be explained by the added stability conferred upon it by intramolecular hydrogen bonding.

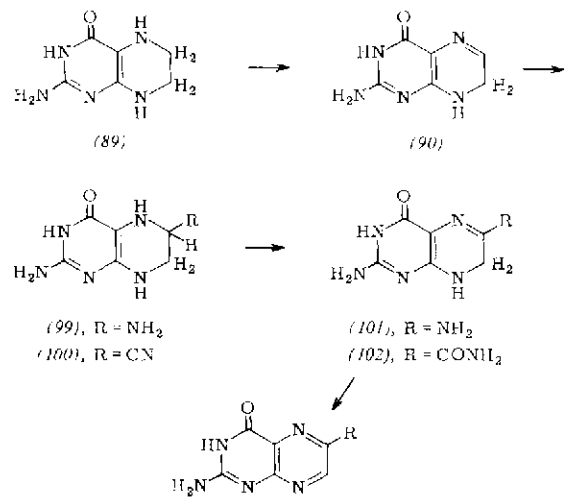
The reduction of 2-hydroxypteridine *(41)* to 3,4-dihydro-2-hydroxypteridine *(98)* [142] in alkaline medium was the first example showing that the pyrimidine ring can be reduced before the pyrazine ring is attacked.



*(41)* *(98)*

### 4. Derivatives of 7,8-Dihydropterin

Partially hydrogenated pteridines are chemically interesting and may be of biochemical significance [146, 153]. Reoxidation of 5,6,7,8-tetrahydropterin *(89)* in the presence of nucleophilic agents gives rise to 6-substituted pterins *(103)* [145, 146, 154–156]. This reaction probably proceeds via the 7,8-dihydropterin *(90)* [146] as an intermediate, since the latter is the most electrophilic compound.



*(89)* *(90)*

*(99)*, R = $NH_2$
*(100)*, R = CN

*(101)*, R = $NH_2$
*(102)*, R = $CONH_2$

*(103)*, R = $NH_2$, $CONH_2$, OH, $SO_3H$, SR'

This reaction sequence is confirmed, on the one hand, by the ready addition of ammonia onto *(90)* to form 6-amino-5,6,7,8-tetrahydropterin *(99)* and the oxidation of the latter via 6-amino-7,8-dihydropterin *(101)* to 6-aminopterin [*(103)* R – $NH_2$], and on the other, by the reaction of *(89)* [155] or of *(90)* [146] with KCN in the presence of oxidants. It was previously assumed that 5,8-dihydropterin-6-carboxamide was formed via *(100)* in the latter reaction; however, actually it is the relatively stable 7,8-dihydro derivate *(102)* that is formed [157]. Analogous additions of bisulfite [145], hydroxyl ions [156], thiols [146], and carbanions [146], as well as the oxidative conversion of the products into the corresponding 6-substituted pterins [*(103)*; R = $SO_3H$, OH, or SR] all serve to underline the general nature of this reaction.

### V. Naturally Occurring Pteridines

The widespread interest in the pteridines, which dates from the fundamental studies of *H. Wieland*, *C. Schöpf*, and *R. Purrmann*, is undoubtedly due to their widespread occurrence in both the animal and plant kingdoms. Naturally occurring pteridines can be recognized directly as pigments in the wings of insects, and in the eyes and skin of fish, amphibia, and reptiles [158]. Moreover, they usually possess a very characteristic fluorescence with allows them to be readily seen and identified. Consequently, it is not surprising that the number of pteridine compounds known has increased by leaps and bounds in recent years. However, it has been possible to determine the structures of only some of these newly described compounds. Although refined analytical and chromatographic techniques have simplified the isolation and purification of the pteridines enormously, potentially productive studies are limited by the small quantities of material normally available. It must therefore be considered fortunate that the three best-known butterfly pigments, *viz.* leucopterin *(31)*, xanthopterin *(4)*, and isoxanthopterin *(5)*, occur in relatively large concentrations in the wings of these insects. Hence, no better starting material could be found for the initial studies on the isolation and structure of the natural pteridines.

A great many other natural materials studied so far as potential sources of pteridines, including the skin of *Rana nigromaculata* frogs [159], of green snakes [160], of the fire salamander [161], or of various ornamental (tropical) fish [162], the larvae and eggs of the silkworm *Bombyx mori* [159, 163, 164], fruit-flies *Drosophila* [165, 166], the scales of Japanese carp [167], human urine [168], red ants [169], the flour moth *Ephestia kühniella* [170], various genotypes of *Plodia interpunctella* [171], and the heads and eyes of various *Lepidoptera* species [172], contain isoxanthopterin *(5)* in

[153] *H. S. Forrest* [14].

[154] *C. van Baalen* and *H. S. Forrest*, J. Amer. chem. Soc. *81*, 1770 (1959).

[155] *H. S. Forrest*, *C. van Baalen*, *M. Viscontini*, and *M. Piraux*, Helv. chim. Acta *43*, 1005 (1960).

[156] *M. Viscontini* and *M. Piraux*, Helv. chim. Acta *45*, 615 (1962).

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[159] *S. Nawa*, *M. Goto*, *S. Matsuura*, *H. Kakizawa*, and *Y. Hirata*, J. Biochemistry (Tokyo) *41*, 657 (1954).

[160] *J. A. Blair* and *J. Graham*, Chem. and Ind. *1955*, 1158.

[161] *Th. Kauffmann* and *K. Vogt*, Chem. Ber. *92*, 2855 (1959).

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[163] *S. Nawa* and *T. Taira*, Proc. Imp. Acad. (Tokyo) *30*, 632 (1954).

[164] *R. Tschesche* and *F. Korte*, Chem. Ber. *87*, 1713 (1954).

[165] *M. Viscontini*, *M. Schoeller*, *E. Loeser*, *P. Karrer*, and *E. Hadorn*, Helv. chim. Acta *38*, 397 (1955).

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[168] *J. A. Blair*, Biochem. J. *68*, 385 (1958).

[169] *G. H. Schmidt* and *M. Viscontini*, Helv. chim. Acta *45*, 1571 (1962).

[170] *M. Viscontini*, *A. Kühn*, and *A. Egelhaaf*, Z. Naturforsch. *11b*, 501 (1956).

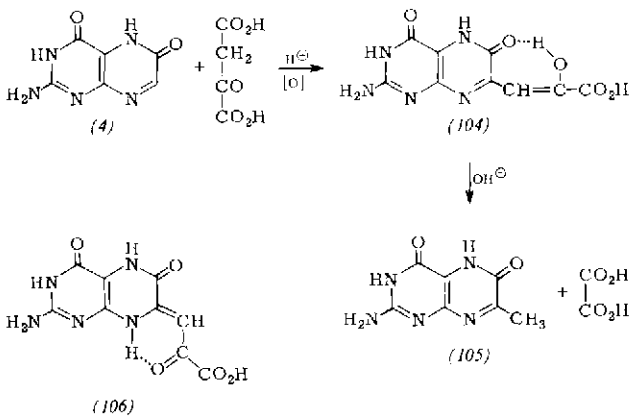
[171] *E. Möhlmann*, Z. Vererbungslehre *89*, 651 (1958); *F. F. de Almeida*, Z. Naturforsch. *13b*, 687 (1958); *A. Kühn* and *F. F. de Almeida*, Z. Vererbungslehre *92*, 126 (1961).

[172] *U. Grossbach*, Z. Naturforsch. *12b*, 462 (1957).

only small concentrations and only extremely minute quantities of the less common compound xanthopterin [171, 170, 172].

### 1. Erythropterin, Pterorhodin, Ekapterin, and Lepidopterin

Because the concentrations of erythropterin *(104)* that occur in the South American butterfly *Catopsilia argante* are relatively large, it has been possible to isolate this orange-red wing pigment first described by *Schöpf* and *Becker* [173] in pure form and to determine its structure [174]. Alkaline degradation to 7-methylxanthopterin *(105)* and oxalic acid served to confirm the existence of the pyruvate side chain which, in view of the optical behavior of the compound, is likely to exist in a tautomeric form, most probably the enol. Proton resonance spectra confirmed the absence of a $CH_2$ group and led to the proposal of formula *(106)* [134].

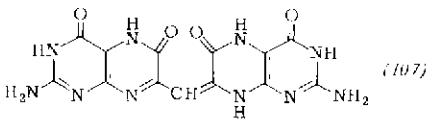


The synthesis of erythropterin *(104)* from xanthopterin *(4)* and oxaloacetic [175] or pyruvic acid [176, 177] makes use of the ability of the $\Delta^7$-double bond to add on nucleophilic agents.

It is very likely that compound *(104)* occurs in tubercle bacilli [179]; its occurrence in *Ephestia kühniella* Zeller [176, 178] and in *Pyrrhocoris apterus* L. [180] has been verified by chemical isolation.

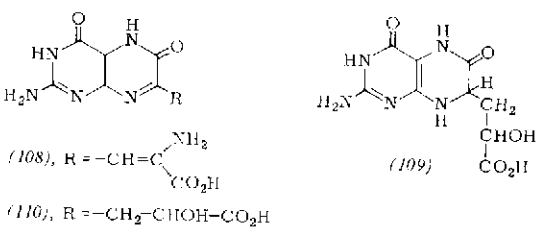
Chrysopterin [181], which has been identified as a 7-methylxanthopterin *(106)*, is not a naturally occurring wing pigment, but must be considered as a product of hydrolysis of the erythropterin localized in the discoidal spot of the brimstone butterfly *Gonepteryx rhamni* [182].

Pterorhodin *(107)* is a newly isolated natural pigment found in butterfly wings [183]. In conjunction with erythropterin, it causes the intense red color of the wings of *Appias nero*, a pierid native to the islands of Java and Ceylon. Comparisons with synthetic materials [185–187] have shown that the red pigment found in the eyes of *Ephestia* and *Ptychopoda* [184] is also pterorhodin.



*(107)*

Knowledge of the true structure of erythropterin has helped in understanding the structure of ekapterin *(110)* and lepidopterin *(108)* [176–178]. As both of these pterins occur together with erythropterin in *Ephestia kühniella*, a structural relationship appeared likely. The conversion of *(104)* into *(108)* with $NH_3$, as well as its reduction to tetrahydroerythropterin *(109)* and the oxidation of the latter to *(110)* can be considered as evidence for the proposed structures.



*(108)*, R = $-CH=C(NH_2)-CO_2H$

*(110)*, R = $-CH_2-CHOH-CO_2H$

*(109)*

### 2. Biopterin and Ichthyopterin

A widely occurring natural pterin that was first isolated from human urine by *Patterson* et al. [188] and designated as biopterin has also been isolated from the fruit-fly *Drosophila melanogaster* [165, 189–191], from the crayfish *Astacus fluviatilis* [192], from the Mediterranian flour moth *Ephestia kühniella* [170], and from the royal jelly of the bee [193]. It also occurs in amphibia


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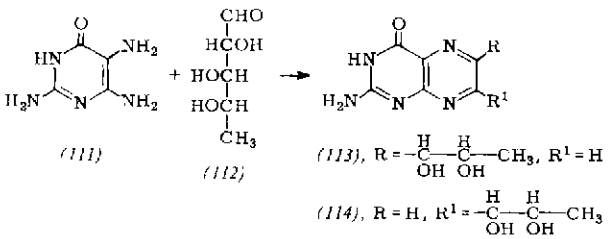
[190] *M. Viscontini*, *E. Loeser*, *P. Karrer*, and *E. Hadorn*, Helv. chim. Acta *38*, 1222 (1955).

[191] *M. Viscontini*, *E. Loeser*, *P. Karrer*, and *E. Hadorn*, Helv. chim. Acta *38*, 2034 (1955).

[192] *M. Viscontini*, *H. Schmid*, and *E. Hadorn*, Experientia *11*, 390 (1955).

[193] *A. Butenandt* and *H. Rembold*, Hoppe-Seylers Z. physiol. Chem. *311*, 79 (1958).

[194–196], in fish [197], and in red ants [169]. Synthesis confirmed that the structure of biopterin *(113)* is 6-(L-*erythro*-1′,2′-dihydroxypropyl)pterin [198].



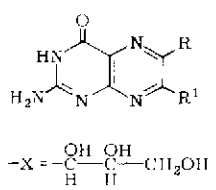
*(111)* *(112)*

*(113)*, R = $-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-CH_3$, $R^1 = H$

*(114)*, R = H, $R^1 = -\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-CH_3$

When 2,4,5-triamino-6-oxodihydropyrimidine *(111)* is condensed with rhamnotetrose *(112)*, the product is always a mixture of two isomers, *(113)* and *(114)* [133, 193, 198, 199, 201, 202]. The isomer ratio is largely independent of the conditions of the reaction [200] and is practically unaffected by addition of hydrazine [205], boric acid [198], or *p*-toluidine [206], all of which induce formation of the 6-isomers from hexoses but do not affect the corresponding reaction with pentoses [203, 204]. Partition chromatography on either silica gel [200, 201] or cellulose phosphate [202] has been used recently to isolate and purify the 15–30 % of biopterin present in the mixture.

It took a chromatographic study of the reactions [44] to show just how complex the condensation of compound *(111)* with carbohydrates really is. Although the reaction of *(111)* with 1-deoxy-1-(*p*-toluidino)-D-fructose *(115)* in the presence of hydrazine leads to the formation of a single compound, *viz.* 6-(D-*arabo*-tetrahydroxybutyl)pterin *(116)* [204], as many as six pterins [*(116)*–*(121)*] may be formed simultaneously under other conditions [44].



*(116)*, R = $-\underset{OH}{\overset{H}{C}}-X$, $R^1 = H$

*(117)*, R = H, $R^1 = -\underset{OH}{\overset{H}{C}}-X$

*(118)*, R = $-CH_2-X$, $R^1 = H$

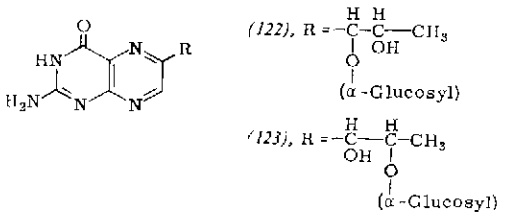
*(119)*, R = H, $R^1 = -CH_2-X$

*(120)*, R = X, $R^1 = CH_3$

*(121)*, R = $CH_3$, $R^1 = -X$

Biopterin differs from most of the other known simple pteridine derivatives by virtue of its biochemical activity. It stimulates growth in the flagellate *Crithidia fasciculata* [188, 207] and probably plays an important role in the process determining the transformation of a bee larva into a queen [133, 208–210]. Details of the special functions of biopterin are still unknown. The mere need of biopterin exhibited by *C. fasciculata* [211] and bee larvae does not indicate in what form the compound is found in the cell. Biopterin is not noticeably transformed to other fluorescent pterins in the process of selection of the queen bee [212]; it may therefore be assumed that biopterin itself is not the metabolically active form. It presumably acts as a cofactor in hydrogen transfers via the system tetrahydrobiopterin ⇌ dihydrobiopterin.

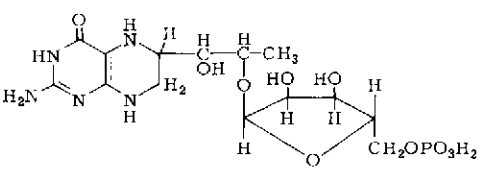
This hypothesis is supported by the fact that a derivative of tetrahydrobiopterin [213, 214] occurs as an extremely photosensitive compound in the eyes and skin of insects, in the skin of amphibia and fish [215 to 217], and in all likelihood also in algae [218]. An α-glucoside of biopterin has been isolated from the blue-green alga *Anacystis nidulans* [219]. Its structure is either *(122)* or *(123)*. Moreover, analogous biopterin glycosides, which differ in the carbohydrate moiety of the molecule, have also been isolated from blue-green algae [220]. Both of these observations may perhaps be



*(122)*, R = $-\underset{OH}{\overset{H}{C}}-\underset{O}{\overset{H}{C}}-CH_3$ (α-Glucosyl)

*(123)*, R = $-\underset{OH}{\overset{H}{C}}-\underset{O}{\overset{H}{C}}-CH_3$ (α-Glucosyl)

interpreted as indications of the structure of active biopterin. If it is true, as has been alleged [213], that ribose and phosphoric acid are linked to the photolabile tetrahydrobiopterin derivative, then a structure like that of compound *(124)* appears possible.



*(124)*

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[210] *H. Rembold*, Umschau Wiss. Techn. *17*, 488, 524 (1961).

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[212] *H. Rembold* and *G. Hanser*, Hoppe-Seylers Z. physiol. Chem. *319*, 213 (1960).

[213] *I. Ziegler*, Z. Naturforsch. *15b*, 460 (1960).

[214] *I. Ziegler* [14].

[215] *H. Ziegler* and *I. Ziegler*, Z. Naturforsch. *10b*, 642 (1955).

[216] *I. Ziegler-Gründer*, Z. Naturforsch. *11b*, 493 (1956).

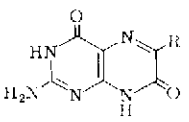
[217] *T. Hama* [14].

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From a chemical point of view, biopterin *(113)* closely resembles ichthyopterin *(126)* [221], a compound first isolated in 1943 as the principal pigment of the blue-violet fluorescent materials found in the skin of *Cyprinidae* (carp). It occurs widely in the skin of whitefish [158,197,222–224] and ornamental tropical fish [162].



*(125)*, R = $-CH_2-CO-CH_3$
*(126)*, R = $-CHOH-CHOH-CH_3$

The structure of ichthyopterin was determined by its synthesis [225] from 6-acetonylisoxanthopterin *(125)*, the acetonyl grouping being converted into the 1′,2′-dihydroxypropyl side chain. Although it has proved possible to confirm the identity of the synthetic and natural compound by chromatography and ultraviolet spectroscopy [226], the absolute configuration of the side chain remains unknown. Until the hypothetical L-*erythro*-configuration of the side chain is confirmed, it would be best to speak of ichthyopterin as 6-(1′,2′-dihydroxypropyl)isoxanthopterin, rather than to designate it as 7-hydroxybiopterin.

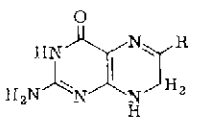
### 3. Drosophila Pterins (Sepia-, Isosepia-, Droso-, Isodroso-, and Neodrosopterin)

The yellow to red pterins from the fruit-fly *Drosophila melanogaster* constitute another important group of natural pteridine derivatives. They represent some of the fluorescent materials which *Hadorn* et al. used to study the effects of genes in *Drosophila* [227] and *Ephestia* [228]. It was possible to show by means of chromatography that the *Drosophila* pterins consist of the yellow compounds sepiapterin [229] and isosepiapterin [230], as well as of the orange to red compounds drosopterin, isodrosopterin, and neodrosopterin [231–233]. A number of papers describing their distribution in nature have been published [234–242].

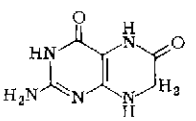
Sepiapterin *(127)* was isolated in the form of yellow crystals from *D. melanogaster*, whose *sepia* mutant accumulates it in large concentrations [243]. This pigment is occasionally designated as "yellow pterin" and is also found in amphibian skin [195,196,216,217,244 to 246], in fish [217,247–249], and in the epidermis of the *lem* mutant of the silk moth *Bombyx mori* [163]. The structure of sepiapterin *(127)* was determined by analysis of the products of its oxidative degradation, *viz.* 7,8-dihydroxanthopterin *(128)* and lactic acid. Under mild degradation conditions, the products were 7,8-dihydropterin-6-carboxylic acid *(129)* and acetaldehyde [250].

Because of this clear-cut chemical proof, previously proposed structures [230,232,233,243,251–253] must be abandoned in favor of that of 6-lactoyl-7,8-dihydropterin *(127)*. Additional confirmation of this structure comes from the close structural relationship between sepiapterin and isosepiapterin; NMR studies [254] confirmed the 7,8-dihydro structure of isosepiapterin *(130)*.

From a biochemical point of view, sepiapterin *(127)* may serve as the dihydro component in the hydrogen transfer system tetrahydrobiopterin ⇌ sepiapterin [213,214,217,255]. This hypothesis derives some support from the growth-promoting activity of compound *(127)* observed for *Crithidia fasiculata* [256,257].



*(127)*, R = $-CO-CHOH-CH_3$
*(129)*, R = $-COOH$

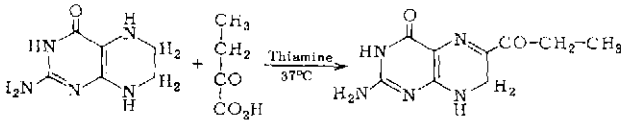


*(128)*

The other yellow fluorescent component, isosepiapterin *(130)*, was also isolated in crystalline form for the first time from the *sepia* mutant of *Drosophila* [230]. At first, structural studies were not very successful and merely indicated a partially hydrogenated pteridine


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[230] *M. Viscontini* and *E. Möhlmann*, Helv. chim. Acta *42*, 836 (1959).
[231] *M. Viscontini*, *E. Hadorn*, and *P. Karrer*, Helv. chim. Acta *40*, 579 (1957).
[232] *M. Viscontini*, Ind. chim. belge *10*, 1181 (1960).
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[234] *B. De Lerma* and *M. DeVincentiis*, Boll. Zool. *22*, 1 (1955).
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[241] *E. Hadorn*: Proceedings Xth International Congress of Genetics, Montreal 1959. University of Toronto Press, Vol. I, p. 337.
[242] *E. Hadorn*, Sci. American *1962*, 101.
[243] *H. S. Forrest* and *H. K. Mitchell*, J. Amer. chem. Soc. *76*, 5656, 5658 (1954).
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[245] *I. Ziegler-Günder*, Experientia *15*, 429 (1959).
[246] *I. Ziegler*, Biochem. Z. *334*, 425 (1961).
[247] *J. Matsumoto*, *T. Kajishima*, and *T. Hama*, Genetics *45*, 1177 (1960).
[248] *T. Hama*, *J. Matsumoto*, and *M. Obika*, Proc. Imp. Acad. (Tokyo) *36*, 217 (1960).
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[250] *S. Nawa*, Bull. chem. Soc. Japan *33*, 1555 (1960).
[251] *M. Viscontini* and *H. Möhlmann*, Helv. chim. Acta *42*, 1679 (1959).
[252] *H. S. Forrest*, *D. Hatfield*, and *C. van Baalen*, Nature (London) *183*, 1269 (1959).
[253] *H. S. Forrest*: XVIIth IUPAC Congress, Munich 1959. Verlag Chemie, Weinheim 1960, Vol. 2, p. 40.
[254] *H. S. Forrest* and *S. Nawa*, Nature (London) *196*, 372 (1962).
[255] *I. Ziegler*, Advances in Genetics *10*, 349 (1961).
[256] *I. Ziegler* and *H. A. Nathan*, Z. Naturforsch. *16b*, 260 (1961).
[257] *H. A. Nathan* and *I. Ziegler*, Z. Naturforsch. *16b*, 262 (1961).

derivative with a $C_3$ side chain at position 6 [230,251]. These studies were advanced considerably when somewhat larger concentrations of isosepiapterin were found in the blue-green alga *Anacystis nidulans* [258], thus permitting chemical degradation and transformation studies. However, unequivocal proof that isosepiapterin has the structure of 6-propionyl-7,8-dihydropterin *(130)* came only recently with the aid of NMR spectroscopy [254]. Isosepiapterin and sepiapterin exhibit similar




*(89)* *(130)*

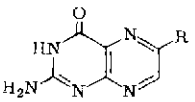
optical behavior. This can be considered as an additional argument for structural similarity between the two. The first synthesis of isosepiapterin was achieved starting from 5,6,7,8-tetrahydropterin *(89)*, α-ketobutyric acid, and thiamine [153,259]; this synthesis is of both chemical and biocbemical interest, as it may be the biosynthetic pathway for the formation of *Drosophila* pterins [153].

*Viscontini* [231] was the first to separate the water-soluble red eye-pigments of *Drosophila* [260] into drosopterin, isodrosopterin, and neodrosopterin. Structural studies [251,261,262], which were largely based on oxidative degradation and on reduction and reoxidation reactions, led to the suggestion that by analogy to sepiapterin and isosepiapterin, the three red pigments, also had a dihydropterin structure with a $C_3$ side chain at position 6. However, all of the structural formulae proposed so far [232,233,251,263] are not very convincing, since they fail to explain the characteristic absorption in the 475--505 mμ region of the spectrum.

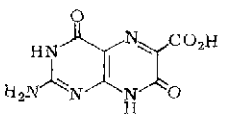
Consideration of the optical behavior of these compounds, in conjunction with the small $R_F$ values they exhibit in the usual solvents, suggests that the red pigments may not be simple pteridines, but rather dipteridyl derivatives. It is conceivable that these highly colored compounds constitute a new class of natural pigments, since they occur in the eyes of certain *Drosophila* mutants, in the skin of some fish [162,217] and amphibia [217], as well as in the skin folds of various reptiles [264].

### 4. Other Natural and Synthetic Pteridines

Pterin *(2)* itself occurs widely as a natural pteridine derivative [160,165,166,168–171,192,195]. From a biosynthetic viewpoint, it is a precursor of isoxanthopterin *(5)* and therefore usually occurs in association with it. Pterin-6-carboxylic acid *(131)* [160,165,166,195] is more likely to be an artefact than a natural product, as it can very readily be formed from 6-substituted pterins by photolytic and oxidative degradation.



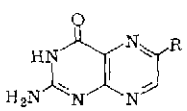
*(131)*, R = COOH
*(132)*, R = $NH_2$



*(133)*

The 6-aminopterin [54] isolated from *D. melanogaster* and from the algae *Anacystis nidulans* and *Nostoc muscorum* G. is also very probably an artefact. Its formation can be explained by assuming an addition of ammonia onto a 7,8-dihydropterin derivative with subsequent oxidation. Isoxanthopterincarboxylic acid *(133)* is a natural fish pterin and was first isolated from the scales of the Japanese carp [167].

Further indications of the widespread and diverse occurrence of the natural pterin derivatives came from the identification of hydroxymethylpterin *(134)* [220], which occurs as a glucose compound in the alga *Synchocystis*, of 6-(1′,2′,3′-trihydroxypropyl)pterin *(135)*, which has frequently been described as "bufochrome" [217] and which may be identical with the neopterin found in bee pupae [265], and finally of 6-(1′,2′,3′-trihydroxypropyl)pterin-3′-phosphate *(136)* [266] from *Escherichia coli*.



*(134)*, R = $-CH_2OH$
*(135)*, R = $-(CHOH)_2-CH_2OH$
*(136)*, R = $-(CHOH)_2-CH_2O[PO_3H_2]$

The constitution of urothione, the yellow urine pigment containing sulfur, is unknown. Attempts to solve the problem by synthesis [267–271] have failed to clarify the picture.

New aspects of pteridine chemistry have come from the work of *Masuda*, who isolated two new pteridine derivatives [*(137)* and *(138)*] from *Eremothecium ashbyii* [272,273]; later, these were also reported to occur in *Ashbya gossypii* [274,275]. Structural studies [276,277] and syntheses [274,275,278–282] later showed that

[258] *H. S. Forrest, C. van Baalen*, and *J. Myers*, Science (Washington) *125*, 699 (1957); *C. van Baalen, H. S. Forrest*, and *J. Myers*, Proc. nat. Acad. Sci. USA *43*, 701 (1957); *H. S. Forrest, C. van Baalen*, and *J. Myers*, Arch. Biochem. Biophysics *83*, 508 (1959).

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[272] *T. Masuda*, Pharmac. Bull. (Tokyo) *4*, 71, 72 (1956).

[273] *T. Masuda, T. Kishi*, and *M. Asai*, Pharmac. Bull. (Tokyo) *5*, 598 (1957).

[274] *G. W. E. Plaut* and *G. F. Maley*, Arch. Biochem. Biophysics *80*, 219 (1959).

[275] *G. F. Maley* and *G. W. E. Plaut*, J. biol. Chemistry *234*, 641 (1959).

[276] *T. Masuda*, Pharmac. Bull. (Tokyo) *5*, 375 (1957).

[277] *T. Masuda, T. Kishi*, and *M. Asai*, Chem. pharmac. Bull. (Tokyo) *6*, 291 (1958).

[278] *T. Masuda, T. Kishi, M. Asai*, and *S. Kuwada*, Chem. pharmac. Bull. (Tokyo) *7*, 361 (1959).

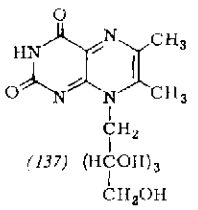
[279] *T. Masuda, T. Kishi, M. Asai*, and *S. Kuwada*, Chem. pharmac. Bull. (Tokyo) *7*, 366 (1959).

[280] *W. Pfleiderer* and *G. Nübel*, Chem. Ber. *93*, 1406 (1960).

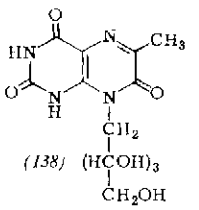
[281] *R. M. Cresswell* and *H. C. S. Wood*, J. chem. Soc. (London) *1960*, 4768.

[282] *J. Davoll* and *D. D. Evans*, J. chem. Soc. (London) *1960*, 5041.

*(137)* and *(138)* are not derivatives of pterin *(2)*, but of 2,4-pteridinedione *(43)*, *i.e.* of lumazine. This demonstrated that the pterins are not the only natural products in the pteridine series, but that the possibility of varying the substituents on the pyrimidine nucleus is as great as in the case of the closely related purines.

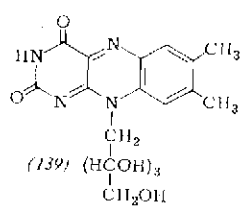


*(137)*

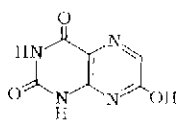


*(138)*

The hypothesis [275, 283–285] that 8-ribityl-6,7-dimethyllumazine *(137)* is an intermediate in the biosynthesis of riboflavin, but that 8-ribityl-6-methyl-7-oxodihydrolumazine *(138)* does not take part in this biosynthesis, [286], is based on numerous studies of the enzymatic transformation of *(137)* into riboflavin [287]. Two molecules of 8-ribityl-6,7-dimethyllumazine *(137)* are joined by the catalytic action of the enzyme riboflavin synthetase to form one molecule of riboflavin *(139)* plus an unknown compound [288, 289]. Compound *(137)* reacts in this unusual biochemical reaction both as a donor and acceptor for a $C_4$ intermediate which consists of both the methyl groups and carbon atoms 6 and 7. Various 8-ribityl-6,7-dialkyl- and 8-glycityl-6,7-dimethyllumazines were synthetized in order to test the substrate specificity of this enzyme [290]. With the exception of 8-(D-5′-deoxyribityl)-6,7-dimethyllumazine, none of these substrates were transformed into an isoalloxazine derivative [289, 290], although they are all competitive inhibitors in the enzymatic transformation of *(137)* into *(139)*.



*(139)*



*(140)*

Very recently, a purely chemical synthesis of riboflavin *(139)* was achieved [291] by heating *(137)* for 15 hours in phosphate buffer at pH 7.3 under nitrogen; a 55 % yield of riboflavin was obtained. The isolation of 7-hydroxylumazine *(140)* [180] from *Pyrrhocoris apterus* C. indicates that in the future, derivatives of 2,4-pteridinedione will also have to be considered.

*Xenopus* larvae [292] are probably able to transform purines into pteridines. This observation provided the first experimental basis for the reasonable supposition that purines are precursors of pteridines. Earlier reports [293] had already suggested a possible biogenetic relationship between purines and riboflavin, and the transformation of purine into pteridine has been discussed [286, 294–301]. It was only recently that definitive proof was obtained [302] that the entire purine nucleus, with the exception of carbon atom 8, is incorporated into the pyrimidine and pyrazine moieties of riboflavin *(137)*, which is produced via 8-ribityl-6,7-dimethyllumazine. Inasmuch as natural pteridine derivatives, *i.e.* pterins and lumazines, are ultimately derivatives of 4-hydroxypteridine, it is possible that the latter is an intermediate in the biosynthesis of pteridine [303], particularly as 4-hydroxypteridine undergoes enzymatic oxidation to 7-hydroxylumazine *(140)* via lumazine *(43)* [304]. Purines have also been reported to play a role in the biosynthesis of folic acid [305, 306].

The present-day picture of the purine → pteridine transformation is the result of many years of study of the biosynthesis of leucopterin by *Weygand* et al. [307, 308]. By using $^{14}C$-labelled precursors in the caterpillars or pupae of the cabbage butterfly (*Pieris*), and as a result of degradation studies of the leucopterin isolated from the resultant butterfly wing pigment, it proved possible to establish the origin of the carbon atoms of the pteridine nucleus (the carbon atoms of the pyrimidine nucleus are derived from the same precursors as the corresponding carbon atoms of guanine, while carbon atoms 6 and 7 come from a pentose). The following picture emerged from this work (Scheme 1).

The first step results in the elimination of C-8 from either guanosine or guanylic acid *(149)*. Subsequently, the ribosyl residue of 2,5-diamino-4-β-D-ribofuranosyl-6-pyrimidone


[283] *T. Masuda*, Pharmac. Bull. (Tokyo) *5*, 136 (1957).

[284] *S. Kuwada, T. Masuda, T. Kishi*, and *M. Asai*, J. Vitaminol. (Kyoto) *4*, 217 (1958).

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[288] *G. W. E. Plaut*, J. biol. Chemistry *235*, PC 41 (1960).

[289] *G. W. E. Plaut* [14].

[290] *C. H. Winestock* and *G. W. E. Plaut*, J. org. Chemistry *26*, 4456 (1961).

[291] *T. Rowan* and *H. C. S. Wood*, Proc. chem. Soc. (London) *1963*, 1.

[292] *I. Ziegler-Günder, H. Simon*, and *A. Wacker*, Z. Naturforsch. *11b*, 82 (1956).

[293] *G. W. E. Plaut*, J. biol. Chemistry *208*, 513 (1954).

[294] *W. S. McNutt*, J. biol. Chemistry *219*, 365 (1956).

[295] *H. S. Forrest* and *W. S. McNutt*, J. Amer. chem. Soc. *80*, 951 (1958).

[296] *F. Korte, H. U. Aldag*, and *H. G. Schicke*, Z. Naturforsch. *13b*, 463 (1958).

[297] *F. Korte, H. U. Aldag, G. Ludwig, W. Paulus*, and *K. Striko*, Liebigs Ann. Chem. *619*, 70 (1958).

[298] *M. Al-Khaldidi*, Fed. Proc. *17*, 180 (1958).

[299] *E. G. Brown, T. W. Goodwin*, and *O. T. G. Jones*, Biochem. J. *68*, 40 (1958).

[300] *W. S. McNutt*, J. Amer. chem. Soc. *82*, 217 (1960).

[301] *T. W. Goodwin* and *A. A. Horten*, Nature (London) *191*, 772 (1961).

[302] *W. S. McNutt*, J. Amer. chem. Soc. *83*, 2303 (1961).

[303] *H. S. Forrest, E. W. Hanley*, and *J. M. Lagowski*, Biochim. biophysica Acta *50*, 596 (1961).

[304] *F. Bergmann* and *H. Kwietny*, Biochim. biophysica Acta *33*, 29 (1959).

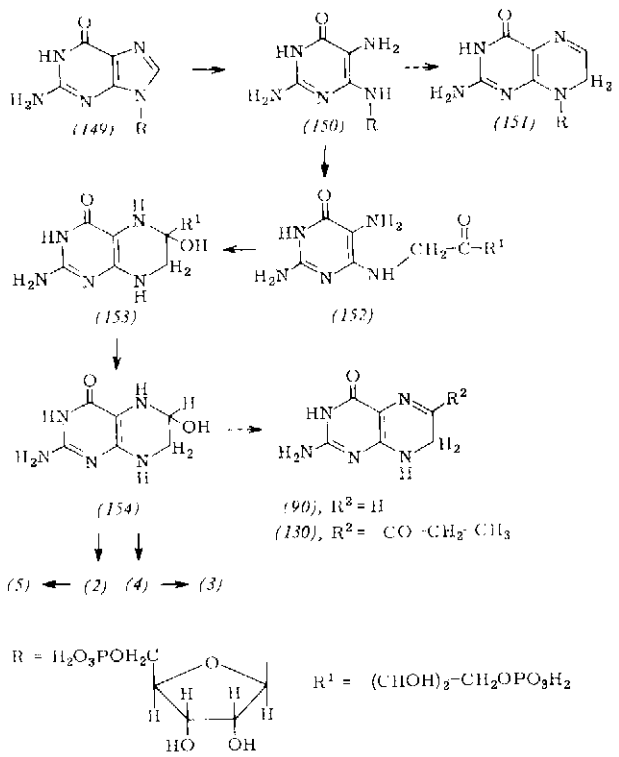
[305] *S. Aaronson* and *E. Rodriguez*, J. Bacteriol. *75*, 660 (1958).

[306] *E. Vierira* and *E. Shaw*, J. biol. Chemistry *236*, 2507 (1961).

[307] *F. Weygand, H. Simon, G. Dahms, M. Waldschmidt, H. J. Schliep*, and *H. Wacker*, Angew. Chem. *73*, 402 (1961).

[308] *H. Simon* [14].

*(150)* is used for the formation of the pyrazine ring, presumably after an Amadori rearrangement [309] favored by the adjacent amino group. The $C_3$ side chain is then split off from *(153)*, and the resultant 6-hydroxy-5,6,7,8-tetrahydropterin *(154)* is transformed via xanthopterin *(4)* into leucopterin *(3)*, with attendant dehydrogenation and hydroxylation.

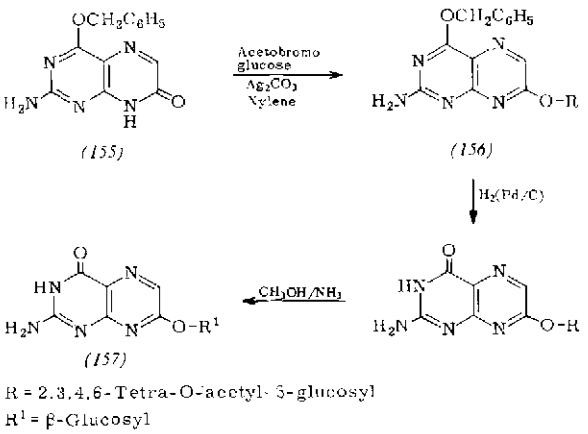



Scheme 1. Conversion of guanylic acid into pteridines.

Studies *in vitro* [310] have given support to the above reaction sequence. Attempts to isolate *(152)* have merely resulted in the isolation of 7,8-dihydroxanthopterin, formed by cyclization, elimination, and oxidation. According to Scheme 1, there is a possibility that *(154)* is dehydrated and that the resulting highly reactive 7,8-dihydropterin *(90)* is utilized for the synthesis of more complex pteridines, in analogy to the processes shown to occur in the isosepiapterin synthesis [153, 259].

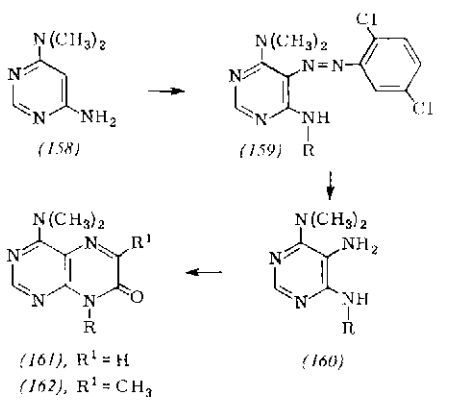
An interesting variation of the purine → pteridine conversion occurs when the pyrazine ring is closed not by the ribosyl residue, as with *(150)*, but by a $C_2$ fragment obtained from a pentose. In that case, a pteridine-*N*(8)-riboside or ribotide *(151)* would then be the biosynthetic intermediate [311]. Attempts have been made to synthetize such pteridine derivatives in order to elucidate their chemical and physical properties [311].

Direct glycosidation of 7-pteridones with halogenated sugars by the methods used in nucloside synthesis yielded only 7-*O*-glycosides [312]. These are labile in both acid and alkali, with the result that isoxanthopterin-7-*O*-β-D-glucopyranoside *(157)* [83] can only be obtained from 2-amino-4-benzyloxy-7-pteridone *(155)* via *(156)*, which requires debenzylation and deacetylation.

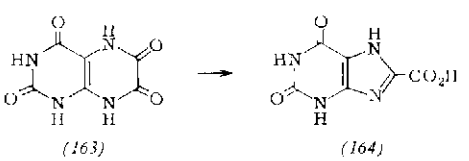



A true pteridine-*N*(8)-glycoside was first synthetized [314] by an approach analogous to the Todd purine nucleoside synthesis [313]:

The first step was glucosidation of 4-amino-6-dimethylaminopyrimidine *(158)*, followed by transformation by coupling and acetylation into 5-(2′,5′-dichlorophenylazo)-6-dimethylamino-4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylamino)-pyrimidine *(159)*. After reduction to *(160)*, the latter was condensed directly (without further isolation) with glyoxylic or pyruvic ester to form 8-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosyl)-4-dimethylamino-7-pteridone *(161)* or its 6-methyl analogue *(162)*.




Because these products exhibit the stability to alkalies and moderate stability to acids known for purine nucleosides, it is to be expected that if pteridine-*N*(8)-ribosides do occur in nature, they will be relatively stable compounds, capable of isolation. In connection with the enzymatic degradation of the pteridines, mention should also be made of the conversion of xanthopterin *(4)* and isoxanthopterin *(5)* into xanthine-8-carboxylic acid [315]. Cultures of the bacterium *Alkali-*




[309] *F. Micheel* and *I. Dijong*, Liebigs Ann. Chem. *658*, 120 (1962).

[310] *A. Stuart* and *H. C. S. Wood*, Proc. chem. Soc. (London) *1962*, 151.

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[314] *D. Söll*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1962.

[315] *M. S. McNutt* [14].

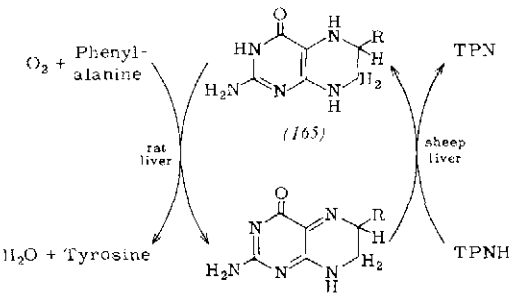
*genes faecalis*, which utilize *(4)* and *(5)* as sources of nitrogen and carbon, deaminate these substances to the respective lumazine derivatives, which then undergo oxidation to 2,4,6,7-pteridinetetraone *(163)*. The isomerization of *(163)* to xanthine-8-carboxylic acid *(164)* is achieved enzymatically.

### VII. The Biochemical Role of Unconjugated Pteridines

By his study of the enzymatic hydroxylation of phenylalanine to form tyrosine, *Kaufman* [317] has made a valuable contribution to the knowledge of the biochemistry of the pteridines [316]. He was able to show [317,318] that two enzymes are involved in the overall reaction

$$H^+ + TPNH + O_2 + \text{phenylalanine} \rightarrow TPN^+ + H_2O + \text{tyrosine}$$

(where TPN = triphosphopyridine nucleotide and TPNH = reduced TPN). One of the enzymes, isolated from rat liver, catalyses the hydroxylation; it contains a tetrahydrogenated, unconjugated pteridine as a cofactor. The second enzyme, obtained from sheep liver, acts in conjunction with TPNH to induce rehydrogenation of the dihydropteridine to the tetrahydro stage. Details of the structure of the cofactor are still unknown. The fact that the cofactor can be replaced by either 6-methyl- or 6,7-dimethyl-5,6,7,8-tetrahydropterin [319] or by tetrahydrobiopterin indicates that a 6-substituted tetrahydropterin is involved. The partially hydrogenated pteridine derivative [320] produced in the course of the hydroxylation is neither a 5,8- nor a 7,8- nor most probably a 5,6-dihydropterin. Hence, it is likely that an oxidation-reduction system is involved. This system may have compounds *(165)* and *(166)* as components.




*(165)*

*(166)*

This first example in which a simple unconjugated pteridine plays the role of a cofactor can be considered to be the beginning of a new chapter in the development of pteridine chemistry. It does not seem improbable that other biological functions of the pteridines will be discovered in the near future.

Received, March 11th, 1963 [A 335/134 IE]
German version: Angew. Chem. *75*, 993 (1963)

[316] *S. Kaufman* [14].
[317] *S. Kaufman*, J. biol. Chemistry *226*, 511 (1957).
[318] *S. Kaufman*, J. biol. Chemistry *230*, 931 (1958).
[319] *S. Kaufman*, J. biol. Chemistry *234*, 2677, 2683 (1959).
[320] *S. Kaufman*, J. biol. Chemistry *236*, 804 (1961).

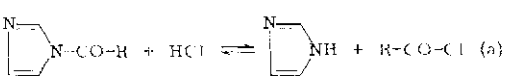
# COMMUNICATIONS

## Formyl Chloride

By Prof. Dr. H. A. Staab and Dipl.-Chem. A. P. Datta

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Heidelberg (Germany)

When dry HCl is passed into a solution of an imidazolide [1] in chloroform or methylene chloride, an acid chloride is obtained as a result of acylation of the hydrogen chloride. Although the transacylation reaction (a) is reversible, as is shown by the formation of imidazolides from acid chlorides and imidazole, the acid chlorides are formed in practically quantitative yield, since imidazolium chloride formed in a subsequent reaction precipitates out. Acid chlorides whose synthesis by the usual methods is attended by difficulties can be prepared by this route, since imidazolides are readily accessible from carboxylic acids and 1,1'-carbonyldiimidazole.




The long sought for formyl chloride *(1)* has now been obtained on a preparative scale for the first time. We passed HCl into a solution of 1-formylimidazole [2] in $CHCl_3$ at −60 °C and filtered off the quantitative precipitate of imidazolium chloride formed in the cold through a sintered glass filter in a closed apparatus. The chloroform solution of *(1)* obtained as filtrate was stable for one hour at −60 °C. After addition of methanol, methyl formate was isolated in 65–70 % yield. At −40 °C, we obtained only 9 % ester under otherwise identical conditions. The thermal decomposition of *(1)* into CO and HCl, which is still being investigated quantitatively, was also followed by direct determination of the carbon monoxide evolved.

Received, August 16th, 1963; publication withheld until now at the request of the authors. [Z 563/445 IE]
German version: Angew. Chem. *75*, 1203 (1963)

[1] See *H. A. Staab*, Angew. Chem. *74*, 407 (1962); Angew. Chem. internat. Edit. *1*, 351 (1962).
[2] *H. A. Staab* and *B. Polenski*, Liebigs Ann. Chem. *655*, 95 (1962).

## Dicyclopentadienyleuropium

By Prof. Dr. E. O. Fischer and Dipl.-Chem. H. Fischer

Institut für Anorganische Chemie der Universität München
(Germany)

Treatment of the blue solution of metallic europium in liquid ammonia with cyclopentadiene in a ratio of 1:3.1, thermal degradation of the yellow reaction residue at 200 °C *in vacuo*, and rapid heating to 420–440 °C affords yellow dicyclopentadienyleuropium in 20 % yield in the form of a crystalline sublimate. This is the first "sandwich" compound prepared

which contains a divalent lanthanide. The complex is formed in accordance with the equation

$$Eu + 3\,C_5H_6 \xrightarrow{\text{liq. } NH_3} Eu(C_5H_5)_2 + C_5H_8$$

It is soluble in liquid ammonia and in dimethylformamide, is extremely sensitive to air and moisture, and has a magnetic moment of 7.62 B.M. [1]. Its paramagnetism is thus practically equal to that anticipated for the $Eu^{2+}$ ion (7.9 B.M.). The salt-like character of the complex, which must be assumed on the basis of this observation, is only slightly affected by covalent centric $\sigma$-bonding contributions, as is shown by the position of the $\gamma_{CH}$-frequency at 739 $cm^{-1}$ in the infrared spectrum. The presence of symmetrical five-membered rings follows from the $\nu_{CH}$-band at 3077 $cm^{-1}$, the $\omega_{CC}$-band at 1435 $cm^{-1}$, and the $\delta_{CH}$-absorption at 1007 $cm^{-1}$. The similarity between $r_{Eu^{2+}} = 1.09$ and $r_{Sr^{2+}} = 1.10$ Å, and the comparable bond character are reflected in the agreement between the corresponding frequencies of $Sr(C_5H_5)_2$ [2] (739, 3077, 1435, and 1008 $cm^{-1}$) and of $Eu(C_5H_5)_2$.

Received, November 22nd, 1963 [Z 621/452 IE]
German version: Angew. Chem. 76, 52 (1964)

[1] According to investigations of *K. E. Schwarzhans.*

[2] *E. O. Fischer* and *G. Stölzle*, Chem. Ber. *94*, 2107 (1961).

## Hydrothermal Sintering

By Prof. Dr. R. Brill and I. Melczynski

Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin (Germany)

Various methods for thermal sintering of metal powders are known. A similar effect may be obtained with some metal powders by treating them with water. This effect was discovered accidentally, when we tried to wash iron carbonyl powder with water in a Soxhlet apparatus. After extraction for several hours, the metal powder had formed a firmly cohering cake. We found that the iron particles always cake together if they are placed in close contact with one another and then treated with warm water or boiled with water. The hydrothermally sintered solids are strong enough to be turned on a lathe; the exposed surface acquires the typical appearance of iron. The surface may also be polished to a high gloss, but under the microscope the polished surface exhibits a grained structure. There are some particles with a strong, metallic lustre besides some weakly reflecting ones and some dark, void spaces. The X-ray diagram shows not only the lines for $\alpha$-iron, but also those of iron spinel. On heating with water, the surface of the iron particles has therefore evidently reacted with the water, yielding the anhydrous spinel phase $Fe_3O_4$ as the effective product which firmly cements the individual iron particles together.

Closely similar effects have been observed with aluminum and zinc, starting with commercial Al and Zn powders. X-Ray studies showed that the metal particles are joined together by Böhmite and ZnO respectively.

It is interesting that the caking of the above metal powder particles produces structures that have enough mechanical strength for considerable amounts of other metals, which do not sinter hydrothermally on their own, or even of inert substances to be embedded in the cake. The mechanical strength of hydrothermally sintered solids does not appear to be high enough for engineering purposes. During their preparation they may, however, be easily combined with non-metals such as paper and plastics.

We do not intend to continue studies on hydrothermal sintering effects from either the scientific or the commercial point of view.

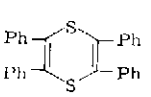
Received, November 25th, 1963 [Z 622/450 IE]
German version: Angew. Chem. 76, 52 (1964)

## Characterization and Stabilization of Dithiobenzil by Complex Formation

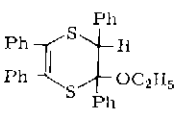
By Priv.-Doz. Dr. G. N. Schrauzer and H. W. Finck

Institut für Anorganische Chemie der Universität München (Germany)

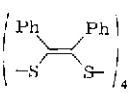
According to *Mitra* [1], three compounds are formed in the reaction between benzoin and $H_2S$ in ethanolic HCl, *viz.* *(1)*, m.p. 195 °C, *(2)*, m.p. 126 °C, and *(3)*, m.p. 97 °C. As this author regarded *(3)* as monomeric dithiobenzil, we felt it desirable to check his claims, particularly since we were interested in *(3)* as a possible starting material for a new synthesis of bis(dithiobenzil)nickel *(4)*, which can also be obtained, for example, from nickel sulfide and tolane [2]. Although we were able to confirm *Mitra*'s results, a revision of the structures he suggests is necessary. In agreement with *R. Mayer* and *Nitzschke* [3], we found that *(1)* is tetraphenyldithiacyclohexadiene and that *(2)* is 5-ethoxy-2,3,5,6-tetraphenyl-1,4-dithiacyclohexene; however, we also



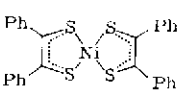
*(1)*



*(2)*



*(3)*



*(4)*

Ph = $C_6H_5$

succeeded in isolating *(3)* (softening point 105–110 °C, yield: 3 % based on benzoin) in solid, analytically pure, but non-crystalline form [4]. Molecular-weight determinations show that *Mitra*'s dithiobenzil is actually tetrameric. In the proton magnetic resonance spectrum only signals of the phenyl protons were detectable. Therefore, a cyclic structure with S–S bonds could be present. When heated, *(3)* decomposes into sulfur and tetraphenylthiophene. On treatment with $Ni(CO)_2 \cdot 2P(C_6H_5)_3$ in xylene, *(3)* gives the nickel complex *(4)* in good yield. The same complex is formed when benzoin is reacted with $H_2S$ under the above conditions in the presence of $NiCl_2$ (yield 10 % based on benzoin). In this reaction, the unstable precursor of *(3)*, dithiobenzoin, is trapped by the added metal salt.

Received, November 25th, 1963 [Z 632/460 IE]
German version: Angew. Chem. 76, 143 (1964)

[1] *S. K. Mitra*, J. Indian chem. Soc. *15*, 58 (1938).

[2] *G. N. Schrauzer* and *V. Mayweg*, J. Amer. chem. Soc. *84*, 3221 (1962); Z. Naturforsch. Scr. b, in the press.

[3] *R. Mayer* and *M. Nitzschke*, Chem. Ber. *96*, 2539 (1963).

[4] Compound *(3)* forms minute, pale yellow, transparent globules.

## 1,2- and 1,4-Hydrostannation of Conjugated Dienes

By Priv.-Doz. Dr. W. P. Neumann and Dipl.-Chem. R. Sommer

Chemisches Institut der Universität Gießen (Germany)

Hydrostannation of $\alpha$-olefins [1] proceeds by way of radicals [1a, 2]. Therefore, it seemed worthwhile to examine the behavior of conjugated dienes in this reaction. Butadiene, substituted butadienes *(2)*, and cyclopentadiene are readily hydrostannated by a radical mechanism at 60–80 °C. Radical scavengers inhibit, radical-producing agents accelerate the reaction. The main product is the 1,4-adduct

*(3)* shown in Equation (a), together with only a small quantity of the 1,2-adduct *(4)* [3]. The product *(3)* has mainly the *trans*-configuration (strong absorption at 950 to 960

(a) $R_3SnH$ + $H_2C{=}CR^1{-}CR^2{=}CHR^3$ ⟶
*(1)* *(2)*
$R_3Sn{-}CH_2CR^1{=}CR^2{-}CH_2R^3$ + $R_3Sn{-}CH_2{-}CHR^1{-}CR^2{=}CHR^3$
*(3)* *(4)*

$cm^{-1}$). The trialkylstannyl group adds preferentially to the unsubstituted end of the conjugated system *(2)*. If, as in Equation (b), a primary carbon atom can become a radical center ($R^3 = H$), this reacts preferentially with the H of a further molecule of *(1)*; about 80 % of the 1,4-adduct *(3)* as obtained. If only secondary carbon atoms are radical centers

(b) $R_3Sn{-}CH_2{-}\dot{C}R^1{-}CR^2{=}CHR^3 \leftrightarrow R_3Sn{-}CH_2{-}CR^1{=}CR^2{-}\dot{C}HR^3$

($R^3$ = methyl), the yield of 1,2-adduct *(4)* rises to ca. 35 %. With dimethylbutadiene ($R^1 = R^2 = CH_3$), the tertiary carbon atom is apparently favored as a radical center [left-hand limiting structure in (b)], leading to an increased proportion of *(4)*. The same effect in the case of phenylbutadiene ($R^3 = C_6H_5$) probably causes its tendency to form the styrene system. Diisobutylstannane reacts analogously to *(1)*.

For analysis of the mixtures *(3)* + *(4)*, among other methods, titration with iodine at 0–20 °C was used for the selective estimation of *(3)*, for iodine splits off the allylic alkylstannyl group rapidly and quantitatively. We have also prepared a number of possible isomers by independent synthesis.

Table 1. Hydrostannation of dienes according to Reaction (a) at 70–75 °C. Catalyst: azoisobutyronitrile; excess of diene: 100 %.

| Diene | Organotin hydride | Adduct (Yield *(3)* + *(4)* = 75–96 %) b.p. [°C/mm Hg] | % 1,4- *(3)* | % 1,2- *(4)* |
|---|---|---|---|---|
| $H_2C{=}CH{-}CH{=}CH_2$ | $(C_2H_5)_3SnH$ | 120–122/44 | 80 | 20 |
| $H_2C{=}CH{-}C(CH_3){=}CH_2$ | $(C_2H_5)_3SnH$ | 103–106/12 | 81 [a] | 19 |
| $H_2C{-}(CH_3)C{-}C(CH_3){-}CH_2$ | $(C_2H_5)_3SnH$ | 109–111/12 | 68 | 32 |
| $H_2C{=}CH{-}CH{-}CH{-}CH_3$ | $(C_2H_5)_3SnH$ | 100–103/12 | 66 | 34 |
| $H_2C{=}(CH_3)C{-}C(CH_3){=}CH_2$ *(5)* | $(C_4H_9)_3SnH$ | 100–101/0.1 | 72 | 28 |
| *(5)* | $(C_6H_5)_3SnH$ | m.p. 69 °C [b] | ≥ 95 | ≤5 |
| *(5)* | $(i\text{-}C_4H_9)_2SnH_2$ | 180–185/12 | 70 | 30 |
| $H_2C{-}CH{-}CH{=}CH{-}C_6H_5$ | $(C_6H_5)_3SnH$ | — | 64 | 36 |
| Cyclopentadiene | $(C_2H_5)_3SnH$ | 110–113/12 | 87 [c] | 13 |
| Cyclopentadiene | $(C_6H_5)_3SnH$ | m.p. 84 °C [b] | ≥ 94 | ≤6 |

[a] Contains very little of the inverse 4,1-adduct.

[b] From ethanol.

[c] By-product: adduct formed with dimeric cyclopentadiene, b.p. 167 °C/12 mm.

Received, November 26th, 1963 [Z 623/453 IE]
German version: Angew. Chem. 76, 52 (1964)

[1] *J. G. Noltes* and *G. J. M. van der Kerk*, Chimia *16*, 122 (1962), where further references are given.

[1a] *W. P. Neumann*, *H. Niermann*, and *R. Sommer*, Angew. Chem. *73*, 768 (1961); Liebigs Ann. Chem. *659*, 27 (1962).

[2] *W. P. Neumann* and *R. Sommer*, Liebigs Ann. Chem., in the press.

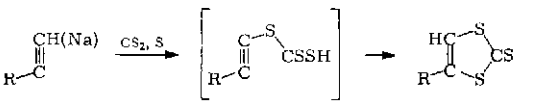
[3] *D. J. Cooke*, *G. Nickless*, and *F. H. Pollard* (Chem. and Ind. *1963*, 1493) expected to obtain only the 1,2-adduct on addition of trimethylstannane onto piperylene, without considering the possibility of 1,4-addition. They assumed that the geometric isomerism of piperylene was the reason for the appearance of several products.

## Synthesis of 1,3-Dithiole-2-thiones ("Isotrithiones")

By Prof. Dr. Roland Mayer, Dipl.-Chem. B. Gebhardt, Dipl.-Chem. J. Fabian, and A. K. Müller

Institut für Organische Chemie
der Technischen Universität Dresden (Germany)

1,3-Dithiole-2-thiones (1,3-dithiacyclopentene-2-thiones) arise by the simultaneous action of carbon disulfide and sulfur on acetylene in polar solvents at somewhat elevated temperatures or from sodium acetylides with carbon disulfide and sulfur (*e.g.* in acetonitrile) at room temperature. Mercaptoethynyl compounds [1], which are produced by the action of sulfur on sodium acetylides, also add on carbon disulfide in polar solvents at room temperature, and are cyclized by nucleophilic attack of the thiolic sulfur of the trithiocarbonate group on the triple bond.




*(1)*: R = $C_6H_5$
*(2)*: R = H

Average yields of 50–70 % are obtained. Thus, sodium phenylacetylide affords 60 % phenyl-1,3-dithiole-2-thione *(1)* when the reaction is performed in acetonitrile. The parent compound, *viz.* 1,3-dithiole-2-thione *(2)*, is accessible in 25 % yield from acetylene or sodium acetylide [2].

Received, December 2nd, 1963 [Z 630/456 IE]
German version: Angew. Chem. 76, 143 (1964)

[1] *L. Brandsma*, *H. Wijers*, and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *81*, 583 (1962); *M. Schmidt* and *V. Potschka*, Naturwissenschaften *50*, 302 (1963).

[2] Cf. *R. Mayer* and *B. Gebhardt*, Chem. Ber., in the press, where an introduction to the literature of isotrithiones is also given.

## Cyclopentadienyl-(benzene)-molybdenum

By Prof. Dr. E. O. Fischer and Dipl.-Chem. F. J. Kohl

Institut für Anorganische Chemie
der Universität München (Germany)

In the course of an investigation of the behavior of $[C_5H_5MC_6H_6(CO)]^+$ ions (M = Mo or W) [1] toward nucleophilic reagents, we discovered a new type of synthesis for $C_5H_5MC_6H_6$ π-complexes. If red $[C_5H_5MoC_6H_6(CO)]PF_6$ is treated with hydride ions as nucleophilic reagent, the carbonyl group is eliminated and cyclopentadienyl-(benzene)-molybdenum, m.p. 216–218 °C, is obtained according to the equation:

$$[C_5H_5MoC_6H_6(CO)]PF_6 \xrightarrow[0\,^\circ C]{LiAlH_4/THF} C_5H_5MoC_6H_6$$

The red compound is soluble in organic solvents, sublimes *in vacuo* above 50 °C, and is extremely sensitive to air. Evidence for its sandwich structure is provided by its infrared spectrum. In agreement with earlier studies carried out on $C_5H_5CrC_6H_6$ [2], typical absorptions are observed at 1404, 1096, 996, 814, and 791 $cm^{-1}$ for the covalently bonded, symmetrical $C_5H_5$-ligand (sym. $C_5v$) in Nujol/Hostaflon. Absorption bands at 1404, 977, 950, 838, and 761 $cm^{-1}$ may be assigned to the π-bonded undistorted benzene-ligand (sym. $C_6v$). The paramagnetism of the compound (1.68 B.M.) [3] corresponds to the value for one unpaired electron. The substance $C_5H_5(C_6H_6)MoH$ which would be a feasible intermediate between $(C_5H_5)_2MoH_2$ [4] and $(C_6H_6)_2Mo$ [5] in the isoelectronic series, was not observed.

Received, December 5th, 1963 [Z 627/457 IE]
German version: Angew. Chem. 76, 98 (1964)

[1] *E. O. Fischer* and *F. J. Kohl*, Z. Naturforsch. *18b*, 504 (1963).

[2] *J. Manchot*, Ph. D. Thesis, Technische Hochschule München, 1963; *E. O. Fischer* and *H. P. Kögler*, Z. Naturforsch. *13b*, 197 (1958).

[3] Measurements carried out by *K. Schwarzhans*.

[4] *M. L. H. Green*, *C. N. Street*, and *G. Wilkinson*, Z. Naturforsch. *14b*, 738 (1959); *E. O. Fischer* and *Y. Hristidu*, Z. Naturforsch. *15b*, 135 (1960).

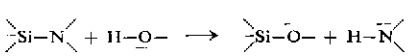
[5] *E. O. Fischer* and *H. O. Stahl*, Chem. Ber. *89*, 1805 (1956).

## Conversion of Si—O into Si—N Bonds [1]

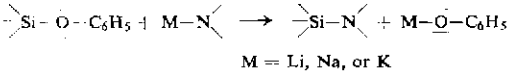
By Prof. U. Wannagat, Dr. P. Geymeyer,
and Dipl.-Ing. G. Schreiner

Institut für Anorganische Chemie
der Technischen Hochschule Graz (Austria)

Silicon-nitrogen compounds are considered – sometimes mistakenly – to react with water; they are converted into silicon-oxygen compounds by alcohols and especially by acids.



We found that the reverse of this process occurs when phenoxysilanes are treated with alkali metal derivatives of amines.



M = Li, Na, or K

Stoichiometric amounts of the components in 400–500 ml of petroleum ether or benzene are heated to boiling for 2–3 hours for molar charges; the Na or K phenoxide formed precipitates out quantitatively and is then filtered off ($LiOC_6H_5$ is best converted with $(CH_3)_3SiCl$ into LiCl and $(CH_3)_3SiOC_6H_5$), the SiN compounds being obtained in over 75 % yield by fractional distillation.

$LiN(C_2H_5)_2$, $NaN[Si(CH_3)_3]_2$, or $KN(C_6H_5)_2$ removes only one phenoxyl group per Si atom; this limitation does not hold for $NaNH_2$.

A selection of previously unknown SiN compounds prepared by this procedure is given in Table 1.

Table 1. New Si–N compounds prepared from phenoxysilanes and substituted alkali amides

| Starting materials R = $CH_3$, R′ = $C_2H_5$, R″ = n-$C_3H_7$ | | Si—N compounds | B. p. [°C/mm] |
|---|---|---|---|
| $R_2Si(OC_6H_5)_2$ | $LiNR''_2$ | $R_2(C_6H_5O)SiNR''_2$ | 95–97/1 |
| $RSi(OC_6H_5)_3$ | $KN(C_6H_5)_2$ | $R(C_6H_5O)_2SiN(C_6H_5)_2$ | 162/2 |
| $R_2Si(OC_6H_5)NR'_2$ | $NaNH_2$ | $R_2Si(NH_2)NR'_2$ | 38–39/13 |
| $R_2Si(OC_6H_5)NHR'$ | $NaNH_2$ | $[R_2(R'NH)Si]_2NH$ | 46–48/1 |
| $[R_2(C_6H_5O)Si]_2NH$ | $LiNR'_2$ | $R'_2NR_2SiNHSiR_2OC_6H_5$ | 98–99/2 |
| $R_2Si(OC_6H_5)_2$ | $NaN(SiR_3)_2$ | $(R_3Si)_2NSiR_2OC_6H_5$ | 103/1 |

Received, December 16th, 1963 [Z 629/458 IE]
German version: Angew. Chem. 76, 99 (1964)

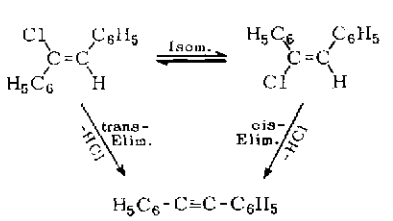
[1] Communication No. 36 on Silicon Nitrogen Compounds; Communication No. 31: *H. Bürger* and *U. Wannagat*, Mh. Chem. *94*, 761 (1963); Communications Nos. 31–35; Mh. Chem., in the press.

## Elimination of HCl from Gaseous cis- and trans-Chlorostilbene [1]

By Dr. P. Andréu, Lic. E. Schmitz, and Dr. H. Noller [2]

Physikalisch-Chemisches Institut der Universität München (Germany)

The loss of HCl from alkyl halides in the liquid phase is a *trans*-α,β-elimination with an ionic mechanism. Eliminations on catalysts have so far been little studied.



We have now examined the elimination of HCl from *cis*- and *trans*-chlorostilbene (1,2-diphenylchloroethylene) in the vapor phase on several salt and oxide catalysts. Which mode of elimination occurs or is favored invariably depends upon the different reactivities of the two isomers. Both modes of elimination give rise to tolane (diphenylacetylene).

Table 1. The elimination of HCl from *cis*- and *trans*-chlorostilbene on various catalysts.

| Catalyst | Substrate | Arrhenius parameters E [kcal/mole] | Arrhenius parameters A (relative) | Temp. [°C] | Yield of [*] Tolane [%] | Yield of [*] Isomer [%] |
|---|---|---|---|---|---|---|
| $MnO_2$ | *cis*-chlorostilbene | 8 | $1.2\times10^5$ | 250 | 14 | 0 *trans*-chlorostilbene |
| | *trans*- | 24 | $4.8\times10^9$ | 250 | 5 | 0 *cis*- |
| $BaCl_2$ | *cis*- | 11 | $2.2\times10^6$ | 250 | 17 | 19 *trans*- |
| | *trans*- | 20 | $3.2\times10^8$ | 250 | 8 | 4 *cis*- |
| CdO | *cis*- | 9 | $5.5\times10^5$ | 260 | 100 | 0 *trans*- |
| | *trans*- | 8 | $1.5\times10^5$ | 260 | 8 | 1 *cis*- |
| MgO | *cis*- | 9 | $2.6\times10^5$ | 250 | 35 | 2 *trans*- |
| | *trans*- | 10 | $2.1\times10^5$ | 250 | 26 | 1 *cis*- |
| CaO | *cis*- | 9 | $7.8\times10^5$ | 283 | 11 | 0 *trans*- |
| | *trans*- | 7 | $5.6\times10^4$ | 283 | 12 | 0 *cis*- |
| $CaCl_2$ | *cis*- | 7 | $2.1\times10^5$ | 350 | 41 | 24 *trans*- |
| | *trans*- | 8 | $1.4\times10^5$ | 350 | 22 | 0 *cis*- |
| $Al_2O_3$ | *cis*- | – | – | 250 | 100 | 0 *trans*- |
| neutral | *trans*- | 10 | $1.4\times10^6$ | 250 | 0 | 0 *cis*- |

[*] The rest of the material was unchanged.

As Table 1 shows, the *cis*-isomer reacts more readily and, with few exceptions, its activation energy is lower. This means that both *cis*- and *trans*-elimination can occur, but that *cis*-elimination is favored.

Isomerization does not occur to any considerable extent on oxide catalysts, presumably because the HCl formed (without which isomerization cannot take place) is bound on the surface of the catalyst. Isomerization does occur on chlorides, but it is nevertheless apparent that the *cis*-isomer reacts directly and more easily.

Measurements were carried out by gas chromatography at 230–430 °C using the pulse technique; the catalyst chamber was interposed in the carrier-gas train before the chromatography column. The residence time of the chlorostilbene on the catalyst was about 0.1 sec. The amount of reactant injected as a saturated acetone solution was 1.0–1.5 µl for the *cis*-isomer and 3.0 µl for the *trans*-isomer; the amount of catalyst was about 2.5 g.

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German version: Angew. Chem. 76, 184 (1964)

[1] The Mechanism of Eliminations on Catalysts, Part III. Part II: *H. Noller*, *W. Löw*, and *P. Andréu*, Naturwissenschaften, in the press.

[2] We thank Dr. *G.-M. Schwab* for his continual interest in this work, and the Deutsche Forschungsgemeinschaft and the Fonds der Chemie for financial support.

## Azlactones as 1,3-Dipoles; A New Pyrrole Synthesis

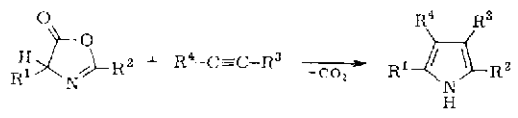
By Prof. Dr. R. Huisgen, Dr. H. Gotthardt,
and Dr. H. O. Bayer

Institut für Organische Chemie der Universität München (Germany)

When the azlactone *(1)*, $R^1 = R^2 = C_6H_5$, is heated with dimethyl acetylenedicarboxylate in xylene at 100 °C, dimethyl 2,5-diphenylpyrrole-3,4-dicarboxylate *(2)* is formed in 83 % yield within 2 hr. Alkaline hydrolysis and decarboxylation of *(2)* lead to 2,5-diphenylpyrrole.

5-Oxazolones *(1)* with either aromatic or aliphatic substituents can be used in this reaction, and the acetylene dicarboxylic ester can be replaced by methyl propiolate. The same pyrrole derivative *(5)* is obtained from the azlactones

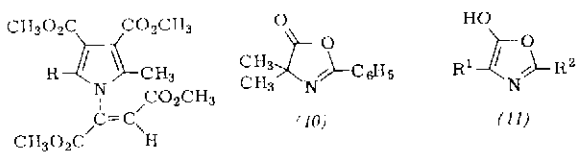
of either *N*-benzoylalanine or *N*-acetylphenylglycine. The preparative application of this new pyrrole synthesis is simplified by the fact that alkyloxazolones, which are unstable and difficult to purify [1], can be used *in situ*. Thus, *(5)* is obtained by the reaction of phenylglycine or *N*-acetylphenylglycine with dimethyl acetylenedicarboxylate in acetic anhydride.



*(1)* *(2)* to *(7)*

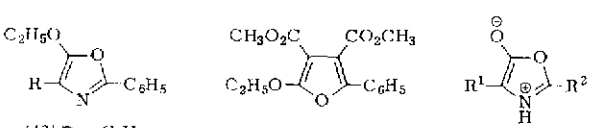
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield [%] | M.p. [°C] |
|---|---|---|---|---|---|---|
| *(2)*: | $C_6H_5$ | $C_6H_5$ | $CO_2CH_3$ | $CO_2CH_3$ | 83 | 149–150 |
| *(3)*: | $o$-$NO_2C_6H_4$ | $C_6H_5$ | $CO_2CH_3$ | $CO_2CH_3$ | 60 | 158–160 |
| *(4)*: | $C_6H_5$ | $p$-$CH_3OC_6H_4$ | $CO_2CH_3$ | $CO_2CH_3$ | 98 | liquid |
| *(5)*: | $CH_3$ | $C_6H_5$ | $CO_2CH_3$ | $CO_2CH_3$ | 72 | 127–128 |
| *(5)*: | $C_6H_5$ | $CH_3$ | $CO_2CH_3$ | $CO_2CH_3$ | 78 | 127–128 |
| *(6)*: | $C_6H_5$ | $C_6H_5$ | $CO_2CH_3$ | H | 55 | 172–173 |
| *(7)*: | $CH_3$ | $C_6H_5$ | ($CO_2CH_3$, H) | | 98 | liquid |

The pyrrole derivatives which are formed similarly *in situ* from 2,4-dimethyl- or 4-benzyl-2-methyloxazolone and dimethyl acetylenedicarboxylate undergo nucleophilic addition onto a second molecule of the acetylenic ester to give *(8)* and *(9)*, respectively.



*(8)* R = $CH_3$
*(9)* R = $C_6H_5$–$CH_2$

This surprising pyrrole synthesis is similar to the 1,3-dipolar additions of sydnones, which yield pyrazoles with elimination of $CO_2$ [2]. The oxazolones *(1)* cannot be 1,3-dipoles as long as the 4-position retains its $sp^3$-character. The fact that the 4,4-disubstituted oxazolone *(10)* does not react with dimethyl acetylenedicarboxylate at 180 °C suggests that the preliminary stage is tautomerization of the oxazolone. 5-Hydroxyoxazole *(11)* cannot be the intermediate, as the 5-ethoxyoxazoles *(12)* and *(13)* react with dimethyl acetylenedicarboxylate by Diels-Alder addition and subsequent fission to give dimethyl 2-ethoxy-5-phenylfuran-3,4-dicarboxylate *(14)* and benzonitrile or acetonitrile



*(12)* R = $C_6H_5$
*(13)* R = $CH_3$
*(14)*
*(15)*

A moderate equilibrium concentration of the mesoionic tautomer *(15)* is essential for the 1,3-dipolar cycloaddition leading to pyrrole formation to occur [3].

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German version: Angew. Chem. *76*, 185 (1964)

[1] Review: *H. E. Carter*, Org. Reactions *3*, 198 (1947).

[2] *R. Huisgen, R. Grashey, H. Gotthardt*, and *R. Schmidt*, Angew. Chem. *74*, 29 (1962); Angew. Chem. internat. Edit. *1*, 48 (1962); *R. Huisgen, H. Gotthardt*, and *R. Grashey*, Angew. Chem. *74*, 30 (1962); Angew. Chem. internat. Edit. *1*, 49 (1962).

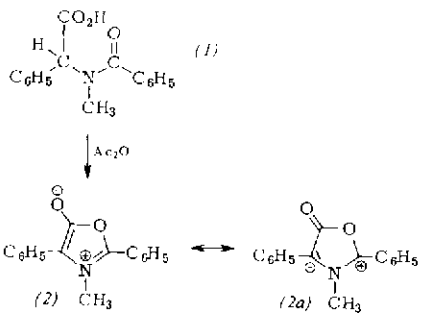
[3] *R. Huisgen, H. Gotthardt, H. O. Bayer*, and *F. C. Schaefer*, Angew. Chem. *76*, 185 (1964); Angew. Chem. internat. Edit. *3*, 136 (1964).

## A New Type of Mesoionic Aromatic Compound and Its 1,3-Dipolar Cycloaddition Reactions with Acetylene Derivatives

By Prof. Dr. R. Huisgen, Dr. H. Gotthardt, Dr. H. O. Bayer, and Dr. F. C. Schaefer

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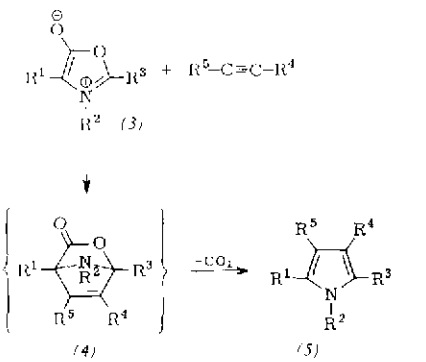
If *N*-benzoyl-*N*-methylphenylglycine *(1)* is treated with acetic anhydride at 55 °C for a few minutes, bright yellow crystals of the mesoionic compound *(2)* are obtained in 90 % yield. The synthesis of oxazole derivatives of this type, which can be formulated only as zwitterionic structures, is analogous to that of the sydnones from *N*-nitroso-*N*-alkylamino acids [1].



*(1)*
*(2)* $CH_3$ *(2a)* $CH_3$

The mesoionic [2] derivatives *(3)* of azlactones are readily hydrolysed and undergo the Dakin-West reaction with acetic anhydride at elevated temperatures; it is probably for these reasons that they have previously escaped notice. Anhydro-5-hydroxyoxazolium hydroxides *(3)* may provide the key to an understanding of the Dakin-West reaction [3].

The mesoionic oxazolones *(3)* undergo cycloadditions with acetylenecarboxylic esters at 0–70 °C to produce *N*-substituted pyrroles *(5)* with liberation of carbon dioxide. Phenyl- and alkyl-substituted acetylenes also react at 70–100 °C.



*(3)*
*(4)*
*(5)*

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield [%] | M.p. [°C] |
|---|---|---|---|---|---|---|
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | $CO_2CH_3$ | $CO_2CH_3$ | 92 | 147–148 |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | $CO_2CH_3$ | H | 95 | 99–100 |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | H | 93 | 178–179 |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 21 | 210–211 |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | $CO_2C_2H_5$ | 87 | 170–171 |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | n-$C_4H_9$ | H | 81 | oil |
| $CH_3$ | $C_6H_5$ | $CH_3$ | $CO_2CH_3$ | $CO_2CH_3$ | 80 | 87–88 |
| $CH_3$ | $C_6H_5$ | $CH_3$ | $C_6H_5$ | $CO_2C_2H_5$ | 80 | 82–84 |
| $CH_3$ | $CH_3$ | $C_6H_5$ | $CO_2CH_3$ | $CO_2CH_3$ | 83 | 94–95 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | $CO_2CH_3$ | $CO_2CH_3$ | 90 | 94–95 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | ($C_6H_5$, $CO_2C_2H_5$) | | 75 | 117–119 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | ($C_6H_5$, H) | | 77 | 144–145 |
| H | $CH_3$ | $CH_3$ | $CO_2CH_3$ | $CO_2CH_3$ | 37 | 88–89 |
| H | $C_6H_5$ | H | $CO_2CH_3$ | $CO_2CH_3$ | 92 | 117–118 |
| $-(CH_2)_3-$ | | $CH_3$ | $CO_2CH_3$ | $CO_2CH_3$ | 76 | 102–103 |

The intermediate *(3)* need not be isolated. Since the cycloaddition reaction proceeds more rapidly than the Dakin-West reaction, the *N*-acyl-*N*-alkyl- or -*N*-arylamino acid *(1)*

is simply treated with the alkyne in acetic anhydride. Thus, dimethyl 5-methyl-1,2-trimethylenepyrrole-3,4-dicarboxylate is obtained in 76 % yield by merely warming proline with dimethyl acetylenedicarboxylate in acetic anhydride at 130 °C for 1 hr.

The kinetics of the release of carbon dioxide indicate that the acetylenic dipolarophile first combines with *(3)*, presumably to form the bicyclic adduct *(4)*; the elimination of $CO_2$ from *(4)* is a rapid subsequent reaction. Compound *(3)* belongs to the azomethine-ylide class of 1,3-dipoles [4], cf. the sextet structure *(2a)*; here the 1,3-dipole system is part of an aromatic ring. *H. Staudinger* [5] has proposed the term "nitrenes" for azomethine ylides. The first representatives have recently been described [6].

Received, December 20th, 1963 [Z 642/469 IE]
German version: Angew. Chem. 76, 185 (1964)

[1] *J. C. Earl* and *A. W. Mackney*, J. chem. Soc. (London) *1935*, 899.

[2] Mesoionic compounds: *W. Baker* and *W. D. Ollis*, Quart. Reviews (chem. Soc., London) *11*, 15 (1957).

[3] *H. D. Dakin* and *R. West*, J. biol. Chemistry *78*, 91, 757 (1928); *R. H. Wiley* and *O. H. Borum*, J. Amer. chem. Soc. *72*, 1626 (1950); *A. Lawson* and *C. E. Searle*, J. chem. Soc. (London) *1957*, 1556.

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

[5] *H. Staudinger* and *K. Miescher*, Helv. chim. Acta *2*, 554 (1919).

[6] *R. Huisgen*, *R. Grashey*, and *E. Steingruber*, Tetrahedron Letters *1963*, 1441.

## Tris(biphenylenevinyl)methane [1]

By Prof. Dr. Richard Kuhn and Dr. Herbert Fischer

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Bis(biphenylene)pentadienone *(1)* reacts with iodomethylenetriphenylphosphorane to give yellow needles of *(2)*, m.p. 152–153 °C. Condensation of *(2)* with fluorene in dimethylformamide in the presence of sodium hydroxide yields a hydrocarbon which crystallizes in colorless prisms, m.p. 235–237 °C (decomp.), molecular weight 540. This is tris(biphenylenevinyl)methane *(3a)*, somewhat contaminated by its structural isomer *(3b)*, judging by its ultraviolet spectrum [2]. The new hydrocarbon is about 300 times more acidic than the bis(biphenylene)pentadiene *(4)* described in our third communication [1] (pK of *(3a)* [*] in a 1:1 acetone/pyridine mixture: 6.2; pK of *(4)*: 8.8). The anion of *(3a)* has an absorption maximum at 645 mμ ($\varepsilon = 10^5$), *i.e.* at only slightly longer wavelength than that of the anion of *(4)* ($\lambda_{max}$ = 633 mμ). The high acidity of the hydrocarbon and the absorption band of the anion are in agreement with the predictions of the molecular orbital theory [3] (delocalization energy of *(4)*: 2.22 β, delocalization energy of *(3a)*: 2.50 β; calculated absorption band for the anion of *(3a)*: *ca.* 630 mμ).

$$(\text{BiphC=CH})_2\text{CO} + \text{Ph}_3\text{P=CHI} \rightarrow (\text{BiphC=CH})_2\text{C=CHI}$$
*(1)* *(2)*

$$\xrightarrow[\text{DMF/OH}^{\ominus}]{\text{BiphCH}_2} (\text{BiphC=CH})_3\text{CH} + (\text{BiphC=CH})_2\text{C=CH—CHBiph}$$
*(3a)* *(3b)*

$(\text{BiphC=CH})_2\text{CH}_2$ *(4)*

Biph = Biphenylene

The preparation of 1,1,5,5-bis(biphenylene)-3-(diphenylvinyl)-pentadiene *(6)* from 1,1-diphenyl-5,5-biphenylenepentadienone *(5)* was achieved similarly. In addition to *(6)*, two structural isomers are possible, one of which can also be expected to have geometric isomers. The anion of *(6)* absorbs at 675 mμ.

$$(\text{Ph})_2\text{C—CH—CO—CH=CBiph} \xrightarrow{\text{as above}} (\text{BiphC=CH})_2\text{CH—CH=CPh}$$
*(5)* *(6)*

1,1,5,5-Bis(biphenylene)-3-phenylpentadiene *(7)* was prepared by condensation of styrylfluorenol and methylfluorenol by the method of *Wawzonek* [4, 1] as colorless rods [5], m.p. 192–193 °C, and is at least 100 times less acidic than the pentadiene *(4)* (pK of *(7)* in a 1:1 acetone/pyridine mixture *ca.* 11). Its anion absorbs at 686 mμ ($\varepsilon = 82\times10^3$).

$$\underset{\text{OH}}{\text{BiphC—CH=CH—Ph}} + \underset{\text{OH}}{\text{CH}_3\text{—CBiph}} \rightarrow (\text{BiphC=CH})_2\text{CH—Ph} \quad (7)$$

The hydrocarbon *(3a)* is an analogue of tris-(β,β-diphenylvinyl)methane, which requires treatment with phenylisopropylpotassium to convert it into an anion [6].

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German version: Angew. Chem. 76, 146 (1964)

[1] Communication No. 4 on Highly Acidic Hydrocarbons; Communication No. 3: *R. Kuhn*, *H. Fischer*, *F. A. Neugebauer*, and *H. Fischer*, Liebigs Ann. Chem. *654*, 64 (1962).

[*] Somewhat contaminated with *(3b)*.

[2] Starting from bis(biphenylene)pentadiene and biphenylenevinyl bromide, both *(3a)* and *(3b)* have been obtained: m.p. (decomp.) 268–270 °C and 229–230 °C, respectively; $\lambda_{max}$ in tetrahydrofuran 319 mμ ($\varepsilon = 53\times10^3$) and 342 mμ ($\varepsilon = 35\times10^3$), respectively. Both give the same anion (*R. Kuhn* and *D. Rewicki*).

[3] *J. N. Murrel* and *H. Fischer*, in preparation.

[4] *S. Wawzonek* and *E. Dufek*, J. Amer. chem. Soc. *78*, 3530 (1956).

[5] On ozonolysis, 1.4 molar equivalents of fluorenone and some phenylacetic acid were obtained.

[6] *G. Wittig* and *H. Kosack*, Liebigs Ann. Chem. *529*, 167 (1937).

## Bis(trimethylsilyl)aminodimethylarsine and Tris(dimethylarsino)amine

By Dr. O. J. Scherer and Prof. Dr. Max Schmidt

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In connection with studies of hetero-tris(trimethylsilyl)amines [1], we have prepared bis(trimethylsilyl)aminodimethylarsine *(1)* in 75 % yield from dimethylchloroarsine and sodium bis(trimethylsilyl)amide [2] in dry ether according to the equation:

$$[(\text{CH}_3)_3\text{Si}]_2\text{NNa} + \text{ClAs}(\text{CH}_3)_2 \rightarrow \underset{(\text{CH}_3)_3\text{Si}}{\overset{(\text{CH}_3)_3\text{Si}}{\text{N—As}(\text{CH}_3)_2}} + \text{NaCl}$$
*(1)*

The product is a liquid (m.p. −46 to −44 °C, b.p. 45–46 °C/1 mm) which is colorless, sensitive toward oxygen and moisture, and is cleaved at the As–N bond by methyl-lithium with formation of $[(\text{CH}_3)_3\text{Si}]_2\text{NLi}$ and $\text{As}(\text{CH}_3)_3$. The NMR spectrum of *(1)* [two signals, area ratio 1 ($\delta = -77.8$ cps) : 3 ($\delta = -10.0$ cps)] shows that there is no migration of the silyl group from the nitrogen to the arsenic. Compound *(1)* is not cleaved even at 120 °C by excess chloroarsine.

$$(1) + 2\ \text{ClAs}(\text{CH}_3)_2 \not\rightarrow 2\ (\text{CH}_3)_3\text{SiCl} + \underset{\text{As}(\text{CH}_3)_2}{\overset{(\text{CH}_3)_2\text{As}}{\overset{|}{\text{N}}}}\!\!\diagdown\!\!\diagup\!\!\text{As}(\text{CH}_3)_2$$
*(2)*

We obtained tris(dimethylarsino)amine in 50 % yield as colorless prisms, m.p. 22–25 °C, b.p. 57–58 °C/1 mm, by heating bis(trimethylsilyl)amine with dimethylchloroarsine without solvent for 6 hours at 100–120 °C. Its NMR spectrum shows only one signal ($\delta = -69.0$ cps). Compound *(2)* is extremely sensitive towards oxygen and moisture.

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German version: Angew. Chem. 76, 144 (1964)

[1] *O. J. Scherer* and *M. Schmidt*, Angew. Chem. *75*, 642 (1963); Angew. Chem. internat. Edit. *2*, 478 (1963); J. organometall. Chem., in the press.

[2] *U. Wannagat* and *H. Niederpruem*, Chem. Ber. *94*, 1540 (1961).

## Preparation of Trimethyltin Methoxide

By Priv.-Doz. Dr. E. Amberger, Dr. Maria-Regina Kula, and Dipl.-Chem. J. Lorberth

Institut für Anorganische Chemie der Universität München (Germany)

Pure trimethyltin methoxide *(1)* cannot be secured by the reaction of trimethyltin chloride with sodium methoxide [1]. The pure product can however be prepared by careful methanolysis of trimethyltin diethylamide in diethyl ether at −50 °C.

$$(CH_3)_3SnN(C_2H_5)_2 + CH_3OH \rightarrow \underset{(1)}{(CH_3)_3SnOCH_3} + HN(C_2H_5)_2$$

After removal of volatile matter *in vacuo* at −50 to −10 °C, trimethyltin methoxide is left as a colorless powder in 95 % yield. It can be obtained as needles and prisms by sublimation at 0.1 mm. It decomposes gradually above 45 °C and, depending on the rate of heating, melts within the range 45 to 75 °C. Its NMR spectrum (Varian A 60, 32 °C, saturated solution in $CCl_4$) displays two peaks with an area ratio of 1 : 3 which are displaced about 209 and 21.5 cps to lower fields relative to TMS as internal standard. The spin-spin coupling constants are $J_{^{119}SnCH_3} = 56.7$ cps and $J_{^{117}SnCH_3} = 54.9$ cps. Coupling with the protons of the methyl group bound to the oxygen was not observed.

The infrared spectrum in Nujol has an Sn–O–C vibration at 1035 $cm^{-1}$, in accordance with earlier results [1].

Received, January 2nd, 1963 [Z 637/462 IE]
German version: Angew. Chem. *76*, 145 (1964)

[1] *E. Amberger* and *M.-R. Kula*, Chem. Ber. *96*, 2562 (1963). We wish to thank the Deutschen Forschungsgemeinschaft and the Fond der Chemie for generous financial support.

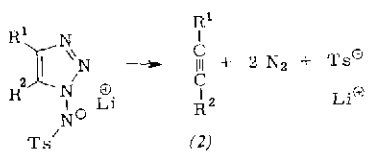
## Photolysis of 1-Tosylamino-1,2,3-triazole Anions; A New Synthesis of Alkynes

By Dr. F. G. Willey [1]

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der Universität Heidelberg (Germany)

On photolysis of compounds containing more than two nitrogen atoms in a ring, expulsion of one mole-equivalent of nitrogen at the most has hitherto been observed [2].

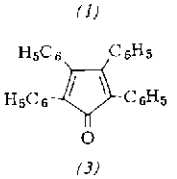
Unsubstituted 1,2,3-triazoles, or those bearing only hydrocarbon groups at positions 4 and 5, are both thermally and photochemically stable [3]. 1-Amino-1,2,3-triazoles, the corresponding 1-sulfonylamino derivatives [4], and the salts of these sulfonamides *(1)* are also quite stable to heat. Thus, *(1a)* and *(1e)* are recovered unchanged after refluxing in ethylene glycol, but they lose nitrogen slowly on heating in the solid state to ca. 300 °C.



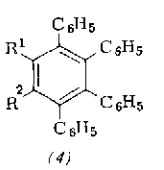
*(1)*



*(2)*



*(3)*



*(4)*

| | $R^1$ | $R^2$ |
|---|---|---|
| *(1a)*: | $C_6H_5$ | $C_6H_5$ |
| *(1b)*: | $-(CH_2)_4-$ | |
| *(1c)*: | $-(CH_2)_5-$ | |
| *(1d)*: | $-(CH_2)_6-$ | |
| *(1e)*: | $CH_3$ | $CH_3$ |

Ts = $H_3C-C_6H_4-SO_2$

| | $R^1$ | $R^2$ |
|---|---|---|
| *(4b)*: | $-(CH_2)_4-$ | |
| *(4c)*: | $-(CH_2)_5-$ | |
| *(4d)*: | $-(CH_2)_6-$ | |
| *(4e)*: | $CH_3$ | $CH_3$ |

Photolysis, on the other hand, of *(1)* [no maximum above 210 mμ, absorption begins at ca. 300 mμ, $\varepsilon_{220} = 3000-7000$] results in evolution of two mole-equivalents of nitrogen, with formation of an alkali metal toluenesulfinate and the corresponding alkyne, which can be trapped if necessary with tetraphenylcyclopentadienone *(3)*; cf. Table 1. Results obtained so far are summarized in Table 1.

| Experiment | Starting material | Conditions [b] | Yield of *(2)* [%] [a] | Yield of *(4)* [%] [a] |
|---|---|---|---|---|
| 1 | *(1a)* | [c] | 85 | — |
| 2 | *(1a)* [*] | [a] | 85 | ... |
| 3 | *(1b)* | [c,e] | — | *(4b)*, 54 |
| 4 | *(1c)* | [c,e] | — | *(4c)*, 56 |
| 5 | *(1c)* | [f] | . | *(4c)*, 26 |
| 6 | *(1d)* | [c] | — | *(4d)*, 77 |
| 7 | *(1e)* | [c,e] | — | *(4c)*, <2 |

[*] Cation K instead of Li.

[a] Based on nitrogen evolved or on starting material decomposed. Evolved $N_2$ + recovered starting material = 100 %.

[b] Irradiated with a Q 81 immersion lamp (Quarzlampengesellschaft m.b.H. Hanau, Germany) in a nitrogen atmosphere at 35–40 °C, unless otherwise specified.

[c] In absolute dioxan.

[d] In 90 % dioxan/10 % water.

[e] In the presence of one equivalent of *(3)*.

[f] In diglyme at ca. −25 °C.

In experiments 5 and 6, *(1c)* and *(1d)* respectively were irradiated, the lamp was switched off, and about two minutes later a solution of *(3)* was injected into the apparatus. Experiment 5 thus represents the first definite observation of free cycloheptyne, since here, as well as with *(1b)*, control experiments showed that no adduct was formed via thermal decomposition of *(1c)* or *(1b)*. Irradiation of *(1e)* leads to 2-butyne, which reacts only slowly with *(3)*; *(1e)*, *(1b)*, and *(1c)*, or any intermediates formed from them prior to nitrogen loss, would be expected to exhibit similar reactivities toward *(3)*. The low yield of adduct obtained upon irradiation of *(1e)* in the presence of *(3)* thus indicates that the adducts *(4)* are formed by reaction of free alkynes, and not of some nitrogenous intermediates, with *(3)*.

This method is of interest as a general synthesis of alkynes, particularly symmetrical ones. The results obtained support earlier work in which the formation of cycloalkynes was also postulated [4b, 5].

Further work on the mechanism of this decomposition, and on its extension to the generation of arynes is anticipated.

Received, December 9th, 1963 [Z 635/459 IE]
German version: Angew. Chem *76*, 144 (1964)

[1] U.S. National Science Foundation Postdoctoral Fellow, 1963. The author wishes to thank Prof. *G. Wittig* for the hospitality extended to him during the past year.

[2] *W. Kirmse*, Angew. Chem. *71*, 381 (1959); *W. Kirmse*, Chem. Ber. *93*, 2353 (1960); *B. Jambar*, Agrokemia es Talajtan *5*, 89 (1956); Chem. Abstr. *51*, 1150 (1957); *R. Kuhn* and *D. Jerchel*, Liebigs Ann. Chem., *578*, 1 (1952).

[3] *W. Kirmse*, Angew. Chem. *71*, 537 (1959). Some 1,2,3-triazoles decompose only very slowly on irradiation; well-defined products were not obtained (*W. Kirmse*, personal communication).

[4] Readily available from the corresponding 1,2-bistosylhydrazones: cf. a) *W. R. Bamford* and *T. S. Stevens*, J. chem. Soc. (London) *1962*, 4735; b) *G. Wittig* and *A. Krebs*, Chem. Ber. *94*, 3260 (1961).

[5] *G. Wittig* and *R. Pohlke*, Chem. Ber. *94*, 3276 (1961) and publications cited therein.

# Hauptversammlung der Gesellschaft Deutscher Chemiker (General Meeting of the German Chemical Society)

**Heidelberg, September 9th–14th, 1963**

A General Meeting of the German Chemical Society is held every two years. Over 2700 chemists from Germany and abroad participated in the 1963 meeting, at which 9 plenary lectures were delivered and 202 short papers were read. The following is a selection of the most important results presented at this meeting.

## Preparation of Red α-Rhombohedral Boron

*E. Amberger* and *W. Dietze*, München (Germany)

Pyrolysis of boron triiodide on tantalum wires of 0.2–2 mm diameter at 800–1000 °C causes formation of a layer of coarse crystalline α-rhombohedral boron which has a thickness of up to 5 mm and which contains small amounts of amorphous glass-like black boron as tiny islands. The ruby-red transparent boron crystals are 2 mm long. Some warts of a grey tetragonal modification of boron are occasionally formed on the surface of the boron layer. The separation of red B can only be reproduced if certain experimental conditions are observed: use of purest grades of boron iodide, extremely pure pyrolysis atmosphere and Ta surface (in particular, free from O and C), and a constant wire temperature (the absolute value is however not critical). $BI_3$ is prepared by treating $LiBH_4$ with $I_2$ in n-hexane and is frozen out. It is then purified by zone melting. Foreign atoms were not detected by spectral analysis in either the $BI_3$ or the α-B. In the preparative method described, the α-boron is not formed from the vapor phase on the surface of the boron deposit to the same extent as the boron is formed pyrolytically from the $BI_3$, but crystallizes out in a secondary process from the very pure X-ray-amorphous boron which is initially formed. A further purification probably takes place thereby. If slightly less pure $BI_3$ is used to prepare the α-B, only microcrystalline α-B with significant proportions of impure boron is formed whereas $BI_3$ purified by zone melting forms predominantly coarsely crystalline α-B.

## Determination of Lithium by Activation Analysis

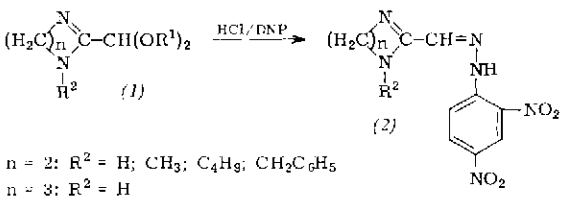
*D. C. Aumann* and *H. J. Born*, München (Germany)

A process for the determination of both traces of lithium and macroscopic lithium contents has been worked out, the nuclear reactions $^6Li(n,\alpha)^3H$ and $^{16}O(t,n)^{18}F$ being utilized. The irradiated specimens were worked up chemically in order to purify the fluoride obtained. Oxygen-free specimens were either mixed with an oxidizing agent or converted into oxygenated compounds before irradiation. The limit of detection of the method lies at $3\times10^{-8}$–$6\times10^{-8}$ g of lithium at a neutron flux of $5\times10^{12}$ n/cm²/sec. The dependence of the induced $^{18}F$ activity per unit weight of lithium on the number of oxygen atoms per cm³ ($N_0$) and on the range of the tritium nuclei (R) in the substance under investigation may be compensated using calculated values of the product $N_0\times R$. The substance to be alanysed and the standard need not have similar compositions; on the contrary, a pure lithium compound may serve as the standard.

## Fragmentations in the Imidazoline Series

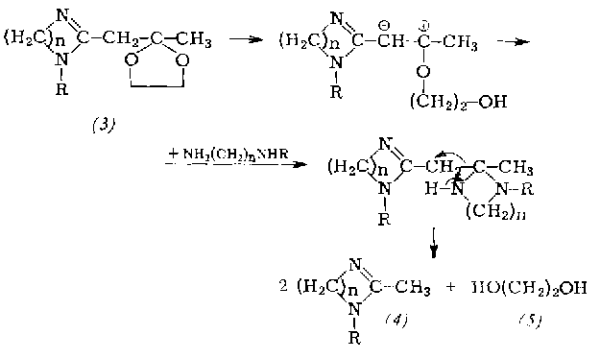
*H. Baganz*, Berlin (Germany)

Following hydrolysis of acetals of the imidazoline and tetrahydropyrimidine series *(1)* in the presence of dinitrophenylhydrazine, the 2-carboxaldehydes were isolated as their dinitrophenylhydrazones *(2)*. In the absence of the carbonyl reagent, the aldehydes decomposed during hydrolysis in the strongly acidic medium, with regeneration of the original diamine and formation of formic acid, $CO_2$, and CO.



n = 2: $R^2$ = H; $CH_3$; $C_4H_9$; $CH_2C_6H_5$
n = 3: $R^2$ = H

On the assumption that the influence of the imidazoline system on the hydrolysis of an acetal or ketal group decreases with increasing distance, an attempt was made to obtain compounds of type *(3)* by treating ketals of β-ketocarboxylic esters with ethylenediamine derivatives or with trimethylenediamine. In these reactions, however, fragmentation of the molecule into lysidine derivatives *(4)* and ethylene glycol *(5)* in a ratio of 2:1 was invariably observed. On the basis of detailed experiments, it is assumed that, after formation of the imidazoline ring, the dioxolane ring is cleaved, and the ethylenediamine attacks the polarized double bond, with simultaneous elimination of ethylene glycol. The intermediate imidazoline ring is thereupon stabilized by prototropy.



n = 2: R = H, $CH_3$; $C_4H_9$; $CH_2C_6H_5$
n = 3: R = H

On the other hand, farther separation of the imidazoline ring from the carbonyl group has a stabilizing effect on the ethyleneketal structure. Thus, 3-(*N*-butyl-2-imidazolylethyl) methyl ketone ethyleneketal can be obtained and is convertible, after hydrolysis, into the γ-carbonyl compound.

## Systematic Examination of the System EuO-$Eu_2O_3$

*H. Bärnighausen*, Freiburg/Breisgau (Germany)

A new method for the preparation of EuO from europium oxide halides in accordance with the equation

$$EuOX + LiH \rightarrow EuO + LiX + {}^1/_2\,H_2$$

has been developed. Samples with higher oxygen content were obtained by annealing finely powdered EuO–$Eu_2O_3$ mixtures of variable compositions at 800–900 °C in an

atmosphere of a carefully purified inert gas. X-ray identification of the annealed products showed that $Eu_3O_4$, which crystallizes in the orthorhombic system, occurs between EuO and $Eu_2O_3$.

To carry out the analysis, a current of nitrogen containing bromine is passed over the samples at 400 °C. The divalent europium is converted into EuOBr so that it is possible to calculate the original composition from the increase in weight. X-ray examination of the system $EuOBr-Eu_2O_3$ led to the new compound $Eu_3O_4Br$, which also crystallizes in the orthorhombic system (a = 11.986, b = 11.854, c = 4.124 Å; possible space groups: Bbmm and $Bb2_1m$). EuOBr is isostructural with PbFCl.

## New Phosphorus Sulfide and Selenide Halides

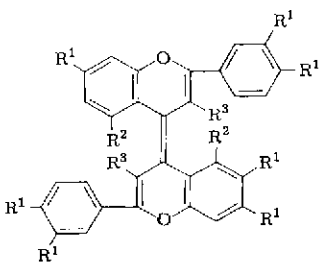
*M. Baudler, G. Fricke*, and *K. Kipker*, Köln (Germany)

Diphosphorus tetraiodide and phosphorus(III) iodide react with sulfur in boiling $C_6H_6$ or $CS_2$ in diffuse daylight to form $P_4S_7$ and $I_2$. On standing for several days at room temperature with complete exclusion of light on the other hand, a different reaction takes place which leads to the formation of the new phosphorus sulfide iodides $P_2S_2I_4$, $P_2SI_4$, and $PSI_3$. These can also be obtained more simply by direct interaction of the elements in stoichiometric amounts in $CS_2$, on standing for several days with exclusion of light at room temperature or, in the case of $PSI_3$, at 0 °C. $P_2SI_4$ is the first inorganic compound in which a trivalent and a pentavalent phosphorus atom are bound directly to each other. The crystalline phosphorus sulfide iodides undergo disproportionation at room temperature within a short time to form $P_4S_7$ and $PI_3$; either $I_2$ or $P_2I_4$ is formed in addition. This transformation is strongly promoted by heat and in particular by light. $P_2S_2I_4$ and $P_2SI_4$ react with oxygen to form the polymeric phosphorus oxide iodide $(P_3I_2O_6)_n$ among other products. Reaction of the phosphorus iodides with selenium yields phosphorus selenide iodides $P_2Se_2I_4$, $P_2SeI_4$, and $PSeI_3$, which are also best obtained directly from the elements.

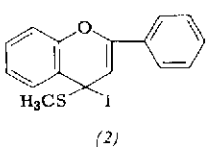
## Synthesis and Properties of Substituted Diflavylenes and Quercetylenes

*Ernst Bayer*, Tübingen (Germany)

Diflavylenes are normally prepared from thioflavones by dimerization with copper powder or Raney nickel. These methods fail when there are substituents adjacent to the connecting double bond, *e.g.* with *(1)* where $R^2$ and $R^3$ = $OCH_3$. The steric hindrance can be overcome if methyl iodide is added during the dimerization. The compound *(2)* thereby formed then contains the sulfur on a tetrahedral carbon atom and the attack of the reagent is sterically possible.



*(1)*



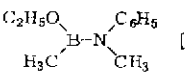
*(2)*

The diflavylenes are yellow but turn red on rubbing and assume partial free radical character. The latter phenomenon is termed piezomagnetism by analogy with piezochromism. Piezochromism and piezomagnetism fade away reversibly on standing. Neither effect occurs with the sterically strongly hindered derivative decamethylquercetylene [*(1)*, $R^1 = R^3 = OCH_3$]. The conversion of the yellow into the red form is attributed to conformational isomerism between a doubly folded and a twisted form, like that assumed by *Kortüm* and *Theilacker* [1] for dehydrodianthrone. It is to be concluded from the piezomagnetism that the rearrangement proceeds through a biradical.

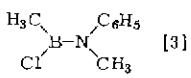
## Structural Investigations of Phenylated Aminoboranes

*H. J. Becher*, Stuttgart (Germany)

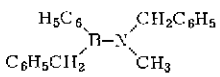
Proton magnetic resonance measurements show that an equilibrium exists in the asymetrically substituted aminoboranes



[2]



[3]



[4]

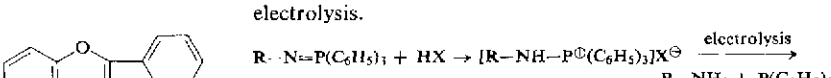
between the conformational isomers. The isomer ratio differs substantially in the three compounds listed, and evidently depends on the steric, inductive, and mesomeric effects of the substituents. Since all three compounds have phenyl groups on either the boron or the nitrogen atom, the interaction of these ligands with the B N bond was examined by evaluating vibrational spectra and by carrying out dipole measurements. The skeletal vibrations of the aminoboranes $(CH_3)_2BN(CH_3)_2$ and $(C_6H_5)_2BN(CH_3)_2$ as well as of $Cl_2BN(CH_3)_2$ and $Cl_2BN(C_6H_5)_2$ exhibit lowering of the B–N vibration frequency only in the case of the *N*-phenyl groups and not with the *B*-phenyl groups [5]. The dipole moments of the compounds $Cl_2BN(CH_3)_2$ and $Cl_2BN(C_6H_5)_2$ were found to be 2.95 and 2.57 Debye units, respectively [6]. The difference between these two values may be explained on the basis of inductive effects and does not justify the assumption that significant resonance takes place between the B–N bond and the phenyl groups.

## The Reaction of Alkylidenephosphoranes with C–C and C–N Double Bonds

*H. J. Bestmann* and *F. Seng*, München (Germany)

Alkylidenephosphoranes *(1)* can react with compounds having an activated double bond *(2)* to form cyclopropane derivatives or to give new alkylidenephosphoranes by a Michael addition [7]. The stereochemistry of the cyclopropane ring formed gives an indication of the nature of the primary product obtained from *(1)* and *(2)*.

With suitable substituents on the C=P double bond, alkylidenephosphoranes give olefins and iminophosphoranes with Schiff bases [8] in a manner analogous to a Wittig reaction. Triphenylphosphine can be recoverd by treating iminophosphoranes *(3)* with mineral acids followed by electrolysis.



[1] *G. Kortüm*, Angew. Chem. *70*, 14 (1958); *W. Theilacker, G. Kortüm*, and *G. Friedheim*, Chem. Ber. *83*, 508 (1950).

[2] *H. J. Becher* et al., Symposium on Boron-Nitrogen Chemistry, Durham, N.C. (U.S.A.), 1963.

[3] *M. Kubo* et al., [2].

[4] *W. Brey* et al., [2].

[5] Cf. *H. T. Baechle*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1963.

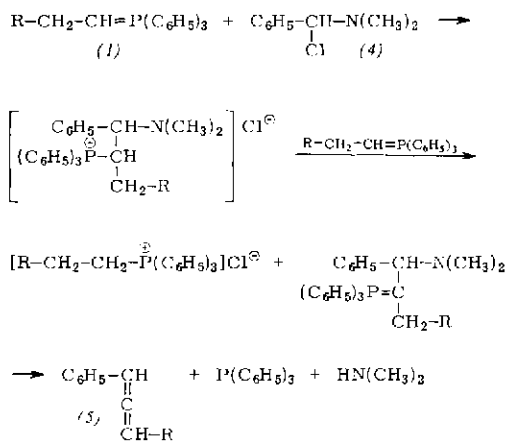
[6] *H. J. Becher* and *H. Diehl*, unpublished results.

[7] *H. J. Bestmann* and *F. Seng*, Angew. Chem. *74*, 154 (1962); Angew. Chem. internat. Edit. *1*, 116 (1962).

[8] *H. J. Bestmann* and *F. Seng*, Angew. Chem. *75*, 475 (1963); Angew. Chem. internat. Edit. *2*, 393 (1963).

If the alkylidenephosphorane has a $CH_2$ group in the β-position relative to the phosphorus atom, reaction with Schiff bases first gives rise to an isolatable product which can be decomposed thermally to an amine, triphenylphosphine, and an allene.

The same allene *(5)* is obtained by treating alkylidenephosphoranes *(1)* with α-aminobenzyl chlorides *(4)*, for instance



## The Reactivity of the P=N Double Bond

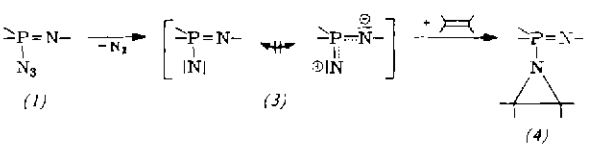
*H. Bock* and *W. Wiegräbe*, München (Germany)

Energetically favored addition reactions onto the P=N double bond of phosphazenes are intermolecular if the coordination number of the phosphorus is low. Otherwise they are intramolecular.

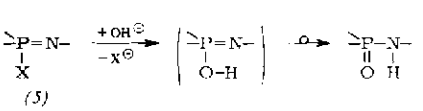
The aminophosphazenes $R_2N-PO=NR$ with a phosphorus of coordination number 3, which are described as monomers in the literature, were found to be dimeric with four-membered P–N rings. *P,P*-Diphenyl-*N*-tosylphosphazenyl azide *(1)* was prepared for the first time and does not exist in the phosphatetrazole form *(2)* according to infrared spectroscopic investigations.



The azene *(3)* remaining after thermal decomposition does not react as a 1,3-dipole. An ethyleneimine structure *(4)* was proved for the reaction product with dicyclopentadiene.



According to the hypothetical $S_N2$-mechanism, hydrolysis of phosphazene derivatives *(5)* should formally involve an intramolecular addition. Substituents showed remarkable effects on the rate of hydrolysis.



Comparison of the P=N stretching frequency of twenty new representative phosphazenes showed band shifts which are mainly caused by substituents on the nitrogen. The transfer of conjugation via the phosphorus atoms and the question whether suitable substituents increase the apparently low reactivity of the P=N double bond are still under investigation.

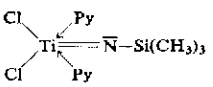
## Preparation of Titanium-Nitrogen Compounds by Addition and Substitution Reactions

*H. Bürger*, Graz (Austria)

Trialkoxytitanium chlorides *(1)* are not ammonolysed by liquid $NH_3$; instead, they form salt-like $NH_4^+[(RO)_3TiClNH_2 \cdot NH_3]^-$, which is converted into $(RO)_3TiCl \cdot NH_3$ at 40–60 °C and reverts to *(1)* via 3 $(RO)_3TiCl \cdot 2\,NH_3$ on further heating. With phenylhydrazine, *(1)* gives a 1:1 adduct (R = $C_2H_5$, m.p. 108 °C; R = i-$C_3H_7$, m.p. 76–77 °C). Dimethylhydrazine binds two molecules of *(1)* to form $(RO)_3TiCl-H_2NN(CH_3)_2-ClTi(OR)_3$. The chlorine in *(1)* is readily substituted by alkali disilylamides. Thus, *(1)* (in the following, R = i-$C_3H_7$) reacts with $NaN[Si(CH_3)_3]_2$ to form $(RO)_3Ti-N[Si(CH_3)_3]_2$, b.p. 93 °C/1 mm, and with $NaN[Si(OR)_3]_2$ to give $(RO)_3Ti-N[Si(OR)_3]_2$. Repeated substitution to yield $[(CH_3)_3Si]_2N-Ti(OR)_2-N[Si(CH_3)_3]_2$, m.p. 189 °C, is also possible. The extremely unstable compound *(2)*, which is formed in accordance with the equation

$$3\,TiCl_4 + 2\,NaN[Si(CH_3)_3]_2 \rightarrow Na_2TiCl_6 + 2\,Cl_3Ti-N[Si(CH_3)_3]_2 \quad (2)$$

is split by pyridine to give $(CH_3)_3SiCl$ and



Hexamethyldisilazane adds on 2 $TiCl_4$ below 20 °C, but reacts only at elevated temperatures to give $Cl_3Ti-NH-Si(CH_3)_3$. On heating the Ti–N Si compounds, which are not very thermostable, the Ti–N bond splits first; the same occurs on hydrolysis.

## Crystal Growth of Compounds with Incongruent Melting Points

*J. Bärmeister*, Aachen (Germany)

A new type of crystallizer, consisting of a storage vessel connected by a capillary to a small crucible-crystallizer, was described. The temperature of each component of the apparatus is independently variable. A melt with the composition of the desired compound is kept in the storage vessel. If solid is withdrawn from the crucible, equalization of the composition in the crucible by diffusion from the storage vessel is prevented by the capillary, and a composition corresponding to the peritectic transition point in the melt is established, which is in equilibrium with the desired compound. This method has been used successfully for the preparation of single crystals of thallium telluride ($Tl_2Te_3$).

## Fragmentation of Substituted Pyrrolidinium Salts

*H. Daniel*, München (Germany)

Quaternary pyrrolidinium salts are cleaved by phenyllithium into ethylene and vinylamine in a fragmentation reaction. The course of this reaction was studied with tritium-labelled pyrrolidinium salts; this excluded one possible mechanism involving a proton transfer from the α-position of the pyrrolidine ring to the *N*-methyl group. According to the kinetic isotopic effect of 1.4, the fragmentation is a two-stage reaction with formation of an α-ylide as the rate-determining primary step. Further attempts were made to influence the reaction by various substituents on the nitrogen or carbon of the pyrrolidine ring. Hexahydroisoindolinium salts gave long-chain unsaturated aldehydes. Increasing substitution causes side reactions, such as Hofmann elimination, substitution reactions, and Sommelet rearrangements.

Hofmann elimination and fragmentation are competing reactions with pyrrolidinium salts which contain β-hydrogen

atoms in addition to the β-hydrogen atom of the pyrrolidine ring, which cannot take part in the Hofmann elimination. The extent of the elimination increases with rising mobility of the β-carbon atoms.

### Preparation and Properties of Azide Chlorides

*K. Dehnicke*, Stuttgart (Germany)

Gaseous chlorazide reacts with anhydrous metal chlorides to form well-defined monoazide chlorides, *e.g.*:

$$TiCl_4 + ClN_3 = TiCl_3N_3 + Cl_2$$

The reactions are exothermic and proceed mildly below room temperature without side reactions. The reaction may be applied to the preparation of $SnCl_3N_3$, $VOCl_2N_3$, and $CrO_2ClN_3$. The azide chlorides are hygroscopic solids which explode when heated rapidly or struck. According to their infrared spectra, homopolarly bound azide groups with a tetrahedral structure around the metal atoms are mainly present.

Azide chlorides serve as starting materials for the preparation of nitrides, *e.g.*:

$$TiCl_3N_3 \rightarrow TiNCl + N_2 + Cl_2$$
$$VOCl_2N_3 \rightarrow VON + N_2 + Cl_2$$

Such reactions can be carried out carefully in boiling $CCl_4$. Provided care is taken to avoid fluctuations of pressure, work can be safely carried out with chlorazide diluted with nitrogen.

### Application of Chloronitrate for the Preparation of Oxide Fluorides

*K. Dehnicke, J. Weidlein*, and *K. Krogmann*, Stuttgart (Germany)

Well-defined fluoride nitrates were prepared using the following methods:

1. From mixed fluoride chlorides:

$$SbFCl_4 + 4\ ClNO_3 = SbF(NO_3)_4 + 4\ Cl_2$$

2. From lower fluorides:

$$SnF_2 + 2\ ClNO_3 = SnF_2(NO_3)_2 + Cl_2$$

The infrared and Raman spectra disclose in addition to the uniformity of the fluoride nitrates a certain intertwining of the $NO_2$ groups. Thermal decomposition leads directly to the oxide fluorides:

$$SbF(NO_3)_4 = SbO_2F + 4\ NO_2 + O_2.$$

In this manner, the oxide fluorides $SbOF_3$, $SbO_2F$, $SnOF_2$, $Sn_2OF_6$, InOF, and TlOF, most of which were unknown up to now, were obtained. $SnF_4$ and $SbOF_3$ are not isotypic. In contrast to $SnF_4$ (tetragonal, coordination number = 6; d = 4.78 g/cm³) [9], the powder diagram of $SbOF_3$ can be interpreted as being indicative of a cubic structure, with a lattice constant of a = 10.09 Å. The extinctions, the density (d = 3.70 g/cm³), and the infrared spectrum point to a coordination number of 4 for the antimony.

### Investigations of the Racemization of L-Amino Acid Derivatives

*H. Determann*, Frankfurt/Main (Germany)

It was shown by the Anderson test that racemization of acylated L-amino acids on activation of their carboxyl group by condensation with esters of chloroformic acid can be avoided by preparing the mixed anhydride rapidly in tetrahydrofuran at −15 °C and using the solution within a few minutes. About 50 % racemization occurs even after only 20 minutes. Of two suggested explanations – anhydride mesomerism or intermediate formation of oxazoles – only the latter is in accordance with all the experimental facts. The explanation of the differing effects that various acyl residues on the amino group have on the rate of racemization resides in the differing tendencies toward oxazole formation. The position of the carbonyl band in the infrared spectrum of the anilides of carbonic monoesters (ca. 1720 $cm^{-1}$) and of other acids (ca. 1680 $cm^{-1}$) indicates that the carbonyl oxygen is more nucleophilic in the latter. Amino acids protected with urethane groups do not therefore tend to cyclize and hence to racemize, whereas all other acylamino acids racemize to some extent when activated, a process that has been followed quantitatively in the case of L-phenylalanine derivatives.

### Preparation and Properties of Organometallic Onium Salt Complexes

*R. Dötzer*, Erlangen (Germany)

The addition of compounds RX, which undergo heterolytic cleavage, onto donor-acceptor molecule systems is favored energetically and leads to a simple method for preparing organometallic onium salt complexes, which are of interest as low-melting electrolytes for the galvanic separation of metals. Ammonium, phosphonium, stibonium, and telluronium salt complexes were prepared, alkyl compounds of Zn, Al, Ga, In, and Sn being used as acceptor molecules, in accordance with the equation

$$(C_2H_5)_3N + CH_3Cl + Al(C_2H_5)_3 \rightarrow [(CH_3)(C_2H_5)_3N][C_2H_5)_3AlCl]$$

The coordination compounds and the RX/acceptor or RX/donor molecule mixtures are also capable of yielding colorless electrolytes which are sometimes no longer spontaneously inflammable in air:

$$(CH_3)_3N{:}Ga(C_2H_5)_3 + C_6H_5CH_2F \rightarrow [(CH_3)_3(C_6H_5CH_2)N][(C_2H_5)_3GaF]$$

$$(C_2H_5)_3Sb/C_2H_5Br + Al(C_2H_5)_3 \rightarrow [(C_2H_5)_4Sb][(C_2H_5)_3AlBr]$$

Melting ranges: −62 to −65 °C, and −18 to −20 °C, respectively.

Although the starting materials are non-conductors or poor conductors of electricity, the onium salt complexes exhibit specific conductivities of $10^{-3}$ to $10^{-2}$ mho/cm in the temperature range 20–160 °C.

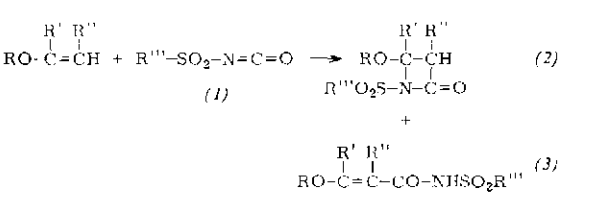
Onium salts that are difficult to prepare can be obtained by solvolysis of onium salt complexes, for instance in accordance with the reaction

$$[(C_2H_5)_4Sb][(C_2H_5)_3AlBr] + 3\ CH_3OH \rightarrow [(C_2H_5)_4Sb]Br + Al(OCH_3)_3 + 3\ C_2H_5$$

### Reaction of Vinyl Ethers and Ketene Acetals with Isocyanates and *N*-Sulfinyl Compounds

*F. Effenberger* and *R. Gleiter*, Stuttgart (Germany)

Sulfonyl isocyanates *(1)* react rapidly and quantitatively with vinyl ethers to give 4-alkoxyacetidin-2-one derivatives *(2)* or β-alkoxyacrylamide derivatives *(3)*. The proportions of *(2)* and *(3)* formed depend on the substituents and the reaction conditions.



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

[9] *R. Hoppe* and *W. Dähne*, Naturwissenschaften *49*, 254 (1962).

Alkyl, aryl, and acyl isocyanates do not react thus with vinyl ethers. Ketene diethylacetal (1,1-diethoxyethylene) reacts with sulfonyl and also with alkyl, aryl, and acyl isocyanates to give *N*-substituted carbamidoketene acetals (1,1-diethoxy-2-carbamidoethylenes) in good yields.

Reaction also takes place between *N*-sulfinyl compounds and vinyl ethers. The investigations carried out indicate that only cycloaddition occurs. The structure of the reaction product was discussed in the light of its infrared spectrum. The compounds resulting from the cycloaddition undergo various cleavage reactions.

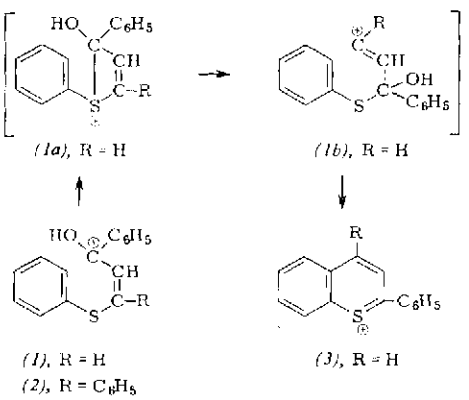
## A New Synthesis of 1-Thianaphthalenium Salts [10]

*N. Engelhard* and *A. Kolb*, Freiburg/Breisgau (Germany)

1-Thianaphthalenium perchlorate, which was hitherto accessible only by a multi-stage process, can now be obtained by cyclization of readily available β-(phenylthio)acrolein with perchloric acid. The synthesis is capable of general extension.

During the cyclization of 3-phenylthio-1-phenylprop-2-en-1-one, a new rearrangement was observed. It does not yield the expected 4-phenyl-, but instead 2-phenyl-1-thianaphthalenium perchlorate *(3)*. In contrast, 3-(3,4-dimethoxyphenylthio)-1-phenylprop-2-en-1-one can be cyclized with the expected result.

The carbonium ion *(1)* resulting from protonation probably alkylates the sulfur with formation of an unstable thiacyclobutene derivative *(1a)*. The carbonium ion *(1b)* is thus rendered sufficiently electrophilic to cyclize with the benzene ring to give *(3)*.There is a competition between this cyclization and the normal ring closure which occurs when the nucleus



*(1a)*, R = H — *(1b)*, R = H

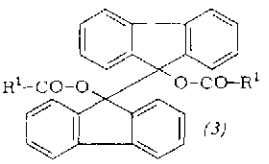
*(1)*, R = H
*(2)*, R = $C_6H_5$ — *(3)*, R = H

becomes more nucleophilic than the sulfur by the introduction of methoxy groups. In the condensation of thiophenol with dibenzoylmethane, the postulated intermediate *(2)* can be isolated; on treatment with water this is rapidly converted into 3-phenylthio-1,3-diphenylprop-2-en-1-one.

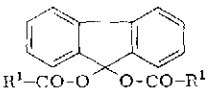
## The Reaction of Diazo Compounds with Diaroyl Peroxides

*E. Fahr* and *H. Lind*, Würzburg (Germany)

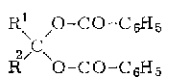
Diazofluorene *(1)* reacts with diaroyl peroxides $R^1CO-O_2-OCR^1$ *(2)*, where $R^1=C_6H_5$, $p$-$CH_3-C_6H_4$, or $p$-$H_3CO-C_6H_4$, to give derivatives of 9,9'-dibenzoyloxy-9,9'-bifluorenyl *(3)*. On the other hand, other diaroyl peroxides *(2)*, where $R^1 = p$-$O_2N-C_6H_4$ and $p$-$Cl-C_6H_4$, afford the 9,9-dibenzoyloxy derivatives *(4)* on reaction with *(1)*. Similarly, phenyldiazomethane and diphenyldiazomethane form the phenylated dibenzoyloxymethane derivatives *(5)* on reaction with benzoyl peroxide, while diazoketones ($R^2-CO-CHN_2$) and diazoacetic ester ($R^2OOC-CHN_2$) react with *(2)* to give the compounds $R^2$-CO-$CH_2$-O-CO-$R^1$ and $R^2OOC-CH_2-O-CO-R^1$, respectively.



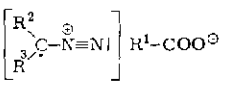
*(3)*



*(4)*



*(5)*



*(6)*

Determination of the order of reaction and of the rate constants of the reaction in relation to the substituents in the diaroyl peroxides shows that the diazo compound does not decompose into the corresponding carbene, which then reacts further with the peroxide or the radicals derived therefrom, but that compounds *(3)* to *(5)* are formed via an intermediate product, probably of structure *(6)*.

## Thermochemistry and Polymorphism of Selenium

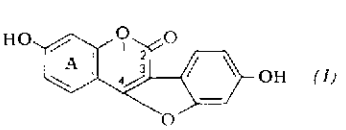
*G. Gattow*, Göttingen (Germany)

Combustion of various highly purified grades of selenium in the calorimeter bomb was used to ascertain the enthalpy of formation of $SeO_2$ at 25.0 °C and to compute the heats of transformation of selenium for feasible and hypothetical modification changes. Determinations of the heat contents by means of the drop method between −160 and + 280 °C showed that the individual types of selenium pass through several, hitherto unknown, reversible transformations, before turning into the thermodynamically stable modification of hexagonal selenium. Vitreous selenium: −145 °C ($L_t$ = 40 ± 20 cal/g-atom), + 11 °C ($L_t$ = 30 ± 20 cal/g-atom), and + 30 °C ($L_t$ = 0 ± 20 cal/g-atom); red amorphous selenium: −134 °C ($L_t$ = 160 ± 20 cal/g-atom) and + 10 °C ($L_t$ = 60 ± 20 cal/g-atom); monoclinic selenium (α + β): −120 °C, + 15 °C, and + 30 °C (with $L_t$ = 0 ± 20 cal/g-atom in each case). Hexagonal selenium, which melts at 221 °C, has a reversible transformation point at 106 °C ($L_t$ = 0 ± 20 cal/g-atom), which is reflected in the change in the lattice dimensions with temperature (c-constant).

## Investigations on the Biosynthesis of Coumestrol in Alfalfa

*H. Grisebach* and *W. Barz*, Freiburg/Breisgau (Germany)

Coumestrol *(1)*, which is isolated from leguminosae because of its estrogenic properties, belongs to the group of coumarano-coumarins.



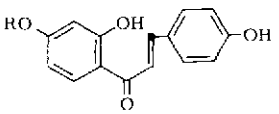
*(1)*

The biosynthesis of *(1)* was investigated by administration of $^{14}C$-labelled precursors to alfalfa (*Medicago sativa* L.). The radioactivity of *carboxy*[$^{14}C$]cinnamic acid becomes localized in C-2 of *(1)*. On the other hand, after addition of [1-$^{14}C$]-acetate, the total activity is found in the ring A. The biosynthesis of *(1)*, therefore, proceeds analogously to that of the isoflavones and not like that of normal coumarins [11].

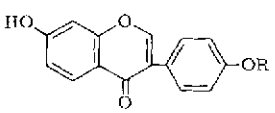
[10] Thia-aromatics, Part VIII; Part VII: *A. Lüttringhaus, M. Mohr*, and *N. Engelhard*, Liebigs Ann. Chem. *661*, 84 (1963).

[11] *H. Grisebach* and *W. D. Ollis*, Experientia (Basel) *11*, 4 (1961).

On administration of the labelled (•) chalcone-*O*-glucoside *(2)*, compound *(1)* is formed with a specific radioactivity which is of the same order of magnitude as that of the isoflavones, formononetin *(3)* and daidzein *(4)*, which also occur in alfalfa. The glucoside *(2)* is a common precursor for coumestrol and the isoflavones.



R = Glucose
*(2)*

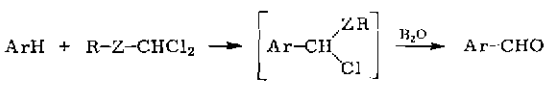


*(3)*, R = $CH_3$
*(4)*, R = H

## New Syntheses of Aldehydes and Carboxylic Acids Using α-Halogen Ethers

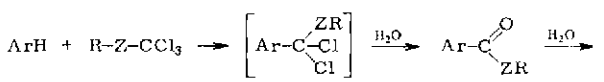
*H. Gross*, Berlin-Adlershof (Germany)

Aromatic hydrocarbons, phenols, phenyl ethers, and aromatic heterocyclics can be formylated or carboxylated easily by treatment with α-chloro ethers or α-chloro thioethers under Friedel-Crafts conditions. Dichloromethyl alkyl ethers or sulfides, for instance, give the corresponding aldehydes in good yield:



(Z = O, S)

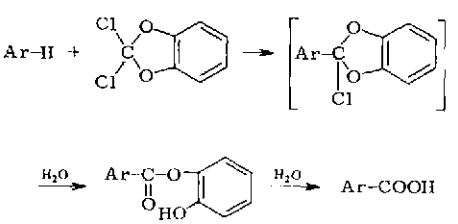
Polyhydroxybenzenes can be formylated smoothly with orthoformates and $AlCl_3$. Trichloromethyl alkyl ethers and sulfides react analogously to form carboxylic acids.



(Z = O, S)

Ar–COOH

The 1,2-*O*-dichloromethylene ether of pyrocatechol is particularly suitable for direct carboxylations. The pyrocatechol orthoester of the aromatic acid chloride is obtained first and is then smoothly hydrolysed by alkali to give the carboxylic acid.



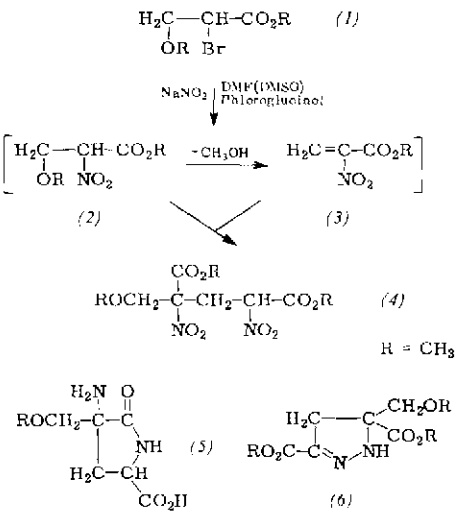
## Investigations of α-Nitro-β-alkoxypropionic Esters; α-Nitroacrylic Ester as Intermediate

*K. D. Gundermann*, Münster (Germany)

The reaction of methyl α-bromo-β-methoxypropionate *(1)* with sodium nitrite in dimethylformamide or dimethyl sulfoxide in the presence of phloroglucinol (Kornblum method [12]) gives dimethyl α-methoxymethyl-α,α′-dinitroglutarate *(4)*, which is formed from methyl α-nitro-β-methoxypropionate *(2)* and methyl α-nitroacrylate *(3)* by Michael addition as a non-isolable intermediate.

[12] *N. Kornblum, R. K. Blackwood*, and *J. W. Powers*, J. Amer. chem. Soc. 79, 2507 (1957).

The diester *(4)* is also obtained by oxidation of methyl α-oximino-β-methoxypropionate, which is prepared from *O*-methyl-DL-serine methyl ester, again via *(2)* and *(3)*. The structure of *(4)* is afforded by its reduction and hydrolysis to give α-methoxymethyl-α,α′-diaminoglutarolactam *(5)* which was synthetized independently by hydrogenation of *(6)*.



## Cinnoline Compounds as By-products in the Formation of Osazones from Aldoses

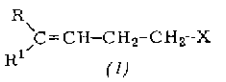
*H. J. Haas*, Heidelberg (Germany)

When glucose phenylosazone is prepared from D-glucose and phenylhydrazine in dilute acetic acid by the method of *E. Fischer*, 3-(D-*arabo*-tetrahydroxybutyl)cinnoline *(1)* is obtained as a by-product. The yield of *(1)* can be increased to 20 % by working in dilute hydrochloric acid. The structure was confirmed by degradation to 3-methylcinnoline which is known. The same by-product is formed in the preparation of glucosazone from D-mannose, but not from D-fructose, 1-deoxy-1-*p*-toluidino-D-fructose, or the hydrochlorides of D-glucosamine or D-isoglucosamine. 3-(D-*lyxo*-Tetrahydroxybutyl)-cinnoline and 3-(D-*threo*-trihydroxypropyl)-cinnoline are formed in addition to the osazones when D-galactose and D-xylose are treated with phenylhydrazine. Their structures were confirmed by degradation to cinnoline-3-carboxaldehyde.

## Investigations on Cyclopropane Compounds

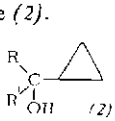
*M. Hanack, H. Eggensperger, K. Görler, S. Kang*, and *H. J. Schneider*, Tübingen (Germany)

Homoallyl compounds of general structure



*(1)*

rearrange under the conditions of a kinetically controlled reaction, with anchimeric assistance of the double bond, to form cyclopropyl carbinol derivatives. This reaction was studied: Homoallyl halides of structure *(1)* (R = $CH_3$, $R^1$ = H; R = $R^1$ = $CH_3$; R = H, $R^1$ = $C_6H_5$; R = H, $R^1$ = $FC_6H_4$; R = H, $R^1$ = cyclopropyl; R = $R^1$ = cyclopropyl; X = Cl and Br) rearrange practically quantitatively on hydrolysis with aqueous potassium carbonate or with silver oxide to give cyclopropyl carbinols of structure *(2)*.



*(2)*

Solvolysis of homoallyl tosylates [*(1)*, X = OTos] in methanol leads to only 30–40 % of the cyclopropyl carbinol owing to the more nucleophilic nature of the solvent. In addition, some

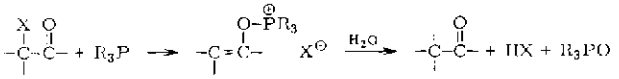
non-rearranged homoallyl ether [*(1)*, X = $OCH_3$] is formed. The anchimeric assistance of the double bond in open-chain homoallyl derivatives is shown in the solvolysis of 5-(*p*-nitrobenzoyloxy)-2-methyl-2-pentene *(1)*, R = $R^1$ = $CH_3$; X = $OCOC_6H_4NO_2^-$. The alkyl-oxygen bond is split and cyclopropylisopropanol [*(2)*; R = $R^1$ = $CH_3$] is formed.

When the naphthylsulfonate of 2-cyclopentenyl carbinol is rearranged in methanol, glacial acetic acid, or dioxan/water, anchimeric assistance of the double bond occurs and bicyclo[3,1,0]hexan-2-ol as well as $\Delta^3$-cyclohexenol are formed. The influence of the solvent on the course of the reaction in comparison with the deamination of 2-cyclopentenyl carbinylamine is being investigated. Furthermore, the kinetics of the reaction with various substituted homoallyl naphthylsulfonates in several solvents, were examined and compared with those of the saturated compound. Although the anchimeric assistance of the double bond leads to cyclopropyl carbinol compounds, the rate of solvolysis of the homoallyl compounds is only slightly increased.

## Reductive Dehalogenations Using Tertiary Phosphines

*H. Hoffmann* and *H. J. Diehr*, Mainz (Germany)

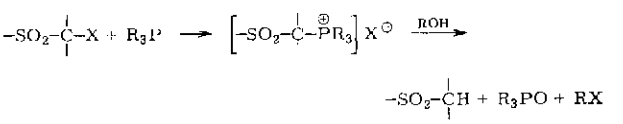
Tertiary phosphines react with various α-halogenocarbonyl compounds, to give enol phosphonium salts. These compounds are very susceptible to hydrolysis. They are decomposed with water to the simple dehalogenated carbonyl compounds, hydrogen halide, and tertiary phosphine oxides.



During the formation of the enol phosphonium salt, the halogen is split off as a cation, as in the analogous Perkow reaction. α,β-Dihalogenocarbonyl compounds react with tertiary phosphines to yield α,β-unsaturated carbonyl compounds and phosphine dihalides.

α-Halogenophosphonium salts and α-halogenophosphine oxides are dehalogenated by tertiary phosphines in the presence of protons.

α-Halogenosulfones are dehalogenated in the presence of water or alcohol, but in benzene or acetonitrile are converted into *C*-phosphonium salts.

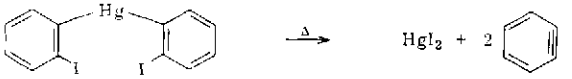


## Detection of Dehydrobenzene in the Gas Phase

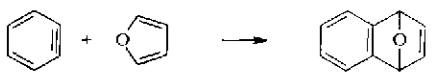
*R. W. Hoffmann* and *H. F. Ebel*, Heidelberg (Germany)

The intermediate existence of dehydrobenzene in solution can now be considered as assured. It remained, however, unestablished to what extent the dehydrobenzene molecule is stabilized in solution by solvation or complex formation. In order to prove the existence of free dehydrobenzene, it had to be prepared in the vapor phase and identified by chemical means.

Bis-(*o*-iodophenyl)mercury was evaporated in a stream of argon of 8 mm Hg and then decomposed at 700 °C.



The gases leaving the zone of decomposition were cooled and then brought into contact with furan vapor. Dihydronaphthalene-*endo*-oxide was formed and was then isomerized

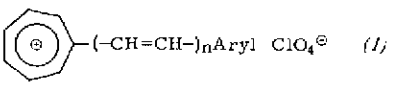


and identified as α-naphthol. It was ascertained by experiment and by calculation that the amount of furan which diffuses against the gas flow into the zone of decomposition is considerably smaller than the actual yield of naphthol. As the zones of decomposition of the substrate and of reaction with the trapping agent are far apart, the existence of a reactive particle, which is considered to be dehydrobenzene, must be postulated.

## Preparation and Investigation of Substituted Tropylium Salts

*Ch. Jutz*, München (Germany)

The cations *(1)* with the tropylium system as acceptor and substituted aryl residues as donors were used as relatively simple models for studying the stability (pK values) and color (spectra) of this type of salt.



Such salts (n = 0, aryl = $-C_6H_4-X$) were obtained via the corresponding tropilidines by treating arylmagnesium bromides with 7-methoxytropilidine or by electrophilic substitution of phenol or anilines with tropylium ion (from methoxytropilidine in acetic acid) followed by dehydrogenation. Salts of *(1)* with n = 1 (aryl = substituted phenyl, naphthyl, phenanthryl, anthranyl) and n = 2, 3, 4 (aryl = diphenyl) were obtained by condensation of aldehydes with methyltropylium perchlorate. The pK values (measured in acetonitrile/water, 1:1) of the ions of *(1)* with n = 0, aryl = $C_6H_4$–X (with X = H, *p*-$CH_3$, *m*-$CH_3$, *p*-$C(CH_3)_3$, *p*-$OCH_3$, *m*-$OCH_3$, *p*-OH, *p*-$OCOC_6H_5$, *p*-$C_6H_5$, *m*-$C_6H_5$, *p*-$N(CH_3)_2$, *p*-$NHCOC_6H_5$, *p*-F, *p*-Cl, *p*-Br, *m*-F, *m*-Cl, *m*-Br, *m*-$CF_3$) follow the Hammett σ-relationship closely with ρ = + 2.4.

## Chelate Complexes of Plutonium with 8-Hydroxyquinoline

*C. Keller* and *S. Eberle*, Karlsruhe (Germany)

In their ability to form metal chelates with 8-hydroxyquinoline (oxine) and some of its derivatives, the transuranium elements exhibit a significant difference from the remaining

| Reaction of | Oxine | 5-Chlorooxine | 5,7-Dichlorooxine | 2-Methyloxine |
|---|---|---|---|---|
| with: Np(IV) | $Np(R^1)_4$ | $Np(R^2)_4$ | $Np(R^3)_4$ | $Np(R^4)_4$ [a] |
| Np(VI) | Reduction | Reduction | Reduction | Reduction |
| Pu(III) | $Pu(R^1)_3$ | $Pu(R^2)_3$ | | |
| Pu(IV) | $Pu(R^1)_4$ | $Pu(R^2)_4$ | $Pu(R^3)_4$ | $Pu(R^4)_4$ [a] |
| Pu(V) | $H_2[PuO_2(R^1)_3]$ | $H_2[PuO_2(R^2)_3]$ | $H_2[PuO_2(R^3)_3]$ | $H[PuO_2(R^4)_2]\cdot H_2O$ |
| Pu(VI) | Reduction | Reduction | Reduction | Reduction |
| Am(III) | $Am(R^1)_3$ | $Am(R^2)_3$ | $Am(R^3)_3$ | |

[a] Basic chelates $R^4$: M = 3.2–3.7.

actinide elements, thorium and uranium. Pu(VI) and Np(VI) solutions are reduced to Pu(V) and Np(V) by 8-hydroxyquinoline at pH ≈ 2. $HPuO_2R^1_3$, which *Harvey* et al. [13] regarded as a Pu(VI) chelate, is actually a chelate of Pu(V): $H_2[PuO_2(R^1)_3]$.

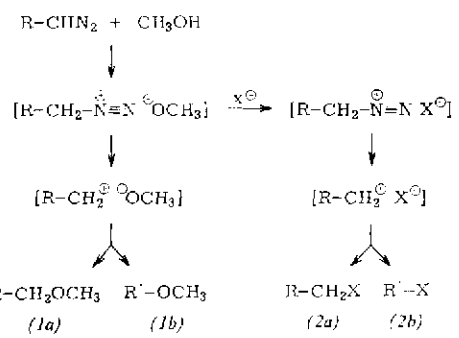
Precipitation of a Pu(IV) salt from its buffered solution with 8-hydroxyquinoline produces basic chelates $Pu(OH)_x(R^1)_{4-x}$, which are soluble in chloroform up to $x = 2$.

$Pu(R^1)_4$ and $Np(R^1)_4$ are obtained by precipitating a buffered solution of 8-hydroxyquinoline with an acidified solution of Pu(IV) or Np(IV). When oxygen is excluded, Pu(III) forms the complex $Pu(R^1)_3$. The table lists the chelates of transuranium elements obtained.

## Substitution of Aliphatic Diazonium Groups

*W. Kirmse*, Marburg/Lahn (Germany)

The reaction of aliphatic diazonium ions with nucleophilic reagents was investigated by the following method: aliphatic diazo compounds are protonated by alcohols even in alkaline medium to form primarily diazonium alkoxide ion pairs from which ethers *(1)* are obtained. Anions $X^-$ (halides, azide, thiolates) added in the form of their lithium salts can only be effective after displacement of the alkoxide since the acid HX does not occur under the conditions chosen.




The following systems are particularly instructive:

a) The isobutyl system. Besides isobutyl derivatives, t- and s-butyl derivatives ($R'-OCH_3$, $R'-X$) are formed in this case by rearrangement of the carbonium ion. The formation of the substitution products *(2)* is accompanied by less isomerization than the formation of the ethers *(1)* [*(2a)*: *(1a)* > *(2b)*:*(1b)*]. With increasing nucleophilicity of the added anion, the rearrangement is increasingly supressed and the yield of substitution products *(2)* increases.

b) The crotyl/methallyl system. The fraction of crotyl derivative formed from 1-diazo-2-butene increases with increasing nucleophilicity of the added anion. An analogous effect is not observed with 3-diazo-1-butene.

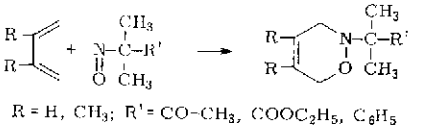
These results indicate an anion exchange at the stage of the diazonium ion, not at the carbonium ion stage. Some results are best explained by partial $S_N2$-character of the substitution; however, the assumption of an ion-pair process is generally adequate.

## Diels-Alder Syntheses with Nitroso Compounds

*D. Klamann, P. Weyerstahl*, and *M. Fligge*, Hamburg (Germany)

The hitherto known Diels-Alder syntheses using *C*-nitroso compounds are limited to aromatic nitroso and aliphatic geminal chloronitroso and cyanonitroso compounds; nitrosoisobutane does not react with dienes. Aliphatic α-nitroso ketones, α-nitrosocarboxylic esters, and aromatically substituted aliphatic nitroso hydrocarbons react with dienes to yield 3,6-dihydro-1,2-oxazines.

9-Nitrosotriptycene is thermally extremely stable but is sterically hindered and thus reacts by the Diels-Alder method only under vigorous conditions. Trichloronitrosomethane reacts smoothly with dienes in the presence of alcohols even



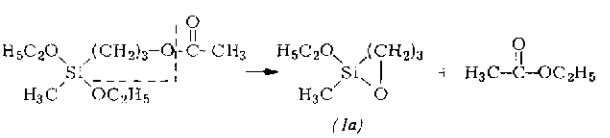

R = H, $CH_3$; R' = $CO-CH_3$, $COOC_2H_5$, $C_6H_5$

down to −25 °C to give 3,6-dihydro-1,2-oxazines (95 % yield) and tetraalkyl orthocarbonates. Aliphatic 1,1-nitronitroso compounds react in an analogous step, even in the presence of excess urea, to give *N*-nitroso-3,6-dihydro-1,2-oxazines and the appropriate ketals. The Diels-Alder reaction is synonymously influenced by increases in the positivity of the nitrogen atom and thermal stability of the nitroso compounds. Inorganic nitroso compounds, such as nitrosylsulfuric acid, yield the salts of the corresponding 1,2,6*H*-oxazines with 2,3-dimethylbutadiene after 1,4-addition and spontaneous rearrangement with ring closure. All the oxazines prepared or their derivatives may be hydrogenated in good yields to the isomer-free 1,4-aminobutanols.

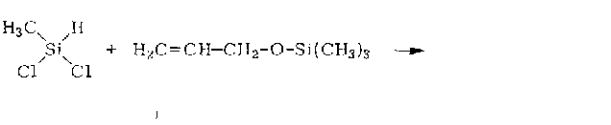
## Synthesis and Polymerization of 1-Oxa-2-silacyclopentane Derivatives

*G. Koerner* and *G. Rossmy*, Essen (Germany)

1-Oxa-2-silacycloalkanes [14,15] can be obtained by two new routes, leading to *(1a)* and *(1b)*.




*(1a)*




*(1b)*

Both syntheses allow many variations. The 1-oxa-2-silacyclopentane derivatives polymerize on standing at room temperature. The polymers can be quantitatively reconverted into the monomers by heating.

An equilibrium is established in solution in inert solvents, *e.g.* $CCl_4$. Solutions of *(1a)* have a constant monomer content of 24 g/l at total concentrations of over 100 g/l. The presence of dimeric compounds (ten-membered rings) was also established in some compounds.

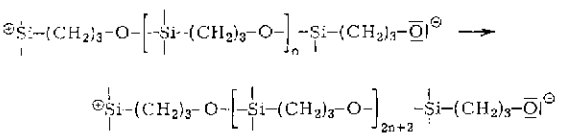
The viscosity of catalyst-free samples of *(1)* which were, stored in sealed vessels at room temperature shows considerable increases after the monomer content has fallen to its final value. This is presumably caused by the appearance of intermediate zwitterions.

[13] *B. G. Harvey, H. G. Heal, A. G. Maddock*, and *E. L. Rowley*, J. chem. Soc. (London) *1947*, 1010.

[14] *W. H. Knoth* and *R. V. Lindsey*, J. Amer. chem. Soc. *80*, 4106 (1958); *J. L. Speier, M. P. Davind*, and *B. A. Eyon*, J. org. Chemistry *25*, 1637 (1960).

[15] U.S.-Pat. 2983745 (May 9th, 1961), Dow Corning Corp., inventor: *J. L. Speier*; U.S.-Pat. 2888454 (May 26th, 1959), Union Carbide Corp., inventor: *D. L. Bailey*.

The fact that strong bases alkoxides or Lewis acids ($AlCl_3$) accelerate the polymerization (but also cause depolymerisation) is in agreement with this picture.



## Structure of Anomalous Oxalato Complexes of Platinum

*K. Krogmann*, Stuttgart (Germany)

The crystal structures of $K_2[Pd(C_2O_4)_2] \cdot 4\ H_2O$, $K_2[Pt(C_2O_4)_2] \cdot 2\ H_2O$ ("yellow salt"), and $K_{1.6}[Pt(C_2O_4)_2] \cdot 2.5\ H_2O$ ("violet salt") were examined. The yellow salt and the Pd compound contain isolated planar complex ions. In the violet salt, the complex ions are superposed one upon another; this leads to short Pt-Pt distances (2.75 Å). The Pt thereby has a mean oxidation number of 2.4. It is not possible to distinguish crystallographically between $Pt^{2+}$ and $Pt^{4+}$. The same oxidation number is observed in the "violet acid" $H_{1.6}[Pt(C_2O_4)_2]$and in the new compounds $H_{1.6}[Pt(OH)_2C_2O_4$ and $H_{1.6}[Pt(OH)_4]$. The "yellow acid" $H_2[Pt(C_2O_4)_2]$, which is only stable in the absence of air, was also prepared for the first time. On contact with air it forms the "violet acid". The reactions of these compounds in solutions, which have been regarded as rearrangements, can be interpreted on the basis of these new results.

## Refining of Titanium and Titanium Alloys by Melt Electrolysis Using a Liquid Lead Electrode

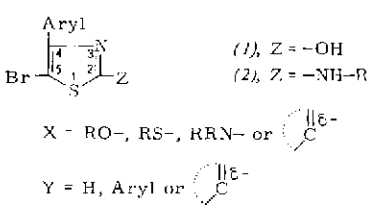
*H. Kühnl*, Gießen (Germany)

Crude titanium or titanium alloys were refined by melt electrolysis in a cell in which two separate chambers were connected through a liquid lead bielectrode. The electrolyte consisted of an NaCl melt at 850 °C containing dissolved lower titanium chlorides. The current densities at the mechanically stirred bielectrode amounted to 0.05 A/cm² at the most. The lead content of the refined titanium was below 0.005 %. About 0.1–0.3 % Fe contaminant was derived from the material of the crucible. When a titanium alloy with 5 % manganese was refined, only 0.7 % Mn was deposited in comparison with 2.71 % Mn in a conventional electrolysis cell. When a titanium alloy with 5 % chromium was used, a maximum of 0.05 % Cr passed over into the refined titanium (without the lead electrode, the amount is more than 0.8 % Cr).

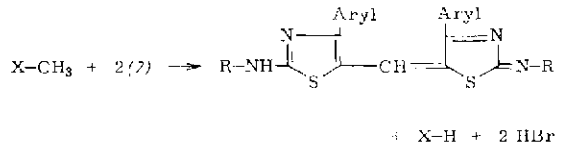
## "Thiazolizations" Using 2-Hydroxy- or 2-Amino-4-aryl-5-bromothiazole

*W. Lässig*, Leverkusen (Germany)

2-Hydroxy- *(1)* or 2-amino-4-aryl-5-bromothiazole *(2)* reacts in the melt at approximately 160 °C with compounds of general formula $X-CH_2-Y$.




One or both hydrogen atoms in $X-CH_2-Y$ are substituted by the thiazoyl residue, with vigorous evolution of hydrogen bromide. This new reaction may be suitable for the preparation of bis-5,5'-(2-aminothiazolyl)methane dyes according to the equation




## Cyclic Methylenephosphoranes

*G. Märkl*, Würzburg (Germany)

The synthesis of 1,1-diphenyl-1-phosphanaphthalene [16] and 1,1-diphenyl-1-phosphabenzene *(1)* [17] demonstrated that it is possible to obtain stable methylenephosphoranes of a new type by introduction of the $d_\pi$-$p_\pi$-double bond into a cyclic conjugated system.

An illustration of the bond proportions is attempted in Figure 1. Using the concepts developed by *Dewar* [18], linear combination of both the $d_{xz}$ and $d_{yz}$ orbitals concerned in the formation of the $d_\pi$-$p_\pi$-double bond yields two new orbitals $d_{\pi a}$ and $d_{\pi b}$ in the direction of the σ-bond axes; each of these can only interact with the pz orbital of a neighboring carbon atom. This regulation causes the phosphorus atom to act as an insulator in the cyclic conjugated

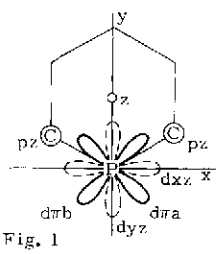
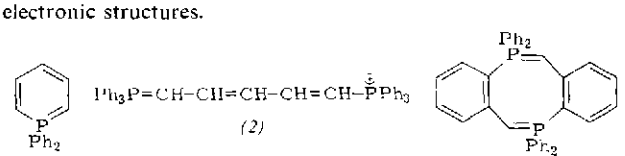
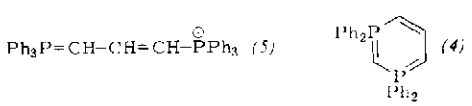


Fig. 1

system. As both of the d-orbitals together have only one electron to contribute, stabilization by means of the mesomeric energy gain of a delocalized π-electron system can be envisaged; these d-orbitals can participate as either electron donors or acceptors. Such a system of bonding should be regarded as an "internal cyanine". The close similarity between the ultraviolet spectra of *(1)* ($\lambda_{max}$ = 409 mμ in $CHCl_3$) and of the open-chain pentamethinephosphacyanine *(2)* ($\lambda_{max}$ = 432 mμ in $CHCl_3$) confirm the analogy of the electronic structures.




The working hypothesis that cyclic conjugated methylenephosphoranes are stabilized independently of the size of the ring if "internal cyanine" structures are possible is supported by the formation of *(3)* and *(4)* in aqueous solutions of the corresponding phosphonium salts. The resemblance of the ultraviolet spectra of the trimethinephosphacyanine *(5)* ($\lambda_{max}$ = 349 mμ in $CHCl_3$) and of *(4)* ($\lambda_{max}$ = 384 mμ in ether) is in accordance with the views expressed.

[16] *G. Märkl*, Angew. Chem. *75*, 168 (1963); Angew. Chem. internat. Edit. *2*, 145 (1963).

[17] *G. Märkl*, Angew. Chem. *75*, 669 (1963); Angew. Chem. internat. Edit. *2*, 479 (1963).

[18] *M. J. S. Dewar, E. A. C. Lucken*, and *M. A. Whitehead*, J. chem. Soc. (London) *1960*, 2423.

## The Existence and Constitution of Ternary Compounds between PbO, $SiO_2$, and Lead Halides

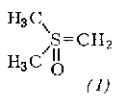
*L. Merker*, Würzburg (Germany)

Starting with melts of composition 2 $PbO{\cdot}SiO_2$, it is possible to replace about one-quarter of the molar PbO content by lead halides without the formation of two phases or without impairing solidification to a glass. These halogen-containing glasses exhibit pure anion conductivity. Devitrification experiments between 375 and 450 °C lead in all four series (F, Cl, Br, and I) to separations of hitherto unknown hexagonal pyromorphite-like structures. The dependence of the lattice constants a and c on the composition of the melts and the type of halogen as well as on the chemical behavior (substitutability of the surface halogen in the iodine-containing phase by ethoxyl; detected by Zeisel's method) suggests that the substances separated are a series of mixed crystals lying between the limiting compositions of $Pb_5(SiO_4)(SiO_3Hal)_2$ and $Pb_5(SiO_3Hal)_3Hal$, by analogy with the compounds $Pb_5(SiO_4)(PO_4)_2$ and $Pb_5(PO_4)_3Hal$, which form crystals of the pyromorphite type. Crystalline compounds, in which partial substitution of the oxygen contained in the $SiO_4$ tetrahedron by halogen must evidently be assumed, have thus been prepared for the first time.

## Reactions of Sulfur Ylides [19]

*H. Metzger*, Ludwigshafen/Rhein (Germany)

On the basis of the observation of *Corey* et al. that dimethyloxosulfonium methylide *(1)* reacts with carbonyl compounds



*(1)*

to form oxiranes, reactions of *(1)* with some C=N multiple bond systems and with α,β-unsaturated amides were investigated. Whereas *(1)* yields mainly aziranes [20] with *N*-benzylideneaniline and benzaldazine, it reacts with benzaldehyde phenylhydrazone to form benzaldehyde *N*-methyl-*N*-phenylhydrazone. Aliphatic and aromatic isocyanates yield 1:1 and 1:2 adducts with *(1)*, depending on the reaction conditions. In this way, new sulfur ylides are formed which are stable even towards hot water; these are dimethyloxosulfurylene-acetamides and -malonamides, and they can be reductively desulfurized to the acetamides and malonamides. As expected, the 1:1-adducts were converted into 1:2-adducts with further isocyanate. Certain aromatic nitriles react with *(1)* by 1:1 addition to yield (β-amino-β-aryl)-vinyldimethyloxosulfonium salts. These can be hydrolysed to ketones. In this way, for example, benzonitrile can be converted into acetophenone [20a].

When *(1)* was treated with α,β-unsaturated amides, cyclopropanecarboxamides or, by ring closure, pyrrolidone derivatives were obtained, depending on the nature of the amide. In this reaction, the yield of pyrrolidones is best with acrylamides. Cinnamanilide yielded a mixture of cyclopropane derivatives and pyrrolidone derivatives, whereas cinnamamide yielded only phenylcyclopropanecarboxamide [20].

## Isomerization of Cyclic Mono- and Diolefins during the Koch Carboxylic Acid Synthesis

*K. E. Möller*, Mülheim/Ruhr (Germany)

If cycloalkenes are subjected to the Koch carboxylic acid synthesis [21], carboxylic acids containing an additional carbon atom or their methyl esters are formed by condensation with CO and $H_2O$ or $CH_3OH$, respectively, in the presence of strongly acidic catalysts. Starting from cyclopentene, cyclohexene, or cyclododecene it is possible to obtain the corresponding secondary cycloalkanecarboxylic acids exclusively or preponderantly when catalysts containing boron fluoride are used; however, with cycloheptene, over 90 % tertiary 1-methylcyclohexane-1-carboxylic acid is formed by isomerization with ring contraction. Cyclooctene yields exclusively 1-methylcycloheptane-1-carboxylic acid and 1-ethylcyclohexane-1-carboxylic acid. In addition to only 10 % of a mixture of tertiary $C_{11}$ acids, the reaction of cyclododecene gives 32 % higher acids and – presumably by hydride transfer [22] – 22 % of a mixture of *cis*- and *trans*-decalin-9-carboxylic acids.

*cis*-Bicyclo[3,3,0]octane-1-carboxylic acid (pentalanecarboxylic acid) is formed under extremely mild conditions from 1,5-cyclooctadiene. Both 1,5- [23] and 1,6-cyclodecadiene [24] can be converted into *cis*- and *trans*-decalin-9-carboxylic acids in very good yields. A mixture containing 82 % 1,2,3,4,5,6,7,8-octahydronaphthalene and 18 % 2,3,4,5,6,7,8,10-octahydronaphthalene is obtained almost quantitatively by isomerization of the cyclodecadienes in boiling *n*-hexane with boron trifluoride etherate as catalyst.

## The Szilard-Chalmers Process in $K_2ReBr_6/K_2OsCl_6$ Mixed Crystals

*Horst Müller*, Freiburg/Breisgau (Germany)

Following neutron activation of $K_2ReBr_6$ and dissolution of the target, 28 % of the radioactive rhenium atoms obtained are present as perrhenate, the remainder as hexabromorhenate (retention). In order to elucidate the cause of the retention, the chemical reactions following the $^{185}Re(n,\gamma)^{186}Re$ nuclear process were investigated in $K_2ReBr_6/K_2OsCl_6$ mixed crystals. At low rhenium contents, 37 % of the active rhenium atoms are found in the form of perrhenate, the remainder as $ReCl_nBr_{6-n}$ ($6 \geqslant n \geqslant 0$), *viz.* 14 % $ReBr_6^{2-}$, 4 % $ReCl_6^{2-}$, and 45 % mixed hexa(chloro/bromo)rhenates. This shows that of the three mechanisms under discussion, *viz.* 1) no bond rupture, $*ReBr_6^{2-}$ is preserved, 2) billiard impact: $*Re + OsCl_6^{2-} \rightarrow *ReCl_6^{2-} + Os$, and 3) hot-zone reaction: $*Re + nCl^- + (6-n)Br^- \rightarrow *ReCl_nBr_{6-n}^{2-}$, the third is the main one, while the second is inefficient. The marked enrichment of the bromine in the complex ions representing the retention fraction relative to the bromide content of the mixed crystals leads to the conclusion that the formation of the retention fraction occurs in a very small zone around the original position of the recoil atom, the diameter of which can be estimated at 5 Å. The non-statistical distribution of the mixed hexa(chloro/bromo)rhenates proves that the atoms remain unmixed within the reaction zone.

## Disproportionation Reactions of Diboron Compounds

*H. Nöth, P. Fritz, K. H. Hermannsdörfer, W. Meister, H. Schick*, and *G. Schmidt*, München (Germany)

Diboron compounds decompose in accordance with the disproportionation scheme:

$$nB_2X_4 \rightarrow n\,BX_2 + B_{n+2}X_{n+4}$$

In addition boron(I) compounds $[BX]_m$ and products that are even richer in boron are formed.

When X = OR, $NR_2$, or R, decompositions and elimination reactions involving hydrogenation compete with the disproportionation. The order of stability

$$B_2[N(CH_3)_2]_4 > B_2(OR)[N(CH_3)_2] > B_2Cl[N(CH_3)_2]_3 \approx B_2Cl_2[N(CH_3)_2]_2 > B_2R[N(CH_3)_2]_3 > B_2R_2[N(CH_3)_2]_2 > B_2H[N(CH_3)_2]_3 > B_2F_4 > B_2Cl_4 > B_2R_2(OR)_2$$

[19] The observations described in this paper were originally submitted to Angewandte Chemie as a short communication on August 16th, 1963.

[20] *H. Metzger* and *K. Seelert*, Z. Naturforsch. *18b*, 335 (1963); Angew. Chem. internat. Edit. *2*, 624 (1963).

[20a] *H. Metzger* and *H. König*, Z. Naturforsch. *18b*, 976, 987 (1963).

[21] *H. Koch*, Brennstoff-Chem. *36*, 321 (1955); Fette, Seifen einschl. Anstrichmittel *59*, 493 (1957).

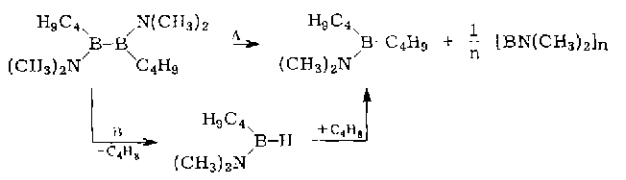
[22] *W. Haaf* and *H. Koch*, Liebigs Ann. Chem. *638*, 122 (1960).

[23] *G. Wilke*, Angew. Chem. *75*, 10 (1963).

[24] *G. Wilke* and *P. Heimbach*, unpublished results.

indicates the influence exerted by polarity and by π-bonds on the tendency towards disproportionation, which increases with any decrease in the electron density on the boron atoms.

The decomposition products which can be isolated depend on the reaction conditions.



+ polymeric products

A: sealed tube, 230°C
B: ambient pressure, 250°C

Polymeric products are formed via low molecular-weight straight-chain boron subcompounds, *e.g.* $C_4H_9[(CH_3)_2N]$-B–B[$N(CH_3)_2$]–B[$N(CH_3)_2$]$C_4H_9$, which can be isolated.

Dehalogenation of $B_2Cl[N(CH_3)_2]_3$ with liquid Na/K alloy leads to a tetraboron hexakisdimethylamide, $B_4[N(CH_3)_2]_6$, which on thermal decomposition yields $B_2[N(CH_3)_2]_4$ as a readily volatile main decomposition product together with a small amount of $B[N(CH_3)_2]_3$.

## Ring Syntheses Using Enamines and Ketene-N,N-acetals

*G. Opitz*, Tübingen (Germany)

Cycloaddition of ketenes onto enamines yielding 3-aminocyclobutanones proceeds smoothly in the aliphatic series. Although hetero-substituents in the ketene are not detrimental, aromatic substituents in ketenes and at the nitrogen atom of the enamine exert an inhibiting effect. Starting from ketene-*N,N*-acetals [$H_2C$=$C(NR_2)_2$] and ketene, 4-dialkylamino-6-methylcoumalines are obtained; these yield 1,3,5-triphenylbenzene with phenylmagnesium bromide and are degraded by sodium hydroxide, by way of triacetic acid, into acetone, acetic acid, and the dialkylamine.

Sulfenes, which are produced either from aliphatic sulfonyl chlorides and triethylamine or from a diazoalkane and $SO_2$ *in situ*, react with diazoalkanes to yield ethylenesulfones, and with enamines to yield β-aminotrimethylenesulfones. Cyclization to four-membered rings also occurs with 3-dialkylaminovinyl ketones and dienamines. On treatment with mesyl chloride-triethylamine, 1,1-dimorpholinoethylene yields 3-morpholinothietene-1,1-dioxide, via a cycloaddition and elimination of amine.

β-Amino-β-lactams, which are accessible from enamines and isocyanates, are also formed by cycloaddition of ketenes (produced *in situ*) onto amidines.

## Method for the Preparation of Complex Compounds of Elements in Higher Valence States

*Sw. Pajakoff*, Vienna (Austria)

The desired complexes are obtained by dissolving the stabilized and active oxides, oxo- and fluorometallates (*i.e.* oxocerate, fluoroterbate, *etc.*) of tetravalent Ce, Pr, Tb, Pb, Mn, Co, Ni, and Ag in complexing agents such as polyacetic acid, citric acid, trihydroxyglutaric acid, or aconitic acid, particularly in solutions of pH 8–10. The metal : ligand ratio in the solid complexes has a value of 1 : 1.

Stable fluorometallates of these tetravalent elements are obtained by fluorination of a mixture of the fluorides of the elements, alkali halides, and thermostable alkali fluorometallates at temperatures above 500 °C. The solid complex compounds of tetravalent Ce, Pr, Tb, Pb, Mn, Co, Ni, and Ag are very strong oxidizing agents; they are stable in air and are readily soluble in weakly alkaline solutions of pH $\leq$10. Above pH 11, the oxide hydrates of Ce(IV), Pr(IV), Tb(IV), and Pb(IV) [all yellow], and of Co(IV) [red-brown] precipitate out. On acidification of the complex solutions of tetravalent Ce, Pr, Tb, and Pb, which have a pH of 8.4–8.6, the sparingly soluble fluorides of tetravalent Pr, Ce, Tb, and Pb separate out in the form of yellow amorphous precipitates. Dioxides of Ce, Pr, Tb, Pb, Ni, Co, and Ag are obtained by thermal decomposition of the lower-valent metal nitrates in an oxidizing alkali nitrate melt. Individual reaction products are isolated by organic solvents, in particular, tributyl phosphate *(1)*. In this manner, tetravalent prascodymium and terbium nitrates and oxonitrates were isolated for the first time:

$Pr(NO_3)_4 \cdot 2BuO_3PO$; $PrO(NO_3)_2$; $Tb(NO_3)_4 \cdot 2BuO_3PO$; $TbO(NO_3)_2$.

Selective extraction of mixtures of higher oxides of Ce, Pr, Tb, Mn, Pb, Co, Ni, or Ag in complexing solutions yields the very pure dioxides of these elements. In the selective extraction of the oxoterbate $Tb_4O_7$ with 0.1 M EDTA solution, a reddish-brown highly colloidal oxoterbate(IV) was isolated. The method is also suitable for the preparation of pure oxometallates of the transition elements in higher oxidation stages [25]. Alkaline earth hydroxides in excess are very rapidly and completely removed with dilute complexing solutions of pH 9–9.5.

## Alkylgallium Derivatives

*G. Raab*, Erlangen (Germany)

Coordination compounds of tertiary amines with gallium trialkyls or dialkylgallium halides were prepared.

| Compound | B.p. [°C/mm Hg] | M.p. [°C] |
|---|---|---|
| $(C_2H_5)_3Ga \cdot N(CH_3)_3$ | 92/15 | – 28 |
| $(C_2H_5)_3Ga \cdot N(C_2H_5)_3$ | 52–54/$10^{-2}$ | – 6 |
| $(C_2H_5)_3Ga \cdot NC_5H_5$ | 62–65/$10^{-2}$ | ca. –40 |
| $(nC_4H_9)_3Ga \cdot N(CH_3)_3$ | 70/$10^{-3}$ | ca. –50 |
| $Cl(C_2H_5)_2Ga \cdot N(CH_3)_3$ | 74/$10^{-3}$ | ca. 0 |
| $Cl(C_2H_5)_2Ga \cdot NC_5H_5$ | 95–100/$10^{-2}$ | – 5 |
| $Cl(C_2H_5)_2Ga \cdot H_2NC_2H_4NH_2$ | | 170–180 (decomp.) |
| $Cl(nC_4H_9)_2Ga \cdot N(CH_3)_3$ | 80–85/$10^{-3}$ | ca. 0 |

Whereas pure gallium trialkyls and dialkylgallium halides possess practically no conductivity ($<10^{-8}$ mho/cm), the amine coordination compounds of these substances exhibit specific conductivities which are sometimes quite substantial and which are due to the amine-stabilized dialkylgallium ions.

$$2\ ClR_2Ga \cdot NR'_3 \rightleftarrows [R_2Ga(NR'_3)_2]^+ + [R_2GaCl_2]^-$$

This interpretation is confirmed for instance by the salt-like properties of the compound $[(C_2H_5)_2Ga\ en]^+\ Cl^-$ (en = ethylenediamine).

In the case of the alkylgallium dihalides, which also exhibit conductivity, ion formation is presumably caused by the strong tendency to form the $[GaX_4]^-$ ion and by the stabilization of $[R_2Ga]^+$ made possible by this ion.

$$(RGaX_2)_2 \rightleftarrows [R_2Ga]^+ + [GaX_4]^-$$

The following order of specific conductivities was determined:

| Compound | [mho/cm] at 80 °C |
|---|---|
| $(C_2H_5)_3Ga \cdot NC_5H_5$ | $6.0 \times 10^{-7}$ |
| $Cl(C_2H_5)_2Ga \cdot N(CH_3)_3$ | $1.3 \times 10^{-4}$ |
| $Cl(C_2H_5)_2Ga \cdot NC_5H_5$ | $8 \times 10^{-4}$ |
| $(C_2H_5)GaCl_2$ | $5.3 \times 10^{-3}$ |

[25] *R. Scholder* and *W. Klemm*, Angew. Chem. 66, 461 (1954).

## A Synthesis of Vomicine

*P. Rosenmund*, Frankfurt/Main (Germany)

According to *H. Wieland* and *R. Robinson*, the structure of vomicine, a minor alkaloid of *Strychnos nux vomica* L., is that of 4-hydroxy-*N*-methylpseudostrychnine. This formula has been confirmed by synthesis. 2-Bromostrychnine was nitrated in the 4-position [26], and the resulting bromonitrostrychnine was reduced with sodium amalgam to 4-aminostrychnine. The latter was converted on diazotization and boiling into 4-hydroxystrychnine in good yield, obviously thanks to a neighboring group effect. 4-Hydroxypseudostrychnine can be obtained through the *N*-oxide of this compound by a chromate-catalysed Polonovski reaction, and then be methylated by methyl iodide in methanol to give vomicine in 15 % yield. The ultraviolet absorption curves show that the deviation in absorbance of vomicine from that of 4-hydroxystrychnine is due to the methylation (the last step of the synthesis) and can be explained by the approach of the negatively charged oxygen atom of the zwitterionic form closer to the benzene nucleus.

## A Novel Decomposition of Peresters

*C. Rüchardt* and *H. Schwarzer*, München (Germany)

t-Butyl 2,4,6-cycloheptatrieneperoxycarboxylate *(1)* [27] and t-butyl 2,3-dipropylcyclopropenylperoxycarboxylate *(2)* are split into t-butanol, $CO_2$, and tropylium or dipropylcyclopropenium cations respectively by acid catalysis.

$$R{-}CO{-}O{-}O{-}t\text{-}C_4H_9 \xrightarrow[\text{Acetonitrile}]{HClO_4,\ 0\,^\circ C} R^+ + CO_2 + t\text{-}C_4H_9{-}OH$$

t-Butyl 2,3-benzo-2,4-norcaradiene-7-peroxycarboxylate *(3)*, 7*H*-cycloprop[*a*]acenaphthylene-7-peroxycarboxylate *(4)*, diphenylperoxyacetate *(5)*, and *exo*-bicyclo[2,2,1]hept-5-ene-2-peroxycarboxylate *(6)* do not undergo this fragmentation.

The thermal decomposition of *(1)* and *(2)* proceeds via a radical fission, since the rate of decomposition is little

$$R{-}CO{-}O{-}O{-}t\text{-}C_4H_9 \rightarrow R^\cdot + CO_2 + t\text{-}C_4H_9O^\cdot$$

influenced by the polarity of the solvent and since no cycloheptatrienyl methyl ether or dipropylcyclopropenyl methyl ether could be detected when the decomposition was carried out in methanol. In inert solvents compound *(1)* decomposes sixty times faster than *(5)*, and *(2)* ten times faster than *(5)* [28]; this is due to the more favorable entropy of activation of *(1)* and *(2)* and to a polar effect [29]. Esters *(3)* and *(4)* undergo thermolysis solely by fission of the peroxide bond in the rate-determining step of the reaction.

## Attempts to Prepare $C_6O_6$

*J. Sauer*, München (Germany)

Judging from kinetic studies [30], it might be expected that the double anhydride $C_6O_6$ *(1)* of ethylenetetracarboxylic acid *(2)* would exhibit dienophilic activity comparable to that of tetracyanoethylene *(3)*. Various methods of preparing *(1)* from *(2)* by dehydration failed. The Diels-Alder adduct *(4)* of $C_6O_6$ and 9,10-dimethoxyanthracene was prepared in 85 % yield by an independent route and decomposed in $10^{-3}$ M solution in dioxan to give about 20 % dimethoxyanthracene *(5)* and *(1)*; in the presence of one mole equivalent of cyclopentadiene, the decomposition proceeds even in $10^{-4}$ M solution in up to 95 % conversion and is strictly of the first-order; *(1)* accordingly possesses considerable dienophilic activity.

In preparative experiments, *(1)* may be trapped from decomposing *(4)* with dienes in the form of Diels-Alder adducts: cyclopentadiene (81 % adduct), 2,3-dimethylbutadiene (91 %), dimethylfulvene (56 %), diphenylfulvene, chloroprene (60 %), and 1,4-diphenylbutadiene (81 %); *(5)* resulting from *(4)* was isolated to 80–100 %. With bicycloheptadiene, the homo-Diels-Alder adduct (81 %) resulted. On boiling *(4)* in dioxan or toluene, up to 78 % of a pure isomerization product was isolated to which the structure of a Diels-Alder adduct of *(1)* at the 1,4-positions of *(5)* was assigned. Compound *(3)* is unable to undergo 1,4-addition under analogous conditions. The Diels-Alder adducts of *(3)* and 9-phenyl-, 9-chloro-, 9-methoxy-, and 9,10-dimethoxyanthracene are cleaved in dioxan at 20 °C partly spontaneously and partly at a measurable rate. Attempts to prepare solutions of free *(1)* are in progress.

[26] *P. Rosenmund* and *H. Franke*, Chem. Ber. *96*, 1741–1746 (1963).

[27] *C. Rüchhardt* and *H. Schwarzer*, Angew. Chem. *74*, 251 (1962); Angew. Chem. internat. Edit. *1*, 217 (1962).

[28] *P. D. Bartlett* and *R. R. Hiatt*, J. Amer. chem. Soc. *80*, 1398 (1958).

[29] *P. D. Bartlett* and *C. Rüchhardt*, J. Amer. chem. Soc. *82*, 1753 (1960).

[30] *J. Sauer*, *H. Wiest*, and *A. Mielert*, Z. Naturforsch. *17b*, 203 (1962).

## Compounds of Niobium with Elements of the 5th and 6th Main Groups

*H. Schäfer* and *W. Fuhr*, Münster (Germany)

The compounds NbX and $NbX_2$ (X = S, Se, or Te) can be transported chemically with iodine in a temperature gradient (900/1050 °C). NbX migrates to the higher and $NbX_2$ to the lower temperature zone.

$$NbX + 2\,I_2,\ g = NbI_4,\ g + 0.5\,X_2,\ g;\ \Delta H\,^\circ(R)\ \text{negative}$$

$$NbX_2 + 2\,I_2,\ g = NbI_4,\ g + X_2,\ g;\ \Delta H\,^\circ(R)\ \text{positive}$$

This makes it possible to carry out syntheses and separations and to grow crystals. The arsenides and antimonides of niobium can also be transported with iodine.

If closely neighboring compounds are present, or if non-stoichiometric (or doped) phases of definite composition are to be obtained, it is advisable to effect transportation with a "buffered gas phase", *e.g.* to transport the niobium oxides with a $Br_2$–$NbBr_4$–$NbBr_5$ gas phase.

## Preparation of New N-Silylaminosulfanes by Nucleophilic Rupture of S—S Bonds

*O. Scherer* and *Max Schmidt*, Marburg/Lahn (Germany)

In connection with the problem of strengthening the bond between the nitrogen and silicon in the silylated alkali amides prepared by *Wannagat* and collaborators [31] by means of the lone pair of electrons on the nitrogen, we studied the nucleophilic behavior of these substances toward sulfur-sulfur bonds. It was thereby found that sodium bistrimethylsilylamide $NaN[Si(CH_3)_3]_2$ is not only suitable for effecting removal of elemental sulfur [32] but also splits disulfanes even under mild conditions. In addition to the sodium thioxide, a considerable number of new types of *N*-silylaminosulfanes are thereby made readily accessible according to the equation

$$[R_3Si]_2NNa + x{-}S{-}S{-}x \rightarrow (R_3Si)_2N{-}S{-}x + Na{-}S{-}x$$

x = $C_2H_5$; n-$C_4H_9$; $C_6H_5$; $C_6H_5CO$; $C_2H_5{-}O{-}CO$; i-$C_3H_7{-}O{-}CS$; $(CH_3)_2N{-}CS$ and NC

As is to be expected, replacement of R = $CH_3$ by i-$C_3H_7O$ leads to a substantial decrease in the reactivity of the silylamide towards sulfur, on account of the greater demand placed by the silicon on the lone electron pair of the nitrogen.

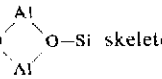
[31] For example, *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

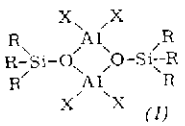
[32] *O. Scherer* and *M. Schmidt*, Naturwissenschaften, in the press.

## Trimethylsiloxychloroalane, a Crystalline, Distillable Compound with a Four-membered Ring Structure

*H. Schmidbaur* and *F. Schindler*, Marburg/Lahn (Germany)

Molecular-weight determinations and infrared as well as NMR spectroscopic investigations carried out on trialkylsiloxydichloro- and trialkylsiloxydibromoalanes have proved that these compounds possess a dimeric structure

with a $d_\pi$-$p_\pi$-stabilized planar  skeleton and the formula *(1)*.



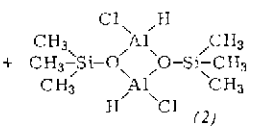
*(1)*

R = alkyl, X = Cl, Br

Cleavage of hexaalkyldisiloxanes with $AlI_3$ has now made it possible to prepare the isostructural diiodo compounds (X = I), which were hitherto regarded as being non-existent, in a pure state in the form of stable crystalline substances.

Treatment of such compounds *(1)* with $LiAlH_4$ and subsequent decomposition by distillation of the aluminohydride complexes formed have revealed a pathway to new types of stable aluminum-hydrogen compounds. Thus, trimethylsiloxydichloroalane *(1)*, R = $CH_3$, X = Cl, reacts with two equivalents of $LiAlH_4$ to form polymeric aluminohydride as well as *(2)*, m.p. 20.5 °C, b.p. 63–65 °C, the structure of which was determined by analysis, molecular-weight determination, and infrared and NMR spectra.

$$[(CH_3)_3SiOAlCl_2]_2 + 2\ LiAlH_4 \longrightarrow 2\ LiCl + 2\ (AlH_3)_n$$



*(2)*

Compound *(2)* can be methylated with $LiCH_3$ to give stable trialkylsiloxyalkylaluminohydrides [*(1)*, R = $CH_3$, X = H, $CH_3$] and can be hydrogenated further.

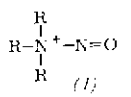
## Alkoxydiazenium Salts

*A. Schmidpeter*, München (Germany)

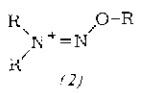
Methyl iodide reacts with dimethylnitrosamine according to the equation

$$2\ CH_3I + (CH_3)_2NNO \rightarrow [(CH_3)_4N]I + NO + \tfrac{1}{2}I_2$$

This suggests an initial alkylation of the nitrosamine at the amino nitrogen *(1)*. On the other hand, Lewis acids generally add the to the oxygen of the nitrosamine system [33] and therefore, by analogy, *O*-alkylation *(2)* was to be expected.



*(1)*



*(2)*

Trialkyloxonium hexachloroantimonates and dialkylnitrosamines yield salts of the composition $[R_3N_2O]SbCl_6$. Proton magnetic resonance spectra establish the dissimilarity of the three alkyl groups and hence structure *(2)*. In contrast to the trialkylnitrosylammonium salts *(1)*, the new 1,1-dialkyl-2-alkoxydiazenium salts *(2)* are very stable.

A simple way to prepare compounds of type *(2)* is the reaction of dimethyl sulfate with dialkylnitrosamines at room temperature.

$$(CH_3)_2SO_4 + R_2NNO \rightarrow [R_2NNOCH_3]SO_4CH_3$$

The reaction is reversible; the starting compounds are recovered by vaccum distillation. Crystalline methoxydiazenium salts are precipitated from solutions of the resulting 1,1-dialkyl-2-methoxydiazenium methyl sulfates by anions such as $SbCl_6^-$, $TeCl_6^{2-}$, $PF_6^-$, and $B(C_6H_5)_4^-$.

The course of the protonation of dialkylnitrosamines is of interest in view of their acid-catalysed hydrolysis. The crystalline compound obtained by addition of HCl onto dimethylnitrosamine is shown by its PMR spectrum to have the proton bound to the oxygen. HCl combines with the dimethylnitrosamine/antimony pentachloride adduct to give a compound which decomposes again *in vacuo*.

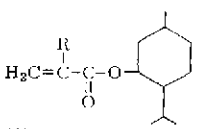
$$(CH_3)_2NNOSbCl_5 + HCl \rightleftarrows [(CH_3)_2NNOH]SbCl_6$$

Its reaction with diazomethane to the methoxy compound $[(CH_3)_2NNOCH_3]SbCl_6$ shows that the adduct is 1,1-dimethyl-2-hydroxydiazenium hexachloroantimonate.

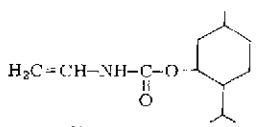
## Radiochemical Polymerization of Some Optically Active Monomers

*R. C. Schulz*, Mainz (Germany)

The optically active monomers *(1)*–*(3)* were obtained by treating L-menthol with acrylic acid, methacrylic acid, or vinyl isocyanate.



*(1)*: R = H
*(2)*: R = $CH_3$



*(3)*

Esters *(1)* and *(2)* can be polymerized in bulk or in solution with azoisobutyrodinitrile, Grignard reagents, or $\gamma$-radiation from a Co source. Compound *(3)* also undergoes radical polymerization either in the melt or in solution; it could also be polymerized by $\gamma$-radiation in solution, but not in the crystalline state.

All the polymers of *(1)*–*(3)* are optically active. The direction of rotation is the same as with the monomers, but the value of the rotation is less. It is possible to obtain translucent, optically active molded solids by bulk polymerization initiated by radiation.

## Formation of Novel Organotin-Phosphorus Compounds by Reactions of Tetraphenyltin with Elemental Phosphorus

*H. Schumann*, *H. Köpf*, and *Max Schmidt*, Marburg/Lahn (Germany)

Tetraphenyltin and phosphorus react in an evacuated sealed tube at temperatures up to about 260 °C to form diphenylstannylenetriphenylphosphorane $(C_6H_5)_2Sn{-}P(C_6H_5)_3$, which on working up in air gives rise to diphenyltin oxide and triphenylphosphine oxide. Between 260 and 280 °C, depending on the quantitative ratio, triphenylphosphine and various phenyltin phosphides are obtained which are oxidized to organotin phosphates with air. Triphenylstannyldiphenylphosphine $(C_6H_5)_3Sn{-}P(C_6H_5)_2$ and polymeric phenyltin phosphides $[(C_6H_5)SnP]_x$ can be isolated. Their structure is proved by cleavage of the oxidation products with alcoholic sodium hydroxide:

$$(C_6H_5)_3Sn{-}P(C_6H_5)_2 \xrightarrow{O_2} (C_6H_5)_3Sn{-}O{-}\overset{O}{\overset{\|}{P}}{-}(C_6H_5)_2$$

$$\xrightarrow{OH^\ominus} (C_6H_5)_3SnOH + (C_6H_5)_2\overset{O}{\overset{\|}{P}}{-}ONa$$

$$[(C_6H_5)SnP]_x \xrightarrow{2\,O_2} [(C_6H_5)SnPO_4]_x \xrightarrow{OH^\ominus}$$

$$(C_6H_5)SnOONa + Na_3PO_4$$

[33] *A. Schmidpeter*, Chem. Ber. *96*, 3275 (1963).

Triphenylstannyldiphenylphosphine is also obtained from triphenylchlorostannane and lithiodiphenylphosphine or from triphenylstannyl-lithium and diphenylchlorophosphine. Above 280 °C, tetraphenyltin and phosphorus form only triphenylphosphine and alloy-like tin phosphides of variable composition.

### The Constitution of the Horse-Chestnut Saponin Aescin

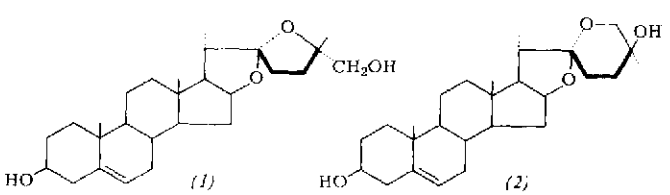
*R. Tschesche, U. Axen,* and *G. Snatzke,* Bonn (Germany)

When aescin is completely hydrolysed, it yields aescigenin, glucose, xylose, glucuronic acid, tiglic acid, and acetic acid [34]. Following acidic hydrolysis of aescin, in addition to aescigenin, a product was isolated which still contained both fatty acids in the genin. The structure of this "deglycoaescin" was determined by chemical reactions to be that of 28-(α-methyl-β-acetoxybutyryl)aescigenin; this was confirmed by its mass spectrum. The linkage of the sugar was elucidated by methylation and subsequent hydrolysis of the unaltered glycoside, of the glycoside after reduction at the carboxyl group of the glucuronic acid moiety, and of the partially hydrolysed glycoside. It appears that the xylose is attached at C-2 and the glucose at C-4 of the glucuronic acid. The glucuronic acid is probably bound glycosidically to the OH at C-3 of the aescigenin.

### The Constitution of a Cholegenin Analogue from the Vegetable Kingdom

*R. Tschesche* and *K. H. Richert,* Bonn (Germany)

A saponin was isolated from the roots of *Solanum sisymbriifolium* which was not precipitated with cholesterol. On hydrolysis with acid, this yielded a new genin, nuatigenin *(1)*, $C_{27}H_{42}O_4$, the first cholegenin analogue of plant origin. Mineral acids rearrange it to the structural isomer isonuatigenin *(2)*. This was related via its 24,25-anhydro compound to diosgenin and tigogenin. The constitutional formula suggested is that of *(20S,22S,25S)*-Δ⁵-spirostene-3β,25-diol.




From this it follows that the structure of nuatigenin is that of *(20S,22S,25S)*-22,25-epoxy-Δ⁵-furostene-3β,27-diol, as inversion of configuration at C-25 is excluded in the rearrangement of *(1)* to *(2)*.

### Geometrically Isomeric Pairs with Preferred cis-Configurations Among Substituted Ethylenes and 1,3-Butadienes

*H.-G. Viehe,* Brussels (Belgium)

Until now, it has been generally accepted that, under equilibrium conditions, the substituents on the spine of a molecule of both saturated and olefinic compounds prefer to take up positions furthest removed from one another. In the case of geometric isomers at least, this picture is false in many instances. Instead, the following can be considered as a first working hypothesis: the forces of attraction predominate between substituents, provided H–H interaction (as in pure hydrocarbons) or extreme overcrowding are absent.

Thermal isomerization of 2-bromo-1-iodoethylene at 175 and 225 °C proves that the *cis*-isomer is the more stable, contrary to previous steric descriptions. Moreover, of the ten possible 1,2-dihalogenoethylenes, *trans*-configuration is favored only in 1,2-diodoethylene. Furthermore, when 2-bromo-1-iodoethylene is warmed, an equilibrium is attained between the isomeric pairs of 1,2-dibromo-, 1,2-diodo-, and 2-bromo-1-iodoethylene via intermolecular halogen exchange. The equilibrium is experimentally attainable from all sides. 2-Fluoro-1-iodoethylene is formed analogously from 2-fluoro-1-bromoethylene by warming the latter with sodium iodide, and its formerly unknown *trans*-isomer can be isolated. Photochemical addition of 2-fluoro-1-iodoethylene onto ethylene and fluoroethylene permits the synthesis of 1-fluoro-1,3-butadiene and 1,4-difluoro-1,3-butadiene. Like their chloro analogues, both show *cis*-preference when subjected to isomerization with iodine in benzene solution.

### The Structure of the so-called "Alkali Carbonyls"

*E. Weiss* and *W. Büchner,* Geneva (Switzerland)

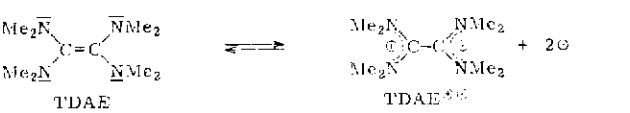
In liquid ammonia, carbon monoxide and alkali metals interact to give highly reactive, pyrophoric products of gross formula $(MCO)_x$ where M = Na, K, Rb, or Cs. These consist of an organometallic compound plus the metal derivative of dihydroxyacetylene $MOC{\equiv}COM$ (main constituent). On hydrolysis, both substances yield glycolic acid. The dihydroxyacetylene derivatives crystallize tetragonally (space group I 4/mmm-$D_{4h}^{17}$) with two formula units to each cell. The most important structural element is the linear anion $^{\ominus}|\overline{O}-C{\equiv}C-\overline{O}|^{\ominus}$ with approximate interatomic distances of C–C = 1.20 Å and C–O = 1.28 Å. Each oxygen atom is surrounded by five cations (tetragonal pyramid with O at the center of the base). The same environmental relationships occur in potassium methoxide (space group P 4/nmm-$D_{4h}^{7}$; 2 $KOCH_3$ per cell). Sodium methoxide, however, crystallizes in the $LiOCH_3$ lattice form, where each oxygen atom is surrounded by four cations. When, on the other hand, about 30 % NaOH is introduced (statistical distribution by partial hydrolysis of $NaOCH_3$), the $KOCH_3$ lattice is formed.

### Chemistry of Tetrakis(dimethylamino)ethylene

*N. Wiberg* and *J. W. Buchler,* München (Germany)

Tetrakis(dimethylamino)ethylene (TDAE) is a strong electron donor. Depending on the nature of the electron acceptor, the electron pair of (a) the double bond, (b) the nitrogen atom, or (c) the complete electronic system may be involved in the following reactions.

a) Strong oxidizing agents [35] convert TDAE into the dication $TDAE^{\oplus\oplus}$:

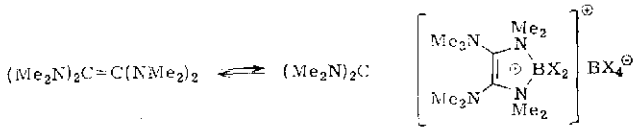



From the chemical point of view, TDAE is thus opposed to tetracyanoethylene (TCNE), which takes up electrons with extreme ease. Accordingly, TDAE reacts with TCNE with complete electron transfer, to yield the salt $[TDAE^{\oplus\oplus}][TCNE^{\ominus}]_2$. The radical cation $TDAE^{\oplus\ominus}$, corresponding to the radical anion $TCNE^{\ominus}$, was identified by mass spectroscopy.

[34] See *J. Wagner* and *J. Bosse,* Hoppe-Seylers Z. physiol. Chem. *320,* 27 (1960), where further references are given.

[35] *N. Wiberg* and *J. W. Buchler,* Angew. Chem. *74,* 490 (1962); Angew. Chem. internat. Edit. *1,* 406 (1962); Chem. Ber. *96,* 3223 (1963).

b) With Lewis-acids [36], *e.g.* $BX_3$, where X = F or H, TDAE forms cyclic "borazylammonium" salts *(1)*. This type of reaction (b), together with (a), disproves the existence of a carbene equilibrium.



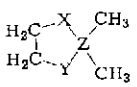
*(1)*

c) A compound in which the entire electron system of TDAE is involved in bond formation is encountered in the crystalline electron donor-acceptor complex $TDAE(TNB)_2$, where TNB = *s*-trinitrobenzene. Spectroscopic results suggest a sandwich arrangement of the molecules.

## New Heterocycles Containing Germanium and Silicium

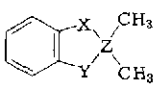
*M. Wieber* and *Max Schmidt*, Marburg/Lahn (Germany)

Bifunctional halogenoalkyl-germanes and -silanes may be converted practically quantitatively into the heterocycles *(1)* by means of glycol or its monothio or dithio analogue.



*(1)* Z = Ge or Si; X = Y = O; X = Y = S; X = O, Y = S

Catechol or its amino or thio analogue similarly furnish the new ring-compounds fused onto a benzene ring.

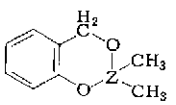


Z = Ge or Si; X = Y = O; X = Y = NH; X = O, Y = NH; X = S, Y = NH

*(2)*

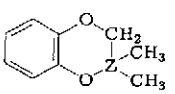
*o*-Hydroxybenzyl alcohol yields heterocycles of type *(3)*. Their isomeric molecules *(4)* are formed from chloromethyl-dimethyl-chlorogermane or -chlorosilane and catechol.

*(3)*



Z = Ge or Si

*(4)*



## Novel Dienylation Reactions

*D. Wittenberg*, Ludwigshafen/Rhein (Germany)

Hardly any substitution reactions on dienes have been reported up to now. Novel types of dienylation reactions were reported in which a 1,3-diene is added onto carbon-carbon multiple bonds in the form of the dienyl and hydrogen radical.

$$CH_2{=}CH{-}CH{=}CH_2 + RCH{=}CHR' \rightarrow CH_2{=}CH{-}CH{=}CH{-}CHR{-}CH_2R'$$

*(1)*: R = H, R' = H

*(2)*: R = $-CH{=}CH_2$, R' = H

*(3)*: R = H, R' = $-COOR''$

The brown solutions of "cobalt – diene complexes" formed on reduction of cobalt compounds with metal alkyls in the presence of 1,3-dienes are used as catalysts.

Butadiene is converted into a mixture of straight-chain oligomers. The reaction can be controlled so as to give 3-methyl-1,4,6-heptatriene *(2)* and 1,3,6-octatriene as main products. Butadiene and ethylene form 1,3-hexadiene *(1)*, butadiene and acrylic esters give 4,6-heptadiene-1-carboxylic esters *(3)*. Isoprene and acrylic ester give 6-methyl-4,6-heptadiene-1-carboxylic ester. 1,8-Diphenyl-1,3,5,7-octatetraene, the product of two-fold dienylation, is formed from phenylacetylene and butadiene.

Hydrocarbons and ether are used as solvents. The preferred reaction temperature lies between 30 and 100 °C.

[VB 750/109 IE]

German version: Angew. Chem. *75*, 1106 (1963)

[36] *N. Wiberg* and *J. W. Buchler*, J. Amer. chem. Soc. *85*, 243 (1963); Chem. Ber. *96*, 3000 (1963).

## Isomerism of Hydroxylamine Derivatives

*O. Exner*, Prague (Czechoslovakia)

The infrared spectra of hydroxylamine derivatives confirm the correctness of the formula R–CO–NHOH preferred today for hydroxamic acids rather than R–C(NOH)OH; however, a new formula had to be put forward for the anion. It had previously been assumed that the hydrogen linked to the oxygen dissociates; thus, all the *O*-derivatives were called esters. However, it was shown by comparison of the dissociation constants (in 80 % methyl cellosolve) of *O*- and *N*-substituted benzhydroxamic acids that it is the hydrogen atom bound to the nitrogen that is acidic. If the pK values of a number of *O*-substituted benzhydroxamic acids are plotted against the Taft inductive constants of the substituents, the point for the unsubstituted acid lies on the same streight line. On the other hand, the *N*-derivatives are mostly much weaker acids; their acidity depends not only on the inductive but also on the steric effects of the substitutents. The Hammett ρ-constant for benzhydroxamic acids that are substituted in the nucleus, as well as for *O*-benzoylbenzhydroxamic acid derivatives, is about equal to that of benzoic acids, because the acidic hydrogen atom in all of these compounds bears the same relationship to the benzene nucleus. As expected, the ρ-constant for *N*-methylbenzhydroxamic acid derivatives is about half as great.

The structure of the hydroxamic acid anion $R{-}CO{-}\overset{\ominus}{N}OH$ was further proved by its infrared spectrum in Nujol suspension and dioxan solution. The presence of the OH-group in the lithium salt followed from comparison with *O*- and *N*-derivatives as well as with deuterated compounds. Finally, it appears from the ultraviolet spectra of *p*-nitrobenzhydroxamic acid and its *O*- and *N*-derivatives in neutral and alkaline media that the structure of the unsubstituted acid and of the *O*-derivatives alters in the same way on dissociation, whereas the *N*-derivatives show no alteration.

[GDCh-Ortsverband Marburg (Germany), November 8th, 1963] [VB 767/113 IE]

German version: Angew. Chem. *76* (1964), in the press.

## Mass-Spectroscopy of Inorganic Systems at High Temperatures [1]

*P. Goldfinger*, Brussels (Belgium)

The vaporization equilibria of numerous inorganic substances have been examined by mass spectroscopy during the last ten years [1a].

A narrow molecular beam of the vapor under examination effuses from a Knudsen cell of a few ml volume, in which a solid/gas or liquid/gas equilibrium is established. The

[1] Sponsored in part by the Aeronautical Systems Division, AFSC, through the European Office, Aerospace Research, U. S. Air Force.

[1a] *M. G. Ingram* and *J. Drowart*: High Temperature Technology. McGraw-Hill, New York 1960; *P. Goldfinger*: Compound Semiconductors. Reinhold, New York 1962; *J. Drowart* and *P. Goldfinger*, Annual Rev. Phys. Chem. *13*, 459 (1962).

molecules are ionized in the ion source of a mass spectrometer by electrons of variable energy, accelerated to about 2000 volt, submitted to magnetic mass analysis in a 60° sector instrument (radius of curvature: 20 cm), and the intensities measured with a secondary electron amplifier. The qualitative composition of the gaseous phase in the Knudsen cell is determined from the mass of the ions, their isotope distribution, and their appearance potentials. The quantitative composition and absolute pressure are obtained from the ion intensities, the total quantity of substance effused, and the relative ionization cross-sections [2].

Our results are summarized in Table 1. It was possible to determine the dissociation energies of $S_2$ and $Se_2$ [3], which have been the subject of long-standing controversy, from the equilibrium values (a) and (b); M = Ca, Sr, or Ba. The results can be corroborated by means of the equilibrium values (r) to (u) and other data. The equilibrium values (f) to (h) and (i) to (l) yield the dissociation energy of SO.

Table 1. Energies of formation of gaseous compounds.

| | Equilibrium | Compound formed | ΔH [kcal/mole] | Ref. |
|---|---|---|---|---|
| a | 2/3 MS(sol) + 2 S ⇌ 2/3 M + 4/3 $S_2$ [*] | $S_2$ | 97.5 ± 4.5 | [4] |
| b | M + $S_2$ ⇌ MS + S | MgS | 55 | [4] |
| c | | CaS | 74 ± 4.5 | [4] |
| d | | SrS | 74 ± 4.5 | [4] |
| e | | BaS | 95 ± 4.5 | [4] |
| f | M + $O_2$ ⇌ MO + O | MgO | 77 ± 5 | [5] |
| g | | CaO | 83 ± 5 | [5] |
| h | | SrO | 92 ± 5 | [5] |
| i | M + SO ⇌ MO + S | CaO | 84 ± 6 | [4] |
| k | | SrO | 92 ± 6 | [4] |
| l | | BaO | 130 ± 6 | [4] |
| m | BaS(sol) + BaS ⇌ $Ba_2S_2$ | $Ba_2S_2$ | 114 ± 5 [**] | [4] |
| n | $Se_2$ ⇌ 2 Se | $Se_2$ | 75 ± 2 | [6] |
| o | MO(sol) ⇌ MO | GeO | 157 ± 2.5 | [7] |
| p | | SnO | 127 ± 3 | [7] |
| q | | PbO | 91 ± 2 | [7] |
| r | MS(sol) ⇌ MS | SnS | 111 ± 2.5 | [7] |
| s | | PbS | 79 ± 2.5 | [7] |
| t | MSe(sol) ⇌ MSe | SnSe | 95 ± 1.5 | [7] |
| u | | PbSe | 71 ± 2.5 | [7] |
| v | MTe(sol) ⇌ MTe | GeTe | 93 ± 2.5 | [7] |
| w | | SnTe | 80 ± 1.5 | [7] |

[*] Solid substances are denoted by "(sol)"; all others are gaseous.

[**] Dissociation energy $Ba_2S_2$ ⇌ 2 BaS.

[Karlsruher Chemische Gesellschaft, Karlsruhe (Germany), November 7th, 1963] [VB 765/112 IE]

German version: Angew. Chem. 76, 150 (1964)

## The Structure of Silicate Glasses

*H. Wondratschek*, Freiburg/Breisgau (Germany)

It has been customary for some time to consider the hypotheses of *Zachariasen* on the structure of glasses as outmoded. Two assertions always seem to recur; 1. a three-dimensional (Si,Al)-O lattice is not necessarily present in silicate glasses, and 2. the glass constituents are not homogeneously distributed in the glass, but form clusters. There is even occasional mention of complete phase separation. Examination of *Zachariasen*'s work shows that he did not postulate a three-dimensional lattice, nor did he make any assertions on the homogeneity of the distribution of glass constituents. Criticism of his views on that score is therefore unfounded.

When the details of the glass structure that are known with certainty are assembled, and the reliability of the analytical procedures employed is investigated, it soon becomes apparent that the evidence derived from the results obtained up to now has been highly overrated. Using X-ray crystallographic analysis, for instance, it is not possible to determine the coordination number of Si in silica glass more closely than "as lying between 3 and 5". Other procedures are equally uncertain, with the possible exception of the chromatographic method for the determination of the length of the phosphate chains in high-alkali $P_2O_5$ glasses. Most promising are feasibility studies in which glasses are compared with crystals of corresponding composition.

Electron micrographs of glass-fracture planes are often cited as evidence for inhomogeneity and phase separation. There are glasses which will actually give complete phase separation after sufficiently long time intervals, but statistical experiments show that even a completely random distribution of the different kinds of particles in the glass leads to relatively great inhomogeneity. It is not known how the fracture planes of such glasses would appear. Furthermore, cluster formation can already occur above the critical separation point, that is, certainly in the uniphase region, without phase separation ever taking place. It is at present not possible to distinguish with certainty between such a tendency to separate and statistical distribution or incipient separation.

Certain far-reaching assertions on the structure of the vitreous state, which are frequently encountered, should therefore be viewed with considerable caution. New and unexpected results (*e.g.* with glasses in the system $Pb_2SiO_4/PbSO_4$, examined in conjunction with *L. Merker*, or with the $Pb_2SiO_4/PbHal_2$ glasses found by *Merker*) show again how uncertain predictions in the field of glass chemistry can often be.

[GDCh-Ortsverband Saar (Germany), November 8th, 1963] [VB 761/110 IE]

German version: Angew. Chem, 76 (1964), in the press.

## The Constitution of Rifamycins

*V. Prelog*, Zürich (Switzerland)

Rifamycins (formerly known as rifomycins) are metabolic products isolated from cultures of *Streptomyces mediterranei*. Under certain growth conditions, rifamycin B is the main product of this group of compounds. It is, however, unstable and is oxidized in buffered neutral solutions by mild oxidizing agents, or even in air, to rifamycin O with loss of two hydrogen atoms. Rifamycin S is obtained from rifamycin O by treatment with acid in aqueous solution, one molecule of glycolic acid being removed hydrolytically. Rifamycin O is transformed by mild reducing agents, *e.g.* ascorbic acid, into rifamycin B; rifamycin S undergoes the same reaction to give rifamycin SV, the sodium salt of which has found clinical application under the commercial name rifocin®.

Extensive investigations by *W. v. Oppolzer* in our laboratory have led to the constitutional formulae *(1)*–*(4)* for the four rifamycins mentioned above. These are based mainly on the results of chemical degradations of rifamycin S (methanolysis of the iminomethyl ether of rifamycin S; degradation of rifamycin S by ozone and subsequent treatment with performic acid; oxidation of tetrahydrorifamycin S with nitric acid) and on the analysis by NMR spectroscopy of the molecule and its degradation products obtained by these and other reactions.

[2] *R. Colin*, Ind. chim. belge *26*, 51 (1961).

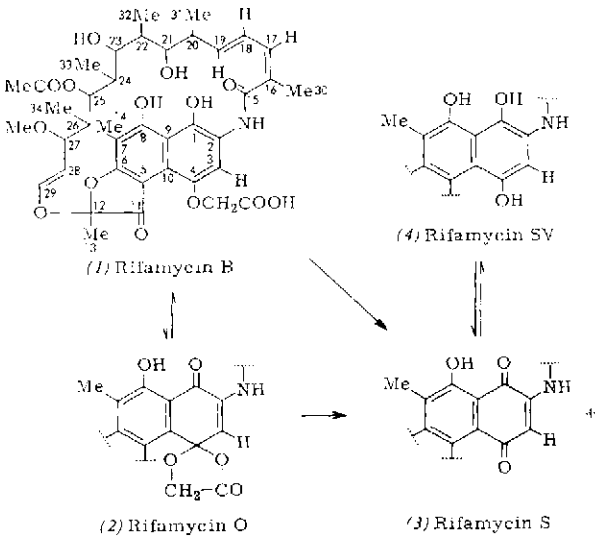
[3] *P. Goldfinger*, *W. Jeunehomme*, and *B. Rosen*, Nature (London) *138*, 205 (1936).

[4] *R. Colin*, *P. Goldfinger*, and *M. Jeunehomme*, Trans. Faraday Soc., in the press.

[5] *G. Verhaegen*, *J. Drowart*, and *G. Exsteen*, Trans. Faraday Soc., in the press.

[6] *D. Detry*, Ind. chim. belge *28*, 752 (1963).

[7] *R. Colin* and *J. Drowart*, Technical Note No. 10, contract AF 62 (052)–225 (1963); available from ASTIA, Arlington Hall Station, Arlington, Virginia (U. S. A.).



*(1)* Rifamycin B

*(2)* Rifamycin O

*(3)* Rifamycin S

*(4)* Rifamycin SV

+ $HOCH_2CCOH$

According to formulae *(1)–(4)*, the rifamycins represent naturally occurring ansa-compounds in which an aliphatic bridge spans an aromatic system. One consequence of this ansa-constitution is that methyl groups of the aliphatic bridge are placed in the magnetic field of the aromatic π-electron current, and are therefore more or less shielded, depending on their exact positions. The doublets attributed to two of the four $CH_3CH$-groups of rifamycins O and S do indeed lie at unusually high magnetic fields, *viz.* $\delta = 0.22$ and 0.67 ppm.

Their constitutions suggest that biogenetically the rifamycins are built up largely from acetate and propionate or their biochemical equivalents.

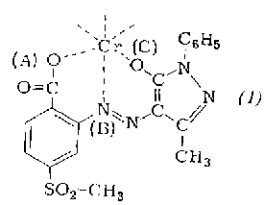
[GDCh-Ortsverband Mannheim-Ludwigshafen (Germany) December 12th, 1963] [VB 773/116 IE]

German version: Angew. Chem. *76*, 193 (1964)

# SELECTED ABSTRACTS

**Decarbobenzoxylation with liquid hydrogen bromide** was achieved by *M. Brenner* and *H. Ch. Curtius*. They treated carbobenzoxyamino acids and peptides with 10–20 parts of condensed HBr at −80 °C and evaporated off the HBr by removal of the coolant, moisture being excluded. The resultant hydrobromide was then recrystallized. This method is particularly suitable for labile compounds and sparingly soluble carbobenzoxy peptides, for liquid HBr is an excellent solvent and can be removed under mildest conditions. Peptides containing thioester groups, for instance, can be decarbobenzoxylated to give pure compounds in 70–90% yield. / Helv. chim. Acta *46*, 2126 (1963) / –Dc. [Rd 792/208 IE]

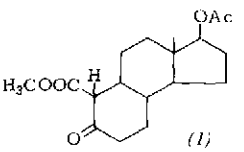
**The steric configuration of 1:2-metal-dye complexes** with 6-coordinate metal central ions ($Cr^{3+}$, $Co^{2+}$) was studied by *G. Schetty*. Diarylazo and diarylazomethine dyes (*e.g.* 2-hydroxy-6-carboxyazobenzene) were used as tridentate ligands. By incorporation of the central ion, each dye molecule forms either two annelated six-membered rings or a five-membered ring annelated with a six-membered ring via its three coordinating atoms A, B, and C. In the 6-6 rings, the dye molecules of the complex lie one on top of the other in a sandwich structure; in the 5-6 rings, the molecule planes are perpendicular to each other. Both these structural possibilities (A, B, and C are at the corners of an equilateral or isosceles triangle) are also apparent in atomic models. With the aid of the bonding angles and interatomic distances, the dimensions of the ABC coordination triangles can be calculated and compared with the theoretical values of the coordination octahedron. The complex *(1)* is a borderline case in which both



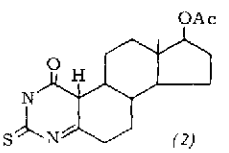
*(1)*

structures are feasible. The 6-6 systems are more labile and yield stereoisomers; they are further distinguished from the 5-6 systems by their ultraviolet absorption spectra. Chemically as well as stereoisomerically differing complexes may be separated chromatographically on Alox columns. The 6-6- and 5-6 systems can be differentiated by means of possibly stereoisomeric mixed complexes (there are two different dye molecules in the complex). Equilibria between 1:2- and 1:1-complexes and the free dye were determined optically. / Helv. chim. Acta *46*, 1132 (1963) / –Jg. [Rd 781/203 IE]

**Heterocyclic steroids in which ring A is replaced by a pyrimidine ring** have been prepared for the first time by *E. Caspi* and *D. M. Piatak*. Degradation of 19-nortestosterone was performed by condensation with ethyl formate, acetylation to form 17-β-acetoxy-2-acetoxymethylene-Δ⁴-oestren-3-one, and ozonolysis to yield the γ-keto acid, followed by conversion



*(1)*

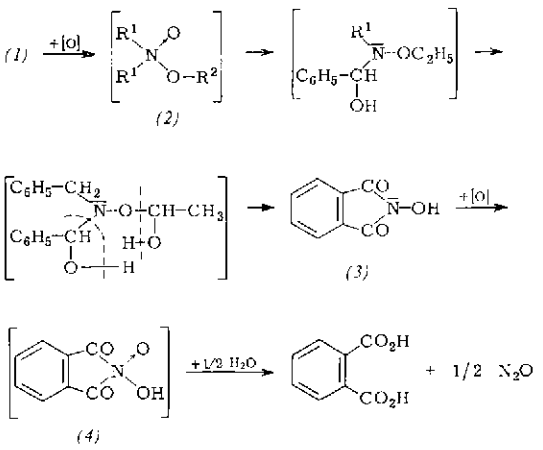


*(2)*

into a diphenyleneketo steroid; splitting of the diphenylene ketal with $RuO_4/NaIO_4$ then led to *(1)*, the key intermediate. Compound *(1)* can be condensed with thiourea to give 17-β-acetoxy-2,4-diaza-Δ⁴-oestren-1-one-3-thione *(2)*, $C_{18}H_{24}N_2O_3S$, m.p. > 300 °C, $\lambda_{max} = 219$ (ε = 12000) and 280 mμ (21000) in methanol. / Experientia (Basel) *19*, 465 (1963) / –De. [Rd 779/202 IE]

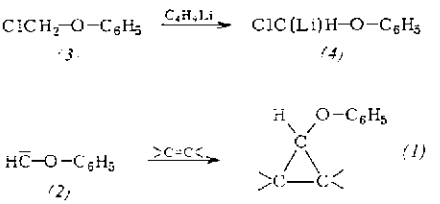
**The effect of liquid $NH_3$ on phosphoric esters** has been investigated by *R. Klement* and *A. Wild*. On ammonolysis, $OP(OR)_3$ (R = alkyl) yields $NH_4PO_2(OR)_2$ after some weeks at room temperature, but more rapidly at 60–70 °C. The C–O–P bond is therefore cleaved between the C and the O, in contrast to aryl esters, which yield $OP(NH_2)_2$, the C–O–P bond being cleaved between the P and the O. The ammonolysis appears to proceed step-wise. Tetraethyl pyrophosphate yields quantitatively the ammonium salt and amide of diethylphosphoric acid. The tetraphenyl ester produces phosphoric triamide and ammonium diphenylphosphate. The reaction products were examined by paper chromatography. / Chem. Ber. *96*, 1916 (1963) / –Kr. [Rd 778/201 IE]

**The possibility of the existence of dialkyl- and diacylnitronic acids** was investigated by *F. Klages, R. Heinle, H. Sitz,* and *E. Specht.* All attempts to prepare dialkyl- and diacylnitronic acids, $R_2NOOH$, led to side reactions, but the reaction products indicated intermediate formation of compounds of the desired formula. Decomposition also occurs even under very mild conditions, but the different courses of this reaction could largely be elucidated. Nitronic acids with two organic substituents on the nitrogen atom are not capable of existence.



Reaction of *N,N*-dibenzyl-*O*-ethylhydroxylamine *(1)* with less than the theoretical amount of peroxyacetic acid yielded equimolar amounts of benzaldehyde and acetaldehyde (20 to 25 %) as well as *N*-benzylhydroxylamine (75 %), probably by oxidation of *(1)* to dibenzylnitronic acid *(2)* followed by rearrangement. Oxidation of *N*-hydroxyphthalimide *(3)* with $H_2O_2$ or $PbO_2$ gave $N_2O$ and phthalic acid, possibly via the primarily formed nitronic acid derivative *(4)*. *N,N*-Di-t-butylhydroxylamine and its *O*-acetyl derivative always gave a nearly quantitative yield of 2-nitroisobutane with peroxycarboxylic acids. An intermediate blue color seems to indicate transient formation of 2-nitrosoisobutane. / Chem. Ber. *96*, 2387 (1963) / –Ma. [Rd 733/204 IE]

**The synthesis of phenoxycyclopropanes** (1) from phenoxycarbene *(2)* and olefins is reported by *U. Schöllkopf, A. Lerch,* and *J. Paust.* The carbene *(2)* is produced in the reaction mixture by elimination of hydrogen chloride from chloromethyl phenyl ether *(3)* with butyl-lithium, lithiochloromethyl phenyl ether *(4)* probably occurring as an intermediate.



The carbene *(2)* apparently acts as an electrophilic reagent, for the yields of cyclopropane compounds are greater, the higher the electron-density at the olefinic double bond. The addition takes place stereospecifically as *cis*-addition. / Chem. Ber. *96*, 2266 (1963) / Sk. [Rd 775/199 IE]

# BOOK REVIEWS

**Atlas d'équilibres électrochimiques à 25 °C** (Atlas of Electrochemical Equilibria at 25 °C), by *M. Pourbaix*, in collaboration with a number of scientists. Gauthier-Villars and Cie., Paris 1963. 1st edit. 644 pp., numerous illustrations, linen, NF. 140.– (about $ 28. –).

This atlas presents equilibrium data for a large number of electrochemical reactions, which characterize the behavior of metals and metaloids in aqueous solutions at 25 °C. The equilibria are, in general, represented graphically, the reversible electrode tension being plotted against pH (tension-pH diagrams). For every element, a number of reactions, particularly those involving hydroxide or oxide formation, has been considered in most cases.

In the introduction, *Van Rysselberghe* develops concisely and clearly the thermodynamic fundamentals of the book; he uses the concepts of chemical, electrochemical, and electrical tension, recommended by the CITCE nomenclature commission, which allow elegant derivation of the main basic relationships. In a further section, *Pourbaix, Valensi, Charlot, Hoar,* and *Garrels* discuss the most important applications of the tension-pH diagrams. These are primarily of interest in connection with corrosion, but also with general inorganic chemistry, analytical chemistry, the deposition and dissolution of metals by electrolysis, and even geology. Numerous diagrams show the regions in which metals corrode and those in which they are immune or passive (immunity being understood as the state in which corrosion by an adjacent liquid is thermodynamically impossible, whereas in the case of passivity, corrosion is prevented by a change in the surface characteristics of the metal, owing, for instance, to the formation of a compact surface layer). In general, the equilibrium diagrams and analytical relationships given allow one to state whether, for a given set of conditions, an electrochemical reaction can take place or not. This does not mean, of course, that a thermodynamically possible reaction will in fact occur, because its rate may be impracticably slow.

However, this restriction in the use of the diagrams is also encountered in the utilization of all the usual chemical free energy tables in general. Compared to the latter, which even to-day are often rather incomplete, the number of data collected in the atlas under review is remarkable. Virtually all the elements have been covered. This is the fruit of years of relentless efforts on the part of *M. Pourbaix* and of the Cebelcor [*] of which he is director. This comprehensive, well arranged volume will be welcome, particularly to those interested in corrosion and passivity. The printing and general appearance are good, the price can be regarded as modest for a book of this kind. *N. Ibl* [NB 135/63 IE]

[*] Centre Belge d'Etude de la Corrosion.

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# Protonic States in Chemistry [*]

BY PROF. DR. H. ZIMMERMANN [**]

PHYSIKALISCH-CHEMISCHES INSTITUT
DER TECHNISCHEN HOCHSCHULE MÜNCHEN (GERMANY)

*Dedicated to Prof. Dr. G. Scheibe on the occasion of his 70th birthday*

*Protons are subject to the wave/particle dualism of matter. Hitherto, only the corpuscular picture has been generally used in chemistry for describing protons. In contrast, the wave picture is considered in the present article. Protonic states, proton delocalization, and the tunnel effect in chemistry are discussed and illustrated by examples.*

## I. Introduction

Of all the elementary particles, electrons and protons claim special interest in chemistry. The electrons in atoms, ions, and molecules occupy well-defined states that may be computed, in principle, as solutions of the Schrödinger equation. According to wave mechanics, it is not possible to indicate accurately the position occupied by an electron at a given time. All that can be made is a statement of the probability of its location. In the view of wave mechanics, therefore, the electron is not located at any definite spot but is delocalized, *i.e.* distributed, over the whole range of the electronic state.

Fundamentally, any elementary particle may be described as a wave or as a corpuscle. For the treatment of problems concerning electrons in chemistry, the wave-mechanical approach has proved particularly helpful. Conversely, the corpuscular picture is of less importance in describing electrons. The opposite situation prevails in the treatment of problems concerning protons in chemistry. The proton as the nucleus of the hydrogen atom is generally represented as a corpuscle, which is fixed in a definite position in a molecule. This differentiated treatment of electrons and protons seems appropriate because of the difference in mass of the particles, *viz.* $M_{H^+}/M_e = 1836$. However, the proton, in turn, differs from the atoms and ions of the remaining elements of the periodic system. In the form of a bare atomic nucleus, it has a radius of the order of $10^{-13}$ cm, whereas atoms and ions generally have radii of the order of $10^{-8}$ cm. Accordingly, the proton is smaller by about five orders of magnitude than other atoms. It is therefore to be expected that it exhibits properties that, on the one hand, differ from those of other atoms and ions and, on the other, show analogies to the behavior of electrons. It therefore seems reasonable, to base the description of protons in chemistry on the wave picture as well. According to this view, states are supposed to exist for protons, much as in the case of electrons, in which protons are delocalized. States of this kind will be discussed in the following with several examples.

## II. Protonic States of a Harmonic Oscillator

The simplest model for the discussion of protonic states is the harmonic oscillator. This will now be briefly discussed [1,2].

Let us consider a molecule A–H, in which a hydrogen atom H is linked by a homopolar bond to a residue A. The bonding electrons are derived from the residue A as well as from the hydrogen atom. The proton is held in the negatively charged electron cloud of the bonding

[*] Excerpts from this paper were given in a lecture to the annual meeting of DECHEMA, Frankfurt/Main (Germany), 1962.

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[1] *W. Finkelnburg:* Einführung in die Atomphysik. Springer, Berlin, Göttingen, Heidelberg 1956, p. 193.

[2] *G. Herzberg:* Molecular Spectra and Molecular Structure II, Infrared and Raman Spectra of Polyatomic Molecules. Van Nostrand, New York 1960, p. 61.

electron state. If the bond is stable, the proton is placed in a potential trough, the shape of which in the neighborhood of the potential minimum can be easily estimated.

According to classical mechanics, a particle reaches its lowest energy state at the potential minimum. If it deviates from its position of rest by an amount x, a force K is generated which tends to return the particle to its equilibrium position and is approximately proportional to x:

$K = -f\,x$, where f = directing force.

A shift dx causes the particle to gain the potential energy $dU = -K\,dx$. This yields the potential function

$$U = \tfrac{1}{2} f x^2,$$

As a particle of mass m deviates from its position of rest, it can be excited to undergo harmonic vibrations around its equilibrium position, with the frequency

$$\nu = \frac{1}{2\pi}\sqrt{f/m}$$

According to classical mechanics, vibrations of any amplitude and, therefore, of any energy are feasible.

If the proton in its ground state were to remain at the potential minimum, as is postulated by classical mechanics, the position (x = 0), momentum (p = 0), and energy (E = 0) of the particle would be clearly defined. However, the proton is an elementary particle and as such is subject to Heisenberg's uncertainty principle, according to which both the position and the momentum of any particle cannot be accurately known at the same time.

We must therefore discard the classical view and employ wave mechanics. For this purpose, we must look for solutions of the Schrödinger equation which we obtain for a proton moving in a parabolic potential. The limiting condition that the proton is always at a finite distance from the equilibrium position implies quantization of its energy. In contrast to classical mechanics, the proton cannot possess any indescriminate energy of vibration, but can only assume discrete energy levels (energy eigenvalues):

$E_n = h\nu\,(n + \tfrac{1}{2})$, where $n = 0, 1, 2, \ldots$.

In its lowest energy state (n = 0), the proton has still got a minimum amount of energy, its zero-point energy, as a direct consequence of the uncertainty principle.

A place-dependent eigenfunction $\Psi_n(x)$ may be ascribed to each of the discrete protonic energy states $E_n$. These eigenfunctions are obtained as solutions of the Schrödinger equation. By substituting $\xi = 2\pi x\sqrt{m\nu/h}$, eigenfunctions of the following type result:

$$\Psi_n(\xi) = \exp(-\xi^2/2)\cdot P_n(\xi).$$

The Hermite polynomials $P_n(\xi)$ for the lowest states are given by

$P_0(\xi) = 1$

$P_1(\xi) = \xi$

$P_2(\xi) = \xi^2 - 1$

The square of the eigenfunction $\Psi_n(x)$ or $\Psi_n(\xi)$ is a measure of the probability of the presence of the proton in the n-th state at position x or $\xi$, respectively (Fig. 1).

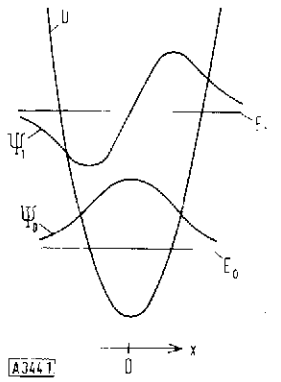



Fig. 1. Potential U, energy eigenvalues E, and eigenfunctions $\Psi$ of a harmonic oscillator.

Figure 1 shows the lowest energy eigenvalues and eigenfunctions (n = 0, 1) for a proton moving in a parabolic potential field. Let us consider the ground state of the particle. As can be seen from Figure 1, $\Psi_0(x)$, and therefore also $\Psi_0(x)^2$, has a maximum at the position of the potential minimum (x = 0). This is, therefore, where the proton is most probably to be found. This shows a certain analogy to classical mechanics, according to which the particle in its ground state should be at the potential minimum. In contrast to the classical view, the proton pictured by wave mechanics has a finite probability of occurrence even on either side of the maximum $\Psi_0(0)^2$. It may even penetrate into the potential wall, a phenomenon that contradicts classical mechanics and can only be understood in terms of wave mechanics. The proton, therefore, is not fixed at a definite location but is delocalized over the range of the protonic state. Protons, in other words, behave just like electrons. A very good illustration is given by comparison of the different protonic states $\Psi_n(x)$ with the vibration states of the molecule A–H. Energy absorption and emission can cause proton transitions between these states. These transitions can be determined experimentally by means of infrared and Raman spectroscopy.

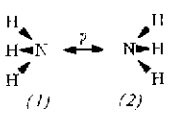
Protonic states occur widely in nature in the form just described. They are present whenever there is only one potential trough for a proton in a molecule. In particular cases, several potential troughs for a solitary proton can also exist. Protonic states are then probably formed that extend over a range encompassing all of these potential troughs. Such protonic states will be dealt with in the following, as they are of particular importance in chemistry.

## III. Protonic States of the Ammonia Molecule

The ammonia molecule is the classical example for the discussion of protonic states extending over two potential troughs [3]. Ammonia has a pyramidal structure with the nitrogen atom at the peak, and with three valence

[3] *G. Herzberg*, [2], p. 221.

bonds to the hydrogens radiating downward from it. This arrangement is not rigid, however, *i.e.* the molecule can invert, in which case the hydrogen atoms pass from one side of the nitrogen to the other. This inversion is a very common occurrence. It can be shown that the life period of any configuration is only $10^{-11}$ sec (approx.) [3]. The actual state of the molecule must therefore be described by superimposition of configurations *(1)* and *(2)* which are only limiting structures of the molecule. A similar situation is therefore encountered in describing the protonic states of the ammonia molecule as with the electronic states of molecules. Electronic states may be tentatively described by quantum-mechanical superimposition of basic functions (*viz.* by superimposition of mesomeric structures in the valence bond (VB) method or by linear combination of atomic eigenfunctions in the LCAO method). Protonic states may be represented by superimposition of basic functions formed from the various configurations of the molecule. This tentative description of protonic states by linear combination of protomeric structures of the molecule shall be called protomerism and characterized by the symbol $\overset{P}{\leftrightarrow}$.



*(1)* *(2)*

Quantum-mechanical calculations of the protonic states of ammonia have been carried out by various authors [4–10]. Their treatments differ essentially in the potentials used in the calculations. The following illustration is intended to clarify the close connection between the treatment of protonic states and electronic states according to the LCAO method. Since inversion is not limited to ammonia alone, it is better to examine the general problem of a pyramidal molecule $AH_3$.

A molecule may be in its ground state or in an excited vibrational state. The law of conservation of the centre of gravity holds for all states of the molecule. Since A is considerably larger in mass than the proton, it is primarily the protons that will be in motion in an excited vibration state, while A is approximately at rest. For a tentative consideration of inversion it will therefore suffice to follow the motion of the protons.

Let us consider a proton of the molecule $AH_3$, and let us first suppose that configurations *(1)* and *(2)* have an infinite life period. The proton will have two stable positions, *i.e.* there are two potential troughs $U_I$ and $U_{II}$ for the proton, which may be ascribed to the two configurations *(1)* and *(2)*. $U_I$ and $U_{II}$ can be roughly described by parabolic potentials such as we have met in the treatment of the harmonic oscillator (Fig. 2). Energy eigenvalues $E_{In}$ and $E_{IIn}$ as well as eigenfunctions $\Psi_{In}$ and $\Psi_{IIn}$ may be ascribed to the potential troughs, ($n = 0, 1, 2 \ldots$). Configurations *(1)* and *(2)* being energetically equivalent, the two energy eigenvalues $E_{In}$ and $E_{IIn}$ for any given value of n are equal for each pair and are thus degenerate ($E_{In} - E_{IIn} - E_n$).

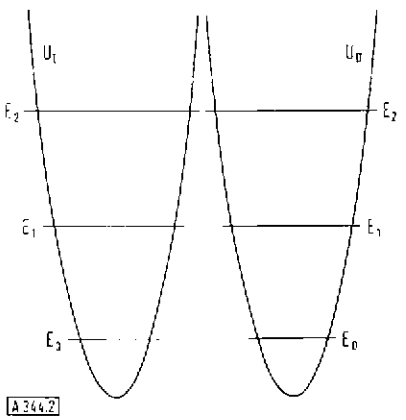



Fig. 2. Potential U and energy states E of a system consisting of two non-interacting harmonic oscillators.

If we now consider the case that configurations *(1)* and *(2)* interconvert rapidly, a change in position of the proton between the potential troughs $U_I$ and $U_{II}$ must occur. The proton will move in a potential that may be represented by superimposition of the partial potentials $U_I$ and $U_{II}$ (Fig. 3). The resulting potential has two minima of equal height, separated by a wall. Generally, there are two possible mechanisms for this change in position.

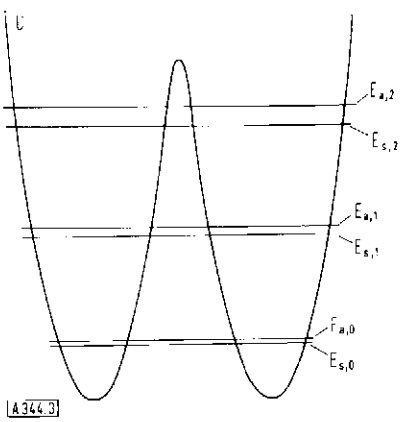



Fig. 3. Potential U and energy states E of a system consisting of two interacting harmonic oscillators.

The proton is either supplied with activation energy and leaps over the potential wall, or it penetrates through the potential wall (tunnel effect), in which case no activation energy is required. It can be shown that the proton transfer actually takes place by means of the tunnel effect in the case of the ammonia molecule [11].

Let us consider a pair of degenerate protonic states $\Psi_{In}$ and $\Psi_{IIn}$ that are ascribed to the neighboring potential troughs $U_I$ and $U_{II}$. Since protons are able to penetrate into a potential wall to a certain extent, the states $\Psi_{In}$ and $\Psi_{IIn}$ extend into the range of the potential wall sep-

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arating the potential troughs. If the potential wall is sufficiently thick, there is no substantial overlapping of $\Psi'_{In}$ and $\Psi'_{IIn}$; the states are independent of each other. However, if the potential wall is thin, $\Psi'_{In}$ and $\Psi'_{IIn}$ may overlap, *i.e.* the states $\Psi'_{In}$ and $\Psi'_{IIn}$ interact. Fresh eigenfunctions have to be set up in order to describe this system. These may be adequately represented, in close approximation, by linear combination of $\Psi'_{In}$ and $\Psi'_{IIn}$. $\Psi'_{In}$ and $\Psi'_{IIn}$ are thus basic functions of the protonic state. Since the potential is arranged symmetrically around the centre, $\Psi'_{In}$ and $\Psi'_{IIn}$ may be linearly combined either symmetrically (s) or anti-symmetrically (a). Two fresh eigenfunctions result for each value of n, by interaction of the protomeric structures (N = normalizing constant):

$$\Psi'_{s,n} = N(\Psi'_{In} + \Psi'_{IIn})$$

$$\Psi'_{a,n} = N(\Psi'_{In} - \Psi'_{IIn})$$

Figure 4 shows the states $\Psi'_{s,n}$ and $\Psi'_{a,n}$ for n = 0, 1. All the states extend over both potential troughs. The probability of the occurrence of the proton is equal for the

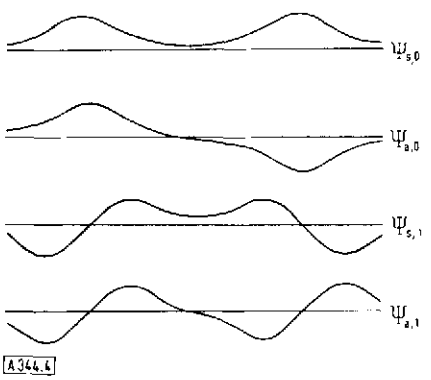



Fig. 4. Protonic states for a potential with a symmetrical double minimum.

two potential minima. It is impossible, in wave mechanics, to state in which potential trough the proton will be at a given time. The proton is delocalized over the range of both potential troughs and changes its position between the two potential minima by means of a tunnel effect.

An energy $E_{s,n}$ or $E_{a,n}$ may be ascribed to each of the states $\Psi'_{s,n}$ and $\Psi'_{a,n}$ with the aid of the Schrödinger equation,

$$E = \int \Psi_H \Psi d\tau / \int \Psi^2 d\tau .$$

Starting approximately from orthogonally normalized eigenfunctions $\Psi'_{In}$ and $\Psi'_{IIn}$, one obtains in simple fashion

$$E_{s,n} = E_n + \omega_n$$

$$E_{a,n} = E_n - \omega_n$$

$$E_{s,n} - E_{a,n} = 2\omega_n$$

The integral

$$\omega_n = \int \Psi'_{In} H \Psi'_{IIn} d\tau$$

describes the interaction between the protomeric structures $\Psi'_{In}$ and $\Psi'_{IIn}$.

Without going into detail about the special form of the Hamiltonian operator H, $\omega_n$ may be easily considered qualitatively. A measure of the interaction between $\Psi'_{In}$ and $\Psi'_{IIn}$ is the tunnel effect. The latter is facilitated by increased interaction, depends on thickness and height of the potential wall, and occurs the more readily, the thinner and lower the potential wall (calculated from the energy level of the particle). It follows from this that the value of $\omega_n$ increases on approaching the peak of the potential wall, *i.e.* the higher the quantum numbers n. In this way, the term system of the proton may be considered qualitatively.

If no interaction occurs between $\Psi'_{In}$ and $\Psi'_{IIn}$, *i.e.* if configurations *(1)* and *(2)* have long lives, no tunnel effect is in operation, *i.e.* the proton is able to occupy only one of the doubly degenerate energy states $E_{In} = E_{IIn} = E_n$ at a time. If there is interaction between $\Psi'_{In}$ and $\Psi'_{IIn}$, however, *i.e.* if configurations *(1)* and *(2)* have short lives, then there is a tunnel effect, *i.e.* the degeneracy of the terms disappears. In place of the degenerate terms $E_{In}$ and $E_{IIn}$, the split terms $E_{s,n}$ and $E_{a,n}$ are observed (inversion doubling). The splitting of the terms, namely

$$E_{s,n} - E_{a,n} = 2\omega_n$$

increases with rising n (Fig. 3). The splitting of the terms has been determined experimentally for ammonia [11]. This renders it certain that, during inversion, the protons of the molecule move in potentials with a double minimum and that the proton transfer takes place by means of the tunnel effect.

## IV. Protonic States in Hydrogen Bonds

An intermolecular or intramolecular hydrogen bond arises from the interaction of the particles A–H and B.

$$A{-}H\cdots|\,B \qquad (3)$$

A–H supplies a proton to the hydrogen bond and is called a proton donor. B supplies a free electron pair to the bond and is described as an electron donor.

A hydrogen bond therefore represents the joining of a Brönsted acid/base pair. Accordingly, it is reasonable to suppose that proton transfer may take place within the bond from A–H to B, resulting in a polar form of the bond:

$$\overset{\ominus}{A}|\cdots H{-}\overset{\oplus}{B} \qquad (4)$$

If there is conduction between A and B through a π-electron system within a molecule with intramolecular hydrogen bonds, charge equalization can take place by means of an electron shift.

Some limiting conditions can be given for the potential and for the proton states in the bond:

1. The potential has two minima around A and B.

1a) For weak proton donors and acceptors, the potential trough at A is considerably lower than that at B. The proton, in its ground state, remains around A. The bond

is characterized by the limiting structure *(3)*. Only energy absorption enables the proton to reach the potential trough B (Fig. 5a).

1b) For strong proton donors and acceptors, the potential trough at B is considerably lower than that at A. The proton, in its ground state, remains in the potential trough at B. The bond is characterized by the limiting structure *(4)*. Energy absorption makes proton transfer into the potential trough at A possible (Fig. 5b).

1c) For medium-strength proton donors and acceptors, the two potential troughs may have the same or almost the same height. The probabilities of occurrence of the proton in the two potential minima are approximately equal. The bond can be characterized by superimposition of the limiting structures *(3)* and *(4)*. Proton transfer is possible by a proton leap or by the tunnel effect (Fig. 5c).

2. In extremely short hydrogen bonds, the two potential minima may merge to one joint potential trough. The proton in its ground state stays about half-way between A and B (Fig. 5d).

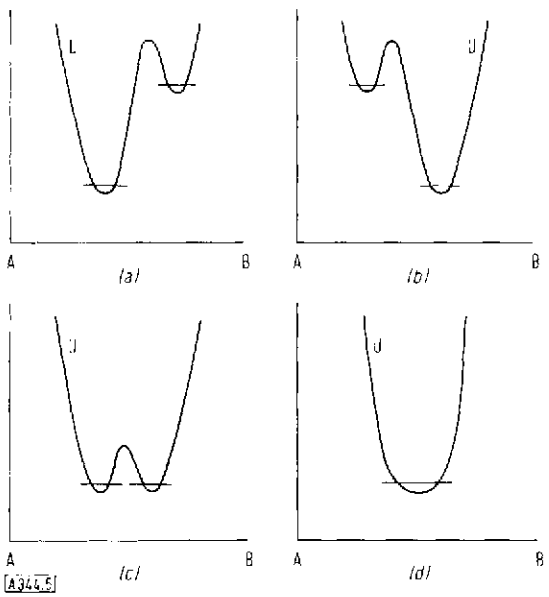



Fig. 5. Limiting states for the potential of the proton in a hydrogen bond.
(a) Hydrogen bond between weak proton donor (A) and weak proton acceptor (B).
(b) Hydrogen bond between strong proton donor (A) and strong proton acceptor (B).
(c) Hydrogen bond between medium-strength proton donor and acceptor.
(d) Extremely short hydrogen bond.

The potentials and the protonic states of hydrogen bonds have been investigated by numerous authors, both theoretically [12–25] and experimentally [12, 13, 26–45]. For a discussion of proton delocalization, those bonds are of particular interest in which proton transfer takes place by a tunnel effect between two roughly equal potential troughs. The proton states may be represented, by analogy to the ammonia molecule, by protomerism between the structures *(3)* and *(4)* of the bond.

$$\underset{(3)}{A{-}H\cdots|B} \overset{p}{\leftrightarrow} \underset{(4)}{A^{\ominus}|\cdots H{-}B^{\oplus}}$$

The tunnel effect in hydrogen bonds with double minima has formed the subject of several studies [33, 34, 37, 40–46]. It ought to be possible to detect the tunnel effect experimentally by splitting of the vibrational terms of the bond. However, it is extremely difficult to identify this splitting in the spectrum.

In the case of the hydrogen bond of imidazole, by combination of various experimental methods, it was possible to detect a potential with a double minimum and to furnish strong indications of the tunnel effect of the proton [43, 44].

Imidazole associates in non-polar solvents by means of intermolecular hydrogen bonds to form *(5)* [47, 48]. Each molecule is able to act as both a proton donor and a proton acceptor, and the degree of association is thus high.


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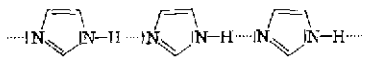
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Crystalline imidazole, too, contains associated molecules. It was possible to determine the structure of the molecular chains both in solution and in the crystalline state by means of X-ray analysis [49, 50].



(5)

Infrared and Raman spectra of crystalline imidazole were used to ascertain the frequencies of the vibrational bands of the hydrogen bond. Analysis of these bands led to a term system for the vibrational states of the bond [43], which exhibits normal and combination vibrations. The terms of the normal vibrations are represented in Figure 6a. For the interpretation of the term system, the possible vibrational states of a hydrogen bond have to be considered.

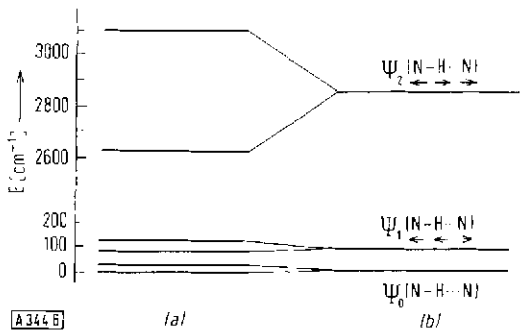



Fig. 6. (a) Experimental and (b) theoretical term system of the hydrogen bond of imidazole.

X-ray structural analysis showed that the hydrogen bond of imidazole is almost linear. A linear three-mass system can undergo the following normal vibrations [51]:

$\Psi'_1$ (N–H···N) ← ← →

$\Psi'_2$ (N–H···N) ← → →

$\Psi'_3$, $\Psi'_4$ (N–H···N) ↓ ↑ ↓

$\Psi'_2$ must be considered as an NH-valence vibration that is modified to some extent by the hydrogen bond. The nitrogen and hydrogen atoms of the NH-group are linked by a normal covalent $\sigma$-bond. Accordingly, their excited vibrational state is rich in energy (Fig. 6b). $\Psi'_1$ is to be regarded as a valence vibration of the hydrogen bond. This bond is very weak. Little energy is required to excite its vibration. The term $\Psi'_1$ lies just above the ground state $\Psi'_0$.

$\Psi'_3$ and $\Psi'_4$ are degenerate deformational vibrations of the hydrogen bond. Deformational vibrations are generally much less rich in energy than valence vibrations. Since it is already difficult to detect even the low energy valence vibration $\Psi'_1$ of the hydrogen bond, there is little hope of experimental detection of the even lower energy deformational vibrations $\Psi'_3$ and $\Psi'_4$.

Thus, only the three states $\Psi'_0$, $\Psi'_1$, and $\Psi'_2$ should appear in the experimental term system. In actual practice, however, six terms are observed, but these are due to term splitting (Fig. 6) [43].

A similar type of term splitting of vibrational states has already been discussed in connection with the inversion of the ammonia molecule. It was explained by supposing that the protons of the molecule move in potential fields with double minima and are carried from one potential trough to the other by a tunnel effect. It must therefore be concluded from the term splitting of the vibrational states of the hydrogen bond of imidazole that the hydrogen bond proton also moves in a potential field with a double minimum. The term system shows that the two potential minima lie at about the same height. The distance between the potential troughs and the height of the potential wall may be estimated to be comparable to those for the ammonia molecule. Accordingly, the change of position of the proton in the hydrogen bond should again be caused by the tunnel effect. Protonic states will then be formed that extend over the range of both potential troughs and in which the proton is delocalized. These states may be described by linear combination of the protomeric structures of the bond. The ground state is then given by

$$\Psi' = a\,\Psi'(\mathrm{NH\cdots N}) + b\,\Psi'(\overset{\ominus}{\mathrm{N}}\cdots\overset{\oplus}{\mathrm{HN}}).$$

The basic functions $\Psi'(\mathrm{NH\cdots N})$ and $\Psi'(\overset{\ominus}{\mathrm{N}}\cdots\overset{\oplus}{\mathrm{HN}})$ are energetically not absolutely equivalent. They share in the linear combination to different extents a and b, but a and b do not differ much, since the two potential minima of the bond have practically the same height.

The tunnel effect depends on the mass of the tunnelling particle and is inhibited if the hydrogen atom of the bond is replaced by deuterium. In view of the fact that the tunnel effect is also responsible for the term splitting, it ought to be possible to produce spectroscopic evidence for an isotope effect in the term splitting. It is, in fact, possible to recognize spectral differences in the infrared bands of hydrogen and deuterium bonds, which may be attributed to a reduction in the term splitting in the deuterium bond. This result shows that the tunnel effect is most probably operative in the bond [43].

The proton states of the bridge bond have been described by linear combination of protomeric structures. One structure is strongly polar. This form shares in the linear combination to about the same extent as the non-polar structure. The resulting protonic state should exhibit a large dipole moment. Dipole-moment measurements have shown that the hydrogen bond of imidazole is, in fact, exceptionally strongly polar [43].

The change in position of the proton between the two potential troughs within the hydrogen bond can be proved by measurement of its nuclear resonance. Generally speaking, NH-groups show very broad signals as a result of interaction between the proton and the nitrogen nucleus. It is known from model experiments, however, that the proton and the nitrogen nucleus become uncoupled by rapid changes in the position of the pro-

[49] *H. Zimmermann*, Liebigs Ann. Chem. *612*, 193 (1958).
[50] *G. Will*, Nature (London) *198*, 575 (1963).
[51] *G. Herzberg* in [2], p. 111.

ton [52,53]; the NH-signal is sharpened as a result. A sharp NH-signal is observed for the NH···N hydrogen bond of imidazole [43,44]. It must be concluded that the proton in the hydrogen bond changes its position between the two potential troughs.

Proton delocalization is also encountered in the proton states in aqueous solution and in ice. In aqueous solution, a proton first becomes attached to a water molecule with formation of a $H_3O^{\oplus}$ ion, which promotes the formation of hydrogen bonds to three further water molecules. In this process, a $H_9O_4^{\oplus}$ complex is formed, which is solvated by further, loosely bonded molecules of water (Fig. 7) [54–57]. Kinetic investigations of the neutralization reaction [58,59] and investigations of the infrared

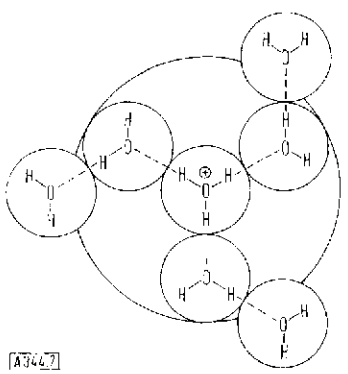
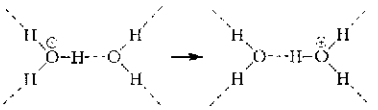


Fig. 7. Hydrated proton in aqueous solution [54].

spectra of strong acids in aqueous solutions have shown that the "excess" proton in the $H_9O_4^{\oplus}$ ion has virtually free movement. The same result was obtained by infrared spectroscopic measurements on hydrated polystyrenesulfonic acid, in which $H_7O_3^{\oplus}$ complexes are formed [60,61]. The excess proton is delocalized in the $H_7O_3^{\oplus}$ ion just as in the $H_9O_4^{\oplus}$ complex. Proton delocalization may be described by superimposition of the appropriate limiting structures [60].

Proton conductivity is observed in ice. The rate-determining factor for the conductivity is the proton transfer in a hydrogen bond with a double minimum [56,62,63].



The mobility of protons in ice is remarkably high, being only less by one or two powers of ten than the mobility of electrons in metals. The protons in ice therefore resemble electrons rather than other ions. Moreover, the mobility of the proton, and hence the proton transfer in the hydrogen bond, is almost independent of temperature [63]. This suggests that the proton transfer takes place by means of the tunnel effect.

## V. Protonic States in Prototropic Reactions

Finally, the proton transfer occurring in a Brönsted acid/base pair will be considered. Let us suppose that the reaction

$$A{-}H + B \rightleftharpoons A^{\ominus} + B{-}H^{\oplus}$$

be divided into the following partial steps:

1. Formation of a complex between the acid and the base, with participation of a hydrogen bond;
2. Proton transfer within the hydrogen bond;
3. Decomposition of the complex.

$$A{-}H + B \rightleftharpoons A{-}H\cdots B \rightleftharpoons A^{\ominus}\cdots H{-}B^{\oplus} \rightleftharpoons A^{\ominus} + B{-}H^{\oplus}$$

(Charges of the individual forms are not shown.)

The proton in the bond of the complex has two positions of maximum proton density and, again, moves in a potential field with a double minimum. If the two potential minima lie close to each other and are of approximately equal height, proton transfer can take place by the tunnel effect.

These conditions are only fulfilled in exceptional cases. Let us therefore consider, quite generally, a reaction in which the potential troughs are so far apart and have such unequal heights that the tunnel effect cannot take

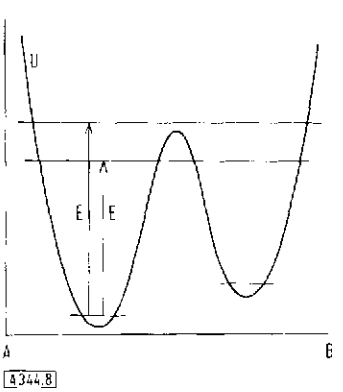



Fig. 8. Potential U and energy states E in a prototropic reaction $AH + B \rightleftharpoons A + BH$.

place in the ground state of the complex (Figs. 5a and 5b, Fig. 8). The proton is located in either one or the other potential trough and A-H···B and A···H-B are molecular entities of long life.


[52] *J. D. Roberts:* Nuclear Magnetic Resonance. McGraw Hill, New York 1959, p. 83.

[53] *N. Joop* and *H. Zimmermann*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 440 (1962).

[54] *E. Wicke, M. Eigen*, and *Th. Ackermann*, Z. physik. Chem. N.F. *1*, 340 (1954).

[55] *M. Eigen* and *L. De Maeyer*, Proc. Roy. Soc. (London), Ser. A *247*, 505 (1958).

[56] *M. Eigen* and *L. De Maeyer* in *W. J. Hamer:* The Structure of Electrolytic Solutions. Wiley, New York 1959, p. 64.

[57] *H. D. Beckey*, Z. Naturforsch. *14a*, 712 (1959); *15a*, 822 (1960).

[58] *M. Eigen* and *L. De Maeyer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 986 (1955).

[59] *G. Ertl* and *H. Gerischer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 629 (1961); *66*, 560 (1962).

[60] *G. Zundel, H. Noller*, and *G. M. Schwab*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 129 (1962).

[61] *G. Zundel* and *G. M. Schwab*, J. physik. Chem. *67*, 771 (1963).

[62] *M. Eigen*, Angew. Chem. *75*, 489 (1963); Angew. Chem. internat. Edit. *3*, 1 (1964).

[63] *H. Chr. Spatz*, Diploma Thesis, Universität Göttingen, 1962.

The proton has to change its position between the two potential minima in this reaction. For this purpose, it will make use of any protonic states linking the two potential troughs. As can be readily appreciated, corresponding terms exist above the peak of the potential wall. These states may be occupied with the help of an activation energy E. From the classical standpoint, the reaction is described as a proton leap, and the velocity constant obeys Arrhenius' law:

$$k = A \exp(-E/RT)$$

Below the peak of the potential wall, however, there are similar states covering both potential troughs, since there the potential barrier is sufficiently thin to permit a tunnel effect. If the reaction passes beyond these states, less activation energy is required than would be expected according to the classical approach ($E' < E$).

According to these considerations, the prototropic reaction again passes through states in which protons are free to move within the range of both potential troughs. The proton delocalization in the transition state may be approximately described by a linear combination of the wave functions:

$$\Psi = a\,\Psi_{(A-H\cdots B)^*} + b\,\Psi_{(A\cdots H-B)^*}$$

The protomeric states $\Psi$(A-H···B)* and $\Psi$(A···H-B)* are formed by excited vibrational states of the complex. The transition state is therefore characterized by the participation of all the reactants.

It was possible to confirm the classical proton leap mechanism experimentally by numerous examples [64]. However, indications were also obtained of the occurrence of tunnel effects in prototropic reactions [64].

It is possible to distinguish between the two mechanisms on the basis of the following considerations. Proton transfer will be easier in states above the potential barrier than in states below the peak of the potential wall, where proton transfer is feasible only by way of the tunnel effect. At sufficiently high temperatures, the reaction should therefore proceed predominantly according to the classical proton leap mechanism, as long as the terms above the potential barrier remain adequately occupied by absorption of energy. At low temperatures, however, the high energy states are only sparsely occupied, in comparison with the low energy terms below the peak of the potential wall. The tunnel effect then competes with the classical mechanism. In the presence of a tunnel effect, the activation energy E*, measured as the mean value of E and E' ($E' < E$), is therefore always smaller than would be expected according to the classical mechanism ($E^* < E$). E* consequently diminishes with decreasing temperature.

It can be shown similarly that the frequency factor A* is smaller in the presence of a tunnel effect than would be expected on the basis of the classical mechanism ($A^* < A$) (literature see [64]). Conclusions about the tunnel effect may therefore be drawn from the influence of temperature on E* and A*. However, the reaction velocity must be followed very accurately over a large temperature range in order to obtain experimental data on the deviations from the classical Arrhenius' law.

A second experimental possibility for investigating the tunnel effect in prototropic reactions is afforded by the isotope effect (literature see [64]). Deuterons penetrate a potential wall much less easily than protons do. Deuterium transfer therefore proceeds predominantly according to the classical mechanism ($A_D^* \approx A_D$). The condition for proton transfer however is $A_H^* < A_H$. If the tunnel effect is neglected, the theory yields a ratio of the frequency factors $A_H/A_D \approx 0.5$–$1.0$; if the tunnel effect is taken into account, $A_H^*/A_D^* < 0.5$–$1.0$. Thus, the influence of the tunnel effect in any reaction becomes apparent in an unusually low ratio $A_H^*/A_D^*$.

On the basis of these criteria, it was possible to demonstrate the existence of a tunnel effect in the base-catalysed bromination of 2-ethoxycarbonylcyclopentanone. The rate-determining step is the proton transfer from the substrate to the catalyst [64–66]. Examination of the reaction kinetics showed that the rate of reaction at low temperatures is much higher than is to be expected according to the classical mechanism. This deviation from Arrhenius' law points to a non-classical effect. The existence of a tunnel effect of the proton was also strongly suggested in other reactions [64].

The tunnel effect of the proton has so far been given little consideration in chemistry as it can only be detected by means of extremely careful and painstaking measurements. A more sophisticated approach toward reaction mechanisms, however, will make it indispensable to allot it due consideration.

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[64] *R. P. Bell*: The Proton in Chemistry. Methuen, London 1959.

[65] *R. P. Bell, J. A. Fendley*, and *J. R. Hulett*, Proc. Roy. Soc. (London) Ser. A *235*, 453 (1956).

[66] *J. R. Hulett*, Proc. Roy. Soc. (London) Ser. A *251*, 274 (1959).

# Structure and Aromatic Character of Non-benzenoid Cyclically Conjugated Systems

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*Dedicated to Professor Dr. Karl Ziegler on the occasion of his 65th birthday*

*The chemistry of aromatic compounds was originally confined to benzenoid hydrocarbons and their derivatives but has been enriched in the last decade by the discovery of numerous non-benzenoid, cyclically conjugated systems that are more or less like benzene in their properties. This has necessitated a new conception of "aromatic character". Theoretical and experimental studies have been applied to this problem. In this connection, several selected representatives of this class of compound are described, mostly from studies by the author's own group, and relationships between structure and "aromatic character" are indicated.*

## Introduction

At an early stage in organic chemistry the characteristic differences in physical properties and chemical reactivity between benzenoid hydrocarbons and their acyclic analogues induced *Kekulé* [1] to make his fundamental studies on the structure of benzene. Since that time, the theory of "aromatic character" has attracted the interest of organic chemists to an ever-increasing degree. Alongside the benzenoid compounds numerous non-benzenoid heterocyclic and carbocyclic systems with very similar properties have appeared, which have robbed the classical aromatic substance, benzene, of its special position and have necessitated a wider and deeper definition of the concept of "aromatic character". In this thorough studies of the chemical and physical properties of new kinds of non-benzenoid, cyclically conjugated compounds and numerous theoretical investigations have made very significant contributions [2].

The theory of "aromatic character" has thereby undergone manifold changes. The empirical generalization of the "aromatic sextet" [3] was followed by Hückel's rule [4], which was based upon quantum-mechanical considerations. According to this rule, benzenoid properties should be displayed not only by compounds with a $\pi$-electron sextet but also by any fully conjugated, planar, monocyclic polyolefin with $4n-2$ $\pi$-electrons ($n = 0, 1, 2, 3, 4, \ldots$).

Chemical reactivity was often the preferred criterion of "aromatic character", *i.e.* "aromaticity" was associated with thermal stability and reluctance to undergo addition reactions; as a result, it was the energy content of the excited state which was chiefly considered. However, more recently, greater importance has been assigned to those physical quantities which depend upon the extent of delocalization of the $\pi$-electrons of a cyclically conjugated system and which permit statements concerning its ground state. Thus "aromatic" compounds are characterized not only by the shift of their light absorption to longer wavelengths compared with olefinic systems, but also by a ready polarizability, by anisotropy of their diamagnetic susceptibility, by changes in bond lengths and charge distribution related to delocalization of the $\pi$-bonds, and by their resonance energy. This latter criterion of "aromatic character" in particular allows a limited statement only, despite its widespread use, because the value for the resonance energy is empirical, derived as it is from thermochemical data. The total stabilization represented by the thermochemical data is certainly not only related to the dynamic behavior of the electrons, which largely determines the properties of a molecule [5].

Recent investigations of cyclically conjugated, non-benzenoid compounds have revealed the difficulties associated with the definition of "aromatic character" and the often very different behavior of non-benzenoid, cyclically conjugated molecules in the ground and excited states. A high degree of electron delocalization, *i.e.* a strong ring current of the $\pi$-electrons, does not always guarantee benzene-like reactivity and stability. It therefore appears justified to distinguish between "aromatic character" of the ground state and "aromatic" reactivity and stability. This is impressively borne out *inter alia* by the investigations of annulenes [6] and the

[1] *A. Kekulé*, Bull Soc. chim. France (2) *3*, 98 (1865); Liebigs Ann. Chem. *137*, 129 (1866); *162*, 77 (1872).

[2] a) *D. Ginsburg:* Non-Benzenoid Aromatic Compounds. Interscience, New York 1959; b) *M. E. Vol'pin*, Russian chem. Reviews *29*, 129 (1960); c) *W. Baker* and *J. F. W. McOmie*, in *J. W. Cook:* Progress in Organic Chemistry. Butterworths, London 1955, Vol. 3, p. 44; d) *W. v. E. Doering:* Theoretical Organic Chemistry. Butterworths, London 1959; e) *A. Streitwieser:* Molecular Orbital Theory for Organic Chemists. J. Wiley, New York 1961.

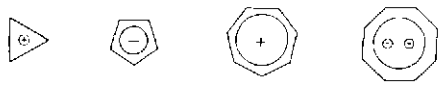
[3] *J. W. Armit* and *R. Robinson*, J. chem. Soc. (London) *121*, 827 (1922); *127*, 1604 (1925); *R. Robinson*, Tetrahedron *3*, 323 (1958).

[4] *E. Hückel*, Z. Physik *70*, 204 (1931); Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin 1938.

[5] *R. B. Turner:* Theoretical Organic Chemistry. Butterworths, London 1959; *C. A. Coulson*, J. physic. Chem. *56*, 311 (1952).

[6] *L. M. Jackman, F. Sondheimer, Y. Amiel, D. A. Ben-Efraim, Y. Gaoni, R. Wolovsky*, and *A. A. Bothner-By*, J. Amer. chem. Soc. *84*, 4307 (1962), where further references are given.

manifold studies of cyclically conjugated systems with either 4n+2 or 4n π-electrons; among these, special interest was attached to the charged ring systems, the cyclopropenium cation *(1)* [7], the cyclopentadienyl anion *(2)* [8], the tropylium cation *(3)* [9], and the most recently discovered cyclooctatetraenyl dianion *(4)* [10].



*(1)* *(2)* *(3)* *(4)*

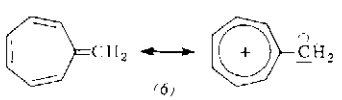
Investigations of various compounds derived from these monocyclic systems have broadened our knowledge of the relationships existing between structure and "aromatic character". In this connection the relationships between derivatives of the cross-conjugated fulvene system and their isomeric benzenoid counterparts were summarized from this point of view in a recent article [11]. Investigations of several mono- and polycyclic conjugated 5- and 7-membered ring systems are described in the following discussion.

## Cross-conjugated 7-Membered Ring Systems

The cross-conjugated fulvene system *(5)* [11] should be compared with that of heptafulvene *(6)* [12]. Like fulvene itself, the 7-membered ring system synthetized by



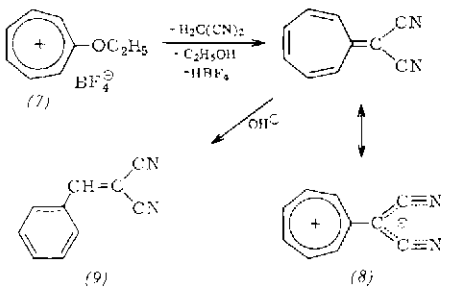
*(5)*



*(6)*

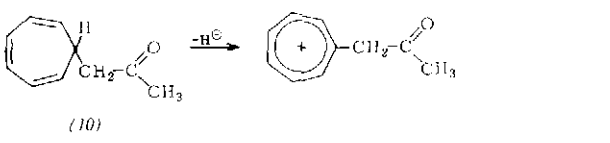
*Doering* and *Wiley* [13] is distinguished by its very low thermal stability, which for a long time prevented its isolation.

Nevertheless, introduction of electron acceptors on the exocyclic carbon atom of heptafulvene *(6)* effects an increase in the cyclic conjugation of the 7-membered ring together with a considerably greater chemical stability just as the electron sextet in fulvene is stabilized by electron donors on the exocyclic carbon atom. This is shown particularly clearly by 8,8-dicyanoheptafulvene *(8)* [14,15], which is stable up to 300 °C and reacts neither with dienophiles nor with electrophilic reagents. Com-

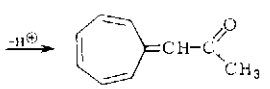


*(7)* *(9)* *(8)*

pound *(8)* is obtained by condensation of the alkoxytropylium fluoroborate *(7)* [14] with malononitrile. In contrast to its inertness toward the reagents already mentioned, it undergoes ring contraction to give the dicyanostyrene *(9)* under the influence of bases. Similar but smaller sextet stabilization in the 7-membered ring occurs in several other heptafulvenes [15] with one or two electron-attracting substituents on the exocyclic carbon atom. The 8-acetyl derivative *(11)* [16] obtained from tropylacetone *(10)* is the simplest stable representative



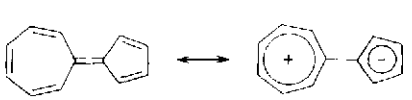
*(10)*



*(11)*

of this class of compounds; another example is 8,8-diphenylheptafulvene, which was prepared by *Dauben* [16a] in a similar way.

Surprisingly, it has not yet been possible to isolate sesquifulvalene *(12)*, for which theory predicts [12, 17] a



*(12a)* *(12b)*

high delocalization energy and which should be stabilized by the two sextet systems in the dipolar structure *(12b)*. Only some benzo- and polyphenyl-substituted

[7] *J. D. Roberts, A. Streitwieser,* and *C. M. Regan,* J. Amer. chem. Soc. *74*, 4579 (1952); *R. Breslow, H. Hover,* and *H. W. Change,* ibid. *84*, 3168 (1962), and earlier publications.

[8] *J. Thiele,* Ber. dtsch. chem. Ges. *34*, 69 (1901).

[9] *M. J. S. Dewar,* Nature (London) *155*, 50 (1945); *W. v. E. Doering* and *L. H. Knox,* J. Amer. chem. Soc. *76*, 3203 (1954); *W. v. E. Doering* and *H. Krauch,* Angew. Chem. *68*, 661 (1956).

[10] *T. J. Katz,* J. Amer. chem. Soc. *82*, 3784, 3785 (1960); *T. J. Katz* and *H. L. Strauss,* J. chem. Physics *32*, 1873 (1960); *T. J. Katz, W. H. Reinmuth,* and *D. E. Smith,* J. Amer. chem. Soc. *84*, 802 (1962); *H. L. Strauss, T. J. Katz,* and *G. K. Fraenkel,* ibid. *85*, 2360 (1963).

[11] *K. Hafner, K. H. Häfner, C. König, M. Kreuder, G. Ploß, G. Schulz, E. Sturm,* and *K. H. Vöpel,* Angew. Chem. *75*, 35 (1963); Angew. Chem. internat. Edit. *2*, 123 (1963).

[12] *G. Berthier* and *B. Pullman,* Trans. Faraday Soc. *45*, 484 (1949); *E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman,* and *B. Pullman,* Bull. Soc. chim. France *18*, 684 (1951); *G. E. Wheland* and *D. E. Mann,* J. chem. Physics *17*, 264 (1949); *A. Julg,* J. Chim. physique *52*, 50 (1955); *A. Julg* and *B. Pullman,* ibid. *52*, 481 (1955).

[13] *W. v. E. Doering* and *D. W. Wiley,* Tetrahedron *11*, 183 (1960).

[14] *K. Hafner, H. W. Riedel,* and *M. Danielisz,* Angew. Chem. *75*, 344 (1963); Angew. Chem. internat. Edit. *2*, 215 (1963).

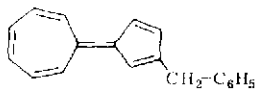
[15] *T. Nozoe,* in *J. W. Cook* and *W. Carruthers:* Progress in Organic Chemistry. Butterworths, London 1961, Vol. 5, p. 159; *T. Mukai, T. Nozoe, K. Osaka,* and *N. Shishido,* Bull. chem. Soc. Japan *34*, 1384 (1961).

[16] *K. Hafner* and *W. aus der Fünten,* unpublished results.

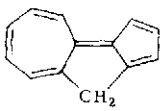
[16a] *H. J. Dauben, Jr.,* personal communication.

[17] *J. F. Tinker,* J. chem. Physics *19*, 981 (1951).

derivatives of this hydrocarbon possess the expected thermal stability [18]. 8-Benzylsesquifulvalene *(13)*



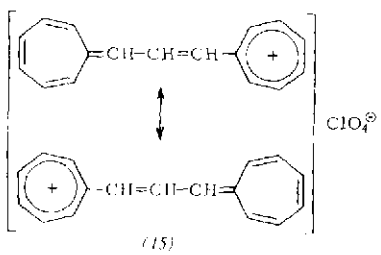
*(13)*



*(14)*

neatly prepared by *Prinzbach* and *Rosswog* [19] has poor stability and polyene character; this suggests that the parent substance *(12)* itself may lack the supposed resonance stabilization, possibly owing to a non-planar arrangement of the 5- and 7-membered rings relative to one another. Such twisting of the central C-C bond should be inhibited in the tricyclic derivative *(14)*, a non-benzenoid isomer of fluorene, in which resonance in the sesquifulvalene moiety might perhaps confer some stability.

In contrast to *(12)*, the heptafulvene system with a resonance-stabilized sextet typified by the deeply colored



*(15)*

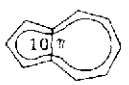
polymethine salt *(15)* [14] is distinguished by remarkable stability. Compound *(15)* reacts only with nucleophilic reagents with loss of conjugation [20].

## Azulene

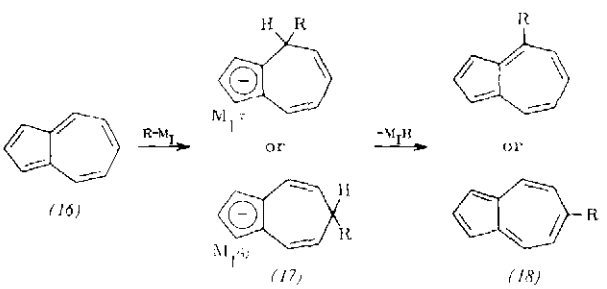
A formal combination of two charged monocyclic sextet systems, *viz.* the cyclopentadienyl anion and the tropylium cation, is encountered in the 10 π-electron system of azulene *(16)* [2a–c,2e,21], whose properties are largely determined by structures with charge separation. The ultraviolet spectrum [22] of azulene and its electron delocalization energy [22] of *ca.* 35 kcal/mole indicate a state of bonding very similar to that



*(16)*

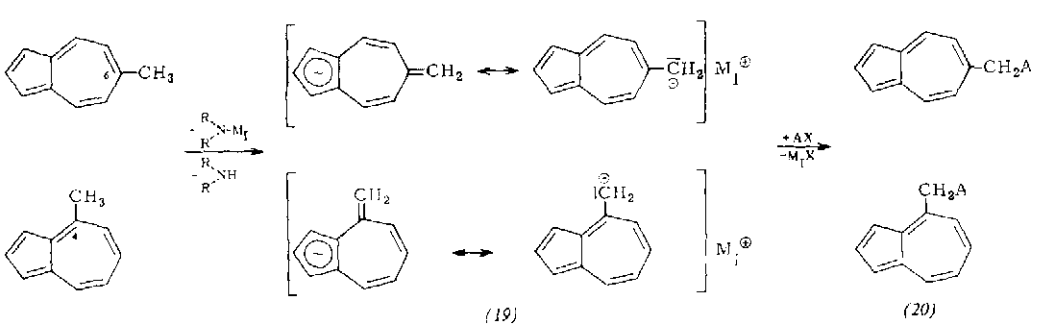


in benzenoid systems and show the relationship of this non-alternant hydrocarbon to its isomer naphthalene. The similarity between azulene and the cyclopentadienyl anion is made particularly clear by two characteristic reactions of the bicyclic hydrocarbon. With organometallic compounds of the alkali metals it reacts readily to form isolable cyclopentadienylmetal compounds of type



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

*(17)* [23] which are intermediates in the nucleophilic substitution at the 4-, 6-, or 8-position of the 7-membered ring, since they reafford the bicyclic decet system *(18)* with loss of a molecule of alkali metal hydride. The second reaction depends upon the acidity of primary or secondary alkyl groups in the 4-, 6-, and 8-positions, the positions of least electron density in azulene. The alkyl groups are activated by the positively polarized 7-membered ring of the azulene. Strong bases are able to extract a proton from these positions to form resonance-



*(19)* *(20)*

stabilized alkylideneazulenate salts *(19)* [24], in which the heptafulvene system is fused to the cyclically conjugated 5-membered ring. These salts react with electro-

[18] *B. Pullman, A. Pullman, E. D. Bergmann, H. Berthod, E. Fischer, Y. Hirshberg, D. Lavie,* and *M. Mayot,* Bull. Soc. chim. France *19*, 73 (1952); *H. Prinzbach* and *D. Seip,* Angew. Chem. *73*, 169 (1961).

[19] *H. Prinzbach* and *W. Rosswog,* Angew. Chem. *73*, 543 (1961).

[20] See also *Ch. Jutz,* Angew. Chem. *74*, 502 (1962).

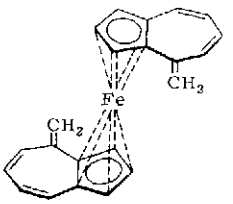
[21] *W. Treibs, W. Kirchhof,* and *W. Ziegenbein,* Fortschr. chem. Forsch. *3*, 334 (1955); *K. Hafner,* Angew. Chem. *70*, 419 (1958); *T. Nozoe* and *S. Itô,* in *L. Zechmeister,* Fortschr. chem. org. Naturstoffe *19*, 32 (1961).

[22] *E. Heilbronner* in [2a].

[23] *K. Hafner* and *H. Weldes,* Liebigs Ann. Chem. *606*, 90 (1957); *K. Hafner, C. Bernhard,* and *R. Müller,* ibid. *650*, 35 (1961).

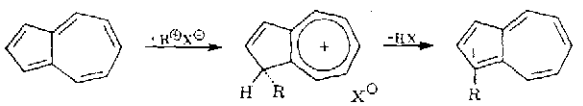
[24] *K. Hafner, H. Pelster,* and *H. Patzelt,* Liebigs Ann. Chem. *650*, 80 (1961).

philic reagents reforming the azulenoid system *(20)*; with ferrous chloride, on the other hand, the heptafulvene structure is fixed in the blue-green ferrocene derivative *(21)* [25] which is formed.



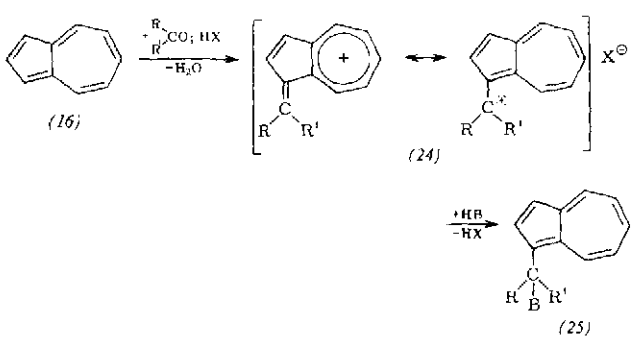

*(21)*

Conversely, it is also possible for azulene to form the tropylium cation. Addition of protons or onium ions at the 1- or 3-positions of the 5-membered ring – the positions of highest electron density – yields isolable azulenium salts of type *(22)* [26], which as intermediates in the electrophilic substitution readily give up a proton to reform the bicyclically conjugated system *(23)*. Condensation with carbonyl compounds in presence of acids




*(16)* *(22)* *(23)*

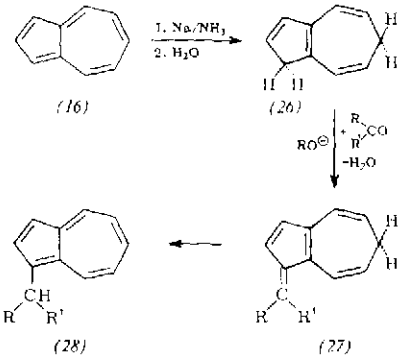
can also convert the decet system into the sextet system of the tropylium cation via a hydroxyalkylation. The alkylideneazulenium salts *(24)* [27] thereby obtained contain the cross-conjugated fulvene system fused to the cyclically conjugated 7-membered ring. With nucleophilic reagents these compounds can reform the bicyclic azulene system *(25)*.




*(16)* *(24)* *(25)*

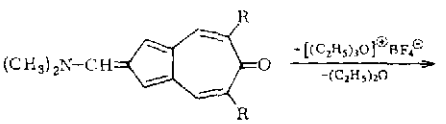
These conversions of the 5- and 7-membered fulvenoid systems of conjugation into the azulenoid system are evidently energetically favored, and furthermore the bicyclic system of 10 $\pi$-electrons is less favored energetically than the benzenoid sextet. These factors determine the reactivity of the fulvenoid system which will be illustrated by three further examples.

The dihydro derivative *(26)* is readily accessible by Birch reduction [28] of azulene with sodium in liquid ammonia [29]. This derivative reacts with carbonyl compounds in the presence of base to yield stable fulvenes of structure *(27)*, which are readily rearranged into the

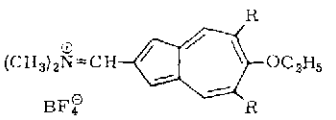



*(16)* *(26)* *(28)* *(27)*

azulenoid system *(28)* (formally by migration of a hydride ion) in the presence of suitable hydride-ion acceptors and donors [29]. This simple conversion of the cross-conjugated fulvene system into the cyclically conjugated decet system is also encountered in the alkylation



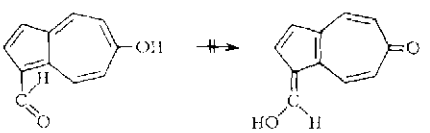

*(29)*




*(30)*

of fulvenotropones of structure *(29)*, which are thereby rapidly transformed into the azulene system of conjugation *(30)* [30].

As expected, the reverse transformation of the azulene derivative *(31)* into the fulvenotropone system *(32)* by proton migration [31] is not possible.




*(31)* *(32)*

However, the cyclic conjugation of the azulenoid system of 10 $\pi$-electrons is readily disrupted if a possibility exists of forming the benzenoid sextet. This is borne out not only by the thermal isomerization [32] of azulene to naphthalene, but also by the synthesis of the tricyclic hydrocarbon *(35)*. The product expected from intramolecular ring-closure of the ketone *(33)* is *(34)*, in which the azulene is fused to a cyclohexadiene system.

[25] *K. Hafner, H. Pelster*, and *W. aus der Fünten*, unpublished experiments.

[26] *K. Hafner, A. Stephan*, and *C. Bernhard*, Liebigs Ann. Chem. *650*, 42 (1961).

[27] *K. Hafner, H. Pelster*, and *J. Schneider*, Liebigs Ann. Chem. *650*, 62 (1961).

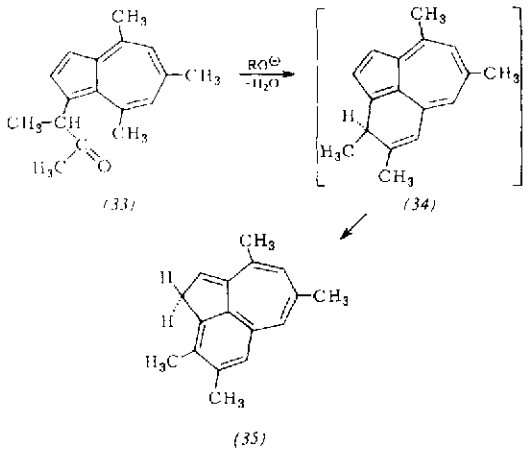
[28] *A. J. Birch*, Quart. Reviews (chem. Soc., London) *4*, 69 (1950).

[29] *K. Hafner* and *W. Klinner*, unpublished experiments.

[30] *K. Hafner, K. H. Vöpel, G. Ploß*, and *C. König*, Liebigs Ann. Chem. *661*, 52 (1963).

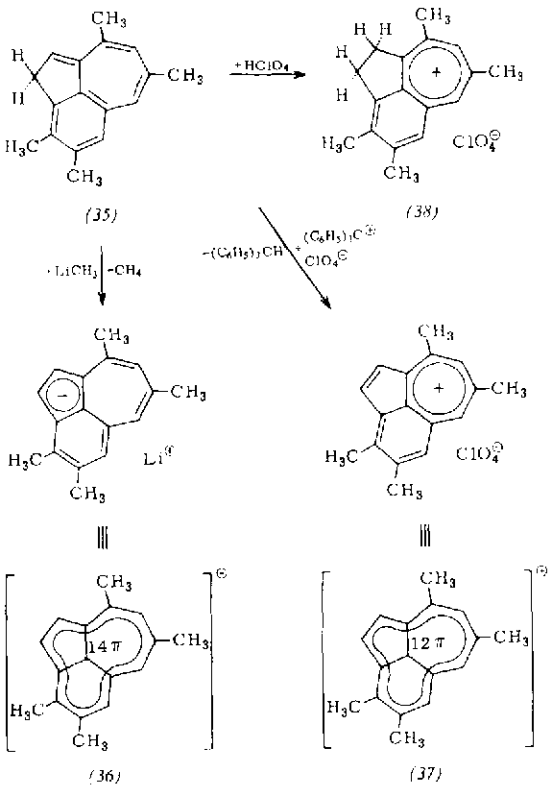
[31] *H. Kaiser*, Ph. D. Thesis, Universität Marburg/Lahn, 1959.

[32] *E. Heilbronner, P. A. Plattner*, and *K. Wieland*, Experientia *3*, 70 (1947); *E. Heilbronner* and *K. Wieland* Helv. chim. Acta *30*, 947 (1947).



(33) (34) (35)

Isolation of this compound is prevented by its isomerization to the benzoheptafulvene derivative *(35)* [33] with loss of the bicyclic conjugation of azulene. Compound *(35)* is a non-benzenoid isomer of phenalene [34], and like the latter, can be transformed by proton-abstraction with strong bases into the anionic system *(36)*



(35) (38) (36) (37)

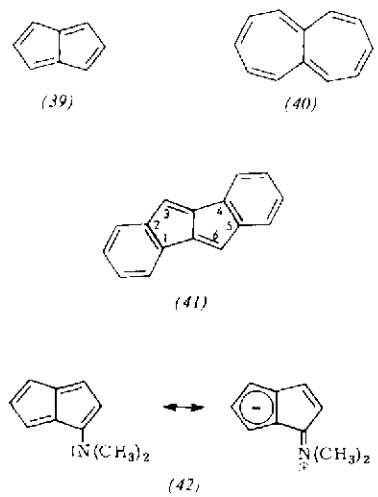
containing 14 π-electrons, and can form the cation *(37)* [35] containing 12 π-electrons under the influence of hydride-ion acceptors. The heptafulvene system in *(35)* is stabilized in a characteristic manner by addition of a proton to give the benzotropylium ion *(38)* [33].

[33] *K. Hafner* and *H. Schaum*, Angew. Chem. *75*, 90 (1963); Angew. Chem. internat. Edit. *2*, 95 (1963).

[34] *R. Pettit*, Chem. and Ind. *1956*, 1306; J. Amer. chem. Soc. *82*, 1972 (1960); *V. Boekelheide* and *C. E. Larrabee*, J. Amer. chem. Soc. *72*, 1245 (1950).

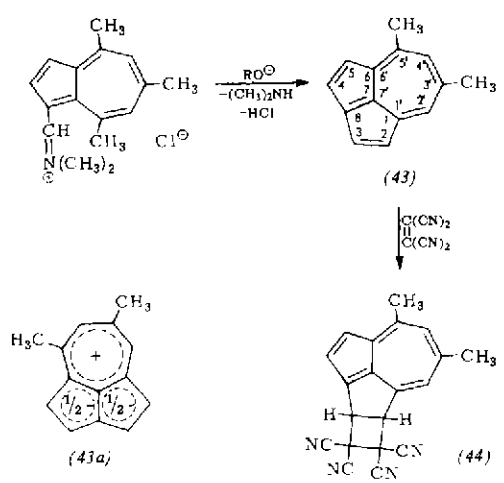
[35] *K. Hafner* and *H. Schaum*, unpublished experiments. MO-LCAO calculations for the cation, anion, and free radical of *(35)* have recently been carried out by *R. Zahradnik*, *C. Parkanyi*, and *J. Michl*, Prague (personal communication from Dipl.-Ing. *R. Zahradnik*).

The two non-alternant hydrocarbons, pentalene *(39)* and heptalene *(40)*, are cyclically conjugated systems of 8 and 12 π-electrons, respectively, and therefore belong



(39) (40) (41) (42)

to the systems of 4n π-electrons which, according to Hückel's rule, should possess no "aromatic character", *i.e.* only low delocalization energy and no benzene-like reactivity. Although this hypothesis was confirmed by the experimental results of several groups of workers, theoretical calculations led to different conclusions [36]. The marked olefinic properties of dibenzo[*a*,*e*]pentalene *(41)* [37] (ring-closed *trans*-1,4-diphenyl-1,3-butadiene) suggest that the resonance stabilization lacking in pentalene (in contrast to azulene) may be compensated by electron-releasing substituents, as, for example, in *(42)*. Pentalene derivatives of type *(42)* are not yet known, however. Nevertheless, the tricyclic pentalene derivative *(43)* was synthetized by attachment of a 5-membered ring across the 1,8-positions of azulene [38]. The 7-membered ring in this derivative can formally accept a partial positive charge, whereas the two 5-membered rings are



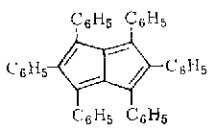
(43) (43a) (44)

[36] *E. D. Bergmann* in [2a].

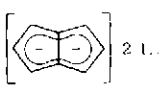
[37] *C. T. Blood* and *R. P. Linstead*, J. chem. Soc. (London) *1952*, 2255, 2263; *C. C. Chuen* and *S. W. Fenton*, J. org. Chemistry *23*, 1538 (1958).

[38] *K. Hafner* and *J. Schneider*, Lichigs Ann. Chem. *624*, 37 (1959).

negatively polarized according to formula *(43a)*. Probably as a result of the angle strain at carbon atom 6 or 7 caused by the ethylene bridges in the 2,3- or 4,5-positions, the hydrocarbon does not show the properties of its underlying azulene system, but behaves like a polyolefin, which is prone to spontaneous addition of dienes or dienophiles onto one of the double bonds in the two 5-membered rings, with reformation of the cyclic conjugation of azulene *(44)* [38]. This behavior of the "stabilized" pentalene derivative *(43)* as well as that of the hydrocarbon *(41)* confirms the theoretical predictions, according to which no "aromatic character" is to be expected of the parent substance *(39)*, whose synthesis has not yet been accomplished despite numerous attempts. Neither hexaphenylpentalene *(45)*, which was recently prepared by *Le Goff* [39], nor the pentalene dianion *(46)*, which contains 10 π-electrons and was prepared by *Katz* [40], permit assertions concerning the unsubstituted, uncharged bicyclic system *(39)*.

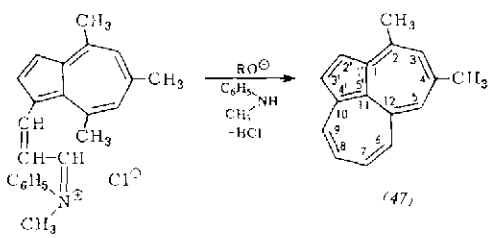


*(45)*

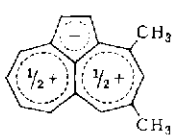


*(46)*

It was also possible in the case of heptalene *(40)* [36] to confirm predictions based on the relations between constitution and "aromatic character". In the tricyclic heptalene derivative *(47)* [38,41,42], the 5-membered ring bears a partial negative charge which should stabilize the bicyclic heptalene to a certain extent by affording an additional opportunity for resonance in the sense of the collective structure *(47a)*; compound *(47)*



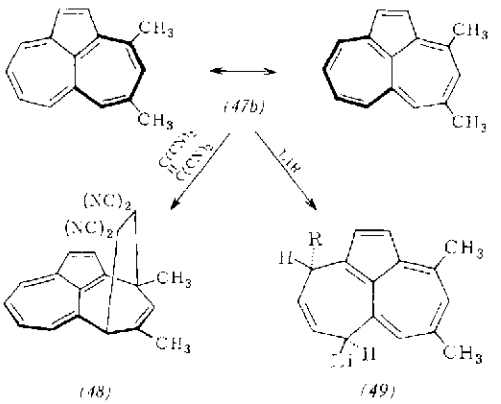
*(47)*



*(47a)*

allowed valuable statements to be made about the parent substance, which have recently been confirmed by an elegant synthesis of the latter [43].

The thermally stable hydrocarbon *(47)* is readily accessible by fusion of a further 7-membered ring onto azulene across the 1,8-positions and shows chemical and spectroscopic properties unlike those expected of the analogue of acenaphthylene, "aceheptylene" [44], since the ethylene bridge forming the 5-membered ring has no olefinic character. In accord with MO-LCAO calculations [45], *(47)* is much more like an azulene with a diene bridge across the 1,8-positions, in which the π-electrons of the conjugated diene participate more or less

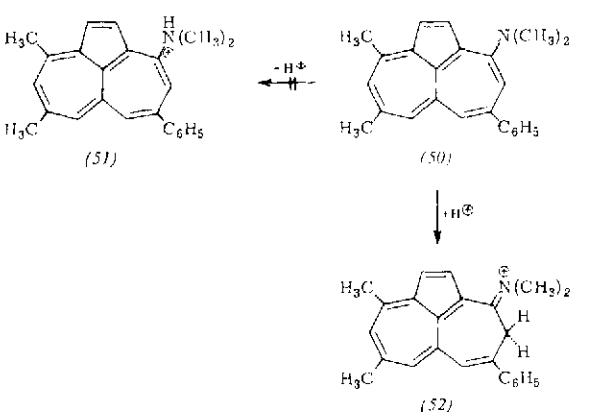


*(47b)* *(48)* *(49)*

in the resonance of the bicyclic decet system of the azulene *(47b)*.

This is indicated by the electrophilic substitution which takes place at the 3'-carbon atom of the 5-membered ring, the Diels-Alder reaction of the diene system of the dimethylated 7-membered ring with tetracyanoethylene (or similarly with maleic anhydride) to give the adduct *(48)*, the formation of blue azulene derivatives of type *(49)* by 1,4-addition of lithium alkyls onto the more electrophilic unsubstituted 7-membered ring, and the bathochromically shifted absorption spectrum of the hydrocarbon, which is nevertheless characteristic of the azulene system [38,41].

This picture is further confirmed by the course of the protonation of the dimethylamino derivative *(50)*. Formation of the ammonium salt *(51)* with tricyclic conjugation does not occur; instead, compound *(50)* reacts as an enamine adding a proton at the β-position relative to the amino group, whereby the system of 14 π-electrons is transformed into the preferred decet system of the azulene *(52)* [42].



*(51)* *(50)* *(52)*

[39] *E. LeGoff*, J. Amer. chem. Soc. *84*, 3975 (1962); see also ibid. *84*, 1505 (1962).

[40] *T. J. Katz* and *M. Rosenberger*, J. Amer. chem. Soc. *84*, 865 (1962).

[41] *K. Hafner* and *G. Schneider*, Liebigs Ann. Chem. *672* (1964), in the press.

[42] *K. Hafner* and *K. F. Bangert*, Liebigs Ann. Chem. *650*, 98 (1961).

[43] *H. J. Dauben, Jr.* and *D. J. Bertelli*, J. Amer. chem. Soc. *83*, 4659 (1961).

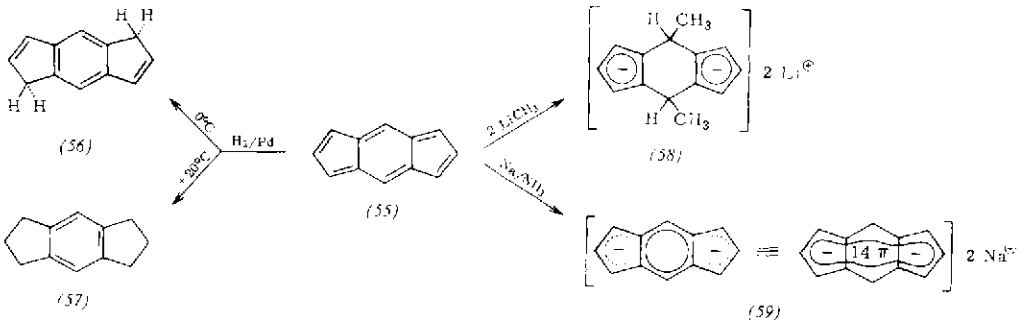
[44] Nomenclature proposed by Prof. *H. J. Dauben*.

[45] *M. Asgar Ali* and *C. A. Coulson*, Molecular Physics *4*, 65 (1961); *A. Rosowsky, H. Fleischer, S. T. Young, R. Partch, W. H. Saunders, Jr.*, and *V. Boekelheide*, Tetrahedron *11*, 121 (1960); *A. Streitwieser* [2e].

The energetic advantage of the π-electron decet of azulene over the 12 π-electron system of heptalene is confirmed by the typically olefinic character of the very thermolabile parent substance *(40)*, and by its NMR spectrum, in which the location of the ring-proton signals in the frequency range that is characteristic of olefinic protons (between 4 and 5 τ) [43] indicates very little π-electron delocalization.

protons. Catalytic hydrogenation below 0 °C rapidly transforms the hydrocarbon into the benzenoid derivative, 1,5-dihydro-*s*-indacene *(56)*, and hydrogenation at 20 °C gives *s*-hydrindacene *(57)* [49], with gains in resonance energy.

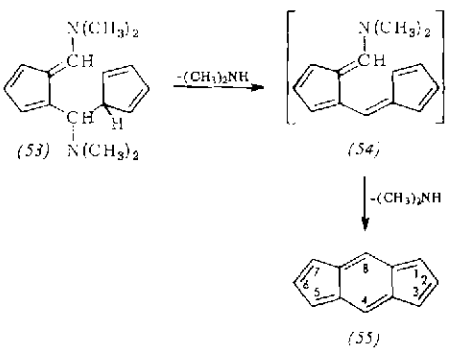
In agreement with *Brown*'s predictions [47], nucleophilic attack takes place at the 4- and 8-positions of the tricyclic system. The reaction profits from the energy gain




## *s*-Indacene

*s*-Indacene *(55)* [46] was often the subject of theoretical and experimental studies, because it is a further example of a system of 4n π-electrons related to the still unknown pentalene and one which allows the relations between structure and "aromatic character" to be clearly recognized. According to LCAO calculations carried out by *R. D. Brown* [47], this hydrocarbon should possess an electron delocalization energy similar to that of the tropylium cation, yet the system can be expected to show high reactivity on account of the low energy difference between its ground and excited states. A simple synthesis of *s*-indacene was effected recently [11] which has allowed the theoretical predictions to be tested.

The surprisingly great tendency of the fulvene *(53)* to form the tricyclic compound *(55)* by way of the non-isolable intermediate *(54)* even below −30 °C (a fine




example of the effectiveness of the "principle of rigid groups" [48]) stands in contrast to the remarkably small thermal stability of this system. Limited π-electron delocalization is indicated by the NMR spectrum of *s*-indacene, which displays signals between 2.4 and 3.7 τ in the intensity ratio 1:2:1 corresponding to the 8 ring

associated with the formation of the two isolated sextet systems of cyclopentadienyl anions. Compound *(55)* reacts with methyl-lithium even at −30 °C to give the stable, isolable lithium salt *(58)* [50]. Birch reduction [28] of *s*-indacene *(55)* with sodium in liquid ammonia leads to the disodium salt *(59)* of the tricyclic system. As befits a system of 14 π-electrons obeying Hückel's rule, like the dianion *(4)* with 10 π-electrons prepared in the same way by *Katz* et al. [10] from cyclooctatetraene, the salt *(59)* can be isolated as a thermally stable, but air-sensitive, colorless compound [50]. On hydrolysis, it yields 1,5-dihydro-*s*-indacene *(56)* of established structure. As a cyclopolyene, *(55)* reacts with silver nitrate to form a red, crystalline metal π-complex of only low thermal stability [50].

The properties of *s*-indacene *(55)* give reason to suppose that its still unknown asymmetrical isomer *(60)* [47, 51] is subject to even less resonance stabilization. In contrast to the two equivalent Kekulé structures of *s*-indacene, the asymmetrical isomer can be described only as a resonance hybrid of the two canonical forms *(60a)* and *(60b)*, which are *p*- and *o*-quinonoid, respectively.




## Heterotropilidenes

Whereas bi- and polycyclic non-benzenoid systems of 4n π-electrons (such as pentalene derivatives, heptalene, and *s*-indacene) have been synthetized and recognized (by their ultraviolet and NMR spectra, thermochemical

[46] *A. Streitwieser* [2e]; *D. P. Craig* in [2a].

[47] *R. D. Brown*, J. chem. Soc. (London) *1951*, 2391.

[48] *W. Baker*, Ind. chim. Belge *17*, 633 (1952).

[49] *R. T. Arnold* and *E. Rondestvedt*, J. Amer. chem. Soc. *67*, 1265 (1945).

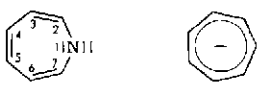
[50] *E. Sturm*, unpublished experiments.

[51] *A. Etienne* and *A. LeBerre*, C. R. hebd. Séances Acad. Sci. *242*, 1453 (1956); *O. Chalvet* and *J. Peltier*, Bull. Soc. chim. France *1956*, 1667.

properties, and reactivities) as representatives of a class of compounds that differ considerably from the systems with 4n+2 π-electrons, only a few observations are available concerning monocyclic conjugated systems with 4n π-electrons. These include studies by different groups of workers on compounds which are isoelectronic with the cycloheptatrienyl anion *(64)* and which differ from it in replacement of one of the methine groups by a hetero-atom. These are oxepine *(61)*, thiepine *(62)*,



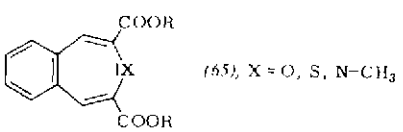
*(61)* *(62)*



*(63)* *(64)*

and azepine *(63)*. None of these three heterotropilidenes has been prepared as yet. On the other hand, the cycloheptatrienyl anion *(64)* was recently detected by *Dauben* [52], and its heptaphenyl derivative by *Breslow* and *Chang* [53]. Both systems of 8 π-electrons prove to be thermally very unstable. Further investigations of the fine structure and reactivity in these octet systems are necessary in order to recognize similarities to and differences from the corresponding tropylium cations.

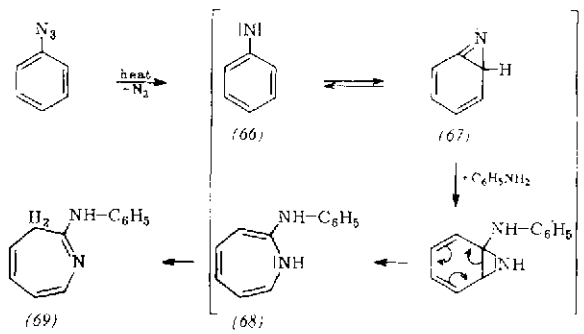
So far only several mono-, di-, and tribenzo derivatives of the three heterotropilidenes *(61)* to *(63)* have been prepared as well as some polysubstituted derivatives stabilized by additional opportunities for resonance, and various dihydro derivatives [54, 55]. Only limited conclusions are permissible from the chemical and physical



*(65)*, X = O, S, N–$CH_3$

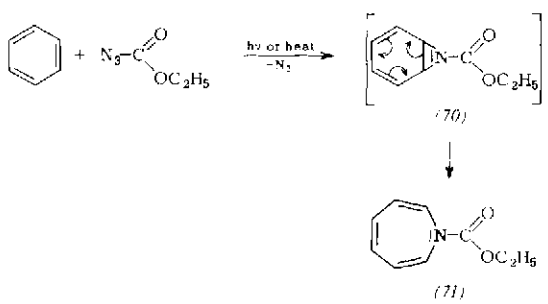
behavior of the benzoheterotropilidenes *(65)* studied by *Dimroth* and *Freyschlag* [54] concerning the properties of the hypothetical monocyclic compounds *(61)* to *(63)*, because in the bicyclic derivatives *(65)* stabilization of the benzene moiety by its electron sextet presumably far outweighs any stabilization of the heterocyclic 7-membered ring.

On the other hand, the investigations of *Huisgen* et al. [55] are of greater significance in this connection. Thermolysis of phenyl azide in aniline yielded a monocyclic isomer of azepine, the cyclic amidine or azatropilidene derivative *(69)* [*]. According to these workers' findings, the aryl nitrene *(66)*, *i.e.* the reactive intermediate arising from the aryl azide by elimination of nitrogen, is supposedly converted in an equilibrium reaction into the similarly highly reactive bicyclic azirine *(67)*, which then undergoes a first (but still incomplete) stabilization to 2-anilino-1*H*-azepine *(68)* by addition of one mole of aniline and subsequent isomerization to the 7-membered ring. The 1*H*-azepine *(68)* rapidly rearranges into the tautomeric form *(69)* which is energetically favored by amidine resonance.



*(66)* *(67)* *(69)* *(68)*

A synthesis recently discovered in our laboratory [56] of a simple azepine derivative and a study of its properties give an answer to the question of the "aromatic character" of this octet system. *N*-Ethoxycarbonylazepine *(71)* can be prepared readily by either photochemical or thermal ring-expansion of benzene with ethyl azidoformate in a reaction analogous to that of *Buchner* [57]. The azepine derivative *(71)* is presumably formed by way of the intermediate aziridine *(70)*, its valence-isomer.



*(70)* *(71)*

The NMR spectrum of this heterocycle displays a multiplet at 4.0–4.7 τ due to the six ring protons. Compared with the spectrum of the homologous *N*-ethoxycarbonylpyrrole (ring-proton signals at 3.0 and 4.0 τ), this indicates some π-electron delocalization (ring current), the extent of which has still not been determined exactly,

[52] *H. J. Dauben, Jr.*, J. Amer. chem. Soc. *85*, 3041 (1963).

[53] *R. Breslow* and *H. W. Chang*, J. Amer. chem. Soc. *84*, 1484 (1962).

[54] *K. Dimroth* and *H. Freyschlag*, Chem. Ber. *89*, 2602 (1956); *90*, 1623, 1628 (1957); *K. Dimroth* and *G. Lenke*, ibid. *89*, 2608 (1956); *K. Dimroth* and *G. Pohl*, Angew. Chem. *73*, 436 (1961); *R. H. F. Manske* and *A. E. Ledingham*, J. Amer. chem. Soc. *72*, 4797 (1950); *F. A. L. Anet* and *P. M. G. Bavin*, Canad. J. Chem. *35*, 1084 (1957); *R. Huisgen, E. Laschtuvka*, and *F. Bayerlein*, Chem. Ber. *93*, 392 (1960); *R. Huisgen, E. Laschtuvka, J. Ugi*, and *A. Kamnermeier*, Liebigs Ann. Chem. *630*, 128 (1960); *E. D. Bergmann* and *M. Rabinovitz*, J. org. Chemistry *25*, 827 (1960); *G. Westöö*, Acta chem. scand. *13*, 604 (1959).

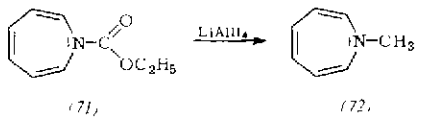
[55] *R. Huisgen, D. Vossius*, and *M. Appl*, Chem. Ber. *91*, 1 (1958); *R. Huisgen* and *M. Appl*, ibid. *91*, 12 (1958); *M. Appl* and *R. Huisgen*, ibid. *92*, 2961 (1959).

[*] According to more recent investigations and contrary to earlier statements, *(69)* possesses the constitution of 2-anilino-3*H*-azepine (personal communication from Prof. *R. Huisgen*).

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

[57] *E. Buchner* and *Th. Curtius*, Ber. dtsch. chem. Ges. *18*, 2377 (1885); see also *G. O. Schenck* and *H. Ziegler*, Liebigs Ann. Chem. *584*, 221 (1953).

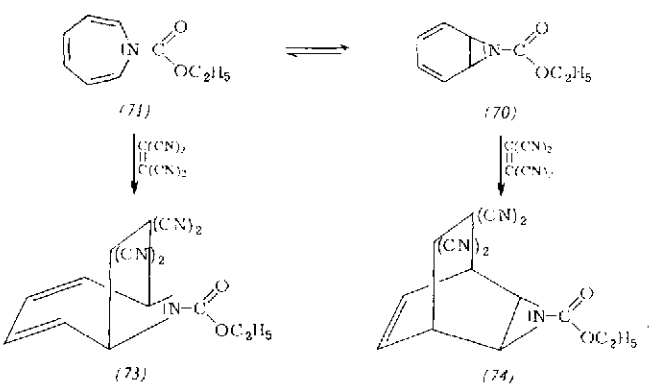
and thus a difference in degree only, but not in kind, between systems with 4n+2 and 4n π-electrons. At the same time, however, the urethane resonance also contributes to the stabilization of *(71)*. This is borne out by the extreme thermal instability of *N*-methylazepine *(72)*,



*(71)* *(72)*

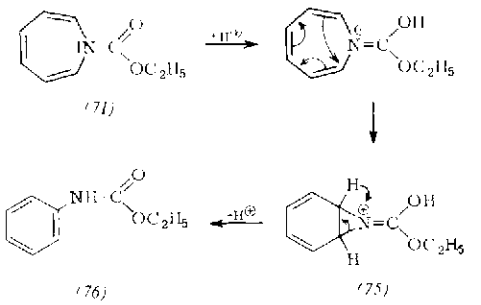
which is accessible by reduction of the azepine derivative *(71)* with lithium aluminum hydride, and whose cyclic system of 8 π-electrons is not stabilized by functional groups. The structureless ultraviolet spectrum of this vinylogue of *N*-methylpyrrole is like that of the 5-membered parent heterocycle with a π-electron sextet but shifted bathochromically by about 30mμ, in accordance with the extension of the conjugated system [58].

In contrast to the 7-membered carbocyclic sextet systems, the ethoxycarbonylazepine *(71)* reacts rapidly with dienophiles to form adducts. According to present findings, the product obtained with tetracyanoethylene [58] is the 1,6-adduct *(73)*, and not the equally conceivable tricyclic Diels-Alder adduct *(74)* which could arise from a mobile equilibrium of the two valence-isomeric



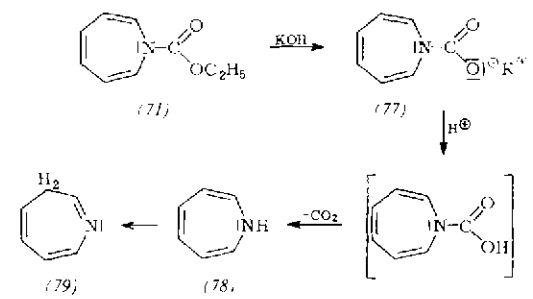
*(71)* *(70)* *(73)* *(74)*

forms *(70)* and *(71)* analogous to the comparable reaction of tropilidene [59]. The lower stability of the π-electron octet than that of the benzenoid π-electron sextet is confirmed by the reaction of *N*-ethoxycarbonylazepine *(71)* with acids. This rapidly leads to ethyl *N*-phenylurethane *(76)*, which is presumably formed after initial protonation of the oxygen by way of the aziridine intermediate *(75)*, from which the benzenoid system is then formed irreversibly with a considerable gain in resonance energy [60].



*(71)* *(76)* *(75)*

Alkaline hydrolysis of the azepine derivative *(71)* offers a route to 1*H*-azepine *(78)* itself. The alkali metal salt of the carbamic acid *(77)* which is initially formed decarboxylates readily under the influence of dilute acids.



*(71)* *(77)* *(79)* *(78)*

1*H*-Azepine *(78)* thereby obtained in solution is thermally very unstable; spectroscopically, like its *N*-methyl derivative, it resembles pyrrole. Its formation is followed rapidly by a rearrangement, presumably into the tautomeric 3*H*-azepine *(79)* [61], effecting stabilization as in the preparation of *Wolff* and *Huisgen*'s azepine derivative *(69)* [55], although the latter compound also profits from the gain in resonance energy associated with the formation of the amidine system. On the other hand, the driving force for the transformation of the double enamine *(78)* with its 8 π-electrons into the azatriene system *(79)* should possibly be sought in the accompanying rebybridization of the nitrogen atom and its involvement in the conjugation.

*I wish to thank my coworkers Dr. K. F. Bangert, Dr. M. Danielisz, W. aus der Fünten, W. Klinner, Dr. C. König, Dr. H. Patzelt, Dr. H. Pelster, Dr. H. Riedel, H. Schaum, Dr. G. Schneider, Dr. J. Schneider, Dr. A. Stephan, E. Sturm, Dr. H. Weldes, M. Woschée, and D. Zinser. Our investigations were generously supported by Professor K. Ziegler, the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Badische Anilin- und Sodafabrik, and Degussa.*

Received, September 17th, 1963 [A 339/140 IE]
German version: Angew. Chem. *75*, 1041 (1963)

[58] *K. Hafner* and *G. Schneider*, unpublished experiments.

[59] *K. Alder* and *G. Jacobs*, Chem. Ber. *86*, 1528 (1953); *K. Alder, K. Kaiser*, and *M. Schumacher*, Liebigs Ann. Chem. *602*, 80 (1957); vgl. auch *E. Vogel*, Angew. Chem. *74*, 829 (1962); Angew. Chem. internat. Edit. *2*, 1 (1963).

[60] *K. Hafner* and *D. Zinser*, unpublished experiments.

[61] *K. Hafner* and *W. aus der Fünten*, unpublished experiments.

# Transformations of Organoboranes at Elevated Temperatures

BY DR. R. KÖSTER
BASED ON WORK CARRIED OUT BY G. BENEDIKT, R. KÖSTER, W. LARBIG, K. REINERT, AND G. ROTERMUND

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*Dedicated to Professor Dr. Karl Ziegler with respect and gratitude on the occasion of his 65th birthday*

*Trialkylboranes with identical or different groups on the boron are stable to alkyl exchange at room temperature. Mixed trialkylboranes only undergo disproportionation in the presence of catalysts such as aluminum trialkyls and boron-hydrogen compounds. At temperatures above 100 °C, organoboranes such as trialkylboranes and B-alkylboracyclanes isomerize as a result of migration of the boron along the aliphatic hydrocarbon radical via dehydroboration-hydroboration equilibria. Alkyl, cycloalkyl, as well as aralkyl and certain arylboranes can be converted irreversibly by pyrolysis at 200–300 °C into other organoboranes (methylboranes and boron-heterocycles of various structures).*

## Introduction

Advances made in organic preparative methods have rendered organoboranes, in particular trialkylboranes, much more readily accessible [1,2]. This has led to a growing interest in these substances in recent years.

In some of their chemical properties, trialkylboranes exhibit certain analogies to trialkylaluminum [3,4], *e.g.* exchange with olefins (displacement reactions), as well as oxidation and hydrogenation of B-C bonds. In many respects, however, they differ from the aluminum compounds. In particular, the catalytic properties exhibited by organoaluminum compounds with regard to the transformation of olefins [5] are only observed to a very slight extent in the corresponding boron compounds (addition of the boron-carbon bond onto C=C double bonds). The transformation of organoboron compounds at elevated temperatures sometimes also leads to products completely different from those obtained with organoaluminum compounds – mainly on account of the greater thermal stability of the B-C and B-H bonds.

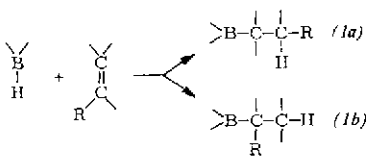
Besides isomerization, the most important thermal reaction of organoboron compounds, in which boron is bound only to carbon, is the splitting of C-C or C-H bonds leading to widely differing boron compounds, especially boron heterocycles. Since generally mixtures are obtained, analysis of the products is of great importance. Gas-chromatographic separation of boron compounds [6–8] and their identification by mass spectrometry [9] and infrared spectroscopy has proved to be particularly satisfactory.

## I. Organoboranes at Room Temperature

Boron-carbon bonds are mainly formed in two ways: 1. by the reaction of alkylmetal or arylmetal with boron halides or with boric esters [4]; 2. in the aliphatic series, by addition of B-H compounds onto alkenes or alkynes, *i.e.* by hydroboration [10,11].

An essential factor governing the composition and structure of organoboron compounds is the temperature of their formation. In addition, the agent used for hydroboration (*e.g.* diborane or alkyldiborane) exerts an influence. *H. C. Brown* and collaborators [11] have made a detailed study of the rules governing hydroboration.

If, for instance, an α-olefin is hydroborated at room temperature with diborane, uniform tri-1-alkylboranes




[1] *E. Frankland* and *B. F. Duppa*, Proc. Roy. Soc. (London) *10*, 568 (1859).

[2] Cf. *M. F. Lappert*, Chem. Reviews *56*, 959 (1956).

[3] *K. Ziegler* et al., Liebigs Ann. Chem. *629*, 14, 53, 121 (1960).

[4] *R. Köster*, Liebigs Ann. Chem. *618*, 31 (1958).

[5] *K. Ziegler*, Angew. Chem. *64*, 323 (1952); *68*, 721 (1956); *K. Ziegler* et al., Liebigs Ann. Chem. *629*, 172 (1960).

[6] *G. Schomburg*, *R. Köster*, and *D. Henneberg*, Z. analyt. Chem. *170*, 285 (1959).

[7] *G. Schomburg*, *R. Köster*, and *D. Henneberg*, Mitteilungsbl. chem. Ges. DDR, Tagungsber., special issue 1960 (Analytische Chemie).

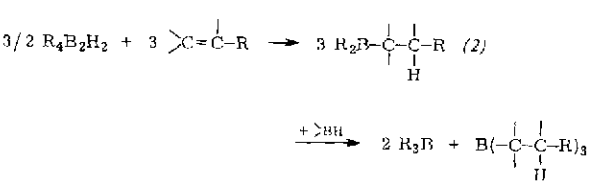
[8] *G. Schomburg* in: Gas Chromatography 1962. Butterworths, London 1962, p. 292; Chem. Abstr. *59*, 8771g (1963).

[9] *D. Henneberg*, *H. Damen*, and *R. Köster*, Liebigs Ann. Chem. *640*, 52 (1961).

[10] *D. T. Hurd*, J. Amer. chem. Soc. *70*, 2053 (1948).

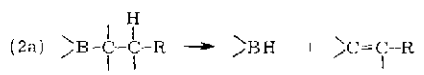
[11] Review: *H. C. Brown:* Hydroboration. W. A. Benjamin Inc., New York 1962.

*(1a)* are not obtained, since addition may take place in two ways. The amount of 2-alkylboranes *(1b)* formed is, however, generally not very great. Practically pure tri-1-alkylboranes *(1a)* are formed when hydroboration is carried out with tetraalkyldiborane [12,13] followed by catalytic disproportionation at a lower temperature of the mixed trialkylboranes *(2)* initially formed [12,14].



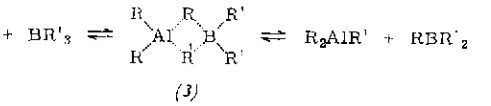
In contradiction to the opinion put forward by *Brown* and *Zweifel* [13], the use of bulky alkyl groups is not essential for selective hydroboration [12,27], since tetraethyldiborane and other tetra-1-alkyldiboranes react with α-olefins to give almost exclusively primary alkyl groups on the boron.

If an α-olefin is hydroborated above 100 °C, *e.g.* with trialkylamine-boranes [16,41], the proportion of secondary alkyl groups on the boron in the final product is usually considerably higher than in the product of hydroboration at low temperatures. This is due to the dehydroboration [4,15,16] which then becomes possible [Equation (2a)]. The reaction conditions during formation suffice to lead to thermal equilibria between different trialkylboranes.



In contrast to trialkylaluminum, trialkyl- and triarylboranes do not exchange hydrocarbon radicals [17] at room temperature. For this reason, it is possible to obtain pure, stable, constant boiling samples of mixed trialkylboranes ($R_2BR'$), which can be readily differentiated from mixtures of two different uniform trialkylboranes ($2R_3B + R'_3B$) having the same overall composition. This significant difference between boron and aluminum trialkyls may be related to the fact that associated aggregates containing electron-deficient bonds bring about the exchange. Such associated forms have been known for a long time in the case of organoaluminum compounds but have not been observed with trialkylboranes. Trialkylboranes have always been found to be completely monomolecular [18,19]. The non-occurrence of rapid spontaneous alkyl exchange between trialkyl- and triarylboranes may be regarded as a final absolute proof that these compounds are not associated even in traces (*i.e.* below the limit of detection).

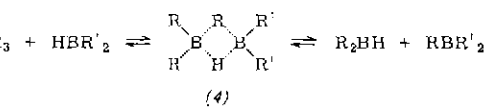
Trialkylboranes exchange alkyl groups with trialkylaluminum at a rate corresponding to that of ionic reactions [17]. This leads to the conclusion that the formation of mixed associates *(3)* with electron deficient bonds between aluminum and boron trialkyls is possible. Aluminum trialkyls are therefore extremely effective catalysts for alkyl exchange between trialkylboranes. Addition of minute amounts of trialkylaluminum to a mixture of $BR_3$ and $BR'_3$ leads to establishment of the equilibrium [17]:



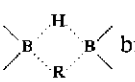
*(3)*

$$BR_3 + BR'_3 \overset{AlR_3}{\rightleftharpoons} R_2BR' + RBR'_2$$

Besides $AlR_3$, boron hydrides also catalyse mutual ligand exchange between boron compounds [17,20,21]. The formation of associated forms such as *(4)* must therefore be assumed as an intermediate stage in this equilibration.



*(4)*

Since catalytically active B-H compounds must necessarily be present during the hydroboration of olefins, exchange of alkyl groups on the boron must also take place simultaneously. The composition of the trialkylboranes formed depends on the rate of exchange as well as on the composition of the equilibrium mixture. Alkyl groups with secondary carbon atoms on the boron (*e.g.* 2-propyl groups) are transferred from one boron atom to the other via the  bridge in *(4)* much more slowly than primary alkyl groups, evidently for steric reasons [20].

## II. Transformations of Organoboranes at Elevated Temperatures

### 1. Thermal Isomerizations

Trialkylboranes isomerize at temperatures above 100 °C via dehydroboration-hydroboration equilibria to give mixtures of trialkylboranes containing primary and seconday alkyl groups on the boron [20,22,23], the $B\text{-}C_{primary}$ bond *(5a)* being strongly preferred to the $B\text{-}C_{secondary}$ bond *(5b)*.

[12] *R. Köster* and *G. Griasnow*, Angew. Chem. *73*, 171 (1961).

[13] *H. C. Brown* and *G. Zweifel*, J. Amer. chem. Soc. *82*, 3222 (1960); *83*, 1241 (1961).

[14] *R. Köster*, Angew. Chem. *73*, 66 (1961).

[15] *L. Rosenblum*, J. Amer. chem. Soc. *77*, 5016 (1955).

[16] *E. C. Ashby*, J. Amer. chem. Soc. *81*, 4791 (1959).

[17] *R. Köster* u. *G. Bruno*, Liebigs Ann. Chem. *629*, 89 (1960).

[18] *A. Stock* and *F. Zeidler*, Ber. dtsch. chem. Ges. *54*, 531 (1921).

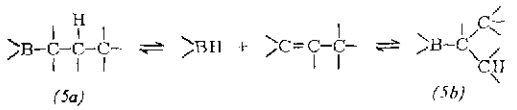
[19] *C. H. Bamford*, *D. L. Levi*, and *D. M. Newitt*, J. chem. Soc. (London) *1946*, 468.

[20] *R. Köster* and *G. Schomburg*, Angew. Chem. *72*, 567 (1960).

[21] *R. Köster*, *G. Bruno*, and *P. Binger*, Liebigs Ann. Chem. *644*, 1 (1961).

[22] *G. F. Hennion*, *P. A. McCusker*, *E. C. Ashby*, and *A. J. Rutkowski*, J. Amer. chem. Soc. *79*, 5190 (1957).

[23] *H. C. Brown* and *B. C. Subba Rao*, J. org. Chemistry *22*, 1137 (1957).



(5a) (5b)

$B\text{-}C_{tertiary}$ bonds generally cannot be detected in the isomerized products since these bonds are evidently subject to dehydroboration at about room temperature [23a, 23b] and are converted into $B\text{-}C_{primary}$ or $B\text{-}C_{secondary}$ bonds. The rate-determining process in attaining the equilibrium is the elimination of the olefin (dehydroboration) [15]. The addition of B-H compounds, *e.g.* alkyldiboranes, onto the C=C double bonds of olefins (hydroboration) takes place very rapidly, even at room temperature [24–27], whereas dehydroboration generally takes place to a significant extent only above 100 °C. The composition of equilibrium mixtures of the simplest trialkylboranes (tripropylborane, tributylborane) can be determined by gas chromatography [6–8] (cf. Table 1).

Table 1. Equilibrium mixtures of simple trialkylboranes at 160 °C.

| Tri-n-propylborane | Tri-n-butylborane |
|---|---|
| 83 % ppp | 94 % bbb |
| 16 % ppi | 6 % bbs |
| 1 % pii | 0 % bss |

p = 1-propyl; i = 2-propyl; b = 1-n-butyl; s = 2-n-butyl.

The attainment of equilibrium, *e.g.* with the tripropylboranes, can also be readily followed by gas chromatography [8] (cf. Fig. 1).

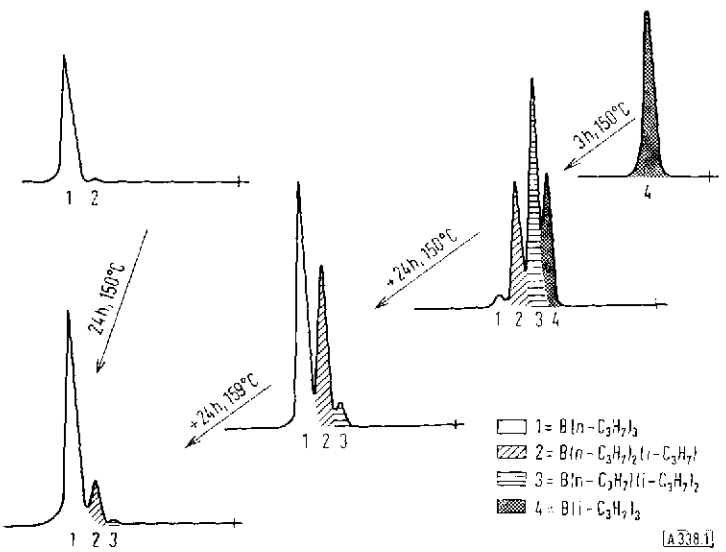
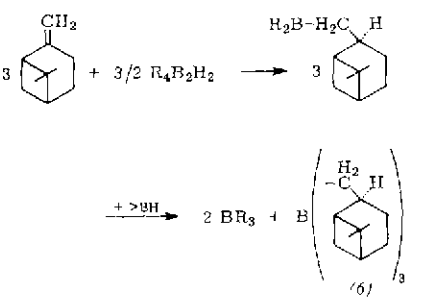



Fig. 1. Thermal isomerization of tripropylboranes. Gas-chromatographic analysis (column: silicone oil DC 710 on Chromosorb 0.3–0.4 mm; 90 °C; He current velocity: 105 ml/min; approx. 5 µl sample).

With increasing temperature, the proportion of boron bound to secondary carbon atoms in the equilibrium mixture increases slightly. Thus, in the case of tripropylborane, the ratio of 1-propyl to 2-propyl groups is of the order of 16:1 at 160 °C, but about 12:1 at 220 °C [17].

Trialkylboranes with longer alkyl chains contain predominantly 1-alkyl groups together with a small amount of 2-alkyl groups at equilibrium. Boron is practically not bound to carbon atoms further away from the terminal position. It is therefore possible to prepare alkylboranes with terminal boron atoms from olefins containing a C–C double bond in the interior of a long alkyl chain. Subsequent olefin exchange (displacement reaction [26, 28–30]) makes it possible to split off the olefins with the terminal C=C double bond from the thermally isomerized trialkylborane.

If the alkyl chain of the alkylboranes is branched, the boron atom is preferably bound to that carbon atom which is furthest removed from the point of branching. Frequently, however, the tendency of the boron atoms to become attached to different chain ends is too similar and an alkylborane cannot therefore be readily converted quantitatively into another one.



In the meantime, considerable knowledge has been gained about the thermal migration of boron atoms along alkyl chains of alkylboranes [31]. It is interesting to note that thermal isomerizations occur in which the boron atom remains bound to a given carbon atom of an alkyl group and simply changes its steric position with respect to it [32]. Thus, tri-(*cis*-myrtanyl)borane *(6)* is obtained at room temperature from tetraethyldiborane and β-pinene by hydroboration followed by disproportionation in the presence of excess B-H groups [27]. Compound *(6)* is formed by *cis*-addition of the B-H group onto the terminal C–C double bond [32]. If the pure crystalline compound *(6)* (m.p. 94 °C) is heated above its melting point, it undergoes isomerization to form tri-(*trans*-myrtanyl)borane *(6a)*, which is a liquid at room temperature. This rearrangement is due to differences in the rates of the dehydroboration and hydroboration reactions [27] (cf. Scheme 1).


[23a] *P. Heimbach*, Ph. D. Thesis, Technische Hochschule Aachen, 1960, pp. 21, 69, 70. Formation of *cis*-myrtanylboranes on hydroboration of β-pinene at room temperature.

[23b] *G. Zweifel* and *H. C. Brown*, J. Amer. chem. Soc. *85*, 2066 (1963).

[24] *P. Binger*, Ph. D. Thesis, Technische Hochschule Aachen, 1959.

[25] *H. C. Brown* and *G. Zweifel*, J. Amer. chem. Soc. *83*, 1241 (1961).

[26] *R. Köster*, Angew. Chem. *68*, 383 (1956).

[27] *R. Köster, G. Griasnow*, and *P. Binger*, Liebigs Ann. Chem. *672* (1964), in the press.

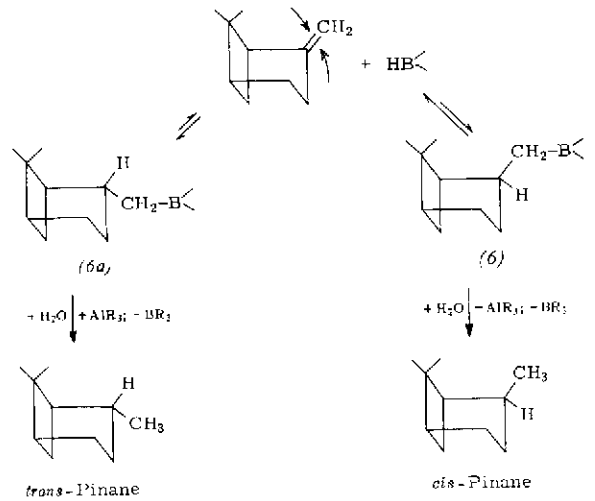
[28] *R. Köster*, Angew. Chem. *70*, 413 (1958).

[29] *R. Köster*, Liebigs Ann. Chem. *618*, 31 (1958).

[30] *H. C. Brown* and *B. C. Subba Rao*, J. org. Chemistry *22*, 1137 (1957); J. Amer. chem. Soc. *81*, 6434 (1959).

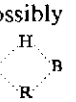
[31] See [11], pp. 136 et seq.

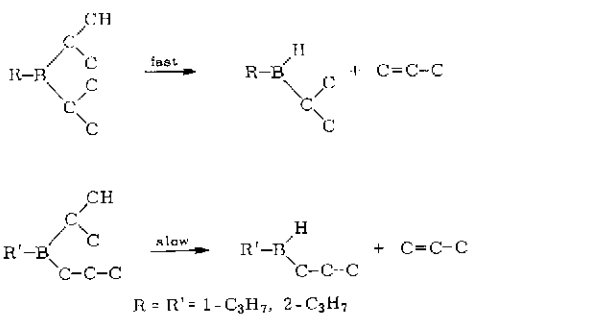
[32] *J. C. Braun* and *G. S. Fisher*, Tetrahedron Letters *21*, 9 (1960).



Scheme 1. The formation of sterically isomeric pinanes via trimyrtanylboranes as intermediate products.

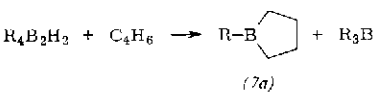
The boron atom thus passes from the sterically more hindered side (isopropylidene group) to the less hindered side of the same carbon atom.

The recently observed thermal isomerization of trialkylboranes catalysed by B-H compounds [33] is possibly due to the fact that alkyl group exchange via the  bridge precedes the rate-determining dehydroboration. The di-s-alkylmono-1-alkylboranes and tri-s-alkylboranes which are formed anew in the mixtures evidently split off olefin much more rapidly than the mono-s-alkyldi-1-alkylboranes or tri-1-alkylboranes (cf. Scheme 2).



Scheme 2. Rate of dehydroboration as a function of the degree of branching of the alkyl groups.

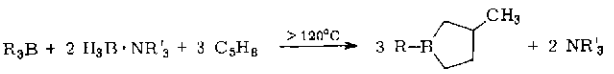
Equilibria similar to those prevailing in the case of the simple trialkylboranes also occur with simple boron heterocycles, *e.g.* the *B*-alkylboracyclanes *(7a)* and *(7b)* [20,27,38]. The compounds are readily prepared



*(7a)*

by hydroboration of dienes with alkyldiboranes at low temperatures [27] or with trialkylamine-boranes in the presence of trialkylboranes above 120 °C [20,38,41].

The alkyl group of the *B*-alkylboracyclanes occupying the third valence of the boron atom also isomerizes at elevated temperatures. However, here the equilibrium mixture contains a larger amount of secondary groups



*(7b)*

than is observed with boranes containing only open-chain substituents; this may be due to steric effects [35]. Thus, in the case of *B*-n-butylborolane, about 15 % of the butyl groups are secondary at 160 °C, as compared to about 6 % of the "third" butyl groups in tri-n-butylborane.

This side-chain isomerization of alkyl radicals bound to boron is accompanied in boron heterocycles by isomerizations in which rings of different sizes are interconverted. The same influences are in operation here as in the side-chain isomerization, *viz.* dehydroborationhydroboration equilibria and steric factors. Different boracyclanes are therefore in equilibrium with one another at elevated temperatures as a result of ring contraction or ring enlargement. Seven-membered as well as five- and six-membered rings are formed. In addition, stereoisomerism due to the rings is observed [27].

General statements regarding the relative stabilities of boracyclanes cannot be made readily, since the ring stability depends on the ring size as well as on the type of the B–C bonds. At all events, it can be stated that boracyclanes in which the formation of a six-membered ring with two $B-C_{primary}$ bonds or with a $B-C_{primary}$ bond and a $B-C_{secondary}$ bond is possible possess the greatest thermal stability. The difference in the rates of dehydroboration is involved here. In fact, the stabilizing influence of the ring size may be so great that $B-C_{tertiary}$ bonds are formed in some particularly favorable cases (cf. Table 2).

Table 2. Distribution [a] in equilibrium at 160 °C of the *B*-ethylboracyclanes which are formed in the hydroboration of dienes with tetraethyldiboranes

| Diene | Five-membered ring [%] | Six-membered ring [%] | Seven-membered ring [%] |
|---|---|---|---|
| Isoprene | 100 % | — | — |
| 2,3-Dimethyl-1,3-butadiene | 30:70 [b] | — | — |
| 1,4-Pentadiene | 2.8 | 97.2 | — |
| 1,5-Hexadiene | 1.0:2.7 [b]; 3.8 | 79.9 | 12.6 |
| 2,5-Dimethyl-1,5-hexadiene | 66.3 | 23.0 [c] | 10.7 |

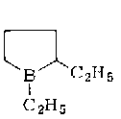
[a] Gas-chromatographic analyses; the percentage areas of the peaks from the gas chromatograms correspond approximately to the percentages by weight of the isomers.
[b] Cis-trans isomers.
[c] Contains an unknown amount of a borepane isomer.

Thus, when 1,5-hexadiene is hydroborated with tetraethyldiborane at low temperature,

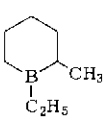
$$C_6H_{10} + (C_2H_5)_4B_2H_2 \rightarrow C_2H_5BC_6H_{12} + B(C_2H_5)_3,$$

[33] See [11], pp. 137–138.
[34] *K. A. Saegebarth*, J. Amer. chem. Soc. *82*, 2081 (1960).
[35] *R. Köster* and *G. Rotermund*, unpublished work; cf. [43].

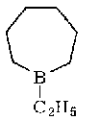
the triethylborane formed is accompanied by a mixture of boracyclanes, $C_2H_5BC_6H_{12}$, not containing any five-membered rings. The reason for this is that the formation of five-membered rings from the olefin requires a dehydroboration step which proceeds at a significant rate only above 120 °C. The hydroboration mixture obtained at low temperatures therefore consists of 97 % of the seven-membered ring compound, *B*-ethylboracycloheptane *(10)*, together with 3 % of the six-membered ring compound, *B*-ethyl-2-methylboracyclohexane *(9)* [27]. At 160 °C, a 7.5 %:79.9 %:12.6 % mixture of the *B*-ethylboracyclanes, *(8)*, *(9)*, and *(10)*, is obtained [20] (cf. Table 2).



*(8)*

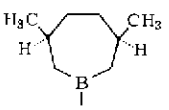


*(9)*

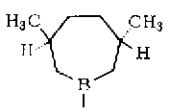


*(10)*

Hydroboration of 2,5-dimethyl-1,5-hexadiene with tetraethyldiborane at low temperature yields the two sterically isomeric *B*-ethyl-3,6-dimethylboracycloheptanes *(11a)* and *(11b)* in a molar ratio of 1:1 [36].

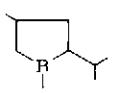


*(11a), cis*

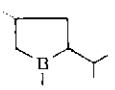


*(11b), trans*

Following oxidative degradation with alkaline hydrogen peroxide, only 2,5-dimethyl-1,6-hexanediol is isolated, but this presumably consists of a mixture of the racemate and the *meso*-form which cannot be separated by gas chromatography. On heating to temperatures above 120 °C, isomerization takes place. At elevated temperatures, the proportion of the two seven-membered ring compounds changes first of all. Subsequently, the six-membered ring compound can be detected. After about 3 hours at 120 °C, the five-membered ring compound appears which finally, at 160 °C, forms the main constituent of the isomeric mixture and which can be split into the *cis*- and *trans*-isomers *(12a)* and *(12b)*.



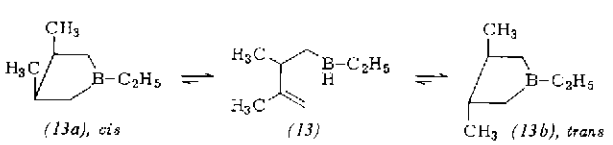
*(12a), cis*



*(12b), trans*

Oxidation followed by hydrolysis of the boracyclane mixture also yields a 1,4- and 1,5-diol in addition to 1,6-diols. The six-membered boracyclane which is the parent compound of the 1,5-diols, can only result when the boron atom is bound to a tertiary carbon atom.

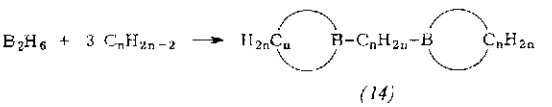
A further good example involving steric isomerism is the borolane formed from 2,3-dimethyl-1,3-butadiene and ethyldiboranes [37]. At low temperatures, the *cis*- and *trans*-*B*-ethyl-3,4-dimethylborolanes *(13a)* and *(13b)* (b.p. 55–56 °C/50 mm) are obtained in a 1:1 ratio. If this mixture is heated for 4 hours at 160 °C, the ratio changes to about 3:7. The equilibrium is attained via the dehydroboration stage *(13)*.



*(13a), cis* *(13)* *(13b), trans*

This change in the composition is probably due to a difference in the rates of dehydroboration of the two isomers; the hydroboration rate is likely to be practically the same for both compounds also at elevated temperatures. The change of the isomer ratio is then due to the difference in the influence exerted on the borolane ring by the two vicinal methyl groups when in *cis*- and in *trans*-relationship.

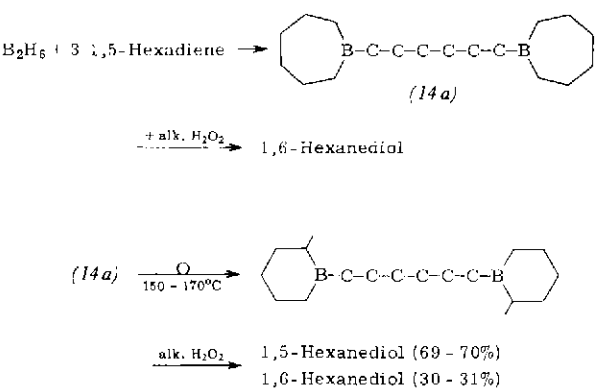
Bis-*B*-boracyclylalkanes *(14)* [34,38] are readily prepared by hydroboration of dienes with diborane at low temperature [34] or with trialkylamine-boranes at elevated temperatures [38] but isomerize on heating in an



*(14)*

analogous manner to the *B*-alkylboracyclanes. The composition of the compounds $B_2(C_nH_{2n})_3$ (n = 5 or 6) was examined before and after thermal isomerization by oxidation to the diols [34].

A bis-*B*-boracyclylalkane which was prepared at room temperature from 1,5-hexadiene or 1,4-hexadiene and diborane and then heated to 160 °C yielded on oxidation and subsequent hydrolysis two-thirds 1,5-alkanediol together with about one-third 1,6-alkanediol. The 1,5-alkanediol is probably derived mainly from the resultant six-membered heterocycles, and the 1,6-alkanediol from the alkylene group to which the two boron atoms are attached in the bis-*B*-boracyclylalkane. The composition of the compounds prepared at room temperature from diborane and 1,3-pentadiene, 1,4-pentadiene, and 1,5-hexadiene [34] was investigated. On oxidation and hydrolysis, the product prepared at low temperature from 1,5-hexadiene *(14a)* yields mainly 1,6-hexanediol. Thus, here again the seven-membered ring with two $B-C_{primary}$ bonds is preferred in the first instance. Six-membered ring compounds are hardly formed in the low-temperature hydroboration of 1,5-hexadiene.




Exact determination of the thermal equilibria of bis-*B*-boracyclylalkanes *(14)* and generally of mixtures containing compounds with several boron atoms is more difficult than in the case of simple *B*-alkylboracyclanes, since gas-chromatographic separation is no longer possible on account of the low vapor pressures.

On heating of bis-*B*-boracyclylalkanes, migration of the *B*-borolane ligand along the alkylene chain between the two boron atoms (side-chain isomerization) might be anticipated in addition to ring isomerization. However, isomerization of bis-(3'-methyl-*B*-borolanyl)-2-methylbutane *(15)* evidently proceeds not only in this direction [39]. This isomerization is accompanied by dispropor-

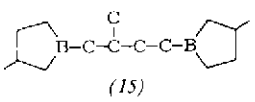
[36] *R. Köster* and *W. Larbig*, unpublished work.

[37] *R. Köster* and *W. A. Dorochow*, unpublished work.

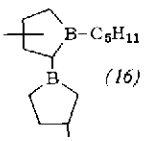
[38] *R. Köster*, Angew. Chem. *71*, 520 (1959).

[39] *R. Köster* and *K. Iwasaki*, unpublished work.

tionation of the alkylene radicals. Mono- and trifunctional groups are formed from the bifunctional alkylene

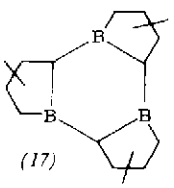


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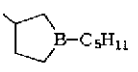


(16)

groups. Starting from *(15)*, a compound of constitution *(16)* is obtained which on further heating is converted into a boron compound (mol. weight 240) containing 3 boron atoms; this must be a triboracylohexane derivative *(17)*. *B*-Isopentyl-3-methylborolane *(18)* is formed as a further disproportionation product.

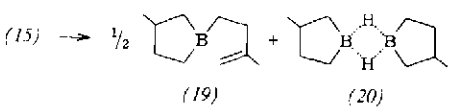


(17)



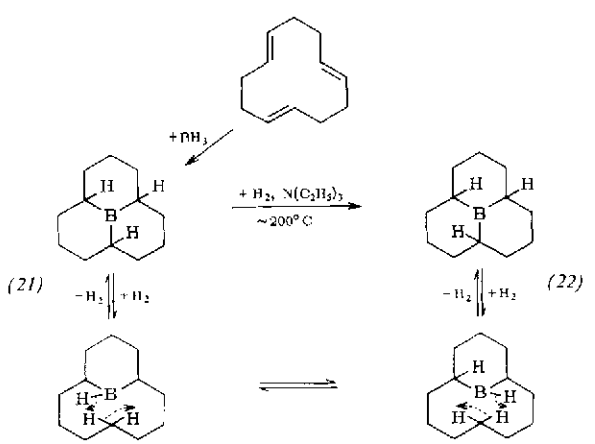
(18)

The postulated first step, *viz.* dehydroboration of the bicyclic boron compound *(15)*, can be realized experimentally. At reduced pressure, *B*-isopentenyl-3-methylborolane *(19)* is obtained together with bis-(3-methylborolane) *(20)* at about 150 °C [39,40].



(19) (20)

*cis,cis,cis*-Perhydro-9$^b$-boraphenalene *(21)* [41] may be prepared by hydroboration of *trans,trans,trans*-1,5,9-cyclododecatriene [51] and may be converted into an isomeric form by treatment with hydrogen under pressure for several hours at 200–220 °C in the presence of a tertiary aliphatic amine, *e.g.* triethylamine [42.43]. The liquid



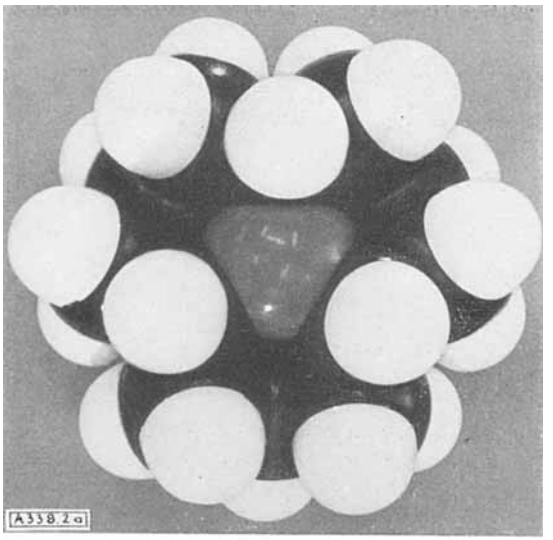
(21) (22)

[40] *R. Köster:* New Results in the Field of Organoboron Compounds. Symposium on Current Trends in Organometallic Chemistry, Cincinnati, Ohio (U.S.A.), June 1963. Abstracts of Papers, p. 19.

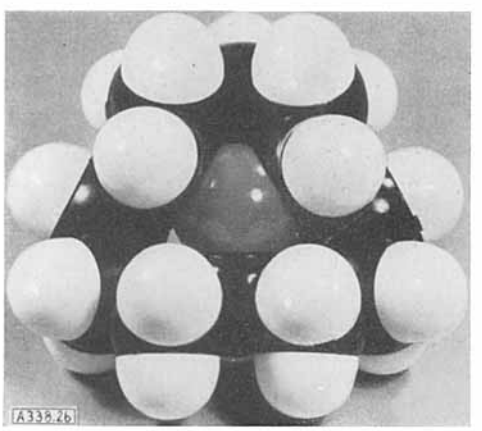
[41] *R. Köster*, Angew. Chem. *69*, 684 (1957).

[42] *G. Rotermund* and *R. Köster*, Angew. Chem. *74*, 329 (1962); Angew. Chem. internat. Edit. *1*, 269 (1963).

[43] *G. Rotermund*, Ph. D. Thesis, Technische Hochschule Aachen, 1962.



(a)



(b)

Fig. 2. Stuart-Briegleb models of the isomeric perhydro-9$^b$-boraphenalenes.

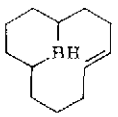
(a): *cis,cis,cis*-perhydro-9$^b$-boraphenalene; (b): *cis,cis,trans*-perhydro-9$^b$-boraphenalene.

compound *(21)* yields an isomer of identical composition, b.p. 110 °C/9 mm, which forms beautiful crystals, m.p. 31 °C. Hydrogen and amine are not consumed during this transformation. The crystalline isomer is *cis, cis, trans*-perhydro-9$^b$-boraphenalene *(22)*. In this case, isomerization probably takes place via hydrogenation of a B–C bond [21,26], followed by a conformational change and transanular dehydrogenation. The infrared spectra of the two centroboron compounds *(21)* and *(22)* exhibit characteristic differences.

During the attainment of the hydrogenation-dehydrogenation equilibrium between the two isomers, the trialkylamine probably acts as a stabilizer for the boron-hydrogen compounds formed as intermediates. In the absence of amine, the boron-carbon bonds undergo hydrogenation, and cyclododecane is then isolated together with other saturated hydrocarbons (particularly methane as well as ethane, propane, butane, *etc.*) [43].

Isomerization of the two perhydro-9$^b$-boraphenalenes cannot be achieved simply by heating since these boron heterocycles evidently only undergo dehydroboration at temperatures at which the intermediates (13-borabi-

cyclo[7,3,1]tridecenes) *(23)* decompose irreversibly. This example therfore indicates the limits of the thermal transformation of organoboranes.



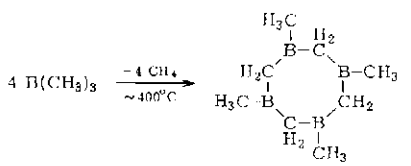
*(23)*

## 2. Irreversible Reactions

On heating alkyl- or aralkylboranes to 200 °C and above, varying structures are obtained – depending on the type and length of the groups bound to the boron – as a result of an irreversible reaction.

a) *Pyrolysis of Trialkylboranes with Small Alkyl Groups (Methylboranes)*

On pyrolysis, trimethylborane [44] forms boron heterocycles in addition to polymeric compounds of varying composition. Among the numerous reaction products formed at about 400 °C, an eight-membered ring containing four carbon and four boron atoms can be



*(24)*

isolated *(24)*. Other low trialkylboranes can be converted into trialkylboranes containing new alkyl groups at comparatively low temperatures, sometimes in surprisingly good yield [45].

Pyrolysis at about 300 °C of trialkylboranes containing more than one, but fewer than four carbon atoms in the main alkyl chain (*e.g.* triethyl-, tripropyl-, and tri-isobutylborane) yields methyl- and other alkylboranes by dehydroboration via dialkylborohydrides as a result of C-C splitting [45].

Triethylborane yields ethylene and methylethylboranes, while tri-isobutylborane gives isobutene and methylpropylboranes:

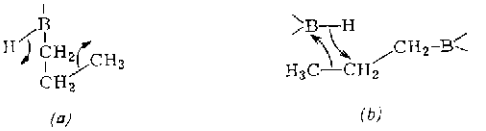
$$B(i\text{-}C_4H_9)_3 \rightarrow BH(i\text{-}C_4H_9)_2 + i\text{-}C_4H_8 \rightarrow i\text{-}C_4H_9B(CH_3)(C_3H_7).$$

As a result of the simultaneous occurrence of alkyl exchange on the boron atom, mixtures of all possible trialkylboranes are isolated after pyrolysis. Propyl groups bound to boron are present partially in the form of 1-propyl groups and partially in the form of 2-propyl groups (equilibrium mixture [20]). The pyrolysis products generally do not contain any B–H bonds, yet boron hydrogen compounds such as *(25)* constitute the actual reactive intermediates of the thermal transformation of trialkylboranes.



*(25)*

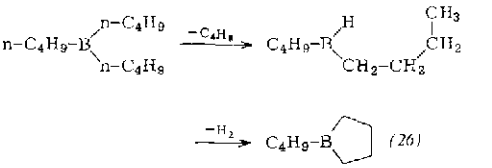
It has not yet been proved whether C–C splitting in the presence of B–H compounds is an intramolecular (a) or intermolecular (b) process.



*(a)* *(b)*

b) *Pyrolysis of Trialkylboranes with Medium-Sized and Long Alkyl Groups (Mono- and Bicyclic Boron Heterocycles)*

Trialkylboranes containing at least four carbon atoms in the main alkyl chain may be converted in high yields into boron heterocycles by heating to 200–300 °C [46, 48]. As a result of dehydroboration (elimination in particular of 2-butene) a mixture of *B*-butylboracyclopentanes $C_4H_9BC_4H_8$ *(26)* is obtained at about 300 °C in yields of up to 90 % together with hydrogen. The mixture consists of two isomers which can be separated by



*(26)*

gas chromatography [7], *viz.* 85 % 1-n-butylborolane and 15 % 2-n-butylborolane. Oxidation and hydrolysis (for instance with alkaline $H_2O_2$) yields 1-n-butanol and 2-n-butanol, as well as 1,4-butanediol.

The composition of the products of pyrolysis of trialkylboranes becomes progressively more complex with increasing numbers of carbon atoms in the alkyl groups. With an increase in the length of the alkyl chain bound to the boron, a lower pyrolysis temperature can be chosen (*e.g.* tri-n-hexylborane undergoes rapid decomposition with elimination of hydrogen at about 280 °C; with tri-n-undecylborane, this takes place at about 220 °C) [43].

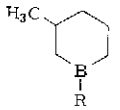
High yields are obtained when the products of pyrolysis are removed as rapidly as possible from the hot zone. In addition the work must be carried out with only partial conversion, particularly when it is not possible to separate off the cyclic compounds immediately after pyrolysis. Reaction mixtures containing higher trialkylboranes assume a brown color at about 75–80 % conversion and those of the triaralkylboranes (cf. p. 182) at about 90 % conversion. The simple cyclization products are then accompanied by polymeric boron compounds. In the initial stages of pyrolysis, the trialkylborane

[44] *J. Goubeau* and *R. Epple*, Chem. Ber. *90*, 171 (1957).
[45] *R. Köster* and *W. Larbig*, Angew. Chem. *73*, 620 (1961).
[46] *R. Köster* and *G. Rotermund*, Angew. Chem. *72*, 138 (1960).
[47] *R. Köster* and *G. Rotermund*, Angew. Chem. *72*, 563 (1960).

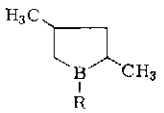
is present in large excess and substantially prevents intramolecular reactions of the heterocycles formed (dilution effect).

On pyrolysis, most trialkylboranes yield mixtures of cyclic isomers, as is to be anticipated on the basis of the thermal equilibria observed with boracyclanes (cf. p. 178) [46,47]; thus, the number of atoms in the ring (n = 5,6,7) and the position at which the side chain is attached to the boron differ (cf. p. 177).

Tri-(2-methyl-1-pentyl)borane yields four isomers of empirical formula $C_6H_{13}BC_6H_{12}$, with elimination of hydrogen and, predominantly, 2-methyl-2-pentene; these isomers contain about 80 % isohexylboracyclohexanes *(27a)* (2 compounds, two different hexyl radicals R) and about 20 % isohexylmethylboracyclopentane *(27b)* (4 compounds, 2 different



*(27a)*

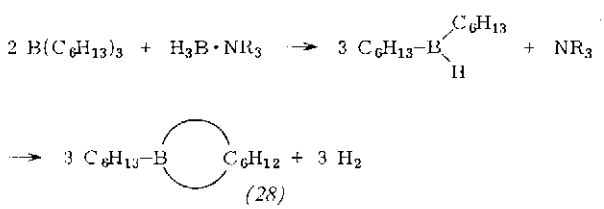


*(27b)*

hexyl radicals R; *cis*- and *trans*-isomers) [46]. As a result of migration of the boron atom to the other end of the carbon chain, R also consists of the 4-methyl-1-pentyl group [46].

Tri-(2-ethyl-1-hexyl)borane [35] can be converted in a similar manner into a fairly complex mixture of boron heterocycles which has not been examined in detail up to now. It is likely to consist of mainly six-membered rings. Three different alkyl groups come mainly into consideration for the side chain R; in addition to the 2-ethyl-1-hexyl group, 3-methyl-1-heptyl radicals and, in particular, 5-methyl-1-heptyl radicals are present after heating. Alkyl radicals in which the boron atom is bound to a non-terminal carbon atom cannot be detected. On the other hand, the olefin mixture obtained in the pyrolysis contains almost exclusively branched alkenes with a non-terminal C=C double bond: 3-methyl-2-heptene and 3-methyl-3-heptene.

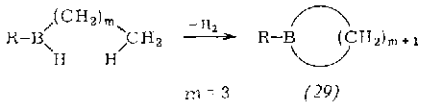
Boracyclanes can also be prepared by pyrolysis of a mixture of trialkylboranes and trialkylamine-boranes [35, 46]. Thus, if 1 mole of triethylamine-borane and 2 moles of tri-n-hexylborane are heated at about 200 °C, an isomeric mixture of three boron heterocycles *(28)* is obtained. No olefin is formed. The five-membered (borolane) and six-membered (borinane) rings are accompanied by a small amount of the seven-membered boracyclane (borepane) (cf. p. 178). Oxidation (*e.g.* with



*(28)*

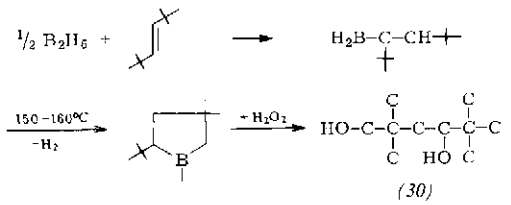
alkaline $H_2O_2$) yields, in addition to 1,4-hexanediol and 1,6-hexanediol, mainly 1,5-hexanediol. The side chain R consists predominantly of the 1-hexyl group. Secondary hexyl groups on the boron are present only to a small extent.

Dialkylboranes are intermediates in the pyrolysis of trialkylboranes to boron heterocycles, since alkyldiboranes $B_2H_{6-n}R_n$ (n = 1–4) are converted into boron heterocycles *(29)* at 150–200 °C with elimination of hydrogen [46,47,50].



*(29)*

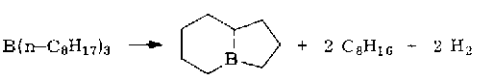
Diborane and 1,2-di-t-butylethylene (*trans*-2,2,5,5-tetramethyl-3-hexene), for instance, react to give an alkyldiborane which on prolonged heating (20 hours, 160–165 °C) forms a heterocyclic boron compound from which 2,2,5,5-tetramethyl-1,4-hexanediol *(30)* is formed on oxidation with hydrogen peroxide [49].



*(30)*

Although dialkylboranes are evidently intermediates in the preparation of heterocycles from trialkylboranes, the trialkylboranes nevertheless give better yields [46]. Apparently the concentration of the B–H groups must not be high since otherwise polymers and other by-products (*e.g.* methylboranes) are readily formed. In the presence of trialkylamine-boranes as B–H group source, aminoboranes $R_2B{-}NR_2$ are also isolated [43].

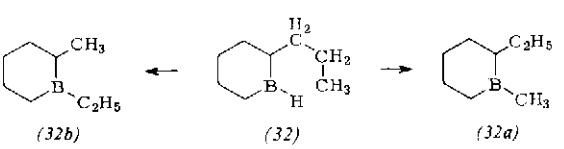
In the pyrolysis of trialkylboranes and alkyldiboranes with eight and more carbon atoms in the main alkyl chain, bicyclic as well as monocyclic boron compounds are formed [43,47]. Starting from tri-n-octylborane one obtains 8-borahydrindane *(31)*, albeit in small yields, via octylborohydrides after loss of two moles of hydrogen.



*(31)*

The octenes given off contain predominantly non-terminal C–C double bonds. The reaction products also include polymers. Furthermore, it is impossible to avoid C–C bond splitting.

If the carbon chain is not long enough – as is the case with tri-n-octylborane – the second stage of the pyrolysis involves methylborane formation [43], as is also observed with the lower trialkylboranes [45] (cf. p. 180). The



*(32b)* *(32)* *(32a)*

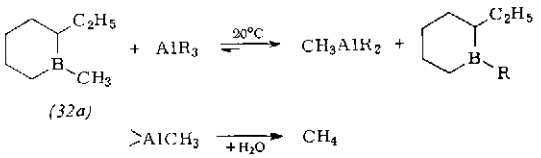
molecular weights of these secondary products can be determined by mass spectrometry [43]. Furthermore, the

[48] *P. F. Winternitz* and *A. A. Carotti*, J. Amer. chem. Soc. *82*, 2430 (1960).

[49] *T. J. Logan* and *T. J. Flautt*, J. Amer. chem. Soc. *82*, 3446 (1960).

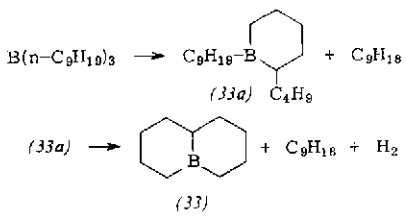
[50] *R. Köster* and *G. Rotermund*, Angew. Chem. *74*, 252 (1962); Angew. Chem. internat. Edit. *1*, 217 (1962).

newly formed small alkyl groups present on the boron *(32a)* can be readily detected by alkyl exchange with aluminum trialkyls. Methyl groups are particularly



*(32a)*

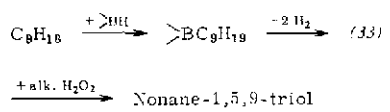
readily detected thereby since they are preferably bound to aluminum in the $BR_3/AlR_3$ equilibrium mixture [17]. These complexes play a less significant part in the pryolysis of tri-n-alkylboranes with more than eight carbon atoms in the alkyl groups. Under suitable conditions (cf. p. 180), 9-boradecalin *(33)* is obtained between 250 and 300 °C from tri-n-nonylborane in 80 % yield [47].



The monocyclic boranes *(33a)* are formed first as intermediates. As the pyrolysis progresses, *(33a)* is then converted into the bicyclic compound.

Higher trialkylboranes are converted by pyrolysis to 1-alkyl-9-boradecalins (*e.g.* tri-n-undecylborane → 1-ethyl-9-boradecalin) [42,43].

1,5,9-Alkanetriols are readily prepared from the 9-boradecalins *(33)*. A method is thus available for synthetizing well-defined alkanetriols from monoolefins, *e.g.* 1,5,9-nonanetriol from n-nonene, in accordance with the reaction scheme:



c) *Pyrolysis of Tricycloalkylboranes (Boron Heterocycles with endo-Boron Atoms)*

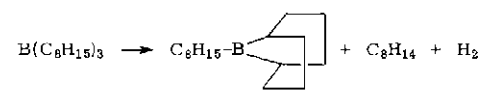
Cycloalkylboranes rapidly split off cycloolefins at 180 to 200 °C, first forming dicycloalkylborane [50]. The further course of the reaction depends on the ring size of the cycloalkyl group.

Tricyclohexylborane yields cyclohexane, cyclohexene, hydrogen, and polymeric products containing boron:

$$B(C_6H_{11})_3 \rightarrow [C_6H_{11}B]_x + C_6H_{10} + C_6H_{12} \quad \text{(also: } C_6H_{10} + H_2\text{)}$$

7-Borabicyclo[2.2.1]heptane is not formed.

Tricyclooctylborane on the other hand yields *B*-cyclooctyl-9-boratricyclo[3.3.1]nonane *(34)* [50] in good yields:



*(34)*

The cyclooctyl compounds are best pyrolyzed in the presence of a trialkylborane, $BR_3$. The third boron valence which does not participate in the ring is then saturated with the group R, as for instance in *(34)*.

When heated to 220 °C, 1 mole of tricyclododecylborane yields a perhydro-9$^b$-boraphenalene *(21)* [50] with elimination of 2 moles of cyclododecene (*cis*- and *trans*-isomers) and 2 moles of hydrogen in accordance with the equation:

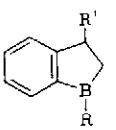
$$B(C_{12}H_{23})_3 \rightarrow 2\,C_{12}H_{22} + (21) + 2\,H_2$$

Compound *(21)* is also formed on hydroboration of *trans,trans,trans*-cyclododeca-1,5,9-triene (cf. p. 179) [42,51].

d) *Pyrolysis of Aralkylboranes (1-Boraindanes and 1-Boratetralins)*

Although alkyldiboranes and olefins are formed when trialkylboranes are heated above 180 °C (dehydroboration), certain triaralkylboranes cannot be converted into aralkyldiboranes at elevated temperatures, even under strongly reduced pressure [4]. The olefin (arylalkene) produced is accompanied by hydrogen [52]. The presence of B–H bonds cannot be proved in the boron-containing dehydroboration products of the triaralkylboranes. On heating aralkylboranes, boron heterocycles are often obtained directly in yields of over 90 %. The temperatures required for cyclization lie between 180 and 250 °C.

For instance, 1 mole of tri-(2-phenylpropyl)borane decomposes at 180–200 °C and a pressure of $10^{-1}$–$10^{-3}$ mm to form 1 mole of α-methylstyrene and 1 mole of hydrogen as well as a boron compound $BC_{18}H_{21}$, a colorless liquid which is sensitive to air and which has a well defined boiling point [52]. The compound was identified as *B*-(2-phenylpropyl)-3-methylboraindane *(35a)* [52] and has a $B-C_{aryl}$ bond which is readily detected by its reaction with mercuric chloride [53].



*(35a)*: R = $CH_2$–$CH(CH_3)$–$C_6H_5$, R' = $CH_3$
*(35b)*: R = $CH_2$–$CH_2$–$C_6H_5$, R' = H

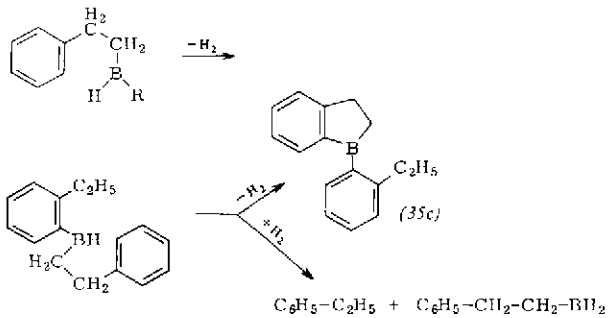
Tri-(2-phenethyl)borane is converted similarly into *B*-(2-phenethyl)boraindane *(35b)*, ethylbenzene being formed in addition to styrene and hydrogen. The hydrocarbon evidently arises as a result of hydrogenation of the aralkylborane and not from styrene produced by dehydroboration, since pyrolysis of 2-phenethylboron compounds yields not only boraindanes with aralkyl groups on the boron, but also derivatives *(35c)* with alkaryl (*e.g.* 2-ethylphenyl) groups. This indicates that dehydrogenations and hydrogenations in accordance with Scheme 3 take place during pyrolysis.

Direct elimination of hydrocarbons (*e.g.* ethylbenzene) is also possible but evidently plays a decisive part only in


[51] *G. Wilke*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

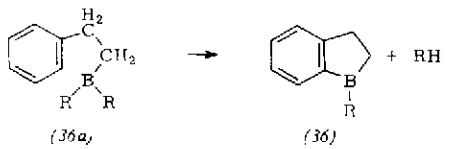
[52] *R. Köster* and *K. Reinert*, Angew. Chem. *71*, 521 (1959).

[53] *G. Wittig, C. Keicher, A. Rückert*, and *P. Raff*, Liebigs Ann. Chem. *563*, 110 (1949).



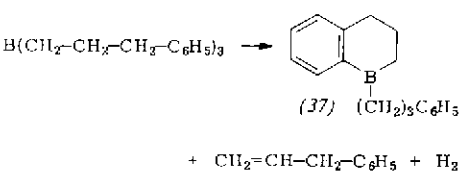
Scheme 3. Hydrogenations and dehydrogenations taking place during the pyrolysis of tri-(2-phenethyl)borane.

special cases (cf. p. 184), since RH-elimination [*(36a)* → *(36)*] proceeds at a substantially slower rate than the liberation of hydrogen from B–H compounds.



*(36a)* *(36)*

The six-membered rings corresponding to *(36)* (1-boratetralins) can be prepared by the same method. Tri-(3-phenylpropyl)borane and tri-(2-methyl-3-phenylpropyl)-borane split off hydrogen and allylbenzene and methallylbenzene, respectively, at temperatures above 200 °C under reduced pressure. *B*-(3′-Phenylpropyl)boratetralin *(37)* and *B*-(2′-methyl-3′-phenylpropyl)-3-methylboratetralin, respectively, are obtained.



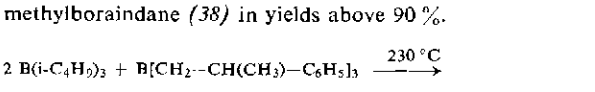
*(37)*



1-Boraindanes or 1-boratetralins are always formed pyrolytically if at least one aralkyl group bound to the boron is suitable for formation of the five- or six-membered ring. The two other ligands on the boron may be different; but one of them should, on account of the reasons mentioned, either be a B–H group or be capable of conversion into a B–H group by dehydroboration. The third valence of the boron compound may be varied as desired. It determines the group attached to boron outside the ring in boron heterocycles.

For this reason, mixed dialkylmonoaralkylboranes, as well as triaralkylboranes may be converted into boraindanes and boratetralins [52]. Instead of the compound with different ligands, mixtures of a trialkylborane and a triaralkylborane may be used (exchange of ligands). In this manner all the aralkyl groups can be utilized for the formation of the boron heterocycles.

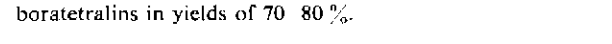
At about 230 °C, 2 moles of tri-isobutylborane and 1 mole of tri-(2-phenylpropyl)borane interact to form 1-isobutyl-3-methylboraindane *(38)* in yields above 90 %.



*(38)*

Since the isobutene which is given off thereby is volatile, the reaction can be carried out at atmospheric pressure.

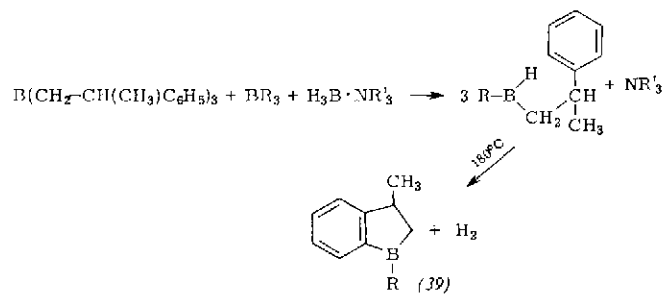
1-Aralkylboraindanes *(35a, b)* and 1-aralkylboratetralins *(37)* are readily converted into any 1-alkyl compound [54]. Tetraalkyldiboranes or a mixture of trialkylamine-borane and trialkylborane react at about 180–190 °C with elimination of hydrogen to give 1-alkylboraindanes *(39)* or 1-alkylboratetralins in yields of 70–80 %.



*(39)*

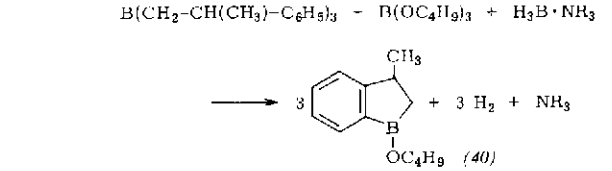
Aralkyldiboranes form 1-boraindanes or 1-boratetralins at about 150 °C with elimination of hydrogen. This method of preparation is, however, not very convenient from a practical point of view, since too many side reactions (*e.g.* formation of polymeric products) take place at high borohydride concentrations. If, however, the borohydrides are stabilized by Lewis bases such as trialkylamines, useful results are obtained. Practically no aminoboranes are formed if the mixtures (*e.g.* triaralkylborane + triethylamine-borane) are not exposed to high temperatures for excessively long periods.

As a result of exchange of the substituents on the boron, a mixture of equimolar amounts of triaralkylborane, trialkylborane, and triethylamine-borane reacts like a monoaralkyl-monoalkylborane to give 1-alkyl-1-boraindanes *(39)* or 1-alkyl-1-boratetralins [52].



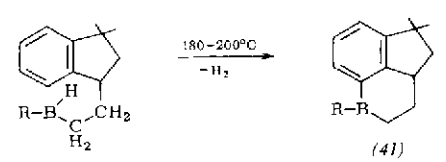
*(39)*

When the trialkylboranes are replaced by trialkoxyboranes, 1-alkoxy-1-boraindanes are formed directly. At 190 °C, for instance, one obtains 1-n-butoxy-3-methyl-1-boraindane *(40)* in approximately 85 % yield [55].



*(40)*

The ring-closure method is of a very general application. Thus, in the presence of tri-isobutylborane, a mixture of tri-[2-(3′,3′-dimethylindanyl)ethyl]borane and triethylamine-borane forms a tricyclic compound *(41)* [55].



*(41)*

e) *Pyrolysis of Arylboranes (9-Borafluorenes)*

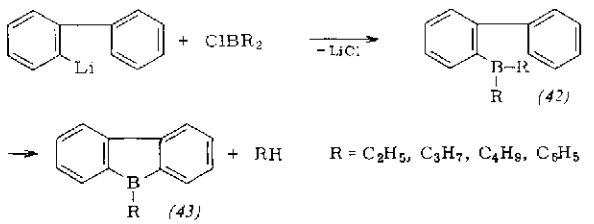
On heating 2-biphenylyldialkylboranes *(42)* or 2-biphenylyldiphenylborane, 9-borafluorenes *(43)* [56] are formed with elimination of alkane or benzene.

[54] *R. Köster*, unpublished work.

[55] *R. Köster* and *K. Reinert*, unpublished work.

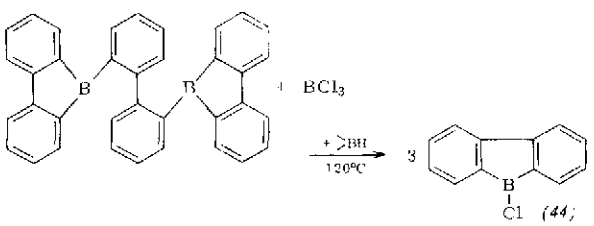
[56] *R. Köster* and *G. Benedikt*, Angew. Chem. *75*, 419 (1963); Angew. Chem. internat. Edit. *2*, 323 (1963).

On heating 2-biphenyldiethylborane, which is readily prepared from 2-biphenylyl-lithium and diethylchloroborane, at about 180 °C, 9-ethylborafluorene is obtained in the form of an intensely yellow crystalline compound in approx. 65 % yield [56].

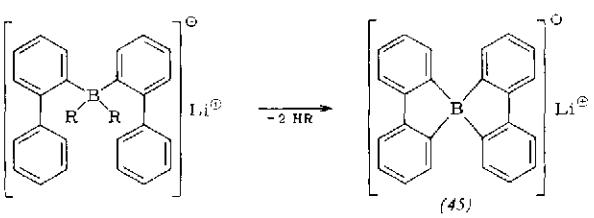


As a result of pyrolytic dehydroboration, compounds containing higher alkyl radicals (*e.g.* propyl or isobutyl) also yield alkenes and B–H compounds which are then converted into 9-alkylborafluorenes with elimination of hydrogen. The $B-C_{aryl}$ bond is thereby partly hydrogenated with elimination of biphenyl (yields: 42 % 9-propylborafluorene, 40 % 9-isobutylborafluorene). 9-Alkylborafluorenes are also formed from biphenylyl-monoalkylboranes even at 120 °C, only hydrogen being evolved [56a].

2-Biphenylyldiphenylborane (m.p. 31 °C; prepared from 2-biphenylyl-lithium and diphenylchloroborane) gives off benzene only at 280–300 °C, yielding yellow 9-phenylborafluorene in approx. 55 % yield. The orange-yellow products obtained as residue in the pyrolysis yielded yellow 9-chloroborafluorene *(44)* when trichloroborane was passed in at about 120 °C in the presence of B–H compounds [14].



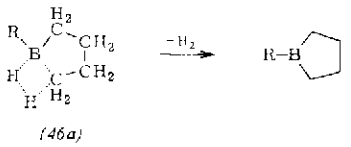
When 2-biphenylyl-lithium and dialkyl- or diarylchloroborane are heated in a molar ratio of 2:1 [56], the lithium salt of the known bis-(2,2'-biphenylidene)boranate *(45)* [57] is obtained, in which the boron atom is bound as in a spirane.



## III. Mechanism of Pyrolytic Ring Formation

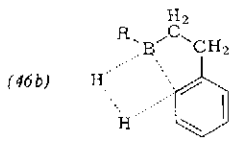
A radical mechanism of the type initially discussed [48] does not appear to be likely for the pyrolysis. Pyrolysis of some trialkylboranes (such as tri-1-butylborane and tri-1-nonylborane) may proceed extremely smoothly in one direction. A reaction involving a radical mechanism should, however, yield a large number of decomposition products. Thus, it would be anticipated, for instance, that not only certain definite C–H bonds and C–C bonds would undergo splitting. The relatively low pyrolysis temperature of about 200 °C also forms evidence against the likelihood of a radical mechanism.

Elimination of hydrogen from dialkylboranes evidently proceeds via a concerted mechanism, *e.g.* a four-center transition state *(46a)*.



*(46a)*

The formation of boron heterocycles containing $B-C_{aryl}$ bonds (pp. 182–184) which takes place with elimination of hydrogen or hydrocarbons (alkane, benzene) is also likely to be based on a concerted mechanism involving an intramolecular four-center transition state *(46b)*.



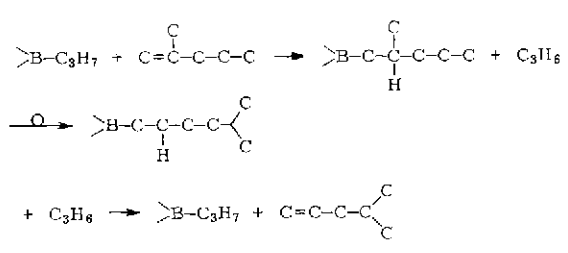
*(46b)*

The fact that intramolecular ring closure with formation of boraindanes, boratetralins, borafluorene, *etc.* takes place particularly readily becomes more understandable if it is assumed that the conformation required is particularly easily attained by interaction of the π-electrons of an aromatic ring with the unoccupied orbital of the $sp^3$-hybridized boron.

Intermolecular reactions between aromatic hydrocarbons and borohydrides do take place but of course at a much slower rate than the cyclizations dealt with here [58, 59].

## Outlook

At the beginning it was pointed out that the migration of boron along alkyl chains that is brought about via dehydroboration-hydroboration equilibria can be used for isomerizing alkenes or for preparing certain functional derivatives of hydrocarbons (*e.g.* alcohols) from alkenes via alkylboranes. The method can, however, be applied only in those cases where the equilibria of the alkylboranes formed are accurately known. The following reaction sequence can then often be employed in accordance with Scheme 4: alkyl-olefin exchange → isomerization → alkyl-olefin exchange (displacement):



Schema 4. Sequence of olefin-exchange and isomerization reactions of alkylboranes.

[56a] *R. Köster* and *G. Benedikt*, unpublished work.

[57] *G. Wittig* and *W. Herwig*, Chem. Ber. *88*, 962 (1955).

[58] *D. T. Hurd*, J. Amer. chem. Soc. *70*, 2053 (1948).

[59] *R. Köster*, *K. Reinert*, and *K. H. Müller*, Angew. Chem. *72* 78 (1960).

In addition to thermal isomerization, pyrolytic reactions also make it possible to convert alkenes into compounds (*e.g.* diols and triols) in which the functional groups are bound to certain carbon atoms depending on the boron heterocycles formed as intermediates.

The pyrolytic transformations of organoboranes are not limited to compounds containing B–C and B–H bonds. Well-defined B–N heterocycles can also be prepared from organic compounds containing boron-nitrogen bonds [60]. In the case of compounds containing oxygen in addition to boron, the possibilities of preparing the corresponding B–O heterocycles appear to be slight. In this case, boroxines are mostly formed instead of heterocycles containing boron and oxygen as well as carbon.

Received, September 25th and October 4th, 1963 [A 338/137 IE]
German version: Angew. Chem. 75, 1079 (1963)

[60] *R. Köster* and *K. Iwasaki:* New Compounds Containing Boron-Nitrogen Bonds. International Symposium on Boron-Nitrogen Chemistry, Durham, N.C. (U.S.A.), April 1963. Preprints of Papers. p. 123.

# Coordination Chemistry and Catalysis

## Investigations on the Synthesis of Cyclooctatetraene by the Method of W. Reppe

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*The relationship between the structure and the catalytic activity of nickel(II) complexes in the synthesis of cyclooctatetraene by the method of W. Reppe is discussed. The cyclotetramerization of acetylene takes place within labile Ni(II)-acetylene π-complexes. Inhibition tests have made it probable that four molecules of acetylene are grouped around the nickel ion in the transition state, in a configuration which favors the formation of the eight-membered ring.*

### Introduction

The synthesis of cyclooctatetraene discovered in 1940 by *Reppe* [1] belongs to the most fascinating reactions of modern chemistry. The simple starting material acetylene is converted by means of certain nickel(II) complexes into cyclooctatetraene, the unsaturated hydrocarbon which *Willstätter* [2] managed to prepare only in small quantities from pseudo-pelletierine at the beginning of the century by an extremely tedious and laborious sequence of reactions. *Reppe*'s synthesis permits production of this compound on a technical scale. Since benzene is the main product of uncatalysed thermal polymerization of acetylene, it is particularly surprising that largely selective cyclotetramerization takes place under substantially milder conditions in the presence of nickel(II) complexes. *Reppe* [1] suggested that the formation of the eight-membered ring occurs within labile nickel-acetylene complexes. More detailed investigations on the mechanism of this reaction were not reported until very recently. The attempts made by various authors to explain the reaction remained necessarily speculative, since decisive new knowledge of the complex chemistry of nickel was only obtained in recent years. The observation [3,4] that cyclooctatetraene was also formed in the presence of certain Ni(0) complexes, *e.g.* bis(acrylonitrile)Ni(0), was the starting point of our own investigations, first reports on which appeared in 1961 and 1962 [5,6]. Meanwhile, further data have been obtained, so that the present comprehensive report contains hitherto unpublished material.

[1] *W. Reppe, O. Schlichting, K. Klager,* and *T. Toepel,* Liebigs Ann. Chem. *560,* 1 (1948).

[2] *R. Willstätter* et al., Ber. dtsch. chem. Ges. *44,* 3428 (1911), and subsequent papers.

[3] *G. N. Schrauzer,* J. Amer. chem. Soc. *81,* 5310 (1959).

[4] *G. N. Schrauzer,* Chem. Ber. *94,* 1403 (1961).

### I. Conditions and Scope of Reaction

The formation of cyclooctatetraene occurs between 80 and 120 °C (optimum at 85–95 °C) at an acetylene pressure of 15–25 atm. The Ni(II) complexes most commonly used as catalysts are the acetylacetonate, cyanide, salicylaldehydate and the enolates of acetoacetic esters [1,7]. Cyclooctatetraene is obtained in 70 % yield (calculated on the quantity of acetylene used) together with varying amounts of benzene (up to 15 %), a resinous polymer, and a dark brown, insoluble, cuprene-like mass ("niprene") [1]. Small quantities of styrene, 1-phenyl-1,3-butadiene, vinylcyclooctatetraene [1,8,9], and traces of azulene are also formed.

[5] *G. N. Schrauzer,* Angew. Chem. *73,* 546 (1961).

[6] *G. N. Schrauzer* and *S. Eichler,* Chem. Ber. *95,* 550 (1962).

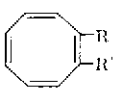
[7] *N. Hagihara,* J. chem. Soc. Japan, pure Chem. Sect. *73,* 323 (1952); Chem. Abstr. *47,* 10490i (1953).

[8] *L. E. Craig* and *C. Larrabee,* J. Amer. chem. Soc. *73,* 1191 (1951).

[9] *A. C. Cope* and *S. W. Fenton,* J. Amer. chem. Soc. *73,* 1195 (1951).

The reaction has no induction period and the catalysts need not be subjected to any contact development. All the catalysts known up to the present are relatively short-lived. Of the side-reactions which deactivate the catalysts, that leading to the formation of niprene is particularly noteworthy.

The reaction is essentially confined to unsubstituted acetylene. Under the same conditions, substituted acetylenes always yield linear polymers or derivatives of benzene. However, a few mono- and disubstituted cyclooctatetraene derivatives have been produced catalytically by mixed cyclooligomerization of acetylene with monosubstituted and disubstituted alkynes. Up to now, only one substituted alkyne could be incorporated into the eight-membered ring at a time [10, 11], to give the compounds *(1a)* to *(1e)*.

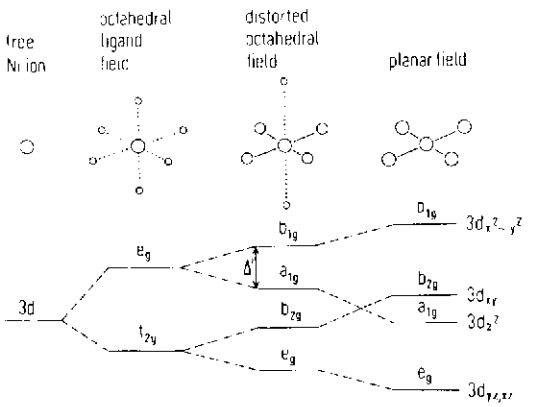


| | R | R' |
|---|---|---|
| *(1)*: | H | H |
| *(1a)*: | n-$C_4H_9$ | H |
| *(1b)*: | $C_6H_5$ | H |
| *(1c)*: | $CH_3$ | H |
| *(1d)*: | $(CH_2)_3OH$ | H |
| *(1e)*: | $CH(OH)CH_3$ | H |
| *(1f)*: | $CH_3$ | $CH_3$ |
| *(1g)*: | $C_6H_5$ | $C_6H_5$ |

## II. Properties of the Catalysts

All hitherto known catalytically active Ni(II) complexes have octahedral or planar structures. In octahedral complexes, the 3d level is split to give one triply degenerate ($t_{2g}$) and one doubly degenerate ($e_g$) term. Since there are eight 3d electrons available in the Ni(II) ion, the $e_g$ level contains only two electrons and the complexes are therefore paramagnetic. The degeneracy of the levels is destroyed by any distortion of the octahedral symmetry, or by unequal changes in the ligand strength [12]. Particular importance is attached to the cases where the coordination octahedron is distorted axially or the ligand strength is increased tetragonally on the octahedral base. In the extreme case, in which the axial ligands are completely removed, or where the tetragonal ligand strength is greatly increased, the splitting of the levels becomes that of a diamagnetic planar complex (Scheme 1).

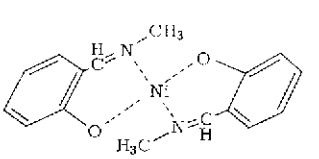
Examples of these two extreme types of complexes are the paramagnetic bis(acetylacetonato)Ni(II) with its octahedral configuration in the solid state, and planar, diamagnetic bis(dimethylglyoximato)Ni(II). When the distortions of the octahedral symmetry are only small, the paramagnetism is maintained; this status prevails until the distance $\Delta'$ becomes so large that thermal promotion to a higher level is no longer possible.



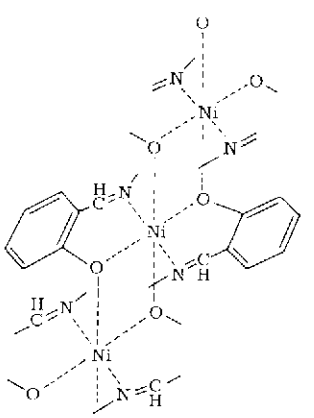

Scheme 1. Tetragonal distortion of octahedral complexes.

A large number of Ni(II) complexes lie in the immediate vicinity of the singlet-triplet transition point; either of the two states may then become the ground state, since the energy difference between them is very small. Complexes of this type exhibit markedly anomalous magnetic behavior. Particular examples of such compounds are the Ni complexes of *N*-alkylsalicylaldimine. Initially, we shall consider only complexes containing straight-chain alkyl groups.

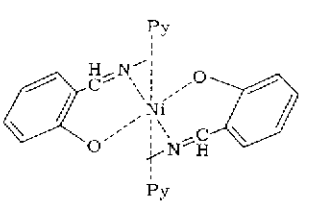
The *N*-methyl derivative *(2)* crystallizes in two diamagnetic low-temperature modifications, and forms a buff colored, insoluble, and paramagnetic high-temperature modification *(3)*, in which the coordination number of the nickel ion is probably 6 [13, 14]. However, in this and in other cases, the transition from the planar diamagnetic form into the paramagnetic modification takes place immediately on dissolution. The paramagnetism of the dissolved complex may be caused either by solvation, association, or a combination of these two ef-



*(2)*



*(3)*



*(4)*

[10] *A. C. Cope* and *H. Campbell*, J. Amer. chem. Soc. *73*, 3536 (1951); 74, 179 (1952).

[11] *A. C. Cope* and *D. S. Smith*, J. Amer. chem. Soc. *74*, 5136 (1952); *A. C. Cope* and *D. F. Rugen*, ibid. *75*, 3215 (1953); *A. C. Cope* and *R. M. Pike*, ibid. *75*, 3220 (1953).

[12] For general information on Ni(II)-complexes, see, for example, the review articles: *C. J. Ballhausen*: Introduction to Ligand Field Theory. McGraw-Hill, New York 1962, pp. 261 et seq.; *J. R. Miller*, *H. J. Emeleus*, and *A. G. Sharpe*: Advances in Inorganic Chemistry and Radiochemistry. Academic press, New York 1962, Vol. 4, pp. 133 et seq.

[13] *C. M. Harris*, *S. E. Livingstone*, and *I. E. Reege*, Austral. J. Chem. *11*, 331 (1958).

[14] *L. Sacconi*, *P. Paoletti*, and *R. Cini*, J. Amer. chem. Soc. *80*, 3583 (1958).

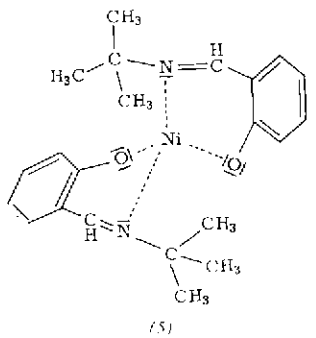
fects. With pyridine, for example, bis(*N*-methylsalicylaldiminato)Ni(II) forms a paramagnetic 1:2-adduct *(4)* [15].

However, the same complex is also paramagnetic in non-coordinating solvents, but the magnetic moment depends on the concentration and the temperature. Molecular-weight determinations indicate the presence of associated species in which the nickel ion achieves the axial perturbation by interaction with the oxygen atoms of adjacent molecules [16]. The anomalous magnetic behavior was traced back to the dependence of the degree of association on temperature, concentration, and solvent [17].

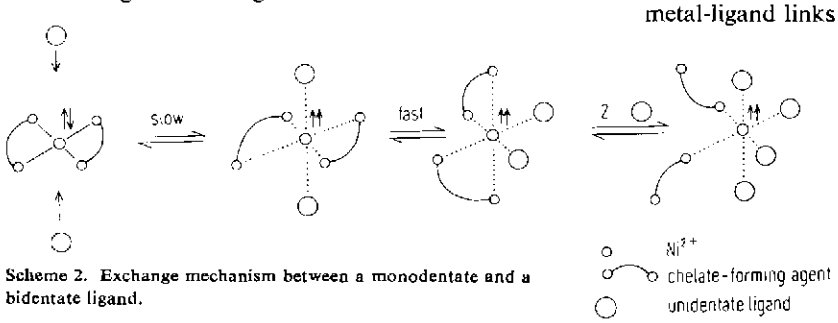
In the synthesis of cyclooctatetraene, the only complexes that are catalytically active are those which are octahedral, or which can easily assume this configuration (Table 1). Complexes with extremely strong tetrahedral coordination are inactive, since in contrast to the octahedral complexes, they are largely inert with respect to ligand-exchange reactions. Ligand-exchange reactions are still possible with planar nickel complexes with moderately strong coordination, since the energy required for their conversion into the octahedral type of complex is only small. The spin decoupling of planar Ni(II) complexes takes place with participation of polar solvents [18] and leads to a weakening of the original nickel-ligand bonds. A somewhat simplified representation of a ligand-exchange is shown in Scheme 2.

Table 1. Classification of cyclooctatetraene catalysts containing divalent nickel [6].

| | Weak ligand field | Intermediate range | Strong ligand field |
|---|---|---|---|
| Configuration | octahedral | octahedral and planar | planar |
| Magnetic behavior | paramagnetic | anomalous | diamagnetic |
| Ligand exchange | rapid | moderately rapid to rapid | very slow |
| Catalytic activity | active | active | inactive |
| Examples | Ni-salicylaldehyde<br>Ni-acetylacetonate | Ni-bis-(*N*-alkylsalicylaldimine)<br>$Ni(CN)_2$ | Ni-phthalocyanine<br>Ni-dimethylglyoxime |



*(5)*




Scheme 2. Exchange mechanism between a monodentate and a bidentate ligand.

Whereas *N*-alkylsalicylaldiminato complexes with straight-chain alkyl groups may occur only in the octahedral and the planar configuration, it has recently been shown [18–20] that the analogous complexes with branched hydrocarbon residues also form tetrahedral structures. Thus, the bis-(*N*-cyclopentyl)-, bis-(*N*-cyclohexyl)-, and bis-(*N*-cyclooctylsalicylaldiminato)Ni(II) complexes are diamagnetic and planar in the solid state, but more or less strongly paramagnetic in solution. In this case, the spin decoupling is caused not only by association, but also by the rearrangement into the tetrahedral configuration. Although the formation of tetrahedral complexes of Ni(II) is not energetically favored, this configuration may still be realized if the ligands carry bulky substituents. Thus, bis-(*N*-t-butylsalicylaldiminato)Ni(II) *(5)*, exists almost completely in the tetrahedral form both in solution and in the solid state [18]. The tetrahedral bis-(*N*-alkylsalicylaldiminato)Ni complexes undergo relatively rapid ligand exchange and are also active catalysts for the formation of cyclooctatetraene, a property which will be described in greater detail.

## III. Transition State and Rate-Determining Step

If the formation of cyclooctatetraene is to occur within a nickel-acetylene complex, the original coordinate nickel-ligand bonds must first be broken and new such bonds must be formed with acetylene molecules. It was therefore assumed [5,6] that the loosening of coordinate metal-ligand links is the rate-determining step for both the ligand-exchange reaction and the cyclooctatetraene synthesis. This appears to be indeed the case and may be illustrated by two examples: The paramagnetic and kinetically labile bis(salicylaldehydato)Ni(II) is a good catalyst for the formation of cyclooctatetraene, whereas the bis(salicylaldiminato)Ni(II) is kinetically inert and virtually ineffective as a catalyst.

[15] *H. C. Clark* and *A. L. Odell*, J. chem. Soc. (London) *1955*, 3431.

[16] *R. H. Holm*, J. Amer. chem. Soc. *83*, 4683 (1961); *J. P. Packler* and *F. A. Cotton*, ibid. *82*, 5005 (1960); *83*, 2818 (1961).

[17] *R. H. Holm* and *T. M. McKinney*, J. Amer. chem. Soc. *82*, 5506 (1960).

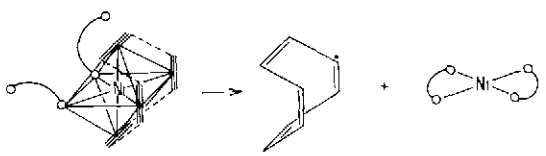
[18] *L. Sacconi*, *P. Paoletti*, and *M. Ciampolini*, J. Amer. chem. Soc. *85*, 411 (1963).

[19] *L. Sacconi*, *P. L. Orioli*, and *M. Ciampolini*, Proc. chem. Soc. (London) *1962*, 255.

[20] *R. H. Holm* and *K. Swaminathan*, Inorg. Chem. *2*, 181 (1963).

As early as 1952, *Hagihara* [21] suspected a connection between the magnetic properties and the catalytic activity of Ni(II) complexes in the synthesis of cyclooctatetraene, but an interpretation of his results has only recently become possible.

Since the polar solvent participates in the ligand exchange reactions of Ni(II) chelates (the reactions proceed more rapidly in tetrahydrofuran, for example, than in benzene), the formation of cyclooctatetraene also depends on the polarity of the medium [5,6]. The yields are generally larger in dioxan than in tetrahydrofuran, and are least in benzene. More strongly solvating solvents than dioxan or tetrahydrofuran are unsuitable, since the acetylene may no longer displace the solvent molecules that are clustered around the Ni(II) ion; thus, no cyclooctatetraene is formed in solvents such as pyridine, benzonitrile, or water. Four coordination sites can be made available in the nickel complexes by cleavage of the coordinate linkages, and these can be occupied by acetylene molecules. In the resultant, approximately octahedral complex, these molecules can assume a steric configuration which favors the formation of cyclooctatetraene (Scheme 3).




Scheme 3. Assumed transition state in the formation of cyclooctatetraene on Ni(II) complexes.

The basic strengths of the lower straight-chain alkylamines alternate. *Sacconi* et al. [22] were able to show that the magnetic moments of the bis-(*N*-alkylsalicylaldiminato)Ni(II) chelates alternate in parallel with the basic strengths of the alkylamines. The yield of cyclooctatetraene from acetylene with these chelates as catalysts also varies with the effective ligand field strengths. The N-methyl compound is the most strongly paramagnetic chelate of this series and gave the highest yields [5,6]. This result shows that the same rate determining step is involved in the formation of cyclooctatetraene and in the apparently entirely unrelated ligand exchange reaction. This step is most probably the reaction of the catalyst with the first acetylene molecule, during which the coordination number of the Ni(II) ion may vary from four to six, with the simultaneous conversion into the paramagnetic form. This view is supported by the results of recent measurements of the kinetics of the reaction between bis-(*N*-alkylsalicylaldiminato)Ni(II) and dimethylglyoxime. The reaction, in which bis(dimethylglyoximato)Ni(II) is the product, is of second order. The rate is controlled by the addition of the first molecule of dimethylglyoxime to the original Ni(II) complex, which would also explain why small differences in the effective ligand strengths have such a pronounced effect on the rate [23].

[21] *N. Hagihara*, J. chem. Soc. Japan, pure chem. Sect. *79*, 323 (1952); Chem. Abstr. *47*, 10490i (1953).

[22] *L. Sacconi*, *P. Paoletti*, and *G. Delre*, J. Amer. chem. Soc. *79*, 4062 (1957).

[23] *G. N. Schrauzer* and *P. Glockner*, unpublished work.

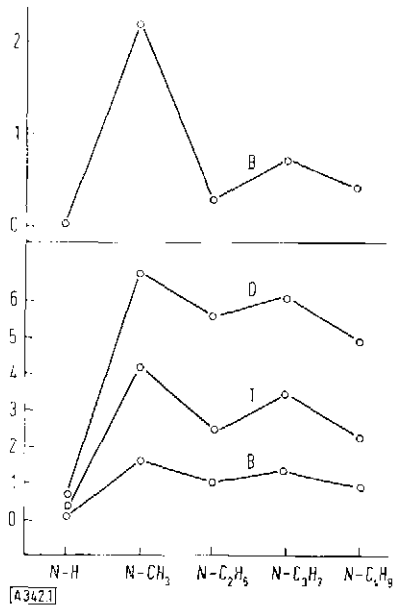



*Fig. 1.* Magnetic moments and catalytic activities of bis-(*N*-alkylsalicylaldiminato)Ni(II) chelates for the synthesis of cyclooctatetraene in various solvents [6], in relation to the size of the alkyl groups. Experimental conditions: Reaction temperature: 95 °C, acetylene pressure: 25 atm; amount of catalyst: 5 mmoles (with benzene as solvent: 10 mmoles); reaction time: 15 hours.

B: in benzene
C: in tetrahydrofuran
D: in dioxan
Upper ordinate: magnetic moment at 20 °C [Bohr magnetons]
Lower ordinate: yield of cyclooctatetraene [g]

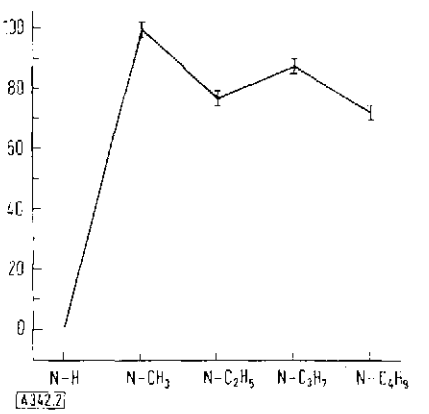
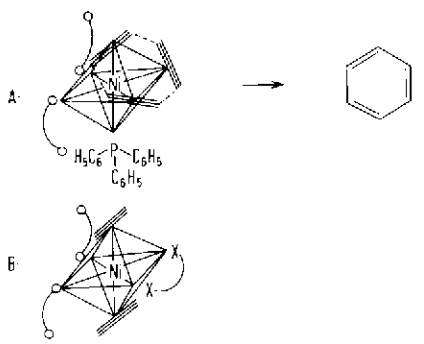



*Fig. 2.* Relative rate of ligand exchange of dimethylglyoxime with bis(*N*-alkylsalicylaldiminato)Ni(II) complexes in tetrahydrofuran [6].
Ordinate: Relative rate of exchange (*N*-methyl compound = 100)

## IV. Synthesis of Benzene by Inhibition of the Formation of Cyclooctatetraene

Since the rate of formation of cyclooctatetraene is controlled by a slow ligand-exchange process, no evidence regarding the structure of the transition state can be gained from kinetic measurements. If the transition state is in fact that represented by Scheme 3, the synthesis of cyclooctatetraene should be effectively inhibited by electron donors. When the reaction is carried out with acetylene and the usual catalyst in the presence of triphenylphosphine (molar ratio 1:1 to the catalyst), no cyclooctatetraene is produced, but instead, benzene is obtained in high yield [5,6]. Benzene formation is not in-

hibited by the addition of even large amounts of triphenylphosphine. Triphenylphosphine is evidently capable of blocking a coordination site in the complex in the manner represented by Scheme 4A. The interaction of triphenylphosphine with the catalysts was also directly demonstrated by preparative methods [23]. The reaction of triphenylphosphine with $Ni(CN)_2$ in alcohol yields a pale yellow, diamagnetic bis(triphenylphosphine)nickel cyanide. The triphenylphosphine is only loosely bonded in this compound, and is re-eliminated in refluxing benzene. It is a powerful catalyst for the polymerization of acetylene, but produces only benzene. The analogous complex of the more strongly basic diphenylethylphosphine is more stable and a much less effective trimerization catalyst [23].



Scheme 4. Inhibition of the formation of cyclooctatetraene (A) by the association of competing electron donors with the Ni(II) ion (cf. Scheme 3). With bifunctional electron donors, even benzene is no longer formed (B).

Inhibitors which block not only one, but two *cis*-positions in the active complex, *e.g.* $\alpha,\alpha'$-bipyridyl, 1,10-phenanthroline, or 1,2-bis(diphenylphosphino)ethane $[(C_6H_5)_2P-C_2H_4-P(C_6H_5)_2]$, completely poison all catalysts. Even benzene is no longer formed, and no acetylene is consumed. The effect of basic additives increases in the order:

(Dioxan) < trimethylamine < pyridine < triphenylphosphine < diphenylethylphosphine < tributylphosphine.

The order of this series permits certain conclusions to be drawn regarding the bonding of the acetylene in the active complex. Relatively weak $\sigma$-bonds with only small $\pi$-bond contributions are formed between the acetylene and the Ni(II) ion, since the formation of cyclooctatetraene is inhibited even by trimethylamine or pyridine, both of which are $\sigma$-donors but at most only weakly $\pi$-bonding ligands. *Yamazaki* and *Hagihara* [24] recently established a similar series: dimethylaniline < pyridine < $Bi(C_6H_5)$ < $Sb(C_6H_5)_3$ < $As(C_6H_5)_3$ < $P(C_6H_5)_3$. Under the conditions of the cyclooctatetraene synthesis, the acetylene behaves towards the Ni(II) ion as a ligand with a weak field. The Ni(II) ion should therefore remain paramagnetic in the transition state and should exist in an approximately octahedral ligand field.

Water is also an inhibitor, but its effect is much weaker than that of the weakly $\pi$-bonding pyridine. In tetrahydrofuran, with bis(acetylacetonato)Ni(II) as catalyst, about 50 moles of water per mole of catalyst are required to reduce the yield of cyclooctatetraene to one-half, whereas only 2 moles of pyridine are necessary to achieve the same result.

In the synthesis of benzene on triphenylphosphine-poisoned catalysts, the same process is rate-determining as in the absence of the inhibitor. The dependence of the yield of benzene on the magnetic moments of the bis(*N*-alkylsalicylaldiminato)Ni(II) complexes is shown in Figure 3.

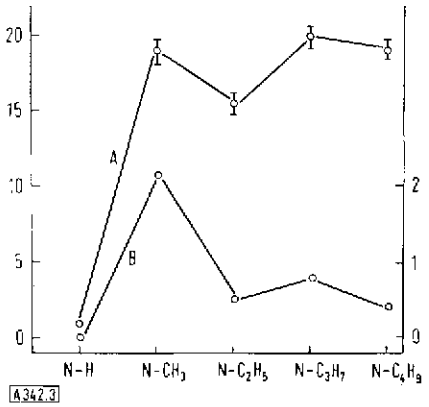
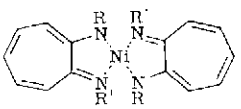


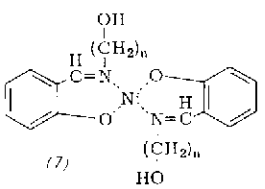

Fig. 3. Dependence of the yield of benzene (in tetrahydrofuran at 95 °C and a $C_2H_2$ pressure of 25 atm) on the magnetic moments of the bis-(*N*-alkylsalicylaldiminato)Ni(II) chelates. Left-hand ordinate (for curve A): yield of benzene [g] per 5 mmoles of catalyst in 15 hours. Right hand ordinate (for curve B): Magnetic moments [Bohr magnetons] of the catalyst complexes in dioxan.

## V. Influence of the Structure of the Catalyst

The *N*-alkylsalicylaldimine-Ni(II) chelates with branched alkyl residues, which exist in equilibrium with tetrahedral structures, are also active catalysts for the formation of cyclooctatetraene. The yields of cyclooctatetraene are again roughly proportional to the rate of ligand exchange with dimethylglyoxime. It is noteworthy that benzene is produced in somewhat larger quantities (up to 30 % relative to the yield of cyclooctatetraene) than with the analogous catalysts containing straight-chain alkyl groups. Evidently the bulkier branched substituents partially inhibit the formation of the transition state required for the cyclotetramerization of acetylene.



*(6a)*: R = R' = $CH_3$
*(6b)*: R = R' = $C_2H_5$



*(7)*

The bis-(*N*,*N'*-dialkylaminotroponiminato)Ni(II) complexes *(6)* recently described contain tetrahedral chelates with stronger ligand fields than those of the *N*-alkylsalicylaldimines. Compound *(6a)* is diamagnetic

[24] *H. Yamazaki* and *N. Hagihara*, J. chem. Soc. Japan, ind. Chem. Sect. *61*, 21 (1958); Chem. Abstr. *53*, 18885e (1959).

and planar; *(6b)* is paramagnetic and, again for steric reasons, tetrahedral [25]. Both complexes undergo ligand exchange only slowly in inert solvents, and react with acetylene to yield only traces of cyclooctatetraene [23]. Thus, the catalytic activity of Ni(II) complexes for the cyclization of acetylene is essentially a function of the effective ligand-field strengths.

Complexes of type *(7)* with n = 2, 3, 5, and 6 are not at all or only slightly active. For n = 4, a relatively large quantity of benzene (about 40 % relative to the yield of cyclooctatetraene) is formed in addition to cyclooctatetraene. Additional chelate rings are presumably formed between the nickel ion and the oxygen atoms of the side-chains; these may be exceptionally stable for n = 4, and thus block one coordination site in the transition state much more frequently (cf. Fig. 4) [23].

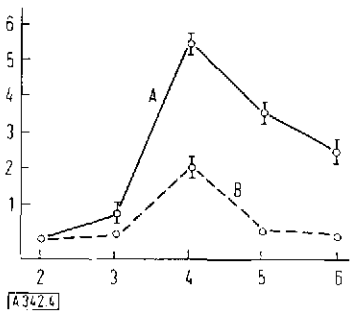
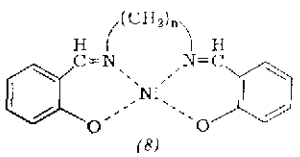



Fig. 4. Yields of cyclooctatetraene (curve A) and benzene (curve B) with catalysts of type *(7)*, in tetrahydrofuran at 95 °C and a $C_2H_2$ pressure of 25 atm.
Ordinate: Yield [g] per 5 mmoles of catalyst in 15 hours.
Abscissa: Chain length [number of carbon atoms].

Complete inactivity results if the mobility of the ligands around the Ni(II) ion is restricted, as with chelates of type *(8)* in which n = 6. At n = 7 and n = 8, the com-

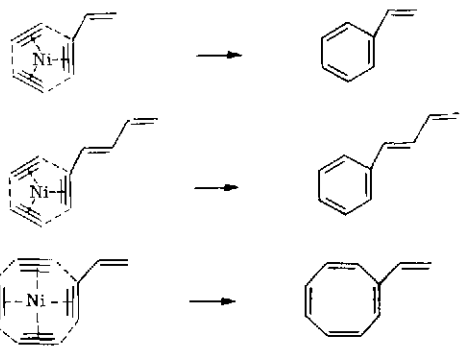



*(8)*

plexes again become slightly active and yield small quantities of cyclooctatetraene [23].

## VI. Formation of By-products

As shown by the inhibition experiments, the cyclooctatetraene synthesis can be easily "switched over" to yield only benzene. It is therefore not surprising that small quantities of benzene are almost always produced as a by-product. The formation of styrene, phenylbutadiene, and vinylcyclooctatetraene can be attributed to mixed cyclooligomerization of acetylene with vinylacetylene and higher linear oligomers of acetylene, which are formed in small quantities under the conditions of the reaction [26] (Scheme 5). The formation of niprene is a metal-catalysed polymerization of acetylene, brought about either by the nickel catalyst itself or by its decomposition products (metallic nickel).




Scheme 5. Formation of the by-products styrene, phenylbutadiene, and vinylcyclooctatetraene.

## VII. Formation of the New Carbon-Carbon Bonds

To explain the above results one has to assume that cyclooctatetraene and benzene are formed within labile acetylene-Ni(II) π-complexes. In the transition state the acetylene molecules appear to be both activated and drawn closely together. Activation of the acetylenic carbon atoms presumably occurs with formation of the π-complex, whereby the sp-hybridized carbon atoms acquire a larger amount of p-character. This would facilitate their rehybridization to $sp^2$, which gives the acetylene molecule the reactivity of a biradical. It is likely that the formation of the products does not involve any further intermediate, even if the new carbon-carbon bonds are not all formed simultaneously.

## VIII. The Cyclobutadiene Hypothesis

Another aim of the present work was to search for some indication of the intermediate formation of cyclobutadiene. No such indication was found; on the contrary, some of the observations were incompatible with this hypothesis. *E. D. Bergmann* [27] was the first to suggest the possibility that cyclooctatetraene is formed from acetylene by dimerization of two molecules of cyclobutadiene. *Kuri* and *Shida* [28] subsequently postulated the formation of cyclobutadiene as an intermediate in the photo-polymerization of acetylene, which yields benzene plus a small quantity of cyclooctatetraene. In their famous paper on the possible existence of π-complexes of cyclobutadiene, *Longuet-Higgins* and *Orgel* [29] also expressed the opinion that cyclooctatetraene is obtained

[25] *D. R. Eaton, W. D. Phillips,* and *D. J. Caldwell,* J. Amer. chem. Soc. *85*, 397 (1963). The author is indebted to Dr. *R. E. Benson,* Wilmington, Del. (U.S.A.), for two samples of these complexes.

[26] *E. C. Herrick* and *J. C. Sauer,* U.S.-Patent 2667520; Chem. Abstr. *48*, 6162f (1954).

[27] *E. D. Bergmann:* The Chemistry of Acetylene and Related Compounds. Interscience, New York 1948, p. 93.

[28] *Z. Kuri* and *S. Shida,* Bull. chem. Soc. Japan *25*, 116 (1952); Chem. Zbl. *127*, 10689 (1956).

[29] *H. C. Longuet-Higgins* and *L. E. Orgel,* J. chem. Soc. (London) *1956*, 1969.

from two molecules of cyclobutadiene that are formed on the nickel catalyst. *Criegee* and *Schroeder* were able to verify this hypothesis by thermolysis of tetramethylcyclobutadiene-$NiCl_2$ [30], but a temperature of 190 °C was required. Although traces of cyclooctatetraene are actually formed in the reaction of "cyclobutadiene-mercury" with bis(acetylacetonato)nickel it is not certain whether these really arise by dimerization of cyclobutadiene [31].

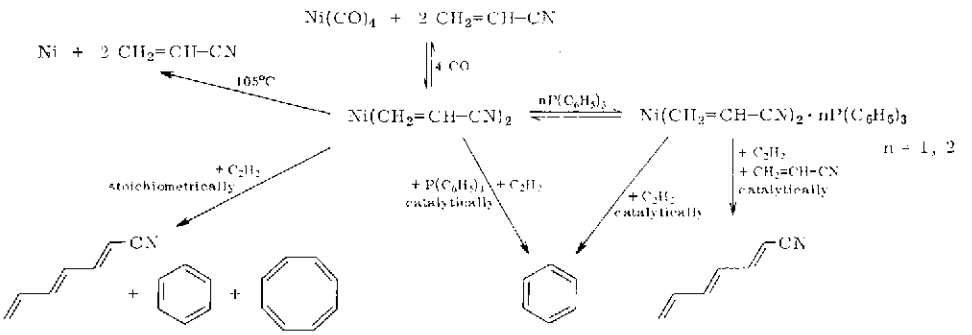
As a consequence of its electronic structure, cyclobutadiene must be considered a strongly π-bonding ligand. Intermediate cyclobutadiene-Ni(II) complexes would therefore be diamagnetic and kinetically more stable than the parent catalyst molecules. The rate of cyclooctatetraene formation would then be controlled by the consecutive reactions of the cyclobutadiene complex, a fact which cannot be reconciled with the experimental evidence.

The results of the inhibition experiments are likewise incompatible with the cyclobutadiene hypothesis. There is no logical explanation for the assumption that the cyclobutadiene formed in catalytic quantities on the nickel catalyst should dimerize selectively to cyclooctatetraene, despite the large excess of acetylene present, yet in the presence of triphenylphosphine should yield almost exclusively benzene. It must be concluded that the formation of cyclooctatetraene in *Reppe*'s synthesis does not involve cyclobutadiene as an intermediate.

## IX. The Formation of Cyclooctatetraene on Ni(0) Complexes

Bis(acrylonitrile)nickel(0) is a coordinately unsaturated π-complex, and reacts with acetylene to form heptatriene nitrile, benzene, and cyclooctatetraene [3,4] (Scheme 6).

However, the yields are only approximately stoichiometric. On reaction with acetylene, the complexes of the 1,1-dicyano- and 1,1,2-tricyanoethylene derivatives – which have meanwhile been isolated – [32] also give small quantities of benzene and cyclooctatetraene. In these complexes, the catalytically active particle is the zerovalent nickel atom, which rapidly loses its activity [4,33] because it is difficultly resolvated by acetylene.




Scheme 6. Reactions of bis(acrylonitrile)nickel(0).

Electron donors such as triphenylphosphine stabilize atomic nickel [4,33] and thereby catalyse the formation of both heptatriene nitrile and benzene [4]. The yield of benzene can be considerably increased in this way, but the formation of cyclooctatetraene is completely suppressed. Trialkylphosphines also inhibit the formation of benzene on Ni(0) catalysts, since with the latter they form more stable complexes [34] than, for example, triphenylphosphine. Ni(0) complexes of the type $Ni(PX_3)_4$ (where X = Cl or F) cyclize acetylenemonocarboxylic esters mainly to benzene derivatives, but small quantities of 1,2,4,6- and 1,3,5,7-tetraalkoxycarbonylcyclooctatetraenes are also formed [35]. The yields of cyclooctatetraene and benzene in the reaction of acetylene with the Ni(0) complexes of unsaturated nitriles, dinitriles, and trinitriles were found to be independent of the polarity of the solvent. They remain practically the same in benzene, tetrahydrofuran, and dioxan [34]. It can therefore be concluded that in these reactions the catalytically active species is the unchanged nickel atom.

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German version: Angew. Chem. 76, 28 (1964)

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[33] *G. Wilke*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

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[35] *J. R. Leto* and *M. F. Leto*, J. Amer. chem. Soc. *83*, 2944 (1961).

# Oxidative Condensation of Quaternary Phenolic Bases [*]

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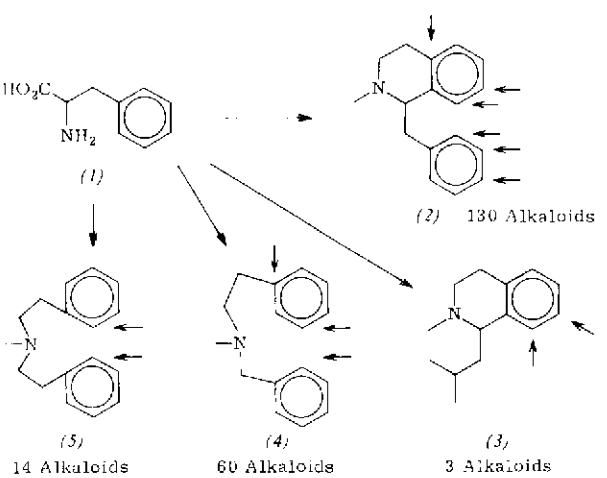
*Dedicated to Prof Dr. H. Brockmann on the occasion of his 60th birthday*

*Provided they contain quaternary nitrogen, simple phenolic bases can undergo oxidative condensation under conditions similar to those of biogenesis to form alkaloids of the isoquinoline series with good yields. By means of such oxidative condensations, more than sixty alkaloids of various structural types have become more easily obtainable. Of the numerous possible condensations of the intermediate mesomeric radicals only those which lead to naturally occurring alkaloids give good yields and few by-products. The results suggest that oxidative condensations of quaternary bases are also involved in the biosynthesis of alkaloids in the plant cell.*

## I. Introduction

The structures of some 1700 naturally occurring alkaloids are known at present. More than 200 of these can be formed in plant cells by oxidative condensation of simple phenolic bases, which are derived from the amino acid phenylalanine [1,2,4–8]. No simple syntheses have yet been devised for these alkaloids, which include morphine and the tube curare poisons [3]. Despite their methodical ingenuity, the multistep syntheses described up to now seem unsatisfactory when compared to the paths used by nature. This problem has intrigued many workers, and numerous attempts have been made to imitate the biosynthesis and to form the alkaloids via oxidative condensation of simple precursors such as tertiary [9–13], secondary [14], or *N*-acylated [15] bases. In all of these attempts, the condensation either failed to give the desired products or the yields were lower than one percent.

In the course of systematic studies of the alkyl- and benzyltetrahydroisoquinoline alkaloid series, we have discovered a method for carrying out these long-sought biogenetic-type alkaloid syntheses, which is of interest both for preparative reasons as well as for an understanding of the fundamental processes involved in alkaloid biosynthesis.




Scheme 1. Alkaloid precursors formed from phenylalanine *(1)* by condensation with an aldehyde. The alkaloids are formed from these by oxidative condensation at the positions shown by arrows.

[*] Based on lectures delivered at the International Symposium on Organic Chemistry held by the Societé Chimique de Belgique in Brussels, June 15th, 1962, the XIXth IUPAC Congress in London, July 11th, 1963, a Gordon Research Conference in New Hampton, August 2nd, 1963, and at several American universities and research institutes.

[**] Address: Institut für Organische Chemie der Universität Kiel (Germany).

[1] *R. Robinson:* The Structural Relations of Natural Products. Clarendon Press, Oxford 1955.

[2] *K. Mothes* and *H. R. Schütte*, Angew. Chem. *75*, 265, 357 (1963); Angew. Chem. internat. Edit. *2*, 341, 441 (1963).

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[4] *D. H. R. Barton* and *T. Cohen* in: Festschrift A. Stoll. Birkhäuser, Basel 1957, p. 122.

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[8] *H. G. Boit:* Ergebnisse der Alkaloid-Chemie bis 1960. Akademie-Verlag, Berlin 1961.

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[12] *D. H. R. Barton* and *G. W. Kirby*, Proc. chem. Soc. (London) *1960*, 392; J. chem. Soc. (London) *1962*, 806; *D. H. R. Barton, G. W. Kirby, W. Steglich*, and *G. M. Thomas*, Proc. chem. Soc. (London) *1963*, 203.

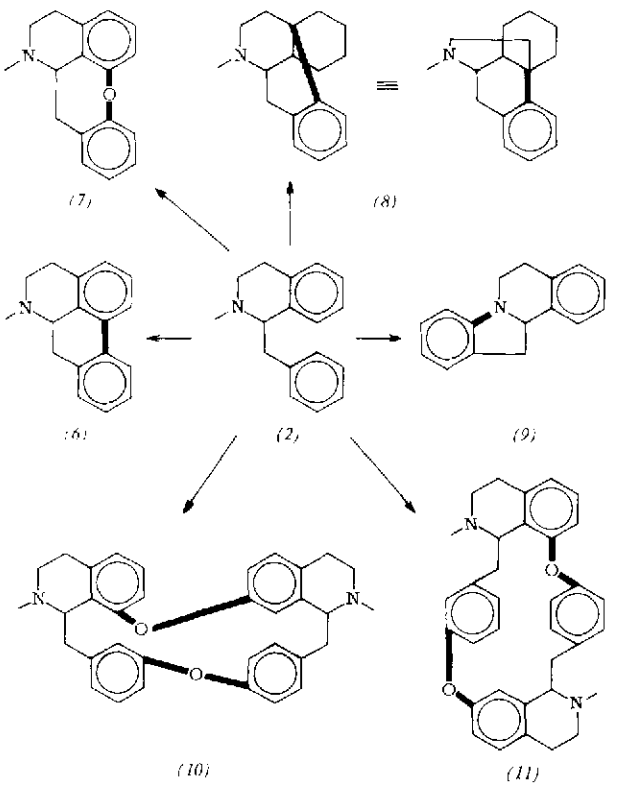
[13] *J. Knabe*, Angew. Chem. *70*, 576 (1958).

[14] *J. Harley-Mason*, J. chem. Soc. (London) *1953*, 1465.

[15] *H. Plieninger*, personal communication; *A. Feinauer*, Ph. D. Thesis, Universität Heidelberg, 1958.

Before describing this work, let us consider in a simplified, schematic way the role of oxidative condensation in the biosynthesis of alkaloids. These biogenetic relationships have been described in greater detail in some excellent reviews [2, 4, 7]. Scheme 1 shows the precursors of the benzyltetrahydroisoquinoline alkaloids *(2)*, the cactus alkaloids of the lophocerine type *(3)*, the *Amaryllidaceae* alkaloids *(4)*, and the *Erythrina* alkaloids *(5)*, all of which can be derived from phenylalanine *(1)* by condensation with an aldehyde. On oxidative condensation at the positions indicated by the arrows, these precursors yield the representatives of these classes of alkaloids so far known (the number of individual compounds of known constitution in each class is shown below the respective formulae).

As can be seen in Scheme 2, the possibilities for oxidative condensations are extremely versatile in the biosynthesis of the benzyltetrahydroisoquinoline alkaloids [1, 4, 6, 7]. These alkaloids are derived from the simple benzyltetrahydroisoquinoline skeleton *(2)* by formation of either additional

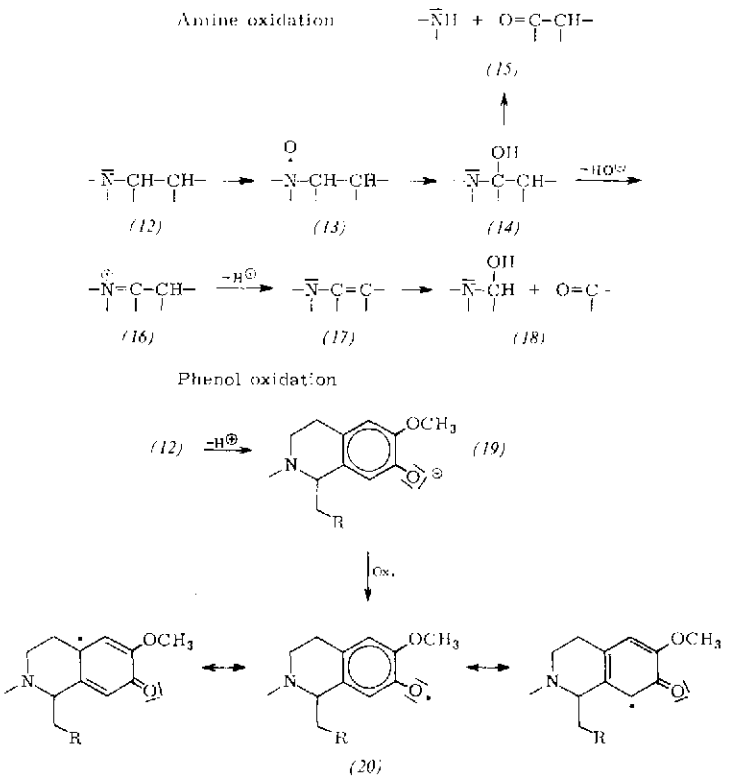


Scheme 2. Oxidative condensations which lead from benzyltetrahydroisoquinoline *(2)* to alkaloids. Bonds formed by oxidative condensations are denoted by heavy lines.

carbon-carbon bonds or new ether bridges as indicated in formulae *(6)* to *(11)* by heavy lines. The 80 monomeric condensation products of this class include alkaloids of the aporphine *(6)*, cularine *(7)*, morphine *(8)*, and cryptaustoline *(9)* types. The dimeric condensation products have more complex structures; more than 60 of these are known. In such structures the two benzyltetrahydroisoquinoline units are linked together by ether bridges either in a parallel [berbamine type *(10)*] or an antiparallel [tubocurarine type *(11)*] arrangement.

## 2. Oxidation Experiments

In the past, oxidative condensations have given unsatisfactory results chiefly because of side reactions at the nitrogen. Oxidizing agents which react with phenolic bases can cause either amine oxidation at the nitrogen



or phenol oxidation at the aromatic nucleus. The oxidation of secondary and tertiary amines *(12)* may lead, possibly via the *N*-oxides *(13)* [16, 17], to the α-hydroxylamines *(14)* [17], which can undergo cleavage to give *(15)* [11, 18], dehydration to form *(16)* or *(17)* [17, 19], or further oxidation with elimination of the C-1 substituents in the form of aldehydes to yield *(18)* [11]. On the other hand, phenols may be transformed via the phenolate anion *(19)* into mesomeric radicals *(20)*, which can condense with other radicals at the phenolic oxygen or at the *o*- or *p*-carbon atoms [4]. Many combinations are possible in the condensation, since each phenolic hydroxyl group may produce as many as four different radical positions in this manner.

Thus, to achieve a biogenetic-type alkaloid synthesis by oxidative condensation, it appeared necessary to suppress the amine oxidation and to promote the phenol oxidation. We attempted to solve this problem by:

1. varying the conditions of oxidation,
2. reducing the oxidizability of the nitrogen,
3. promoting and directing the condensation in the phenolic moiety, by varying the number and position of the free hydroxyl groups.

We investigated the behavior of more than twenty benzyltetrahydroisoquinolines in 25 oxidation systems, whereby the oxidizability of the precursor was varied in a systematic fashion. The best oxidizing agents proved to be manganese dioxide, potassium ferricyanide, and ferric chloride. The reaction mixtures, which were frequently dark and tarry, were

[16] *E. Wenkert*, Experientia (Basel) *10*, 436 (1954).

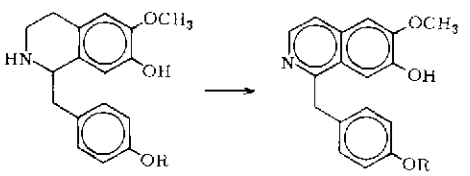
[17] *H. B. Henbest* and *M. J. W. Stratford*, Chem. and Ind. *1961*, 1170.

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[19] *N. J. Leonard* and *W. K. Musker*, J. Amer. chem. Soc. *82*, 5148 (1960).

resolved by means of paper and thin-layer chromatography. The analytical results showed that these oxidations actually proceed much better than had been expected on the basis of first impressions. If the oxidation conditions were chosen sufficiently mild, so that about 20 % of the starting material remained unchanged at the end of the reaction, the product consisted of only a few components, which could almost always be separated by simple means.

Initially we attempted to synthetize dimeric condensation products of the berbamine *(10)* or tubocurarine *(11)* types. Thus, coclaurine *(21)* and similar secondary bases were oxidized, since in these cases intramolecular condensation is unlikely because of the arrangement of the hydroxyl groups. These oxidations proceeded best when a fivefold quantity (by weight) of active manganese dioxide [20] was used in boiling chloroform [21]. Coclaurine *(21)* and 4′-*O*-methylcoclaurine *(22)* yielded compounds with intensely green fluorescence in addition to polymeric, poorly soluble products. They were purified by partition chromatography on cellulose powder impregnated with potassium dihydrogen phosphate using butanol/1 % formic acid as solvent. The compounds proved to be isoquinoline derivatives *(23)* of coclaurine, which had been formed by dehydrogenation.




*(21)*, R = H
*(22)*, R = $CH_3$

*(23)*

This same dehydrogenation also took place in other secondary tetrahydroisoquinolines under extremely mild conditions, even on standing in air. It therefore seemed impossible to avoid amine oxidation in the secondary bases. Tertiary amines [22] and *N*-acylated bases [15, 22] behaved similarly. Further systematic investigations showed, however, that phenolic bases may be condensed in a biogenetic-type alkaloid synthesis, provided the following conditions are observed [23]:

a) To prevent condensations or dehydrogenation at the nitrogen, the latter must be quaternary.

b) The oxidizing agent should be ferric chloride or potassium ferricyanide. The oxidation should be conducted in aqueous solution at 20 °C using at the most one equivalent of oxidizing agent for intermolecular, or two equivalents for intramolecular condensations.

c) The phenyl nuclei undergoing condensation must be derived from pyrocatechol or guaiacol. Monohydroxyphenyl residues do not condense under mild conditions resembling those of biosynthesis.

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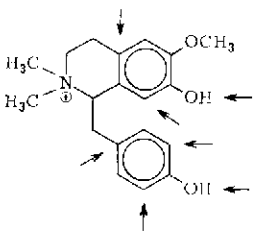
[22] *B. Franck* and *G. Schlingloff*, unpublished work.

[23] *B. Franck*, *G. Blaschke*, and *G. Schlingloff*, German Patent Application F 36207 IVd/12p (March 6th, 1962).

## 3. Dimeric Isoquinoline Ether Alkaloids

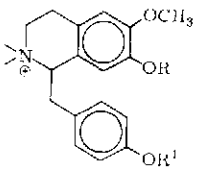
The quaternary coclaurine *(24)*, which occurs in various kinds of magnolia as magnocurarine, is accessible in large quantities by nine conventional synthetic steps, starting from vanillin. Its oxidation with potassium ferricyanide gave a crystalline dehydrogenation product, m.p. 225 °C [24]. We shall now proceed to consider various possibilities for its structure.

With its two free phenolic hydroxyl groups, magnocurarine can have seven potential radicals sites (shown by arrows), by which a total of 28 dimerization products can conceivably be formed. This number may be even higher if more than one new bond is created during the dimerization.




*(24)*

In order to establish how the two magnocurarine monomers are bonded to each other, the two magnocurarine derivatives *(25)* and *(26)*, which differ in the position of the non-methylated hydroxyl group, were oxidized under identical conditions. Only 4′-*O*-methylmagnocurarine *(25)* gave an oxidation product, armepavine




*(25)*, R = H, $R^1 = CH_3$
*(26)*, R = $CH_3$, $R^1$ = H

methiodide *(26)* remained unchanged. Therefore, oxidation occurs exclusively at the free hydroxyl group of the isoquinoline residue. Thus the oxidation products of *(24)* and *(25)* can contain only one bond between the isoquinoline residues and should both yield an identical pentamethyl ether. This was indeed the case.

What remained to be explained was whether the linkage between the two magnocurarine molecules is a carbon-carbon or an ether bond. If the latter were the case, then it would be possible to conceive of condensation products which would contain more than two benzyltetrahydroisoquinoline units per molecule. The well-established method of determining the structure of isoquinoline ether alkaloids by selective aryl ether cleavage of the permethylated alkaloids, using sodium or potassium in liquid ammonia [25–27], is applicable only to tertiary bases. The identification of the quater-

[24] *B. Franck*, *G. Blaschke*, and *G. Schlingloff*, Tetrahedron Letters *162*, 439.

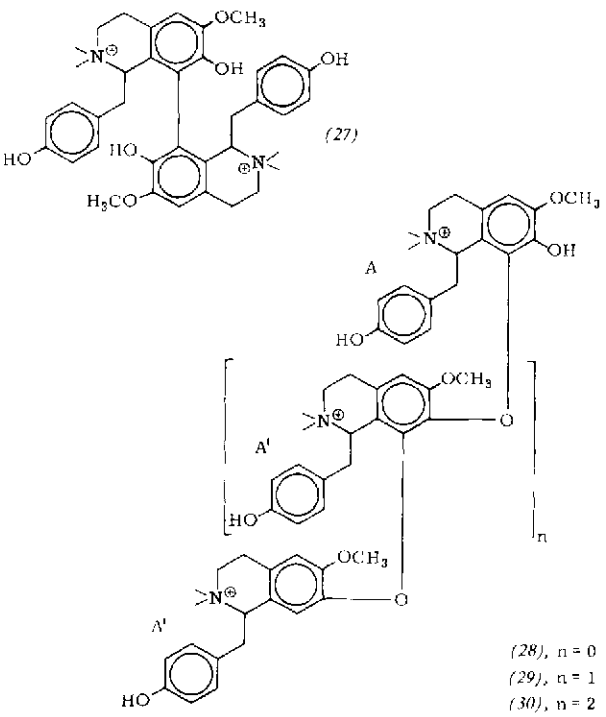
[25] *R. H. F. Manske*, J. Amer. chem. Soc. *72*, 55 (1950).

[26] *M. Tomita*, Progress Chem. org. Natural Products *9*, 175 (1952), particularly p. 184.

[27] *C. Djerassi*, *S. K. Figdor*, *J. M. Bobbitt*, and *F. X. Markley*, J. Amer. chem. Soc. *79*, 2203 (1957).

nary oxidation products described here and in later sections was accomplished more simply and reliably by proton resonance measurement in deutcrated sodium hydroxide solution. This method can be carried out rapidly with small quantities and without the need for model substances. Unlike degradation reactions [28], it permits reliable determination of the number of monomer units contained in an isoquinoline ether alkaloid. The nuclear magnetic resonance data, which by themselves are sufficient for the structural determination, were confirmed by methylation experiments and infrared spectra.

As shown in Table 1, the possible structures *(27)* to *(30)* for our dehydrogenation product can be distinguished by the number and intensity ratios of the $OCH_3$ signals



*(27)*

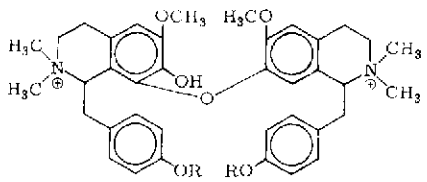
*(28)*, n = 0
*(29)*, n = 1
*(30)*, n = 2

Table 1. Identification of condensed benzyltetrahydroisoquinoline derivatives of the magnocurarine type by $OCH_3$ proton resonance, methylation, and the symmetrical diaryl ether C—O—C stretching frequency.

| Structure | δ-Values (ppm) and number of $OCH_3$ protons | | Methylatable OH groups/ N atoms | $^{\nu}$C—O—C (sym) at 1070 $cm^{-1}$ |
|---|---|---|---|---|
| | 5.52 | 5.66 | | |
| *(27)* | 6 | -- | 4/2 | — |
| *(28)* | 3 | 3 | 3/2 | + |
| *(29)* | 3 | 6 | 4/3 | + |
| *(30)* | 3 | 9 | 6/5 | + |

to be expected in the NMR spectrum, by the number of methylatable hydroxyl groups per nitrogen, and by a symmetrical diaryl ether vibration at 1070 $cm^{-1}$.

In the case of a C-C linkage *(27)*, four methylatable hydroxyl groups and only one signal in the NMR spectrum would be expected, since both $OCH_3$ groups would be in identical surroundings. The two $OCH_3$ groups of the dimeric isoquinoline ether *(28)* are no longer equivalent, and should be identifiable by two NMR signals of equal intensity at 5.52 ppm (at ring A) and 5.66 ppm (at ring A') [29]. In addition to this, only three methylatable hydroxyl groups would be present and the infrared spectrum should contain a C—O—C absorption band. The oxidation product of magnocurarine actually



*(31)*, R = H
*(32)*, R = $CH_3$

exhibits the properties just enumerated. Trimeric *(29)* and tetrameric *(30)* isoquinoline ethers may be excluded from consideration since they would exhibit different intensity ratios of the $OCH_3$ signals as well as a different number of methylatable hydroxyl groups.

Thus, the oxidation product of magnocurarine has structure *(31)*. The dehydrogenation product of 4'-*O*-methylmagnocurarine has the analogous structure *(32)*. In these compounds the two isoquinoline systems are linked by an ether bridge, as they are in berbamine and in seventeen naturally occurring alkaloids similar to berbamine. In addition, most of these alkaloids contain an ether bridge between the benzyl residues.

## 4. Pilocereine and Isopilocereine

The pillar cacti of the Arizona desert grow as tall as a house. Because of their giant size, they are among the natural wonders of the United States. *Djerassi* et al. [30–32] isolated the alkaloid pilocereine from *Lophocereus* species, which belong to the same cactus family, and tentatively ascribed to it the dimeric structure *(36)* [27].

*Djerassi* recently determined the structure of this new type of alkaloid. It has actually the trimeric structure *(38)*, and the dimeric formula *(36)* was then assigned to isopilocereine, a degradation product obtained by treatment of pilocereine with potassium in liquid ammonia. As far as the ether bond between the isoquinoline groups is concerned, pilocereine and isopilocereine correspond to the oxidation product *(31)* of magnocurarine. We therefore attempted to prepare the methiodides *(35)* and *(37)* of isopilocereine and of pilocereine by mild biogenetic-type oxidation of the monomer, quaternary lophocerine *(33)*. Since pilocereine *(38)* was isolated together with lophocereine *(34)* from *Lophocereus schottii*, it is highly probable that its biosynthesis proceeds from a lophocereine-like compound via this oxidation route [32].

When lophocerine *(33)* was oxidized in the form of its methiodide in the same fashion as magnocurarine *(24)*

[28] *C. Djerassi, H. W. Brewer, C. Clarke,* and *L. J. Durham,* J. Amer. chem. Soc. *84*, 3210 (1962).

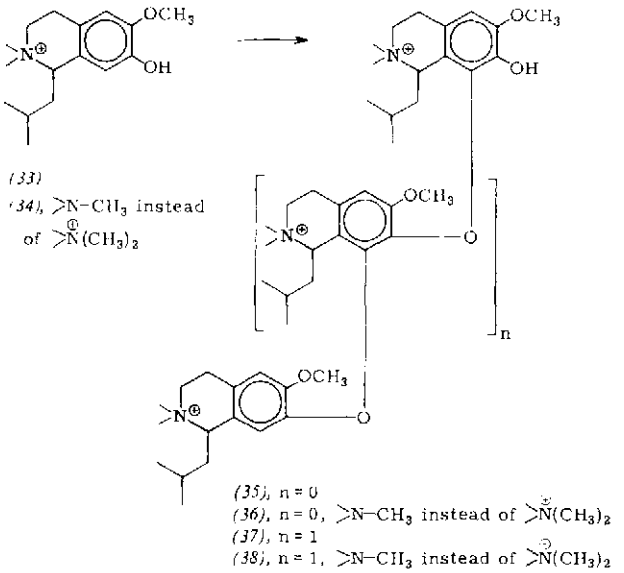
[29] The assignment of the $OCH_3$ signals in the NMR spectrum agrees with the findings of *I. R. C. Bick,* J. *Harley-Mason, N. Sheppard,* and *M. J. Vernengo,* J. chem. Soc. (London) *1961*, 1896.

[30] *C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. K. Figdor,* and *H. Estrada,* J. Amer. chem. Soc. *76*, 3215 (1954).

[31] *C. Djerassi, N. Frick,* and *L. E. Geller,* J. Amer. chem. Soc. *75*, 3632 (1953).

[32] *C. Djerassi, T. Nakano,* and *J. M. Bobbitt,* Tetrahedron *2*, 58 (1958).

with one mole of potassium ferricyanide at 20 °C in dilute sodium carbonate, a 45 % yield of a product was obtained which must have arisen by oxidative dimerization through a carbon-carbon or an ether linkage.



*(33)*
*(34)*, $>N-CH_3$ instead of $>\overset{\oplus}{N}(CH_3)_2$

*(35)*, n = 0
*(36)*, n = 0, $>N-CH_3$ instead of $>\overset{\oplus}{N}(CH_3)_2$
*(37)*, n = 1
*(38)*, n = 1, $>N-CH_3$ instead of $>\overset{\oplus}{N}(CH_3)_2$

In contrast with the starting material, it does not form an azo dye with diazotized sulfanilic acid and hence cannot have a free phenolic hydroxyl group together with unoccupied *o*- or *p*-positions. Just as in the determination of the structure of the magnocurarine dehydrogenation product, the NMR spectrum in deuterated sodium hydroxide was again helpful. This spectrum indicates three isolated aromatic protons and two non-equivalent methoxy groups. This, the results of elemental analysis, and the ultraviolet and infrared spectra show that only the dimeric structure *(35)* is acceptable. The structure of the compound was, therefore, confirmed by comparison with isopilocereine methiodide [33] from naturally occurring pilocereine [34].

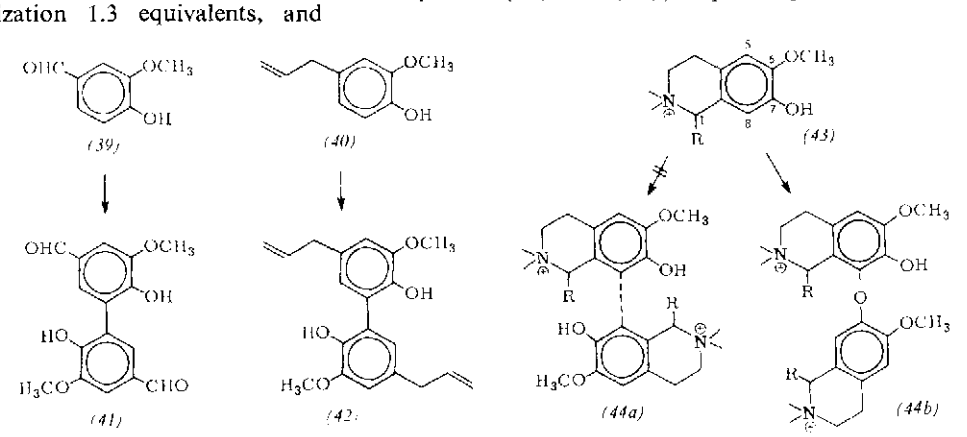
Oxidative dimerization of phenolic compounds requires one equivalent, trimerization 1.3 equivalents, and oxidative polymerization two equivalents of oxidizing agent per molecule of phenol. Hence at least 1.3 moles of potassium ferricyanide must be used in order to trimerize lophocerine methiodide *(33)* to pilocereine methiodide *(37)*. When analysed by thin-layer chromatography, the product obtained on oxidation of lophocerine methiodide with two moles of potassium ferricyanide contained isopilocereine methiodide plus a slower moving fraction in a ratio of 2:3. The latter fraction was in fact identical with pilocereine methiodide *(37)* [33].

These oxidations yielded almost no polymeric products. There are kinetic reasons for this. The dimer *(35)* and the trimer *(37)* cannot generate any condensable carbon radicals on further oxidation and consequently cannot condense with themselves. Thus, they can only condense with any monomer *(33)* that is still available, forming ether bridges. Polymerization could only occur as a series of single steps, and for this reason, as well as on steric grounds, it practically does not take place because the monomers condense much faster with themselves.

These biogenetic-type syntheses of quaternary isopilocereine and pilocereine from lophocerine methiodide [34] show that the actual plant-cell synthesis of these alkaloids could proceed via this route. In an independent study, *Bobbitt* et al. [35] were able to prepare isopilocereine *(36)* and pilocereine *(38)* by oxidation of the tertiary compound lophocerine *(34)*. *Tomita* [36] recently described a multistep synthesis of *O*-methylisopilocereine, which does not resemble that occurring in nature.

## 5. Specificity of the Isoquinoline Ether Formation

In view of current concepts of phenol oxidations [4, 37], it is surprising that the intermolecular condensation of the quaternary coclaurine and lophocerine derivatives *(43)* proceeds exclusively via C–O linkage and thus leads to naturally occurring alkaloids. One would rather expect a C–C condensation to form the biphenyl derivative *(44a)*, just as in the oxidation of other guaiacol derivatives. For example, vanillin *(39)* [38] and eugenol *(40)* [39] are dehydrogenated to give the C–C dimeric compounds *(41)* and *(42)*, respectively. The unusual



*(39)* *(40)* *(43)*
*(41)* *(42)* *(44a)* *(44b)*

[33] We are extremely grateful to Prof. Dr. *C. Djerassi*, Stanford, for the samples of isopilocereine and pilocereine.

[34] *B. Franck* and *G. Blaschke*, Tetrahedron Letters *1963*, 569.

[35] *J. M. Bobbitt*, *R. Ebermann*, and *M. Schubert*, Tetrahedron Letters *1963*, 575.

[36] *M. Tomita*, *T. Kikuchi*, and *K. Bessho*, Tetrahedron Letters *1962*, 127.

[37] *H. Erdtman* and *C. A. Wachtmeister* in: Festschrift A. Stoll. Birkhäuser, Basel 1957, p. 144.

[38] *J. M. Gulland* and *G. U. Hopton*, J. chem. Soc. (London) *1932*, 439.

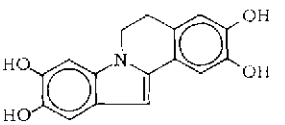
[39] *H. Erdtman*, Biochem. Z. 258, 172 (1933).

formation of diphenyl ethers *(44b)* on dehydrogenation of the quaternary tetrahydroisoquinoline *(43)* has steric causes. The carbon radical at C-8 of the isoquinoline moiety, which is produced in the oxidation, is sterically hindered by substituents at C-1 and C-7. It can apparently condense with a second isoquinoline residue *(44b)* only if the latter is held at a distance by an interposed oxygen atom. It is perhaps for this reason that in all of the 64 bisalkyl- and bisbenzyltetrahydroisoquinoline alkaloids identified so far, the isoquinoline residues are linked via ether bridges.

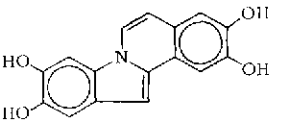
## 6. Synthesis of an Aporphine

In 1932, *Schöpf* and *Thierfelder* [9] and independently, *Robinson* and *Sugasawa* [10] attempted to condense laudanosoline *(45)* oxidatively to form morphine *(46)* and aporphine derivatives *(47)*. However, instead of the desired C–C linkage, they obtained the dibenzotetrahydropyrrocoline derivative *(48)*, formed by nucleophilic addition of the nitrogen onto the *o*-quinone grouping in the benzyl moiety of *(45)*, which occurs as an intermediate stage. Twenty years later, the alkaloid cryptaustoline *(49)*, which also has the structure of *(48)*, was isolated from the Australian *Lauraceae* species *Cryptocarya bowiei* [40], thus proving that the C–N condensation of laudanosoline also plays a role in alkaloid biosynthesis.

On oxidation, the secondary norlaudanosoline [*(45)*, >NH in place of >N–$CH_3$] behaved similarly to laudanosoline, in that it was dehydrogenated to tetrahydroxydibenzodihydropyrrocoline *(50a)*. This was rapidly oxidized further by atmospheric oxygen to form violet dibenzopyrrocoline *(50b)* [41].

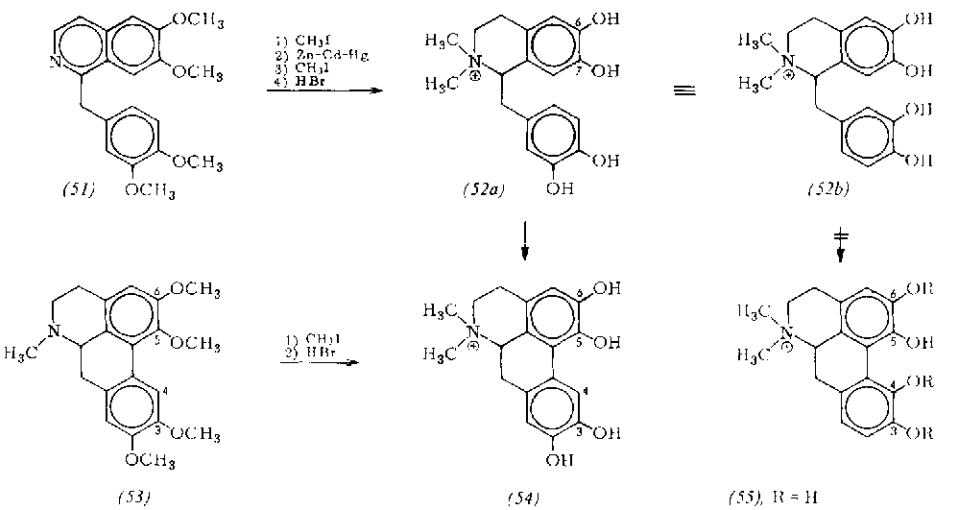


*(50a)*



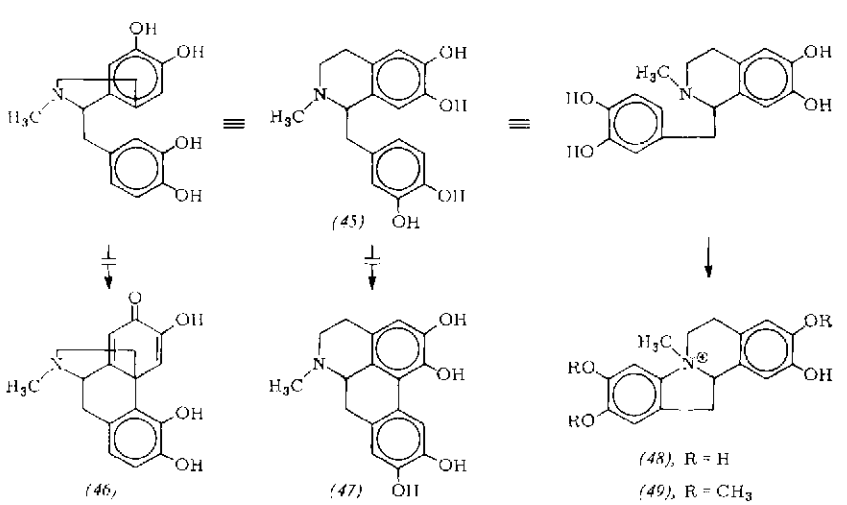
*(50b)*

By using quaternary laudanosoline undesirable C–N condensation should be inhibited. To test this idea, laudanosoline methiodide *(52)* was prepared in four simple steps from papaverine *(51)* and treated in aqueous solution at 20 °C with the calculated amount of ferric chloride in order to remove two electrons. After



*(51)* *(52a)* *(52b)* *(53)* *(54)*

*(55)*, R = H
*(56)*, R = $CH_3$; >N–$CH_3$ instead of $\overset{\oplus}{N}(CH_3)_2$



*(46)* *(47)* *(45)* *(48)*, R = H *(49)*, R = $CH_3$

[40] *J. Ewing, G. K. Hughes, E. Ritchie*, and *W. C. Taylor*, Nature (London) *169*, 618 (1952); Austral. J. Chem. *6*, 78 (1953).

[41] *J. Harley-Mason*, J. chem. Soc. (London) *1953*, 1465.

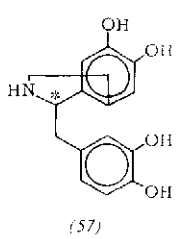
20 hours the solution was evaporated and the dehydrogenated product crystallized out in a yield of 62 %. Judging from the characteristic ultraviolet spectrum of this compound, the long-sought aporphine condensation had occurred [42].

However, the formation of two aporphines, *viz. (54)* and *(55)*, was possible. These differ in the position of the hydroxyl groups on the benzyl moiety and correspond, respectively, to the naturally occurring alkaloids glaucine *(53)* and corydine *(56)*. The two alkaloids are readily distinguishable by their ultraviolet spectra, since the biphenyl system of corydine *(56)* is more strongly twisted by the substituents at the 4- und 5-positions than that of glaucine *(53)*, where C-4 is unsubstituted. The central absorption band of corydine, at 268–270 mμ, is thus some 14 mμ lower than that of glaucine, which lies at 282 mμ [43].

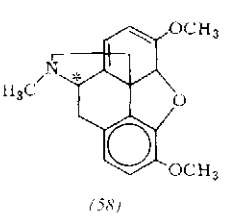
The ultraviolet spectrum and all the other properties of the dehydrogenation product obtained from laudanosoline methiodide were identical with those of the quaternary *O*-demethyl base *(54)* of glaucine *(53)*, which was prepared by a Pschorr phenanthrene synthesis according to the method of *Gadamer* [44] and has therefore the structure *(54)*. Accordingly, the oxidative condensation of quaternized laudanosoline proceeds preferably from the sterically less hindered conformation *(52a)*. In the non-biogenetic type method of glaucine synthesis, the yield of the Pschorr phenanthrene ring closure is much lower, being only 15 %.

## 7. The Oxidative Ring Closure of Morphinane

For methodological and biosynthetic reasons, it would be of great interest to see whether morphine alkaloids could also be prepared by oxidative condensation. In this case, the oxidation of a laudanosoline derivative *(52)* would have to lead to a condensation at the *p*-position of the isoquinoline moiety (relative to the activating hydroxyl group at C-7) rather than at the *o*-position. Such a ring closure appears to be possible in the plant cell, since *Battersby* [7,45] found that [1-$^{14}$C]-norlaudanosoline *(57)* is successively transformed into



*(57)*

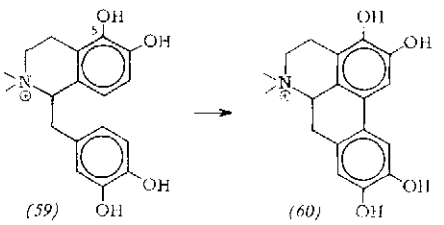


*(58)*

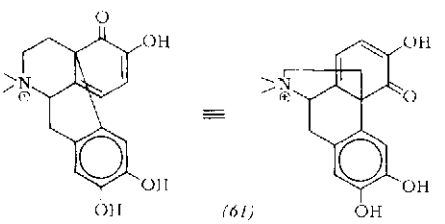
thebaine *(58)*, codeine, and morphine in the poppy (*Papaver somniferum*) and the position of the labelled carbon atom is in agreement with the assumption of an oxidative condensation.

For this reason, we investigated the oxidation of two laudanosoline derivatives, *(59)* and *(62)*, with ferric chloride, in which altered positions of the hydroxy groups would be expected to favor a morphinane ring closure [46]. Both compounds are conceivable biogenetic precursors.

Compound *(59)* has a hydroxyl group at C-5, *i.e.* in *o*-position to the carbon atom at which the morphinane ring closure should occur. Its dehydrogenation could lead either to an aporphine *(60)* or to a morphinane derivative *(61)*. In fact, a crystalline monomeric oxidation product was formed, which proved to be the aporphine *(60)* [47]. Since no further dehydrogenation products were obtained, morphinane ring closure could not have taken place.



*(59)* *(60)*



*(61)*

The second laudanosoline derivative *(62)* has an additional hydroxyl group at C-8. Here, the apparently easy condensation to aporphine should not be possible, so that either a cularine alkaloid *(63)* or a morphinane derivative *(64)* should be formed. Compound *(62)* was prepared for the first time in large quantity from trimethoxybenzaldehyde via mescaline [47]. Its oxidation with ferric chloride again gave a crystalline dehydrogenation product, which was, surprisingly, neither a cularine nor a morphinane derivative. Instead, it was identical with the aporphine alkaloid *(54)* obtained by oxidation of laudanosoline methiodide *(52)* [47]; elimination of the 8-hydroxyl group of *(62)* must therefore have occurred.

It is possible that condensation to give the morphinane derivative *(64)* does in fact occur as a first step in the oxidation of *(62)*. The resulting dienone could then rearrange in the acidic oxidation medium, aromatize, and lose a hydroxyl cation to form the aporphine derivative *(54)*. This is analogous to the morphine/apomorphine rearrangement. Since a hydroxyl cation is finally eliminated, the overall reaction effected by ferric chloride is not an oxidation, but merely a condensation with elimination of water. Those aporphines *(54)* and *(60)* formed from the laudanosoline derivatives *(52)* and *(59)* could also have arisen by rearrangement of an initially produced morphinane derivative, *e.g. (61)*, just as in the oxidation of *(62)*. Further experiments are needed to

[42] *B. Franck* and *G. Schlingloff*, Liebigs Ann. Chem. *659*, 123 (1962).

[43] *M. Shamma*, Experientia (Basel) *16*, 484 (1960).

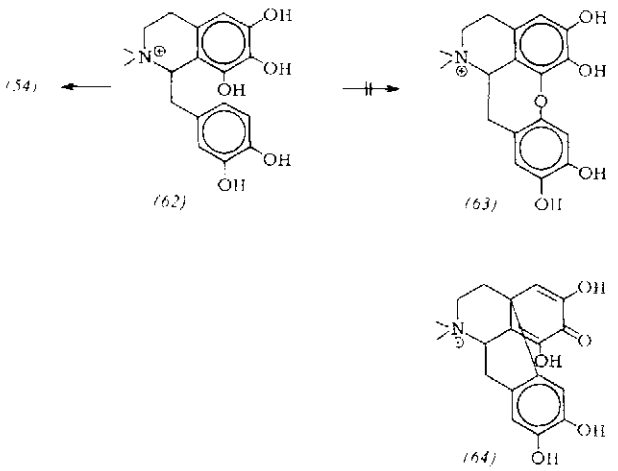
[44] *J. Gadamer*, Arch. Pharmaz. *249*, 680 (1911).

[45] *A. R. Battersby* and *R. Binkes*, Proc. chem. Soc. (London) *1960*, 360.

[46] *B. Franck* and *G. Blaschke*, unpublished work.

[47] *G. Blaschke*, Ph.D. Thesis, Universität Göttingen, to appear in 1964.

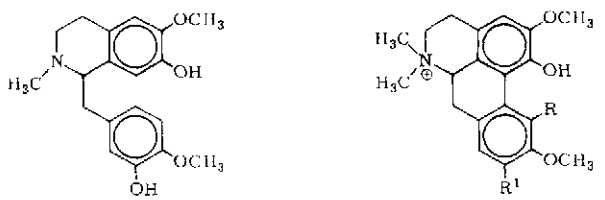
show whether the dienone system of such a morphinane can be obtained by especially careful isolation or stabilization through reduction of its carbonyl group.



(54) (62) (63) (64)

## 8. Biosynthesis of the Aporphine Alkaloids

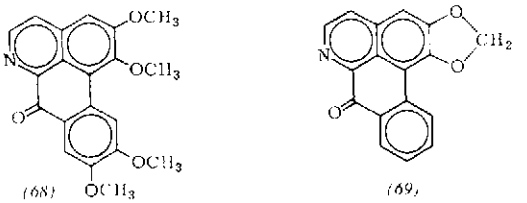
The biogenetic-type aporphine syntheses described here permit the assumption that aporphine alkaloids can arise in the plant cell by oxidative condensation of quaternary benzyltetrahydroisoquinolines. This assumption is impressively confirmed by the occurrence in nature of definite classes of alkaloids:



(65) (66), R = H, $R^1$ = OH
(67), R = OH, $R^1$ = H

1. The alkaloids coclanoline *(65)* [48], laurifoline *(66)* [49], and magnoflorine *(67)* [50] have been isolated from *Cocculus laurifolius*. Of these, the aporphines *(66)* and *(67)* are quaternary, conforming to the requirements for their formation by oxidative condensation. Furthermore, their structures correspond exactly to the two possible modes of condensation of coclanoline. Holewort (*Corydalis cava*) also contains both of these condensation species in the form of glaucine *(53)* and corydine *(56)*.

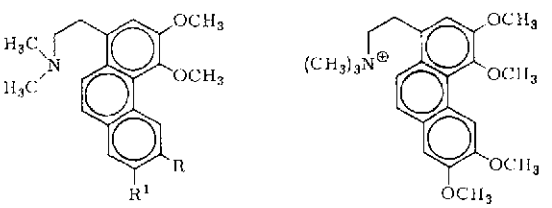
2. If aporphines do arise by oxidative condensation, products of further oxidation should also occasionally occur in plants. This is the case in the magnolia tree (*Liriodendron tulipifera* L.) which occurs abundantly in the Eastern USA. The decorative yellow color of its wood is caused by two colored alkaloids *(68)* and *(69)*, whose structure has recently been elucidated by *Taylor*



(68) (69)

[51]. These alkaloids are oxidized aporphine derivatives *(68)* one of which could be formed from the major alkaloid glaucine *(53)* which is also present in the magnolia tree. If the nitrogen atom of the aporphine derivative that is initially formed in *L. tulipifera* were quaternary, this oxidation would not occur, as the experiments described above showed. Thus, the wood would be colorless.

3. Quaternary aporphines readily undergo Hofmann elimination, since the double bond formed is fitted into a stable phenanthrene system. Thus, for example, de-*O*-methylglaucine methiodide *(54)* is transformed under mild, weakly alkaline methylation conditions into the phenanthrene derivative *(72)* [42]. If aporphines



(70), R = $R^1$ = H
(71), R, $R^1$ = –O–$CH_2$–O–
(72)

arise in quaternary form during biosynthesis, the occurrence of such Hofmann elimination products in plants should be expected. Such alkaloids, *e.g. (71)*, have indeed been found in *Thalictrum thunbergii* [52] together with quaternary aporphines, *e.g. (67)* [53], and benzyltetrahydriosoquinolines [54]. They were also found in *Cryptocarya angulata (70)* [55].

## 9. Conclusion

The studies described here show that simple tetrahydroisoquinoline precursors need only be quaternized for the long-sought biogenetic-type oxidative condensations to alkaloids to be carried out. Up to now, this surprisingly smooth condensation has made it possible to execute simple syntheses of six skeletal types in the isoquinoline alkaloid family, thus making more than sixty alkaloids more readily accessible. Sir *Robert Robinson*, to whom the modern chemistry of natural products is indebted for many stimulating predictions, indicated this possibility thirty years ago [10]. If the phenolic hydroxyl

[48] *F. Kusuda*, Pharm. Bull. (Japan) *1*, 189 (1953); Chem. Abstr. *1955*, 4683.

[49] *M. Tomita* and *F. Kusuda*, Pharm. Bull. (Japan) *1*, 1 (1953); Chem. Abstr. *1954*, 12131.

[50] *T. Nakano* and *M. Uchiyama*, Pharm. Bull. (Japan) *4*, 407 (1956); Chem. Abstr. *1957*, 10004.

[51] *W. I. Taylor*, Tetrahedron *14*, 42 (1961).

[52] *E. Fujita* and *T. Tomimatsu*, J. pharm. Soc. Japan *79*, 1252 (1959); Chem. Abstr. *1960*, 4643.

[53] *E. Fujita* and *T. Tomimatsu*, Pharm. Bull. (Japan) *4*, 489 (1956); *6*, 107 (1958); Chem. Abstr. *1957*, 13886; *1959*, 5588.

[54] *E. Fujita* and *T. Tomimatsu*, J. pharm. Soc. Japan *79*, 1082 (1959); Chem. Abstr. *1960*, 4643.

[55] *R. G. Cooke* and *H. F. Haynes*, Austral. J. Chem. *7*, 99 (1954); Chem. Abstr. *1955*, 3212.

groups are located at the correct positions and are activated by *o*-hydroxy or *o*-methoxy groups, the desired alkaloids are formed in good yield and with hardly any by-products.

The greater the complexity of the natural products which can be isolated and structurally identified by modern techniques, the more important does it become to learn to synthetize them as simply and as rapidly as in the cell. The photosynthesis experiments of *Calvin* [56] have shown that starting from $CO_2$, algae can perform a total synthesis of complicated natural products within ten seconds. Only by imitating such synthetic methods can the increasing demand for physiologically active biological products be met more efficiently than by the time-consuming extraction from the plant cell.

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German version: Angew. Chem. *75*, 957 (1963)

[56] *M. Calvin*, Angew. Chem. *68*, 253 (1956).

# New Chemical and Biochemical Developments in the Vitamin $B_{12}$ Field

BY PROF. DR. K. BERNHAUER, DR. OTTO MÜLLER, AND DR. FRITZ WAGNER

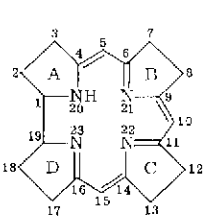
LEHRSTUHL FÜR BIOCHEMIE DER TECHNISCHEN HOCHSCHULE STUTTGART (GERMANY)

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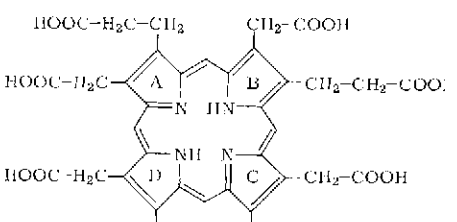
About 8000 publications have appeared in the 15 years following the isolation of crystalline vitamin $B_{12}$ by *Folkers* and coworkers [1] in the USA and by *E. L. Smith* and *Parker* [1a] in England (see reviews [1b–8]). This field has recently received new impetus because of partial chemical syntheses and the discovery and elucidation of the structures of coenzyme forms of the Vitamin $B_{12}$ group.

## A. Nomenclature [9, 10]

Vitamin $B_{12}$ contains a macro-ring with four nitrogen atoms. This macro-ring was named **corrin** *(1)*. Compounds containing this ring system are called **corrinoids**. All the corrinoids found so far in nature contain cobalt as the central atom. They also have acetic and



*(1)*



*(2)*

[1] *E. L. Rickes, N. G. Brink, F. R. Koniuszy, T. R. Wood*, and *K. Folkers*, Science (Washington) *107*, 396 (1948).

[1a] *E. L. Smith* and *L. F. J. Parker*, Biochem. J. *43*, Proc. VIII (1948).

[1b] *H. Knobloch:* Chemie und Technik der Vitamine. 3rd Edit., Enke, Stuttgart 1955, p. 266.

[2] *W. Stepp, J. Kühnau*, and *H. Schroeder:* Die Vitamine und ihre klinische Anwendung. Enke, Stuttgart 1957, Vol. 2, p. 557.

[3] Vitamin $B_{12}$ und Intrinsic Factor, 1. Europ. Symposium, Hamburg 1956. Enke, Stuttgart 1957.

[4] *W. Friedrich* and *K. Bernhauer* in *K. Fr. Bauer:* Medizinische Grundlagenforschung. Thieme, Stuttgart 1959, Vol. 2, p. 662.

[5] *E. L. Smith:* Vitamin $B_{12}$. 2nd Edit., Methuen, London 1963.

[6] Vitamin $B_{12}$ und Intrinsic Factor, 2. Europ. Symposium, Hamburg 1961. Enke, Stuttgart 1962.

[7] *W. Friedrich* in *R. Ammon* u. *W. Dirscherl:* Fermente, Hormone, Vitamine. Thieme, Stuttgart, Vol. 3, in the press.

[7a] Conference on Vitamin-$B_{12}$-Coenzymes, New York, April 1963; Ann. N.Y. Acad. Sci., in the press.

[8] Reviews on Vitamin $B_{12}$ in annual periodicals, *e.g.* Ann. Rev. Biochem., Vitamins and Hormons, Ann. Rev. Microbiol., *etc.*

[9] IUPAC Nomenclature of Biological Chemistry, J. Amer. chem. Soc. *82*, 5582 (1960).

[10] *E. L. Smith* in [6], p. 764.

propionic acid groups in the same positions as type III porphyrins and are especially similar in this respect to uroporphyrin III *(2)*. However, ring C of the corrinoids has a methyl group instead of an acetic acid residue.

Cobyrinic acid *(3)* has six additional methyl groups –which are underlined in formula *(2a)* of the basic skeleton [*] – and six double bonds. All further compounds of this series can be named as derivatives of cobyrinic acid. Trivial names are used for the most important substances [formulae *(3)* to *(10)*]: When all the carboxyl groups except the one at position f in *(2a)* are amidated, the compound is called cobyric acid *(4)* [10] (Factor $V_{1a}$). In cobinic acid *(5)*, the carboxyl group at f is amidated with D$_g$-(–)-1-aminopropan-2-ol, while the other carboxyl groups are free. In cobinamide *(6)*, the f-carboxyl group is amidated with 1-aminopropan-2-ol and all the others are amidated with ammonia. In cobamide *(7)*, the hydroxyl group of cobinamide is esterified with 3'-phospho-D-ribofuranose [R = H in *(7)*]. However, corrinoids containing an *N*-glycosidylimidazole base whose second nitrogen atom is coordinated with the Co atom are also called cobamides; these cobamides may contain a benzimidazole, naphthimidazole, imidazole, or purine base. When the base is 5,6-dimethylbenzimidazole, the compound is called cobalamin *(8)*. Other ligands on the Co may be water or anions: *e.g.* in cyano-5,6-dimethylbenzimidazolylcobamide [cyanocobalamin *(8)*, L = $CN^{\ominus}$], hydroxo(aquo)adenylcobamide *(7)* [L = $HO^{\ominus}$ or $H_2O$, OR = adenine bound to N-7], diaquocobinamide, and monocyanomonoaquocobyric acid [10a].

*(3)*, R = R' = OH
*(4)*, R = $NH_2$, R' = OH
*(5)*, R = OH,

R' = –NH–$CH_2$–C(H)(–OH)–$CH_3$

*(6)*, R = $NH_2$,

R' = –NH–$CH_2$–C(H)(–OH)–$CH_3$

*(9)*, R = $NH_2$,

R' = NH–$CH_2$–C(H)($H_3C$)–O–P(OH)(=O)–OH

*(2a)*

*(7)*

*(8)*

The basis for characterization and classification of corrinoids is the presence (or absence) of a hetero base which is capable of coordination. When such a base is present, the corrinoids are said to be complete, in its absence, they are said to be incomplete [11]. The two groups have significantly different physicochemical properties [11].

The coenzyme forms of the corrinoids do not contain water or anion ligands, but instead have a 5'-deoxyadenosyl residue. Thus, the simplest designation for the vitamin $B_{12}$ coenzyme *(10)* is *Co*-(5'-β-deoxyadenosyl)-cobalamin.

*(10)*

[*] In this article, the designation [Co] will be used henceforth to indicate the ring system *(2a)*. In some cases with substituents, as in *(3)* to *(6)*, the meaning of [Co] is evident from the text.

## B. Natural Corrinoids and Their Biogenetic Relationships [12]

So far, no naturally occurring, cobalt-free corrinoids have been isolated. The corrin ring is apparently biosynthetized in the same manner as the porphyrin ring. Thus, the explanations for the "reverse" order of acetic and propionic acid residues on ring C of the porphyrins [13, 14] should also hold for the corrinoids. The

[10a] Designations such as benzimidazolyl- or adenylcobamide cyanide are considered unconventional, at least in German nomenclature, since the substitution involves an *N*-glycosidic linkage. Furthermore, it is customary to use the prefix (*e.g.* "cyano-" and not "cyanide") in the chemistry of inorganic complex ions functioning as ligands. See *H. Remy*, Angew. Chem. *71*, 515 (1959).


[11] *K. Bernhauer* and *W. Friedrich*, Angew. Chem. *66*, 776 (1954).

[12] *K. Bernhauer*, *O. Müller*, and *F. Wagner* in [6], p. 37.

[13] *K. D. Gibson*, *M. Matthew*, *A. Neuburger*, and *G. T. Tait*, Nature (London) *192*, 204 (1961).

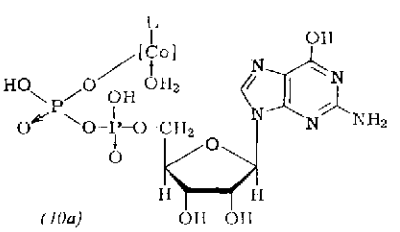
[14] *J. H. Mathewson* and *A. H. Corwin*, J. Amer. chem. Soc. *83*, 135 (1961).

additional methyl groups of the corrinoids are introduced by direct C-methylation. However, it is not yet known at which point of the biosynthesis this happens. It is also unclear when rings A and D are interlinked, when the Co atom is introduced, and when the acetic acid group originally probably present at C-12 is decarboxylated [14a, b]. The first part of the biosynthesis of corrinoids can be considered complete with the formation of cobyrinic acid *(3)*, even though this compound has not yet been found in nature.

The carboxyl groups a to e and g in *(3)* are amidated stepwise, and the f-carboxyl group is connected to D-(−)-1-aminopropan-2-ol, which is produced by decarboxylation of L-threonine. The intermediates produced in these reactions are cobyric acid *(4)*, several partly amidated cobinic acids *(5)*, and incompletely amidated cobyric acids. Experiments *in vivo* and *in vitro* with *P. shermanii* seem to indicate that cobyrinic acid *(3)* and its monoamide are not natural intermediates [14c]. Complete amidation leads to cobinamide *(6)*, which is the most ubiquitous intermediate in the biosynthesis of cobamides.

Occasionally a nucleotide or a part of a nucleotide is connected with a partially amidated cobinic acid, as shown by the appearance of mono-, di-, and tricarboxylic acids of cobalamin in cultures of *Propionibacterium shermanii*. It is probable that the carboxyl group e is the last to be amidated.

Cobinamide *(6)* is not directly combined with nucleotides, *e.g.* with α-ribazole phosphate at the formation of vitamin $B_{12}$. However, α-ribazole [14d] is incorporated directly at its biosynthesis [15] and was also found in cultures of *P. shermanii* [16]. In *Nocardia rugosa*, both cobinamide phosphate *(9)* and cobinamide pyrophosphate-guanosine *(10a)* are used for the biosynthesis of cobamides. It cannot yet be decided whether the pyrophosphate is the immediate precursor of the cobamides. For example, in experiments comparing the effect of acetone powders of *P. shermanii* on *(6)*, *(9)*, or *(10a)*,



*(10a)*

with 5,6-dimethylbenzimidazole, α-ribazole, or α-ribazole phosphate added, the highest conversion was obtained with the combination of *(9)* and α-ribazole [17].

Another possibility is that the initial product is cobamide *(7)*, R = H, and that its synthesis is followed by attachment of a hetero-base to the Co atom, the final step being the combination of this base with the ribose moiety via a glycosidic linkage. Several findings support this pathway. A final decision as to the mechanism will be afforded by the use of labelled substrates, which are now accessible by chemical synthesis (see below). It is quite possible that the incorporation of the nucleotide moiety follows a different pathway in the benzimidazole and purine series; it may also depend on the type of microorganism used.

It is the bases of the nucleotide moiety which account for the great variety of the cobamides, as well as for their differing physicochemical and biological properties. The strength of the bond between the bases and the Co atom decreases from a high value in 5,6-dimethylbenzimidazole and linear naphthimidazole to intermediate values in other benzimidazoles and imidazoles and a low value in the purines, thus roughly paralleling the biological activity of the respective cobamides [4]. Which base can be incorporated depends on its structure and on the type of microorganism involved [18–20]. A plausible picture of the biogenesis of benzimidazole and naphthimidazole bases emerges when it is assumed that this biosynthesis proceeds analogously to the synthesis of the benzenoid ring in riboflavin [12]. It is remarkable that under anaerobic conditions, *P. shermanii* synthetizes almost solely cobinamide *(6)*. However, in the presence of small amounts of oxygen, the same organism synthetizes 5,6-dimethylbenzimidazole and thus cobalamin *(8)* [21]. The bases of the purine series probably originate as 9-β-nucleotides, which are then hydrolysed to the free bases so that these can be incorporated into the cobamide molecule by a 7-α-glycosidic linkage.

## C. Syntheses in the Vitamin $B_{12}$ Field [22]

Recent studies in this field were aimed at the synthesis of the macrocyclic corrin system and at partial syntheses of corrinoids. The object was to obtain intermediates of the biosynthesis of vitamin $B_{12}$, as well as compounds with new biological properties.

### I. The Corrin Ring

Several routes have been followed for the synthesis of corrin and its derivatives. *Todd* and coworkers [23, 24] studied the reactions of $\Delta^1$-pyrroline-1-oxides, which yield dipyrrolinylmethane derivatives by condensation with the activated methyl group of 2-methyl-$\Delta^1$-pyrroline-1-oxide. In the presence of strong bases, the $\Delta^1$-pyrroline-1-oxides dimerize to 2,2′-dipyrrolidinyl derivatives. So far no one has reported the combining of pairs of the dipyrrolinylmethane or the 2,2′-dipyrrolidinyl derivatives or the introduction of the six adjoining and three isolated asymmetric centers into the corrin system.

[14a] *R. C. Bray* and *D. Shemin*, J. biol. Chemistry *238*, 1501 (1963).

[14b] *D. Shemin* and *R. C. Bray* in [7a].

[14c] *K. Bernhauer*, *P. Rietz*, and *F. Wagner*, unpublished results.

[14d] α-Ribazole = 5,6-Dimethylbenzimidazole-1-α-D-ribofuranoside.

[15] *P. Barbieri*, *G. Boretti*, *A. Di Marco*, *A. Migliacci*, and *C. Spalla*, Biochem. biophysica Acta *57*, 599 (1962).

[16] *H. S. Friedmann* and *D. L. Harris*, Biochem. biophysic. Res. Commun. *8*, 164 (1962).

[17] *F. Wagner*, unpublished work, Stuttgart 1962.

[18] *S. K. Kon* and *J. Pawelkiewicz:* Fourth International Congress of Biochemistry. Pergamon Press, London 1959, Vol. XI, p. 115.

[19] *D. Perlman*, Adv. appl. Microbiol. *1*, 87 (1959).

[20] *D. Perlman*, *J. M. Barrett*, and *P. W. Jackson* in [6], p. 58.

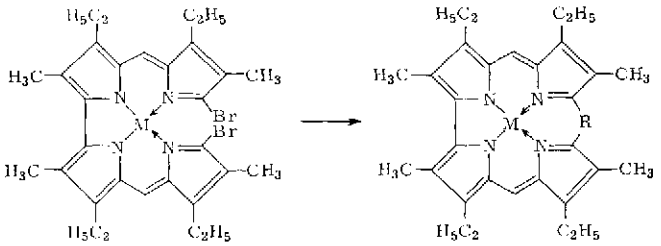
[21] US.-Pat. 2951017 (Aug. 30th, 1960), inventors: *J. D. Speedie* and *G. W. Hull*.

[22] For a review of previous work, see [5].

[23] For a review, see *A. W. Johnson* in [6], p. 1.

[24] *V. M. Clark*, Angew. Chem. *74*, 881 (1962).

*Johnson* and coworkers [23] synthetized pentadehydrocorrin derivatives. Even though macrocyclic compounds of structure *(11a)* were prepared from *(11)* in the presence of palladium or copper salts, these compounds



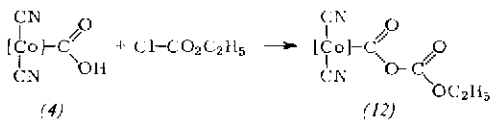
*(11)* *(11a)*

R = O, NH, N–$CH_3$, N–$NH_2$, S

contain an oxygen, nitrogen, or sulfur bridge between rings B and C. However, it was impossible as yet to introduce a methine bridge [24a]. The stereoselective synthesis of rings A and D of corrin is being attempted [24b].

## II. Partial Synthesis of Corrinoids

Almost all partial syntheses start with cobyric acid *(4)*. The latter was isolated from digested sewage sludge [25] and obtained in crystalline form [26]; it also appears as an intermediate in the biosynthesis of vitamin $B_{12}$ by *P. shermanii* [27] and a *N. rugosa* mutant [28]. For purely chemical syntheses [29], the carboxyl group of cobyric acid is activated by treatment with ethyl



*(4)* *(12)*

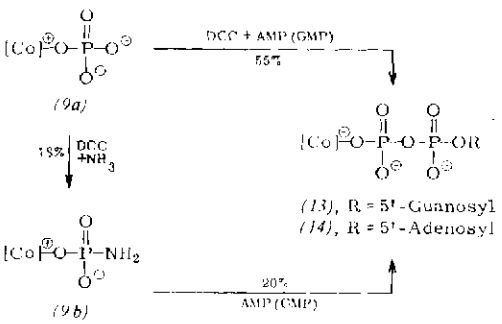
chloroformate in anhydrous dimethylformamide in the presence of triethylamine to give the mixed anhydride *(12)*, which is treated with a nucleophilic reagent without preliminary isolation. This procedure, well known in peptide chemistry, gives the best yields and is superior to the carbodiimide method [30].

### 1. *Incomplete Corrinoids*

Treatment of *(12)* with D-(−)-1-aminopropan-2-ol yields natural cobinamide [30]. This reaction also serves as a proof of the structure of cobyric acid *(4)*. Similarly, reactions of *(12)* with other alkanolamines yield a series of cobinamide analogues [31, 32], some of which are very strong competitive antagonists of cobinamide in *Escherichia coli* 113-3 (see below).

Reactions of *(12)* with α-amino-β-hydroxycarboxylic acids (*e.g.* serine or threonine) yield the corresponding cobinamide carboxylic acids [33]; with α-amino-β-hydroxycarboxylic acids with phosphorylated hydroxyl groups, the phosphoric esters are obtained [34]. These compounds are not metabolized by *P. shermanii* and therefore cannot be biosynthetic intermediates [34].

Cobinamide phosphate and *P*(1)-cobinamide-*P*(2)-guanosine-5′-pyrophosphate were isolated during the study of the biosynthesis of vitamin $B_{12}$ [35]. Synthesis of these compounds from cobyric acid *(4)* proved their structure. Thus DL-cobinamide phosphate *(9a)* [*] [36] was obtained in good yield by treatment of *(12)* with DL-1-amino-2-propyl phosphate, and was in turn converted into DL-cobinamide phosphoamide *(9b)* by treatment with ammonia and *N*,*N*′-dicyclohexylcarbodiimide (DCC) [37]. Both of these substances can be used for the synthesis of *P*(1)-DL-cobinamide-*P*(2)-guanosine-5′-pyrophosphate *(13)* and *P*(1)-DL-cobinamide-*P*(2)-adenosine-5′-pyrophosphate *(14)*. The reaction of DL-cobinamide phosphate with adenosine-5′-phosphate



*(9a)* *(9b)*

*(13)*, R = 5′-Guanosyl
*(14)*, R = 5′-Adenosyl

(AMP) or with guanosine-5′-phosphate (GMP) in the presence of DCC does – contrary to expectation [38, 39] – not yield symmetric DL-cobinamide pyrophosphate [37] since DL-cobinamide phosphate is dipolar and ionic. Recently, natural cobinamide *(6)* was phosphorylated directly by condensing it with β-cyanoethyl phosphate and DCC in anhydrous dimethylformamide/pyridine to yield β-cyanoethylcobinamide phosphate, which gave cobinamide phosphate *(9)* upon alkaline hydrolysis [40].


[24a] *A. W. Johnson, J. T. Kay,* and *R. Rodrigo,* J. chem. Soc. (London) *1963*, 2326.

[24b] *R. B. Woodward,* Lecture in Basel (Switzerland), June 1963; Abstract: Angew. Chem. *75*, 871 (1963).

[25] *K. Bernhauer, H. Dellweg, W. Friedrich, G. Gross, F. Wagner,* and *P. Zeller,* Helv. chim. Acta *43*, 693 (1960).

[26] *K. Bernhauer, F. Wagner,* and *D. Wahl,* Biochem. Z. *334*, 279 (1961).

[27] *K. Bernhauer, E. Becher, G. Gross,* and *G. Wilharm,* Biochem. Z. *332*, 562 (1960).

[28] *A. Di Marco, M. P. Marnati, A. Miggliacci, A. Rusconi,* and *C. Spalla* in [6], p. 69.

[29] *K. Bernhauer* and *F. Wagner* in [6], p. 28.

[30] *K. Bernhauer, F. Wagner,* and *P. Zeller,* Helv. chim. Acta *43*, 696 (1960).

[31] *K. Bernhauer* and *F. Wagner,* Hoppe-Seylers Z. physiol. Chem. *322*, 184 (1960).

[32] *K. Bernhauer, F. Wagner, D. Wahl,* and *D. Glatzle,* unpublished results.

[33] *K. Bernhauer* and *F. Wagner,* Hoppe-Seylers Z. physiol. Chem. *332*, 194 (1960).

[34] *K. Bernhauer* and *F. Wagner,* Biochem. Z. *335*, 325 (1962).

[35] See review [12].

[36] *K. Bernhauer, F. Wagner, H. Dellweg,* and *P. Zeller,* Helv. chim. Acta *43*, 700 (1960).

[37] *K. Bernhauer* and *F. Wagner,* Biochem. Z. *335*, 453 (1962).


[*] DL-Cobinamide phosphate is the short designation for cobyryl-(DL-2-hydroxypropyl)amide. Cobinamide denotes the natural product.


[38] *H. G. Khorana,* Fed. Proc. *19*, 931 (1960).

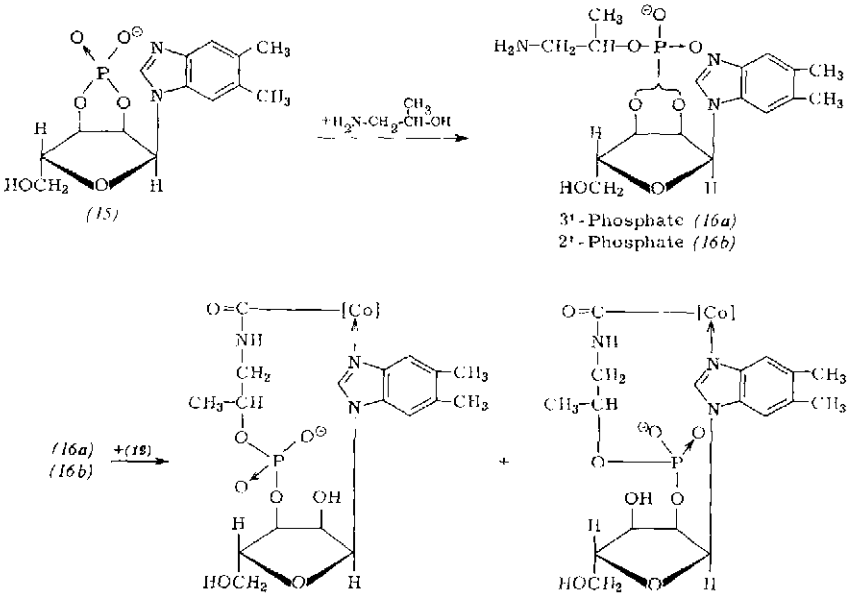
[39] *F. Cramer,* Angew. Chem. *72*, 236 (1960).

[40] *F. Wagner,* Biochem. Z. *336*, 99 (1962).

These methods permitted preparation of other phosphorylated cobinamide derivatives, including radioactively labelled preparations. These are valuable for elucidating the mode of biosynthesis of the nucleotide moiety of the complete cobamides.

### 2. *Complete Corrinoids*

*Friedrich* et al. [41] were the first to synthetize cobalamin *(8)*, starting from cobyric acid *(4)*: α-ribazole phosphate [(1-α-D-ribofuranosyl-5,6-dimethylbenzimidazolyl)-3′-dihydrogen phosphate] was converted into α-ribazole-2′,3′-cyclophosphate *(15)* by reaction with dicyclohexylcarbodiimide. Compound *(15)* was then




reated with a large excess of an alkanolamine (*e.g.* D-1-aminopropan-2-ol in the synthesis of cobalamin) in the presence of sodium butoxide. This gave a 70 % yield of a mixture of equal parts of the 3′- and 2′-nucleotide esters *(16a)* and *(16b)*. The next reaction, in which the mixture was treated with one mole of *(12)* in anhydrous dimethylformamide, was complete at 0 °C within a few seconds giving a 60–70 % yield of the complete corrinoid [43].

This same method [41] was used to prepare 5-methoxybenzimidazolylcobamide and 2-methyladenylcobamide [42]. The complete cobamides obtained by treatment of the 3′-(D-1-amino-2-propyl)nucleotide ester proved to be identical with the corresponding natural products. This is a further proof for the structure determined analytically.

The mixture of isomers *(16a)* and *(16b)* can be separated by chromatography on DEAE-cellulose or on paper. Alternatively, the mixture is treated with *(11)* and the 3′- and 2′-vitamin $B_{12}$ derivatives are separated by paper electrophoresis at pH 2.7 [43].

This synthetic pathway permits the preparation of numerous vitamin $B_{12}$ derivatives [43] in which the D-1-aminopropan-2-ol group of cobalamin is replaced by other alkanolamines (see below). These products, which are not found in nature, may help in the elucidation of the biochemical function of the D-1-aminopropan-2-ol group. Some of these compounds were shown to be exceptionally strong competitive antagonists of cobalamin (see below).

In addition to the purely synthetic 2′-isomer of cobalamin [41], the 5′-isomer of cobalamin was recently prepared [40] by condensation of cobinamide phosphate and 2′,3′-isopropylidene-α-ribazole with dicyclohexylcarbodiimide, followed by removal of the isopropylidene group. The 5′-isomer was also synthetized by condensation of α-ribazole-5′-phosphate with 1-(benzyloxycarbonylamino)-2-propanol in the presence of dicyclohexylcarbodiimide, hydrogenolytic cleavage of the carbobenzoxy group and reaction of the diester so obtained with *(12)* [43a]. Direct phosphorylation of cobalamin by the method described for cobinamide yields cobalamin-5′-phosphate [40].

## D. Coenzyme Forms of the Corrinoids

The commercial cyano form of cobalamin is an artefact. It is obtained by the action of cyanide ions on natural precursors of the vitamin during the isolation of the latter. Only the hydroxo (aquo) form can be isolated from natural substrates, provided cyanide ions are rigidly excluded. Because of its good depot properties, it is preferred over the cyano form [44–45], and it is in that form that vitamin $B_{12}$ is commonly used. However, the naturally occurring vitamin actually exists in the coenzyme form discovered several years ago.

[41] *W. Friedrich, G. Gross, K. Bernhauer*, and *P. Zeller*, Helv. chim. Acta *43*, 704 (1960).

[42] *W. Friedrich* and *H. C. Heinrich*, Biochem. Z. *333*, 550 (1961).

[43] *W. Friedrich* in [6], p. 8.

[43a] *W. Friedrich*, Z. Naturforsch. *18b*, 455 (1963).

[44] *E. E. Gabbe* and *H. C. Heinrich* in [6], p. 116.

[44a] *G. B. J. Glass, H. R. Skeggs, D. H. Lee, E. L. Jones*, and *W. W. Hardy* in [6], p. 673.

[45] *G. B. J. Glass, D. H. Lee, H. R. Skeggs*, and *J. L. Stanley*, Fed. Proc. *21*, 471 (1962).

## I. Occurrence and Isolation of the Coenzymes [46]

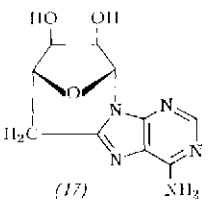
The corrinoid coenzymes were discovered by *Barker* et al. [47] during a study of the enzymatic conversion of glutamic acid into β-methylaspartic acid. The enzyme is light-sensitive and is deactivated by daylight or by cyanide ions. The coenzyme forms of 5,6-dimethylbenzimidazolylcobamide, benzimidazolylcobamide, and adenylcobamide were the first to be isolated [47]. Later, coenzyme forms of cobinamide [48,49], cobinamide-pyrophosphate-guanosine [48], cobyric acid [50], and several biosynthetic cobamides [51,52] were isolated from microorganisms. Vitamin $B_{12}$ also exists in its coenzyme form *(10)* in the liver of humans, sheep, rabbits, and chickens [53].

To isolate the coenzyme forms, bacteria are extracted with boiling 70–80 % ethanol or a neutral aqueous buffer [46], or with 60 % aqueous acetone at room temperature [54]. Acetone powders of bacteria are extracted with water [48]. After concentration, the solutions are extracted with mixtures of phenol and chloroform or *o*-dichlorobenzene (40:60 w/w). The organic phase is washed several times with water, treated with chloroform and n-butanol. The corrinoid coenzymes can then be extracted with water. Residual phenol is removed with chloroform. The aqueous solution is concentrated *in vacuo*, and usually contains mixtures of the coenzymes. These can be separated by column chromatography on cellulose, by paper electrophoresis, or by ion exchange [46, 54].

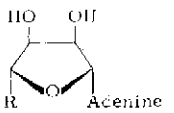
## II. Properties and Degradation of the Coenzymes

The extreme sensitivity to light of the isolated coenzymes and their peculiar cleavage by cyanide are their most remarkable properties. The coordinate bond between cobalt and the imidazole nitrogen is ruptured at pH $< 6$ if the hetero base is a purine and at pH $< 2.5$ if the coenzyme contains benzimidazole [46].

It is concluded from the valence of the cobalt in the cobalamin coenzyme (see below) and from the appearance of a reduced form of cobalamin ($B_{12r}$) after exposure to light in the absence of oxygen [55,56] that the ligand containing adenine is split off as a radical. In the absence of oxygen, the radical is stabilized by formation of the cyclic nucleoside *(17)* [57,57a]. In air, the 8,5′-cyclic adenosine is only partially formed; some of the radicals react with oxygen to form adenosine-5′-aldehyde *(18)* [58] or adenosine-5′-carboxylic acid *(19)* [59]. In air, vitamin $B_{12r}$ is oxidized within a few seconds to hydroxo (aquo) cobalamin. The corrinoid coenzymes are much more stable when bound to proteins than in their free form.

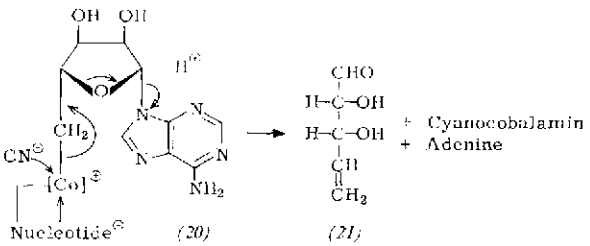



*(17)*




*(18)*, R = CHO
*(19)*, R = COOH

Cyanide converts the cobalamin coenzyme *(20)* [= *(10)*] into cyanocobalamin [46,59,59a] by splitting off adenine and *erythro*-3,4-dihydroxy-1-penten-5-al *(21)*. This reaction is not affected by atmospheric oxygen [55].




*(20)* *(21)*

The other corrinoid coenzymes are cleaved by light and cyanide in the same manner as the cobalamin coenzyme, but at considerably different rates [60].

The action of iodine on the cobalamin coenzyme in aqueous solution results in the formation of iodinecobalamin and 5′-iodo-5′-deoxyadenosine [54].

## III. Structure of the Coenzymes

The structure of the cobalamin coenzyme *(10)* was first elucidated by means of X-ray analysis [61] and was then confirmed by partial synthesis (see below).

In the cobalamin coenzyme, the 5′-deoxyadenosyl residue assumes the sixth coordination position, which is occupied by cyanide in vitamin $B_{12}$. It is connected to the Co atom by a covalent bond at C-5′. X-ray diffraction studies on the cobalamin coenzyme have shown that, like vitamin $B_{12}$, it contains $Co^{3+}$ [62]. This is in agreement with its electrophoretic behavior. The presence of $Co^{3+}$ is further indicated by the electron spin resonance spectrum of the cobalamin coenzyme [62a].


[46] *H. A. Barker* in [6], p. 82.

[47] *H. A. Barker, H. Weissbach,* and *R. D. Smyth,* Proc. nat. Acad. Sci. USA *44,* 1093 (1958).

[48] *J. Pawelkiewicz, B. Bartosiński,* and *W. Walerych,* Bull. Acad. polon Sci., Sér. Sci. biol. *8,* 123 (1960).

[49] *K. Bernhauer, P. Gaiser, O. Müller,* and *O. Wagner,* Biochem. Z. *333,* 106 (1960).

[50] *A. Migliacci* and *A. Rusconi,* Biochim. biophysica Acta *50,* 370 (1961).

[51] *K. Bernhauer, O. Müller,* and *G. Müller,* Biochem. Z. *335,* 37 (1961).

[52] *J. I. Toohey, D. Perlman,* and *H. A. Barker,* J. biol. Chemistry *236,* 2119 (1961).

[53] *J.I.Toohey* and *H. A. Barker,* J. biol. Chemistry *236,* 560 (1961).

[54] *K. Bernhauer, P. Gaiser, E. Irion, G. Müller, O. Müller,* and *O. Wagner,* unpublished results.

[55] *K. Bernhauer* and *O. Müller,* Biochem. Z. *334,* 199 (1961).

[56] *R. O. Brady* and *H. A. Barker,* Biochem. biophysic. Res. Commun. *4,* 373 (1961).

[57] *H.P.C. Hogenkamp* and *H.A. Barker,* Fed. Proc. *21,* 470 (1962).

[57a] *H. P. C. Hogenkamp,* J. biol. Chemistry *238,* 477 (1963).

[58] *H. P. C. Hogenkamp, J. N. Ladd,* and *H. A. Barker,* J. biol. Chemistry *237,* 1950 (1962).

[59] *A. W. Johnson* and *N. Shaw,* Proc. chem. Soc. (London) *1961,* 447.

[59a] *A. W. Johnson* and *N. Shaw,* J. chem. Soc. (London) *1962,* 4608.

[60] *O. Müller* and *G. Müller,* Biochem. Z. *336,* 299 (1962).

[61] *P. G. Lenhert* and *D. Crowfoot-Hodgkin,* Nature (London) *192,* 937 (1961).

[62] *D. Heintz,* Diploma Thesis, Universität München 1962.

[62a] *H. P. C. Hogenkamp, H. A. Barker,* and *H. S. Mason,* Arch. Biochem. Biophysics *100,* 353 (1963).

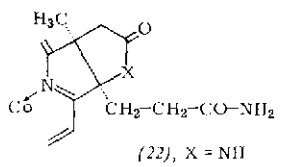
Thus, magnetochemical results which were obtained with aqueous solutions of the cobalamin and cobinamide coenzymes and which indicate $Co^{2+}$ [63–65] are probably due to other phenomena.

The cobinamide coenzyme contains a hydroxo (aquo) group instead of the nucleotide. The cobinamide coenzyme obtained by degradation of cobalamin coenzyme *(10)* with cerium(III) hydroxide [66] is identical with the natural product; this proves the position of the nucleoside.

At first it was not clear whether the corrin ring of the coenzyme forms had the usual six double bonds. The bond system and the number of hydrogen atoms in the corrin skeleton of the cobalamin coenzyme cannot be determined exactly by X-ray analysis [61]. The partial synthesis of the coenzyme forms involves reduction of the Co atom and thus, does not yield any definite conclusions about the structure of the corrin ring.

The synthesis of *Co*-methylcobalamin in water-containing tritium leads to a radioactive product [67] with tritium in the methyl group bound to the cobalt. This was shown [67a] by aerobic photolysis and trapping of the produced formaldehyde in the form of its adduct with dimedone. This results seems to indicate that the conjugated system of the corrin ring in the coenzyme form is identical with that of the cyano forms [67a].

It was shown, however [67], that the coenzyme forms do not undergo the same reactions as cyano- or hydroxocobalamin do on account of activation of C-8 (CN double bond in the allylic position). Thus, in alkaline solution, cyanocobalamin *(8)*, L = CN, is dehydrogenated by atmospheric oxygen to the lactam *(22)* [68] while cobalamin coenzyme, cobalamin sulfonate or *Co*-methylcobalamin are not dehydrogenated under the same conditions. Equimolar

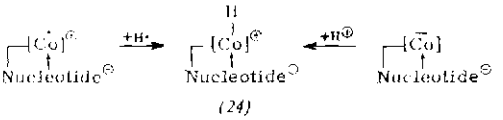


*(22)*, X = NH
*(23)*, X = O

quantities of chloramine-T or bromine water oxidize cyanocobalamin to the lactone *(23)*. Halogenation occurs only when chloramine-T or bromine water is present in excess. On the other hand, the coenzyme forms are not oxidized by one mole of chloramine-T, but are converted into a uniform monochloro derivative [67]. The first equivalent of bromine water or *N*-bromosuccinimide has an analogous effect [68a].

## IV. Partial Chemical Syntheses of Corrinoid Coenzymes and Their Analogues

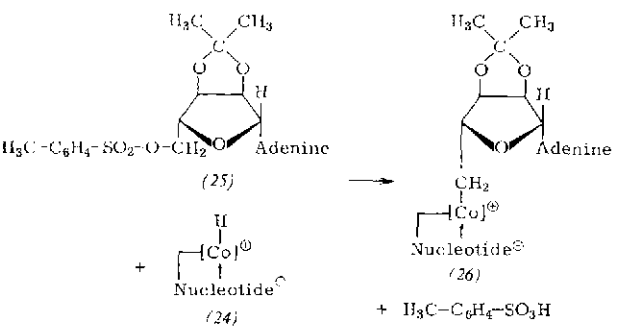
When vitamin $B_{12}$ is reduced with zinc in $NH_4Cl$ [69], NaOH, or acetic acid solution, yellow $B_{12r}$ is initially formed, provided oxygen is rigorously excluded. After prolonged reaction times, the reduction proceeds further, yielding a light blue to green product. This product can also be obtained with other reducing agents, *e.g.* chromium(II) salts or sodium borohydride [70, 71]. Cobalamin reduced in this way reacts with diazomethane to yield *Co*-methylcobalamin and is thus a cobalt hydride *(24)* [60]. It is formed in the reaction of the $Co^{2+}$-complex with nascent hydrogen, or from the intermediate $Co^{I}$-complex by addition of a proton. The addition reactions of the reduced product also seem to indicate a cobalt-hydrogen bond.



*(24)*

Provided oxygen is absent, cobalamin hydride is stable in aqueous solution. In air, it is converted within a few seconds to hydroxo(aquo)cobalamin.

Hydrides of other corrinoids, such as benzimidazolylcobamide, adenylcobamide, and cobinamide, can be obtained in a similar manner. The reduction to the hydride causes the cobalt atoms of the corrinoids to become nucleophilic and thus to react with compounds having an electrophilic center.



*(25)* *(26)* *(24)*

The synthesis of the cobalamin coenzyme proceeds by reaction of cobalamin hydride *(24)* with 2′,3′-isopropylidene-5′-tosyladenosine *(25)* to yield *(26)*, followed by removal of the isopropylidene group with dilute acid [60, 72, 73, 73a]. Similarly, reaction of cobalamin hydride and 2′,3′-isopropylidene-5′-tosylinosine yields the hypoxanthine analogue [72, 74] of the cobalamin coenzyme. This analogue had been previously prepared by deamination of the cobalamin coenzyme [75]. The uridine [72] and guanosine [74] analogues of cobalamin coenzyme have also been obtained. It is noteworthy that synthetic cobinamide coenzyme is identical with the natural product. This implies that the hydrogen atom attached to the Co in the hydrides is always on the same side of the molecule.


[63] *A. W. Johnson* and *N. Shaw*, Proc. chem. Soc. (London) *1960*, 420.

[64] *L. Nowicki* and *J. Pawelkiewicz*, Bull. Acad. pol. Sci., Sér. Sci. biol. *8*, 433 (1960).

[65] *K. Bernhauer, P. Gaiser, O. Müller, E. Müller*, and *F. Günter*, Biochem. Z. *333*, 560 (1961).

[66] *K. Bernhauer* and *O. Müller*, Biochem. Z. *335*, 44 (1961).

[67] *F. Wagner* and *P. Renz*, Tetrahedron Letters *1963*, 259.

[67a] *F. Wagner* and *K. Bernhauer* in [7a].

[68] *R. Bonnet, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith*, and *A. R. Todd*, J. chem. Soc. (London) *1957*, 1158.

[68a] *F. Wagner* and *V. Koppenhagen*, unpublished results.

[69] *O. Schindler*, Helv. chim. Acta *34*, 1356 (1951).

[70] *R. N. Boos, J. E. Can*, and *J. B. Conn*, Science (Washington) *117*, 603 (1953).

[71] *F. P. Siegel*, Ph. D. Thesis, University of Illinois, USA, 1955.

[72] *E. L. Smith, L. Merwin, A. W. Johnson*, and *N. Shaw*, Nature (London) *194*, 1175 (1962).

[73] *K. Bernhauer, O. Müller*, and *G. Müller*, Biochem. Z. *336*, 102 (1962).

[73a] *A. W. Johnson, N. Shaw*, and *E. L. Smith*, J. chem. Soc. (London) *1963*, 4146.

[74] *O. Müller* and *G. Müller*, Biochem. Z. *336*, 299 (1962).

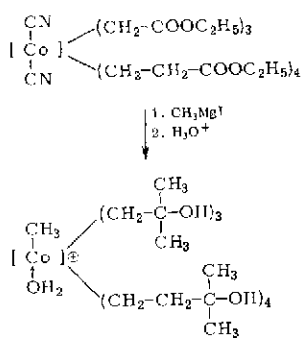
[75] *O. Müller* and *G. Müller*, Biochem. Z. *335*, 340 (1962).

## V. Other Corrinoids with Cobalt-Carbon Bonds

Alkylated cobalamin compounds are obtained by treatment of cobalamin hydride with alkyl halides, dialkyl sulfates, or *p*-toluenesulfonic esters [60, 72–74]. At room temperature, the reactions are finished within a few minutes. Sulfonium compounds such as methylmethionine or *S*-adenosylmethionine can also be used to prepare *Co*-methylcobalamin [74, 75a]. In addition, acetylenic and olefinic compounds add onto cobalamin hydride. For example, reaction with acrylic acid yields *Co*-β-carboxyethylcobalamin [73a, 75b], while that with tetrahydrofuran yields *Co*-δ-hydroxybutylcobalamin [74]. As expected from their structures, the properties of the *Co*-alkylcorrinoids resemble those of the corrinoid coenzymes. In air, they are photolysed to the corresponding hydroxo(aquo)corrinoids. The ultraviolet absorption spectra of the *Co*-alkylcorrinoids are also very similar to those of the corresponding corrinoid coenzymes. However, in contrast to the coenzymes, the *Co*-alkylcorrinoids are not cleaved by cyanide.

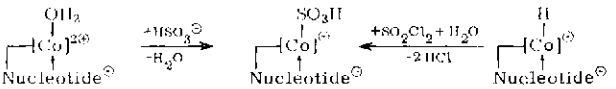
The corrinoid hydrides also react with acylating agents such as acid anhydrides and acyl halides, producing acyl *Co*-derivatives. These are also sensitive to light and cyanide and, in addition, to alkali [60]. It is noteworthy that the ultraviolet spectrum of *Co*-ethoxycarbonylcobalamin, which is obtained by the reaction of cobalamin hydride with ethyl chloroformate, is much more similar to the ultraviolet spectrum of cyanocobalamin than to that of the coenzyme forms [74].

But even Cyano- or hydroxocorrinoids with $Co^{3+}$ as central atom can be directly converted into coenzyme-like derivatives, when compounds are used which are soluble in inert solvents and which can therefore be reacted with Grignard reagents or lithium alkyls. For example, treatment of heptaethyl cobyrinate with excess methylmagnesium iodide in tetrahydrofuran/ether and decomposition of the reaction product with diluted acetic acid yields a *Co*-methyl derivative of the corresponding tertiary alcohol [67a].



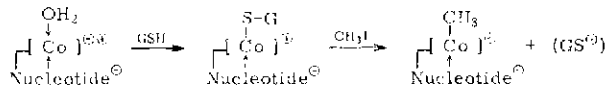

## VI. Corrinoids with Cobalt-Sulfur Bonds

The action of sulfite or sulfurous acid on cyano- or hydroxo(aquo)corrinoids yields substances which are very similar to the corrinoid coenzymes [76–80]. These are again light-sensitive, have similar ultraviolet spectra, and are converted by cyanide into cyanocorrinoids. The derivatives of cobalamin and cobinamide were obtained in crystalline form [76, 79, 79a]. These same products are also produced on treatment of cobalamin hydride or cobinamide hydride with sulfuryl chloride [79]. These reactions, as well as the appropriate infrared spectra, show that these corrinoids contain a cobalt-sulfur bond. Until the nomenclature of this new class of compounds is fixed, we will designate these substances respectively




as cobalamin *Co*-sulfonate and cobinamide *Co*-sulfonate. *Co*-*p*-Toluenesulfonyl- and *Co*-benzenesulfonylcobinamides were prepared in the same manner. However, these compounds are not light-sensitive [79].

Treatment of aquocobalamin with glutathione (GSH) yields *Co*-(*S*-glutathionyl)cobalamin as intermediate which reacts with electrophilic agents, *e.g.* with methyl iodide to give *Co*-methylcobalamin [67a].




## VII. Biosynthesis of the Corrinoid Coenzymes

All the corrinoids occurring in nature apparently exist in the coenzyme form. This form presumably arises soon after the synthesis of the corrin ring and the incorporation of the Co atom, perhaps at the stage of a pentacarboxylic acid *(3)*, which, just like other related polycarboxylic acids, can be converted enzymatically into its coenzyme form [81]. Further biogenesis to the complete cobamides probably takes place at the coenzyme level. Alternatively, it may involve forms having the essential characteristics of the coenzyme structure (see below).

The biosynthesis of the 5′-deoxyadenosyl moiety and its binding to the Co atom was studied mainly with enzymes obtained from microorganisms. These studies were first conducted with acetone powders [82–84], later with extracts of bacteria [85–89], and finally with


[75a] *W. Friedrich* and *E. Königk*, Biochem. Z. *336*, 444 (1962).

[75b] *E. L. Smith* and *L. Merwyn*, Biochem. J. *86*, 2 P (1963).

[76] *K. Bernhauer, O. Müller*, and *O. Wagner* in [6], p. 110.

[77] *K. Bernhauer, P. Renz*, and *F. Wagner*, Biochem. Z. *335*, 443 (1962).

[78] *Ph. George, D. H. Irvine*, and *St. C. Glauser*, Ann. New York Acad. Sci. *88*, 393 (1960).

[79] *K. Bernhauer* and *O. Wagner*, Biochem. Z. *337*, 366 (1963).

[79a] *D. H. Dolphin, A. W. Johnson*, and *N. Shaw*, Nature (London) *199*, 170 (1963).

[80] *J. A. Hill, J. M. Pratt*, and *R. J. P. Williams*, J. theoret. Biol. *3*, 423 (1962).

[81] *K. Bernhauer, H. Beisbarth, P. Rietz*, and *F. Wagner*, unpublished results.

[82] *K. Bernhauer, P. Gaiser, O. Müller*, and *O. Wagner*, Biochem. Z. *333*, 106 (1960).

[83] *J. Pawelkiewicz, B. Bartosiński*, and *W. Walerych*, Bull. Acad. polon. Sci., Sér. Sci. biol. *8*, 123 (1960).

[84] *J. Pawelkiewicz, B. Bartosiński*, and *W. Walerych*, Acta biochim. polon. *8*, 131 (1961).

[85] *H. Weissbach, B. G. Redfield*, and *A. Peterkofsky*, J. biol. Chemistry *236*, PC40 (1961).

[86] *R. O. Brady* and *H. A. Barker*, Biochem. biophysic. Res. Commun. *4*, 464 (1961).

a purified enzyme preparation which had been enriched 337 times [90]. When this preparation is used, the synthesis of the coenzyme requires $Mn^{2+}$, $K^+$, reduced flavin-adenine dinucleotide and a sulfhydryl compound, in addition to a corrinoid and ATP. Studies with ATP labelled with radiocarbon show that this is the source of the 5′-deoxyadenosyl residue of the coenzyme [87–90]. However, the manner in which the 5′-deoxyadenosyl residue is transferred is unknown. The enzymatic conversion of cyanocobalamin into the cobalamin coenzyme is supposed to take place in one step [91]. However, by starting with cobinamide, it was possible to isolate a labile, light-sensitive, yellow, apparently reduced intermediate, with physicochemical properties reminiscent of reduced cobinamide. This product then yielded the cobinamide coenzyme in a second reaction step which took place in the presence of ATP and dihydroflavin mononucleotide ($FMNH_2$) [92,93].

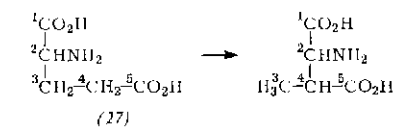
## E. Enzymatic Functions of Vitamin $B_{12}$

### I. Intramolecular Rearrangements in which Cobamide Coenzymes are Involved

The enzymatic reactions in which cobamide coenzymes participate are mainly intramolecular isomerizations.

#### 1. *Conversion of Glutamate into Methylaspartate*

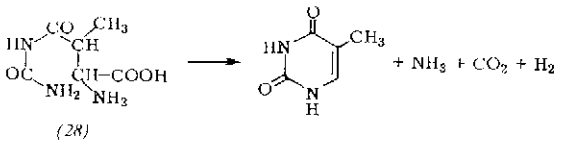
The study of this reaction in *Clostridium tetanomorphum* led to the discovery of the coenzyme forms of the cobamides [46]. The glutamate isomerase reaction can be conceived as an intramolecular reversible transfer of a glycine group from the β- to the α-carbon of the propionic acid moiety of glutamic acid *(27)*, with simultaneous shift of a hydrogen atom in the opposite direction



*(27)*

[46]. Only cobamide coenzymes are active in this reaction; the incomplete forms are inactive [94,94a].

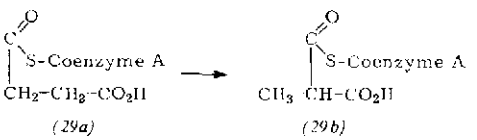
In protozoa, the carbamyl derivative *(28)* of methylaspartate is a precursor of thymine, which may explain why vitamin $B_{12}$ is required for DNA synthesis [95]. However, this pathway of thymine biosynthesis does not apply to rats [96].



*(28)*

#### 2. *Conversion of Succinyl-CoA into Methylmalonyl-CoA*

This reaction is catalysed by methylmalonyl-coenzyme-A isomerase and involves transfer of the thioester group from the β- to the α-carbon of the propionic acid moiety of the molecule [*i.e. (29a)* → *(29b)*], as was shown with labelled substrates [97,98]. When purified isomerase



*(29a)* *(29b)*

was used, the reaction product did not take up tritium from labelled water [99]. For the reaction mechanism, see also [99a,b].

This reaction plays an important role in the biological utilization of propionic and other fatty and amino acids [100–102b]. It is noteworthy that in human megaloblastic anemia, ten to twenty times the normal amount of methylmalonate is excreted in the urine. Thus, accumulation of methylmalonate in the tissues could be the cause of the symptoms of pernicious anemia [103].

#### 3. *Conversion of 1,2-Diols into Deoxyaldehydes*

This intramolecular redox reaction was realized with cell-free extracts of *Aerobacter aerogenes* or *Clostridium perfringens* in the presence of some cobamide coenzymes; examples are: propane-1,2-diol → propionaldehyde and ethylene glycol → acetaldehyde [104,104a]. During this study, it was shown by experiments with heavy water that the rearrangement involves an intramolecular shift of hydrogen (as hydride ion) with simul-

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[88] *A. Peterkofsky* and *H. Weissbach,* Fed. Proc. *21,* 470 (1962).

[89] *B. Bartosiński* and *J. Pawelkiewicz,* Bull. Acad. polon. Sci. Sér. Sci. biol. *10,* 121 (1962).

[90] *R. O. Brady, E. G. Castanera,* and *H. A. Barker,* J. biol. Chemistry *237,* 2325 (1962).

[91] *H. Weissbach, B. G. Redfield,* and *A. Peterkofsky,* J. biol. Chemistry *237,* 3217 (1962).

[92] *B. Bartosiński,* Bull. Acad. polon. Sci., Sér. Sci. biol. *10,* 189 (1962).

[93] For the conversion of $B_{12r}$ to $B_{12}$-coenzyme, see [88].

[94] *H. A. Barker,* Fed. Proc. *20,* 956 (1961).

[94a] *H. A. Barker, F. Suzuki, A. Iodice,* and *V. Rooze* in [7a].

[95] *H. D. Isenberg, E. Seifter,* and *J. I. Berkman,* Biochim. biophysica Acta *39,* 187 (1960).

[96] *R. E. Webb, S. Kirschfeld,* and *B. C. Johnson* in [6], p. 198.

[97] Review: *P. Overath* in [6], p. 155.

[98] *C. S. Hegre, S. J. Miller,* and *M. D. Lane,* Biochem. biophysica Acta *56,* 538 (1962).

[99] *P. Overath, G. M. Kellermann, F. Lynen, H. P. Fritz,* and *H. J. Keller,* Biochem. Z. *335,* 500 (1962).

[99a] *H. G. Wood* in [7a].

[99b] *J. D. Erfle, J. M. Clark, Jr.,* and *B. C. Johnson* in [7a].

[100] *P. Overath, E. R. Stadtman, G. M. Kellerman,* and *F. Lynen,* Biochem. Z. *336,* 77 (1962).

[101] *W. A. Ayers,* Arch. Biochem. Biophysics *96,* 210 (1962).

[102] *H. R. V. Arnstein* and *A. M. White,* Biochem. J. *79,* 3P (1961); *83,* 264 (1962).

[102a] *S. Ochoa* in [7a].

[102b] *F. Lynen* in [7a].

[103] *A. M. White,* Biochem. J. *84,* 41P (1962).

[104] *R. H. Abeles* and *H. A. Lee, Jr.,* J. biol. Chemistry *236,* PC1 (1961); *236,* 2347 (1961).

[104a] *H. A. Lee* and *R. H. Abeles,* J. biol. Chemistry *238,* 2367 (1963).

taneous displacement of an OH group [105]. Recently, acetaldol was suggested as an intermediate in the reation [106]. Extracts of lactobacillus convert glycerol to β-hydroxypropionaldehyde [106a, b].

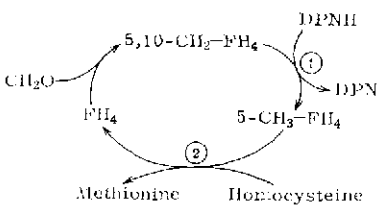
### II. Degradation of Lysine to Fatty Acids and Ammonia

$$H_2N-(CH_2)_4-CH(NH_2)-CO_2H \rightarrow H_3C-(CH_2)_2-CO_2H + H_3C-CO_2H + 2NH_3$$

To accomplish this reaction, which is effected by *Clostridia*, cell preparations that have been aged or treated with activated charcoal require pyruvate, diphosphopyridine nucleotide, $Fe^{2+}$, acetyl coenzyme A, and cobalamin coenzyme [107, 107a].

### III. The Role of Vitamin $B_{12}$ in Methionine Synthesis

A cobalamin enzyme is involved, in addition to several other co-factors, in the transfer of a methyl group from *N*(5)-methyltetrahydrofolic acid to homocysteine [108 to 112a]. This process is part of a cycle which explains the close biochemical relationship known to exist between folic acid and vitamin $B_{12}$ (Scheme 1).




Scheme 1. The role of vitamin $B_{12}$ in the transfer of a methyl group in the synthesis of methionine.

(1) 5,10-methyleneetetrahydrofolate reductase
(2) $B_{12}$-enzyme, DPNH, $FADH_2$, ATP, $Mg^{2+}$

It is possible that this enzymatic system is a main metabolic function of vitamin $B_{12}$ in animal cells and perhaps even the key to various anemias, for in vitamin $B_{12}$ deficiency, the level of methyltetrahydrofolic acid in blood rises to a value several times above the normal. Thus the synthesis of many cell components (purines, pyrimidines) may be inhibited by blockage of the folic acid cycle [112].

In methionine synthesis, the active portion of the vitamin $B_{12}$ enzyme appears to be *Co*-methylcobalamin. If this is incubated with homocysteine and a purified apovitamin $B_{12}$ enzyme, methionine is synthetized and the methyl group bound to cobalt is utilized [113, 113a].

Methionine can also be synthetized nonenzymatically by anacrobic photolysis of *Co*-methylcobalamin in the presence of homocysteine. Under identical conditions, homocysteine is converted by the cobalamin coenzyme into *S*-adenosylhomocysteine [114]. These photolytic reactions can be explained by a free radical mechanism.

The activity of the coenzyme forms in the above enzyme systems explains only a part of the manifold and vital functions of vitamin $B_{12}$ [115]. Moreover, the vitamin also acts as a cofactor in the reduction of ribonucleosides to deoxyribonucleosides [116–118], in the incorporation of amino acids into protein [119, 120], and in carbohydrate and fat metabolism [121, 122].

### IV. Enzymatic Synthesis of Methane

In the presence of pyruvate, an enzyme system from *Methanosarcina barkeri* converts the methyl group of *Co*-methylcobalamin stoichiometrically to methane, as was shown with labelled substrates [122a]. The same reaction occurs with extracts of *Methanobacillus omeianskii* in the presence of ATP [122b].

## F. Molecular Biology of Vitamin $B_{12}$

The biochemical function of the various portions of the vitamin $B_{12}$ molecule was elucidated primarily – as for other vitamins – by demonstration of the biological activity of analogues which were prepared chemically. Analogues with antagonistic activity may be suitable for the treatment of leukemia or other malignant diseases (for reviews, see [123, 124]).


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[106] *B. Zagalak* and *J. Pawelkiewicz*, Life Sci. *8*, 395 (1962).

[106a] *K. L. Smiley* and *M. Sobolov*, Arch. Biochem. Biophysics *97*, 538 (1962).

[106b] *K. L. Smiley* and *M. Sobolov* in [7a].

[107] *T. C. Stadtman*, Fed. Proc. *21*, 470 (1962).

[107a] *T. C. Stadtman*, J. biol. Chemistry *238*, 2766 (1963).

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[112a] *J. M. Buchanan* in [7a].

[113] *J. R. Guest, S. Friedman, D. Woods*, and *E. L. Smith*, Nature (London) *195*, 340 (1962).

[113a] *J. R. Guest, S. Friedman, M. J. Dilworth*, and *D. D. Woods* in [7a].

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[116] *L. A. Manson* in [6], p. 191.

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[120] *H. R. V. Arnstein* and *A. M. White* in [6], p. 211.

[121] *C.-T. Ling* and *B. F. Chow* in [3], p. 127.

[122] *D. K. Biswas* and *B. C. Johnson* in [6], p. 210.

[122a] *B. A. Blaylock* and *Th. C. Stadtman*, Biochem. biophys. Res. Commun. *11*, 34 (1963).

[122b] *M. J. Wolin, E. A. Wolin*, and *R. S. Wolfe*, Biochem. biophys. Res. Commun. *12*, 464 (1963).

[123] *E. L. Smith* in [6], p. 226.

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## I. The Cobalt Atom and the Corrin Ring

In contrast to the porphyrins, the metal atom in vitamin $B_{12}$ is held so tightly that it has not yet been possible to remove it without destroying the molecule. The Co atom participates in the resonance of the corrin ring system. When coordinated nucleotides are present, the Co atom is so deeply imbedded in the cobamide coenzymes that it cannot come into direct contact with substrate. Contact is probably made via a peripheral part of the molecule [46, 125].

The difference in reactivity of the two coordination positions of the Co atom in incomplete corrinoids gave the first insight into the significance of the corrin ring. Thus, X-ray analysis has shown that the cyano group in the monocyanomonochlorohexacarboxylic acid [126] or in monocyanomonoaquocobyric acid *(4)* [127] is coordinated at the same position as the nucleotide in cobalamin *(8)*. Furthermore, in dicyanocobinamide *(6)*, which has two CN groups as ligands, one CN group is bound tightly and the other loosely [77]. It is remarkable that the coenzyme form obtained by chemical synthesis from cobinamide is identical with the natural product and that no other isomer is obtained [74]. Parallel to this, *P. shermanii* converts synthetic *Co*-butylcobinamide into the same *Co*-butylcobalamin as can be synthetized directly from cobalamin [74]. Thus, hydride formation in cobinamide can take place only in the "upper" coordination position in the formulae shown here; this requirement must hold for both incomplete and complete corrinoids. It is possible that the not exact planarity of the corrin ring [126] or the *trans*-effect [128] is of importance in this connection.

## II. The 1-Aminopropan-2-ol Group

Surprisingly, the 1-aminopropan-2-ol group is of special molecular-biological significance, as was shown by experiments with many analogues containing a modified alkanolamine moiety [124]. The most important representatives are shown in Table 1. The stimulation of the growth of *E. coli* 113-3 by chemically and in part biochemically synthetized analogues is similar to that by cobalamin [130] and cobinamide [32], provided the C-1 of the 1-aminoethan-2-ol group carries no substituent (Table 1). If they are not too large, substituents on C-2 do not reduce growth stimulation significantly, compared with the natural products. However, substitution on C-1 results in strong competitive antagonism. This is also true for the coenzyme forms of cobinamide analogues

Table 1. Effect of cobalamin and cobinamide analogues on *E. coli* 113-3 (tube-test experiments).

| 1-Aminoethan-2-ol group with substituent on | | Effect on growth, compared to | | Inhibition Index [129] | |
|---|---|---|---|---|---|
| C-1 | C-2 | Cobalamin = 100 | Cobinamide = 100 | Cobalamin | Cobinamide |
| H | H | 83 | 71 | – | – |
| H | $CH_3$ (D) | 100 | 100 | – | – |
| H | $CH_3$ (L) | 60 | 80 | – | – |
| H | Phenyl (DL) | 0.01 | 0.01 | 17 | 32 |
| H | 2 $CH_3$ | 45 | 36 | – | – |
| $CH_3$ | $CH_3$ | 1 | 36 | – | – |
| $CH_3$ | H | 0.1 | 0.01 | 6 | 7 |
| $C_2H_5$ | H | – | 0.01 | – | 5 |
| 2 $CH_3$ | H | 0.1 | 0.01 | 3 | 3 |

[32] and of cobalamin analogues [130a]. Cobalamin antimetabolites also inhibit the growth of *Ochromonas malhamensis* and are antierythropoetic in decompensated pernicious anemia patients [130]. Cobinamide analogues which stimulate the growth of *E. coli* are converted into cobalamin analogues by *P. shermanii* in the presence of 5,6-dimethylbenzimidazole. This is not so with cobinamide antagonists [32].

## III. The Carboxamide Groups

The carboxyl groups in positions a–e and g [see formula *(2a)*] must be amidated for vitamin $B_{12}$ to be biochemically active; cobalamincarboxylic acids are inactive or antagonistic towards *E. coli* [123, 131]. The individual carboxamide groups are, however, of differing biochemical significance. The strongest antagonist to *E. coli* [123, 132] is the cobalaminmonocarboxylic acid which is the last intermediate in the biosynthetic amidation [81, 132] and is also the one which is the predominant product of mild acidic hydrolysis of cobalamin. Its carboxyl group in position e is presumed to be the one that is free [81]. Its inhibition index (see [129]) with *E. coli* is 40 [133]. The alkylamides of cobalamin which are synthetized by alkylamidation of the carboxylic acids are also antagonistic to *E. coli*. The most active representatives are the monomethylamide and the hydrazide of that monocarboxylic acid which is the main product of hydrolysis of cobalamin (inhibition index = 50) [123].

## IV. The Nucleotide Moiety

Only cobamide coenzymes which contain nucleotides apparently have biochemical activity *in vivo*; the incomplete forms are only intermediates of the biosynthesis. In biological systems in which the incomplete forms are active (*e.g.* in growth tests), they are converted beforehand into complete cobamide coenzymes.

[125] *H. A. Barker*, Fed. Proc. *20*, 956 (1961).

[126] *D. C. Hodgkin* et al., Nature (London) *176*, 325 (1955).

[127] *D. C. Hodgkin*, personal communication.

[128] *J. V. Quagliano* and *L. Schubert*, Chem. Reviews *50*, 201 (1952).

[129] The inhibition index indicates the mole ratio of antagonist to cobalamin (or cobamide) which inhibits the growth stimulated by the latter to 50%.

[130] *H. C. Heinrich*, *W. Friedrich*, and *P. Riedel*, Biochem. Z. *334*, 284 (1961).

[130a] *W. Friedrich*, *H. C. Heinrich*, *E. Königk*, and *P. Schulze* in [7a].

[131] *E. L. Smith* in [3], p. 1.

[132] *K. Bernhauer*, *E. Becher*, *G. Gross*, and *G. Wilharm*, Biochem. Z. *332*, 562 (1960).

[133] *A. M. Kelemen*, *E. Czanyi*, and *A. Simon*, Acta physiol. Acad. Sci. hung. *21*, 177 (1962).

The nature of the base in the nucleotide portion is of minor importance in bacteria, but is very important in the protozoon *O. malhamensis* and in animals. Here, only cobamides of the benzimidazole and naphthimidazole series are active. Although many cobamide analogues containing various non-naturally occurring bases have been synthetized [4, 18, 19], it was impossible to obtain a cobalamin antagonist with a good inhibition index in this way. The 3′-phosphoric acid bond in the nucleotide permits the base to coordinate with the cobalt [see formula *(8)*], so that the molecule becomes "complete" – a fact which appears to be of biochemical importance. The 2′-analogues, in which the bond between Co and the imidazole ring is weakened, are biologically less active [124].

V. The 5′-Deoxyadenosyl Group of the Coenzyme Forms

The 5′-deoxyadenosyl group is necessary for the activity of the coenzyme forms in the enzyme systems mentioned above. Its replacement by other ligands, such as 5′-deoxyinosine, 5′-deoxyuridine, or alkyl groups, leads to loss of activity or to competitive antagonism [72, 100]. However, the presence of the 5′-deoxyadenosyl group is not necessary for the biosynthesis of the vitamin $B_{12}$ molecule, for *Co*-ethyl- and especially *Co*-butylcobinamide are converted into the *Co*-alkylcobalamines by *P. shermanii in vivo* if 5,6-dimethylbenzimidazole is present. Only afterwards they are converted into cobalamin coenzymes [74].

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# New Methods of Preparative Organic Chemistry IV [*]

## Cyclization of Dialdehydes with Nitromethane [1]

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*Dedicated in memoriam to Hermann O. L. Fischer, whose initiative started the developments in this field*

*Condensation of nitromethane with suitable dialdehydes in alkaline medium provides a general method of cyclization, in which the methyl group of the nitromethane is incorporated into the ring. This method leads to 5-, 6-, and 7-membered rings and is equally applicable to aliphatic, aromatic, and sugar dialdehydes. For example, glyoxal is converted into 1,4-dideoxy-1,4-dinitro-neo-inositol, and glutaraldehyde into trans-2-nitrocyclohexane-1,3-diol, while the corresponding cyclization of xylo-trihydroxyglutaraldehyde leads to deoxynitroinositols having the scyllo, myo-1, and muco-3 configurations. – In the case of aromatic dialdehydes, the cyclization is accompanied by elimination of water. Thus, phthalaldehyde, naphthalene-2,3-dicarboxaldehyde, and homophthalaldehyde yield, respectively, 2-nitroindenol, 2-nitrobenzindenol, and 2-nitronaphthalene. – Application of the method to sugar dialdehydes (aldehydic diglycol derivatives of monosaccharides formed by periodate oxidation) constitutes an excellent synthesis of 3-amino sugars, since 3-deoxy-3-nitropyranoses are formed smoothly on cyclization, and the corresponding 3-amino derivatives are obtained by hydrogenation. Thus, the reaction sequence: periodate oxidation → cyclization with nitromethane → hydrogenation, leads in the case of α- and β-D-pentosides to 3-amino-3-deoxy-D- and -L-pentosides, respectively, with ribo, xylo, and arabino configurations. α-D-Hexosides afford 3-amino-3-deoxy derivatives of glucose, mannose, and talose, while β-D-hexosides give derivatives with gluco, manno, and galacto configurations. 3-Amino-3,6-dideoxyglucosides of the D- and L-series are obtained from 6-deoxy-D- or -L-hexosides, respectively, and 3-aminohexosans with gulo, ido, and altro configurations are obtained from 1,6-anhydro sugars. Cyclization of the dialdehydes obtained from sedoheptulose and methyl 4,6-O-ethylidene-α-D-glucoside by periodate oxidation, leads to 3-nitro and, after hydrogenation, to 3-amino derivatives of 3-deoxyheptopyranoses.*

### Introduction

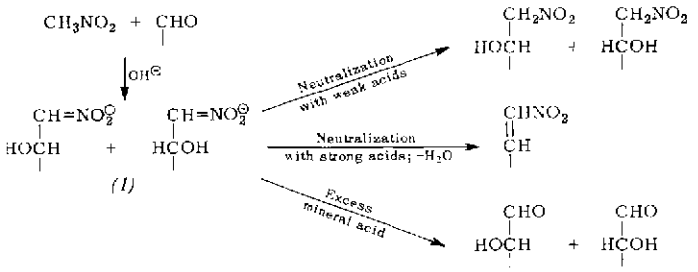
The base-catalysed condensation of an aldehyde with nitromethane, a reaction analogous to the aldol condensation, has been used for the synthesis of a variety of products since its discovery by *Henry* [2] in 1895. The primary products of the reaction are *aci*-nitro salts *(1)*. Neutralization of the latter with weak acids results in a

[*] The preceding papers of this series have been published in a revised and extended form in three volumes by Verlag Chemie GmbH., Weinheim/Bergstr. (Germany), and by Academic Press, New York and London.

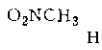
[1] Extended version of lectures given at the Department of Biochemistry, University of California, Berkeley (May, 1961), the Department of Agricultural Chemistry, University of Kyoto (July, 1961), the meeting of chemistry lecturers at Bonn (September, 1962), and at the Technische Hochschule, Darmstadt (November, 1961 and December, 1962).

[2] *L. Henry*, C. R. hebd. Séances Acad. Sci. *120*, 1265 (1895).

mixture of two epimeric nitro alcohols [3–5], while strong acids generally produce nitro olefins with elimination of water [4]. On treatment of the *aci*-nitro salts with excess mineral acid, the Nef reaction [6] occurs, resulting in a mixture of epimeric hydroxy aldehydes. This reaction has attained great importance, principally in sugar chemistry, where it has been used to synthetize aldoses [5,7,8], 2-deoxyaldoses [5], and aldosamines [5,9], which are otherwise difficultly accessible.




With suitable dialdehydes, a cyclizing nitromethane condensation can occur. This was first demonstrated in 1910 in the case of *o*-phthalaldehyde [10]. Condensation of this compound with nitromethane in the presence of alcoholic potassium hydroxide, followed by acidification, yields a 2-nitroindenol. In 1952, *McCasland* et al. [11] obtained a cyclic product from the reaction of glutaraldehyde with nitromethane, although in impure form and only 3 % yield. Stepwise cyclizations of dialdehydes



with nitromethane, starting with trihydroxy- or aminodihydroxyglutaraldehydes blocked at one aldehyde group, were described by *Grosheintz* and *Fischer* [12], and by *Wolfrom* et al. [13]. In these cases, condensation with nitromethane and subsequent release of the second aldehyde group produced mixtures of 6-nitrohexoses or 6-nitrohexosamines, respectively. Under the influence of alkali, the carbonyl and nitromethylene functions of these compounds cyclize intramolecularly to form nitroinositols [12] or nitroinosamines [13].

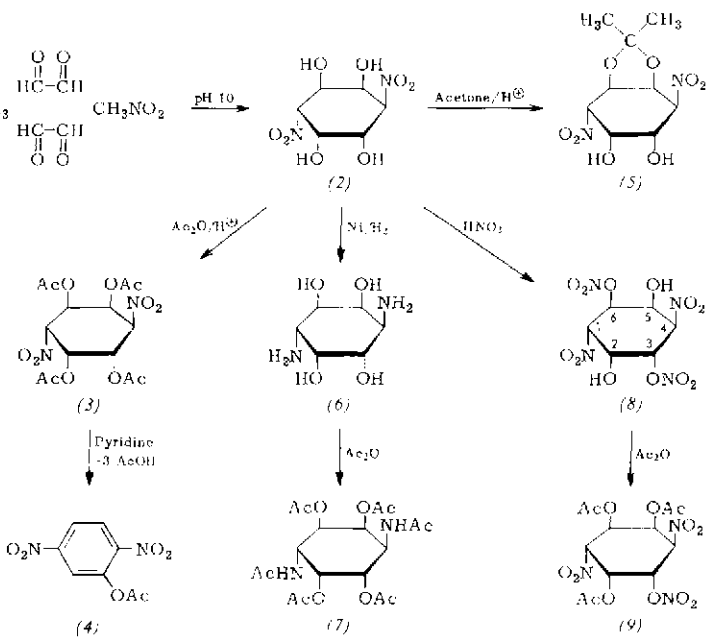
*Baer* and *Fischer* [14] postulated that direct combination of sugar dialdehydes with nitromethane should likewise lead to cyclization, and demonstrated this for the first time with the dialdehydes derived from methyl pentosides by periodate oxidation. Since then, this synthetic method has been extended to many dialdehydes – partly derived from sugars – and has resulted in the preparation of 2-nitro- and 2-amino-1,3-diols which are otherwise inaccessible.

This article presents a survey of the development and the scope and limitation of cyclizing condensations with nitromethane [*].

## I. Cyclization of Aliphatic Dialdehydes

### 1. Glyoxal

Condensation of nitromethane in aqueous sodium carbonate with glyoxal, whose tendency to form cyclic products is well known [15], led to cyclization and the formation of a mixture of isomeric 1,4-dideoxy-1,4-dinitroinositols. Because of its insolubility in water, one uniform isomer was isolated [16]; of the fourteen theoretically possible configurations (eight *meso* and six racemic forms), the *neo*-1,4-configuration *(2)* was assigned to this isomer [17].




The proof of the configuration of *(2)* is based on the following experiments:

1. *(2)* yielded a tetraacetate *(3)* on acid-catalysed acetylation; on treatment with pyridine, *(3)* aromatized to *O*-acetyl-2,5-dinitrophenol *(4)*, with elimination of three moles of acetic acid [17].

[3] *B. M. Vanderbilt* and *H. B. Hass*, Ind. Engng. Chem., ind. Edit. *32*, 34 (1940).

[4] *H. B. Hass* and *E. F. Riley*, Chem. Reviews *32*, 406 (1943).

[5] *J. C. Sowden*, Advances Carbohydrate Chem. *6*, 291 (1951).

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[8] *J. C. Sowden* and *R. R. Thompson*, J. Amer. chem. Soc. *77*, 3160 (1955); *80*, 2236 (1958); *J. C. Sowden* and *D. R. Strobach*, ibid. *82*, 954, 956 (1960); *R. K. Hulyalkar*, *J. K. N. Jones*, and *M. B. Perry*, Canad. J. Chem. *41*, 1490 (1963).

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[11] *G. E. McCasland*, *T. J. Matchett*, and *M. Hollander*, J. Amer. chem. Soc. *74*, 3430 (1952).

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[13] *M. L. Wolfrom*, *S. M. Olin*, and *W. J. Polglase*, J. Amer. chem. Soc. *72*, 1724 (1950).

[14] *H. H. Baer* and *H. O. L. Fischer*, Proc. nat. Acad. Sci. USA *44*, 991 (1958); J. Amer. chem. Soc. *81*, 5184 (1959).

[*] Abbreviations used: Ac = $CH_3CO$– (acetyl residue); Ms = $CH_3SO_2$– (mesyl residue).

[15] *B. Homolka*, Ber. dtsch. chem. Ges. *54*, 1393 (1921); *R. Kuhn*, *G. Quadbeck*, and *E. Röhm*, Liebigs Ann. Chem. *565*, 1 (1949); *F. Weygand*, *K. G. Kinkel*, and *D. Tietjen*, Chem. Ber. *83*, 395 (1950).

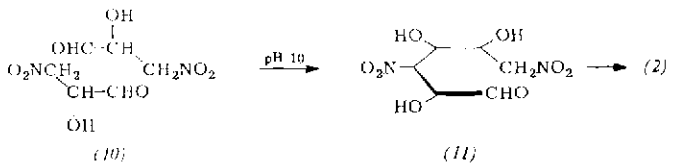
[16] The yield of *(2)* is 10 % if it is assumed that the 30 % aqueous glyoxal used contains only monomer, but is 72 % when based on the actual content of monomeric glyoxal in solution [17].

[17] *F. W. Lichtenthaler* and *H. O. L. Fischer*, J. Amer. chem. Soc. *83*, 2005 (1961).

2. Treatment of *(2)* with acetone yielded a mono-*O*-isopropylidene derivative, the ketal *(5)*. This establishes the presence of a *cis*-diol grouping at one side of the ring, but does not exclude a second such grouping at the other side, even though its presence cannot be proved by formation of a di-*O*-isopropylidene compound (the latter would require the compound to transform from its chair form to the thermodynamically unstable boat form with an axial nitro group [17]). The elimination of a nitrate ester group [18] on acetylation of the dinitrate *(8)* to give *(9)* may be similarly attributed to steric hindrance [19].

3. The NMR spectrum of the tetraacetate *(3)* [20] has two signals of equal intensity at 7.88 and 7.98 τ, which have to be ascribed to two axial and two equatorial acetoxy groups. The six ring hydrogens gave a 1:2:1 intensity triplet at 3.78 τ, indicating two equatorial hydrogen atoms flanked on both sides by axial hydrogen atoms, as well as four doublets of equal intensity in the region of 5.0–4.0 τ, which denote four axial ring protons. The data can be correlated only with the *neo*-1,4-configuration. Analogous results were obtained from the NMR spectrum of the hexaacetylinosadiamine *(7)* produced by hydrogenation of *(2)* to *(6)* and subsequent acetylation of *(6)* [17].

The first intermediate in the cyclization of glyoxal with nitromethane is probably 3-nitrolactaldehyde *(10)*, which may condense either directly via intermediate *(11)* to form *(2)*, or may react with glyoxal to give the intermediate 2,5-dihydroxy-3-nitroglutaraldehyde, which likewise leads via *(11)* to *(2)*. The aldehyde *(10)* was in fact prepared by *Fischer* et al. [21,22] and subsequently cyclized in sodium carbonate solution to give a mixture of isomeric dinitroinositols, from which *(2)* was isolated in 17 % yield [23].

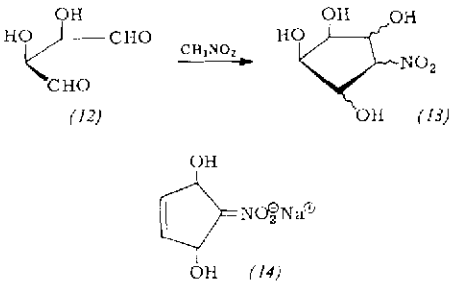



*(10)* *(11)*

## 2. 1,4-Dialdehydes

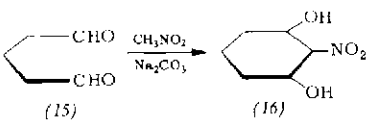
Cyclization of tartaraldehyde *(12)* with nitromethane afforded a mixture of isomeric nitrocyclopentanetetraols *(13)* [24], whose configurations are still unclear.

Maleic aldehyde yielded an *aci*-nitro salt of probable structure *(14)* on condensation with nitromethane in sodium methoxide. The 2-nitrocyclopentadienol expected by analogy with the *o*-phthalaldehyde-nitromethane condensation could not, however, be isolated even on careful neutralization, since it polymerizes extremely readily [23].

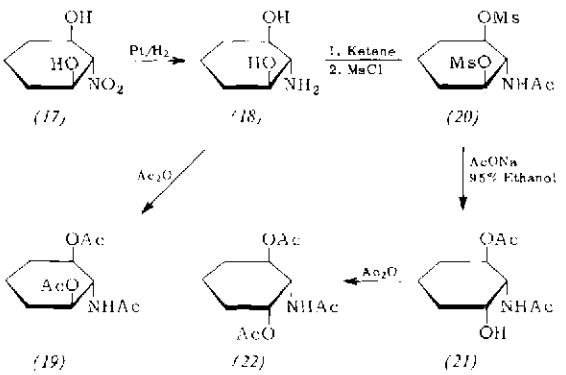



## 3. 1,5-Dialdehydes

Glutaraldehyde *(15)* condenses with nitromethane in sodium carbonate solution to yield a mixture of isomeric 2-nitrocyclohexane-1,3-diols *(16)*, from which a chromatographically uniform isomer can be isolated in 51 % yield by extraction with ether. Three configurations (*trans*, DL, and *cis*) are theoretically possible, but the compound was assigned the *trans*-configuration *(17)* on the basis of NMR evidence [25].




The diacetate of *(16)* gives a sharp peak in the NMR spectrum at 7.99 τ, which indicates two equatorial acetoxy groups. The triacetate *(19)*, obtained by hydrogenation of *(17)* followed by acetylation, shows a doublet with a 2:1 intensity ratio in this region – a proof of the equatorial position of the two acetoxy (7.95 τ) and the acetamino (8.07 τ) groups.




The inversion of sulfonic ester groups which are *trans* to a vicinal acetamido group [26] has repeatedly been used [31,51 55] as a chemical proof of an all-*trans*-configuration, such as

[18] On the basis of its infrared spectrum, the dinitrate, which has four theoretically possible configurations, is assigned configuration *(8)* (esterification of equatorial hydroxyl groups in the 3,6-position [19]).

[19] *E. R. Bissel*, General Chemistry Technical Note Nr. 45 (1961), Lawrence Radiation Laboratory, Livermore, California.

[20] All NMR data are given in τ values [*G. V. D. Tiers*, J. physic. Chem. *62*, 1151 (1958)].

[21] *H. O. L. Fischer*, *E. Baer*, and *H. Nidecker*, Helv. chim. Acta *18*, 1079 (1935).

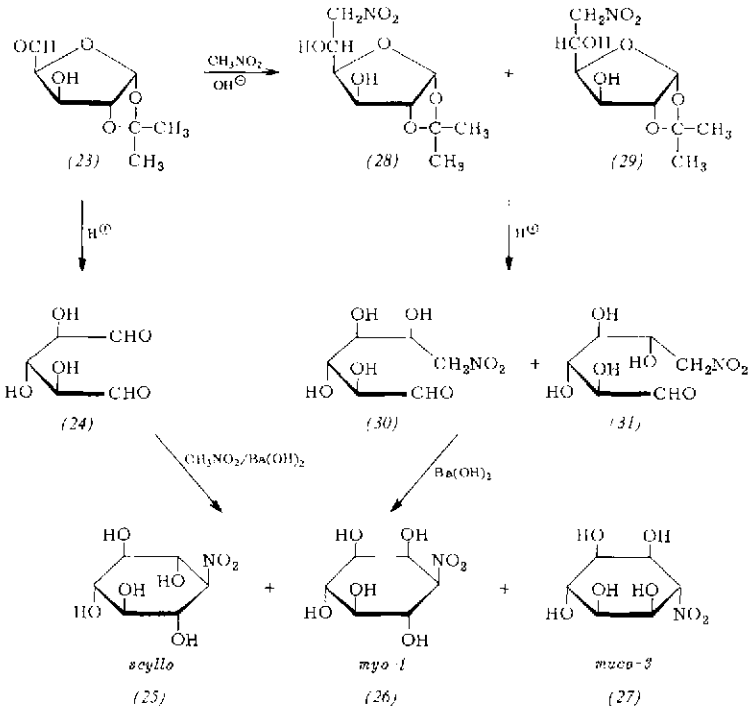
[22] In his Ph. D. Thesis (University of Basel, 1937), *H. Nidecker* described the reaction of *(10)* with barium hydroxide, but did not obtain definite products on subsequent acidification of the barium salt formed in the reaction. In the preparation of the diethylacetal of *(10)* from glyoxal semiacetal and nitromethane, he obtained 2,5-dinitrophenol as a by-product. Undoubtedly, under the conditions of the reaction (20 min at 110 °C in concentrated potassium carbonate solution), the acetal groups were partially hydrolysed, so that 2,5-dinitrophenol was produced via the intermediates *(10)*, *(11)*, *(2)* and subsequent aromatization of *(2)*.

[23] *F. W. Lichtenthaler*, unpublished results.

[24] *S. J. Angyal*, personal communication (January 25th, 1962).

[25] *F. W. Lichtenthaler*, Angew. Chem. *73*, 654 (1961); Chem. Ber. *96*, 845 (1963).

[26] *G. E. McCasland*, *R. K. Clark*, *Jr.*, and *H. E. Carter*, *J.* Amer. chem. Soc. *71*, 637 (1949); *S. Winstein* and *R. Boschan*, ibid. *72*, 4669 (1950); *B. R. Baker* and *R. E. Schaub*, J. org. Chemistry *19*, 646 (1954); J. Amer. chem. Soc. *77*, 5902 (1955); *B. R. Baker*, *R. E. Schaub*, and *J. H. Williams*, ibid. *77*, 9 (1955); *R. E. Schaub* and *M. J. Weiß*, ibid. *80*, 4683 (1958); *R. W. Jeanloz* et al., ibid. *79*, 2591, 4215 (1957); J. org. Chemistry *26*, 532, 537 (1961); *J. F. Codington*, *R. Fecher*, and *J. J. Fox*, ibid. *27*, 163 (1962); *W. Meyer zu Reckendorf* and *W. A. Bonner*, Chem. Ber. *95*, 996, 1917 (1962).



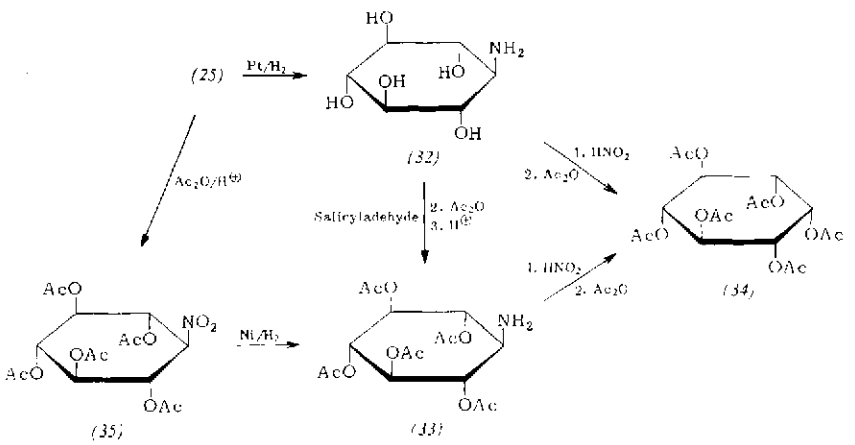
that shown in *(18)*. When this procedure was applied to the *N*-acetyl dimesylate *(20)*, both mesyl groups were indeed eliminated, but the expected *N*-acetyl-*cis*-diol was not obtained. Instead, the product was 3-*O*-acetyl-DL-2-acetamidocyclohexane-1,3-diol *(21)*. The DL-structure was established on the basis of the NMR spectra of *(21)* and *(22)*. The acetyl signals at 7.90, 7.97, and 8.08 τ indicate an axial and an equatorial acetoxy group adjacent to the equatorial acetamido group. Thus, in the case of the dimesylate *(20)*, one mesyl group was eliminated with inversion, the other with retention of configuration, apparently because of the greater mobility of the cyclohexane ring in comparison with the more highly substituted systems of *(36)*, *(75)*, and *(92)* [25].

*xylo*-Trihydroxyglutaraldehyde *(24)* [27], which is obtained from 1,2-isopropylidene-α-D-glucofuranose by oxidation with periodate [28] to *(23)* and removal of the acetone moiety of *(23)* in acidic solution [29,30], undergoes condensation with nitromethane and barium hydroxide to yield a mixture of *aci*-nitro barium salts. On acidification, these yield three deoxynitroinositols with *scyllo*- *(25)*, *myo*-1- *(26)*, and *muco*-3-configurations *(27)*, respectively [30]. The same mixture of isomers had been prepared earlier [12,31] by condensation of *(23)* with nitromethane to form *(28)* and *(29)*, followed by hydrolytic removal of the isopropylidene group to yield a mixture of 6-deoxy-6-nitrohexoses having the L-ido- *(30)* and D-*gluco*-configurations *(31)* [32] and, finally, intramolecular cyclization of the latter with barium hydroxide. If the cyclization of the dialdehyde *(24)* or of the nitrohexose mixture *(30)* *(31)* is carried out with sodium hydroxide, the nitroinositol mixture contains only the *scyllo* *(25)* and *myo*-1 *(26)* isomers [12,30].

The proof of the configurations of the three deoxynitroinositols *(25)*, *(26)*, and *(27)* is based on the following data.

1. Deoxynitro-*scyllo*-inositol *(25)*: Hydrogenation in acidic solution yields an inosamine identical with the *scyllo*-inosamine *(32)* prepared by other means [33,34]. Furthermore, *(32)* can be converted by direct deamination [34] (8 % yield) or, better, by deamination of its penta-*O*-acetyl derivative *(33)* and subsequent acetylation (70 % yield) into hexaacetyl-*myo*-inositol *(34)* [35,36]. The reaction sequence: *(23)* → *(28)* + *(29)* → *(30)* + *(31)* → *(25)* → *(32)* → *(33)* → *(34)* [35], as well as its simplification [36] in the last steps, *i.e.* *(25)* → *(35)* → *(33)* → *(36)*, has been used for the preparation of [2-$^{14}$C]*myo*-inositol by introducing $^{14}$C-labelled nitromethane at the step *(23)* → *(28)* + *(29)*.

2. 1-Deoxy-1-nitro-DL-*myo*-inositol *(26)*: The inosamine obtained by catalytic hydrogenation of *(26)* in acidic medium differed in chromatographic behavior from the *scyllo*-, *myo*-2-, *myo*-4-, *neo*-2-, and *muco*-3-isomers, but was identical



[27] In solution, *(23)* probably exists predominantly in a cyclic hemialdal form [cf. *R. D. Guthrie*, Advances Carbohydrate Chem. *16*, 105 (1961)].

[28] *R. Schaffer* and *H. S. Isbell*, J. Res. nat. Bur. Standards 56, 191 (1956).

[29] *K. Iwadare*, Bull. chem. Soc. Japan *16*, 40 (1941); Chem. Zbl. *1942*, I, 1753.

[30] *F. W. Lichtenthaler*, Angew. Chem. *75*, 93 (1963); Angew. Chem. internat. Edit. *1*, 662 (1962).

[31] *F. W. Lichtenthaler*, Chem. Ber. *94*, 3071 (1961).

[32] In the crystalline state *(31)* exists in the α-D-glucopyranose form. Its configuration was proved by its mutarotation from $[\alpha]_D$ = +45 ° to +25 ° [12]. Its infrared spectrum showed the presence of the pyranose ring: OH absorption at 3550 cm$^{-1}$ and, hence, the essentially complete absence of hydrogen bridges. If the furanose form were present, strong hydrogen bonds would exist between the nitro and the C-5 OH groups, resulting in a shift of the OH absorption to longer wavelengths; cf., for example, those in *(29)* (OH bands at 3530 and 3300 cm$^{-1}$) [23].

[33] *H. E. Carter*, *R. K. Clark, Jr.*, *B. Lythe*, and *G. E. McCasland*, J. biol. Chemistry *175*, 683 (1948); *L. Anderson* and *H. A. Lardy*, J. Amer. chem. Soc. *72*, 3141 (1950).

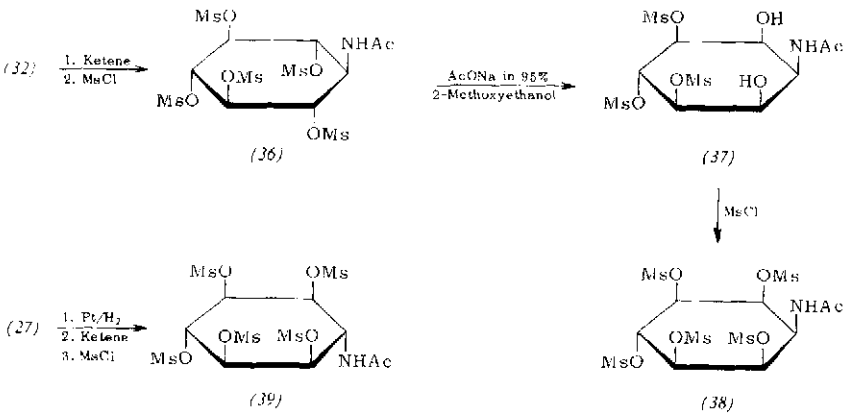
[34] *T. Posternak*, Helv. chim. Acta *33*, 1597 (1950).

[35] *T. Posternak*, *W. H. Schopfer*, and *R. Huguenin*, Helv. chim. Acta *40*, 1875 (1957).

[36] *G. J. Drummond*, *J. N. Aronson*, and *L. Anderson*, J. org. Chemistry *26*, 1601 (1961).

with the *myo*-1-inosamine prepared independently [37]. The NMR spectrum of the hexaacetate likewise indicated the *myo*-1-configuration [31].

3. 3-Deoxy-3-nitro-*muco*-inositol *(27)*: The formation of a di-*O*-isopropylidene compound from *(27)* demonstrated the presence of two *cis*-(e,a)-hydroxyl groups on each side of the ring above the plane, which is possible only with the *muco*-3- or the *epi*-3-configuration. The latter could be rejected, however, firstly because the penta-*O*-mesyl-*N*-acetyl derivative of *epi*-3-inosamine *(38)* – prepared from *scyllo*-inosamine *(32)* via *(36)* and *(37)* – was not identical with the pentamesylate *(39)* prepared from *(27)*, and secondly, because good agreement in physical properties was observed between genuine hexaacetyl-*muco*-3-inosamine synthetized independently [38] and the compound obtained from *(27)* by hydrogenation and acetylation.




## II. Cyclization of "Sugar Dialdehydes"

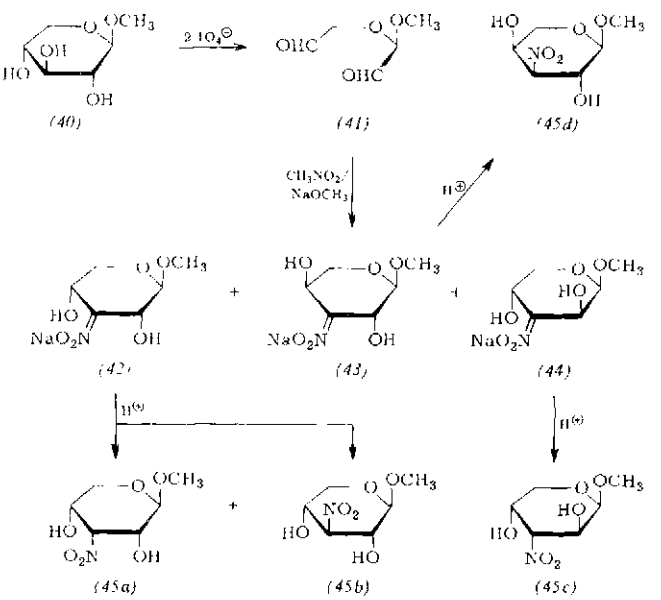
### 1. L′-Methoxydiglycolaldehyde

L′-Methoxydiglycolaldehyde *(41)*, which is easily obtainable by periodate oxidation of methyl β-D-xylopyranoside *(40)* [39], cyclizes smoothly with nitromethane/sodium methoxide in aqueous alcohol. The product is a mixture of isomeric sodium salts of methyl 3-*aci*-nitro-3-deoxy-β-D-pentoside, from which one isomer can be isolated in crystalline form in 43 % yield. Configuration *(42)* must be ascribed to this isomer, since the nitropentoside mixture obtained on acidification by trituration with solid potassium hydrogen sulfate consists predominantly of methyl 3-deoxy-3-nitro-β-D-riboside *(45a)* plus an admixture of some 3-nitroxyloside *(45b)* [14]. In the mother liquors remaining after removal of *(42)* there are two other *aci*-nitro salts of configurations *(43)* and *(44)*, respectively. These were not isolated, but their existence is established by the formation of methyl 3-deoxy-3-nitro-β-D-arabinoside *(45c)* and methyl 3-deoxy-3-nitro-α-L-arabinoside *(45d)* on acidification [40].

Proof of the configurations of these compounds was based on comparison of the 3-aminopentosides obtained therefrom by catalytic hydrogenation with the corresponding known [41, 42] 3-amino sugar derivatives.

There are four theoretically possible *aci*-nitro salts. Since one of these, namely *(42)*, is formed in 43 % yield, this cyclization possesses a considerable stereospecificity. The preferred equatorial orientation of the hydroxyl group on C-2 in *(42)* and in its derivatives *(45a)* and *(45b)* is attributable to the effect of the substituents at C-1 and can be deduced from Cram's rule [43]. However, no similar directing effect applies in the orientation of the hydroxyl on C-4; thus the *aci*-nitro salts present in the condensation solution would be expected to contain a compound with an axial hydroxyl on C-4 besides compound *(42)*, whose 4-hydroxyl is equatorial. This prediction is confirmed by the occurrence of *(45d)* in the nitropentoside mixture.

On the other hand, the steric course of the acidification of the *aci*-nitro salt *(42)* is surprising. In contrast to all




[37] *G. G. Post*, Ph. D. Thesis, University of Wisconsin, 1959; *S. J. Angyal* and *L. Anderson*, Advances Carbohydrate Chem. *14*, 207 (1959).

[38] *M. Nakajima*, *N. Kurihara*, and *A. Hasegawa*, Chem. Ber. *95*, 141 (1962).

[39] *E. L. Jackson* and *C. S. Hudson*, J. Amer. chem. Soc. *59*, 994 (1937); *63*, 1229 (1941).

[40] *H. H. Baer* and *A. Ahamad*, Canad. J. Chem. *41*, 2931 (1963).

[41] *G. W. Waller*, *P. W. Fryth*, *B. L. Hutchings*, and *J. H. Williams*, J. Amer. chem. Soc. *75*, 2025 (1953); *B. R. Baker* and *R. E. Schaub*, J. org. Chemistry *19*, 646 (1954); *B. R. Baker*, *R. E. Schaub*, and *J. H. Williams*, J. Amer. chem. Soc. *77*, 7 (1955).

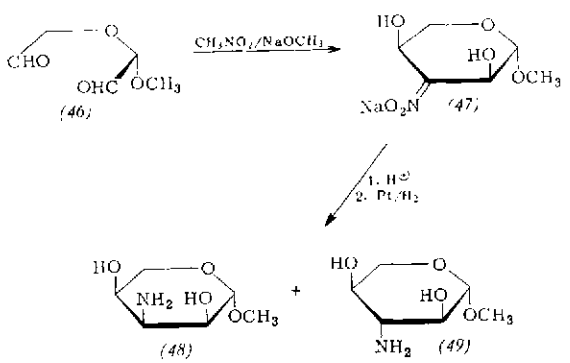
[42] *R. E. Schaub* and *M. J. Weiß*, J. Amer. chem. Soc. *80*, 4683 (1958); *C. D. Anderson*, *L. Goodman*, and *B. R. Baker*, ibid. *80*, 5247 (1958).

[43] *G. Baschang*, Liebigs Ann. Chem. *663*, 167 (1963).

other nitromethane cyclizations previously investigated, which yield products having equatorial nitro groups, the main product of acidification of *(42)* is not the all-equatorial *xylo*-compound *(45b)*. Instead, the product is *(45a)*, which has an axial nitro group. This phenomenon has not as yet been explained.

### 2. D'-Methoxydiglycolaldehyde

A stereochemically analogous course is followed in the cyclization of D'-methoxydiglycolaldehyde *(46)*, which is obtained from methyl α-D- or β-L-pentopyranosides by oxidation with periodate [39]. Condensation with nitromethane/sodium methoxide yields a mixture of *aci*-nitro salts, from which a uniform isomer can be isolated in crystalline form. It has configuration *(47)*, since on acidification and subsequent catalytic hydrogenation it is converted into methyl 3-amino-3-deoxy-β-L-ribopyranoside *(48)* and methyl 3-amino-3-deoxy-β-L-xylopyranoside *(49)* [14]. Acidification of the mother liquor remaining after isolation of *(47)* results in isolation of two further isomers. These are the β-L- and α-D-arabinopyranoside derivatives [40].

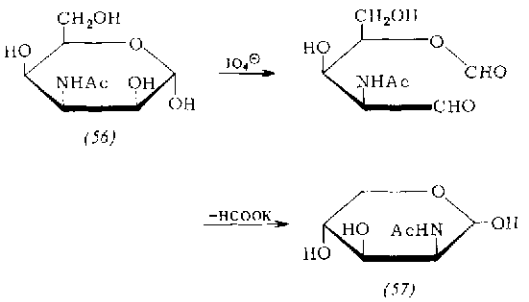


### 3. D'-Methoxy-D-hydroxymethyldiglycolaldehyde

The dialdehyde *(51)*, which is readily accessible by periodate oxidation of methyl α-D-glucopyranoside *(50)* (or methyl α-D-pentopyranosides) [44] yields an *aci*-nitro compound upon condensation with nitromethane/sodium methoxide in methanolic solution. When the *aci*-nitro compound is acidified with a cation exchange resin, a mixture of isomeric methyl 3-deoxy-3-nitro-α-D-hexopyranosides *(52)* is obtained in 75 % yield. This mixture does not crystallize, but three crystalline 3-aminohexosides are formed on catalytic hydrogenation. These have the *manno- (53)*, *gluco- (54)*, and *talo- (55)* configurations [45,46].

The three compounds were isolated and their configurations determined in the following manner [45,46]:

Methyl-3-amino-3-deoxy-α-D-mannopyranoside *(53)*: A methyl 3-amino-3-deoxyhexoside crystallized in 33–36 % yield from the mixture of isomers obtained by hydrogenation of *(52)* [47]. On acid hydrolysis and *N*-acetylation, a 3-acetamido-3-deoxyhexose was obtained. This was identical with a 3-acetamido-3-deoxymannopyranose synthetized by independent means [48]. Methyl 3-amino-3-deoxy-α-D-gluco- and -D-talopyranosides *(54)* and *(55)*: The mother liquor remaining after removal of *(53)* was chromatographed on a cellulose column giving two crystalline 3-amino-3-deoxyhexoside hydrochlorides in addition to *(53)*. Acetylation of one of these hydrochlorides produced a tetraacetate identical with methyl 2,4,6-*O*-3-*N*-tetraacetyl-3-amino-3-deoxy-α-D-glucopyranoside [49]. The other aminohexoside hydrochloride was subjected to hydrolysis with acid and *N*-acetylation, giving *(56)*, which was oxidized with periodate to *N*-acetyl-D-lyxosamine *(57)*. Since the reaction conditions were such that *(57)* could have been produced only from 3-acetamido-3-deoxy-D-talose or -galactose, and since the latter possesses different physical properties, the isomer in question must have the *talo*-configuration *(55)*.



[44] Compounds *(51)* and *(63)* do not exist in the open-chain dialdehyde form, but have either a hemiacetal or a hemialdal structure [cf. *R. D. Guthrie*, Advances Carbohydrate Chem. *16*, 124 (1961)].

[45] *H. H. Baer* and *H. O. L. Fischer*, J. Amer. chem. Soc. *82*, 3709 (1960); *H. H. Baer*, Angew. Chem. *73*, 532 (1961).

[46] *H. H. Baer*, J. Amer. chem. Soc. *84*, 83 (1962).

[47] Larger quantities of *(53)* can be prepared by this method via the simplified procedure of *A. C. Richardson* [J. chem. Soc. (London) *1962*, 373]. This gives *(53)* in 20–30 % yield.

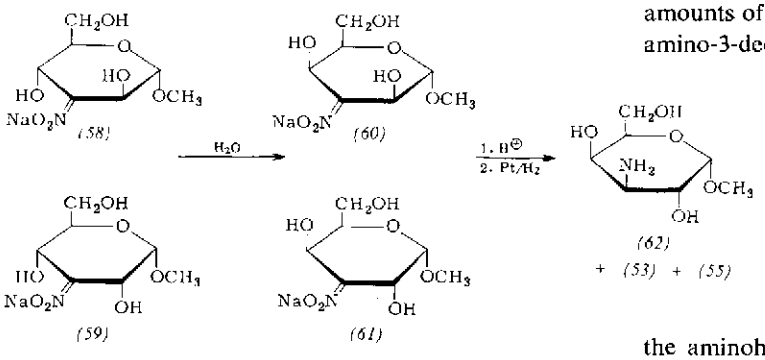
[48] *R. Kuhn* and *G. Baschang*, Liebigs Ann. Chem. *628*, 206 (1959).

[49] *S. Peat* and *L. F. Wiggins*, J. chem. Soc. (London) *1938*, 1810; *H. Ogawa*, *T. Ito*, *S. Kondo*, and *S. Inoue*, Bull. agric. chem. Soc. Japan *23*, 289 (1959); *R. D. Guthrie*, Proc. chem. Soc. (London) *1960*, 387.

Condensation of *(51)* with nitromethane and potassium bicarbonate in aqueous solution yielded a mixture of nitrohexosides of similar composition. After catalytic hydrogenation, the 3-aminomannoside *(53)* was isolated in 23–31 % yield, while *(54)* was obtained in 30 % yield in the form of its tetraacetate. Further column chromatographic fractions which also contained *(54)* brought its total yield up to about 60 % [46].

An aminohexoside mixture of totally different composition is obtained if *(51)* is condensed with nitromethane and sodium methoxide in methanol and the resulting *aci*-nitro salt comprising mostly *(58)* and *(59)* – is dissolved in water. Over a period of 90 hours, mutarotation from $[\alpha]_D = +4.33°$ to $+5.95°$ takes place. Acidification and catalytic hydrogenation yielded only 10–12% of the 3-aminomannoside *(53)* plus traces of *(54)*; the major products were *(55)* and a new isomer, methyl 3-amino-3-deoxy-α-D-galactopyranoside *(62)*, which were obtained in 40 % and 30 % yields, respectively. Thus, it must be concluded that the dissolution of the mixture of *(58)* and *(59)* in water resulted in extensive epimerization at C-4 to give *(60)* and *(61)*. The mechanism of this reaction, which is probably induced by the change in pH, has not yet been explained [46].

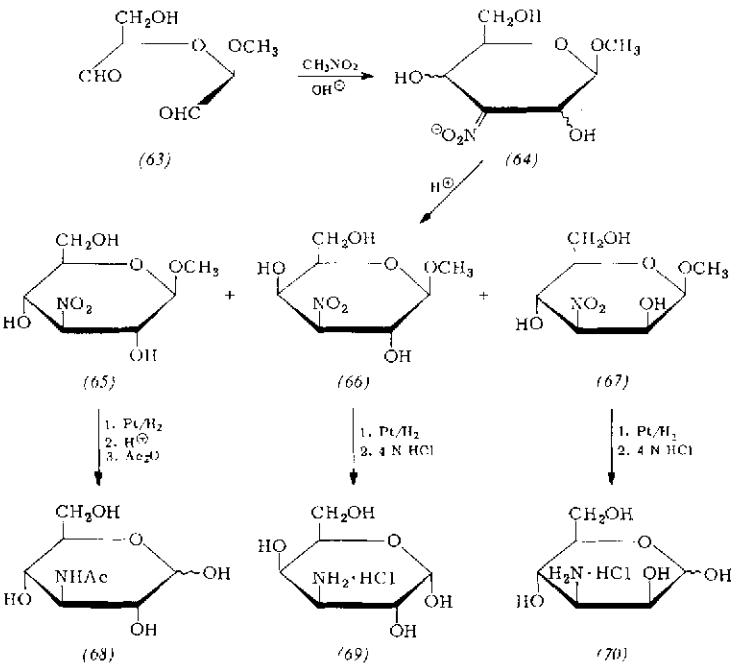
As far as the steric course of the cyclization is concerned, the configurations at C-2 and C-4 in the main product should be predictable from Cram's rule [43]. Application of the rule to the dialdehyde *(57)* indicates that the most favorable isomer is the *aci*-nitro salt having the *manno*-(*altro*)-configuration *(58)*; *i.e.* the nitrohexoside mixture obtained on acidification should contain principally the mannoside or altroside isomers. However, the yields of aminohexosides actually isolated show that the nitrohexoside mixture obtained by direct condensation contains only about 30 % of the mannoside isomer, the main product (60 %) being the glucoside compound.



The acidification of the *aci*-nitro salt mixture, however, proceeds via a definite stereochemical path. Whether obtained directly by condensation or by subsequent epimerization, the exclusive products are nitro- or aminohexosides with *manno*-, *gluco*-, *talo*-, and *galacto*-configurations, *i.e.* compounds with equatorial nitro or amino groups. No C-3 epimeric compounds with *altro*-, *allo*-, *ido*-, and *gulo*-configurations, *i.e.* with the nitro group in the axial orientation, are formed. Thus, the nitro group obtained by acidification of the *aci*-nitro salts preferentially assumes the equatorial position; *i.e.* the proton is attached from the axial side [46].

### 4. L'-Methoxy-D-hydroxymethyldiglycolaldehyde

The dialdehyde *(63)* which is obtained by oxidation of methyl β-D-hexopyranosides or methyl β-D-pentofuranosides with periodate [44] can be cyclized analogously with nitromethane. A mixture of isomeric 3-nitrohexosides is formed via the *aci*-nitro salt *(64)*. The composition of the mixture varies, depending on the solvent or condensing agent used [50a, b].



On condensation with sodium methoxide in methanol and subsequent acidification with cation exchange resin, the product crystallizing in 40 % yield from the mixture of nitrohexoside isomers is methyl 3-deoxy-3-nitro-β-D-glucopyranoside *(65)*. The residue contains large amounts of the galactoside isomer *(66)*, since methyl 3-amino-3-deoxy-β-D-galactoside *(69)* was isolated from the aminohexoside mixture after hydrogenation [50a]. Cyclization with potassium bicarbonate in water proceeds via a stereochemically similar path since it was possible to isolate 32 % of the nitroglucoside *(65)* after acidification of the nitrohexoside mixture [50a].

On the other hand, if the *aci*-nitro salt mixture obtained by condensation with sodium methoxide in methanol is allowed to stand in water before acidification, or if the cyclization is conducted from the outset in aqueous solution in the presence of a molar equivalent of sodium hydroxide, then only 25 % of the nitroglucoside *(65)* can be isolated. The major product becomes methyl 3-deoxy-

[50a] *H. H. Baer*, Chem. Ber. *93*, 2865 (1960).

3-nitro-β-D-galactoside *(66)* – 34 % yield of crystals – along with about 13% methyl 3-deoxy-3-nitro-β-D-mannoside *(67)*.

The configurations of the three nitrohexosides were determined in the following manner [50b, 51].

Methyl 3-deoxy-3-nitro-β-D-glucopyranoside *(65)*: Catalytic hydrogenation of *(65)* yielded an aminohexoside, which was converted by acid hydrolysis and *N*-acetylation into an *N*-acetate identical with 3-amino-3-deoxy-D-glucose *(68)* (*N*-acetylkanosamine [52]). In addition, *(68)* was transformed by periodate oxidation and alkaline hydrolysis into the known compound *N*-acetyl-β-D-arabinosamine.

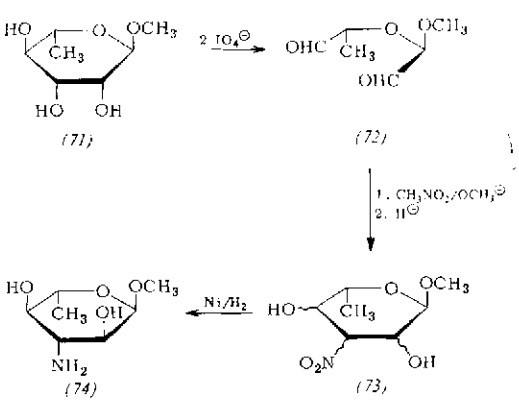
Methyl 3-deoxy-3-nitro-β-D-galactopyranoside *(66)*: In this case, catalytic hydrogenation followed by acid hydrolysis gave a 3-aminohexose hydrochloride, which was identical with the known compound [53] 3-amino-3-deoxy-D-galactose hydrochloride *(69)*.

Methyl 3-deoxy-3-nitro-β-D-mannopyranoside *(67)*: The *manno*-configuration of this isomer was established from the identity of the product of its hydrogenation and acid hydrolysis with the 3-amino-3-deoxy-D-mannose hydrochloride *(70)* obtained by other means [45].

Cram's rule [43] predicts that the cyclization of dialdehyde *(63)* should yield the *gluco*-isomer *(65)* as the principal component of the nitrohexoside mixture. The fraction actually obtained (40 %) in condensations with potassium bicarbonate and sodium methoxide agrees well with this prediction.

### 5. L'-Methoxy-L-methyldiglycolaldehyde

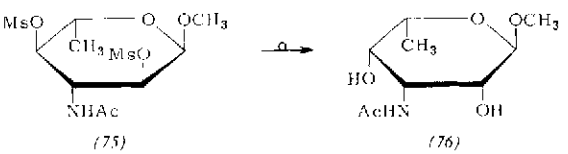
Dialdehyde *(72)* is readily prepared by periodate oxidation of methyl-α-L-rhamnoside *(71)* [54]. Nitromethane condensation of *(72)* with sodium methoxide, followed by acidification (addition of cation exchange resin in the $H^+$ form), yielded a 3-nitropyranoside mixture *(73)* which failed to crystallize. Catalytic hydrogenation of the mixture on Raney nickel gave a mixture of 3-aminopyranosides, from which methyl 3-amino-3,6-dideoxy-α-L-glucoside *(74)* crystallized in 25–31 % yield [based on *(71)*]. No other crystalline compounds have as yet been isolated from the mother liquor of *(74)* [55a, 55b].




The L-*gluco*-configuration of *(74)* was established from the following data [55a, 55b]:

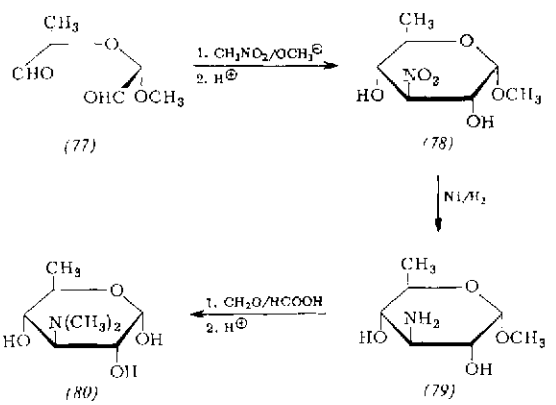
1. The NMR spectrum of the triacetate of *(74)* showed the peak distribution expected for the L-*gluco*-configuration, with signals at 8.10 τ (equatorial acetamido group) and at 7.91 and 7.93 τ (two equatorial acetoxy groups). Furthermore, the NMR signals of the two epimeric tetraacetyl-3-amino-3,6-dideoxypyranoses formed from *(74)* by hydrolysis with acid and acetylation are explainable only by assuming *gluco*-configuration for *(74)*.

2. The *N*-acetyl-2,4-di-*O*-mesyl derivative *(75)* is obtained from *(74)* by *N*-acetylation and subsequent mesylation. Inversion of mesyl groups, which are *trans* to an acetamido group causes elimination of the mesyl groups [26, 31]. Such elimination occurs with *(75)*, hence, both its sulfonic ester groups must be *trans* to the acetamido group, a requirement which is consistent only with the L-*gluco*- or L-*ido*-configuration. Comparison of the molecular rotation of *(74)* and that of the *N*-acetate and triacetate of *(74)* with the $[M]_D$ values of related gluco- and idopyranosides excluded the L-*ido*-configuration. Hence, *(75)* possesses the L-*gluco*-, and *(76)* the L-*talo*-configuration.




### 6. D'-Methoxy-D-methyldiglycolaldehyde

Application of the nitromethane cyclization to the corresponding dialdehyde of the D-series *(77)* [54], prepared by periodate oxidation of methyl 6-deoxy-α-D-glucoside, resulted in a mixture of isomeric 3-nitropyranosides. This contained at least 25 % of the 3-nitroglucoside *(78)*, since catalytic hydrogenation produced methyl 3-amino-3,6-dideoxy-α-D-glucoside *(79)*. The infrared spectrum of the latter was identical with that of *(74)* [56]. Dimethylation of the amino group with formaldehyde/formic acid followed by acid hydrolysis produced *(80)* in good yield. Since *(80)* was identical with the amino sugar derivative mycaminose isolated from





[50b] *H. H. Baer*, J. Amer. chem. Soc. *83*, 1882 (1961).

[51] *H. H. Baer* and *F. Kienzle*, Canad. J. Chem. *41*, 1606 (1963).

[52] *M. J. Cron, D. L. Evans, F. M. Palermiti, D. F. Whitehead, I. R. Hooper, P. Chu*, and *R. U. Lemieux*, J. Amer. chem. Soc. *80*, 4741 (1958).

[53] *R. Kuhn* and *G. Baschang*, Liebigs Ann. Chem. *636*, 164 (1960).

[54] The dialdehydes *(72)* and *(77)* are not open-chain compounds, but possess the hemidial structure [cf. *I. J. Goldstein, B. A. Lewis*, and *F. Smith*, J. Amer. chem. Soc. *80*, 939 (1958)].

[55a] *A. C. Richardson*, Proc. chem. Soc. (London) *1961*, 255.

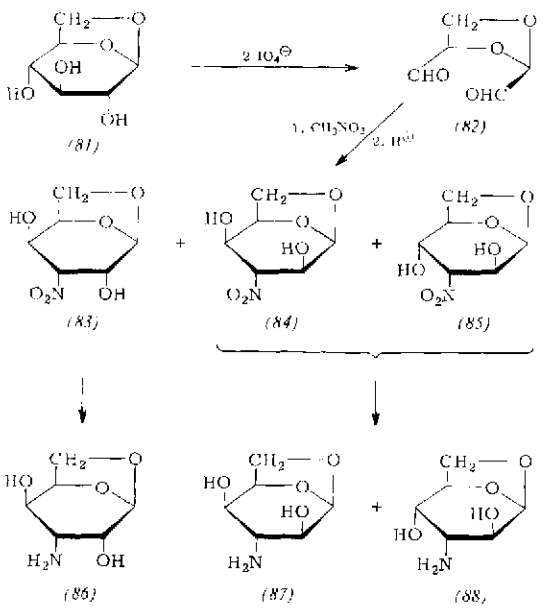
[55b] *A. C. Richardson* and *K. A. McLauchlan*, J. chem. Soc. (London) *1962*, 2499.

[56] *A. C. Richardson*, Proc. chem. Soc. (London) *1961*, 430; J. chem. Soc. (London) *1962*, 2758.

the antibiotic magnamycin [57], its configuration is established as 3-dimethylamino-3,6-dideoxy-D-glucose *(80)* [56].

### 7. cis-1,3-Dioxolan-2,4-dicarboxaldehyde

This dialdehyde *(82)* is readily obtainable by periodate oxidation of levoglucosan *(81)* [58]. Cyclization with nitromethane/sodium methoxide and subsequent acidification produced a mixture of 3-nitrohexosans having the *gulo- (83)*, *ido- (84)*, and *altro- (85)* configurations [59].

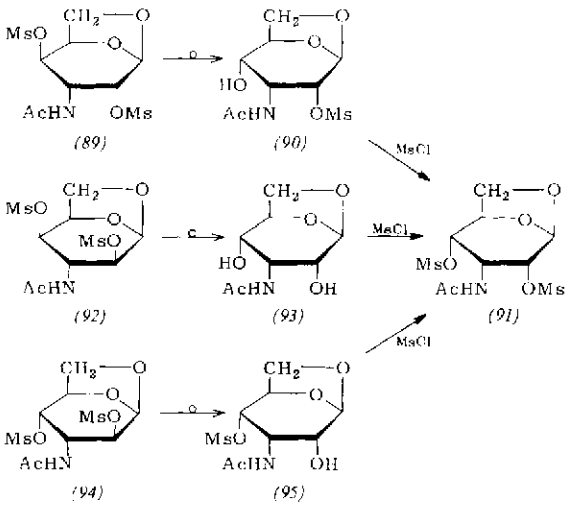


The isolation of and assignment of configuration to the nitro compounds *(83)*, *(84)*, and *(85)* or the corresponding amino derivatives were carried out as follows [59]:

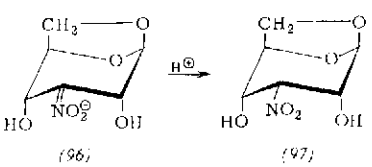
1,6-Anhydro-3-deoxy-3-nitro-β-D-gulopyranose *(83)*: A crystalline isomer was isolated from the 3-nitrohexosan mixture in 13.5 % yield [based on *(81)*]. Catalytic hydrogenation of this isomer yielded a 3-aminohexosan *(86)*, whose optical rotation indicated the D-*gulo*-configuration. The exact proof was accomplished by inversion of the mesyl group *trans* to a vicinal acetamido group [26,31]. The required 3-*N*-acetyl-2,4-di-*O*-mesyl derivative *(89)* is easily prepared from *(86)* by *N*-acetylation and subsequent *O*-mesylation. The *O*-mesyl group at C-4 was eliminated by heating with sodium acetate in 95 % 2-methoxyethanol, 3-acetamido-2-*O*-mesyl-allosan *(90)* being formed. The product of mesylation *(91)* of this compound was identical with 1,6-anhydro-3-acetamido-3-deoxy-2,4-di-*O*-mesyl-β-D-allopyranose *(91)*, which was also obtained in a similar way from *(92)* and *(94)*.

1,6-Anhydro-3-amino-3-deoxy-β-D-idopyranose *(87)*: Compound *(84)* was present in the nitrohexosan mixture to the extent of at least 7.5 %, since catalytic hydrogenation of the mother liquor remaining after removal of *(86)* gave a 7.5 % yield of 3-aminoidosan *(87)*. Since the product of acetylation of *(87)* was identical with the triacetate of *(87)* which was prepared by other means [60], and since demesylation of the 3-*N*-acetyl-2,4-di-*O*-mesyl derivative *(92)* gave 3-acetamido-allosan *(93)*, compound *(87)* must have the *ido*-configuration.

1,6-Anhydro-3-amino-3-deoxy-β-D-altropyranose *(88)*: Acidification with HCl of the aminohexosan mixture remaining after isolation of *(87)* resulted in crystallization of the hydrochloride of *(88)* in 15 % yield [based on *(81)*]. The altro pyranose structure was indicated by comparison of *(88)* with a genuine sample [61], as well as by conversion of the 3-*N*-acetyl-2,4-di-*O*-mesyl derivative *(94)* into the 3-aminoallosan derivatives *(95)* and *(91)*.



The fact that only cyclization products with *gulo- (83)*, *ido- (84)*, and *altro- (85)* configurations were isolated, as well as the relative proportions of the individual isomers in the mixture, leads to some interesting stereochemical conclusions [59]. Since the dialdehyde *(82)* is relatively rigid because of the 1,6-anhydro bridge, one would expect the substituents at C-6 and C-1 (vicinal to the aldehyde groups) to have a much greater effect here on the configuration at C-2 and C-4 than the corresponding substituents in the cyclization of dialdehydes derived from simple hexoses or pentoses. Thus, according to



Cram's rule [43], the most probable product of cyclization would be 3-*aci*-nitro-3-deoxy-*allo(gulo)*hexosan *(96)*, in which both hydroxyl groups are axial. In addition, the nitro group should assume the equatorial position on acidification. Thus, the principal product should be the *allo*-isomer *(97)*. The *gulo* and *altro*-isomers, each have one equatorial hydroxyl group and should occur in smaller, but approximately equal amounts, while the *ido*-compound, with its two equatorial hydroxyl groups, should be formed in only very small yield. Although a compound with the *allo*-configuration *(97)* has not been isolated from the products of cyclization, the observed ratio of the other three isomers supports the above assumptions. The yields of *gulo-* and *altro*-compounds amounted to about 15 % each, while that of the *ido-*

[57] *F. A. Hochstein* and *K. Murai*, J. Amer. chem. Soc. *76*, 5080 (1954); *F. A. Hochstein* and *P. P. Regna*, ibid. *77*, 3353 (1955).

[58] *E. L. Jackson* and *C. S. Hudson*, J. Amer. chem. Soc. *62*, 958 (1940).

[59] *A. C. Richardson* and *H. O. L. Fischer*, Proc. chem. Soc. (London) *1960*, 341; J. Amer. chem. Soc. *83*, 1132 (1961).

[60] *S. P. James*, *F. Smith*, *M. Stacey*, and *F. Wiggins*, J. chem. Soc. (London) *1946*, 625.

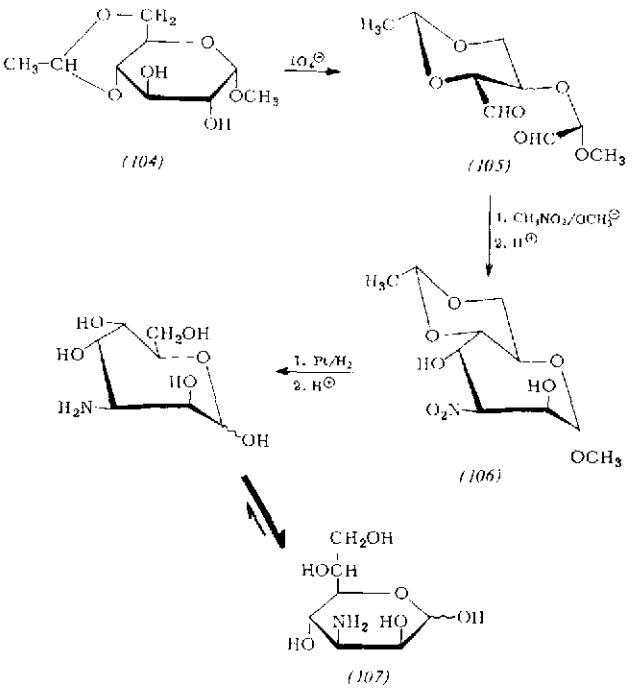
[61] *L. F. Wiggins*, J. chem. Soc. (London) *1947*, 18.

hexosane was 8 %. It is, therefore, probable that the remaining 60 % of the condensation mixture contained a considerable amount of the *allo*-isomer *(97)*.

### 8. 2-Hydroxymethyl-cis-1,3-dioxolan-2,4-dicarboxaldehyde

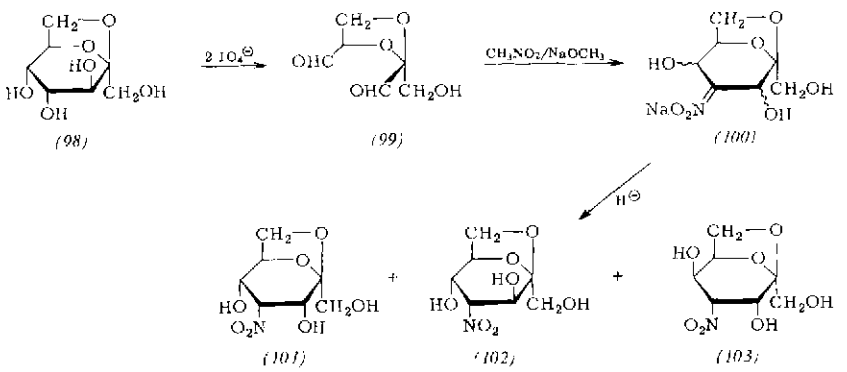
The dialdehyde *(99)*, which is related to *(82)* and which is readily obtainable from sedoheptulosan *(98)* by periodate oxidation, also undergoes cyclization with nitromethane. The condensation carried out with sodium methoxide in methanol affords a mixture of isomeric *aci*-nitro salts *(100)*, which can be partially isolated in crystalline form. When treated with a cation exchange resin in the $H^+$ form, the mixture yields a total of three pure 2,7-anhydro-4-nitro-4-deoxy-D-D-heptulosans [62]. The NMR spectra of the tetraacetyl-4-amino-4-deoxyheptulosans obtained on catalytic hydrogenation and acetylation show that the compounds have the *allo*- *(101)*, *altro*- *(102)*, and *gulo*- *(103)* configurations [62a].

The cyclization with nitromethane can also be carried out in aqueous solution in the presence of a molar equivalent of sodium hydroxide; the 4-nitroheptulosan mixture is then formed directly upon acidification [62].




*(104)* *(105)* *(106)* *(107)*

*(106)*, followed by acid hydrolysis, affords a syrup of 3-amino-3-deoxy-D-glycero-D-mannoheptopyranose *(107)*, which can, however, be crystallized as its *N*-acetate.



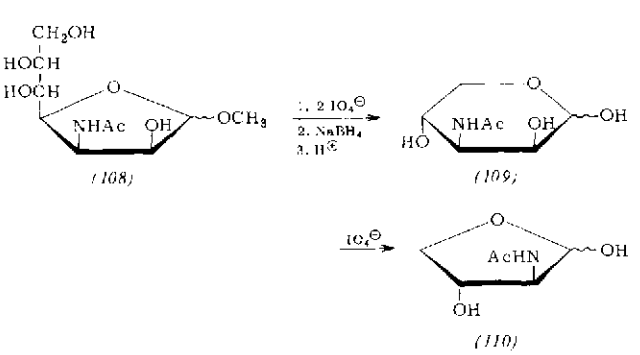

*(98)* *(99)* *(100)* *(101)* *(102)* *(103)*

### 9. Dialdehyde from Methyl 4,6-O-Ethylidene-α-D-glucoside

Cyclization of 1,6-dialdehydes by condensation with nitromethane should lead to seven-membered rings provided ring closure were to occur at all. Although such a cyclization has not yet been achieved with simple aliphatic dialdehydes, *Baschang* [43] was able to verify this hypothesis on the dialdehyde *(105)* obtained from methyl 4,6-*O*-ethylidene-α-D-glucoside *(104)* by periodate oxidation. On condensation of *(105)* with nitromethane/sodium methoxide and subsequent acidification with a cation exchange resin, he obtained a 41 % yield of a single nitroheptoside which has the configuration of methyl 3-deoxy-3-nitro-5,7-*O*-ethylidene-D-glycero-D-α-mannoseptanoside *(106)*. Catalytic hydrogenation of

On the basis of Cram's rule, the principal product of the condensation of *(105)* would be expected to have the D-*glycero*-D-*talo*- or the D-*glycero*-D-*manno*-configuration. The exact proof in favor of the D-*glycero*-D-*manno*-configuration for *(106)* and *(107)* was furnished by the following results [43]:

The optical rotation (mutarotation from +3 ° to −11 °) of the *N*-acetate of *(107)* was not identical with any of the four known 3-acetamidoheptoses. The chromatographic behavior of *(107)*, too, did not correspond to that of the 3-acetamidoheptoses. Of the four possible isomers remaining, three could




*(108)* *(109)* *(110)*

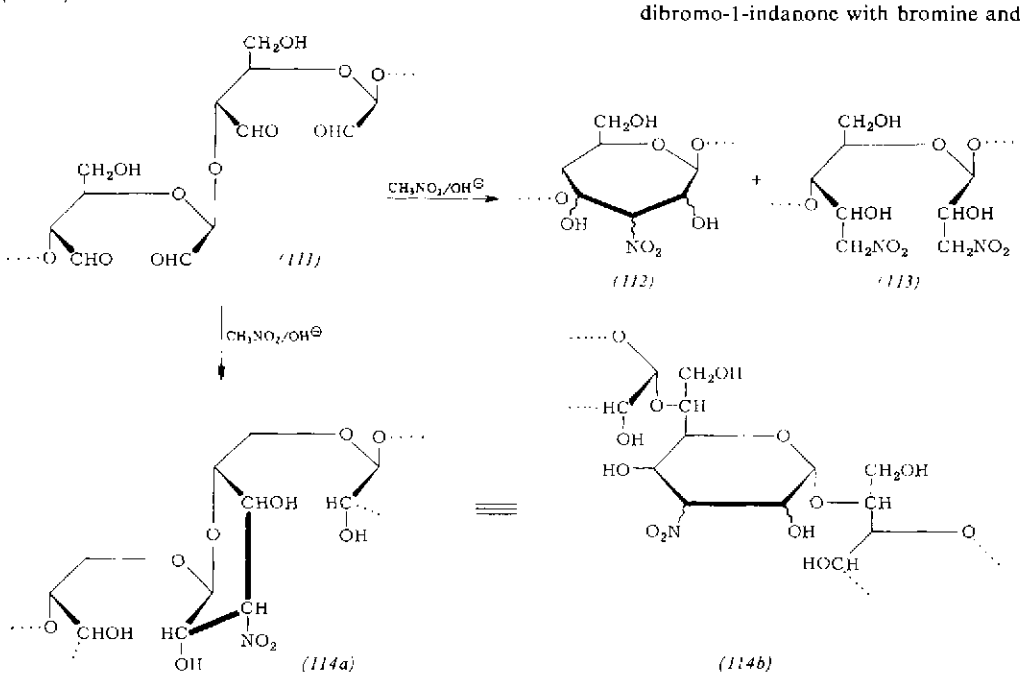
[62] *H. H. Baer*, J. org. Chemistry *28*, 1287 (1963).

[62a] *H. H. Baer*, Lecture at the General Meeting of the Gesellschaft Deutscher Chemiker in Heidelberg, September 1963; cf. Angew. Chem. *75*, 1124 (1963).

be eliminated by conversion of *(107)* into a derivative of 3-aminolyxose *(109)*: treatment of the *N*-acetate of *(107)* with methanolic HCl leads to a 3-acetamidoheptofuranoside *(108)*, subsequent periodate oxidation, reduction with sodium borohydride, and mild hydrolysis to a 3-acetamidopentose, whose *lyxo*-configuration *(109)* was proved by its chromatographic behavior as well as by periodate degradation to 2-acetamido-2-deoxy-D-threose *(110)*. These results can only be explained by assuming the D-*glycero*-D-*manno*-configuration for *(106)* and *(107)*.

### 10. Poly(dialdehydes) from Cellulose

Treatment of the poly(dialdehyde) *(111)* formed by periodate oxidation of cellulose with nitromethane and sodium hydroxide in aqueous solution gave products which contained 3.4–5.0 % nitrogen, depending on the concentration of alkali (0.32–1.44 %) and the reaction time at room temperature (20–48 hours). The structure of these products has not been defined unequivocally [63]. It was assumed that the major reaction was cyclization to a seven-membered ring *(112)*, together with the formation of products of the type *(113)* and of compounds resulting from condensation of two cellulose dialdehyde chains [63]. However, cyclization of the aldehyde groups of neighboring "glucose dialdehyde" units seems more likely. This would lead to the sterically more favorable six-membered ring. The condensation product *(114a)* formed in this way would then be a polysaccharide chain composed of D-heptopyranoside units *(114b)*.

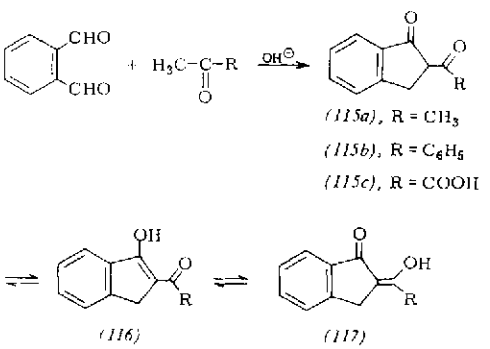



The condensation of starch dialdehyde with nitromethane had been investigated some time ago by *H. O. L. Fischer* and co-workers [64], but this also led to ill-defined products.

## III. Cyclization of Aromatic Dialdehydes

### 1. *o*-Phthalaldehyde

The studies of *Thiele* [65–67] on the condensation products of *o*-phthalaldehyde had shown that treatment with reactive methylene compounds such as acetone, acetophenone, and pyruvic acid resulted in ready cyclization, with formation of 2-acyl derivatives of 1-indanone *(115)*.




The condensation products give a positive ferric chloride reaction, which indicates at least partial existence of the enol forms *(116)* and *(117)*. The structures *(115)*, *(116)*, *(117)* for these compounds were proved by the following observations:

1. Being a β-diketone, *(115c)* is readily cleaved with alkali to give 1-indanone and oxalic acid, and can be resynthetized from the cleavage products [66, 68].

2. All three compounds *(115a)*, *(115b)*, and *(115c)* give 2,2-dibromo-1-indanone with bromine and alkali [65–67].

3. The NMR spectra of *(115b)* and *(115c)* and of the enol acetates of *(115b)* and *(115c)* show a signal around 6 τ which corresponds to the two protons of a $CH_2$ group [69].


[63] *Z. I. Kuznetsova, U. S. Ivanova*, and *N. N. Shorygina*, Dokl. Akad. Nauk SSSR *1962*, 2087.

[64] *J. S. Sowden*, Advances Carbohydrate Chem. *17*, 12 (1962).

[65] *J. Thiele* and *K. G. Falk*, Liebigs Ann. Chem. *347*, 112 (1906).

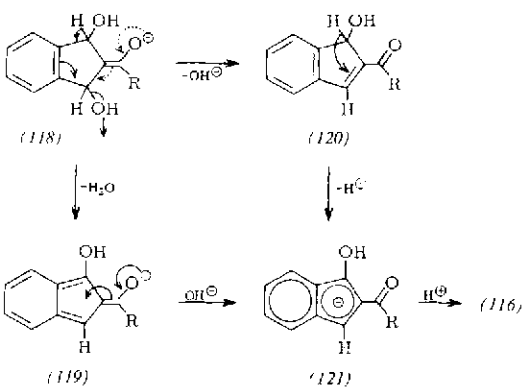
[66] *J. Thiele* and *J. Schneider*, Liebigs Ann. Chem. *369*, 287 (1909).

[67] *J. Thiele* and *E. Weitz*, Liebigs Ann. Chem. *377*, 1 (1910).

[68] *H. Leuchs* and *G. Kowalski*, Ber. dtsch. chem. Ges. *58*, 2289 (1925).

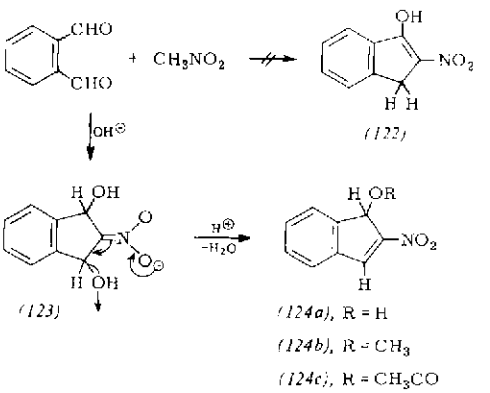
Compounds *(115)* ⇌ *(116)* ⇌ *(117)* are, however, not direct condensation products, but are produced by rearrangement following cyclization. The mechanism of this process can be readily explained by assuming that the primary cyclization product *(118)* is transformed in alkaline solution via the intermediates *(119)* or *(120)* into the stable indenyl anion *(121)*. The product formed from *(121)* on acidification, however, is not the 1-hydroxyindene derivative *(120)*, but the 3-derivative *(116)*.

The fact that the 3-hydroxyindene *(116)* must be the more stable compound is shown by the alkali-induced (and evidently irreversible) rearrangements of 1-alkylindene derivatives to the corresponding 3-alkylindenes [70]. These rearrangements may be readily explained by assuming the intermediate formation of an indenyl anion, just as in the case of formation of 1-alkylidene-3-hydroxyalkylindene derivatives by reaction of indene with benzaldehyde [71–73], *p*-nitro- or *p*-methoxybenzaldehyde [72], cinnamaldehyde [71], furfural [74], and acetone [75]. The rearrangement of 5-indenylhydroxyacetic acid to the 6-isomer proceeds by an analogous mechanism [76]. The same applies to the last step in the formation of terracinoic acid by alkaline degradation of terramycin [77].



In contrast, when *o*-phthalaldehyde is cyclized with nitromethane/alcoholic potassium hydroxide [67], the reaction product obtained on acidification with mineral acid is not 2-nitro-3-indenol *(122)* or its ketone, as would be expected by analogy to *(116)* [67, 78], but instead 2-nitro-1-indenol *(124a)*. This was shown unequivocally by the NMR spectra of compounds *(124a)*–*(124c)* [69].

The NMR peaks of *(124a)*, *(124b)*, and *(124c)* indicated four aromatic hydrogen atoms plus an olefinic proton at about $\tau$ = 2.1 and another signal, corresponding to one proton, at $\tau$ = 4.36 [*(124a)*], 4.53 [*(124b)*], and 3.16 [*(124c)*]. This

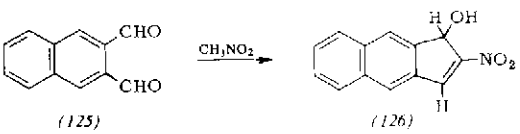


peak can only be ascribed to the α-proton of a secondary alcohol. If structure *(122)* were present, a signal would be observed at 6 $\tau$ corresponding to two protons, as required for a $CH_2$ group, in much the same manner as with *(115b)*.

Hence, the *o*-phthalaldehyde/nitromethane cyclization does not proceed via an indenyl anion. This is evidently due to the stronger electron attraction of the nitro group compared to the acyl residue *(118)*. Thus acidification of the primary cyclization product *(123)* with mineral acid leads to direct dehydration and formation of *(124a)*.

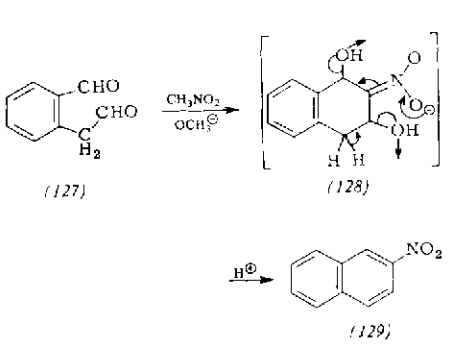
### 2. Naphthalene-2,3-dicarboxaldehyde

Like *o*-phthalaldehyde, naphthalene-2,3-dicarboxaldehyde *(125)* undergoes ready cyclization with nitromethane/sodium methoxide in dioxan to form 2-nitrobenzinden-1-ol *(126)* in 77 % yield upon acidification with mineral acid. Condensation with acetophenone gave 2-benzoylbenzinden-3-ol. The structure was again proved by NMR spectra [69].



### 3. Homophthalaldehyde

Owing to the ease of aromatization of the intermediate nitrotetralin-1,3-diol *(128)*, the condensation of homophthalaldehyde *(127)* with nitromethane led to 2-nitronaphthalene *(129)* in 25 % yield and auto-condensation




[69] *F. W. Lichtenthaler*, Tetrahedron Letters *1963*, 775.

[70] *C. Courtot*, C. R. hebd. Séances Acad. Sci. *160*, 523 (1915); Ann. Chimie *5*, 79 (1916).

[71] *J. Thiele*, Ber. dtsch. chem. Ges. *33*, 3395 (1900); *G. S. Whitby* and *M. J. Katz*, J. Amer. chem. Soc. *50*, 1170 (1928).

[72] *J. Thiele* and *A. Bühner*, Liebigs Ann. Chem. *347*, 258 (1906).

[73] *H.-M. Wüest*, Liebigs Ann. Chem. *415*, 303 (1918); *C. Courtot*, Ann. Chimie *4*, 199 (1915).

[74] *H.-M. Wüest*, Liebigs Ann. Chem. *415*, 318 (1918).

[75] *J. Thiele* and *K. Merck*, Liebigs Ann. Chem. *415*, 257 (1918).

[76] *C. F. Koelsch* and *R. A. Scheiderhauer*, J. Amer. chem. Soc. *65*, 2311 (1943).

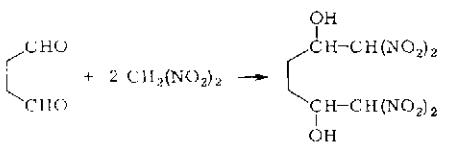
[77] *F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternak, P. N. Gordon, F. J. Pilgrim, K. J. Brunings*, and *R. B. Woodward*, J. Amer. chem. Soc. *75*, 5459 (1953).

[78] *R. D. Campbell* and *C. L. Pitzer*, J. org. Chemistry *24*, 1531 (1959).

products of *(127)* [69]. The mechanism proposed for the formation of *(129)* from *N*-methylisoquinolinium iodide and nitromethane [79] is thus proved to be correct.

## IV. Concluding Remarks

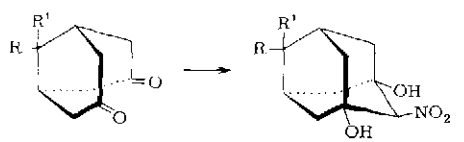
In view of the variety of modifications which the condensation of nitromethane with monoaldehydes can assume by using nitroethane, nitroethanol, *etc.* [5], extension of the dialdehyde/nitromethane cyclization to other nitromethylene compounds is an obvious development. This possibility has not yet been studied in detail. However, the presence of three reactive hydrogens may possibly be required for a cyclizing condensation to occur (two hydrogen atoms for linking the two C-C bonds and one atom for the formation of the *aci*-nitro salt). It is perhaps for this reason that the condensation of dinitromethane with glyoxal or succinaldehyde does not lead to cyclization, but rather to a condensation at each aldehyde group giving the dicondensation products 1,1,4,4-tetranitrobutane-2,3-diol and 1,1,6,6-tetranitrohexane-2,5-diol *(130)*, respectively [80].



n = 2, 3 *(130)*

However, the condensation of dialdehydes with acetonitrile should produce cyclic 2-cyano-1,3-diols. Preliminary experiments [23] indicated that cyclization does in fact occur under suitable conditions, but further work is required to develop a preparatively useful method.

In view of the ability of nitromethane to condense with ketones, especially alicyclic ketones [81], a cyclizing condensation of nitromethane with suitable diketones should also be theoretically possible. This reaction has already been verified with the two bicyclo[1,3,3]nonane-3,7-diones *(131a)* and *(131b)*, which on treatment with nitromethane/sodium methoxide afforded the corresponding 2-nitroadamantane-1,3-diols *(132)* in 79 % and 63 % yield, respectively [82]. Further experiments are required to determine whether this reaction can be extended to other diketones whose carbonyl groups are not as favorably oriented for cyclization.



*(131a)*, R = R' = H *(132)*

*(131b)*, R = $CH_3$; R' = $CHCl_2$

## V. Preparative Procedures

1,4-Dideoxy-1,4-dinitro-*neo*-inositol *(2)* [17]:

A mixture of 200 ml of nitromethane, 500 ml of 30 % aqueous glyoxal, 1000 ml of methanol, and 1000 ml of water is cooled in ice, and a solution of 210 g of sodium carbonate in 800 ml of water is added with stirring over a period of 10 minutes. On scratching the walls of the vessel with a glass rod, a precipitate begins to separate. After standing for 5 h at 5 °C, the latter is suction filtered, washed with copious quantities of water, and dried over $P_4O_{10}$. The yield of *(2)* is 30–35 g. After storage overnight in a refrigerator, additional 5 g of *(2)* can be isolated from the mother liquor, which contains some 500 ml of wash water. The yield of crude *(2)* is 10 % [16]. Recrystallization from methanol (20 g/liter) gives crystals which become brown at 250 °C and decompose at about 270 °C.

*neo*-Inosadiamine 1,4-dihydrochloride *(6)* [17]:

A solution of 20 g of dinitroinositol *(2)* in 250 ml of dimethyl formamide is mixed with 250 ml of glacial acetic acid and hydrogenated at normal pressure over 15 g of nickel T-4 catalyst [83]. After 5 h (consumption of 11.2 l of hydrogen) the mixture is filtered, the residue (the inosadiamine is insoluble in DMF/acetic acid) is carefully treated with 2 N hydrochloric acid and filtered by suction. Ethanol is added to the filtrate until incipient turbidity and the solution is stored overnight at 5 °C. The precipitated inosadiamine dihydrochloride is then sucked off and washed with ethanol. Yield of *(6)* as dihydrochloride: 14.1 g. Evaporation of the mother liquor to dryness, dissolution of the greenish residue in a little water, and addition of ethanol yields additional 7.5 g. The total yield of *(6)* as the dihydrochloride is 90 %.

2-Nitrobenzinden-1-ol *(126)* [23]:

A solution of 2.4 g of naphthalene-2,3-dicarboxaldehyde *(125)* [84] in 100 ml of dioxan is treated with 1.4 ml nitromethane. A solution of 0.3 g of sodium in 20 ml of methanol is added dropwise with cooling in ice. Stirring is continued for 1.5 hours, 100 ml of water is added, and the mixture is neutralized with 1 N hydrochloric acid. The yellow precipitate is suction filtered, washed with water, and dried over $P_4O_{10}$. The yield of *(126)* is 77 %. Decomposition point 182–185 °C. Recrystallization from chloroform affords yellow needles which decompose at 190–195 °C.

Methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride *(53)* [47]:

Sodium metaperiodate (220 g) is slowly added with stirring to a solution of 100 g of methyl α-D-glucoside in 500 ml of water, the temperature being kept below 20 °C by addition of ice as needed. Stirring is continued for 1 h, the formic acid produced is neutralized with 40 g of sodium bicarbonate, and the mixture, from which sodium iodate has crystallized out, is poured into 500 ml of ethanol and filtered with suction. The filtrate is concentrated to a thin syrup, taken up in 800 ml of ethanol and refiltered. Nitromethane (60 ml) is added, followed by a solution of 12 g of sodium in 600 ml of meth-


[79] *N. J. Leonard* and *G. W. Leubner*, J. Amer. chem. Soc. *71*, 3405 (1949).

[80] U.S. Pat. 2544103 (March 6th, 1951), inventor: *H. Plaut*; Chem. Abstr. *45*, 7587 (1951).

[81] *H. B. Fraser* and *G. A. R. Kon*, J. chem. Soc. (London) *1934*, 604; *A. Lambert* and *A. Lowe*, ibid. *1947*, 1517; *C. A. Grob* and *W. von Tscharner*, Helv. chim. Acta *33*, 1072 (1950); *H.-J. Dauben, R. J. Ringold, R. H. Wade*, and *A. G. Anderson*, J. Amer. chem. Soc. *73*, 2359 (1951); *T. F. Wood* and *R. J. Cadorin*, ibid. *73*, 5504 (1951); *F. F. Blicke, N. J. Doorenbos*, and *R. H. Cox*, ibid. *74*, 2925 (1952); *D. V. Nightingale* et al., J. org. Chemistry *15*, 782 (1950); *17*, 1005 (1952); *23*, 236 (1958); *28*, 642 (1963); *F. I. Carroll, J. D. White*, and *M. E. Wall*, ibid. *28*, 1240 (1963).

[82] *H. Stetter* and *J. Mayer*, Angew. Chem. *71*, 430 (1959); *H. Stetter* and *P. Tacke*, Chem. Ber. *96*, 694 (1963).

[83] *S. Nishimura*, Bull. chem. Soc. Japan *32*, 61 (1959).

[84] *W. Ried* and *H. Bodem*, Chem. Ber. *89*, 708 (1956).

anol. The mixture is left standing at room temperature for 20 min, and approximately 700 ml of Amberlite IR-120 in its $H^+$ form are added with stirring to effect neutralization. After filtration, the solution is concentrated to an oil, treated with 400 g of hot ethyl acetate, insoluble material removed by filtration, and the filtrate once again concentrated to a wine-red syrup. A solution of this syrup in 300 ml of ethanol is hydrogenated over 10–20 g of nickel T-4 catalyst [83] at an initial pressure of 4 atm [85]. At the end of the hydrogenation (1–8 hours), the catalyst is removed and the filtrate treated with 30 ml of conc. hydrochloric acid, whereupon *(53)* slowly crystallizes out and is filtered off after 1 h at 0 °C. The yield of *(53)* is 21 %; decomposition range 210–240 °C; $[\alpha]_D^{20} = +60°$ (c = 2 in water).

Methyl 3-deoxy-3-nitro-β-D-glucopyranoside *(65)* [50a]:

Sodium metaperiodate (2.14 g), 1.0 g of potassium carbonate, and 0.55 ml of nitromethane are mixed with about 40 ml of water and stirred at 0 °C. Methyl β-D-ribofuranoside [86] (1.64 g) is then added in portions, resulting in a clear solution within a few minutes. The temperature of the solution is allowed to rise gradually to 23 °C, and is kept there for 3 hours. The pH of the solution is then brought to about 4 with a just sufficient amount of Amberlite IR-120 in its $H^+$ form. Addition of a threefold volume of ethanol precipitates most of the inorganic salts. The filtrate is concentrated, again treated with ethanol, filtered, and the process repeated once more. The final product is a colorless syrup, which crystallizes on scratching. After two evaporations in ethyl acetate, the crude product is allowed to stand overnight at 0 °C under some ethyl acetate, and a 32 % yield of *(65)* is obtained in the form of colorless, needle-like prisms, m.p. 200–201 °C (decomp.), $[\alpha]_D^{20} = -14.4°$ (c = 1.5 in water). Recrystallization from ethyl acetate/methanol gives a purified product, m.p. 202–204 °C (decomp.), $[\alpha]_D^{24} = -12.4°$.

[85] At normal pressure, too, the hydrogenation is complete in 5–8 hours (*F. W. Lichtenthaler* and *B. Küspert*, unpublished results).

[86] *R. Barker* and *H. G. Fletcher, Jr.*, J. org. Chemistry *26*, 4607 (1961).

Methyl 3-amino-3,6-dideoxy-α-L-glucoside *(74)* [55b]:

A stirred solution of 25 g of methyl α-L-rhamnopyranoside *(71)* [87] in 250 ml of water is treated portionwise with 60 g of sodium metaperiodate, the temperature being kept at 20–30 °C by addition of ice. After 1 h, the mixture is carefully neutralized with 11.5 g of sodium bicarbonate and poured into 750 ml of ethanol; the salts precipitated are removed by suction filtration, and the filtrate is concentrated to a syrup which is extracted first with 250 ml and then with 120 ml of ethanol. After standing overnight in a refrigerator, the combined extracts are filtered and treated with 20 ml of nitromethane followed by a solution of 4 g of sodium in 300 ml of methanol. After standing for 40 min at room temperature, the solution is neutralized by stirring with about 250 g of Amberlite IR-120 resin in its $H^+$ form, filtered, and evaporated to dryness. The oily residue is taken up in 200 ml of ether, filtered through Hyflo-Supercel to remove insoluble material, and concentrated to a golden-red syrup. This is hydrogenated in 300 ml of methanol over about 10 g of nickel T-4 catalyst [83] at an initial pressure of 3 atm. The hydrogenation is complete after about 30 min. The catalyst is filtered off and washed with methanol. Evaporation of the filtrate leaves a crystalline residue, which is refluxed with 100 ml of ethyl acetate for 5 min. Although solution is not complete, the mixture is now cooled, allowed to stand overnight in the refrigerator, and filtered. Pale colored crystals of *(74)*, m.p. 175–176 °C, are obtained. The yield is 7.8 g (31 %). One recrystallization from ethanol gave pure *(74)*, m.p. 177–178 °C, $[\alpha]_D^{20} = -145°$ (c = 1.9 in water).

*The author's own work described in portions of this paper was aided by the United States Public Health Foundation and the Deutsche Forschungsgemeinschaft. I wish to thank Prof. Dr. F. Cramer for his interest and generous support and Miss G. Olfermann for her most skillful assistance.*

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German version: Angew. Chem. *76*, 84 (1964)

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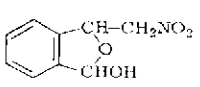
# COMMUNICATIONS

## Synthesis of the Isoquinoline System from o-Phthalaldehyde and Nitromethane

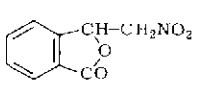
By Prof. Dr. H. H. Baer and Barbara Achmatowicz, M. Sc.

Department of Chemistry, University of Ottawa, Ottawa (Canada)

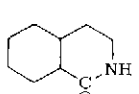
The primary product of the condensation of *o*-phthalaldehyde and nitromethane, *viz.* 2-(1-hydroxy-2-nitroethyl)benzaldehyde *(1)*, becomes stabilized as the intramolecular hemiacetal *(2)*, m.p. 121–123 °C, in the absence of hydroxylic solvents. The condensation proceeds with 80 % yield in excess nitromethane within 15 h. at room temperature in the presence of dry sodium carbonate. With 2,4-dinitrophenylhydrazine, *(2)* yields a red, highly insoluble 2,4-dinitrophenylhydrazone derived from *(1)*, m.p. 205–207 °C. Oxidation of *(2)* with potassium dichromate and sulfuric acid produces the nitrolactone *(3)*, m.p. 132 °C, in 80 % yield. Catalytic hydrogenation of *(3)* over Pt affords first the corresponding aminomethyl lactone, which can be isolated as its hydrochloride, m.p. approx. 260 °C, and then octahydroisocarbostyril *(4)*, m.p. 147 °C. In order to characterize *(4)* further, it was reduced with $LiAlH_4$ to decahydroisoquinoline, the picrate of the *cis*-form, m.p. 150 °C, being isolated [1].



(2)

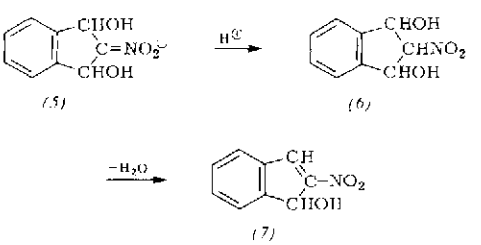


(3)



(4)

Alcoholic alkali causes instantaneous rearrangement of *(2)* to the nitronate *(5)* of 1,3-dihydroxy-2-nitroindane *(6)*. On acidification with aqueous HCl, the colorless nitronate *(5)* produces yellow 2-nitro-3-hydroxyindene *(7)*, m.p. 148 °C. On the other hand, deionization with a methanolic suspension of Amberlite IR-120 ($H^+$) gives a separable mixture of *(7)* and colorless *(6)*, m.p. 163–165 °C. The structures of *(6)* and *(7)* were proved by the NMR spectra of their crystalline acetates, m.p. 90–91 °C and 130 °C, respectively. 2-Nitro-1-hydroxyindene [2] is not formed [3].



(5) (6) (7)

Received, November 15th, 1963 [Z 617/446 IE]
German version: Angew. Chem. *76*, 50 (1964)

[1] *B. Witkop*, J. Amer. chem. Soc. *70*, 2617 (1948).

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[3] See also *F. W. Lichtenthaler*, Tetrahedron Letters *1963*, 775.

## Differentiation of Strong Acids by Conductometric Titration in Glacial Acetic Acid

By Dr. B. Sansoni

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Strong acids are buffered by water to the acid strength of the hydroxonium ion $OH_3^{\oplus}$, so that titration of a mixture of $HClO_4$, $H_2SO_4$, $HNO_3$, and $CCl_3COOH$ with $OH^{\ominus}$ ion produces only a single end-point. On the other hand, in glacial acetic acid which is a substantially more weakly basic solvent, the solvated hydrogen ion $CH_3COOH_2^{\oplus}$ is more acidic than $OH_3^{\oplus}$ in water, and an equilibrating buffer effect begins only at correspondingly higher acid strength. In glacial acetic acid, $HClO_4$, $H_2SO_4$ (first dissociation stage), $p$-$CH_3$–$C_6H_4$–$SO_3H$, and HCl have pK values of 4.87, 7.24, 8.46, and 8.55, respectively, and according to other data [1], the relative strengths of 0.005 N $HClO_4$, HBr, $H_2SO_4$, HCl, and $HNO_3$ are 400:160:30:9:1. These differences in acid strength, as well as the differing tendencies of the individual acids to undergo ion association to ion pairs or triple ions [2], make it possible to achieve conductometric differentiation of strong acids in glacial acetic acid.

Titration of $H_2SO_4$ in glacial acetic acid yields two distinct equivalence points corresponding to $HSO_4^{\ominus}$ and $SO_4^{2\ominus}$; differentiation of binary mixtures, for example of $H_2SO_4$ and HCl, is also possible [3]. Conductometric titration with 0.5 M sodium acetate in glacial acetic acid can be used to differentiate complex mixtures of strong acids. The apparatus used entailed a high-precision bridge with logarithmic indicating amplifier (Type WBR + TAV) and unplatinized Pt-electrodes, and measurements were made in analytical grade glacial acetic acid (0.1–0.2 % $H_2O$) in an adjustable cell at 20.0 ± 0.1 °C with exclusion of moisture. The mixtures $HClO_4/H_2SO_4/HSO_4^{\ominus}$, $HClO_4/HNO_3$, $H_2SO_4$ + HBr/$HSO_4$, $HClO_4/H_2SO_4/HNO_3/HSO_4^{\ominus}$ and $HClO_4/H_2SO_4/HNO_3/HSO_4^{\ominus}/CCl_3COOH$ all gave reproducible, analytically evaluable points of inflection. Finally, as many as six points of inflection are recognizable in the titration of the mixture $HClO_4/p$-$CH_3$–$C_6H_4$–$SO_3H/H_2SO_4/HNO_3/HSO_4^{\ominus}/CCl_3COOH$ (Fig. 1).

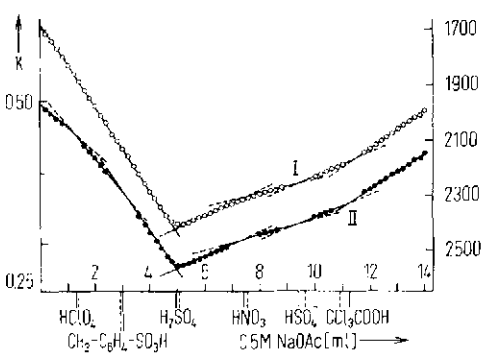



Fig. 1. Conductometric titration of a mixture of 0.69 mmole of $HClO_4$ (70 %)/0.78 mmole of $p$-$CH_3$–$C_6H_4$–$SO_3H$/1.05 mmole of $H_2SO_4$ (97 %)/1.23 mmole of $HNO_3$ (100 %)/0.62 mmole of $CCl_3COOH$ in 99 ml of glacial acetic acid + 1 ml of water with 0.5 M $CH_3COONa$.

——— experimental measurements.

- - - - - - - - theoretical equivalence points.

Curve I (left-hand ordinate) × [$10^4$ mho $cm^{-1}$].

Curve II (right-hand ordinate) scale degrees (measurements were a nonlinear function of ×).

The sequence of equivalence points generally corresponds roughly to the acid strengths in glacial acetid acid. The best conditions were obtained with the addition of about 1 % water. Figure 1 shows the most extensive differentiation of strong acids known to us that has been obtained using acid-base titrations [4]. A mixture of the acids $CH_2ClCOOH/CHCl_2COOH/CCl_3COOH$ gave three equivalence points; commercial $H_4P_2O_7$, containing mono- to pentaphosphoric acids as impurities (from Messrs. Riedel De Haen), gave four points of inflection.

Corresponding titrations in propionic acid with sodium propionate proceeded unfavorably; probably both the acidity and dissociation are too low in this case. Formic acid also proved unsuitable; it is, of course, a stronger acid than glacial acetic acid, but its high autoprotolysis constant ($1.0 \times 10^{-6}$, cf. acetic acid: $3.5 \times 10^{-15}$) [1], indicates a very high basic strength. This produces a buffering effect similar to that which occurs in water.

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[*] Part 4 of a series on Separations in Non-aqueous Solvents; Part 3: Angew. Chem. *75*, 418 (1963); Angew. Chem. internat. Edit. *2*, 615 (1963). Work carried out in collaboration with the following students: *U. Murawski*, *H.-B. Kuhnhen*, *B. Berrang*, *H. Arold*, *H. Cuntze*, and *E. Sebastiani* and reported in a lecture in March 1963 at the H. C. Ørsted Institute, University of Copenhagen (Denmark).

[1] *S. Bruckenstein* and *I. M. Kolthoff* in *I. M. Kolthoff*, *Ph. J. Elving*, and *B. B. Sandell:* Treatise on Analytical Chemistry. The Interscience Encyclopedia Inc., New York 1959, part I, Vol. 1, p. 475.

[2] *R. M. Fuoss* and *C. A. Kraus*, J. Amer. chem. Soc. *55*, 2387 (1933); *R. Stolz*, Ph. D. Thesis, Universität Marburg, 1963.

[3] *G. Jander* and *G. Mass*, Fortschr. chem. Forsch. *2*, 619 (1953); *T. Higuchi* and *C. R. Rehm*, Analytic. Chem. *27*, 408 (1955); *A. M. Shodkin* and *N. A. Izmailov*, Zh. obshch. Khim. *20*, 39 (1950).

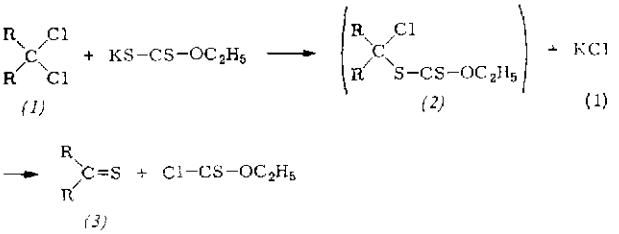
[4] *D. B. Bruss* u. *G. E. A. Wild*, Analytic. Chem. *29*, 232 (1957); *W. Stuck*, Z. analyt. Chem. *177*, 338 (1960).

## Reaction of Potassium Xanthate with Diaryldichloromethanes, a New Thioketone Synthesis [*]

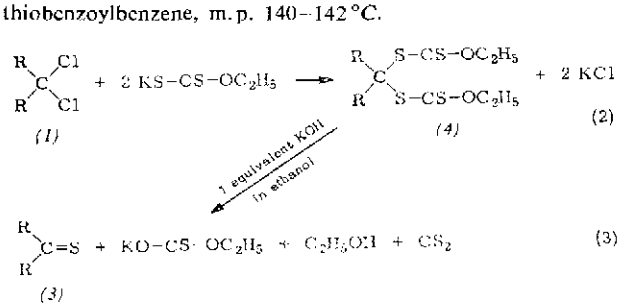
By Prof. Dr. A. Schönberg and Dipl.-Chem. E. Frese

Fakultät für allgemeine Ingenieurwissenschaften der Technischen Universität Berlin (Germany)

Diaryldichloromethanes *(1)* react with one equivalent of potassium xanthate to give diarylchloromethyl xanthates *(2)*, which cannot be isolated; these decompose exothermically according to Equation (1) to form thioketones *(3)* and *O*-ethyl chlorothioformate. The reaction in boiling petroleum (b.p. 100–140 °C) or in hot dimethylformamide, in which potassium xanthate is readily soluble, is complete in ca. 1 h; at room temperature, it requires ca. 24 hours. The yields of the resultant thioketones, which were shown by melting-point determination and analysis to be almost pure, are consistently greater than 90 %.




Examples of compounds prepared by this route are $p,p'$-dimethoxythiobenzophenone, xanthione, and 1-thioxanthione, and the previously unknown deep blue-green, solid 1,4-bis-thiobenzoylbenzene, m.p. 140–142 °C.



Reaction of two equivalents of potassium xanthate with diaryldichloromethanes according to Equation (2) gives the little-known *gem*-dixanthoylmethanes *(4)*, examples of which are diphenyldixanthoylmethane, m.p. 156 °C and bis-(4-methoxyphenyl)dixanthoylmethane, m.p. 146 °C.

These react with one equivalent of ethanolic potassium hydroxide according to Equation (3) to give thioketones *(3)*, *O*-potassium *O'*-ethyl thiocarbonate, and xanthic acid, which decomposes spontaneously into ethanol and $CS_2$. Thermolysis of the above dixanthoylmethanes also yields thioketones *(3)*.

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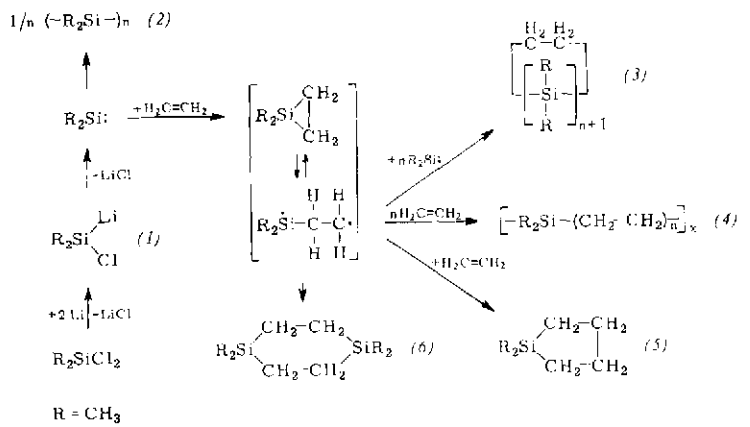
[*] The recent publications of *R. Mayer* and *H. Berthold*, Chem. Ber. *96*, 3096 (1963), and *F. Asinger* et al., Angew. Chem. *75*, 1050 (1963), Angew. Chem. internat. Edit. *3*, 19 (1964), prompted us to report some of our own results.

## The Formation and Reactions of Dimethylsilylene, a Silicon-Analogue of the Carbenes

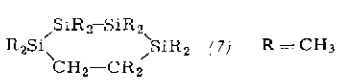
By Dr. O. M. Nefedov and cand. chem. M. N. Manakov

N. D. Zelinskii Institute of Organic Chemistry of the Academy of Sciences of the U.S.S.R., Moscow (U.S.S.R.)

When dimethyldichlorosilane is treated with lithium in tetrahydrofuran at 0–10 °C and ethylene is passed through the reaction mixture, 1,2-dimethyl-1-silacyclopentane *(5)* and 1,1,4,4-tetramethyl-1,4-disilacyclohexane *(6)* are obtained in small yields (2–5 %) in addition to solid and liquid high molecular-weight silicon hydrocarbons *(3)* and *(4)*. Compounds *(5)* and *(6)* are also formed from $(H_3C)_2SiCl_2$, metallic sodium in benzene, and $C_2H_4$ in an autoclave at temperatures of 105–120 °C, as well as on thermal degradation of polydimethylsilylene *(2)* [1] at 300 °C in the presence of $C_2H_4$. The formation of the Si-containing heterocycles *(5)* and *(6)*, the telomers *(3)*, and the polymers *(4)* can only be explained by the assumption of transient formation of dimethylsilylene, since Li does not add onto the C–C double bond of monoolefins under the conditions employed [2], and ethylene does not react at 105–120 °C with Si-Li bonds such as those in *(1)* [3].



When ethylene is replaced by isobutylene, 1,1,2,2,3,3,4,4,5,5-decamethyl-1,2,3,4-tetrasilacyclohexane *(7)*, m.p. 44–45 °C, separates out, whereas the presence of cyclohexene or 1-hexene leads to the formation of liquid telomers containing oxygen, such as $C_6H_{10}[Si(CH_3)_2]_4O_2$, b.p. 74 °C/0.3 mm, or $C_7H_{14}[Si(CH_3)_2]_4O_2$, b.p. 96 °C/2 mm.



Intermediary formation of silylenes must always be expected when diaorganyldichlorosilanes are treated with alkali metals [1,4]. Dimethylgermene can be formed from $R_2GeCl_2$ with Li and added onto olefins analogously.

Received, December 9th, 1963 [Z 633/465 IE]
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[2] *P. Vaculik:* Chemie der Monomeren (Chemistry of Monomers), Academy of Czechoslovakia, Prague 1956, Vol. I.

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## Autoxidative Ring Closure of ω,ω'-Bis(triphenylphosphorylidene)alkanes

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The action of oxygen on alkylidenetriphenylphosphoranes of structure $R-CH=P(C_6H_5)_3$ yields olefins $R-CH=HC-R$ [1]. Under the same conditions, autoxidation of ω,ω'-bis(triphenylphosphorylidene)alkanes *(1)* can lead to cycloalkenes *(2)*. Examples are given in Table 1.

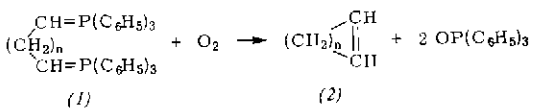
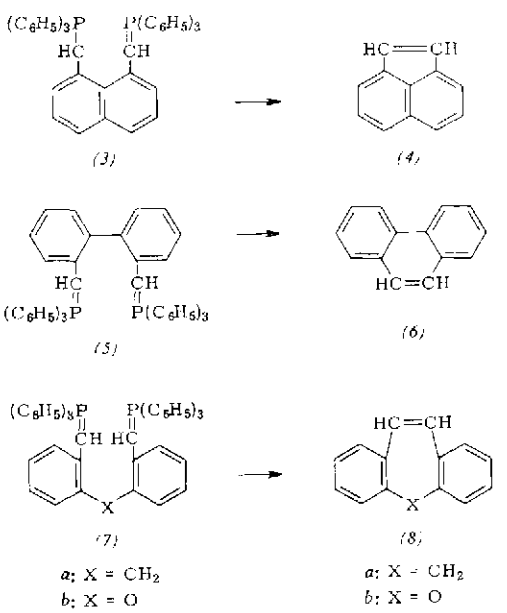


Table 1. Cycloalkenes *(2)* obtained by autoxidation of ω,ω'-bis(triphenylphosphorylidene)alkanes *(1)*.

| n | Cycloalkene *(2)* | Yield of *(2)* [%] |
|---|---|---|
| 5 | Cycloheptene | 61 |
| 4 | Cyclohexene | 60 |
| 3 | Cyclopentene | 68 |
| 2 | 1,5-Cyclooctadiene | 52 |

When n = 2, cyclizing dimerization occurs to give the eight-membered ring. Polycyclic rings can be synthetized analogously:



Acenaphthylene *(4)* is obtained in 30 % yield from the naphthalene derivative *(3)*, and phenanthrene *(6)* in 45 %

yield from the biphenyl derivative *(5)*. On autoxidation, *(7a)* gives dibenzo[*a*,*e*]cyclohepta-1,3,5-triene *(8a)*, m.p. 133 °C (45 %), and *(7b)* gives dibenzo[*e*,*f*]oxepin *(8b)*, m.p. 111 °C (52 %).

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[1] *H. J. Bestmann* and *O. Kratzer*, Chem. Ber. *96*, 1899 (1963).

## Cocarcinogen A 1 — the First Pure, Highly Active Constituent of Croton Oil

By Doz. Dr. E. Hecker, Dipl.-Chem. H. Bresch, and Dipl.-Chem. Ch. v. Szczepanski

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The pharmacologically active principle of croton oil [1,2] contains the substance groups A and B which cause the toxic, inflammatory, and cocarcinogenic activity [3] of the oil. Substance group A can be separated further by countercurrent distribution into the inactive component A2, m.p. 72 °C, and the pure, highly active component A1.

The pure cocarcinogen A1 [*] $C_{36}H_{56}O_8$ is a colorless resin, that is insoluble in water but dissolves in nearly all organic solvents; $[\alpha]_D^{24} = +49°$ (1 % in dioxan); $\lambda_{max} = 232$ and 333 mμ, $\varepsilon_{max} = 5400$ and 73 in ethanol; infrared spectrum in KBr: hydroxyl 2.96 μ, ester carbonyl 5.75 μ, ketone carbonyl 5.80–5.85 μ, C=C double bonds 6.15 μ; NMR spectrum δ = 0.9, 1.3, 1.7, 2.1, 2.5, 3.2, 3.9, 4.3, 5.2, 5.4, 5.6, 7.5 ppm (in $CCl_4$ with tetramethylsilane as internal standard).

Cocarcinogen A1 is not aromatic, contains an α,β-unsaturated carbonyl group that does not react with 2,4-dinitrophenylhydrazine or semicarbazide, as well as three free and two esterified hydroxyl groups. The latter carry an acetic and a myristic acid residue, respectively [2]. One of the free hydroxyl groups may be esterified practically quantitatively with 4'-nitroazobenzene-4-carbonyl chloride [4]. Fission of this ester ($C_{49}H_{63}O_{11}N_3$), m.p. 86–87 °C [2], with $KMnO_4$ affords the corresponding ester of glycolic acid. The esterifiable hydroxyl group is therefore primary and occurs in an allyl configuration; the two remaining free hydroxyl groups are tertiary. Other chemical data (see [5]) have been obtained for compounds which have not yet been shown to be pure.

Cocarcinogen A1 may be degraded by fission of the ester linkages to give a crystalline parent alcohol $C_{20}H_{28}O_6$, m.p. 238–40 °C, $[\alpha]_D^{29} = +116°$ (0.4 % in dioxan); $\lambda_{max} = 234$ and 335 mμ, $\varepsilon_{max} = 5000$ and 75 in ethanol; infrared spectrum in KBr: hydroxyl 2.87 and 3.05 μ, carbonyl 5.88 μ, C=C double bonds 6.10 μ; NMR spectrum: δ = 0.52, 0.88, 1.10, 1.67, 2.32, 2.91, 3.77, 4.17, 5.44, 7.52 ppm (in perdeuterodimethyl sulfoxide, standard: tetramethylsilane). A triacetate $C_{26}H_{34}O_9$, $[\alpha]_D^{28} = +68°$ (1 % in dioxan), is obtained by acetylation. The spectral and chemical properties of the parent alcohol show that it is not aromatic and contains a carbonyl as well as five hydroxyl groups, one of which is primary and allylic; two other are tertiary.

The natural product A1 proved to be highly active in the toxicity test in frogs ($LD_{50}$), in the inflammation test on mouse ears (I.U.), and in the cocarcinogen test on the back skin of mice, but does not produce any papillomas within 12 weeks without pretreatment with subthreshold doses of a carcinogen. The substance loses its biological activity on treatment with acids or alkalies. The parent alcohol *(1)* is not active in the amounts applied (Table 1), while the triacetate *(2)* shows a strongly decreased — but still significant — activity compared with A1.

Table 1. Biological activity of the pure cocarcinogen A1, of its parent alcohol *(1)*, and of the triacetate *(2)* of *(1)*. Tests according to [3].

| Substance | $LD_{50}$ [μg/50 g] | I. U. [μg/ear] | Cocarcinogen test [a] | |
|---|---|---|---|---|
| | | | μg/application [b] | papilloma/mouse [c] |
| A 1 | 10 | 0.009 | 10 | 9 |
| *(1)* | 5000 | 2.4 | 500 | 0 |
| *(2)* | 150 | 1.5 | 50 | 0.1 |

[a] Carcinogen: 1 μmole of 9,10-dimethylbenzanthracene.

[b] Application: twice weekly for 12 weeks.

[c] After 12 weeks.

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[*] Formerly denoted by "a" (cf. [2]).

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## Deaminothiamine Pyrophosphate, a Strong Carboxylase Inhibitor [1]

By Dr. habil. A. Schellenberger and Dr. W. Rödel

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Deaminothiamine *(1)* was synthetized as follows: 4-Chloro-5-ethoxycarbonylmethyl-2-methylpyrimidine [2] was converted with NaSH into the 4-mercapto compound, m.p. 185 °C, in 91 % yield. Elimination of the mercapto group with Raney nickel in boiling water gave 5-ethoxycarbonylmethyl-2-methylpyrimidine, b.p. 104 °C/3 mm, in 34 % yield; this was converted via the hydrazide, m.p. 160 °C, 98 % yield, by twofold treatment with $NaNO_2$ into 5-hydroxymethyl-2-methylpyrimidine, m.p. 105 °C, in 31 % yield. Heating this with HBr and glacial acetic acid at 100 °C gave the bromide which reacted unpurified with 5-(β-hydroxyethyl)-4-methyl thiazole to give deaminothiamine bromide (hydrobromide?). When this was shaken with a suspension of AgCl in methanol, the chloride (hydrochloride?) was produced and was purified by chromatography on a cellulose column (Schleicher and Schüll, No. 123a). The product crystallized after standing for several weeks. Deaminothiamine can be obtained analytically pure as its perchlorate, m.p. 204 °C (decomp.), which crystallizes well.

Phosphorylation of *(1)* with anhydrous orthophosphoric acid [3] yielded a mixture of the mono-, di-, and triphosphoric esters in addition to inorganic phosphate. This mixture was separated using paper or thin-layer electrophoresis. The separated fractions were eluted with water.

If deaminothiamine pyrophosphate is added to resynthetized carboxylase in a molar ratio cocarboxylase:deaminococarboxylase = 0.96:1, the activity of the enzyme is reduced by 84 % (optical assay according to [4]). If, however, the inhibitor is added in the resynthesis of carboxylase before thiamine pyrophosphate, then the inhibition is almost complete.

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German version: Angew. Chem. 76, 226 (1964)

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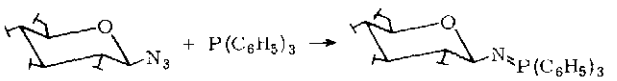
[4] *E. Holzer*, *H.-D. Söling*, *H.-W. Goedde*, and *H. Holzer*, in *H. U. Bergmeyer:* Methods of enzymatic Analysis. Verlag Chemie, Weinheim/Bergstr., and Academic Press, New York 1963, p. 602.

## Triphenylphosphine N-Acetylglycosylimides and N,N'-Bis(acetylglycosyl)carbodiimides

By Dr. A. Messmer, Dipl.-Chem. I. Pintér, and Dipl.-Chem. F. Szegö

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Research on the application to sugar chemistry of the phosphine imide reaction of *Staudinger* [1] led to the synthesis of phosphine-imido derivatives of sugars. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl azide *(1)* [2] reacts with triphenylphosphine *(2)* in absolute ether even at room temperature with loss of a molecule of nitrogen to give triphenylphosphine *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)imide *(3)* which forms macroscopic crystals. The structure of *(3)* was proved by Zemplén hydrolysis [3] and by its reaction with *p*-nitrobenzaldehyde to give *N*-(*p*-nitrobenzylidene)-2,3,4,6-tetra-*O*-acetyl-β-D-glucosylamine [4].



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

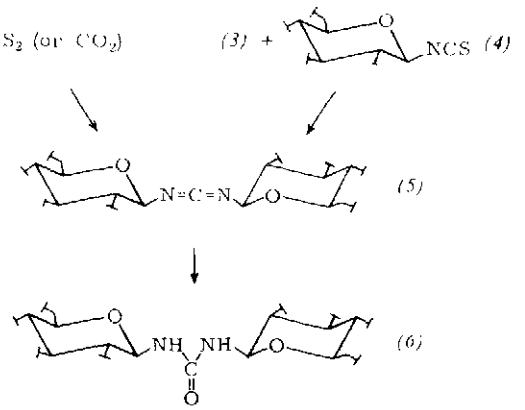
The triphenylphosphine-imido derivatives of acetylated sugars prepared in this way are shown in Table 1.

Table 1. Properties of triphenylphosphine *N*-acetylglycosylimides.

| R = | R–N=P(C$_6$H$_5$)$_3$ M.p. [°C] | $[\alpha]_D$ in dioxan [°] | Yield [%] |
|---|---|---|---|
| 2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl- | 136 | −18.2 | 85 |
| 2,3,4,6-Tetra-*O*-acetyl-β-D-galactosyl- | 129 | −4.1 | 82 |
| 2,3,4-Tri-*O*-acetyl-β-D-xylosyl- | 128 | −23.8 | 89 |
| 2,3,6,2',3',4',6'-Hepta-*O*-acetyl-β-D-cellobiosyl- | 90–95 (amorph.) | +15.7 | 70 |

By analogy to the aliphatic phosphine imides [1], triphenylphosphine *N*-(tetraacetyl-β-D-glucosyl)imide *(3)* reacts with $CO_2$ or $CS_2$ to give a high yield of the same crystalline substance as is formed from *(3)* and tetraacetyl-β-D-glucosyl isothiocyanate *(4)* [5]. The analytical data tally with the formula of *N,N'*-bis-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)-carbodiimide *(5)*, although the compound is not converted into a diglucosylurea derivative *(6)* like a normal carbodiimide when treated with water [6] or acids, or with methanol in the presence of CuCl [7].

Thus, as well as *(5)*, the isomeric *N,N*-bis(tetraacetyl-β-D-glucosyl)cyanamide structure must be considered. The infrared spectrum does not permit a decision, for the absorption line at 2180 cm$^{-1}$ may come from either the carbodiimide or the cyano group. Like bistriphenylmethylcarbodiimide [8], *(5)* adds on a molecule of water in benzene/glacial acetic acid, and *N,N'*-bis-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)urea *(6)* [9] is formed in 98% yield. This proves the carbodiimide structure.



The syrupy product obtained from *(5)* by Zemplén hydrolysis is to be regarded as *N,N'*-bis-(β-D-glucosyl)isourea methyl ether and the crystalline substance obtained from this by acetylation as *N,N'*-bis-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)-isourea methyl ether (m.p. 161 °C, $[\alpha]_D = -2.7°$ in $CHCl_3$). The bisglycosylcarbodiimides prepared and the bisglycosylurea derivatives obtained under *Bredereck*'s conditions [8] are shown in Table 2.

Table 2. Properties of bis(acetylglycosyl)carbodiimides and bis(acetylglycosyl)carbamides.

| R = | R–N=C=N–R M.p. [°C] | $[\alpha]_D$ in $CHCl_3$ [°] | Yield [%] | R–NH–C(=O)–NH–R M.p. [°C] | $[\alpha]_D$ in $CHCl_3$ [°] | Yield [%] |
|---|---|---|---|---|---|---|
| 2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl- | 178 | −43.0 | 86 | 162 | −3.6 | 98 |
| 2,3,4,6-Tetraacetyl-β-D-galactosyl- | syrup | | | 225 | −16.7 | 67 |
| 2,3,4-Tri-*O*-acetyl-β-D-xylosyl- | 139 | −16.9 | 47 | 250 | −7.7 | 97 |
| 2,3,6,2',3',4',6'-Hepta-*O*-acetyl-β-D-cellobiosyl- | 130–145 (amorphous) | −19.5 | 12 | 228–232 (amorphous) | −15.1 | 50 |

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German version: Angew. Chem. *76*, 227 (1964)

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[2] *A. Bertho*, Ber. dtsch. chem. Ges. *63*, 836 (1930).

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## The Cyclodecapentaene System

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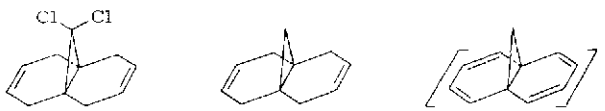
Cyclodecapentaene *(1)*, which contains 10 π-electrons, can be expected according to *Hückel*'s rule [1] to possess aromatic character. High resonance stabilization does not, however, seem possible in *(1)*, since the hydrocarbon cannot assume a planar configuration because of overlapping of the van der Waals radii of the hydrogen atoms at positions 1 and 6 on the *trans* double bonds.



*(1)* *(2)*

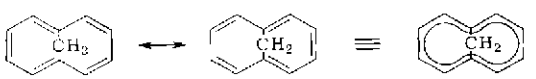
Atomic models indicate that replacement of the two internal hydrogen atoms in *(1)* by a methylene group should result in the formation of an almost, if not completely planar structure of the cyclodecapentaene skeleton.

The synthesis of 1,6-methanocyclodecapentaene *(2)* [or of (5)] started from 1,4,5,8-tetrahydronaphthalene [2]. The triene adds on dichlorocarbene (generated from $CHCl_3$ and K-t.-butoxide) at the central double bond with a high degree of selectivity [3] affording *(3)*, m.p. 83–84 °C. Sodium in liquid ammonia converts *(3)* into *(4)*, b.p. 80–81 °C/11 mm, and this reacts with bromine in the cold to form a tetrabromide, m.p. 128–129 °C. This compound reacts with bases, *e.g.* alcoholic KOH, to give a good yield of the desired hydrocarbon $C_{11}H_{10}$ as colorless crystals, m.p. 28–29 °C.



*(3)* *(4)* *(5)*

Three structures of the hydrocarbon are possible: a) *(5)*; b) *(2)* with a fluctuating structure according to *(6)* ⇌ *(5)* ⇌ *(7)*; and c) *(2)* with a delocalized π-electron system [*(6)*–*(8)*].



*(6)* *(7)* *(8)*

The ultraviolet spectrum of the hydrocarbon has maxima at 256 mμ (ε = 68000), 259 mμ (ε = 63000), and 298 mμ (ε = 6200); this suggests an extensive conjugated system [not compatible with *(5)*]. The NMR spectrum is particularly revealing: it shows an $A_2B_2$ system (8 protons) in the range 2.5–3.2 τ, centred at 2.8 τ, and a sharp signal at 10.5 τ (2 protons). The absorption of the olefinic protons at very low field, combined with strong shielding of the $CH_2$-protons above the peripheral ten-membered ring, can be considered as evidence [4] for the presence of a ring current and, therefore, for the 1,6-methanocyclodecapentaene structure *(6)* to *(8)* [5]. 1,6-Methanocyclodecapentaene is highly strained, however, and is certainly not an aromatic compound in the classical sense, because it exhibits olefinic reactivity just like the [18]- and [30]annulenes [6].

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German version: Angew. Chem. 76, 145 (1964)

[1] *T. J. Katz*, J. Amer. chem. Soc. *82*, 3784 (1960); *T. J. Katz* and *P. J. Garratt*, ibid. *85*, 2852 (1963), and *E. A. LaLancette* and *R. E. Benson*, ibid. *85*, 2853 (1963) described negatively charged 10-π-electron carbocycles with aromatic character, *viz.* the cyclooctatetraene dianion and the cyclononatetraenyl anion.

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[5] A fluctuating structure seems unlikely in view of the position of the olefinic protons in the NMR spectrum; however, it remains a possibility.

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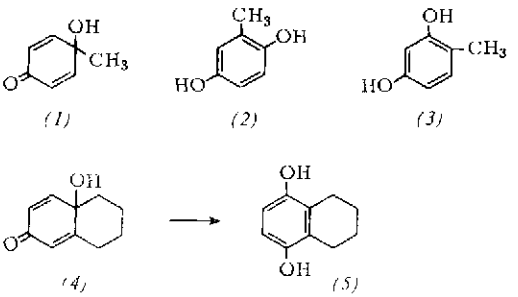
## Rearrangements of *p*-Quinols in Trifluoroacetic Anhydride

By Doz. Dr. E. Hecker and E. Meyer

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*p*-Alkylphenols of biochemical importance are oxidized during intermediary metabolism to *p*-quinols [1], which rearrange to alkylhydroquinones under the influence of enzymes.

Rearrangements of *p*-quinols in trifluoroacetic anhydride yield the same products. The *p*-quinolide compound is dissolved in trifluoroacetic anhydride at room temperature and, after some time, the reagent is evaporated. On short hydrolysis with dioxan/water, the phenolic products of rearrangement are usually obtained in quantitative yield and in pure form. Some of the labile trifluoroacetates of the phenolic products of rearrangement can be isolated before hydrolysis.



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

*(4)* *(5)*

*p*-Toluquinol *(1)* yields toluhydroquinone *(2)* and resorcinol *(3)*, but rearrangement of the methyl and tetrahydropyranyl ethers of *p*-toluquinol yields only the hydroquinone and no resorcinol derivative. Tetralin-*p*-quinol *(4)* and its ethers rearrange exclusively to 5,8-dihydroxytetralin *(5)* or its monoethers, with 1,3-migration of the alkyl substituent. The acetates and benzoates of *p*-toluquinol and tetralin-*p*-quinol are converted exclusively into the monoesters of the corresponding resorcinol derivatives.

The rearrangements can be explained by assuming that even at room temperature trifluoroacetic anhydride contains a sufficient concentration of $CF_3CO^{\oplus}$ ions to cause electrophilic attack on the carbonyl group of the dienone system and thereby to initiate anionic migration of substituents and consequent aromatization. With *p*-quinols and their ethers, the alkyl group migrates preferentially; with quinol esters, the acyl group migrates considerably faster than the alkyl group. The exceptional behavior of *p*-toluquinol (and other monocyclic *p*-quinols) can be explained by assuming that esterification of the hydroxyl group competes with the migration of the alkyl group, and that subsequent rapid migration of the attached trifluoroacetyl group occurs. The high rate of esterification [2] of *p*-toluquinol and the small rate of migration of the alkyl group can be established by kinetic measurements [3].

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[1] *E. Hecker* and *S. M. A. D. Zayed*, Hoppe-Seylers Z. physiol. Chem. *325*, 209 (1961); cf. Angew. Chem. *71*, 744 (1959); *E. Hecker* and *F. Marks*, Naturwissenschaften *50*, 304 (1963).

[2] *E. Hecker* and *R. Lattrell*, Chem. Ber. *96*, 639 (1963).

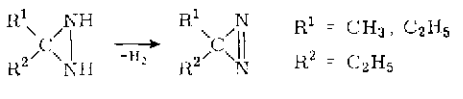
[3] *E. Hecker* and *E. Meyer*, Chem. Ber., in the press.

## Thermal Dehydrogenation of C,C-Dialkyldiazacyclopropanes

By Dr. A. Jankowski and Dr. S. R. Paulsen

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*C,C*-Dialkyldiazacyclopropanes *(1)* are dehydrogenated by oxidizing agents (yellow mercuric oxide, permanganate, chromic acid) to give *C,C*-dialkyldiazacyclopropenes *(2)* [1,2].



$R^1 = CH_3, C_2H_5$
$R^2 = C_2H_5$

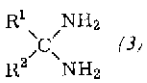
*(1)* *(2)*

We have found that compounds of type *(1)* can also be dehydrogenated to *(2)* simply by heating to 125 °C. In addition to *(2)*, ammonia and a high molecular-weight nitrogenous residue are formed.

On addition of Cu(I) or Cu(II) salts to solvent-free *(1)*, strongly exothermic dehydrogenation starts, according to the type of the groups R, either spontaneously at room temperature or on warming to 60 °C. In the presence of water and copper or copper salts, 1 mole of *(1)* is converted in 96.5 % yield into 0.5 mole of *(2)*, 1 mole of $NH_3$, and 0.5 mole of a ketone with the same carbon skeleton as *(1)*.

The products were separated by distillation and identified by infrared spectroscopy, gas chromatography, and refractive indices.

We assume that in this reaction 1 molecule of *(1)* is dehydrogenated by a second molecule of *(1)*, giving rise to *(2)* and the *C,C*-diamino compound *(3)*. The latter condenses to high molecular-weight compounds with loss of



*(3)*

ammonia or, in the presence of water, is hydrolysed to the ketone and ammonia.

Received, January 3rd and 29th, 1964 [Z 655/480 IE]
German version: Angew. Chem. *76*, 229 (1964)

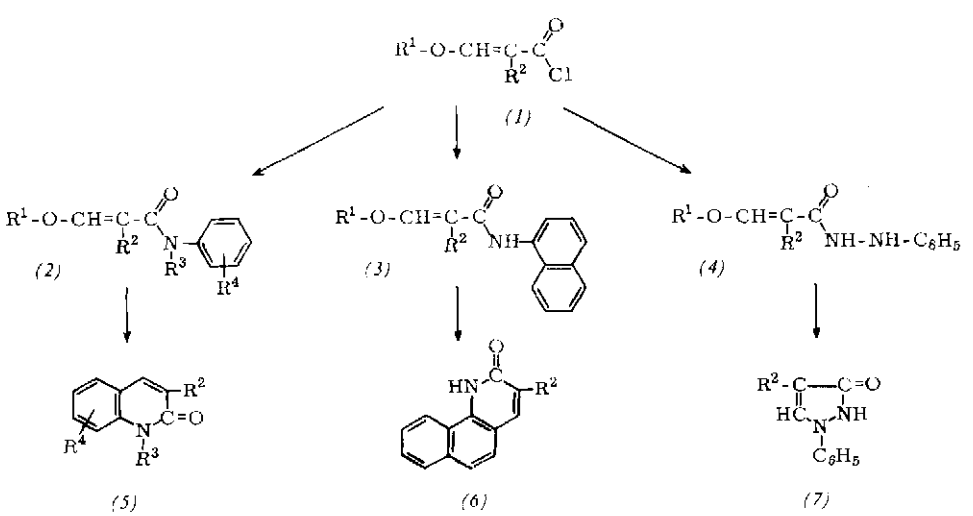
[1] *S. R. Paulsen*, Angew. Chem. *72*, 781 (1960).
[2] *E. Schmitz* and *R. Ohme*, Chem. Ber. *94*, 2166 (1961).

## Syntheses with β-Alkoxyacrylyl Chlorides

By Dr. F. Effenberger and Dipl.-Chem. W. Hartmann

Institut für Organische Chemie und Organisch-Chemische Technologie der Technischen Hochschule Stuttgart (Germany)

The interaction of β-alkoxyacrylyl chlorides *(1)* [1] with alcohols, phenols, thiophenols, hydrazines, and amines has afforded new derivatives of β-alkoxyacrylic acids, some of which are suitable for the synthesis of otherwise difficultly accessible heterocyclic compounds.



When the anilides *(2)* are ground with concentrated mineral acids, carbostyrils *(5)* are obtained smoothly within a few minutes in good yields. Table 1 gives a list of examples.

The action of concentrated acids on the naphthalides *(3)* gave benzoquinolones *(6)* [$R^2$ = H, m.p. 257 °C, 100 % yield; $R^2$ = $CH_3$, m.p. 240 °C, 95 % yield] and on the phenylhydrazides *(4)* gave 1-phenylpyrazol-3-ones *(7)* [$R^2$ = H, m.p. 153 °C, 98 % yield].

Table 1. Examples of the reaction *(2)* → *(5)*

| Anilide *(2)* $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield of *(5)* [%] | M.p. [°C] |
|---|---|---|---|---|---|
| $C_2H_5$ | H | H | H | 100 | 199 |
| $C_2H_5$ | H | $CH_3$ | H | 73 | 72 |
| $C_2H_5$ | $CH_3$ | H | H | 82 | 238 |
| $C_2H_5$ | H | H | *p*-$CH_3$ | 100 | 241 |
| $C_2H_5$ | H | H | *o*-$CH_3$ | 89 | 224 |
| $C_2H_5$ | H | H | *p*-Cl | 100 | 275 |
| $C_2H_5$ | H | H | *o*-Cl | 100 | 210 |
| $C_2H_5$ | $CH_3$ | H | *o*-$CH_3$ | 98 | 180 |

Starting with aminoanthracene or aromatic diamines, we obtained more highly condensed ring systems.

Received, January 2nd, 1964 [Z 648/475 IE]
German version: Angew. Chem. *76*, 188 (1964)

[1] U.S. Pat. 2768174 (Oct. 23rd, 1956) Societé des usines chimiques Rhône-Poulenc, inventors: *R. E. Paul* and *S. Tchelitcheff*; Chem. Abstr. *51*, 5818 (1957).

## Inversion of the Triphenylamine Molecule

By Dipl.-Phys. P. Knobloch and Dipl.-Phys. M. Stockhausen

Physikalisches Institut der Universität Mainz (Germany)

Conclusions can be drawn from the relaxation time of dipole orientation in dilute solution about the mechanism by which the electrical moment of a polar molecule orientates in the applied electrical field. Moments that are rigidly incorporated into the molecule can only orientate by rotation of the whole molecule, resulting in a relatively long relaxation time. However, if intramolecular adjustment can occur making more rapid dipole orientation possible, without the whole molecule having to move, the relaxation time is less.

Table 1. Relaxation times $\tau$ of the dipole orientation and dipole moments $\mu$ of triaryl derivatives of Group V elements in benzene.

| Compound | $\tau$ [sec] | $\mu$ [Debye] |
|---|---|---|
| Triphenylarsine | $77 \times 10^{-12}$ | 1.18 |
| Triphenylphosphine | $60 \times 10^{-12}$ | 1.52 |
| Triphenylamine | $0.7 \times 10^{-12}$ (approx.) | 0.66 |
| Tribenzylamine | $70 \cdot 10^{-12}$ | 0.7 |

Our relaxation measurements [1] yielded direct information about the different modes of behavior of triphenylamine and the triaryl derivatives of the higher elements of Group V. Results obtained for solutions in benzene are shown in Table 1.

Relaxation times of the magnitude shown for the first two substances in Table 1 were to be expected, in view of the rotatory orientation of the entire molecule. This could be

estimated from the molecular volumes and data derived from a large amount of experimental material [2]. In contrast, the considerably shorter relaxation time for triphenylamine can only be explained by internal mobility. Evidently inversion takes place, facilitated by the arrangement of the N-Ph bonds in a pyramid that is flatter than those of the other two molecules. The low dipole moment of triphenylamine also implies very close approximation to a flat structure, with valence angles greater than the tetrahedral angle. These determinations assure that any inversion in triphenylarsine and triphenylphosphine should be at least 100 times less probable than in the amine. Moreover, the values for tribenzylamine show that inversion evidently occurs only when the nitrogen is linked to an aromatic ring [*].

The relaxation times were determined by microwave absorption. For this purpose, dilute solutions (about 1 mole-%) in benzene were examined at 20 °C at frequencies varying between 500 Mc ($\lambda$ = 60 cm) and 115 Gc ($\lambda$ = 2.6 mm).

Received, January 8th, 1964 [Z 651/482 IE]
German version: Angew. Chem. 76, 186 (1964)

[1] For apparatus and methods of measurement, see *H. Kramer*, Z. Physik *157*, 134 (1959); *F. Hufnagel* and *G. Klages*, Z. angew. Physik *12*, 202 (1960).

[2] *F. Hufnagel*, Z. Naturforsch. *15a*, 723 (1960); *F. Hufnagel*, *G. Klages*, and *P. Knobloch*, ibid. *17a*, 96 (1962), where further references are given.

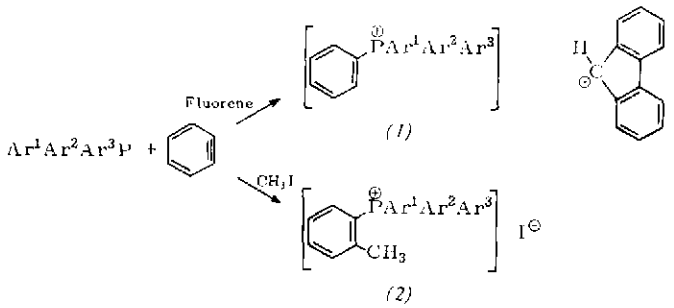
[*] This may be explained as follows: The bonding state of the nitrogen atom may contain $sp^2$-hybridization which is energetically favored because of mesomeric interaction between the phenyl groups and the lone electron pair at the nitrogen atom. Since the gain in energy due to mesomerism is greatest in the planar form of the molecule, inversion will be facilitated.

## A New Approach to Tetraarylphosphonium Salts

By Prof. Dr. G. Wittig and Dipl.-Chem. H. Matzura

Institut für Organische Chemie der Universität Heidelberg (Germany)

A recent note dealing with the interaction of dehydrobenzene with diphenylmethylphosphine [1] prompts us to report results we obtained some time ago. *o*-Fluorophenyl-lithium prepared according to *Gilman* and *Gorsich* [2] does not react with triarylphosphine at −75 °C. On being allowed to thaw in the presence of fluorene, the reaction mixture affords the tetraarylphosphonium salt at −40 °C in 67 % yield. Analogous reactions with methyl iodide in place of the fluorene produce the *o*-methyl derivatives, also in good yield.




*(1)* *(2)*

a) $Ar^1 = Ar^2 = Ar^3$ = phenyl
b) $Ar^1$ = phenyl, $Ar^2$ = p-tolyl, $Ar^3$ = p-biphenylyl

Compound *(1a)* was characterized as its bromide, m.p. 288–290 °C, and iodide, m.p. 330–332 °C. The structures of the iodides *(2a)*, m.p. 294–296 °C, and *(2b)*, m.p. 271–273 °C, were confirmed by elemental analyses and infrared spectra. The new method [3] is being applied principally for the preparation of pentaarylphosphoranes with five non-identical substituents for the purpose of studying their stereochemistry.

Received, January 17th, 1964 [Z 645/473 IE]
German version: Angew. Chem. 76, 187 (1964)

[1] *D. Seyferth* and *J. M. Burlitch*, J. org. Chemistry *28*, 2463 (1963).

[2] *H. Gilman* and *R. D. Gorsich*, J. Amer. chem. Soc. *78*, 2217 (1956).

[3] For an analogous synthesis of ammonium salts, see *G. Wittig* and *E. Benz*, Chem. Ber. *92*, 1999 (1959).

## The Crystal Structure of Titanium Phosphide $Ti_5P_3$

By Prof. Dr. G. Brauer, Dr. K. Gingerich, and Dipl.-Chem. M. Knausenberger [1]

Chemisches Laboratorium der Universität Freiburg/Breisgau (Germany)

and The Pennsylvania State University, Dept. of Chemistry, University Park, Penns. (U.S.A.)

We have found a hitherto unknown Ti/P phase with about 68.5 % (by weight) Ti and 30.3 % P. The X-ray powder diagrams of samples of this and similar composition display a consistently characteristic diffraction pattern, which is easily distinguishable from those of neighboring phases. A single crystal was isolated from one of the samples. X-ray examination of this crystal and of the powdered material indicated a hexagonal unit cell with dimensions a = 7.234 Å; c = 5.090 Å; c/a = 0.704 Å. The phase appears to have a range of homogeneity. From the density of the substance (d = 4.85 g/cm³) we calculated that the unit cell contains 10 Ti and 6 P atoms. This leads to the formula $Ti_5P_3$ and a crystal structure of the $D8_8$ type ($Mn_5Si_3$); space group $P6_3/mcm$. This structure was confirmed by intensity measurements on integrated Weissenberg photographs. The free parameters $x_{Ti}$ = 0.251 and $x_P$ = 0.610 of the six-fold point of symmetry (g) in the space group $P6_3/mcm$ were obtained from the electron density distribution along the line parallel to the x-axis and passing through the point $0,0,{}^1/_4$ (unidimensional Fourier analysis using three-dimensional data).

Received, January 21st, 1964 [Z 650/472 IE]
German version: Angew. Chem. 76, 187 (1964)

[1] We wish to thank Dr. *H. Bärnighausen* for assistance with the X-ray investigations.

## Methylgermylamines

By Dr. Ingeborg Ruidisch and Prof. Dr. Max Schmidt

Institut für Anorganische Chemie der Universität Marburg (Germany)

We have obtained 1,1,1,3,3,3-hexamethyldigermazane *(1)* in dry ether as a colorless liquid, b.p. 47 °C/17 mm, which reacts readily with the slightest trace of moisture to yield the isosteric germoxane and ammonia.

$$2\,(CH_3)_3GeCl + 3\,NH_3 \rightarrow (CH_3)_3Ge\cdot NH\cdot Ge(CH_3)_3 + 2\,NH_4Cl$$

*(1)*

The NMR spectrum of *(1)* has $\delta_{(CH_3\text{-}Ge)}$ as a sharp singlet at −13 cps, $J_{^1H,^{13}C}$ = 126.5 cps [1,2]; its infrared spectrum has peaks at 3390, 2960, 2861, 1405, 1234, 1183, 819, and 780 $cm^{-1}$ [3]. Trisdimethylchlorogermylamine *(2)* is obtained from $(CH_3)_2GeCl_2$ under analogous conditions according to the equation

$$3\,(CH_3)_2GeCl_2 + 4\,NH_3 \rightarrow [(CH_3)_2GeCl]_3N + 3\,NH_4Cl$$

*(2)*

(together with polymeric dimethylgermazanes and amines) as colorless crystals, m.p. 62 °C, subl. p. ≈ 75 °C/2 mm, which are quantitatively hydrolysed by water, albeit more slowly than *(1)*.

Its NMR spectrum has $\delta_{(CH_3\text{-}Ge)}$ sharp at −63.5 cps, $J_{^1H\text{-}^{13}C}$ = 130.0 cps [1]; its infrared spectrum has characteristic bands at 1247, 839, and 816 $cm^{-1}$ [3].

With methyl-lithium, *(2)* reacts according to the equation

$$[(CH_3)_2GeCl]_3N + 3\ LiCH_3 \rightarrow \underset{\displaystyle N}{\overset{(CH_3)_3Ge}{\overset{|}{}}}\!\!\!\!\!\!\!\!\begin{matrix} Ge(CH_3)_3 \\ | \\ Ge(CH_3)_3 \end{matrix} + 3\ LiCl \qquad (3)$$

to form tristrimethylgermylamine *(3)*, a colorless liquid (b.p. 60 °C/2 mm), which is slowly decomposed by moisture into germoxane and ammonia. The NMR spectrum of *(3)* has $\delta_{(CH_3\text{-}Ge)}$ sharp at −18 cps, $J_{^1H\text{-}^{13}C}$ = 126.5 cps [1]; its infrared spectrum has peaks at 2985, 2924, 1441, 1235, 817, and 754 $cm^{-1}$ [3].

Received, January 27th, 1964 [Z 653/479 IE]
German version: Angew. Chem. 76, 229 (1964)

[1] In 5% solution in $CCl_4$, Varian A 60 (60 Mc); standard: tetramethylsilane.

[2] An N–H proton signal is not observed on account of the strong broadening due to H-$^{14}$N coupling.

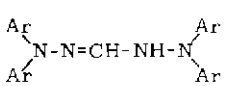
[3] Perkin-Elmer Infracord spectrophotometer, Model 137; the spectrum of *(2)* was taken in Nujol suspension.

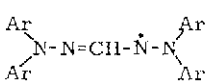
## Tetraazapentenyl Radicals

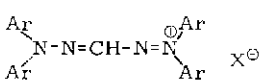
By Prof. Dr. Richard Kuhn, Dr. F. A. Neugebauer, and H. Trischmann

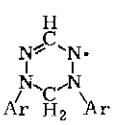
Institut für Chemie, Max-Planck-Institut
für Medizinische Forschung, Heidelberg (Germany)

Condensation of orthoformic esters with N,N-diphenylhydrazine in the presence of $BF_3$ affords the colorless compound 1,1,5,5-tetraphenyl-1,2,4,5-tetraaza-2-pentene *(1)*, m.p. 121–123 °C (decomp.), in 69 % yield. On dehydrogenation (*e.g.* with $O_2$, $PbO_2$, or $Ag_2O$), *(1)* gives the bluish-green free radical 1,1,5,5-tetraphenyl-1,2,4,5-tetraazapentenyl *(2)*, which crystallizes from benzene/petroleum ether as nearly black prisms, m.p. 115–116 °C (decomp.); its magnetic moment $\mu_{eff}/\mu_B$ = 1.65 (found), its electron spin resonance spectrum has a very large number of lines (> 64) at intervals of about 0.7 gauss [1].

*(1)* 

*(2)* 

*(3)* 



*(4)*

In their chemical and physical behavior, the new free radicals of type *(2)* are closely related to the cyclic verdazyl radicals *(4)* [2]. Like these substances they undergo disproportionation to form leuco compounds *(1)* and violet salts *(3)* in the presence of acids. Their longest-wavelength absorption maxima are:

| Ar | Radicals *(2)* in dioxan | Cations *(3)* in formic acid |
|---|---|---|
| Phenyl | 631 mμ | 537 mμ |
| *p*-Tolyl | 646 mμ | 567 mμ |
| *p*-Bromophenyl | 645 mμ | 566 mμ |

In accordance with theoretical expectations, the fact that the tetraazapentenyls can be prepared shows that the $CH_2$-bridge in the verdazyls (through which no ring current can pass) is only of limited importance for the remarkable readiness with which they are formed and for their great stability [2].

The open-chain free radicals *(2)* are, however, much less stable. On melting or on prolonged standing in solution, radical *(2)* (R = phenyl) decomposes to give diphenylamine, an orange red azo compound (m.p. 240–241 °C), and polymeric products:

$$(2) \longrightarrow Ar\text{–}NH\text{–}Ar + (Ar)_2N\text{–}N{=}CH\text{–}N\text{–}N\text{–}CH{=}N\text{–}N(Ar)_2$$

Received, February 3rd, 1964 [Z 657/485 IE]
German version: Angew. Chem. 76, 230 (1964)

[1] Measured by Prof. *K. H. Hausser*.

[2] *R. Kuhn* and *H. Trischmann*, Angew. Chem. 75, 294 (1963); Angew. Chem. internat. Edit. 2, 155 (1963); Mh. Chem., in the press.

## Preparation of P(III) and P(III/V) Oxides

By Prof. Dr. E. Thilo, Dr. D. Heinz, and Dr. K.-H. Jost

Institut für Anorganische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Adlershof, and I. Chemisches Institut der Humboldt-Universität, Berlin (Germany)

Large quantities of the hitherto only difficultly accessible phosphorus(III) oxide $P_4O_6$ have been prepared by a continuous process in yields of up to 50 % by oxidation of white phosphorus with $N_2O$ at *ca.* 70 mm and 600 °C [1].

Attempts to obtain $(PO_2)_n$ [2] by thermal decomposition of $P_4O_6$ resulted in the formation of at least two phosphorus(III/V) oxides with different compositions and crystal structures. Rhombohedral mixed crystals of $P_4O_9$ and $P_4O_8$ molecules (α-form) and monoclinic mixed crystals of $P_4O_8$ and $P_4O_7$ molecules (β-form) were obtained. This was demonstrated by examination of the hydrolysis products [P(III) acids, P(III)–O–P(III) and P(III)–O–P(V) acids or compounds, and mono-, di-, tri-, and trimeta-phosphoric acids] [3] and X-ray structural investigations [4]. The stoichiometric composition of the α-form is $P_4O_{8-9}$, and that of the β-form is $P_4O_{7-8}$. Pure $P_4O_7$ has not yet been prepared. The $P_4O_9$, $P_4O_8$, and $P_4O_7$ molecules are structurally similar to the $P_4O_{10}$ molecule but lack respectively one, two, or three of the terminal oxygen atoms. The lattice constants are independent of the composition, but the densities vary accordingly.

The phosphorus(III/V) oxides are diamagnetic. Their mean molecular weights in the vapor phase corresponds to the compositions found.

Phosphorus(III/V) oxides can also be obtained by the reaction between phosphorus(V) oxide and elemental phosphorus in an inert gas atmosphere.

Received, January 30th, 1964 [Z 656/484 IE]
German version: Angew. Chem. 76, 229 (1964)

[1] East German Pat. 26660 (June 11th, 1960), inventors: *D. Heinz* and *E. Thilo*.

[2] *T. E. Thorpe* and *A. E. Tutton*, J. chem. Soc. (London) *49*, 833 (1886); *57*, 545 (1890); *C. A. West*, ibid. *81*, 923 (1902); *P. H. Emmet* and *J. F. Schulz*, Ind. Engng. Chem. *31*, 105 (1939).

[3] *D. Heinz*, Z. anorg. allg. Chem., in the press.

[4] *K.-H. Jost*, Acta crystallogr., in the press.

# Third International Congress of Chemotherapy

The Third International Congress of Chemotherapy was held in conjunction with the first general meeting of the International Society for Chemotherapy in Stuttgart (Germany) from July 22nd to 27th, 1963. The congress was attended by over 1000 scientists from 43 countries and included 376 papers; this represents a considerable increase in support for the society, which was founded only a few years ago. The previous meetings were at Geneva in 1959 with about 400 participants and 18 papers, and at Naples in 1961 with 600 participants and 186 papers.

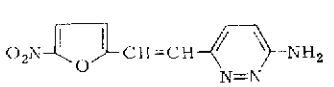
The congress was principally concerned with the chemotherapy of bacterial infections (including tuberculosis), virus diseases, and neoplasmata. In addition, the chemoprophylaxis and chemotherapy of radiation damage, the chemotherapy of tropical and autoimmune diseases, to a lesser extent the chemotherapy of mycosis and haemochromatosis, the relation of chemotherapy to embryopathies, *etc.*, were discussed. Outside the actual agenda were questions on the control of drugs and especially on the international exchange of information on antibiotics.

A considerable part of the proceedings was taken up with questions of the practical application of drugs, their actions and side-effects, dosages, the possibilities of combination therapy, the circumvention of resistance phenomena, the distribution of drugs in the tissues, experimental assay methods, *etc.* A large number of contributions was devoted to the scientific basis of chemotherapy, including investigations of the biochemistry of drug action, the kinetics of drug action, the causes of resistance, and the improvement of clinical testing methods. A third and smaller part of the proceedings dealt with new chemotherapeutic agents. Only this part will be reported below; some of the newer preparations and their specific actions will be described [*].

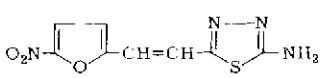
## New Chemotherapeutic Agents for the Treatment of Bacterial Infections

With regard to drugs for treating bacterial infections, there were reports on new nitrofuran compounds and sulfonamides as well as on various other synthetic compounds and some new antibiotics.

The *in vitro* and *in vivo* bactericidal and bacteriostatic action of two new nitrofuran derivatives, designated HB 115 *(1)* and HB 126 *(2)*, was described by *W. Vömel*, Mannheim (Germany). These substances showed $10^1$–$10^2$ times higher antibacterial activity *in vitro* than known nitrofuranes. Full use



*(1)*

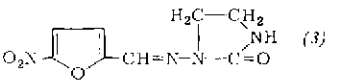


*(2)*

can be made of this increase in external applications. Oral administration results in a high antibacterial activity in the excreta; both substances are thus best suited for treating urinary and intestinal infections. Levels effective against general bacterial infections are not attained in blood or tissues.

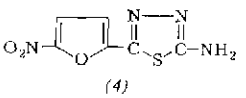
[*] The proceedings of the congress will be published by Thieme-Verlag, Stuttgart (Germany), and are due to appear early in 1964.

*J. R. O'Connor* and coworkers, Norwich (England), also introduced a new nitrofuran compound with urinary activity, *viz.* NF 246 *(3)*; this differs from Furadantin® by replacement of the hydantoin ring by an imidazolidinone ring. NF 246 is especially suitable for the treatment of chronic urinary infections which, in contrast to acute infections, can only be treated with difficulty.

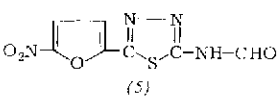


*(3)*

*K. Skagius*, Uppsala (Sweden), and other workers reported on investigations with 5-(5′-nitro-2′-furyl)-2-amino-1,3,4-thiadiazoles. The most active proved to be 2-amino-5-(5′-nitro-2′-furyl)-2-amino-1,3,4-thiadiazole *(4)* and 2-formylamino-5-(5′-nitro-2′-furyl)-1,3,4-thiadiazole *(5)*, which were tested under the code numbers Ph 778/1B and Ph 778/78. They have



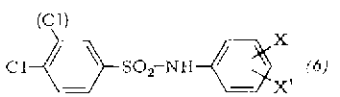
*(4)*



*(5)*

been used with considerable success in the treatment of intestinal infections by *Coli*, *Salmonella*, and *Schigella* bacteria.

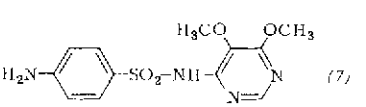
Among the reports on new sulfonamides was that of *E. Jeney* and *T. Zsolnai*, Debreczen (Hungary), dealing with the bacteriostatic action of *N*-arylmethanesulfonamides and *N*-aryl-3,4-dichlorobenzenesulfonamides. Some of these compounds with a halogen substituent in the *m*- and/or *p*-position of the *N*-aryl ring have a more or less bacteriostatic action both on *Staphylococcus aureus* strains that are sentitive to sulfanilamides and on resistant *Staph. aureus* and *Staph. albus* strains. They are ineffective against Gram-negative bacteria. The majority of compounds investigated also showed fungistatic activity. On the basis of results obtained *in vitro*,



*(6)*

some of the halogen substituted [X = X′ = halogen in *(6)*] *N*-phenyl derivatives of 4-chloro- and 3,4-dichlorobenzenesulfonamides are at present being tested clinically against pyodermias, which are caused by Gram-positive bacteria, and for local treatment of skin mycosis.

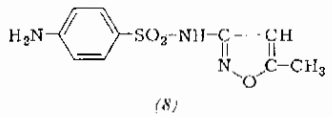
*E. Böhni* and coworkers, Basel (Switzerland), investigated the relationships between constitution and chemotherapeutic action in substituted 2-, 4-, and 5-sulfanilamidopyrimidines. Activity is closely related to structure. Only methyl, methoxy, dimethoxy, methyl plus methoxy, halogen, or halogen plus methoxy substituents in the pyrimidine ring raise the activity of the standard preparation, sulfadiazine. 4-Sulfanilamidopyrimidines with a methoxy group in the 6- or two methoxy groups in the 5- and 6-positions are most active. 4-Sulfanilamido-5,6-dimethoxypyrimidine *(7)* has been tested



*(7)*

clinically for some time now as the preparation Ro 4-4393, and several reports on it were given. It is characterized by an especially long lasting action. Sulfonamide activity was observed up to a week after doses of 1 to 1.5 g.

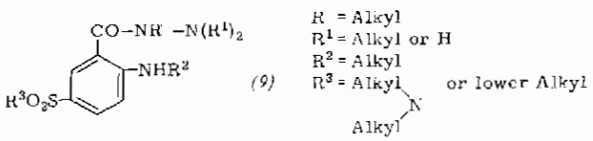
A promising sulfonamide, sulfamethoxazole or 5-methyl-3-sulfanilamidoisoxazole *(8)*, is being tested clinically under the test designation Ro 4-2130 (Gantanol®). According to a



*(8)*

report from *J. H. Peters*, Lackland Air Force Base, it has proved to be especially suitable for treating acute febrile pharyngitis caused by *Streptococci*.

Among the new synthetic compounds, chemotherapeutically active anthranilohydrazides having a dialkylsulfamyl residue *para* to the amino group appear to be interesting. These substances were the subject of a report by *P. Schmidt* and

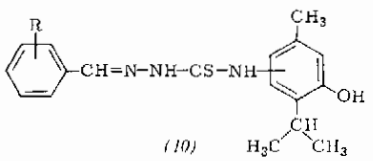


*(9)*

$R$ = Alkyl
$R^1$ = Alkyl or H
$R^2$ = Alkyl
$R^3$ = Alkyl, Alkyl, Alkyl or lower Alkyl

*I. Neipp*, Basel (Switzerland). The compounds *(9)* are active against *Staph. aureus* and *Diplococcus pneumoniae*, but activity is restricted to compounds with small alkyl groups.

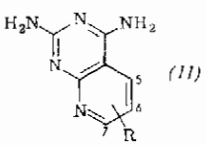
Another new group of active substances are the thymolylthiosemicarbazones *(10)*, which were described by *B. Prescott* and coworkers, Bethesda, Md. (U.S.A.). Fourteen



*(10)*

derivatives showed definite action against *Staph. aureus*. Four thymolylthiosemicarbazones, namely those of salicylaldehyde, 5-chlorosalicylaldehyde 5-nitrosalicyclaldehyde, and 3-ethoxy-4-hydroxybenzaldehyde, showed marked antibacterial activity at concentrations of 4 μg/ml.

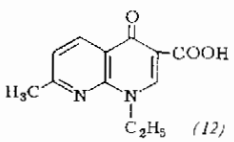
*G. H. Hitchings* and coworkers, Tuckahoe, N.Y. (U.S.A.), presented 2',4'-diaminopyrido[2.3-*d*]pyrimidines *(11)* as a new group of antibacterial agents that are effective both *in vitro* and *in vivo*. Like other 2,4-diaminopyrimidines, these



*(11)*

are regarded as folic reductase inhibitors. Investigations with the 5-, 6-, and 7-alkyl, -aryl, or -aralkyl substituted compounds showed that activity is markedly dependent on the form and size of the 6-substituent and somewhat less on those of the 5-substituent. The influence of 7-substituents is slight.

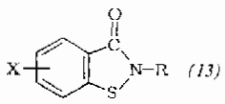
*G. Y. Lesher* and coworkers, Rensselaer, N.Y. (U.S.A.), reported on investigations of 1-alkyl-1,8-naphthyridine-4-one-3-carboxylic acids. By far the most active of these compounds was 1-ethyl-7-methyl-1,8-naphthyridine-4-one-3-carboxylic acid, or nalidixinic acid *(12)*, which has been successfully



*(12)*

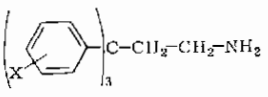
tested *in vitro* and *in vivo* against Gram-negative bacteria, especially *E. coli*, *Proteus rettgeri*, *P. mirabilis*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Pasteurella multocida*, *Shigella flexneri*, and *Salmonella typhimurium*. Several reports confirmed that nalidixinic acid is well tolerated by man.

The bacteriostatic and fungistatic actions of derivatives of 1:2-benzisothiazolones *(13)* were investigated by *R. Fischer*, Bern (Switzerland). Suitably substituted compounds have a wide spectrum of action against both Gram-positive and Gram-negative bacteria and against fungi. 6-Chloro-1,2-benzisothiazolone [X = 6-Cl, R = H in *(13)*] is especially active.

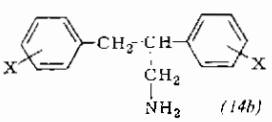


*(13)*

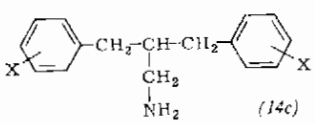
The halogenoaralkylamine derivatives *(14a)* to *(14c)* dealt with by *M. Schorr*, Frankfurt (Germany), also have high chemotherapeutic activity and show pronounced antibacterial and antimycotic actions.



*(14a)*



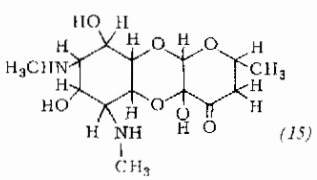
*(14b)*



*(14c)*

With regard to antibiotics, the semi-synthetic penicillins produced from 6-aminopenicillanic acid were well to the fore. Actinospectacin and fusidinic acid were introduced as new antibiotics.

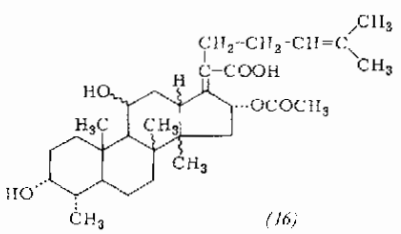
*G. M. Savage*, Kalamazoo, Mich. (U.S.A.), obtained good results using actinospectacin *(15)*, a broad-spectrum antibiotic isolated from *Streptomyces spectabilis*. It shows hardly



*(15)*

any side effects and no clinically significant toxicity, but can only be applied parenterally.

*J. Meyer-Rohn*, Hamburg (Germany), reported on the successful application of fusidinic acid *(16)* to the treatment of staphylococcal skin infections and other pyodermias. Only

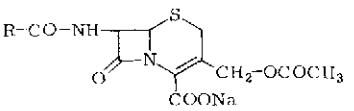


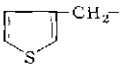
*(16)*

one out of 200 *Staphylococcus* strains proved resistant to fusidinic acid. This antibiotic (m.p. 193 °C) was isolated from the mold *Fusidium coccineum*.

*R. S. Griffiths*, Indianapolis, Ind. (U.S.A.), obtained favorable results using cephalothin *(17a)*, a product developed from the antibiotic cephalosporin C *(17b)*. It was active against Gram-positive and Gram-negative bacteria and has proved especially effective clinically against urinary infections.

Resorption is very small on oral administration, but adequate concentrations are easily attained by parenteral application. Cross resistance with other antibiotics was not observed.

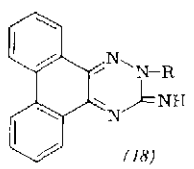


*(17a)*: R = 

*(17b)*: R = $HOOC-CH(NH_2)-(CH_2)_8-$

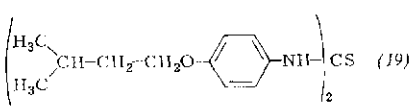
## Chemotherapy of Tuberculosis

*H. Umezawa* and coworkers, Tokyo (Japan), reported on a new antibiotic, ilamycin, which inhibits mycotic bacteria. Ilamycin is isolated together with another antibiotic, ilamycin B, from *Streptomyces islandicus*. L-Alanine, L-leucine, L-*N*-methylleucine, and L-3-nitro-4-hydroxyphenylalanine were detected after hydrolysis of ilamycin. Ilamycin inhibits the growth of *Mycobact. tuberculosis* at a concentration of 0.5 μg/ml. However, investigations on experimental tuberculoses did not give consistent results, and ilamycin is thus still of no practical importance.



*(18)*

2-Alkyl-3-iminophenanthrotriazines *(18)* have strong tuberculostatic activity *in vitro* and were discussed by *W. H. Wagner*, Frankfurt (Germany). They also show distinct activity against tuberculosis in mice. The highest activity was obtained with 2-ethyl-3-imino[9,10-*e*]phenanthro-1,2,4-triazine hydrochloide, a yellow microcrystalline substance (m.p. 183 °C), which showed stronger inhibition of the human and bovine tubercle bacilli strains investigated in the various media than INH did. However, the prophylatic and therapeutic action in mice infected with tubercle bacilli is less than that of INH or streptomycin. Hardly any therapeutic action was demonstrable against tuberculosis in guinea pigs and rabbits.



*(19)*

4,4'-Diisoamyloxythiocarbanilide, DATC, or (isoxyl) *(19)*, is a new antitubercular agent of the thiocarbanilide series and was presented by *L. Eidus* and *E. J. Hamilton*, Ottawa, Canada. It is well tolerated, but since it attains only low blood levels, it must be used in combination with other drugs.

## Therapy of Neoplastic Growths

In the field of the chemotherapeutic treatment of neoplasmata, the contributions were mainly concerned with further details of known carcinostatic substances, *e.g.* of alkylating compounds, antimetabolites, steroids, carcinostatic antibiotics, and some plant materials, such as the vinca alkaloids. In addition, various new antineoplastic antibiotics and synthetic substances were described; however, these mostly showed no marked advantage over previous materials.

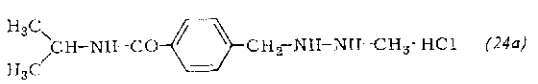
Two new antibiotics with pronounced antineoplastic activity are enomycin and pbleomycin, which were investigated by *H. Umezawa*, Tokyo (Japan), and coworkers. Enomycin is obtained from a culture filtrate of *Streptomyces mauvecolor* mainly by chromatographic separation. It is a peptide with a molecular weight of 2000–5000 and produced a clear antitumor action in subtoxic doses against the Ehrlich ascites tumor and Yoshida sarcoma. Phleomycin consists of a mixture of antibiotics containing copper and is produced from cultures of *Streptomyces verticillus*. It is active against experimental animal tumors, *e.g.* Ehrlich carcinoma in mice, and inhibits growth of hela cell cultures and Yoshida sarcoma cells. It influences the synthesis of DNA but not protein synthesis.

*G. F. Gause*, Moscow (U.S.S.R.), reported on recent results obtained by *M. G. Brazhnikova* and coworkers with the new antitumor antibiotic, olivomycin. This antibiotic is isolated from *Actinomyces olivoreticuli* by extraction with butyl acetate at pH 5.0. It markedly inhibits growth of many animal tumors, and has also given positive results in clinical trials on a series of malignant tumors, *e.g.* melanoma and bronchial carcinoma. Olivomycin crystallizes in yellow needles. It consists of at least three different substances.

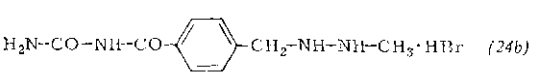
*A. di Marco*, Milan (Italy), reported on daunomycin, a new antibiotic of the rhodomycin group. This also acts against animal tumors, especially against Ehrlich carcinoma, sarcoma 180, Yoshida sarcoma, hepatoma AH 130, and myeloma. It clearly increased the period of survival of animals with tumors.

Iyomycin, another new antitumor antibiotic was described by *H. Kentaro*, Tokyo (Japan). It is extracted from a culture medium containing *Streptomyces pheoverticulatus* and is a marcomolecular substance. The antitumor activity is distinctly higher and the toxicity lower than that of other antitumor antibiotics, *e.g.* carcinophilin, mitomycin, and melanomycin. Sarcoma 180 can be reduced or healed by daily intraperitoneal or intravenous subtoxic doses. Iyomycin is therefore a very promising new substance.

*W. Bollag*, Basel (Switzerland), introduced methylhydrazine compounds as a new class of syntbetic cytostatic agents. 1-Methyl-2-(*p*-isopropylcarbamoyl)benzylhydrazine hydrochloride *(24a)* and 1-methyl-2-(*p*-allophanoyl)benzylhydrazine hydrobromide *(24b)* proved to be most active. These preparations (Ro 4-6467 and Ro 4-6824) inhibit the growth of



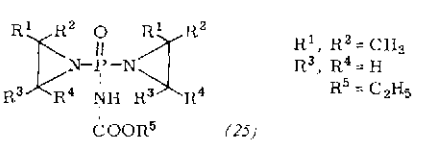
*(24a)*



*(24b)*

Ehrlich carcinoma, Ehrlich ascites carcinoma, Crocker sarcoma S 180, Walker carcinosarcoma 256, and uterus ephithelioma T8 after parenteral and oral administration.

*T. J. Bardos* and coworkers, Buffalo, N.Y. (U.S.A.), described new cytostatic agents of the alkylated carbamate type. In particular, preparation AB-132 *(25)* was found to be active against various transplanted and virus-induced tumors

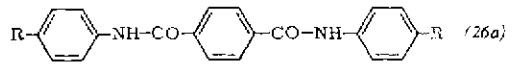


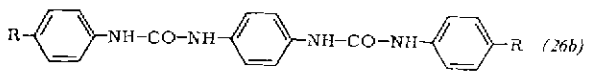
$R^1, R^2 = CH_3$
$R^3, R^4 = H$
$R^5 = C_2H_5$

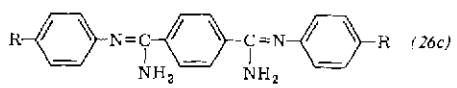
*(25)*

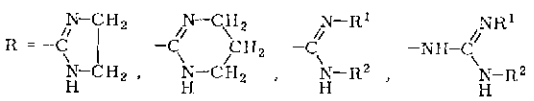
in rodents, with very little toxic action on the hematopoetic system. On hydrolysis, AB-132 yields urethane, 2-amino-t-butanol and a substance containing phosphorus that is structurally similar to cholinesterase inhibitors, which also contain phosphorus. AB-132 therefore acts like a cholinesterase inhibitor. At present attempts are being made to avoid these side effects by addition of antagonists to the cholinesterase inhibition.

*R. Hirt*, Bern (Switzerland), described polybasic compounds with antileucaemic activity. Derivatives of the structural types *(26a)* to *(26c)* were the most active of a series of several hundred substances. They have a strong inhibitory action on leucaemia induced experimentally in mice with L 1210. Some of these substances are at present undergoing clinical trials in the U.S.A.


*(26a)*


*(26b)*


*(26c)*



*H. Fujimori*, Osaka (Japan), described the antitumor action of cobalt protoporphyrin (COPP), which has already been tested clinically for stomach, lung, and uterus cancer. Regression of the tumors was found in about 39 % and subjective improvement in 50 % of the cases. Side effects occur comparatively infrequently and only with too high dosages. Liver function is not affected, and there were no noticeable changes in the blood constituents.

## Oncolysis

A fundamentally new approach to cancer therapy was presented by investigations reported by *J. R. Möse*, Graz (Austria), into the oncolysis produced by *Clostridia*. In these experiments, spores of an anaerobe, *e.g. Clostridium butyricum* strain 55, were administered intravenously to animals with tumors. The spores then germinated selectively in the tumor tissue and multiplied there extremely rapidly. They thus destroyed the surrounding tissue by proteolysis so that it could be sucked off after a few days as a liquid necrotic material. Since oncolysis depends on the type of tumor and the species of animal (*e.g.* only some mice tumors respond, rat tumors are insensitive), an attempt is at present being made to find spores that are better suited to individual types of tumor. According to investigations by *G. E. Boxer* and *H. Thiele*, Rahway, N.J. (U.S.A.), good results were obtained in the therapy of experimental animal tumors if the treatment with spores was combined with the use of cytostatics. Tumor regression was accelerated, and the loss of weight encountered with spore treatment alone was eliminated. *D. Gericke* and *K. Engelhart*, Frankfurt (Germany), established that tumors have a high porphyrin content, which stimulates the resporulation of *Clostridia* both *in vitro* and *in vivo* and so brings the oncolytic process to a standstill. Porphyrin formation can be blocked by parenteral and para- or intratumoral administration of heavy metal compounds. By this means, the extent and speed of tissue breakdown is considerably raised. Since there are still many unsolved problems relating to clostridial oncolysis, *e.g.* the completeness of oncolysis or the elimination of toxic by-products, it is still too early to assess its future importance in practical carcinotherapy.

## Therapy of Virus Diseases

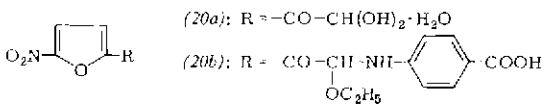
Some new approaches to the problems of chemotherapy in virus diseases were discussed, but successful treatment can still only be claimed in a few cases.

*H. Kaufman*, Gainesville, Fla. (U.S.A.), reported on the already well established treatment of *Herpes simplex* keratitis with 5-fluoro- and 5-iodouracil deoxyribosides. These act as thymidine antagonists and block the DNA synthesis of the viruses, thus inhibiting their multiplication. However, this action is limited to viruses containing DNA and no activity is obtained against RNA forms. On account of the high toxicity of the ribosides, only external application is possible. The drugs are used for example in *vaccinia* and *herpes* keratitis of the rabbit and human eye and in *Herpes labialis*.

Another nucleoside, cytosine arabinoside (CA), was tested by *G. E. Underwood*, Kalamazoo, Mich. (U.S.A.), against *herpes* keratitis in the rabbit and against *vaccinia* virus infections. Cytosine arabinoside is comparable to 5-iodouracil deoxyriboside in its virostatic activity.

*J. Wollensak*, Erlangen (Germany), tested other materials for the treatment of virus diseases of the cornea. He reported favorable results with *p*-fluorophenylalanine, 3,6-diaminoacridine (proflavine), and 4-ethylthio-2-aminobutyric acid (ethionine). However, it was not possible to confirm the initial extremely favorable therapeutic results completely on a great number of herpetic diseases of the cornea. There are obviously strains of *Herpes simplex* which are not completely inhibited by the above antimetabolites.

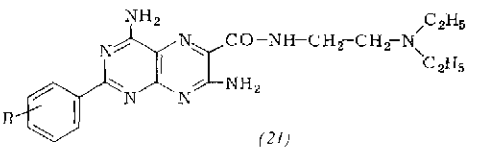
The activity of derivatives of 5-nitro-2-furylglyoxal against two strains of influenza virus in chick embryos were tested by *B. Babudieri* and coworkers, Rome (Italy). While some of the compounds show virostatic action only if they are applied simultaneously with the virus, others, such as *(20a)* and *(20b)*, are also active if they are administered after virus infection.


*(20a)*: R = $-CO-CH(OH)_2 \cdot H_2O$

*(20b)*: R = $-CO-CH(OC_2H_5)-NH-C_6H_4-COOH$

*W. Cutting* and *E. Furasawa*, Stanford, Calif. (U.S.A.), reported on investigations with propionin, a virostatic material which was discovered in *Bacterium propioni Freudenreichii*. Application of the crude extract to mice infected with Columbia SK virus reduced the average mortality by 70 %. Propionin could not yet be produced pure.

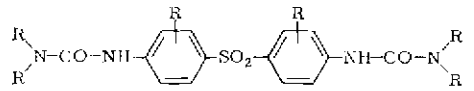
*C. P. Hegarty* and coworkers, Radnor (Wales), observed a clear increase in the period of survival in mice experimentally infected with Columbia SK, Semliki-Forest, *Herpes simplex*, and influenza PR-8 and NWS viruses when treated with 2-aryl-4,7-diamino-*N*-dialkylaminoalkyl-6-pteridinecarboxamide derivatives *(21)*. Small chemical changes in the


*(21)*

aryl ring effect specific alterations in the spectrum of activity towards the various viruses. Thus a reproducible relation between constitution and activity was found. All these substances proved to be inactive in tissue cultures.

A new antibiotic, julimycin B 11, possessing a chemoprophylactic action against polio infection in mice, was isolated by *K. Katagiri* and *J. Shoji*, Osaka (Japan), from cultures of *Streptomyces* No. 222; it was obtained as orange-yellow crystals. Its virostatic activity *in vitro* is very low. Julimycin has also an inhibitory action on the development of Ehrlich ascites tumors as well as on various bacteria.

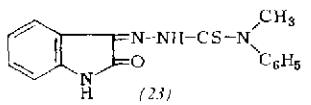
*G. Michael*, Stolberg (Germany), described the actions of diphenyl sulfone derivatives against model virus infections in tissue cultures and *in vivo*. Urea derivatives *(22)* of the diphenyl sulfone B 662, which were tested clinically under the



(22)

designation CG 662, have proved especially useful. As several of the reports given indicated, the cure of *Herpes simplex* and *Herpes zoster* infections and of viral influenza was noticeably accelerated by the use of diphenyl sulfone derivatives.

*D. G. O'Sullivan* and coworkers, London (England), dealt with the virostatic activities of the β-(4',4'-dialkylthiosemicarbazones) of isatin. These show high chemotherapeutic activity against *Ectromelia* virus after subcutaneous application to mice. Isatin β-(4'-methyl-4'-phenylthiosemicarbazone) *(23)* proved to be the most active agent of this class.



(23)

## General Discussion on the Chemotherapy of Virus Diseases

Some subjects of the Congress had also been discussed at an informal round-table meeting at Schloss Reinhartshausen on July 20th, 1963, for which Farbwerke Hoechst had invited a number of scientists. In addition to oncolysis, the discussion was on the chemotherapy of virus diseases, with *A. Wacker*, Frankfurt (Germany), in the chair.

*H. J. Eggers*, New York (U.S.A.), reported his investigations with 2-(α-hydroxybenzyl)benzimidazole (HBB) and guanidine. These two substances have the property of selectively inhibiting RNA-containing, lipid-free viruses of the Picorna group, without any toxic damage to the cells themselves. It accomplishes complete inhibition of RNA and protein synthesis in the virus, and that even only within the cell. Inhibition of extracellular viruses with these substances is not possible. The course of RNA synthesis in the virus can be followed using tritium-labelled nucleotides if RNA synthesis in the cell has first been inhibited by actinomycin. The selective inhibition of the RNA synthesis in the virus by HBB can be followed in this system. Apparently, the formation of a specific RNA polymerase occurs shortly before the maturation of the virus and is independent of the intracellular DNA; this polymerase is found only in the ribosome fraction of infected cells and has a short life. The polymerase fraction can be concentrated by various purification procedures from the ribosomes and has the ability of incorporating nucleoside triphosphates into a polymeric RNA in a cell-free system in the presence of ATP. Whether this is identical with virus RNA has still to be proved.

Some observations indicate that it is the virus-induced polymerase which synthetizes the specific virus RNA. Nothing is known as yet of the mechanism of HBB inhibition. It is however possible that HBB attacks specific positions on the RNA, so that the gene or cystrone occurring there is no longer capable of forming polymerase. In any case, the high specificity of the inhibitor is remarkable; thus, for example, the benzimidazole nucleus is absolutely essential. All the HBB derivatives previously tested have less activity. Changes at the asymmetric carbon atom also diminish the inhibitory action. The discussion of the significance of these observations for use in virus chemotherapy did not give room for great expectations, since HBB acts only on RNA-containing viruses of the Picorna group and resistant mutants are also often found. Finally, a marked depression of total protein synthesis is observable in later stages of the experiments and the infected cells die.

*A. D. Welch*, New Haven, Conn. (U.S.A.), referred to the possibility of chemotherapy with 5-iododeoxyuridine (IUDR), 5-iododeoxycytidine (ICDR), and the corresponding monophosphates. Normally, thymidine is incorporated into the DNA inside the cell via the mono-, di-, and triphosphates with the help of the polymerase. Monophosphotymidylic acid (TMP) is formed in turn by the action of a thymidylic synthetase from deoxyuridyl monophosphate. If IUDR or its monophosphate is provided, the iodinated compound enters into the metabolism instead of the TMP and is incorporated into the DNA as a false constituent. ICDR acts in a similar way; it is deaminated in the cell to IUDR and is then incorporated as above.

Local treatment of *Herpes simplex* infections in rabbit eyes with IUDR produces complete inhibition of the virus, even though the mechanism does not appear to proceed by incorporation of the antimetabolite into virus DNA, as was shown later. On the basis of these results, *H. Kaufman* developed a therapy for corneal keratitis in man using IUDR and has achieved a large number of excellent cures.

Further exeprimental results were presented on the inhibition of *vaccinia* virus in rabbit skin by IUDR. The strongest inhibition was obtained with a dose of 80 mg/kg at 8 hour intervals. No toxic side-effects were produced with this dosage.

Further investigations were carried out on new-born hamsters which were infected with *adenovirus* type 12 shortly after birth. If 0.5 mg of IUDR is given at the same time as the virus inoculation and treatment is continued for 30–60 days, tumor formation is definitely inhibited. Repeated subcutaneous application is also clearly successful. Similarly, a single dose of IUDR reduces the number of neoplasms formed in the experimental series. Even if the treatment with IUDR begins a day after the virus infection, there is still a destinct reduction in the number of tumor-bearing animals. ICDR shows similar inhibition of tumors after intraperitoneal doses of 1 mg (5 injections), because it undergoes slow deamination to give IUDR. Experiments with hela cells indicate selective inhibition of the virus DNA replication by IUDR.

*R. Thiel*, Frankfurt (Germany), remarked that IUDR found application in his clinic not only for herpetic corneal infections, but also for patients with tumors in order to secure restriction of X-ray therapy.

An extensive discussion developed on the possible teratogenic action of IUDR. According to *A. D. Welch*, an intravenous dose of 120 mg/kg in man produced toxic effects, including loss of hair, stomatitis, and disturbances of bone marrow function. IUDR induces a definite increase in the rate of mutation in bacteria and a microscopically detectable change in the chromosomes in *Drosophila*. On the other hand, IUDR is degraded very rapidly after subcutaneous application, iodide being released.

*H. Kaufman* mentioned that there had never been any sign of cancer formation or similar disturbances as a result of IUDR treatment for corneal ceratitis in a great number of adults and children. It was shown that no radioactivity was detectable in the blood only 4 hours after administration of 120 mg of $^{125}$IUDR. Iodine was then found only in the bone marrow, but not bound to DNA.

Isatin thiosemicarbazone was favorably accredited with regard to any possible eventual teratogenic side-effects. It is a virus inhibitor with which DNA and protein synthesis apparently continue normally but which prevents maturation of the virus.

Later in the discussion, *J. Škoda*, Prague (Czechoslovakia), gave a review of his work with 6-azauridine (AzUR). This compound is converted into its monophosphate in the cell; this inhibits the normal metabolic conversion of orotidyl monophosphate into uridyl monophosphate. AzUR, but not azauracil or the corresponding deoxyriboside, has an antileucaemic action. On injection into animals with tumors, AzUR is taken up predominantly by the tumor tissue and accumu-

lates there. In some cases, there is thus a reduction of neoplastic tissue during the period of treatment. This substance is exceptionally well tolerated; 40 g per day in man is without toxic side-effects. AzUR also causes sharp reduction of the uridine kinase activity in *vaccinia* viruses. *Mycosis fungoides* (apparently a form of skin cancer) is completely healed with AzUR. Mention must also be made of the antiseptic, antiepileptic, and abortive actions of this compound. Administration is by intravenous injection, the blood level of the antimetabolite falling to practically nil within four hours. With 2,3,5-triacetyl-AzUR a high blood level can be maintained for a longer period after oral administration.

*H. Kaufman* spoke on his clinical experience in the treatment of *Herpes simplex* ceratitis of the eyes using IUDR. He indicated that there were many compounds which destroyed viruses in cultures. However, this was mostly a matter of specific anticulture activity, and these compounds have no therapeutic interest. Earlier work on folic acid antagonists was unsuccessful as they only worked if they were already present before the virus infection. On the other hand, destruction of the virus without simultaneously killing the host cell is hardly conceivable. The search for a compromise acceptable from all points of view calls for combined scientific efforts.

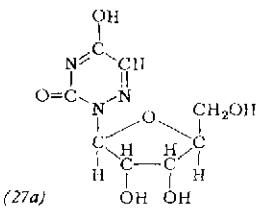
*Kaufman* dealt further with the mechanism of IUDR action, stating that this compound is apparently not incorporated as a false constituent into virus DNA. Thus, for example, cytosine acts in a similar fashion to IUDR and is not incorporated into DNA. On the other hand, 5-fluorodeoxyuridine (FUDR) has no inhibitory effect on virus development. It is known that cytosine arabinoside and cytidine inhibit the phosphorylation of deoxycytidine in the cell. From this and other considerations, the action of IUDR, and also to a lesser extent of BUDR and CUDR, is to be sought in the possible specific inhibition of phosphorylation of nucleosides and of nucleotide polymerization.

This view was supported by *A. D. Welch*, who mentioned that AzUR acts via its 5'-phosphate to block the phosphorylation of orotic acid or the decarboxylation to give uridylic acid. FUDR inhibits the conversion of deoxyuridine monophosphate into thymidine monophosphate, and IUDR inhibits the incorporation of thymidine monophosphate into DNA. From these findings, virus chemotherapy with two combined antimetabolites seems especially promising. The combination of IUDR and FUDR and to a lesser extent of IUDR and AzUR in the treatment of *Herpes simplex* syndromes yields a considerable increase in activity. Thus, the activity of IUDR can be increased almost one-hundredfold by addition of FUDR.

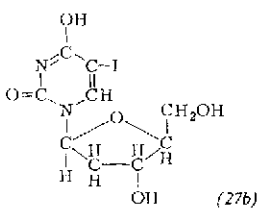
Another substance, which was successfully used for the inhibition of viruses, is the amino acid analogue, *p*-fluorophenylalanine.

*G. E. Boxer*, Rahway, N.J. (U.S.A.), indicated the possibility of using a hydroxylamine derivative HO–NH–CH($CH_3$)–COOH to inhibit the synthesis of AMP in the cell in a competitive fashion.

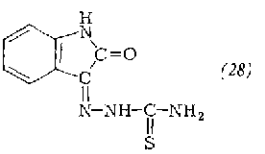
In conclusion, *K. Herzberg*, Frankfurt (Germany), recalled his earlier experiments on the inhibition of *vaccinia* virus in rabbit skin with metal salts plus dyes. Methylene blue with silver salts seemed especially suitable, the metal salt being absolutely essential. His impressive color slides showed that complete inhibition of the virus infection and healing of the erythema were obtained by this treatment. Since the process takes place under the skin of the animal and the animals were kept in the dark, the influence of visible light on the course of the cure was eliminated.



*(27a)*



*(27b)*



*(28)*

The World Health Organisation is at present preparing large scale experiments which are to be carried out in India with the object of investigating the chemotherapy of virus diseases on a broad front. Compounds which are to be used in particular are 6-azauridine *(27a)*, 5-iododeoxyuridine *(27b)*, and isatin thiosemicarbazone *(28)*.

[VB 749/106 IE]

German version: Angew. Chem. *75*, 1178 (1963)

# Joint Meeting of Swiss and Austrian Chemists

## Innsbruck (Austria), October 3rd–5th, 1963

From the proceedings:

### Chemical Investigation of Interferon

*G. Bodo* and *C. Jungwirth*, Vienna (Austria)

Two interferon preparations produced by different virus strains (Influenza A MEL and Influenza B LEE) in chorioallantoic membranes of hen's eggs were subjected to an initial purification [1]. The behavior of the two preparations during column chromatography on sulfoethylcellulose at pH 2.0 and on DEAE-cellulose at pH 6.6 and 4.5 was quite identical. Starch-gel electrophoresis of the purified preparations yielded several protein bands. On account of the adsorption of interferon onto starch gel, it was not possible to elute the biologically active components. It was evident that this method of purification did not yield pure interferon preparations.

Effective purification was obtained by column chromatography on Sephadex G-100 of preparations subjected to preliminary purification. The molecular weight of the interferon was estimated by comparing the position of the maximum of biological activity in the elution pattern with the elution behavior of pure proteins. On this basis, the main components of both preparations were found to have molecular weights between 25000 and 35000. This relatively low molecular weight is in contrast to earlier determinations (*Burke* [1]: 63000) and agrees with recent data obtained with the ultracentrifuge (*Lampson* et al. [2]: 20000–34000; *Rotem* et al. [3]: 20000–25000).

[1] *D. C. Burke*, Biochem. J. *78*, 556 (1961).

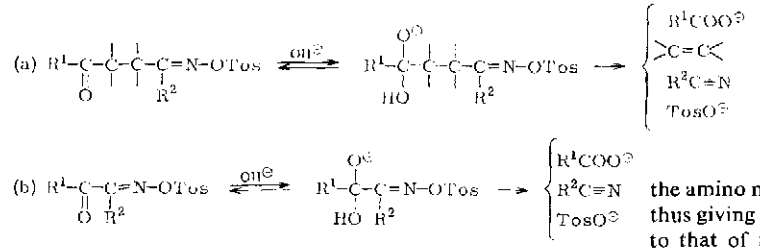
[2] *G. P. Lampson, A. A. Tytell, M. M. Nemes*, and *M. R. Hilleman*, Proc. Soc. exp. Biol. Med. *112*, 468 (1963).

[3] *Z. Rotem* and *P. A. Charlwood*, Nature (London) *198*, 1066 (1963).

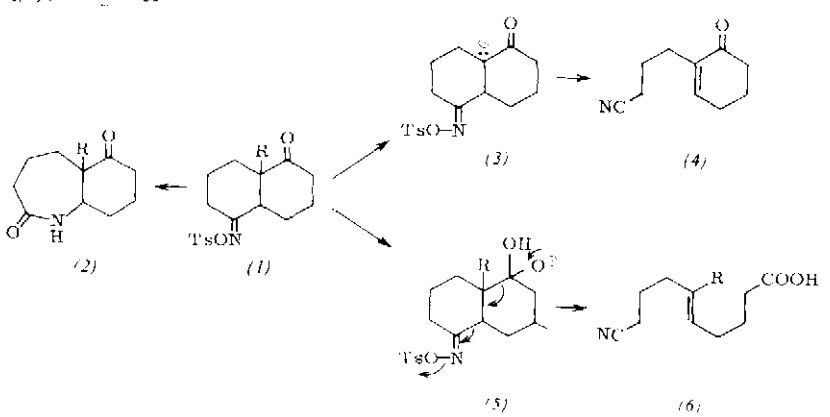
## Five- and Seven-Center Fragmentation of γ-Oximino Ketones

*C. A. Grob, W. Eisele,* and *E. Renk,* Basel (Switzerland)

γ-Oximino ketones (see Reaction a) are ethylogues of α-oximino ketones (see Reaction b), the *p*-toluenesulfonic esters (tosylates) of which are decomposed by hydroxide ion to give an acid, a nitrile, and tosylate ion. While the second fragmentation reaction (b) involves five atomic centers, seven centers participate in the fragmentation of the γ-tosyloximinoketones (a), which give an olefinic fragment in addition.



In order to test whether the originally hypothetical reaction (a) was actually possible, the *p*-toluenesulfonic esters of 1-oxo-5-oximino-*trans*-decalin [*(1)*, R = H] and its 9-methyl derivative [*(1)*, R = $CH_3$] were prepared and treated with a number of bases in aqueous ethanol. The tosyl oximino compound *(1)*, where R = H, reacted with strong bases such as potassium t.-butoxide to give 2-(γ-cyanopropyl)cyclohexen-2-one *(4)* by 5-center fragmentation of the mesomeric anion *(3)*. With hydroxide and cyanide ions, 7-center fragmentation to give 9-cyano-5-nonenoic acid [*(6)*, R = H] also occurred to a small extent. With the 9-methyl derivative [*(1)*, R = $CH_3$], which cannot undergo the competing 5-center fragmentation because of the absence of a hydrogen atom on C-9, hydroxide ion effected as major reaction the desired 7-center fragmentation to 9-cyano-6-methyl-5-nonenoic acid [*(6)*, R = $CH_3$].



In the absence of base, both γ-tosyloximino ketones [*(1)*, R = H or $CH_3$] undergo only Beckmann rearrangement to the lactams [*(2)*, R = H or $CH_3$]. Both the 5- and 7-center fragmentations are thus base-induced, indicating the occurrence of the anionic intermediates *(3)* and *(5)*.

## The Behavior of Some Indicators in Aprotic Solvents

*V. Gutmann* and *H. Hubacek,* Vienna (Austria)

A number of indicators, chiefly those of the sulfophthalein class, give reversible color changes in phosphorous oxychloride, thionyl chloride, and acetyl chloride which are determined by the activity of the chloride ions of the solution. In acidic media, which are poor in chloride ion, these indicators are red, whereas in basic media, which are rich in chloride ion, they are yellow. The absorption spectra are independent of the nature of the chloride ion acceptor or the chloride ion donor and show the same characteristics as those in aqueous medium. The indicators react in phosphorous chloride such that two phenolic hydrogen atoms are replaced by $[POCl_2]$-groups (formation of a symmetrical molecule). In basic medium, a $[POCl_2]$-group is split off with reformation of undissociated $POCl_3$ (formation of an asymmetrical molecule).

Crystal violet gives reversible color changes not only in the acid chlorides mentioned but also in solvents which do not normally ionize, such as acetone or acetonitrile. Chloride ion acceptors, such as $SbCl_5$, are thereby coordinated directly at the amino nitrogen, and this group is simultaneously blocked thus giving rise to the spectrum of malachite green and finally to that of the triphenylcarbonium ion. On adding chloride ions, the color change takes place in the opposite direction since the formation of a chloro-complex is favored by the appropriate donation of chloride ions.

## Polymerization of Germanic Acid

*J. Haas, Nelly Konopik, F. Mark,* and *A. Neckel,* Vienna (Austria)

To elucidate the polymerization behavior of germanic acid in aqueous solution, high-precision potentiometric titrations were carried out on 0.00159 -0.02388 M solutions of germanic acid at 25 °C and constant ionic strength (0.5 M $NaClO_4$), using a glass electrode. The Ge concentration was kept constant during a given titration.

A special measuring method made it possible to obtain hydrogen ion concentrations from the measured potentials. The concentration of free germanic acid, which could not be determined experimentally, and the total concentration of complex molecules were calculated. These data make it possible to evaluate the number of hydroxyl groups taken up per Ge atom, as well as the mean charge of the complexes and the mean degree of polymerization. These values indicate that only a few combinations of complexes carrying different amounts of negative charge and having different degrees of polymerization are probable. The combination which best reproduced the experimental results was selected from these by the least-squares curve fitting method, using an electronic computer. The mathematical analysis gave the following results: in solutions of concentration greater than 0.004 M, the undissociated monomeric species $Ge(OH)_4$, and the monomeric ions $GeO(OH)_3^-$ and $GeO_2(OH)_2^{2-}$ are accompanied by a polymeric anion containing eight Ge atoms and carrying a charge of −3. The

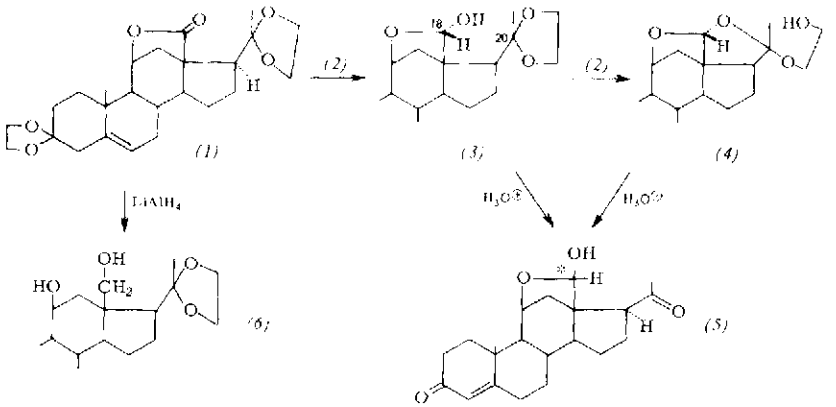
following equilibrium reactions and constants were determined:

$$Ge(OH)_4 + OH^- \rightleftharpoons GeO(OH)_5^- + H_2O \quad \log K_{11} = 4.71_1 \pm 0.002$$
$$Ge(OH)_4 + 2\,OH^- \rightleftharpoons GeO_2(OH)_2^{2-} + H_2O \quad \log K_{21} = 6.00 \pm 0.25$$
$$8\,Ge(OH)_4 + 3\,OH^- \rightleftharpoons (Ge(OH)_4)_8(OH)_3^{3-} \quad \log K_{38} = 29.55 \pm 0.01$$
$$-\log K_W\ (0.5\ M\ NaClO_4) = 13.72 \pm 0.01$$

## A Novel Intramolecular Displacement Reaction

*J. Schmidtlin* and *A. Wettstein*, Basel (Switzerland)

When the strongly hindered lactone *(1)* is reacted with a quarter of a mole equivalent of lithium aluminum hydride in tetrahydrofuran, mainly full reduction to the diol *(6)* occurs, thus leaving about half the amount of the starting material unchanged [1]. Thus, the desired cyclohemiacetal *(3)* is formed as a by-product only. However, if the reduction of *(1)* is carried out with diisobutyl aluminum hydride $(i\text{-}C_4H_9)_2AlH$ *(2)* or triisobutyl aluminum [2] in toluene at −20 °C, the hitherto difficultly accessible cyclohemiacetal *(3)* is produced in excellent yield.

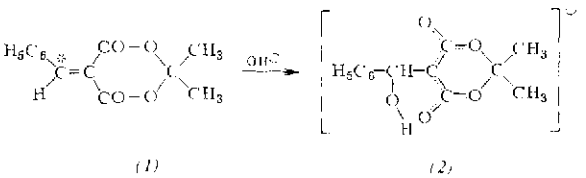


The reduction of the lactonic carbonyl group in *(1)* with *(2)* proceeds stereospecifically as shown by the subsequent conversion of *(3)* into the hydroxyethyl ketal *(4)* in the reaction solution even at room temperature. The molecular models reveal that such a transformation requires *(3)* to have the *(18S)*-configuration. As expected, both compounds *(3)* and *(4)* are smoothly deketalized by acid hydrolysis to the diketocyclohemiacetal *(5)* with still unknown configuration at C-18. Prerequisites for the aprotic intramolecular displacement reaction *(3)* → *(4)* are the immediate proximity of hydroxyl oxygen and C-20 and the presence of a Lewis acid, such as the diisobutyl aluminum cation which can form a complex with one of the ketalic oxygens. The structures of the isomeric compounds *(3)* and *(4)* and the corresponding *O*-acetyl derivatives have been confirmed by their proton resonance spectra.

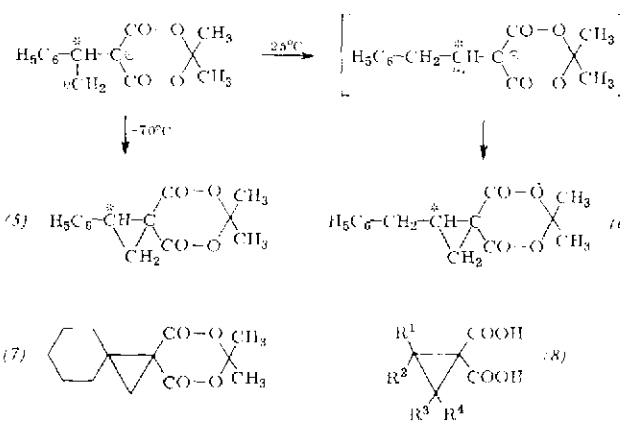
## A New Class of Acidic Compounds and Their Use in the Synthesis of Cyclopropane Derivatives

*F. Wessely* and *A. Eitel*, Vienna (Austria)

Condensation of aldehydes or ketones with cyclic acylals affords compounds, *e.g. (1)*, which can be titrated in aqueous methanol as monobasic acids. On acidification of the alkaline solution, compound *(1)* is recovered almost quantitatively. It contains no active hydrogen. Formulation of the anion present in the alkaline solution as structure *(2)* agrees with quantummechanical calculations made by *O. E. Polansky*. In addition to *(1)*, analogous compounds were synthetized with various ketones, *e.g.* with cyclopentanone *(3)* or cyclohexanone *(4)*. All can be titrated as monobasic acids.



Solutions in ether of *(1)*, *(3)*, and *(4)* react vigorously with diazomethane without a catalyst, with evolution of nitrogen. However, this reaction does not yield pyrazoline compounds, which might be expected on the basis of the α,β-unsaturated ester constitution of *(1)*. Instead, *(1)* yields the cyclopropane derivatives *(5)* and *(6)* at −75 and 25 °C, respectively. These were characterized by synthesis of the two compounds by another route, and by degradation experiments using $^{14}C$-labelled *(1)*. These experiments also showed that after addition of the first methylene group onto *(1)*, migration of the phenyl anion leads to a new electrophilic centre which reacts further with diazomethane to give the cyclopropane derivative *(6)*. The formation of *(7)* from *(3)* is explained in a similar manner.



Other diazoalkanes, *e.g.* dimethyldiazomethane and diazoacetic ester, also react with *(1)* to give analogous compounds. Since the primary reaction products of the diazoalkanes can be hydrolysed to the corresponding cyclopropane-1,1-dicarboxylic acids, it is in principle possible to use cyclic acylals and the described reaction sequence to prepare compounds of general structure *(8)*, which can naturally be further altered by known methods.

[VB 757/108 IE]

German version: Angew. Chem. 76, 105 (1964)

[1] *J. Schmidlin* and *A. Wettstein*, Helv. chim. Acta *42*, 2636 (1959).

[2] *K. Ziegler*, *K. Schneider*, and *J. Schneider*, Angew. Chem. *67*, 425 (1955).

## New Types of Low Molecular-Weight Heterosiloxanes

*H. Schmidbaur*, Marburg (Germany)

Low molecular-weight model substances of well-defined composition were prepared for the first time in connection with an investigation of the principles of structure and bonding in heterosiloxanes. Examples of such compounds are $R^1_3SiOXR^2_3$, $(R^1_3SiO)_2XR^2_2$, $(R^1_3SiO)_3XR^2$, and $(R^1_3SiO)_4X$, where X = Si, Ge, Sn, or Pb, $R^1 = CH_3$ or $C_2H_5$, and $R^2 = CH_3$, $C_2H_5$, *etc.* Specific heterolytic cleavage reactions with Lewis acids or nucleophilic reagents, as well as infrared and NMR spectroscopic examinations carried out on such heterosiloxanes have shown that, within the Si–O–X grouping, the X–O– bond invariably possesses the greater polarity and the lower proportion of π-bond character. In particular, the regular changes in the chemical shifts and the coupling constants of the NMR spectra demonstrate that this polarization is in accordance with $\rightarrow Si-O \leftarrow X \leftarrow$ and increases regularly in the order X = Si < Ge < Sn < Pb. This result is thus in contradiciton to the assumption that the electronegativities of these elements alternate [1]. The NMR spectra have particularly high numbers of peaks as a result of the presence of the magnetically active isotopes $^1H$, $^{13}C$, $^{29}Si$, $^{117}Sn$, $^{119}Sn$, and $^{207}Pb$.

Heterosiloxanes of the trivalent elements of group V of the periodic table, which are of the general type $R^1_3SiOYR^2_2$ (Y = P, As, or Sb) with a lone pair of electrons on the heteroatom, are very sensitive to hydrolysis and oxidation and belong to the thermally least stable types of heterosiloxanes. Derivatives of the same elements in the pentavalent state $[R^1_3SiOYR^2_4$ and $(R^1_3SiO)_2YR^2_3]$ on the other hand exhibit high thermal stability (in particular if Y = Sb).

Heterosiloxanes of the elements of group III, $R^1_3SiOZR^2_2$ (Z = Al or Ga), with an electron deficiency on the hetero-atom occur exclusively in the dimeric form. The planar four-membered ring systems *(1)* exhibit comparatively high thermal and chemical stability on account of the stabilization which is possible with this arrangement.

*(1)* 

[Inorganic Chemistry Colloquium, Universität Marburg (Germany), December 13th, 1963, and Technische Hochschule Aachen (Germany), November 19th, 1963] [VB 769/114 IE]

German version: Angew. Chem. *76*, 234 (1964)

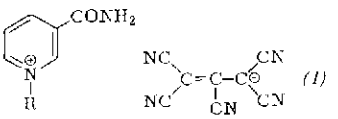
## Recent Developments in Cyanocarbon Chemistry

*K. Wallenfels*, Freiburg/Breisgau (Germany); experimental work with *G. Bachmann*, *H. Diekmann*, *K. Friedrich*, *D. Hofmann*, and *R. Kern*

1. *Dihydropyridines and Tetracyanoethylene*: Reduced diphosphopyridine nucleotide (DPNH) and model compounds (PyH) reduce tetracyanoethylene (TCNE) to the radical anion $TCNE^{\cdot\ominus}$, which can be detected and determined quantitatively by its characteristic "coxcomb spectrum", which contains twelve maxima between 350 and 500 mμ. The intensity of this absorption depends upon the apparent redox potential of the corresponding $Py^{\oplus} \rightleftharpoons PyH$ system [2]. The transient deep coloration which occurs on mixing PyH with TCNE can be explained by the formation of a charge-transfer complex. The reduction to a radical is interpreted as a hydride-ion transfer. This leads to $TCNEH^{\ominus}$, which equilibrates with TCNE.

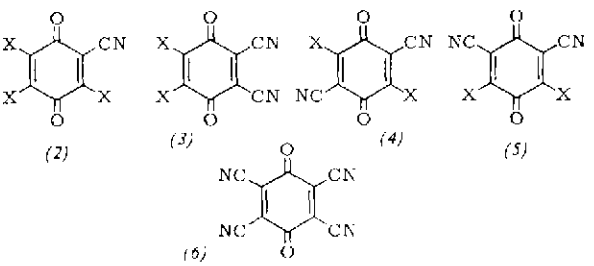
$$TCNEH^{\ominus} + TCNE \rightleftharpoons 2\,TCNE^{\cdot\ominus} + H^{\oplus}$$

This system is the aliphatic analogue of a quinone/hydroquinone equilibrium for which the high stability of the semiquinone stage is characteristic. Treatment of PyH with 4 moles of TCNE in acetonitrile and subsequent dilution with water yield crystalline pyridinium pentacyanopropenide *(1)* in approx. 90 % yield.



*(1)*

2. *Cyanoquinones*: Of the six possible cyano-substituted benzoquinones, the compounds *(2)*–*(6)*, where X = Cl, Br, I, OH, or OR, were synthetized. The electron affinity of the halogeno- or hydrogeno-substituted compounds increases with increasing substitution by CN; the dissociation of the hydroxylated quinones and hydroquinones increases correspondingly.



*(2)* *(3)* *(4)* *(5)* *(6)*

3. *Cyanoarenes*: Similar changes in the physical properties are found with increasing substitution of the benzene ring with cyano groups. Pentacyanotoluene shows high C–H acidity; it forms a deep blue anion which is unstable in the presence of water. The pyrene complexes of tetracyano-*m*-xylene, pentacyanotoluene, and hexacyanobenzene [3] are yellow, red, and blue-green, respectively (color of solution in acetonitrile). In a differential thermoanalysis, hexacyanobenzene was found to be stable up to 475 °C. It sublimes rapidly without decomposition at this temperature.

[Organic Chemistry Colloquium, Universität Basel (Switzerland), November 29th, 1963] [VB 772/115 IE]

German version: Angew. Chem. *76*, 275 (1964)

## Electron Spin Resonance Measurements on Irradiated Bacteriophages and Their Nucleic Acids

*A. Müller*, Karlsruhe (Germany)

Bacteriophages are particularly suitable for studying radiation damage because of their primitive organization, high nucleic-acid content, and great sensitivity to radiation. Radicals were produced in dry bacteriophages and nucleic acid prepared therefrom, by irradiation with X-rays (50 kr/min) or γ-rays ($^{60}Co$; 10 krep/min) and examined qualitatively and quantitatively by means of their ESR absorption spectra; the results were compared with measurements on phage proteins and nucleic-acid components (nucleotides, nucleosides, free bases).

In whole phages of strains T1 and T2, radicals which show different ESR-spectral types are produced in high yield (G = 2–10) by irradiation. Radicals are formed in comparable yield from T2-phage nucleic acids and give ESR spectra which correspond to those observed in whole phages. The radical concentration in irradiated phage nucleic acid increases with dose according to an exponential function up to a saturation value lying between $10^{18}$ and $10^{19}$ radicals/g (63 % of the saturation concentration is reached after doses of 0.4–1.4 Mr).

[1] Cf. also *H. Schmidbaur*, Lecture delivered at the VII. European Congress on Molecular Spectroscopy, Budapest 1963, Abstract p. 86.

[2] *K. Wallenfels*, *H. Diekmann*, and *F. Kuhowitz*, Liebigs Ann. Chem. *621*, 174 (1959).

[3] *K. Wallenfels* and *K. Friedrich*, Tetrahedron Letters *1963*, 1223.

The radicals of the T2-protein are equal in concentration and spectral frequency to those of other sulfur-free proteins (*e.g.* gelatin). D-2-Deoxyribose gives a radical yield of G = 4. The radicals produced in the nucleosides do not show a spectrum typical of D-2-deoxyribose, but spectra which are similar to those of the free bases.

Whilst the radical yield of irradiated nucleotides corresponds to that from nucleic acids (G = 2–15), the radical yield in the case of irradiated nucleosides is less (G = 0.4–1.0) and still smaller in the case of the pure nucleic-acid bases (G = 0.1 to 1.0). The radical yield increases particularly strongly on passing from thymine via thymidine to thymidine-5-monophosphate. Directly after irradiation, the spectrum of the phosphate, like that of thymine, has a large number of lines, but on keeping changes into a quartet, which appears very like that of stored nucleic acid.

The radical concentrations in the bases, nucleosides, and nucleotides show a similar dependence on the radiation dose as those in the nucleic acid and all the other substances investigated. It is probable that the primary radiation damage occurs at the thymine unit of the nucleic acid.

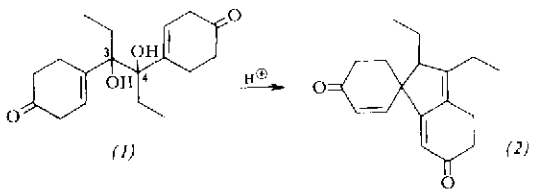
[Physikalisches Colloquium, Heidelberg (Germany), November 8th, 1963] [VB 763/111 IE]

German version: Angew. Chem. *76*, 233 (1964)

## Investigations on Highly Substituted Glycols

*H. H. Inhoffen*, Braunschweig (Germany)

Birch reduction of 3,4-di-*p*-anisylhexane-3,4-diol gives a bis-enol-ether which is converted into *(1)* by mild treatment with acid. The reaction of *(1)* with alcoholic sulfuric acid affords a mixture from which a racemate of molecular formula $C_{18}H_{22}O_2$, m.p. 70–71 °C, and with ultraviolet maxima at $\lambda = 303$ mμ, $\varepsilon = 19000$, and $\lambda = 224$ mμ, $\varepsilon = 14300$, can be isolated in 30 % yield. This compound was shown to have the *spiro*-ketone structure *(2)*.



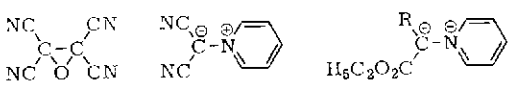
*(1)* *(2)*

[GDCh-Ortsverband Süd-Württemberg, Tübingen (Germany) December 13th, 1963] [VB 774/122 IE]

German version: Angew. Chem. *76*, 235 (1964)

# SELECTED ABSTRACTS

**Tetracyanoethylene oxide** has been synthetized by *A. Rieche* and *P. Dietrich*. Tetracyanoethylene reacts with hydrogen peroxide in ether at room temperature to give tetracyanoethylene oxide *(1)*, m.p. 174 °C (sealed tube), in quantitative yield. Compound *(1)* is also formed from tetracyanoethylene and alkyl hydroperoxides in warm benzene. Hydrolysis of *(1)* readily affords a black product (polymeric hydrocyanic acid). With pyridine bases, *(1)* forms crystalline pyridinium

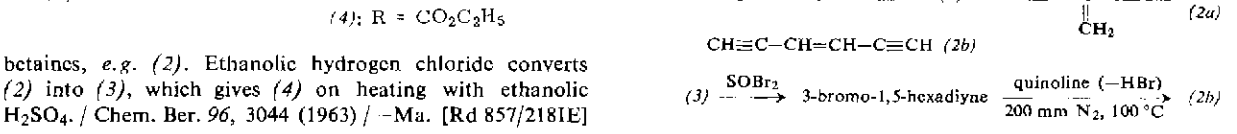


*(1)* *(2)* *(3)*: R = CN; *(4)*: R = $CO_2C_2H_5$

betaines, *e.g.* *(2)*. Ethanolic hydrogen chloride converts *(2)* into *(3)*, which gives *(4)* on heating with ethanolic $H_2SO_4$. / Chem. Ber. *96*, 3044 (1963) / –Ma. [Rd 857/218IE]

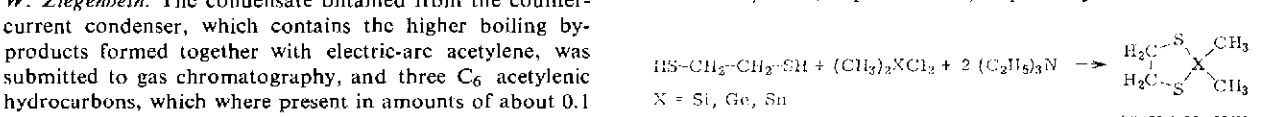
**The most potent animal venom known** is found in the skin of the Columbian arrow-poison (kokoi) frog *Phyllobates bicolor*. *F. Märki* and *B. Witkop* found that 0.05 γ of the 60-fold enriched poisonous principle was sufficient to kill a mouse of 10 g weight. The poison is a chloroform-soluble base with a mol. weight of 399240. Molecular weight and elemental composition have recently been determined on a sample of only 40 γ with the aid of a double-focussing mass spectrometer. / Experientia *19*, 329 (1963) / W. [Rd 794/214 IE]

**The isolation, identification, and synthesis of isomeric hexene-diynes from electric-arc acetylene** is reported by *T. Böhm-Gössl*, *W. Hunsmann*, *L. Rohrschneider*, *W. M. Schneider*, and *W. Ziegenbein*. The condensate obtained from the counter-current condenser, which contains the higher boiling by-products formed together with electric-arc acetylene, was submitted to gas chromatography, and three $C_6$ acetylenic hydrocarbons, which where present in amounts of about 0.1 to 1.0 %, were isolated. Ultraviolet, infrared, and mass spectra showed that triacetylene was present. The main component (1.3 %) ($\lambda_{max}$ = 270, 255, and 242 mμ) had a mass spectrum corresponding to $C_6H_4$. It contained a vinyl double bond in conjugation with an acetylenic bond, a central and a terminal acetylenic group, and two types of protons, bound to doubly and triply bonded carbon. The ratio of acetylenic to olefinic protons was 1:3 and corresponds to the formula of 1-hexene-3,5-diyne *(1)*. The NMR spectrum excludes all other possible constitutions. The third $C_6$ acetylene (0.1 %) was separated on polypropylene glycol as stationary phase. Structures *(2a)* and *(2b)* were possible according to infrared and mass spectra. Compound *(2a)* was synthetized from 1,4-pentadiyne-3-ol, and *(2b)* from 1,5-hexadiyne-3-ol *(3)*. The results obtained indicated that *trans*-3-hexene-1,5-diyne *(2b)* is present in electric-arc acetylene.



*cis*-3-Hexene-1,5-diyne could not be isolated from crude acetylene. It may occur in traces and be removed with the triacetylene during gas chromatography. / Chem. Ber. *96*, 2504 (1963) / –Ma. [Rd 791/210 IE]

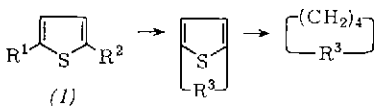
**Five-membered heterocyclics containing Si, Ge, or Sn,** and sulphur in the ring have been synthetized by *M. Wieber* and *M. Schmidt*, who have previously built up the corresponding six-membered rings. Dithioglycol reacts with equivalent quantities of triethylamine and dimethylchloro-silane, -germane, and -stannane in boiling benzene to form 2,2-dimethyl-2-sila-1,3-dithiacyclopentane, b.p. 75–77 °C/12 mm, 2,2-dimethyl-2-germa-1,3-dithiacyclopentane, b.p. 87–93 °C/12 mm, and 2,2-dimethyl-2-stanna-1,3-dithiacyclopentane, b.p. 113–115 °C/5 mm, m.p. 82–83 °C, respectively.



Yields are satisfactory. The compounds have unpleasant odors and are rapidly decomposed by hot water. / Z. Naturforsch. *18b*, 846 (1963) / –Ma. [Rd 789/207 IE]

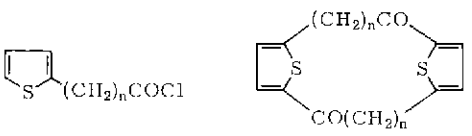
**A new metalating agent** – **naphthalene magnesium** – is reported by *C. Ivanoff* and *P. Markov*. When Mg powder and naphthalene are stirred together vigorously in liquid $NH_3$, a green color is produced, which is intensified by addition of ether, with simultaneous dissolution of the Mg. The solution is decolorized by the addition of ethanol, and 1,4-dihydronaphthalene, m.p. 24–25 °C, can then be isolated from the mixture. This decomposition reaction suggests the formation of naphthalene magnesium, which can be used as a metalating agent in a manner analogous to naphthalene sodium. It reacts with compounds containing activated methylene groups, such as benzyl cyanide, from which one obtains α-phenylbutyronitrile, b.p. 122–123 °C, on subsequent treatment with ethyl iodide. Metalation of ethyl phenylacetate in absolute benzene instead of in ether leads to the formation of ethyl α,γ-diphenylacetoacetate, m.p. 77.5–78.5 °C, in 61 % yield. / Naturwissenschaften *50*, 688 (1963) / - Ma. [Rd 790/209 IE]

**Syntheses of higher alicyclic systems** were achieved by *Ya. L. Goldfarb, S. Z. Taits*, and *L. I. Belenskii*, starting with thiophene derivatives such as *(1)*. A ring was formed from substituents $R^1$ and $R^2$, *e.g.* by acyloin condensation with Na/K alloy at only 50–60 °C. The sulfur bridge of the resulting bicyclic thiophene derivative was removed with Raney nickel.

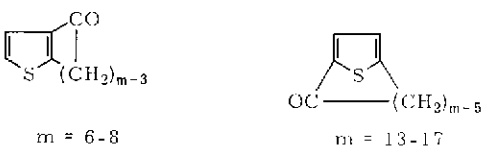


*(1)*

2,5-Dialkylthiophenes with ester groups in the 3- or 4-positions of the alkyl chains are particularly suitable for the acyloin condensation. Ring closure of *(1)* is also favored when $R^1$ = $C_2H_5OOCCH_2CO$ and $R^2$ = $(CH_2)_nHal$. Acid chlorides, such as *(2)*, form mono- and diketones as well as polymeric condensation products with Na/K.



*(2)*, n = 3-12 *(3)*, n = 5-9

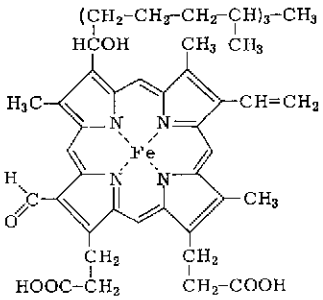


m = 6-8 m = 13-17

A sulfur-free diketone with 28 carbon atoms was made from *(3)* with n = 9. / Tetrahedron *19*, 1851 (1963) / –Kr. [Rd 846/215 IE]

**A new method for identifying substances by gas chromatography** has been developed by *J. Franc* and *S. Michajlova*. The sample for analysis is distributed simultaneously to four columns which are charged with different stationary phases. The gas streams from the four columns pass into a common detector connected to a recorder which prints the elution curves of the four columns in the form of spectra. In the ideal case, *i.e.* when the retention times of the four columns are different, a 'spectrum' is obtained with four maxima. The substance can then be identified by comparison with standard chromatograms. The following stationary phases have proved especially useful: the 3,5-dinitrobenzoyl ester of trimethyleneglycol butyl ether, polyethyleneglycol adipate, Silicone Elastomer E 301 (Griffin & George, London), and distillation residues of methylphenylsilicone oil. / 4th Symp. on Gas Chromatography, Leuna (Germany) 1963, Abstracts p. 32 / –Ko. [Rd 795/211 IE]

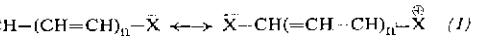
**The constitution of cytohaemin,** whose importance in cell respiration has been known for some time, has been elucidated by *M. Grassl, U. Coy, R. Seyffert*, and *F. Lynen*. Cytohaemin *(1)*, was isolated from beef hearts in the form of its hydrochloride and was converted into cytoporphyrin by hydrogenation with $H_2$/Pd in HCOOH. The degradation products resulting from oxidation of cytoporphyrin with $CrO_3$ were haematinic acid, methylethylmaleimide, and a lipophilic maleimide that is identical with recently synthetized methyl-(5,9,13-trimethyltetradecyl)maleimide [b.p. 167–171 °C/ $10^{-5}$ mm (oil bath), $n_D^{20}$ – 1,4835]. Methylethylpyrroledicarboxylic acid is obtained by oxidation of *(1)* with $KMnO_4$.



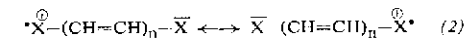
*(1)*

The nature of the degradation products and the mass-spectrometric and gas-chromatographic determinations carried out on them, together with spectroscopic data and the findings of other authors, indicate that *(1)* is the structural formula for cytohaemin. / Biochem. Z. *338*, 771 (1963) / –De. [Rd 793/213 IE]

**New free radical ions** were obtained by *S. Hünig, H. J. Friedrich, D. Scheutzow*, and *W. Brenninger*. It is known that a substance with an odd number of methine groups between key atoms X *(1)* has maximum delocalization of its π-electrons. This condition is also achieved with an even number of methine groups if the system *(2)* has free-radical character.



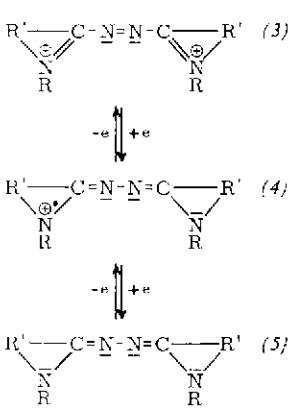
*(1)*



*(2)*

X = –N, –S–, –O–

Application of these facts led to the synthesis of new, stable free radical ions with, for example, 2-benzthiazolyl, 2-pyridyl-, 4-quinolyl, and 9-acridyl substituents according to the general formula *(3)* + *(5)* ⇌ 2 *(4)*.



*(3)*

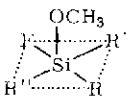
*(4)*

*(5)*

Some results in recent publications can also be explained by assumption of stable radical ions [1]. / Tetrahedron Letters *1964*, 181 / –Kr. [Rd 847/216 IE]

[1] *M. Fraser* and *D. H. Reid*, J. chem. Soc. (London) *1963*, 1421.

**The racemization of an optically active fluorosilane** was investigated by *L. H. Sommer* and *P. G. Rodewald*. Optically active methyl-α-naphthylphenylfluorosilane ($R_3Si^*F$) is quickly racemized when methanol is added to its solution in pentane or t-butanol. The racemization is not caused by traces of HF, for additions of HF retard the reaction, nor is it due to the formation of $F^\ominus$ ions by ionization of the $R_3Si^*F$, for the racemization is slower in the strongly polar solvent formic acid than in the weakly polar one pentane. The methoxy derivative $R_3Si^*OCH_3$ does not occur as an intermediate, for in a mixture of $R_3Si^*F$ and $R_3Si^*OCH_3$ only the former is racemized. The reaction is of the first order with regard to $R_3Si^*F$, and of about the fourth order with regard to $CH_3OH$. An intermediate that corresponds to these observations is the pentacovalent anion *(1)*, which is



*(1)*

formed by addition of the $CH_3O^\ominus$ ion (present in the methanol owing to dissociation) to $R_3Si^*F$. Displacement of the $CH_3O$ ligand from *(1)* is much faster than the alternative reaction to form $R_3Si^*OCH_3$ by elimination of $F^\ominus$, for after the time required to complete racemization, the methoxy compound could not be found in the reaction mixture. The formation of a hexacovalent intermediate is also possible, though less likely. / J. Amer. chem. Soc. *85*, 3898 (1963) / –Ko. [Rd 851/217 IE]

**Porous glasses as stationary phases in adsorption gas chromatography** were investigated by *Ya. I. Yaschin*, *S. P. Zhdanov*, and *A. V. Kiselev*. The porous glasses obtained by treatment of alkali borosilicate glasses with acids and water are characterized by a uniform pore structure which can be modified by the composition of the starting glass and by the leaching conditions. Moreover, the surface of porous glasses may be easily chemically modified. Glasses with very fine pores (pore diameter ≈ 10 Å) act as molecular sieves and permit the separation of low boiling gases. Glasses of average pore diameter 30 to 100 Å are suitable for the analysis of low boiling gases and vapors, *e.g.* light hydrocarbons. Large-pore glasses (pore diameter 300–500 Å) can be employed for the separation of liquids with boiling points of up to about 200 °C. / 4th Symp. on Gas Chromatography, Leuna (Germany) 1963, Abstracts p. 402 / –Ko. [Rd 796/212 IE]

# BOOK REVIEWS

**Thermodynamische Elektrochemie** (Thermodynamic Electrochemistry). By *Erich Lange* and *H. Göhr*. Alfred Hüthig Verlag GmbH., Heidelberg 1962. 1st Edit., 429 pp., 193 figs., clothbound, DM 39.–.

There are textbooks where the voice of Science herself seems to be heard, and others which make the reader believe, that he is constantly face with the author. The present book is of the latter kind. It was evolved from *E. Lange*'s famous article in Vol. 12 of the Handbuch der Experimentalphysik (Handbook of Experimental Physics). Here we are confronted with the outcome of decades of discussions between the author and his students, in an attempt to put electrochemistry on a firm footing of systematic thermodynamics. The concept thermodynamics is treated generously, irreversible processes being encompassed as well.

The introduction indicates the proper place of electrochemistry in the system of sciences. The text, composed together with his collaborator of many years standing, *H. Göhr*, begins with a discussion of single phases without and with current-flow. This is followed by treatment of the equilibria of simple electrodes and galvanic cells, and a section on thermocouples. An intermediate chapter describes the principles of "concentration" and "activation" overvoltage. The main part of the book is formed by the discourse on double and multiple electrodes, single and twofold protective-layer electrodes, including passivity, and by an additional chapter on scrape effects.

The authors frequently repeat in a generalizing manner the relations they have mentioned earlier, but this can only be welcome to the reader. It offers him a chance to get used to the terminology, which differs considerably from the customary jargon, and gradually to comprehend the rigorous system of symbols given here entwined with indices. In an appendix *E. Lange* has recapitulated his views on several general questions, particularly terminology, but not everybody will agree with this.

The book is not easy to read, but every electrochemist will gain a solid foundation for his science from a tussle with it.

*W. Jaenicke* [NB 136/64 IE]

**Atomphysik und menschliche Erkenntnis** (Atomic Physics and Human Understanding), by *Niels Bohr*. Series: Die Wissenschaft (Science), Collections of monographs from all fields of natural science. Edited by W. Westphal. Verlag Friedr. Vieweg & Sohn, Braunschweig 1958. 1st Edit. XIII, 104 pp., 8 figs., bound, DM 9.40 (about $ 2.50).

*Niels Bohr*'s essays from the years 1933–57, which are collected in this volume, serve essentially to define the importance of the concept of complementarity introduced by him into physics, and its applicability to other fields of knowledge such as biology, psychology, sociology, and anthropology. Ontologically the concept of complementarity is founded on the trend towards completeness manifested in several ways by reality, a trend which makes it impossible to draw a permanent sharp distinction between subject and object. In biology the notion of complementarity leads to a balance between the mechanistic and vitalistic attitudes. For its application to psychology, *Bohr* points to the complementarity of thought and feeling, particularly between the conscious deliberation on the motives of an action and the experience of an emotion governed by the will. The complementarity of instinct and reason is a frontier common to all the ultraphysical sciences mentioned. Lastly there is a very general level, on which we find the complementarity between the use of any given concept and attempts to define it precisely. It is in this very connection that *Bohr* manifests his sharp consciousness of the possibilities and limitations of all scientific method.

*E. Scheibe* [NB 143/65 IE]

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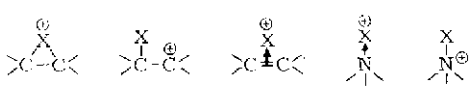
# Polar Addition of Hydrogen Halides onto Olefins [1]

BY PROF. DR. J. S. DEWAR AND DR. R. C. FAHEY [2]

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS, AUSTIN, TEXAS (U.S.A.)

*Various structures have been proposed for the intermediates of electrophilic additions onto olefins; these include halonium ions, classical carbonium ions, π-complexes (i.e. non-classical carbonium ions), and π-complexes with back-coordination. It is shown here that it is impossible to use any one of these entities alone to explain all such electrophilic additions; the electrophile itself determines the nature of the transition state formed. Polar addition of hydrogen halides onto olefins appears to proceed via a classical carbonium ion which does not occur as the free ion but as an undissociated ion pair. Various other mechanisms have been excluded by studies reported here of the stereochemical course of such additions.*

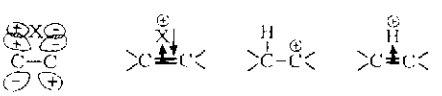
Electrophilic addition reactions have long been recognized [3] to proceed via intermediates with the composition of carbonium ions. It is also known that these intermediates, in certain cases at least, are not simple carbonium ions since the reactions are stereospecific, the products being formed by exclusive *trans*-addition onto the olefin. This observation was explained some time ago by *Roberts* and *Kimball* [4] for halogen addition by the assumption that the intermediate is a halonium ion *(1)* rather than a carbonium ion *(2)*; the product is formed by nucleophilic attack on the intermediate with opening of the three-membered ring, and this reaction, in effect an $S_N2$ reaction, takes place by attack of the nucleophile *trans* to the "leaving group", here $X^{\ominus}$.



*(1)* *(2)* *(3)* *(4)* *(5)*

This formulation of the intermediate is, however, open to criticism [5], for it does not explain the orientation of addition onto unsymmetrically substituted olefins (*i.e.* Markownikoff's rule), and one of us accordingly suggested [5] some years ago that the intermediate might be better represented as a π-complex *(3)* in which the filled π-orbital of the olefin is used to form a dative bond by interaction with the empty valence orbital of the acceptor $X^{\oplus}$. This structure is formally analogous to that of an ammonium salt formed by addition of $X^{\oplus}$ to ammonia or an amine; such a complex could be written equivalently as a donor-acceptor complex *(4)* or as an ammonium ion *(5)*.

If the acceptor $X^{\oplus}$ has unshared p- or d-electrons or π-electrons, these can be used to form a reverse dative bond to the olefin by interaction with the empty antibonding π-molecular orbital of the latter *(6)* [6].



*(6)* *(7)* *(8)* *(9)*

The group $X^{\oplus}$ is then attached to the olefin by a double bond composed of two opposed dative bonds involving π-molecular orbitals *(7)*. This structure differs from *(1)* only in the state of hybridization of the olefinic carbon atoms, since the bond between them is only partly double. It is therefore somewhat difficult to distinguish between the two tentative structures *(3)* and *(7)*.

Recent physical evidence [7] indicates that analogous metal complexes, *e.g.* Zeise's salt, are in fact double-bonded π-

[1] This work was supported by a grant from the National Science Foundation.

[2] National Science Foundation Predoctoral Fellow; present address: Department of Chemistry, University of California at San Diego, La Jolla, Calif. (U.S.A.).

[3] See *E. S. Gould:* Structure and Mechanism in Organic Chemistry. Henry Holt and Co., New York 1959.

[4] *I. Roberts* and *G. E. Kimball*, J. Amer. chem. Soc. *59*, 947 (1937).

[5] *M. J. S. Dewar:* The Electronic Theory of Organic Chemistry. Clarendon Press, Oxford 1949.

[6] *M. J. S. Dewar*, Bull. Soc. chim. France *18*, 71 (1951).

[7] See *S. Maricic, C. R. Redpath*, and *J. A. S. Smith*, J. chem. Soc. (London) *1963*, 4905.

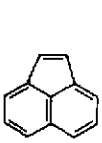
complexes of type *(7)*, the olefinic moiety being coplanar and the carbon atoms multiply linked.

This ambiguity would be avoided if $X^{\oplus}$ were a group without electrons capable of forming a reverse dative bond, for stereospecific *trans*-addition would then indicate very clearly that the intermediate was a π-complex or "non-classical carbonium ion" *(3)*. The study of such reactions is therefore of considerable theoretical interest, both on its own merits and in view of the current controversy concerning the status of such "non-classical carbonium ions" as reaction intermediates. Addition of $X^{\oplus}$ onto an olefin would be expected to give the more stable of the two possible species directly; the course of such reactions should therefore indicate definitely whether or not such "non-classical carbonium ions" or π-complexes *(3)* are more stable than the isomeric classical carbonium ions *(1)*.

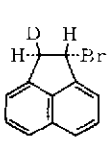
The groups $X^{\oplus}$ that are obviously suitable for this study are carbonium ions or protons; experimental considerations make the latter the more attractive choice. The problem is then to decide whether the electrophilic addition of acids, *e.g.* HBr, onto olefins takes place stereospecifically *trans*; if it does, it may be concluded that classical carbonium ions such as *(8)* are less stable than the isomeric π-complexes such as *(9)*.

It has often been assumed [3] that such additions do take place stereospecifically *trans*, although evidence for this view is somewhat meagre. Hydrogen iodide is known [8] to add *trans* onto certain α,β-unsaturated acids, and *Hammond* and his collaborators [9] have shown that hydrogen bromide adds almost exclusively *trans* onto 1,2-dimethylcyclohexene, and that hydrogen chloride adds predominantly (92 %) *trans* onto 1,2-dimethylcyclopentene. However, these isolated findings cannot be generalized, for there is doubt as to whether the addition reactions of acids are electrophilic in nature, and additions onto cyclic compounds might be subject to conformational effects. We therefore investigated the stereochemistry of the polar addition of hydrogen halides onto olefins where no such complications could arise.

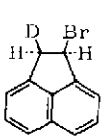
We first examined [10] the addition of hydrogen bromide onto acenaphthylene *(10)*. In order to determine the stereochemistry of the reaction we labelled the atoms isotopically by using deuterium bromide as the reagent.



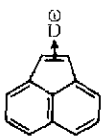
*(10)*



*(11)*

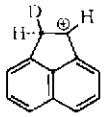


*(12)*

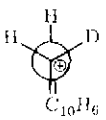


*(13)*

Addition via a π-complex *(13)* should give exclusively *trans*-adduct *(11)*. Addition by a "classical" mechanism would involve a carbonium ion *(14)* which has a plane of symmetry [cf. the Newman projection *(15)*]; if this ion can exist freely in solution, it should combine more or less randomly with bromide ions to give an approximately equimolar mixture of *(11)* and *(12)*. Any difference in the proportions of *(11)* and *(12)* could be due only to secondary isotope effects and would not exceed 10–20 %.



*(14)*



*(15)*

The reaction product was analysed in two different ways, *viz.* by nuclear magnetic resonance, and by elimination. The NMR analysis involved measurement of the splitting of the CHBr proton signal due to interaction with the adjacent CHD proton. The magnitude of this spin-spin splitting should depend on the dihedral angle between the corresponding CH bonds, which is approximately 120° in *(11)* and 0° in *(12)*. The expected splittings, according to *Karplus* [11], are approximately 2 cps and 8 cps, respectively. The difference is thus quite large. The second method of analysis entailed $E_N2$ elimination of HBr or DBr by base (potassium t-butoxide) to regenerate acenaphthylene. Since eliminations from halogenoacenaphthenes are known [12] to take place almost exclusively *trans*, *(11)* should give acenaphthylene free from deuterium, while *(12)* should give acenaphthylene containing one deuterium atom.

The NMR spectrum of the adduct indicated immediately that the reaction was not stereospecific, for the CHBr proton resonance showed four lines, corresponding to the presence of both *cis*- and *trans*-isomers. This interpretation was confirmed by a change in the spectrum with time; the weaker pair of lines increased in intensity at the expense of the stronger, implying gradual conversion of the one isomer into the other. The change was not due to a chemical reaction, for the bromide could be recovered unchanged [*(11)* and *(12)* are of course physically equivalent]. The separations of the pair of lines also corresponded quite closely to *Karplus'* calculations, being 2.7 cps and 6.8 cps, respectively. There seemed therefore little doubt concerning their identification, but much to our surprise it was the pair with $\tau$ – 6.8 cps corresponding to the *cis*-isomer, that was the stronger! Contrary to predictions the reaction had apparently led predominantly to *cis*-adduct. This unexpected conclusion was confirmed by the data from elimination; the recovered acenaphthylene contained nearly one atom of deuterium, showing that the bromide must have been mainly the *cis*-isomer *(12)*.

The proportions of isomeric adducts formed in various solvents were determined quantitatively, by both NMR and elimination. The results are shown in Table 1, together with data for the addition of deuterium chloride. The results of the two methods of analysis always

[8] See *W. R. Vaughan, R. L. Craven, R. Q. Little,* and *A. C. Schoenthaler,* J. Amer. chem. Soc. *77*, 1994 (1955).

[9] *G. S. Hammond* and *T. D. Nevitt,* J. Amer. chem. Soc. *76*, 4121 (1954); *G. S. Hammond* and *C. H. Collins,* ibid. *82*, 4323 (1960).

[10] *M. J. S. Dewar* and *R. C. Fahey,* J. Amer. chem. Soc. *85*, 2245 (1963).

[11] *M. Karplus,* J. chem. Physics *30*, 11 (1959); see also *F. A. L. Anet,* Canad. J. Chem. *39*, 789 (1961).

[12] *S. J. Cristol, F. R. Stermitz,* and *P. S. Ramsey,* J. Amer. chem. Soc. *78*, 4939 (1956).

agreed within the limits of experimental error; some complications arose in the NMR analysis due to long-range couplings with ring protons [13] but these could be eliminated by spin decoupling techniques.

Table 1. Addition of DBr onto acenaphthylene.

| Reagent | Solvent | Temp. [°C] | *cis*-Adduct [*] [%] |
|---|---|---|---|
| DBr | Pentane | −78 | 87 |
| | Pentane | 0 | 89 |
| | $CH_2Cl_2$ | −78 | 84 |
| | $CH_2Cl_2$ | 0 | 85 |
| | DOAc | 25 | 74 |
| DCl | $CH_2Cl_2$ | 0 | 85 |
| | DOAc | 25 | 85 |

[*] In the reaction product before isomerization begins.

We proved that the reactions under our conditions were of the polar rather than of the free radical type by carrying out the addition with HBr in the presence of styrene; free radical additions of HBr involve intermediate bromine atoms, and these would lead to the formation of phenethyl bromide $C_6H_5CH_2CH_2Br$ from the styrene. No trace of this could be detected in the reaction product although this contained large amounts of the "normal" polar adduct $C_6H_5CHBrCH_3$. We also established that the *trans*-isomer formed was a primary reaction product, and was not formed by secondary isomerization, by allowing the reaction mixture to stand for various lengths of time before work-up. The *trans*- → *cis*-isomerization of the bromide was extremely slow; that of the chloride was faster, but we were able to extrapolate the isomer ratios to zero time to find the proportions of *cis*- and *trans*-isomers formed in the initial reaction. These figures are listed in the last column of Table 1. We also demonstrated that the *trans*-isomer was not formed by a concomitant free radical process, for the proportions of *cis*- and *trans*-adducts remained unchanged when the reaction was run under strong illumination. This would have selectively accelerated any free radical processes.

These results showed unambiguously that the addition of hydrogen halides onto acenaphthylene does not involve intermediate π-complexes. However, acenaphthylene is not a typical olefin, and so we extended our studies to indene [14] and *cis*- and *trans*-1-phenylpropene [15]. The stereochemistry of the addition of deuterium bromide onto indene was studied by NMR only, since we could not reconvert 1-bromoindane into indene quantitatively by elimination. The stereochemistry of the adducts obtained from deuterium bromide and the phenylpropenes could not of course be determined by NMR spectroscopy since their molecular skeletons are not rigid; however elimination with potassium t-butoxide converted them quantitatively into mixtures of olefins from which the predominant isomer (*trans*-1-phenylpropene) was separated by gas chromatography. Estimation of the deuterium in this enabled the proportions of isomers in the adduct to be deduced. The results are shown in Table 2.

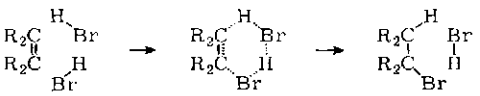
Table 2. Addition of DBr onto indene and *cis*- and *trans*-1-phenylpropene.

| Olefin | Solvent | Temp. [°C] | *cis*-Adduct [%] |
|---|---|---|---|
| Indene | Pentane | −78 | 80 |
| | $CH_2Cl_2$ | −78 | 81 |
| *cis*-1-Phenylpropene | $CH_2Cl_2$ | 0 | 88 |
| *trans*-1-Phenylpropene | $CH_2Cl_2$ | 0 | 88 |

In these experiments it was easy to establish the nature of the addition reactions since the products from radical ("peroxide effect") addition are different from those of polar addition. Indene gave exclusively 1-bromoindane under our conditions, indicating polar addition. The phenylpropenes gave some anti-Markownikoff product (1-phenyl-2-bromopropane) when treated with hydrogen bromide in methylene chloride alone, but this side reaction could be completely suppressed by adding hydroquinone.

These results show conclusively that the additions of hydrogen halides onto acenaphthylene, indene, and *cis*- and *trans*-1-phenylpropene do not proceed via π-complexes or free carbonium ions as intermediates, for in the former case the products would have been exclusively *trans*-adducts and in the latter case approximately equimolar mixtures of the *cis*- and *trans*-adducts.

One possible mechanism for *cis*-addition would be a Diels-Alder-type mechanism involving a cyclic transition state *(16)*. However this mechanism would be



*(16)*

expected to lead to a second order reaction depending on the concentration of hydrogen halide, whereas the observed order in reactions of this kind is usually three [16]. It would also be impossible to account in this way for the formation of *trans*-adduct as a primary product in proportions which seem to be independent of the concentration of hydrogen halide, because the order with respect to hydrogen halide would certainly differ for *cis*- and *trans*-addition, being necessarily much higher for the latter. The only solution is then to assume different mechanisms for the *cis*- and the *trans*-addition. In this case, the *trans*-addition would have to involve ionic intermediates (*e.g.* π-complexes) and would therefore show a solvent dependence entirely different from that of the non-ionic *cis*-addition. In practice, the proportion of *cis*-adduct was found to change remarkably little with the polarity of the solvent (Table 1), so this mechanism must also be rejected.

The only remaining possibility is a mechanism in which an intermediate classical carbonium ion is formed, but not as a free ion. This is in fact extremely reasonable;

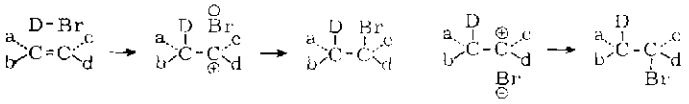
[13] *M. J. S. Dewar* and *R. C. Fahey*, J. Amer. chem. Soc. *85*, 2704 (1963).

[14] *M. J. S. Dewar* and *R. C. Fahey*, J. Amer. chem. Soc. *85*, 2248 (1963).

[15] *M. J. S. Dewar* and *R. C. Fahey*, J. Amer. chem. Soc. *85*, 3645 (1963).

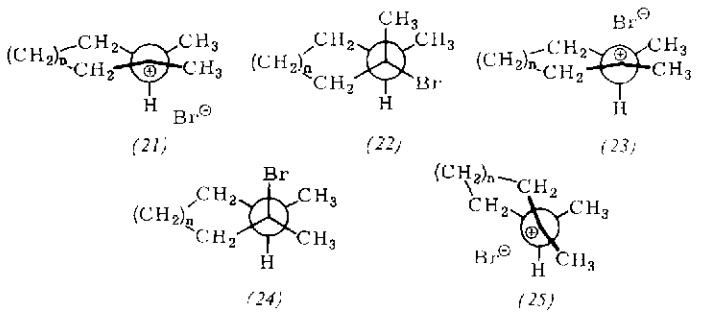
[16] *F. R. Mayo* and *J. J. Katz*, J. Amer. chem. Soc. *69*, 1339 (1947).

because in the solvents used by us, salts exist mainly as ion pairs, and hydrogen halides are undissociated. The reaction of undissociated deuterium bromide with an olefin should then give first an ion pair in which the bromide ion is retained on the same side of the olefin as the deuterium; collapse of this ion pair *(17)* would give exclusively *cis*-adduct *(18)*. The *trans*-adduct *(20)* is formed only if the ion pair survives long enough for the bromide ion to migrate to the opposite side of the planar carbonium ion *(19)*; if collapse of *(17)* is fast, *cis*-addition will predominate. The probability of isomerization should increase with increasing solvent polarity since this will prolong the life of the intermediate ion pair; the addition of deuterium bromide onto acenaphthylene did infact give increased amounts of *cis*-adduct in less polar solvents (Table 1), but the data for the other reactions were not accurate enough to confirm or refute such a trend. Finally, the high order of the reaction with respect to hydrogen halide can be attributed to solvation; the formation of ions from neutral molecules in a relatively non-polar solvent is a very unfavorable process, and it is very reasonable that solvation of the nascent halide ion by additional molecules of hydrogen halide is needed as a driving force.



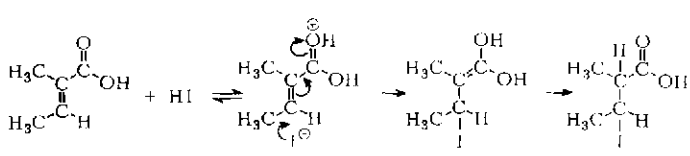
*(17)* *(18)* *(19)* *(20)*

In the reactions studied by us, *cis*-addition predominated; our mechanism can also provide a satisfactory explanation for the *trans*-addition reported by *Hammond* and his collaborators [9] for the additions of hydrogen halides onto 1,2-dimethylcyclohexene and 1,2-dimethylcyclopentene. Here the intermediate carbonium ion is first formed in the conformation represented in Newman projection in *(21)*. Collapse to give the *cis*-adduct *(21)* would then take place through an intermediate configuration in which the methyl groups are



*(21)* *(22)* *(23)* *(24)* *(25)*

eclipsed. This conformational effect should hinder *cis*-addition and encourage isomerization of the primary ion pair to the isomer *(23)*, which can collapse freely to the *trans*-adduct *(24)*. In order to form the *cis*-adduct easily, the initial ion *(21)* would have to isomerize to *(25)*; this isomerization would however be inhibited by the conformational requirements of the remaining carbon atoms in the ring. These requirements are of course less for a five-membered ring than for a six-membered ring; this explains why addition of hydrogen bromide onto 1,2-dimethylcyclohexene gave no detectable trace of *cis*-adduct, whereas 8 % *cis*-adduct was formed in the reaction between hydrogen chloride and 1,2-dimethylcyclopentene. One might also expect *cis*-addition to occur more easily with unsubstituted cyclic olefins, where collapse of the initial ion pair *(26)* involves eclipsing of protons rather than of methyl groups; *Smirnov-Zamkov* and *Piskovitina* [17] reported that the addition of deuterium bromide onto cyclohexene does indeed give large amounts of *cis*-adduct.

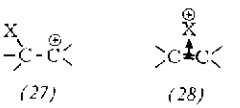


*(26)*

The only other example of *trans*-addition of hydrogen halides onto olefins, namely, the reaction of HI and α,β-dimethylacrylic acid, is also easily explained. Hydrogen iodide is a very strong acid, and the carboxyl group has significant basic properties; it therefore seems likely that the addition of hydrogen iodide onto α,β-unsaturated acids is an acid-catalysed Michael (nucleophilic) addition rather than an electrophilic addition. If so, this reaction has no bearing on the mechanism of electrophilic substitution, and the stereochemistry of the product is determined solely by the final prototropic shift. It is easily seen [14] that here steric effects will favor formation of the *trans*-adduct.

These arguments suggest that the normal course of addition of hydrogen halides onto olefins is a polar electrophilic process involving classical carbonium ions as intermediates and leading mostly, but not exclusively, to *cis*-adducts. A direct corollary would be that classical carbonium ions such as *(8)* are normally more stable than isomeric π-complexes with apical protons *(9)*. The problem is then why some electrophilic additions to olefins take place via π-complexes, while others involve carbonium ions as intermediates.

If we consider the heat of isomerization (ΔH) involved in the transformation of the classical carbonium ion *(27)* to the π-complex *(28)*, we see that in *(27)*, the



*(27)* *(28)*

whole positive charge resides on the carbon; whereas in *(28)*, a part δq of it resides on X. If $E_{C-C}$, $E_{C=C}$, and $E_{C-X}$ are the bond energies of the C–C, C=C, and C–X bonds, $E_\pi$ that of the dative bond in *(28)*, and $I_C$ and $I_X$ the ionization potentials of carbon and X, then:

$$\Delta H = E_{C=C} + E_\pi - E_{C-C} - E_{C-X} + \delta q(I_C - I_X)$$
$$= C + E_\pi - E_{C-C} - E_{C-X} - \delta q \cdot I_X$$

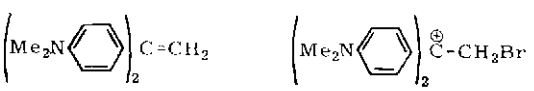
where C is a constant for attack on a given olefin by different reagents X. This equation shows that the π-complex structure will be all the more favored, the

[17] *J. V. Smirnov-Zamkov* and *G. A. Piskovitina*, Ukr. Khim. Zh. *28*, No. 4 (1962), and personal communication from Professor *Smirnav-Zamkov*.

weaker the bond C–X, and the less electronegative X, because the dative bond will be relatively weak, and variations in its (relatively small) bond energy are likely to be relatively unimportant.

To this we must add two further considerations. First, if X has π-electrons, or unshared p- or d-electrons, the π-complex will be selectively stabilized by back-coordination [cf. *(6)* and *(7)*]. Second, the carbonium ion will be selectively stabilized [18] by –E or ±E [18a] substituents, for these will have much smaller effects on the π-complex, as might be expected from their greater charge dispersion and can be demonstrated by molecular orbital calculations.

Now let us consider the experimental facts. Additions involving initial attack by $I^{\oplus}$, $Br^{\ominus}$, or $RS^{\oplus}$ give *trans*-adducts in all the cases that have been studied; the intermediates here are definitely π-complexes or, in the case of $RS^{\oplus}$, the equivalent cyclic structures *(1)*. This is in agreement with evidence [19] from neighboring group participation in solvolytic reactions, which indicates that here the classical ions *(2)* are less stable than *(1)* or *(3)*. The only exceptions appear with molecules in which the carbonium ion is stabilized by strong –E substituents; *e.g.* the olefin *(29)* reacts with bromide to give the ion *(30)* [20].

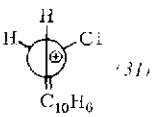


*(29)* *(30)*

In all these cases, the group X in *(1)* or *(3)* has unshared p-electrons, and the C–X bond is weak (CBr, CI) or X is only weakly electronegative (RS). It is therefore not surprising to find a strong bias in favor of π-complex intermediates.

The situation is different when X is chlorine. While simple olefins, *e.g.* 2-butene [21], seem to add on chlorine stereospecifically *trans*, stilbene gives a mixture of *cis*- and *trans*-dichlorides [22], and acenaphthylene *(10)* adds on chlorine predominantly *cis* [23]. These apparent inconsistencies can be explained if the balance between carbonium ion and π-complex is close, so that a single ±E group (phenyl or α-naphthyl) is enough to displace the balance in favor of the carbonium ion. This conclusion is also supported by solvolytic studies [19] which show that chlorine is a poor neighboring group. The arguments given above would require chlorine to differ in this way from bromine or iodine, for the C–Cl bond is much stronger than that of C–Br or C–I, and chlorine is more electronegative than bromine or iodine.

It is interesting that acenaphthylene *(10)* reacts with iodobenzene dichloride to give mainly *trans*-dichloroacenaphthene [23]; this can again be explained in terms of an intermediate ion pair containing the cation *(31)* and the anion $(C_6H_5ICl)^{\ominus}$. Steric effects due to the bulk of the latter could hinder collapse to *cis*-dichloride and so favor isomerization of the initial ion pair to the *trans*-dichloride.



*(31)*

These considerations suggest that *(1)* should definitely be the more stable form of the ion when X is fluorine. There are no data available for the stereochemistry of the addition of fluorine onto olefins, but fluorine has never been reported to show neighboring group effects.

The position of hydrogen is now intelligible. The C–H bond is extremely strong, and hydrogen possesses no unshared p- or d-electrons and is quite strongly electronegative. It is not surprising to find that π-complexes with apical protons seem to be generally less stable than the isomeric classical carbonium ions.

It appears then that the conventional picture of electrophilic addition is oversimplified. Many such reactions do involve π-complex intermediates, but many others take place by a "classical" mechanism involving intermediate carbonium ions. It will clearly be necessary to reinvestigate many of these reactions in detail in order to delineate the areas where each of the two mechanisms dominates.

One particularly interesting case, which has so far not been studied at all, is that when X in *(1)* or *(3)* is an alkyl group. We know from solvolysis studies [19] that the π-complex is commonly more stable when X is an aryl group with π-electrons; and we know that the π-complex is more stable in certain polycyclic systems in which the carbonium ion is selectively destabilized by ring strain. We do not, however, know the relative stabilities of the π-complex and carbonium ion in simple aliphatic systems. The lack of neighboring group effects throws no light on this problem, for it could well be that the classical carbonium ions and "non-classical" π-complexes are separated by energy barriers. If so, their relative stabilities could be established only by a study of addition reactions where the ion is formed by addition of a carbonium ion to an olefin. The stereochemistry of such reactions has not yet been investigated except in certain cyclizations where conformational effects could have determined the stereochemistry (cf. the cases of dimethylcyclohexene and dimethylcyclopentene discussed above). The evidence concerning addition of protons to olefins allows no speculation on the outcome of such reactions, for alkyl groups are less electronegative than protons, and the C–C bond is much weaker than the C–H linkage. There is dire need for data concerning the stereochemistry of additions to olefins where the primary reagent is a carbonium ion.


[18] Cf. *M. J. S. Dewar*, J. Amer. chem. Soc. *74*, 3357 (1952).

[18a] Cf. *M. J. S. Dewar*, J. Amer. chem. Soc. *74*, 3350 (1952).

[19] See *A. Streitwieser:* Solvolytic Displacement Reactions. McGraw-Hill, New York 1962.

[20] *P. Pfeiffer* and *R. Wizinger*, Liebigs Ann. Chem. *461*, 132 (1928).

[21] *H. J. Lucas* and *C. W. Gould*, J. Amer. chem. Soc. *63*, 2541 (1941).

[22] *S. J. Cristol* and *R. S. Bly*, J. Amer. chem. Soc. *82*, 142 (1960).

[23] *S. J. Cristol, F. R. Stermitz*, and *P. S. Ramsey*, J. Amer. chem. Soc. *78*, 4939 (1956).



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# Synthesis of Naturally Occurring Unsaturated Fatty Acids by Sterically Controlled Carbonyl Olefination

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*It is shown that carbonyl olefination, i.e. the reaction of carbonyl compounds with alkylidene phosphoranes, can be sterically controlled. In some cases cis-olefins can be obtained by proper choice of the reaction conditions; trans-olefins are formed only in the presence of suitable structural factors. These cis- and trans-olefination reactions have opened new, stereospecific routes to unsaturated and polyunsaturated fatty acids with differing positions and sequences of cis- and trans-double bonds and to ω-hydroxy and branched chain fatty acids.*

I. Introduction

II. Steric control of carbonyl olefination

III. Application of *cis*- and *trans*-olefination to the synthesis of naturally occurring unsaturated fatty acids

1. *cis*-Alkenoic acids $CH_3(CH_2)_mCH=CH(CH_2)_nCOOH$
2. Conjugated polyenoic acids $CH_3(CH_2)_m(CH=CH)_x(CH_2)_nCOOH$
3. Acids of the *cis,cis*-divinylmethane type $CH_3(CH_2)_mCH=CH-CH_2-CH=CH(CH_2)_nCOOH$
4. Polyenes of the divinylethane type
5. Unsaturated ω-hydroxy acids
6. Higher branched-chain carboxylic acids

## I. Introduction

Unsaturated fatty acids are attracting considerable attention of late, mainly in their capacity as constituents of lipids, in particular of the various phospholipids which play an essential part in basic biological processes as the building material of cellular and subcellular membranes. Numerous new acids of this type have been discovered during the last two decades in the lipids of brain, liver, heart, and other mammalian organs, in fish oils, and also in lipids of plant origin [1, 2]. However this period has seen no marked advance in the synthesis of these acids. As a rule, the conventional synthetic methods are complicated, require difficultly available starting materials, and give only minute ultimate yields [3]. For instance, one of the shortest routes to oleic acid [4] involves seven stages and the yield is only 2 % with respect to the starting material pimelic acid. The ways described in the literature for synthetizing polyolefinic acids, *e.g.* the ten-stage synthesis of α-cleostearic acid [5] are even more complicated. Furthermore, most methods for the preparation of unsaturated fatty acids (excepting those starting from acetylenic derivatives) are not stereospecific, the *trans*-isomer usually predominating; natural unsaturated fatty acids usually have the *cis*-configuration. The development of straightforward, stereospecific routes to higher unsaturated fatty acids is therefore a primary objective in lipid chemistry.

Recently new methods have been developed in our institute for the synthesis of the principal types of naturally occurring unsaturated fatty acids. These utilize readily available materials, require only a few stages, and are highly stereospecific. The methods are based on the principles discovered some years ago by the authors and their coworkers [5a] for steric control of the reactions between carbonyl compounds and alkylidenetriphenylphosphoranes [6] or dialkyl phosphonate and diphenylphosphine oxide ions [7] to give olefins.

$$R_2CO + Ph_3P{=}CHR \longrightarrow R_2C{=}CHR + Ph_3PO$$

$$R_2CO + (C_2H_5O)_2\overset{O^{\ominus}}{\underset{|}{P}}{=}CHR \longrightarrow R_2C{=}CHR + (C_2H_5O)_2POO^{\ominus}$$

$$R_2CO + Ph_2\overset{O^{\ominus}}{\underset{|}{P}}{=}CHR \longrightarrow R_2C{=}CHR + Ph_2POO^{\ominus}$$

[*] Previous contributions to this series are collected in three volumes, published by Verlag Chemie, Weinheim/Bergstraße (Germany), and by Academic Press, New York and London.

[1] Cf. *F. D. Gunstone* in: Progress in Organic Chemistry. Butterworths, London 1958, Vol. 4, p. 1.

[2] *J. Assellineau* and *E. Lederer*, Ann. Reviews Biochem. *30*, 71 (1961).

[3] See review *W. J. Gensler*, Chem. Reviews *57*, 191 (1957).

[4] *W. F. Huber*, J. Amer. chem. Soc. *73*, 2730 (1951).

[5] *L. Crombie* and *A. G. Jacklin*, J. chem. Soc. (London) *1957*, 1632.

[5a] *L. D. Bergelson*, *V. A. Vaver*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1960*, 1900, and later publications.

[6] *L. D. Bergelson* and *M. M. Shemyakin*, Tetrahedron *19*, 149 (1963).

[7] *L. D. Bergelson*, *V. A. Vaver*, *L. I. Barsukov*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, in the press.

These reactions, which can be designated collectively as carbonyl olefinations, have found widespread use in various fields of organic chemistry as a general means for the synthesis of unsaturated compounds. The newly discovered possibility of their steric control extends their scope even further, especially for the synthesis of natural products.

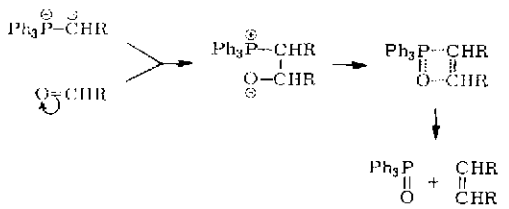
## II. Steric Control of Carbonyl Olefination

The stereochemistry of carbonyl olefination has hitherto received no systematic attention. The reaction of carbonyl compounds with alkylidenetriphenylphosphoranes, *i.e.* the Wittig reaction [8,9], has generally been considered to be non-stereospecific and, since it yields mainly *trans*-olefins, it appeared to be of little promise for the synthesis of naturally occurring unsaturated fatty acids. No data are to be found in the literature regarding the stereochemistry of the reaction between carbonyl compounds and dialkyl phosphonate or diphenylphosphine oxide anions [10, 11].

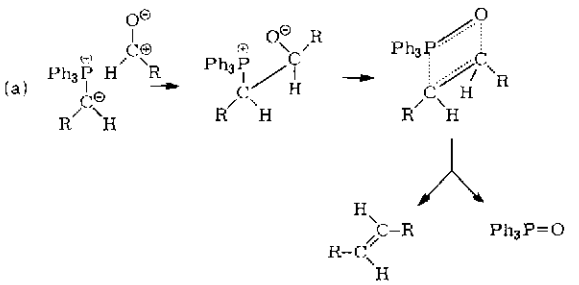
In a systematic investigation of the reaction of aldehydes with alkylidenetriphenylphosphoranes [6], we were able to show that its stereochemistry can be controlled by suitable reaction conditions and structural factors. The following gives a description of the fundamental stereochemical relationships established in the course of this investigation and of how they can be used for the directed stereospecific synthesis of unsaturated compounds.

1. *In the reaction between aldehydes and alkylidenetriphenylphosphoranes, the presence of a sufficiently nucleophilic Lewis base promotes cis-olefin formation.*

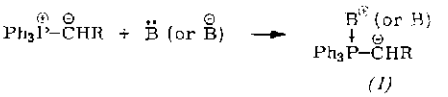
The reaction of Wittig reagents with carbonyl compounds is generally assumed to begin with an electrophilic attack of the carbonyl carbon on the negatively polarized phosphorane carbon [8,9] (although nucleophilic attack on the positively polarized phosphorus atom by the carbonyl oxygen cannot be excluded).



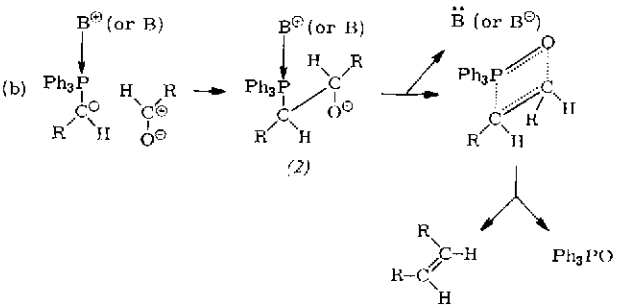
In the absence of Lewis bases and in non-polar media, dipole-dipole interaction and mutual repulsion of the substituents R on the reactants lead predominantly to *trans*-olefins (a).



The effect of Lewis bases (B: or $B^{\ominus}$) on the steric course of the reaction is due to their ability to interact with the phosphorus atom, which tends to expand its electronic octet to a decet [6].



The phosphorus is less electrophilic and at the same time sterically less accessible in the resultant complex *(1)* than in the initial alkylidenephosphorane, so that dipole-dipole interaction of the phosphorane with the aldehyde will no longer exert a decisive influence on the orientation of the reactants. These then orientate themselves mainly as in *(2)* and the reaction proceeds with formation of the *cis*-olefin.



This *cis*-directing effect of Lewis bases is observed in the reaction of various aldehydes and alkylidenetriphenylphosphoranes. However, its manifestation may also depend upon the nature of the reactants, in particular upon the stability of the phosphoranes and the branching of the groups R. Efficient Lewis bases are halogenide ions ($Br^{\ominus}$ and especially $I^{\ominus}$) and certain amines. With Lewis bases of the same species, the relative yield of *cis*-isomers is augmented in proportion to their nucleophilicity, *i.e.* in the order Cl < Br < I or ethyl *p*-aminobenzoate < aniline < phenylhydrazine < *N,N*-dimethyl-*p*-phenylenediamine. However, with amines the yield of *cis*-isomer also depends strongly upon steric factors, falling sharply in the order butylamine > diethylamine > triethylamine. It should be noted that, while promoting formation of the *cis*-isomer, Lewis bases retard the overall rate of reaction [6,13,17].

2. *The relative yield of cis-isomer increases when the aldehydes are treated with alkylidenetriphenylphosphoranes in a polar aprotic solvent.*

The *cis*-directing effect increases with the polarity, of the solvent, *e.g.* in the order benzene < ether < tetra-

[8] *U. Schöllkopf*, Angew. Chem. *71*, 260 (1959).

[9] *S. Tripett* in: Advances in Organic Chemistry. Interscience, New York, London 1961, Vol. 1, p. 83.

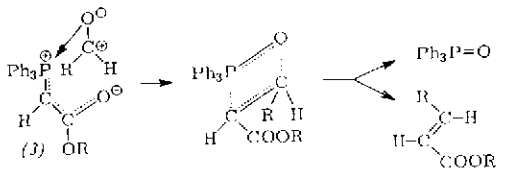
[10] *L. Horner, H. Hoffman*, and *H. G. Wippel*, Chem. Ber. *91*, 61 (1958).

[11] *L. Fieser* and *M. Fieser:* Topics in Organic Chemistry. Reinhold, New York 1963, p. 482.

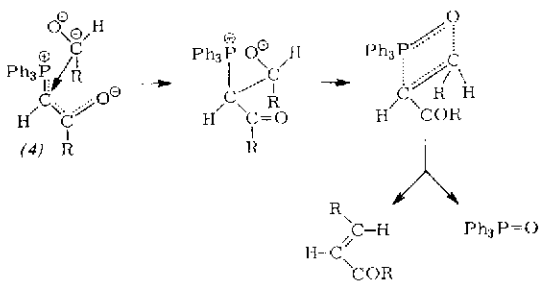
hydrofuran < dimethylformamide [12, 13]. This effect can be explained by assuming that polar solvents solvate the phosphorus and the carbonyl oxygen, thus facilitating the formation of the intermediate *erythro*-compound *(2)*.

3. *Alkylidenetriphenylphosphoranes with a carbonyl group at the α-carbon atom react with aldehydes to form largely trans-olefins.*

The α-C-atom of such phosphoranes [see *(3)* and *(4)*] has a lower nucleophilicity. Therefore the possibility exists that the carbonyl oxygen attacks the phosphorus atom, although direct evidence for such a mechanism is still lacking.



However, it can readily be seen that a C → C attack in the reaction of *(3)* or *(4)* with aldehydes also leads to *trans*-olefins, formation of the *cis*-isomer being hindered by mutual repulsion of negative groups.



It is noteworthy that the steric course of this reaction depends neither upon the polarity of the solvent nor upon Lewis bases.

Obviously, not only alkylidenetriphenylphosphoranes of type *(3)* but also their vinylogues $Ph_3P{=}CH(CH{-}CH)_n{-}COOR$ [14], as well as β,γ-unsaturated compounds of type $Ph_3P{=}CHCH{-}CHR$ [15] will promote *trans*-olefination.

4. *Alkylidenephosphoranes with sufficiently low positive charge on the phosphorus atom give predominantly trans-olefins with aldehydes, independent of the reaction conditions.*

The positive charge on the phosphorus can be reduced by introducing a substituent of strong −I effect. Compounds of this type, for example dialkyl alkylidenephosphonate and diphenylphosphine oxide anions [7] or alkylidenetricyclohexylphosphoranes [16], cannot form complexes with Lewis bases. They therefore react with aldehydes according to Equation (a) to form predominantly *trans*-olefins, regardless of the polarity of the solvent and the presence of halide ions.

Proper combination of these four principles enables stereoselective syntheses of various unsaturated aliphatic compounds, from simple mono-olefins to complicated polyenic systems, to be carried out. Thus, our study of the influence of environmental factors on the reaction between alkylidenetriphenylphosphoranes and aldehydes led to a stereospecific modification that gives predominantly *cis*-olefins [17]. The reaction is best carried out in a polar aprotic solvent (optimally dimethylformamide) with $I^{\ominus}$ or $Br^{\ominus}$ as Lewis bases. Under such conditions, the amount of *trans*-olefin in the product usually does not exceed 5–6 %. We therefore call this reaction *cis*-olefination.

On the other hand, *trans*-olefination requires favorable structural factors. Thus, dialkyl alkylidenephosphonate or diphenylphosphine oxide anions, react with aldehydes to afford *trans*-olefins, but the relative instability of the dialkyl alkylidenephosphonate anions limits their use for this purpose [11].

Another method of *trans*-olefination takes advantage of the behavior of alkylidenetriphenylphosphoranes with carbonyl groups at the α-carbon atom. For instance, *trans*-α,β-unsaturated acids *(6)* can be prepared by condensation of aldehydes with α-alkoxycarbonylalkylidenetriphenylphosphoranes *(5)* [6].

$$RCHO + Ph_3P{=}CH{-}COOR \longrightarrow \overset{\text{trans}}{RCH{=}CH{-}COOH}$$

*(5)* *(6)*

Use of the corresponding vinylogues *(7)* leads to all-*trans*-polyenoic acids *(8)* [14].

$$RCHO + \overset{\text{trans}}{Ph_3P{=}CH{-}(CH{=}CH)_n{-}COOR} \quad (7)$$

$$\downarrow$$

$$\overset{\text{trans}}{R{-}(CH{=}CH)_{n+1}{-}COOH} \quad (8)$$

Utilizing the principles of sterically controlled carbonyl olefination, it is comparatively easy to carry out directed syntheses of various stereoisomers of 1,4-substituted 1,3-butadienes, RCH−CHCH−CHR. Thus, condensation of saturated aldehydes with *trans*-β-alkenylidenetriphenylphosphoranes *(9)* affords *trans,trans*-dienes [15], whereas condensation with *cis*-β-alkenylidenetriphenylphosphoranes *(9a)* gives *trans,cis*-dienes. Another way to *trans,cis*-dienes is the reaction of *trans*-α,β-

$$RCHO + \overset{\text{trans}}{Ph_3P{=}CH{-}CH{=}CHR} \longrightarrow \overset{\text{trans}}{RCH{=}CH{-}CH{=}CHR}$$

*(9)*

$$RCHO + \overset{\text{cis}}{Ph_3P{=}CH{-}CH{=}CHR} \longrightarrow \overset{\text{trans}}{RCH{=}CH{-}CH{=}CHR}$$

*(9a)*

$$\overset{\text{trans}}{RCH{=}CH{-}CHO} + Ph_3P{=}CHR \xrightarrow[I^{\ominus}]{DMF} \overset{\text{trans}}{RCH{=}CH{-}CH{=}CHR}$$

[12] *L. D. Bergelson, V. A. Vaver*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1961*, 729.

[13] *M. M. Shemyakin, V. A. Vaver*, and *L. D. Bergelson*, Ind. Chim. Belges *27*, 547 (1962).

[14] *L. D. Bergelson, E. V. Dyatlovitskaya*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 388.

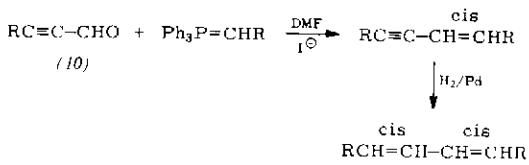
[15] *L. D. Bergelson, V. D. Solodovnik*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, in the press.

[16] *H. J. Bestmann* and *O. Kratzer*, Chem. Ber. *95*, 1894 (1962).

[17] *L. D. Bergelson, V. A. Vaver, L. I. Barsukov*, and *M. M. Shemyakin*, Doklady Akad. Nauk SSSR *143*, 111 (1962).

unsaturated aldehydes with alkylidenetriphenylphosphoranes under the conditions of selective *cis*-olefination [18].

*cis,cis*-Dienes should also be available by condensation of alkylidenetriphenylphosphoranes with *cis*-α,β-unsaturated aldehydes; however, owing to the tendency of the latter to isomerize, it is more feasible to start with substituted propiolaldehydes *(10)*.

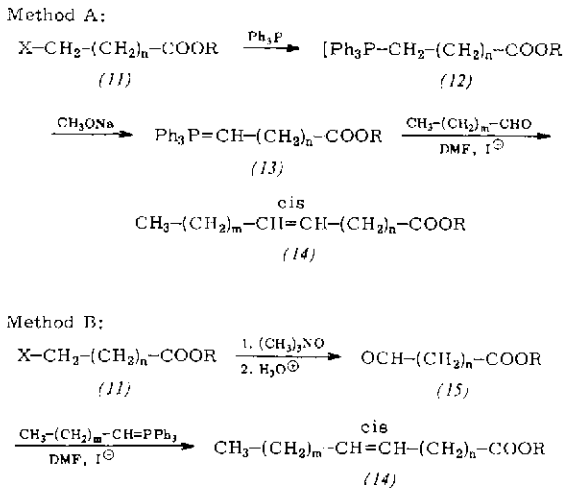


The following is a brief description of the application of sterically controlled carbonyl olefination to the synthesis of the principal types of naturally occurring unsaturated fatty acids.

## III. Application of cis- and trans-Olefination to the Synthesis of Naturally Occurring Unsaturated Fatty Acids

### 1. cis-Alkenoic Acids

The starting materials for the synthesis of higher *cis*-alkenoic acids $CH_3-(CH_2)_m-CH=CH-(CH_2)_n-COOH$ are aliphatic aldehydes (or alkyl halides) and ω-chloroalkanoic acids $Cl(CH_2)_nCOOH$, which are readily available as industrial products [19]. They are obtained by hydrolysis of the telomerization products of $CCl_4$ and ethylene, so that only acids with an odd number of carbon atoms are commercially available. Acids with even numbers of carbon atoms can be synthetized from the latter by chain extension according to *Arndt* and *Eistert* or by degradation according to *Barbier* and *Wieland*.



Scheme 1. Conversion of ω-chloroalkanoic acids into higher *cis*-alkenoic acids

[18] *L. D. Bergelson, V. D. Solodovnik, E. V. Dyatlovitskaya*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 683.

[19] *R. Kh. Freidlina* and *E. I. Vasilieva*, Khim. Nauka i Promyshlennost *2*, 2 (1957).

The transformation of ω-chloroalkanoic acids *(11)*, where R=H, X=Cl, into higher *cis*-alkenoic acids is carried out according to one of the two methods shown in Scheme 1.

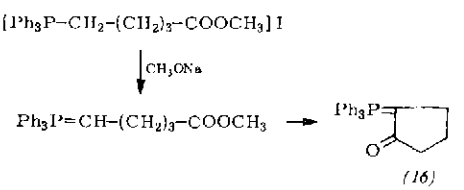
Method A [20,21]

The ω-chloroalkanoic acids are purified by distillation of their methyl or ethyl esters. ω-Chloroalkanoic esters *(11)*, where R = $CH_3$ or $C_2H_5$, X = Cl, react with triphenylphosphine only on heating in dimethylformamide, whereas the ω-iodo esters, which are readily prepared by refluxing the chloro esters with KI in methyl ethyl ketone, react in benzene. It is better to convert the ω-chloro esters into the iodo derivatives also because the ω-alkoxycarbonylalkyltriphenylphosphonium chlorides *(12)*, where X=Cl, have a greater tendency than the corresponding iodides to undergo partial decomposition to triphenylphosphine during their conversion into the phosphoranes *(13)* with sodium alkoxide. Finally, $I^{\ominus}$ is the Lewis base required for the formation of the *cis*-isomer.

ω-Alkoxycarbonylalkyltriphenylphosphonium iodides *(12)*, where X = I, are comparatively inert. Unlike the α-alkoxycarbonylalkyltriphenylphosphonium salts [8], they do not pass over to the corresponding phosphoranes with alkoxides or sodamide in ether or benzene, but do react quite readily in tetrahydrofuran, diglyme, or dimethylformamide. The latter proved to be most suitable; the phosphorane *(12)* is formed and subsequently reacts with aldehydes in DMF at room temperature.

Studies of the reaction conditions showed that satisfactory yields of unsaturated esters *(14)* are obtained only when the phosphonium salt is in large excess, because it is partially decomposed by the alkoxide with formation of triphenylphosphine. Separation of *(14)* from the latter can be achieved by chromatography on low-activity alumina or by conversion of the crude ester into the acid which can then be easily separated from the triphenylphosphine by chromatography on silica gel or by extraction of its sodium salt with ether.

Method A was employed for the preparation of *cis*-alkenoic acids of type *(14)*, where R = H, with n = 6, 7, or 9, which are found in various animal and plant lipids (see Table 1). However, the procedure proved to be unsuitable for acids of type *(14)* with n = 3, because the ω-alkoxycarbonylalkylidenephosphorane *(13)* with n = 3 behaves anomalously [22] and un-



*(16)*

[20] *L. D. Bergelson, V. A. Vaver, V. Yu. Kovtun, L. B. Senyavina*, and *M. M. Shemyakin*, Zh. Obshchei Khimii *32*, 1802 (1962).

[21] *L. D. Bergelson, V. A. Vaver, L. I. Barsukov*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 1417.

[22] *H. O. House* and *H. Babad*, J. org. Chemistry *28*, 90 (1963); *L. D. Bergelson, V. A. Vaver, L. I. Barsukov*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 1135.

dergoes intramolecular acylation to give 2-oxocyclopentylidenetriphenylphosphorane *(16)* immediately after its formation [22a].

### Method B [21]

In order to prepare $\Delta^5$-unsaturated acids *(14)*, where R = H and n = 3, a variant of the stereospecific synthesis of *cis*-alkenoic acids was devised, according to which alkylidenetriphenylphosphoranes are condensed with ω-alkoxycarbonyl aldehydes *(15)*. The latter can be obtained by Rosenmund reduction of ω-alkoxycarbonylalkylcarbonyl chlorides [23] but undesirable impurities that react with the alkylidenephosphoranes are formed as by-products. Since these impurities are difficult to remove, owing to the low stability of the alkoxycarbonyl aldehydes, the latter are secured more conveniently by treating trimethylamine-*N*-oxide with ω-iodoalkanoic esters *(11)*, where X = I, followed by mild acid hydrolysis [24]. After simple distillation, the resultant ω-alkoxycarbonylaldehydes *(15)* are sufficiently pure and can be used directly for olefination.

Method B was found to be useful not only for the synthesis of $\Delta^5$-unsaturated acids but also of higher acids of type *(14)* with m > 11, the higher alkyl bromides being often more readily available than the corresponding aldehydes. Using this method, unsaturated higher fatty acids that are found as minor components in plant seeds and in the lipids of marine sponges have been synthetized (see Table 1).

Methods A and B are somewhat less specific than the only stereospecific synthesis of higher *cis*-alkenoic acids (via acetylenic derivatives) hitherto available. For instance, ethyl oleate prepared by method A contained up to 6 % elaidic ester [20], whereas in an oleic ester sample obtained by hydrogenation of the corresponding acetylenic compound the *trans*-isomer content was only 2 % [25].

### Preparation of the Starting Materials

a) ω-Methoxycarbonylalkyltriphenylphosphonium Iodides *(12)*, R = $CH_3$, X = I [20].

A mixture of 0.15 mole of anhydrous sodium iodide and 150 ml of dry methyl ethyl ketone is heated for 30 min. at 80 °C; 0.1 mole of methyl ω-chloroalkanoate *(11)*, R = $CH_3$, X = Cl, [31] is added, and heating is continued for further 10 hours with periodic shaking. The cooled solution is filtered, and most of the solvent is distilled off. The residue is diluted with 150 ml of benzene, the solution washed with water, 5 % sodium thiosulfate, again with water, and dried over magnesium sulfate. After evaporating the filtered solution to a volume of 100 ml, 0.12 mole of triphenylphosphine is added, and the mixture is heated at 80 °C for 10 hours. The benzene is then distilled off and the residue thoroughly stirred with 100 ml of absolute ether. The phosphonium salt which crystallizes out on addition of the ether is filtered off, washed with absolute ether, and dried *in vacuo*; yield: 80–90 %.

b) ω-Methoxycarbonyl Aldehydes *(15)*, R = $CH_3$ [21].

To a solution of 0.108 mole of anhydrous trimethylamine-*N*-oxide in 50 ml of dry chloroform is added a chloroform solution of methyl ω-iodoalkanoate prepared from the corresponding chloroester as described above. The mixture is refluxed for 2 hours, cooled, and treated consecutively with 2 N hydrochloric acid, 5 % sodium bicarbonate, and water. The ω-methoxycarbonyl aldehyde *(15)* is purified by distillation; yield, 50–60 %.

Table 1. Unsaturated fatty acids of the type $CH_3-(CH_2)_m-CH=CH-(CH_2)_n-COOH$.

| Acid | Prepd. by Method | Yield [%] | Natural Source | M. p. of acids [°C] | |
|---|---|---|---|---|---|
| | | | | Synthetic | Natural |
| *cis*-8-Hexadecenoic (m = 6, n = 6) | A | 56 | Herring oil | < −10 | [a] |
| Palmitoleic (m = 5, n = 7) | A | 64 | Higher animal fats and vegetable oils | 0 -1 | 0.5–1 [26] |
| Palmitvaccenic (m = 3, n = 9) | A | 59 | Lipids of *Streptococci* | 69–70 [b] | [a] |
| *cis*-7-Octadecenoic (m = 9, n = 5) | A | 53 | Human faeces [c] | 85–86 [b] | [a] |
| Oleic (m = n = 7) | A | 73 | Lipids of most animals and plants | 11 -13 | 13 [27] |
| *cis*-Vaccenic (m = 5, n = 9) | A | 71 | Lipids of bacteria, plants, and higher animals | 10–12 | 10–12 [28] |
| Gadoleic (m = 9, n = 7) | A | 60 | Fish oils and marine-animal fats | 21.5–22.5 | 24.5 [27] |
| *cis*-11-Eicosenoic (m = 7, n = 9) | A | 67 | *Cruciferae* seed oil; fish oils | 21–22 | 22 [29] |
| Cetoleic (m = n = 9) | A | 54 | Marine animal fats | 29–30 | 33 [30] |
| *cis*-5-Docosenoic (m = 15, n = 3) | B | 47 | *Limmanthes douglasii* seed oil | 32–34 | [a] |
| *cis*-9-Hexacosenoic (m = 15, n = 7 | B | 31 | Marine sponge lipids | 43–45 | [a] |

[a] Natural product not isolated in the pure state. [b] M. p. of amide. [c] Configuration of the natural product not established.

[22a] Compound *(16)* is a stable substance which reacts readily with aldehydes and which served as the basis for a new synthesis of α-substituted cyclopentanones, starting from ω-chlorovaleric acid [22].


[23] *E. Mosettig* and *R. Mozingo*, Org. Reactions *4*, 362 (1948).

[24] *V. Franzen* and *S. Otto*, Chem. Ber. *94*, 1360 (1961).

[25] *D. E. Ames* and *P. J. Islip*, J. chem. Soc. (London) *1961*, 351.

[26] *H. Bull*, Ber. dtsch. chem. Ges. *39*, 3570 (1906).

[27] *T. P. Hilditch:* The Chemical Constitution of Natural Fats. London, Chapman and Hall, 1956.

[28] *I. D. Morton* and *A. R. Todd*, Biochem. J. *47*, 327 (1950).

[29] *W. Karrer:* Konstitution und Vorkommen der organischen Pflanzenstoffe. Birkhäuser, Basel 1958, p. 306.

[30] *Y. Toyama*, J. Soc. chem. Ind. Japan *30*, 597 (1927).

[31] *A. N. Nesmeyanov* and *L. I. Zakharkin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1955*, 224.

### Synthesis of *cis*-Alkenoic Acids *(14)*, R = H, by Method A [20,31a]

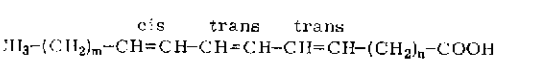
A solution of 25 mmoles of ω-methoxycarbonylalkylidenetriphenylphosphonium iodide *(12)*, where R = $CH_3$ and X = I, in 40 ml of dry dimethylformamide is quickly added to 20 mmoles of dry sodium methoxide and the mixture is stirred for 1 hour at room temperature. The orange-red solution of alkylidenetriphenylphosphorane *(13)* is cooled with ice water, and a solution of 0.15 mmole of aldehyde in 10 ml of dimethylformamide is added, stirring being continued for 2–3 hours. The mixture is then allowed to stand overnight at 20 °C. It is then diluted with water and extracted with hexane. The residue obtained after concentration of the extract is refluxed for 1–1.5 hours with 25 ml of 5 % NaOH in 80 % methanol. After removal of the solvent, the residue is extracted with ether, acidified and chromatographed on a silica-gel column (500 × 15 mm). The triphenylphosphine formed is eluted with hexane and the unsaturated acid *(14)*, R = H, with a 1:1 hexane/ether mixture.

### Synthesis of *cis*-Alkenoic Acids *(14)*, R = H, by Method B [21]

A solution of 12 mmoles of alkyltriphenylphosphonium bromide or iodide in 30 ml of dimethylformamide is added to 10 mmoles of dry sodium methoxide. After 30 min, 7.5 mmoles of the ω-methoxycarbonyl aldehyde *(15)*, R = $CH_3$, are added to the reddish-brown alkylidenetriphenylphosphorane solution formed; the mixture is stirred for 3 hours and left overnight at 20 °C. After evaporation of the solvent, the residue is extracted with hexane, concentrated, and chromatographed in hexane on a column of 250 g neutral alumina (activity grade IV). After separation of the triphenylphosphine, the unsaturated ester *(14)*, R = $CH_3$, is eluted and saponified as described above.

## 2. Conjugated Polyenoic Acids

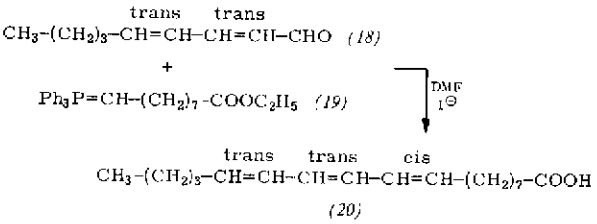
The lipids of some higher plants contain $C_{18}$-acids with a system of 3 conjugated bonds. These include α-eleostearic acid *(20)*, the principal fatty acid of tung oil [27], catalpa acid *(17)*, where m = 3 and n = 7, isolated from the tree *Catalpa ovata* [32], and its *cis*, *trans*,*cis*-isomer, punicic acid, obtained from the seed oil of the pomegranate *Punica granatum* and of plants of the *Trichosanthes* family [32a]. Closely related to these acids are calendic acid *(17)*, where m = 4 and n = 6, from the marigold *Calendula officinalis* [33], and its *cis*,*trans*,*cis*-isomer, jacaranda acid, isolated from the jacaranda tree *Jacaranda mimosifolia* [34].



*(17)*

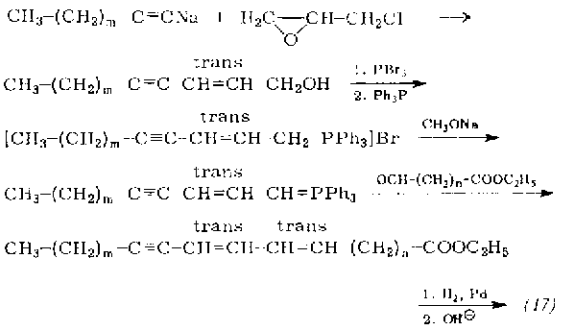
Sterically controlled carbonyl olefination makes it possible to carry out directed syntheses of these stereoisomeric alkatrienoic acids. Isomerization is avoided by introducing the *cis*-double bond only at the last stage of the synthesis.

Thus, α-eleostearic acid *(20)* was prepared by condensation of nona-*trans*-2,*trans*-4-dienal *(18)* [35] with 8-ethoxycarbonyloctylidenetriphenylphosphorane *(19)* under conditions leading to selective formation of the *cis*-double bond [36].



*(20)*

Catalpa acid *(17)*, m = 3, n = 7, and calendic acid *(17)*, m = 4, n = 6, were synthetized by means of the *trans*-olefination reaction according to the following scheme [36a]:



### Synthesis of α-Eleostearic Acid [36,36b]

Two grams (4.5 mmoles) of nona-*trans*-2,*trans*-4-dienal [35] are added in the course of 20 min to a solution of 8-ethoxycarbonyloctylidenetriphenylphosphorane *(19)* [prepared from 16.55 g (29 mmoles) of 8-ethoxycarbonyloctyltriphenylphosphonium iodide, see p. 254] in 35 ml of dimethylformamide. The mixture is stirred for 15 hours, and 50 ml of water are added, the whole being then extracted with light petroleum (5 × 50 ml). The extract is dried over magnesium sulfate. After removal of the solvent *in vacuo*, the 4.85 g of oil obtained are chromatographed in hexane on 750 g of neutral alumina (activity grade IV) in a column with a 2:1 hexane/benzene mixture as eluant. The first fractions (90 ml) contain triphenylphosphine; this is followed by ethyl α-eleostearate. The ester is purified by distillation at 135 °C/5 × $10^{-2}$ mm and then saponified with alcoholic sodium hydroxide at 20 °C to give α-eleostearic acid *(20)*, m.p. 46.5–48 °C (from light petroleum).

## 3. Acids of the cis,cis-Divinylmethane Type

The *cis*,*cis*-divinylmethane pattern *(21)* is characteristic of a large group of biologically important unsaturated fatty acids isolated from the phosphatides of various human and animal tissues, as well as from numerous plants [37,38].

[31a] The preparation and reactions of alkylidenetriphenylphosphoranes *(13)* must all be carried out under dry nitrogen.

[32] *C. Y. Hopkins* and *M. J. Chisholm*, J. chem. Soc. (London) *1962*, 573.

[32a] See [5] and the literature cited therein.

[33] *M. J. Chisholm* and *C. Y. Hopkins*, Canad. J. Chemistry *38*, 2501 (1960).

[34] *M. J. Chisholm* and *C. Y. Hopkins*, J. org. Chemistry *27*, 3137 (1962).

[35] *E. L. Pipen* and *M. Nonaka*, J. org. Chemistry *23*, 1580 (1958).

[36] *L. D. Bergelson*, *V. D. Solodovnik*, and *M. M. Shemyakin*, Izv. Acad. Nauk SSSR, Otdel. Khim. Nauk *1962*, 1315.

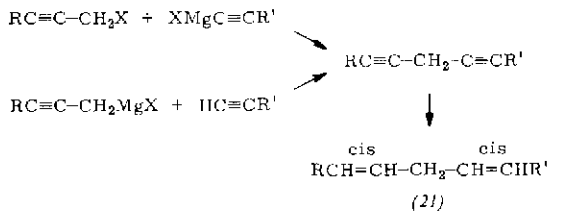
[36a] *L. D. Bergelson*, *V. D. Solodovnik*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, in the press.

[36b] The entire synthesis is carried out under dry nitrogen.

[37] *E. Klenk* and *H. Debuch*, Annual Rev. Biochemistry *28*, 42 (1959).

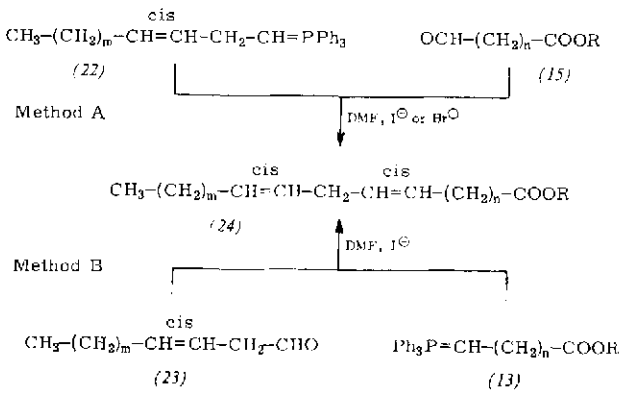
[38] *J. Asselineau* and *E. Lederer*, Annual Rev. Biochemistry *30*, 71 (1961).

All the syntheses of such acids so far reported are based on the condensation of propargyl halides with acetylenes [39–51].



*(21)*

A fundamentally new way of synthetizing polyunsaturated acids of this type has been developed on the basis of stereospecific *cis*-olefination reactions, starting with either the saturated aldehydic esters *(15)* and γ-alkenylidenetriphenylphosphoranes *(22)* and using Method A, or starting with β,γ-unsaturated aldehydes *(23)* and ω-alkoxycarbonylalkylidenetriphenylphosphoranes *(13)* and using Method B [52].



Linoleic acid and its analogues have been synthetized by these two methods. The methods can also be used for the synthesis of higher fatty acids containing three, four, and more double bonds with alternating methylene groups.

[39] *R. A. Raphael* and *F. Sondheimer*, J. chem. Soc. (London) *1950*, 2100.

[40] *H. M. Walborsky, R. N. Davis*, and *D. R. Howton*, J. Amer. chem. Soc. *73*, 2590 (1951).

[41] *W. J. Gensler* and *G. R. Thomas*, J. Amer. chem. Soc. *73*, 4601 (1951).

[42] *G. A. Serebryannikova, T. K. Mitrofanova, A. A. Kraevskii, I. K. Sarycheva*, and *N. A. Preobrazhenskii*, Dokl. Akad. Nauk SSSR *140*, 1083 (1961).

[43] *Yu. B. Pyatnova, I. A. Kovtun, M. G. Pleshakov, A. A. Kraevskii, I. K. Sarycheva*, and *N. A. Preobrazhenskii*, Zh. Obschei Khimii *32*, 138 (1962).

[44] *I. K. Sarycheva, G. I. Myagkova*, and *N. A. Preobrazhenskii*, Zh. Obshchei Khimii *29*, 2318 (1959).

[45] *A. A. Kraevskii, Yu. B. Pyatnova, G. I. Myagkova, I. K. Surycheva*, and *N. A. Preobrazhenskii*, Dokl. Akad. Nauk SSSR *146*, 1349 (1962).

[46] *J. M. Osbond, P. G. Philpott*, and *J. C. Wickens*, J. chem. Soc. (London) *1961*, 2779.

[47] *J. M. Osbond*, J. chem. Soc. (London) *1961*, 5270.

[48] *D. E. Ames* and *F. J. Islip*, J. chem. Soc. (London) *1961*, 4409.

[49] *S. S. Nigam* and *B. C. L. Weedon*, J. chem. Soc. (London) *1956*, 4049.

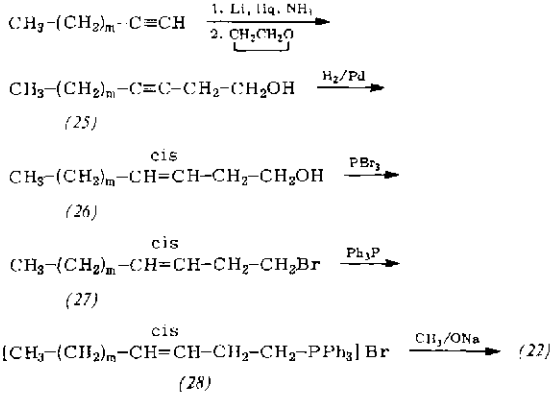
[50] *A. I. Rachlin, W. Wasyljiw*, and *M. M. Goldberg*, J. org. Chemistry *26*, 2688 (1961).

[51] *S. N. Ege, R. Wolovsky*, and *W. J. Gensler*, J. Amer. chem. Soc. *83*, 3080 (1961).

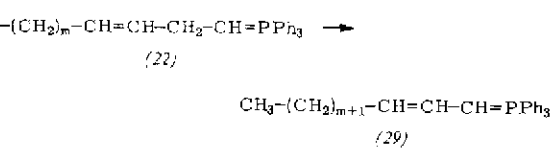
[52] *L. D. Bergelson, V. A. Vaver*, and *M. M. Shemyakin*, Izv. Acad. Nauk SSSR, Otdel. Khim. Nauk *1962*, 1894.

## Method A

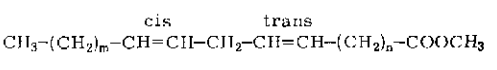
The starting materials for the synthesis of divinylmethane-type fatty acids by this method are ω-alkoxycarbonylalkanals *(15)* (cf. p. 254) and *cis*-$\Delta^3$-alkenyl bromides *(27)*, which can be readily prepared from alkylacetylenes and ethylene oxide.



The catalytic hydrogenation of 3-alkyn-1-ols *(25)* to the *cis*-3-alken-1-ols *(26)* is known to be accompanied by the formation of a certain amount of the *trans*-isomer (see *e.g.* [53]). The latter can be conveniently removed at the phosphonium salt *(28)* stage, the salt usually lending itself to purification by simple recrystallization. The phosphonium salts can be prepared by heating $\Delta^3$-alkenyl bromides *(27)* with triphenylphosphine in benzene in a sealed tube. An undesirable side reaction that occurs during the further conversion of these salts *(28)* into the γ-alkenylidenetriphenylphosphoranes *(22)* is the isomerization of the latter to the conjugated β-alkenylidenephosphoranes *(29)*.



This isomerization is promoted by alkaline agents, elevated temperatures, and light, but if sodium methoxide is carefully added to the dimethylformamide solution of the phosphonium salt in the cold and in the dark γ-alkenylidenephosphoranes *(22)* can be obtained that are only little contaminated with the conjugated isomer *(29)*. Condensation of *(22)* with ω-methoxycarbonyl aldehydes *(15)* in the presence of $Br^{\ominus}$ or $I^{\ominus}$ as Lewis bases yields *cis,cis*-divinylmethane-type esters *(24)*, where R = $CH_3$, usually containing less than 10 % of the *trans,cis*-isomer *(30)*.



Separation of the isomers, as well as isolation of the unsaturated ester from triphenylphosphine (see p. 255) can be achieved by chromatography on neutral, low-activity alumina in an atmosphere of nitrogen.

[53] *F. Sondheimer*, J. chem. Soc. (London) *1950*, 877.

Method B

According to this method, the *cis,cis*-divinylmethane-type acids are synthetized by condensation of ω-alkoxycarbonylalkylidenetriphenylphosphoranes *(13)* (cf. p. 255) with *cis*-3-alkenals *(23)*. The latter can be prepared [54] from alkyl halides and the sodium derivative of methoxybutenyne *(31)* according to Scheme 2.

$$CH_3-(CH_2)_m-X + NaC\equiv C-CH=CHOCH_3 \longrightarrow$$
*(31)*

$$CH_3-(CH_2)_m-C\equiv C-CH=CHOCH_3 \xrightarrow{H_2/Pd}$$
*(32)*

$$CH_3-(CH_2)_m-\overset{cis}{CH=CH}-CH=CHOCH_3 \xrightarrow{H_3O^+}$$
*(33)*

$$CH_3-(CH_2)_m-\overset{cis}{CH=CH}-CH_2-CHO$$
*(23)*

Scheme 2. Synthesis of *cis*-3-alkenals *(23)*.

Isomerization of the aldehyde *(23)* to the α,β-unsaturated aldehyde can be avoided if the acid hydrolysis of the methoxydiene *(33)* is carried out under mild, strictly controlled conditions, but a small amount of the conjugated isomer is formed on subsequent condensation of *(23)* with the ω-alkoxycarbonylalkylidenephosphorane *(13)*. Moreover, the *cis,cis*-alkadienoic esters *(24)*, where R = $CH_3$, contain, the *trans,cis*-isomer *(30)* (resulting from the incomplete stereospecificity of the *cis*-olefination) and also the *cis,trans*- *(34)* and the *trans,trans*-isomer *(35)* owing to the small amount of difficultly removable *trans*-isomer invariably present in the *cis*-methoxydiene *(33)* prepared by catalytic hydrogenation. Method B therefore usually leads to less pure products than method A.

$$CH_3-(CH_2)_m-\overset{trans}{CH=CH}-CH_2-\overset{cis}{CH=CH}-(CH_2)_n-COOCH_3$$
*(34)*

$$CH_3-(CH_2)_m-\overset{trans}{CH=CH}-CH_2-\overset{trans}{CH=CH}-(CH_2)_n-COOCH_3$$
*(35)*

Synthesis of Methyl Linoleate by Method A

A mixture of 1.37 g (6.7 mmoles) of *cis*-3-nonenyl bromide *(27)*, m = 4, 2.10 g (8 mmoles) of triphenylphosphine and 20 ml of absolute benzene is heated for 10 hours at 120 °C. The resultant mass is cooled and triturated with 15 ml of absolute ether. The crystalline phosphonium bromide *(28)*, m = 4, is filtered off, washed with absolute ether, and dried *in vacuo*. Yield 2.93 g (94 %), m.p. 111–114 °C.

The phosphonium salt (6.3 mmoles) is dissolved in 15 ml of dimethylformamide and added to a suspension of sodium hydride (5.5 mmoles) in 2.5 ml of dimethylformamide [54a]. The dark red solution of the *cis*-3-nonenylidenetriphenylphosphorane *(22)*, m = 4, formed is stirred for 1 hour at room temperature, and 0.83 g (4.5 mmoles) of ω-methoxycarbonyloctanal *(15)*, n = 7, R = $CH_3$, in 2.5 ml of dimethylformamide is then added. The mixture is allowed to stand for 24 hours at 20 °C, heated for 1 hour at 100 °C, and after evaporation of the solvent *in vacuo*, the residue is extracted with ether. The extract is washed with water, dried over magnesium sulfate, and vacuum distilled. Methyl linoleate is isolated by means of preparative thin-layer chromatography on neutral alumina (activity grade IV) in the system heptane/ether (10:1), 500 mg portions of crude product are applied to 18 × 24 $cm^2$ plates each bearing 100 g of alumina. Yield of methyl linoleate (97 % pure, according to gas chromatography): 0.92 g (71 %).

4. Polyenes of the Divinylethane Type

Substances with the divinylethane pattern $-CH-CHCH_2CH_2CH-CH-$ have frequently been found among various unsaturated naturally occurring compounds. Thus, the leaves of the violet *Viola odorata* contain nona-*trans*-2,*cis*-6-dienal [55], and the corresponding alcohol is one of the odoriferous principles of the flowers of this plant [56]. Some polyunsaturated *N*-butylamides isolated from the pellitory of Spain *Anacyclus pyrethrum*, *Heliopsis longipes*, and other plants also possess the divinylethane structure [1]. Finally, the fats of marine animals contain polyenic acids that yield succinic acid on oxidative degradation; it has thus been concluded that these acids contain a system of double bonds separated by two methylene groups [57–59a]. Sterically controlled carbonyl olefination has provided a new stereospecific route to the *cis,cis*- and *trans,cis*-divinylethane systems.

The synthesis of compounds with the *cis,cis*-divinylethane grouping has been achieved according to Scheme 3 [60].

The principal starting material is the readily available compound 4-bromobutyl acetate [63], which with triphenylphosphine gives a phosphonium salt that is converted into 4-acetoxybutylidene triphenylphosphorane *(36)* in the presence of sodium methoxide. Condensation of *(36)* with an aldehyde under *cis*-olefination conditions (see p. 255) then leads to acetates of $\Delta^4$-unsaturated alcohols *(38)*, usually containing more than 90 % of the *cis*-isomer. Approximately the same stereoisomer ratios result from the condensation of alkylidenetriphenylphosphoranes with 4-acetoxybutanal *(37)*, which is formed by the action of trimethyl-

[54] *H. H. Inhoffen, F. Bohlman*, and *G. Rummert*, Liebigs Ann. Chem. *569*, 226 (1950).

[54a] Beginning with this stage, the synthesis is carried out in an atmosphere of pure nitrogen.

[55] *L. Ruzicka* and *H. Schinz*, Helv. chim. Acta *25*, 760 (1942).

[56] *L. Ruzicka* and *H. Schinz*, Helv. chim. Acta *18*, 381 (1935).

[57] *Y. Toyama* et al., Bull. chem. Soc. Japan *4*, 83 (1929).

[58] *Y. Toyama* et al., Bull. chem. Soc. Japan *10*, 192, 232, 296, 441 (1935).

[59] *Y. Toyama* et al., Bull. chem. Soc. Japan *11*, 745, 751 (1936).

[59a] A more detailed study has shown that at least some of the so-called divinylethane acids are actually of the divinylmethane type [61, 62].

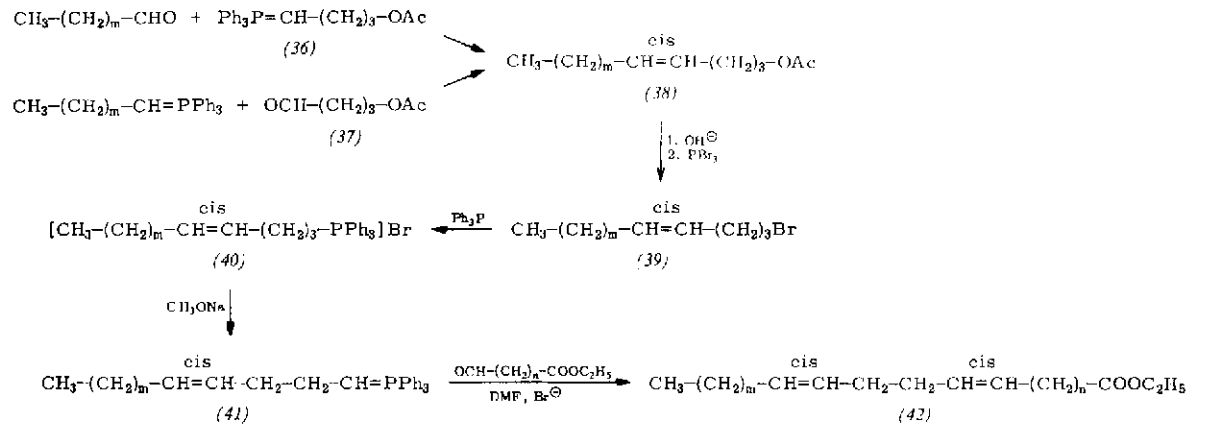
[60] *L. D. Bergelson, V. A. Vaver, A. A. Bezzubov*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, in the press.

[61] *Y. Toyama* et al., Fette, Seifen, Anstrichmittel *61*, 846 (1959).

[62] *E. Klenk* and *W. Bongard*, Hoppe-Seylers Z. physiol. Chem. *292*, 51 (1953).

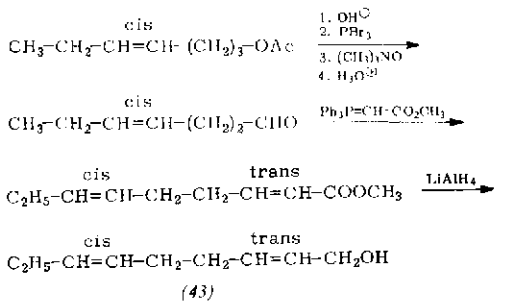
[63] *L. M. Smorgonskii* and *Ya. L. Gol'dfarb*, Zh. Obshchei Khimii *10*, 1113 (1940).

amine-*N*-oxide on 4-acetoxybromobutane [24]. The unsaturated acetates *(38)* and bromides *(39)* are oils, hence the isomers can be best separated at the stage of the crystalline phosphonium salts *(40)*. The *cis*-$\Delta^4$-alkenylidenetriphenylphosphoranes *(41)* obtained from *(40)* condense with ω-ethoxycarbonylalkanals *(15)* (see p. 254) in the presence of $Br^{\ominus}$ in dimethylformamide to give *cis,cis*-divinylethane-type esters *(42)* containing only small amounts of the *trans,cis*-isomers.



Scheme 3. Synthesis of compounds containing the *cis,cis*-divinylethane grouping.

The *trans,cis*-divinylethane system can also be constructed analogously utilizing the *trans*- and *cis*-olefination methods. For instance, a constituent of the odoriferous principle of violets, nona-*trans*-2,*cis*-6-dien-1-ol *(43)*, was synthetized by the short route shown in Scheme 4, starting from *cis*-4-heptenyl acetate *(38)*, m = 1 [64].

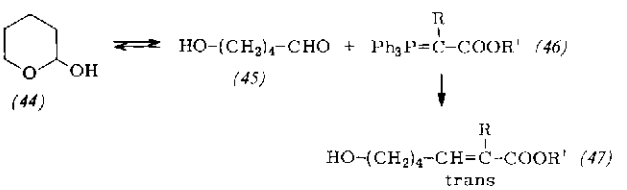


Scheme 4. Synthesis of nona-*trans*-2,*cis*-6-dien-1-ol *(43)*.

## 5. Unsaturated ω-Hydroxy Acids

The naturally occurring unsaturated fatty acids include a number of representatives with an ω-hydroxyl group, *e.g.* the 10-hydroxy-*trans*-2-decenoic acid isolated from the royal jelly of the honey-bee [65], the ω-hydroxyoleic acid isolated from the bark of the cork-oak *Quercus suber* [66], the ambrettolic acid $HO(CH_2)_8CH{=}CH(CH_2)_5COOH$ [67] which is found in the seeds of *Hibiscus abelmoschus* as the macrocyclic lactone, and the ω-hydroxy-α-eleostearic (α-camlolenic) acid *(51)* from the seed oil of spurge *Euphorbiaceae* [68,69].

Some of these unsaturated ω-hydroxy acids can be prepared with the aid of the reaction between alkylidenephosphoranes and 2-hydroxytetrahydropyran *(44)* [14,70,71]. This compound is known [72] to react with malonic acid in its tautomeric form, *viz.* 5-hydroxypentanal *(45)*. The results with ω-alkoxycarbonylalkoxyalkylidenetriphenylphosphoranes *(13)* are unsatisfactory, however, because 2-hydroxytetrahydropyran is much less reactive than the aliphatic aldehydes, and the phosphoranes of type *(13)* decompose gradually during the time required for the reaction. However, 2-hydroxytetrahydropyran does condense well with the stabler α-alkoxycarbonylalkylidenetriphenylphosphoranes *(46)*, where R = H or $CH_3$, to give esters of *trans*-α,β-unsaturated ω-hydroxy acids *(47)*, R = H or $CH_3$, although this reaction occurs less readily than the condensation of *(46)* with aliphatic aldehydes [70].



This reaction has been used for the synthesis of lower homologues of 10-hydroxy-*trans*-2-decenoic acid (royal jelly acid), namely *(47)*, R = R′ = H, and *(47)*, where R = $CH_3$ and R′ = H [71].

Steric control of carbonyl olefination has also made it possible to carry out the total synthesis of α-camlolenic acid *(51)* starting from 2-hydroxytetrahydropyran *(44)* [14]. Condensation of *(44)* with 3-methoxycarbonyl-*trans*-$\Delta^2$-propenylidenetriphenylphosphorane *(48)* led

[64] *L. D. Bergelson, V. A. Vaver*, and *L. I. Ilyukhina*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, in the press.

[65] *A. Butenandt* and *H. Rembold*, Hoppe-Seylers Z. physiol. Chem. *308*, 284 (1957).

[66] *I. Ribas* and *Seoane*, An. Fis. Quim. *50B*, 971 (1954); Chem. Abstr. *50*, 806 (1956).

[67] *M. Kerschbaum*, Ber. dtsch. chem. Ges. *60*, 902 (1927).

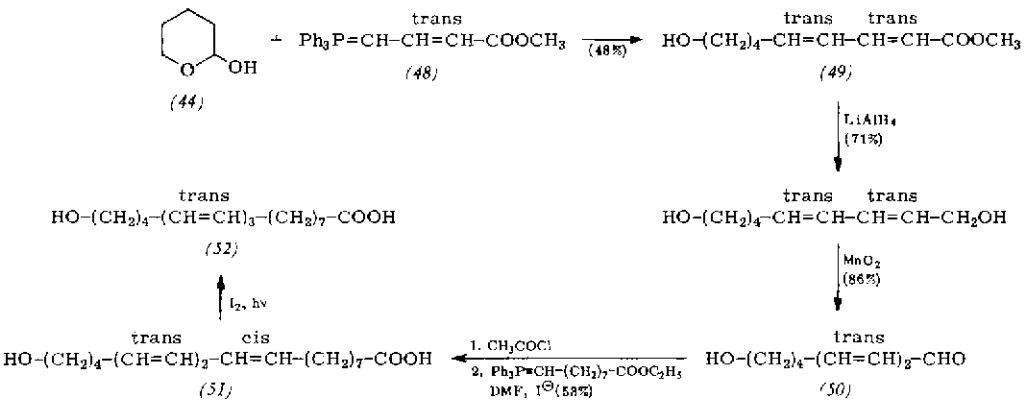
[68] *L. Crombie* and *J. L. Tayler*, J. chem. Soc. (London) *1954*, 2816.

[69] *S. D. Gupta* and *J. S. Aggarwal*, J. Amer. Oil Chem. Soc. *32*, 501 (1955).

[70] *L. D. Bergelson, E. V. Dyatlovitskaya*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 506.

[71] *L. D. Bergelson, E. V. Dyatlovitskaya*, and *M. M. Shemyakin*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1963*, 506.

[72] *G. I. Fray, R. H. Jaeger, E. D. Morgan, R. Robinson*, and *A. D. B. Sloan*, Tetrahedron *15*, 18 (1961).



to 9-hydroxynona-*trans*-2,*trans*-4-dienoic ester *(48)*, which was converted into the corresponding aldehyde *(50)*, the acetate of which was condensed under *cis*-olefination conditions with 8-ethoxycarbonyloctylidenetriphenylphosphorane. The resultant α-camlolenic acid *(51)* was then isomerized to β-camlolenic acid *(52)*.

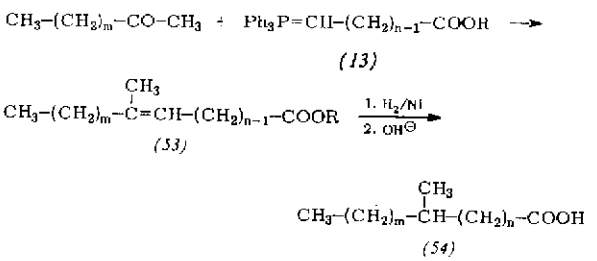
### 6. Higher Branched-Chain Carboxylic Acids

Certain lipids contain not only normal fatty acids but also acids with branched chains. For instance, acids terminated by isopropyl or s-butyl groups (so-called iso- or anteiso-acids) have been isolated from degras and from butter. Branched-chain acids play an important part in the metabolism of some bacteria, particularly mycobacteria. Thus, it has been found that all the known strains of mycobacteria form tuberculostearic acid, *i.e.* D-(−)-10-methylstearic acid. Polymethyl-substituted acids have been isolated from mycobacterial lipids [73].

The specific biological activity and unusual biosynthetic pathways of these compounds have attracted considerable attention. Various methods have been employed for their synthesis [73], but as a rule these involved a large number of stages and gave only small yields of the ultimate product.

The data accumulated during our elaboration of the new carbonyl olefination routes to unsaturated acids pointed out the way for adapting this principle in order to prepare higher branched-chain acids. The synthesis was achieved according to Scheme 5 [74].

In contrast to aldehydes, ketones condense with ω-alkoxycarbonylalkylidenephosphoranes *(13)* only with difficulty, even when the reaction is carried out in dimethylformamide. However, a satisfactory yield (based on the ketone) can usually be obtained with a twofold excess of *(13)*. Hydrogenation and subsequent saponification of the resultant unsaturated esters *(53)* led to the branched acids *(54)* in the yields shown in Table 2.



Scheme 5. Method for synthetizing higher branched-chain acids.

As in the case of aldehydes, reaction of *(13)* with ketones in dimethylformamide is accompanied by the formation of triphenylphosphine, which can best be separated, after hydrolysis of the esters to the sodium salts of the acids, by extraction of their aqueous solution with ether.

Table 2. Branched-chain fatty acids $CH_3-(CH_2)_m-\underset{\displaystyle CH_3}{\underset{|}{CH}}-(CH_2)_n-COOH$

| Acid | m | n | Yield [%] | M.p. of acid [°C] | | M.p. of amide [°C] | |
|---|---|---|---|---|---|---|---|
| | | | | Synthetic | Natural | Synthetic | Natural |
| 12-Methyltridecanoic [a] | 0 | 10 | 55 | 52–53 | 50.5–51 [77] | 105–107 | 107 [78] |
| 12-Methyltetradecanoic [b] | 1 | 10 | 42 | 24.5–26 | 25.8 [79] | 85–86 | 86 [79] |
| 10-Methylheptadecanoic [c] | 6 | 8 | 26 | 16–18 | — | 76–77 | — |
| 10-Methyloctadecanoic [d] | 7 | 8 | 32 | 18–20 | 20–21 [80] | 76.5–77 | 75–76 [80] |

[a] An iso-acid whose (+)-isomer has been isolated from butter.
[b] An anteiso-acid whose (+)-isomer occurs in animal fats.
[c] On the basis of indirect evidence, the dextrorotatory $C_{18}$-acid isolated from butter (m.p. 33.5 °C) [75] and from goose fat [76] was assigned the structure of 10-methylheptadecanoic acid.
[d] = (±)-Tuberculostearic acid.


[73] *E. Lederer*, Angew. Chem. *72*, 372 (1960).

[74] *L. D. Bergelson, V. A. Vaver, A. A. Bezzubov*, and *M. M. Shemyakin*, Zh. Obshchei Khimii *32*, 1807 (1962).

[75] *R. P. Hansen, F. B. Shorland*, and *N. J. Cooke*, Chem. and Ind. *1951*, 839.

[76] *G. Weitzel*, Fette, Seifen, Anstrichmittel *58*, 667 (1956).

[77] *C. R. Fordyce* and *J. R. Johnson*, J. Amer. chem. Soc. *55*, 3368 (1933).

[78] *R. P. Hansen, F. B. Shorland*, and *N. J. Cooke*, Biochem. J. *53*, 374 (1953).

[79] *E. V. Truter*, Quart. Reviews *5*, 390 (1951).

[80] *M. A. Spielman*, J. biol. Chemistry *106*, 87 (1934).

Synthesis of (±)-Tuberculostearic Acid *(54)*, m = 7, n = 8

A solution of 25 mmoles of methyl octyl ketone in 15 ml of dimethylformamide is added during one hour in an atmosphere of nitrogen to a solution of 8-methoxycarbonyloctylidenetriphenylphosphorane *(13)*, n = 7 (prepared from 0.55 mmole of phosphonium salt; see p. 255) in 40 ml of dimethylformamide. The mixture is stirred for 5 hours and then left to stand for 30 hours at room temperature. The dimethylformamide is distilled off *in vacuo*, and the residue obtained is extracted with ether. The extract is concentrated by evaporation, diluted with 100 ml of hexane, quickly filtered through a column (200 × 15 mm) containing 60 g of $Al_2O_3$ and then washed through with 300 ml of hexane. The unsaturated ester obtained after evaporation of the solvent is saponified by heating with 5 % sodium hydroxide in 80 % methanol; the methanol is then partially distilled off and the residue diluted with water, extracted with ether, and acidified.

Treatment with diazomethane gives the methyl ester *(54)*, where R = $CH_3$, m = 7, n = 8, b.p. 151–155 °C/1.5 mm, $n_D^{20}$ = 1.4557. Hydrogenation of this ester in the presence of Raney nickel at 20 °C followed by saponification with 5 % NaOH in 80 % methanol (refluxing for 2 hours) affords (±)-tuberculostearic acid, m.p. 18 20 °C, which is purified by crystallization from hexane at −20 °C.

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# Tetramethylurea as a Solvent and Reagent [1]

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*Respectfully dedicated to Prof. Karl Ziegler on the occasion of his 65th birthday*

*Tetramethylurea is an excellent solvent for organic substances, particularly aromatic compounds. It is suitable as reaction medium for base-catalysed isomerizations, alkylations, acylations, and other condensation reactions. Being inert toward Grignard compounds, it is a useful solvent for reactions of the latter with compounds that are sparingly soluble in ether. Several industrially feasible syntheses of tetramethylurea are discussed.*

## Introduction

In view of the importance achieved in recent years by solvents such as dimethyl sulfoxide, dimethylformamide, dimethylacetamide, and *N*-methylpyrrolidone it is surprising that tetramethylurea (abbreviated: temur [2]), which is related to the amides cited above, has so far received little attention. Literature references to its use as a solvent are only sporadic. For example, it has been mentioned as a solvent for acetylene [3,4] and for polyacrylonitrile [5]. While studying the accelerating effect of dimethylformamide and similar amides on alkylations, *Zaugg* et al. [6] also compared the effect of tetramethylurea. We first directed our attention to tetramethylurea in the course of systematic studies concerning the dipole moments [7] and infrared spectra [8] of carbonyl compounds and the corresponding thiocarbonyl derivatives. These studies were later extended by *Günthard*, *Béguin*, and *Gäumann* [9]. *Kohlrausch* and *Pongratz* [10] have investigated the Raman spectrum of tetramethylurea.

The aim of our preliminary studies [11,12] was to determine the ability of tetramethylurea to dissolve inorganic, organic, and macromolecular compounds and to establish its value as a medium for alkylations, acetylations, and other coupling reactions, including those involving organometals. To provide a more thorough chemical characterization of tetramethylurea, several reactions were carried out with this compound as a reagent. Finally, we were prompted to work out an industrially feasible process for its synthesis.

## I. Physical Properties

Tetramethylurea is one of the few urea derivatives that are liquid at room temperature. This undoubtedly arises from the fact that the normally strong association of

[1] Communication No. IV "On the Structure of Solutions". – Communication No. III: *A. Lüttringhaus* and *Dagmar Berrer*, Tetrahedron Letters *1959*, No. *10*, 10.

[2] We propose an abbreviation for "tetramethylurea" derived from the English name "TEtraMethylUREa", *viz.* temur; we feel that such mnemonic abbreviations are more desirable than those abominable acronyms consisting of initials, for example TMU. Moreover, TMU has three syllables whereas "temur" has only two. Again, for example, DMS means either "dimethyl sulfoxide" or, in the phrase "DMS Card Index", "Documentation of Molecular Spectroscopy".

[3] German Pat. 748245 (1937), DuPont de Nemours, inventors: *N. D. Scott* and *C. R. Harris*.

[4] *P. Hölemann* and *R. Hasselmann*, Forsch.-Ber. Wirtsch.- u. Verkehrsminist. Nordrhein-Westfalen, No. *109*, 27 (1954).

[5] US.-Pat. 2683128 (1954), Koppers, inventor: *G. F. d'Alelio*.

[6] *H. E. Zaugg*, *B. W. Horrom*, and *S. Borgwardt*, J. Amer. chem. Soc. *82*, 2895 (1960).

[7] *A. Lüttringhaus* and *J. Grohmann*, Z. Naturforsch. *10b*, 365 (1955).

[8] *Ro. Mecke*, *Rei. Mecke*, and *A. Lüttringhaus*, Z. Naturforsch. *10b*, 367 (1955).

[9] *C. Béguin* and *Hs. H. Günthard*, Helv. chim. Acta *42*, 2262 (1959).

[10] *K. W. Kohlrausch* and *A. Pongratz*, Mh. Chem. *70*, 226 (1937).

[11] *H.-W. Dirksen*, Diploma Thesis, Universität Freiburg, 1959.

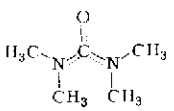
[12] *H.-W. Dirksen*, Ph. D. Thesis, Universität Freiburg, 1961.

amides due to hydrogen bridges involving the hydrogen on the amide nitrogen is lacking here. Tetramethylurea thus acts only as a hydrogen-bond acceptor. However, its boiling point (176.5 °C/760 mm) [13], when compared with that of the isosteric compound diisopropyl ketone (b.p. 125 °C/760 mm), points to strong dipole association, despite the expected hindrance by the four methyl groups. This is in agreement with the relatively high dipole moment, which is of the same order of magnitude as those of the formamides and acetamides, which are shown for comparison in Table 1.

Table 1. Boiling points, dielectric constants, and electric dipole moments of formamides, acetamides, and tetramethylurea.

| | Mol. wt. | B.p. [°C/760 mm] | Dielectric constant | μ [Debye] |
|---|---|---|---|---|
| Formamide | 45 | 210 (decomp.) | 109 | 3.37 |
| Acetamide | 59 | 221 | 74 | 3.6 |
| *N*-Methylformamide | 59 | 185 | 182 | |
| *N*-Methylacetamide | 73 | 206 | 183 | |
| *N*,*N*-Dimethylformamide | 73 | 153 | 36.7 | 3.8 |
| *N*,*N*-Dimethylacetamide | 87 | 165.5 | 37.8 | 3.8 |
| Tetramethylurea | 116 | 176.5 | 23.06 | 3.28–3.66 |

Our measurements show the dipole moment μ of tetramethylurea in benzene to be 3.37 Debye units [7]; recent measurements [14] gave μ = 3.28–3.66 D, depending on the solvent used. These values are high for a trigonal structure in which, because of the amide resonance *(1)* which tends to increase the moment, the three electronegative hetero-atoms are undoubtedly symmetrically



*(1)*

arranged, *i.e.* they do not deviate much from a 120° arrangement around the more positive carbon atom. As in other *N*,*N*-dimethylamides, the dielectric constant of tetramethylurea is markedly lower than that of *N*-unsubstituted amides and, in particular, of *N*-monomethylamides, partly because of the absence of association via hydrogen bridges. We cannot entirely accept the view of *Béguin* [9, 14] and *Zaugg* [6] that the coplanarity of the whole molecule, including the four methyl groups, which is necessary for maximum resonance, is hindered. The Stuart-Briegleb atomic model (Fig. 1) shows no strain, although rotation of both the lower methyl groups is slightly hindered. Moreover, some experimental data indicate that it should be considered that the radius of the hydrogen atoms too large in this type of model by 5 % [17] or 10 % [18]. The resonance energy of tetramethylurea, calculated from

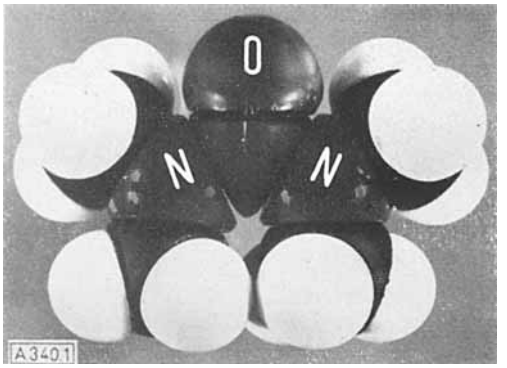



Fig. 1. Stuart-Briegleb atomic model of tetramethylurea.

the calorimetric data given in Table 2, is about 45 kcal/mole [12]; the highest value reported for urea is 41 kcal/mole [21]. However, our value is not to be considered as being very accurate, since we used the heat of formation of ketones for that of the C=O bond and this may introduce additional errors.

Table 2. Physical constants of tetramethylurea.

| | Our measurements [11, 12] | Other workers' measurements |
|---|---|---|
| B.p. [°C] 760 mm | | 176.5 [13] |
| 740 mm | 174.5 | |
| 12 mm | 63–64 | |
| M.p. [°C] | −1.2 | |
| Flash point [°C] | ca. 75 | |
| Density, 20 °C/4 °C | 0.9687 | |
| 15 °C/4 °C | | 0.972 [15] |
| $n_D^{23}$ | 1.4496 | |
| $n_D^{25}$ | | 1.4493 [6] |
| Dielectric constant | 23.1 | 23.06 [16] |
| μ [Debye] | 3.37 [7] | 3.28–3.66 [14] |
| Ultraviolet absorption, | | |
| $\lambda_{max}$ [mμ] | 217.5 | |
| $\varepsilon_{max}$ | 1940 | |
| Infrared absorption [cm⁻¹] | 1640 [8] | 1639.7–1668 [9] |
| ν(C=O) [cm⁻¹] | | 1639 [20] |
| Basicity: $pK_B$ | 12 | 11.8–12.0 [39] |
| Specific conductivity κ [mho/cm] | $<0.6 \cdot 10^{-7}$ | |
| Heat of combustion [cal/g] | | −7046 [19] |
| Heat of combustion [kcal/mole] | −819.3 | |
| Heat of formation [kcal/mole] | −60.8 | |

The marked solvent dependence of the dipole moment [9] (Table 3) and approximately corresponding CO frequency shifts in the infrared spectrum [14] (Table 4)

Table 3. Electric dipole moment of tetramethylurea in different solvents as a function of their dielectric constants [9]

| Solvent | Dielectric constant | μ [Debye] |
|---|---|---|
| Hexane | 1.901 | 3.47 |
| Heptane | 1.917 | 3.43 |
| Cyclohexane | 2.014 | 3.40 |
| *trans*-Decalin | 2.137 | 3.34 |
| Dioxan | 2.229 | 3.49 |
| Carbon tetrachloride | 2.238 | 3.66 |
| Benzene | 2.278 | 3.47 |
| *m*-Xylene | 2.354 | 3.29 |
| Toluene | 2.371 | 3.34 |
| Cumene | 2.375 | 3.28 |

[13] *W. Mischler* and *C. Escherich*, Ber. dtsch. chem. Ges. *12*, 1164 (1879).
[14] *C. Béguin* and *T. Gäumann*, Helv. chim. Acta *41*, 1971 (1958).
[15] *A. P. N. Franchimont*, Recueil Trav. chim. Pays-Bas *3*, 226 (1884).
[16] *T. Gäumann*, Helv. chim. Acta *41*, 1956 (1958).
[17] *A. Lüttringhaus* and *G. Eyring*, Liebigs Ann. Chem. *604*, 111 (1957).
[18] *W. Theilacker*, Z. Naturforsch. *3b*, 233 (1948).
[19] Determined in the Analytical Laboratory of E. Merck AG., Darmstadt (Germany).
[20] *H. A. Staab*, Liebigs Ann. Chem. *609*, 75 (1957).
[21] *L. F.* and *M. Fieser*: Organic Chemistry. 2nd Edit., Heath, Boston 1950, p. 1124.

are noteworthy. *Béguin* and coworkers find that the Kirkwood-Magat-Bauer theory is only roughly satisfied in this case; they consider that the direct effect and the conformation of the solvent molecules which are the immediate neighbors of the tetramethylurea molecule are more important than the dielectric effect. It has been demonstrated with long-chain paraffins that such solvent effects can have drastic influences on the conformational structure [22,23].

The differences between the infrared spectra of tetramethylurea in the dissolved, liquid, and crystalline state [14] (see Tables 2 and 4) are large. However, these differences do not reflect basic structural differences in the different phases [14]. The strong intermolecular forces existing in the crystal lead to pronounced coupling of the normal internal vibrations, and the resulting mechanical disharmonicity markedly broadens and modulates the band contours. Of the urea derivatives lacking hydrogen bonds investigated by them, *Günthard, Gäumann,* and *Béguin* [9,14] found that only tetramethylurea showed this effect.

Table 4. Solvent dependence of the C=O vibration of tetramethylurea, according to *Béguin* and *Günthard* [9].

| Solvent | $\nu_{C=O}$ [cm$^{-1}$] |
|---|---|
| Heptane | 1668 |
| Cyclohexane | 1666.7 |
| Dioxan | 1650.9 |
| Carbon tetrachloride | 1651.7 |
| *p*-Xylene | 1656.9 |
| Benzene | 1651.8 |
| Chlorobenzene | 1649.1 |
| Methylene chloride | 1639.7 |
| Nitrobenzene | 1648.5 [12] |
| Acetonitrile | 1643.3 |

In the plot of the C=O frequency against the "y" function of the Kirkwood-Magat-Bauer theory, aromatics dissolved in tetramethylurea occupy a special position [12]. Obviously, there is some correlation with the surprisingly high solvent power of tetramethylurea for aromatics (see below). The interaction due to the marked electron delocalization in both species is obviously not so strong as to result in actual charge transfer. Nevertheless, the ultraviolet absorption spectra of simple aromatic hydrocarbons in tetramethylurea show a 3 mμ bathochromic shift of the maxima, compared to corresponding cyclohexane solutions; this is true for both phenanthrene, which is readily soluble, and anthracene, which is exceptionally sparingly soluble [12] (Fig. 2). Analogous shifts toward longer wavelengths amount to 11 mμ for nitrobenzene, 35 mμ for trinitrotoluene, 29 mμ for picric acid, and 20 mμ for *p*-nitrophenol. Tetramethylurea is not sufficiently basic (see below) to promote formation, for example, of the nitrophenoxide ion by accepting a proton.

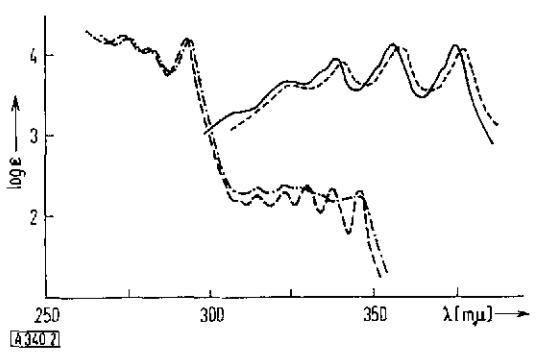



Fig. 2. Effect of the solvent on the ultraviolet absorption spectra of anthracene and phenanthrene.
Anthracene in cyclohexane ———
Anthracene in tetramethylurea — — —
Phenanthrene in cyclohexane ———
Phenanthrene in tetramethylurea —·—·—

For a urea derivative, tetramethylurea has a very high carbonyl absorption maximum (ε = 1940) at λ = 217.5 mμ (π → π*-transition) and a rather broad band (participation of an n → π* transition) (Fig. 3). Hence, measurements of ultraviolet spectra in tetramethylurea at wavelengths below 260 mμ are not accurate.

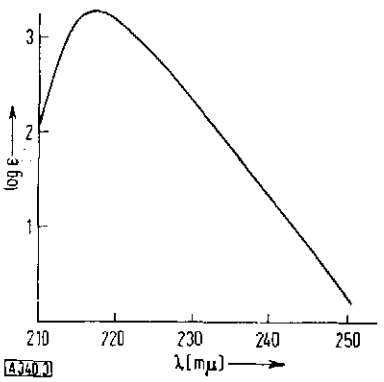



Fig. 3. Ultraviolet absorption spectrum of tetramethylurea in cyclohexane.

The specific conductivity of tetramethylurea is very low, as is to be expected of an aprotic solvent. We determined the density of tetramethylurea/water mixtures and found a maximum ($d_{20}$ = 1.0170 g/cm$^3$) at 86 mole-% water. This corresponds exactly to a water:tetramethylurea molar ratio of 6:1 (Fig. 4), which obviously indicates the optimum hydration number for tetramethylurea.

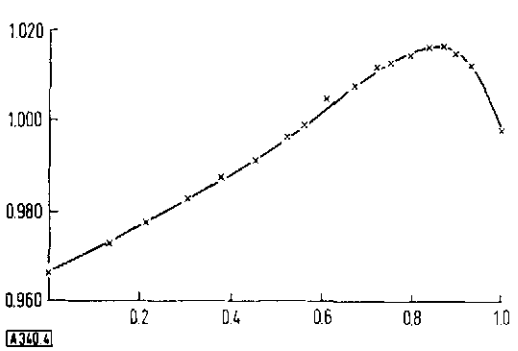



Fig. 4. Density of tetramethylurea/water mixtures at 20 °C.
Ordinate: Density [g/cm$^3$]
Abscissa: Mole fraction of water.

[22] *A. Lüttringhaus* and *I. Sichert-Modrow*, Makromolekulare Chem. *18/19*, 511 (1956); see also *G. Salomon*, Helv. chim. Acta *19*, 743 (1936); *A. Lüttringhaus*, Naturwissenschaften *30*, 40 (1939).

[23] *R. Worthmann* and *A. Lüttringhaus*, Makromolekulare Chem. *18/19*, 522 (1956).

## II. Dissolving Power

Like pyridine, tetramethylurea is miscible in all proportions not only with water but also with all common organic solvents including petroleum ether. At this point, it is worthwhile mentioning the other (also liquid) lower tetralkylureas. Thus, *N,N*-dimethyl-*N'*,*N'*-diethylurea is still completely miscible with water at 20 °C; at the same temperature, methyltriethylurea is soluble to the extent of 1 g/10 ml of water and 1 g of tetraethylurea (b.p. 94–95 °C/12 mm) dissolves in about 25 ml of water [24].

### 1. For Inorganic Compounds

Since tetramethylurea shows a substantially lower dielectric constant than other simple carboxamides (Table 1) with approximately the same dipole moment, and since the interaction of these two parameters is responsible for ion solvation, it is understandable that the dissolving power for salts of pronounced ionic character is not great, approximating that of acetone. Thus, the dissolving power is poor for alkali and alkaline earth chlorides, moderate for the bromides, and good for the iodides. As usual, the sulfate ion confers only low solubility, whereas many nitrates have surprisingly good solubilities. This indicates that anion solvation, too, affects the dissolving power. The low solubilities of alkali cyanides, cyanates, thiosulfates, and surprisingly, also acetates, are disappointing; on the other hand, many salts of transition metals show good solubilities (Table 5).

Table 5. Solubilities of inorganic compounds in tetramethylurea at 22 °C (g per 100 g of tetramethylurea).

| | [g/100 g] | | [g/100 g] |
|---|---|---|---|
| NaCl | 0.14 (75 °C) | $NH_4Cl$ | 0.72 |
| NaBr | 5.8 | $NH_4NO_3$ | 32 |
| NaI | 92 | $CuSO_4$ | 0.22 |
| NaCN | 0.27 | $AgNO_3$ | good |
| $NaNO_3$ | 3.8 | $CaCl_2$ | 2.0 |
| $Na_2S_2O_3 \cdot 5\ H_2O$ | 0.47 | $ZnSO_4 \cdot 7\ H_2O$ | 0.39 |
| Na acetate·3 $H_2O$ | 0.26 | $Cd(NO_3)_2 \cdot 4\ H_2O$ | >60 |
| KCl | 0.15 (75 °C) | $H_3BO_3$ | 12 |
| KBr | 0.11 | $MnCl_2 \cdot 4\ H_2O$ | 85 |
| KI | 14.2 | $FeCl_3$ | 6.9 |
| KCN | 0.25 | $Co(NO_3)_2 \cdot 6\ H_2O$ | >60 |
| KOCN | 0.16 | $Ni(NO_3)_2 \cdot 6\ H_2O$ | 74 |
| KSCN | 29.4 | $NbCl_5 \cdot 2$ DMF | good |
| $K_2S_2O_5$ | 0.45 | *(1)*·HCl [*] | good |
| K acetate | 0.21 | *(1)*·HBr [*] | moderate |

[*] Formation of a compound.

To what extent the formation of solvate complexes affects the solubility of inorganic compounds in tetramethylurea remains to be determined. Since such complexes have been found to exist in the case of dimethylformamide [25] and other amides [26], their existence in tetramethylurea is to be expected. This is also indicated by the negative temperature coefficient of the solubility and by the color effects observed with transition metals.

### 2. For Organic Compounds

The miscibility of tetramethylurea with nearly all classes of organic liquids mentioned already points to a good dissolving power. The fact that a polar liquid which is miscible in all proportions with water also shows a high dissolving power for hydrocarbons is not surprising if one considers the tetramethylurea model shown in Figure 1. The surface of this model is formed mainly by the four lipophilic methyl groups which shield the carbonyl oxygen to a large extent. As shown by experience, the ellipsoid form by itself, under equal conditions of polarity, tends to increase the dissolving power. On the other hand, the model shows that the ability of the carbonyl oxygen to accept hydrogen bridges is hardly impaired; this explains the good solubility of uni- and polyvalent hydroxy compounds and carboxylic acids (Table 6).

Even more striking is the generally excellent dissolving power of tetramethylurea for aromatic hydrocarbons and their halogeno and nitro derivatives, phenols, and aromatic carboxylic acids, *etc.* (Table 6). Among the few exceptions are anthracene and anthraquinone,which are also sparingly soluble in other solvents. Anthracene is very soluble in hot tetramethylurea and can be efficiently crystallized from it. All nitro and polynitro compounds show excellent solubilities. We have already discussed (see p. 262) the fact that the spectra of these solutions show bathochromic shifts. However, this fact should not be accepted indiscriminately because the very pronounced color changes which may occur in tetramethylurea solutions of polynitro compounds are due to the presence of dimethylamine admixtures. This phenomenon may even be used as a criterion of purity. The few examples in Table 6 suffice to demonstrate the good solubilities of heterocyclics in tetramethylurea. The probable reasons for the remarkable dissolving power of tetramethylurea for aromatics have already been discussed in Section I. This solvency is probably derived from the van der Waals forces due to the methyl groups, from the interactions between the resonance systems of the solvent and that of the solute, and from a favorable molecular structure of tetramethylurea. The low solubilities of amino acids, even those of aromatic nature, shown in Table 6, are noteworthy. These low solubilities are undoubtedly related to the zwitterionic structure of these compounds, because they increase as this property decreases. Salt formation, for example the formation of cysteine hydrochloride (see Table 6), and especially electronegative substituents (*e.g.* dinitrophenyl residues) on the amino group lower its basicity and increase the solubility of the compound. Amino acids that do not afford zwitterions [27], *e.g.* *p*-aminobenzoic acid or anthranilic acid, show excellent, nearly 1:1 solubilities,

[24] *J. A. Äschlimann* in: Barell-Festschrift. Basel *1936*, p. 252; Chem. Zbl. *1936*, II, 2943.

[25] *A. Maillard* and *W. Rosenthal*, C. R. hebd. Séances Acad. Sci. *234*, 2546 (1952).

[26] *G. Winkler*, Ph. D. Thesis, Technische Universität Berlin, 1959.

[27] *H. Hünecke*, Ber. dtsch. chem. Ges. *60*, 1451 (1927); see also *E. J. Cohn* and *J. T. Edsall*: Proteins, Amino Acids and Peptides. New York 1943, p. 99.

Table 6. Solubilities of organic compounds in tetramethylurea at 22 °C (g per 100 g of tetramethylurea).

| | | | |
|---|---|---|---|
| **Aliphatic and cycloaliphatic derivatives** | | | |
| Acetylene (18atm) [3,4] | 50 | Sebacic acid | 36 |
| Petroleum ether | c.m. | Citric acid | 12.3 |
| n-Octadecane | c.m. | Acetamide | 44.7 |
| Cyclohexane | c.m. | Dimethylformamide | c.m. |
| Methanol | c.m. | *N*-Methylpyrrolidone | c.m. |
| Ethanol | c.m. | Caprolactam | 81 |
| 1,10-Decanediol | 26.4 | Urea | 2.5 |
| Ethyl acetate | c.m. | Glucose | 1.1 |
| Ethyl acetoacetate | c.m. | Carbon tetrachloride | c.m. |
| Diethyl sebacate | c.m. | Chloroform | c.m. |
| Acetone | c.m. | Methylene chloride | c.m. |
| Paraformaldehyde | 0.05 | Carbon disulfide | c.m. |
| Urotropin | 0.32 | Thiourea | 7.2 |
| Acetic acid | c.m. | | |
| **Aromatic derivatives** | | | |
| Benzene, toluene, xylenes | c.m. | 2,4-Dinitrotoluene | s. |
| Naphthalene | s. | 1,3,5-Trinitrobenzene | s. |
| Phenanthrene | 50 | 2,4,6-Trinitrotoluene | s. |
| Anthracene | 3.8 | Benzoic acid | 67 |
| Pyrene | 73 | 2-Aminobenzoic acid | 85 |
| Biphenyl | 77 | 4-Aminobenzoic acid | 80 |
| Acenaphthene | 26 | 1,2-Diaminobenzene | 46 |
| Phenol | c.m. | 2-Aminophenol | 40 |
| *o*-Cresol | c.m. | 1,3-Diaminobenzene-4-sulfonic acid | 0.3 |
| Hydroquinone | 40 | Diphenyl carbonate | 79 |
| 4-Iodotoluene | v.s. | Benzoquinone | 60 |
| 1-Iodonaphthalene | v.s. | Anthraquinone | 0.25 |
| Nitrobenzene | c.m. | Diphenylene oxide | 72 |
| 4-Nitrotoluene | 115 | Azobenzene | 65 |
| 1,3-Dinitrobenzene | s. | | |
| **Heterocyclic derivatives** | | | |
| Tetrahydrofuran | c.m. | Caffeine | 1.7 |
| Dioxane | c.m. | Benzimidazole | 50 |
| Pyridine | c.m. | Antipyrine | 28 |
| Quinine | 39 | Benzotrithione | 20 |
| **Amino acide** | | | |
| Glycine | 0.02 | Phenylglycine | 0.25 |
| DL-Valine | 0.03 | Phenylalanine | 0.66 |
| DL-Leucine | 0.13 | DL-Tyrosine | 0.08 |
| Cysteine·HCl | 3.5 | DL-Tryptophan | 0.19 |
| Cystine | 0.07 | L(−)Histidine | s.s. |
| DL-Methionine | 0.13 | *N*-Dinitrophenylglycine | s. |
| Lysine (crude) | 1.1 | *N*-Dinitrophenylalanine | s. |
| Glutamic acid | 0.38 | | |

c.m. = completely miscible; v.s. = very soluble
s = soluble; s.s. = sparingly soluble

whereas 2,4-diaminobenzenesulfonic acid, which is zwitterionic, is only sparingly soluble.

The low solvency for zwitterionic amino acids may be explained by the low solvating power of tetramethylurea both for anionized carboxylic groups (low solubility of Na and K acetate, cf. Table 5) and for the ammonium group (ammonium chloride is very sparingly soluble in tetramethylurea; cf. Table 5); the high solubility of ammonium nitrate is obviously due to the nitrate ion, since nitrates generally show remarkably high solubilities (cf. Table 5).

The solubility in tetramethylurea therefore yields useful preliminary information on whether or not acids with basic groups exist preferentially as zwitterions. The remarkable differences in solubility between amino acids and their derivatives suggest the use of tetramethylurea in the analysis of proteins. It has also been used as a component of solvent systems for paper chromatography [28].

[28] We thank Prof. Dr. *O. Westphal*, Freiburg/Breisgau, for having these studies carried out in his Institute.

Table 7 gives a list of the solubilities of a few macromolecular compounds. Polyethylene, polypropylene, and high molecular-weight polyamides of the Perlon

Table 7. Solubilities of macromolecular substances (g per 100 g of tetramethylurea).

| | Temp. [°C] | Solubility |
|---|---|---|
| Low-pressure polyethylene | 22 | — |
| | 75 | 0.06 |
| High-pressure polyethylene | 22 | — |
| | 75 | 0.11 |
| Polypropylene | 22 | |
| | 75 | 0.14 |
| Poly(vinyl chloride) | 22 | Swells and dissolves |
| Rhovyl (RHODIACETA) | 22 | Sol. [a] |
| PCU (RHODIACETA) | 22 | Sol. [a] |
| Poly(vinylidene dicyanide) (GOODRICH, USA) | 22 | Sol. [a] |
| Poly(acrylonitrile) | 175 | — |
| Polycaprolactam | 175 | — |
| Nylon (RHODIACETA) | 100 | — [a] |
| Viscose (American ENKA) | 100 | — [a] |
| Viscose, crosslinked (COURTAULDS) | 100 | — [a] |
| Cuprammonium rayon (CUPRESA, BAYER) | 100 | — [b] |
| Cellulose 2,5-acetate (RHODIACETA) | 22 | Sol. [a] |
| Cellulose triacetate (RHODIACETA) | 22 | Sol. [a] |
| Polymethacrylate | 22 | Swells and dissolves |
| Polyester (Tergal, RHODIACETA) | 100 | — [a] |
| Polyester (Terylene) | 125 | 5–10 |
| Polycarbonate (BAYER) | 22 | swells and dissolves [b] |
| Polyurethane (BAYER) | 175 | swells and dissolves |
| Polystyrene | 22 | ca. 30 |
| Novolak | 22 | ca. 15 |
| Bakelite | 175 | — |

[a] Data kindly furnished by Dr. *Weigand*, Deutsche Rhodiaceta AG., Freiburg/Breisgau (Germany)

[b] Data kindly furnished by Drs. *Reichle* and *Prietzsch*, Farbenfabriken Bayer AG., Dormagen (Germany).

and nylon-6,6 type are practically insoluble at 22 °C; the polyamides are insoluble even at temperatures exceeding 100 °C. As expected, cellulose esters and poly(vinyl dicyanide) exhibit high solubilities, as do (after swelling) poly(vinyl chlorides) that are chlorinated to various degrees. On the other hand, we found pure polyacrylonitrile to be practically insoluble, in contrast to the observation of *d'Alelio* [5] of solubility. It is possible that his measurements were carried out on copolymers, for example, on copolymers with aromatic components. Good solubility is generally observed for aromatic polymers as polystyrene, polyurethane, Makrolon, and the Novolaks. The highly crosslinked bakelites, on the other hand, are insoluble. Among the polyesters, branched polymethacrylate is soluble, whereas Tergal (Rhodiaceta) is not; the aromatic nature of polyterephthalate accounts for its solubility. It should also be noted that tetramethylurea strongly promotes crystallization of certain polymers, *e.g.* polycarbonate (Makrolon) [29].

[29] Communication from Drs. *Reichle* and *Prietzschk*, Bayer-Werk, Dormagen (Germany).

## III. Chemical Properties and Reactions

Urea has a $pK_B$ of 13.8. As might be expected, tetramethylurea appears to be more basic. Its behavior toward hexacarbonylchromium(0) and hexacarbonylmolybdenum(0) suggests a $pK_B$ greater than 11 [30]. The half-wave potential (560 mv [31]; 546 mv [32]) for a potentiometric titration of tetramethylurea in acetic anhydride with perchloric acid in glacial acetic acid shows a $pK_B$ of 11.8–12.0 [32], based on a calibration curve [33]. This is in agreement with our value for $pK_B$ of 12.0 (Table 2).

Accordingly, protonation occurs readily in the presence of strong acids. Whether this occurs on the nitrogen or oxygen atom has been the subject of numerous studies involving amides and ureas [34]. Since *O*-protonation has been demonstrated both for *N,N*-dialkylamides [35] and for urea [36], it is assumed that it also occurs with tetramethylurea. However, we were unable to find unequivocal support of *O*-protonation in either the infrared or the NMR spectrum of crystalline tetramethylurea hydrobromide (in dioxan or excess tetramethylurea). The adducts with hydrogen chloride, sulfuric acid, and chlorosulfonic acid could not be obtained in the crystalline form whereas the hydrobromide and hydroiodide could (unfortunately, the latter discolors rapidly). Hexachloroantimonic acid also gives a crystalline adduct. However, this adduct is an "anomalous" basic salt, as indicated by its formula, *viz.* (tetramethylurea)$_2$·$HSbCl_6$. Analogous salts are known with urea [36]. These adducts of urea are the opposite of the "acidic" salts formed with carboxylic acids and other acidic organic substances. The long-suspected proton bridge [37] required for symmetry seems to be characteristic of both series of adducts.

Tetramethylurea hydrobromide, $C_5H_{12}N_2O \cdot HBr$ (197.1) [12], is formed nearly quantitatively when 100 ml each of 0.34 M solutions of HBr and tetramethylurea in absolute ether are simultaneously added dropwise to 50 ml of absolute ether with agitation and external ice cooling, in an atmosphere of dry nitrogen. The salt is extremely hygroscopic [m.p. 130.5–131 °C (decomp.)]. HBr: Calcd. 41.06 %; found 40.99 %.

Tetramethylurea hemihydrohexachloroantimonate, $(C_5H_{12}N_2O)_2$·$HSbCl_6$ (567.8) [12], is obtained by dropwise addition of 5.12 g (0.44 mmole) of tetramethylurea in 5 ml of absolute acetone to 9.46 g (22 millimoles) of $HSbCl_6$·4.5 $H_2O$ in 10 ml of absolute acetone, slow cooling to −15 °C, filtration by suction, and recrystallization from acetone cooled to −70 °C. The compound forms lemon-yellow crystals, m.p. 125–127 °C. Calcd. C 21.15 %, H 4.41 %, Cl 37.6 %; Found C 20.85 %, H 4.66 %, Cl 37.6 %.

Tetramethylurea does not form the sparingly soluble oxalate and nitrate which are characteristic of urea. Nitric acid causes rapid oxidative decomposition of tetramethylurea with formation of dimethylammonium nitrate, carbon dioxide, and dimethylnitramine [15]. The adduct of tetramethylurea with $BF_3$ is a liquid that crystallizes below −15 °C.

As might be expected from their salt character, the adducts with acids show electrical conductivity in excess tetramethylurea. As shown in Figures 5 and 6, these compounds are weak electrolytes.

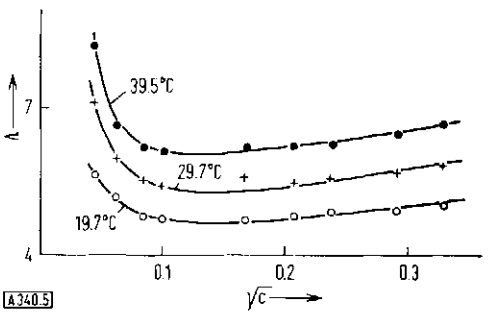



Fig. 5. Equivalent conductivity of HCl in excess tetramethylurea
Ordinate: Equivalent conductivity [mho/cm per equiv./ml]
Abscissa: $\sqrt{c}$, with c in equiv./ml

Solutions of carbonyl halides in anhydrous tetramethylurea are also electrically conductive; however, the rate of addition is markedly slower [12] than, for example, for dimethylformamide. This is obviously due to the shielding effect exerted by the methyl groups on the carbonyl oxygen, which in this case is much more pronounced than in additions involving a small proton.

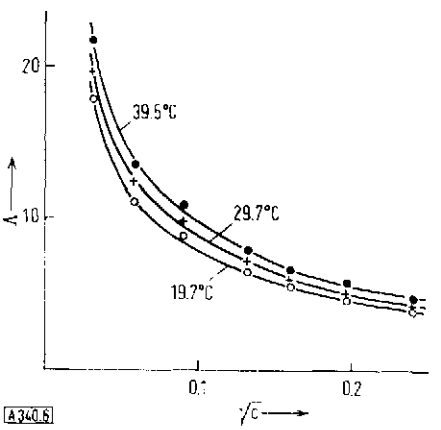
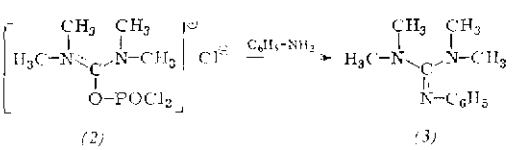



Fig. 6. Equivalent conductivity of HBr in excess tetramethylurea
Ordinate: Equivalent conductivity [mho/cm per equiv./ml]
Abscissa: $\sqrt{c^{-1}}$, with c in equiv./ml

Tetramethylurea gives an adduct with phosphorus oxychloride which is sparingly soluble in ether; to this adduct has been assigned structure *(2)* [38].




*(2)* *(3)*

[30] *W. Kullick*, Ph. D. Thesis, Universität Freiburg, 1960.

[31] *D. C. Wimer*, Analytic. Chem. *30*, 77 (1958).

[32] *H. E. Zaugg*, J. Amer. chem. Soc. *82*, 2903 (1960); *83*, 837 (1961).

[33] *C. A. Streuli*, Analytic. Chem. *30*, 997 (1958).

[34] *R. Huisgen* and *H. Brade*, Chem. Ber. *90*, 1432 (1957); additional references are to be found therein.

[35] *G. Fraenkel*, *C. Niemann*, and *C. Franconi*, Proc. natl. Acad. Sci. USA. *44*, 688 (1958); J. Amer. chem. Soc. *82*, 4478 (1960).

[36] *R. Mecke* and *W. Kutzelnigg*, Chem. Ber. *94*, 1706 (1961).

[37] *A. Lüttringhaus* and *G. v. Sääf*, Liebigs Ann. Chem. *557*, 35 ff. (1945).

[38] *H.* and *K. Bredereck*, Chem. Ber. *94*, 2278 (1961) and earlier publications.

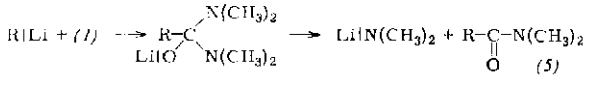
It lends itself well to the preparation of pentasubstituted guanidines. With aniline, for example, *N,N,N',N'*-tetramethyl-*N''*-phenylguanidine *(3)* is obtained.

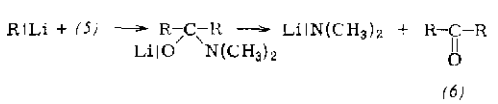
The reaction of tetramethylurea with phosgene results in the replacement of the carbonyl oxygen by two chlorines [39]. This reaction gives high yields of the

$$(CH_3)_2N{-}CO{-}N(CH_3)_2 + COCl_2 \rightarrow CO_2 + (CH_3)_2N{-}CCl_2{-}N(CH_3)_2$$
*(1)* *(4)*

dichloride *(4)*, shown here in its covalent form. Pentasubstituted guanidines are also produced by reaction of tetramethylurea with primary amines. With NaSH, tetramethylthiourea is obtained, while alkoxides yield bis(dimethylamino)dialkoxymethanes, *i.e.* representatives of the interesting group of urea acetals. When a large amount of alkoxide is used, one dimethylamino residue can be replaced with formation of a trialkyl *N*-dimethylorthocarbamate $(CH_3)_2N{-}C(OR)_3$ [39].

The strong shielding of the carbonyl group is also reflected in the behavior of tetramethylurea towards organometallic compounds. Thus, in the reaction with Grignard compounds, no attack on the carbonyl group takes place even at elevated temperatures. On the other hand, the lithium compounds, which are more reactive, normally afford *(5)* and *(6)*. Thus, depending on the molar ratio of the reactants, a symmetrical ketone *(6)*





or the corresponding dimethylcarboxamide *(5)* may be prepared from an organolithium compound in good yields. The reaction yielding *(5)* has preparative value. When the dimethylcarboxamide is the desired product, this reaction makes it unnecessary to prepare the corresponding carboxylic acid intermediately by carboxylation with $CO_2$. The second step leading to the ketone *(6)* corresponds to the synthesis of ketones from dialkylcarboxamides and organolithium compounds worked out by *Izzo* and *Safir* [40].

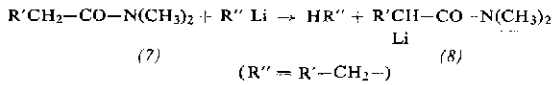
For example, *N,N*-dimethylbenzamide is obtained in 80 % yield by dropwise addition of a solution of phenyl-lithium in ether to a six-fold molar excess of tetramethylurea in ether at −30 °C, decomposition of the organometallic complex with a small amount of water, and direct vacuum distillation of the mixture to recover the excess tetramethyurea [12].

Benzophenone is prepared in 63 % yield by dropwise addition of 175 ml of a 0.36 M solution (0.63 mole) of phenyl-lithium in ether to 36.6 g (0.315 mole) of tetramethylurea in 100 ml of absolute ether over 1 hour, with agitation and external ice-cooling. The mixture is then allowed to stand for additional 4 hours at 0 –15 °C, is decomposed with 20 % sulfuric acid with cooling, is worked up in the usual manner, and distilled *in vacuo* [12].

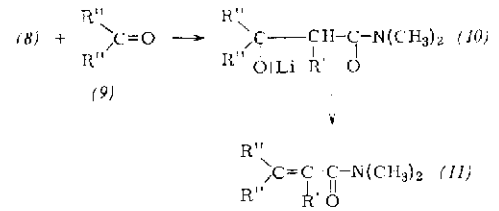
[39] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960).

[40] *P. T. Izzo* and *S. R. Safir*, J. org. Chemistry *24*, 701 (1959).

Lower yields are obtained when this ketone synthesis is applied to primary or secondary aliphatic lithium compounds. This is because the primary product *(7)* as a result of the



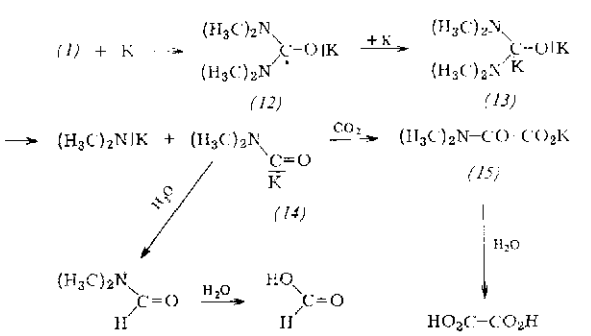
acidifying effect of the carboxamido group, undergoes partial metalation to give *(8)*, which then reacts further with the nascent ketone *(9)* in a manner similar to the modified [41] Reformatsky reaction of esters and affords a β-hydroxy-*N*-dimethylcarboxamide *(10)*. Acid hydrolysis of the latter



followed by distillation then gives the substituted α,β-unsaturated carboxamide *(11)*. Thus, butyl-lithium and tetramethylurea give 40 % 5-nonanone plus *N,N*-dimethyl-2-propyl-3-n-butyl-2-heptenamide (b.p. 158–160 °C/11 mm).

Tetramethylurea also reacts with the still more reactive organosodium compounds, but not with tritylsodium, as indicated by the fact that the red color of this compound remains unaltered in tetramethylurea. This is readily accounted for by steric hindrance in each of the two reactants.

The behavior of tetramethylurea toward alkali metals is noteworthy. Vigorous shaking of this compound with liquid K/Na alloy, in an inert solvent if necessary, produces a dark-blue solution within in a few seconds. Presumably, a system similar to that formed by alkali metals in ammonia and certain ethers is initially formed. At room temperature, this color then rapidly changes to light yellow. Further addition of K to the ketyl radical anion *(12)* yields *(13)*, which undergoes cleavage to give potassium dimethylamide and *(14)*. The formation of *(14)* is demonstrated by its ability to undergo carboxylation to form the oxalic acid derivative *(15)* and hydrolysis to yield formic acid.



The metalating action of K/Na alloy in tetramethylurea on relatively acidic compounds such as triphenylmethane is similar to that of typical radical anion formers, *e.g.* naphthalenesodium [42]; it manifests itself under con-

[41] *P. J. Hamrick* and *Ch. R. Hauser*, J. Amer. chem. Soc. *81*, 2096 (1959).

[42] *H. Normant* and *B. Angelo*, Bull. Soc. chim. France *1960*, 354; *L. Horner* and *H. Güsten*, Liebigs Ann. Chem. *652*, 99 (1962).

ditions where no reaction occurs in the absence of tetramethylurea [12]. Tetramethylurea also has a marked accelerating effect on the metalation of triphenylmethane with sodamide. Sodium hydride in tetramethylurea may also he used for metalation reactions [12]; however, according to *Corey* [43], dimethyl sulfoxide is the preferred medium in this case.

The role of tetramethylurea as a source of hydride hydrogen in the reduction of diazonium hexafluorophosphates [45] merits attention. The reaction is carried out hy adding the solid salt in 50 g portions to 200 ml of tetramethylurea at 20 °C and allowing the exothermic reaction and the evolution of nitrogen to take place. The reaction mixture may be warmed slightly without exceeding 65 °C. The replacement of the diazotized amino group with hydrogen by this method is particularly smooth for nitro- and halogenoanilines and *o*- and *p*-aminobenzoic acids; in some cases, this procedure gives better yields than those involving classical reducing agents (alcohol, stannite, alkaline formaldehyde, hypophosphorous acid). The mechanism is obviously ionic, resembling that formulated by *Meerwein* [46] for the reduction of diazonium tetrafluoroborates with dioxan, dioxolans, ethylene glycol dimethyl ether, or tetrahydrofuran.

## IV. Tetramethylurea as a Reaction Medium

*Zaugg* and coworkers [6,32,47] conducted thorough investigations of the accelerating effect of sulfoxides, amine oxides, phosphine oxides, *etc.* and particularly, of *N,N*-dialkylcarboxamides, on *C*-alkylation of alkali enolates. These enolates, *e.g.* ethyl sodioacetoacetate, exist in benzene as highly associated ion pairs. Addition of even a small amount (5–10 %) of dimethylformamide, *N*-methylpyrrolidone, tetramethylurea, *etc.* has an antiassociating and an unusual accelerating effect on the alkylation of enolates, for example of the industrially important monosubstituted sodiomalonate derivatives. These findings and the physical properties of these amides indicate that the high $\pi$-electron density in the amide group, particularly in the $\pi$-orbital of the carbonyl oxygen, accounts for the remarkable solvation of alkali metal ions. On the basis of this concept, tetramethylurea with its two dimethylamino groups should be the most effective agent. The fact that it is not quite as effective as dimethylformamide is explained by *Zaugg* [32] on the basis of the hypothesis of *Günthard* [9,14] (cf. page 261), which assumes that the bulk of the methyl groups hinder the coplanar arrangement of the tetramethylurea molecule and thus prevent it from attaining its full mesomerism. However, it is also conceivable that molecules with a more readily accessible oxygen atom, *e.g.* dimethylformamide, are capable of surrounding an $Na^+$ ion with more molecules and thus form a denser solvation shell than that provided by tetramethylurea.

As a rough guide, the use of dimethylformamide in place of benzene as reaction medium leads to an approximately 1000-fold, [47] and the use of tetramethylurea to a 200-fold [12] increase in the rate of otherwise identical alkylations.

Ethyl α-n-butylacetoacetate [12]: 30 g of a 20 % suspension of NaH in mineral oil (0.25 mole) are added with agitation to 100 ml of tetramethylurea at 0 °C; 32.5 g of ethyl acetoacetate are added dropwise over a period of 20 min, and the mixture is allowed to warm up. Next, 35.5 g of 1-bromobutane are slowly added and agitation continued for 4 hours at 100 °C. Most of the tetramethylurea is distilled off at about 14 mm pressure. Extraction of the residue with ether and working up the extract in the usual manner afford 35 g (75.5 %) of ethyl n-butylacetoacetate (b.p. 121–122 °C/25 mm; $n_D^{23} = 1.4307$). If dimethylformamide is the reaction medium the yield is 60 % [47].

Good yields and particularly high degrees of purity have been achieved also in the alkylation of tertiary heterocyclic amines in tetramethylurea [48]; in this case, too, the high dissolving power of the latter proved to be beneficial. The preparation of mono- and difunctional phosphonium salts from tertiary phosphines can also be advantageously carried out in tetramethylurea [12].

The behavior of tetramethylurea toward carbonyl halides leads to the conclusion that tetramethylurea/carbonyl chloride mixtures are suitable as acylation media. This has been demonstrated in the case of alcohols, phenols, and amines. By following these acylations conductometrically, a high degree of conversion has been demonstrated [12]. Kinetic data indicate that tetramethylurea participates in the reaction by combining with the hydrogen chloride formed.

Pentachlorophenyl acetate, m.p. 150–151 °C, is produced in 83 % yield by adding a mixture of 1 g of acetyl chloride and 10 ml of tetramethylurea to 2.66 g of pentachlorophenol in 15 ml of tetramethylurea, heating the mixture for 30 min at 100 °C, and pouring it into ice water.

Tetramethylurea is also a useful medium for accelerating base-catalysed prototropic double bond shifts, for example that promoted by potassium alkoxides in fatty acids with multiple double bonds [49]. The reason for this is that it combines a solvating power for alkali ions with the ability to combine, via hydrogen bridges, with the interfering free alcohol formed in the reaction [32,50].

It was already mentioned at the end of the preceding section that tetramethylurea is a useful medium for direct metalations with free alkali metals by way of radical ions, with alkali amides or alkali hydrides, or with triphenylmethylsodium. Since it is also inert toward Grignard compounds, it can be used, for example, as the

[43] *E. J. Corey* and *M. Chaykovzky*, J. Amer. chem. Soc. *84*, 866 (1962); J. org. Chemistry *28*, 255 (1963); *C. Walling* and *L. Bollykry*, J. Amer. chem. Soc. *84*, 866 (1962).

[44] *N. Kornblum* and *D. L. Kendall*, J. Amer. chem. Soc. *74*, 5782 (1952).

[45] *K. Rutherford* and *W. A. Redmond*, J. org. Chemistry *28*, 568 (1963).

[46] *H. Meerwein, H. Altendörfer, P. Beckmann, F. Kunert, H. Morschel, F. Pawellck*, and *K. Wunderlich*, Angew. Chem. *70*, 211 (1958).

[47] *H. E. Zaugg, D. A. Dunmigan, R. J. Michaelis, L. R. Swett, T. S. Wang, A. H. Sommers*, and *R. W. DeNet*, J. org. Chemistry *26*, 644 (1961).

[48] Communication from Dr. *A. Wenz*, E. Merck AG., Darmstadt (Germany).

[49] *J. Ugelstad, B. Jenssen*, and *P. C. Mörk*, Acta chem. scand. *16*, 323 (1962).

[50] Cf. also *D. J. Cram* et al., J. Amer. chem. Soc. *81*, 5774 (1959); *83*, 3688 (1961).

solvent in determinations of active hydrogen by the Zerewitinoff method. The advantage of tetramethylurea over anisole and amyl ether is its better dissolving power, and over pyridine is its lower vapor pressure. However, direct preparation of Grignard reagents in tetramethylurea is not possible.

Since it boils within the required range, tetramethylurea can also be used as diluent in the Ullmann synthesis of biaryls from aryl halides. Since its boiling point is 23 °C higher than that of dimethylformamide, which is normally used [44], its use is recommended when higher reaction temperatures are needed.

## V. Methods of Preparation

The classical preparation of tetramethylurea from dimethylamine and phosgene [13] proceeds via *N,N*-dimethylcarbamyl chloride *(16)*, which is readily isolable.

$$2\,(CH_3)_2NH + COCl_2 \rightarrow (CH_3)_2NH_2^{\oplus}Cl^{\ominus} + (CH_3)_2N{-}COCl \quad (16)$$

$$(16) + 2(CH_3)_2NH \rightarrow (CH_3)_2NH_2^{\oplus}Cl^{\ominus} + (1)$$

For large-scale preparative purposes, this process has several disadvantages. The considerable heat of reaction is difficult to control in practice. Moreover, since tetramethylurea is miscible with water in all proportions, it is difficult to separate it completely from the salts formed in the process. If this procedure is nevertheless to be used, it is advantageous to isolate the dimethylcarbamyl chloride (b.p. 164–165 °C) first.

The troublesome formation of dimethylammonium chloride is readily circumvented by treating phosgene with trimethylamine [51, 52]:

$$(CH_3)_3N + COCl_2 \rightarrow [(CH_3)_3N{-}COCl]^{\oplus}Cl^{\ominus} \rightarrow CH_3Cl + (16)$$

The primary adduct is readily cleaved into methyl chloride and *(16)*; only a small amount of tetramethylammonium chloride is formed. Trimethylamine can also be used in the second step to produce tetramethylurea and methyl chloride [52]; however, the reaction of trimethylamine with *(16)* is slower than that of phosgene. In contrast, the reaction of *(16)* with dimethylamine is too vigorous. However, 40 % aqueous dimethylamine may be used and the formation of $(CH_3)_2NH_2Cl$ prevented by addition of NaOH. This procedure simultaneously permits complete utilization of the dimethylamine [11].

A 500-ml, four-neck flask equipped with a stirrer and two dropping funnels is charged with 135 g (1.17 moles) of 40 % aqueous dimethylamine, and 107 g (1 mole) of dimethylcarbamyl chloride are added dropwise, with external cooling with a freezing mixture to keep the temperature below −10 °C. After the first 20 ml of the chloride have been added, the addition of 100 ml of 40 % sodium hydroxide is started and is so controlled that the two dropping funnels are emptied at about the same rate. Then, 60 g of sodium hydroxide are added resulting in the formation of two layers. The upper layer is separated and freed from residual salts by vacuum distillation. The lower layer contains about 10–15 % tetramethylurea and is extracted three times with benzene; the benzene extracts are combined with the distillate. The benzene is distilled off, the residual dimethylamine and water being removed azeotropically by this process, and the residue is rectified at 10–20 mm through a short column. The yield, based on acid chloride, lies between 78 and 85 %.

Some potential preparative methods, such as the transamination of urea or the dehydration of dimethylammonium dimethylcarbamate, fail in practice. The oxidative desulfurization of tetramethylthiourea is a possible [53], but probably uneconomical process. The same is true for other methods of preparation [54]. Oxidation of bis(dimethylamino)methane, which is readily prepared from dimethylamine and formaldehyde, with common oxidizing agents to give tetramethylurea shows little promise [12]; catalytic oxidation with air might be better.

Aminolysis of aromatic carbonates such as di-*o*-cresyl carbonate was found to be particularly useful. This reaction is best carried out with diphenyl carbonate, which is used by Farbenfabriken Bayer for the commercial synthesis of Makrolon by the Schnell process [55].

$$(C_6H_5O)_2CO + HN(CH_3)_2 \rightarrow C_6H_5OH + C_6H_5O{-}CO{-}N(CH_3)_2 \quad (17)$$

$$(17) + HN(CH_3)_2 \rightarrow C_6H_5OH + (CH_3)_2N{-}CO{-}N(CH_3)_2$$

The conversion is satisfactory at 200 °C, and the residual urethane *(17)*, which does not react quantitatively, can be reused in the next batch. The phenol formed must be removed in the form of the phenoxide, since it forms a high-boiling azeotrope with tetramethylurea (43 mole-% tetramethylurea [12]).

Gaseous dimethylamine is introduced into 2140 g (10 moles) of diphenyl carbonate (cooled externally with water) until the increase in weight is 1150 g (25 moles). The mixture is then heated for 4 hours at 200 °C in an autoclave (about 20 atm). After cooling, 7 l of 5 N sodium hydroxide are added, and the mixture is extracted with ether for at least 24 hours. The residue is rectified through a short column and the fraction boiling between 60 and 66 °C at 13 mm collected. Yield: 850 g of tetramethylurea. Further distillation of the residue affords 345 g of the urethane, which can be reused [12]

Pure tetramethylurea is obtained by distilling it through a long column. After this distillation, the material is dry and does not react with calcium hydride and should thus be stored over the latter. Amine-free tetramethylurea is obtained if the material is first subjected to azeotropic distillation with benzene/water [12]; it then gives only a weak pink color with trinitrotoluene (see p. 263).

In conclusion, we wish to stress that, in its dissolving power and general miscibility, *tetramethylurea* is closest to *pyridine*. It has the advantage over the latter that it is not accompanied by homologues, a frequent nuisance in the case of pyridine; moreover, it has a more con-

[51] *V. A. Rudenko, A. Y. Yakubovich,* and *T. Y. Nikiforawa,* Zh. Obschei Khimii *17*, 2256 (1947); Chem. Abstr. *42*, 4918 (1948).

[52] German Pat. 888689 (1951), Farbenfabriken Bayer, inventors: *E. Stein* and *O. Bayer.*

[53] *H. Lecher* and *K. Gubernator,* J. Amer. chem. Soc. *75*, 1087 (1953).

[54] *H. Lecher, F. Graf,* and *C. Hensk,* Liebigs Ann. Chem. *438*, 165, 184 (1924).

[55] *H. Schnell,* Angew. Chem. *68*, 633 (1956).

venient boiling point and can be made practically anhydrous by simple distillation. Another important advantage over pyridine is its weak and pleasant odor and its low toxicity; the intravenous $LD_{50}$ was found to be 1.1 g/kg in rats [56]. It would be gratifying if tetramethylurea were available commercially [57].

*We wish to thank Dr. A. Wenz, Director of E. Merck AG., Darmstadt, for organizing the production of several kilograms of tetramethylurea, Prof. Dr. O. Hotovy †, E. Merck AG., Darmstadt, for the toxicological testing, Prof. Dr. O. Westphal, Director of the Max-Planck-Institut für Immunbiologie, Freiburg/Breisgau, for the paper-chromatographic studies, Dr. H. Schnell, Director of the Bayerwerk Uerdingen, for furnishing diphenyl carbonate, Dr. A. Reichle, Dr. A. Prietzschk, Bayerwerk Dormagen, and Dr. H. Weigand, Rhodiaceta AG., Freiburg/Breisgau, for solubility determinations on several macromoleculars substance. We are indebted to the "Fonds der Chemie" for supporting our Institute.*

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German version: Angew. Chem. *75*, 1059 (1963)

[56] Determined by Prof. Dr. *O. Hotovy* †, E. Merck AG., Darmstadt (Germany).

[57] Produced by Grand River Chem. Division of John Deere and Co., Grand River, Oklahoma (U.S.A.); cf. [45].

# The Peroxyester Reaction

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*The reactions of t-butyl peroxyesters with various classes of compounds in the presence of a catalytic amount of copper ions produce well-defined acyloxy derivatives. This peroxyester reaction, discovered by Kharasch and Sosnovsky, can be used to effect one-step oxidation of saturated and unsaturated hydrocarbons, alcohols, aldehydes, esters, ethers, sulfides, organosilicon compounds, etc. The reaction can be highly selective: in most cases only one specific carbon atom is attacked. However, with some ethers and sulfides the reaction can take a more complex course, other products being formed in addition to the acyloxy derivatives. The mechanism of the reaction has been extensively investigated, and several concerted and chain mechanisms have been proposed.*

## Introduction

In 1956, *Kharasch* and *Sosnovsky* [1] investigated the autooxidation of nitriles catalyzed by metal ions. As an outgrowth of this work, they then studied [2] the reaction of nitriles with t-butyl hydroperoxide and found that the reaction of phenylacetonitrile with t-butyl hydroperoxide in the presence of cobalt or copper ions produces a mixture consisting mainly of oxygen, t-butyl alcohol, hydrogen cyanide, benzoic acid, t-butyl benzoate, and t-butyl peroxybenzoate. The formation of the last three products was interpreted to proceed by reaction of benzoyl cyanide with water, t-butyl alcohol, and t-butyl hydroperoxide.

Another explanation for the formation of t-butyl benzoate, advanced by Sosnovsky [3], is that t-butyl peroxybenzoate is converted into the benzoate by the metal salt catalyst. To test this hypothesis, t-butyl peroxybenzoate was decomposed in boiling benzene in the presence of cuprous bromide. Instead of the t-butyl benzoate expected, methyl benzoate was actually obtained. The formation of this product was later explained by the following chain mechanism [4]:

$$H_5C_6{-}CO{-}O{-}OC(CH_3)_3 + Cu^+ \rightarrow H_5C_6{-}CO{-}OCu^{+(II)} + {\cdot}OC(CH_3)_3$$

$${\cdot}OC(CH_3)_3 \rightarrow {\cdot}CH_3 + H_3C{-}CO{-}CH_3$$

$$H_5C_6{-}CO{-}O{-}OC(CH_3)_3 + {\cdot}CH_3 \rightarrow H_5C_6{-}CO{-}OCH_3 + {\cdot}OC(CH_3)_3$$

Scheme 1. Formation of methyl benzoate from t-butyl peroxybenzoate by a chain reaction.

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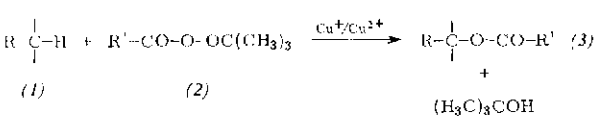
[1] *M. S. Kharasch* and *G. Sosnovsky*, Tetrahedron *3*, 97 (1958).

[2] *M. S. Kharasch* and *G. Sosnovsky*, Tetrahedron *3*, 105 (1958).

[3] *G. Sosnovsky*, unpublished (1957).

[4] *M. S. Kharasch, G. Sosnovsky*, and *N. C. Yang*, J. Amer. chem. Soc. *81*, 5819 (1959).

These results initiated a series of studies of the decomposition of t-butyl peroxyesters in various substrates [5, 6]. It was found that compounds of the general formula *(1)* react with t-butyl peroxyesters *(2)* in the presence of a catalytic amount of copper ions to give acyloxy derivatives *(3)*.



*(1)*: H = primary, secondary, or tertiary
R = cyclic, acyclic, aromatic, or hetero group
*(2)*: R' = $CH_3$ or $C_6H_5$

The peroxyester reaction can be highly selective: in most cases only one specific carbon atom is oxidized.

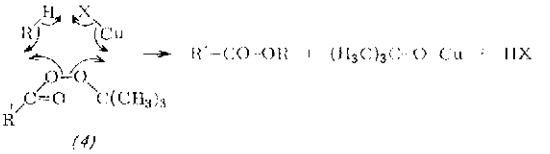
Although the metal-catalysed reaction of t-butyl hydroperoxide or α-cumyl hydroperoxide [2, 7, 8] can also be used for selective oxidation of carbon atoms, the peroxyester reaction is more selective, more versatile, and has greater preparative utility. The products of the peroxyester reaction – esters – can be more readily converted into various derivatives than the products of the hydroperoxide reaction – unsymmetrical peroxides. However, the hydroperoxide reaction supplements the peroxyester reaction because it can still be used where the peroxyester reaction fails. For example, diphenylacetonitrile [9] and cyclohexanone [10] undergo no reaction with peroxyesters, but both react [2, 7, 8] with t-butyl or α-cumyl hydroperoxide to yield unsymmetrical peroxides.

## Mechanisms

In the absence of a catalyst, the thermal decomposition of t-butyl peroxyesters in various substrates usually proceeds with multiple-bond cleavage, resulting in a complex mixture of products [4, 11]. In the presence of a copper salt catalyst, however, the reaction is more selective and proceeds at a faster rate.

For example, uncatalysed thermal decomposition of a peroxyester in a terminal olefin usually produces ill-defined products plus a large quantity of gases, but the reaction catalysed by copper salts yields mainly 3-acyloxy derivatives with little or no primary allylic esters [4, 5] and little or no gas is evolved. Similarly, the catalysed reaction of peroxyesters with cyclic olefins [4, 5], aralkanes [4, 7], aldehydes [10], and benzylic esters [10], sulfides [12–14], etc. proceeds at a faster rate and often yields products entirely different from those obtained in the conventional uncatalysed free-radical reaction.

These results were previously considered [4–6] as evidence against the occurrence of free radicals or carbonium ions as intermediates. The displacement of hydrogens by the acyloxy radical was postulated by *Kharasch, Sosnovsky,* and *Yang* [6, 10] to occur by a concerted mechanism involving the transition state *(4)*.



*(4)*

At a later stage of their studies [4], these authors favored a chain mechanism involving concerted steps (Scheme 2).

$$H_5C_6{-}CO{-}O{-}OC(CH_3)_3 + Cu^+ \rightarrow H_5C_6{-}CO{-}OCu^{+}(II) + {\cdot}OC(CH_3)_3$$

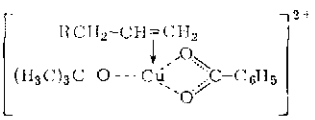
$${\cdot}OC(CH_3)_3 + RH \rightarrow (H_3C)_3COH + R{\cdot}$$

$$R{\cdot} + H_5C_6{-}CO{-}OCu^{+}(II) \rightarrow H_5C_6{-}CO{-}OR + Cu^+$$

Scheme 2. Chain mechanism for the replacement of hydrogen by acyloxy groups.

*Denney* and coworkers [15] showed that t-butyl [*carbonyl*-$^{18}$O]peroxybenzoate reacts with cyclohexene to give a cyclohexenyl benzoate in which the two oxygen atoms are completely equilibrated. Hence any mechanism which does not permit such an equilibration, such as that via *(4)*, must be excluded. Furthermore, the reaction of t-butyl peroxyester with 3-deuterio-3-phenylpropene showed an isotope effect ($K_H/K_D$) of 4.3 [15]. This value is larger than would be predicted ($K_H/K_D < 2.67$) for a simple hydrogen abstraction from allylbenzene by the t-butoxy radical [15, 15a].

*Denney, Denney,* and *Feig* [15] therefore proposed a mechanism involving a complex between the copper ion and the t-butoxy and acyloxy radicals, which, in turn, coordinates with an olefin to give a π-complex *(5)*.



*(5)*

One of the hydrogen atoms α to the double bond is abstracted by the t-butoxy radical; the acyloxy radical then enters at this position. Complex *(5)* accounts for the isotope effect, since a complexed t-butoxy radical is less reactive than a free t-butoxy radical. In addition, it is harder to abstract a hydrogen from a complexed olefin than from an uncomplexed olefin. This mechanism also explains the equilibration of $^{18}O$ and the lack of $CO_2$ evolution. However, this mechanism does not explain the reaction of peroxyesters with substrates which do not form π-complexes with copper ions.

*Berglund* and *Lawesson* [14] studied the reaction of t-butyl peroxybenzoate with 1,4-dioxane in the presence of $CuCl_2$ and found complex bonded $Cu^{++}$ ion (identified by electron spin resonance) during the reaction and a trace of $Cu^{++}$ ion

[5] *M. S. Kharasch* and *G. Sosnovsky*, J. Amer. chem. Soc. *80*, 756 (1958).

[6] *M. S. Kharasch* and *G. Sosnovsky*, Abstract of Papers, 134th Meeting Amer. chem. Soc., Chicago, Sept. 1958, p. 7P.

[7] *M. S. Kharasch* and *A. Fono*, J. org. Chemistry *23*, 324 (1958).

[8] *M. S. Kharasch* and *A. Fono*, J. org. Chemistry *24*, 72 (1959).

[9] *G. Sosnovsky*, unpublished results (1958).

[10] *G. Sosnovsky* and *N. C. Yang*, J. org. Chemistry *25*, 899 (1960).

[11] *P. D. Bartlett* and *R. R. Hiatt*, J. Amer. chem. Soc. *80*, 1398 (1958).

[12] *G. Sosnovsky*, J. org. Chemistry *26*, 281 (1961).

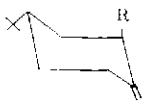
[13] *G. Sosnovsky*, Tetrahedron *18*, 15 (1962).

[14] *C. Berglund* and *S.-O. Lawesson*, Ark. Kemi *20*, 225 (1963).

[15] *D. B. Denney, D. Z. Denney*, and *G. Feig*, Tetrahedron Letters, *15*, 19 (1959).

[15a] *K. B. Wiberg* and *L. H. Slaugh*, J. Amer. chem. Soc. *80*, 3033 (1958).

at the end of the reaction. When CuCl was used as catalyst, they found no $Cu^{++}$ at the end of the reaction. They concluded that valence changes occur that cast doubt upon the validity of the $\pi$-complex mechanism *(5)*. A stereochemical study by *Cross* and *Whitham* [16] of the reaction of t-butyl peroxybenzoate with 1-methylene-4-t-butylcyclohexane *(6)* in the presence of CuCl showed that primarily the axial benzoyloxy isomer *(7)* was formed. Although this result can be explained by a free radical mechanism, a mechanism involving a complex explains it better.

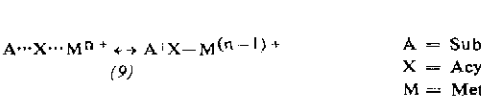


*(6)*: R = H
*(7)*: R = $-O-CO-C_6H_5$
*(8)*: R = OH

The mechanism of metal ion catalysed reactions of peroxides has been thoroughly investigated by *Kochi* [17, 18]. The mechanism he proposed contains essentially the same steps as those shown in Scheme 2.

His mechanism also involves a catalyst capable of undergoing rapid redox reactions. In both mechanisms, the first step is reduction of the peroxyester by a cuprous ion, the second is abstraction of the hydrogen atom of a substrate by the alkoxy radical, and the third is oxidation of the substrate radical to the acyloxy derivative with regeneration of $Cu^{+}$. The difference between the two mechanisms is small; *Kochi* believes that the radicals formed are free and that the $Cu^{++}$ is in the form of a true salt, whereas *Kharasch*, *Sosnovsky*, and *Yang* believe that at least some of the radicals form a complex with the metal ion catalyst.

*Kochi*'s hypothesis is based mainly on the reactions of peroxyesters with 1-butene, *cis*- and *trans*-2-butene, or 1-pentene; each reaction produces a mixture consisting of 84–94 % 3-acyloxy derivative and 6–15 % 1-acyloxy derivative in good yield. To explain the effect of the catalytic amount of copper salt, *Kochi* elaborated the last step in his scheme. He proposed that the redox reaction between the substrate radical and the cupric salt proceeds via a resonance hybrid *(9)* which involves contributions from electron-transfer and ligand-transfer processes.

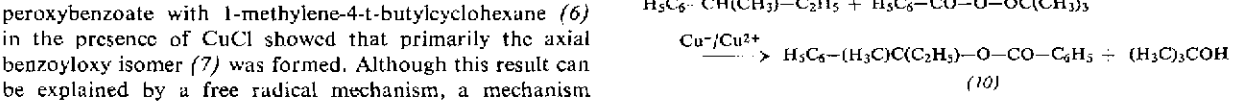


*(9)*

A = Substrate radical
X = Acyloxy radical
M = Metal

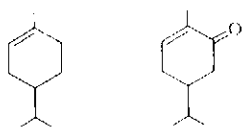
The ligand-transfer and electron-transfer processes are supposed to be extremely rapid; this then precludes the occurrence of the usual chain transfer processes of free radical reactions and confers great selectivity on the peroxyester reaction.

*Hallgarten*, *Wang*, and *Yang* [19, 20] studied the stereochemistry of the rection of t-butyl peroxybenzoate with optically active 2-phenylbutane. Reduction of the reaction product *(10)* with lithium aluminum hydride yielded inactive 2-phenylbutan-2-ol, indicating the occurrence of conventional free radical intermediates during the formation of *(10)*.



*(10)*

A similar conclusion can be made from the result obtained by *Denney* et al. [21] in the reaction of t-butyl peroxyacetate with optically active $\Delta^1$-*p*-menthene *(11)*. In the presence of a copper salt the reaction gave a mixture of acetates, which on hydrolysis and subsequent oxidation yielded the optically inactive ketone *(12)*.

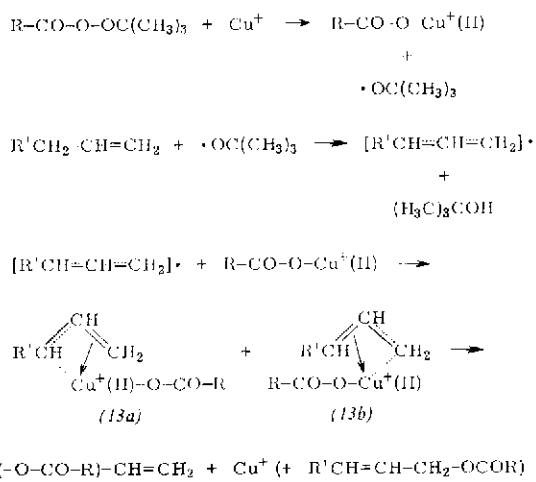


*(11)* *(12)*

*Barnard* and *Yang* [22] found that the rate of the reaction of cyclohexene with t-butyl peroxybenzoate in the presence of cupric ions is of the first order with respect to both peroxyester and olefin. The rate of decomposition of the peroxyester increases with increasing concentration of copper ions at low copper ion concentrations. The rate of the catalysed reaction is several hundred times that of the uncatalysed reaction. These results indicate that the first step of the reaction is reversible or proceeds through a complex. Thus, although free radical species are actually involved in the peroxyester reaction with olefins, a normal free-radical mechanism cannot explain the abnormally high isomer ratio in favor of the allylic ester (see above).

With this consideration in mind, *Yang* and coworkers [19, 20] proposed the mechanism outlined in Scheme 3.

A similar mechanism was considered by *Sosnovsky* in 1958 but was not published because experimental evidence was insufficient at the time.



Scheme 3. Copper-catalysed reaction of olefins with peroxyesters according to *Yang*, *Wang*, and *Hallgarten* [19, 20].

[16] *B. Cross* and *G. H. Whitham*, J. chem. Soc. (London) *1961*, 1650.

[17] *J. K. Kochi*, Tetrahedron *18*, 483 (1962).

[18] *J. K. Kochi*, J. Amer. chem. Soc. *84*, 774 (1962).

[19] *P. A. Hallgarten*, *T. I. Wang*, and *N. C. Yang*, personal communication, 1963.

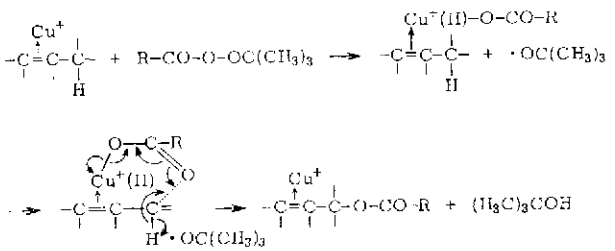
[20] *T. I. Wang*, Roles of Metal Salts in Free Radical Reactions, Ph. D. Thesis, University of Chicago, 1962.

[21] *D. Z. Denney*, *A. Appelbaum*, and *D. B. Denney*, J. Amer. chem. Soc. *84*, 4969 (1962).

[22] *P. W. C. Barnard* and *N. C. Yang*, Chem. and Ind. *39*, 1573 (1961).

The first two steps are essentially the same as those of Scheme 2. In the last step, the allylic radical reacts with copper ions to form complex *(13)*. Of the two possible forms *(13a)* and *(13b)* of this intermediate, the one with the double bond in the terminal position *(13a)* ought to be more stable, since copper ions form stronger complexes with less substituted olefins [23]. The complex then collapses to form the product, with regeneration of the cuprous ion.

*Beckwith* and *Evans* [24] expressed the belief that no single mechanism can explain all peroxyester reactions. Under experimental conditions which do not favor formation of a copper ion/olefin complex, *e.g.* high dilution of the olefin or high temperatures, the reaction probably proceeds through an oxidation-reduction sequence to yield rearranged products. However, copper-catalysed reactions of peroxyesters with high concentrations of olefins probably do involve complexes as transition states. On the basis of the products obtained, *Beckwith* and *Evans* therefore proposed the mechanism shown in Scheme 4.



Scheme 4. Mechanism proposed by *Beckwith* and *Evans* for the peroxyester reaction.

Although cupric ion/olefin complexes have not been isolated, there are indications that such complexes exist [24]. Copper(I) forms π-complexes with olefins. Similar mechanisms involving complexes between copper ions and oxygen or sulfur atoms can be written to account for the products of the reactions of peroxyesters with ethers and sulfides.

In summary, it appears that no single mechanism can account for all results of the peroxyester reaction. It is not unreasonable to assume that various mechanisms are operative, depending on the nature of the substrate and on the experimental conditions [*].

[23] *F. Basolo* and *R. G. Pearson*, Mechanism of Inorganic Reactions, Wiley, New York 1958, p. 352.

[24] *A. L. J. Beckwith* and *G. W. Evans*, Proc. chem. Soc. (London) *1962*, 63.

[*] In this connection two papers [24a, b] are of interest which appeared after this paper was submitted. *Walling* and *Zavitsas* [24a] conducted experiments to test the mechanism of the peroxyester reaction similar to that proposed by *Kochi*. 1-n-Pentene, 2-n-pentene, 1-n-hexene, 1-n-octene, cyclohexene, 1,5-cyclooctadiene, cumene, allylbenzene, and β-methylstyrene were converted with t-butyl peroxyacetate into the corresponding acetates. It was found that the distribution of allylic acetates is in good agreement with *Kochi*'s results. *Walling* and *Zavitsas* favor an electron transfer process with a "free" carbonium ion rather than a ligand transfer process. In another communication [24b] *Sosnovsky* reported the photochemical reactions of peroxyesters in the presence of copper ions. Thus, ethyl ether, dioxan, tetrahydrofuran, dimethylformamide and cyclohexene were converted with peroxyesters at 35 °C to the corresponding acyloxy derivatives. From a preparative viewpoint the photochemical reaction has an advantage over the thermal peroxyester reaction in those cases where thermally unstable acyloxy derivatives are produced. The reactions catalyzed by light only, or copper ions only, proceeded at a much slower rate than the reactions catalyzed by both light and copper ions. The combined effect of light and copper ions on the decomposition of peroxyesters suggests the following interpretation: The first step in the peroxyester reaction is the formation of a complex between the peroxyester and the copper ion. Since less energy is required to dissociate the O-O bond of the complexed peroxyester than that of the uncomplexed peroxyester, the copper-ion catalysed reactions proceed at a faster rate.

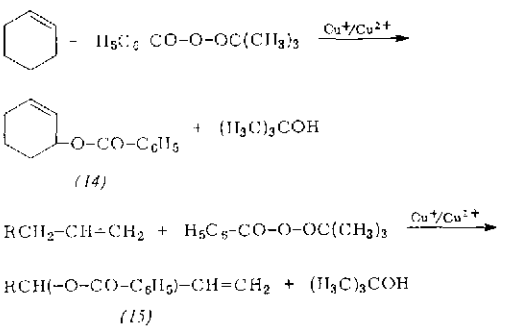
[24a] *C. Walling* and *A. Zavitsas*, J. Amer. chem. Soc. *85*, 2084 (1963).

[24b] *G. Sosnovsky*, J. org. Chemistry *28*, 2934 (1963).

## III. Reactions of Peroxyesters with Various Classes of Compounds

### 1. Olefinic Hydrocarbons

Generally, radical reactions of peroxides with olefins result in complex mixtures of products [11], thus rendering the reactions of no preparative value. *Kharasch* and *Sosnovsky* [5,6] found that the reaction of peroxyesters with cyclic and terminal olefins containing allylic hydrogen atoms is modified by a trace of copper ions to give well-defined products with little or no isomerization of the original olefin. For example cyclohexene, 1-hexene, and 1-octene each react with t-butyl peroxybenzoate to give predominantly the corresponding α-acyloxy derivative [*(14)* and *(15)*].



Later other olefins were converted into their acyloxy derivatives in this way [4]. However, the derivatives obtained from 2-octene, 2,4,4-trimethyl-1-pentene, 1-acetoxy-1-cyclohexene, 4-vinylcyclohexene, and α-pinene were not completely characterized.

Since only t-butyl peroxyacetate and t-butyl peroxybenzoate are commercially available, the type of esters which can be readily prepared is limited. However, the scope of the reaction can be increased by adding an excess of an aliphatic acid to the reaction mixture; the allylic ester of this acid is then obtained [4]. For example, the reaction of cyclohexene with t-butyl peroxybenzoate in excess propionic acid yielded 1-cyclohexenyl propionate instead of the benzoate.

The selectivity of the peroxyester reaction observed by *Kharasch* et al. with 1-octene [4–6], cyclohexene [4–6], and allylbenzene [10] was partly confirmed by *Denney* et al. [15] with cyclohexene and allylbenzene, and by *Beckwith* and *Evans* [24] with 1-octene and allylbenzene. However, *Beckwith* and *Evans* found that, in the presence of a solvent, t-butyl peroxybenzoate reacted with allylbenzene to give a small amount of cinnamyl benzoate in addition to the 3-acyloxy derivative.

The stereospecificity of the peroxyester reaction was investigated by *Cross* and *Whitham* [16] using 1-methylene-4-t-butylcyclohexane *(6)*, a cyclic olefin containing a terminal double bond. The reaction of *(6)* with t-butyl peroxybenzoate yielded a benzoyloxy derivative which was hydrolysed to give mainly 2-methylene-*trans*-5-t-butylcyclohexanol *(8)* with an axial hydroxyl group plus only a trace of the corresponding *cis*-isomer, thus confirming the stereospecificity of the reaction.

Working with 1-butene and 1-pentene in solvents, *Kochi* [18] found that exclusive formation of the 3-acyloxy derivative without isomerization is not a general phenomenon of the peroxyester reaction, since he always obtained a small amount of the 1-acyloxy isomer. Furthermore, he found that aliphatic olefins containing an internal double bond and no secondary α-hydrogen atoms undergo the peroxyester reaction with isomerization, yielding predominantly 3-acyloxy derivatives with a terminal double bond. For example, the reaction of 2-butene with either t-butyl peroxyacetate or peroxybenzoate produces a mixture of 84–94 % 3-acyloxy-1-butene *(16)* and 6–15 % crotyl ester *(17)* in high yield.

$$H_3C{-}CH{=}CH{-}CH_3 + R{-}CO{-}O{-}OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}}$$

$$H_3C{-}CH(O{-}CO{-}R){-}CH{=}CH_2 \quad (16)$$

$$+ H_3C{-}CH{=}CH{-}CH_2{-}O{-}CO{-}R + (H_3C)_3COH \quad (17)$$

$R = CH_3, C_6H_5$

A similar rearrangement was observed by *Denney* and coworkers [21] with higher substituted internal olefins. Thus, trimethylethylene and tetramethylethylene each reacted with t-butyl peroxybenzoate to give mainly the benzoyloxy derivative of the rearranged olefin, *viz.* 2-methyl-1-buten-3-yl benzoate *(18)*, and 2,3-dimethyl-3-benzoyloxy-1-butene *(19)*, respectively.

$$H_3C{-}C(CH_3){=}CH{-}CH_3 + H_5C_6{-}CO{-}O{-}OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}}$$

$$H_2C{=}C(CH_3){-}CH(CH_3){-}O{-}CO{-}C_6H_5 \text{ (and isomers)} + (H_3C)_3COH$$

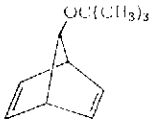
*(18)*

$$(H_3C)_2C{=}C(CH_3)_2 + H_5C_6{-}CO{-}O{-}OC(CH_3)_3$$

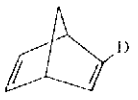
$$\xrightarrow{Cu^+/Cu^{2+}} H_2C{=}C(CH_3){-}C(CH_3)_2{-}O{-}CO{-}C_6H_5 \quad (19)$$

The following conclusions can be drawn from these results: The reaction of peroxyesters with cyclic and terminal olefins containing secondary hydrogen atoms in the α-position relative to the double bond yields products with the acyloxy group located either predominantly or exclusively in this position. The reaction of peroxyesters with aliphatic olefins containing internal double bonds with no secondary α-hydrogen atoms, *e.g.* 2-butene, trimethylethylene, and tetramethyl ethylene yields predominantly or exclusively an acyloxy derivative of the rearranged olefin with a terminal double bond.

An interesting deviation from the general pattern of the peroxyester reaction was observed by *Story* [25–27] with norbornadiene. Instead of the expected benzoate, 7-t-butoxynorbornadiene *(20)* was isolated in 26 % yield.




*(20)*




*(21)*

*Story* [25, 26] first proposed a mechanism involving abstraction of a hydrogen atom from C-7 to form a 7-norbornadienyl radical. However, his recent study [27] with [2-D]norbornadiene *(21)* ruled out such a hydrogen abstraction; the reaction of *(21)* with t-butyl peroxybenzoate in the presence of $CuBr_2$ yielded 7-t-butoxynorbornadiene with deuterium at all skeletal positions in approximately statistical distribution. This indicates attack of the t-butoxy radical at all four olefinic carbons, followed by rearrangement of the norbornadiene skeleton. The possible formation of t-butoxy benzoates which eliminate benzoic acid to form the t-butyl ether is unlikely because the yield of the product did not increase with reaction time.

### 2. Non-Olefinic Hydrocarbons

Only hydrocarbons with benzylic hydrogens have been used as substrates. Cumene [7] and optically active 2-phenylbutane [19, 20] each react with t-butyl peroxybenzoate to yield 2-phenyl-2-benzoyloxypropane and inactive 2-phenyl-2-benzoyloxybutane, respectively. 2-Phenyl-2-acetoxypropane (b.p. 93 °C/10 mm, $n_D^{20}$ = 1.4950) was isolated in 36 % yield from the reaction between cumene and t-butyl peroxyacetate [28] [*]. No reaction occurred with triphenylmethane [4] and t-butyl peroxybenzoate. The corresponding reaction of diphenylmethane [14] yielded 1,1,2,2-tetraphenylethane instead of an acyloxy derivative. Tetralin [10] reacts with t-butyl peroxybenzoate to yield 1-benzoyloxytetralin.

### 3. Organosilicon Compounds

Only the following reactions of organosilicon compounds have been investigated [29–31]: in the presence of cuprous bromide, 3-trimethylsilyl-1-propene reacts with t-butyl peroxybenzoate to give the acyloxy derivative *(22)*, 3-trimethylsiloxy-1-propene reacts with t-butyl peroxybenzoate to give the 3-acyloxy derivative *(23a)*, and 1-trimethylsiloxypropane reacts with t-butyl peroxyacetate to give the 1-acyloxy derivative *(23b)*.

$$(H_3C)_3Si{-}CH(-O{-}CO{-}C_6H_5){-}CH{=}CH_2 \quad (22)$$

$$(H_3C)_3Si{-}O{-}CHR{-}O{-}CO{-}R' \quad (23a),\ R = HC{=}CH_2,\ R' = C_6H_5$$

$$(23b),\ R = C_2H_5,\ R' = CH_3$$

[25] *P. R. Story*, J. Amer. chem. Soc. *82*, 2085 (1960).
[26] *P. R. Story*, J. org. Chemistry *26*, 287 (1961).
[27] *P. R. Story*, Tetrahedron Letters *9*, 401 (1962).
[28] *G. Sosnovsky*, unpublished results (1959–1962).
[*] Note added in proof: this compound has recently also been described by *Walling* and *Zavitsas* [24a].
[29] *G. Sosnovsky* and *H. J. O'Neill*, C. R. hebd. Séances Acad. Sci. *254*, 704 (1962).
[30] U.S. Pat. 3047603 (1962), inventor: *G. Sosnovsky*.
[31] *G. Sosnovsky* and *H. J. O'Neill*, Chem. Engng. News *39*, No. 50, 48 (1961).

## 4. Alcohols

The uncatalyzed reaction of alcohols with t-butoxy radicals yields 1,2-dihydroxy derivatives by dimerization [32–34]; with acyloxy radicals, carbonyl compounds are obtained [35]. t-Butyl peroxybenzoate decomposes slowly in alcohols in the absence of CuCl. Thus, benzyl alcohol yields benzaldehyde and benzoic acid [10, 36] either by fragmentation of the hemiacylal *(24)* or by disproportionation of the benzyl alcohol radical *(25)*.

$$H_5C_6-CHOH-O-CO-C_6H_5 \rightarrow H_5C_6-CHO + H_5C_6-COOH \quad (24)$$

$$2\ H_5C_6-\dot{C}HOH \rightarrow H_5C_6-CHO + H_5C_6-CH_2OH \quad (25)$$

In the presence of CuCl, t-butyl peroxybenzoate decomposes rapidly in primary and secondary alcohols. With n-butyl or benzyl alcohol as substrates, the products are n-butyraldehyde and its di-n-butylacetal, or benzaldehyde and its dibenzylacetal [36]. Secondary alcohols such as s-butanol [36] and α-phenethyl alcohol [36] react with t-butyl peroxybenzoate to give the corresponding ketones but no ketals. The decomposition of t-butyl peroxybenzoate in t-butanol [36] is very slow and only a small amount of methyl benzoate is obtained.

## 5. Aldehydes

By heating t-butyl peroxide and benzaldehyde together in the absence of a catalyst, a high yield of 1,2-diphenylethylene dibenzoate *(26)* is obtained [37]. Compound

$$OC(CH_3)_3 + H_5C_6-CHO \rightarrow (H_3C)_3COH + H_5C_6-\dot{C}=O$$

$$H_5C_6-\dot{C}=O + H_5C_6-CHO \rightarrow$$

$$H_5C_6-CO-O-\dot{C}H-C_6H_5 \rightarrow [H_5C_6-CO-O-CH(C_6H_5)-]_2 \quad (26)$$

*(26)* is also obtained from t-butyl peroxybenzoate and benzaldehyde without a catalyst [10]. In the presence of CuBr, the same reagents yield benzoic anhydride as the main product [10].

$$H_5C_6-CHO + H_5C_6-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} (C_6H_5-CO)_2O + (H_3C)_3COH \quad (27)$$

With n-butyraldehyde as substrate, no well-defined products are found; it was assumed that disproportionation of an intermediate mixed anhydride occurred [10].

## 6. Ketones, Nitriles, Thiols, Phenols, and Thiophenols

The reactions of ketones or nitriles with t-butyl peroxyesters do not produce well-defined products. Reaction of methyl ethyl ketone [28], cyclohexanone [10], 2-methylcyclohexanone [10], or diphenylacetonitrile [9] with peroxyesters has not been achieved. The reactions of t-butyl peroxyesters with thiols [34] and thiophenols [10] apparently are not modified by copper salt catalysts, since the only products are disulfides. The oxidation of 2,6-di-t-butylphenol to diphenoquinone by t-butyl peroxyesters is accelerated by copper ions [38].

## 7. Esters

Reactions of aliphatic esters such as methyl propionate [28] with t-butyl peroxybenzoate have not been successful. The reaction proceeds slowly, and a complex mixture of products, including a large volume of gas, is obtained. Diethyl malonate [14] and ethyl acetoacetate [14] react with t-butyl peroxybenzoate to form the t-butoxy derivatives *(28)* and *(29)* in 26 % and 22 % yield, respectively. In addition, a 16 % yield of diethyl benzoyloxymalonate is obtained in the reaction of diethyl malonate.

$$(H_3C)_3CO-CH(CO-OC_2H_5)_2 \quad (28)$$

$$H_3C-CO-CH(CO-OC_2H_5)-OC(CH_3)_3 \quad (29)$$

The reaction of t-butyl peroxybenzoate with ethyl i-propylcyanoacetate in the presence of CuCl produces only a small amount of dimer [39]. Cholesteryl benzoate reacts with t-butyl peroxybenzoate to give an equal quantity of 3β,7α-dibenzoyloxy-$\Delta^5$-cholestene and 3β,7β-dibenzoyloxy-$\Delta^5$-cholestene plus a trace of the rearranged product, 3β,6β-dibenzoyloxy-$\Delta^4$-cholestene [24]. This reaction provides a new route to $\Delta^{5,7}$-cholestadien-3β-ol.

Benzylic esters react smoothly with peroxyesters to give the corresponding acylals [10]. Thus, benzyl acetate reacts with t-butyl peroxybenzoate to give α-acetoxybenzyl benzoate *(30)*. The same product is obtained from

$$H_5C_6-CH_2-O-CO-CH_3 + H_5C_6-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} H_5C_6-CH(O-CO-CH_3)-O-CO-C_6H_5 + (H_3C)_3COH \quad (30)$$

t-butyl peroxyacetate with benzyl benzoate. Correspondingly, benzylidene diacetate [10] can be prepared from benzyl acetate and t-butyl peroxyacetate. Without a copper salt, the reaction takes a typical free-radical course leading to dimers.

## 8. Ethers

### a) Dialkyl and Aryl Alkyl Ethers

Dialkyl ethers react smoothly with t-butyl peroxyesters in the presence of a cuprous salt to give alkyl α-acyloxyalkyl ethers *(31)* [40–43].

$$RCH_2-O-CH_2R + R^1-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} RCH_2-O-CHR-O-CO-R^1 \quad (31)$$

$R^1 = CH_3, C_6H_5$


[32] *W. H. Urry, F. W. Stacey, E. S. Huyser,* and *O. O. Juveland,* J. Amer. chem. Soc. *76,* 450 (1954).

[33] *K. Schwetlick, W. Geyer,* and *H. Hartman,* Angew. Chem. *72,* 779 (1960).

[34] *S.-O. Lawesson* and *C. Berglund,* Acta chem. scand. *15,* 36 (1961).

[35] *H. Gelissen* and *P. H. Hermans,* Ber. dtsch. Chem. Ges. *58,* 765 (1925).

[36] *S.-O. Lawesson* and *C. Berglund,* Ark. Kemi *17,* 485 (1961).

[37] *F. F. Rust, F. H. Seubold,* and *W. E. Vaughan,* J. Amer. chem. Soc. *70,* 3258 (1948).

[38] *J. K. Kochi,* personal communication (1963).

[39] *S.-O. Lawesson* and *C. Frisell,* Ark. Kemi *17,* 409 (1961).

[40] *G. Sosnovsky,* J. org. Chemistry *25,* 874 (1960).

[40a] *S.-O. Lawesson* and *C. Berglund,* Acta chem. scand. *14,* 1854 (1960).

[41] *S.-O. Lawesson, C. Berglund,* and *S. Grönwall,* Acta chem. scand. *15,* 249 (1961).

[42] *G. Sosnovsky,* Tetrahedron *13,* 241 (1961).

[43] *S.-O. Lawesson* and *C. Berglund,* Ark. Kemi *17,* 465 (1961).

With excess alcohol, an acetal *(32)* is obtained from *(31)*, thus providing a convenient way of transforming ethers into aldehydes [43].

$$(31) + R^2OH \rightarrow RCH_2-O-CHR-OR^2 \xrightarrow{R^2OH} RCH(OR^2)_2 \quad (32)$$

The reaction of ethers containing one or two tertiary α-hydrogen atoms with peroxyesters does not yield acyloxy derivatives, however [43]. It was assumed that the tertiary hydrogen atom is infact substituted first, but that the acyloxy group is immediately eliminated as the corresponding acid. When excess alcohol is present, the corresponding ketals are formed [43], *i.e.* the acyloxy group is replaced by an alkoxy group.

Aryl alkyl ethers [41] react smoothly with t-butyl peroxybenzoate in the presence of copper ions to yield aryl α-benzoyloxyalkyl ethers *(33)*. Phenyl isopropyl ether

$$H_5C_6-O-CH_2R + H_5C_6-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} H_5C_6-O-CHR-O-CO-C_6H_5 + (H_3C)_3COH \quad (33)$$

[41] reacts with t-butyl peroxybenzoate, but no benzoate *(33)* is obtained; the course of the reaction is probably the same as that in the case of dialkyl ethers derived from secondary alcohols (see above).

### b) Benzylic Ethers

Benzylic ethers do not undergo dimerization or fragmentation when they react with t-butyl peroxybenzoate in the presence of CuCl; instead, the benzoyloxy group is introduced, giving the acylal *(34)* [14,44].

$$H_5C_6-CH_2-OR + H_5C_6-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} H_5C_6-CH(OR)-O-CO-C_6H_5 \quad (34)$$

$R = CH_3, C_2H_5, CH(CH_3)_2, C(CH_3)_3, C_6H_5$

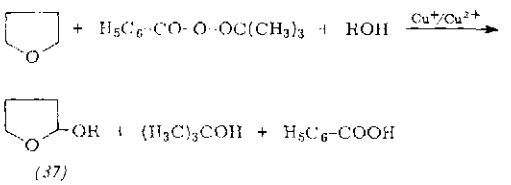
With dibenzyl ether, no acyloxy derivative is isolated, benzaldehyde and its dibenzyl acetal being obtained instead. The first step of this reaction is probably the introduction of the benzoyloxy group into the ether, giving *(35)*. In the following step, t-butanol may react with *(35)* by heterolysis of the alkyl-oxygen bond to give the unsymmetrical acetal *(36a)*, which, by reacetalization, yields the symmetrical acetal *(36b)*.

$$H_5C_6-CH(O-CO-C_6H_5)-O-CH_2-C_6H_5 \quad (35) \xrightarrow{ROH} H_5C_6-CH(OR)-O-CH_2-C_6H_5$$

*(36a)*, $R = C(CH_3)_3$
*(36b)*, $R = CH_2-C_6H_5$

### c) Cyclic Ethers

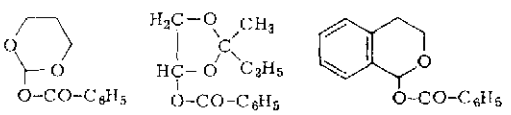
Decomposition of t-butyl peroxyesters in tetrahydrofuran in the presence of cuprous salt gives 2-t-butoxytetrahydrofuran [40,42,45] as the main product. *Sosnovsky* [40,42] postulated that the product formed first is 2-acyloxytetrahydrofuran, which, by thermal elimination of the corresponding acid, yields 2,3-dihydrofuran; addition of t-butanol onto the 2,3-dihydrofuran would then produce 2-t-butoxytetrahydrofuran. *Lawesson* and *Berglund* [40a,45] offered another explanation: the 2-acyloxytetrahydrofuran undergoes alkyl-oxygen heterolysis with t-butanol to give 2-t-butoxytetrahydrofuran directly. They showed that an excess of an alcohol ROH other than the t-butyl alcohol present in the reaction mixture introduced the alkoxy group of this alcohol *(37)*.



*(37)*

Simular results were obtained with t-butyl peroxyesters in tetrahydropyran [40,40a,42,45].

1,4-Dioxan reacts rapidly with t-butyl peroxybenzoate in the presence of a copper salt to give 2-benzoyloxydioxan in good yield [10,14]. Upon prolonged heating, 2-t-butoxydioxan is obtained in poor yield [14,42]. Similarly, 1,4-dioxan reacts with t-butyl peroxyacetate to give 2-acetoxy-1,4-dioxane [28]. The reactions of 1,3-dioxane [14], 2-methyl-2-ethyl-1,3-dioxolan [14], and isochroman [14] with peroxyesters give the products *(38)*, *(39)*, and *(40)* respectively.



*(38)* *(39)* *(40)*

## 9. Sulfides

### a) Straight-Chain Aliphatic and Benzylic Sulfides

Dialkyl sulfides react smoothly with t-butyl peroxyesters in the presence of a copper salt to give α-acyloxyalkyl alkyl sulfides *(41)* [12,13,34,41] without oxidation of the sulfur atom.

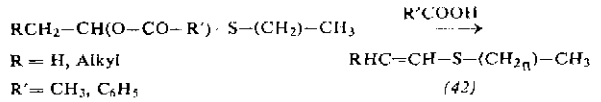
$$RCH_2-S-CH_2R + R'-CO-O-OC(CH_3)_3 \xrightarrow{Cu^+/Cu^{2+}} R-CH(O-CO-R')-S-CH_2R \quad (41)$$

$R' = CH_3, C_6H_5$

In contrast to the α-acyloxy ethers, the α-acyloxy derivatives of straight-chain aliphatic sulfides do not give alkoxy sulfides on heating with an alcohol; instead, mercaptals are isolated [12,46]. For example, the α-acyloxy derivatives of diethyl sulfide, di-n-propyl sulfide, and di-n-butyl sulfide yield acetaldehyde diethylmercaptal, propionaldehyde dipropylmercaptal, and butyraldehyde dibutylmercaptal, respectively. Pyrolysis of the acyloxy derivatives of aliphatic sulfides at temperatures from

[44] *S.-O. Lawesson* and *C. Berglund*, Ark. Kemi *16*, 287 (1960).
[45] *S.-O. Lawesson* and *C. Berglund*, Ark. Kemi *17*, 475 (1961).
[46] *G. Sosnovsky*, Tetrahedron *18*, 903 (1962).

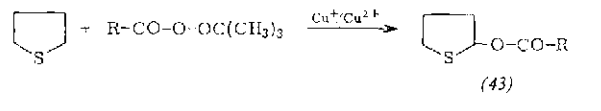
115 to 175 °C produces vinyl sulfides *(42)* and a carboxylic acid [12,41, 47].




*(42)*

b) Cyclic Sulfides

Tetrahydrothiophene [12–14,48] reacts with t-butyl peroxyesters in the presence of a copper salt to give 2-acyloxytetrahydrothiophene *(43)* in good yield. Pyrolysis of *(43)* yields 2,3-dihydrothiophene *(36)* [12,46], which can be isolated if distilled off immediately after its formation; otherwise its dimer *(44)* is obtained [12, 14, 46, 48].

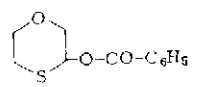



*(43)*




*(44)*

1,4-Thioxan [14] reacts with t-butyl peroxybenzoate in the presence of CuCl to give mainly 3-benzoyloxy-1,4-thioxan *(45)*.

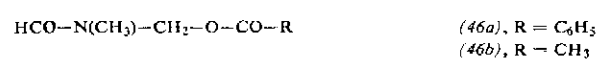



*(45)*

10. Amines and Amides

Attempts [28] to cause peroxyesters to react with aromatic and aliphatic amines have not been successful. The peroxyester decomposes rapidly, with production of the corresponding acid in quantitative yield. However, dimethylaniline undergoes an anomalous reaction which is independent of catalysis to give bis-(*p*-dimethylaminophenyl)methane [10].

Among the amides, only dimethylformamide has been investigated, with CuCl [14] or CuBr [28] as catalyst.




*(46a)*, R = $C_6H_5$
*(46b)*, R = $CH_3$

The reaction with t-butyl peroxybenzoate produces *N*-benzoyloxymethyl-*N*-methylformamide *(46a)* in 35 % yield [14]. The analogous reaction with peroxyacetate produces *N*-acetoxymethyl-*N*-methylformamide *(46b)*, b.p. 66 °C/0.1 mm, $n_D^{25} = 1.4412$, in 25 % yield [28].

[47] *G. Sosnovsky* and *H. J. O'Neill*, J. org. Chemistry *27*, 3469 (1962).

[48] *C. Berglund* and *S.-O. Lawesson*, Acta chem. scand. *16*, 773 (1962).

## General Experimental Procedures for the Peroxyester Reaction

### 1. Reagents

To date, the peroxyester reaction has been carried out only with t-butyl peroxyacetate and t-butyl peroxybenzoate. The peroxyacetate is usually marketed as a 75 % solution in benzene, the peroxybenzoate as the undiluted liquid. Both reagents are stable at room temperature. At 100 °C, the half-life of t-butyl peroxyacetate is 12.5 hours, and that of t-butyl peroxybenzoate is 18 hours. Both compounds can be distilled at reduced pressure; t-butyl peroxyacetate, b.p. 35 °C/8 mm, $n_D^{25} = 1.4022$; t-butyl peroxybenzoate, b.p. 75 -76 °C/0.2 mm, $n_D^{25} = 1.4978$ [9].

### 2. Catalyst

*Kharasch*, *Sosnovsky*, and *Yang* [4] postulated that the peroxyester reaction required as catalyst a metal salt which can undergo rapid redox reactions, and most later investigators agree. Copper salts are the most efficient; either Cu(I) or Cu(II) salts can be used. Cobalt salts are less effective [4], and salts such as $ZnCl_2$ and $MgBr_2$ are ineffective [4].

The reaction is largely independent of the solubility of the catalyst or the nature of the anion [4], although reactions of peroxyesters in the presence of complex copper salts (*e.g.* 1,10-phenanthroline- or α,α-bipyridyl-Cu complexes) show decreased specificity compared with reactions catalysed by simple copper salts [49]. The following catalysts have been used most frequently: CuCl [14], CuBr [4] cupric 2-ethylhexanoate [4], and cupric 3,3,5-trimethylhexanoate [21]. When inorganic salts are used, they are slowly converted during the reaction into organic salts and the reaction proceeds by homogeneous catalysis [4].

### 3. Practical Procedure [4]

The peroxyester is added dropwise to a stirred mixture of the substrate and the copper salt catalyst in a molar ratio of 10:(15 to 40):0.01. A solvent such as benzene can be used if desired. Depending on the nature of the substrate and the stability of the products, the reaction mixture is maintained under an atmosphere of nitrogen at temperatures ranging from 65 to 115 °C [*].

The progress of the reaction can be followed by periodic examination of the infrared spectrum of the mixture ($\nu_{C=O}$ for peroxyacetate = 1785 $cm^{-1}$; $\nu_{C=O}$ for peroxybenzoate = 1775 $cm^{-1}$; acyloxy products usually absorb in the region 1720–1735 $cm^{-1}$) or by titration of the iodine liberated from sodium iodide with a sample of the reaction mixture. If the reaction proceeds according to plan, *i.e.* with formation of an acyloxy product, little or no gas is evolved.

The cooled reaction mixture is washed with a solution of sodium carbonate or sodium hydroxide to remove the carboxylic acid. The remaining organic phase is then washed with water and dried. The excess substrate or solvent or both are removed *in vacuo*, and the product is then purified, usually by distillation.

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German version: Angew. Chem. *76*, 218 (1964)

[49] *J. K. Kochi*, J. Amer. chem. Soc. *84*, 3271 (1962).

[*] Recently it was found [24b] that the reaction can be also carried out at lower temperatures (around 35 °C), when the reaction mixture is irradiated with ultraviolet light.

# Aliphatic Thioketones [1]

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*The methods described in the literature for the synthesis of aliphatic thioketones are examined critically in the light of the authors' own work; new practical methods of preparation are reported, and characteristic properties of thioketones are described.*

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2. From ketones and hydrogen sulfide
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## I. Introduction

In contrast to the corresponding aromatic compounds, monomeric aliphatic thioketones *(1)* [2] have been little studied since there were no general methods for their preparation until recently, and some schools have been forced to abandon work they had started because of the foul and penetrating odor of these compounds. One of the greatest difficulties we had to contend with, however,was the extent of contradictory and erroneous information present in the literature.

In this first review, the present state of work in this field will be summarized, the methods of synthesis critically examined, and, as far as is possible at present, mistakes in the literature will be rectified and characteristic properties of aliphatic thioketones described.

## II. Preparation of Aliphatic Thioketones

### 1. From Ketones and Phosphorus Sulfides or Magnesium Bromide Hydrogen Sulfide

A method often used in the past, and proclaimed as a standard procedure for the conversion of C=O into C=S, involved the action of phosphorus sulfides ($P_2S_3$, $P_4S_{10}$) on carbonyl compounds. The reaction was carried out in the presence or absence of solvent, and at high or low temperatures. It is not suitable as a general method for the preparation of monomeric aliphatic thioketones, however, as numerous side reactions occur.

Nevertheless, several authors have claimed to have obtained monomeric thioketones by this method, *e.g.* from dipropyl ketone [3], diisobutyl ketone [3], menthone [4], fenchone [5], and perfluoro-4-heptanone [6]. For a discussion of supposed dimeric thioketones [3,7,8] see [9], and for the action of $P_4S_{10}$ on perfluorocyclobutanone see [10].

MgBrSH was also thought [11] to be a universal reagent for substituting sulfur into carbonyl groups, but as the result of numerous experiments, we were forced to conclude that this method is unsatisfactory for the preparation of unconjugated aliphatic thioketones. Not even traces of thioketones were formed from cyclic ketones.

### 2. From Ketones and Hydrogen Sulfide

Although aldehydes generally react readily with hydrogen sulfide, ketones are almost unaltered [12,13] in the absence of a catalyst. The formation of traces of thio-

[1] Communication No. 27 on "Sulfur Heterocycles and Intermediates". – Communication No. 26: *R. Mayer* and *J. Jentzsch*, J. prakt. Chem., in the press.

[2] The tautomeric thioenol form has been disregarded in the formulae of the compounds.

[3] *A. J. Kretov* and *J. F. Kommissarov*, Zh. Khim. Ser. A, Zh. obshchei Khim. *5* (67), 388 (1935).

[4] *N. Speranskii*, J. Russ. physico-chem. Soc. *38*, 1346 (1906); Chem. Zbl. *1907*, I, 1746.

[5] *C. N. R. Rao* and *R. Venkataraghavan*, Spectrochim. Acta *18*, 541 (1962).

[6] *E. G. Howard* and *Wm. J. Middleton*, U.S.-Pat. 2970173 (1961); Chem. Abstr. *55*, 14311 (1961).

[7] *J. Wislicenus*, Z. Chem. *12*, 324 (1869); *W. Spring*, Bull. Soc. chim. France, Mém. *40* (2), 67 (1883); Bull. Acad. roy Méd. Belgique *5* (3), 236 (1883); *W. Autenrieth*, Ber. dtsch. chem. Ges. *20*, 373 (1887).

[8] *E. Fromm* and *E. Baumann*, Ber. dtsch.chem.Ges.*22*, 1035(1889).

[9] *H. Böhme*, *H. Pfeiffer*, and *E. Schneider*, Ber. dtsch. chem. Ges. *75*, 900 (1942).

[10] *D. C. England*, Angew. Chem. *74*, 726 (1962).

[11] *Q. Mingoia*, Gazz. chim. ital. *55*, 713 (1925); *56*, 839 (1926).

[12] *R. W. Borgeson* and *J. A. Wilkinson*, J. Amer. chem. Soc. *51*, 1453 (1929).

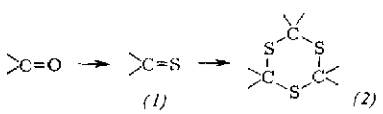
[13] *E. Baumann* and *E. Fromm*, Ber. dtsch. chem. Ges. *28*, 895 (1895).

ketones and other sulfur-containing compounds is indicated only by changes in color [12, 14] and by the smell [12, 14, 15] of the thioketones. Reaction occurs only with ketones having electron-attracting substituents [16, 16a], or at pressures of 65 to 8500 atm [17]; thioketones are still not formed even then; only *gem*-olthiols or *gem*-dithiols result.

If catalysts are added, however, thioketones are produced. Apart from the procedure described in an American patent [18], in which hydrogen sulfide reacts with ketones on an alumina catalyst at 450 °C to give thioketones, and which enables diisobutyl ketone, for example, to be converted into diisobutyl thioketone, it is usual to carry out the reaction between hydrogen sulfide and ketones at low temperatures either in an acidic medium (alcohol saturated with hydrogen chloride is so far the preferred solvent) or in the presence of amines.

### a) With Acidic Catalysts

This method, introduced by *Fromm* and *Baumann* [8], yields mainly 1,3,5-trithianes *(2)*, *i.e.* trimeric thioketones. In this way, trimeric thioacetone [8, 9, 19–21] is

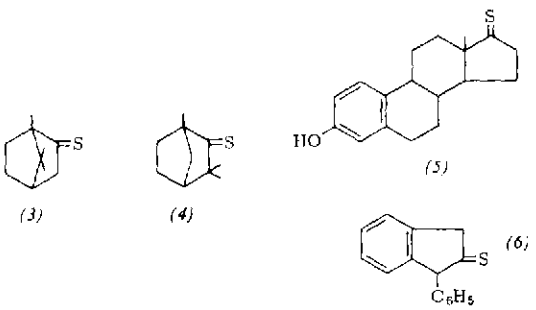


*(1)* *(2)*

formed from acetone, the presence of monomer being merely presumed [20] from the disgusting smell. We have recently [22] isolated monomeric thioacetone itself for the first time by a different method involving cleavage of acetone diethylketal with $H_2S$. The smell of this unstable red oil [23] is indeed almost indescribable. In our opinion, only traces of this compound or of the *gem*-dithiol could have been obtained in the earlier work, since the monomeric thioketone is unstable under the conditions used.

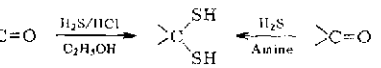
Methyl ethyl ketone behaves similarly to acetone; the main product is the trimeric thioketone [24, 25].

Higher aliphatic ketones, such as methyl hexyl ketone or methyl pentadecyl ketone, do not appear to be converted into thioketones or their trimers by $H_2S$ in acidic medium [13]; this should, however, be checked, since we were able to obtain similar thiones by other methods [22]. On the other hand, thiocamphor *(3)* [26, 27], thiofenchone *(4)* [28], thioestrone *(5)* [29], 1-phenyl-2-indanethione *(6)* [30], and 1,1,3-triphenylthioacetone [30] are readily obtainable from the corresponding ketones with $H_2S$ and acidic catalysts.



*(3)* *(4)* *(5)* *(6)*

The literature on monocyclic thioketones is contradictory; with cyclopentanone [31], cyclohexanone [31], and 4-methylcyclohexanone [31], the first attempts to prepare thioketones led to trimers. This reaction has also recently been observed with cycloheptanone [30] [*]. According to *Sen* [32, 33] (cf. [26]), however, the action of hydrogen sulfide on cyclopentanone, cyclohexanone, 2-methylcyclohexanone, and menthone in ethanol saturated with hydrogen chloride yields monomeric thioketones, as was confirmed by analysis and the preparation of derivatives. The trimers were mentioned as by-products from ketones with five- and six-membered rings, and dimenthenyl sulfide as a by-product from menthone (cf. [34]). This method of *Sen* has until very recently often been quoted and described as a standard procedure for preparing monomeric thioketones. It is in fact of very limited application for preparing monomeric aliphatic thioketones, since *gem*-dithiols *(7)* are formed preferentially.



*(7)*

We have made an extensive study of the reaction with cyclohexanone. If cyclohexanone is treated with hydrogen sulfide in ethanolic hydrochloric acid in an attempt to prepare cyclohexanethione *(1a)* by the method of *Sen* [33], the main product is a foul-smelling sulfur compound whose infrared spectrum exhibits a strong SH frequency at 2550 $cm^{-1}$ but lacks the C=C and =C–H absorption bands that one would expect for a thioenol. Furthermore, the molecular formula $C_6H_{12}S_2$ of the

[14] *R. Mayer* and *J. Morgenstern*, unpublished work.

[15] *W. E. Barch*, U.S.-Pat. 2594379 (1952); Chem. Zbl. *1953*, 1900.

[16] *J. F. Harris*, J. org. Chemistry *25*, 2259 (1960).

[16a] *T. J. Kealy*, U.S.-Pat. 3069397 (1962); Chem. Abstr. *59*, 1489 (1963).

[17] *T. L. Cairns, G. L. Evans, A. W. Larchar*, and *B. C. McKusick*, J. Amer. chem. Soc. *74*, 3982 (1952).

[18] *D. E. Winkler* and *S. A. Ballard*, U.S.-Pat. 2437985 (1948), Chem. Abstr. *43*, 349 (1949).

[19] *W. J. C. de Kok, J. J. Leendertse*, and *H. I. Waterman*, Chem. Weekbl. *37*, 617 (1940); Chem. Zbl. *1941*, I, 2792.

[20] *E. Baumann* and *E. Fromm*, Ber. dtsch. chem. Ges. *22*, 2592 (1889).

[21] *S. Kambara, N. Yamazaki*, and *R. Nitinomi*, J. chem. Soc. Japan, ind. Chem. Sect. *54*, 673 (1951); Chem. Abstr. *47*, 7248 (1953).

[22] *H. Berthold*, Diploma Thesis, Technische Universität Dresden, 1963; *R. Mayer* and *H. Berthold*, Chem. Ber. *96*, 3096 (1963).

[23] Not violet, cf. [13].

[24] *F. Leteur*, C. R. hebd. Séances Acad. Sci. *136*, 1459 (1903); Chem. Zbl. *1903*, II, 281.

[25] *H. Brintzinger* and *H. W. Ziegler*, Chem. Ber. *81*, 380 (1948).

[26] *P. C. Ray*, Nature (London) *134*, 1010 (1934); Chem. Zbl. *1935*, I, 1557.

[27] *D. C. Sen*, J. Indian chem. Soc. *12*, 647 (1935); Chem. Zbl. *1936*, I, 4916.

[28] *D. C. Sen*, J. Indian chem. Soc. *14*, 214 (1937); Chem. Zbl. *1937*, II, 4320.

[29] *R. M. Dodson* and *P. B. Sollman*, U.S.-Pat. 2840577 (1958); Chem. Abstr. *53*, 453 (1959).

[30] *E. Campaigne* and *B. E. Edwards*, J. org. Chemistry *27*, 3760 (1962).

[*] See [31] for an interesting fission reaction of pulegone.

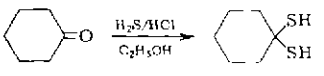
[31] *E. Fromm*, Ber. dtsch. chem. Ges. *60*, 2090 (1927).

[32] *D. C. Sen*, Sci. and Cult. *1*, 582 (1936); Chem. Zbl. *1936*, II, 972.

[33] *D. C. Sen*, J. Indian chem. Soc. *13*, 268 (1936); Chem. Zbl. *1936*, II, 3414.

[34] *E. Fromm*, Ber. dtsch. chem. Ges. *41*, 3661 (1908).

compound contains one mole of $H_2S$ more than is required by the thione *(1a)*. We were able to characterize the product [35] as 1,1-dimercaptocyclohexane *(8)* by comparison with an authentic sample that we obtained by a different method, and also by its reactions.



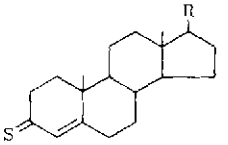
*(8)*



*(1a)*

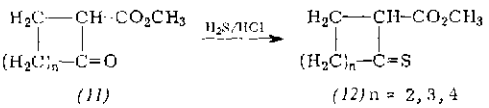
Since subsequent reactions of *(8)* and *(1a)* sometimes yield identical products, and in particular, since *(8)* undergoes the reactions used to characterize *(1a)* [36], it is not possible to say whether *Sen* isolated the pure thioketone. Although *Janssen* [37] considers that the spectroscopic data cast doubt on the purity of cyclohexanethione obtained by *Sen*'s method, *Rosengren* regards a lower boiling fraction as the pure thioketone [38].

An acid-catalysed formation of a dithiol had indeed been noted previously [40], but was experimentally confirmed only considerably later by the isolation of 1,3-diphenyl-2,2-propanedithiol [30,39], 1,3-dichloro-2,2-propanedithiol [41], and other dithiols [42]. Although monochloroacetone [9,25,43] and β-diketones [44] react differently, unsaturated thioketones such as $\Delta^4$-cholestene-3-thione *(9)* [45] and 17β-hydroxy-$\Delta^4$-androstene-3-thione *(10)* [46], as well as β-thioxocarboxylic esters [47–55] and β-thioxocarboxamides [56], are accessible by this method.



*(9)*; R = $C_8H_{17}$
*(10)*; R = OH

According to *Mitra* [49], thioacetoacetic ester was obtained in 85 % yield by passing $H_2S$ at 0 °C into a solution of acetoacetic ester in alcohol saturated with hydrogen chloride. Our own research group has recently made a very thorough investigation of the conversion of β-oxocarboxylic esters into β-thioxocarboxylic esters, and has studied the chemistry of the latter. This work is described elsewhere [52,53], and here we only wish to mention that cyclic β-oxocarboxylic esters *(11)* are especially easy to convert into the corresponding thioxocarboxylic esters *(12)* using hydrogen sulfide in an acidic medium.



*(11)* *(12)* n = 2, 3, 4

### b) With Basic Catalysts

An alkaline medium also promotes the formation of *gem*-dithiols *(7)* very strongly [57]. We devised a simple, general synthesis giving good yields of this interesting class of compounds; ketones are treated with hydrogen sulfide in the presence of amines in a polar solvent at 0–20 °C [57,58].

Basic ketones such as *N*-methylpiperidone do not give thioketones with hydrogen sulfide, but react to form *gem*-dithiols [59], whereas cycloheptanone, methyl cyclohexyl ketone, and a few other ketones also give moderate yields of thioketones [57,60]. It has not yet been determined whether the latter should be regarded as primary or secondary products. The action of $H_2S$ on acetylacetone in the presence of morpholine yields monothioacetylacetone, which exists partly as a thioenol [57].

Our experience so far indicates that these base-catalysed reactions are useful for preparing *gem*-dithiols, but not for preparing thiones.

Ammonium polysulfide cannot be used to convert aliphatic ketones into thioketones, not even if excess hydrogen sulfide is passed in; instead, tetrathianes *(13)* and pentathiepanes *(14)* [61] or reduction products [17,62,63] are formed.

Even thiocamphor *(3)*, which is normally formed very readily, is not obtained directly using ammonium polysulfide,

[35] *J. Jentzsch*, Ph. D. Thesis, Technische Universität Dresden, 1963.

[36] *R. Mayer* and *J. Fabian*, unpublished work.

[37] *M. J. Janssen*, Recueil Trav. chim. Pays-Bas *79*, 464 (1960).

[38] *Kj. Rosengren*, Acta chem. scand. *16*, 1401 (1962).

[39] *G. A. Berchtold, B. E. Edwards, E. Campaigne*, and *M. Carmack*, J. Amer. chem. Soc. *81*, 3148 (1959).

[40] *W. A. Lazier* and *F. K. Signaigo*, U.S.-Pat. 2402639 (1946).

[41] *R. Gottfried*, Diploma Thesis, Technische Hochschule Dresden, 1961.

[42] *B. Magnusson*, Acta chem. scand. *17*, 273 (1963).

[43] *H. Böhme* and *E. Schneider*, Chem. Ber. *82*, 208 (1949).

[44] *A. Brändström*, Ark. Kemi *3*, 41 (1951); Chem. Abstr. *45*, 7574 (1951); *A. Fredga* and *A. Brändström*, Ark. Kemi *1*, 197 (1949); Chem. Abstr. *44*, 3898 (1950); *A. Fredga* and *A. Brändström*, Ark. Kem., Mineralog. Geol., Ser. B *26*, 5 (1948); Chem. Abstr. *44*, 7243 (1950); *E. Fromm* and *P. Ziersch*, Ber. dtsch. chem. Ges. *39*, 3599 (1906); *F. Leteur*, C. R. hebd. Séances Acad. Sci. *133*, 48 (1901).

[45] *R. Bourdon*, Bull. Soc. chim. France *1958*, 722.

[46] *F. A. Kincl*, Chem. Ber. *93*, 1043 (1960).

[47] *S. K. Mitra*, J. Indian chem. Soc. *15*, 31 (1938); Chem. Zbl. *1938*, II, 1577.

[48] *S. K. Mitra*, J. Indian chem. Soc. *10*, 491 (1933); Chem. Zbl. *1934*, I, 1185.

[49] *S. K. Mitra*, J. Indian chem. Soc. *10*, 71 (1933); Chem. Zbl. *1933*, II, 1335.

[50] *K. Chandra, N. K. Chakrabarty*, and *S. K. Mitra*, J. Indian chem. Soc. *19*, 139 (1942); Chem. Abstr. *38*, 4951 (1944).

[51] *S. K. Mitra*, J. Indian chem. Soc. *15*, 129 (1938); Chem. Zbl. *1938*, II, 3390.

[52] *R. Mayer* and *S. Bleisch*, unpublished work; *R. Mayer* and *P. Barthel*, Chem. Ber. *93*, 428 (1960).

[53] *R. Mayer* and *G. Wenschuh*, unpublished work.

[54] *Ch. F. Ferraro, J. J. Draney*, and *M. Cefola*, J. Amer. chem. Soc. *75*, 1206 (1953).

[55] *P. Raoul* and *J. Vialle*, Bull. Soc. chim. France *1959*, 1670.

[56] *J. Goerdeler*, and *W. Mittler*, Chem. Ber. *96*, 944 (1963).

[57] *R. Mayer, G. Hiller, M. Nitzschke*, and *J. Jentzsch*, Angew. Chem. *75*, 1011 (1963); Angew. Chem. internat. Edit. *2*, 370 (1963), where further references are given.

[58] *J. Jentzsch, J. Fabian*, and *R. Mayer*, Chem. Ber. *95*, 1764 (1962).

[59] *H. Barrera* and *R. E. Lyle*, J. org. Chemistry *27*, 641 (1962).

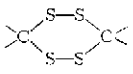
[60] *G. Hiller*, Diploma Thesis, Technische Universität Dresden 1963.

[61] *C. Willgerodt*, Ber. dtsch. chem. Ges. *20*, 2467 (1887); *F. Asinger* and *M. Thiel*, Angew. Chem. *70*, 667 (1958); *A. Fredga*, Acta chem. scand. *12*, 891 (1958); *B. Magnussan*, ibid. *13*, 1031 (1959).

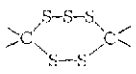
[62] *C. Böttinger*, Ber. dtsch. chem. Ges. *18*, 486 (1885); *Y. Yukawa* and *Y. Kishi*, Mem. Inst. sci. ind. Res., Osaka Univ. *8*, 163 (1951); J. chem. Soc. Japan, pure Chem. Sect. *72*, 371 (1951); Chem. Abstr. *46*, 7061 (1952).

[63] *H. Wuyts*, Ber. dtsch. chem. Ges. *36*, 863 (1903).

as previously claimed [64], but is produced in a very impure state by secondary pyrolysis [63, 65, 66]. The same applies to thiofenchone *(4)* [66].



*(13)*



*(14)*

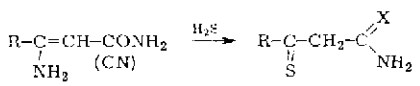
### 3. From Ketone Derivatives and Hydrogen Sulfide

#### a) From Enamines

The recently published [67] synthesis of monomeric cyclohexanethione and cyclopentanethione from the corresponding enamines and $H_2S$ could not be repeated [58, 68, 69]. *gem*-Dithiols *(7)* are formed [57], just as with the enamines of other ketones [69].

Thiocarbonyl compounds can, however, be obtained from some α-substituted enamines. Thus, reaction of 1-cyclopentenylmorpholine [70] with acetyl chloride and subsequent treatment with $H_2S$ yielded α-acetylcyclopentanethione, which was characterized by its reactions [36].

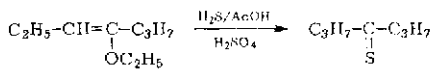
In this connexion, the preparation of β-thioxocarboxylic esters [52], β-thioxocarboxamides *(15a)* [56] and β-thioxothiocarboxamides *(15b)* [71] has also been reported.



*(15a)*; X = O
*(15b)*: X = S

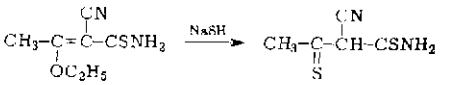
#### b) From Enol Ethers or α,β-Unsaturated Chlorides

Recently we found that enol ethers could be converted into thioketones in the presence of catalytic amounts of sulfuric acid in glacial acetic acid [22]. For example, dipropyl thioketone *(1b)* was obtained in 30 % yield from 4-ethoxy-3-heptene *(16)*.



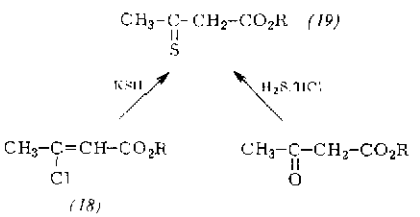
*(16)* *(1b)*

A similar conversion in alkaline medium has so far only been used for the synthesis of an α-cyano-β-thioxothiocarboxamide *(17)* [72].



*(17)*

In contrast to enol ethers, α,β-unsaturated chlorides are not satisfactory starting materials for the synthesis of aliphatic thioketones. The thioacetoacetic esters *(19)* that were prepared from β-chlorocrotonic esters *(18)* and alkali hydrogen sulfides [73–75] can be obtained more conventiently nowadays from β-oxocarboxylic esters by the method of *Mitra* already described [49].



*(18)*

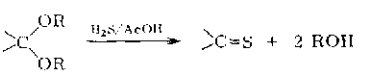
#### c) From Azomethines, Oximes, or Phenylhydrazones

The remarks about enamines apply equally, *mutatis mutandis*, to azomethines. Although diaryl thioketones [76] and thioacetophenone [42] can be prepared from azomethines and hydrogen sulfide, the method fails in the aliphatic series. The ketimines that have so far been examined yielded *gem*-dithiols [42, 77]. Only camphor, the *gem*-dithiol of which is not known, could be converted into thiocamphor by this method [78].

There is still no way known of splitting oximes or phenylhydrazones to get thioketones or *gem*-dithiols, although numerous attempts have been made (cf. [79]).

#### d) From Ketals

We recently discoverd [22] that monomeric thioketones, particularly the lower aliphatic thioketones not previously known in the pure state, can be prepared under mild conditions in average yields of 50 % by cleavage of ketals *(20)*, preferably diethylketals, which are readily accessible from ketones and ethyl orthoformate, with hydrogen sulfide in an acidic medium.



*(20)* *(1)*

[64] *W. Schlebusch*, Ber. dtsch. chem. Ges. *3*, 591 (1870).

[65] *J. Houben* and *H. Doescher*, Ber. dtsch. chem. Ges. *39*, 3503 (1906).

[66] *E. Rimini*, Gazz. chim. ital. *39*, II, 196 (1909); Chem. Zbl. *1909*, II, 1646.

[67] *Y. Nomura* and *Y. Takeuchi*, Bull. chem. Soc. Japan *33*, 1743 (1960); Sci. Pap. Coll. gen. Educat., Univ. Tokyo *11*, 183 (1961); Chem. Abstr. *58*, 4433 (1963).

[68] *C. Djerassi* and *B. Tursch*, J. org. Chemistry *27*, 1041 (1962).

[69] *M. Demuynck* and *J. Vialle*, Bull. Soc. chim. France *1962*, 2126.

[70] *S. Hünig*, *E. Benzing*, and *E. Lücke*, Chem. Ber. *90*, 2833 (1957).

[71] *J. F. Cavalla*, J. chem. Soc. (London) *1962*, 4664.

[72] *M. A. McCall*, J. org. Chemistry *27*, 2433 (1962).

[73] *H. Scheibler* and *W. Bube*, Ber. dtsch. chem. Ges. *48*, 1445 (1915).

[74] *S. K. Mitra*, J. Indian chem. Soc. *8*, 471 (1931); Chem. Zbl. *1931*, II, 3329.

[75] *H. Scheibler*, *H. T. Topouzada*, and *H. A. Schulze*, J. prakt. Chem. (2) *124*, 1 (1930).

[76] *W. Fehrmann*, Ber. dtsch. chem. Ges. *20*, 2844 (1887); *G. Reddelien* and *H. Danilof*, ibid. *54*, 3132 (1921).

[77] *B. Magnusson*, Acta chem. scand. *16*, 1536 (1962).

[78] *T. Tukomoto*, J. pharmac. Soc. Japan *59*, 37 (1939); Chem. Zbl. *1939*, II, 4246.

[79] *T. L. Cairns*, *A. W. Larchar*, and *B. C. McKusick*, J. org. Chemistry *18*, 748 (1953).

The reaction can be carried out either in the presence of a very small amount of an acidic catalyst ($ZnCl_2$, inorganic acids) with or without solvent, or in an anhydrous organic acid. In either case it is advantageous to add a little hydroquinone as stabilizer.

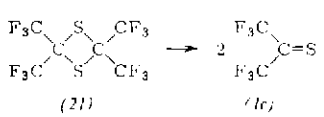
This method is much superior to any of the others mentioned so far. The alcohol is liberated from the ketal even at room temperature and is removed continuously from the equilibrium by distillation under reduced pressure or, for less sensitive thioketones, under ordinary pressure. Cyclic ketals derived from glycols are less convenient starting materials owing to the high boiling points of glycols.

### 4. Pyrolysis and Photolysis of Compounds Containing Sulfur

Trithianes *(2)* are readily accessible from thiones, *gem*-dithiols, or ketones and $H_2S$ in an acidic medium, and by analogy with the oxygen derivatives it should be possible to cleave (depolymerize) them to thioketones *(1)*. However, no instance of this is yet known in the aliphatic series, since compounds of type *(2)* are either very stable or decompose only under conditions so drastic that the thiones *(1)* would be unstable or undergo other reactions [8,9,31]. Success was first achieved in the pyrolysis of aryl alkyl thioketones [13]; whereas trimeric thioacetone distils unchanged under reduced pressure [8], trimeric thioacetophenone decomposes above its melting point into the monomer and other products.

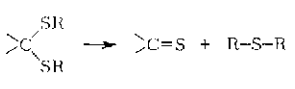
Trimeric diaryl thioketones are apparently unknown. *Schönberg* has studied the different stabilities of various trimeric thioketones to pyrolysis [80].

It is interesting that a dimeric thioketone, perfluorotetramethyl-1,3-dithietane *(21)*, can be partly converted into the monomer *(1c)* by pyrolysis at 600 °C [6].



*(21)* *(1c)*

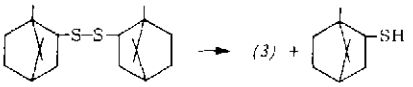
The pyrolysis of simple aliphatic *gem*-bis(alkylthio) compounds *(22)* does not give the desired products [20].



*(22)*

Pyrolysis could sometimes be used to obtain aromatic thioketones, even though side reactions always occurred [81,82]. Aliphatic monosulfides [*], which are relatively stable, have never yet yielded well-defined thioketones on pyrolysis.

Although disulfides are more thermolabile than monosulfides, it has not yet been possible to devise a general method for the preparation of aliphatic thioketones by pyrolysis of disulfides. The only example that works is dibornyl disulfide *(23)*, which is converted into highly impure thiocamphor *(3)* by pyrolysis [63–66,83].

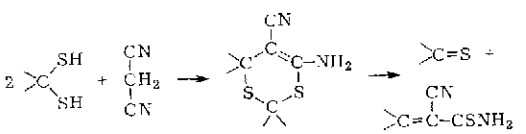


*(23)*

This reaction is evidently a homolytic disulfide fission [84]. Monomeric aliphatic thioaldehydes and thioketones have been detected spectroscopically in the products of photolysis of various disulfides [38,85, cf. 86].

Any pyrolytic process that is to be used for the preparation of aliphatic thioketones must proceed under conditions in which the thiones are stable and will not undergo secondary reactions with other fission products. As we have already seen, this leads to considerable difficulties with trithianes, simple *gem*-bis(alkylthiol) derivatives, monosulfides, and disulfides. The simplest method would be the removal of gaseous hydrogen sulfide from *gem*-dithiols *(7)*, however only fluorinated dithiols (or olthiols) have been converted in this way [16a].

We have therefore chosen an indirect route which has proved to be very successful, and which we use particularly for the preparation of monomeric cyclic thiones in yields of about 60 %: the *gem*-dithiol *(7)* is first treated with malonodinitrile to give an adduct *(24)*, and this

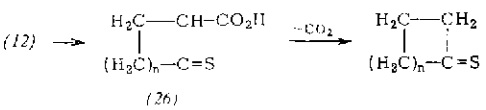


*(7)* *(24)* *(25)*

is then decomposed above its melting point to give the thioketone, which distils off, and a residue of thioamide *(25)* [87].

### 5. Decarboxylation of β-Thioxocarboxylic Acids

As already mentioned, β-thioxocarboxylic esters *(12)* are formed smoothly from β-oxocarboxylic esters *(11)* and hydrogen sulfide in an acidic medium. Careful hydrolysis gives the free acids *(26)*.



*(26)*

Although thioketones had previously been thought to be by-products of this hydrolysis [52,75,88], we were only

[80] *A. Schönberg*, Ber. dtsch. chem. Ges. *62*, 195 (1929).

[81] *A. Schönberg* and *O. Schütz*, Liebigs Ann. Chem. *454*, 47 (1927); Ber. dtsch. chem. Ges. *62*, 2322 (1929).

[82] *A. Schönberg*, *O. Schütz*, *V. Bruckner*, and *J. Peter*, Ber. dtsch. chem. Ges. *62*, 2550 (1929).

[*] See [82] for the fission of diaryl sulfides.

[83] *J. Haraszti*, J. prakt. Chem. (2) *149*, 301 (1937).

[84] *W. E. Lyons*, Nature (London) *162*, 1004 (1948); *W. H. C. Rueggenberg*, *J. Chernack*, *I. M. Rose*, and *E. E. Reid*, J. Amer. chem. Soc. *70*, 2292 (1948); *M. S. Kharasch*, *W. Nudenberg*, and *T. H. Meltzer*, J. org. Chemistry *18*, 1233 (1953); *S. F. Birch*, *T. V. Cullum*, and *R. A. Dean*, J. Instn. Petroleum Technologists *39*, 206 (1953).

[85] *Kj. Rosengren*, Acta chem. scand. *16*, 2284 (1962).

[86] *P. V. Laakso*, Suomen Kemistilehti *13*, 8 (1940); Chem. Zbl. *1940*, II, 1709.

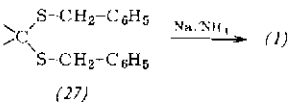
[87] *R. Mayer* and *J. Jentzsch*, Angew. Chem. *74*, 292 (1962); Angew. Chem. internat. Edit. *1*, 217 (1962); J. prakt. Chem. (4) *18*, 211 (1962).

[88] *Z. Reyes* and *R. M. Silverstein*, J. Amer. chem. Soc. *80*, 6367 (1958).

recently [53] able to demonstrate their presence conclusively and to prepare cyclopentanethione, cyclohexanethione, and cycloheptanethione in very pure samples that were, in particular, free from *gem*-dithiols *(7)*, by decarboxylation of the isolated β-thioxocarboxylic acids *(26)*. The thiones thus obtained can be kept for several days as monomers.

### 6. Special Methods

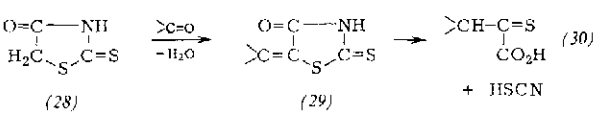
Certain thiosteroids can be obtained from the corresponding *gem*-bis(benzylthio) derivatives *(27)* by fission with sodium in liquid ammonia [29,89–91].



*(27)* *(1)*

There are no references to similar experiments with *S,S'*-disubstituted *gem*-dithiols leading to simple aliphatic ketones, but a *gem*-dithiol was isolated [92] from the fission of a tetrathiane *(13)* under similar conditions.

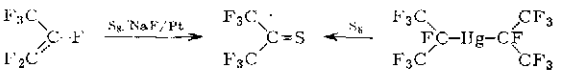
Another especially interesting reaction is the alkaline hydrolysis of the compounds *(29)* obtained by condensation of aldehydes or ketones with rhodanine *(28)*, which leads to derivatives of thiopyruvic acid *(30)* [93–96].



*(28)* *(29)* *(30)*

Finally, the action of elementary sulfur on organic compounds may be mentioned, since sulfur should be able to oxidize methylene groups to thiocarbonyl groups. Of course, under the drastic conditions that are necessary, the thiones that are first formed in the main are rapidly dehydrogenated. The reaction can only be used for practical preparative purposes if the thione is not enolizable and hence cannot react further and is to some extent resistent to dehydrogenation. In the aromatic series, for example, diphenylmethane can be converted into thiobenzophenone by elementary sulfur in 30 % yield.

Aliphatic thiones cannot be prepared by this method; however, hexafluorothioacetone *(1c)* was obtained by treatment of hexafluoropropene *(31)* [6] or bis(heptafluoroisopropyl)mercury *(32)* [6,97] with sulfur.



*(31)* *(1c)* *(32)*

## III. Chemical and Physical Properties of Aliphatic Thioketones

All the known thioketones and related compounds are listed in Table 1.

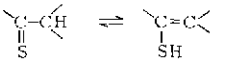
The stability of thiones is very variable; whereas, for instance, dipropyl thioketone [22] and thiocamphor *(3)* [14] will keep for some weeks, thioacetone [22] changes within a few minutes. The other simple thioketones also have only limited stability and polymerize after a time even in the absence of acidic catalysts.

A connection between the instability of thioketones and their photochemical reactivity was noted some time ago [99]. More recently it has been pointed out that photoexcited carbonyl and carbonyl-like groups can be regarded as true biradicals [100,101].

Simple thioketones of low molecular weight are generally red oils with very intensive, unpleasant smells. Only solid thiocamphor and thiofenchone have more pleasant, sulfurous, mint-like odors.

All the thiones we have prepared dissolve readily in nonpolar solvents. Monocyclic thioketones decompose very rapidly in protonating solvents.

If there is at least one hydrogen atom on the carbon atom adjacent to the C=S group, prototropic tautomerism of the thioketone is possible. This can be detected spectroscopically [36]; the thioenol tautomer can



be recognized from infrared bands at 1640 $cm^{-1}$ ($\nu_{C=C}$), 2550 $cm^{-1}$ ($\nu_{SH}$), and 3020 $cm^{-1}$ ($\nu_{=C-H}$), whilst a small amount of the thioketone tautomer is evident from its characteristic color ($\lambda_{max} \approx 500$ mμ). It can be shown in this way that some thioketones exist completely, or nearly so, as the thioenols, *e.g.* β-thioxocycloalkanecarhoxylic acids *(26)* and their esters *(12)* [36], β-thioxothiocarboxamides *(15)* [71,72], derivatives of thiopyruvic acid [93], cyclohexanethione [36], and 1,1,3-triphenylthioacetone *(6)* [30] (in the last compound, the thioenol form was also confirmed by its nuclear magnetic resonance spectrum). On the other hand, some thio-

[89] *R. M. Dodson* and *P. B. Sollman*, U.S.-Pat. 2753361 (1956), U.S.-Pat. 2763669 (1956); Chem. Zbl. *1959*, 1555.

[90] *R. M. Dodson* and *P. B. Sollman*, U.S.-Pat. 2837539 (1958), Chem. Zbl. *1959*, 8986.

[91] *C. Djerassi* and *D. Herbst*, J. org. Chemistry *26*, 4675 (1961).

[92] *B. Magnusson*, Acta chem. scand. *16*, 772 (1962).

[93] *E. Campaigne*, Chem. Reviews *39*, 20 (1946); *E. Campaigne* and *R. E. Cline*, J. org. Chemistry *21*, 32 (1956).

[94] *N. Campbell* and *J. E. McKail*, J. chem. Soc. (London) *1948*, 1251, where further references are given; *G. G. Allan*, *D. Maclean*, and *G. T. Newbold*, ibid. *1952*, 5053.

[95] *O. E. Emerson*, U.S.-Pat. 2863915 (1958); Chem. Zbl. *1961*, 16658.

[96] *W. I. Maimind* and *A. Ya. Berlin*, Zh. obshchei Khim. *20*, (82), 1626 (1950); Chem. Zbl. *1955*, 6957.

[97] *W. J. Middleton*, *E. G. Howard*, and *W. H. Sharkey*, J. Amer. chem. Soc. *83*, 2589 (1961).

[98] *D. C. Sen*, Sci. and Cult. *4*, 134 (1938); Chem. Zbl. *1939*, 1, 3552.

[99] *G. N. Lewis* and *M. Kasha*, J. Amer. chem. Soc. *67*, 994 (1945).

[100] *D. Brück* and *G. Scheibe*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 901 (1957).

[101] *F. Dörr*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 950 (1957).

Table 1. Known monomeric aliphatic thioketones [2]

| Thioketone | Preparation | M.p. [°C] | B.p. [°C/mm] | $n_D^{20}$ | Ref. |
|---|---|---|---|---|---|
| Thioacetone | ketal/$H_2S$ | | 80/760 | 1.4690 | [22] |
| Methyl ethyl thioketone | ketal/$H_2S$ | | 120—124/760 | 1.4800 | [22] |
| Diethyl thioketone | ketal/$H_2S$ | | 55—65/57 | 1.4776 | [22] |
| Di-n-propyl thioketone | ketal/$H_2S$ | | 52—62/12 | 1.4752 | [22] |
| | ketone/$P_4S_{10}$ | | 135—150/40 | | [3] |
| Diisobutyl thioketone | ketone/$P_4S_{10}$ | | 105—110/10 | | [3] |
| Methyl cyclohexyl thioketone | ketone/$H_2S$/amine | | 62/2 | 1.5158 (25 °C) | [57] |
| Cyclopentanethione | ketal/$H_2S$ | | 60—67/18 | | [22] |
| | ketone/$H_2S$/HCl | | 86—88/10 | | [33] |
| | pyrolysis | | 56/11 | | [87] |
| | decarboxylation | | 92—95/12 | 1.5630 | [53] |
| Cyclohexanethione | ketal/$H_2S$ | | 81—84/17 | 1.5375 | [22] |
| | ketone/$H_2S$/HCl | | 75/15 | | [33] |
| | | | 66/16 | | [38] |
| | pyrolysis | | 74/11 | | [87] |
| | decarboxylation | | 64—68/28 | 1.5445 | [53] |
| 2-Methylcyclohexanethione | ketone/$H_2S$/HCl | | 95/10 | | [32] |
| Thiomenthone | ketone/$H_2S$/HCl | | 215—216/763 | | [32] |
| | ketone/$P_2S_3$ | | 217—220/760 | | [4] |
| Thiocamphor | ketone/$H_2S$/HCl | 145 | | | [27] |
| | imine/$H_2S$ | 118 | | | [78] |
| | pyrolysis of disulfide | 119 | 104/15 | | [63] |
| | | 125—130 | | | [83] |
| 1,1'-Bis-thiocamphor [*] | thiocamphor | 180 | | | [98] |
| Thiofenchone | ketone/$H_2S$/HCl | | 92/5 | | [28] |
| | pyrolysis of disulfide | | 207—208/734 | | [66] |
| Cycloheptanethione | ketone/$H_2S$/amine | | 62/3 | 1.5563 (25 °C) | [57] |
| 17-Androstanethione | *gem*-bisbenzylthio derivative | 102—104 | | | [91] |
| $\Delta^4$-Androsten-3-one-17-thione | *gem*-bisbenzylthio derivative | 140—141 | | | [89] |
| $\Delta^4$-Pregnen-3-one-20-thione | *gem*-bisbenzylthio derivative | 145 | | | [90] |
| 3β-Hydroxy-$\Delta^5$-pregnene-20-thione | *gem*-bisbenzylthio derivative | 113—115 | | | [90] |
| 3-Hydroxy-$\Delta^{1,3,5(10)}$-estratriene-17-thione | *gem*-bisbenzylthio derivative | 212—213 | | | [29] |
| 3β-Hydroxy-$\Delta^5$-androstene-17-thione | *gem*-bisbenzylthio derivative | 162—163 | | | [91] |
| Perfluorothioacetone [**] | sulfuration | 8 (?) | | | [97] |
| | | | 107/760 | | [6] |
| Perfluoro-4-heptanethione | ketone/$P_4S_{10}$ | | 84—88/760 | | [6] |
| 1,1,1,3,3,4,4-Heptafluoro-2-butanethione | sulfuration | | 20—27/760 | | [6] |
| 4-Chloroheptafluoro-2-butanethione | sulfuration | | | | [6] |
| Perfluoro-2-hexanethione | sulfuration | | | | [6] |
| Perfluoro-2-heptanethione | sulfuration | | | | [6] |
| Perfluoro-2-octanethione | sulfuration | | | | [6] |
| Perfluoro-2-nonanethione | sulfuration | | | | [6] |
| 1,1,1,3,3-Pentafluoro-2-butanethione | sulfuration | | | | [6] |
| Thioacetylacetone | ketone/$H_2S$/amine | | 68/14 | 1.559 (25 °C) | [60] |
| Methyl thioacetoacetate | keto ester/$H_2S$/HCl | | 68—69/12 | 1.5222 (29.5 °C) | [75] |
| Ethyl thioacetoacetate | keto ester/$H_2S$/HCl | | 75—80/12 | | [49] |
| | α,β-unsat. chloride/NaSH | | 77/18 | 1.5375 (29.5 °C) | [75] |
| Ethyl α-methylthioacetoacetate | keto ester/$H_2S$/HCl | | 95/10 | | [47] |
| Ethyl α-ethylthioacetoacetate | keto ester/$H_2S$/HCl | | 85/14 | | [48] |
| Ethyl α-isobutylthioacetoacetate | keto ester/$H_2S$/HCl | | 122/5 | | [47] |
| Methyl α-benzylthioacetoacetate | α,β-unsat. chloride/NaSH | | | | [75] |
| Diethyl thioacetylmalonate | keto ester/$H_2S$/HCl | | 120/4 | | [47] |
| Diethyl thioacetone-1,3-dicarboxylate | keto ester/$H_2S$/HCl | | | | [49] |
| Methyl cyclopentane-1-thione-2-carboxylate | keto ester/$H_2S$/HCl | | 73/2 | 1.5385 | [53] |
| Ethyl — | keto ester/$H_2S$/HCl | | 110/5.5 | | [50] |
| Methyl cyclohexane-1-thione-2-carboxylate | keto ester/$H_2S$/HCl | | 103—105/3 | 1.5405 | [53] |
| Ethyl — | keto ester/$H_2S$/HCl | | 112/6 | | [50] |
| Methyl cycloheptane-1-thione-2-carboxylate | keto ester/$H_2S$/HCl | | 101—102/2.5 | 1.5315 | [53] |
| Cyclopentane-1-thione-2-carboxylic acid | ester | 160—161 | | | [52] |
| Cyclohexane-1-thione-2-carboxylic acid | ester | 108 | | | [53] |
| Cycloheptane-1-thione-2-carboxylic acid | ester | 154—156 | | | [53] |
| Phenylthiopyruvic acid | rhodanine | 133—134 | | | [93] [cf. 94, 95] |
| Dimethylthiopyruvic acid | rhodanine | 78.5-79 | | | [96] |
| 1,1,3-Triphenylthioacetone | ketone/$H_2S$/HCl | 90—91 | | | [30] |
| 1-Phenylindanone-2-thione | ketone/$H_2S$/HCl | | | | [30] |
| α-Cyano-α-thioacetylthioacetamide | enolether/NaSH | 102—106 | | | [72] |

[*] In 1,1'-bis-thiocamphor two molecules of thiocamphor are joined through the 1 C-atoms.

[**] Note added in proof: for further fluorinated thioketones, see [16a].

ketones, such as dipropyl thioketone, methyl cyclohexyl thioketone, and thiocamphor exist largely as the thiones. It can be shown by means of the infrared and ultraviolet spectra of cycloalkanethiones prepared from ketals, that the concentration of thioketone decreases on standing in favor of that of the thioenol.

The composition of the mixture of tautomers, previously determined iodometrically [33,103], should be checked by a physicochemical method if opportunity occurs.

The dependence of the color of thioketones upon temperature has been related to a shift in the tautomerization equilibrium [33,75], and can still be observed under nitrogen (see, however, [88]). The absorption in the visible part of the spectrum shows that only the intensity of the color alters [37]; it is thus true thermochromism that occurs.

There are considerable difficulties in determining the C=S frequency by infrared spectrometry, since it lies in a very crowded part of the spectrum. Complications also arise from the enolization and instability of some of the compounds. Doubt must be cast on the infrared bands between 1300 and 1550 $cm^{-1}$ cited in the literature [104]. More recent experience indicates that the C=S frequency should be expected to lie between 1100 and 1300 $cm^{-1}$ [*], although only the C–S stretching vibrations of two non-enolizable thioketones are known, *viz.* at 1120 $cm^{-1}$ for di-t-butyl thioketone [105] and at 1180 $cm^{-1}$ for thiofenchone [5]. In spite of spectroscopic comparisons and studies of the influence of the solvent, we have not yet been able to locate the C=S frequency of aliphatic thioketones unequivocally [36].

Aliphatic monothioketones exhibit characteristic absorptions in the visible and ultraviolet regions [106]. Thiofenchone and the enolizable thioketones already mentioned that exist largely in the thioketone form have absorption bands at 488–508 mμ (Type I), 230–244 mμ (Type II), and 214–215 mμ (Type III) in aliphatic hydrocarbon solvents (Fig. 1).

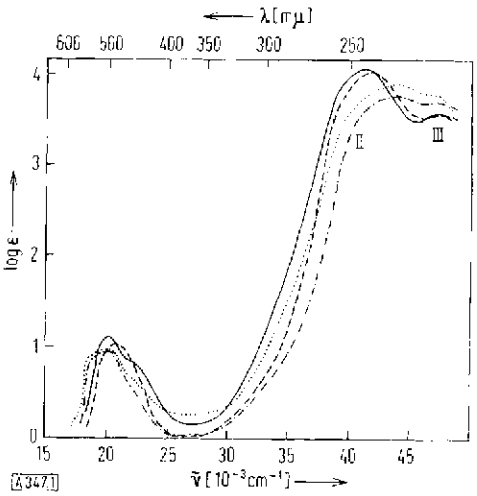



Fig. 1. Absorption spectra of some thioketones (ε = extinction coefficient) Concentrations: $10^{-2}$–$10^{-4}$ M; solvent: cyclohexane or hexane; room-temperature.

– Thiocamphor · · Dipropyl thioketone
– – – Thiofenchone ····· Methyl cyclohexyl thioketone
Roman numerals indicate band types.

Table 2. Fine structure (wavelengths and intensities) of the longwave band (n → π* transition) in the ultraviolet spectrum of aliphatic thioketones.

| Thio compound | Solvent | Wavelength [mμ] [*] | log ε [**] | Ref. |
|---|---|---|---|---|
| Thioacetone | cyclohexane | 411*, 436*, 449, 460, *499*, 511, 527*, 565* | | [36] |
| Methyl ethyl thioketone | cyclohexane | 451*, *500*, 575* | | [36] |
| Dipropyl thioketone | cyclohexane | 450* *503* | 0.95 | [36] |
| Methyl cyclohexyl thioketone | cyclohexane | *508*, 516*, 570* | 1.00 | [36] |
| Cyclopentanethione | cyclohexane | 445*, 472*, 497*, *512*, 522*, 543, 580 | < 1 | [36] |
| Cyclohexanethione | cyclohexane | 450*, 462*, 505*, *512*, 528*, 569 | < 1 | [36, 112] |
| Cycloheptanethione | cyclohexane | 455*, *512*, 576 | < 1 | [36] |
| Thiocamphor | cyclohexane | 450*, *493*, 515*, 551* | 1.09 | [36, 102] |
| Thiofenchone | hexane | 445*, *488*, 501* | 1.04 | [36, 102] |
| 17-Androstanethione | dioxane | *492* | 1.11 | [91] |
| 3β-Hydroxy-$\Delta^5$-androstene-17-thione | dioxane | *492.5* | 1.15 | [91] |
| $\Delta^5$-Pregnen-3-one-20-thione | dioxane | *493* | | [91] |
| Hexafluorothioacetone | methylene dichloride | *580* | | [97] |
| Ethyl cyclopentane-1-thione-2-carboxylate | – | *512* | | [36] |
| Methyl cycloheptane-1-thione-2-carboxylate | – | *512* | | [36] |
| 17β-Hydroxy-$\Delta^4$-androstene-3-thione | ethanol | *514* | 1.92 | [46] |

[*] Asterisks denote shoulders on main peaks. Numbers in italics indicate the position of the main peak.
[**] log ε values refer to the main peaks.

All the thioketones examined showed characteristic weak absorption at 500 mμ, which often exhibited a distinct vibrational fine structure. Table 2 gives the wavelengths and some of the intensities of these long-wave bands.

[102] Cf. [28], also *P. C. Ray*, Nature (London) *138*, 548 (1936); Chem. Zbl. *1937*, I, 883. $\lambda_{max}$ (in benzene): 495 mμ.

[103] *S. K. Mitra*, J. Indian chem. Soc. *15*, 205 (1938).

[104] *N. B. Colthup*, J. opt. Soc. America *40*, 397 (1950); *F. A. Miller*, in *H. Gilman:* Organic Chemistry. Wiley New York, 1953, Vol. III, p. 149; *Sh. Kambara* and *N. Murashima*, J. Soc. Rubber Ind. Japan *29*, 951 (1956); Chem. Abstr. *51*, 18678 (1957).

[*] The figure given for cyclohexanethione (1130 $cm^{-1}$) [67] is naturally erroneous, as it was determined on 1,1-dimercaptocyclohexane.

[105] *W. Maier*, Beckman Report No. 3, p. 3 (1961).

[106] *J. Fabian* and *R. Mayer*, Spektrochim. Acta, in the press.

The figures in italics indicate the strongest absorptions. The positions of the bands depend upon the solvent. The following mean band shifts were observed with four thioketones in passing from cyclohexane to ethanol: Type I: $\Delta \approx 500\ cm^{-1}$ (hypsochromic); Type II: $\Delta \approx 400\ cm^{-1}$ (bathochromic); Type III: $\Delta \approx 500\ cm^{-1}$ (hypsochromic). On the basis of their intensities and solvent dependencies [107] we would assign the bands of Type I to the prohibited transition $n \rightarrow \pi^*$ ($^1U \leftarrow {}^1A$), of Type II to the allowed transition $\pi \rightarrow \pi^*$, and of Type III to the allowed transition $n \rightarrow \sigma^*$ ($^1W \rightarrow {}^1A$) (see [107] for terminology).

The interpretation of the ultraviolet absorption of strongly enolizing monothioketones presents difficulties, since the thioenol configuration exhibits an intense absorption maximum at 220 mμ and hence a superimposed spectrum results [106]. The absorption in the visible region at 500 mμ remains unaffected except for a reduction in its intensity. Substitution of an alkyl residue by an unsaturated residue or by the strongly inductive $CF_3$ group leads to a bathochromic shift (cf. Table 2). Since p-π conjugation of the C=S group causes a marked hypsochromic shift in comparison with dialkyl thioketones, whereas π-π conjugation causes a strong bathochromic shift of the long-wavelength band [108] (Fig. 2), simple aliphatic thioketones can be recognized with some certainty.

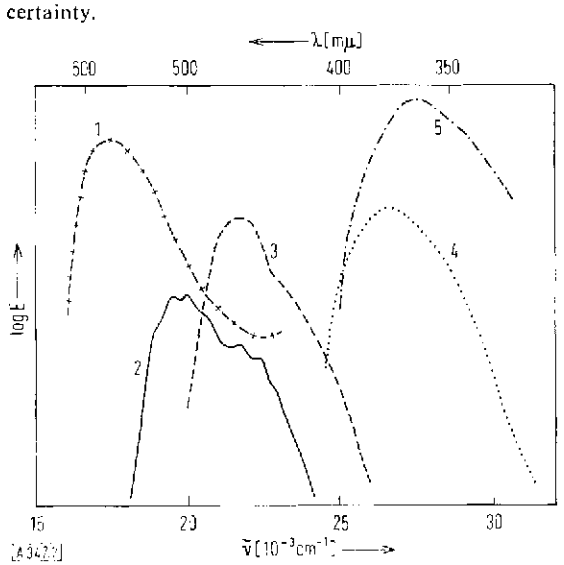
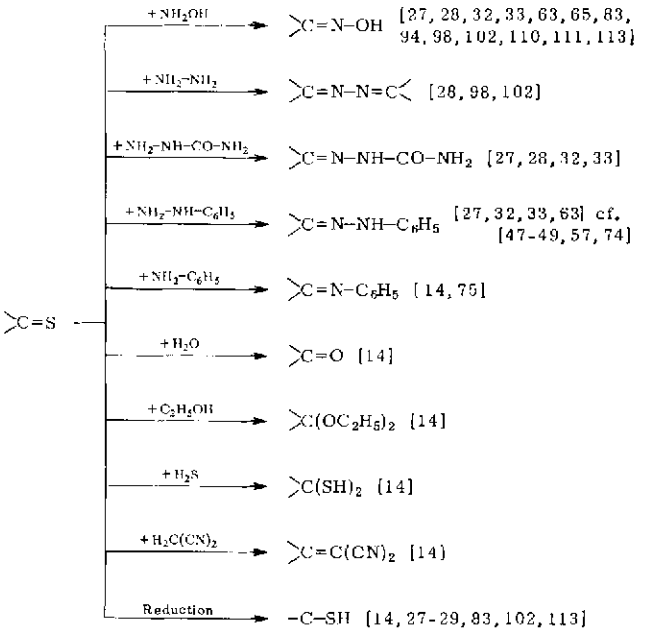



Fig. 2. Relationship between structure and n → π* transition (Type I band) in some thio compounds. E = Extinction.
Concentrations: ca. $10^{-2}$ M; solvent: cyclohexane, room-temperature.
1: $H_3C-CS-C_6H_5$ 4: $H_3C-CS-OC_2H_5$ [37]
2: $H_3C-CS-CH_3$ 5: $H_3C-CS-N(CH_3)_2$
3: $H_3C-CS-SC_2H_5$ [37]

## IV. Chemical Properties of Aliphatic Thioketones

### 1. Reactions with Nucleophilic Reagents

Aliphatic thioketones react with nucleophilic compounds by elimination of hydrogen sulfide in close analogy with ketones (Scheme 1); keto-enol tautomerism is of secondary importance here. Some reactions of thioenol ethers that follow a similar course are also known [32, 33, 109].




Scheme 1. Reactions of thioketones with nucleophilic reagents.

It is not yet possible to say to what extent it is advantageous to use thioketones in reactions instead of their oxygen analogues, but since condensations of thioketones proceed without a catalyst, new possibilities are opened up.

Thiones can be characterized as oximes, semicarbazones, and hydrazones, but it should be noted that *gem*-dithiols react similarly. Reduction of sulfur derivatives with sodium borohydride is of special interest in steroid chemistry [29, 89]. As we found [14], particularly with cyclohexanethione, the thione group is hydrolysed to the carbonyl group by hot water, hydrogen sulfide adds onto thiones smoothly to form 1,1-dithiols, and primary aliphatic amines (ammonia) from perhydro-1,3,5-dithiazines.

A remarkable property of aliphatic thioketones is their strong tendency to form polymeric products. In some cases [6, 10], or under certain conditions [14], dimers are observed instead of the more usual trimers [8, 9, 14, 19–21, 24–26, 30–33].

### 2. Reactions with Electrophilic Reagents

Nearly all the thioketones so far examined react at the sulfur atom with electrophilic reagents to give derivatives of the thioenol. This opens up numerous synthetic possibilities. Strongly enolized thioketones undergo the reactions shown in Scheme 2 with particular ease.

Electrophilic attack at the α-carbon atom of the thioketone only occurs occasionally. Because it is only slightly enolized, thiocamphor reacts in this way under the influence of alkaline condensing agents with benzaldehyde

[107] *J. W. Sidman*, Chem. Reviews *58*, 689 (1958).

[108] *S. F. Mason*, Quart. Reviews *15*, 314 (1961).

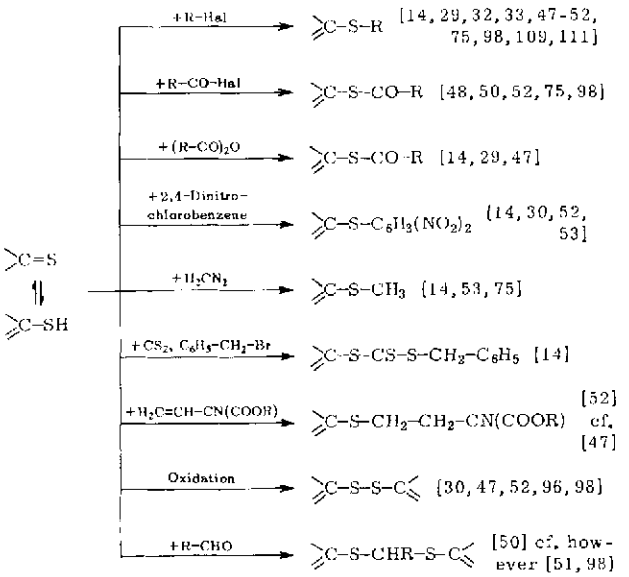
[109] *P. C. Ray, S. K. Mitra*, and *N. N. Ghosh*, J. Indian chem. Soc. *10*, 75 (1933).

[110] *D. C. Sen*, J. Indian chem. Soc. *15*, 537 (1938); Chem. Zbl. *1939*, I, 3552.

[111] *D. C. Sen*, J. Indian chem. Soc. *13*, 523 (1936); Chem. Zbl. *1937*, I, 1952.

[112] Cf. [37]: $\lambda_{max}$ (in cyclohexane) = 504 mμ; also [38]: $\lambda_{max}$ (in isopentane/3-methylpentane) = 505 mμ.

[113] *D. C. Sen*, Sci. and Cult. *1*, 435 (1935); Chem. Zbl. *1936*, I, 4015.




Scheme 2. Reactions of thioketones with electrophilic reagents.

to give α-benzylidenethiocamphor [111, 113] and with isoamyl nitrite to give α-isonitrosothiocamphor [98, 110, 114, 115]. Ester condensations should also be possible at the adjacent methylene group [116], but we have not yet been able to confirm this.

Finally we should mention that the alkali and heavy metal salts that are usually readily obtainable from the thioenolic form of thioketones are important for their detection and purification and for preparative work.

Our research group recently studied the products of further reactions of cyclopentanethione-2-carboxylic ester [52, 53] and of cyclohexanethione [14], but owing to the wealth of information collected we prefer to report these special results elsewhere.

## V. Summary

Although several alternative methods of formation of aliphatic thioketones are known, there is no general method of preparation. Many of the thioketones reported in the literature were found to be impure and some are actually *gem*-dithiols. Well-defined monomeric aliphatic thioketones are nearly always branched at the α-position. Among the stable cyclic thioketones, those ring sizes predominate that are sterically favorable to the formation of trigonal carbon. Neither phosphorus sulfides nor magnesium bromide hydrogen sulfide is satisfactory for the preparation of aliphatic thioketones from ketones.

Thioketones can only occasionally be obtained by the action of hydrogen sulfide on ketones in acidic medium, since trimers or *gem*-dithiols are formed predominantly; the method is only satisfactory for β-thioxocarboxylic esters. Mainly *gem*-dithiols and only occasionally thioketones are also formed in basic medium, even when enamines or ketimines are used as starting materials. On the other hand, ketals and enol ethers are cleaved by hydrogen sulfide in the presence of acidic catalysts to give thioketones; only a few examples yield *gem*-dithiols. Fission of ketals and enol ethers with hydrogen sulfide is the most general and useful method of preparation of aliphatic thioketones yet known.

Most of the methods for preparing aliphatic thioketones by pyrolysis are of doubtful value. Only thermal fission of the adducts of the now readily accessible *gem*-dithiols with malonodinitrile yields thioketones smoothly. Lower alicyclic thioketones are easily obtainable by this method. Very pure thioketones result from decarboxylation of β-thioxocarboxylic acids.

The red color ($\lambda_{max} \approx 500$ mμ) and the very penetrating, unpleasant odor of the lower homologues are characteristic of the unconjugated aliphatic thioketones. Strongly enolized members are almost colorless.

Chemically, thioketones behave like ketones toward nucleophilic reagents and often yield the same products, often even in the absence of catalysts. Nearly all the thioketones so far examined react with electrophilic reagents at the sulfur atom to form thioenol derivatives.

*We wish to record our thanks for generous State support for our work. Special thanks are due to our colleagues, coworkers, and neighbors of the Institute and of our station in Pirna-Copitz for enduring the nuisance of the smell with forbearance.*

Received, July 11th, 1963 [A 347/146 IE]
German version: Angew. Chem. 76, 157 (1964)

[114] *D. C. Sen*, Sci. and Cult. *1*, 158 (1935); Chem. Zbl. *1936*, I, 4916.

[115] *D. C. Sen*, J. Indian chem. Soc. *12*, 751 (1935); Chem. Zbl. *1936*, II, 1354.

[116] *N. K. Chakrabarty* and *S. K. Mitra*, Sci. and Cult. *4*, 472 (1939).

# Organosodium and Organopotassium Compounds

## Part I: Properties and Reactions [1]

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A. Properties
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2. Color and spectra
3. Conductivity and electrolysis
4. Configurational and structural stability

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f) Hetero-substituted aromatic compounds
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i) Eliminations leading to carbenes
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d) CC Multiple bonds
e) Polymerizations

G. Rearrangements
1. Charge transfer to nitrogen
2. Charge transfer to oxygen
3. Charge transfer to another carbon atom

## A. Properties

### 1. Bond and Polarity

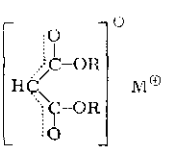
The typical organometallic bond links a saturated, non-polar hydrocarbon residue to a strongly electropositive alkali or alkaline earth metal. The limiting structures *(1)* and *(3)* represent the two possible extremes of the state of the bond.

$M{-}CR_3$ $M{\blacktriangleleft}CR_3$ $[:CR_3]^{\ominus}\ M^{\oplus}$.

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

The actual state *(2)* of the metal-carbon bond in metal alkyls lies between these two limiting structures. This representation of a covalent, but more or less polarized, bond is intended to indicate that the negative charge is concentrated in the vicinity of the carbon atom.

Two factors contribute to this strong polarization of the bond. One is the high electropositivity of the metal, and the other is the stabilization of the electron pair on the carbon atom which occurs as a result of inductive and mesomeric effects. The mesomeric effects are the more pronounced. Organometallic compounds capable of forming a resonance-stabilized carbanion are mostly present as ion pairs – *e.g.* malonic ester derivatives *(4)* – and thus react only with strong electrophiles. The corresponding hydrogenated compounds behave as Brönstedt acids.



*(4)*

The incompatibility of carbon and an alkali metal as components of a bond is the reason for the extraordinary reactivity and the unusual reactions exhibited by or-

[*] Present address.

[1] For earlier reviews see [1a–1g].

[1a] *C. B. Wooster*, Chem. Reviews *11*, 1 (1932).

[1b] *G. Wittig*, Angew. Chem. *53*, 241 (1940).

[1c] *A. A. Morton*, Chem. Reviews *35*, 1 (1944).

[1d] *F. Runge:* Organometall-Verbindungen. Wissenschaftl. Verlagsgesellschaft, Stuttgart 1944.

[1e] *H. Gilman* in: Organic Reactions (The Metalation Reactions with Organolithium Compounds). Wiley, New York 1954, Vol. VIII, p. 258.

[1f] *E. G. Rochow, D. T. Hurd*, and *R. N. Lewis:* The Chemistry of Organometallic Compounds. Wiley, New York 1957.

[1g] *R. A. Benkeser, D. J. Foster, D. M. Sauve*, and *J. F. Nobis*, Chem. Reviews *57*, 867 (1957).

ganoalkali compounds. This incompatibility exists when the organic residue cannot stabilize the negative charge sufficiently. The dependence of the properties of organometallic compounds on the nature of the alkali metal is particularly strong for those with covalent bond character. The increase in electropositivity observed on going from lithium to sodium to potassium is clearly reflected in a striking increase in reactivity. In ionic organometallic compounds, on the other hand, the metal cation does not play an active part [2].

The reactivity is not necessarily directly related to the bond polarity, as indicated by the fact that the electropositivity of the metal, which tends to increase the basicity, and the resonance stabilization of the carbanion, which tends to reduce it, both exert polarizing effects. For example, amylpotassium is more polar and more reactive than amyl-lithium which, in turn, is far more reactive than sodiomalonic ester which is fully ionized.

Although unequivocal, sharp differentiation between true and salt-like organoalkali-metal compounds is not possible, differences in their chemical and physical behavior allow them to be grouped as follows [3]:

Group A: 1. Alkyl-, vinyl-, and aryl-lithium derivatives; 2. Alkyl, vinyl, and aryl derivatives of higher alkali metals.

Group B: 1. Benzylalkali-metal compounds; 2. Alkali-metal derivatives of acidic and highly acidic hydrocarbons; 3. Alkali metal-aromatic complexes and ketyls.

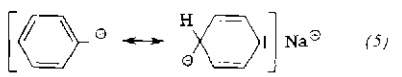
Group C: 1. Metal salts of allylic and cyclopentadienyl compounds; 2. Metal salts of ketones, esters, and nitriles; 3. Metal salts of acetylenes and hydrogen cyanide.

On the basis on this classification, we shall now consider in detail the bond character in organoalkali-metal compounds.

Group A: On passing from organolithium to organic compounds of the higher alkali metals, there are immense changes in properties, even though the electropositivity and the atomic radii increase continuously from lithium to cesium. This unusual behavior is obviously due to the great tendency of lithium compounds to undergo association [4].

Lithium derivatives are colorless, crystallizable substances that are volatile *in vacuo*. Their solutions in ether are stable at 0 °C. Lithium alkyls, with the exception of methyllithium, are readily soluble in hydrocarbons. Derivatives of higher alkali metals are also colorless but are not volatile and possess no definite melting points. They are practically insoluble in hydrocarbons and are rapidly decomposed by ethers.

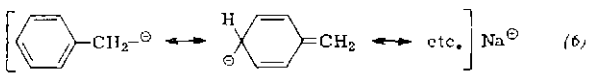
This diversity in behavior is often interpreted as indicating that the bond between lithium and an alkyl or aryl group is polarized, yet covalent, whereas all organosodium and organopotassium compounds [*e.g.* the ion pair *(5)*] are salt-like [5].



*(5)*

This assumption is not consistent with the observation that amylpotassium is more reactive than amylsodium [6]. Dipole measurements cannot be used to investigate the bond character here, because the lithium alkyls and aryls tend to associate [7], and the corresponding sodium and potassium derivatives are insoluble. It is to be hoped that infrared and nuclear resonance spectroscopy will soon provide further insight into the polarity of the organometallic bond.

Group B: All intensely colored alkali derivatives belong to this group. It is apparent that the benzyl group, sometimes substituted, is a common structural characteristic of these derivatives. The gain in energy due to mesomerism according to *(6)* is so great that the metal-carbon bond is cleaved.



*(6)*

As will be shown below, it appears that all benzylalkali-metal compounds exist as ion pairs. As a result, variation of either the alkali metal (triphenylmethyl-lithium, -sodium, -potassium) or the substituent (benzyl-, dimethylphenyl-, triphenylmethyl-sodium) produces no drastic alterations in properties but rather a series of gradual difference from compound to compound. The decrease in basicity in going from sodium alkyls to benzylsodium is much more pronounced than that resulting from the introduction of a second or third phenyl group capable of resonance. All benzylalkali compounds are soluble and rather stable in ether, although the monophenyl derivatives, in contrast to the polyphenyl compounds [8], are not entirely stable, but cause slow decomposition of the ether [9].

The high dipole moment of triphenylmethylsodium ($\mu = 7.11$ D in dioxan) [10] supports its formulation as an ion pair. The tetramethylammonium salts *(7)* and *(8)* possess completely free anions [11].

$[H_5C_6\text{–}\underline{C}H_2]^{\ominus}[N(CH_3)_4]^{\oplus}$ *(7)*

$[(H_5C_6)_3C]^{\ominus}[N(CH_3)_4]^{\oplus}$ *(8)*

Any enlargement of the resonance system results in further decrease in basic strength of the anions; the acidity of the corresponding acids increases corre-

[2] In its ionic form, the alkali metal can, however, also affect the course of reaction. For example, because of its complex-forming cation, lithium hydroxide is a more effective catalyst of the benzilic acid rearrangement than other alkali hydroxides [*W. H. Puterbaugh* and *W. S. Gaugh*, J. org. Chemistry *26*, 3513 (1961)].

[3] Based on a classification used by *K. Ziegler* [*K. Ziegler* et al., Liebigs Ann. Chem. *473*, 1 (1929)].

[4] *F. Hein* and *H. Schramm*, Z. physik. Chem. A *151*, 234 (1930); *G. Wittig*, *F. J. Meyer*, and *G. Lange*, Liebigs Ann. Chem. *571*, 167 (1951); *M. T. Rogers* and *R. L. Brown*, J. physic. Chem. *61*, 366 (1957); *R. West* and *W. Glaze*, J. Amer. chem. Soc. *83*, 3580 (1961); *T. L. Brown*, *D. W. Dickerhoof*, and *D. A. Bafus*, ibid. *84*, 1371 (1962); *P. A. Fowell* and *C. T. Mortimer*, J. chem. Soc. (London) *1961*, 3793.

[5] *A. A. Morton*, Chem. Reviews *35*, 2 (1944).

[6] *H. Gilman* and *R. V. Young*, J. org. Chemistry *1*, 315 (1936); *H. Gilman* in: Organic Chemistry. 2nd Ed., Wiley, New York 1943, Vol. I, p. 520.

[7] *T. L. Brown*, *D. W. Dickerhoof*, and *D. A. Bafus*, J. Amer. chem. Soc. *84*, 1371 (1962).

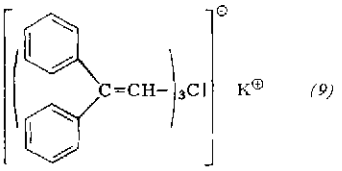
[8] Diphenylmethylsodium is stable towards ether [*W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *464*, 1 (1928)].

[9] *K. Ziegler* and *O. Schäfer*, Liebigs Ann. Chem. *479*, 150 (1930).

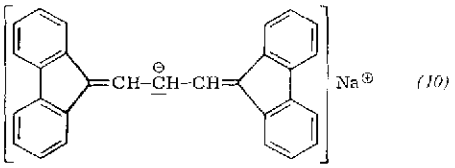
[10] *L. M. Nazarova*, Zh. fiz. Khim. *28*, 36 (1954); Chem. Abstr. *48*, 10396 g (1954).

[11] *W. Schlenk* and *J. Holtz*, Ber. dtsch. chem. Ges. *50*, 274 (1917).

spondingly [12]. Compounds *(9)* [13] and *(10)* [14] are salts of acidic and highly acidic hydrocarbons.

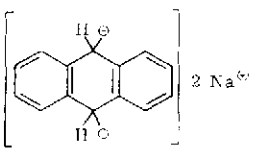


*(9)*

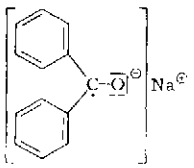


*(10)*

The adducts resulting from the addition of an alkali metal onto aromatic compounds, olefins, carbonyl compounds, or azomethines, *e.g.* anthracenedisodium *(11)* or the sodium ketyl of benzophenone *(12)*, do not possess the reactivity of organometallic compounds [15].

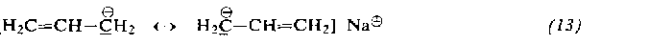


*(11)*



*(12)*

Group C: The members of this group, although colorless, have ionic structures similar to that of the benzylic derivatives. Because of the complete delocalization of its free electron pair, the allylic anion *(13)* shows high resonance stabilization and is similar in this respect to the triphenylmethyl anion.

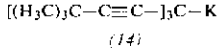


*(13)*

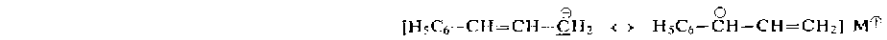
The anions of enols, esters, and nitriles have considerably less energy because the negative charge encompasses the electronegative hetero-atoms as well. On the other hand, the stability of acetylides and cyanides is not due to mesomerism but to the intrinsic acidity of hydrogens on sp-hybridized carbon atoms. Acetylides and cyanides are too weakly basic to be considered as true organometallic compounds.

## 2. Color and Spectra

No unequivocal correlation has yet been established between the color and the structure of organoalkali compounds. The rule of thumb that benzyl anions are colored is not without exception. Tris-(3,3-dimethyl-1-butynyl)methylpotassium *(14)* [16,17] is bright red; metal derivatives of alkyl-substituted styrenes *(15)* are colorless.



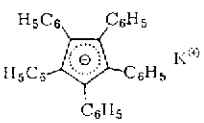
*(14)*



*(15)*

The color phenomena observed are consistent with the following hypothesis: The chromophore is an anion delocalized by resonance. The π-electron system with which the carbanion is in resonance must belong to a hydrocarbon with multiple unsaturation, preferably an aromatic compound. A vinyl group is not sufficient as is indicated by the fact that allylmetal compounds do not absorb in the visible region.

An appreciable portion of the negative charge must be transferred to the resonance system. Compound *(15)* and pentaphenylcyclopentadienylpotassium *(16)* [18] are colorless, because the probability of residence of the free electron pair in the benzene rings is too low.



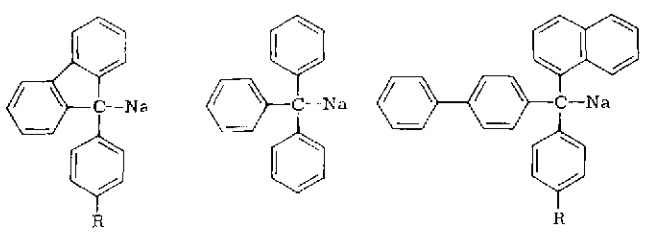
*(16)*

Any increase in the size of the resonance system causes a shift in absorption toward longer wavelengths. In the case of the polymethine carbanion *(17)* [19], this shift amounts to 33 mμ per vinylene group.



*(17)*

The effect of aryl substituents on color was visually established for derivatives *(18)* through *(22)* [20].



*(18)* (orange-red), R = H
*(19)* (red), R = $OCH_3$

*(20)* (red)

*(21)* (blue-purple), R = H
*(22)* (dark-purple), R = $C_6H_5$

If, as suspected, the color arises from the free resonating carbanion, then the light absorption should be independent of the cation [21]. Identical spectra were in

[12] *G. W. Wheland* [J. chem. Physics 2, 474 (1934)] represents the acidity as a linear function of the difference between the energy of conjugation of the hydrocarbon and that of its carbanion.

[13] *G. Wittig* and *H. Kosack*, Liebigs Ann. Chem. *529*, 167 (1937).

[14] *R. Kuhn, Herbert Fischer, F. A. Neugebauer*, and *Hans Fischer*, Liebigs Ann. Chem. *654*, 64 (1962).

[15] *C. B. Wooster*, Chem. Reviews *11*, 37 (1932); *D. J. Morantz*, and *E. Warhurst*, Trans. Faraday Soc. *51*, 1375 (1955); *R. O. C. Norman, G. A. Thompson*, and *W. A. Waters*, J. chem. Soc. (London) *1958*, 175.

[16] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 1 (1928).

[17] *P. L. Salzberg* and *C. S. Marvel*, J. Amer. chem. Soc. *50*, 1737 (1928).

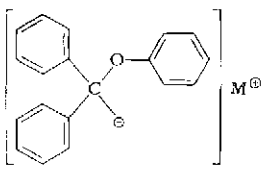
[18] *K. Ziegler* and *L. Ewald*, Liebigs Ann. Chem. *473*, 163 (1929), p. 192; cf. the purple color of the heptaphenylcycloheptatriene anion [*R. Breslow* and *H. W. Chang*, J. Amer. chem. Soc. *84*, 1484 (1962)].

[19] *K. Hafner* and *K. Goliasch*, Angew. Chem. *74*, 118 (1962); Angew. Chem. internat. Edit. *1*, 114 (1962).

[20] *W. Schlenk* and *E. Marcus*, Ber. dtsch. chem. Ges. *47*, 1664 (1914).

[21] The lighter color of benzyl-lithium compared to benzyl sodium and its greater stability towards ether may be due to a partially covalent C—Li bond.

fact obtained for the lithium-, sodium-, and potassium-substituted benzhydryl ethers *(23)*. The Lambert-Beer law is satisfied [22].



*(23)*, M = Li, Na, K

The infrared absorption of allylic anions [23] and the electron-spin resonance of benzophenone ketyls [24] are also independent of the alkali metal. On the other hand, the infrared spectra of phenyl-lithium, phenylsodium, and phenylpotassium show not only common bands but also bands whose positions depend on the alkali metal [25, 26]. One of these groups of bands was tentatively assigned to the carbon-metal bond [26]; for another [25], a linear dependence on the reduced mass of the metal atom was established. These infrared spectroscopic data provide support for the argument that strongly polarized, yet still covalent, organometallic bonds exist in compounds of group A.

## 3. Electrical Conductivity and Electrolysis

Because of their small dielectric constants, ordinary nonpolar solvents do not separate a salt into individual ions. This can be demonstrated, for example, by measurements of the electrical conductivity. Thus, in ether, the carbon-metal bond in group B and group C compounds is fully ionized as the internal ion pair *(24)*, but by no means dissociated into a solvent-separated ion pair *(25)*. In *(24)*, the alkali cation and the carbanion are held together by electrostatic attraction and are surrounded by a common solvent shell. Not even benzophenone ketyls are dissociated in 1,2-dimethoxyethane, as is indicated by ESR measurements [24].

$[M^{\oplus}CR_3^{\ominus}]_{solv}$ *(24)* $\qquad [M(Solv)_m]^{\oplus}[R_3C(Solv)_n]^{\ominus}$ *(25)*

Triphenylmethylsodium has a low conductivity which vanishes with decreasing concentration [20]. A 0.005 M solution of triphenylmethylpotassium in ether is essentially non-conducting [27]. This phenomenon is plausibly explained by the following transport mechanism [20]: Free cations and anions, incapable of existing in ether, add on triphenylmethylsodium affording the complex ions *(26)* and *(27)*. The conductivity of lithium iodide in ether is also very low and that of the sodium salt of acetophenone is immeasurably small [27].

$[Na\{NaC(C_6H_5)_3\}_m]^{\oplus}$ *(26)* $\qquad [\{NaC(C_6H_5)_3\}_nC(C_6H_5)_3]^{\ominus}$ *(27)*

In strongly solvating media such as ammonia, pyridine, or dimethyl sulfoxide, triphenylsodium and triphenylmethylpotassium have identical equivalent conductivities, which are inversely proportional to the concentration, and are as large as those of strong inorganic electrolytes [28].

Organoalkali-metal compounds of group A are apparently all non-conductors [29]. Earlier statements to the contrary are, without exception, based on electrolyses in which a zinc dialkyl was used as solvent. Under these conditions, however, the conductivity is due to the formation of a complex $M(ZnR_3)$ [30].

*Ziegler* [31] recently worked out an industrially interesting synthesis of tetraethyl-lead which is based on the electrolysis of such an $M(ZnR_3)$ complex. Sodium tetraethylaluminate, which behaves chemically as a mixture of ethylsodium and triethylaluminum, is subjected to electrolysis with a mercury cathode and a lead anode, the latter reacting with the ethyl radicals. Tetraethyl-lead distills off along with triethylaluminum. The ethylsodium consumed is regenerated by the reaction of the sodium liberated at the cathode with hydrogen and ethylene; the overall reaction is thus as follows:

$$Pb + 2\,H_2 + 4\,H_2C{=}CH_2 \xrightarrow{\text{electrical energy}} Pb(C_2H_5)_4.$$

## 4. Configurational and Structural Stability

Until now, the studies carried out on optically active lithium alkyls [32], lithium cyclopropyl derivatives [33], and geometrically isomeric vinyl-lithium derivatives [34] have not been extended to the corresponding sodium and potassium derivatives.

Optically active carbanions have been detected as short-lived intermediates in base catalysed deprotonations of hydrocarbons and sulfones, in the cleavage of secondary alkoxides and in the decarboxylation of carboxylic acids. Neutralization proceeds with retention, inversion, or racemization, depending on the protonating solvent applied [35].

Organometallic compounds with $\beta$-hydrogens undergo thermal decomposition with particular ease. Ethylsodium [36] decomposes mainly as follows:

$$Na{-}C_2H_5 \xrightarrow{100\,^{\circ}C} H_2C{=}CH_2 + NaH\ .$$

Higher homologues *e.g.* propylsodium [37] and amylsodium [38], also decompose gradually at room temperature, and rapidly between 50 and 100 °C. In addition to the olefin, this process usually yields the saturated hydrocarbon as a by-product; in some instances it even becomes the major product. An interpretation of this thermal decomposition in terms of a free-radical

[22] *G. Wittig* and *E. Stahnecker*, Liebigs Ann. Chem. *605*, 69 (1957).

[23] *E. J. Lanpher*, J. Amer. chem. Soc. *79*, 5578 (1957).

[24] *P. B. Ayscough* and *R. Wilson*, Proc. chem. Soc. (London) *1962*, 229.

[25] *M. Margoshes* and *V. A. Fassel*, Spectrochim. Acta *7*, 14 (1955).

[26] *E. J. Lanpher*, J. org. Chemistry *21*, 830 (1956).

[27] *D. C. Hill, J. Burkus, S. M. Luck*, and *C. R. Hauser*, J. Amer. chem. Soc. *81*, 2787 (1959).

[28] *K. Ziegler* and *H. Wollschitt*, Liebigs Ann. Chem. *470*, 123 (1930).

[29] For example, fused ethyl-lithium is not electrically conductive (*G. E. Coates:* Organo-Metallic Compounds. Wiley, New York 1956, p. 7).

[30] *G. Wittig, F. J. Meyer*, and *G. Lange*, Liebigs Ann. Chem. *571*, 167 (1951); *G. Wittig*, Angew. Chem. *70*, 65 (1958).

[31] *K. Ziegler*, Angew. Chem. *72*, 565 (1960).

[32] *R. L. Letsinger*, J. Amer. chem. Soc. *72*, 4842 (1950).

[33] *H. M. Walborsky* and *F. J. Impastato*, J. Amer. chem. Soc. *81*, 5835 (1959); *D. E. Applequist* and *A. H. Peterson*, ibid. *83*, 863 (1961).

[34] *D. Y. Curtin* and *W. J. Koehl*, J. Amer. chem. Soc. *84*, 1967 (1962).

[35] Review: *G. Köbrich*, Angew. Chem. *74*, 453 (1962); Angew. Chem. internat. Edit. *1*, 382 (1962).

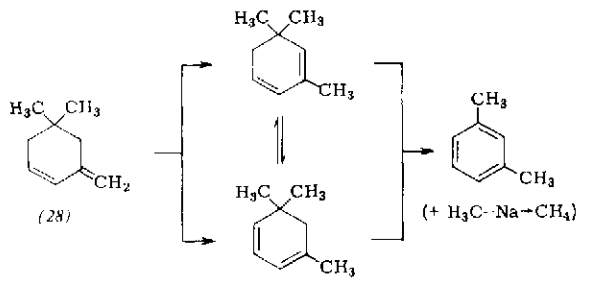
[36] *W. H. Carothers* and *D. D. Coffman*, J. Amer. chem. Soc. *51*, 588 (1929); *52*, 1254 (1930).

[37] *R. L. Letsinger* and *D. F. Pollart*, J. Amer. chem. Soc. *78*, 6079 (1956).

reaction [38] was proved by *Bryce-Smith* [39] to be incorrect. For example, decomposition in the presence of cumene affords no 2,3-diphenyl-2,3-dimethylbutane. It is possible that the alkane formation is due to a disproportionating autometalation [36] of the alkylsodium [40]. Methylsodium decomposes at 200 °C into methane, sodium, and sodium carbide. The thermolysis of methylpotassium, although vigorous at 100 °C, goes to completion only at 250 °C. This suggests the formation of thermally more stable intermediates [36,41]:

$$K{-}CH_3 \xrightarrow{100\,^\circ C} (K_2CH_2) \rightarrow (K_3CH) \xrightarrow{250\,^\circ C} (K_4C) \rightarrow (K_2C_2)\ .$$

Neopentylsodium is also devoid of β-hydrogens. Its decomposition at 144 °C gives, in addition to resins, 17% neopentane, 8% methane, 45% methylsodium, and 0.5% i-butenylsodium [42]. Obviously, a β-elimination of methylsodium is involved, as was observed for the base-catalysed rearrangement of 1,1,3-trimethylcyclohexadienes *(28)* to *m*-xylene [43].



*(28)*

## B. Replacement of the Metal by Hydrogen

### 1. Neutralization with Compounds Containing Active Hydrogen

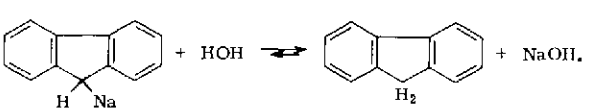
Suitable coreactants for organoalkali compounds, regardless of their bond polarity, are X–Y compounds in which Y can become an anion and X is capable of neutralizing the latent or free carbanion by the formation of a stable, covalent bond.

$$\overset{\delta\oplus\ \ \delta\ominus}{M{-}CR_3} + X{-}Y \rightarrow M^{\oplus} + Y^{\ominus} + X{-}CR_3.$$

In the simplest case, X is hydrogen and Y an acid anion:

$$H_5C_6{-}\underset{(29)}{C(CH_3)_2{-}K} + H{-}Cl \rightarrow H_5C_6{-}CH(CH_3)_2 + KCl;$$

$$H_5C_6{-}Na + H{-}P(C_6H_5)_2 \rightarrow C_6H_6 + Na{-}P(C_6H_5)_2;$$



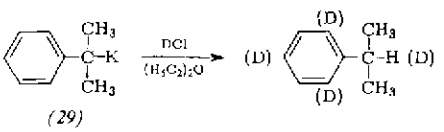
*(30)*

In the third example, the neutralization of a weak organometallic base *(30)* with a weak proton donor ($H_2O$), an equilibrium is observed that is shifted to the right [44].

### 2. Neutralization with Compounds Containing Active Deuterium

On neutralization with heavy water, the metal is replaced by deuterium; thus, a hydrocarbon labelled in a specific position is obtained.

This selectivity is not observed with carbanions with delocalized negative charge. Phenylisopropylpotassium *(29)* reacts with deuterium chloride in ether to afford cumene in which 69% of the α-, 5% of the *ortho*-, and 15% of the *para*-positions are substituted by deuterium. Mass spectrograms indicate that 58% of the product are monodeuterated, 14% dideuterated, and 1% trideuterated; 14% contain no deuterium [45].



*(29)*

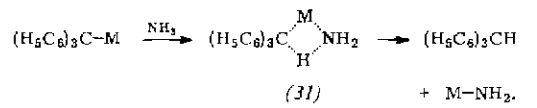
Heavy water [45], carbon dioxide, and dimethyl sulfate [46], on the other hand, attack *(29)* exclusively at the α-position. Even deuterium chloride effects only α-substitution when the more polar solvent 1,2-dimethoxyethane or pentane (in heterogeneous phase) is used instead of ether [45].

### 3. Aminolysis

A "reverse" order of reactivity has been established for the reactions of triphenylmethylalkali-metal compounds with ammonia or piperidine yielding triphenylmethane and alkali amide [47,48]:

$$(H_5C_6)_3C{-}Li > (H_5C_6)_3C{-}Na > (H_5C_6)_3C{-}K$$

This may be due to the greater tendency of the lower alkali metals to form complexes, which might promote the formation of an intermediate *(31)* [48].



*(31)*

### 4. Hydrogenolysis

Molecular hydrogen cleaves organometallic compounds into hydrocarbons and metal hydrides. Whereas the hydrogenolysis of organolithium compounds [49] pro-

[38] *A. A. Morton* and *E. J. Lampher*, J. org. Chemistry *21*, 93 (1936).

[39] *D. Bryce-Smith*, J. chem. Soc. (London) *1955*, 1712.

[40] On the other hand, the photolytic decomposition of organoalkali-metal compounds seems to proceed by a radical process [cf. [22] as well as *H. Linschitz, M. G. Berry*, and *D. Schweitzer*, J. Amer. chem. Soc. *76*, 5833 (1954)].

[41] The isolation of methylenedilithium, $Li_2CH_2$, after mild thermolysis of methyl-lithium has been accomplished [*K. Ziegler, K. Nagel*, and *M. Patheiger*, Z. anorg. allg. Chem. *282*, 345 (1955); Chem. Abstr. *52*, 1203 h (1958)].

[42] *R. A. Finnegan*, Chem. and Ind. *1962*, 895.

[43] *H. Pines* and *H. E. Eschinazi*, J. Amer. chem. Soc. *78*, 5950 (1956).

[44] *R. Weissgerber*, Ber. dtsch. chem. Ges. *34*, 1659 (1901).

[45] *G. A. Russell*, J. Amer. chem. Soc. *81*, 2017 (1959).

[46] *K. Ziegler* and *B. Schnell*, Liebigs Ann. Chem. *437*, 227 (1934).

[47] *C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh*, and *F. C. Frostick*, J. org. Chemistry *20*, 1531 (1955).

[48] *G. Wittig*, Experientia *14*, 389 (1958).

[49] *H. Gilman, A. L. Jacoby*, and *H. Ludeman*, J. Amer. chem. Soc. *60*, 2336 (1938).

ceeds smoothly only under pressure, potassium derivatives [50] react quite readily even under normal conditions. For example:

$$H_5C_6K + H_2 \rightarrow H_6C_6 + KH\ .$$

## 5. Metalations

Pure hydrocarbons also act as proton donors for organometallic compounds. Reactions in which a new organometallic base is produced by replacement of organic hydrogen with a metal atom from another organometallic base are called "metalations" [51]; the term "anionization" denotes proton abstraction from distinctly acidic reactants such as inorganic acids, alcohols, enols, esters, or nitriles. In metalations, as in other acid-base reactions, the weaker organometallic base and the less acidic hydrocarbon are generally produced:

$$H_5C_6{-}Na + H_3C{-}CH{=}CH_2 \rightarrow H_6C_6 + [H_2C{-}CH{=}CH_2]^{\ominus}Na^{\oplus}$$

For sodium and potassium compounds, the differences in acidity can be rather small. Thus, phenyl-lithium is a poor metalating agent even for triphenylmethane, whereas phenylpotassium reacts readily with toluene.

Table 1 gives a list of several representative hydrocarbons, and Table 2 of a few amines and alcohols, arranged according to their acidic strengths [52a–52d].

Table 1. Acid strengths of acidic hydrocarbons.

| Proton donor | $pK_a$ |
|---|---|
| $R_3CH$ (R=H, alkyl) | 40 [*] |
| $H_2C{=}CH_2$ | 39 [*] |
| $C_6H_6$ | 39 [*] |
| $H_5C_6{-}CH(CH_3)_2$ | 37 |
| $H_5C_6{-}CH_3$ | 37 |
| $H_2C{=}CH{-}CH_3$ | 37 [*] |
| $(H_5C_2)_2CH_2$ | 35 |
| $(H_5C_6)_3CH$ | 33 |
| Fluorene | 25 |
| Indene | 21 |
| $H_5C_6{-}C{\equiv}C{-}H$ | 21 |

[*] Extrapolated values.

Table 2. Acid strength of amines and alcohols.

| Proton donor | $pK_a$ |
|---|---|
| $NH_3$ | 36 |
| $H_5C_6{-}NH_2$ | 27 |
| $(H_5C_6)_2NH$ | 23 |
| $(H_3C)_3COH$ | 19 |
| $H_3COH$ | 16 |

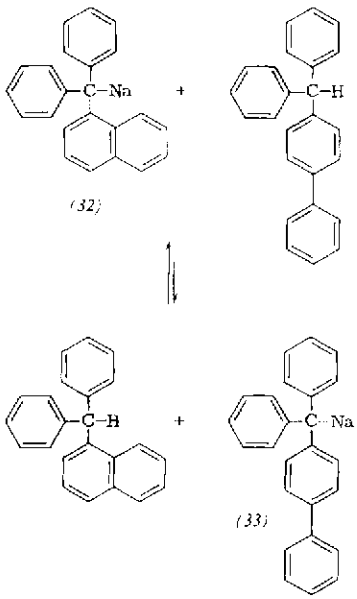
In accordance with experimental results, the following order of basic strengths for organosodium and organopotassium compounds can be derived from Table 1:

$$\text{alkyl-M} > \text{aryl-M} > \text{benzyl-M} > (H_5C_6)_3C{-}M\ .$$

The more subtle differences established for organolithium compounds are probably also applicable to the higher alkali metals:

$$\text{tert.alkyl-M} > \text{sec.alkyl-M} > \text{prim.alkyl-M} > C_6H_5{-}M > H_3C{-}M\ .$$

If the hydrocarbons involved in an acid-base reaction are nearly equal in acidity, an equilibrium will result which for potassium derivatives is attained within a few hours and for sodium derivatives [*(32)* ⇌ *(33)*] only after one month [52a].




### a) *Allylic Compounds*

Propylene reacts readily with amylsodium to afford the allyl anion, which can be characterized by carboxylation to give vinylacetic acid *(34)*; in addition, 15 % of a dicarboxylic acid formed by dimetalation is obtained [53].

$$H_2C{=}CH{-}CH_3 \xrightarrow{H_{11}C_5{-}Na} [H_2C{=}CH{-}CH_2]Na$$

$$\xrightarrow[2.\ H_2O]{1.\ CO_2} H_2C{=}CH{-}CH_2{-}COOH\ \textit{(34)},\ 69\ \%$$

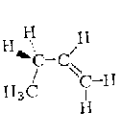
The isomerization of olefins discovered by *Morton* [54] is promoted by catalytic amounts of organometallic compounds and proceeds by way of such allylic anions:

1-Pentene → *trans*-2-pentene

1-Octene → *trans*-2-octene

β-Pinene → α-pinene

The double-bond shift can be followed readily in reactions catalyzed with potassium t-butoxide in dimethyl sulfoxide [55]. Thus 1-butene first yields mainly *cis*-2-butene, which then slowly rearranges to the thermodynamically more stable isomer *trans*-2-butene. Apparently, the removal of a proton from a conformation such as *(35)*, resulting in a *cis*-anion and a *cis*-olefin, is particularly easy.



*(35)*

[50] *K. Clauss* and *H. Bestian*, Liebigs Ann. Chem. *654*, 8 (1962).

[51] *H. Gilman* and *G. F. Wright*, Chem. Reviews *11*, 1323 (1932). – It is not possible to differentiate sharply between metalation and anionization, in view of the gradual transition from strong to weak organometallic bases.

[52a] *J. B. Conant* and *G. W. Wheland*, J. Amer. chem. Soc. *54*, 1212 (1932).

[52b] *W. K. McEwen*, J. Amer. chem. Soc. *58*, 1124 (1936).

[52c] *A. Streitwieser*, Tetrahedron Letters *1960*, No. 6, 23.

[52d] Cf. the new, more extensive list of $pK_a$ values compiled by *D. J. Cram*, Chem. Engng. News *41*, No. 33, p. 93 (1963).

[53] *A. A. Morton* and *M. E. T. Holden*, J. Amer. chem. Soc. *69*, 1675 (1947).

[54] *A. A. Morton* and *E. J. Lanpher*, J. org. Chemistry *20*, 839 (1955).

[55] *A. Schriesheim* and *C. A. Rowe*, Tetrahedron Letters *1962*, 405.

b) *Benzylic Compounds*

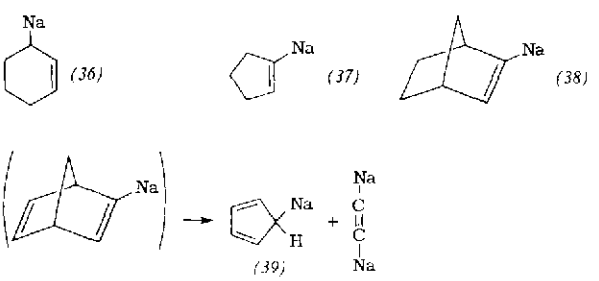
Amylsodium metalates toluene instantaneously to give benzylsodium [56]. Phenylsodium is less basic and therefore reacts quantitatively with toluene only on prolonged boiling, whereas the reaction with diphenyl- and triphenylmethane occurs in the cold. The reaction of amylsodium with ethylbenzene is slower than that with toluene. In the reaction of amylsodium with cumene substitution no longer takes place at the sterically protected α-position but instead, preferentially at the more readily available ring hydrogens (55 % *meta*, 42 % *para*). *Benkeser* [57] differentiates between kinetically and thermodynamically controlled reactions. Thus, after 3 hours' treatment with amylpotassium, cumene gives 42 % α-, 39 % *meta*-, and 19 % *para*-metalated product; however, a 20 hour reaction period affords exclusively phenylisopropylpotassium.

c) *Olefins*

The acidity of a C–H bond increases with increasing s-character ($sp > sp^2 > sp^3$) [58]. Accordingly, alkali alkyls replace an olefinic hydrogen by a metal atom, provided that, as in ethylene [59] or 3,3-dimethyl-1-butene [59], more readily metalated allylic hydrogens are absent.

$$(H_3C)_3C-CH=CH_2 \xrightarrow{H_{11}C_5-Na} (H_3C)_3C-CH=CH-Na \quad (61\,\%).$$

Ring strain also enhances the s-character of exocyclic bonds. Whereas cyclohexene and amylsodium interact to form an allylic anion *(36)*, cyclopentene [60], norbornene [61], and norbornadiene [62] undergo metalation with increasing ease to the derivatives *(37)*, *(38)*, and *(39)*, respectively [63a,63b], with ring opening in the last case.



The olefinic hydrogen in 2,3,3-trimethyl-1-cyclopropene [64] is nearly as active as the hydrogen in acetylene; hence, it is replaced even with methyl-lithium. Cyclopropane [65] reportedly reacts with amylsodium to give cyclopropylsodium [66].

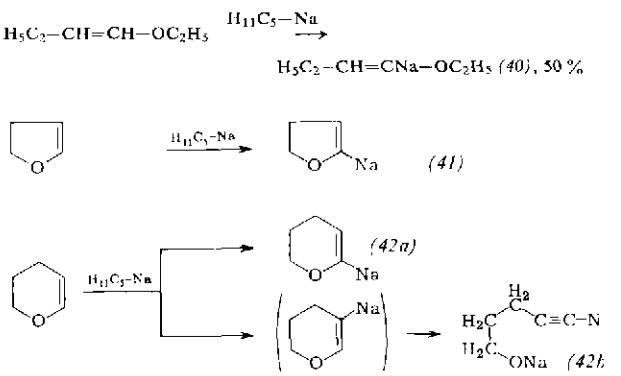
d) *Aromatic Compounds*

Benzene hardly reacts with n-butyl-lithium [67] but is metalated by amylsodium at elevated temperatures to give a 90 % yield of phenylsodium; a small amount of phenylenedisodium is formed as by-product. *m*-Phenylenedisodium is reportedly obtained in 85 % yield if benzene is used in less than the stoichiometric amount [68].

The acidity of polyphenyls and naphthalene differs only slightly from that of benzene. These hydrocarbons, therefore, cannot be metalated at all or only to a slight extent [69,70]. The reaction of naphthalene with amylsodium produces a mixture of the α- and β-isomers of mono-, di-, and trimetalated products [71].

e) *Heterosubstituted Olefins and Heterocycles*

Because of the electron attraction of the hetero-atom, metalation of vinyl ethers involves the alpha rather than the allylic hydrogen, leading for example, to *(40)*, *(41)*, *(42a)*, and *(42b)* [72].



In the case of dihydropyran, the formation of the stable α-metalated derivative is accompanied by a ring opening promoted by β-metalation. The pseudoaromatics furan

[56] *A. A. Morton* and *I. Hechenbleikner*, J. Amer. chem. Soc. *58*, 2599 (1936).

[57] *R. A. Benkeser* and *T. V. Liston*, J. Amer. chem. Soc. *82*, 3221 (1960).

[58] Cf. *F. Bohlmann*, Angew. Chem. *69*, 82 (1957).

[59] *A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little*, and *R. L. Letsinger*, J. Amer. chem. Soc. *72*, 3785 (1950).

[60] *A. A. Morton* and *R. A. Finnegan*, J. Polymer Sci. *38*, 19 (1959).

[61] *R. A. Finnegan* and *R. S. McNees*, Chem. and Ind. *1961*, 1450.

[62] *R. A. Finnegan* and *R. S. McNees*, Tetrahedron Letters *1962*, 755.

[63a] Cf. *A. Streitwieser* and *R. A. Caldwell*, J. org. Chemistry *27*, 3360 (1962).

[63b] *G. Schröder*, personal communication; studies on base-catalysed deuterium exchange have confirmed the cited increase in acidity.

[64] *G. L. Closs* and *L. E. Closs*, J. Amer. chem. Soc. *83*, 1003 (1961).

[65] For information concerning the unsaturated character of cyclopropane, see *H.A. Staab*: Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim 1959, p. 54; and *E. Vogel*, Fortschr. chem. Forsch. *3*, 430 (1955).

[66] *E. J. Lanpher, L. M. Redmen*, and *A. A. Morton*, J. org. Chemistry *23*, 1370 (1958).

[67] *R. V. Young*, Iowa State Coll. J. Sci. *12*, 177 (1937); quoted from *H. Gilman* and *J. W. Morton* in: Organic Reactions. Wiley, New York 1954, Vol. VIII, p. 265.

[68] *A. A. Morton, E. L. Little*, and *W. O. Strong*, J. Amer. chem. Soc. *65*, 1339 (1943); cf. *D. Bryce-Smith* and *E. E. Turner*, J. chem. Soc. (London) *1953*, 861.

[69] *A. A. Morton, J. T. Massengale*, and *G. M. Richardson*, J. Amer. chem. Soc. *62*, 126 (1940).

[70] *H. Gilman* and *R. L. Bebb*, J. Amer. chem. Soc. *61*, 109 (1939).

[71] *A. A. Morton, J. B. Davidson, T. R. P. Gibb, E. L. Little, E. W. Clarke*, and *A. G. Green*, J. Amer. chem. Soc. *64*, 2250 (1942).

[73, 74] and thiophene [75] undergo substitution of the α-hydrogens by metal with surprising ease. With excess amylsodium, both heterocycles give the 2,5-dimetalated derivatives, thiophene reacting more readily than furan [76].

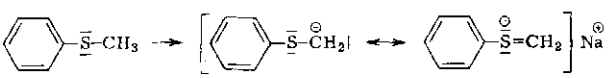
f) *Heterosubstituted Aromatic Compounds*

More remote hydrogens can also be activated by electronegative hetero-atoms, albeit to a lesser extent. This activation accounts for the ease of metalation of *ortho*-hydrogens in aryl halides, aryl ethers, and benzotrifluoride [77].

The ability of ring hydrogens to undergo metalation is strongly enhanced by hetero-atoms of the first period which obey the octet rule, indicating inductive effects. Substituents can be arranged in the order of their acidifying effect, as follows:

$$F > F_3C > H_5C_6O > H_3CO > Cl > Br > (H_3C)_2N > H\,.$$

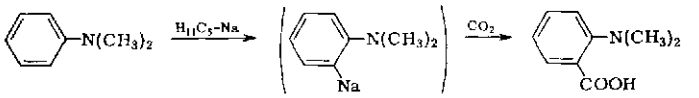
Anisole [56, 70], diphenyl ether [78], and diphenyl sulfide [70] are metalated in the *ortho*-position. With methyl phenyl sulfide, the side chain is more reactive because the d-orbitals of the sulfur participate in the resonance *(43)* [79].



*(43)*

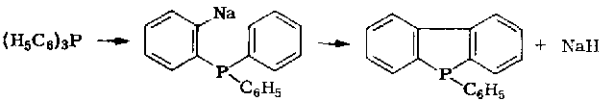
The behavior of dibenzothiophene is similar to that of the acyclic diphenyl sulfide, *i.e.* it is metalated by strong organometallic compounds in one of the two *ortho*-positions [70]. The *ortho*-positions in dibenzofuran are far more activated. This compound is attacked even by methyl-lithium, and benzylsodium, a relatively weak base, converts it into the *o,o'*-disodio derivative in 80 % yield [80].

Aniline [81] and its derivatives [56, 70, 82] are also metalated in the *ortho*-position [*e.g. (44)*].



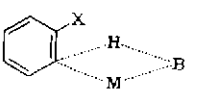
*(44)*

Under drastic conditions, n-butyl-lithium slowly attacks triphenylamine [83], triphenylphosphine [84], and triphenylarsine [85] at the *meta*-position. At 70 °C, phenylsodium converts triphenylphosphine into diphenylenephenylphosphine *(45b)* [86] presumably by intramolecular elimination of sodium hydride from the *ortho*-metalated form *(45a)*. The *meta*-metalated compound formed undergoes subsequent hydrolytic decomposition.

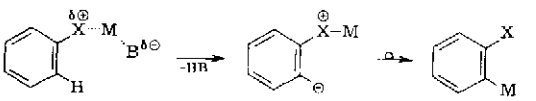


*(45a)* *(45b)*, 15%

The seeming randomness with which organometallic bases bring about metal-hydrogen exchange – sometimes in the *ortho*- and sometimes in the *meta*-position – has prompted extensive discussions of the underlying mechanism. The interpretation of metalation as an electrophilic reaction [87] or as a free-radical process [88] is obsolete. It is now known that the reaction occurs by a nucleophilic, or more correctly, a protophilic [89], attack by the base. According to the concept developed by *Huisgen* [90], the process has a concerted mechanism (F 2) involving a four-centered transition state *(46)* and does not entail an associated precursor *(47)* [77].



*(46)*



*(47)*

g) *Eliminations Leading to Arynes*

Studies involving trapping and symmetrizing reactions have demonstrated the striking readiness with which *ortho*-metalated aryl halides [91–93] release the oppositely polarized substituent and thus afford arynes such as dehydrobenzene *(48)*, which cannot be isolated as such.

[72] *R. Paul* and *S. Tchelitcheff*, C. R. hebd. Séances Acad. Sci. *235*, 1226 (1952); Bull. Soc. chim. France, Documentat. *19*, 808 (1952).

[73] *H. Gilman* and *F. Breuer*, J. Amer. chem. Soc. *56*, 1123 (1934).

[74] *A. A. Morton* and *J. T. Massengale*, J. Amer. chem. Soc. *65*, 1346 (1943).

[75] *J. W. Schick* and *H. D. Hartough*, J. Amer. chem. Soc. *70*, 286 (1948).

[76] *A. A. Morton* and *C. E. Claff*, J. Amer. chem. Soc. *76*, 4935 (1954).

[77] *J. D. Roberts* and *D. Y. Curtin*, J. Amer. chem. Soc. *68*, 1658 (1946).

[78] *A. Lüttringhaus* and *G. v. Sääf*, Angew. Chem. *52*, 578 (1939); Liebigs Ann. Chem. *542*, 241 (1939).

[79] *H. Gilman* and *F. J. Webb*, J. Amer. chem. Soc. *71*, 4062 (1949).

[80] *H. Gilman*, *F. W. Moore*, and *O. Baine*, J. Amer. chem. Soc. *63*, 2479 (1941).

[81] *A. A. Morton* and *R. L. Letsinger*, unpublished data; taken from [1c]; cf. also [82].

[82] *H. Gilman*, *G. E. Brown*, *F. J. Webb*, and *S. M. Spatz*, J. Amer. chem. Soc. *62*, 977 (1940).

[83] *H. Gilman* and *G. E. Brown*, J. Amer. chem. Soc. *62*, 3208 (1940).

[84] *H. Gilman* and *G. E. Brown*, J. Amer. chem. Soc. *67*, 824 (1945).

[85] *H. Gilman* and *C. G. Stuckwisch*, J. Amer. chem. Soc. *63*, 3532 (1941).

[86] *G. Wittig* and *G. Geissler*, Liebigs Ann. Chem. *580*, 50 (1953). An analogous ring closure leading to dibenzothiophene had been accomplished previously by *A. Lüttringhaus*, *G. Wagner*, *G. v. Sääf*, *E. Sucker*, and *G. Borth*, Liebigs Ann. Chem. *557*, 54 (1947).

[87] *A. A. Morton*, Chem. Reviews *35*, 23 et seq. (1944); J. Amer. chem. Soc. *69*, 969 (1947).

[88] *A. A. Morton*, *C. E. Claff*, and *F. W. Collins*, J. org. Chemistry *20*, 428 (1955).

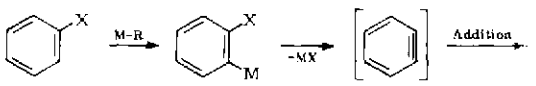
[89] *D. Bryce-Smith*, J. chem. Soc. (London) *1954*, 1079; *D. Bryce-Smith*, *V. Gold*, and *D. P. N. Satchell*, ibid. *1954*, 2743.

[90] *R. Huisgen*, Angew. Chem. *72*, 100 (1960).

[91] *G. Wittig*, Naturwissenschaften *30*, 699 (1942); Angew. Chem. *69*, 245 (1957).

[92] *E. F. Jenny*, *M. C. Caserio*, and *J. D. Roberts*, Experientia *14*, 349 (1958).

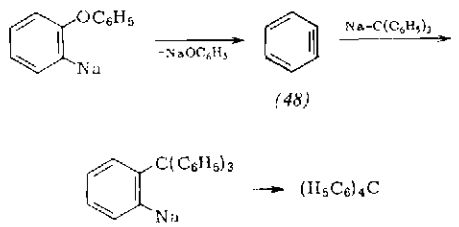
[93] *R. Huisgen* in *H. Zeiss*: Organometallic Chemistry. Reinhold Publ. Corp., New York 1960, p. 36 et seq.



(48)

The metalating agents most frequently used in investigations of arynes were organolithium reagents and lithium amide [94]. However, intermediate formation of *o*-phenylene in the reaction of amylsodium with chlorobenzene was already discussed by *Morton* [95] in order to explain the formation of triphenylene and amylbenzene.

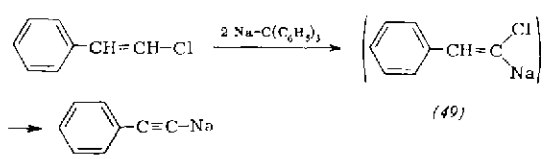
*o*-Halogenophenylalkali-metal compounds lose alkali halide even below 50 °C. *ortho*-Metalated diaryle thers eliminate phenoxide ion only on heating, because of the stronger bond between the aryloxy group and the ring. The elimination of this group as an anion is facilitated by a high electron density at the adjacent position. For this reason, *o*-phenoxyphenylsodium decomposes at 60 °C faster than *o*-phenoxyphenyl-lithium [96,97]. The dehydrobenzene *(48)* formed can be trapped *in situ* with triphenylmethylsodium [96].



(48)

h) *Eliminations Leading to Acetylenes*

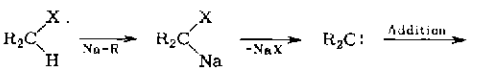
Acyclic acetylenes are lower in energy than the arynes which have a strained triple bond [98]. Accordingly, metalated intermediates could not yet be detected in the dehydrohalogenation of vinyl chlorides with organosodium reagents [99]. The analogous metalation of vinyl ethers and model reactions [100], however, suggest primary attack on the α-hydrogen with formation of *(49)*.



(49)

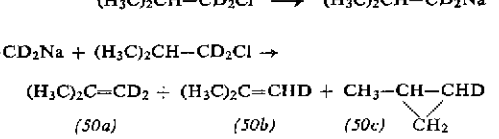
i) *Eliminations Leading to Carbenes*

The carbenes [101], like the arynes, are short-lived electrophiles that are extremely rich in energy and can hence be detected only by means of trapping reactions. The organometallic precursors of the carbenes are obtained by α-metalation of heterofunctional aliphatics and bear on the same carbon oppositely polarized substituents which are released by α-elimination.



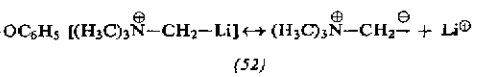
Haloforms [102] and α-chloroalkyl thioethers [103] are sufficiently acidic to be metalated even by alkoxides. On the other hand, the introduction of a metal into α-chloroalkyl ethers [104], dihalogenomethanes [105], and particularly alkyl halides requires the strongest organometallic bases. Thus, methylene is reported to be formed by action of phenylsodium on methyl chloride and to add on in the nascent state to cyclohexene affording norcarane in 1 % yield [106].

*Kirmse* and *Doering* [107] used isotope techniques and collected valuable information concerning the reaction of sodium with primary, secondary, or tertiary butyl halides. Following α-elimination, the carbene is stabilized by either a hydride shift *(50b)* or cyclopropane ring closure *(50c)*; β-elimination to yield *(50a)* also occurs, but no γ-elimination.



α-Elimination increases when potassium is used in place of sodium but is negligibly small with lithium.

Carbene precursors with sodium and chlorine on the same carbon are unstable even at very low temperatures. Replacement of the halogen by a poorer leaving group makes it possible to trap the metalated carbene precursor, for example *(51)* and *(52)*.



In tetrahydrofuran or 1,2-dimethoxyethane, *(51)* undergoes isomerization to triphenylmethoxide (Wittig rearrangement). In ether or petroleum ether, decomposition to diphenylcarbene and phenoxide seems to occur [22,108].

[94] Particular attention is called to the studies of *R. Huisgen* et al., Chem. Ber. *92*, 192 (1959); *93*, 412 (1960).

[95] *A. A. Morton, J. B. Davidson,* and *B. L. Hakon,* J. Amer. chem. Soc. *64*, 2242 (1942).

[96] *A. Lüttringhaus* and *K. Schubert*, Naturwissenschaften *42*, 17 (1955); *A. Lüttringhaus* and *H. Schuster*, Angew. Chem. *70*, 438 (1958).

[97] *G. Wittig* and *L. Pohmer*, Chem. Ber. *89*, 1334 (1956).

[98] With regard to the nature of the aryne bond see *R. Huisgen*, Angew. Chem. *72*, 107 (1960).

[99] *G. Wittig* and *H. Witt*, Ber. dtsch. chem. Ges. *74*, 1474 (1941); *G. Wittig* and *G. Harborth*, ibid. *77 B*, 306, 315 (1944); *G. Wittig* and *M. Schlosser*, unpublished work.

[100] *S. J. Cristol* and *R. S. Bly*, J. Amer. chem. Soc. *83*, 4027 (1961).

[101] Reviews: *W. Kirmse*, Angew. Chem. *71*, 537 (1959); *73*, 161 (1961).

[102] *J. Hine*, J. Amer. chem. Soc. *72*, 2438 (1950); *J. Hine, R. C. Peek,* and *B. D. Oakes*, ibid. *76*, 827 (1954); *W. v. E. Doering* and *A. K. Hoffmann*, ibid. *76*, 6162 (1954).

[103] *U. Schöllkopf* and *G. J. Lehmann*, Tetrahedron Letters *1962*, 165.

[104] *U. Schöllkopf, A. Lerch,* and *W. Pitteroff*, Tetrahedron Letters *1962*, 241.

[105] *G. L. Closs* and *L. E. Closs*, J. Amer. chem. Soc. *81*, 4996 (1959).

[106] *L. Friedman* and *J. G. Berger*, J. Amer. chem. Soc. *82*, 5758 (1960).

[107] *W. Kirmse* and *W. v. E. Doering*, Tetrahedron *11*, 266 (1960); cf. *L. Friedman* and *J. G. Berger*, J. Amer. chem. Soc. *83*, 492, 500 (1961); *P. S. Skell* and *A. P. Krapcho*, ibid. *83*, 754 (1961); and [95].

[108] Cf. *U. Schöllkopf* and *M. Eisert*, Angew. Chem. *72*, 349 (1960).

The function of the organometallic bond as an electron reservoir becomes manifest in the cleavage of nitrogen ylides *(52)*. Ylides prepared with phenyl-lithium or in the presence of lithium salts are stable [109]; more electropositive metals, *e.g.* Na *(52a)*, promote cleavage of the ylides into amine and carbene [109a]. Sulfonium ylides are unstable and decompose similarly [110a, 110b].

$$(H_3C)_4N^{\oplus}Br^{\ominus} \xrightarrow{Na-C_6H_5} (H_3C)_3\overset{\oplus}{N}-\overset{\ominus}{C}H_2\cdots Na \rightarrow (H_3C)_3N + :CH_2$$

*(52a)*

k) *Eliminations Leading to Olefins*

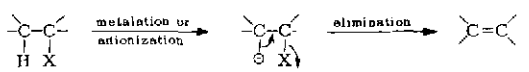
The reaction of organometallic compounds with alkyl halides yields carbenes or, as will be discussed later, results in either halogen-metal exchange or condensations leading to hydrocarbons. If the prerequisites for one of these three types of reaction are not entirely satisfied, concurrent β-elimination occurs and may often become the main reaction, *e.g.* as with *(60)*.

$$n\text{-}H_{13}C_6-Cl + H_5C_2-Na \rightarrow n\text{-}H_9C_4-CH=CH_2 + C_2H_6 + NaCl$$

*(60)*, 46 % [111]

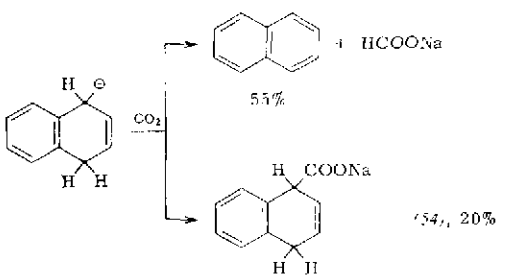
β-Eliminations [112] take place either by the carbanion or the concerted mechanism.

The characteristic of the carbanion mechanism (E 1cB) is an anionic intermediate *(53)* formed by loss of an acidic hydrogen from *(53a)*. The electronegative substituent X is eliminated in a second, rate-determining step.




*(53a)* *(53)*

The elimination of hydrogen chloride from β-chloro sulfones [113] has been explained on the basis of this mechanism. If the substituent to be removed as an anion, *e.g.* a hydride ion, is not a good leaving group, then the anionic intermediate *(53)* can be secured. Thus, 1,4-cyclohexadiene reacts with amylsodium affording a diallyl anion which reacts with carbon dioxide to form

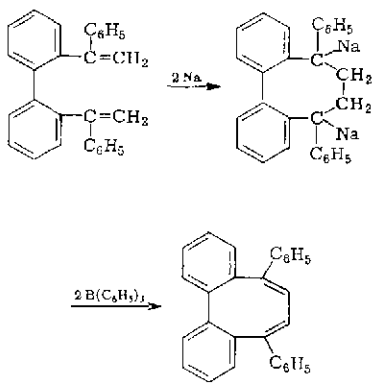



benzene and sodium formate. Carboxylation of the corresponding metalation product obtained from 1,4-dihydronaphthalene affords naphthalene and 1,4-dihydro-1-naphthoic acid *(54)* [114].

If aromatization is precluded, as with *(55)* and *(56)*, elimination of alkali-metal hydride is possible only in the presence of hydride acceptors such as triphenylborane [115].

$$(H_5C_6)_2C-CH_2-H + B(C_6H_5)_3 \rightarrow (H_5C_6)_2C=CH_2 + [HB(C_6H_5)_3]K$$

*(55)*, 73 %



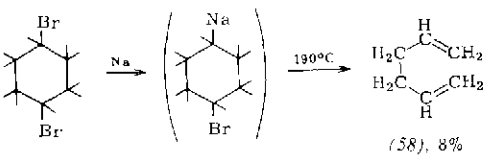

*(56)*, 64%

Sometimes the leaving anion is a carbanion. 3,3,3-Triphenyl-n-propylsodium *(57)* [116] evolves ethylene even in liquid ammonia, whereas the analogous decomposition of 3,3-dimethyl-3-phenyl-n-propylpotassium takes

$$(H_5C_6)_3C-CH_2-CH_2I \xrightarrow[NH_3]{Na} \underset{(57)}{(H_5C_6)_3C-CH_2-CH_2Na} \rightarrow$$

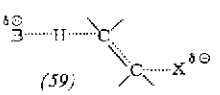
$$(H_5C_6)_3C-Na + CH_2=CH_2$$

place only in boiling cyclohexane [117]. The 1,4-elimination leading from 4-bromocyclohexylsodium to diallyl *(58)* must be effected in boiling decalin.




*(58)*, 8%

Eliminations involving a concerted mechanism (E 2) are much more frequent. The simultaneous bond cleavage and formation circumvents the formation of the high-energy intermediate *(53)* and leads directly to the stable olefinic end product via the transition state *(59)* which is similarly favorable as the transition state occurring in $S_N2$ processes [118].



*(59)*


[109] *G. Wittig* and *M. H. Wetterling*, Liebigs Ann. Chem. *557*, 201 (1944).

[109a] *V. Franzen* and *G. Wittig*, Angew. Chem. *72*, 417 (1960); *G. Wittig* and *S. Krauß*, unpublished work.

[110a] *V. Franzen*, *H. J. Joschek*, and *C. Mertz*, Liebigs Ann. Chem. *654*, 82 (1962).

[110b] *V. J. Hruby* and *A. W. Johnson*, J. Amer. chem. Soc. *84*, 3586 (1962).

[111] *F. C. Whitmore* and *H. D. Zook*, J. Amer. chem. Soc. *64*, 1783 (1942).

[112] Review: *J. Hine*: Physical Organic Chemistry. McGraw-Hill, New York 1956; *J. F. Bunnett*, Angew. Chem. *74*, 731 (1962); Angew. Chem. internat. Edit. *1*, 225 (1962).

[113] *H. L. Goering*, *D. L. Town*, and *B. Dittmar*, J. org. Chemistry *27*, 736 (1962).

[114] *R. Paul* and *S. Tchelitcheff*, C. R. hebd. Séances Acad. Sci. *239*, 1222 (1954).

[115] *G. Wittig* and *W. Stilz*, Liebigs Ann. Chem. *598*, 85, 93 (1956).

[116] *C. B. Wooster* and *R. A. Morse*, J. Amer. chem. Soc. *56*, 1735 (1934).

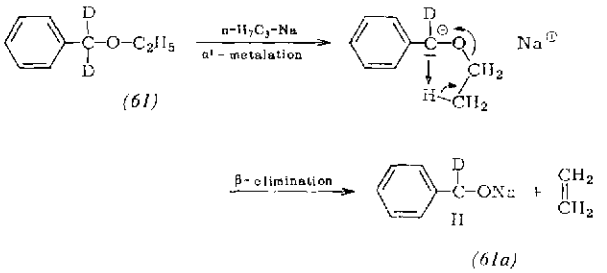
[117] *H. Pines* and *L. Schaaf*, J. Amer. chem. Soc. *80*, 4379 (1958).

Strictly speaking, such concerted eliminations should not be considered as metalation reactions, because, in contrast to all the eliminations discussed so far, metalated, even if short-lived, intermediates are no longer formed.

The cleavage of aliphatic ethers by strong organometallic reagents mentioned above also proceeds by β-elimination [119].

$$H_3C-CD_2-OR \xrightarrow{n\text{-}H_7C_3-Na} H_2C=CD_2 + NaOR + n\text{-}C_3H_8 .$$

Benzyl ethers *(61)* [119], ammonium salts [120], and sulfonium salts [121] are degraded to olefins via α′,β-elimination. The organometallic base attacks the more acidic α′-hydrogens, and the resulting carbanions then undergo a rapid intramolecular β-elimination to form the more stable end product, *e.g. (61a)*.



*(61)* *(61a)*

## C. Replacement of Metal by Halogen

### 1. Halogenolysis

Donors of positive halogen, like active-proton compounds, are capable of heterolysing the organometallic bond. In the chemistry of organolithium compounds, for example, iodolysis has found wide application in both analysis and synthesis [122]. There are no reports that true organosodium and organopotassium derivatievs undergo analogous reactions, although the reaction of iodine with the sodio derivative of ethyl acetate is known [123]:

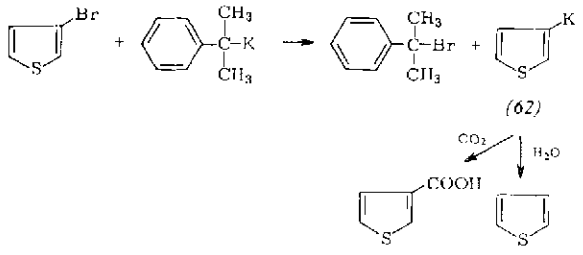
$$H_5C_2OOC-\overset{\ominus}{C}H_2\ Na^{\oplus} \xrightarrow[2.\ \text{Saponification}]{1.\ I_2} I-CH_2-COOH \quad (25\,\%)$$

### 2. Halogen-Metal Interconversion

The reaction of an organic halide with an organometallic compound effecting metathesis of the substituents is referred to as halogen-metal interconversion. If R′H is a stronger acid than RH, the reaction proceeds from left to right:

$$R-M + R'X \rightarrow R-X + R'M .$$

Halogen-metal interconversion is characteristic of organolithium compounds [124] since their associating power is strong enough to give rise to the intermediate complex [125], which is probably responsible for the reaction. Only a few metathesis reactions involving compounds of the higher alkali metals are known; these include n-butylsodium/1-bromonaphthalene [80]; amylsodium/*o*-bromotoluene, bromobenzene, 1-bromonaphthalene [126]; and amylsodium/methyl iodide [95].



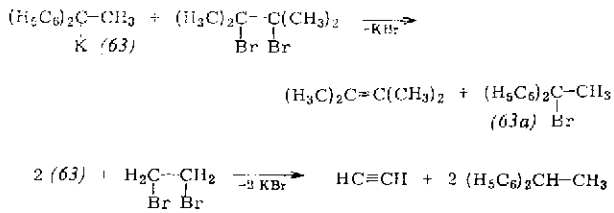
*(62)*



*(62b)*, 62% *(62a)*, 93%

The reaction of 3-bromothiophene with phenylisopropylpotassium to give 3-thienylpotassium *(62)* is surprisingly smooth; *(62)* can then be hydrolysed to thiophene *(62a)* or can be carboxylated to 3-thiophenecarboxylic acid; the phenylisopropyl bromide formed as by-product reacts with excess phenylisopropylpotassium to give 2,3-diphenyl-2,3-dimethyl-n-butane [127].

2,3-Dibromo-2,3-dimethylbutane is a very effective brominating agent. It converts 1,1-diphenylethylpotassium *(63)* into the corresponding bromide *(63a)* which, in turn, reacts with excess *(63)*, to yield 70 % 2,2,3,3-tetraphenyl-n-butane. The reaction of *(63)* with 1,2-dibromoethane, on the other hand, occurs predominantly with elimination [46].



*(63)* *(63a)*

## D. Replacement of the Metal by Carbon and Other Non-Metals

### 1. Alkyl and Aryl Halides

#### a) *Condensations* [128]

The organometallic bond reacts not only with acidic hydrogen or positively charged halogen but also with the positive carbon of organic halides. This C–C coupling proceeds satisfactorily only with alkyl deri-

[118] *C. Ingold*, Proc. chem. Soc. (London) *1962*, 265.

[119] *R. L. Letsinger*, Angew. Chem. *70*, 154 (1958).

[120] *F. Weygand, H. Daniel*, and *H. Simon*, Chem. Ber. *91*, 1691 (1958); Liebigs Ann. Chem. *654*, 111 (1962).

[121] *V. Franzen* and *C. Mertz*, Chem. Ber. *93*, 2819 (1960).

[122] *G. Wittig, D. Hellwinkel*, and *G. Klar*, unpublished work; *H. Gilman* and *J. F. Nobis*, J. Amer. chem. Soc. *67*, 1479 (1945); *E. H. Braye, W. Hübel*, and *I. Caplier*, ibid. *83*, 4406 (1961); *S. Gronowitz* and *R. Håkansson*, Ark. Kemi *16*, 309 (1961).

[123] *E. Müller, H. Gawlick*, and *W. Kreutzmann*, Liebigs Ann. Chem. *515*, 109 (1934).

[124] *R. G. Jones* and *H. Gilman* in: Organic Reactions (The Halogen-Metal-Interconversion Reaction with Organolithium Compounds), Wiley, New York 1951, Vol. VI, p. 339.

[125] *G. Wittig* and *U. Schöllkopf*, Tetrahedron *3*, 91 (1958).

[126] *A. G. Lindstone* and *I. A. Morris*, Chem. and Ind. *1958*, 560.

[127] *G. Wittig* and *V. Wahl*, unpublished work.

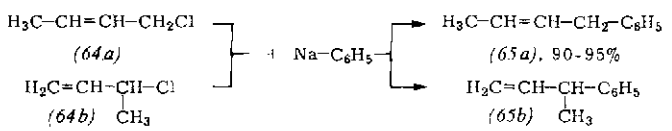
[128] Condensation generally implies a union of two reactants with loss of an electropositive substituent from the one and of an electronegative substituent from the other. The concept of coupling should be restricted to use in the chemistry of dyes.

vatives which are easily substituted. Compounds that are particularly suitable are alkyl iodides [129] and sulfuric esters, *e.g.* dimethyl sulfate [129a].

$$H_5C_6{-}Na + CH_3I \rightarrow C_6H_5{-}CH_3 + NaI$$

Alkyl bromides and chlorides condense so slowly [130] that side reactions, particularly eliminations, predominate. Phenylsodium and n-octyl bromide yield a mixture of condensation product and olefins. Phenyl-lithium is a milder reagent and reacts more slowly, but without undesirable olefin formation [131].

Allyl and benzyl halides are unusually reactive because of the labile halogen they contain. It is noteworthy that the reaction of phenylsodium with the isomeric methylallyl chlorides *(64a)* gave nearly identical mixtures of the two isomeric phenylbutenes *(56a)* and *(56b)* [132].




The extraordinary tendency of alkali-metal derivatives of benzyl, benzhydryl, and triphenylmethyl compounds to give condensation reactions demonstrates that the rate of C–C coupling depends less on basicity than on bond polarity. For example:

$$(H_5C_6)_3C{-}Na + CH_3I \rightarrow (H_5C_6)_3C{-}CH_3 \quad [20, 133]$$

$$(H_5C_6)_2CH{-}Na + CH_2Cl_2 \rightarrow (H_5C_6)_2CH{-}CH_2Cl \quad [134]$$

$$(H_5C_6)_2C(CH_3){-}K + CH_2Cl_2 \rightarrow (H_5C_6)_2C(CH_3){-}CH_2Cl \quad [135]$$

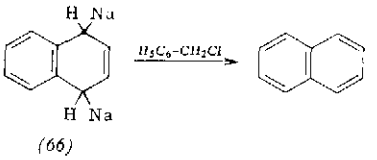
Condensations between benzyl-metal compounds and benzyl halides, *i.e.* between a free carbanion and a labile halogen, are immeasurably fast. The same is true for the following reactions:

$$(H_5C_6)_3C{-}Na + Cl{-}CH_2OCH_3 \rightarrow (H_5C_6)_3C{-}CH_2OCH_3 \quad [136]$$

$$(H_5C_6)_3C{-}Na + Cl{-}COOC_2H_5 \rightarrow (H_5C_6)_3C{-}COOC_2H_5 \quad [137]$$

Steric hindrance sometimes causes elimination to occur rather than condensation. For example, because of its bulk, triphenylmethylsodium only splits off hydrogen chloride from isopropyl chloride [136].

Organometallic derivatives formed by addition of the elemental metal onto unsaturated compounds generally do not undergo condensation; instead, they regenerate the initial hydrocarbon, *e.g. (66)* [138].




*(66)*

b) *The Wurtz-Fittig Reaction*

The Wurtz reaction is a preparative variation of the condensations described under D. 1a). An alkyl halide, preferably an iodide, is treated with metallic sodium to promote C–C coupling of two alkyl radicals. Sodium alkyls are formed [139] which then undergo condensation with unreacted halide.

$$R{-}I \xrightarrow{Na} (R{-}Na) \xrightarrow{R{-}I} R{-}R.$$

With alkyl chlorides, the condensation reaction can be effectively suppressed by applying special conditions; instead, the formation of organosodium compounds is achieved [140].

Intramolecular Wurtz condensations with 1,3- or 1,4-dihalogenoalkanes yield cyclopropanes or cyclobutanes. The scope of intermolecular reactions is restricted, for only symmetrical hydrocarbons can be formed in good yields. If two different alkyl halides, RX and R′X, are used, a mixture of three products, R–R′, R–R, and R′–R′, will result.

The special variant of this condensation discovered by *Fittig* [141], *i.e.* the halogenation of a mixture of aryl and alkyl halides, leads predominantly to unsymmetric products; pure aliphatic derivatives or diaryls are hardly formed [142]. This selectivity arises from pronounced differences in the reactivities of the coreactants. Aryl halides react with sodium faster than alkyl halides. On the other hand, aliphatic halogen can be more easily substituted than aromatic halogen.

c) *Stereochemistry of the Condensations*

When optically active alkyl and benzyl halides were treated with organometallic compounds, sometimes hydrocarbon formation occurred with complete racemization, and sometimes the racemization was accompanied by inversion. Table 3 gives a summary of the stereochemical course of the condensation of various organometallic compounds with ( )-2-bromooctane.

Simple sodium alkyls, *e.g.* n-butylsodium, condense with optically active alkyl bromides with total loss of

[129] *A. A. Morton* and *F. Fallwell*, J. Amer. chem. Soc. *59*, 2387 (1937).

[129a] *D. Bryce-Smith* and *E. E. Turner*, J. chem. Soc. (London) *1950*, 1975.

[130] The ease of condensation of various butyl halides with n-butyl-lithium was investigated by *K. Ziegler* and *H. Colonius*, Liebigs Ann. Chem. *479*, 135 (1930).

[131] *W. H. Puterbaugh* and *C. R. Hauser*, J. org. Chemistry *24*, 416 (1959).

[132] *S. J. Cristol* and *W. C. Overhaults*, J. Amer. chem. Soc. *73*, 2932 (1951).

[133] *C. B. Wooster* and *N. W. Mitchell*, J. Amer. chem. Soc. *52*, 688 (1930).

[134] *C. R. Hauser*, *W. G. Kofron*, *D. R. Dunnavan*, and *W. F. Owens*, J. org. Chemistry *26*, 2627 (1961).

[135] *H. E. Zimmerman* u. *A. Zweig*, J. Amer. chem. Soc. *83*, 1196 (1961).

[136] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *464*, 1 (1928).

[137] *J. B. Conant* and *A. H. Blatt*, J. Amer. chem. Soc. *51*, 1227 (1929).

[138] *N. D. Scott*, *J. F. Walker*, and *V. L. Hansley*, J. Amer. chem. Soc. *58*, 2442 (1936).

[139] Cf. *J. Hine:* Physical Organic Chemistry. McGraw-Hill, New York 1956.

[140] *A. A. Morton* and *I. Hechenbleikner*, J. Amer. chem. Soc. *58*, 1697 (1936).

[141] *R. Fittig* and *J. König*, Liebigs Ann. Chem. *144*, 277 (1867).

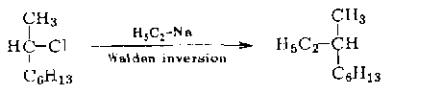
[142] For information on the different, but invariably slow, rates of condensation of phenyl halides and phenyl-lithium, see *G. Wittig*, *G. Pieper*, and *G. Fuhrmann*, Ber. dtsch. chem. Ges. *73*, 1193 (1940).

Table 3. Condensation of organometallic compounds R—M with (−)-2-bromooctane (R′—Br).

| R—M | R—R′ [%] | Racemate [%] | Ref. |
|---|---|---|---|
| Benzylmagnesium bromide | | | |
| $H_2C$=CH—$CH_2$—Na | 83 | 13 [*] | [143] |
| $H_2C$=CH—$CH_2$—MgBr | 78 | 13 [*] | [143] |
| $H_5C_6$—$CH_2$—Na | 81 | 30 [*] | [144] |
| $H_5C_6$—$CH_2$—MgBr | 17 | 91 [*] | [143] |
| $H_5C_2$—Na | 25 | 97 [*] | [145] |
| n-Butylsodium | 35 | 100 | [144] |
| 2-Octylsodium | — | 100 | [145] |

[*] The configuration of the remainder of R—R′ is opposite to that of R′—Br.

activity, whereas the latter is preserved in condensations with the analogous alkyl chlorides, although inversion takes place. Thus, the reaction of (+)-2-chlorooctane with ethylsodium affords (+)-3-methylnonane *(67)* with only 20 % racemization.




$\alpha = +26{,}61°$ *(67)*, 6 %; $\alpha = +5{,}16°$

Two hypotheses have been advanced to explain the racemization observed in the case of alkyl bromides. According to the one theory, the sodium ion causes the alkyl bromide to dissociate into a carbonium ion [146a, 146b], while in the other, the racemization is supposed to be preceded by a rapid halogen-metal interconversion and to proceed by way of a carbanion [119].

### 2. Non-Metal Halides

Phenylsodium condenses with boron trichloride to give triphenylborane (50 %) or with silicon tetrachloride at −40 °C to form a mixture of trichlorophenylsilane (38 %), dichlorodiphenylsilane (14 %), and tetraphenylsilane (35 %). Phosphorus trichloride reacts with phenylsodium to give triphenylphosphine, and with benzylsodium to give tribenzylphosphine (84 %) [147]. Silane [148a] and triarylsilanes [148b] condense with organoalkali-metal compounds resulting in elimination of alkali-metal hydride.

[143] *R. L. Letsinger* and *J. G. Traynham*, J. Amer. chem. Soc. *72*, 849 (1950).

[144] *R. L. Letsinger*, J. Amer. chem. Soc. *70*, 406 (1948).

[145] *N. G. Brink*, *J. F. Lane*, and *E. S. Wallis*, J. Amer. chem. Soc. *65*, 943 (1943).

[146a] *S. E. Ulrich*, *F. H. Gentes*, *J. F. Lane*, and *E. S. Wallis*, J. Amer. chem. Soc. *72*, 5127 (1950).

[146b] *J. F. Lane* and *S. E. Ulrich*, J. Amer. chem. Soc. *72*, 5132 (1950).

[147] *J. F. Nobis*, *L. F. Moormeier*, and *R. E. Robinson:* Organosodium Compounds for Preparation of Other Carbon-Metal Bonds in Metalorganic Compounds. Advances in Chemistry Series, No. 23, published by the Amer. Chem. Soc., Washington D.C. 1959, p. 63 et seq.

[148a] *J. S. Peake*, *W. H. Nebergall*, and *Y. T. Chen*, J. Amer. chem. Soc. *47*, 1526 (1925).

[148b] *R. A. Benkeser* and *F. J. Riel*, J. Amer. chem. Soc. *73*, 3472 (1951).

## E. Replacement of the Metal by Another Metal

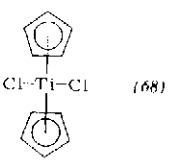
### 1. Reactions with Metal Halides [149]

The substitution of an alkali-metal atom in an organometallic compound by another less electropositive one occurs quantitatively with inorganic salts. This represents a convenient and effective method for preparing Grignard reagents in hydrocarbon solution [150].

$$MgBr_2 + H_5C_6—Na \rightarrow H_5C_6—MgBr + NaBr$$

Similarly, lithium halides or alkoxides transform phenylsodium into phenyl-lithium, and the reaction of aluminum trichloride with butylsodium yields dibutylaluminum chloride [147].

The synthesis of π-complexes from the weak base cyclopentadienylsodium and transition metal salts falls into the same category as these reactions. Ferrocene can be synthetized in this way [151] from ferrous chloride, and titanocene *(68)* [152] from titanium(IV) chloride, both in 90 % yield.




*(68)*

### 2. Reactions with Metals

When the substituting metal is used in elemental form, the nobler (*i.e.* less electronegative) metal separates out also in elemental form. This phenomenon is applied for the preparation of potassium derivatives from organolithium or organosodium compounds [153].

$$K\cdot + n\text{-}H_9C_4—Li \xrightarrow{-Li\cdot} (n\text{-}H_9C_4—K) \xrightarrow[86\,\%]{H_5C_6} H_5C_6—K\,.$$

## F. Addition Reactions

In all the reactions discussed so far, the residue Y in polarizable compounds X—Y was displaced by a carbanion (cryptoanion):

$$M—CR_3 + X—Y \rightarrow X—CR_3 + M^{\oplus}Y^{\ominus}.$$

The reactions dealt with in the following all have the common feature that the organoalkali compound adds onto an electron-deficiency site *(69)* or across a multiple bond *(70)*.

[149] These reactions could also be considered as condensations of metal halides with organoalkali-metal compounds.

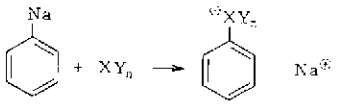
[150] US.-Pat. 2795626 (June 11th, 1957) and 2914578 (Nov. 24th, 1959) National Distillers and Chem. Corp., inventors: *J. F. Nobis* and *R. E. Robinson*; cf. Chem. Abstr. *54*, 15318h (1960).

[151] *W. F. Little*, *R. C. Koestler*, and *R. Eisenthal*, J. org. Chemistry *25*, 1435 (1960).

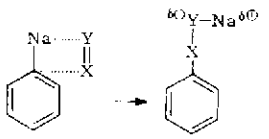
[152] *G. Wilkinson* and *J. M. Birmingham*, J. Amer. chem. Soc. *76*, 4281 (1954).

[153] *D. Bryce-Smith* and *E. E. Turner*, J. chem. Soc. (London) *1953*, 861.

These reactions, too, can be interpreted in terms of the broad concept of charge neutralization. The driving force behind the reaction is provided by the tendency of the carbon to transmit its negative charge to a more electronegative atom or another, less basic, carbon.



*(69)*



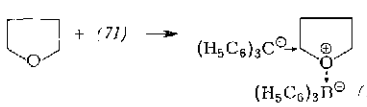
*(70)*

## 1. Lewis Acids

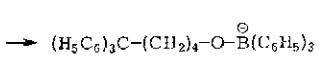
Phenylsodium combines with triphenylborane to form sodium tetraphenylborate (Kalignost®), a useful analytical reagent that is not affected by water or alcohol [154]. Phenylisopropylpotassium also gives a corresponding borate complex [114], and the bulky base triphenylmethylsodium gives adducts *(71)* that are in equilibrium with their components [155].

$$Na{-}C(C_6H_5)_3 + B(C_6H_5)_3 \rightleftarrows [(H_5C_6)_3C{-}B(C_6H_5)_3]Na \qquad (71)$$

Solutions of such antagonist pairs exhibit simultaneous electrophilic and nucleophilic reactivity resulting, for example, in the formation of *(72a)* and *(72b)* [156].

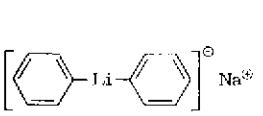


*(72a)*

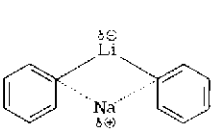


*(72b)*

Organic derivatives of many elements from different groups of the periodic system (Be, Mg, Zn, B, Al, Si, Sb) undergo addition with organoalkali compounds. Surprisingly, even organolithium bases can act as Lewis acids for other organoalkali compounds. Phenyl-lithium gives a 1:1 complex [*(73a)* or *(73b)*] with phenylsodium which can be crystallized from ether.



*(73a)*



*(73b)*

This complex *(73a)* ↔ *(73b)* reacts vigorously with butyl iodide until the phenylsodium is completely consumed; the residual phenyl-lithium continues to react slowly, with a half-life of 9 hours [157].

The addition of even a few per cent of phenyl-lithium to a suspension of phenylsodium (or phenylpotassium, phenylrubidium, or phenylcesium) stabilizes the latter towards ether [158]. Small amounts of phenyl-lithium are evidently sufficient to complex the entire amount of dissolved phenylsodium. Phenylsodium that is moderated in this manner is less active than the lithium-free reagent prepared in hydrocarbons; however, this loss in activity is compensated by the polarity of the ether (see Table 4).

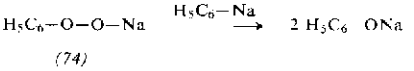
Table 4. Metalation of anisole with phenylalkali-metal compounds at about 20 °C.

| R–M | Solvent | Reaction time [hrs] | Metalation [%] | Ref. |
|---|---|---|---|---|
| $H_5C_6{-}Li + LiBr$ | Ether | 20 | 0 | [159] |
| $H_5C_6{-}Li$ | Ether | 20 | 17 | [159] |
| $[H_5C_6{-}Li \quad C_6H_5]Na$ | Ether | 20 | 71 | [159] |
| $H_5C_6{-}Na$ | Benzene | 24 | 44 | [70] |
| $H_5C_6{-}Na$ | Benzene | 48 | 64 | [70] |

Because of their electron-sextet, carbenes are extremely active Lewis acids. Until now, their reaction with organic derivatives of the higher alkali metals have been reported only sporadically [160]. This reaction is analogous to the frequently observed insertion of carbenes into carbon-lithium bonds [101].

## 2. Oxygen and Sulfur Functions

Molecular oxygen cleaves organoalkali-metal compounds with formation of a peroxide, *e.g. (74)*, which in turn, oxidizes a second molecule of the organometallic



*(74)*

compound [161]. Peroxides of resonance-stabilized organoalkali-metal compounds decompose with elimination of alkali peroxide, for example, to give *(75a)* and *(75b)*.

$$2\,(H_5C_6)_3C{-}Na \xrightarrow{O_2} 2\,(H_5C_6)_3C{-}O{-}O{-}Na \rightarrow (H_5C_6)_3C{-}O{-}O{-}C(C_6H_5)_3 + Na_2O_2 \quad [20, 162]$$

*(75a)*

$$2\,(H_5C_6)_2CH{-}Na \xrightarrow{O_2} (H_5C_6)_2CH{-}CH(C_6H_5)_2 + Na_2O_2 \quad [163]$$

*(75b)*

The reactions of sulfur and sulfur compounds with organoalkali-metal compounds have not yet been systematically studied. The reaction of triphenylmethylsodium with sulfur

[154] *G. Wittig* and *P. Raff*, Liebigs Ann. Chem. *573*, 195 (1951).

[155] *G. Wittig*, *H. G. Reppe*, and *T. Eicher*, Liebigs Ann. Chem. *643*, 47 (1961).

[156] *G. Wittig* and *O. Bub*, Liebigs Ann. Chem. *566*, 113 (1950); *G. Wittig* and *G. Kolb*, Chem. Ber. *93*, 1469 (1960).

[157] *G. Wittig*, *R. Ludwig*, and *R. Polster*, Chem. Ber. *88*, 294 (1955); German Pat. 955596 (Jan. 3rd, 1957) BASF, Ludwigshafen/Rh., inventor: *G. Wittig*; Chem. Abstr. *53*, 13108h, 16064b (1959).

[158] *G. Wittig*, Angew. Chem. *70*, 65 (1958).

[159] *G. Wittig* and *E. Benz*, Chem. Ber. *91*, 874 (1958).

[160] *A. P. Krapcho*, *P. S. Huyffer*, and *I. Starer*, J. org. Chemistry *27*, 3096 (1962).

[161] *H. Hock* and *H. Kropf*, Angew. Chem. *69*, 315, 317 (1957).

[162] *C. A. Kraus* and *R. Rosen*, J. Amer. chem. Soc. *47*, 2739 (1925).

[163] According to *C. B. Wooster*, Chem. Reviews *11*, 14 (1932).

dioxide affords triphenylmethyl sulfinate [163], and that with diphenyl sulfoxide gives a red-violet adduct [164]. Phenylsodium and diphenyl sulfoxide give diphenylene sulfide [165]. The reaction of sultones with organosodium reagents takes place with ring-opening and leads to sulfonates [166].

### 3. Nitrogen Functions

The N≡N triple bond of molecular nitrogen does not react with organometallic compounds. However, phenylpotassium does add onto the N=N double bond of azobenzene to give *(76)*.

$$H_5C_6-N=N-C_6H_5 \xrightarrow{H_5C_6-K} (C_6H_5)_2N-N(C_6H_5)-K \qquad (76)$$

Phenylcalcium iodide also adds onto azobenzene, whereas phenylsodium, phenyl-lithium, and phenylmagnesium bromide act predominantly as reducing agents yielding, respectively, 25%, 52%, and 62% hydrazobenzene [167].

Nitroso and nitro compounds and most nitrogen oxides react with organometallic compounds so vigorously and give reaction products of such high reactivity that the reaction is uncontrollable; for preparative purposes, less reactive organometallic compounds are therefore used [168]. Nitrous oxide reacts only with organoalkali bases, *e.g.* with triphenylmethylsodium, to yield a diazotate *(77)* which liberates nitrogen on hydrolysis [136].

$$(H_5C_6)_3C-Na \xrightarrow{N_2O} (H_5C_6)_3C-N=N-ONa \xrightarrow{ROH}$$

*(77)*

$$(H_5C_6)_3C-OH + N_2 + RONa$$

### 4. Carbon Functions

#### a) *Carbon Oxides*

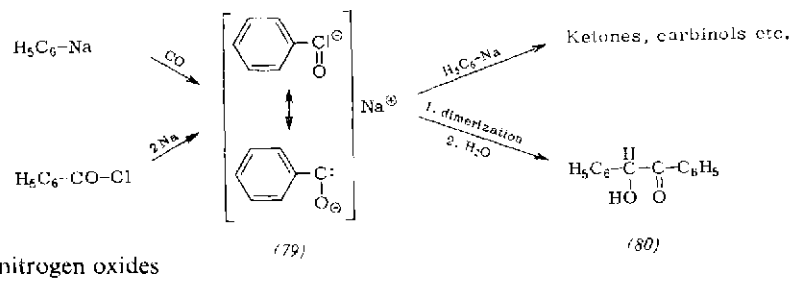
Carboxylation converts organometallic compounds smoothly into carboxylates *(77)* [169]. However, a local excess of the organometallic compound can cause transmetalation and consequent formation of dicarboxylic acids *(78)* [170]; under suitable conditions, the latter can be obtained in high yields [171].

$$H_5C_6-CH_2-Na \xrightarrow{<1\ CO_2} H_5C_6-CH_2-COONa \quad (77),\ 99\%$$

$$H_5C_6-CH_2-Na \xrightarrow{>1\ CO_2} H_5C_6-CHNa-COONa \longrightarrow H_5C_6-CH(COOH)_2$$

*(78)*, 70%

Prolonged treatment of phenylsodium suspensions with carbon monoxide leads to the acyl anion *(79)* and thence to benzophenone, triphenylmethanol, and benzoic acid [172, 173]. A mechanism involving the same anion *(79)* has been postulated to explain the formation of acyloins *(80)* in the reaction of sodium-aromatic complexes with acid chlorides [174].




*(79)* *(80)*

The lower resonance structure predicts the properties of a nucleophilic carbene for the acyl anion *(79)* [175]; however, it does not add onto olefins or acetylene derivatives [176].

Free triphenylmethylsodium does not react with carbon monoxide [20], but does form a dark-colored adduct with it in the presence of triphenylborane [177].

#### b) *Carbonyl and Carboxylic Compounds*

Sodium alkyls and sodium aryls combine with aldehydes or ketones with extreme rapidity. Triphenylmethylsodium undergoes normal addition onto benzaldehyde [20], phenyl isocyanate [178], and phenyl isothiocyanate

[164] *K. Fuchs* and *P. Gross*, Ber. dtsch. chem. Ges. *63*, 1009 (1930).

[165] *K. Fuchs*, Mh. Chem. *53/54*, 443 (1929).

[166] German Pat. 895598 (Oct. 22nd, 1953), Böhme Fettchemie GmbH., inventor: *J. H. Helberger* and *R. W. F. Heyden*; Chem. Abstr. *48*, 4234f (1954).

[167] *H. Gilman* and *J. C. Bailie*, J. org. Chemistry *2*, 84 (1937).

[168] Cf., for example, the preparation of nitroso compounds from nitrosyl chloride and organomercury halides [*L. I. Smith* and *F. L. Taylor*, J. Amer. chem. Soc. *57*, 2460 (1935)].

[169] *J. F. Nobis* and *L. F. Moormeier*, Ind. Engng. Chem. *46*, 539 (1954).

[170] Cf., for example, *H. Gilman* and *H. A. Pacevitz*, J. Amer. chem. Soc. *62*, 1301 (1940).

[171] *J. F. Nobis* and *L. F. Moormeier*. Ind. Engng. Chem. *46*, 539 (1954).

[172] *H. H. Schlubach*, Ber. dtsch. chem. Ges. *52*, 1910 (1919). Participation of organomercury compounds cannot be excluded in view of the method by which phenylsodium is prepared [cf. *W. Schoeller*, *W. Schrauth*, and *W. Essers*, Ber. dtsch. chem. Ges. *53*, 62 (1920)].

[173] For corresponding reactions of carbon monoxide with organolithium compounds, see *G. Wittig*, Angew. Chem. *53*, 241 (1940) (footnote [58]); for reactions with Grignard compounds, see *F. G. Fischer* and *O. Stoffers*, Liebigs Ann. Chem. *500*, 253 (1933).

[174] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 19 (1928).

[175] *H. W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1962).

[176] *M. Schlosser*, unpublished work.

[177] *G. Wittig* and *H. Vogel*; *G. Wittig* and *L. Gonsior*, unpublished work.

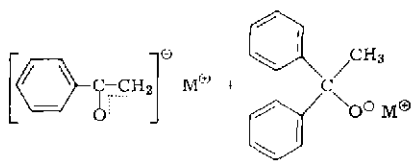
[178] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *464*, 1 (1928).

[178]; the reaction with benzophenone, however, involves an unusual radical formation [179].

$$(H_5C_6)_3C{-}Na + (H_5C_6)_2C{=}O \rightleftharpoons (H_5C_6)_3C\cdot + (H_5C_6)_2C{-}ONa\,.$$

The attack of organoalkali-metal compounds on enolizable aldehydes and ketones is also influenced by steric factors. Secondary and tertiary alkoxide formation from bulky bases [180], particularly from triphenylmethylsodium [181], is suppressed in favor of enolate formation. The dependence of the enolate/alkoxide ratio on the nature of the metal has been investigated by *Hauser* [182]. Lithium and magnesium, which undergo complex formation, promote addition [→ *(82)*] via a concerted mechanism with a four-centered transition state [183]; sodium and potassium, on the other hand, favor deprotonation [→ *(81)*] (Table 5).

$$H_5C_6{-}CO{-}CH_3 + H_5C_6{-}M \xrightarrow{in\ H_5C_2{-}O{-}C_2H_5}$$



*(81)* *(82)*

Table 5. Effect of the metal in the phenylmetal compound on the formation of *(81)* and *(82)* from acetophenone.

| M | Enolate: carbinolate |
|---|---|
| K | 10:1 |
| Na | 2:1 |
| Li | 1:23 |
| BrMg | 1:∞ |

Nonpolar solvents such as benzene impair metalation and thus promote carbinolate formation [182].

α,β-Unsaturated compounds react as 1,2- or 1,4-dipolar structures with organometallic compounds; the type of addition (1,2- or 1,4-) occurring depends on the metal [182, 184]. Magnesium promotes 1,4-addition via a chelate; other metals give predominantly 1,2-addition (Table 6).

Table 6. 1:1-Addition of $C_6H_5{-}M$ onto β-benzoylstyrene ($H_5C_6CH{=}CHCOC_6H_5$).

| $C_6H_5{-}M$ | 1,2-Adduct [%] | 1,4-Adduct [%] |
|---|---|---|
| + $H_5C_6{-}K$ | 67 | — |
| + $H_5C_6{-}Na$ | 60 | 14 |
| + $H_5C_6{-}Li$ | 75 | 14 |
| + $H_5C_6{-}MgBr$ | — | 94 |

Benzylsodium derivatives *(83)* undergo exclusively 1,4-addition onto α,β-unsaturated esters [185, 186].

$$H_5C_6{-}CH_2{-}COOH \xrightarrow[NH_3]{2\ NaNH_2} H_5C_6{-}\underset{\underset{Na}{|}}{CH}{-}COONa$$

*(83)*

$$(83) + H_5C_6{-}CH{=}CH{-}COOC_2H_5 \xrightarrow{Hydrolysis}$$

$$H_5C_6{-}\underset{\underset{H_5C_6{-}\underset{\underset{COOH}{|}}{CH}}{|}}{CH}{-}CH_2{\cdot}COOC_2H_5$$

(erythro + threo)

The reactions of organoalkali-metal compounds with carboxylic acids [187], carbonyl chlorides, anhydrides, and esters proceed in the manner of a normal Grignard reaction.

### c) *CN Multiple Bonds*

Azomethines (Schiff bases) react with organoalkali compounds in the same way as the isoelectronic carbonyl compounds, and isonitriles behave like carbon monoxide. Heterocyclic compounds containing CN double bonds, *e.g.* pyridine, undergo a variety of organometallic addition and substitution reactions resulting in numerous different products [188]. The reaction of nitriles with organometallic compounds represents a useful ketone synthesis [189]. For practical purposes, the readily available Grignard or organolithium compounds are mostly used. In contrast to phenyl-lithium, phenylsodium does not add onto butyronitrile, but produces the anion instead [189a].

### d) *CC Multiple Bonds*

The highly strained triple bond in arynes and lower cycloalkynes is not the only one capable of undergoing nucleophilic additions [190]. Organometallic compounds also add onto linear acetylenes, although not quite as smoothly.

$$H_5C_6{-}C{\equiv}C{-}C_6H_5 \xrightarrow{H_5C_6{-}C(CH_3)_2K} \underset{H_5C_6{-}C(CH_3)_2\ K}{\overset{H_5C_6}{\overset{|}{C}}{=}\overset{C_6H_5}{\overset{|}{C}}}$$

*(84)*

Methylphenylacetylene behaves like tolane *(84)*. Purely aliphatic acetylenes with a non-terminal triple bond undergo isomerization to 1-alkynes [191] instead.

The addition of organoalkali compounds onto conjugated double bonds was discovered and studied ex-


[179] *W. Schlenk* and *R. Ochs*, Ber. dtsch. chem. Ges. *49*, 608 (1916).

[180] *B. F. Landrum* and *C. T. Lester*, J. Amer. chem. Soc. *76*, 5797 (1954).

[181] *E. Müller*, *H. Gawlick*, and *W. Kreutzmann*, Liebigs Ann. Chem. *515*, 97 (1934).

[182] *W. I. O'Sullivan*, *F. W. Swamer*, *W. J. Humphlett*, and *C. R. Hauser*, J. org. Chemistry *26*, 2306 (1961).

[183] *J. Mathieu*, *A. Allais*, and *J. Valls*, Angew. Chem. *72*, 74 (1960).

[184] *P. G. Stevens* et al., J. Amer. chem. Soc. *57*, 1112 (1935); *C. F. Koelsch* and *R. H. Rosenwald*, ibid. *59*, 2166 (1937); *H. Gilman* and *R. H. Kirby*, ibid. *63*, 2046 (1941); *A. Lüttringhaus* et al., Liebigs Ann. Chem. *557*, 70 (1947); *G. Wittig* and *O. Bub*. ibid. *566*, 121 (1950).

[185] *C. R. Hauser* and *M. T. Tetenbaum*, J. org. Chemistry 23, 1146 (1958).

[186] *R. B. Meyer* and *C. R. Hauser*, J. org. Chemistry *26*, 3183 (1961).

[187] *J. F. Nobis*, unpublished work; quoted from *R. A. Benkeser* et al., Chem. Reviews *57*, 867 (1957), p. 891 et seq.

[188] Review: *R. Gaertner*, Chem. Reviews *45*, 493 (1949).

[189] *C. Moureu* and *G. Mignonac*, C. R. hebd. Séances Acad. Sci. *156*, 1801 (1913).

[189a] U.S.-Pat. 2012372 (Aug. 27th, 1935), Winthrop Chem. Co., inventor: *M. Bockmühl* and *G. Ehrhart*.

[190] Review: *G. Wittig*, Angew. Chem. *74*, 479 (1962); Angew. Chem. internat. Edit. *1*, 415 (1962).

[191] *K. Ziegler* and *H. Dislich*, Chem. Ber. *90*, 1107 (1957).

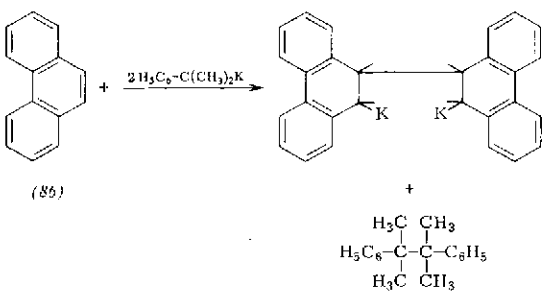
tensively using phenylisopropylpotassium by *Ziegler* [192a–192c].

$$H_5C_6\text{-}CH{=}CH{-}R + H_5C_6{-}C(CH_3)_2K \rightarrow H_5C_6{-}CHK{-}CHR{-}C(CH_3)_2{-}C_6H_5$$

R = H, $CH_3$, $C_6H_5$ *(85)*

Phenylisopropylpotassium reacts with styrene, β-methylstyrene, stilbene, α-methylstyrene, 1,1-diphenylethylene, and several fulvenes. Other olefins are metalated to allylic derivatives. These include ethylene derivatives with only alkyl substituents, styrenes that are doubly substituted with alkyl groups, α-methylstilbene, and 2-methyl-1,1-diphenylethylene. Monosubstituted styrenes seem to represent the dividing line between predominant addition and predominant metalation. In pentane, the more active reagent amylsodium gives 85 % hydrogen-metal interconversion with α-methylstyrene and 29 % with β-methylstyrene [193]. Substitution of the methyl group with long-chain alkyl groups causes a further increase in metalation at the expense of addition.

A third, free-radical reaction of multiple CC bonds has been observed with phenanthrene *(86)* [192a, 192b].




*(86)*



Although phenylsodium [194] and vinylsodium [59] do not react with 1,1-diphenylethylene in nonpolar solvents, both benzylsodium [194], which is less basic, and the alkali-metal amyls, which are more basic, do (relative reaction rates for amyl-lithium, amylsodium, and amylpotassium = 0.03:1:3 [194]).

Addition of a second molecule of olefin onto the addition product *(87a)* obtained from the olefin and amylsodium affords *(87b)* [194].

$$(H_5C_6)_2C{=}CH_2 \xrightarrow{n\text{-}H_{11}C_5{-}Na} Na{-}C(C_6H_5)_2{-}CH_2{-}(n\text{-}C_5H_{11})$$

*(87a)*

$$(H_5C_6)_2C{=}CH_2 + (87a) \rightarrow Na\text{-}C(C_6H_5)_2{-}CH_2{-}C(C_6H_5)_2{-}CH_2{-}(n\text{-}C_5H_{11})$$

*(87b)*

Additions can often be accomplished with catalytic amounts of organometallic compounds; the resulting adducts, *e.g. (88)*, give rise in turn to new addends by hydrogen-metal interconversion [195].

$$H_5C_6{-}CH{=}CH{-}CH_3 \xrightarrow[\text{in } H_5C_6{-}CH_3]{H_5C_6{-}CH_2K} H_5C_6\text{-}CH_2{-}CH(CH_3){-}CH_2{-}C_6H_5 + H_5C_6{-}CH_2{-}K$$

*(88)*

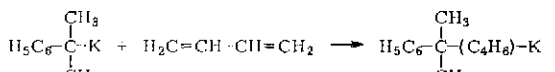
Organoalkali-metal compounds also add onto cycloheptatriene [196] and cyclooctatetraene [197]. Butadiene adds on amylsodium and benzylsodium but not phenylsodium [198]. Phenylpotassium seems to add even onto benzene [198a].

Tri- and tetraarylethylenes do not add on organoalkali compounds. With this exception, obviously due to steric hindrance, additions proceed smoothly whenever a weaker base is formed from a stronger one. For example, the reaction of phenylisopropylpotassium with 1,1-diphenylethylene produces a more highly resonance-stabilized benzhydrylpotassium derivative.

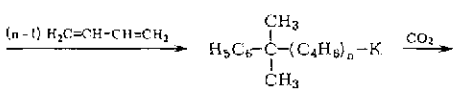
On the other hand, when ethylene reacts with benzylsodium, a stronger base, 3-phenylpropylsodium, results, from which propylbenzene (36 %) and 3-phenyl-n-pentane (37 %) are produced [199]. This reaction requires heat and pressure (100 °C, 200 atm) in contrast to the additions of isopropyllithium or t-butyl-lithium onto ethylene, which take place even at −60 °C, because they lead to weaker bases [200].

### e) *Polymerizations* [201a–203]

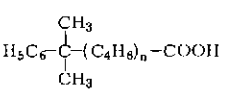
The study of addition reactions provided the key to an understanding of anionic polymerization, recognized by *Ziegler* [201a] to be "an organometallic synthesis on the largest scale". In this polymerization, an organometallic compound adds onto a butadiene- or styrene-type olefin giving rise to another organometallic compound which, in turn, can add on further molecules of olefin. Thus, chain growth *(89b)* takes place by recurring additions of butadiene onto the allylpotassium end-group of the butadiene-isopropylpotassium adduct *(89a)*. After all the monomer is consumed, the reactive



*(89a)*



*(89b)*, n = 0 to 10



[192a] *K. Ziegler* and *K. Bähr*, Ber. dtsch. chem. Ges. *61*, 253 (1928).

[192b] Electron transfer to unsaturated systems via organoalkali-metal compounds has been observed in several other cases [*G. Wittig* and *D. Wittenberg*, Liebigs Ann. Chem. *606*, 8 (1957); *K. Ziegler* and *H. Kleiner*, ibid. *473*, 70 (1929)].

[192c] *K. Ziegler*, *F. Crössmann*, *H. Kleiner*, and *O. Schäfer*, Liebigs Ann. Chem. *473*, 1 (1929).

[193] *A. A. Morton* and *E. Grovenstein*, J. Amer. chem. Soc. *74*, 5437 (1952).

[194] *A. A. Morton* and *H. C. Wohlers*, J. Amer. chem. Soc. *69*, 167 (1947).

[195] *J. Shabtai*, *E. M. Lewicki*, and *H. Pines*, J. org. Chemistry *27*, 2618 (1962).

[196] *K. Hafner* and *W. Rellensmann*, Angew. Chem. *72*, 918 (1960).

[197] *A. C. Cope* and *M. R. Kinter*, J. Amer. chem. Soc. *73*, 3424 (1951).

[198] *A. A. Morton*, *G. H. Patterson*, *J. J. Donovan*, and *E. L. Little*, J. Amer. chem. Soc. *68*, 93 (1946).

[198a] *A. A. Morton* and *E. J. Lanpher*, J. org. Chemistry *23*, 1639 (1958).

[199] US.-Pat. 2548803 (April 10th, 1951), du Pont de Nemours, inventor: *E. L. Little*; *H. Pines*, *J. A. Vesely*, and *V. N. Ipatieff*, J. Amer. chem. Soc. *77*, 554 (1955).

[200] *P. D. Bartlett*, *S. Friedman*, and *S. Stiles*, J. Amer. chem. Soc. *75*, 1771 (1953).

[201a] *K. Ziegler*, Angew. Chem. *49*, 499 (1936).

[201b] *C. E. H. Bawn* and *A. Ledwith*, Quart. Rev. *16*, 386 (1962).

[202] *K. Ziegler* and *H. Kleiner*, Liebigs Ann. Chem. *473*, 57 (1929).

[203] *K. Ziegler*, *E. Eimers*, *W. Hechelhammer*, and *H. Wilms*, Liebigs Ann. Chem. *567*, 43 (1949).

chain ends remain intact, provided hydrolytic agents are excluded. Subsequent introduction of dienes results in avid absorption and addition (living polymers).

The reaction can be stopped at an early stage by using low monomer concentrations [202] or scavengers [203] that are inert toward the chain-initiating organoalkali-metal compounds. The products of the initial addition *(89b)* have been isolated and confirm the postulated mode of chain growth.

In the polymerization of butadiene with n-butyl-lithium, *(90a)* and *(90b)* were identified as the products of the second addition step.

$$n\text{-}H_9C_4\text{—}Li + H_2C\text{=}CH\text{—}CH\text{=}CH_2 \xrightarrow[25\,^\circ C]{i\text{-}H_7C_3\text{—}Cl}$$

$$n\text{-}H_9C_4\text{—}CH_2\text{—}CH(i\text{-}C_3H_7)\text{—}CH\text{=}CH_2 \quad (90a)$$

$$+\ n\text{-}H_9C_4\text{—}CH_2\text{—}CH\text{=}CH\ \ CH_2\text{—}(i\text{-}C_3H_7) \quad (90b)$$

The mechanism of the polymerization of butadiene or styrene initiated by phenylsodium or triphenylmethyl-sodium was revealed by an elegant, effective scavenging method using diethylamine and yielding *(91a)* and *(91b)*.

$$(H_5C_6)_3C\text{—}Na + H_2C\text{=}CH\text{—}CH\text{=}CH_2 \xrightarrow{HN(C_2H_5)_2}$$

$$(H_5C_6)_3C\text{—}CH_2\text{—}CH\text{=}CH\text{—}CH_3 \quad (91a)$$

$$+\ (H_5C_6)_3C\text{—}CH(CH_3)\text{—}CH\text{=}CH_2 \quad (91b)$$

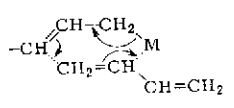
The initiators appear to act as true catalysts, since they are not detectably consumed; but here, too, organometallic addition is the actual initiating step; however, this process is extremely slow in comparison to the rate of chain growth. Polymers of high molecular weight can be obtained by preventing chain termination [202, 203]. Occasionally the scavenger increases the reactivity of the olefin by complex formation. Thus, 2,3-dimethylbutadiene adds onto triphenylmethylsodium only in the presence of triphenylborane and with exclusive formation of the 1,2-adduct [204].

$$(H_5C_6)_3C\text{—}Na + H_2C\text{=}\underset{\displaystyle H_3C}{\overset{}{C}}\text{—}\underset{\displaystyle CH_3}{\overset{}{C}}\text{=}CH_2 \xrightarrow{B(C_6H_5)_3}$$

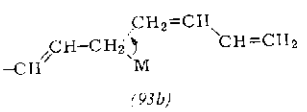
$$\left[(H_5C_6)_3C\text{—}CH_2\text{—}\underset{\displaystyle H_3C}{\overset{}{C}}\text{—}\underset{\displaystyle CH_3}{\overset{}{C}}\text{=}CH_2\ \ \ominus B(C_6H_5)_3\right]\ Na^{\oplus}$$

*(92)*

The polymerization of butadiene does not give stereochemically uniform chains. 1,2-Addition predominates at low temperature (90 % at −70 °C) almost independently of the nature of the organometallic initiator and the solvent, whereas at high temperature, 1,4-linked polymers are primarily produced (85 % at 110 °C). These results possibly reflect the competition between abnormal *(93a)* and normal *(93b)* allylic addition [203].



*(93a)*



*(93b)*

[204] *G. Wittig* and *H. Schloeder*, Liebigs Ann. Chem. *592*, 38 (1955).

The stereochemistry of isoprene polymerization depends on both the solvent and the alkali-metal initiator. In polymerizations carried out in hydrocarbons, lithium behaves differently from the other alkali metals. This difference disappears with increasing polarity of the solvent (Table 7) [205].

Table 7. Isoprene polymerization with alkali metals or their organometallic derivatives.

| Solvent | Metal | Polymer [%] | | | |
|---|---|---|---|---|---|
| | | 1,2 | 3,4 | *cis*-1,4 | *trans*-1,4 |
| n-Heptane | Li | — | 6 | 94 | — |
| n-Heptane | Na | 10 | 42 | | 48 |
| n-Heptane | K | 7 | 35 | — | 58 |
| THF | Li | 14 | 52 | — | 34 |
| THF | Na | 15 | 51 | — | 34 |
| THF | K | 17 | 35 | — | 48 |

In practice, it is immaterial whether the metal is used in elemental form or as the alkyl, aryl, or benzyl derivative, since polymerization is effected identically in all cases. Thus, with isoprene, sodium gives the disodium adduct and then isoprenylsodium, which is the actual chain initiator. In the presence of toluene, benzylsodium is the initiator, as indicated by the hydrocarbon *(94)* isolated after premature hydrolysis [206].

$$H_5C_6\ \ CH_2\text{—}(C_5H_8)_n\text{—}H \qquad (94),\ n = 1\ \text{to}\ 5$$

The details of the polymerization of butadiene with sodium are not entirely clarified. In contrast to the known rules of organometallic polymerization, the structure of the Buna rubber polymer is fairly independent of the temperature of polymerization. On the other hand, its structure is quite different from that of the polymer obtained by the free-radical process using azobisbutyronitrile [203].

Polymerizations promoted by alfin catalysts [59, 207] or Ziegler catalysts [208] cannot be discussed here.

## G. Rearrangements

Intramolecular rearrangements provide another route for the conversion of organoalkali-metal compounds into less basic, and hence more stable compounds.

### 1. Charge Transfer to Nitrogen

The Stevens rearrangement *(95)* [209] effectively "short-circuits" the charges condensed in the ylides of nitrogen, arsenic, and antimony. The corresponding high energy

[205] *A. V. Tobolsky* and *C. E. Rogers*, J. Polymer Sci. *40*, 73 (1959).

[206] *R. E. Robertson* and *L. Marion*, Canad. J. Res. Sect. B 26, 627 (1948).

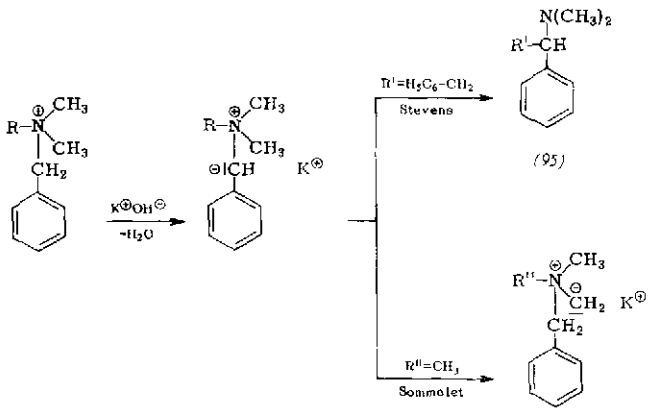
[207] *A. A. Morton*, *E. E. Magat*, and *R. L. Letsinger*, J. Amer. chem. Soc. *69*, 950 (1947).

[208] *C. D. Nenitzescu*, *C. Huch*, and *A. Huch*, Angew. Chem. *68*, 438 (1956); Rev. Chim. (Bucaresti) *7*, 573 (1956); cf. *K. Ziegler*, Angew. Chem. *68*, 581 (1956).

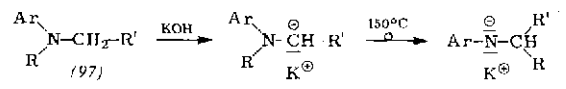
[209] Reviews: *G. Wittig*, Angew. Chem. *63*, 15 (1951); *66*, 10 (1954); Acta chim. Acad. Sci. hung. *12*, 347 (1957); *G. Köbrich*, Angew. Chem. *74*, 453 (1962); Angew. Chem. internat. Edit. *1*, 382 (1962).

gain also promotes the competing Sommelet rearrangement *(96)* [209,210].

In the base-promoted isomerization of tertiary amines *(97)*, also studied by *Stevens* [211], the negative charge is transferred to a previously uncharged nitrogen atom.



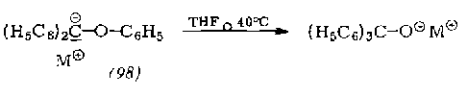
Consequently, here the tendency towards rearrangement is less pronounced, and higher temperatures are required.



Ar = $C_6H_5$; R = $H_5C_6$–$CH_2$; R' = $H_5C_8$–CO

## 2. Charge Transfer to Oxygen

The Wittig rearrangement [22,48,212] of metalated ethers is analogous to the above rearrangement of tertiary amines. This rearrangement generally takes place in the cold; strongly resonance-stabilized metalates, *e.g. (98)*, require slight heating to effect isomerization.

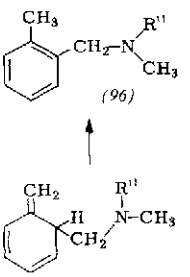


Although the alkali metal M is bound only electrostatically, it exerts an effect on the rate of rearrangement. The kinetic data obtained were measured with relatively concentrated solutions, and, hence, the decrease in reactivity Li > Na, K [22] may be due to a salt effect. The alternative cleavage of metalated ethers in non-polar solvents leading to carbenes has been discussed above.

According to a mechanism postulated by *Schöllkopf* [213a, 213b] for s-alkyl benzyl ethers, the Wittig rearrangement proceeds in two steps, but chiefly by an intramolecular process via an internal ion pair. Competition experiments [213b] show that intermolecular rearrangement is still negligible at −56 °C. t-Alkyl benzyl ethers possibly react according to an $S_Ni$ mechanism [214].

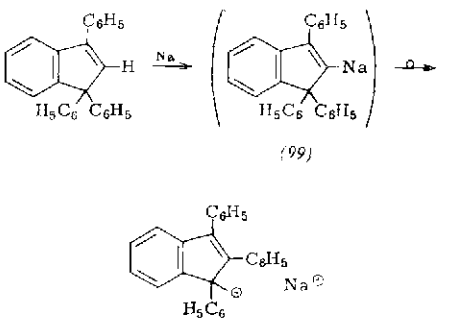
## 3. Charge Transfer to Another Carbon Atom

The isomerization of a metalated hydrocarbon *(99)* was observed thirty-five years ago by both *Schlenk* [215] and *Ziegler* [216].



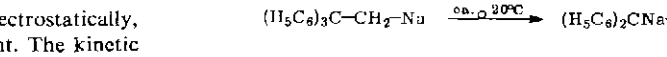


The rearrangements of β-substituted di- and triarylethylalkali-metal compounds have been investigated recently [135,217,218].





The ease with which the organometallic bond can shift within hydrocarbon molecules is surprising in view of what is known about the nitrogen- and oxygen-containing compounds. The isomerization is initiated by a



weakening of the metal-carbon bond, as indicated by the effect of the metal M on this phenomenon (K > Na > Li ≫ Mg, Hg). When several residues are available for migration, the course of the rearrangement depends more on their tendency to migrate than on the stability of the final product. The following order of decreasing mobility has been observed [217,218]: R = benzyl > phenyl > p-tolyl > methyl.

For example, 2,2-diphenyl-n-propylpotassium [R = $CH_3$; M = K] does not afford the more stable isomer 1,1-

[210] *F. N. Jones* and *C. R. Hauser*, J. org. Chemistry *26*, 2979 (1961).

[211] *W. F. Cockburn, R. A. W. Johnstone*, and *T. S. Stevens*, J. chem. Soc. (London) *1960*, 3340; *R. A. W. Johnstone* and *T. S. Stevens*, ibid. *1960*, 3346.

[212] *G. Wittig* and *L. Löhmann*, Liebigs Ann. Chem. *550*, 260 (1942); *G. Wittig* and *H. Schlör*, Suomen Kemistilehti B *31*, 2 (1958).

[213a] *U. Schöllkopf* and *W. Fabian*, Liebigs Ann. Chem. *642*, 1 (1961).

[213b] *U. Schöllkopf* and *D. Walter*, Liebigs Ann. Chem. *654*, 72 (1962).

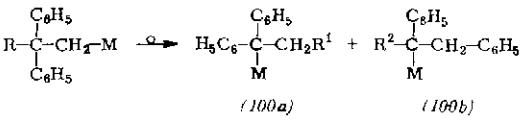
[214] *P. T. Lansbury* and *V. A. Pattison*, J. org. Chemistry *27*, 1933 (1962).

[215] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 98 (1928).

[216] *K. Ziegler* and *F. Crössmann*, Ber. dtsch. chem. Ges. *62*, 1768 (1929).

[217] *H. E. Zimmerman* and *F. J. Smentowski*, J. Amer. chem. Soc. *79*, 5455 (1957).

[218] *E. Grovenstein*, J. Amer. chem. Soc. *79*, 4985 (1957); *E. Grovenstein* and *L. P. Williams*, ibid. *83*, 2537 (1961).



*(100a)* *(100b)*

$R^1 = H_5C_6{-}CH_2,\ H_5C_6$
$R^2 = H_5C_6,\ p\text{-}H_3C{-}C_6H_4,\ H_3C$

diphenyl-n-propylpotassium *(100a)*; instead, 1,2-diphenylisopropylpotassium *(100b)* is produced [217]. However, these rearrangements, too, reflect the tendency of more strongly basic organoalkali-metal compounds to undergo conversion into less basic ones, thus satisfying a principle established for the chemistry of organosodium and organopotassium compounds.

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# COMMUNICATIONS

## Hindered Internal Rotation in Cyanine Dyes

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The proton magnetic resonance of the chain chromophores of *N,N*-dimethylaminoproenylylidene- *(1a)*, *N,N*-dimethylaminopentadienylylidene- *(1b)*, and *N,N*-dimethylaminoheptatrienylylidene-dimethylammonium perchlorates *(1c)* corresponds to the $AX_2$, $A_2X_2Y$, or $AB_2X_2Y_2$ type, respectively. It is the *all-trans*-configuration that occurs in the ground state [1].

$(H_3C)_2N{-}CH(=CH{-}CH)_n{=}\overset{\oplus}{N}(CH_3)_2$

*(1)*

*(1a)*, *(1b)*, *(1c)*: n = 1, 2, or 3

At room temperature in neutral medium, the methyl groups of the auxochromes of *(1a)* and *(1b)* each supply two signals of equal intensity (see Table 1). This splitting of the methyl signals is independent of temperature and is an approximately linear function of the field strength, *e.g.* for *(1a)* in $CHCl_3$: 11.75 cps at 60 Mcps; 4.4 cps at 25 Mcps. It is largely independent of the nature of the solvent in neutral medium. Any external ions added have no influence on the splitting. These results imply that the internal rotation of the *N,N*-dimethylamino groups around the N=C(α) bond is hindered [2, 3], a phenomenon described by *Gutowsky* et al. [4] for carbonyl compounds of the type R-CO-$N(CH_3)_2$. Like all *cis-trans*-rearrangements, the internal rotation is acid-catalysed. When the rotation of the *N,N*-dimethylamino groups is inhibited, the protons of the two freely rotating methyl-groups lie in fields of different intensities. The height of the energy barrier $E_a$ to rotation around the N–C(α) bond was estimated by the method of *Gutowsky* [4] (see Table 1). $E_a$ and $T_{coin}$ (*i.e.* the temperature at which the two methyl signals coincide) decrease with increasing chain length, *e.g.* *(1c)* shows only one methyl-group signal at room temperature (see Table 1).

Table 1. Proton magnetic resonance signals (δ = chemical shift), coupling coostants (J), and activation energies ($E_a$) of dimethylaminopolyenylylidenedimethylammonium perchlorates. External standard: tetramethylsilane.

| | *(1a)* | *(1b)* | *(1c)* |
|---|---|---|---|
| $\delta_\alpha$ [ppm] [*] conc./solvent | −7.49; doublet 0.5 M/$D_2O$ | −7.17; doublet 0.1 M/$CD_3COCD_3$ | −7.16; doublet 0.05 M/$CD_3COCD_3$ |
| $J_{\alpha\beta}$ [cps] | 11.8 | 11.8 | 11.8 |
| $\delta_\beta$ [ppm] conc./solvent | −5.19; triplet 0.5 M/$D_2O$ | −5.33; quartet 0.1 M/$CD_3COCD_3$ | −5.31; quartet 0.05 M/$CD_3COCD_3$ |
| $J_{\beta\gamma}$ [cps] | | 12.7 | 12.7 |
| $\delta_\gamma$ [ppm] conc./solvent | | −7.0; triplet 0.1 M/$CD_3COCD_3$ | −6.88; quartet 0.05 M/$CD_3COCD_3$ |
| $J_{\gamma\delta}$ [cps] | | | 12.6 |
| $\delta_\delta$ [ppm] conc./solvent | | | −5.69; triplet 0.05 M/$CD_3COCD_3$ |
| $\delta CH_3$ [ppm] conc./solvent | −3.23 and −3.03 0.5 M/$D_2O$ | −2.79 and −2.59 0.1 M/$CD_3COCD_3$ | −2.7 0.05 M/$CD_3COCD_3$ |
| $E_a$ [kcal/mole] solvent | 17 $(C_6H_5)_2CO$ | 10 $(C_6H_5)_2CO$ | 7 $CH_3CN/CCl_4$ |
| $T_2$ [sec/rad] [**] | 0.227 | 0.274 | 0.227 |

[*] The carbon atoms of the chain are designated according to their positions relative to the nitrogen atoms as α,β,γ,δ.

[**] $T_2$ is the transverse relaxation time in seconds/radian and is estimated from the linear width $\Delta\omega_{1/2}$.

Addition of acid lowers the activation energy for reorientation, (0.11 % by vol. of $H_2SO_4$ in 0.2 M aqueous solution reduced $E_a$ for *(1a)* from 17 to 8.6 kcal/mole). The NMR spectrum of the protons of the chain carbons remains unchanged, *i.e.* the *trans*-linkage of the cyanine chain is retained. However, proton exchange in β-position of the cyanine chain does take place. In $D_2O$ with addition of about 0.1 % by vol. of $D_2SO_4$ it is slow enough that its kinetics can be examined. The β-position becomes occupied by deuterium; and a singlet replaces the α-doublet. The rate constant in 0.04 N $D_2SO_4$ is $k \approx 2\times10^{-4}$ sec$^{-1}$.

Hindered rotation of *N,N*-dialkylamino groups was also observed in compounds of types *(2)* and *(3)*.

$R_2^1N{-}CH{=}CR^2{-}CH{=}\overset{\oplus}{N}R_2^1$ $R_2^1N{-}CH{=}CR^3{-}CR^2{=}CR^3{-}CH{=}\overset{\oplus}{N}R_2^1$

*(2)* *(3)*

*(2a)*: $R_2^1 = -(CH_2)-$; $R^2 = H$

*(2b)*: $R^1 = CH_3, C_2H_5$; $R^2 = H, CH_3, CH{=}\overset{\oplus}{N}(CH_3)_2$

*(3)*: substituents as in *(2b)*; $R_2^3 = H + H$, $o\text{-}C_6H_4$

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[1] *G. Scheibe*, Chimia *15*, 10 (1961)

[2] *G. Scheibe* et al., Ber. Bunsenges. physik. Chem. *67*, 560 (1963); *W. Seiffert*, Ph. D. Thesis, Technische Hochschule München, 1962.

[3] *G. S. Hammond* et al., J. physik. Chem. *67*, 1655, 1659 (1963).

[4] *H. Gutowsky* et al., J. chem. Physics *25*, 1228 (1956).

## The Furfuryloxycarbonyl Group, an N-Protecting Group for Peptide Syntheses

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Urethane groups have proved useful as *N*-protecting groups in peptide syntheses: they can be removed under mild conditions.

Systematic studies with new urethane groupings have shown that the furfuryloxycarbonyl (carbofuroxy or Cfo) residue is extremely acid-labile and is removed nearly quantitatively from the amino group at room temperature after 3 min with two equivalents of HBr in glacial acetic acid at a concentration of 85 mg/cm³ (corresponding about to a 6 % solution); cf. Table 1. The fission also proceeds quickly and quantitatively at 0 °C.

Table 1. Acidolysis of Cfo-glycine benzyl ester *(1)*, glycine benzyl ester *(2)*, and Cbo-glycine *(3)* at 20 °C in HBr/AcOH.

| Substance | equiv. of HBr per equiv. of *(1)*, *(2)*, or *(3)* | HBr [mg/cm³] | Proportion [%] of *(1)*, *(2)*, or *(3)* split after 1 | 1.5 | 2 | 3 | 5 | 10 | 15 min |
|---|---|---|---|---|---|---|---|---|---|
| *(1)* | 2 | 450 | 90 | 90 | 90 | 90 | | | |
| *(1)* | 2 | 200 | 87 | 91 | 92 | 91 | | | |
| *(1)* | 2 | 85 | 79 | 85 | 87 | 90 | 92 | 92 | |
| *(1)* | 1 | 85 | 65 | 75 | 79 | 84 | 87 | 90 | 91 |
| *(1)* | 2 | 50 | 21 | 30 | 40 | 54 | 70 | 83 | 85 |
| *(1)* | 1 | 50 | 15 | 24 | 30 | 43 | 59 | 73 | 77 |
| *(2)* | 2 | 85 | <1 | | <1 | | <1 | | <1 |
| *(3)* | 2 | 85 | 0 | | 0 | | 2 | | 4 |

Under these conditions, *N*-Cbo- and *C*-benzyl ester groups remain absolutely intact. In contrast, Cfo and Cbo residues are removed with almost equal rate in neutral solution by hydrogenolysis.

The high speed of acidolysis of the Cfo residue is due to the formation of the strongly mesomerically stabilized furfuryl cation. Being vinylogous acetals, furfuryl esters are just as sensitive to acids as acetals.

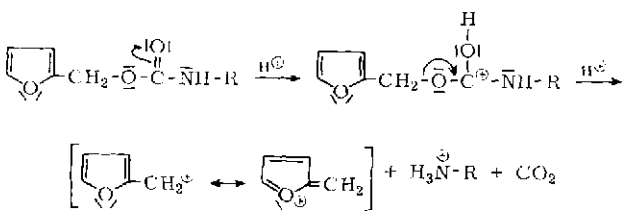


Table 2. Cfo-amino acids, dipeptides, and dipeptide benzyl esters

| Cfo compound [a] | M.p. [°C] |
|---|---|
| Cfo-glycine | 76–77 |
| Cfo-DL-alanine | 82 |
| Cfo-DL-valine | 100–101 |
| Cfo-DL-leucine | 95–96 |
| Cfo-DL-phenylalanine | 100–102 |
| Cfo-glycylglycine | 125 |
| Cfo-glycyl-DL-alanine | 155–156 |
| Cfo-glycyl-DL-valine | 106–107 |
| Cfo-glycyl-DL-phenylalanine | 146–147 |
| Cfo-DL-valylglycine benzyl ester | 132 |
| Cfo-DL-phenylalanyl-glycinebenzyl ester | 118–120 |
| Cfo-DL-leucylglycine benzyl ester | 79–80 |

[a] The Cfo-dipeptides were prepared by the nitrophenyl ester method, the Cfo-dipeptide benzyl esters by the carbodiimide method.

*N*-Cfo-amino acids are formed by the reaction of furfuryl alcohol with the esters of α-isocyanofatty acids and subsequent saponification [1], or directly from amino acids and furfuryl chloroformate, which is produced at −60 °C in toluene from equivalent amounts of furfuryl alcohol, phosgene, and triethylamine. The Cfo compounds are isolated as their dicyclohexylammonium salts. Table 2 shows examples.

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[1] *F. C. McKay* and *N. F. Albertson*, J. Amer. chem. Soc. *79*, 4686 (1957); *St. Goldschmidt* and *M. Wick*, Liebigs Ann. Chem. *575*, 217 (1952).

## Contribution of an Intermolecular Charge-Transfer Band to the Optical Activity of Electron-Donor/Acceptor Complexes

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If the electron donor or acceptor in electron-donor/acceptor (EDA) complexes [1] is optically active, the following influences of EDA interaction on rotatory dispersion and circular dichroism may be expected:

1. Change in the partial rotational strength [2] of a given absorption band which is responsible for the optical activity of the optically active component.

2. Rotatory dispersion and circular dichroism should be detectable within the range of the charge-transfer (CT) band.

3. Any absorption band characteristic for the optically inactive component should exhibit circular dichroism as a result of loss of symmetry.

Since the charge transfer is a permissible electrical dipole transfer, the dissymmetry factor $g = \frac{\Delta\varepsilon}{\varepsilon} = \alpha \frac{\mu_m}{\mu_e}$ [*] is very small. On the other hand, since $\mu_e$ is relatively large, the intensity of absorption of the CT band will be correspondingly large. It is therefore necessary for measurements within the range of the CT band to select the product [concentration] × [layer thickness] relatively small, so that the effects measured (difference in optical activity between the components and the EDA complex [3]), are extremely small. The measuring apparatus required has to be particularly sensitive. Furthermore, EDA complexes with as low CT band intensities as possible have to be used.

In practice, a high transmission polarimeter with an accuracy of $\pm 2\times10^{-3}$ degrees was assembled according to an electronic measuring principle described by *Wenking* [4]. For the measurement of circular dichroism, a method based on the principle of *Senarmont* [5] was developed. The ellipticity was measured with an accuracy of $\pm 2\times10^{-5}\times2\pi$.

Seven EDA complexes which have all relatively small charge-transfer moments within the range of the CT band, were examined.

With the first complex, (+)-camphor tetracyanoethylene *(1)*, in heptane, a negative Cotton curve and negative circular dichroism were found for the EDA portion, within the frequency range of the CT band. By way of contrast, the complex (+)-fenchone tetracyanoethylene *(2)* yielded a positive Cotton curve and positive circular dichroism in heptane. The rotational strengths were calculated to be $R_1 = -1.2\times10^{-40}$ [cgs] and $R_2 = 1.1\times10^{-40}$ [cgs], respectively. The dissymmetry factors $g_1 = -3.7\times10^{-4}$ and $g_2 = 4.4\times10^{-4}$ are of the magnitude expected for the charge-transfer moments of EDA complexes [1]. Also, the circular dichroism calculated from the amplitude of the Cotton curve according to an expression given by *Kuhn* [6] is in agreement with the experimental values.

It has thus been proved for the first time with the complexes *(1)* and *(2)* that the EDA-CT band in EDA complexes with an optically active component can develop circular dichroism and contribute to optical activity.

As stated above, the optically active part of a charge transfer is extremely small. Accordingly, this effect could not be detected with another EDA complex, (+)-methylcyclohexanone tetracyanoethylene *(3)*, in heptane.

Plain dispersion curves [2] with a superimposed positive Cotton curve were obtained for the EDA complexes of methyl (−)-α-[2,4,5,7-tetranitrofluorenylideneaminooxy]propionate as optically active acceptor with 2-methylnaphthalene *(4)* or stilbene *(5)* in benzene and carbazole *(6)* in dioxan. Methyl (+)- and (−)-α-[2,4,5,7-tetranitrofluorenylideneaminooxy]propionates with anthracene *(7)* in benzene yielded plain dispersion curves with a superimposed positive or negative Cotton curve, respectively. Circular dichroism could not be observed, within the limits of accuracy, for the EDA complexes *(4)*–*(7)*. The effect referred to under 1. above, *viz.* change in the absorption band of the optically active component responsible for the optical activity, comes into play in the case of complexes *(4)*–*(6)*. This leads to a change in the rotatory dispersion in the appropriate frequency range of the CT band.

As regards complex *(7)*, it is a moot point whether its positive Cotton curve is a result of the effect referred to under 1. above or is due to a partial contribution of the CT band.

While effect 1. is clearly in operation in the case of complexes *(4)*–*(7)*, it is not noticeable, within the limits of experimental accuracy, for *(1)*–*(3)*. This may however be explained by the octant rule [2], since tetracyanoethylene lies in one of the planes of symmetry of the carbonyl orbital and should therefore have only a minor effect on the optical activity of the carbonyl band.

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German version: Angew. Chem. 76, 228 (1964)

[1] Summary on EDA interaction, cf. *G. Briegleb*: Elektronen-Donator-Acceptor-Komplexe. Springer, Berlin-Göttingen-Heidelberg 1961.

[2] Definitions and nomenclature, cf. *F. S. Mason*, Molecular Physics *5*, 343 (1962); *W. Moffit* and *A. Moscowitz*, J. Chem. Physics *30*, 648 (1959); *C. Djerassi*; Optical Rotatory Dispersion. McGraw-Hill, New York 1960.

[M] is the molecular rotation. The circular dichroism is the difference in the molecular absorption coefficients of left and right circularly polarized light, respectively.

[*] $\varepsilon$ = decadic extinction coefficient.
$\mu_m$ = magnetic dipole-transition moment.
$\mu_e$ = electric dipole-transition moment.

[3] The contribution made to rotation by the EDA band is the difference $\Delta[M] = [M_{EDA}] - [M_{opt.\,act.}]$, where $[M_{EDA}]$ and $[M_{opt.\,act}]$ are the [M]-values of the EDA complex and of the pure, optically active component, respectively, within the range of the EDA band. The strength (R) of rotation is the imaginary part of the product of electrical and magnetic charge-transition moments.

[4] *H. Wenking*, Z. Instrumentenkunde *66*, 1 (1958).

[5] *H. G. Jerrard*, J. opt. Soc. America *38*, 35 (1948).

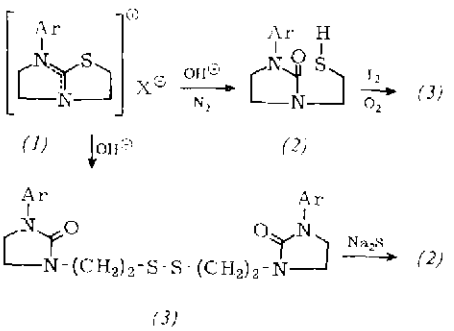
[6] *W. Kuhn* et al., Annual Rev. physic. Chem. *9*, 417 (1958).

## Formation and Behavior of 2,3,5,6-Tetrahydro-7-arylimidazo[2,1-b]thiazolium Salts [1]

By Dr. H. Dorn

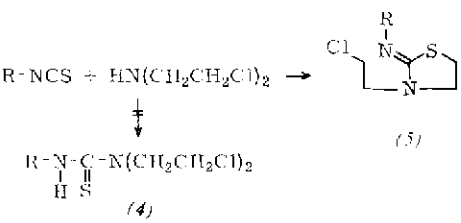
Institut für Organische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Adlershof (Germany)

The bicyclic system imidazo[2,1-*b*]thiazole [2] and 6,7-dihydro-5*H*-imidazo[2,1-*b*]thiazolium salts [3] are accessible from 2-mercaptoimidazole or imidazoline-2-thione and α-halogeno ketones. Aryl isothiocyanates and bis-(β-chloroethyl)amine react in benzene at room temperature to give 2,3,5,6-tetrahydro-7-arylimidazo[2,1-*b*]thiazolium chlorides, which are convertible into other salts, *e.g. (1)*, Ar = $C_6H_5$, X = Cl: m.p. 96–97 °C [*]; *(1)*, Ar = $C_6H_5$, X = $HSO_4$: m.p. 168–169 °C; *(1)*, Ar = $C_6H_5$, X = $ClO_4$: m.p. 145–146 °C. The structure of *(1)* is supported by the absence of non-ionic chlorine, by C=N absorption in the infrared, and by its degradation reactions. The salts *(1)* react with a small excess of alkali on contact with air to yield the thiol *(2)* and, as a by-product, the disulfide *(3)*, *e.g.* Ar = $C_6H_5$: m.p. 157 °C.



*(3)*

Under nitrogen, however, the only product is 1-(β-mercaptoethyl)-3-arylimidazolid-2-one *(2)*, *e.g.* Ar = $C_6H_5$: m.p. 71.5 °C, which is oxidized by air or iodine quantitatively to *(3)*. The disulfide *(3)* is reducible under nitrogen to the thiol *(2)*.



*(4)*

*(5)*

The claim [4] that thioureas *(4)* arise from isothiocyanates and bis-(β-chloroethyl)amine must be treated with reserve. We succeeded in isolating an intermediate of the bicyclic product *(1)*, *viz.* the 2-iminothiazolidine derivative *(5)*, R = 2,3,4,6-tetra-*O*-acetyl-1-β-D-glucosyl, and its salts.

Received, January 20th, 1964 [Z 673/497 IE]
German version: Angew. Chem. 76, 301 (1964)

[1] Potential Cytostatics, Part 2. – Part 1: *H. Dorn*, Mber. dtsch. Akad. Wiss. Berlin *3*, 683 (1961).

[2] *E. Ochiai*, Ber. dtsch. chem. Ges. *69*, 1650 (1936); *H. Andersag* and *K. Westphal*, Ber. dtsch. chem. Ges. *70*, 2044 (1937).

[3] *W. Wilson* and *R. Woodger*, J. chem. Soc. (London) *1955*, 2943.

[*] *(1)*, Ar = $C_6H_5$, X = Cl, crystallizes with 1 $H_2O$. On heating to 75–77 °C, water is lost and three modifications melting at 96–97 °C, 124–125 °C and 138–139 °C are obtained.

[4] *F. D. Popp* and *H. Swarz*, J. org. Chemistry *26*, 4764 (1961).

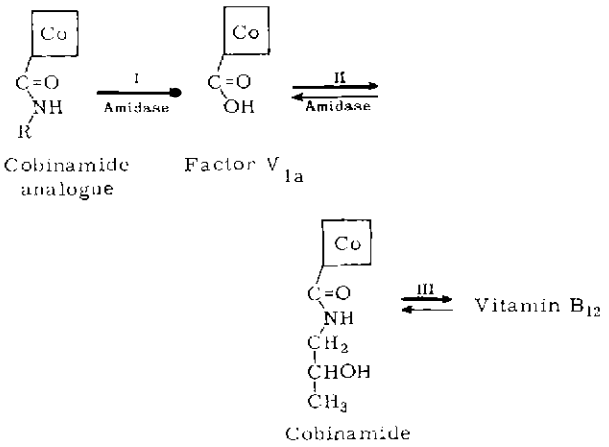
## Cleavage of the f-Amide Bond in Cyanocobalamin Analogues by Propionibacterium shermanii

By Doz. Dr. W. Friedrich and Dr. E. Königk
in collaboration with Waltraud Sandeck

Physiologisch-Chemisches Institut
der Universität Hamburg (Germany)

In the biosynthesis of vitamin $B_{12}$ analogues [1] by *Propionibacterium shermanii* from cobinamide analogues, whose alkanolamine residues are fluorinated, often practically all the starting material is converted into vitamin $B_{12}$ if cobalt-free media are used. This is especially noticeable when the alkanolamine residue is 1-amino-2-hydroxy-2-(*o*-fluorophenyl)ethane, 1-amino-2-hydroxy-2-(*p*-fluorophenyl)ethane, or 1-amino-2-hydroxy-3,3,4,4,5,5,5-heptafluoropentane.

*P. shermanii* obviously produces an amidase, which splits the amide link of the cobinamide analogue giving factor $V_{1a}$ [2] and which then converts this into vitamin $B_{12}$.




The conversion of factor $V_{1a}$ into cobinamide and vitamin $B_{12}$ has already been observed [3]. In order to find out whether the amidase can also convert cobinamide into factor $V_{1a}$, *i.e.* whether Reaction II is reversible, we added factor $V_{1a}$ and [$^{60}$Co]cobinamide to fermentation flasks with *P. shermanii*, and interrupted the experiments at various times. Reversibility of Reaction II should cause factor $V_{1a}$ to become radioactive. The fermentation flasks each contained 7.2 g of corn steep liquor, 10 g of glucose, and ca. 90 ml of tap water. After fermenting for 5 days, 2 mg of factor $V_{1a}$ and 30 nC of [$^{60}$Co]cobinamide were added. After further 12, 24, 36, 48, and 60 h, the fermentation products were worked up; the corrinoids were separated by paper chromatography [4] and their radioactivity measured.

At first the $^{60}$Co appears principally in the vitamin $B_{12}$, *i.e.* Reactions II and III go to the right. Later most of the radioactivity appears in factor $V_{1a}$ [5]; this indicates the reversibility of Reactions II and III. The results show moreover that both [$^{60}$Co]cobinamide and [$^{60}$Co]vitamin $B_{12}$ (and unlabelled factor $V_{1a}$) can serve as precursors for the production of [$^{60}$Co]factor $V_{1a}$ [6].

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Publication deferred until now at the authors' request
German version: Angew. Chem. 76, 272 (1964)

[1] For reviews on the chemistry and biochemistry of vitamin $B_{12}$ and its analogues, see *W. Friedrich* and *K. Bernhauer* in [4]; *K. Bernhauer, O. Müller*, and *F. Wagner*, Angew. Chem. *75*, 1145 (1963); Angew. Chem. internat. Edit. *3*, 200 (1964); *R. Bonnett*, Chem. Reviews *63*, 573 (1963).

[2] *K. Bernhauer, H. Dellweg, W. Friedrich, G. Gross, F. Wagner*, and *P. Zeller*, Helv. chim. Acta *43*, 693 (1960).

[3] *K. Bernhauer, E. Becher, G. Gross*, and *G. Wilharm*, Biochem. Z. *332*, 562 (1960).

[4] *W. Friedrich* and *K. Bernhauer*, in *K. F. Bauer:* Medizinische Grundlagenforschung. Thieme, Stuttgart 1959, Vol. II, p. 661.

[5] Ca. 10000 counts/min per mg of factor $V_{1a}$.

[6] Our thanks are due to the Deutsche Forschungsgemeinschaft for supporting the above work and to Dr. *E. E. Gabbe* for the radioactivity measurements.

## Differentiation of Primary, Secondary, and Tertiary Alcohols by Near Infrared Spectroscopy

By Dr. G. Habermehl

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der Technischen Hochschule Darmstadt (Germany)

Primary, secondary, and tertiary alcohols are normally distinguished by infrared spectroscopy on the basis of the vibrational band due to C–O valence vibration, which occurs near 1050 cm$^{-1}$ for primary alcohols, near 1100 cm$^{-1}$ for secondary alcohols, and near 1150 cm$^{-1}$ for tertiary alcohols [1]. However, since these bands lie in the same region of the spectrum as the vibrational bands of the carbon skeleton of the molecule, their allocation is sometimes difficult. The range from 7000 to 7080 cm$^{-1}$ has been assigned to the first overtone of the OH valence vibration [2–4], but here primary, secondary, and tertiary alcohols have not previously been differentiated.

Now it was found that primary alcohols absorb in the range from 7090 to 7115 cm$^{-1}$, secondary alcohols from 7067 to 7078 cm$^{-1}$, and tertiary alcohols from 7042 to 7053 cm$^{-1}$, independent of whether the hydroxylated carbon atom is substituted with either methyl or phenyl groups (Table 1). The small frequency differences involved demand very careful recording at low speed in the region of the band, in order to pin-point the correct frequency of the band maximum. The exact value of the band maximum has to be read from the frequency counter, otherwise errors of 5–10 cm$^{-1}$ can occur. The recorded frequencies were measured in 1–5% solution in spectroscopically pure $CCl_4$. The concentration of the solutions had no effect on the recorded position of the bands.

Table 1. Absorption of some alcohols in the near infrared [5].

| | Frequency [cm$^{-1}$] |
|---|---|
| *Primary alcohols* | *7090–7115* |
| Methanol | 7115 |
| Ethanol | 7090 |
| 1-Propanol | 7095 |
| 1-Butanol | 7095 |
| 1-Pentanol | 7095 |
| Isoamyl alcohol | 7105 |
| 2-(*N*-Methylamino)ethan-1-ol | 7100 |
| 2-Amino-2-methylpropanol | 7100 |
| *Secondary alcohols* | *7067–7078* |
| 2-Propanol | 7070 |
| 2-Butanol | 7075 |
| Cyclohexanol | 7075 |
| 1-Aminopropanol | 7078 |
| Sedamine | 7067 |
| Samandarine | 7074 |
| Cholesterol | 7070 |
| *Tertiary alcohols* | *7042–7053* |
| t-Butanol | 7050 |
| Triphenylmethanol | 7051 |
| 1-Phenylcyclohexanol | 7042 |
| 1-Phenylcyclopentanol | 7043 |
| 1-Methyl-1-phenylpropanol | 7049 |
| 1,1-Dimethylpropanol | 7053 |

Received, February 3rd, 1964 [Z 664/493 IE]
German version: Angew. Chem. 76, 271 (1964)

[1] *L. J. Bellamy:* The Infrared Spectra of Complex Molecules. Methuen, London 1958, p. 96.

[2] *R. F. Goddu* and *D. Delker*, Analytic. Chem. *32*, 140 (1960).

[3] *W. Kaye*, Spectrochim. Acta *6*, 257 (1954).

[4] *O. H. Wheeler*, Chem. Reviews *59*, 629 (1959).

[5] Perkin-Elmer Model 125.

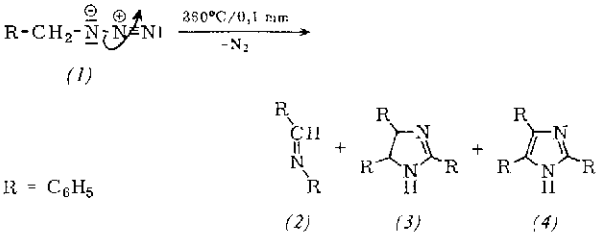
## Pyrolysis of Benzyl Azide in the Gas Phase

By Dr. R. Kreher and Dipl.-Ing. D. Kühling

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

The thermal decomposition of azides is significantly affected by the solvent [1]. We have investigated the pyrolysis of benzyl azide *(1)* in the gas phase at 360 °C/0.1 mm with nitrogen as diluent, and have so far succeeded in isolating by chromatography, *N*-benzylideneaniline *(2)*, m.p. 53 to

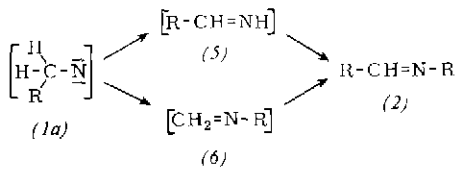
54 °C, in 20 % yield, 4,5-dihydro-2,4,5-triphenylimidazole *(3)* in 29 % yield (m.p. of picrate 258 °C), and 2,4,5-triphenylimidazole *(4)*, m.p. 274–275 °C, in 12 % yield.



*(1)*

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

The formation of *(2)* can be explained by assuming that benzyl azene *(1a)* rearranges to both benzylideneimine *(5)* and *N*-methyleneaniline *(6)*. The azomethines *(5)* and *(6)* interact to form *(2)*, volatile methyleneimine, $[CH_2{-}NH]$, being eliminated.



*(1a)* *(5)* *(6)* *(2)*

It is probable that *(3)* is not produced directly from *(1a)* but is formed from *(5)*, for when benzaldehyde was treated under comparable conditions in an ammonia atmosphere, it gave rise to *(3)* [2], which was characterized as its picrate [3]. Compound *(4)* is presumably formed by dehydrogenation of *(3)*.

According to these preliminary results, benzyl azene is stabilized predominantly by hydrogen migration to give benzylideneimine *(5)*, which reacts further to give *(2)*, *(3)*, and *(4)* [4]. Migration of the phenyl residue to give the unisolable *N*-methyleneaniline *(6)* occurs to only a minor extent; this determines the yield of *(2)*.

Received, February 5th, 1964 [Z 665/491 IE]
German version: Angew. Chem. *76*, 272 (1964)

[1a] *Th. Curtius* and *G. Ehrhart*, Ber. dtsch. chem. Ges. *55*, 1559 (1922); [b] *Th. Curtius* and *W. Klavehn*, J. prakt. Chem. *125*, 464 (1930); [c] *Th. Curtius* and *K. Raschig*, ibid. *125*, 466 (1930).

[2] The formation of *(3)* from *(5)* in liquid $NH_3$ has also been observed; cf. *H. Smith:* Organic Reactions in Liquid Ammonia. Interscience, New York, London 1963, Vol. 1/2, p. 286.

[3] *D. Kühling*, Diploma Thesis, Technische Hochschule Darmstadt, 1963.

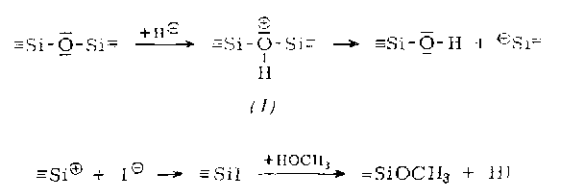
[4] Thermal decomposition of benzyl azide in diethyl succinate also gave *(4)* together with a compound of m.p. 229 °C [1c]. This compound is not 1-benzyl-2,5-diphenyl-1,3,4-triazole, since an analytically pure sample of this compound which we prepared according to the method given by *R. Stollé* and *K. Thomä*, J. prakt. Chem. *73*, 288 (1906), melted at 219 °C.

## Sensitivity of the Siloxane Linkage towards Acidolytic Cleavage

By Dr. K. Damm, Dr. D. Gölitz, and Prof. Dr. W. Noll

Anorganische Abteilung der Farbenfabriken Bayer AG., Leverkusen (Germany)

Linear and cyclic methyl- and phenylpolysiloxanes with a low degree of polymerization are cleaved in methanol by 0.02 N hydrogen iodide:



*(1)*

The reaction may be followed quantitatively by titration of the silanol groups with Karl Fischer reagent [1]:

$$\equiv Si{-}OH + I_2 + SO_2 + 2\,HOCH_3 + \equiv SiOCH_3 + 2\,HI + CH_3HSO_4$$

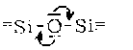
Since this titration of the silanol group proceeds much more rapidly than the splitting of the siloxane linkage (cf. Table 1), the rate of cleavage can also be followed quantitatively. It is thus found that acidolytic cleavage of the siloxane bond is a first order reaction, *i.e.* decomposition of the oxonium complex *(1)* is the rate-determining step.

Table 1. Half-lives ($t_{1/2}$) and disintegration constants (k) for the acidic hydrolysis of various organopolysiloxanes.

| Organopolysiloxane | Abbreviation [2] | $t_{1/2}$ [h] | $k \times 10^3$ [$h^{-1}$] |
|---|---|---|---|
| Diphenylsilanediol [a] | — | 0.05 | — |
| Diethylsilanediol [a] | — | 0.05 | — |
| Hexamethylcyclotrisiloxane | $D_3^{Me}$ | 0.44 | 1575 |
| Hexaphenylcyclotrisiloxane | $D_3^{Ph}$ | 21.5 | 32 |
| Hexamethyldisiloxane | $M_2^{Me}$ | 36 | 19 |
| Octamethylcyclotetrasiloxane | $D_4^{Me}$ | 175 | 3.96 |
| Decamethylcyclopentasiloxane | $D_5^{Me}$ | 310 | 2.2 |
| Octamethyltrisiloxane | $MDM^{Me}$ | 780 | 0.9 |
| Dodecamethylcyclohexasiloxane | $D_6^{Me}$ | 1000 | 0.6 |
| Octaphenylcyclotetrasiloxane | $D_4^{Ph}$ | $\infty$ | 0 |

[a] Silanols for comparison.

The considerable differences in the reaction rates indicate pronounced variations in the stabilities of the siloxane bonds. A partial explanation for this may be found in the fact that different substitution of the silicon ($D_3^{Me} \gg D_3^{Ph}$; $D_4^{Me} > D_4^{Ph}$; $M_2^{Me} > MDM^{Me}$) or valence-angle deformations ($D_3^{Me} > D_4^{Me}$; $D_3 \gg D_4^{Ph}$) cause the lone electron pairs on the oxygen to participate in the formation of a $d_\pi$-$p_\pi$ bond:



The greater this effect, the slower the splitting of the siloxanes (*e.g.* $D_6^{Me}$ or $D_4^{Ph}$) on electrophilic attack by a proton.

Reactive siloxane bonds in silicic-acid xerogels can also be determined quantitatively by titration following acidolytic cleavage. Using a xerogel [3] which had been heated at 200 °C for 4 h, it could be shown that practically all the siloxane bonds formed by condensation are so reactive that they are split by acidolysis.

Received, February 6th, 1964 [Z 659/488 IE]
German version: Angew. Chem. *76*, 273 (1964)

[1] The Karl Fischer titration was carried out automatically using the dead-stop method; the titration curve was also recorded automatically.

[2] $D^{Me} = (CH_3)_2SiO$; $M^{Me} = (CH_3)_3SiO_{1/2}$; $D^{Ph} = (C_6H_5)_2SiO$; cf. *W. Noll:* Chemie und Technologie der Silicone. Verlag Chemie, Weinheim/Bergstr. 1960, p. 3.

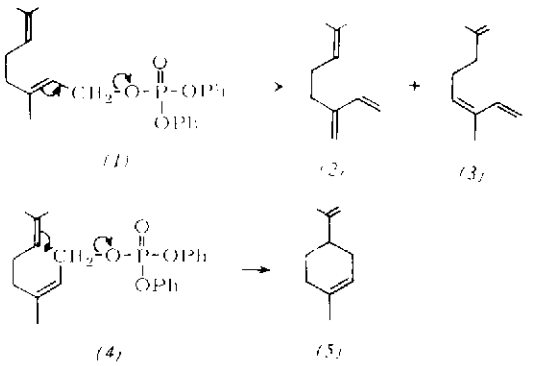
[3] Silica gel from Messrs. Gebrüder Herrmann, Köln (Germany); fraction $< 10\,\mu$.

## A Biogenetic-Type Cyclization of a Terpene Phosphate

By J. A. Miller, B.Sc., and Dr. H. C. S. Wood

Chemistry Department, The Royal College of Science and Technology, Glasgow (Scotland)

Unpublished work by *F. R. Atherton* [1] has shown that geranyl diphenyl phosphate *(1)* decomposes on standing to give $C_{10}$ hydrocarbons which were not identified. We have reinvestigated this reaction and have established that the major products obtained by allowing a solution of 8 g of this ester in 1000 ml of ether to stand at 37 °C for several days were the acyclic terpenes, myrcene *(2)* and ocimene *(3)*. Similar treatment of the diphenyl phosphate ester *(4)* of nerol, which has the *cis*-configuration at the allylic double



(1) (2) (3)



(4) (5)

bond, gave limonene *(5)* in 45 % yield. The phosphates were prepared by the conventional method from the alcohols and diphenylphosphorochloridate in pyridine. The terpene hydrocarbons were separated by preparative gas-liquid chromatography, and were identified by spectroscopic methods and comparison with authentic samples.

These experiments simulate the role played by pyrophosphate esters in the formation of carbon-carbon bonds *in vivo* [2]. They also suggest that the stereochemistry at the allylic double bond in the precursor of monoterpene hydrocarbons may determine the nature of the terpene formed.

Received, February 7th, 1964 [Z 661/483 IE]
German version: Angew. Chem. *76*, 301 (1964)

[1] *F. R. Atherton*, personal communication; also referred to by *A. R. Todd* [2].

[2] *A. R. Todd*, Proc. nat. Acad. Sci. U.S.A. *45*, 1389 (1959); Nature *187*, 821 (1960); Proc. chem. Soc. (London) *1962*, 199; *J. W. Cornforth*, Pure appl. Chem. *2*, 607 (1961); *F. Lynen* and *U. Henning*, Angew. Chem. *72*, 820 (1960).

## Allylbiscyclopentadienyltitanium(III) and -vanadium(III)

By Drs. Hendrik A. Martin and Prof. Dr. F. Jellinek

Laboratorium voor Anorganische Chemie,
Rijksuniversiteit te Groningen (Holland)

No allyl complexes of titanium or vanadium have yet been reported. We have prepared allylbiscyclopentadienyltitanium-(III) *(1)* by the reaction of biscyclopentadienyltitanium(IV) dichloride *(2)* with 2–3 equivalents of allylmagnesium bromide in tetrahydrofuran at room temperature; the original red color of the solution gradually changed into violet. The

*(1)* $(C_5H_5)_2Ti(CH_2{-}CH{=}CH_2)$ $(C_5H_5)_2TiCl_2$ *(2)*

same solution was obtained when *(2)* was first reduced to biscyclopentadienyltitanium(III) monochloride by means of zinc powder [1] and one equivalent of allylmagnesium bromide added to the green solution. The reaction mixture was evaporated *in vacuo*, and the residue extracted with pentane. When the violet pentane solution was concentrated to saturation and cooled to −80 °C, purple crystals of *(1)* precipitated. After two recrystallizations from pentane, pure *(1)*, m.p. 118 °C (decomp.), was obtained in 35 % yield. Reaction of *(1)* with octanol gave propene in 80 % yield.

Allylbiscyclopentadienyltitanium(III) is remarkably stable; the solid compound and its solutions in pentane remained unchanged when kept under nitrogen for several months at room temperature. Solid *(1)* is rapidly oxidized in air, and solutions of *(1)* immediately turn yellow on exposure to air. However, when air is passed through solutions of *(1)* in toluene/HCl, immediate formation of red *(2)* occurs.

The infrared spectrum of *(1)* in KBr has no bands in the 1650–1600 $cm^{-1}$ range, but has a band at 1500 $cm^{-1}$; we conclude, therefore [2], that the allyl group is π-bonded to the metal. Another band at 1435 $cm^{-1}$ is ascribed to the valence vibration of the π-bonded cyclopentadienyl ligands.

Between 400 and 1200 mμ, solutions of *(1)* in hexane show only one rather sharp absorption band at 510 mμ; beyond 400 mμ there is intense absorption. Compound *(1)* is paramagnetic.

The reaction of biscyclopentadienylvanadium(III) monochloride *(3)* with allylmagnesium bromide yielded a brown

*(3)* $(C_5H_5)_2VCl$ $(C_5H_5)_2V(C_3H_5)$ *(4)*

solution. Its absorption spectrum contains bands at 475 mμ and 720 mμ and is similar to that of benzylbiscyclopentadienylvanadium(III) [3]. We assume, therefore, that our reaction product is the analogous allyl compound *(4)*. The compound is unstable and has not yet been isolated. It is also formed, together with *(3)*, by the reaction of biscyclopentadienylvanadium(II) with 0.5 equivalent of allyl chloride. If excess allyl chloride is used, only *(3)* is obtained [4].

Received, February 10th, 1964 [Z 669/487 IE]
German version: Angew. Chem. *76*, 274 (1964)

[1] *J. M. Birmingham, A. K. Fischer*, and *G. Wilkinson*, Naturwissenschaften *42*, 96 (1955).

[2] *W. R. McClellan, H. H. Hoehn, H. N. Cripps, E. L. Muetterties*, and *B. W. Howk*, J. Amer. chem. Soc. *83*, 1601 (1961).

[3] *H. J. de Liefde Meijer, M. J. Janssen*, and *G. J. M. van der Kerk*, Rec. trav. chim. Pays-Bas *80*, 831 (1961).

[4] We wish to thank Dr. *H. J. de Liefde Meijer* for his stimulating advice and Mr. *J. C. de Vries* for his assistance in the experiments.

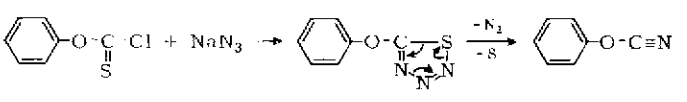
## Phenyl Cyanate

By Dr. D. Martin

Institut für Organische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Adlershof (Germany)

Attempts to prepare cyanic esters result mostly in their trimerization products cyanuric esters; thus, cyanogen halides and alkali phenoxides afford cyanuric esters or iminocarbonic esters. Only phenols with bulky *ortho*-substituents and cyanogen chloride have so far yielded cyanates, *e.g.* 2,6-di-t-butylphenyl cyanate, trimerization of which is sterically hindered [1].

It seemed possible to isolate cyanic esters as products of the fission of thermally labile molecules in which the O–C–N grouping is preformed. Interaction of the thiocarbonic ester chloride *(1)* and sodium azide in aqueous acetone at −5 to 0 °C followed by extraction with ether and concentration of the extract at 0 °C gave 5-phenoxy-1,2,3,4-thiatriazole *(2)*, m.p. 33–34 °C from methanol. Compound *(2)* decomposes exothermically in benzene at room-temperature to afford the previously unknown phenyl cyanate *(3)* in 93 % yield as a colorless liquid with a pungent odor, b.p. 74–75 °C/10 mm. Trimerization does not occur under these conditions.



(1) (2) (3)

Phenyl cyanate is partially hydrolysed by dilute sulfuric acid to phenyl carbamate and thence to phenol. Trimerization at 200 °C yields triphenyl cyanurate.

The ultraviolet spectrum of *(3)* contains two absorption bands. The band of longer wavelength has a distinct fine structure; both it and the band of shorter wavelength are displaced by 11 mμ hypsochromically with respect to the bands of phenyl isocyanate. The infrared spectrum of *(3)* includes bands at 2235 and 2280 $cm^{-1}$ ascribed to the C≡N group [2], and a phenyl ether vibration band at 1190 $cm^{-1}$, which is absent in the spectrum of phenyl isocyanate.

Received, February 10th, 1964 [Z 670/498 IE]
German version: Angew. Chem. *76*, 303 (1964)

[1] *R. Stroh* and *H. Gerber*, Angew. Chem. *72*, 1000 (1960).

[2] *H. Hoyer*, Chem. Ber. *94*, 1042 (1961).

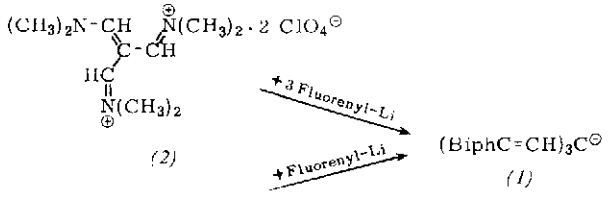
## The Tris(dibenzofulvenyl)methyl Anion, an Extremely Stable Colored Carbanion

By Doz. Dr. C. Jutz and Dipl.-Chem. H. Amschler

Organisch-Chemisches Institut
der Technischen Hochschule München (Germany)

*Dedicated to Professor St. Goldschmidt on the occasion of his 75th birthday.*

We have obtained the deep-blue tris(dibenzofulvenyl)methyl anion *(1)* ($\lambda_{max}$ = 635 mμ) as the Li salt in solution by the action of a) 3 moles of fluorenyl-lithium on 1 mole of the bis-immonium salt *(2)* (colorless crystals, m.p. 220–221 °C from acetonitrile) or b) 1 mole of fluorenyl-lithium on 1 mole of the branched aminofulvene *(3)* (orange-red crystals, m.p. 220–221 °C from benzene/ethanol). The reactants were refluxed under nitrogen in absolute tetrahydrofuran for 30 min. The anion *(1)* is stabilzed by the quasi-aromatic cyclic sextet-conjugation of the five-membered rings and has its charge delocalized over 40 carbon atoms.

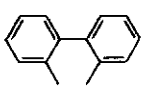



*(2)* *(1)*

$(BiphC{=}CH)_2C{=}CH{-}N(CH_3)_2$

*(3)*

Biph =



The blue solutions of the Li salt of *(1)* are stable in air for over 24 h. Oxidation of *(1)* with $K_3[Fe(CN)_6]$ yields the tris(dibenzofulvenyl)methyl radical, which is brownish-yellow and in solution is sensitive to air. On acidifying the solution of the Li salt of *(1)*, the pale yellow, strongly acidic hydrocarbon [1,3] tris(dibenzofulvenyl)methane, m.p. 225–226 °C from benzene/ethanol [yield from a) 30 %, from b) 90 %], is obtained. It can be chromatographed without decomposition with benzene on $Al_2O_3$ (activity grade II) and has the color of the anion *(1)* on the adsorbent. The bis-immonium salt *(2)* was obtained in 80 % yield by formylation of dimethylaminopropenylidenedimethylimmonium perchlorate with dimethylformamide/phosphorus oxychloride or phosgene [2] (the reaction mixture was worked up with $HClO_4$/ethanol). Heating of *(2)* with fluorene and Na methoxide (molar ratio 1:2:2) in pyridine gave a 90 % yield of *(3)* ($\lambda_{max}$ = 457 mμ, log ε = 4.62 in acetonitrile). For optical studies, solutions of salts with anions of type *(1)* were prepared in which 7*H*-benzo[*c*]fluorene or 2,3-diphenylindene replaced one or two fluorene groups.

Received, February 10th, 1964 [Z 674/504 IE]
German version: Angew. Chem. *76*, 302 (1964)

[1] *R. Kuhn* and *H. Fischer*, Angew. Chem. *73*, 435 (1961); *C. Jutz* and *H. Amschler*, ibid. *73*, 806 (1961); *R. Kuhn*, *H. Fischer*, *F. A. Neugebauer*, and *H. Fischer*, Liebigs Ann. Chem. *654*, 64 (1962).

[2] *Z. Arnold* and *J. Zemlička*, Coll. czechoslov. chem. Commun. *25*, 1318 (1960).

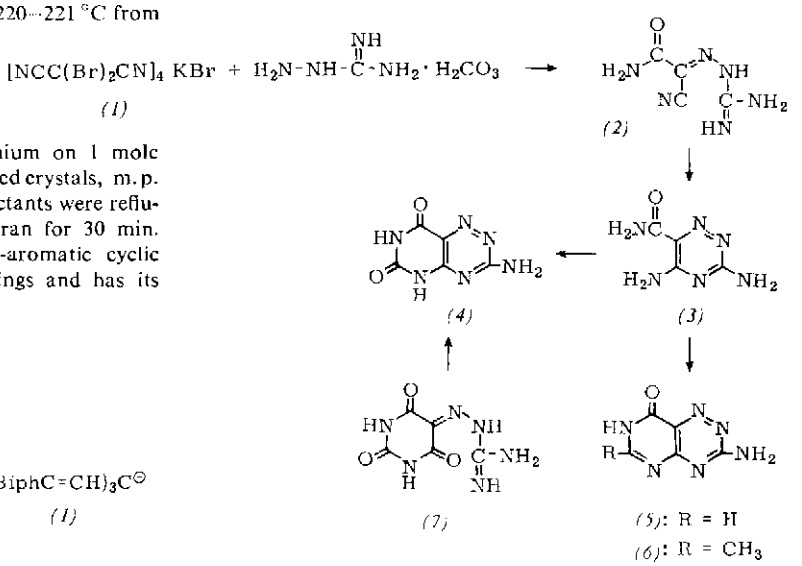
[3] Note added in proof: In the meantime two communications describing tris(dibenzofulvenyl)methane and the anion *(1)* were published: *R. Kuhn* and *H. Fischer*, Angew. Chem. *76*, 146 (1964); Angew. Chem. internat. Edit. *3*, 137 (1964); *R. Kuhn* and *D. Rewicki*, Tetrahedron Letters *1964*, 383. Accordingly to these, the hydrocarbon is an equilibrium mixture of the protomeric hydrocarbons $C_{43}H_{28}$.

## The Synthesis of Pyrimido[4,5-*e*]-as-triazines (6-Azapteridines) [1]

By Prof. Dr. E. C. Taylor and R. W. Morrison, Jr. [2]

Department of Chemistry, Princeton University, Princeton, N.J. (U.S.A.)

The antibiotics toxoflavin and fervenulin, which have recently been recognized to be derivatives of pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) [3], are structurally related to the physiologically important pteridines and alloxazines. We have studied analogous systems hoping to find substances with antibiotic, antiviral, and antimitotic properties, and wish




to report two independent synthetic routes to the isomeric ring system of pyrimido[4,5-*e*]-*as*-triazine (6-azapteridine). Reaction of the dibromomalononitrile/KBr complex *(1)* [4] with aminoguanidinium hydrogen carbonate in ethanol furnished *(2)*, which cyclized on heating in water, dimethylformamide, or 2-ethoxyethanol to give 3,5-diamino-6-aminocarbonyl-*as*-triazine *(3)* [5]. Diethyl carbonate and *(3)* condense in ethanolic sodium ethoxide to afford 3-amino-6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-*e*]-*as*-triazine *(4)* [6], m.p. >360 °C. Similarly, *(3)* reacts with formamide or with acetamide or ethyl acetate to yield the corresponding 6-unsubstituted and 6-methyl derivatives *(5)* and *(6)*, respectively.

The structure of *(4)* was confirmed by an independent synthesis. Alloxan and aminoguanidinium hydrogen carbonate gave *(7)*, which was cyclized by dilute ammonia to *(4)* [7].

Received, February 11th, 1964 [Z 680/502 IE]
German version: Angew. Chem. *76*, 342 (1964)

[1] This work was supported by funds from the National Cancer Institute of the National Institutes of Health, Public Health Service (Grant No. CA-02251), made available to Princeton University.

[2] N. I. H. Predoctoral Fellow, 1961–1964.

[3] *G. Doyle Daves, Jr.*, *R. K. Robins*, and *C. C. Cheng*, J. Amer. chem. Soc. *84*, 1724 (1962) and references cited therein.

[4] *R. A. Carboni*, Org. Syntheses *39*, 64 (1959).

[5] This compound was previously prepared by a less direct method by *H. M. Taylor* (Ph. D. Thesis, University of North Carolina, 1959; Univ. Microfilms, L. C. card. no MIC 59-5587) but he was unable to utilize it as an intermediate.

[6] The preparation of this compound has been claimed by *L. Heinisch*, *W. Ozegowski*, and *M. Mühlstädt* [Chem. Ber. *97*, 5 (1964)], by the action of ammonia on 3-ethylthio-6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-*e*]-*as*-triazine, which was obtained in turn from alloxan and *S*-ethylisothiosemicarbazide hydrochloride. These authors obtained their product only as the hydrate, but we had no difficulty in isolating *(4)* in the anhydrous form. The question of the identity of the two products remains open.

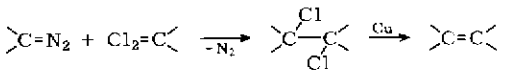
[7] Previous attempts to perform this cyclization with stronger base were reported to result in ring cleavage [5].

## Reactions of Diaryldiazomethanes with Halogeno Compounds [*]

By Prof. Dr. A. Schönberg and Dipl.-Chem. E. Frese

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der Technischen Universität Berlin (Germany)

We have found that diaryldiazomethanes *(1)* in benzene or petroleum ether react briskly at room temperature without irradiation and without decomposition catalysts with some halogeno compounds, *e.g.* diaryldichloromethanes *(2)*.

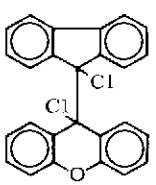


*(1)* *(2)* *(3)* *(4)*

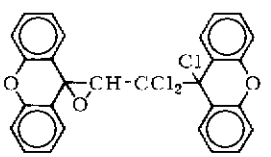
The 1,2-dichloroethanes *(3)* produced are readily dechlorinated with copper powder in boiling ligroin (100–140 °C) to give the corresponding ethylenes *(4)* in ca. 90 % yield.

For example, starting from diazofluorene and 9,9-dichloroxanthene we obtained a 75 % yield of 9-(*o*-biphenylenechloromethyl)-9-chloroxanthene *(5)*, m.p. 176 °C, which was converted into *o*-biphenylenemethylenexanthene [1]. Again, bis-(4-methoxyphenyl)diazomethane and 9,9-dichloroxanthene gave rise to 9-[bis-(4-methoxyphenyl)chloromethyl]-9-chloroxanthene, m.p. 76 °C (from absolute petroleum ether, b. p. 60–70 °C under nitrogen), in ca. 50 % yield, and thence to 9-bis-(4-methoxyphenyl)methylenexanthene [2], m.p. 179 °C (from chloroform/ethanol). Treatment of the reaction product obtained from diazoxanthene and 9,9-dibromofluorene with copper powder also yielded *o*-biphenylenemethylenexanthene.

Diazoxanthene is very reactive; it reacts exothermally with excess $CCl_4$ at room temperature without irradiation to give 9,9'-dichlorobixanthyl, m.p. 203 °C (from petroleum ether, b. p. 90–100 °C), in ca. 35 % yield. With copper powder it is converted almost quantitatively into the known derivative bixanthylene. Its reaction with excess $CHCl_3$ goes just as easily: the 9-chlorobixanthyl formed is converted by ethanol into 9-ethoxybixanthyl, m.p. 145 °C (from ethanol), in ca. 50 % yield.



*(5)*



*(6)*

Diazofluorene and diphenyldiazomethane do not react with $CHCl_3$ or $CCl_4$ under the above conditions. Benzylphenyldiazomethane is somewhat more reactive and decomposes to form over 90 % ketazine.

Diazoxanthene and chloral combine in benzene with evolution of nitrogen to yield a compound $C_{28}H_{17}Cl_3O_3$ (decomp. above 180 °C), for which we propose formula *(6)*. The infrared spectrum of *(6)* in Nujol or $CCl_4$ shows no carbonyl band.

Received, February 13th, 1964 [Z 668/496 IE]
German version: Angew. Chem. *76*, 343 (1964)

[*] A recent publication by *H. Reimlinger*, Chem. Ber. *97*, 339 (1964), has induced us to report some of our results.

[1] *A. Schönberg* and *M. M. Sidky*, J. Amer. chem. Soc. *81*, 2262 (1959).

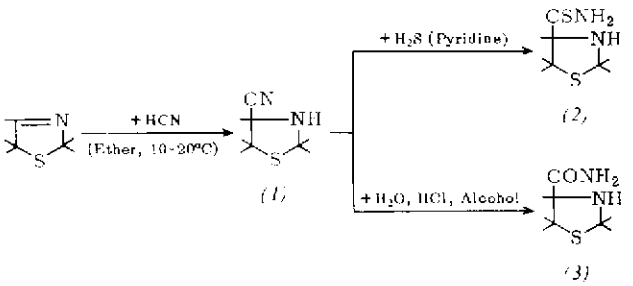
[2] We also obtained 9-bis-(4-methoxyphenyl)methylenexanthene by the reaction of bis-(4-methoxyphenyl)diazomethane with xanthione, the ethylene sulfide formed being desulfurized with copper powder.

## Synthesis of Penicillamine Amide and Penicillamine Thioamide from Thiazolidine-4-carboxamides and -4-thiocarboxamides

By Prof. Dr. F. Asinger, Dr. W. Schäfer, and Dipl.-Chem. E.-Chr. Witte

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der Technischen Hochschule Aachen (Germany)

Gaseous hydrogen cyanide adds on smoothly at room temperature to the azomethine bond of many $\Delta^3$-thiazolines [1, 2]. The stability of the resultant novel thiazolidine-4-carbonitriles *(1)* depends both on their purity and the number and type of substituents on the 2- and 4-positions; they are invariably stable in the form of their hydrochlorides (Table 1).



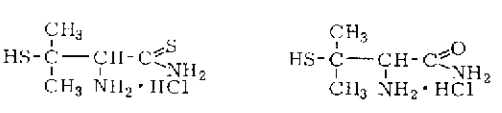

*(1)* *(2)* *(3)*

Table 1. Thiazolidine-4-carbonitriles *(1)*, -thiocarboxamides *(2)*, and -carboxamides *(3)*.

| $\Delta^3$-Thiazoline | *(1)* Yield [%] | *(1)* m.p. [°C] | *(2)* Yield [%] | *(2)* m.p. [°C] | *(3)* Yield [%] | *(3)* m.p. [°C] |
|---|---|---|---|---|---|---|
| 5,5-Dimethyl- | 88 | 57,5 (144)[*] | 79 | 162 | 72 | 177–178 (222) |
| 2,5,5-Trimethyl- | 92 | 58 | 74 | 171 | | |
| 2-Isopropyl-5,5-dimethyl- | 96 | 31 (253) | 62 | 117 | 98 | 97 (236) |
| 2-Phenyl-5,5-dimethyl- | 88 | 109 (167–169) | 25 | 155 | | |
| 2,2,4-Trimethyl- | 93 | 54 | | | 76 | 148 (236) |
| 2,2,5,5-Tetramethyl- | 94 | 73 (171) | 54 | 171 | 47 | 148 (204–205) |
| 2,2-Diethyl-5,5-dimethyl- | 97 | 37 | 34 | 174 | | |
| 2,2-Pentamethylene-5,5-dimethyl- | 92 | 54 (185) | 26 | 177 | 74 | 138 (232) |
| 2,2,4-Triethyl-5-methyl- | 94 | 70 | | | | |

[*] In parentheses: m.p. of the hydrochloride.

The nitriles react with $H_2S$ at 0–10 °C to give the previously unknown, colorless thiazolidine-4-thiocarboxamides *(2)*; the yields increase with decreasing substitution at the 2-position (Table 1). $H_2S$ has not yet been added onto 4-substituted nitriles. Treatment of the nitriles with aqueous-alcoholic HCl gives the hydrochlorides of thiazolidine-4-carboxamides *(3)* (cf. Table 1). Hydrolytic ring opening of the thioamides *(2)*



*(4)* *(5)*

with 2N HCl gives high yields of α-amino-β-mercaptothioamides and oxo compounds. Starting from 2,2,5,5-tetramethylthiazolidine-4-thiocarboxamide, we obtained a quantitative yield of the previously inaccessible compound α-

amino-β-mercaptothioisovaleramide as its hydrochloride *(4)* (penicillamine thioamide hydrochloride, m.p. 169 °C). Similarly, hydrolysis of 2,2,5,5-tetramethylthiazolidine-4-carbonitrile hydrochloride led via the 4-carboxamide to the previously unknown derivative α-amino-β-mercaptoisovaleramide hydrochloride *(5)* (penicillamine amide hydrochloride, m.p. 235 °C) in quantitative yield.

Received, February 14th, 1964 [Z 666/489 IE]
German version: Angew. Chem. 76, 273 (1964)

[1] *F. Asinger* and *M. Thiel*, Angew. Chem. *70*, 667 (1958).
[2] Cf. [1], p. 677.

## Preparation of Silylgermanes

By Prof. Dr. P. Royen and Dipl.-Chem. C. Rocktäschel

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der Universität Frankfurt/Main (Germany)

Attack by 5–6 N HCl on calcium germanide yields an amorphous lower germanium hydride [1] and a mixture of volatile germanium hydrides. Decomposition of the analogous silicide proceeds correspondingly [2]. The formation of mixed volatile hydrides on decomposing solid solutions of the type $Ca_2(Ge,Si)$ and Ca(Ge,Si) was to be expected.

Homogeneous crystalline solid solutions of germanium and silicon in the ratio 1:1 were produced by melting the elements (Ge: 99.999 % pure, Si: 99.999 % pure from Messrs. Schuchardt) together and tempering at 1050–1100 °C for 30 days [3]. This alloy was mixed with the stoichiometric amount of calcium (99.85 % pure from Messrs. Schuchardt), and the mixture welded into a steel crucible [4], evacuated, and fused by heating briefly to 1200 °C. The X-ray patterns of the mixed crystals thus obtained were in accordance with those of the isotypic phases CaSi and CaGe [5] or $Ca_2Si$ and $Ca_2Ge$ [6]. For the reaction, 5–6 N HCl was slowly dropped onto the solid solution with cooling in an evacuated apparatus.

Examination of the gases developed by mass spectrometry [7] showed that $Ca_2(Ge,Si)$ gave rise to the already known volatile hydrides $SiH_4$, $Si_2H_6$, $Si_3H_8$, $GeH_4$, $Ge_2H_6$, $Ge_3H_8$, and $SiGeH_6$ [8] together with the hitherto unknown mixed hydrides $Si_2GeH_8$ and $SiGe_2H_8$. The same hydrides were obtained together with $Si_4H_{10}$ from Ca(Ge,Si).

Received, January 20th and February 17th, 1964 [Z 663/492 IE]
German version: Angew. Chem. 76, 302 (1964)

[1] *P. Royen* and *R. Schwarz*, Z. anorg. allg. Chem. *211*, 412 (1933).
[2] *R. Schwarz* and *F. Heinrich*, Z. anorg. allg. Chem. *221*, 277 (1935).
[3] *H. Stöhr* and *W. Klamm*, Z. anorg. allg. Chem. *241*, 305 (1939).
[4] *A. Weiss* and *G. Rocktäschel*, Z. anorg. allg. Chem. *307*, 1 (1960).
[5] *P. Eckerlin*, *H. J. Meyer*, and *E. Wölfel*, Z. anorg. allg. Chem. *281*, 322 (1955).
[6] *P. Eckerlin* and *E. Wölfel*, Z. anorg. allg. Chem. *280*, 321 (1955).
[7] We wish to thank Dr. *W. Mosch*, Institut für physikalische Chemie, Frankfurt/Main, for the mass-spectrometric identification of the volatile hydrides.
[8] *E. J. Spanier* and *A. G. MacDiarmid*, Inorg. Chem. *2*, 215 (1963); preparation from $SiH_4$ and $GeH_4$ by silent electrical discharge.

## Alcoholysis of Tetraphosphorus Heptasulfide $P_4S_7$

By Dipl.-Chem. H. Petschik and Prof. Dr. E. Steger

Institut für Anorganische und Anorganisch-Technische Chemie und Institut für Spezielle Analytische Chemie der Technischen Universität Dresden (Germany)

The esters $(RO)_2PSSH$, $(RO)_2PSH$, and $(RO)_2PS(SR)$ plus $H_2S$ and some $PH_3$ have been described as the products of alcoholysis of $P_4S_7$ [1]. The NMR spectrum of the reaction mixture of $P_4S_7$ and n-butanol displays 9 signals [2]. We allowed $P_4S_7$ to react in $CS_2$ with ethanol at ≈ 20 °C and analysed the mixture quantitatively by thin-layer chromatography. $(C_2H_5O)_2PS(SC_2H_5)$ *(1)* and $(C_2H_5O)_2PSH$ *(2)* were found to be secondary products. According to our investigations, approximately two atoms of sulfur are split off per $P_4S_7$ as $H_2S$; $(C_2H_5O)_2PS(SH)$ *(3)* is immediately detectable in the infrared spectrum and accounts initially for about half of the phosphorus in solution; hence we consider the main reaction to be:

$$P_4S_7 + 7\,C_2H_5OH \rightarrow \underset{(3)}{2(C_2H_5O)_2PS(SH)} + 2\,H_2S + \underset{(4)}{(C_2H_5O)_2P{-}P(OC_2H_5)SH} \quad (a)$$

*O,O,O'*-Triethyl diphosphonothioate *(4)* is at present only characterized by its position on chromatograms, sensitivity towards water, and strong reducing properties; it decomposes within a few hours. As *(4)* decomposes, the proportion of *(2)* increases until it accounts for nearly one-quarter of the total phosphorus. Ester *(1)* attains this level only after 1–2 days. A substance must therefore be formed by cleavage of *(4)* which alkylates *(3)* to *(1)*, for ethanol does not react with *(1)* under these conditions. From chromatograms and infrared spectra we assume that reactions (b) and (c) occur.

$$\underset{(4)}{(C_2H_5O)_2P{-}P(OC_2H_5)SH} + C_2H_5OH \rightarrow \underset{(2)}{(C_2H_5O)_2PH} + (C_2H_5O)_2PSH \quad (b)$$

$$\underset{(3)}{(C_2H_5O)_2PH} + (C_2H_5O)_2PS(SH) \rightarrow \underset{(1)}{(C_2H_5O)_2PS(SC_2H_5)} + \underset{(5)}{(C_2H_5O)P(O)H_2} \quad (c)$$

$(C_2H_5O)P(O)H_2$ *(5)*, which is unstable at room temperature [3], accounts for the formation of $PH_3$; the proportion of 5–7 % [4] of the total phosphorus found in this form agrees with the maximum amount of 8.33 % to be expected from *(5)*. The other disproportionation product $(C_2H_5O)_2POH$ *(6)* occurs as an impurity that went unrecognized in most of the preparations of *(2)* described, which have $n_D^{20} < 1.4695$ [1, 5] and infrared bands at 550 and 1270 $cm^{-1}$ [6]. It can be isolated from *(2)* by extraction with water; *(2)* and *(6)* are difficult to separate by distillation. In this way, we obtained about 98 % $(C_2H_5S)_2PSH$ *(2)*, b.p. 72.5 °C/13.5 mm, with the refractive index specified. During the alcoholysis, water present converts *(4)* into a more strongly polar substance; the yield of *(2)* falls off correspondingly. This occurs particularly during methanolysis, since the complete esterification of $(CH_3O)_2PS(SH)$ by excess methanol produces water.

The alcoholysis of $P_4S_7$ produces varying yields (≤ 6 %) of a bright yellow, finely powdered substance with P:S = 1:1; this is probably identical with the $(PS)_x$ of *Kuchen* and *Beckers* [7]. This yellow substance, probably mixed with unreacted $P_4S_7$, appears to have been taken for sulfur by several authors [5, 8].

Received, February 18th, 1964 [Z 681/508 IE]
German version: Angew. Chem. 76, 344 (1964)

[1] *M. I. Kabatschnik* and *T. A. Masstryukova*, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk *1952*, 727.
[2] *K. Moedritzer* and *J. R. Van Wazer*, J. Inorg. Nuclear Chem. *25*, 683 (1963).
[3] *M. I. Kabatschnik*, *A. E. Schipov*, and *T. A. Masstryukova*, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk *1960*, 196.
[4] *T. A. Masstryukova*, personal communication.
[5] *R. A. McIvor*, *G. D. McCarthy*, and *G. A. Grant*, Canad. J. Chem. *34*, 1819 (1956).
[6] *R. A. McIvor*, *G. A. Grant*, and *C. E. Hubley*, Canad. J. Chem. *34*, 1611 (1956).
[7] *W. Kuchen* and *H. G. Beckers*, Angew. Chem. *71*, 163 (1959).
[8] *G. Schrader*, *W. Lorenz*, and *R. Mühlmann*, Angew. Chem. *70*, 690 (1958).

## Synthesis and Crystal Structure of Titanium(III) Tetrametaphosphate and Polyphosphate

By Priv.-Doz. Dr. F. Liebau and H. P. Williams, M. Sc.

Max-Planck-Institut für Silikatforschung,
Würzburg (Germany)

Two phosphates of composition $Ti_2O_3 \cdot 3\,P_2O_5$ have been obtained during investigations of phosphates of trivalent titanium.

Metallic titanium was dissolved with exclusion of oxygen in 85 % phosphoric acid, and the solution was then heated until separation began: tetrameta- or polyphosphates were thus obtained, often together in one and the same charge. On heating metallic titanium in molten $NH_4(H_2PO_4)$, also with exclusion of oxygen, only the polyphosphate was formed.

Under these conditions, titanium(III) tetrametaphosphate forms bright blue tetrahedral and octahedral crystals with a maximum length of edge of 1 mm. X-Ray investigations (Guinier, rotating crystal, and Weissenberg photographs) showed it to be isotypic with the cubic aluminum tetrametaphosphate $Al_4(P_4O_{12})_3$ of known crystal structure [1]. $Ti_4(P_4O_{12})_3$ has cyclic anions containing four $PO_4$ tetrahedra. The crystallographic data of titanium and aluminum tetrametaphosphates are:

| | a [Å] | Z | $\rho_{calc.}$ [g/cm³] | Refractive index |
|---|---|---|---|---|
| $Ti_4(P_4O_{12})_3$ | 13.82 | 4 | 2.84 | $1.584_5$ |
| $Al_4(P_4O_{12})_3$ | 13.71 | 4 | 2.64 | 1.545 [2] |

Titanium(III) polyphosphate was obtained as irregular, oblong, purple-blue crystals of about 0.5 mm maximum length. X-Ray powder patterns showed that this phosphate is isotypic with the monoclinic polyphosphates $Fe(PO_3)_3$ [3], $Cr(PO_3)_3$ [3], and $Mo(PO_3)_3$ [4]. It is a polyphosphate of formula $Ti(PO_3)_3$ with chains of $(PO_3)_\infty^{3-}$ anions. The dimensions of the unit cell and the optical data are similar to those of molybdenum polyphosphate:

| | a sin β [Å] | b [Å] | c [Å] | Z | $\rho_{calc.}$ [g/cm³] | Refractive indices $n_\alpha \approx n_\beta$ | $n_\gamma$ | 2 $V_z$ [5] |
|---|---|---|---|---|---|---|---|---|
| $Ti(PO_3)_3$ | 10.42 | 19.35 | 9.54 | 12 | 2.93 | ≈1.635 | 1.651 | ≈10° |
| $Mo(PO_3)_3$ | 10.67 | 19.48 | 9.55 | 12 | 3.34 | 1.660 | 1.680 | 9.5° |

Received, February 21st, 1964 [Z 672/509 IE]
German version: Angew. Chem. 76, 303 (1964)

[1] *L. Pauling* and *J. Sherman*, Z. Kristallogr. *96*, 481 (1937).
[2] *S. B. Hendricks* and *R. W. G. Wyckoff*, Amer. J. Sci. *13*, 491 (1927).
[3] *E. Thilo* and *I. Grunze*, Z. anorg. allg. Chem. *290*, 223 (1957).
[4] *R. M. Douglass* and *E. Staritzky*, Analytic. Chem. *29*, 985 (1957).
[4] *R. M. Douglass* and *E. Staritzky*, Analytic. Chem. *29*, 985 (1957).
[5] 2 $V_z$ is the angle between the primary optical axes.

## Aminoboron Azides [1]

By Dr. P. I. Paetzold and cand. chem. Gert Maier

Institut für Anorganische Chemie
der Universität München (Germany)

*N,N*-Dialkylaminoboron azides are formed in almost quantitative yields from *N,N*-dialkylaminoboron chlorides and lithium azide by stirring for 20 h in boiling benzene. They are isolated by distillation under reduced pressure.

The dialkylaminoboron azides are colorless liquids which are extremely sensitive to hydrolysis but which are more thermostable than diarylboron azides [2] and may be distilled without decomposition. The asymmetric azide valence vibrations ($\nu_1$) lie at higher values than those of diarylboron azides. The B–N valence vibrations of the boron-amine bond ($\nu_2$) lie in the expected region.

$$(R_2N)_{3-n}BCl_n + n\,LiN_3 \rightarrow (R_2N)_{3-n}B(N_3)_n + n\,LiCl$$

| Compound | R | n | B.p. [°C/12 mm] | $\nu_1$ [cm⁻¹] | $\nu_2$ [cm⁻¹] |
|---|---|---|---|---|---|
| *(1)* | $CH_3$ | 1 | 40 | 2151 | 1531 |
| *(2)* | $C_2H_5$ | 1 | 90–93 | 2137 | 1495 |
| *(3)* | $CH_3$ | 2 | 53–55 | 2146 | 1534 |
| *(4)* | $C_2H_5$ | 2 | 75–77 | 2155 | 1504 |

On heating *(1)* for 17 h in a sealed tube at 270 °C, one mole of *(1)* yields 1 mole of nitrogen and 1 mole of dimethylamine, together with insoluble resins; at lower temperatures, the nitrogen is not completely split off. For quantitative decomposition of 1 mole of *(2)* it is necessary to heat it at 280 °C for 18 h; this gives rise to 1 mole of nitrogen plus 0.15 mole of tris(diethylamino)boron and brown products from which no single substance can be isolated. On saponification they yield 10 % 1,1-diethylhydrazine, calculated on the rearrangement:

$$x\,[(C_2H_5)_2N]_2BN_3 \rightarrow x\,N_2 + [(C_2H_5)_2N{-}B{=}N{-}N(C_2H_5)_2]_x$$

in which a diethylamino group moves from boron to the nitrogen atom; analogous reactions of dichloroboron azide [3] and diphenylboron azide [4] led to very high yields of rearrangement products.

On heating the diazides *(3)* and *(4)* to 210 °C, only the nitrogen of one azide group is evolved. Beside tars, salts containing the remaining azide group are formed, namely ammonium azide from *(3)* and diethylammonium azide from *(4)*.

Received, February 24th, 1964 [Z 676/506 IE]
German version: Angew. Chem. 76, 343 (1964)

[1] Contributions to the Chemistry of Boron Azides, Part. 5. Part 4: *P. I. Paetzold*, Z. anorg. allg. Chem. *326*, 64 (1963).
[2] *P. I. Paetzold*, unpublished work.
[3] *P. I. Paetzold*, Z. anorg. allg. Chem. *326*, 47 (1963).
[4] *P. I. Paetzold*, Z. anorg. allg. Chem. *326*, 53 (1963).

## Preparation of Potassium Hexathiocyanatotitanate(IV) and Its Behavior in Liquid $NH_3$

By Prof. Dr. O. Schmitz-DuMont and Dipl.-Chem. B. Ross

Anorganisch-Chemisches Institut
der Universität Bonn (Germany)

When titanium tetrachloride is added to a solution of potassium thiocyanate in acetonitrile in a molar ratio of 1:6.5, the solution turns orange-yellow and then gradually dark red with concurrent separation of potassium chloride. When the potassium chloride is filtered off with exclusion of moisture, and the filtrate is evaporated to dryness *in vacuo* at room temperature, a reddish-black crystalline residue is obtained, which consists of a thiocyanato salt containing acetonitrile, $K_2[Ti(SCN)_6] \cdot CH_3CN$ *(1)*, and excess potassium thiocyanate. To remove the latter, the solution in acetonitrile is treated with the equivalent amount of silver nitrate dissolved in acetonitrile. Silver thiocyanate and potassium nitrate precipitate out. After evaporating the filtered solution under reduced pressure, the pure coordination complex *(1)* is left. This can be freed from acetonitrile by heating *in vacuo* at 95 °C. Compound *(1)* dissolves in ether to give a red solution and crystallises out on concentrating same. Both *(1)* and the acetonitrile-free compound $K_2[Ti(SCN)_6]$ *(2)* dissolve in water to give colorless solutions from which $TiO_2 \cdot aq$ is deposited only on adding ammonia. Both dissolve in liquid ammonia to give a yellow solution, which becomes brown at higher concentrations. The clear concentrated solution becomes turbid when diluted with liquid ammonia, a behavior suggestive of ammonolysis. The turbidity disappears when the solution is concentrated by evaporating ammonia. After complete evaporation of the ammonia, a product

remains which consists of an ammoniate of titanium(IV) thiocyanate and potassium thiocyanate. On dissolving $K_2[Ti(SCN)_6]$ in liquid $NH_3$ the following reaction occurs:

$$K_2[Ti(SCN)_6] + x\ NH_3 \rightarrow 2\ KSCN + Ti(SCN)_4(NH_3)_x\ (x = 4-5)$$

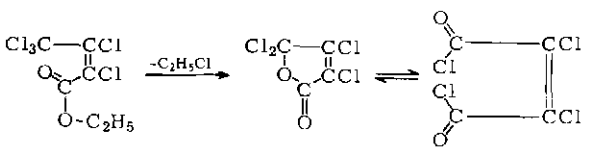
Received, February 24th, 1964 [Z 677/510 IE]
German version: Angew. Chem. 76, 304 (1964)

## Dichloromaleyl Dichloride

By Dr. G. Maahs

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Marl, Krs. Recklinghausen (Germany)

Ethyl perchlorocrotonate *(1)* [1] decomposes on boiling into ethyl chloride and 3,4,5,5-tetrachloro-2-oxodihydrofuran *(2)* [2], the latter rearranging to dichloromaleyl dichloride *(3)*, b.p. 192–194 °C. The product is isolated by distillation. On 100% conversion the yield is over 90%. Like the thermal decomposition of 1-ethoxypentachloro-1,3-butadiene [3], the reaction takes place particularly smoothly in the presence of catalytic amounts (≦ 0.01 %) of iron or iron compounds (Fe-powder, iron oxides, iron-containing boiling chips).




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

By analogy to the well-known thermal decomposition of γ-bromocarboxylic esters [4], a cyclic onium chloride is probably formed as an intermediate.

Received, February 24th, 1964 [Z 675/505 IE]
German version: Angew. Chem. 76, 303 (1964)

[1] *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 1 (1956).
[2] *E. Ott*, Liebigs Ann. Chem. *392*, 245 (1912).
[3] *G. Maahs*, Angew. Chem. *75*, 982 (1963); Angew. Chem. internat. Edit. *2*, 690 (1963).
[4] *J. Weinstock*, J. Amer. chem. Soc. *78*, 4967 (1956).

## Tristriphenylstannylarsine, -stibine, and -bismuthine

By Dr. H. Schumann and Prof. Dr. Max Schmidt

Institut für Anorganische Chemie
der Universität Marburg/Lahn (Germany)

When stoichiometric quantities of triphenylstannyl-lithium *(1)* [1] dissolved in tetrahydrofuran are added slowly dropwise at room temperature with careful exclusion of air and moisture to vigorously stirred solutions of arsenic trichloride, antimony trichloride, or bismuth trichloride in the same solvent, good yields (ca. 80 %) of tristriphenylstannylarsine *(2)*, tristriphenylstannylstibine *(3)* or tristriphenylstannylbismuthine *(4)* result. These are isolated by evaporation of the solvent and recrystallization from pentane.

$$3\,(C_6H_5)_3SnLi + MCl_3 \rightarrow [(C_6H_5)_3Sn]_3M + 3\,LiCl$$

*(1)*

*(2)*, M = As
*(3)*, M = Sb
*(4)*, M = Bi

Reagent *(1)* must not be present in excess or else secondary cleavage reactions occur. Compounds *(2)*, *(3)*, and *(4)* are colorless solids which are sensitive to air and moisture; m.p. 212–216 °C, 214–215 °C, or 138–142 °C (decomp.), respectively.

By using organo-substituted metal halides instead of the pure trichlorides, other organostanyl derivatives of As, Sb, and Bi are easily obtainable. $(CH_3)_3Sn\ As(C_6H_5)_2$, the first representative of this type, was recently prepared by an alternative, but more complicated, method [2].

Received, February 28th, 1964 [Z 683/507 IE]
German version: Angew. Chem. 76, 344 (1964)

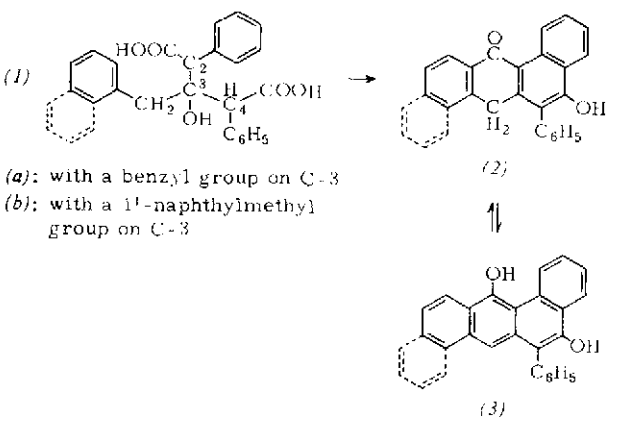
[1] *G. Wittig* and *J. F. Meyer*, Liebigs Ann. Chem. *571*, 167 (1951); *H. Schumann*, *K. F. Thom*, and *M. Schmidt*, J. Organometallic Chem. *1*, 167 (1963).
[2] *K. Jones* and *M. F. Lappert*, Proc. Chem. Soc. *1964*, 22.

## A New Synthesis of Derivatives of Benz[*a*]anthrone and Dibenz[*a*,*d*]anthrone

By Prof. Dr. Ch. Ivanov and L. Mladenova-Orlinova

Institute of Chemical Technology, Sofia (Bulgaria)

As shown previously [1], dehydration of 2,3,4-triaryl-3-hydroxyglutaric acids with conc. sulfuric acid yields 4-aryl-3-hydroxybenzofluorenone. We have found that, in analogous manner, dehydration of the diarylhydroxyglutaric acids *(1a)* and *(1b)*, whose central carbon atom carries an arylmethyl group, yields 4-phenyl-3-hydroxybenz[*a*]anthrone *(2a)* and 4-phenyl-3-hydroxydibenz[*a*,*d*]anthrone *(2b)*, respectively.



*(1)*

*(a)*: with a benzyl group on C-3
*(b)*: with a 1'-naphthylmethyl group on C-3

*(2)*

*(3)*

We obtained the acid *(1b)*, m.p. 167–169 °C (decomp.), in 11.5 % yield by the same method as for *(1a)* [2]; phenylnaphthylacetone, m.p. 58.5–59 °C, was formed simultaneously in 66 % yield.

To carry out the dehydration, *(1a)* is dissolved in conc. sulfuric acid; the solution is then poured into water 15 min later. After washing the precipitate formed to remove sulfonic acids, *(2a)* is obtained in 66 % yield as yellow crystals (from butanol), m.p. 225–225.5 °C (green melt). Its solution in aqueous ethanolic sodium hydroxide is yellow-brown, and turns blue-violet on boiling. Even after prolonged boiling, followed by acidification, a mixture of *(2a)* with orange crystals of 4-phenyl-3-hydroxybenz[*a*]anthranol *(3a)* is always obtained; *(2a)* is not completely rearranged to *(3a)*.

Compound *(2b)* is obtained analogously in 43 % yield as yellow-green crystals, m.p. 216–216.5 °C, which dissolve in aqueous ethanolic sodium hydroxide with an orange-red colour. On prolonged standing or on boiling the alkaline solution, the color turns to blue-violet. On acidification, *(2b)* is reformed, accompanied by orange crystals which are probably those of dibenz[*a*,*d*]anthranol *(3b)*.

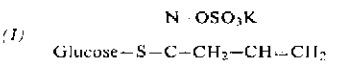
Received, January 22nd, 1964 [Z 660/490 IE]
German version: Angew. Chem. 76, 301 (1964)

[1] *Ch. Ivanov*, C. R. bulg. Sci. 7, 29 (1954).
[2] *D. Ivanoff* and *N. Nicoloff*, Bull. Soc. Chim. *51*, 1331 (1931).

## Isothiocyanates of Natural Derivation

*A. Kjær*, Copenhagen (Denmark)

The isothiocyanate-producing glucosides form a unique and interesting class of natural compounds. Besides the classical representatives, such as sinigrin *(1)* and sinalbin, this class now comprises about 45 glucosides of the same general structure but possessing different side-chains. These can be saturated and unsaturated aliphatic, unbranched ω-methylthioalkyl, unbranched keto-substituted alkyl, aralkyl, aryl, heterocyclic, or β- or γ-hydroxylated alkyl groups.

*(1)* 

The mass-spectra of about 50 individual isothiocyanates, mainly of natural origin, were discussed. Unbranched aliphatic derivatives gave prominent peaks at m/e = 72, attributable to the ion $CH_2NCS^+$ produced by simple β-fission. Strong peaks at m/e = 115 and M-33 obtained with isothiocyanates containing six or more carbon atoms were shown to originate from intramolecular rearrangements. In all methylthioalkyl-substituted derivatives, a strong peak at m/e = 61 was observed due to the ion $CH_3SCH_2^+$. The combination of vapor-phase chromatography and mass spectrometry has proved extremely useful for the rapid and unequivocal identification of small amounts of isothiocyanates of natural origin.

[GDCh-Ortsverband Bonn (Germany), December 12th, 1963]

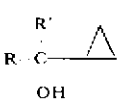
[VB 781/117 IE]

German version: Angew. Chem. *76*, 276 (1964)

## Investigations on Cyclopropane Compounds

*M. Hanack*, Tübingen (Germany)

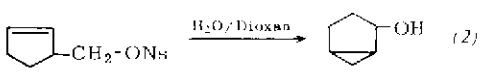
As was already shown previously, cyclopropyl carbinols of the general structure

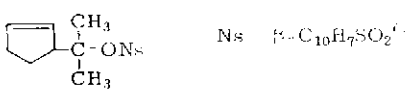


react smoothly with acids and thereby undergo homoallyl rearrangement to the homoallyl halides. If two cyclopropane rings are present in the molecule, the rearrangement proceeds with opening of the substituted cyclopropane ring only. In contrast, halogeno-substituted cyclopropyl carbinols, *e.g.* 2-fluoro-1-cyclopropylethanol, no longer undergo normal homoallyl rearrangement. The fluoro compound is readily obtainable from cyclopropyl diazo ketone via the fluoromethyl cyclopropyl ketone and rearranges with acids to cyclobutane compounds with elimination of fluorine.

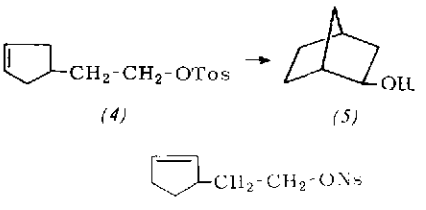
The preparative and kinetic aspects of the formation of cyclopropyl carbinols from homoallyl compounds was studied in several solvents. In weakly nucleophilic solvents, the cyclopropyl carbinyl compound is formed almost quantitatively.

The stability of the isomeric carbonium ions that are produced govern the composition of the products formed by cyclization reactions: for example, *(1)* gives 70 % *(2)*, whereas under the same conditions *(3)* does not isomerize to a cyclopropane compound.

*(1)*  *(2)*

*(3)* 

Under solvolytic conditions, *(4)* gives *(5)* [1], whereas *(6)* does not rearrange to the anticipated 7-norborneol.



*(4)* *(5)*

*(6)*

In connection with the formation of *(2)*, the addition of a methylene group onto the double bond of unsaturated cyclic alcohols by treating them with $CH_2I_2$ according to *Simmons* was investigated further. Cyclopropane compounds are only formed if the OH group lies on a carbon atom adjacent to the double bond or if the molecule can assume a conformation in which the OH group comes into the proximity of the double bond.

[GDCh-Ortsverband Wuppertal-Hagen at Wuppertal-Elberfeld (Germany), December 11th, 1963]

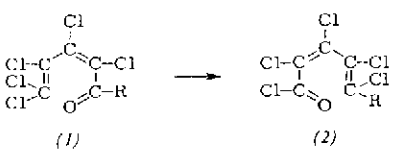
[VB 779/121 IE]

German version: Angew. Chem. *76*, 235 (1964)

## Rearrangement of Vinylogous Carbonyl Chlorides

*A. Roedig*, Würzburg (Germany) [2]

Perchloropentadienal *(1a)* [3], perchlorobutadienyl alkyl ketones, *e.g. (1b)*, and perchlorobutadienyl aryl ketones, *e.g. (1c)*, which can be considered as vinylogues of carbonyl chlorides, are converted irreversibly and quantitatively into the isomeric acid chlorides when heated.



*(1)* *(2)*

*(a)*: R = H; *(b)*: R = $CH_3$; *(c)*: R = $C_6H_5$; *(d)*: V = Cl

Starting from *(1a)* labelled with radiocarbon at C-5, it was shown that the oxygen atom and a δ-chlorine atom change places during the rearrangement. Radioactive *(1a)* can be quantitatively converted into radioactive *(2a)* by heating it for three hours in boiling $CCl_4$. Hydrolysis of the acid chloride, thermal cyclization of the resultant acid to 3,4,5-trichloro-2-pyrone, and decarboxylative Diels-Alder condensation of this with maleic anhydride gives a diene adduct containing all the radioactivity; none is found in the $CO_2$.

The rearrangement of *(1a)* is a first oder reaction, and its rate is practically independent of the dielectric constant of the solvent. Radical formers and radical scavengers have no effect. The activation energy (22.8 kcal/mole) and activation entropy (8–11 cal/deg/mole) are independent of the solvent; the latter is negative.

The results indicate a mechanism involving a cyclic intermediate or transition state but do not show whether the rearrangement proceeds via tetrachloropyran *(3a)* (which

[1] *B. D. Bartlett* and *S. Bank*, J. Amer. chem. Soc. *83*, 2591 (1961); *R. G. Lawton*, ibid. *83*, 2399 (1961).

[2] Work carried out in conjunction with *R. Kohlhaupt*, *G. Märkl*, *G. Röbke*, *W. Ruch*, and *M. Schlosser*.

[3] *A. Roedig* and *G. Märkl*, Liebigs Ann. Chem. *659*, 1 (1962).

cannot be isolated under the reaction conditions) or concertedly via a four-centred transition state *(4a)*.



*(3)* *(4)*

One prerequisite for the rearrangement is a *cis*-configuration of the double bond adjacent to the carbonyl group of *(1)*. *trans*-Perchlorobutadienyl phenyl ketone *(1c)*, prepared together with the *cis*-isomer by treating *(1d)* with phenylmagnesium bromide, does not rearrange to the acid chloride. Work is in progress to determine whether the halogen substituents on the conjugated chain are important and thus whether the rearrangement is generally applicable.

[GDCh-Ortsverband Marl (Germany), December 4th, 1963]

[VB 775/118 IE]

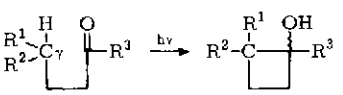
German version: Angew. Chem. *76*, 276 (1964)

## Photochemical Reactions of Steroids

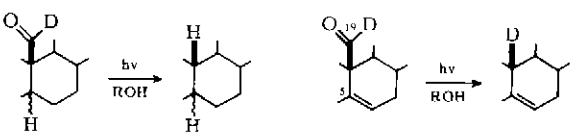
*O. Jeger*, Zürich (Switzerland)

Some novel photochemical reactions of carbonyl compounds were systematically classified according to the structure of the starting compounds and the reaction conditions, using illustrations from the steroid and terpene series.

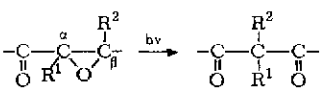
In the photoreaction involving conversion of saturated aldehydes and ketones with a hydrogen atom in the γ-position into secondary or tertiary cyclobutanol derivatives, intramolecular abstraction of the γ-hydrogen occurs and is accompanied by partial retention of the configuration of the γ-carbon atom.



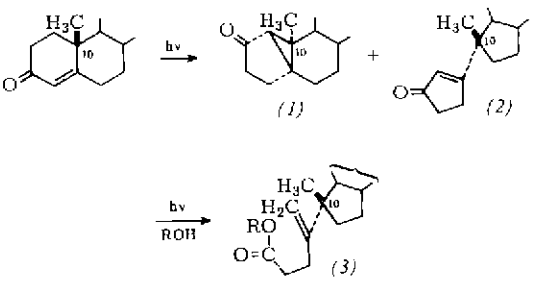
Photolytic decarbonylation (> 2800 Å) of a deuterated homoallylically conjugated 10-formyl steroid led practically exclusively to stereospecific incorporation of the formyl deuterium (R–CDO → RD + CO). In contrast, CDO is ejected from saturated analogues.



α,β-Epoxy ketones isomerize photochemically to β-dicarbonyl compounds. The 1,2-shift of a β-substituent involved can lead to stereospecific molecular rearrangements. The role of the epoxide oxygen can also be played by the ether oxygen of a lactone.



The diverse behavior of cyclohexenones was discussed, taking testosterone as an example. Molecular rearrangements to compounds of types *(1)* and *(2)* are of special interest. The latter is photochemically unstable and is split with participation of the solvent to give *(3)*.



Some of these reactions give very high yields.

[GDCh-Ortsverband Unterfranken at Würzburg (Germany), November 29th, 1963] [VB 778/120 IE]

German version: Angew. Chem. *76*, 275 (1964)

## Syntheses with N-Metalated Silicon-Nitrogen Compounds

*U. Wannagat*, Graz (Austria)

Sodium bistrimethylsilylamide $NaN(SiR_3)_2$ can be prepared directly from $NaNH_2$ and $R_3SiCl$ (R = $CH_3$) by using special starting conditions (5–6 drops of $R_3SiCl$ are allowed to run into the reaction flask and then the whole amount of $NaNH_2$/benzene suspension is added in one gush; stirring and heating are commenced after the addition of further 40 drops of $R_3SiCl$). The reaction can be modified in such a way that yields of up to 80 % or more of hexamethylsilazane $(R_3Si)_2NH$ or tristrimethylsilylamine $N(SiR_3)_3$ are obtained [1]. For this purpose 8 moles of $NaNH_2$ in benzene are placed in the flask using the starting procedure described above and 6 moles (out of a total of 9 moles) of $R_3SiCl$ are added dropwise and the mixture is then heated for 30 minutes.

$$5\ NaNH_2 + 6\ R_3SiCl \rightarrow 3\ (R_3Si)_2NH + NH_3 + NH_4Cl + 5\ NaCl$$

On heating for several hours under reflux, the $(R_3Si)_2NH$ reacts further:

$$3\ NaNH_2 + 3\ (R_3Si)_2NH \rightarrow 3\ (R_3Si)_2NNa + 3\ NH_3$$

If the remaining 3 moles of $R_3SiCl$ are added and the mixture is heated for 2–3 hours, $(R_3Si)_3N$ is formed.

$$3\ (R_3Si)_2NNa + 3\ R_3SiCl \rightarrow 3\ (R_3Si)_3N + 3\ NaCl$$

Hexamethyldisilazane reacts with $NaNH_2$ and with urea to give off ammonia which, according to the results of studies with $^{15}N$, originates from $NaNH_2$ and $(R_3Si)_2NH$ respectively.

$$(R_3Si)_2{}^{15}NH + NaNH_2 \rightarrow NH_3 + (R_3Si)_2{}^{15}NNa$$
$$(R_3Si)_2{}^{15}NH + CO(NH_2)_2 \rightarrow {}^{15}NH_3 + (R_3SiNH)_2CO$$

$NaN(SiR_3)_2$, m.p. 172 °C, b.p. 202 °C/1–2 mm, crystallizes in the hexagonal system. Its solution in benzene and the melt at 200 °C do not conduct electricity, but its solution in liquid $NH_3$ probably does. Up to the present, the reactions of $NaN(SiR_3)_2$ with halides have given rise *inter alia* to the following compounds.

$FB[N(SiR_3)_2]_2$, b.p. 136 °C/11 mm
$ClPO[N(SiR_3)_2]_2$, b.p. 94 °C/0.1 mm
$Cl_3TiN(SiR_3)_2$, m.p. 75–77 °C
$[(R_3Si)_2N]_2V(OSiR_3)(NSiR_3)$, m.p. 68 °C
$Cr[N(SiR_3)_2]_3$, m.p. 120 °C
$Fe[N(SiR_3)_2]_3$, m.p. 135 °C
$Co[N(SiR_3)_2]_2$, m.p. 73 °C

It reacts with phenoxysilanes to form tris(silyl)amines.

$$R'_3SiOC_6H_5 + NaN(SiR_3)_2 \rightarrow NaOC_6H_5 + (R_3Si)_2NSiR'_3$$

Silicon tetracyanate is converted by it into carbodiimides and polysiloxanes.

$$Si(NCO)_4 + 2\ (R_3Si)_2NNa \rightarrow 2\ NaOCN + R_3SiNCNSiR_3 + 1/x[-OSi(OSiR_3)(NCNSiR_3)-]_x$$

[1] This work will be published in detail soon in Mh. Chem.

The preparation of a tricyanatosilylamine could only be accomplished as shown below.

$$(R_3Si)_2NNa \rightarrow (R_3Si)_2NSiCl_3 \rightarrow (R_3Si)_2NSi(NCO)_3 \text{ (b.p. 81 °C/1 mm)}$$

Carbon monoxide is converted into sodium cyanide, disiloxane being eliminated.

$$CO + NaN(SiR_3)_2 \rightarrow (CN)^-Na^+ + O(SiR_3)_2$$

A five-membered SiN ring *(1)* can be built up.

$$ClSiR_2SiR_2Cl + LiNRSiR_2NRLi \rightarrow 2\ LiCl + \begin{matrix} R_2Si{-}SiR_2 \\ | \quad\quad | \\ RN \quad NR \\ \quad Si \\ \quad R \end{matrix} \quad (1)$$

Octamethyl-1,2,4-trisila-3,5-diazacyclopentane melts at −18 °C and boils at 70 °C/13 mm.

[GDCh-Ortsverband Göttingen (Germany), November 25th, 1963, and Marburg (Germany) November 29th, 1963]

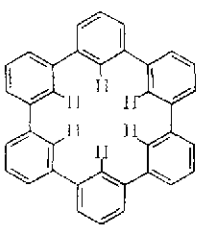
[VB 777/119 IE]

German version: Angew. Chem. 76, 234 (1964)

## Investigations on Aromatic Systems

*H. A. Staab*, Heidelberg (Germany)

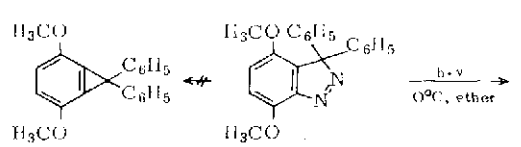
Hexa-*m*-phenylene *(1)*, which has practically the same geometrical arrangement in its inner ring system as [18]-annulene and probably possesses a practically planar structure, has like that compound π-electrons on all the carbon atoms of its inner ring. However, in view of the *meta*-bonding of the phenylene groups, the cyclic π-conjugation should be suppressed. Compound *(1)* was prepared (with *F. Binnig*) from the Grignard compound of 3,3′-dibromodiphenyl with $CoCl_2$ in tetrahydrofuran. It can be distilled



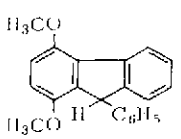
*(1)*

without decomposition at 650 °C/$10^{-4}$ mm Hg; m.p. 509.5 to 511 °C. Its proton resonance (in view of its low solubility, measurements have so far only been carried out in 1-methylnaphthalene at 180 °C) gave no signals at 3.7–7.7 τ and 8.5–18.0 τ; particularly strong shielding of the six inner protons by an aromatic ring current can thus be excluded, as anticipated. In the ultraviolet, *(1)* absorbs practically at the same wavelength (251.2 mμ, ε = 138000 in $CHCl_3$) as biphenyl (251.5 mμ, ε = 18300).

Attempts to prepare the benzocyclopropene *(3)* (with *J. Ipaktschi*) by photochemical elimination of nitrogen from *(2)* did not lead to the desired product. Instead, the 9-phenylfluorene derivative *(4)* was obtained in very good yield.



*(3)* *(2)*



*(4)*

In the course of studies on nine-membered rings containing nitrogen and having 10 π-electrons 1,4,7-dibenzo[*b,h*]triazonines were obtained (with *R. Bader*).

[Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany), January 8th, 1964] [1]

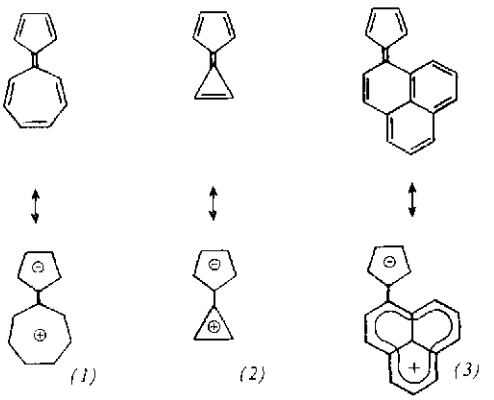
[VB 783/124 IE]

German version: Angew. Chem. 76, 276 (1964)

## New Types of Polyenes with Cyclic Cross-Conjugated Bond Systems

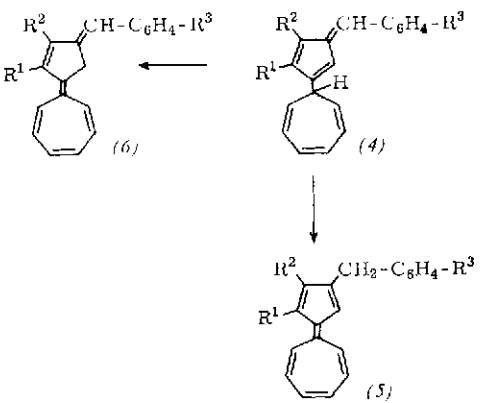
*H. Prinzbach*, Freiburg/Breisgau (Germany)

In the dipolar structural formulae of the hydrocarbons sesquifulvalene *(1)*, calicene *(2)*, and phenafulvalene *(3)*, the central single bond joins, in each case, two relatively stable organic ions.



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

Although *(1)* exists only in solution, it may be estimated accurately by spectrophotometry and by its chemical reactions. On the other hand, doubly annellated derivatives of *(1)*, or those containing four phenyl groups on the five-membered ring, are stable. Simple derivatives are obtained by prototropic rearrangement of fulvenes *(4)*. In contrast to the observation in the annellated series *(4a)*, where only a formal 1,5-hydrogen displacement to give *(5a)* is found, a competition reaction occurs in the analogous rearrangement of *(4b)*, and with increasing acceptor-character of $R^3$, progressively more formation of the vinyloguous heptafulvene *(6b)* takes place. The chemical behavior of this class of compounds – including the smooth addition of acids and bases, the site of the electrophilic attack, and adduct formation – is in agreement with the π-electron delocalization favored in the transition state.



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

*(a)* $R^1R^2 = -C_4H_4$; $R^3 = -CN, -Cl, -H, -OCH_3, -N(CH_3)_2$

*(b)* $R^1 = R^2 = H$; $R^3 = -CN, -Cl, -H, -OCH_3, -N(CH_3)_2$

[1] Also reported January 10th, 1964, at a meeting of the GDCh-Ortsverband Köln (Germany).

NMR-spectroscopic examination of *(4)*, *(5)*, and *(6)*, and of prototypes of *(2)* and *(3)* showed that the π-bonds are largely localized in these cyclic cross-conjugated systems. On the assumption of changes of bond lengths typical for olefins, molecular-orbital calculations by *Nakajima* on *(1)* gave a value for N-V' excitation [*], that is verified experimentally (calculated: 3.20 eV; found: 3.16 eV).

[GDCh-Ortsverband Ruhr, Mülheim/Ruhr (Germany), December 11th, 1963] [VB 782/123 IE]

German version: Angew. Chem. 76, 235 (1964)

## Transport Processes and Equilibria in the Reduction of Oxides

*H. J. Engell*, Clausthal-Zellerfeld (Germany)

In the reduction of metal oxides by gases, a dense layer of the final reaction product can be formed. Then transport processes in this layer can determine the rate of reduction. In the reduction of wustite (FeO) to iron, an outer layer of iron may be formed. The diffusion of oxygen in this layer then determines the rate of reduction, as was shown by comparison of the measured rate with the rate of diffusion of oxygen in iron estimated by other methods. In the reduction of magnetite ($Fe_3O_4$) to wustite (FeO), dense surface layers of wustite are formed. In this case, however, the gas/oxide phase-boundary reaction determines the rate of reaction, since iron diffuses relatively quickly through the wustite layer.

During the reduction of oxide mixed crystals, the oxide phase is decomposed. The extent of this decomposition depends on the equilibrium conditions; its rate depends on transport processes in the oxide, which are controlled by the disorder equilibria. The form of metal precipitation observed here is a result of these equilibria.

[GDCh-Ortsverband Nordwürttemberg, Stuttgart (Germany) January 16th, 1964] [VB 785/126 IE]

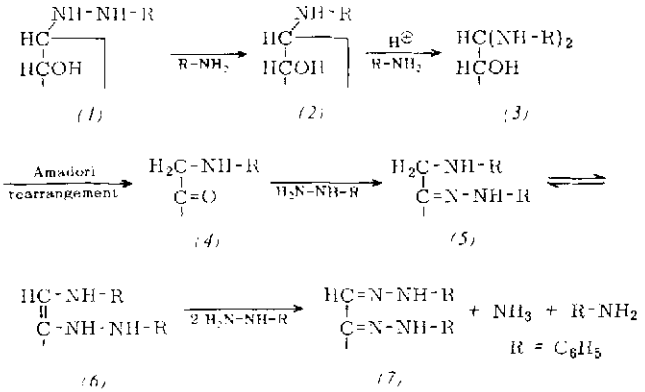
German version: Angew. Chem. 76, 307 (1964)

## Mechanism of Osazone Formation and of the Amadori Rearrangement

*F. Micheel*, Münster/Westfalen (Germany)

The osazone reaction discovered by *Emil Fischer* in 1884 is not initiated by an Amadori rearrangement of an aldose phenylhydrazone; instead, some phenylhydrazine first decomposes in the acidic solution by partial disproportionation into aniline, ammonia, benzene, nitrogen, *etc.* The phenylhydrazone *(1)* reacts with the aniline produced in this manner by transamination to form a 1-phenylamino derivative *(2)* which is readily converted by further aniline and $H^+$-ions into a 1-deoxy-1-phenylaminoketose derivative *(4)* [1]. The Amadori rearrangement proceeds very rapidly in the presence of excess amine; this also shows that the intermediate product is not a Schiff's base but a 1,1-bis-*N*-acetal *(3)* [2].

Compound *(4)* reacts rapidly with phenylhydrazine to give a 1-deoxy-1-phenylaminoketose phenylhydrazone *(5)*, which in turn can react rapidly with excess phenylhydrazine to form the osazone *(7)*. By using $^{14}C$-phenylhydrazine it can be demonstrated [3] that this step does not involve an intramolecular redox reaction but that *(5)* or *(6)* – as a strongly




reducing enediamine [4] – hydrogenates further phenylhydrazine to ammonia and aniline. Aniline formed in this manner accelerates the osazone formation in accordance with the above equation.

[GDCh-Ortsverband Unterfranken, Würzburg (Germany), January 17th, 1964] [VB 787/129 IE]

German version: Angew. Chem. 76, 307 (1964)

## Complex Formation with Polymolybdate Ions

*K. F. Jahr*, Berlin (Germany)

Telluromolybdates can be detected by conductometric, potentiometric, spectrophotometric, and salt-cryoscopic titrations of acidified $Na_2MoO_4$ solutions (1.0–1.6 $H^+/MoO_4^{2-}$) with solutions of $Te(OH)_6$. With increasing concentrations of $Te(OH)_6$ in solutions with 1.0–1.14 $H^+/MoO_4^{2-}$, telluro-1:12-, telluro-1:7-, and telluro-1:6-molybdates are formed successively; at 1.33 $H^+/MoO_4^{2-}$, the 1:7 and then the 1:6 complex are formed. On titrating the molybdate with solutions of $Al^{3+}$ salts, an alumino-1:7- and then an alumino-1:6-molybdate result; here a 1:12 complex cannot be detected.

The telluro-1:6 complex is the familiar heteropolyanion $TeMo_6O_{24}^{6-}$, which consists of a flat ring of six $MoO_6$ octahedra with $Te^{6+}$ at the center. The new 1:7 complex is thought to be an adduct of $H_4TeO_6^{2-}$ and the "paramolybdate ion" $Mo_7O_{24}^{6-}$, while the new 1:12 complex is a 1-tellurium-2-hexamolybdate ion with $Te^{6+}$ as an octahedrally coordinated central ion sandwiched between two superjacent $Mo_6O_{24}$ rings. The 1-tellurium-1-hexamolybdate was shown by salt-cryoscopic measurements to be the most stable complex at two $H^+/MoO_4^{2-}$ ratios (1.14 and 1.50), since it can be formed from two different hexamolybdate ions which predominate at these ratios. Conductometric titration of an acidic molybdate solution (1.5 $H^+/MoO_4^{2-}$) with free $H_3PO_4$ led to a phospho-1:12-molybdate with consumption of $H^+$. This complex condenses to form the well known 1-phosphorus-2-dodecamolybdate ion only in strongly acidic solution and is thought to be an inclusion compound with a phosphate ion inside a hollow spherical dodecamolybdate ion, which in such acid solutions is in equilibrium with a hexamolybdate ion. The fact that the dodecamolybdate ion has a hollow interior suitable for the formation of inclusion compounds is demonstrated by the formation of a 1-(methyl red)-1-dodecamolybdate ion, which was detected by conductometry and spectrophotometry. On adding methyl red to a molybdate solution with 1.5 $H^+/MoO_4^{2-}$, the initially red solution gradually turns yellow as the indicator is converted into the anion by inclusion inside the hollow space within the dodecamolybdate ion. Even large additions of sulfuric acid do not restore the red color of the solution; however, phosphoric acid, displaces the indicator from the cavities to form the more strongly complexed 1-phosphorus-dodecamolybdate ion and colors the solution red with the liberated indicator. When ammonia is added dropwise to the yellow solution of

[*] N-V' excitation is defined as the transition between the highest MO and the lowest excited singlet state.

[1] *F. Micheel* and *I. Dijong*, Liebigs Ann. Chem. *669* 136 (1963).

[2] *F. Micheel* and *I. Dijong*, Liebigs Ann. Chem. *658*, 120 (1962).

[3] *F. Micheel* and *I. Dijong*, unpublished results.

[4] *F. Micheel*, *G. Bode*, and *R. Wiebert*, Ber. dtsch. chem. Ges. *70*, 1862 (1937).

the inclusion compound, the dodecamolybdate ion breaks down into the hexamolybdate ion, thus liberating the indicator and coloring the solution – which is still acidic – red. Inclusion compounds can condense to form true heteropolyacids which are purely inorganic chelate complexes. Naturally only such materials are included or complexed which by virtue of their size, structure, and coordinating ability can pass into the hollows within the isopolyanion.

[GDCh-Ortsverband Braunschweig (Germany), January 20th, 1964] [VB 784/125 IE]

German version: Angew. Chem. 76, 236 (1964)

## Adsorption Phenomena at Gas/Solid Interfaces at Low Gas Pressures

*N. Hansen*, Aachen (Germany)

The isotherms for physical adsorption of argon on different adsorbents in ultrahigh vacuum do not yield the proportionality between pressure and amount of gas absorbed predicted for low coverages. Down to a fraction of the monolayer of $10^{-6}$ and at relative equilibrium pressures $p/p_0$ of $10^{-12}$ or $p = 10^{-10}$ mm, a parabolic isotherm is observed, which may be ascribed to thermodynamic heterogeneity of the surface. Experiments suggest that at even lower coverages linear isotherms are obtained and that at very low coverages there are at least $10^4$ units of very sparsely occupied surface for each unit of closely occupied surface.

The chemisorption of gases on pure metallic surfaces takes place very rapidly and cannot be measured in conventional gas-volumetric apparatus. By means of an "open apparatus" (with continuous admission of gas), it was possible to observe the rate of adsorption over many orders of magnitude. For instance, for carbon monoxide on zirconium films obtained by evaporation, it amounts, at low coverage, to about half the maximum possible rate of impact, which may be calculated from gas kinetics. The rate of adsorption of metal powders with relatively pure surfaces – obtainable from some transition metals by heat treatment *in vacuo* – is therefore determined by the Knudsen molecular flow. If a suitable pore structure is generated in these metal powders, they are adequate for the production of compact arrangements that show large adsorptive capacities for gases at very high adsorption rates and may be used as sorption pumps or getters.

[GDCh-Ortsverband Berlin (Germany), January 21st, 1964] [VB 791/133 IE]

German version: Angew. Chem. 76, 308 (1964)

## Energetics of the Contraction Cycle in Muscle

*W. F. H. M. Mommaerts*, Los Angeles, Calif. (U.S.A.)

Present day knowledge of the biochemical basis of the energetics of muscle contraction rests mainly upon the experimental possibility of interrupting a muscle contraction at any desired stage by rapid freezing of the specimen and of comparing the chemical composition of the latter with that of an unstimulated control. Technically, this has become possible through methodological developments made in our laboratory during the last decade; the limit of the method is set by statistical fluctuations between the compositions of muscles within a pair. Thus, frog sartorius muscle forms 0.4 µmole of creatine and phosphate in a single tetanic contraction of 400 msec, and the same figure is obtained for the activation metabolism per contraction in a series of brief tetani, extrapolated to conditions of zero work performance, although there are cases where this behavior has not yet been demonstrated. When work is done, more hposphocreatine is broken down.

While these two results, in agreement with work by *Carlson*, account for two categories of energy production, a third, *Hill*'s shortening heat, could not be detected in this way. Since there is good reason to assume the existence of a shortening heat, representing the dissipational heat of a work process under non-ideal conditions, this discrepancy represents one of the urgent problems in this field. The recent observation by *Davies* of the primary breakdown of ATP is in accordance with expectations. One interesting aspect of this work, which we seem able to confirm, is that part of the activation metabolism occurs in the relaxation phase of the contraction cycle, while the activation heat occurs earlier. This finding, too, remains to be explained.

With such fundamental aspects of the energetic balance still incompletely explained, it seems premature to try to account for the energetic problems in molecular terms. However, a discussion was given of some such questions with regard to the energetic effects of binding versus splitting of ATP, of the importance of a specific conformation of myosin-adenosine triphosphatase, of the participation of actin, and of the importance of Curie's theorem in biological energetics.

[Biochemisches Colloquium, Universität Heidelberg (Germany), January 23rd, 1964] [VB 795/128 IE]

German version: Angew. Chem. 76, 308 (1964)

## Scattering and Absorption Coefficients in Diffuse Reflection of Powdered Materials

*G. Kortüm*, Tübingen (Germany)

In determining "typical color curves" of powdered materials by means of the Kubelka-Munk function

$$F(R_\infty) = (1-R_\infty)^2/2\,R_\infty = K/S$$

it is assumed that the scattering coefficient S is independent of the wavelength, so that the absorption coefficient K becomes proportional to the true absorption coefficient of the absorbing medium. If the multiple scattering of powders is treated generally on the basis of the Mie theory [1] for simple scattering, it is to be expected that, for particle diameters d that are very small in comparison with the wavelength $\lambda$, the scattering coefficient becomes $S \sim \lambda^{-4}$, and for particle diameters that are large in comparison with the wavelength, S becomes independent of $\lambda$. The scattering coefficients of reference standards (Aerosil, MgO, NaCl, $CaF_2$, cracking catalysts, glass powders, *etc.*) were determined, for the limiting conditions indicated, from the reflectance and transmittance of very thin powder layers and from $R_\infty$. For Aerosil samples of varying particle size, for which $d \ll \lambda$, the scattering coefficients ranged from $S \sim \lambda^{-2.6}$ to $S \sim \lambda^{-3.6}$. The exponential –4, characteristic of simple Rayleigh scattering, was thus not reached, while for $d \gg \lambda$, S is in fact independent of the wavelength in the visible and near ultraviolet regions. For application of the Kubelka-Munk theory to the determination of typical color curves of powders, it follows therefore that no particle size below 2–5 µ should be used, if the spectra of adsorbed substances are to be examined. Otherwise, the scattering coefficients of the adsorbent must first be determined.

As an example, the absorption spectrum of graphite on Aerosil was given from 700 to 250 mµ, the scattering coefficients measured being taken into account. It was shown that the scattering coefficients of the adsorbent are not changed by admixture of 0.1 % graphite, so that the true spectrum of the adsorbed substance may actually be obtained in this way with ultrafine adsorbents [*].

[Chemische Gesellschaft Heidelberg (Germany), January 21st, 1964] [VB 789/130 IE]

German version: Angew. Chem. 76, 308 (1964)

[1] *G. Mie*, Ann. Physik 25, 377 (1908).

[*] This work will soon be published in detail in Zeitschrift für Naturforschung, Section a.

## Bonding in Intermetallic Phases of the Ni-As Type

*H. Wever*, Berlin (Germany)

Among intermetallic phases, the Ni As type represents a transition between mainly metallic and essentially non-metallic phases. The B atoms occupy a close-packed hexagonal unit cell with a c/a ratio of 1.633. Chains of A atoms fit into the octahedral voids. With increasing metallic character of the B partner, both the c/a ratio and the heteropolar forces between the A and B partners decrease. Homopolar forces due to coupling between d-electrons of the A atom are superimposed. The electrical conductivity behavior suggests discrete d-levels for c/a $>$ 1.633, and bands for c/a $<$ 1.633. If the c/a ratio is less than 1.33, then the tetrahedral voids of the hexagonal unit cell can also be filled with A atoms, *i.e.* the structure tends towards $A_2B$. In this way, new coordination and bonding relationships result. Further information can be gained from studies of the electrical and magnetic properties of the phases as well as from electrolytic transport phenomena.

The Ni–Sn and Ni–In systems were also studied. Both phases have a considerable range of homogeneity. Definite compositions ($c_s$) corresponding to the temperature maximum in the phase diagram can be obtained by zone melting. Electrical and magnetic properties are dependent on composition, such that the electrical conductivity of the Ni–Sn phase shows a marked minimum at composition $c_s$. The electrolytic transport shows that for the Ni Sn phase the field force, and for the Ni–In phase the interaction force, is the essential driving force.

A discussion of the experimental results suggests that the d-band is filled increasingly from Ni–In to Ni Sn to Ni Sb. The electrical properties can be understood if an atomic bond between the Ni atoms in the tetrahedral voids and the neighboring B atoms is assumed, for this would lead to a bonding triple band. In the case of the Ni–Sn phase, the band would be completely filled at the composition $c_s$.

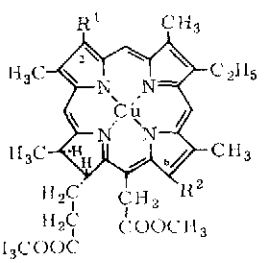
[GDCh-Ortsverband Nord-Württemberg, Stuttgart (Germany), January 23rd, 1964] [VB 786/127 1E]

German version: Angew. Chem. *76*, 353 (1964)

## Acetylation Reactions of Chlorins, a Contribution to the Munich Chlorophyll Chemistry

*H. H. Inhoffen*, Braunschweig (Germany)

By heating the Cu complex of 2-devinylisochlorin $e_4$-dimethyl ester *(1a)* with $SnCl_2(\cdot 2H_2O)$ and acetic anhydride at 100 °C for 10 min, *H. Fischer* et al. [1] obtained the corresponding 2,6-diacetyl derivative *(1b)*. When the copper was removed from *(1b)* and the chlorin residue was allowed to stand at room temperature in pyridine with benzoyl chloride, the Cu-free 2-monoacetyl compound *(1c)* was isolated in 5 % yield. From this *Fischer* concluded that partial deacetylation in the 6-position can be achieved. Compound *(1c)* is an important intermediate in *Strell*'s synthetic reactions for chlorophyll a. On checking these reports, it turned out that acetylation of *(1a)* under *Fischer*'s conditions actually gave a mixture of *(1b)* and *(1c)* in the ratio of 4:1. Pure *(1b)*, *i.e.* free of *(1c)*, could not be partially deacetylated in the 6-position by *Fischer*'s method. Moreover, considerably more vigorous conditions, *e.g.* conc. aqueous HCl at room temperature or at 100 °C, were also without effect upon the 6-acetyl group in *(1b)*.



*(1a)*: $R^1 = R^2 = H$
*(1b)*: $R^1 = R^2 = COCH_3$
*(1c)*: $R^1 = COCH_3$; $R^2 = H$
*(1d)*: $R^1 = H$; $R^2 = COCH_3$

If *(1a)* is acetylated at 0 °C (60 min), a new monoacetyl compound can be isolated in 70 % yield. The product obtained from this by removal of its copper with conc. HCl/glacial acetic acid can be regarded on the basis of extensive deuteration experiments together with nuclear magnetic resonance measurements as being the 6-monoacetyl compound *(1d)* (without Cu). Compound *(1d)* is acetylated under Fischer's conditions to give the known mixture of *(1b)* and *(1c)*.

If *(1a)* is acetylated at 100 °C with subsequent addition of water (1 mole of $H_2O$ to 1 mole of $Ac_2O$), *(1c)* is obtained in 90 % yield.

The Cu-free chlorins were also made from *(1b)*, *(1c)*, and *(1d)*.

[GDCh-Ortsverband Braunschweig (Germany), January 27th, 1964] [VB 793/132 1E]

German version: Angew. Chem. *76* (1964), in the press.

[1] *H. Fischer, F. Gerner, W. Schmelz*, and *F. Balázs*, Liebigs Ann. Chem. *557*, 134 (1944).

## Methanol/Air Fuel Cells

*W. Vielstich*, Bonn (Germany)

Apart from glycol and glycerin, methanol – including its conversion products – is especially suitable as liquid fuel for galvanic fuel cells. Such cells are particularly useful for maintenance-free energy supplies to signal devices, telegraph stations, emergency power generators, *etc.*

The operating voltage varies between 0.5 and 0.8 V at room temperature. Up to 145 ampere-hours were obtained per mole of methanol (theoretical value for conversion to carbonate about 160 amp.h). It is thus possible to store up to 1000 amp.h per l of fuel/electrolyte mixture. For practical purposes, a "hard discharge curve", *i.e.* a flat curve for the voltage as a function of time or the concentration of methanol, is of importance. This may be attained between –10 and +30 °C by suitable choice of catalysts and electrolyte composition.

Information about the individual reaction steps was obtained by means of the potentiostatic triangular voltage method. On anodic oxidation of formic acid on platinum (acid electrolyte), formate radicals are formed in the potential range between +300 and +600 mV (relative to hydrogen). They passivate the electrode by adsorption on the surface. It was shown that formation of oxalate or carbon monoxide does not occur.

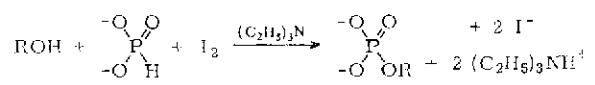
On passing $CO_2$ over a platinum electrode in the potential range $0 < \varphi < +300$ mV against hydrogen, *Giner* [2] observed deposition of an oxidizable reaction product on the electrode. Now it has been shown that, here again, this product is adsorbed formate radicals and not CO.

[GDCh-Ortsverband Bonn (Germany), January 28th, 1964] [VB 792/134 1E]

German version: Angew. Chem. *76* (1964), in the press.

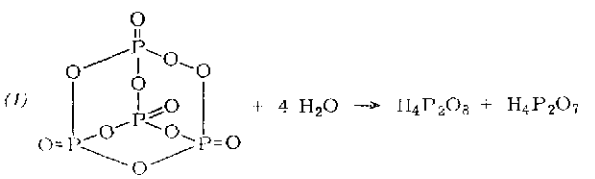
[2] *J. Giner*, Electrochim. Acta *8*, 857 (1963); *9*, 63 (1964).

**A new synthesis of monoalkyl phosphates** has been described by *A. J. Kirby*. They are obtained quantitatively by oxidation of phosphite anion with iodine in alcohol.



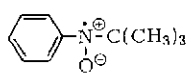
The reactive intermediate is presumably the $IPO_3^{2-}$ anion, or, less likely, monomeric metaphosphate. Alcohols that are easily oxidized by iodine are unsuitable. To carry out the phosphorylation, crystalline phosphorous acid is dissolved in butene-1,4-diol, for example, and triethylamine, and solid iodine is added; an exothermic reaction takes place. The mixture is then poured into acetone, the monophosphate being precipitated as dicyclohexylammonium-4-hydroxy-2-butenyl phosphate in 100 % yield. The method gives good results with the usual aliphatic alcohols. / Chem. and Ind. *1963*, 1877 / –Ma. [Rd 859/234 IE]

**An improved synthesis of phosphorus peroxide** has been described by *P. W. Schenk* and *H. Vietzke*. Phosphorus and oxygen interact in a glow discharge to form a mixture of $P_2O_5$ with a maximum of 15 % peroxide, which separates as a violet deposit on a cold finger. This violet form of the peroxide is only stable at low temperatures and has free-radical character. It is converted by warming into the colorless peroxide $P_4O_{11}$, which decomposes above 130 °C. $P_4O_{11}$ *(1)* reacts with water to yield only peroxodiphospboric acid and diphosphoric acid.



When nitrogen is added under the conditions for peroxide production, a violet product of composition $P_4O_{11} \cdot 2P_4O_{10} \cdot 3NO$ is formed. Hydrolysis of this leads to the formation of a nitric oxide-tetrametaphosphoric acid which is stable in alkaline media. / Z. anorg. allg. Chem. *326*, 152 (1963) / –Kr. [Rd 840/235 IE]

**Phenyl-t-butylnitroxide, a new free radical,** has been synthetized by *H. Lemaire, A. Radssat*, and *A.-M. Ravet* by the action of t-butylmagnesium chloride on nitrobenzene and also by the reaction of phenylmagnesium bromide with nitro-t-butane. The radical was identified by its paramagnetic

*(1)* 

electron resonance spectrum. The lifetime of the radical is about one week, so that its purification is possible. / Bull. Soc. chim. France *1963*, 1980 / –Ma. [Rd 855/236 IE]

**A localized bond between a substituted benzene and a transition metal** has been demonstrated for the first time with certainty in cyclopentadienyl hexakistrifluoromethyl benzenerhodium. The compound was prepared from hexafluoro-2-butyne and cyclopentadienylrhodium dicarbonyl. According to its infrared and NMR spectra and crystal structure (monoclinic; $C_{2h}^5 hP2_1/c$, a = 9.48, b = 12.59, c = 17.79 Å; $\beta = 114.8°$; Z = 4; $\rho_{20\,°C} = 2.27$ g/cm³) the Rh is octahedrally coordinated. Only four atoms of the benzene ring are coordinated with the rhodium, C-1 and C-4 by covalent σ-bonds, and C-2 and C-3 by a π-bond. The Rh–C distance for C-1 and C-4 is 2.15 Å and for C-2 and C-3 2.04 Å; C-5 and C-6 are 3.0 Å away. The original benzene ring is hinged at an angle of 48 ± 2° across the (C-1)-(C-4) axis. The strained coordinate double bond (C-2)=(C-3) is about 0.13 Å long erthan the uninvolved (C-5)–(C-6) bond. Compared with the benzene ligands in a normal complex, the (C-1)-(C-4) distance is reduced from 2.80 to 2.56 Å. / Proc. chem. Soc. (London) *1963*, 365 / –Jg. [Rd 836/341 IE]

**Salts of xenic acid** have been described by *A. D. Kirschenbaum* and *A. V. Grosse*. Free xenic acid $Xe(OH)_6$ was obtained in 30–40 % yield by hydrolysis of $XeF_4$ or xenon oxide fluorides at 0 °C with water. Solutions free from hydrogen fluoride can be prepared by addition of a small excess of $Ca(OH)_2$ or $CaCO_3$ and separation of the resulting $CaF_2$. Xenic acid can be determined by treating it with iodide and titrating the iodine liberated with thiosulfate.

$$Xe(OH)_6 + 6\,KI + 6\,HCl \rightarrow Xe + 6\,H_2O + 3\,I_2 + 6\,KCl$$

Solutions of this very weak acid can be stored for weeks at –20 to –30 °C. Barium xenate $Ba_3XeO_6$ was obtained in quantitative yield as a white, amorphous, sparingly soluble precipitate from $Ba(OH)_2$ and $Xe(OH)_6$ solutions in a molar ratio of 3:1 at 0 °C. The solubility of $Ba_3XeO_6$ in water at 20 °C is 0.25 g/l. Barium xenate is stable for at least a month at room temperature. At 125 °C, it begins to decompose slowly; at 250 °C, thermal decomposition is complete.

$$Ba_3XeO_6 \rightarrow 3\,BaO + Xe + 1.5O_2$$

The sodium and potassium salts of xenic acid were also prepared. Solutions of these salts at 0 °C and pH 7 appear to be stable. / Science (Washington) *142*, 580 (1963) / Ko. [Rd 849/242 IE]

**Solutions of pure nitrous acid** were obtained by *C. S. Scanley* using ion exchange at low $HNO_2$ concentrations and low temperatures (the decomposition of $HNO_2$ is of the 4th order and is very dependent on temperature). A 3 % solution of sodium nitrite in ethylene glycol dimethyl ether/water (2:1) was run through a column of Dowex 50 W-X4 in its acid form at –30 °C. Analysis of the resulting solution showed that it consisted of almost pure $HNO_2$ (Na content ≤4 ppm). These solutions can be used *inter alia* for the production of nitrites by direct neutralization, for nitrosation, and for diazotization reactions. / J. Amer. chem. Soc. *85*, 3888 (1963) / –Ko. [Rd 850/243 IE]

**For routine measurements of the surface area of finely divided materials,** a simple and rapid method developed by *R. Haul* and *G. Dümbgen* based on low-temperature adsorption of nitrogen can be used. Several samples are degassed simultaneously by heating in a stream of nitrogen. Subsequently, standardized measuring vessels with the samples and a reference vessel of equal volume all filled with nitrogen at atmospheric pressure are cooled with liquid nitrogen. The surface area of the sample can be obtained from the pressure difference read on a differential manometer and the initial (atmospheric) pressure without additional measurements of the equilibrium pressure and the use of empirical calibration factors. Each measurement requires about half an hour, the computation a few minutes. Gases other than nitrogen can also be used [*]. / Chem.-Ing.-Techn. *35*, 586 (1963) / –Hl. [Rd 690/244 IE]

[*] A device based on the above principle is available from Messrs. Ströhlein and Co., Düsseldorf (Germany).

**Über den Ablauf organisch-chemischer Reaktionen** (Organic Reaction Mechanisms). By *S. Hauptmann*. WTB, Science Pocket Books. Akademie-Verlag, Berlin, 1963. 1st edit. 175 pp., paperback, DM 12.50 (about $3.25).

This science pocket book deals with the multiplicity of organic reactions on the basis of 'electronic theory'. From this point of view the booklet is excellent. The arrangement is clear, and the individual reactions are grouped in such a way that their common traits are clearly illustrated by application of electronic theory. One example of this is provided by addition reactions (Section 2.1), almost all of which are induced and influenced by mesomeric and inductive effects. Again, the representation of substitution reactions (Section 2.3), in particular the differentiation between the individual reactions on pp. 86–107, is particularly apt.

How do we know, however, that the molecules do in fact react via the structures shown? Do we arrive at these ideas exclusively as a result of experience, that is, empirically? It seems regrettable to have to read in the preface that the molecular orbital method affords the best means of answering these queries, but that it should be left to the physicist to apply it. In actual fact, however, the book contains such a large number of theoretical fragments which have recently found their way into chemistry almost unnoticed that the more knowledgeable reader will perceive a lack of foundation precisely during more fundamental discussions. The few basic principles which are mentioned frequently and which are said to govern the processes can only be explained on a theoretical basis. The basic concepts mentioned in the section on mesomerism are derived from the field of wave mechanics. This provides the only possibility for explaining the numerous exceptions which are in principle not capable of being treated on the basis of electronic theory.

It is unfortunate that the results of the MO–LCAO method (Hückel method) were not utilized in the treatment of organic reaction mechanisms, as they would make it possible to discuss the position at which the reaction is initiated as well as its likely course, particularly with $\pi$-electron systems. In this connection, mention should also be made here of the LCBO-method and the method of valence structures, the latter in particular with regard to excited states. Only brief mention is made of reaction kinetics, and the concepts of transition states, metastable intermediates, and activation energies are described without much method. No comment is made of molecular vibrations, equilibria are not dealt with. The reader necessarily arrives at the conclusion that there is no basis for the discussion of the reaction processes other than that of electronic theory. The table given on p. 7 is misleading since it shows He with the same number of valence electrons as Be or Mg.

The book could have been made more useful if theoretical concepts developed during the last few years had not been deliberately disregarded, thus introducing an unnecessary limitation to the otherwise excellent treatment of the subject matter. The chemist will profit more from the book if he disregards the statement made in the preface that "classical chemical structural formulae (with additional representation of lone pairs of electrons by dashes and of unpaired electrons by dots) will continue to form the simplest and, generally speaking, completely adequate method of representing the constitution of organic compounds and the course of their reactions."

*H. Preuß* [NB 140/67 IE]

**Kern- und Radiochemie** (Nuclear and Radiochemistry). By *R. Lindner*. Basic principles, practical methods, and technical application. Springer-Verlag, Berlin-Göttingen-Heidelberg 1961. 1st edit., XII, 369 pp., 140 illustrations, linen. DM 49.80 (about $12.50).

The first half of this book, which is the outcome of a series of lectures delivered at the Technical College in Göteborg (Sweden), deals with the basic principles of nuclear physics, measuring techniques, nuclear reactors, and radiation protection. The second half is devoted to radiochemistry and applications of radionuclides in science and technology.

The author presents a wealth of scientific information from this wide field in concise and accurate formulations. The book offers a good review of the whole subject and rapid orientation in the individual topics.

Unfortunately only a brief discussion of the extensive topics of radiochemistry (*e.g.* methods of separation and enrichment; processes of radionuclide production; the chemistry of the radioclements and the fission products of uranium and the transuranic elements; chemical nuclear technology, including the problems of processing nuclear fuels; the chemistry of reactor materials and radioactive wastes) is possible within the framework of such a comprehensive treatment which also includes the basic physical principles involved and borderline subjects.

*G. Schulze-Pillot* [NB 141/70 IE]

**Kunststofftechnisches Wörterbuch** (Dictionary of Plastics Technology). By *A. M. Wittfoht*. Technical terms used in the manufacture, processing, and use of plastics, material testing and mold construction. Vol. 4: German-French. Carl Hanser Verlag, Munich 1962. 1st edit. XV, 534 pp., numerous illustrations, linen, DM 72.- (about $18.-).

This dictionary is of great help to those who deal with plastics, especially if they have to carry out technical correspondence in French or German.

One inestimable advantage of this book is that the individual terms have appended explanations to clarify their exact meaning and the sense in which they are used. It is to be welcomed that a book is now available in which engineers, businessmen, and translators can quickly find the right expression for many a technical term. Illustrations and sketches – many of them in fair detail – are of further help. An appendix of methods of molding, pressing, and pressmolding, in addition to initials and abbreviations, as well as conversion tables is extremely useful.

The author and publisher have created a dictionary that is exemplary in contents and lay-out. It can be warmly recommended to all those interested, especially since no work of this kind has been available up to now.

*O. Horn* [NB 142/66 IE]

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# Structure and Specificity of Organic Chelating Agents [*]

BY PROF. DR. ERNST BAYER

BASED ON WORK CARRIED OUT IN COLLABORATION WITH DR. H. FIEDLER, DR. K.-L. HOCK, DR. D. OTTERBACH, DR. G. SCHENK, AND DIPL.-CHEM. W. VOELTER

CHEMISCHES INSTITUT DER UNIVERSITÄT TÜBINGEN (GERMANY)

*Macromolecular chelating agents possessing high selectivity for rare metal ions have been synthetized. One of these, with the complexing group of glyoxal bis-2-mercaptoanil, is suitable for selective enrichment of gold from sea-water, while another is suitable for copper and uranium. – The enrichment of metallic ions in nature is discussed, taking hemocyanin as an example. – Both stereochemistry and isomerism, as well as cyclic conjugation during chelate formation, may influence the selectivity of complexing agents. The quasi-aromatic properties of chelates are discussed.*

More than thirty years ago, *Fritz Haber* [1] published a paper entitled "Gold in Sea-Water" in this Journal, and ended it with the words "I have given up my search for this dubious needle in a haystack". With this sentence, the inventor of the ammonia synthesis abandoned his many years' efforts at extracting gold from sea-water. The process proposed by *Haber* failed because the actual gold content of sea-water averages 0.01 $\gamma$/l, a concentration which is several powers of ten lower than previously published values. Despite their lack of commercial success, the methods developed by *Haber* and *Jaenicke* at that time for the determination of the gold content of the ocean are still admired today.

Even the revised determination of the gold content of the sea indicates a reserve of some 70 million tons – a colossal figure when compared with the world production (*e.g.* 1200 tons for 1937). However, the quantities of other elements present in sea-water also exceed those of their known continental deposits. It is estimated, for instance, that the seas contain some $7\times10^9$ tons of copper and $0.5\times10^9$ tons of uranium. Such figures explain the desire to mobilize these supplies and to find methods for their extraction.

Although at present there are no synthetic substances which would selectively concentrate a single rare metal from the multifarious elements present in sea-water, there are certain living organisms which are capable of achieving this result. In addition to the more abundant elements iron and copper, rarer metals such as molybdenum, cobalt, or vanadium are also found in natural chelates.

An extreme example of the concentration of metals by biological organisms is provided by vanadium, which is a million times more concentrated in the blood cells of the tunicate *Phallusia mamillata* than in sea-water [2,3]. A further example is the concentration of copper in the blood of the cuttlefish *Octopus vulgaris*, by a factor of about one hundred thousand [4].

## I. Specificity of Natural Complexing Agents

In nature, the specifically concentrated metal ions are all bound in organic complexes. Thus, the simplest explanation for the selective concentration appeared to be the hypothesis that the organic complexing agents are specific for only one ion. Selectivity for a single metal ion has not yet been achieved with synthetic chelating agents. Most synthetic chelates bind nearly all metal ions, with the exception of the alkali metal and alkaline earth ions, although different ions are held with varying degrees of strength.

The first task was therefore to determine whether natural complexing agents are in fact absolutely specific for a

[*] Based on lectures given at colleges and institutes in Germany and in the U.S.A.

[1] *F. Haber*, Angew. Chem. *40*, 303 (1927).

[2] *H.-J. Bielig* and *E. Bayer*, Liebigs Ann. Chem. *580*, 135 (1953).

[3] *H.-J. Bielig*, *E. Bayer*, *L. Califano*, and *L. Wirth*, Pubbl. Staz. zool. Napoli *25*, 26 (1954).

[4] *E. Bayer*, Experientia *12*, 365 (1956).

single ion. Up to now, most of these investigations have failed, either because the complexing agent was altered or destroyed when the metallic ion was removed, or because reintroduction of the metal ion was impossible. For example, the complexing ability of hemovanadine is irreversibly changed when the vanadium is removed. However, hemocyanin, the blue pigment responsible for the transport of oxygen in the blood of molluscs, was an excellent example. Up to 75 % of its complexed copper can be removed without destroying the chelate's complex-forming ability, and the metal can then be reintroduced, with complete restoration of the oxygen-binding capacity [5–7]. This resynthesis of hemocyanin from apohemocyanin can be achieved with cuprous but not with cupric salts [7]. Other metal ions cannot be coordinatively bound to apohemocyanin without denaturing the complexing agent [7]. The complex-forming function is therefore specific for one metal.

It remained to be established whether the specificity applies to monovalent or divalent copper. Resynthesis with cuprous salts does not prove the presence of monovalent copper in hemocyanin and oxyhemocyanin, since oxidation may occur at any time up to the incorporation of oxygen. *Klotz* et al. [8] even suggested the coexistence of monovalent and divalent copper in oxyhemocyanin.

The valence of the central atom cannot be determined by classical magnetic methods, since at a copper content of only 0.24 % any paramagnetism due to copper(II) is masked by the diamagnetism of the organic ligand. The temperature-independence of the magnetic susceptibility was the only indication of the occurence of monovalent copper in both hemocyanin and oxyhemocyanin. A final argument in favor of copper(I) was supplied by electron resonance absorption [7]. Apohemocyanin is therefore a specific complexing agent for copper(I).

The next step consisted in the elucidation of the groups which are responsible for this absolute specificity. Hemocyanin derived from *Octopus vulgaris* has a molecular weight of $2.7 \times 10^6$ [9], and elemental analysis indicates that its composition is that of a protein. Amino acids were the sole product which could be detected in the hydrolysate. Thus, hemocyanin contains no prosthetic groups, *i.e.* no low molecular-weight complexing agent, as is the case with all other natural chelates of known constitution. The complex-forming function is therefore part of the macromolecular protein.

The mercapto groups of the cysteine linked by peptide bonds in the protein are known to be the group capable of binding the copper [6, 7]. In addition, the copper may also be fixed by the imidazole nitrogen of histidine, at least in oxygen-free hemocyanin. Neither simple, low molecular-weight complexing agents which contain mercapto groups, such as cysteine, nor cysteine-histidine dipeptides exhibit absolute specificity for copper, so that the steric arrangement of these groups in the macromolecule must be responsible for their selectivity. Consequently, the naturally occurring selectivity cannot be reproduced in low molecular-weight models, since in addition to the sequence of the links, the secondary structure of the protein is likely to play a part.

## II. Synthetic Complexing Agents

Since the selective concentration observed in nature could not be directly reproduced with synthetic models, it was necessary to find organic ligands which would exhibit specificity during chelation by virtue of their steric structure or special bonding features. Even if these experiments could not be expected to result in specific bonding of a single metal, limitation of the complexing power to a few metals would represent a great step forward. Recognized chelating agents such as ethylenediaminetetraacetic acid, 8-hydroxyquinoline, *N,N'*-bis-(*o*-hydroxybenzylidene)ethylenediimine (salicylaldehyde-ethylenediimine), or 1,3-diketo compounds were immediately rejected, since these yield complexes with almost all metallic ions. This behavior is clear from the results of experiments with complexing agents of low molecular weight, and from unsuccessful attempts to enhance the specificity of such groups by incorporating them into ion-exchangers [10, 11].

In attempts to synthetize suitable complexing agents for the concentration of metal ions from sea-water, attention must be paid to their practicability. The complex-forming entity should be built into a macromolecule, so as to obtain compounds which are sufficiently insoluble for column filtration or suspension processes. Furthermore, it should be possible to remove the metal bound by the chelating agent reversibly without destroying the macromolecule, so that the latter can be used again. Only for valuable metals such as gold, could this requirement perhaps be sacrificed. Agents in which hydrogen is replaced by metallic ions when complexing occurs are suitable, since these can be regenerated by treatment with an acid:

$$\text{Complexing agent}-H_2 + M^{2+} \rightleftharpoons \text{Complexing agent}-M + 2H^+$$

The stability constants should be such that the metal is displaced even by dilute acids.

The complex bonding of numerous organic ligands has been studied in detail. In many instances, this study revealed new facts regarding the bonding relationships which have helped to define our practical aim and which will be discussed in connection with the complex-forming groups involved in the concentration of uranium, copper, and gold from sea-water.

### Complexing Agents Prepared from o-Aminophenol and Glyoxal

Condensation of *o*-aminophenols with α,β-dicarbonyl compounds gives rise to complexing agents such as glyoxal bis-2-hydroxyanil *(1b)*, which are particularly suitable for sequestering copper and uranyl ions [12–14].

[5] *F. Kubowitz*, Biochem. Z. *299*, 325 (1938).

[6] *E. Bayer*, Chimia *16*, 333 (1962).

[7] *E. Bayer* and *H. Fiedler*, Liebigs Ann. Chem. *653*, 149 (1962).

[8] *I. M. Klotz* and *T. A. Klotz*, Science (Washington) *121*, 477 (1955).

[9] *I. B. Eriksson-Quensel* and *T. Svedberg*, Biol. Bull. *71*, 498 (1936).

[10] For review, see *G. H. Osborn:* Synthetic-Ion-Exchangers. Chapman & Hall, London 1955, pp. 43 et seq.

[11] *F. Helferich:* Ionenaustauscher. Verlag Chemie, Weinheim 1959, Vol. I, pp. 38 et seq.

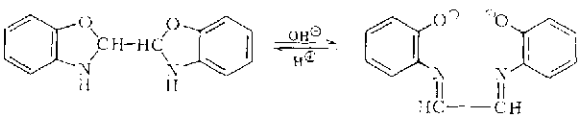
[12] *E. Bayer*, Chem. Ber. *90*, 2325, 2785 (1957).

[13] *E. Bayer* and *H. Möllinger*, Angew. Chem. *71*, 426 (1959).

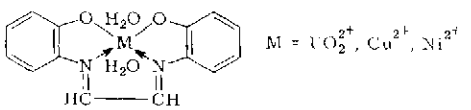
[14] *E. Bayer* and *G. Schenk*, Chem. Ber. *93*, 1184 (1960).

Nickel, uranyl, and copper ions are smoothly and rapidly bound in weakly acidic media at room temperature. Complexes are also formed in weakly alkaline media with $Co^{2+}$, $Zn^{2+}$, and $Cd^{2+}$, and even with the alkaline earth ions. This unusual preference for a few metals at pH less than 7 is connected with the special steric structure and the isomerism of glyoxal bis-2-hydroxyanil.

In the condensation of *o*-aminophenol and glyoxal, the initial product is not the open-chain Schiff base *(1b)*, but principally the isomeric bis-2-benzoxazolinyl *(1a)* [14]. In weakly alkaline media, this ring form *(1a)*, which is incapable of forming complexes, rearranges to form the open-chain form *(1b)*, which is the true complexing agent. In the presence of the most strongly complexing ions $Cu^{2+}$, $UO_2^{2+}$, and $Ni^{2+}$, this rearrangement can occur even in acidic to neutral media. The open-chain isomer, traces of which are present in equilibrium even in acidic media, is removed in the form of the complex *(2)*. Less stable complexes are formed only in weakly alkaline media, in which the complexing agent exists predominantly or exclusively as the double Schiff base *(1b)*. In



*(1a)* *(1b)*



*(2)*

the acidic pH range, these complexes can be completely redissociated to give back the metal ion and the ligand. A Stuart-Briegleb model of the nickel(II) chelate of glyoxal bis-2-hydroxyanil (Fig. 1) shows that its phenolic oxygens cannot approach the metal atom sufficiently closely. Consequently, formation of neither a covalent

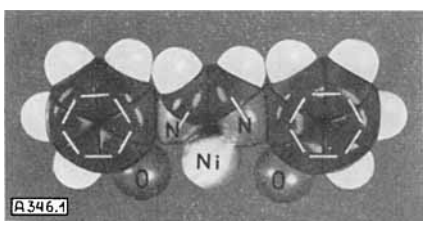
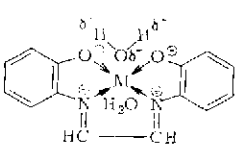



Fig. 1. Stuart-Briegleb model of (glyoxal bis-2-hydroxyanilato)nickel(II).

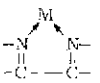
oxygen-metal bond nor a firm electrostatic bond is possible. On the other hand, the arrangement of the nitrogen atoms is exceptionally favorable for covalent bonding. The chelates can therefore be regarded as zwitterions which depend for their stability on the metal-nitrogen bond. This zwitterionic strucutre *(3)* is supported



*(3)*

further by the very firm binding of two molecules of water to the fifth and sixth coordination sites. The polar water molecule is fixed not only by its oxygen to the central atom, but also by its hydrogen to the phenoxide groups. This dual electrostatic bonding also explains the unusual fact that water cannot be removed from (glyoxal bis-2-hydroxyanilato)copper(II) *(2)* by heating without decomposing the molecule. Here the coordination number 6 is therefore preferred to the coordination number 4 which is otherwise formed almost exclusively by copper(II) [15].

Complex formation is thus determined exclusively by the metal-nitrogen bond. If the latter is regarded as being covalent, a formally heterocyclic N–M–N–C–C five-membered ring *(3a)* is obtained, which according to Figure 1 can have a planar structure similar to that of other five-membered heterocyclic rings. Cyclic conjugation seems then possible.



*(3a)*

Many of the properties exhibited by the chelates must be ascribed to this five-membered ring. These include the deep color of the glyoxal bis-2-hydroxyanil complexes, which is due to a new absorption maximum between 550 and 580 mμ and which is not exhibited by the alkali metal salts or the free complexing agent. This maximum lies in the same region for all of the complexes of *(1b)* irrespective of the nature of the central metal atom [12]. For example, the zinc(II) complex shows the same deep color (cf. Fig. 2), and since the d-shell is filled in zinc(II)

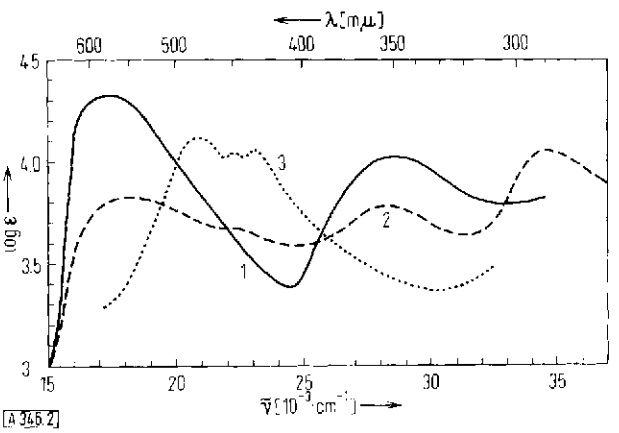
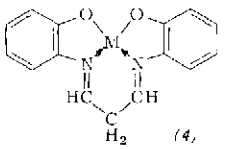



Fig. 2. Absorption spectra (in methanol at 20 °C)
1. (Glyoxal bis-2-hydroxyanilato)nickel(II)
2. (Glyoxal bis-2-hydroxyanilato)zinc(II)
3. (Malonaldehyde bis-2-hydroxyanilato)nickel(II).

the band between 550 and 580 mμ cannot be attributed to d-electron transfer in the single metal ion. Instead, this band is considered to be characteristic of the heterocyclic five-membered ring, as evidenced by arguments given below. The copper, uranium, and nickel complexes exhibit the highest extinctions, since the cyclic conjugation is apparently developed most strongly in these substances. The decisive part played in the absorption mechanism by the cyclic conjugation, and not by the metal

[15] *J. Bjerrum*, Chem. Reviews *46*, 381 (1950).

ion or by the metal-nitrogen bond alone, is demonstrated by comparing the spectra of glyoxal bis-2-hydroxyanil complexes with those of the malonaldehyde bis-2-hydroxyanil complexes *(4)*. Conjugation ist not possible in *(4)*, because of the methylene group and the non-planar structure. Accordingly, no new absorption maximum appears in this case, but the bands – shown by even the sodium salt – are slightly displaced (see Fig. 2) [16].



*(4)*

Another property which can be traced back to the cyclic conjugation is the chemical and spectroscopic behavior of the C=N double bond. Normally Schiff bases can be smoothly hydrogenated by palladium/activated carbon to form secondary amines. In exceptional cases, the hydrogenation can even lead to cleavage of the C=N bond with the formation of primary amines and hydrocarbons. This cleavage proceeds particularly readily with Schiff bases containing *o*-aminophenol components, providing a very mild procedure for the reduction of carbonyl compounds to hydrocarbons [17]. Both C=N bonds in the sodium salt of *(1b)* are readily hydrogenated to give secondary amines.

No hydrogenation could be observed with the stable Cu, Ni, and $UO_2$ complexes of glyoxal bis-2-hydroxyanil. The other metal complexes are catalytically hydrogenated with Pd/activated carbon, although the reaction is slower than that with the sodium salt. However, it can be seen from Figure 3 that even in this case, the rate of

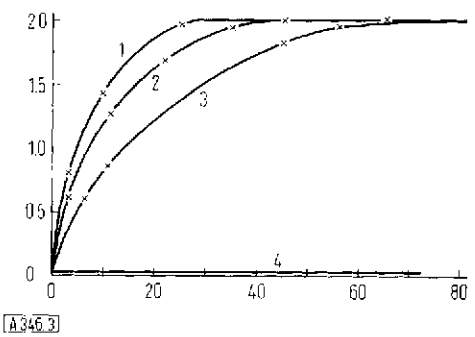



Fig. 3. The rate of hydrogenation of glyoxal bis-2-hydroxyanil complexes (Pd/activated carbon catalyst at 20 °C)

1. Disodium salt
2. Cadmium(II) complex
3. Cobalt(II) complex
4. Nickel(II) complex

hydrogenation decreases with increasing stability of the complex. These experiments show that the C=N double bond in the stable complexes of glyoxal bis-2-hydroxyanil no longer exhibits normal reactivity. In contrast, the complexes of malonaldehyde bis-2-hydroxyanil *(4)* can be hydrogenated in exactly the same manner as the free complexing agent.

[16] *E. Bayer* in *K. Issleib:* Anomalien bei Ionenaustausch-Vorgängen. Akademie-Verlag, Berlin 1962, pp. 305 et seq.

[17] *G. Schenk*, Ph. D. Thesis, Technische Hochschule Karlsruhe. 1961.

The behavior of (glyoxal bis-2-hydroxyanilato)nickel(II), particularly with respect to its lack of susceptibility to hydrogenation, is that of a quasi-aromatic heterocyclic structure. Incidentally, this difference in susceptibility to hydrogenation can be used as the basis of a quantitative determination of nickel in the presence of cobalt. The deeply colored nickel and cobalt complexes *(3)* are formed, the total extinction is measured, and the cobalt complex is selectively hydrogenated with Pd/activated carbon. Since the cobalt compound of the resulting secondary amine is colorless, the nickel content can be determined by remeasuring the extinction (at 556 mμ) after hydrogenation. The difference of the two values obtained is a measure of the absorption due to the cobalt compound.

The change in reactivity of the C=N double bond after chelation can be explained as being due to its acquisition of certain characteristics of a C–N single bond, as would also be expected in the case of cyclic conjugation. A corresponding displacement of the C=N band can in fact be detected in the infrared spectra; again the displacement is greatest for the stable complexes (Table 1).

Table 1. Infrared bands of the C=N bond of various complexes of glyoxal bis-2-hydroxyanil and malonaldehyde bis-2-hydroxyanil.

| Compound | ν [cm⁻¹] |
|---|---|
| GBHA–$Na_2$ [a] | 1635 |
| GBHA–Cd(II) | 1550 |
| GBHA–Co(II) | 1550 |
| GBHA–Ni(II) | 1540 |
| GBHA–Cu(II) | 1535 |
| GBHA–U(VI)$O_2$ | 1515 |
| MBHA–$H_2$ [b] | 1618 |
| MBHA–Ni(II) | 1615 |

[a] GBHA = divalent anion of glyoxal bis-2-hydroxyanil [cf. *(1b)*].
[b] MBHA = divalent anion of malonaldehyde bis-2-hydroxyanil [cf. *(4)*].

With regard to the infrared bands, it can be shown that cyclic conjugation is a prerequisite for the displacement, since, as can be seen from Table 1, the C=N band lies in the usual region in the case of the malonaldehyde bis-2-hydroxyanil complexes.

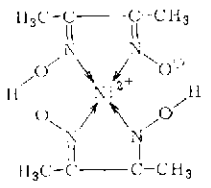
These properties have led us to the working hypothesis that the heterocyclic N–M–N–C–C five-membered ring *(3a)* is not merely formally analogous to quasi-aromatic five-membered heterocyclic structures such as pyrrole, thiophene *etc.*, but actually represents a non-benzenoid, non-classical aromatic system.

## III. Metal Chelates with Quasi-Aromatic Five-Membered Rings

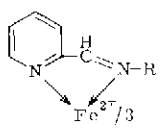
Since the glyoxal bis-2-hydroxyanil complexes are relatively complicated molecules, the properties described cannot be attributed with absolute certainty solely to the N–M–N–C–C five-membered ring *(3a)*. To confirm the quasi-aromatic character of these chelates, simpler complexes had to be studied.

Examination of the known complexing agents reveals that a large number of complexes, which are known from analytical reactions to be specific, can be related to such five-membered rings. These include the red (dimethylglyoxime)nickel complex *(5)* and the red iron(II) complexes of pyridine-2-carboxaldimine *(6)*, α,α′-dipyridyl *(7)*, and 1,2-diketimines and glyoxaldimines *(8)*.

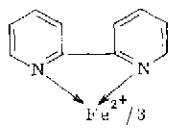
The exceptional stability of these chelates, their specific metal-sequestering ability, and their extraordinarily deep colors have long been among the unsolved mysteries of the chemistry of complexes. The existence of a cyclically conjugated ring provides at least a qualitative explanation.



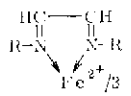
(5)



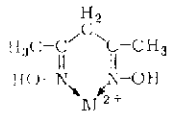
(6)



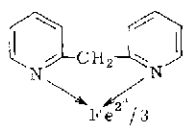
(7)



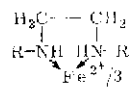
(8)



(9)



(10)



(11)

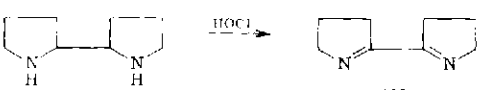
The deep color, high stability, and specificity disappear if structures *(5)* to *(8)* are modified so that cyclic conjugation is no longer possible. The complexes of the saturated ring system analogous to *(8)* that is derived from ethylenediamine are colorless and less stable. Interruption of the conjugation by insertion of a methylene group also produces a reduction in color and stability. In contrast to (dimethylglyoxime)nickel *(5)*, which is deeply colored, and to the α,α′-bipyridyliron complex *(7)*, the corresponding chelates of acetylacetonedioxime *(9)* and dipyridylmethane *(10)* are rather unstable [18]. The deep red complex tris(glyoxal bis-*N*-methylimine)iron(II) chloride *(8)*, where R = $CH_3$ [19], which can be easily prepared from glyoxal, methylamine, and iron(II) salts, can be used for comparative tests. This complex contains no groups capable of resonance other than the five-membered ring.

The great stability of *(8)* is noteworthy. As in the case of (glyoxal bis-2-hydroxyanilato)nickel(II), the C=N bond in *(8)* cannot be hydrogenated. Oxidizing agents attack the complex only under drastic conditions. Bromine oxidizes neither the chelate nor its ferrous iron constituent. The properties of the latter are masked to such an extent in this ring that it cannot be oxidized to ferric iron, for example, without destroying the complex. Even dilute mineral acids do not destroy the complex. These properties are all the more remarkable because the metal-free ligand cannot be prepared – an instructive example of stabilization by chelation.

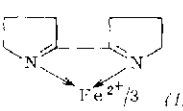
The infrared spectrum *(8)* again shows displacement towards longer wavelengths of the band due to the C=N double bond. The visible light absorption characteristics are surprising (cf. Fig. 4). The longest wavelength band is at 550 mμ, *i.e.* in the same region as that of the glyoxal-bis-2-hydroxyanil complex, which was ascribed to the N–M–N–C–C five-membered ring *(3a)*. There can no longer be any doubt that, in tris-(glyoxal bis-2-methylimine)iron(II) iodide, this band must be associated with the five-membered ring.

It has long been known that alicyclic Schiff bases are considerably more stable than purely aliphatic ones. In the course of our syntheses in the pyrroline series [20], we therefore prepared alicyclic Schiff bases, including α,α′-bipyrrolinyl *(12)*.

As expected, *(12)* forms red iron(II) complexes *(13)* with visible light absorption characteristics similar to that of *(8)*. Comparison of the spectra of the complexing agent and the iron(II) complex (Fig. 4) shows the appearance of a new maximum at 560 mμ after complex formation. The infrared band due to the C=N double bond is again displaced here (Fig. 5).



(12)



(13)

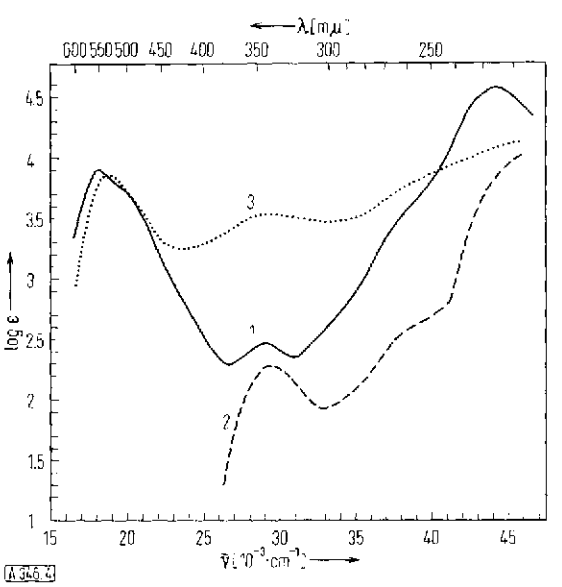



Fig. 4. Absorption spectra (in methanol at 20 °C) of:
1. Tris(glyoxal bis-2-methylimine)iron(II) iodide *(8)*
2. α,α′-Bipyrrolinyl *(12)*
3. Tris-(α,α′-bipyrrolinyl)iron(II) chloride *(13)*


[18] *K. L. Hock*, Ph. D. Thesis, Technische Hochschule Karlsruhe, 1962.

[19] *P. Krumholz*, J. Amer. chem. Soc. *75*, 2163 (1953).

[20] *D. Otterbach*, Ph. D. Thesis, Technische Hochschule Karlsruhe, 1963.

Up to now, it has been assumed that the tris-(α,α′-bipyridyl)iron(II) complex *(7)* can also be regarded as one of these quasi-aromatic chelates. This would mean that two double bonds per pyridine nucleus are not required for complex formation.

each five-membered ring contains a π-electron sextet. Four electrons in each ring are contributed by the two C=N double bonds. The remaining two electrons can only be supplied by the metal ion. The total of six d-electrons in iron(II) is just sufficient for the formation of three π-electron sextets in the three five-membered rings of tris-(α,α′-bipyridyl)iron(II)

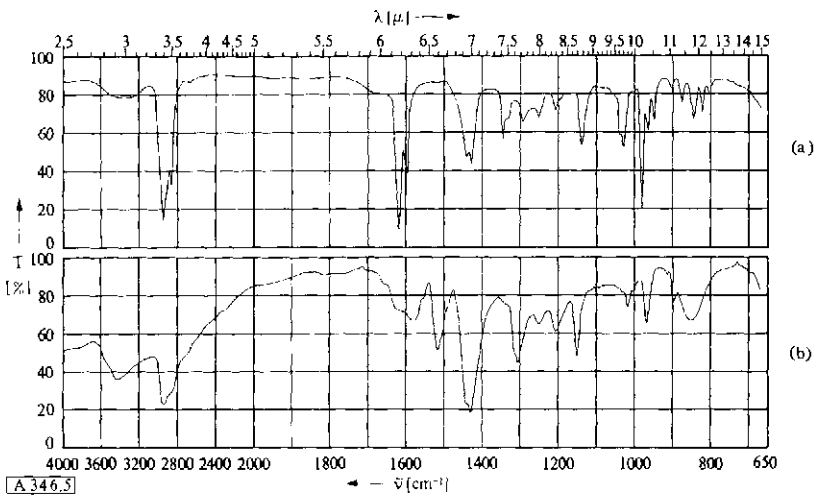
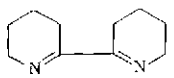



Fig. 5. Infrared spectra of (a) α,α′-bipyrrolinyl *(12)* and (b) its iron(II) complex *(13)* in KBr.

α,α′-Bipiperideinyl *(14)* should therefore form iron(II) complexes with the same properties. α,α′-Bipiperideinyl *(14)* was synthetized by the method given for bipyrrolinyl and yielded the expected red iron(II) complexes. This



*(14)*

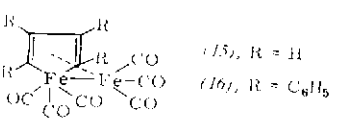
behavior indicates a close generic relationship between these complexes and the iron chelates of α,α′-bipyridyl and phenanthroline. In addition to the characteristic absorption maximum, the infrared spectra of all of these compounds show displacements towards longer wavelengths of the C=N band, corresponding to linkages intermediate between a single and a double bond. Moreover, the susceptibility of the C=N bond to reduction is lost, and the iron(II) chelate cannot be oxidized to an iron(III) chelate.

This stabilization of ferrous iron has long been known for the tris-(α,α′-bipyridyl)iron(II), (phenanthroline)iron(II), and (pyridinecarboxaldimine)iron(II) complexes, and had been attributed to the well-known concept of a filled krypton shell. Some doubt regarding the validity of this explanation had already been expressed by *Bezier* [21], who showed that the redox potential of the hexacyanoiron(II) complex ($E_0$ = + 0.36 V), which is also diamagnetic, is displaced in the expected direction, *i.e.* towards that of iron(II) salts ($E_0$ = + 0.771 V), whilst that of the phenanthroline complex ($E_0$ = + 1.14 V) is displaced in the opposite direction. Enhancement of the stability of the iron(II) is therefore observed only with the phenanthroline complex. Analogous results are obtained with the bipyridyl compound.

This resistance to oxidation can be readily explained by recourse to the concept of the formation of cyclically conjugated quasi-aromatic rings, and by the assumption that

iodide or the tris(glyoxal bis-*N*-alkylimine)iron(II) complexes. Only five d-electrons are available in iron(III), so that not all the rings can be "aromatized". Such non-aromatic complexes should automatically be less stable and this does in fact correspond to the experimental results. The observation that three ligands are preferentially added, the absence of intermediate stages with one or two ligands, and the stabilization of lower valency states of the metal ions which are isoelectronic with divalent iron [22], can also be explained in this way.

There is no reason that a quasi-aromatic five-membered ring should be limited to the N–M–N–C–C structure [cf. *(3a)*]. It should also be possible to replace the nitrogen atoms by carbon, so that the hetero-ring contains only a metal atom. Quasi-aromatic C–C–Fe–C–C five-membered rings would be named ferroles, by analogy with the azoles. *Hübel* et al. [23] and *Stone* et al. [24] treated acetylenes and thiophene with dodecacarbonyltriiron and obtained compounds which can be regarded as complexes of structures *(15)* and *(16)*. These compounds would represent aromatic π-complexes containing the quasi-aromatic ferrole system. Reactions of



*(15)*, R = H
*(16)*, R = $C_6H_5$

2,5-dichloromuconic esters with sodium iron carbonyl yields the ferrole system *(17)* which does not contain the additional tricarbonyliron group present in *(15)* and *(16)* [25]. Compound *(17)* has merely carbon monoxide added on coordinately. Nuclear resonance

[21] *H. Bezier*, J. chem. Physics *41*, 100 (1944).

[22] *S. Herzog*, Z. anorg. allg. Chem. *294*, 155 (1959).

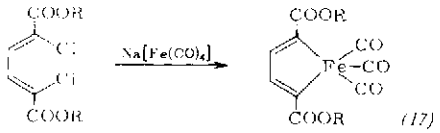
[23] *W. Hübel* and *E. Weiss*, Chem. and Ind. *1959*, 703; *W. Hübel* and *E. H. Braye*, J. inorg. nuclear Chem. *10*, 250 (1959).

[24] *F. G. A. Stone*, *H. D. Kaesz* u. *R. B. King*, J. Amer. chem. Soc. *82*, 4749 (1960).

[25] *E. Bayer*, *H. Brune*, and *K. L. Hock*, Angew. Chem. *74*, 872 (1962); Angew. Chem. internat. Edit. *1*, 552 (1962).

studies show that the signals for the β-protons lie in the normal region for heterocyclically bound protons.

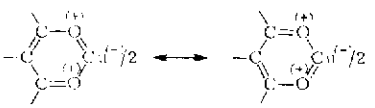
Comparison with cyclobutadiene-nickel complexes [26, 27] shows that *(17)* does not contain a cyclobutadiene system and is therefore intermediate between organometallic compounds, chelates, and quasi-aromatic heterocyclic systems.




*(17)*

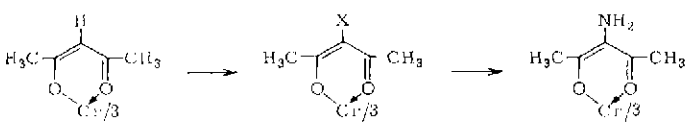
By analogy with ferrole, other metal ions with partially filled d-electron shells from the first long period of the periodic table should also be able to give such five-membered rings. According to studies on models, similar complexes with metals of the second and third long period are no longer planar. Cyclic conjugation is therefore reduced or becomes impossible.

It should also be possible for six-membered rings to exhibit aromatic behavior. *Calvin* et al. [28] postulated quasi-aromatic rings for acetylacetonates and proposed the mesomeric structures *(18a)* ↔ *(18b)*.



*(18a)* *(18b)*

*Collman* et al. [29] succeeded in obtaining confirmation for this view by electrophilic substitution of acetylacetonates. For example, tris(acetylacetonato)chromium *(19)* can be readily halogenated and nitrated [28–31]. The nitro compound *(20a)* can even be catalytically hydrogenated to yield an aminoacetylacetonate chelate [32, 33].



*(19)* *(20a)*, X = $NO_2$ *(21)*

*(20b)*, X = Halogen

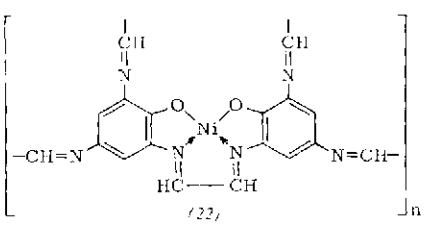
*Collman* and *Yamada* [33] recently succeeded in diazotizing the amino group to a stable diazonium salt.

Since beryllium acetylacetonates also exhibit the properties mentioned for the chromium complex [33a], the d-electrons are not essential for the formation of a quasi-aromatic six-membered ring. For this reason, no specificity associated with a definite number of electrons in the metal ion can be expected from these complexes. This is in agreement with the observation that acetylacetone forms complexes with all metallic ions; even the sodium compound may be regarded as a complex.

## IV. Concentration of Copper and Uranium from Sea-Water

Let us now return to the practical application of complexing agents to the selective concentration of metal ions. According to the foregoing discussion, complexing agents which react with metal ions to yield chelate rings such as that in *(3a)* appear to be particularly promising. The glyoxal bis-2-hydroxyanil grouping can be grafted onto macromolecules by condensing di- and triaminophenols with glyoxal.

The transition from low molecular-weight model substances to macromolecular complexing agents possessing adequate chemical and mechanical stability was a difficult task. The polycondensation is carried out in a weakly alkaline solution with a several-fold excess of glyoxal [34]. For large charges, condensation in the presence of nickel salts, has proved successful; this yields the polymeric nickel complex *(22)* in which the complexing group is protected. The nickel can then be eluted with hydrochloric acid at pH 1–1.5.




*(22)*

These macromolecular complexing agents are used in column or suspension processes, with particle sizes ranging from 0.2 to 0.8 mm. The substances [13] are suitable for selective sequestration of uranium and copper, and can take up as much as 5 % by weight of copper and 20 % by weight of uranium. The sequestered metal ions can be eluted with dilute hydrochloric acid at pH 1–2 without decomposing the complexing agent, which can be regenerated repeatedly.

Despite encouraging results with concentrated solutions, it was not certain whether these substances would actually concentrate the extremely low uranium and copper contents in sea-water. It was not known whether uranium and copper are held in sea-water (pH ≈ 7) in colloidal form, as a dissolved complex, or within microorganisms. Samples of water from the Gulf of Naples contained 4.5–5.0 γ/l of dissolved copper and 0.5 γ/l of dissolved uranium [35]. It was found that it was a simple matter to concentrate the copper and uranium in yields of up to 100 % [35] by passing the sea-water, at the rate of 1.5 l/cm²/hr, through a column packed with the ma-


[26] *R. Criegee* and *G. Schröder*, Angew. Chem. *71*, 70 (1959).

[27] *R. Criegee* and *G. Schröder*, Liebigs Ann. Chem. *623*, 1 (1959).

[28] *R. E. Martell* and *M. Calvin*: Chemistry of the Metal Chelate Compounds. Prentice Hall, New York 1953, pp. 160 et seq.

[29] *J. P. Colman*, *R. A. Moss*, *H. Maltz*, and *C. Heindel*, J. Amer. chem. Soc. *83*, 531 (1961).

[30] *H. Reihlen*, *R. Illig*, and *R. Wittig*, Chem. Ber. *58*, 12 (1925).

[31] *L. Djoidjeric*, *J. Lewis*, and *R. S. Nyholm*, Chem. and Ind. *1959*, 122.

[32] *K. L. Hock*, Diploma Thesis, Technische Hochschule Karlsruhe, 1960; see also Angew. Chem. *73*, 533 (1961).

[33] *J. P. Collman* and *M. Yamada*, Chem. and Ind. *1963*, 692.

[33a] *R. M. Klein* and *J. C. Bailar*, Inorg. Chem. *2*, 1190 (1963).

[34] German Patent 1102397 (Sept. 28th, 1961), inventor: *E. Bayer*.

[35] *E. Bayer* and *H. Fiedler*, Angew. Chem. *72*, 921 (1960).

cromolecular complexing agent. To the best of our knowledge, this was the first time that rare metals had been concentrated from sea-water by a simple process.

## V. Concentration of Gold

Replacement of both the hydroxyl groups in glyoxal bis-2-hydroxyanil by mercapto groups results in a complexing agent in which covalent coordination between the sulfur and the metal ions is conceivable.

A Stuart-Briegleb model (Fig. 6) indicates that, in addition to nitrogen-metal bonds, sulfur-metal bonds are also sterically possible owing to the larger atomic volume of sulfur. Overlapping of the electron orbits of the sulfur and the metal should be exceptionally favorable

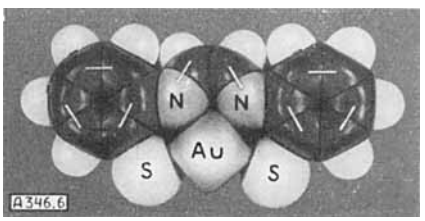
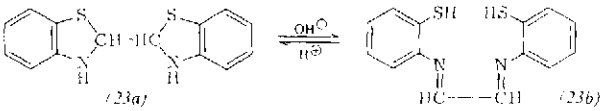



Fig. 6. Stuart-Briegleb model of the (glyoxal bis-2-mercaptoanilato)-gold(III) complex.

with metals possessing larger ionic radii, *e.g.* the transition elements of the second and third long periods. For this reason, and because of the well-known preferential coordination of ligands containing sulfur to metals of the first and second transition groups, it was possible to predict that glyoxal bis-2-mercaptoanil *(23a)* ⇌ *(23b)* would be specific for silver, gold, and mercury ions.

[36] *E. Bayer*, Angew. Chem. *73*, 659 (1961).

Condensation of aminothiophenol and glyoxal first produces bis-2-benzothiazolinyl *(23a)*, which is rearranged by alkalis to the oxidizable form glyoxal bis-2-mercaptoanil *(23b)* [36]. Deep red to violet complexes are formed with gold(III), mercury(II), and silver salts at pH > 1, whilst other metal complexes are formed only




in weakly alkaline media. For practical application, it seems particularly favorable that, owing to the tautomeric ring form *(23a)*, oxidation of the SH groups of the chelating agent cannot occur in preference to the bonding of the metal ions.

Judging from the selectivity of the low molecular-weight model, incorporation of the complex-forming glyoxal bis-2-mercaptoanil group into macromolecular complexing agents should produce substances capable of concentrating gold from sea-water, and so of finding the "needle in the haystack" which *Haber* sought in vain.

Polycondensation of di- and triaminotbiophenols with glyoxal does in fact give macromolecules, by means of which it is possible to concentrate gold specifically from dilute solutions, whithout interference from other metals. It was thus found possible to extract gold from the water of the Gulf of Naples in quantities of 1.4 γ/100 l, corresponding to the gold content determined analytically.

*We wish to express our sincere gratitude to the following organizations for their help in our studies: Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie, Bundesministerium für wissenschaftliche Forschung, and Badische Anilin- und Sodafabrik.*

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Translated by Express Translation Service, London

# Three-Membered Rings Containing Two Hetero-Atoms

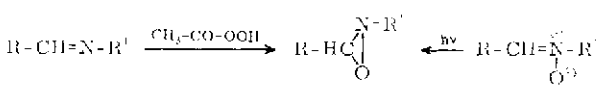
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*Since their discovery five years ago, the diaziridines have become an extensive and easily accessible class of compounds. Hydrolysis of these compounds effects a simple synthesis of hydrazine, alkylhydrazines, and N,N'-dialkylhydrazines. They are also powerful oxidizing agents. The rigidity of the three-membered ring gives rise to a few stereoelectronic peculiarities. Investigations on the mechanism of formation of the three-membered rings led to a new synthesis of oxaziranes and to discovery of the isomeric oximes with a three-membered ring structure. The latter decompose readily to form diimide. Diazirines are cyclic isomers of the aliphatic diazo compounds and are surprisingly easy to obtain by dehydrogenation of suitable diaziridines; they are chemically much more stable than the linear isomers. Grignard reagents add onto the N–N double bond without destruction of the three-membered ring. Thermal decomposition yields carbenes.*

The ease of formation of three-membered rings containing one hetero-atom often led to erroneous postulations of structural formulae with two hetero-atoms in a three-membered ring. Hydrazones, nitrones, and aliphatic diazo compounds were for a long time formulated as three-membered rings. However, we now know that no three-membered rings containing two hetero-atoms had ever been prepared prior to 1950 [1].

The first compounds which proved to be true three-membered rings of this type were the oxaziranes *(1)* prepared in 1952 by *H. Krimm* from Schiff bases and peroxy acids. These were first described in patents [2], but were later discovered independently by *Emmons* [3] and by *Horner* and *Jürgens* [4]. Oxaziranes *(1)* may also be prepared by exposing nitrones to light [5].



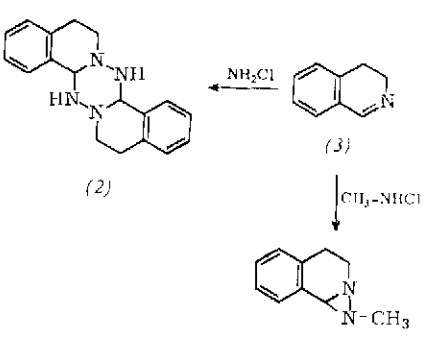
*(1)*

The diaziridines (C–N–N three-membered rings) were discovered independently by three research groups a few years later [6–8].

## Diaziridines

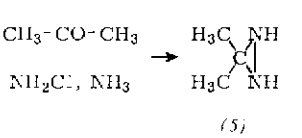
### a) Synthesis of Diaziridines

In 1958, *Schmitz* described the synthesis of a hexahydrotetrazine derivative *(2)* from 3,4-dihydroisoquinoline *(3)* and chloramine [9]. A similar experiment with *N*-chloromethylamine did not yield the expected tetrazine derivative [*(2)* with $N-CH_3$ in place of NH], but instead a compound of the same empirical formula but with only half of the molecular weight. This was formulated as a diaziridine derivative *(4)* [6].



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

In an attempt to carry out the Raschig hydrazine synthesis in the gas phase and to trap the hydrazine formed with acetone, *Abendroth* and *Henrich* [7] obtained an isomer of acetone hydrazone, to which they assigned a C–N–N three-membered ring structure *(5)*. In a patent, *Paulsen* reported corresponding compounds from diethyl ketone and from methyl ethyl ketone [8].



*(5)*

[*] From a plenary lecture at the General Meeting of the Gesellschaft Deutscher Chemiker in Heidelberg on September 13th, 1963, and lectures in Jena (May 22nd, 1963), Leipzig (May 24th, 1963), Marl-Hüls (September 18th, 1963), Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (September 19th, 1963), Budapest (October 11th, 1963) and Freiberg/Sachsen (October 30th, 1963).

[1] Short Review: *E. Schmitz*, S.-Ber. dtsch. Akad. Wiss. *1962*, No. 6.

[2] Review: *H. Krimm*, Chem. Ber. *91*, 1057 (1958).

[3] *W. D. Emmons*, J. Amer. chem. Soc. *79*, 5739 (1957).

[4] *L. Horner* and *E. Jürgens*, Chem. Ber. *90*, 2184 (1957).

[5] *J. S. Splitter* and *M. Calvin*, J. org. Chemistry *23*, 651 (1958); *R. Bonnet*, *V. M. Clark*, and *A. R. Todd*, J. chem. Soc. (London) *1959*, 2102.

[6] *E. Schmitz*, Angew. Chem. *71*, 127 (1959); Chem. Ber. *95*, 676 (1962).

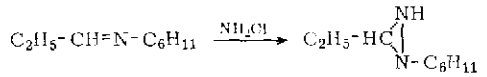
[7] *H. J. Abendroth* and *G. Henrich*, Angew. Chem. *71*, 283 (1959); German Pat. 1082889 (March 17th, 1958).

[8] *S. R. Paulsen*, Belg. Pat. 588352 (March 7th, 1959).

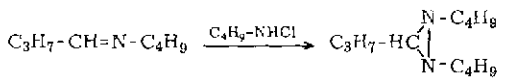
[9] *E. Schmitz*, Chem. Ber. *91*, 1495 (1958).

The three-membered ring structure postulated by the discoverers of this new class of compounds was confirmed by extensive synthetic work carried out between 1959 and 1962. In this work, the smoothness of formation of the C–N–N three-membered ring proved to be just as surprising as the general applicability of the synthesis [10].

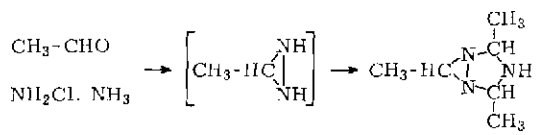
The reaction discovered with the Schiff base 3,4-dihydroisoquinoline *(3)* is quite generally applicable to aliphatic Schiff bases. In all the cases investigated, chloramine in ether transferred its NH residue to the Schiff bases, immaterial whether the latter were derived from aldehydes, ketones, or cyclic ketones [11, 12].



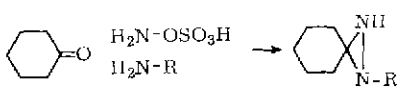
Formation of the three-membered ring also proceeded smoothly if chloramine was replaced by *N*-chloromethylamine or the *N*-chloro derivatives of other primary aliphatic amines [11, 13].



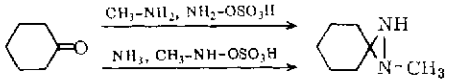
In the reaction of aliphatic aldehydes with ammonia and chloramine, the formation of diaziridines was accompanied by a further condensation leading to a triazolidine ring [14]. This reaction also occurred with benzaldehyde.



Both ketone/ammonia mixtures and Schiff bases react with hydroxylamine-*O*-sulfonic acid to form diaziridines [15, 16]; a mixture of a carbonyl compound and a primary amine may also be used in place of the Schiff base:



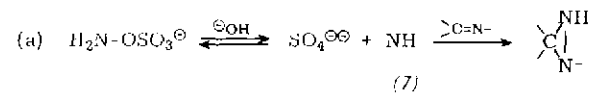
About 50 diaziridines have been prepared by this method [10], generally in yields ranging from 50 to 80 %. During these syntheses a simple proof of the three-membered ring structure was obtained. The reaction of cyclohexanone with methylamine and hydroxylamine-*O*-sulfonic acid leads to the same diaziridine *(6)* as the reaction with ammonia and methylhydroxylamine-*O*-sulfonic acid. The classical method of labelling with methyl groups proved the equivalence of the two nitrogen atoms [17]:



*(6)*

### b) Mechanism of the Formation of Diaziridines

Both the synthesis of cyclopropanes from olefins and carbenes [18] and the old view of the mechanism of the Raschig hydrazine synthesis [19] tempt one to formulate the formation of diaziridines as the addition of an imene *(7)* or alkylimene to a C=N double bond:



*(7)*

This view has often been expressed [20] and appears so plausible that it must be refuted all the more vehemently. The formation of an imene *(7)* with an electron sextet on the nitrogen is impossible during the synthesis of diaziridines. Hydroxylamine-*O*-sulfonic acid in alkaline solution is not in equilibrium with imene and sulfate [Equation (a)], for it does not incorporate radioactive sulfur from a solution of active sulfate by isotope exchange [21]. There is still the possibility that irreversible decomposition of the hydroxylamine-*O*-sulfonic acid into imene and sulfate occurs. If this were so, the formation of diaziridine, in a subsequent reaction should not be rate-determining, but should proceed at the same rate as the decomposition of hydroxylamine-*O*-sulfonic acid in the absence of a Schiff base. However, it is in fact appreciably faster. The formation of diaziridine from cyclohexanone, ammonia, and hydroxylamine-*O*-sulfonic acid is complete within about one hour at 0 °C, whereas only about half of a given amount of the sulfonic acid is decomposed in 0.1 N sodium hydroxide solution after about 20 hours at 20 °C [22]. Thus, the Schiff base does not wait for the irreversible decomposition of the hydroxylamine-*O*-sulfonic acid to occur before reacting with one of the decomposition products, the imene, to form the three-membered ring, but attacks the sulfonic acid as such.

The same is true in the case of chloramine. $^{36}Cl$ is not incorporated: hence there is no equilibrium between the chloramine and imene [23]. Since the rate of formation

[10] Extensive review: *E. Schmitz:* Advances in Heterocyclic Chemistry. Academic Press, New York 1963, Vol. II, pp. 83-130.

[11] *E. Schmitz*, German Pat. 1107238 (Dec. 21st, 1959).

[12] *E. Schmitz* and *D. Habisch*, Chem. Ber. *95*, 680 (1962).

[13] *E. Schmitz* and *K. Schinkowski*, Chem. Ber. *97*, 49 (1964).

[14] *E. Schmitz*, Chem. Ber. *95*, 688 (1962).

[15] *H. J. Abendroth*, Angew. Chem. *73*, 67 (1961).

[16] *E. Schmitz* and *R. Ohme*, Chem. Ber. *94*, 2166 (1961).

[17] *E. Schmitz, R. Ohme*, and *R. D. Schmidt*, Chem. Ber. *95*, 2714 (1962).

[18] *W. v. E. Doering* and *A. K. Hoffmann*, J. Amer. chem. Soc. *76*, 6162 (1954).

[19] *F. Raschig:* Schwefel- und Stickstoffstudien. Verlag Chemie, Berlin 1924.

[20a] *S. R. Paulsen* and *G. Huck*, Chem. Ber. *94*, 968 (1961).

[20b] *J. Harley-Mason*, Chem. and Ind. *1962*, 888.

[20c] *C. G. Overberger* and *J. P. Anselme*, Tetrahedron Letters *1963*, 1405.

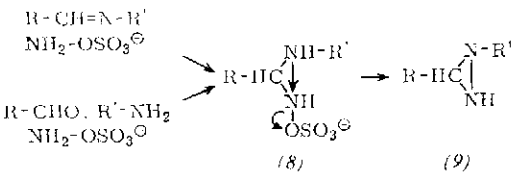
[21] *E. Schmitz, R. Ohme*, and *S. Schramm*, unpublished work.

[22] *E. Schmitz, R. Ohme*, and *R. D. Schmidt*, unpublished work.

[23] *M. Anbar* and *G. Yagil*, J. Amer. chem. Soc. *84*, 1790 (1962).

of diaziridine is again faster by several powers of ten than the rate of decomposition of chloramine, the reaction must be due to attack of the Schiff base on the chloramine.

The closure of the three-membered ring is probably preceded by the formation of a geminal compound *(8)*, which can arise from hydroxylamine-*O*-sulfonic acid either by addition to a Schiff base or by aminoalkylation with a carbonyl compound and an amine.

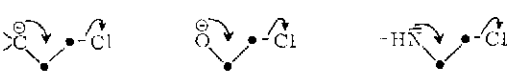


*(8)* *(9)*

The ring closure to form the diaziridine *(9)* is then an intramolecular $S_N2$ reaction. The following observations indicate the intermediate occurrence of the geminal compound *(8)*:

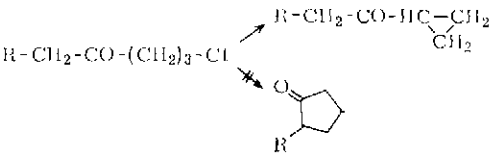
1. The tendency towards opening of the double bond in the series of cyclic ketones passes through a maximum at the six-membered ring [24]. The occurrence of *(8)* as an intermediate in the formation of diaziridine suggests that the optimum should occur with cyclohexanone, as is indeed the case. Cyclopentanone and cycloheptanone react less smoothly than cyclohexanone [25].

2. The majority of the reactions leading to three-membered rings proceed by intramolecular attack of a nucleophilic center on an atom bearing a labile group, generally a halogen. Thus, carbanions [26], alkoxides [27], or amino groups [28] react by rear-side attack on a carbon-halogen bond to form three-membered rings.

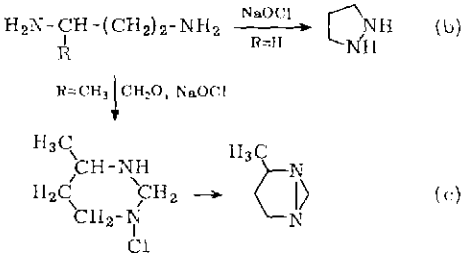


The formation of diaziridine from *(8)* fits into this scheme. A fact which can be inferred from this mechanism, namely that the diaziridine ring-closure should not require a basic catalyst, is in fact realized in practice.

3. The analogy between the formation of cyclopropane by 1,3-elimination and the mode of formation of diaziridine is accentuated by the predominance of the two reactions over the closure of larger rings. Hydrogen halide is eliminated from γ-halogeno ketones by bases to form only three-membered rings; the completely analogous formation of five-membered rings, though conceivable, is not observed in practice [26].



An intramolecular hydrazine synthesis resulting in a five-membered ring [Equation (b)] proceeds with only a moderate yield [29]. However, if the two nitrogen atoms are also linked by formaldehyde, the reaction proceeds in 98 % yield, but this time with formation [Equation (c)] of a three-membered ring [30].



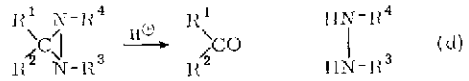
What is the reason for this preferential formation of three-membered rings? In $S_N2$ reactions, nucleophiles react particularly rapidly if they can penetrate their solvation shell easily [31]. However, the latter cannot be of considerable magnitude between the ends of a three-membered chain, for example in *(8)*, so that the chief obstacle to an $S_N2$ reaction is simply avoided.

### c) Reactions of Diaziridines

Diaziridines are weak bases. After their preparation, they are extracted from organic solvents with dilute mineral acids, and are recovered practically without loss by means of alkali [12]. There are at present no quantitative data on their basicities. The pH-dependence of the rate of hydrolysis of 1-methyl-3,3-pentamethylene-diaziridine *(6)* indicates that the compound is almost completely protonated at pH 3, *i.e.* its basicity corresponds roughly to that of aniline (pK of the anilinium ion: 4.58) [32].

Stable salts with the three-membered ring intact have been obtained from some 1,3-dialkyldiaziridines and oxalic acid [12].

When heated with aqueous mineral acids, diaziridines are cleaved to form a carbonyl compound and a substituted hydrazine [Equation (d)]. Some yields are shown in Table 1. Side reactions occur only with the extremely stable diaziridines derived from formaldehyde [33].




[24] *V. Prelog* and *M. Kobelt*, Helv. chim. Acta *32*, 1187 (1949).

[25a] *R. Ohme*, Ph. D. Thesis, Humboldt-Universität, Berlin, 1962.

[25b] *A. Stark*, Diploma Thesis, Humboldt-Universität, Berlin, 1963.

[26] Review: *E. Vogel*, Angew. Chem. *72*, 4 (1960).

[27] *W. Lwowski*, Angew. Chem. *70*, 483 (1958).

[28] *J. S. Fruton*, in *R. C. Elderfield:* Heterocyclic Compounds. Wiley, New York 1950, p. 61.

[29] *A. Lüttringhaus, J. Jander*, and *R. Schneider*, Chem. Ber. *92*, 1756 (1959).

[30] *E. Schmitz* and *R. Ohme*, unpublished work.

[31] *E. S. Gould:* Mechanism and Structure in Organic Chemistry. Holt and Comp. New York 1959.

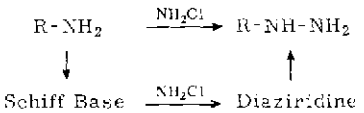
[32] *H. A. Staab:* Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim 1959, p. 637.

[33] *Cs. Szántay* and *E. Schmitz*, Chem. Ber. *95*, 1759 (1962).

Table 1. Hydrolytic cleavage of diaziridines to hydrazines according to Equation (d).

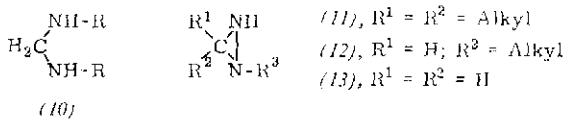
| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield [%] | Ref. |
|---|---|---|---|---|---|
| Ethyl | H | Cyclohexyl | H | 88 | [12] |
| n-Propyl | H | Benzyl | H | 87 | [12] |
| Methyl | Methyl | Isopropyl | H | 83 | [12] |
| Pentamethylene | | Cyclohexyl | H | 87 | [12] |
| n-Hexyl | H | n-Butyl | H | 77 | [12] |
| Pentamethylene | | n-Propyl | H | 88 | [34] |
| n-Propyl | H | Ethyl | n-Butyl | 73 | [13] |
| n-Propyl | H | n-Butyl | n-Butyl | 85 | [13] |
| Ethyl | H | Methyl | Cyclohexyl | 63 | [13] |
| Ethyl | H | Tosyl | Cyclohexyl | 67 | [35] |
| Ethyl | H | $C_6H_5$—NH—CO | Cyclohexyl | 73 | [35] |

Synthesis of a diaziridine and its cleavage to the alkylated hydrazine corresponds in effect to the direct reaction of an amine with chloramine [36] or hydroxylamine-*O*-sulfonic acid [37, 38]. The carbonyl compound introduced with the Schiff base is recovered on cleavage of the diaziridine. However, the detour via the diaziridine is richly repaid. A considerable excess of amine must always be used in the direct reaction in order to suppress further interaction of the alkylhydrazine formed with the aminating agent.

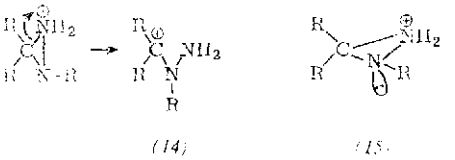



The diaziridines, on the other hand, are insensitive to the aminating agent. Furthermore, the range of application of the hydrazine synthesis via diaziridines is considerably wider: *N*-chlorinated primary amines react just as readily as chloramine itself to form diaziridines, while all attempts to react *N*-chlorinated primary amines with ammonia or amines to form hydrazines have so far proved unsuccessful [29]. An efficient and generally applicable method is thus now available for the synthesis of alkylhydrazines and *N*,*N'*-dialkylhydrazines.

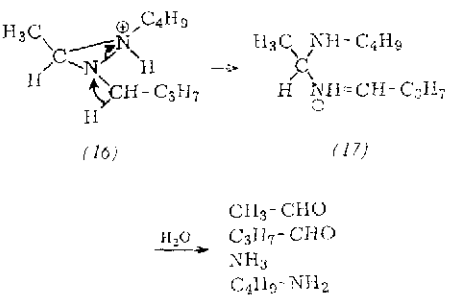
Hydrolysis of diaziridines with acid requires much more vigorous conditions than was expected from experience with open-chain compounds or larger rings. It is well known that open-chain 1,1-diamines *(10)* are decomposed instantaneously by dilute acids [39]. In contrast, diaziridines *(11)* derived from ketones have a half-life of about one hour in mineral acids at room temperature [33]; those *(12)* derived from aldehydes have half-lives of a few days, and those *(13)* derived from formaldehyde of a few weeks. Thus increasing alkyl substitution strongly accelerates the rate of hydrolysis. The magnitude and direction of this substituent effect are characteristic of an $S_N1$ reaction.



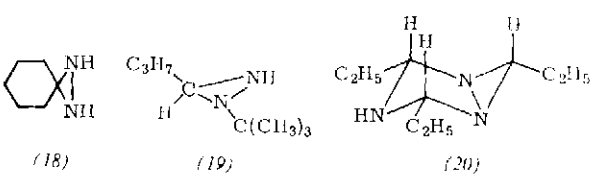

The rate-determining step must therefore be the ionization of a protonated diaziridine to the carbonium ion *(14)*. It can be seen from the spatial representation *(15)* that this ionization receives no help from the lone pair of electrons on the unprotonated nitrogen: the diaziridine molecule is perfectly rigid, and the orbital of this electron pair lies at an angle of about 60° to the plane of the ring; this configuration prevents any synchronous electron displacements.




Hydrolysis to the hydrazine derivative in a strongly solvating solvent is an $S_N1$ reaction. The reaction follows a different path in a weakly solvating solvent; with HCl in carbon tetrachloride, the N–N bond is broken. However, since the formation of an electron sextet on the nitrogen is impossible, the N–N bond can only break if a hydride ion simultaneously migrates over from the adjacent carbon atom [*i.e.* *(16)* → *(17)*]. Thus, one nitrogen atom is also dealkylated, the alkyl residue split off being recovered as the corresponding aldehyde [13].




The possibility of the migration of a hydride ion is a prerequisite for this N–N cleavage. Diaziridines which do not contain a suitable C–H bond do not undergo N–N fission. For example, pentamethylenediaziridine *(18)* is stable to HCl/carbon tetrachloride.




Once again, owing to the rigidity of the three-membered ring, the N–N cleavage is stereoelectronically very demanding. Simultaneous N–N cleavage and hydride migration requires that the two bonds involved be almost parallel. The C–H bond on the ring carbon atom in *(19)* and the axial C–H bonds in *(20)* form such large angles with the N–N bond that they cannot assist N–N cleavage: both compounds are stable to HCl/carbon tetrachloride [13].


[34] *E. Schmitz* and *R. Ohme*, Angew. Chem. *73*, 220 (1961).

[35] *E. Schmitz* and *D. Habisch*, Rev. Chi. (Bukarest), in the press.

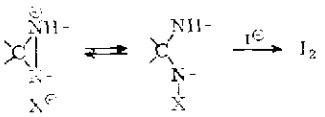
[36] *L. F. Audrieth* and *L. H. Diamond*, J. Amer. chem. Soc. *76*, 4869 (1954).

[37] *G. Gever* and *K. Hayes*, J. org. Chemistry *14*, 813 (1949).

[38] *R. Gösl* and *A. Meuwsen*, Chem. Ber. *92*, 2521 (1959).

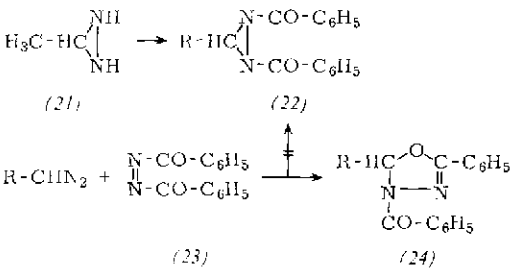
[39] For example, *M. Zief* and *J. Ph. Mason*, J. org. Chemistry *8*, 1 (1943).

The role of the hydride ion in assisting the N–N cleavage of the protonated diaziridine can also be taken over by nucleophilic reagents. Iodide ions cleave the N–N bond quantitatively in acidic solutions [7, 10]. The liberation of two equivalents of iodine in this reaction provides a simple analytical method for the determination of diaziridines.



Evolution of chlorine was observed on heating diaziridines with concentrated hydrochloric acid [20a]. The attack of halide ions on the protonated diaziridine to cleave the N–N bond appears to be the exact reversal of the diaziridine ring closure.

The relatively high stability of diaziridines enables them to undergo reactions in which the three-membered ring remains intact. Benzoylation of 3-methyldiaziridine *(21)* proceeds smoothly to give a dibenzoyl derivative *(22)*, R = $CH_3$, with an undamaged three-membered ring, as shown by its ability to oxidize iodide [35].

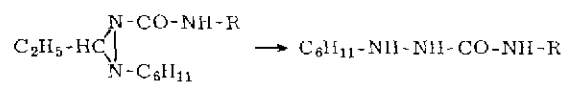


*(21)* *(22)*

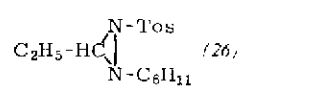
This oxidizing character disproves an earlier, supposed diaziridine synthesis. The diaziridine structure *(22)* had repeatedly been assigned to the product of the reaction between aliphatic diazo compounds and azodicarbonyl compounds *(23)* [40]. However, in contrast to 1,2-dibenzoyl-3-methyldiaziridine *(22)*, R = $CH_3$, these products are not oxidizing, and are thus no diaziridines. The suspected oxadiazoline structure *(24)* [41] has recently been proved by nuclear magnetic resonance [42] and infrared spectroscopy [43].

*(23)* *(24)*

Other acylating agents also react smoothly with diaziridines. Reaction with nitrourea or phenyl isocyanate yields three-membered ring compounds *(25)* which are isomeric with semicarbazones, and toluenesulfonyl chloride gives *(26)*. Hydrolysis of these derivatives



*(25)*, R = H, $C_8H_5$



*(26)*

provides a simple method for the preparation of *N*-alkyl-*N'*-acylhydrazines, which are otherwise difficult to obtain [35].

## Oxaziranes

### a) New Synthesis of Oxaziranes

The same is true of the majority of amination reactions of hydroxylamine-*O*-sulfonic acid as of the diaziridine synthesis: the compounds that are aminated attack the aminating agent; an imene does not occur as an intermediate stage [44]. The reaction with methylamine, for example [Equation (e)], is about ten times as fast as the reaction with hydroxyl ions (Fig. 1). This is also true of the amination of hydroxylamine [diimide formation, Equation (f)] [45].

$$CH_3-NH_2 + NH_2-OSO_3H \rightarrow CH_3-NHNH_2 \quad \text{(e)} \quad [38]$$

$$NH_2OH + NH_2-OSO_3H \rightarrow NH_2-NH-OH \rightarrow HN=NH \quad \text{(f)} \quad [45]$$

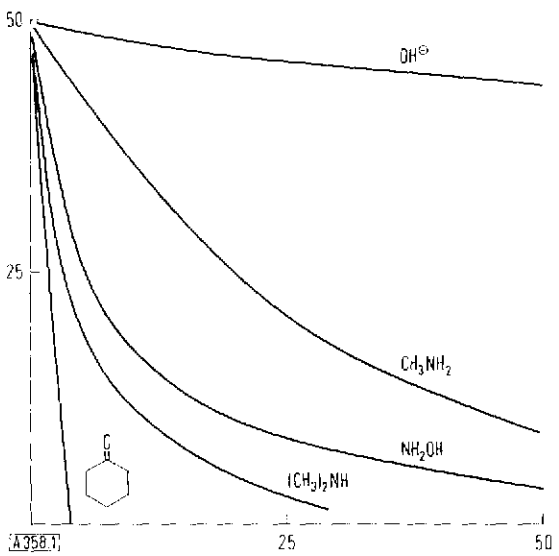



Fig. 1. Rates of some amination reactions with hydroxylamine-*O*-sulfonic acid (0.05 M solution in 0.5 N NaOH at 20 °C; reactants in equivalent quantities) [46].

Ordinates: Initial concentration [mmoles/l].
Abscissae: Time [min]

It was difficult at first to understand why cyclohexanone consumes the hydroxylamine-*O*-sulfonic acid about ten times as rapidly as the other compounds. A detailed investigation showed that this is also due to three-membered ring formation.

When methylhydroxylamine-*O*-sulfonic acid in dilute sodium hydroxide is allowed to act on cyclohexanone, a strongly oxidizing, ether-soluble substance is formed within a few minutes. This was found to be the oxazirane *(28)* [47]. Its properties are analogous to those of oxaziranes prepared by known methods [2–4]. Oxa-

[40] *E. Müller*, Ber. dtsch. chem. Ges. *47*, 3001 (1914); *H. Staudinger* and *A. Gaule*, Ber. dtsch. chem. Ges. *49*, 1961 (1916); *E. Chinoporos*, Chem. Reviews *63*, 235 (1963).

[41] *E. Schmitz*, Angew. Chem. *73*, 23 (1961).

[42] *R. Breslow*, *C. Yaroslawski*, and *S. Yaroslawski*, Chem. and Ind. *1961*, 1961.

[43] *E. Fahr*, Angew. Chem. *73*, 536 (1961).

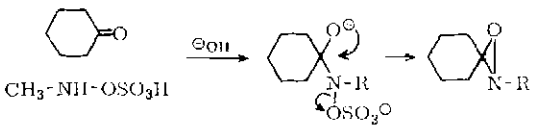
[44] Review on nitrenes: *L. Horner* and *A. Christmann*, Angew. Chem. *75*, 707 (1963); Angew. Chem. internat. Edit. *2*, 599 (1963).

[45] *E. Schmitz* and *R. Ohme*, Angew. Chem. *73*, 807 (1961).

[46] *E. Schmitz*, *R. Ohme*, and *S. Schramm*, unpublished work.

[47] *E. Schmitz*, *R. Ohme*, and *D. Murawski*, Angew. Chem. *73*, 708 (1961).

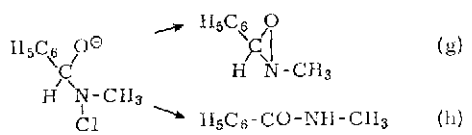
ziranes are also formed from other carbonyl compounds, *e.g.* benzaldehyde. However, the reaction rapidly reaches a limit with increasing size of the *N*-alkyl residue. With cyclohexanone, the yield falls off from 60 % for the *N*-methyl compound *(28)* to 10 % for the *N*-ethyl compound. No oxaziran is formed with *N*-t-butylhydroxylamine-*O*-sulfonic acid. The reason for this behavior becomes clear if the oxaziran ring closure is formulated similarly to the formation of diaziridine.



*(27)* *(28)*, R = $CH_3$

The rear-side attack of the alkoxide oxygen in *(27)* is sterically hindered as the size of the *N*-alkyl residue increases. Thus when R = t-butyl, the leaving group is in the particularly strongly sterically hindered neopentyl position.

The similarity repeatedly observed between the *N*-halogenoamines and the *O*-sulfonic acids of the hydroxylamines suggests that *N*-chloromethylamine should also form oxaziranes with aldehydes. This conjecture was opposed by the observation that benzaldehyde reacts with *N*-chloromethylamine to give *N*-methylbenzamide in 80 % yield [41]. Repetition of this experiment showed that, in addition to the amide, an oxazirane was indeed formed in 15 % yield. Thus, 1,3-elimination to form the oxazirane [Equation (g)] competes with the 1,2-elimination [Equation (h)] to form the amide [47].



(g)

(h)

The yield of oxazirane is tripled on *ortho*-substitution of the benzaldehyde (Table 2). It is possible that the 1,2-elimination is repressed by steric hindrance.

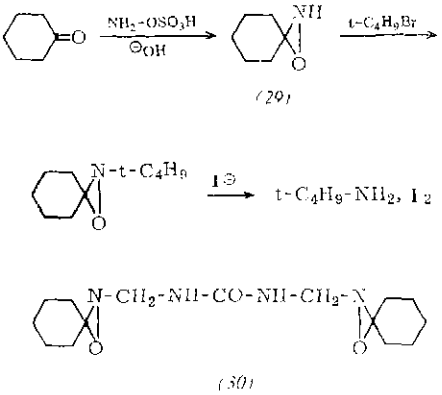
Ketones are more suitable starting materials than aldehydes, since the competition of amide formation is suppressed. Some yields are shown in Table 2. Unfortunately, the synthesis is adversely affected by the sensitivity of the oxazirans to alkalis [3]; the yields with cyclopentanone and simple aliphatic ketones do not exceed 30 %. Once again, the maximum yield is obtained with cyclohexanone. Replacement of *N*-methyl by *N*-ethyl again appreciably reduces the yields.

Table 2. Oxaziranes from carbonyl compounds and *N*-chloroalkylamines

| Carbonyl compound | *N*-Alkyl | Oxazirane yield [%] |
|---|---|---|
| Cyclohexanone | Methyl | 85 |
| 4-Methylcyclohexanone | Methyl | 65 |
| Cyclopentanone | Methyl | 22 |
| Methyl ethyl ketone | Methyl | 30 |
| Acetone | Methyl | 30 |
| Cyclohexanone | Ethyl | 10 |
| Benzaldehyde | Methyl | 15 |
| *o*-Chlorobenzaldehyde | Methyl | 48 |
| *o*-Nitrobenzaldehyde | Methyl | 43 |

### b) Isomeric Oximes with Three-Membered Ring Structures

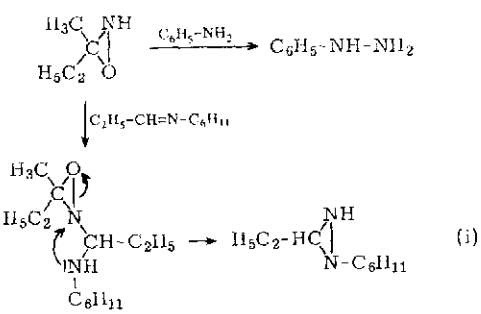
Since alkyl substituents on the nitrogen make oxazirane formation more difficult, it seemed worthwhile to try to omit the alkyl residue completely, and to treat hydroxylamine-*O*-sulfonic acid itself with carbonyl compounds. It was infact possible, with very rapid work, to obtain from cyclohexanone an oxazirane *(29)* unsubstituted on the nitrogen. This is an isomer of cyclohexanone oxime, and is extremely unstable. It yields a crystalline derivative *(30)* with dihydroxymethylurea; its relation to the known oxaziranes is shown by *N*-alkylation with t-butyl bromide.



*(29)*

*(30)*

The isomeric oxime partly duplicates the oxaziranes in its chemical behavior; it oxidizes iodide to iodine; acid hydrolysis yields hydroxylamine. In contrast to the *N*-alkylated compounds, however, the isomeric oximes are strong aminating agents, *e.g.* they convert aniline into phenylhydrazine [48]. The NH group is transferred to Schiff bases to form diaziridines [Equation (i)]. This is an interesting reaction, since the opening of one three-membered ring supplies the energy for closure of a new three-membered ring.



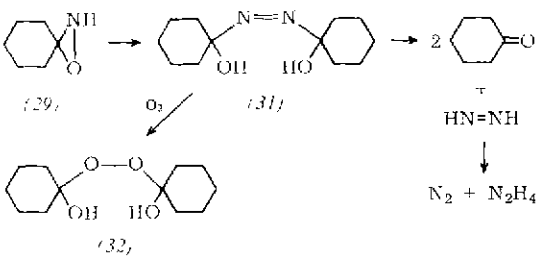
(i)

Pentamethyleneoxazirane *(29)* decomposes almost instantaneously in the presence of alkali, even at room temperature, to cyclohexanone, nitrogen, and hydrazine. Since the three bonds of the nitrogen molecule can hardly be formed in a single reaction step, an intermediate product must occur. This intermediate was isolated in the form of the crystalline azo compound *(31)* [49]. As expected, the azo compound was even less

[48] *E. Schmitz, R. Ohme,* and *S. Schramm,* Z. Chem. *3*, 190 (1963).

[49] *E. Schmitz, R. Ohme,* and *S. Schramm,* Angew. Chem. *75*, 208 (1963); Angew. Chem. internat. Edit. *2*, 157 (1963).

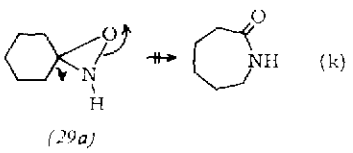
stable than the three-membered ring, for it contains the diimide in a weak hemiacetal like bond. Diimide is liberated from *(31)* even by traces of acid or base, its presence being demonstrated by its hydrogenating action on azobenzene, and by its disproportionation to hydrazine and nitrogen [50].



*(29)* *(31)* *(32)*

Free radical reactions of the azo compound *(31)* have also been observed. A solution of *(31)* in carbon tetrachloride becomes opaque within a few seconds and hydrazine hydrochloride separates. Introduction of oxygen into a solution of *(31)* in benzene results in formation of the peroxide *(32)*, in 80 % yield. The peroxide is obtained in the same yield if crystalline *(31)* is stored for a few days at −15 °C in air.

It was particularly surprising that caprolactam was not formed, even in traces, on thermal decomposition of pentamethyleneoxaziranc *(29)* [Equation (k)]. Attempts to find amides revealed only caproamide *(33)* in about 1 % yield.



(k)

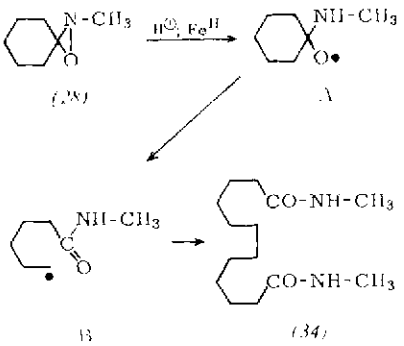
*(29a)*

$CH_3$-$(CH_2)_4$-$CONH_2$

*(33)*

This may again be due to stereoelectronic factors. The three-membered ring in *(29a)* and the two bonds projecting outwards from its carbon atom lie in mutually perpendicular planes. There is thus no possibility of mutual assistance of O–N bond cleavage and migration of the bond from the carbon to the nitrogen [arrows in *(29a)*]. The formation of *(33)*, which probably occurs by way of free radicals, shows very clearly the reluctance of *(29a)* to undergo the stereoelectronically unfavorable rearrangement to caprolactam.

The view that the formation of *(33)* involves opening of the three-membered ring by a one-electron reduction, followed by opening of the six-membered ring, also by a free radical mechanism, is supported by the following experiment: If 2-methyl-3,3-pentamethyleneoxaziranc *(28)* is treated with an iron(II) salt, the bis-*N*-methylamide of a $C_{12}$-dicarboxylic acid *(34)* is obtained in 50 % yield. By analogy with the modes of decomposition of simple oxaziranes [3] and of cyclohexanone peroxides [51], it is probable that the radicals A and B take part in this reaction.



*(28)* A B *(34)*

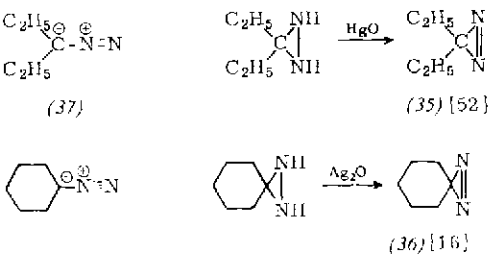
Since *(28)* can be obtained in 85 % yield from cyclohexanone, methylamine, and chlorine, this points to a simple route for the preparation of the $C_{12}$-dicarboxylic acid.

## Cyclic Diazo Compounds (Diazirines)

In the last three years, cyclic diazo compounds with three-membered rings (diazirines) have been added to the ranks of the well-known aliphatic diazo compounds. These became available before their existence was even suspected. Although the three-membered ring structure had previously been widely discussed, it was only in its capacity as a tentative structure for the known diazo compounds. The idea that, in addition to the linear aliphatic diazo compounds, cyclic isomers might exist as a distinct class of compounds had never arisen. The first publications on the existence of cyclic diazo compounds [16,52,57a] were therefore received with some doubt.

Within a year, not only had the three-membered ring structure been proved [17,53], but it has also been shown that the cyclic isomers *(35)* and *(36)* were often more readily available than the linear aliphatic diazo compounds. Whereas, for example, 3-diazopentane *(37)* has never been described, and diazocyclohexane is only known in solution [54], the cyclic isomers are obtained in good yield within a few minutes by dehydrogenation of the saturated three-membered rings. This new class of compounds, in the form of these two examples, was discovered by *Paulsen* [52] and by *Schmitz* and *Ohme* [16,55].

Other members of the class were prepared from acetone, methyl ethyl ketone, 4-heptanone, acetophenone, cyclo-



*(37)* *(35)* [52]

*(36)* [16]

[50] *S. Hünig, H. R. Müller,* and *W. Thier,* Angew. Chem. *75*, 298 (1963); Angew. Chem. internat. Edit. *2*, 214 (1963).

[51] *E. G. E. Hawkins,* J. chem. Soc. (London) *1955*, 3463.

[52] *S. R. Paulsen,* Angew. Chem. *72*, 781 (1960).

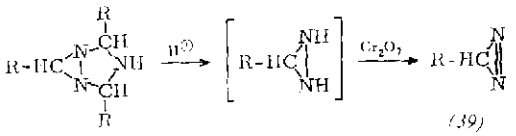
[53a] *E. Schmitz* and *R. Ohme,* Kernenergie *5*, 357 (1962).

[53b] *J. Pierce* and *V. Dobyns,* J. Amer. chem. Soc. *84*, 2651 (1962).

[54] *K. Heyns, A. Heins,* and *G. Seemann,* Liebigs Ann. Chem. *634*, 49 (1960).

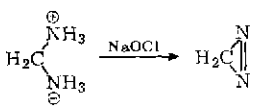
[55] *E. Schmitz* and *R. Ohme,* Angew. Chem. *73*, 115 (1961).

pentanone, and cycloheptanone [10]. Cyclic diazo compounds with primary alkyl residues can be prepared from aldehydes by a two-stage procedure [56]. Intermediates in this process are the bicyclic diaziridines *(38)*, whose five-membered rings can be easily split off by hydrolysis, without damage to the three-membered ring. Hydrolysis in the presence of dichromate yields the cyclic diazo compounds *(39)* directly in 70–95 % yield.



*(38)* *(39)*

The parent compound of this class [57b] is prepared by adding methylenediammonium sulfate *(40)* [58] to hypochlorite solution. This results in neutralization, *N*-chlorination, ring-closure, and dehydrogenation to cyclodiazomethane. The yield is about 30 %.



*(40)* *(41)*

A second synthesis of *(41)* was discovered recently; in it difluoramine is treated with t-butylazomethine [59].

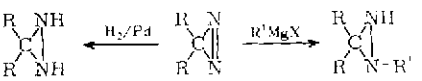
$$CH_2{=}N{-}t.C_4H_9 + HNF_2 \rightarrow (41)$$

A few months after the discovery of diazirine *(41)*, measurements of its bond lengths and bond angles were already available, so that there is no doubt about its three-membered ring structure [53b], particularly since the two nitrogen atoms have been shown to be equivalent by labelling with $^{15}N$ [17].

The preparation of cyclodiazomethane puts an end to the discussions regarding the three-membered ring structure of the "classical" aliphatic diazo compounds. The cyclic diazo compounds differ so markedly from the linear compounds that confusion between the two types is impossible. In certain respects the cyclic diazo compounds do in fact appear to be the exact opposites of their linear isomers.

For instance, the linear aliphatic diazo compounds absorb in the visible region, but the cyclic compounds are colorless. The latter absorb only below 360 mμ [60]. Aliphatic diazo compounds are extremely sensitive to acids, whereas the cyclic isomers are resistent to even strong mineral acids, and are only decomposed by 80–90 % sulfuric acid. The greater part of the nitrogen then appears in molecular form, but considerable quantities of hydrazine also occur, *e.g.* about 0.15 mole in the decomposition of pentamethylenediazirine *(36)* [61].

In the reactions of diazomethane, almost without exception a new bond is attached to the carbon atom. With the cyclic compounds, on the other hand, the view of *Thiele* [62] has been confirmed. He disputed the three-membered ring form of diazomethane on the grounds that addition to the N=N double bond would be expected in the case of a cyclic diazomethane molecule. In fact, both catalytically activated hydrogen [16] and Grignard reagents [34] add onto the double bond. Both reactions give rise to diaziridines, thus providing proof of the three-membered ring structure of diazirines.



The linear aliphatic diazo compounds are among the most reactive substances known in organic chemistry. They mostly behave as nucleophilic reagents. The cyclic isomers, on the other hand, are surprisingly inert. In the few reactions which are known at present, they exhibit electrophilic character. The reaction with Grignard reagents mentioned above, together with hydrolysis of the resulting 1-alkyldiaziridines, provides an efficient synthesis for alkylhydrazines.

Linear aliphatic diazo compounds are stabilized by substituents which can assume a partial negative charge from their α-carbon atom: thus, diazoketones are more stable than unsubstituted aliphatic diazo compounds. Attempts to synthetize a diazoketone with a three-membered ring structure [63] indicated that the cyclic diazo group is destabilized by an adjacent keto group.

However, the two types of diazo compounds have one property in common: they both explode violently on overheating. The diazirines appear to be rather more stable than the linear isomers; the activation energy for the decomposition of dimethyldiazirine was found to be 33.165 kcal/mole [64].

The elimination of nitrogen from diazirine should lead to carbene [65], and from substituted diazirines to alkylcarbenes [66, 67]. The formation of carbenes can be easily demonstrated. Carbenes are characterized by their tendency to attack a β-C-H bond and form cyclopropanes. Cyclodiazoneopentane *(42)* was thermally decomposed to give 80 % dimethylcyclopropane, and cyclodiazoisobutane yielded 40 % methylcyclopropane. Hexamethylenediazirine *(43)* gave norcarane *(44)* plus cycloheptene [67]. The yields correspond to those of the

[56] *E. Schmitz* and *R. Ohme*, Chem. Ber. *95*, 795 (1962).

[57a] *E. Schmitz* and *R. Ohme*, Tetrahedron Letters *1961*, 612.

[57b] *R. Ohme* and *E. Schmitz*, Chem. Ber. *97*, 297 (1964).

[58] *P. Knudsen*, Ber. dtsch. chem. Ges. *47*, 2698 (1914).

[59] *W. H. Graham*, J. Amer. chem. Soc. *84*, 1063 (1962).

[60] *J. A. Merritt*, Canad. J. Physics *40*, 1683 (1962); *A. Lau*, *E. Schmitz*, and *R. Ohme*, Z. physik. Chem. *223*, 417 (1963).

[61] *E. Schmitz* and *G. Schneider*, unpublished work.

[62] *J. Thiele*, Ber. dtsch. chem. Ges. *44*, 2522 (1911).

[63] *E. Schmitz* and *A. Stark*, unpublished work.

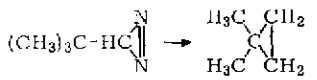
[64] *H. M. Frey* and *I. D. R. Stevens*, J. chem. Soc. (London) *1962*, 3865.

[65] *H. M. Frey* and *I. D. R. Stevens*, Proc. chem. Soc. (London) *1962*, 79.

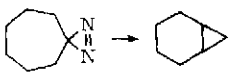
[66] *H. M. Frey* and *I. D. R. Stevens*, J. Amer. chem. Soc. *84*, 2647 (1962).

[67] *E. Schmitz*, *D. Habisch*, and *A. Stark*, Angew. Chem. *75*, 723 (1953); Angew. Chem. internat. Edit. *2*, 548 (1963).

best known sources of carbenes [68]. The inertness of the diazirines may be advantageously applied in reactions requiring carbenes. Thus, for example, in the presence of compounds which react with diazomethane,



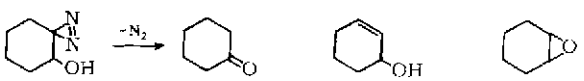
*(42)*



*(43)* *(44)*

the latter cannot be used as a source of carbene but diazirine can. Carbenes are also formed from diazirines in the absence of strong bases, but these must be present in most other reactions yielding carbenes.

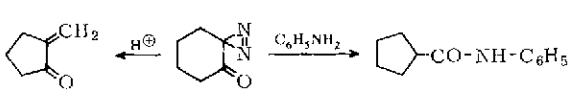
The thermal decomposition of α-hydroxypentamethylenediazirine *(45)* can be formulated to proceed via an α-hydroxycarbene. Cyclohexanone, cyclohexenol, and cyclohexene epoxide were found as the stable end-products [63].



*(45)* 75% 20% 5%

The appreciable sensitivity of *(45)* towards acid was remarkable; 2N sulfuric acid was sufficient to split off its nitrogen quantitatively within a few minutes at 80 °C. The only reaction product was cyclohexanone.

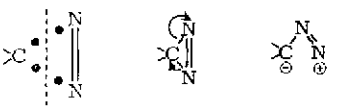
A compound *(46)*, prepared from hydroxydiazirine *(45)* by oxidation with t-butyl hypochlorite, is even more sensitive to acids. Nitrogen is eliminated by dilute acid within a few seconds, even at room temperature. A suspicion that this is actually a linear diazo compound could not be confirmed: its reaction with Grignard reagent yielded a diaziridine, recognized by its ability to oxidize iodide [63].



*(47)* *(46)* *(48)*

Decomposition of the cyclic diazo ketone *(46)* with acid results in ring contraction, with formation of methylenecyclopentanone *(47)*; the dinitrophenylhydrazone of *(47)* was identical with an authentic sample [69]. Thermal elimination of nitrogen from *(46)* takes place even at 40 °C and results a Wolf rearrangement: in the presence of aniline, cyclopentanecarboxanilide *(48)* is formed.

It appears to be interesting for the mechanism of the elimination of nitrogen that the introduction of electron-attracting groups reduces the stability of the diazirines by several orders of magnitude. The α-ketodiazirine *(46)* decomposes in solvents whose protonating capacity is at least $10^6$ times smaller than that of the 80% sulfuric acid required to decompose pentamethylenediazirine *(36)*. Compound *(46)* undergoes thermal decomposition slightly above room temperature, whereas diazirines without additional substituents are only appreciably decomposed above 150 °C. Assuming that a general principle holds good in these cases, some of the possible mechanisms can be neglected.



*(49)* *(50)* *(51)*

If the two C–N bonds are broken homolytically *(49)* as in the case of the aliphatic azo compounds [70], the electron distribution on the carbon atom in the transition state must tend towards a sextet. However, an electron deficiency cannot be stabilized by a withdrawal of electrons.

A simultaneous shift of two electron pairs in the directions of the arrows drawn in *(50)* is equally improbable. Substituent effects of the order of magnitude mentioned above point to a transition state with extensive charge separation. A transition state with a negative charge accumulation on the carbon atom would be stabilized, and hence more easily achieved, as a result of withdrawal of electrons. Thus, the two electron displacements shown by the arrows in *(50)* must be non-synchronous, the first step being the displacement of a pair of bonding electrons to the carbon. This gives rise to *(51)*, the carbanionic limiting structure of an aliphatic diazo compound, which however lacks the linear arrangement of atoms necessary for resonance stabilization.

Further investigations may possibly lead to the discovery of a "no-man's-land" between the two distinct classes of aliphatic diazo compounds known today [71].

*I am sincerely grateful to my colleagues Dr. R. Ohme, D. Murawski, D. Habisch, R. D. Schmidt, S. Schramm, K. Schinkowski, and A. Stark for their contributions to these results; particular attention should be drawn to Dr. Ohme's share. My appreciation is also due to my technical assistants E. Beyer, Ch. Kuck, I. Kapsch, and U. Pieper. I would also like to thank Prof. A. Rieche for his interest and for his assistance in the present study.*

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[68] Recent reviews on carbenes: *Ph. Miginiac*, Bull. Soc. chim. France *1962*, 2000; *E. Chinoporos*, Chem. Reviews *63*, 235 (1963).

[69] *M. N. Kolossov, M. G. Karapetyan*, and *V. Y. Sodionov*, Zh. obshch. Khim. *28*, 2068 (1958).

[70] For example, *J. B. Levy* and *B. K. W. Copeland*, J. Amer. chem. Soc. *82*, 5314 (1960).

[71] Recently *C. G. Overberger* and *J.-P. Anselme* [20c] attempted the preparation of diphenyldiazirine, but could establish only the formation of diphenyldiazomethane. They assumed the intermediate formation of the cyclic diazo compound.

# Reactions of Sodium Hydrazide with Organic Compounds

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*The reactions of sodium hydrazide with organic compounds are reviewed for the first time. The great variety of these reactions is mainly due to the extraordinary ease with which the hydrazide ion adds onto unsaturated compounds, usually to form unstable adducts that achieve stability in various ways.*

1. Addition Reactions
   a) With Alkenes
   b) With Alkynes
   c) With Nitriles
   d) Carbonyl Compounds
2. Substitution Reactions
   a) With Aromatic Heterocycles
   b) With Aryl Halides
3. Reduction Reactions
   a) Reduction of Unsaturated and Aromatic Compounds
   b) Reductive Hydrazination
   c) Reductive Dehalogenation
4. Cleavage Reactions
   a) With Alkenes
   b) With Azomethines
   c) With *N,N*-Dialkylamides
   d) With Esters
   e) With Ethers
5. Dehydrogenative Hydrazination of Dienes
6. Occurrence of Free Radicals
7. Future Developments

## Introduction

Sodium hydrazide is a pale yellow crystalline compound that explodes violently on reaction with oxygen or on heating above 100 °C. It was first prepared in pure form in 1915 by *Schlenk* and *Weichselfelder* [1], but was then neglected for more than four decades. Since the hydrazide ion is much more nucleophilic than hydrazine, it seemed likely to have interesting synthetic possibilities; we have been studying the reactions of sodium hydrazide with organic compounds since 1958, and have discovered many that were completely unexpected.

The reactions described below were carried out in a well-screened splinter-proof apparatus [2]. The sodium hydrazide was not isolated, but was used as a suspension in ether, diisopropyl ether, or benzene; it was prepared by the action of sodamide [3] or sodium hydride [4] on anhydrous hydrazine in an atmosphere of nitrogen [5] at 20 °C, according to the equation

$$NaR + H_2N{-}NH_2 \rightarrow NaNH{-}NH_2 + HR \qquad (R = NH_2 \text{ or } H)$$

[1] *W. Schlenk* and *Th. Weichselfelder*, Ber. dtsch. chem. Ges. *48*, 669 (1915).

[2] *Th. Kauffmann*, *Ch. Kosel*, and *D. Wolf*, Chem. Ber. *95*, 1540 (1962).

[3] *T. W. B. Welsh*, J. Amer. chem. Soc. *37*, 497 (1915).

[4] *Ch. Kosel*, Ph. D. Thesis, Technische Hochschule, Darmstadt 1962.

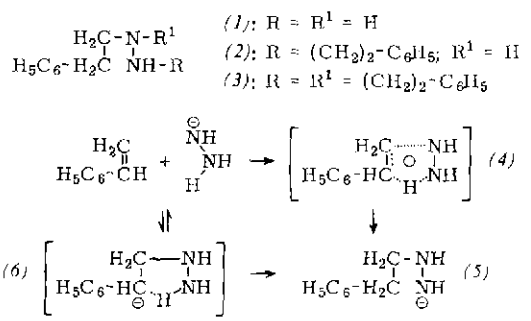
[5] The method of preparation used by *Schlenk* and *Weichselfelder* ($Na + H_2N{-}NH_2$) [1] often leads to explosions even when oxygen is strictly excluded.

## 1. Addition Reactions

### a) With Alkenes

Sodium hydrazide does not attack isolated double bonds, apart from those in which the bond angle is strained [6]. On the other hand, it adds onto C=C double bonds that are conjugated with a phenyl residue or another C=C double bond.

Styrene adds on sodium hydrazide in ether very rapidly even at 0 °C. The sodium derivatives of the bases *(1)* to *(3)* are formed in successive stages; of these, *(1)* can be isolated as the main product by carrying out the reaction in the presence of much free hydrazine, and *(2)* by the use of excess styrene [2] (cf. Table 1).




[6] Bicyclo[2,2,1]hepta-1,5-diene adds on sodium hydrazide slowly at 40 °C [7]. Other olefins with strained double bonds have not yet been investigated.

We ascribe the surprising [8] ease of hydrazide addition and the complete lack of anionic polymerization of styrene to a one-stage mechanism via transition state *(4)* or a two-stage mechanism via intermediate *(6)* in which a hydrogen atom from the uncharged nitrogen atom of the hydrazide ion participates. In conformity with this mechanism, sodium methylhydrazide (probably a mixture of sodium *N'*-methylhydrazide and sodium *N*-methylhydrazide, cf. Section 4a) and sodium *N,N'*-dimethylhydrazide, whose anions, like that of sodium hydrazide, have a hydrogen atom on the uncharged nitrogen atom, also add onto styrene rapidly at 0 °C, whereas sodium *N,N*-dimethylhydrazide and sodium trimethylhydrazide, which have no hydrogen atom on the uncharged nitrogen atom, do not react in this way [2, 9].

Only a catalytic amount of sodium hydrazide need be present for the reaction of styrene with sodium hydrazide plus hydrazine to give phenethylhydrazine *(1)*. Apparently it is continually reformed by metal-hydrogen exchange between the sodium derivative of *(5)* and hydrazine.

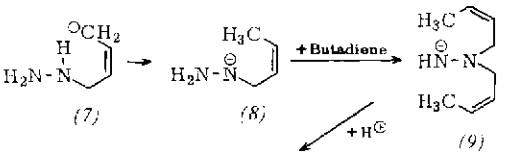
The styrene derivatives numbered 2 to 6 in Table 1 also add on sodium hydrazide in ether at 0 °C but α-benzylstyrene (metalation) and α,α-dimethylstyrene do not. In experiments 2–6, reaction almost ceases after formation of the monosubstituted hydrazine under conditions [2] under which styrene itself gives a mixture of the bases *(1)–(3)*. Like styrene, alkenes that have a double bond allylic to an aromatic ring (allylbenzene, 1,4-dihydronaphthalene) add on the hydrazide ion in the α-position. Probably the strongly basic hydrazide displaces the double bond into conjugation with the ring before addition occurs.

Table 1. Addition of hydrazide onto olefins in ether [a].

| Expt. | Olefin | Product | Yield [%] |
|---|---|---|---|
| 1 | Styrene | Phenethylhydrazine *(1)* | 61 |
| | | or *N,N'*-diphenethylhydrazine *(2)* | 83 |
| 2 | β-Methylstyrene | 1-Hydrazino-2-phenylpropane | 52 |
| 3 | α-Methylstyrene | 2-Hydrazino-1-phenylpropane | 62 |
| 4 | Anethole | 2-Hydrazino-1-(4-methoxyphenyl)propane | 65 |
| 5 | Isoeugenol | 2-Hydrazino-(4-hydroxy-3-methoxyphenyl)propane | 34 |
| 6 | 1,2-Dihydronaphthalene | 2-Hydrazino-1,2,3,4-tetrahydronaphthalene | 82 |
| 7 | 1,4-Dihydronaphthalene | | 81 |
| 8 | Allylbenzene | 2-Hydrazino-1-phenylpropane | 59 |

[a] Experiments 4 and 5 were carried out at 35 °C, the others at about 0 °C.

Butadiene also adds on sodium hydrazide in ether at 0 °C. In addition to nitrogenous polymeric products, up to 50 % *N,N*-di-*trans*-crotylhydrazine *(10)* can be isolated [4] from the reaction mixture after hydrolysis with water. The fact that the disubstituted hydrazine that is formed is unsymmetrical and not, as in the case of styrene (see above), symmetrical may be due to prototropic rearrangement of the mesomeric primary adduct *(7)* via a six-membered ring to the hydrazide ion *(8)*, which reacts with more butadiene to give *(9)*. The *trans*-configuration (infrared spectrum) of *(10)*, which is contrary to this explanation, may occur on subsequent isomerization.




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

*(10)* $H_2N\text{-}N(CH_2\text{-}CH{=}CH\text{-}CH_3)_2$

The other 1,3-dienes studied [10] react with sodium hydrazide in ether or benzene only in the presence of free hydrazine, but here, as will be shown in Section 5, hydrazide addition is always accompanied by dehydrogenation.

### b) With Alkynes

Reactions between sodium hydrazide and alkynes have been little studied. As might be expected, compounds with terminal triple bonds are merely metalated. The isolated triple bond of stearolic acid does not add on sodium hydrazide [11]. On the other hand, tolane takes up hydrazide smoothly in ether at 0 °C [9]. The hydrazone *(11)* is formed in 78 % yield after hydrolysis. One hydrogen atom on the uncharged nitrogen atom of the hydrazide ion apparently also plays an important part in this addition, since sodium methylhydrazide and sodium *N,N'*-dimethylhydrazide also add onto tolane in benzene/ether at 0 °C, whereas sodium *N,N*-dimethylhydrazide and sodium trimethylhydrazide, which do not have a hydrogen atom on the uncharged nitrogen, do not add on even at 50 °C [12].

$$\begin{matrix} & & N\text{-}NH_2 \\ & & \| \\ H_5C_6\text{-} & C & \text{-}CH_2\text{-}C_6H_5 \end{matrix} \quad (11)$$

### c) With Nitriles

The successive action of sodium hydrazide (at 0–20 °C) and water on nitriles produces amidrazones *(12)* [13] in good yields. These compounds are extremely useful for the synthesis of heterocyclic systems but have been

[7] *Th. Kauffmann*, unpublished work.

[8] Sodamide behaves differently, cf. [2].

[9] *Th. Kauffmann, H. Henkler, Ch. Kosel, W. Schoeneck*, and *D. Wolf*, Angew. Chem. *72*, 752 (1960).

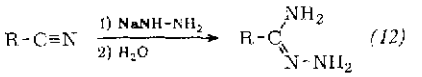
[10] *Th. Kauffmann, H. Müller*, and *Ch. Kosel*, Angew. Chem. *74*, 248 (1962); Angew. Chem. internat. Edit. *1*, 214 (1962); *Th. Kauffmann* and *H. Müller*, Chem. Ber. *96*, 2206 (1963).

[11] *J. Schulz* and *Th. Kauffmann*, unpublished work.

[12] *D. Wolf*, Diploma Thesis, Technische Hochschule Darmstadt, 1961.

[13] *Th. Kauffmann, S. Spaude*, and *D. Wolf*, Angew. Chem. *75*, 344 (1963); Angew. Chem. internat. Edit. *2*, 217 (1963).

comparatively inaccessible [14] until recently, as is evidenced by the fact that in the aliphatic series only acemidtarazone [15] has been described.

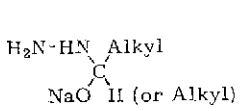


*(12)*

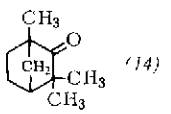
The following were prepared: acetamidrazone (63 %), capramidrazone (87 %), lauramidrazone (85 %), myristamidrazone (100 %), hexadecanecarboxamidrazone (93 %), stearamidrazone (74 %), phenylacetamidrazone (78 %), benzamidrazone (99 %), *o*-hydroxybenzamidrazone (100 %), α-naphthoamidrazone (57 %), and β-naphthoamidrazone (88 %).

### d) With Carbonyl Compounds

Reaction between aliphatic aldehydes or unbranched aliphatic ketones and sodium hydrazide in ether at 20 °C gives colorless precipitates, presumably containing the adducts *(13)*, which when hydrolysed with water with ice cooling give hydrazones [7, 16] in good yield. There is practically no formation of azines, as in the corresponding reactions with hydrazine.



*(13)*



*(14)*

It was not found possible to convert ketones, such as those listed below – which react with hydrazine only at elevated temperatures or not at all – smoothly into their hydrazones using sodium hydrazide, a reaction that would have been of interest in connexion with the *Wolff-Kishner* reduction. The major part of the starting materials were recovered unchanged in the reactions of sodium hydrazide with acetophenone [17] (1 h at 22 °C), t-butyl phenyl ketone (1 h at 60 °C), camphor (1 h at 50 °C), and fenchone *(14)* (4 h at 35 °C); there was little or no evidence for the formation of an intermediate [7].

In the case of enolizable ketones (acetophenone, camphor), an enolate could be formed. With non-enolizable ketones (t-butyl phenyl ketone, fenchone), the failure to form hydrazones can be attributed to steric hindrance of hydrazide addition or to the elimination of hydrazine instead of water during hydrolysis of the adduct.

[14] The best method of preparation hitherto involved the reaction of imido esters (imino ethers) with hydrazine; cf. *A. Pinner*, Liebigs Ann. Chem. *297*, 221 (1897), and [15].

[15] *W. Oberhummer*, Monatsh. Chem. *63*, 285 (1933).

[16] *G. Ruckelshauss*, Diploma Thesis, Technische Hochschule Darmstadt 1964. Hydrazones of aliphatic aldehydes dimerize to 3,6-dialkylhexahydro-*sym*-tetrazines: *Th. Kauffmann, G. Ruckelshauss*, and *J. Schulz*, Angew. Chem. *75*, 1204 (1963); Angew. Chem. internat. Edit. *3*, 63 (1964).

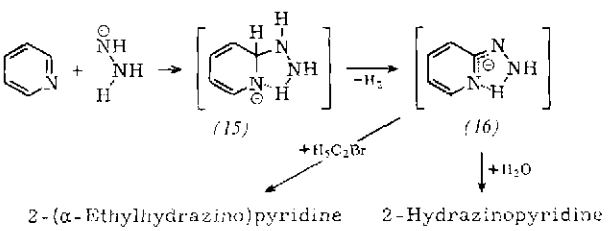
[17] To obtain the corresponding hydrazones, acetophenone must be heated with hydrazine hydrate at 80–100 °C for 3 days, and benzophenone (mentioned in Section 6) in an autoclave at 150 °C for 6 h; cf. *Th. Curtius* et al., J. prakt. Chem. [2] *44*, 540, 194 (1891); *H. Staudinger* et al., Ber. dtsch. chem. Ges. *49*, 1932 (1916).

## 2. Substitution Reactions

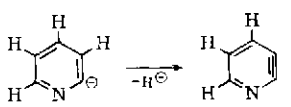
### a) With Aromatic Nitrogen Heterocycles

#### α) *Preparation of Hydrazino Compounds*

Pyridine can be converted directly into 2-hydrazinopyridine by treatment with sodium hydrazide/hydrazine and subsequent hydrolysis with water [18]. Two stages can be clearly distinguished in the hydrazination reaction at room temperature: a rapid first phase, characterized by evolution of heat and the formation of a brown coloration, is succeeded by a second, slow phase, which can be followed by means of the evolution of hydrogen that continues for several hours. The mechanism of this substitution is thus probably analogous to that suggested by *Ziegler* and *Zeiser* [19] for Tschitschibabin amination via the adduct *(15)*:




The aryne mechanism involving the deprotonated pyridine *(17)* and 2,3-dehydropyridine *(18)* [20] recently postulated [21] for the Tschitschibabin amination is highly unlikely. This mechanism demands that, owing to the lower proton affinities of their anions, sodium hydrazide and sodium methylhydrazide should substitute pyridine less readily than sodium *N,N*-dimethylhydrazide or sodamide. The reverse is in fact the case: sodium hydrazide and sodium methylhydrazide react in benzene even at 10–20 °C, whereas sodium *N,N*-dimethylhydrazide and sodamide react only at about 80 °C. If, however, one assumes that the preliminary step in the substitution reaction is adduct formation, the higher reactivities of sodium hydrazide and sodium methylhydrazide are readily understood, since these hydrazides are also characterized by their great tendency to form adducts with styrene, tolane, and *p*-fluorotoluene [cf. Sections 1a), 1b), and 2b)].



*(17)* *(18)*

As can be seen from Table 2, substitution of pyridine by methyl in the 4-position (4-methyl-, 2,4-dimethylpyridine) has a favorable effect on the yield of hydrazination product. This is even more marked in the quinoline series. Almost no 2-hydrazinoquinoline is

[18] *Th. Kauffmann, J. Hansen, Ch. Kosel*, and *W. Schoeneck*, Liebigs Ann. Chem. *656*, 103 (1962).

[19] *K. Ziegler* and *H. Zeiser*, Ber. dtsch. chem. Ges. *63*, 1848 (1930).

[20] It is not certain whether 2,3-dehydropyridine [*R. J. Martens* and *H. J. den Hertog*, Tetrahedron Letters *1962*, 643] adds on bases preferentially at C-2 or C-3; cf. also *Th. Kauffmann* and *F.-P. Boettcher*, Chem. Ber. *95*, 1529 (1962).

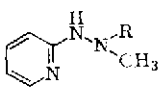
[21] *L. S. Levitt* and *B. W. Levitt*, Chem. and Ind. *1963*, 1621.

formed in the reaction between unsubstituted quinoline and sodium hydrazide/hydrazine, owing to reduction reactions [22] that are apparently initiated by addition of the hydrazide ion in the γ-position [cf. the reduction of quinaldine, Section 3a)]. Isoquinoline, in which the position *para* to the nitrogen is occupied, gives the 1-hydrazino compound in the expected good yield.

Table 2. Hydrazination to give hydrazino compounds.

| Heterocycle | α-Hydrazino compound Yield [%] |
|---|---|
| Pyridine | 36 |
| 2-Methylpyridine | 25 |
| 4-Methylpyridine | 62 |
| 2,4-Dimethylpyridine | 58 |
| Quinoline | 0.5 |
| 4-Methylquinoline | 76 |
| Isoquinoline | 69 (1-hydrazinoisoquinoline) |

Similar hydrazination of pyridine with sodium methylhydrazide gives *(19)*, and with sodium *N,N*-dimethylhydrazide gives *(20)* and *(21)* [18,23].



*(19)*: R = H (26%)
*(20)*: R = $CH_3$ (33%)

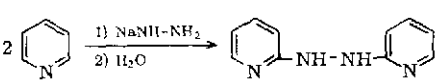


*(21)* (2%)

Compounds of the 2-hydrazinopyridine type are of interest, since they react with a large number of reagents to undergo ring-closure reactions similar to those of *o*-phenylenediamine [24].

### β) *Preparation of Hydrazino Compounds*

If no free hydrazine is present, the reaction of sodium hydrazide with aromatic nitrogenous heterocycles produces hydrazo compounds [11,25], as shown below for pyridine.



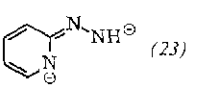
*(22)*

The yields (Table 3) generally correspond to those obtained in the synthesis of hydrazino compounds. Quinoline can be hydrazinated to the hydrazo derivative in far better yield than to the hydrazino compound; this is probably due to the much weaker reducing properties of sodium hydrazide compared with the sodium hydrazide/hydrazine system [cf. Section 2a.α)].

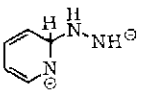
Table 3. Hydrazination to give hydrazo compounds.

| Heterocycle | α,α'-Hydrazo compound Yield [%] |
|---|---|
| Pyridine | 20 |
| 4-Methylpyridine | 64 |
| Quinoline | 45 |
| 4-Methylquinoline | 62 |
| Isoquinoline | 64 (1,1'-hydrazodiisoquinoline) |

It is not clear how the pyridine residue becomes attached during the synthesis of 2,2'-hydrazodipyridine (*N,N'*-di-α-pyridylhydrazine) *(22)*. The anion *(16)*, which can be obtained from 2-hydrazinopyridine and 1 mole of sodamide, and which is presumably the primary product of the reaction of pyridine with sodium hydrazide, does not react with pyridine. If, on the other hand, 2-hydrazinopyridine is treated with 2 moles of sodamide, and then heated with pyridine at 80 °C for 7 h, 2,2'-hydrazodipyridine is formed in 19 % yield [4]. The latter might therefore be formed in the reaction of sodium hydrazide with pyridine through the dianion *(23)*. Linking of the two pyridine rings via the deprotonated intermediate *(24)* formed from the adduct *(15)* is a further possibility.



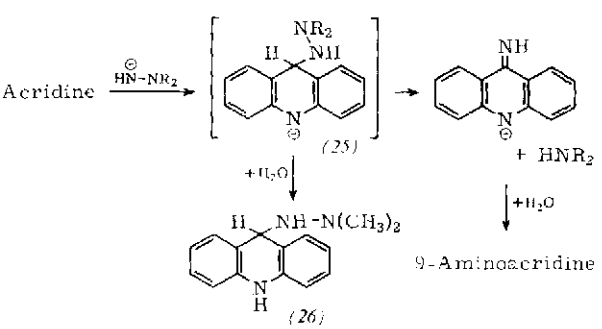
*(23)*



*(24)*

### γ) *Preparation of Amino Compounds*

Although sodamide converts acridine smoothly into 9-aminoacridine [26], corresponding hydrazinations with sodium hydrazide/hydrazine or with sodium hydrazide alone to give 9-hydrazinoacridine or 9,9'-hydrazodiacridine do not occur. 9,10-Dihydroacridine is formed almost quantitatively with sodium hydrazide/hydrazine [27], whereas with sodium hydrazide in the absence of hydrazine, 9-aminoacridine is formed with evolution of ammonia [28]. The formation of 9-aminoacridine must be assumed to proceed via *(25)*, R=H, since 9-aminoacridine (89 %) is also formed, with elimination of dimethylamine, by the action of sodium *N,N*-dimethylhydrazide on acridine. The fact that the adduct *(25)* is an intermediate in this reaction is confirmed by the isolation of the hydrolysis product *(26)*, which in this series is surprisingly stable [28].



In the hydrazinations described above, the adducts are stabilized by dehydrogenation, whereas in this case the

[22] *W. Schoeneck*, Diploma Thesis, Technische Hochschule Darmstadt 1959.

[23] *Th. Kauffmann* and *W. Schoeneck*, Angew. Chem. *71*, 285 (1959).

[24] Cf. *Th. Kauffmann* and *H. Marhan*, Chem. Ber. *96*, 2519 (1963); *K. Vogt*, Ph. D. Thesis, Technische Hochschule Darmstadt 1961.

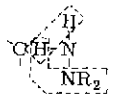
[25] *Th. Kauffmann, H. Hacker*, and *Ch. Kosel*, Z. Naturforsch. *14b*, 602 (1959).

[26] *K. Bauer*, Chem. Ber. *83*, 10 (1950).

[27] *Th. Kauffmann, H. Hacker, Ch. Kosel*, and *W. Schoeneck*, Angew. Chem. *72*, 918 (1960).

[28] *Th. Kauffmann* and *H. Hacker*, Chem. Ber. *95*, 2485 (1962).

second mode of stabilization *(27)* is realized, namely loss of $NH_3$ or dimethylamine [29].



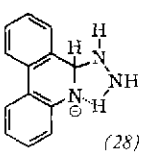
*(27)*, R = H or $CH_3$

It will be seen from Table 4 that amino compounds are also formed on interaction of sodium hydrazide or *N,N*-dimethylhydrazide and other heterocycles; with quinazoline, both an amino group and a hydrazino group are introduced into the molecule [30].

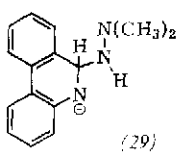
Table 4. Amination of heterocycles with sodium hydrazide and with sodium *N,N*-dimethylhydrazide (yields in parentheses)

| Heterocycle | Amination product | Yield [%] |
|---|---|---|
| Acridine | 9-aminoacridine | 65 (89) |
| Phenanthridine | 9-aminophenanthridine | 2 (85) |
| Quinazoline | 4-amino-2-hydrazinoquinazoline | 16 |
| 2-Methylquinazoline | 4-amino-2-methylquinazoline | 25 |

The yield of 9-amino compound from the reaction between phenanthridine and sodium hydrazide is low (Table 4) because at the temperature of the reaction (60 °C) the adduct *(28)*, in contrast to the adduct *(29)* from sodium *N,N*-dimethylhydrazide, is quite stable. This difference in stabilities indicates that, like most thermal eliminations [31], the elimination of $NH_3$ or amine here is a *cis*-elimination, and therefore occurs only when the β-nitrogen of the hydrazine can approach very close to the hydrogen atom linked to the hydrazinated C atom. In *(28)* this approach may be hindered by the formation of a hydrogen bond with the ring nitrogen.



*(28)*



*(29)*

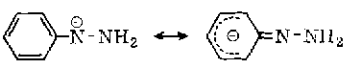
### b) With Aryl Halides

Nearly all the halogeno compounds that have been treated with sodium hydrazide are aromatic, and with these the halogen is replaced either by a hydrazino group or by hydrogen. The latter reaction is discussed in Section 3c).

#### α) *Substitution by an Aryne Mechanism*

*p*-Bromotoluene in ether reacts rapidly with sodium hydrazide/hydrazine even at 0 °C, whereas *p*-chlorotoluene does not react until about 30 °C. Since *m*-tolylhydrazine is always formed alongside *p*-tolylhydrazine, the reaction proceeds via 3,4-dehydrotoluene. The formation of ditolylhydrazines (see below) is further evidence for this. Under similar conditions (molar ratios of halogeno compound:sodium hydrazide:hydrazine = 1:2:4 in ether at 35 °C for 90 min), the ratios of *p*-: *m*-tolylhydrazines are 42:58 and 40:60, respectively [11,32], *i.e.* close to the ratio (38:62) of *p*-: *m*-toluidines produced in the reaction between *p*-chlorotoluene and sodamide in liquid ammonia [33].

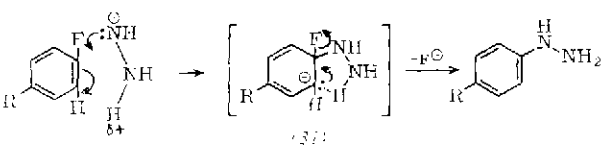
The reactions of bromo- and chlorobenzene with sodium hydrazide/hydrazine (molecular ratios 1:3:15 in ether at 35 °C for 90 min) give not only phenylhydrazine (*ca.* 65 %) but also a mixture of *N,N*- and *N,N'*-diphenylhydrazine (*ca.* 25 %). Since sodium phenylhydrazide [34] does not react with chloro- or bromobenzene [35] under the conditions used, the two diphenylhydrazines can only arise by addition of sodium phenylhydrazide onto dehydrobenzene (benzyne) produced by *o*-metalation of the halides and subsequent elimination of sodium halide. The ratio of *N,N*- to *N,N'*-diphenylhydrazine is about 2.3:1 [11,32]. Thus, the negatively charged α-nitrogen atom (adjacent to the benzene ring) is the more successful of the two nitrogens of the phenylhydrazide ion *(30)* in competing for the extra bond of benzyne.



*(30)*

#### β) *Substitution by an Addition-Elimination Mechanism*

*p*-Fluorotoluene and fluorobenzene also react with sodium hydrazide in ether or benzene containing hydrazine even at only 30 °C. As *p*-tolylhydrazine or phenylhydrazine is formed exclusively [cf. Section 2b.α)], there is no doubt that the reactions proceed entirely by an addition-elimination mechanism [36]. This observation is surprising, since *p*-fluorotoluene reacts with the comparable lithium piperidide/piperidine system entirely by the aryne mechanism [37]; however, it is probably due [36] to the ease of the single-stage process (see formulae below) [38] by which the hydrazine ion attaches itself, aided by a hydrogen atom on the uncharged nitrogen, to the phenyl residue, which is activated by the fluorine atom. The adduct *(31)*, R–$CH_3$ or H, is then stabilized by elimination of fluoride.



*(31)*

[29] For a discussion of why stabilization of the adduct occurs in some cases by elimination of hydrogen and in others by elimination of ammonia or amine, see [28].

[30] *H. Hacker*, Ph. D. Thesis, Technische Hochschule Darmstadt 1961.

[31] Cf. *D. H. R. Barton*, J. chem. Soc. (London) *1949*, 2174.

[32] *H. Henkler*, Ph. D. Thesis, Technische Hochschule Darmstadt 1962.

[33] *J. D. Roberts, C. W. Vaughan, L. A. Carlsmith*, and *D. A. Semenow*, J. Amer. chem. Soc. *78*, 611 (1956).

[34] Because of the possibilities of mesomerism in the anion *(30)*, phenylhydrazine may be quantitatively deprotonated to *(30)* by excess sodium hydrazide.

[35] Attempts to cause sodium phenylhydrazide to react with pyridine, styrene, or tolane were also negative [12,23]. *R. Engelhardt*, J. prakt. Chem. [2] *54*, 143 (1896), described reactions with aromatic nitriles to give *sym*-triazoles.

[36] Cf. *Th. Kauffmann* and *H. Henkler*, Chem. Ber. *96*, 3159 (1963).

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

[38] Cf. *Th. Kauffmann, H. Henkler*, and *J. Schulz*, Angew. Chem. *74*, 502 (1962); Angew. Chem. internat. Edit. *1*, 514 (1962).

This interpretation is supported by the observation that sodium methylhydrazide, with which addition assisted by a hydrogen atom in the β-position to the nucleophilic center is also possible, reacts like sodium hydrazide with *p*-fluorotoluene by an addition-elimination mechanism at *ca.* 30 °C, whereas sodium *N,N*-dimethylhydrazide, whose anion does not possess a hydrogen atom on the β-nitrogen, reacts by the aryne mechanism [36] and requires a temperature of about 80 °C (in benzene).

The hydrazinonaphthalenes that are obtained along with naphthalene by the reaction of monohalogenonaphthalenes with sodium hydrazide/hydrazine [cf. Section 3c)] are also formed by substitution through an addition-elimination mechanism, since the hydrazino group is introduced exclusively into the position previously occupied by the halogen atom [7, 39].

## 3. Reduction Reactions

### a) Reduction of Unsaturated and Aromatic Compounds

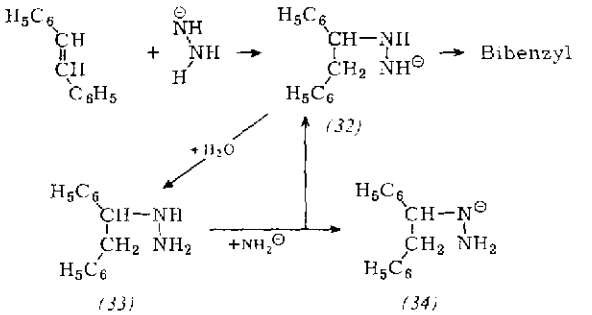
Reductions are often observed in the reactions of sodium hydrazide with unsaturated or polycyclic aromatic hydrocarbons, with nitrogen heterocycles, and with azoxy and nitro compounds [27, 40]. These reductions proceed very smoothly when free hydrazine is present in the reaction mixture. Some examples are shown in Table 5. Intense colors are always formed during the reductions. When compounds of simple structure are reduced, the yields are usually high; with higher aromatic hydrocarbons, mixtures of several reduction products are often formed; some of these are very unstable to oxygen.

Table 5. Reduction of unsaturated and polycyclic aromatic compounds with sodium hydrazide/hydrazine.

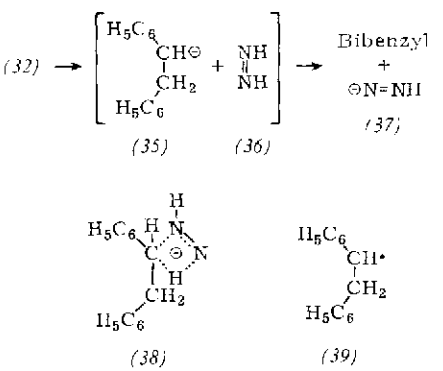
| Compound | Temp. [°C] | Color produced during reaction | Product | Yield [%] |
|---|---|---|---|---|
| Cyclooctatetraene | 34 | black | 1,3,5-cyclooctatriene | 85 |
| *trans*-Stilbene | 0 | brown-black | bibenzyl | 92 |
| Phenanthrene | 50 | green | 9,10-dihydrophenanthrene | 92 |
| Chrysene | 0 | blue | hexahydrochrysene (m.p. 132 °C) [a] | 45 |
| Quinaldine | 0 | red | 1,4-dihydroquinaldine | 84 |
| 2,2'-Azopropane | 40 | yellow | *N,N'*-diisopropylhydrazine | 95 |
| Azoxybenzene | 0 | red | hydrazobenzene | 98 |
| Nitrobenzene | 0 | red | azobenzene | 82 |
| 4-Nitrobiphenyl | 0 | red-black | 4,4'-azoxybiphenyl | 95 |

[a] Structure unknown.

The reduction of *trans*-stilbene to bibenzyl (1,2-diphenylethane) has been studied closely, and probably proceeds through the hydrazide adduct *(32)*, which on hydrolysis yields the product *(33)*, which could be isolated. As expected, sodamide converts *(33)* into bibenzyl (36 %); simultaneous formation of up to 40–50 % toluene and benzaldehyde hydrazone is plausibly explained by fragmentation [cf. Section 4a)] via the ion *(34)*.




Studies that are in progress on the mode of conversion of the intermediate *(32)* into bibenzyl, and the observation that diisopropyldiimide is formed in the reduction of acridine with sodium *N,N'*-diisopropylhydrazide, suggest that the second stage of the reduction takes the course shown below. Whether diimide *(36)* occurs free or as part of a transition complex such as *(38)* remains uncertain. It is very unlikely that *(32)* decomposes via the radical *(39)* [cf. Section 6)], since the stable dimer, 1,2,3,4-tetraphenylbutane [41], of *(39)* could not be detected in the crude product.




In the decomposition of *(32)*, free diimide is formed at the most in very low concentration because, if compounds with isolated C=C double bonds are added [42] to the mixture, they remain unattacked. This does not exclude the possibility that diimide can be split off from *(32)*, since *(36)* should be more strongly "acidic" than hydrazine by analogy with the increase in acidic character in the series ethane<ethylene<acetylene, and then loses a proton immediately to the carbanion *(35)* or to excess hydrazide present in the mixture, giving the diimide anion *(37)*. The latter, in contrast to diimide *(36)*, does not appear to reduce isolated C=C double bonds [43].

[39] *H. Zengel*, Diploma Thesis, Technische Hochschule Darmstadt 1962.

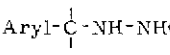
[40] *Th. Kauffmann, Ch. Kosel*, and *W. Schoeneck*, Chem. Ber. *96*, 999 (1963).

[41] *E. Fromm* and *O. Achert*, Ber. dtsch. chem. Ges. *36*, 539 (1903).

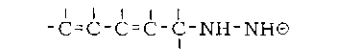
[42] Reduction of such compounds by diimide: cf. for example, *S. Hünig, H.-R. Müller*, and *W. Thier*, Tetrahedron Letters *1961*, 353; *E. E. van Tamelen, R. S. Dewey*, and *R. J. Timmons*, J. Amer. chem. Soc. *83*, 3725 (1961).

[43] The intermediate formation of diimide in the decomposition of benzenesulfonylhydrazine in aqueous alkali is discernible not only from the reduction of added compounds with isolated C=C double bonds [42], but also from the evolution of hydrogen and nitrogen [*F. Raschig*, Angew. Chem. *23*, 972 (1910)]. Benzenesulfonylhydrazine also evolves hydrogen and nitrogen on treatment with sodamide in anhydrous tetrahydrofuran at 60 °C; in this reaction reduction of added compounds containing isolated C=C double bonds could not be detected [11]. Decomposition of the diimide anion: cf. *S. Hünig, H.-R. Müller*, and *W. Thier*, Angew. Chem. *75*, 298 (1963); Angew. Chem. internat. Edit. *2*, 214 (1963).

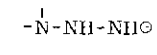
A plausible explanation of the much greater instability of the hydrazide adduct of stilbene *(32)* compared with that of styrene *(5)* is that the (δ-)- or (−)-charge which is produced on the carbon atom shown in bold type in *(32)* during the elimination of the diimide anion *(37)* or of diimide *(36)* is partly transferred to the attached phenyl residue. In general, it may be said that the hydrazido anion $-NH-NH^{\ominus}$ is always easily eliminated when, as in the structures *(40)*–*(42)*, it is attached to a group that can readily accept a negative charge because of its electronegativity or its ability to mesomerize.



*(40)*



*(41)*, e.g. Cyclooctatetraene-hydrazide adduct



*(42)*, e.g. Diisopropyldiimine-hydrazide adduct

Reductions of diaryl ketones and of some nitrogenous compounds appear to proceed through dianions. One example of these reductions, which require excess hydrazide and usually an elevated temperature (*ca.* 50 °C for benzophenone and azobenzene, in comparison with 0 °C for acridine), is that of quinaldine to 1,4-dihydroquinaldine. In this reaction the excess hydrazine is probably necessary in order to convert the adduct *(43)* in which the negative charge does not extend to the β-nitrogen of the hydrazino group [cf. however *(32)*] because of mesomeric distribution in the nitrogenous ring system, into the dianion *(44)*. The fact that *(44)* does not decompose below 50 °C, although it contains the otherwise labile system *(40)*, may be due to refusal of the negatively charged residue to accept an additional (δ-)- or (−)-charge during the elimination of the diimide anion *(37)* or of diimide *(36)*. Because the normal course of reaction is blocked in this way, and because of the tendency of organic dianions to decompose into radicals (discussed in Section 6), the hydrazido group would be expected to be eliminated from *(44)* homolytically with radical formation [cf. *(74)* in Section 6], at least as a side reaction.

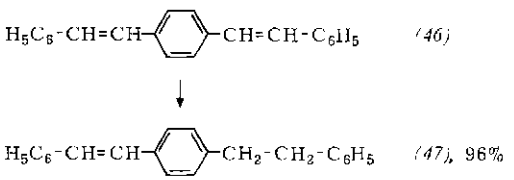


*(43)* *(44)* *(45)*

The dianion *(45)* appears to be stable, although it also contains a system *(40)* that is usually unstable, since acetophenone slowly adds on sodium hydrazide at 60 °C [7] but is not reduced by sodium hydrazide/hydrazine as are aliphatic ketones.

The products obtained in reductions with sodium hydrazide/hydrazine are often the same as those obtained by reduction with Na/liquid $NH_3$ [44] and similar systems. It is therefore interesting that ethers with one or two aromatic residues, which are generally split smoothly by Na/liquid $NH_3$ [44], are very resistant to sodium hydrazide/hydrazine [cf. Section 4e)].

Another interesting use of sodium hydrazide as a reducing agent is in the partial reduction of 1,4-distyrylbenzene *(46)* to *(47)* [40].

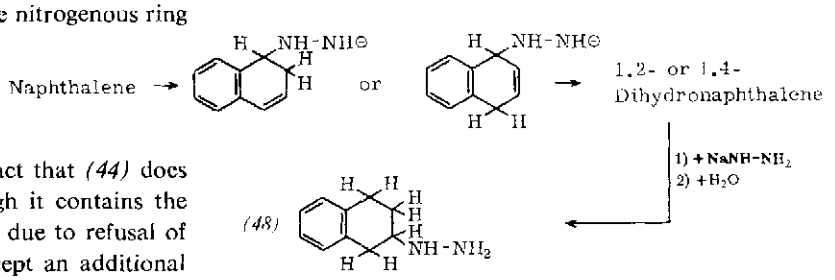


*(46)*

*(47)*, 96%

### b) Reductive Hydrazination

This variant of normal sodium hydrazide reduction occurs when the primary reduction product can form a stable adduct with the excess of sodium hydrazide. We have encountered it in the (slow [45]) reaction between naphthalene and sodium hydrazide/hydrazine in benzene at 50 °C [46]. Up to 72 % of the product consists of 2-hydrazino-1,2,3,4-tetrahydronaphthalene *(48)*. As has already been mentioned, the same compound is obtained in the reaction of 1,2- or 1,4-dihydronaphthalene with sodium hydrazide; *(48)* is therefore probably formed from naphthalene by the following route:




A hydrazinotetrahydro compound (hydrochloride; m.p. 115–118 °C) of unknown structure is formed analogously, but much more rapidly, in 70 % yield by the action of sodium hydrazide/hydrazine on fluoranthene in benzene at 50 °C [46]. Azulenes similarly form hydrazinotetrahydro compounds of unknown constitutions [7], together with other products.

### c) Reductive Dehalogenation

The reaction of sodium hydrazide/hydrazine with the compounds shown in Table 6 and similar [47] aryl halides, unlike that with halogenobenzenes [cf. Section 2b)], results in considerable or exclusive replacement of the halogen by hydrogen [47]. This dehalogenation

[44] Review: *G. W. Watt*, Chem. Reviews *46*, 289 (1950).

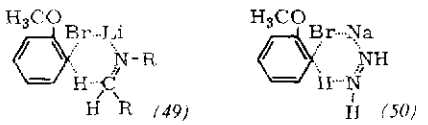
[45] Only 20 % of the naphthalene are used up after 2 h.

[46] *W. Schoeneck*, Ph. D. Thesis, Technische Hochschule, Darmstadt 1962.

[47] *Th. Kauffmann, H. Henkler*, and *H. Zengel*, Angew. Chem. *74*, 248 (1962); Angew. Chem. internat. Edit. *1*, 214 (1962).

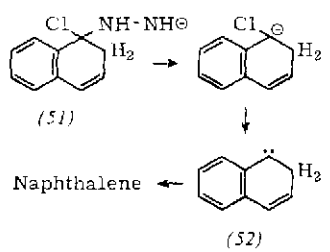
reaction usually occurs even below 20 °C and is accompanied by vigorous evolution of $NH_3$ and $N_2$; in the examples studied, the $NH_3/N_2$ ratio was 1.4-2.0. Excess sodium hydrazide must be added, since it reacts with sodium halides to form 1:1 addition complexes in which the hydrazide is largely deactivated. Deactivation increases in the order NaF < NaCl < NaBr.

The work of *Benkeser* and *DeBoer* [48] has shown that reductive dehalogenation of *o*-bromoanisole with lithium amides probably proceeds through *(49)*, and the transition state *(50)* can therefore be assumed for the



*(49)* *(50)*

analogous reaction with sodium hydrazide. Another possible course of reaction to be considered for halogenonaphthalenes is that formulated below for 1-chloronaphthalene, via the adduct *(51)* and the carbene *(52)*.



*(51)* *(52)*

Replacement of the halogeno by the hydrazino group via the aryne mechanism (*e.g.* with bromoanisole [39] and 3-chloropyridine [32]) or by the addition-elimination mechanism (*e.g.* with 1- and 2-halogenonaphthalenes [7, 39]) usually competes with the reductive dehalogenation.

Table 6. Reductive dehalogenations with sodium hydrazide/hydrazine.

| Halide | Temp. [°C] | Product | Yield [%] |
|---|---|---|---|
| Bromomesitylene | 25 | mesitylene | 82 |
| *o*-, *m*-, *p*-Bromoanisole | 20 | anisole | 58, 30, or 38 |
| 1- or 2-Chloronaphthalene | 0 | naphthalene | 65 or 75 |
| 9-Bromoanthracene | 0 | anthracene | 90 |
| 2,3-Dibromocoumarone | 0 | coumarone | 85 |
| 4-Bromoisoquinoline | 0 | isoquinoline | 57 |
| 1-Chloroferrocene | 0 | ferrocene | 97 |

## 4. Cleavage Reactions

### a) With Alkenes

Sodium hydrazide splits arylethylenes (Table 7) in boiling ether at the olefinic double bond [49–51] according to the equation

$$R(Ar)C{=}CR^1R^2 \xrightarrow[2)\ H_2O]{1)\ NaNH{\cdot}NH_2(35°C)} \begin{matrix} R(Ar)CH_2 \\ + \\ H_2N{-}N{=}CR^1R^2 \end{matrix}$$

The behavior of arylethylenes towards sodium hydrazide is thus analogous to that of carbonyl compounds or azomethines [O or RN instead of R(Ar)C]. Free hydrazine in the reaction mixture usually facilitates the fission, but suppresses it in the case of stilbene by competitive reduction to bibenzyl.

Table 7. Cleavage of C=C double bonds by sodium hydrazide in ether at 35 °C.

| Alkene | Reaction time [h] | Fission [%] |
|---|---|---|
| Styrene | 2 | 81 |
| β-Methylstyrene | 6 | 85 |
| β-Phenylstyrene | 6 | 97 |
| α-Methylstyrene | 6 | 85 |
| α-Ethylstyrene | 6 | 83 |
| α,α-Dimethylstyrene | 8 | 74 |
| α-Methyl-β-phenylstyrene | 6 | 72 |
| *trans*-Stilbene | 1 | 32 |
| 1-Methyl-2-vinylbenzene | 6 | 75 |
| 1,3-Dimethyl-2-vinylbenzene | 6 | 62 |
| 1,3,5-Trimethyl-2-vinylbenzene | 5 | 53 |
| 1-Vinylnaphthalene | 6 | 65 |
| 2-Vinylpyridine [a] | 2 | 63 |
| α,*o*-Dimethyl-β-phenylstyrene | 5 | practically no cleavage |
| 4-Methoxy-1-propenylbenzene | 6 | practically no cleavage |
| 4-Hydroxy-1-propenylbenzene | 6 | practically no cleavage |
| 4-Isopropenylbenzoic acid | 6 | practically no cleavage |

[a] Temperature: 20 °C, product: 2-methylpyridine. Up to 53 % 2-hydrazino-6-methylpyridine is formed at 60 °C.

Isolated C–C double bonds are not split by sodium hydrazide. Double bonds allylic to an aromatic ring represent a special case; they are first displaced into conjugation with the ring, then ruptured.

The new fission reactions could be of value in the elucidation of structures and for syntheses for the following reasons:

1. All known methods for the cleavage of C=C double bonds employ strong oxidizing agents ($O_3$, $RuO_4$, $OsO_4/Pb(OAc)_4$, $KMnO_4/NaIO_4$), follow reaction course (A), and sometimes cause oxidation at other sites in the molecule. In contrast, sodium hydrazide is a reducing agent and fission takes course (B) [formally hydrolysis of a C–C double bond] if followed by hydrolysis with acid.

2. Since fission of the system Aryl–C=C–R (R = alkyl or aryl) with sodium hydrazide leads to a hydrazone, it can be combined with the Huang-Minlon modification [52] of the Wolff-Kishner reduction in a one-step reaction, as an experiment with stilbene has confirmed, resulting in reductive cleavage according to route (C).

3. Since sodium hydrazide does not attack isolated double bonds, it can be used for selective cleavage of C=C double bonds that are conjugated with an aromatic group.

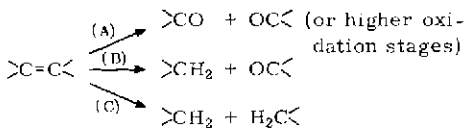
[48] *R. A. Benkeser* and *C. E. DeBoer*, J. org. Chemistry *21*, 281 (1956).

[49] *Th. Kauffmann, H. Henkler, Ch. Kosel, E. Rauch, J. Schulz*, and *R. Weber*, Angew. Chem. *74*, 650 (1962); Angew. Chem. internat. Edit. *1*, 456 (1962).

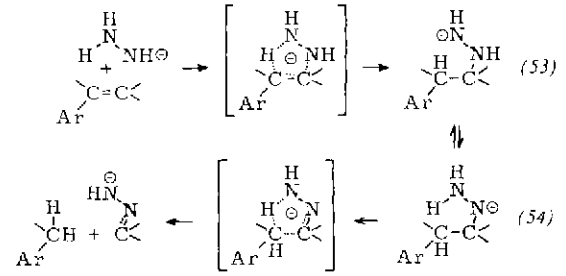
[50] *K. Lötzsch*, Diploma Thesis, Technische Hochschule Darmstadt, 1963.

[51] No hydrazone could be isolated when $R^1 = R^2 = H$.

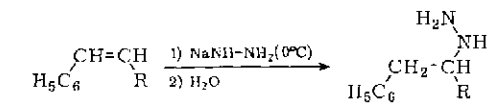
[52] *Huang-Minlon*, J. Amer. chem. Soc. *68*, 2487 (1946). According to *D. J. Cram, M. R. V. Sahyun*, and *G. R. Knox*, J. Amer. chem. Soc. *84*, 1734 (1962), Wolff-Kishner reductions proceed in dimethylsulfoxide at temperatures as low as 20 °C.



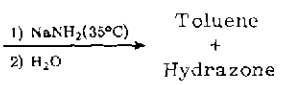
In our opinion, the most likely mechanism for the fission of C=C double bonds by sodium hydrazide (hydrazidolysis) is that shown below, according to which the rupture of both π- and the σ-bond takes place through a 5-membered cyclic transition state, just as with ozonolysis [53].



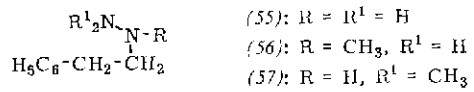
Two facts lend major support of this mechanism: the fissions can be carried out in two stages [4, 54],



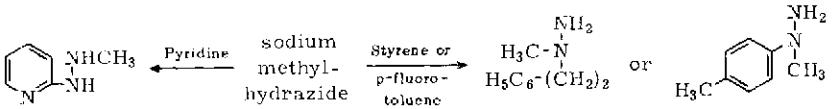
(R = Alkyl, $C_6H_5$)



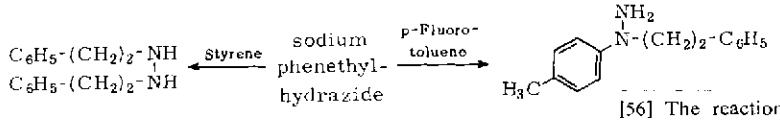
and *(56)*, *(57)*, and phenethylamine, unlike *(55)*, do not split off toluene when treated with sodamide in boiling ether [11, 54].



The supposition that equilibrium is established between *N'*-alkylhydrazide ions *(53)* and *N*-alkylhydrazide ions *(54)* is supported by the addition and substitution reactions of sodium methylhydrazide and sodium phenethylhydrazide formulated below, from which it is evident that these compounds can react both as $NaN(Alkyl)\text{-}NH_2$ and as $NaNH\text{-}NH(Alkyl)$ [2, 18, 36, 54].



*(58)* [55]



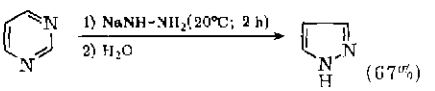
[53] Cf. *R. Huisgen*, Angew. Chem. *75*, 631–633 (1963); Angew. Chem. internat. Edit. *2*, 592–594 (1963).

[54] *D. Wolf*, Ph. D. Thesis, Technische Hochschule Darmstadt, anticipated for 1964.

[55] Structure *(58)* follows from its hydrogenation to give 89% *N*-methyl-*N*-phenethylamine [54]. Since no hydrazone could be obtained with *p*-nitrobenzaldehyde, and sodium phenethylhydrazide gives *(59)* on reaction with styrene, *(58)* was originally assumed to be *N*-methyl-*N'*-phenethylhydrazine [2].

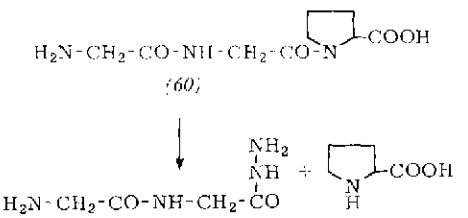
### b) Azomethines

Several recorded data show that sodium hydrazide can also split C=N double bonds: treatment of *N*-benzylideneaniline with sodium hydrazide/hydrazine at *ca.* 0 °C for 2 h splits it into aniline + benzaldehyde hydrazone (85%); similarly, the aromatic azines benzaldazine (dibenzylidenehydrazine) and 4,4'-dimethoxybenzaldazine (bis-4-methoxybenzylidenehydrazine) are split into the hydrazones almost quantitatively [56], although the azine of the aliphatic aldehyde myristaldehyde does not react [11]. Under similar conditions, both C=N double bonds of quinoxaline are ruptured to give *o*-phenylenediamine (85%) [30]. Rupture of one of the C=N double bonds of pyrimidine is probably the first stage in the following interesting ring contraction [30, 57]:



### c) N,N-Dialkylamides

Experiments with *N*-caproylpiperidine, *N*-benzoylpiperidine [59], *N*-benzyl-2-pyrrolidone, diglycyl-L-proline *(60)*, and glycyl-L-4-hydroxyproline show that amides containing the group $-CO-N(Alk)_2$ [A] are split



practically quantitatively within an hour by treatment at 0 °C with sodium hydrazide in ether containing

[56] The reactions were carried out in tetrahydrofuran with azines, and in ether with the other compounds mentioned in Section 4b). If ether is used instead of tetrahydrofuran, the dibenzylidenehydrazine is hydrogenated to *N*-benzylbenzylidenehydrazine (54%) by sodium hydrazide/hydrazine [11].

[57] We wish to reserve the application of this reaction to pyrimidine derivatives for ourselves.

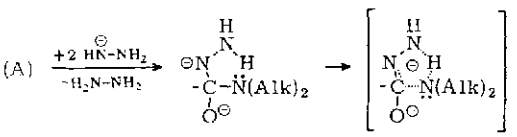
[58] *Th. Kauffmann* and *J. Sobel*, Angew. Chem. *75*, 1177 (1963); Angew. Chem. internat. Edit. *2*, 743 (1963).

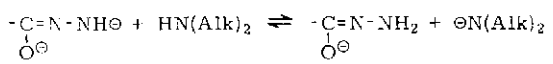
[59] *N,N'*-Dibenzoylhydrazine is formed as well as benzoylhydrazine.

hydrazine, followed by hydrolysis with water, in the manner illustrated by the example *(60)* [60].

Amides (*e.g.* 2-pyrrolidone, diglycylglycine, caproamide, asparagine) which contain a -CO-NH-Alk [B] or -CO-$NH_2$ [C] group and which can form mesomeric anions, are stable under these conditions. The consequent expectation that amides containing a (B) or (C) group as well as an (A) group would be split selectively at (A) has been realized for the combination (A) + (B) in the reaction shown above, in which only traces of glycine hydrazide are formed. Prospects for experiments on the selective fission of proteins [60a] at the amino acids proline and 4-hydroxyproline seem favorable, since anhydrous hydrazine [61] is a solvent equally suitable for sodium hydrazide and for proteins, and since natural amino acids, except those containing sulfur are stable to sodium hydrazide at 0 °C.

The following mechanism can be assumed for the cleavage of *N,N*-dialkylamides with sodium hydrazide by analogy with the fission of non-enolizable ketones with sodamide [62], and with the hydrazidolysis of C=C double bonds mentioned above:



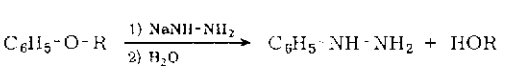


d) Esters [46, 63]

It is not surprising that esters are rapidly split into acyl hydrazides and alcohols by sodium hydrazide at 0 °C, presumably by a route analogous to the above scheme, since esters are usually readily split even by hydrazine hydrate [64]. Sodium hydrazide might be of value for selective cleavage of ester groups (*e.g.* for removal of protecting groups) in molecules that also contain the -CO-$NH_2$ or -CO-NH-Alk amide group.

e) Ethers [46]

Aliphatic ethers are stable to sodium hydrazide at 60 °C. Ethers with one or two aromatic residues are also fairly resistant: when heated at 50 °C for five hours with sodium hydrazide in benzene containing free hydrazine, anisole and diphenyl ether are split to the extent of only 9 % and 21 %, respectively. The course of fission is essentially as follows:

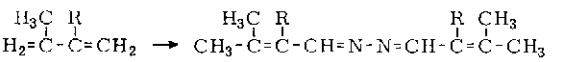


(R = $CH_3$ or $C_6H_5$)

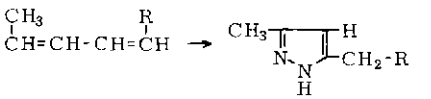
The formation of *N,N*- and *N,N'*-diphenylhydrazines as by-products indicates that benzyne is formed in these reactions, just as in the cleavage of diphenyl ether with phenylsodium [65], by elimination of NaOR from a primary metalation product [cf. Section 2b)].

## 5. Dehydrogenative Hydrazination of Dienes

Although, as already mentioned, 1,3-butadiene adds on sodium hydrazide in ether to form *N,N*-dicrotylhydrazine, isoprene, 2,3-dimethyl-1,3-butadiene, 1,3-pentadiene, and 2,4-hexadiene in ether or benzene only react with sodium hydrazide if free hydrazine is present in the reaction mixture. These reactions usually proceed at room temperature (50–60 °C for hexadiene) with vigorous evolution of $NH_3$ and yield, not substituted hydrazines, but α,β-unsaturated azines, pyrazoles, and pyrazolines, *i.e.* products containing less hydrogen [10]. This dehydrogenation is brought about by the free hydrazine, which is hydrogenated to ammonia. Methyl groups on the central carbon atoms of the butadiene system promote azine formation; on the outer carbon atoms they cause pyrazole formation [66].



63 or 70% yield when R = *H* [67] or $CH_3$



54 or 53% yield when R = H or $CH_3$

These reactions are of particular interest, as there are no other known methods for direct conversion of dienes into azines and pyrazoles.

In the simplest dehydrogenative hydrazination, the conversion of butadiene into 5-methyl-2-pyrazoline *(61)* (in 25 % yield) by the action of sodium hydrazide/hydrazine, 32 % adduct (*N,N*-dicrotylhydrazine) and polymeric nitrogenous compounds are also formed. Here the following mechanism seems likely: Addition of hydrazide ion onto the butadiene gives the *N*-crotylhydrazide ion *(8)*. This is probably [cf. Section 4a)] in

[60] Attempts to effect similar cleavage with sodamide at 0 °C or 35 °C were unsuccessful [58]. According to *B. Witkop* (Advances in Protein Chemistry. Academic Press, New York 1961, Vol. 16, p. 235), "certain *N*-acylhydroxyproline amides", but not ordinary peptides of hydroxyproline, can be split with sodamide + metallic sodium in liquid ammonia.

[60a] Note added in proof: By treating insuline, which contains no 4-hydroxyproline and only one proline residue, with sodium hydrazide at 0 °C in anhydrous hydrazine, we were able to split off selectively the peptide Pro-Lys-Ala-COOH from the carboxyl end of the B-chain [63].

[61] Peptide bonds are split extremely slowly by anhydrous hydrazine at 0 °C.

[62] "Bauer-Haller fission", cf. Org. Reactions *9*, 1 (1957). Degradation of ketones with sodium hydrazide has not yet been observed.

[63] *J. Sobel*, Ph. D. Thesis, Technische Hochschule Darmstadt, anticipated for 1964.

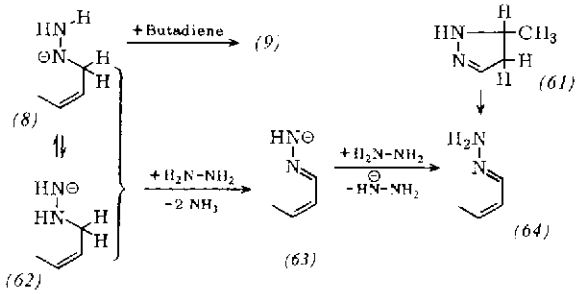
[64] Cf. Org. Reactions *3*, 367 (1947).

[65] *A. Lüttringhaus* and *K. Schubert*, Naturwissenschaften *42*, 17 (1955).

[66] The reaction between dienes with substituents other than methyl groups and sodium hydrazide/hydrazine has not yet been studied.

[67] Up to 15 % 5,5'-dimethyl-2-pyrazoline is also formed.

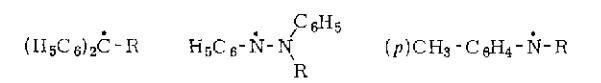
equilibrium with the *N'*-crotylhydrazide ion *(62)*, and can react with further butadiene to form the *N,N*-dicrotylhydrazide ion *(9)*. Either *(8)* or *(62)* is dehydrogenated by hydrazine to the crotylidenehydrazide ion



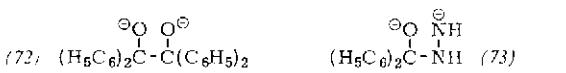

*(63)*, which undergoes ring closure either as such or, after addition of a proton, in the form *(64)*. It is known that crotylidenehydrazine is not stable and rearranges spontaneously to 5-methyl-2-pyrazoline *(61)* [68].

## 6. Occurrence of Free Radicals

Comparison of the dimers (*e.g.* hexaphenylethane) of the radicals *(65)*, *(66)* [69], and *(67)* [70] with the doubly negatively charged dimers, *e.g.* *(72)*, of the anionic radicals *(68)* [71], and *(69)–(71)* [72] shows that, like phenyl groups, anionic groups can labilize neighboring bonds. Dianions, such as could be formed from the hydrazide adducts of aromatic or polyunsaturated compounds, *e.g.* *(44)* or *(73)*, and possibly even the hydrazide adducts themselves, would therefore be expected to dissociate into radicals.



*(65)*, R = $-C_6H_5$ *(66)*, R = $-C_6H_5$ *(67)*, R = $-C_6H_4-CH_3(p)$
*(68)*, R = $-O^{\ominus}$ *(69)*, R = $-O^{\ominus}$ *(70)*, R = $-O^{\ominus}$
*(71)*, R = $-N=NO$

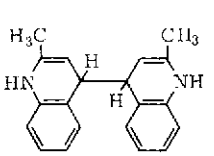


*(72)* *(73)*

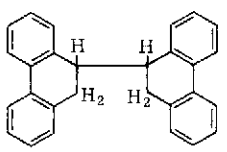
The reaction between benzophenone and excess sodium hydrazide gives rise to a deep blue coloration [73] and was therefore studied from this point of view. According to electron spin resonance measurements [74], the small concentration of radicals present in a suspension of sodium hydrazide in ether containing free hydrazine increases by one-hundred fold on addition of the ketone (at 20 °C). The blue reaction mixture has almost the same ESR spectrum [75] as "sodium benzophenone" (blue; anion *(68)*] and on hydrolysis gives, apart from much benzophenone and other products, a small amount (2 % after reaction for 10 min at 20 °C) of tetraphenylethylene glycol, the characteristic product of hydrolysis [71] of "sodium benzophenone" [76].

It can therefore be assumed that the radical ion *(68)* is formed by the addition of excess sodium hydrazide onto benzophenone. It probably results from homolytic fission of the deprotonated adduct *(73)* of benzophenone and hydrazide. No formation of tetraphenylethylene glycol could be detected in the reduction of benzophenone to benzhydrol (98 %) with excess sodium hydrazide at 55 °C [7].

The by-products *(74)* and *(75)* obtained in 9 and 6 % yields, respectively, in the reductions of quinaldine and phenanthrene indicate that free radicals are also formed in these reductions, which, characteristically, only proceed in the presence of excess hydrazide [cf. Section 3a)]. It is possible that the intense colors observed in reactions with sodium hydrazide are largely due to free-radical by-products or intermediates.



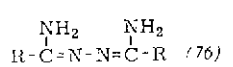
*(74)*



*(75)*

## 7. Future Developments

The most important reactions of sodium hydrazide with organic compounds [77] have probably been discovered in the investigations described above. It cannot be said, however, that the field has been studied exhaustively. It is not yet certain, for instance, how sodium hydrazide reacts with sulfur or phosphorus compounds, or whether liquid ammonia is a suitable solvent for reactions involving sodium hydrazide. It seems particularly attractive to replace the sodium cation with other cations and perhaps discover metal hydrazides that are less explosive, are soluble in organic solvents, or react differently. Preliminary experiments in this direction have shown that dialkylaluminum hydrazides are readily soluble in benzene, are safe to handle, and react differently from sodium hydrazide [cf. Section 1c)] with nitriles, giving $\alpha,\alpha'$-diamino amines *(76)* [78].



*(76)*

[68] *J. Hladik*, Monatsh. Chem. *24*, 434 (1903).

[69] *St. Goldschmidt*, Ber. dtsch. chem. Ges. *53*, 44 (1920).

[70] *H. Wieland*, Liebigs Ann. Chem. *381*, 204 (1911).

[71] *E. Beckmann* and *Th. Paul*, Liebigs Ann. Chem. *266*, 6 (1891); *W. Schlenk* and *T. Weickel*, Ber. dtsch. chem. Ges. *44*, 1182 (1911).

[72] *Th. Kauffmann* and *S. M. Hage*, Angew. Chem. *73*, 680 (1961); *75*, 248, 295 (1963); Angew. Chem. internat. Edit. *2*, 156 (1963).

[73] No blue color is obtained using an equimolar amount of sodium hydrazide.

[74] The ESR spectra were determined by Dr. *H. Fischer* of Deutsches Kunststoff-Institut, Darmstadt, to whom we are very grateful.

[75] *D. Braun* and *I. Löffund*, Makromolekulare Chem. *53*, 221 (1962).

[76] *S. M. Hage*, Ph. D. Thesis, Technische Hochschule Darmstadt, 1964.

[77] To our knowledge, the reaction of sodium hydrazide with inorganic compounds has not yet been studied.

[78] *L. Bàn*, Diploma Thesis, Technische Hochschule Darmstadt, anticipated for 1964.

In 1953, *G. Wittig* [79] wrote: "The progress in the chemistry of organic anions entitles us to expect that it will one day achieve the same status as organic cation chemistry, as soon as the fallow land is cultivated with the intensity devoted to the fertile field of cationic chemistry". The experiments described above have brought a new stretch of this fallow under the plow.

[79] *G. Wittig*, Angew. Chem. *66*, 17 (1954).

*On behalf of his collaborators and himself, the author wishes to thank the Director of the Institut für Organische Chemie of the Technische Hochschule Darmstadt most warmly for his continual and generous encouragement, and the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for valuable material assistance.*

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# Recent Advances in the Synthesis of 19-Norsteroids

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*This review describes approaches for improved preparations of 19-norsteroids. They are based on novel total syntheses of estrone and on intramolecular functionalization and elimination of the C-19 methyl group in androstane derivatives.*

Introduction

A. Total syntheses
1. Synthesis scheme AD → ABCD
2. Synthesis scheme CD → ACD → ABCD
3. Synthesis scheme AB → ABD → ABCD
4. Miscellaneous syntheses

B. Aromatization of ring A

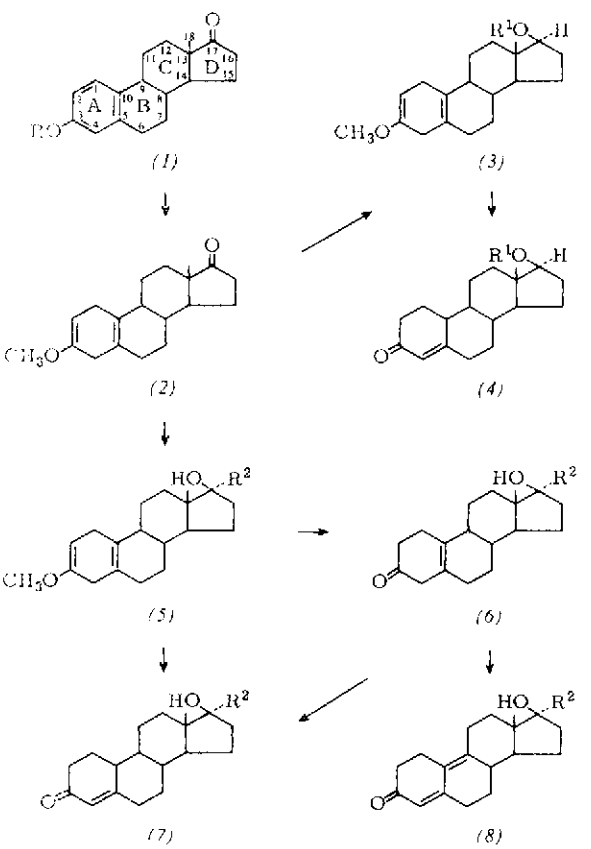
C. Intramolecular functionalization of C-19

D. Practicable syntheses of 19-norsteroids

## Introduction

Nonaromatic 19-norsteroids have gained importance in the last decade as anabolic agents [1] and as progestogens [2] for ovulation control. Some representative anabolic agents with favorable anabolic/androgenic ratios are 19-nortestosterone *(4)*, $R^1$ = H, a number of its esters *(4)*, $R^1$ = acyl, and its 17α-alkyl derivatives such as *(7)*, $R^2 = C_2H_5$. Progestational activity combined with marked gonadotropin inhibition is exhibited by, for example, norethisterone *(7)*, $R^2$ = C≡CH, norethynodrel *(6)*, $R^2$ = C≡CH, and the recently described 19-nor-$\Delta^{4,9(10)}$-androstadien-3-ones *(8)*, $R^2$ = C≡CH [3] and $R^2$ = C≡CCl [4], when administered *per os*.

Until 1961, the preparation of these compounds [5] was based almost entirely on Birch reduction [6] of the only 19-norsteroid generally available, *viz.* estrone *(1)*, R = H, or its methyl ether *(1)*, R = $CH_3$. The dihydroaromatic derivative obtained was then oxidized to reform the




[1] Reviewed by *B. Camerino* and *G. Scala* in *E. Jucker:* Progress in Drug Research. Birkhäuser, Basel 1960, Vol. 2, p. 71.

[2] *G. Pincus* and *A. P. Merrill* in *C. A. Villee:* Control of Ovulation. Pergamon Press, New York 1961, p. 37.

[3] *M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay*, and *R. T. Rapala*, J. Amer. chem. Soc. *82*, 2402 (1960).

[4a] *J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett*, and *S. L. Steelman*, J. Amer. chem. Soc. *83*, 4663 (1961).

[4b] *C. Burgess, D. Burn, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, A. P. Leftwick, J. S. Mills*, and *V. Petrow*, J. chem. Soc. (London) *1962*, 4995.

[5] For a more detailed discussion of these reactions, see *L. F. Fieser* and *M. Fieser:* Steroids. Reinhold Publishing Corp., New York 1959, p. 586.

[6a] *A. J. Birch* and *H. Smith*, Quart. Reviews (chem. Soc. London) *12*, 17 (1958).

[6b] For recent improvements see *H. L. Dryden, G. M. Webber, R. R. Burtner*, and *J. A. Cella*, J. org. Chemistry *26*, 3237 (1961); *B. Pelc*, Coll. czechoslov. chem. Commun. *27*, 2706 (1962).

[6c] Reviewed by *F. J. Kakis* in *C. Djerassi:* Steroid Reactions. Holden-Day, San Francisco 1963, p. 267.

ketonic group at C-17 giving *(2)*, the key intermediate for subsequent synthesis of the various endproducts.

Stereoselective reduction of *(2)*, *e.g.* with $NaBH_4$, afforded the 17β-ol *(3)*, thus providing a short route to 19-nortestosterone *(4)*, R = H, and by esterification to its esters *(4)*, R = acyl. Reaction of *(2)* with the appropriate Grignard or organolithium reagents resulted in a series of 17α-alkyl, vinyl, ethynyl, or chloroethynyl derivatives *(5)* with a protected A-ring. Controlled hydrolysis of these yielded 19-nor-3-keto-$\Delta^{5(10)}$-steroid derivatives *(6)* which could be rearranged to the conjugated 3-keto-$\Delta^4$-steroids *(7)* or dehydrogenated further to give 19-nor-$\Delta^{4,9(10)}$-androstadien-3-ones *(8)*.

The recent increase in medical interest in 19-norsteroids has generated intensive chemical research in this field. Since the problems related to the partial synthesis *(1)* → *(6)*, *(7)*, *(8)* have been solved satisfactorily [5, 6], it became clear that further improvements could only be achieved by either broadening the raw material basis or finding entirely new methods for the preparations of 19-norsteroids. Consequently, efforts were made to develop simpler total syntheses of estrone from readily available starting materials, and, more recently, to effect functionalization and elimination of the C-19 angular methyl group of appropriate androstane derivatives.

## A. Total Syntheses

The classical total synthesis [6d] of estrone by *Cole*, *Johnson*, *Robins*, and *Walker* [7] and the versatile steroid synthesis of *Velluz* and *coworkers* [8] represent probably the ultimate in stereoselectivity attainable at present in this field [9]. However, the number of steps involved limit the applicability of these procedures [10] to large scale production.

A number of seemingly unrelated organic chemical developments, such as availability of 2-methylcyclopentane-1,3-dione [11], a practical method for the preparation of 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol *(25)* [11a], *etc.*, have led over the past few years to several new, relatively short total syntheses in the estrone field, that are also potentially applicable for industrial use.

[6d] The structural formulae in this section show only one enantiomer, and even though (±) is mostly omitted, this text deals only with racemates.

[7a] *J. E. Cole, jr., W. S. Johnson, P. A. Robins*, and *J. Walker*, Proc. chem. Soc. (London) *1958*, 114.

[7b] *J. E. Cole, jr., W. S. Johnson, P. A. Robins*, and *J. Walker*, J. chem. Soc. (London) *1962*, 244.

[8] *L. Velluz, G. Nominé*, and *J. Mathieu*, Angew. Chem. *72*, 725 (1960).

[9a] For previous estrone syntheses, see [5] p. 495.

[9b] For an up-to-date summary of progress in steroid total syntheses, see *I. V. Torgov*, Pure and appl. Chem. *6*, 525 (1963); *G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall*, and *H. Smith*, J. chem. Soc. (London) *1963*, 5072; *L. Velluz, G. Nominé, G. Amiard, V. Torelli*, and *J. Cerede*, C. r. hebd. Séances Acad. Sci. *257*, 3086 (1963).

[10] For recent improvements and developments along the same general lines, see a) *W. Nagata* et al., Chem. Pharmac. Bull. (Tokyo) *9*, 267 (1961) and subsequent papers; b) *D. K. Banerjee* and *K. M. Sivanandaiah*, J. Indian chem. Soc. *38*, 652 (1961); c) *L. J. Chinn* and *H. L. Dryden, jr.*, J. org. Chemistry *26*, 3904 (1961).

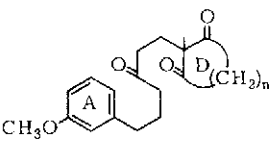
[11] *J. J. Panouse* and *Ch. Sannié*, Bull. Soc. Chim. *1955*, 1036.

[11a] *I. N. Nazarov, I. V. Torgov*, and *G. P. Verkholetova*, Doklady Akad. Nauk SSSR *112*, 1067 (1957).

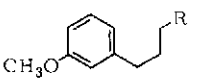
Common characteristics of these new syntheses are a) the use of a preformed five- or six-membered D-ring already containing the potential C-18 methyl group [11b], and b) stereoselective introduction of three (out of four) asymmetric carbon atoms in the last two steps of the synthesis. In the following sections, these new syntheses are systematized according to the sequences used for building up the steroid skeleton.

### 1. Synthesis Scheme AD → ABCD

The availability of 2-methylcyclopentane-1,3-dione [11] added emphasis to an ingenious total synthesis of estrone by *Hughes* and *Smith* [13], which consisted in incorporating preformed rings A and D into a molecule *(12)* suitable for subsequent cyclization. Both *(12a)*



*(12a)*, n = 2
*(12b)*, n = 3

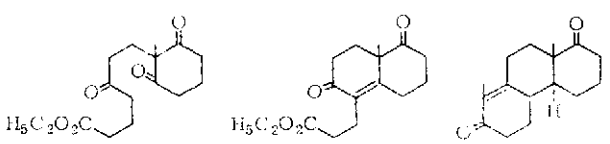


*(13)*, R = Br
*(14)*, R = -C≡CH
*(15)*, R = $-C\equiv C-CH_2-N(C_2H_5)_2$
*(16)*, R = $-CO-(CH_2)_2-N(C_2H_5)_2$
*(17)*, R = $-CO-CH=CH_2$

and *(12b)* were prepared starting from 3-(*m*-methoxyphenyl)propyl bromide *(13)* which was treated with sodium acetylide to give *(14)*.

Mannich condensation of *(14)* with formaldehyd and diethylamine led to *(15)* which after hydration with $H_2SO_4$–$HgSO_4$ gave a mixture of 2-dimethylamino-

[11b] A preformed six-membered D-ring was already used by *Miescher* et al. [12] in their total synthesis of D-homoandrostane-3,17a-dione. These authors condensed 2-methylcyclohexane-1,3-dione and ethyl 7-chloro-5-oxoheptanoate with trimethylamine to give the triketo ester *(9)*,



*(9)* *(10)* *(11)*

which was cyclized to the diketo ester *(10)*. Further transformations through a series of lengthy and mostly non-stereoselective reactions gave D-homoandrostane-3,17a-dione via the tricyclic intermediate *(11)*.

[12] *P. Wieland, H. Ueberwasser, G. Anner*, and *K. Miescher*, Helv. chim. Acta *36*, 376 (1953) and subsequent papers.

[13a] *G. A. Hughes* and *H. Smith*, Proc. chem. Soc. (London) *1960*, 74.

[13b] *G. A. Hughes* and *H. Smith*, Chem. and Ind. *1960*, 1022.

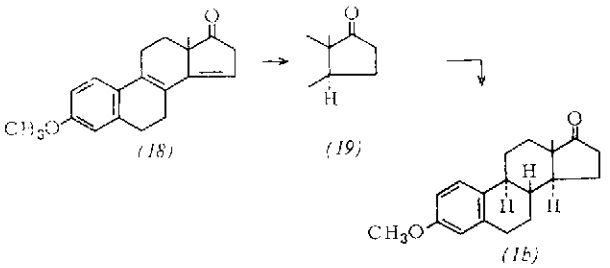
[14a] Michael condensations of 2-methylcyclohexane-1,3-dione and 2-methylcyclopentane-1,3-dione with methyl vinyl ketone or its corresponding Mannich base were previously described by *P. Wieland* and *K. Miescher*, Helv. chim. Acta *33*, 2215 (1950).

[14b] *N. L. Wendler, H. L. Slates*, and *M. Tishler*, J. Amer. chem. Soc. *73*, 3816 (1951).

[14c] *S. Swaminathan* and *M. S. Newman*, Tetrahedron *2*, 88 (1958).

[14d] *W. Acklin, V. Prelog*, and *A. P. Prieto*, Helv. chim. Acta *41*, 1416 (1958).

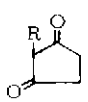
ethyl *m*-methoxyphenylpropyl ketone *(16)* and its elimination product *m*-methoxyphenylpropyl vinyl ketone *(17)*. Michael condensation of a mixture of *(16)*, *(17)*, and 2-methylcyclohexane-1,3-dione gave *(12b)* [14]. Analogous condensation with 2-methylcyclopentane-1,3-dione later yielded *(12a)*. In the preferred version of the *Hughes* and *Smith* synthesis, *(12a)* was cyclodehydrated directly to 3-*O*-methyl-8,14-bisdehydroestrone *(18)*, with *p*-toluenesulfonic acid in boiling benzene. This tetracyclic ketone has become an important intermediate in other total syntheses.



*(18)* *(19)* *(1b)*

Stereoselective hydrogenation of the 14,15-double bond in the presence of palladium on calcium carbonate afforded a high yield of the diastereoisomer *(19)*, having the required C/D-*trans* junction [15]. Correct stereochemistry at C-8 and C-9 was obtained in the next step leading to *(1b)* by reduction of *(19)* with potassium in liquid ammonia, the A-ring being left intact [15a]. Some reduction occurred at C-17, but subsequent reoxidation regenerates the C-17 ketone, to give (±)-3-*O*-methylestrone *(1b)*.

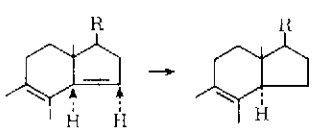
More recently, *Smith*, *Hughes* et al. [15b] reported that *(17)* can also be condensed with higher homologues *(19a)* of 2-methylcyclopentane-1,3-dione the corresponding C-18 homologue of *(12)* and *(18)* being obtained. These were used for the preparation of a number of steroid-like compounds of potential biological interest.



*(19a)*, R = ethyl, n-propyl, isopropyl, etc.

[14e] *C. B. C. Boyce* and *J. S. Whitehurst*, J. chem. Soc. (London) *1959*, 2022.

[15] In the total synthesis of equilenin, *Johnson* et al. [16] achieved preferential hydrogenation by attack from the rear side of the molecule, utilizing the shielding effect of the C-18 methyl group. It was later found by other investigators [17] that a second, β-oriented substituent (R) at C-17 was needed for exclusive formation of the 14α-isomers:



The stereoselective hydrogenation of *(18)* which has a carbonyl group at C-17, is of definite practical importance.

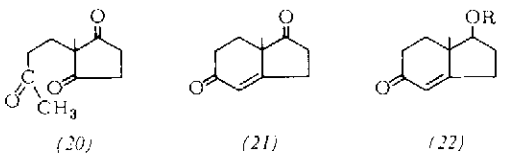
[15a] This method was first used by *Johnson* et al. [18a] in the reduction of a styrene type double bond: *trans*-addition of the hydrogen occurred, leaving the aromatic ring intact. Later, *Johnson* and coworkers [18b] found that addition of lithium to this reaction mixture reduces the aromatic ring as well to give the corresponding dihydroaromatic derivative.

[15b] *H. Smith*, *G. A. Hughes*, *G. H. Douglas*, *D. Hartley*, *B. J. McLoughlin*, and *J. D. Siddall*; *G. R. Wendt*, *G. C. Busby*, *D. R. Herbst*, *K. W. Ledig*, *J. R. McMenamin*, *T. W. Pattison*, *J. Suida*, *J. Tokolics*, and *P. A. Edgren*; *A. B. A. Jansen*, *B. Gadsby*, *D. H. R. Watson*, and *P. C. Phillips*, Experientia *19*, 394 (1963).

## 2. Synthesis Scheme CD → ACD → ABCD

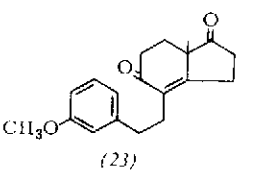
In 1959, *Boyce* and *Whitehurst* [14e] reported the preparation of *(20)* as well as its cyclization to *(21)* in good yields.

Utilization of *(21)* as a CD building block for an estrone synthesis was recently reported by *Crispin* and *Whitehurst* [19], who prepared the tetrahydropyranyl ether *(22)* which was alkylated with *m*-methoxyphenethyl *p*-toluenesulfonate, and yielded *(23)* after hydrolysis



*(20)* *(21)* *(22)*

and reoxidation at C-17 (steroid numbering). Compound *(23)* was then cyclized to 3-*O*-methyl-8,14-bisdehydroestrone *(18)* which had previously been converted into estrone by *Hughes* and *Smith* [13]. Direct alkylation of the ketone *(21)* with 2-*m*-methoxyphenethyl bromide to yield *(23)* is described by *Smith*, *Hughes*, and *McLoughlin* [20].



*(23)*

As no yields were reported in the preliminary communications, the practical value of this route is difficult to compare with the first synthesis of *Smith* and *Hughes* [13], in which high yields are reported for the individual steps.

## 3. Synthesis Scheme AB → ABD → ABCD

In 1957, *Nazarov* and coworkers [11a] successfully reacted the readily available compound 6-methoxy-α-tetralone *(24)* [21] with the vinylmagnesium bromide reagent described by *Normant* [22] and obtained the vinyl carbinol *(25)* in excellent yield.

[16a] *W. S. Johnson*, *J. W. Petersen*, and *C. D. Gutsche*, J. Amer. chem. Soc. *67*, 2274 (1945).

[16b] *R. Hirschmann* and *W. S. Johnson*, J. Amer. chem. Soc. *73*, 326 (1951).

[17a] *D. K. Banerjee*, *S. Chatterjee*, *C. N. Pillai*, and *M. V. Bhatt*, J. Amer. chem. Soc. *78*, 3769 (1956).

[17b] *L. Velluz*, *G. Nominé*, and *J. Mathieu*, Angew. Chem. *72*, 725 (1960).

[17c] *R. A. Barnes* and *R. Miller*, J. Amer. chem. Soc. *82*, 4960 (1960).

[18a] *W. S. Johnson*, *A. D. Kemp*, *R. Pappo*, *J. Ackerman*, and *W. F. Johns*, J. Amer. chem. Soc. *78*, 6312 (1956).

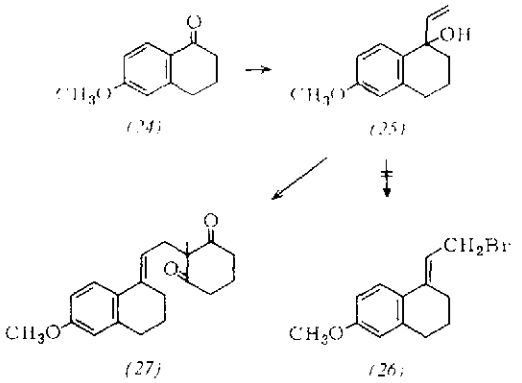
[18b] *W. S. Johnson*, *W. A. Vredenburgh*, and *J. E. Pike*, J. Amer. chem. Soc. *82*, 3409 (1960).

[19] *D. J. Crispin* and *J. S. Whitehurst*, Proc. chem. Soc. (London) *1962*, 356.

[20] *H. Smith*, *G. A. Hughes*, and *B. J. McLoughlin*, Experientia *19*, 178 (1963).

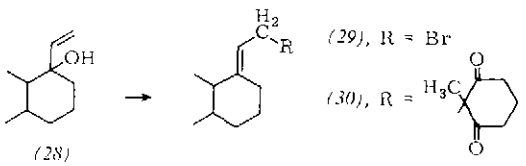
[21] *G. Stork*, J. Amer. chem. Soc. *69*, 576 (1947).

[22] *H. Normant* in *R. A. Raphael*: Advances in Organic Chemistry. Interscience, New York 1960, Vol. II, p. 1.



(24) (25) (27) (26)

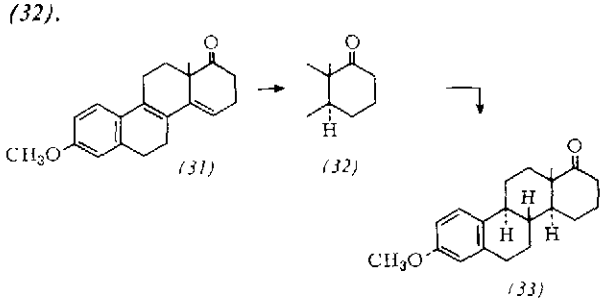
On the basis of their previous model experiments [23, 24], summarized here by the formulae *(28)* → *(29)* → *(30)*, utilization of *(25)* appeared promising for the



(28) (29), R = Br (30), R = $H_3C$

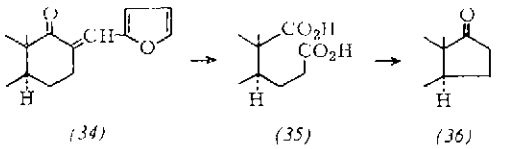
preparation via *(26)* of compounds of the type *(27)*. First attempts to obtain the substituted vinyl bromide *(26)* from *(25)* proved unsuccessful [25]. Later, however, *Ananchenko* and *Torgov* [26] succeeded in preparing *(27)* directly from *(25)* in 50 % yield by condensing *(25)* with 2-methylcyclohexane-1,3-dione in the presence of basic catalysts. The mechanism of this interesting reaction is still not understood.

Subsequently, the Russian workers [27] cyclodehydrated *(27)* to *(31)*, which on selective hydrogenation [15] gave *(32)*.



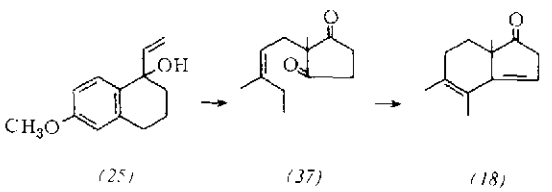
(31) (32) (33)

In the first version of this total synthesis, four additional steps were required to go from *(32)* to 3-*O*-methyl-D homoestrone *(33)*. In a later publication [28], the reduction of *(32)* to *(33)* in 42 % yield using potassium in liquid ammonia is described [cf. *(19)* → *(1b)*]. Conversion of the D-homoestrone methyl ether to (±)-3-*O*-methylestrone *(1b)* was accomplished in three steps [reaction sequence *(34)* → *(35)* → *(36)*] using *W. S. Johnson*'s method of ring D contraction [29].



(34) (35) (36)

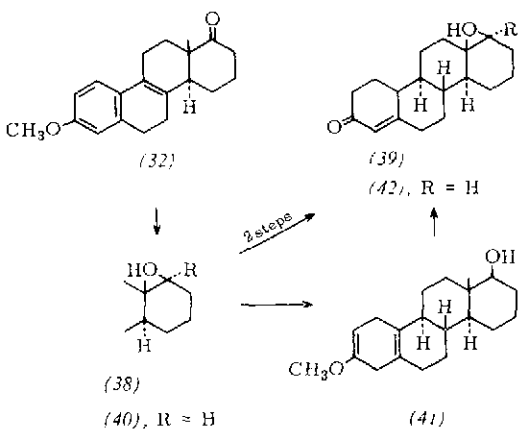
The shortest total synthesis of (±)-estrone methyl ether from readily available starting materials was reported independently in 1963 by five research groups [9b, 15b, 30, 31]. This synthesis follows the AB + D → ABCD scheme [reaction sequence *(25)* → *(37)* → *(18)*].



(25) (37) (18)

Conversion of *(18)* into estrone methyl ether *(1b)* is carried out by the procedure of *Hughes* and *Smith* [13]. Thanks to the high yields in the first steps [30b], this total synthesis seems to compare favorably with that of *Hughes* and *Smith* [13].

The Russian workers [32] subsequently directed their attention to 19-nor-D-homotestosterone *(42)* and its derivatives *(39)*, which reportedly also possess anabolic activity. The more important reactions, starting out from 3-*O*-methyl-9,10-dehydro-D-homoestrone *(32)*, are summarized in the formulae *(38)* through *(42)*; for processes leading to the stereoisomers, see [15a].




(32) (39) (42), R = H (38) (40), R = H (41)


[23] *I. N. Nazarov, S. N. Ananchenko,* and *I. V. Torgov,* Zhur. Obshchei Khim. *26*, 819 (1956).

[24] *I. N. Nazarov, G. P. Verkholetova, S. N. Ananchenko, I. V. Torgov,* and *G. V. Aleksandrova,* Zhur. Obshchei Khim. *26*, 1482 (1956).

[25] *I. N. Nazarov, S. N. Ananchenko,* and *I. V. Torgov,* Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1959*, 103.

[26] *S. N. Ananchenko* and *I. V. Torgov,* Dokl. Akad. Nauk SSSR *127*, 553 (1959).

[27] *S. N. Ananchenko, V. N. Leonov, A. V. Platonova,* and *I. V. Torgov,* Dokl. Akad. Nauk SSSR *135*, 73 (1960).

[28a] *S. N. Ananchenko, Tao-Sen-Yeh,* and *I. V. Torgov,* Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1962*, 298.

[28b] *S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. N. Rzheznikov,* and *I. V. Torgov,* Tetrahedron *18*, 1355 (1962).

[29a] *W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg,* and *L. J. Chinn,* J. Amer. chem. Soc. *74*, 2832 (1952).

[29b] *W. S. Johnson, B. Bannister, R. Pappo,* and *J. E. Pike,* J. Amer. chem. Soc. *78*, 6354 (1956).

[30a] *D. J. Crispin* and *J. S. Whitehurst,* Proc. chem. Soc. (London) *1963*, 22.

[30b] *T. B. Windholz, J. H. Fried,* and *A. A. Patchett,* J. org. Chemistry *28*, 1092 (1963).

[31a] *T. Miki, K. Hiraga,* and *T. Asako,* Proc. chem. Soc. (London) *1963*, 139.

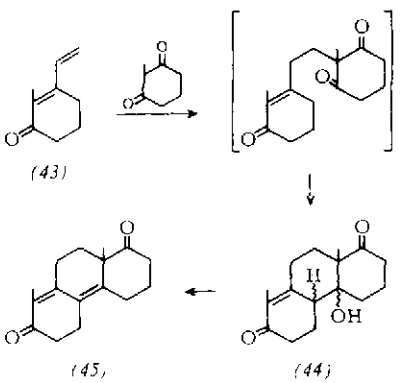
[31b] *S. N. Ananchenko* and *I. V. Torgov,* Tetrahedron Letters *1963*, 1553.

[32] *V. M. Rzheznikov, S. N. Ananchenko,* and *I. V. Torgov,* Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1962*, 465, and [28b].

## 4. Miscellaneous Syntheses

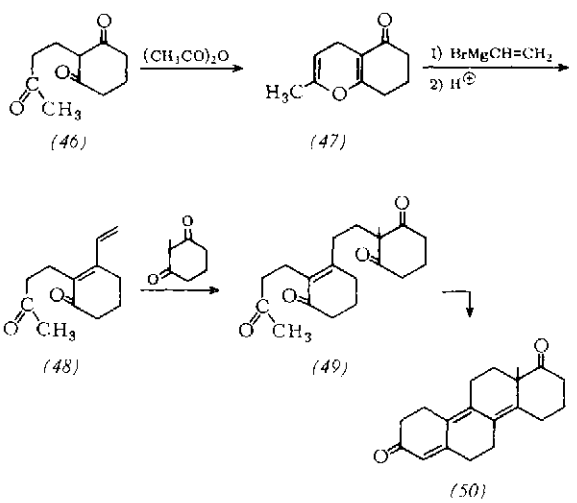
Introduction of a $\Delta^{9(10)}$-double bond *(8)* into steroids of the norethisterone type *(7)* increases their progestational activity [3, 4]. The preparation of a compound with extended conjugation *(54)* was achieved by total synthesis.

This work had its origin in 1953 when *Eschenmoser, Schreiber*, and *Julia* [33] carried out the reaction sequence *(43)* → *(45)* which is based on a vinylogous Michael addition.



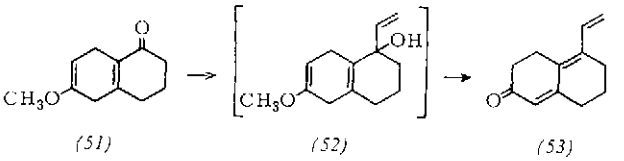
*(43)* *(45)* *(44)*

*Panouse* and *Sannié* [34] performed the same reactions with 2-methylcyclopentane-1,3-dione and obtained a tricyclic compound corresponding to the BCD-rings of a steroid molecule [35]. The importance of this work became evident in 1961, when *Zavialov* et al. [36] prepared *(48)*, an analogue of *(43)* containing a side chain that was eventually used for building up ring A. The preparation of *(48)*, its condensation with 2-methylcyclohexane-1,3-dione, and cyclization of the obtained *(49)* to the final product *(50)* are shown.



*(46)* *(47)* *(48)* *(49)* *(50)*

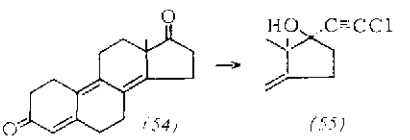
A simpler procedure was found by *Gajdamovich* and *Torgov* [37], who prepared 2,3,4,6,7,8-hexahydro-1-vinylnaphthalen-6-one *(53)* from 1,2,3,4,5,8-hexahydro-1-oxo-6-methoxynaphthalene *(51)* [38] and vinylmagnesium bromide [23] via the carbinol *(52)*.



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

Condensation of *(53)* with methylcyclohexane-1,3-dione then gave a tetracyclic carbinol corresponding to *(44)*, which was subsequently dehydrated to *(50)*, which proved to be identical with the compound prepared by *Zavialov* [36].

Lately *Windholz* et al. [39] prepared (±)-19-nor-$\Delta^{4,8(14),9(10)}$-androstatriene-3,17-dione *(54)* in approx. 17% yield in a one-step reaction from *(53)* and 2-methylcyclopentane-1,3-dione. Ensuing selective chloroethynylation at C-17 gave *(55)*.



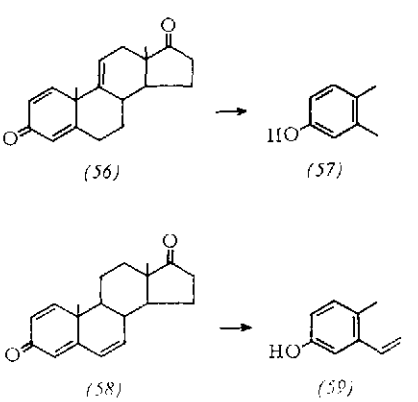
*(54)* *(55)*

The progestational activity of this racemic compound was found to be intermediate between that of *(7)* and *(8)*.

### B. Aromatization of Ring A

In addition to the total syntheses discussed above, another new development, which once again focused attention on the original method of *Inhoffen* for the aromatization of the A-ring [40], will be reported here.

*Tsuda* et al. [41] described an unusually mild method of achieving A-ring aromatization by refluxing an ap-



*(56)* *(57)* *(58)* *(59)*

[33] *Y. Eschenmoser, J. Schreiber*, and *S. A. Julia*, Helv. chim. Acta *36*, 482 (1953).

[34] *J. J. Panouse* and *Ch. Sannié*, Bull. Soc. Chim. *1956*, 1429, 1435.

[35] *Eschenmoser* and coworkers succeeded in converting *(45)* into *(11)* by catalytic hydrogenation followed by rearrangement with acid; *J. Schreiber*, Ph. D. Thesis, E.T.H. Zurich (1953); they also treated *(43)* with 2-methylcyclopentane-1,3-dione and obtained the BCD rings of the steroid molecule; *A. Frey*, Ph. D. Thesis, E.T.H. Zurich (1954); personal communication from *A. Eschenmoser*.

[36] *S. I. Zavialov, G. V. Kondrateva*, and *L. F. Kudryavtseva*, Izv. Akad. Nauk SSSR, Otdel Khim. Nauk *1961*, 529.

[37] *N. N. Gaidamovich* and *I. V. Torgov*, Izv. Akad. Nauk SSSR, Odtel Khim. Nauk *1961*, 1803.

[38] *A. J. Birch, J. A. K. Quartey*, and *H. Smith*, J. chem. Soc. (London) *1952*, 1768.

[39] *T. B. Windholz, J. H. Fried, H. Schwamm*, and *A. A. Patchett*, J. Amer. chem. Soc. *85*, 1707 (1963).

[40] See [5], p. 479.

[41] *K. Tsuda, E. Ohki, S. Nozoe*, and *K. Ikekawa*, J. org. Chemistry *26*, 2614 (1961).

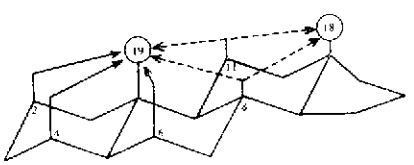
propriate cross-conjugated steroid with zinc in moist pyridine. An impressive 75 % yield of 9-dehydroestrone *(57)* is obtained from *(56)*. However, the much more accessible 3-keto-$\Delta^{1,4,6}$-triene *(58)* gave only 10–15 % of the useful intermediate 6-dehydroestrone *(59)*, thus considerably limiting the applicability of this method.

### C. Intramolecular Functionalization of C-19

Besides the partial syntheses carried out in the late 1950's and described in the introduction, there were two other possibilities for the preparation of 19-norsteroids: a) chemical transformation of naturally occurring steroids with an oxygen function at C-19, *e.g.* strophanthidin, and b) enzymatic oxidation of the C-19 methyl group. Because of the limited supply of potential starting materials in the first case, and because of the nonselective nature of the enzymatic attack in the second case, neither of these methods appeared promising for industrial purposes.

The successful chemical functionalization of the C-18 methyl group [42a - g] achieved during extensive search for a partial synthesis of aldosterone paved the way to spectacular advances in the field of 19-norsteroids. Here, however, besides functionalization, the problem consisted also in developing efficient methods for elimination of the C-19 group without simultaneous aromatization of ring A.

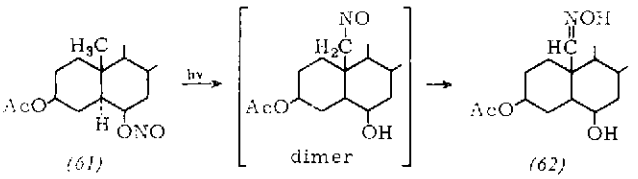
Intramolecular attack on a non-activated $CH_3$ group is initiated by abstraction of one of its hydrogen atoms and is brought about by oxygen radicals generated by homolysis of an –OR bond [R being NO, halogen, or $Pb(OAc)_3$] attached to a γ-carbon atom relative to the methyl group to be functionalized [42 h]. As shown in *(60)*, steroids containing a β-hydroxyl group on carbon atoms 2, 4, 6, 8, or 11 meet the above requirements.



*(60)*

Structure *(60)* also suggests that attack from C-8 and C-11 could lead to simultaneous functionalization of the equidistant C-18 and C-19 positions, hence utilization of substitutents at C-8 and C-11 would be impractical. The 6β-hydroxy steroids are readily accessible and became the natural choice for efficient functionalization of the C-19 methyl group, since 2- and 4-hydroxy compounds are relatively difficult to obtain, and 8-hydroxy compounds practically unknown.

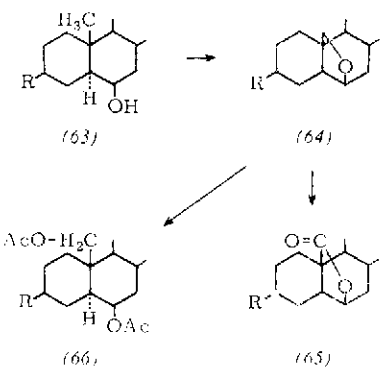
*Barton* and coworkers carried out the pioneer work on hydrogen abstraction from non-activated carbon atoms by photolytic attack in the steroid field [42c, e] and described the following C-6 → C-19 attack as early as 1960 [43a, b].




*(61)* *(62)*

Photolysis of the 6β-nitrite *(61)* to give the 19-oxime *(62)* via a dimeric nitroso derivative was the first known chemical functionalization at C-19, but was not pursued further at that time.

While investigating the reactions of various steroidal secondary alcohols with lead tetraacetate, *Bowers* et al. [44] found that by refluxing *(63)* in benzene for 18 hours, a good yield of the transannular cyclic ether *(64)* could be obtained. This was then either oxidized to the




*(63)* *(64)* *(66)* *(65)*

lactone *(65)* or cleaved with $BF_3$ in acetic anhydride to give *(66)*, a functionalized C-19 derivative.

Excellent yields are reported by *Meystre* et al. [45a] for the 6,19-oxides *(64)* obtained when 6β-alcohols are treated with lead tetraacetate and excess iodine in the presence of light. This reaction has been called the "hypoiodite reaction" and is discussed in detail by *Heusler* and *Kalvoda* [42d].

It has been shown very recently that the reaction *(63)* → *(64)* with lead tetraacetate can also be performed photolytically at 16–18 °C [45b].

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[42a] *K. Schaffner, D. Arigoni*, and *O. Jeger*, Experientia *16*, 169 (1960).

[42b] *K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni*, and *O. Jeger*, Helv. Chim. Acta *44*, 502 (1961).

[42c] *D. H. R. Barton* and *J. M. Beaton*, J. Amer. chem. Soc. *82*, 2641 (1960).

[42d] *K. Heusler* and *J. Kalvoda*, Angew. Chem. *76* (1964) in the press; Angew. Chem. internat. Edit. *3* (1964) in the press.

[42e] *A. L. Nussbaum* and *C. H. Robinson*, Tetrahedron *17*, 35 (1962).

[42f] *L. Velluz, G. Muller, R. Bardoneschi*, and *A. Poitevin*, C. R. hebd. Séances Acad. Sci. *250*, 725 (1960).

[42g] *A. Bowers* and *E. Denot*, J. Amer. chem. Soc. *82*, 4956 (1960).

[42h] For a complete discussion of the mechanistic aspects of intramolecular radical reactions, as well as the detailed stereochemical implications of these procedures, the reader is referred to the comprehensive reviews of *K. Heusler* and *J. Kalvoda* [42d], and *A. L. Nussbaum* and *C. H. Robinson* [42e].

[43a] *D. H. R. Barton, J. M. Beaton, L. E. Geller*, and *M. M. Pechet*, J. Amer. chem. Soc. *82*, 2640 (1960).

[43b] For details on the "Barton Reaction" see [42e].

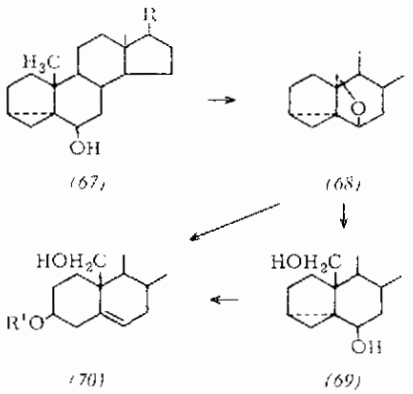
[44a] *A. Bowers, L. C. Ibanez, M. E. Cabezas*, and *H. J. Ringold*, Chem. and Ind. *1960*, 1299.

[44b] *A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas*, and *H. J. Ringold*, J. org. Chemistry *27*, 1862 (1962).

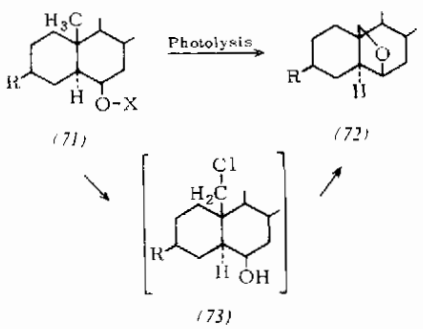
[45a] *C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner*, and *A. Wettstein*, Experientia *17*, 475 (1961).

[45b] *J. Kalvoda* and *K. Heusler*, Chem. and Ind. *1963*, 1431.

The lead tetraacetate reaction was recently applied to 3,5-cyclosteroids *(67)* [46a–c]. The 6,19-oxido-3,5-cyclosteroids *(68)* obtained in 25 % yield were solvolysed directly or via the functionalized 3,5-cyclosteroids *(69)* to the desired derivatives of type *(70)*, in both the androstane and cholestane series.

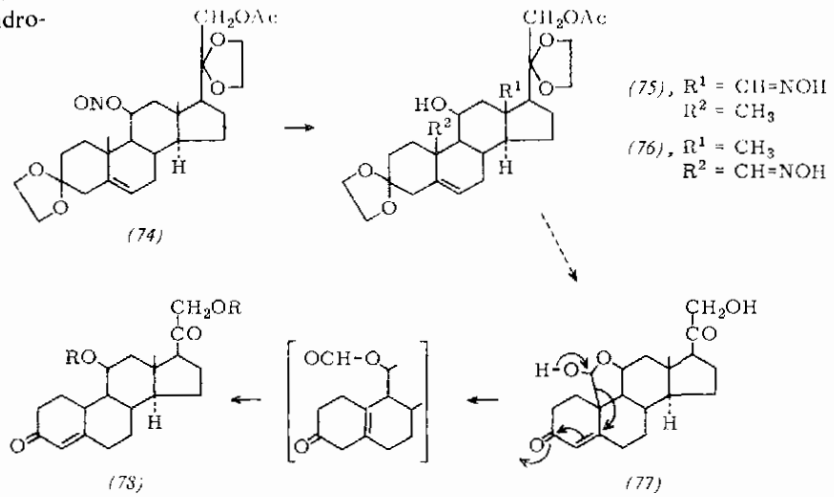


Working independently, *Akhtar* and *Barton* [47], and *Mills* and *Petrow* [48] found that hypochlorites of 6β-hydroxy steroids *(71)* can form 6,19-oxides *(72)* via the intermediate 19-chloro derivatives *(73)* which were not characterized. This reaction apparently has not found practical application so far.

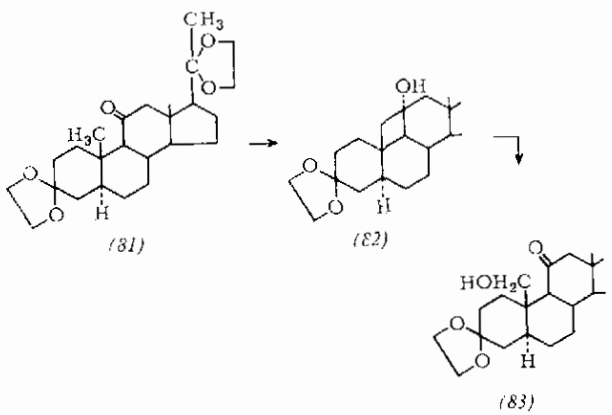


Simultaneous functionalization at C-18 and C-19 using an 11β-substituent was achieved by *Barton* and *Beaton* [49]. Photolysis of the 11β-nitrite *(74)* afforded a mixture of the 18- and 19-oximes *(75)* and *(76)*. Deoximation of *(76)* under the usual conditions with nitrous acid led to the expected hemiacetal *(77)*, a 19-isomer of aldosterone. Alkaline treatment of *(77)* resulted in a retroaldol elimination to yield 19-norcorticosterone *(78)* via the intermediate 11-formate. This represents the first elimination of a chemically functionalized C-19 angular methyl group [49c]. Subsequent photolysis of the 11-nitrite of *(78)* eventually led to the preparation of 19-noraldosterone.

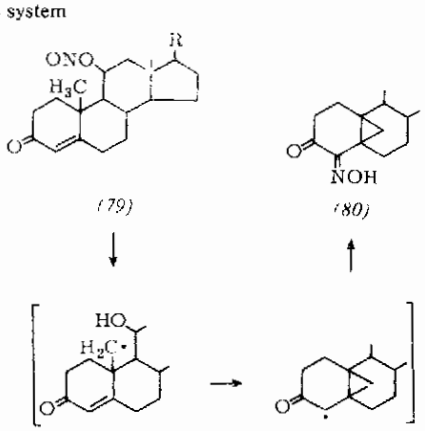
*Jeger* and coworkers, who performed the early work on functionalization of the steroidal C-18 methyl group [42a], used one of their methods [50] for an indirect



functionalization of C-19. In this approach [51], photochemical isomerization of a C-11 carbonyl group *(81)* serves to establish a new C–C bond between C-11 and C-19, with formation of a tertiary cyclobutanol *(82)*.



[49c] A photolysis of an 11-nitrite *(79)* resulting in an attack of C-19 was first described by *Barton* [42c]; however the unprotected 3-keto-Δ -ene system



was responsible for formation of the undesired product *(80)*.


[46a] *K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi*, and *Y. Morisawa*, Chem. Pharm. Bull. (Tokyo) *10*, 1126 (1962).

[46b] *J. Tadanier*, J. org. Chemistry *28*, 1744 (1963).

[46c] *R. M. Moriarty* and *T. D. D'Silva*, J. org. Chemistry *28*, 2445 (1963).

[47] *M. Akhtar* and *D. H. R. Barton*, J. Amer. Chem. Soc. *83*, 2213 (1961).

[48] *J. S. Mills* and *V. Petrow*, Chem. and Ind. *1961*, 946.

[49a] *D. H. R. Barton* and *J. M. Beaton*, J. Amer. chem. Soc. *83*, 750 (1961).

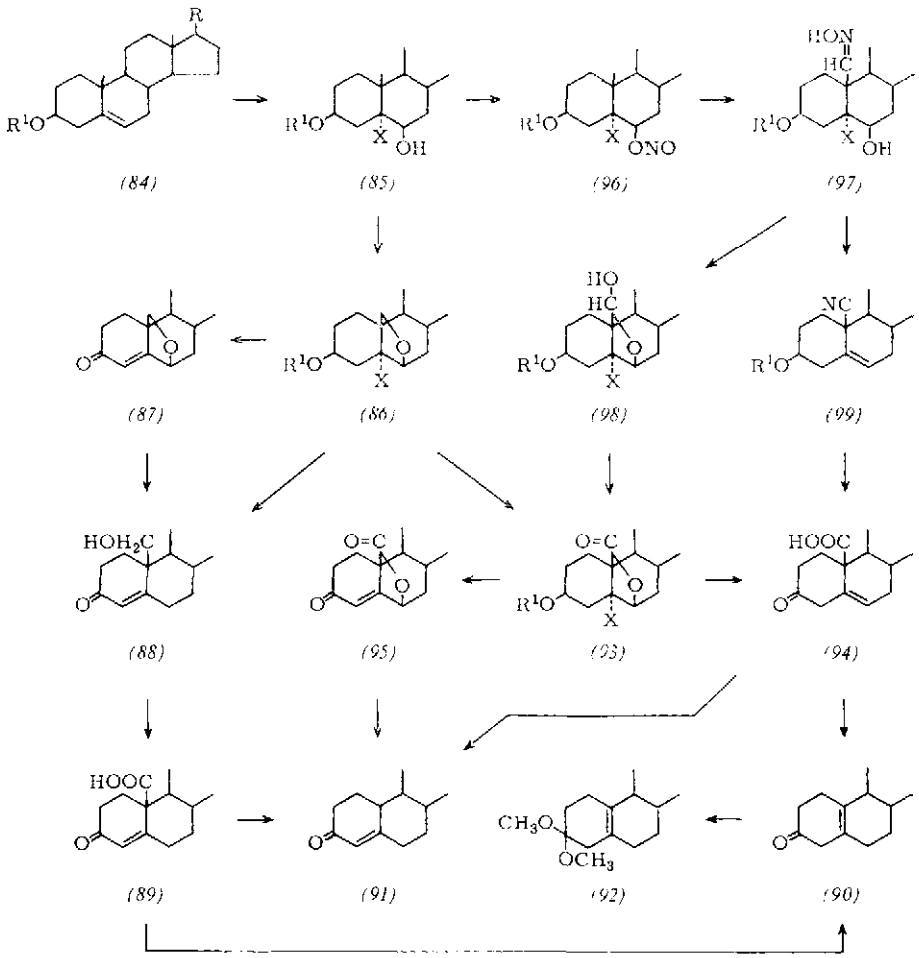
[49b] *D. H. R. Barton* and *J. M. Beaton*, J. Amer. chem. Soc. *84*, 199 (1962).

[50] *P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner*, and *O. Jeger*, Helv. chim. Acta *42*, 2122 (1959).

[51a] *H. Wehrli, M. S. Heller, K. Schaffner*, and *O. Jeger*, Helv. chim. Acta *44*, 2162 (1961).

[51b] *M. S. Heller, H. Wehrli, K. Schaffner*, and *O. Jeger*, Helv. chim. Acta *45*, 1261 (1962).

[51c] *J. Iriarte, K. Schaffner*, and *O. Jeger*, Helv. chim. Acta *46*, 1599 (1963).



Selective fragmentation of the new C–C bond is accomplished with lead tetraacetate, and a 19-hydroxy steroid *(83)* is obtained in good yield.

The intramolecular attack on the C-19 methyl group of 2β- and 4β-hydroxy steroids by various methods is discussed in detail by *Heusler* and *Kalvoda* [42d].

### D. Practicable Syntheses of 19-Norsteroids

Although the functionalizations described above were a prerequisite for the preparation of 19-norsteroids, methods for efficient elimination of the oxygenated angular methyl group still had to be found.

The best preparative solutions to this problem came almost simultaneously and independently from several laboratories in 1961–1963; this explains some unavoidable overlap in the methods used. As early as 1960, *Hagiwara*, *Noguchi*, and *Nishikawa* [52] described the elimination of 19-formyl and 19-carboxyl groups in excellent yields. However, their starting materials, the 19-hydroxy compounds were obtained by microbial oxidation.

The new 19-norsteroid syntheses summarized in the formula scheme apply the best methods of intramolecular functionalization to the readily available 6β-hydroxy steroids *(85)*, followed by smooth elimination of C-19 in such a way as to provide a variety of desired products. Most of these methods are equally well applicable in the androstane, pregnane, and cholestane series; consequently the formulae are generalized, having only an R group at C-17.

Thanks to the high yields of *(58)* obtained by addition of hypochlorous or hypobromous acid to the abundantly available 3β-acetoxy-$\Delta^5$-steroids *(84)*, these 5α-halogeno-6β-hydroxy compounds became the basic starting materials for all practical syntheses.

19-Hydroxy derivatives *(88)* can be obtained from *(85)* by two methods. In the first, developed by the CIBA group [53], *(85)* is treated with lead tetraacetate in the presence of iodine ("hypoiodite reaction") to form the cyclic ether *(86)* [54]. The 3-keto-$\Delta^4$-ene group *(87)* is then introduced and subsequent reductive ring cleavage with zinc/acetic acid leads to *(88)*. The other method was developed by the Syntex group [55] and starts with treatment of *(85)* with lead tetraacetate alone to yield

[52] *H. Hagiwara, S. Noguchi*, and *M. Nishikawa*, Chem. Pharm. Bull. (Tokyo) *8*, 84 (1960).

[53a] *K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner*, and *A. Wettstein*, Experientia *18*, 464 (1962).

[53b] *H. Ueberwasser, K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 344 (1963).

[53c] *J. Kalvoda, K. Heusler, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 1017 (1963).

[53d] *J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 1361 (1963).

[54] Cf. *J. F. Bagli, P. F. Morand*, and *R. Gaudry*, J. org. Chemistry *28*, 1207 (1963).

[55a] *A. Bowers, R. Vilotti, J. A. Edwards, E. Denot* and *D. Halpern*, J. Amer. chem. Soc. *84*, 3204 (1962).

[55b] *B. Berkoz, E. Denot*, and *A. Bowers*, Steroids *1*, 251 (1963).

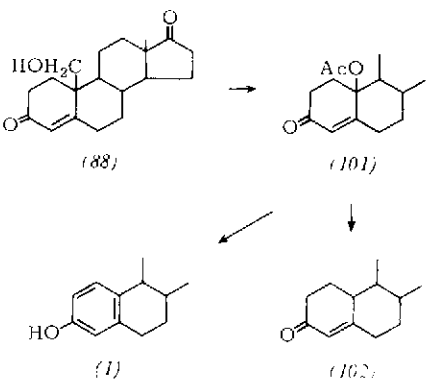
the cyclic ether *(86)*; the epoxide ring is opened under mild conditions with zinc and isopropanol, and the A-ring is then oxidized [*(86)* → *(88)*] in two steps. Oxidation of *(88)* to the 19-carboxy derivative *(89)* and elimination of the angular substituent by treatment with acid gave the required end products *(90)* and *(91)* in good overall yields. The best example of the Syntex procedure so far is the conversion of pregnenolone acetate *(84)*, R = $COCH_3$, into 19-norprogesterone *(91)*, R = $COCH_3$, in 37% yield [55a]. Another industrial application reported by the CIBA group [53b] entailed large scale preparation of *(90)* in the androstane series and its conversion into *(92)*. The latter compound is comparable in its reactions to *(2)*, since it has an easily removable protecting group on the A-ring, and a number of important 19-norsteroids may be obtained from it.

The lactones *(93)* prepared by oxidation of the cyclic ethers *(86)* [53a] can also be transformed into 19-norsteroids by two alternative routes, *viz.* ring opening followed by elimination *(93)* → *(94)* → *(91)* [55], or formation of the 3-keto-$\Delta^4$-ene group in ring A, followed by lactone opening and elimination *(93)* → *(95)* → *(91)* [56].

Compound *(85)* is also used as starting material in practical syntheses based on the Barton reaction [57], in which nitrites *(96)* are smoothly photolysed to the oximes *(97)*. These oximes are converted into the hemiacetals *(98)* according to *Akhtar* and *Barton* [56] and the latter are oxidized in good yields to the lactones *(93)*. The reaction sequence *(93)* → *(95)* → *(91)* then leads to the 19-norsteroids.

*Gardi* and *Pedrali* [58] dehydrated the oximes *(97)* to the angular nitriles *(99)*, which after saponification and oxidation in two steps gave the 19-carboxy compounds *(94)*. The conversion of *(94)* into *(91)* was accomplished by a new and mild method of decarboxylation using Girard T reagent [59a].

Application of the fragmentation of monohydric alcohols with lead tetraacetate to the now easily accessible 19-hydroxy compound *(88)* resulted in yet another elimination reaction [59b]. Good yields are reported for

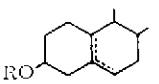



*(88)* *(101)* *(1)* *(102)*

the steps *(88)* → *(101)* → *(102)*. Thermal elimination applied to *(101)* resulted in concomitant aromatization to estrone *(1)* [60].

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German version: Angew. Chem. *76*, 249 (1964)

[59a] A recent improvement of this procedure involves reductive elimination of the 19-cyano group to give an intermediate mixture formulated as *(100)* from which *(91)* is obtained in good yields [58c].




*(100)*

[56] *M. Akhtar* and *D. H. R. Barton*, J. Amer. chem. Soc. *84*, 1496 (1962).

[57] Cf. *T. Jen* and *M. E. Wolff*, J. org. Chemistry *28*, 1573 (1963).

[58a] *R. Gardi* and *C. Pedrali*, Gazz. chim. ital. *91*, 1420 (1961).

[58b] *R. Gardi* and *C. Pedrali*, Gazz. chim. ital. *93*, 514 (1963).

[58c] *R. Gardi*, *C. Pedrali*, and *A. Ercoli*, Gazz. chim. ital. *93*, 525 (1963).

[59b] *M. Amorosa*, *L. Caglioti*, *G. Cainelli*, *H. Immer*, *J. Keller*, *H. Wehrli*, *M. Lj. Mihailovic*, *K. Schaffner*, *D. Arigoni*, and *O. Jeger*, Helv. chim. Acta *45*, 2674 (1962).

[60] For recent aromatization reactions of 19-norsterecids, see *R. Gardi*, *C. Pedrali*, and *A. Ercoli*, Gazz. chim. ital., in the press; *R. Gardi* and *C. Pedrali*, Steroids *2*, 387 (1963).

# Organosodium and Organopotassium Compounds

## Part II: Preparation and Synthetic Applications [1]

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*A selection of well established procedures for the preparation of the most common organosodium and organopotassium compounds is given. The wide synthetic applicability of organoalkali-metal compounds is shown by means of examples. Unlike Part I, Part II deals not only with "true" organoalkali compounds, but also with salt-like compounds such as sodium acetylides and sodiocarboxylic esters, since these possess considerable preparative value.*

A. Preparative Methods
1. From metal derivatives
a) Transmetalation
b) Metalation with alkali amides
c) Other methods
2. Reactions with metals
a) Metal-metal exchange
b) Direct metalation
c) Halogen-metal exchange
d) Cleavage of ethers
e) Cleavage of carbon-carbon bonds
f) Addition of metals to multiple bonds
B. Experimental procedures
1. Alkali metals
2. Organoalkali-metal compounds
3. Syntheses using organoalkali-metal compounds

## A. Preparative Methods

A distinction is to be drawn between methods which lead to the creation of new organometallic bonds by the action of elemental alkali metals, and those which merely effect transfer of the organometallic bond from one organic residue to another. We shall first consider the latter type, in which a readily accessible organometallic compound, or occasionally an alkali metal amide or alkoxide, is used for the preparation of an organometallic reagent.

### 1. From Metal Derivatives

#### a) *Transmetalation*

By analogy with an acid-base reaction, the weaker organometallic base may be obtained from the corresponding hydrocarbon and a more strongly basic organometallic compound. The first transmetalation of this type was observed by *Schorigin* [2] [*(1)* → *(2)*]. Tables 1 and 2 list examples of such transmetalations.

$$\underset{(1)}{\text{i-H}_9\text{C}_4\text{—Na}} + \text{H}_5\text{C}_6 \rightarrow \underset{(2)}{\text{H}_5\text{C}_6\text{—Na}} + \text{i-H}_{10}\text{C}_4$$

[1] Part I: Properties and Reactions: *M. Schlosser*, Angew. Chem. *76*, 124 (1964); Angew. Chem. internat. Edit. *3*, 287 (1964).

[*] Present address.

[2] *P. Schorigin*, Ber. dtsch. chem. Ges. *41*, 2711, 2717, 2723 (1908).

[3] *A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little*, and *R. L. Letsinger*, J. Amer. chem. Soc. *72*, 3785 (1950).

[4] *A. A. Morton, M. L. Brown, M. E.T. Holden, R. L. Letsinger*, and *E. E. Magat*, J. Amer. chem. Soc. *67*, 2224 (1945).

[5] *A. A. Morton* and *M. E.T. Holden*, J. Amer. chem. Soc. *69*, 1675 (1947).

Table 1. Metalation of hydrocarbons.

| Hydrocarbon to be metalated | Metalating agent [a] | Ref. | New compound | Yield [%] [b] |
|---|---|---|---|---|
| Ethylene | *(3)* | [3] | Vinylsodium | [c] |
| Propene | *(3)* | [4, 5] | Allylsodium | 69[d] |
| 1-Butene | *(3)* | [4, 5] | Crotylsodium | 62[d] |
| 2-Butene | *(3)* | [4, 5] | | |
| Isobutene | *(4)* | [6] | 2-Methylallylpotassium | 63 |
| Benzene | *(3)* | [7] | Phenylsodium | 78 |
| Benzene | *(5)* | [8] | | [c] |
| Benzene | *(6)* | [9] | Phenylpotassium | 45 |
| Benzene | *(7)* | [8, 10, 11] | | 83 |
| Cyclohexene | *(3)* | [12] | $\Delta^2$-Cyclohexenylsodium | 38–84 |
| Toluene | *(3)* | [7] | Benzylsodium | 40 |
| Toluene | *(2)* | [13, 14] | | 99 |
| Toluene | *(7)* | [8] | Benzylpotassium | 44 |
| Toluene | *(4)* | [6] | | 70 |
| Indene | *(8)* | [15] | $\Delta^2$-Indenylsodium | 50 |
| Acenaphthene | *(3)* | [16, 17] | 1,5-Acenaphthenylenedisodium | 50 |
| Fluorene | *(3)* | [16, 18] | 9-Fluorenylsodium | 100 |
| Fluorene | *(8)* | [15] | | 40–70 |
| Diphenylmethane | *(3)* | [7, 16] | Diphenylmethylsodium | 92 |
| 1,2-Diphenylethane | *(3)* | [16] | 1,2-Diphenylethylenedisodium | 70 |
| Triphenylmethane | *(3)* | [16] | Triphenylmethylsodium | 93 |
| Triphenylmethane | *(4)* | [19] | Triphenylmethylpotassium | [c] |
| Tri-*o*-tolylmethane | *(4)* | [20] | Tris-(α-potassio-*o*-tolyl)methane | 40 |

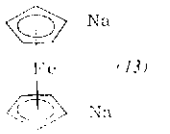
[a] *(3)*: n-Amylsodium; *(4)*: Phenylisopropylpotassium; *(5)*: n-Butylsodium; *(6)*: Ethylpotassium; *(7)*: n-Butylpotassium; *(8)*: Triphenylmethylsodium

[b] The yields given should be regarded as minimum values, since they almost all refer to the carboxylic acids prepared for characterization purposes.

[c] Exact values not given.

[d] The products isolated from the carboxylation were the isomeric carboxylic acids $R\text{—}CH\text{=}CH\text{—}CH_2\text{—}COOH$ and $H_2C\text{=}CH\text{—}CHR\text{—}COOH$, together with small amounts of the α,β-unsaturated acid $R\text{—}CH_2\text{—}CH\text{=}CH\text{—}COOH$ and dicarboxylic acids.

Ferrocene readily undergoes double metalation by reaction with *(2)* or *(3)* to give *(13)* in yields of 47 and 68 %, respectively [30a].




*(13)*

Table 2. Metalation of ethers and thioethers.

| Ether or thioether | Metalating agent [a] | Ref. | New compound | Yield [%] [b] |
|---|---|---|---|---|
| Furan | *(9)* | [21] | 2-Furylsodium | 58 |
| Thiophene | *(2)* | [22] | 2-Thienylsodium | 89 |
| Thiophene | *(3)* | [23] | 2,5-Thienylenedisodium | 50 |
| 2,3-Dihydrofuran | *(3)* | [24] | 2,3-Dihydro-5-furylsodium | 58 |
| Anisole | *(2)* | [25] | *o*-Anisylsodium | 64 |
| Anisole | *(10)* | [26] | *o*-Anisylsodium and -lithium | 71 |
| Anisole | *(11)* | [27] | *o*-Anisylpotassium | 60 |
| Dibenzofuran | *(9)* | [28] | 4,6-Dibenzofurylenedisodium | 80 |
| | *(12)* | [28] | | 88 |
| Dibenzothiophene | *(3)* | [25] | 4-Dibenzothienylenesodium | 37 |
| Diphenyl ether | *(2)* | [29] | *o*-Phenoxyphenylsodium | 10 |
| Diphenyl ether | *(10)* | [30] | *o*-Phenoxyphenylsodium and -lithium (together with *o,o'*-dimetalated derivative) | 50 |
| Diphenyl sulfide | *(2)* | [25] | *o*-Thiophenoxyphenylsodium | 56 |

[a] See footnote [a] of Table 1. In addition:
*(9)*: Benzylsodium *(11)*: Phenylpotassium
*(10)*: Diphenyl-lithium-sodium *(12)*: *p*-Tolylsodium

[b] See footnote [b] of Table 1.

b) *Metalation with Alkali Amides*

True organometallic compounds are not required for the anionization of ketones, nitriles, esters, sulfoxides, and other compounds containing activated hydrogens. The exchange of hydrogen for metal may be accomplished with even relatively weak proton acceptors such as sodium dispersions, potassium hydroxide, sodium hydride, sodium ethoxide, or potassium t-butoxide. Sodamide or potassamide in liquid ammonia are even more effective. However, these amides are too weakly basic to metalate purely aliphatic or monophenylated hydrocarbons [31]. On the other hand, alkali-metal benzyls, *e.g. (9)*, are rapidly ammonolyzed with decolorization by liquid ammonia.

$$\underset{(9)}{H_5C_6{-}CH_2{-}Na} + NH_3 \rightarrow H_5C_6{-}CH_3 + NaNH_2$$

The reactive hydrogens in acetylene [31a] or fluorene [32] are readily metalated by alkali-metal amides. As a rule, alkali-metal benzyls such as *(15)* and *(16)* are obtained smoothly with these amides if at least one additional activating group is present besides one aryl

$$\underset{(13)}{H_5C_6{-}CH_2{-}COOH} + 2\,NaNH_2 \rightarrow \underset{(14)}{H_5C_6{-}CHNa{-}COONa} + 2\,NH_3$$

$$(H_5C_6)_2CH_2 + NaNH_2 \rightarrow \underset{(15)}{(H_5C_6)_2CH{-}Na} + NH_3$$

$$(H_5C_6)_3CH + KNH_2 \rightarrow \underset{(16)}{(H_5C_6)_3C{-}K} + NH_3$$


[6] *K. Ziegler* and *H. Dislich*, Chem. Ber. *90*, 1107 (1957).

[7] *A. A. Morton* and *I. Hechenbleikner*, J. Amer. chem. Soc. *58*, 2599 (1936).

[8] *H. Gilman* and *J. C. Bailie*, J. org. Chemistry *2*, 84 (1937).

[9] *H.Gilman* and *R.H.Kirby*, J. Amer. chem. Soc. *58*, 2074 (1936).

[10] *H. Gilman, A. L. Jacoby*, and *H. Ludeman*, J. Amer. chem. Soc. *60*, 2336 (1938).

[11] *D. Bryce-Smith* and *E. E.Turner*, J. chem. Soc. (London) *1953*, 861.

[12] *A. A. Morton* and *R. A.Finnegan*, J. Polymer Sci.*38*, 19 (1959).

[13] *J. F. Nobis* and *L. F. Moormeier*, Ind. Engng. Chem., analyt. Edit. *46*, 539 (1954).

[14] *H. Gilman, H. A. Pacevitz*, and *O. Baine*, J. Amer. chem. Soc. *62*, 1514 (1940).

[15] *J. B. Conant* and *G. W. Wheland*, J. Amer. chem. Soc. *54*,1212 (1932).

[16] *A. A. Morton* and *E. L. Little*, J. Amer. chem. Soc. *71*, 487 (1949).

[17] *A. A. Morton, J. B. Davidson, T. R. P. Gibb, E. L. Little, E. W. Clarke*, and *A. G. Green*, J. Amer. chem. Soc. *64*, 2250 (1942).

[18] *A.A.Morton* and *F.Fallwell*, J.Amer.chem.Soc.*60*, 1924 (1938).

[19] *K. Ziegler*, Angew. Chem. *49*, 459 (1936).

[20] *P. D. Bartlett* and *J. E. Jones*, J. Amer. chem. Soc. *64*, 1837 (1942).

[21] *H. Gilman* and *F. Breuer*, J. Amer. chem. Soc. *56*, 1123 (1934).

[22] *J. W. Schick* and *H. D. Hartough*, J. Amer. chem. Soc. *70*, 286 (1948).

[23] *A. A. Morton* and *C. E. Claff*, J. Amer. chem. Soc. *76*, 4935 (1954).

[24] *R. Paul* and *S.Tchelitcheff*, C. R. hebd. Séances Acad. Sci. *235*, 1226 (1952).

[25] *H. Gilman* and *R.L. Bebb*, J. Amer. chem. Soc. *61*, 109 (1939).

[26] *G. Wittig* and *E. Benz*, Chem. Ber. *91*, 874 (1958).

[27] *A. A. Morton* and *E. J. Lanpher*, J. org. Chemistry *23*, 1639 (1958).

[28] *H. Gilman, F. W. Moore*, and *O. Baine*, J. Amer. chem. Soc. *63*, 2479 (1941).

[29] *A. Lüttringhaus* und *G. v. Sääf*, Angew. Chem. *52*, 578 (1939); Liebigs Ann. Chem. *542*, 241 (1939); *557*, 25 (1947).

[30] *G. Wittig* and *L. Pohmer*, Chem. Ber. *89*, 1334 (1956).

[30a] *A. N. Nesmeyanov* and *E. G. Perevalova*, Dokl. Akad. Nauk SSSR *112*, 439 (1957); ibid. *120*, 1263 (1958); *S. I. Goldberg, D. W. Mayo, M. Vogel, H. Rosenberg*, and *M. Rausch*, J. org. Chemistry *24*, 824 (1959); *E. O. Fischer* and *H. Brunner*, Z.Naturforsch. *16b*, 406 (1961).

[31] *C. B. Wooster* and *J. F. Ryan*, J. Amer. chem. Soc. *54*, 2419 (1932).

[31a] *R. A. Raphael*: Acetylenic Compounds in Organic Synthesis. Butterworths, London 1955, pp. 192–196.

[32] *R. S. Yost* and *C. R. Hauser*, J. Amer. chem. Soc. *69*, 2325 (1947).

residue. This is illustrated by the preparation of sodium α-sodio-α-phenylacetate *(14)* [33], diphenylmethylsodium *(15)* [31], and triphenylmethylpotassium *(16)* [34].

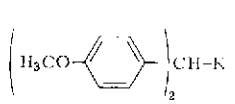
These transformations are equilibrium reactions. In the case of di-*p*-anisylmethane *(17)* [35], the equilibrium lies more to the left.

$$(H_3CO-C_6H_4)_2CH_2 + NaNH_2 \rightleftharpoons (H_3CCO-C_6H_4)_2CH^-Na^+ + NH_3$$

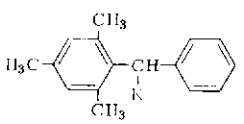
*(17)*

With diphenyl- and triphenylmethane, it is only in the ammonia solution that the equilibrium seems to be shifted completely towards the organometallic compound. Even on careful (vacuum) removal of the ammonia from a solution of triphenylmethylsodium, the residue is simply a mixture of triphenylmethane and sodamide. Addition of an organic solvent before the removal of the ammonia does not prevent the aminolysis [36a, 36b]. In contrast to diphenyl- and triphenylmethylsodium, the corresponding potassium derivatives may be isolated from their ammonia solutions with no difficulty, immaterial of whether the ammonia is evaporated off directly or whether an organic phase is first admixed [36a, 36b]. The fact that here the reversion to the hydrocarbon is suppressed does not necessarily imply that the organopotassium compound is more stable; the phenomenon could also be due to extremely slow attainment of the aminolysis-equilibrium in the case of the organopotassium derivative [37].

Di-*p*-anisylmethylpotassium *(18)* and mesitylphenylmethylpotassium *(19)* are stronger bases. If the attempt is made to isolate them from ammonia solution, they are protonated to regenerate the hydrocarbon just like the organosodium compounds [36a, 36b].



*(18)*



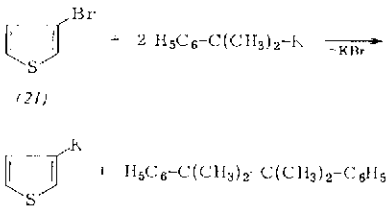
*(19)*

### c) *Other Methods*

New organosodium and organopotassium reagents may also be prepared by the reactions of organosodium and -potassium compounds with olefins *(20)* (addition), with halides *(21)* (halogen-metal interconversion), and with organometallic compounds, particularly those of mercury *(22)* (metal-metal interconversion). None of these reactions is of major preparative significance.

$$(H_5C_6)_2C{=}CH_2 + n\text{-}H_{11}C_5\text{-}Na \longrightarrow (H_5C_6)_2C(n\text{-}C_6H_{13})\text{-}Na \quad [38]$$

*(20)*



*(21)*

$$+ H_5C_6\text{-}C(CH_3)_2\text{-}C(CH_3)_2\text{-}C_6H_5 \quad [39]$$

$$(H_5C_6)_2Hg + 2\ n\text{-}H_9C_4\text{-}Na \longrightarrow 2\ H_5C_6\text{-}Na + (n\text{-}H_9C_4)_2Hg \quad [40]$$

*(22)*

## 2. Reactions with Metals [*]

### a) *Metal-Metal Exchange*

The first organoalkali-metal compounds were prepared from organomercury compounds [*(23)* and Table 3] and sodium [2, 41, 42], and were even isolated [43].

$$(H_5C_6)_2Hg + 2\ Na \rightarrow 2\ H_5C_6\text{-}Na + Na/Hg$$

*(23)*

Lithium and potassium derivatives may be obtained analogously. Since these are equilibrium reactions, the

Table 3. Organosodium and organopotassium compounds obtained from the corresponding mercury derivatives.

| Organic residue of mercury compound | Reference | |
|---|---|---|
| | Na derivative | K derivative |
| Methyl | [43, 44] | [43, 45] |
| Ethyl | [2, 9, 43, 45, 46] | [9] |
| n-Propyl | [46] | -- |
| n-Butyl | [8] [d] | [8, 14] [d] |
| i-Amyl | [2] [d] | - |
| n-Octyl | [43] | - |
| Phenyl | [14, 43] | [47] |
| *o*-Tolyl | [14] [d] | — |
| *m*-Tolyl | [14] [d] | — |
| *p*-Tolyl | [14] [d] | [14] [d] |

[d] Under the reaction conditions used, these organoalkali-metal compounds occur only as intermediates.

[33] *C. R. Hauser* and *M. T. Tetenbaum*, J. org. Chemistry *23*, 1146 (1958).

[34] *C. A. Kraus* and *R. Rosen*, J. Amer. chem. Soc. *47*, 2739 (1925).

[35] *C. R. Hauser* and *P. J. Hamrick*, J. Amer. chem. Soc. *79*, 3142 (1957).

[36a] *R. Levine, E. Baumgarten*, and *C. R. Hauser*, J. Amer. chem. Soc. *66*, 1230 (1944).

[36b] *C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh*, and *F. C. Frostik*, J. org. Chemistry *20*, 1531 (1955).

[37] Cf. *G. Wittig*, Experientia *14*, 392 (1958).

[38] *A. A. Morton* and *H. C. Wohlers*, J. Amer. chem. Soc. *69*, 167 (1947).

[39] *G. Wittig* and *V. Wahl*, unpublished data.

[*] In Anglo-American literature, a distinction is made between exchange reactions between organic halides and organoalkali-metal compounds, and those involving alkali metals, *e.g.*

$R\text{-}Br + R'Na \rightarrow R\text{-}Na + R'Br$ "halogen-metal interconversion"
$R\text{-}Br + 2\ Na \rightarrow R\text{-}Na + NaBr$ "halogen-metal exchange"

See *R. G. Jones* and *H. Gilman* in *R. Adams:* Organic Reactions, Wiley, New York 1951, Vol. 6, p. 339; Chem. Reviews *54*, 835 (1954).

[40] *H. Gilman, W. Langham*, and *A. L. Jacoby*, J. Amer. chem. Soc. *61*, 109 (1939).

[41] *F. S. Acree*, Amer. Chem. J. *29*, 588 (1903).

[42] *G. Buckton*, Liebigs Ann. Chem. *112*, 222 (1859).

[43] *W. Schlenk* and *J. Holtz*, Ber. dtsch. chem. Ges. *50*, 262 (1917).

[43a] *W. Schlenk* and *J. Holtz*, [43], pp. 265 et seq.; cf. *H. Gilman* and *T. C. Wu*, J. org. Chemistry *18*, 759 (1953).

[44] *W. H. Carothers* and *D. D. Coffman*, J. Amer. chem. Soc. *52*, 1254 (1930).

[45] *W. H. Carothers* and *D. D. Coffman*, J. Amer. chem. Soc. *51*, 588 (1929).

[46] *F. C. Whitmore* and *H. D. Zook*, J. Amer. chem. Soc. *64*, 1783 (1942).

[47] *A. A. Morton* and *R. L. Letsinger*, J. Amer. chem. Soc. *69*, 172 (1947).

alkali metal is always introduced in great excess. Often no attempt is made to separate the resulting organoalkali-metal compound from the unused alkali metal and the amalgam, although the separation procedure is a simple one [43a].

Although many organomercury compounds are easily prepared, this method soon fell out of favor, since it is not suitable for the preparation of large quantities of organoalkali compounds. The insidious toxicity of liquid mercury derivatives is a further serious disadvantage. Nowadays the mercury/alkali metal exchange is used only for the preparation of limited amounts of salt-free organosodium or organopotassium compounds when drastic conditions must be avoided.

The displacement method can be applied to other organometallic compounds, provided that the metal to be displaced is more electronegative than sodium. Alkylpotassium compounds are thus obtained elegantly from lithium alkyls and potassium metal in hydrocarbons [48]; transmetalation in benzene leads directly to phenylpotassium *(11)* in 86 % yield [11]:

$$R{-}Li \xrightarrow{K} R{-}K \xrightarrow{Benzene} H_5C_6{-}K \qquad (11)$$

b) *Direct Metalation*

The direct replacement of hydrogen by the elemental metal provides the simplest means of access to organoalkali compounds.

$$R{-}H + M \rightarrow R{-}M + {}^1/_2\,H_2$$

The controlling factors in direct metalation are the acidity of the hydrocarbon, the electropositivity and particle size of the metal used, and the nature of the solvent. The conversion of triphenylmethane into triphenylmethylpotassium by means of molten potassium, which reacts with the hydrocarbon above 200 °C, is accompanied by side reactions [49]. Metalation may be accomplished quite easily, however, with the blue solution of potassium in liquid ammonia [50], or with the corresponding solution of sodium [51]; the latter, however, reacts more sluggishly. Sodium dispersions (see Section B.1) and sodium aromatic complexes [52] are far superior to solid sodium in the anionization of carboxylic esters and aliphatic nitriles. Potassium reacts more vigorously with thiophene [22] than sodium does, and metallic cesium displaces even the hydrogen atoms of paraffins [53]. Table 4 gives a list of some organosodium and organopotassium compounds obtained by hydrogen-metal exchange. The displaced hydrogen is not always liberated as gas. With acetylene [54], fluorene [55], and triphenylmethane [56], the reaction mixtures contain hydrogenation products as well as the appropriate organometallic base. The metalation of toluene to give benzylpotassium *(24)* in the presence of sodium oxide is especially noteworthy in this respect [57].

$$2\,H_5C_6{-}CH_3 + 2\,K + Na_2O \xrightarrow{3^h,\ 110\,^\circ C} 2\,H_5C_6{-}CH_2{-}K + NaH + NaOH$$

*(24)*, 87 %

Table 4. Organosodium and organopotassium compounds obtained by hydrogen-metal exchange.

| Organic residue | Reference | |
|---|---|---|
| | Na derivative | K derivative |
| Ethynyl | [58, 59, 59b] | [59] |
| Ethynylene | [60] | |
| Phenylethynyl | [61] | [61] |
| Pentaphenylcyclopentadienyl | — | [62] |
| Indenyl | [63, 64] | — |
| 9-Fluorenyl | [64] | |
| 9-Fluorenylidene | [c] | [65] [c] |
| Triphenylmethyl | [50] | [49, 50, 55] |
| Diphenylmethylene | — | [66] [c] |
| Benzyl | — | [56] |
| 2-Furyl | | [21] |
| 5-Methyl-2-furyl | — | [21] |
| 2-Thienyl | — | [67] |
| 5-Chloro-2-thienyl | [22] | — |
| 5-Bromo-2-thienyl | [22] | — |
| 5-Iodo-2-thienyl | [22] | |

[c] Apparently the geminally dimetalated derivatives are formed.

The hydrogen atoms bound to the metalloids in germane $GeH_4$, triphenylgermane $(C_6H_5)_3GeH$, and triphenylstannane $(C_6H_5)_3SnH$ are metalated with particular ease by sodium or potassium in liquid ammonia, but not by sodamide [68–70].

c) *Halogen-Metal Exchange*

Derivatives of heavier alkali metals can be prepared in a manner analogous to the synthesis of organomagnesium

[48] *D. Bryce-Smith*, J. chem. Soc. (London) *1954*, 1079.

[49] *M. Hanriot* and *O. Saint-Pierre*, Bull. Soc. chim. France [3], *1*, 775 (1889); *A. Werner* and *A. Grob*, Ber. dtsch. chem. Ges. *37*, 2898 (1904).

[50] *C. B. Wooster* and *N. W. Mitchell*, J. Amer. chem. Soc. *52*, 688 (1930).

[51] *C. A. Kraus* and *T. Kawamura*, J. Amer. chem. Soc. *45*, 2756 (1923).

[52] *L. Horner* and *H. Güsten*, Liebigs Ann. Chem. *652*, 99 (1962).

[53] *E. Marcus*, unpublished data; cited by *W. Schlenk* in *Houben-Weyl:* Die Methoden der organischen Chemie. 2nd Edit. Thieme-Verlag, Leipzig 1924, Vol. IV, p. 946.

[54] *R. A. Raphael:* Acetylenic Compounds in Organic Synthesis. Butterworths, London 1955, p. 1.

[55] *J. J. Eisch* and *W. C. Kaska*, J.org.Chemistry *27*, 3745 (1962).

[56] *H.O.House* and *V.Kramar*, J.org.Chemistry *27*, 4146 (1962).

[57] *C.E.Claff* and *A.A.Morton*, J. org. Chemistry *20*, 440 (1955).

[58] *K. Heß* and *M. Munderloh*, Ber. dtsch. chem. Ges. *51*, 377 (1918).

[59a] *T. H. Vaughn, G. F. Hennion, R. R. Vogt*, and *J. A. Nieuwland*, J. org. Chemistry *2*, 1 (1937).

[59b] *R. A. Raphael:* Acetylenic Compounds in Organic Synthesis. Butterworths, London 1955, pp. 192–196.

[60] *C. Matignon*, C. R. hebd. Séances Acad. Sci. *124*, 775 (1897).

[61] *H. Gilman* and *R.V.Young*, J. org. Chemistry *1*, 315 (1936).

[62] *K. Ziegler* and *L. Ewald*, Liebigs Ann. Chem. *473*, 163 (1929).

[63] *R. Weißgerber*, Ber. dtsch. chem. Ges. *41*, 2913 (1908); *42*, 569 (1909).

[64] U.S.-Pat. 2171867 (Sept. 5th, 1939), inventors: *N. S. Scott, J. F. Walker* and *V. L. Hansley*.

[65] *G. W. H. Scherf* and *R. K. Brown*, Canad. J. Chem. *38*, 697 (1960).

[66] *O. Saint-Pierre*, Bull. Soc. chim. France [3] 6, 292 (1891).

[67] Cf. *K. Ziegler* [87], pp. 1745 et seq.

[68] *C. A. Kraus* and *E. S. Carney*, J. Amer. chem. Soc. *56*, 765 (1934).

[69] *G. K. Teal* and *C. A. Kraus*, J. Amer. chem. Soc. *72*, 4705 (1950).

[70] *C. A. Kraus* and *W. H. Kahler*, J. Amer. chem. Soc. *55*, 3537 (1933).

and organolithium compounds, *i.e.* by the action of the metal on organic halides.

Many years ago, *Schorigin* [2] postulated the occurrence of the alkylsodium compounds *(1)*, which were supposed to be formed by halogen-metal exchange, as intermediates in the Wurtz synthesis and in certain addition reactions:

$$i\text{-}H_9C_4\text{—}Br + Na \rightarrow i\text{-}H_9C_4\text{—}Na \rightarrow \text{Products.}$$

*(1)*

Nevertheless, it was a long time before this procedure became a standard method, surpassing in importance all other preparations of organosodium and organopotassium compounds. The high reactivity of the organometallic compounds at first frustrated any attempts at their isolation; instead, they were consumed by subsequent reactions with the solvent or with unreacted halide.

It was only after the studies of *Morton* [72–75] that it became possible to suppress secondary processes such as transmetalation, elimination, and Wurtz condensation. The use of finely divided sodium, high-speed stirring, and effective temperature control permit the preparation of numerous organosodium compounds in quantitative yield. Thus, a continuous unit [71] is capable of handling more than 1 kg of sodium powder per hour to give phenylsodium in 75 % yield [71].

The greater reactivity of sodium and potassium derivatives, relative to the Grignard and lithium compounds used previously, extends the scope of organometallic reagents in preparative reactions. Furthermore, organometallic compounds may now be prepared economically from sodium and alkyl or aryl chlorides, using cheap solvents, and are thus suitable for industrial applications. Grignard compounds are mostly obtained from expensive bromides or iodides, whereas all of the organoalkali-metal derivatives in Table 5, with but a single exception [84], are derived from chlorides.

*E. Müller* [85] described some interesting exchange reactions of the disodium adduct of tetraphenylethylene, which behaves like dissolved sodium. Thus, *o*-bromofluorobenzene is converted by it into *o*-fluorophenylsodium at −70 °C in tetrahydrofuran; treatment of this with benzophenone leads to a 65 % yield of *o*-fluorophenyldiphenylmethanol. Under the same conditions, *o*-bromophenylsodium, which is obtained similarly from *o*-dibromobenzene, is unstable, dehydrobenzene derived from its decomposition can be trapped with furan in 15–36 % yield.

Table 5. Organosodium and organopotassium compounds obtained by halogen-metal exchange.

| Organic residue | Na derivative | | K derivative | |
|---|---|---|---|---|
| | Ref. | Yield [%] [b] | Ref. | Yield [%] [b] |
| n-1-Propyl | [72] | 26 | — | — |
| n-1-Butyl | [73] | 42 | — | — |
| n-1-Amyl | [3, 74] | 72–80 | [4] | 35 |
| n-1-Octyl | [75] | 64 | — | |
| n-1-Decyl | [75] | 31 | — | — |
| n-1-Dodecyl | [76] | 20 | [76] | 10 |
| n-2-Butyl | [73] | 2 | — | — |
| n-2-Amyl | [73] | 2 | | — |
| Cyclohexyl | [77] | 8 | — | — |
| Triphenylmethyl | [43, 78, 79] | 95-100 | — | |
| Vinyl | [80] | 90 | [80, 81] | 73 |
| 1-Cyclohexenyl | [80] | 60 | — | — |
| α-Styryl | [80] | 21 | — | |
| Phenyl | [13, 14, 82] | 100 | [27] | 55 |
| *p*-Tolyl | [14, 19] | 80 | — | |
| *p*-Biphenyl | [77] | 78 | — | |
| 1-Naphthyl | [83] | 90 | | — |
| 3-Pyrenyl | [83] | 80 | — | — |
| 9-Anthryl | [83] | 55 | — | — |
| 9-Phenanthryl | [83] | 35 | — | — |
| 2-Furyl | [77] | [c] | | |
| 3-Furyl | — | — | [84] | 0.5 |
| 2-Thienyl | [22] | 84 | — | — |

[b], [c]: See corresponding footnotes in Table 1.

d) *Cleavage of Ethers*

The cleavage of ethers by alkali metals [86–88] is formally analogous to the halogen-metal exchange, but differs from it in one significant respect: purely aliphatic ethers are stable toward metals below 200 °C. Only aryl and benzyl ethers are cleaved; with mixed aryl ethers *(25)*, the oxygen remains attached to the aromatic residue, while the alkyl residue becomes part of the organometallic compound. Benzyl aryl ethers *(26)* are decomposed to the more weakly basic benzylalkali-metal compound and alkali phenoxide.


[71] *H. Ruschig, R. Fugmann*, and *W. Meixner*, Angew. Chem. *70*, 71 (1958).

[72] *A. A. Morton, G. M. Richardson*, and *A. T. Hallowell*, J. Amer. chem. Soc. *63*, 327 (1941).

[73] *A. A. Morton, J. B. Davidson*, and *H. A. Newey*, J. Amer. chem. Soc. *64*, 2240 (1942).

[74] *A. A. Morton* and *H. A. Newey*, J. Amer. chem. Soc. *64*, 2248 (1942).

[75] *A. A. Morton, J. B. Davidson*, and *R. J. Best*, J. Amer. chem. Soc. *64*, 2239 (1942).

[76] *R. N. Meals*, J. org. Chemistry 9, 211 (1944).

[77] *A. A. Morton, G. H. Patterson, J. J. Donovan*, and *E. L. Little*, J. Amer. chem. Soc. *68*, 93 (1946).

[78] *W. B. Renfrow* and *C. R. Hauser* in Organic Syntheses. Wiley, New York 1943, Coll. Vol. II, p. 607.

[79] *H. E. Zimmermann* and *F. J. Smentowski*, J. Amer. chem. Soc. *79*, 5455 (1957).

[80] Brit. Pat. 886980 (Oct. 2nd, 1959), Union Carbide Corporation, inventor: *D. J. Foster*.

[81] *R. G. Andersan, M. B. Silverman*, and *D. M. Ritter*, J. org. Chemistry *23*, 750 (1958).

[82] U.S.-Pat. 2012372 (Aug. 27th, 1935), Winthrop Chem. Co., inventors: *M. Bockmühl* and *G. Ehrhart*.

[83] French Pat. 1236912 (June 13th, 1960), Union Carbide Corporation, inventor: *D. J. Foster*.

[84] *H. Gilman* and *G. F. Wright*, J. Amer. chem. Soc. *55*, 2893 (1933).

[85] *E. Müller* and *G. Röscheisen*, Chem. Ber. *90*, 543 (1957).

[86] *P. Schorigin*, Ber. dtsch. chem. Ges. *56*, 176 (1923).

[87] *K. Ziegler* and *F. Thielmann*, Ber. dtsch. chem. Ges. *56*, 1740 (1923).

[88] *A. Lüttringhaus* in *Houben-Weyl*: Die Methoden der Organischen Chemie. 2nd Edit., Thieme-Verlag, Leipzig 1924, Vol. II, p. 424.

$$H_5C_6-O-CH_3 + 2\,K \rightarrow H_5C_6-K + KOCH_3$$
(25)

$$(H_5C_6)_3C-O-C_6H_5 + 2\,K \rightarrow (H_5C_6)_3C-K + KOC_6H_5$$
(26)

A convenient source of metal is a liquid Na/K alloy [87], an excess being used. Cleavage is generally quantitative (see Table 6, K derivatives). Only a few very labile ethers react at low temperatures with pulverized or solid sodium (see Table 6, Na derivatives). Ether cleavage provides a means of degrading complex ethers and thioethers [88,94]. Acetals are cleaved with particular ease. The resulting α-metalated ethers sometimes undergo Wittig rearrangement [91].

Table 6. Organosodium and organopotassium compounds obtained by ether cleavage.

| Organic residue | Reference | |
|---|---|---|
| | Na derivative | K derivative |
| Phenyl | — | [27] |
| Allyl | [89] | [93] |
| Phenylisopropyl | — | [6,90] |
| Dibenzylphenylmethyl | — | [90] |
| Diphenylmethyl | · | [87] |
| 1,1-Diphenylethyl | — | [90] |
| 1,1,2-Triphenylethyl | — | [90] |
| Triphenylpropynyl | — | [90] |
| 1,1,3,3-Tetraphenylprop-2-yl | -- | [90] |
| Methoxydiphenylmethyl | [91] | [87,91] |
| 9-Fluorenyl | [92] | — |
| 9-Phenyl-9-fluorenyl | [57] | — |
| 9-Methoxy-9-fluorenyl | [57] | |

e) *Cleavage of Carbon-Carbon Bonds*

Polyarylethanes *(27)* are reported by *Schlenk* [95] to be cleaved by alkali metals at their weakened central C–C bond, giving two molecules of organometallic compound.

$$(H_5C_6)_3C-C(C_6H_5)_3 \xrightarrow{Na/Hg} 2\,(H_5C_6)_3C-Na$$
(27)

With sodium powder, hexaphenylethane *(27)* is largely irreversibly isomerized to *p*-diphenylmethylphenyltriphenylmethane.

The tendency of the ethane derivatives to dissociate may be roughly estimated from the nature of the metal required for cleavage. Hexaphenylethane reacts even with 1 % sodium amalgam, 9,9′-dimethylbixanthyl requires 40 % sodium amalgam [96], while 1,1,2,2-tetraphenylethane [87] is cleaved only with liquid Na/K alloy to yield diphenylmethylpotassium. Table 7 gives a survey of the organosodium and organopotassium compounds obtained from symmetrical ethanes by such cleavage reactions. The cleavage of unsymmetrical hydrocarbons such as pentaphenylethane [95] and 1,1,1,2-tetraphenylethane [87] is also possible. In this case, mixtures of two organometallic compounds are obtained.

Table 7. Organosodium and organopotassium compounds obtained by cleavage of symmetrical ethanes.

| Organic residue | Reference | |
|---|---|---|
| | Na derivative | K derivative |
| Triphenylmethyl | [95] | |
| Di-*p*-biphenylyl-α-naphthylmethyl | [95] | — |
| Xanthyl | [96] | [96] |
| 9-Methyl-9-xanthyl | [96] | [96] |
| Diphenylmethyl | · | [96] |
| $(H_5C_6)_2(C_6H_5O)C$ | [97] | [97] |
| $(H_5C_6)_2(H_5C_6-C\equiv C)C-$ | [98] | — |
| *p*-Biphenylmethyl | — | [99] |
| $(H_5C_6)_2C=CH-CH_2-$ | -- | [99] |
| $(H_3C)_3C-C\equiv C-$ | · | [100] |

The preparation of triphenylmethylsodium [43] from triphenylmethyl chloride and Na/Hg certainly involves hexaphenylethane as an intermediate. The latter is then cleaved by excess metal to give triphenylmethylsodium. Benzyl chloride does not react with sodium to give benzylsodium, since condensation occurs instantaneously to give 1,2-diphenylethane, which cannot be cleaved [96, 99].

Polyarylated disilanes, digermanes, distannanes, and diplumbanes react with alkali metals in a manner similar to the polyarylethanes. They are cleaved in ether (or, preferably, in liquid ammonia) to give "quasi-organometallic" compounds. For example, hexaphenyldisilane is converted into triphenylsodium [101] and diphenylsilylpotassium [101, 102]. Other preparations of this type include $(CH_3)_3GeNa$ [103–106], $(CH_3)_3SnNa$ [107], $(C_6H_5)_3SnNa$ [108], and $(C_6H_5)_3PbNa$ [109]. The triaryl derivatives are chemically very similar to the triarylmethylalkali-metal compounds.


[89] *R. L. Letsinger* and *J. G. Traynham*, J. Amer. chem. Soc. *70*, 3342 (1948).

[90] *K. Ziegler* and *B. Schnell*, Liebigs Ann. Chem. *437*, 227 (1924).

[91] *G. Wittig* and *W. Happe*, Liebigs Ann. Chem. *557*, 205 (1947).

[92] *A. Kliegl*, Ber. dtsch. chem. Ges. *62*, 1327 (1929).

[93] *A. A. Morton*, *E. E. Magat*, and *R. L. Letsinger*, J. Amer. chem. Soc. *69*, 959 (1947).

[94] *R. L. Burwell*, Chem. Reviews *54*, 673 (1954); *D. S. Tarbell* and *D. P. Harnish*, ibid. *49*, 1 (p. 38 et seq.) (1951); *W. E. Truce*, *D. P. Tate*, and *D. N. Burdge*, J. Amer. chem. Soc. *82*, 2872 (1960).

[95] *W. Schlenk* and *E. Marcus*, Ber. dtsch. chem. Ges. *47*, 1664 (1914).

[96] *J. B. Conant* and *B. S. Garvey*, J. Amer. chem. Soc. *49*, 2599 (1927).

[97] *G. Wittig* and *E. Stahnecker*, Liebigs Ann. Chem. *605*, 69 (1957).

[98] *J. G. Stampfli* and *C. S. Marvel*, J. Amer. chem. Soc. *53*, 4057 (1931).

[99] *G. Wittig* and *M. Leo*, Ber. dtsch. chem. Ges. *63*, 943 (1930).

[100] *P. L. Salzberg* and *C. S. Marvel*, J. Amer. chem. Soc. *50*, 1737 (1928).

[101] *A. G. Brook* and *H. Gilman*, J. Amer. chem. Soc. *76*, 278 (1954).

[102] *H. Gilman* and *T. C. Wu*, J. org. Chemistry *18*, 753 (1953).

[103] *C. A. Kraus* and *L. S. Foster*, J. Amer. chem. Soc. *49*, 457 (1927).

[104] *C. A. Kraus* and *H. S. Nutting*, J. Amer. chem. Soc. *54*, 1622 (1932).

[105] *C. A. Kraus* and *C. S. Sherman*, J. Amer. chem. Soc. *55*, 4694 (1933).

[106] *F. B. Smith* and *C. A. Kraus*, J. Amer. chem. Soc. *74*, 1418 (1952).

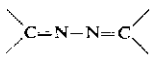
[107] *C. A. Kraus* and *W. V. Session*, J. Amer. chem. Soc. *47*, 2361 (1925).

[108] *R. F. Chambers* and *P. C. Scherer*, J. Amer. chem. Soc. *48*, 1054 (1926).

[109] *H. Gilman* and *J. C. Bailie*, J. Amer. chem. Soc. *61*, 731 (1939).

f) *Addition of Metals to Multiple Bonds*

*Beckman* [110a] was the first to observe that a solution of benzophenone in dry ether acquires a deep blue-violet color when it is shaken with sodium powder or when boiled with sodium wire. A brief induction period precedes the reaction, in which the sodium ketyl *(29)* is formed. The reaction has been studied extensively by *Schlenk* [110b]. Later, numerous other intensely colored metal adducts became known including those of ketones, nitriles, Schiff bases, hydrazones, azo compounds, ketazines



nitrogen heterocycles, and derivatives of styrene, stilbene and tolane (diphenylacetylene), as well as of allenes and polycyclic aromatics [111, 112].

Most of these unsaturated systems also add on organometallic reagents readily. However, a few aromatic hydrocarbons, such as naphthalene, appear to add on only the elemental metals.

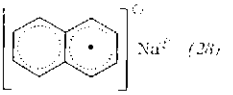
The ability of such compounds to undergo addition reactions increases with the number of their double bonds. Thus, sodium adds much more rapidly onto anthracene than onto naphthalene, while it does not add onto benzene at all at 80 °C. Strong electropositivity of the metal likewise facilitates the reaction. Benzene probably forms an adduct with potassium under drastic conditions [113], but no adduct is obtained with sodium; ethylene will not react with potassium, but it does react with cesium to yield ethylenedicesium [114].

Lithium appears superior to the heavier alkali metals in additions to triple bonds; for example, it is taken up by tolane much faster than other metals [115]; (it is also the only metal which reacts with molecular nitrogen at room temperature to form a nitride [116]).

Depending on the composition of the products obtained, one can distinguish between

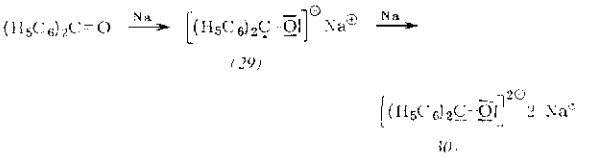
a) 1:1 adducts (radical anions)
b) 2:1 adducts, and
c) 2:2 adducts (dimeric adducts).

A typical 1:1 complex is naphthalenesodium [51, 117a], which exists as the undissociated ion pair *(28)* [112, 117b].



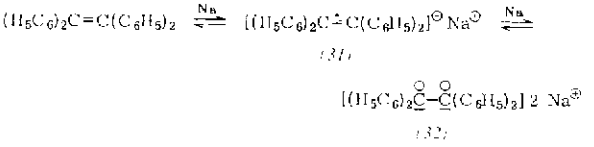
*(28)*

The 1:1 adducts can take up additional atoms of metal, particularly at high temperature. Thus, the blue-violet sodium ketyl *(29)* affords red-violet benzophenone-disodium *(30)* [118a, 118b].



*(29)* *(30)*

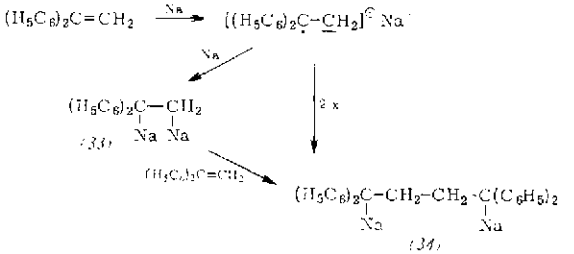
In the case of tetraphenylethylene in ether, the 2:1 adduct *(32)* is so favored that none of the 1:1 adduct *(31)* can be detected, no matter how much olefin is present. It is only when the equilibrium between *(31)* and *(32)* is shifted by changing the solvent (*e.g.* by replacing ether with 1,2-dimethoxyethane) that the radical anion *(31)* can be detected by its ESR signal [119].



*(31)* *(32)*

Many hydrocarbons can bind metal atoms to go beyond the 2:1 adduct, giving highly metalated products such as anthracenedecasodium [120].

With 1,1-diphenylethylenes, adduct formation proceeds by a fundamentally different process. Here, in a formal sense, two radical anions combine to form a dimer that is substituted with metal at the 1- and 4-positions. In this process, however, the 2:2 adduct *(34)* does not appear to be generated by coupling of two radicals, as *Schlenk* assumed [118a, 121], but rather by addition of the organometallic 2:1 complex *(33)* onto a second molecule of olefin, as proposed by *Ziegler* [122].



*(33)* *(34)*

[110a] *E. Beckmann* and *Th. Paul*, Liebigs Ann. Chem. *266*, 1 (1891).

[110b] *W. Schlenk* and *T. Weickel*, Ber. dtsch. chem. Ges. *44*, 1182 (1911); *W. Schlenk* and *A. Thal*, ibid. *46*, 2840 (1913).

[111] Reviewed by *C. B. Wooster*, Chem. Reviews *11*, 37, 48 (1932).

[112] *B. J. Morantz* and *E. Warhurst*, Trans. Faraday Soc. *51*, 1375 (1955); *A. Mathias* and *E. Warhurst*, ibid. *58*, 942, 948 (1962); *D. G. Powell* and *E. Warhurst*, ibid. *58*, 953 (1962).

[113] *H. Abeljanz*, Ber. dtsch. chem. Ges. *5*, 1027 (1872); *9*, 10 (1876); cf. *W. Schlenk* and *H. Meyer*, ibid. *46*, 4060 (1913); cf. *A. A. Morton* and *E. J. Lanpher*, J. org. Chemistry *23*, 1640 (1958).

[114] *L. Hackspill* and *R. Rohmer*, C. R. hebd. Séances Acad. Sci. *217*, 152 (1943).

[115] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 71 (1928).

[116] *F. W. Dafert* and *R. Miklauz*, Mh. Chem. *31*, 981 (1910).

[117a] *N. D. Scott*, *J. F. Walker* and *V. L. Hansley*, J. Amer. chem. Soc. *58*, 2442 (1936).

[117b] *W. Hückel*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *43*, 838 (1937).

[118a] *W. Schlenk*, *J. Appendroät*, *A. Michael*, and *A. Thal*, Ber. dtsch. chem. Ges. *47*, 473 (1914).

[118b] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *464*, 22 (1928).

[119] *J. F. Garst* and *R. S. Cole*, J. Amer. chem. Soc. *84*, 4352 (1962).

[120] U.S.-Pat. 2948762 (August 9th, 1960), Snia Viscosa, Milano, inventors: *W. Muench*, *L. Notarbartolo*, *G. Selvestri*, and *V. Ruoti*.

[121] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 1 (1928).

[122] *K. Ziegler* and *O. Schäfer*, Liebigs Ann. Chem. *479*, 150 (1930).

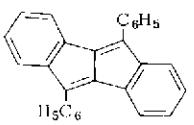
The normally high readiness of a methylene-sodium bond to undergo addition reactions should be even further increased in the adduct *(33)* by the neighboring diphenylmethyl anion. The increase in reactivity due to directly neighboring organometallic bonds[123] may also be responsible for adduct formation in the case of tolane. Compounds *(35)* derived from the monomer presumably appear as intermediates, which promptly take up a second molecule of tolane. In ether, lithium adds smoothly onto tolane, giving tetraphenylbutadiene-1,4-dilithium. The analogous greenish-blue adduct *(36)* is formed with Na/K alloy in dioxan. Its hydrolysis yields, besides tolane (35 %), 1 % diphenyldibenzopentalene *(37)*, 2 % *cis,trans*-1,2,3,4-tetraphenylbutadiene, and 5 % 1-benzyl-2,3-diphenylindane [124].

$$M-(H_5C_6)C=C(C_6H_5)-M$$

*(35)*

$$K-(H_5C_6)C=C(C_6H_5)-(H_5C_6)C=C(C_6H_5)-K$$

*(36)*



*(37)*

The chemical behavior of most of the 1:1 and 2:1 adducts based on the monomeric hydrocarbons is similar to that of a solution of the appropriate alkali metal in an organic solvent. Thus, when stilbene disodium *(38)* is treated with methyl iodide, benzyl chloride, aryl halides, oxygen, sulfur, or arsenic(III) chloride, the original hydrocarbon is always regenerated [121, 125a - 125c].

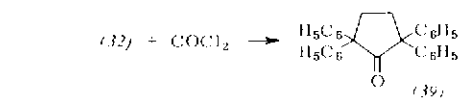
$$\underset{(38)}{H_5C_6-CHNa\ \ CHNa-C_6H_5} \xrightarrow[-2\ NaI]{2\ CH_3I} H_5C_6-CH=CH-C_6H_5 + H_3C-CH_3$$

In other cases, stilbene disodium *(38)* reacts like an organometallic compound. For example, it reacts with proton donors to give diphenylethane, with dimethyl sulfate to give racemic and *meso*-2,3-diphenylbutane, and with carbon dioxide to give *meso*-2,3-diphenylsuccinic acid (together with some racemate) [125a-125c].

Unlike the 1:1 and 2:1 adducts, the dimeric (2:2) adducts find many preparative applications, since they only rarely revert to the parent hydrocarbon; for example, 1,1,4,4-tetraphenylbutylene-1,4-disodium *(34)* may be cleaved with mercury [121, 126], and the analogous dipotassium compound is cleaved with iodine, methylene iodide, or tetramethylethylene dibromide [127], reverting to 1,1-diphenylethylene.

$$\underset{(34)}{Na-(H_5C_6)_2C-CH_2-CH_2-C(C_6H_5)_2-Na} \xrightarrow{Hg} 2\,(H_5C_6)_2C=CH_2 + Na/Hg$$

The other reactions of the 2:2 adducts, including those with alkyl and acyl halides, esters, aldehydes, or nitrosyl chloride, give the corresponding 1,4-disubstituted derivatives, *e.g. (39)* [121].



*(39)*

Under mild conditions, 2:2 adducts of butadiene [128], styrene [129], and α-methylstyrene [129] may also be obtained. To inhibit polymerization, polar ethers such as dimethyl ether, tetrahydrofuran, or dimethoxyethane are used as solvents. In these media, adduct formation occurs with sufficient rapidity even at −30 °C. A small amount of *o*-terphenyl serves as a carrier for the dispersed sodium. The metal is transferred to the olefin via the aromatic sodium complex initially formed.

The dimeric adduct of butadiene *(40)* and sodium is now being produced on an industrial scale. The mixture of unsaturated $C_{10}$ dicarboxylic acids which results from carboxylation of *(40)* is sold commercially in the hydrogenated form [128, 130].

$$H_2C=CH-CH=CH_2 \rightarrow Na-CH_2-CH=CH-CH_2-Na$$

$$\downarrow$$

$$Na-CH_2-CH=CH-CH_2-CH_2-CH=CH-CH_2-Na$$

*(40)*

$\downarrow CO_2, H_2$

2-Ethylsuberic acid 51 %
Sebacic acid 38 %
2,5-Diethyladipic acid 11 %

The alkali metal adducts are important in many reactions, in which they act as intermediates that cannot be isolated. The chief examples are the Birch-Hückel-Ziegler [131] and Bouveault-Blanc [132, 133] reductions using the elemental metals in the presence of proton donors. Related to these is a convenient method for the preparation of diphenylmethyl-type organosodium and organopotassium compounds, in which the metal is added onto derivatives of 1,1-diphenylethylene in liquid ammonia. All the alkali-metal atoms attached to an

[123] This principle was formulated by *K. Ziegler* et al. [Liebigs Ann. Chem. *511*, 64 (1934)] to explain the fact that 2,3 dimethylbutadiene dimerizes – but does not polymerize – in the presence of lithium metal. 1,4-Dilithium-2,3-dimethyl-2-butene, $Li-CH_2-C(CH_3)=C(CH_3)-CH_2-Li$, an adduct with two vinylogously vicinal organolithium bonds, does indeed add more rapidly onto 2,3-dimethylbutadiene than the subsequent products $Li\ CH_2-C(CH_3)-C(CH_3)\ CH_2\ R$, in which the organometallic bond is isolated.

[124] *C. Hoogzand*, personal communication.

[125a] *G. F. Wright*, J. Amer. chem. Soc. *61*, 2106 (1939).

[125b] *G. S. Myers, H. H. Richmond*, and *G. F. Wright*, J. Amer. chem. Soc. *69*, 710 (1947).

[125c] *A. G. Brook, H. L. Cohen*, and *G. F. Wright*, J. org. Chemistry *168*, 447 (1953).

[126] *E. Bergmann*, Ber. dtsch. chem. Ges. *63*, 1617 (1930); *K. Ziegler*, Ber. dtsch. chem. Ges. *64*, 445 (1931).

[127] *G. Wittig* and *F. v. Lupin*, Ber. dtsch. chem. Ges. *61*, 1633 (1928).

[128] *C.E.Frank* and *W.E.Foster*, J.org.Chemistry *26*, 303 (1961).

[129] *C. E. Frank, J. R. Leebrick, L. F. Moormeier, J. A. Scheben*, and *O. Homberg*, J. org. Chemistry *26*, 307 (1961).

[130] U.S.-Pat. 2816916 (Dec. 17th, 1957), U.S. Industrial Chemical Co., inventors: *C. E. Frank* and *W. E. Foster*.

[131] *K. Ziegler, L. Jakob, H. Wollthan*, and *A. Wenz*, Liebigs Ann. Chem. *511*, 64 (1934); *W. Hückel* and *H. Bretschneider*, ibid. *540*, 157 (1939); *A. J. Birch*, Quart. Rev. (chem. Soc., London) *4*, 69 (1950); *G. W. Watt*, Chem. Reviews *46*, 317 (1950); *D. H. R. Barton* and *C. H. Robinson*, J. chem. Soc. (London) *1954*, 3045; *E. A. Benkeser, G. Schroll*, and *D. M. Sauve*, J. Amer. chem. Soc. *77*, 3378 (1955); *A. J. Birch* and *H. Smith*, Quart. Rev. *12*, 17 (1958).

[132] *L. Bouveault* and *G. Blanc*, C. R. hebd. Séances Acad. Sci. *136*, 1676 (1903); *137*, 60, 328 (1903).

[133] *V. L. Hansley*, Ind. Engng. Chem. *39*, 55 (1947).

alkyl or benzyl group of the intermediate 2:1 adduct are immediately replaced by hydrogen, while organometallic bonds with two neighboring aryl groups are resistant to the aminolysis. Examples are given in Table 8.

Table 8. End-products of the reaction of olefins with sodium in liquid ammonia.

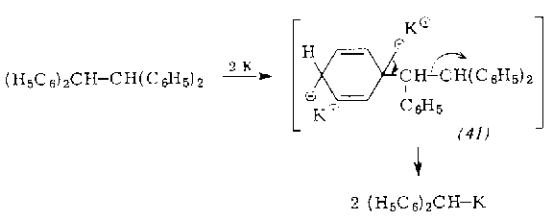
| Olefin | Na derivative | Ref. |
|---|---|---|
| $(H_5C_6)_2C{=}CH_2$ | $(H_5C_6)_2C(CH_3){-}Na$ | [134, 135] |
| $(H_5C_6)_2C{=}CH{-}CH_3$ | $(H_5C_6)_2C(C_2H_5){-}Na$ | [135] |
| $(H_5C_6)_2C{=}CH{-}C_6H_5$ | $(H_5C_6)_2C(CH_2{-}C_6H_5){-}Na$ | [135] |
| $(H_5C_6)_2C{=}CH{-}CH(C_6H_5)_2$ | $(H_5C_6)_2CNa{-}CH_2{-}CH(C_6H_5)_2$ | [135] |
| $(H_5C_6)_2C{=}C{=}C(C_6H_5)_2$ | $Na{-}(H_5C_6)_2C{-}CH_2{-}C(C_6H_5)_2{-}Na$ | [135] |

Addition of the intermediate 1,1-diphenylethylenedisodium onto unreacted 1,1-diphenylethylene resulting in a 10–30% yield of 1,4-disodium-1,1,4,4-tetraphenylbutane competes with its ammonolysis [135].

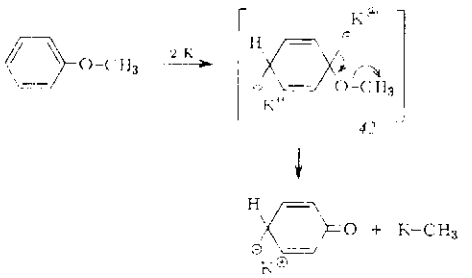
Liquid ammonia promotes the addition of metal to an extraordinary degree. Thus, 1,1-diphenyl-1-propene reacts smoothly with sodium in ammonia, although it forms no sodium adduct in ether [121, 125c]. Moreover, tetraphenylethylenedisodium, which is otherwise stable, seems to be cleaved at the central C–C bond by excess sodium in liquid ammonia [135, 136].

$$(H_5C_6)_2C{=}C(C_6H_5)_2 \xrightarrow{2\,Na} (H_5C_6)_2C(Na){-}C(Na)(C_6H_5)_2 \xrightarrow{2\,Na} 2\,(H_5C_6)_2CNa_2\ (?)$$

It may be presumed that alkali metal/hydrocarbon adducts play a decisive role in the cleavage of carbon-carbon bonds and in the cleavage of ethers. Of course, the reaction of hexaphenylethane with sodium to form triphenylmethylsodium may also be formulated as a dissociation equilibrium producing triphenylmethyl radicals, which are then trapped by the metal (cf. *Paneth*'s demonstration of methyl radicals [137]). However, no corresponding radical mechanism can be postulated for the cleavage of tetraphenylethane or of 1,2-di-*p*-biphenylylethane, since here there is no evidence for a dissociation equilibrium at room temperature. None the less, it may well be that in the first of the above cases a potassium adduct *(41)* occurs as an intermediate from which the two halves of the molecule are separated to form the final product.




In a similar manner, the cleavage of ethers by alkali metals [137a] may be considered as the result of adduct formation *(42)*.




On the other hand, the exchange processes, in which a chlorine, bromine, or iodine atom bound to an organic residue is replaced by a metal, may be completely explained by a nucleophilic attack on the halogen, which is capable of enlargement to an electron decet; this is the reason that aliphatic halides can also react in this way. However, alkali metal adducts must again be assumed as intermediates in the exchange of halogen by metal in fluorinated aromatics [138], in the Emde degradation of ammonium salts [139], and in the analogous cleavage of phosphonium salts [140].

## B. Experimental Procedures

### 1. Alkali Metals

It is advantageous to use sodium in solution in ammonia, as an ether-soluble aromatic/sodium adduct, or as a dispersion [141, 142]. Thirty and fifty per cent sodium stock dispersions are available as mobile suspensions, generally stabilized against sedimentation by small amounts of additives [149]. The preparation of sodium dispersions is described in Procedures 2β and 2δ. The average size of the sodium particles in Procedure 2δ is 2–3 μ. Metallic potassium is generally used as a fine powder or in the form of the readily prepared liquid alloy with sodium [90, 102, 143].

### 2. Organoalkali-Metal Compounds

#### α) Methylsodium [43]

A Schlenk tube is charged under nitrogen with 60 ml of dry ligroin (b.p. *ca.* 80 °C), fine chips of sodium, and 3.0 g (13 moles) of dimethylmercury. The sodium should be present in four-fold excess [9], although still covered by the liquid. The Schlenk tube is sealed and kept for several days in a drying oven at 65 °C. The tube is then placed in an ice-salt mixture, after which it is shaken vigorously to loosen the yellowish incrustations of methylsodium from the unreacted sodium and sodium amalgam. The methylsodium is thus obtained as powder and flakes. The light particles of methylsodium can be decanted off with the ligroin and are washed with petroleum ether [144]. The corresponding preparations of ethylsodium, higher sodium alkyls, and phenylsodium proceeds much more rapidly; the reaction is completed within a few hours at room temperature.

[134] *K. Ziegler, H. Colonius*, and *O. Schäfer*, Liebigs Ann. Chem. *473*, 36 (1929).

[135] *C. B. Wooster* and *J. F. Ryan*, J. Amer. chem. Soc. *56*, 1133 (1934).

[136] The analogous cleavage of *N,N'*-disodiohydrazobenzene at the N-N bond, to yield *N,N*-disodioaniline, is known [*W. Schlenk* and *J. Holtz*. Ber. dtsch. chem. Ges. *50*, 274 (1917)].

[137] *J. H. Simons* and *M. F. Dull*, J. Amer. chem. Soc. *55*, 2696 (1933); cf. *F. O. Rice* and *K. Rice*: The Aliphatic Free Radicals. J. Hopkins Press, Baltimore 1935, p. 58.

[137a] *R. L. Burwell*, Chem. Reviews *54*, 672 (1954).

[138] *H. Gilman* and *T. S. Soddy*, J.org.Chemistry *22*, 1121 (1957).

[139] *H. Emde*, Ber. dtsch. chem. Ges. *42*, 2590 (1909).

[140] *L. Horner, P. Beck*, and *H. Hoffmann*, Chem. Ber. *92*, 2088 (1959).

[141] *V. L. Hansley*, Ind. Engng. Chem., analyt. Edit. *43*, 1760 (1951).

[142] Sodium Dispersions, brochure obtainable from U.S. Industrial Chemical Co., Division of National Distillers and Chemical Corp. (1957).

[143] *H. Lecher*, Ber. dtsch. chem. Ges. *48*, 527 (1915).

[144] It is often possible to omit this rather bothersome separation step, since the presence of sodium and sodium amalgam has no deleterious effect on many of the reactions of sodium alkyls.

β) n-Amylsodium [3,5,73,145]:

A 1-liter three-necked flask with two creases (Morton flask [146a]) is charged under nitrogen with 23 g (1 gram-atom) of sodium, which is then covered with about 300 ml of olefin-free n-octane. This mixture is heated to 110 °C and stirred for at least one minute with a propeller-type agitator (10000 rpm). After cooling, the "sodium sand" (average particle size 25 μ) is allowed to settle, the octane is siphoned off under nitrogen, and the sodium washed several times with dry n-pentane. Such a sodium dispersion in about 200 ml of pentane or octane is mixed with 53.2 g (0.5 mole) of n-amyl chloride, which is added dropwise at −10 °C over a period of one hour while stirring is continued at approx. 5000 rpm [146b]. The mixture usually becomes blue. Finally it is stirred for further 30 min at −10 °C. The yield of n-amylsodium is 80 %. As a safety precaution, it is inadvisable to use more than one gram-atom of sodium at a time.

γ) Phenylsodium/Phenyl-lithium Solution [147]:

Diphenylmercury (0.9 g = 2.5 mmoles) in 15 ml of absolute ether is mixed in a Schlenk tube with 1 g (43.5 mmoles) of sodium wire and 5 ml of a 1 N phenyl-lithium solution prepared from diphenylmercury and lithium chips in ether; glass fragments are added, and the tube is sealed and shaken for 3 h. The solution is decanted from the greyish white precipitate and the lump of amalgam into a storage burette, where it is diluted with 40 ml of absolute ether. The solution decomposes slowly by reacting with the ether.

Variations of this method include the action of Li/Na alloy on diphenylmercury and the combination of phenyl-lithium with phenylsodium. Ether suspensions with higher phenylsodium/phenyl-lithium mole ratios (*e.g.* 5:1) have also been described [147].

δ) Phenylsodium [13,42]:

A Premier Mill laboratory dispersion unit [148,142] (high-speed stirrer with a dispersing head) is filled with nitrogen, and 150 g of dry toluene and 27 g (1.17 gram-atom) of sodium are introduced [149]. The sodium melts when the temperature is raised to 105 °C. The stirrer is then gradually brought to maximum speed (15000–18000 rpm) and maintained there for 5–15 min; the grey mixture is then cooled to room temperature [150]. A mixture of 56.3 g (0.5 mole) of chlorobenzene and 50 g of toluene is then prepared in a dropping funnel and 10–15 ml of it is rapidly added to the sodium mixture with gentle stirring. As a rule, reaction begins suddenly within a few minutes, with a noticeable increase in temperature and the appearance of black particles of phenylsodium. Otherwise the reaction may be initiated with 2 ml of amyl alcohol. The remainder of the chlorobenzene is then added dropwise over 20–30 min, but precaution must be taken to maintain the reaction temperature at 30–35 °C. The yield of phenylsodium is 99–100 %.

ε) Benzylsodium [13]:

A suspension of phenylsodium in toluene is heated for 2 hours under reflux in a nitrogen atmosphere. Benzylsodium is thus obtained in 99–100 % yield. A modification of this procedure is applied for the preparation of benzylsodium in the n-butylbenzene synthesis (cf. Procedure 3 γ).

ζ) Triphenylmethylsodium [78]:

A 1 % sodium amalgam is prepared under nitrogen in a 1 liter Schlenk tube by introducing 5.53 g (0.25 gram-atom) of sodium as small pieces speared on the end of a pointed glass rod into 575 g of pure mercury; (this operation must be performed in a hood). After cooling, 750 ml of absolute ether are added, followed by 31.5 g (0.113 mole) of triphenylmethyl chloride [m.p. 112–113 °C; recrystallized from a 10:1 ligroin (b.p. 100 °C)/acetyl chloride mixture]. The Schlenk tube is sealed off and shaken vigorously, whereupon the solution becomes deep orange. The exothermic reaction is moderated by cooling the tube with wet cloths, or by occasional immersion in ice water. The reaction is largely complete after fifteen minutes' shaking; to obtain total conversion, the tube is shaken for three hours on a horizontal mechanical shaker. After the sodium chloride produced has settled out, the tube is opened under nitrogen, and the organometallic solution is transferred to a storage burette through polyethylene tubing, into which a plug of glass wool has been loosely inserted. The yield is practically quantitative, as shown by titration of a sample with 0.1 N acid. If the mercury is not objectionable, the triphenylmethylsodium can be prepared more simply in a three-necked flask, and then used directly for further reaction [79].

η) Sodium Acetylide [59b,151]:

A one-liter flask is fitted with a glass or Hershberg stirrer (with mercury seal) and a dry-ice condenser (or a freezing mixture at −35 °C). Anhydrous liquid ammonia (300 ml) is added. Acetylene gas is passed through a cold trap at −70 °C and two wash bottles containing conc. sulfuric acid and is bubbled through the liquid. Simultaneously 5.5 g (0.24 gram-atom) of sodium are added slowly in small pieces so that the blue color disappears before the next piece is added. As soon as all of the sodium has been introduced and the solution has lost color, the flow of acetylene is discontinued. This method can be used with only minor variations to produce large quantities of sodium acetylide (13 moles in 6 l of ammonia) [59a,59b]. Large amounts can also be obtained with sodamide in liquid ammonia [152]. The excess acetylene in solution, inevitable in these preparations, generally causes no difficulty in further use.

ϑ) Sodium Phenylacetylide [61]:

A mixture of 3.06 g (30 mmoles) of phenylacetylene, 0.46 g (20 mmoles) of finely divided sodium, and 30 ml of absolute ether is stirred at room temperature. After about 8 h all of the metal is consumed; this is shown by absence of hydrogen evolution when a few drops of the suspension are hydrolysed. The corresponding reaction with potassium, which yields potassium phenylacetylide, usually requires 48 h.

κ) *p*-Tolylpotassium [48]:

A solution of *p*-tolyl-lithium (95 mmoles) in ether is evaporated *in vacuo* (at the end for 30 min at 60 °C) to remove the solvent completely. Dry benzene (45 ml) and an alloy of 7.8 g (0.2 gram-atom) of potassium with 2 g (0.087 gram-atom) of sodium are now added, and the mixture is stirred for 10 h at 20 °C. An aliquot of the dark brown mixture is withdrawn and filtered. A small alkali content of the filtrate indicates that the reaction has been almost quantitative. The preparations of ethyl-, n-propyl-, n-butyl, s-butyl, and t-butylpotassium and other potassium alkyls are analogous [11,48].

[145] *A. A. Morton* and *J. Hechenbleikner*, J. Amer. chem. Soc. *58*, 1697 (1936).

[146a] *A. A. Morton*, Ind. Engng. Chem., analyt. Edit. *11*, 170 (1939); *A. A. Morton* and *D. M. Knott*, ibid. *13*, 650 (1939).

[146b] *A. A. Morton* and *L. M. Redman*, Ind. Engng. Chem., analyt. Edit. *40*, 1190 (1948).

[147] *G. Wittig, R. Ludwig*, and *R. Polster*, Chem. Ber. *88*, 294 (1955).

[148] Premier Mill Co., Geneva, N.Y. (U.S.A.).

[149] It often happens that the dispersion cannot be used at once in further reactions, or must be prepared in benzene or an alkane rather than in toluene. In these cases, it is advisable to intdroduce 1 % oleic acid (based on the weight of sodium) or another additive before making the dispersion.

[150] *O. D. Frampton* and *J. F. Nobis*, Ind. Engng. Chem., analyt. Edit. *45*, 404 (1953).

[151] *A. I. Vogel:* Practical Organic Chemistry. 3rd Edit., Longmans, London 1961, p. 898.

[152] *K. W. Greenly* and *A. L. Henne* in Inorganic Syntheses. Wiley, New York 1946, Vol. 2, pp. 75, 79, 128; *T. L. Jacobs* in Organic Syntheses. Wiley, New York 1949, Vol. 5, pp. 25–40.

λ) α-Phenylisopropylpotassium [6, 153]:

A mixture of α-methylstyrene and methanol in a molar ratio of 1:2) is treated with 0.05 % of its weight of 70 % perchloric acid solution and allowed to stand for 48 h at 50 °C. Aqueous sodium hydroxide is then added, the methanol completely extracted from the oil layer with water, and the oil layer dried with $CaCl_2$. Fractional distillation *in vacuo* yields 26 % unreacted α-methylstyrene (b.p. 64–65 °C/23 mm, $n_D^{20} = 1.5372$) and 62 % methyl α-phenylisopropyl ether (b.p. 83–84 °C/23 mm, $n_D^{20} = 1.4956$) [6]. Methyl α-phenylisopropyl ether (5.0 g, 33 moles), 6 g of potassiumsodium alloy (5:1), and 400 ml of absolute ether are filled into a large Schlenk tube under nitrogen. The tube is sealed off and shaken vigorously. The intense red color of the organopotassium compound develops within two minutes. The reaction is complete after two days' shaking. The tube is opened under nitrogen and the solution transferred to a storage burette through a polyethylene tube containing a plug of glass wool [153]. Phenylisopropylpotassium may also be obtained as a suspension in hydrocarbons or, free of by-products, in solid form [6].

μ) Diphenylmethylpotassium [154]:

A two-liter 3-necked flask, fitted with a dry-ice condenser and a Hershberg stirrer (with a mercury seal), is filled with 800 ml of liquid ammonia, and 21.5 g (0.55 gram-atom) of potassium are added in small pieces with thorough mixing. The deep blue solution is decolorized within two hours, this indicating the formation of potassium amide [155]. A solution of 84.0 g (0.5 mole) of diphenylmethane in 800 ml anhydrous ether is added, and, after the dry-ice condenser has been replaced by a water-cooled condenser, the ammonia is evaporated off on a water bath. Sufficient ether is added to bring the total volume up to 800 ml, and the mixture is refluxed for further two hours. Carboxylation of the orange-red solution gives a 90 % yield of diphenylacetic acid. Alkylation, acylation, and other reactions may also be carried out in the ammonia-ether medium before the ammonia is evaporated off [154]; with diphenylmethyl*sodium*, it is essential that these reactions be performed before evaporation [35].

## 3. Syntheses Using Organoalkali-Metal Compounds

α) Vinylacetic Acid [156]:

A Morton flask is charged under nitrogen with 5.8 g (0.25 gram-atom) of "sodium sand" (see Procedure 2β). The octane is replaced by hexane, and 14.7 g (0.15 mole) of diallyl ether dissolved in an equal volume of hexane are added dropwise over a period of one hour, the mixture being stirred at 5000 rpm and an average temperature of 35 °C being maintained. After further 30 min, the purely white, moderately viscous reaction mixture is transferred from the flask by pressure (via an outlet tube) onto solid carbon dioxide. After addition of 200 ml of water and extraction with ether, 8.3 g of vinylacetic acid (b.p. 61–62 °C/3 mm, $n_D^{23} = 1.4220$) are isolated (77 % yield based on sodium).

β) Phenylmalonic Acid [13]:

A suspension of benzylsodium in toluene, prepared by Procedure 2ε [13] using 112.6 g (1 mole) of chlorobenzene, is carboxylated by introducing carbon dioxide gas with stirring at 30–60 °C. In this operation about half of the theoretical quantity of gas is added during the first ten minutes, stirring is continued for 30 min, and more carbon dioxide is introduced during 80 min to complete the carboxylation slowly. The excess sodium is now destroyed with steam in a hydrolysis apparatus, the aqueous phase removed and decolorized with animal charcoal, and then neutralized with hydrochloric acid at 0 °C [157]. Large quantities of phenylmalonic acid are precipitated. Additional product is obtained by extraction of the mother liquor with ether [157]. The total yield of acid, m.p. 145–148 °C, is 67 % (based on chlorobenzene). The phenylacetic acid (28 %) present as a by-product is previously removed by benzene extraction.

γ) n-Butylbenzene [158]:

A 1-liter three-necked flask is charged under nitrogen with 300 ml of toluene and 27.5 g (1.2 gram-atom) of sodium wire. Over a period of two hours, 68 g (0.6 mole) of chlorobenzene are added dropwise at 30–35 °C with vigorous stirring (blade-type stirrer, mercury seal). The reaction begins quickly. The mixture is then refluxed for 35 min, the heating bath is removed, and 49 g (0.4 mole) of n-propyl bromide are added dropwise to the benzylsodium suspension at 103–105 °C over a period of 20 min. After cooling, any benzylsodium remaining is destroyed with a stream of carbon dioxide, and the excess sodium with water. The toluene layer is separated off, dried, and fractionally distilled twice; 40 g of pure n-butylbenzene (b.p. 181–181.5 °C, $n_D^{20} = 1.4898$) is obtained (74 % yield based on n-propyl bromide). In contrast, the condensation of phenylsodium and n-butyl bromide gives only a 44 % yield of n-butylbenzene.

δ) 1-Chloro-5-nonyne [59b]:

A solution of sodium acetylide in ammonia is prepared from 5.5 g (0.24 gram-atom) of sodium, and 41 g (0.24 mole) of n-propyl iodide are added to it slowly, stirring being continued for four hours. A solution of 0.25 gram-atom of sodamide (prepared from 5.8 g of sodium) in 150 ml of liquid ammonia [59b] is then added in portions to the thoroughly cooled mixture, which is stirred for another hour. Next 41 g (0.24 mole) of 1-chloro-4-bromobutane are slowly added dropwise, and the cooled reaction mixture is stirred for further 12 h. Then 15 g (0.28 mole) of ammonium chloride are added, the ammonia is evaporated off, and the residue is extracted with water and ether. Distillation of the dried organic phase gives 5.3 g (13 %) of unreacted 1-chloro-4-bromobutane and 24.2 g (64 %) of 1-chloro-5-nonyne (b.p. 83–84 °C/13 mm, $n_D^{18} = 1.4620$).

ε) 1,8-Cyclotetradecadiyne [159]:

α,ω-Nonadiyne (0.1 mole) is added with stirring to a solution of 0.2 mole of sodamide [59b] in 1 liter of liquid ammonia. After one hour, 0.1 mole of α,ω-dibromopentane is added, again with agitation. Stirring under a condenser cooled with dry ice is continued for four days, and the ammonia is then removed by evaporation. Water is added, the mixture is extracted with ether, the ether extracts are dried, the ether is evaporated off, and the residue is distilled at 100–110 °C and $10^{-3}$ mm Hg. The diyne thus obtained is crystallized from alcohol and melts at 97–98 °C. The yield (56 %) may be increased to more than 70 % by working in more dilute solution.

ζ) *p*-Nitrophenyl Phenethyl Ketone [160]:

A solution of 1.2 g (4 mmoles) of di-t-butyl benzylmalonate in 25 ml of dry benzene is stirred gently in a three-necked flask under slight reflux and treated with 0.15 g (6 mmoles) of

[153] *K. Ziegler, F. Crössmann, H. Kleiner*, and *O. Schäfer*, Liebigs Ann. Chem. *473*, 20 (1929).

[154] *R. S. Yost* and *C. R. Hauser*, J. Amer. chem. Soc. *69*, 2325 (1947).

[155] *C. R. Hauser* and *T. M. Harris*, J. Amer. chem. Soc. *80*, 636 (1958).

[156] *R. L. Letsinger* and *J. G. Traynham*, J. Amer. chem. Soc. *70*, 3342 (1948).

[157] Above 30 °C decarboxylation may occur.

[158] *D. Bryce-Smith* and *E. E. Turner*, J. chem. Soc. (London) *1950*, 1975.

[159] *J. Dale, A. J. Hubert*, and *G. S. D. King*, J. chem. Soc. (London) *1963*, 73.

[160] *G. S. Fonken* and *W. S. Johnson*, J. Amer. chem. Soc. *74*, 831 (1952).

sodium hydride. As soon as the evolution of gas has ceased (after about 2.5 h), 0.75 g (4 mmoles) of *p*-nitrobenzoyl chloride is added without interrupting the stirring or reflux. One hour later the mixture is cooled, and the excess sodium hydride is decomposed with 0.35 g (2 mmoles) of anhydrous *p*-toluenesulfonic acid. The salts precipitated are filtered off, the benzene is distilled off, and the residual oil is refluxed for one hour with a mixture of 0.1 g of *p*-toluenesulfonic acid in 25 ml of glacial acetic acid containing about 2 % (by volume) of acetic anhydride. The evolution of gas ceases after about 45 min. The mixture is poured onto ice, neutralized with dilute alkali, and the white precipitate is filtered off (0.83 g; 81 % yield). After recrystallization from ethanol, colorless leaflets are obtained which melt at 74.5–75 °C.

### $\eta$) Diphenylenephenylphosphine [161]:

A Schlenk tube is charged under nitrogen with 21.6 g (83 moles) of triphenylphosphine and a suspension of phenylsodium (prepared from 8.5 g of chlorobenzene and 3.5 g of sodium) in 40 ml of benzene, then sealed and shaken for 10 h at 20 °C and for 30 h at 70 °C. After decomposition of unreacted starting material with methanol and addition of water, the benzene layer is dried, the solvent is evaporated, and the residue distilled. Thirteen grams of distillate are collected at 0.05 mm Hg and 155–160 °C. This is mulled with aqueous HCl (2 parts conc. HCl, 1 part $H_2O$) to extract 10.2 g of triphenylphosphine. After recrystallization from methanol, the residue melts at 93–94 °C. The yield varies from 8 to 15 %. For reasons of safety, larger-scale preparations should be carried out in a three-necked flask with thorough mixing (Vibrator).

### $\vartheta$) Tetraphenylgermane [162]:

A mixture of 10 g (47 mmoles) of germanium tetrachloride, 100 ml of toluene, 9 g (39 mg-atom) of sodium and 30 g (190 mmoles) of bromobenzene is carefully heated. As soon as the reaction has begun, cooling must be applied. When the reaction has subdued, the mixture is refluxed for another hour. The hot solution is hydrolysed with hydrochloric acid. Additional 100 ml of warm toluene are added, and the toluene layer is separated off, filtered, and concentrated to a small volume. The dark colored solution yields a precipitate of 9.6 g of purely white crystals (53 % yield).

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Translated by scripta technica, Washington

[161] *G. Wittig* and *G. Geissler*, Liebigs Ann. Chem. *580*, 50 (1953).

[162] *D. E. Worrall*, J. Amer. chem. Soc. *62*, 3267 (1940).

# COMMUNICATIONS

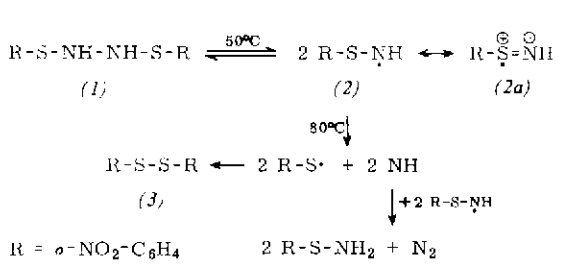
## The o-Nitrophenylsulfenylimine Radical [1]

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Di-(*o*-nitrophenylsulfenyl)hydrazine *(1)* dissociates in toluene at about 50 °C into *o*-nitrophenylsulfenylimine radicals *(2)*. The ESR spectrum shows three lines of equal intensity which indicates a spin density at the nitrogen. As the equidistant line-spacing is only about half as great (11 Gauss) as in the spectrum of diphenylpicrylhydrazyl (DPPH), one must assume a high spin density at an atom without nuclear spin, in this case at the sulfur [formula *(2a)*]. Also, the high g-factor (2.0076) which lies in the region of the values found for sulfur radical ions ($CH_3OC_6H_4-\overset{\oplus}{S}-C_6H_4OCH_3$: g = 2.0079 [2]) and away from the g-values of *N*-radicals (DPPH: g = 2.0036) indicates an important participation of resonance structures with radical sulfur.

On cooling, the signal dies away and appears on reheating, indicating a reversible dissociation. Above 80 °C in toluene, nitrogen is evolved from *(1)*. The sulfenylimine radical *(2)* probably decomposes into a sulfur radical, which recombines to give the disulfide *(3)*, and into imene which reduces the sulfenylimine radical *(2)* to sulfenylamine *(4)*. Compounds *(3)* and *(4)* were identified. Dry decomposition of *(1)* gave rise to *(3)*, $N_2$, and $NH_3$. Decomposition of *(1)* in acrylonitrile resulted in polymerisation.




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[1] Communication No. 7 on Organic Sulfur Radicals. – Communication No. 6: *U. Schmidt, A. Müller*, and *K. Markau*, Chem. Ber. *97*, 405 (1964).

[2] *U. Schmidt, K. H. Kabitzke*, and *K. Markau*, Liebigs Ann. Chem., in the press.

## Formation of Bis-(β-chloro-β-alkoxyethyl) Sulfoxides by Addition of Thionyl Chloride onto Alkyl Vinyl Ethers

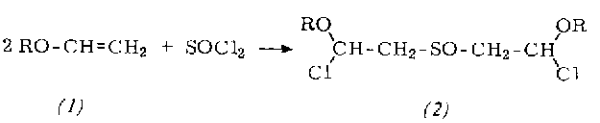
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*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

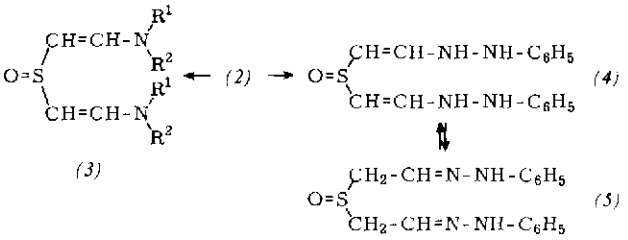
2-Chloro-2-ethoxyethanesulfinyl chloride has been described [1] as the unstable product of the addition of thionyl chloride onto ethyl vinyl ether.

The reaction of thionyl chloride and alkyl vinyl ethers *(1)* in a molar ratio of 1:3 has now yielded bis-(β-chloro-β-alkoxyethyl) sulfoxides *(2)*.




When absolute ether was used as solvent, the sulfoxides *(2)* crystallized directly as colorless compounds that are readily

recrystallizable from $CCl_4$ [R = $C_2H_5$, 97 % yield, m.p. 20 °C (decomp.); R = s-$C_4H_9$, 80 % yield, m.p. 30–32 °C (decomp.); R = n-$C_4H_9$, 90 % yield, m.p. 41–43 °C (decomp.)]. The action of secondary amines on *(2)* yields compounds of type *(3)* [$R^1$ $R^2$ = $(CH_2)_5$, m.p. 78–80 °C, $R^1$ $R^2$ = $(CH_2)_2$–O–$(CH_2)_2$, m.p. 79–81 °C], while phenylhydrazine produces *(4)*, m.p. 118–120 °C, which could also be formulated as *(5)*.



*(3)*

Tertiary amines eliminate hydrogen chloride from *(2)*, R = $C_2H_5$, yielding a product of formula $C_8H_{14}O_3S$, the structure of which has not yet been established.

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[1] *H. E. Simmons, D. C. Blomstrom*, and *R. D. West*, J. Amer. chem. Soc. *84*, 4782 (1962).

## Dependence of the Electron Excitation of Open-Chain Cyanine Dyes on the Valence Angle of Their Nitrogen Atoms

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In contrast to the statements of the simple theories on the light absorption in cyanine dyes, the electron-excitation energy depends not only upon the chain length but also on the angle imposed on the residual valences of nitrogen by its incorporation into rings of varying size. The energy differences amount to about 1 kcal/mole and decrease with increasing

$$[R=\overset{\oplus}{N}=(CH-CH)_n=CH-N=R]\ ClO_4^{\ominus} \qquad (1)$$

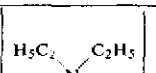
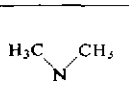
$$[R-N-CH=CH-C(CH_3)=CH-CH=\overset{\oplus}{N}=R]\ ClO_4^{\ominus} \qquad (2)$$

chain length. The cause is probably hybridization of the nitrogen atom, depending on the angle involved; this alters the s-portion of the N–C bond and, therefore, the coupling capacity of the nitrogen. The light absorption of the cyanine dyes therefore yields the series 4-<5-<6-ring for the coupling capacity of the nitrogen as a function of the ring size; this corresponds to the order observed by *Lippert* and *Prigge* [4] for the electron-donor capacity of the nitrogen atom in free cyclic imines.

Further work is in progress, also on cyanine dyes with longer chains.

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Table 1. Electron-excitation energy $\tilde{\nu}_{max}$ and extinction coefficient $\varepsilon_{max}$ of cyanine dyes [2] in ethanol at room temperature. The values for the $\tilde{\nu}_{00}$-bands, measured in ethanol at −180 °C [3], are shown in brackets

| | R–N– |  |  |  |  |  |
|---|---|---|---|---|---|---|
| $\tilde{\nu}_{max}$ $10^{-3}$ [cm$^{-1}$]<br>$\varepsilon_{max}$ $10^{-4}$ | *(1)*, n = 0 | | 42.7<br>1.18 | 43.2<br>1.35 | | 44.6<br>1.45 [1] |
| $\tilde{\nu}_{max}$ $10^{-3}$ [cm$^{-1}$]<br>$\varepsilon_{max}$·$10^{-4}$ | *(1)*, n = 1 | | 31.3 (30.6)<br>5.25 | 31.7 (31.3)<br>5.81 | | 32.2 (31.75)<br>4.82 |
| $\tilde{\nu}_{max}$ $10^{-3}$ [cm$^{-1}$]<br>$\varepsilon_{max}$·$10^{-4}$ | *(1)*, n = 2 | 23.65 (23.45)<br>12.0 | 23.75 (23.5)<br>12.4 | 24.0 (24.0)<br>12.0 | 24.1 | 24.35 (24.15)<br>10.4 |
| $\tilde{\nu}_{max}$ $10^{-3}$ [cm$^{-1}$]<br>$\varepsilon_{max}$·$10^{-4}$ | *(1)*, n = 3 | | 19.15<br>19.7 | 19.35<br>19.4 | | 19.55<br>18.7 |
| $\tilde{\nu}_{max}$ $10^{-3}$ [cm$^{-1}$]<br>$\varepsilon_{max}$·$10^{-4}$ | *(2)* | | 22.525<br>12.5 | 22.75<br>12.4 | 22.85<br>12.3 | 23.05<br>11.2 |

## Synthesis of Ribodinucleotides with Terminal 3′-Phosphate Groups

By Dr. D. Söll [*] and Prof. Dr. H. G. Khorana

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*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

Ribodinucleotides with 3′-phosphate end groups can be polymerized chemically to give ribopolynucleotides, which are of importance for the experimental analysis of the amino acid code.

Using CpUp *(1)* as an example, we wish to describe in the following the simplest and most satisfactory approach yet discovered to dinucleotides with 3′-phosphate end groups. *N*-Acetyl-2,5-di-*O*-acetylcytidine 3′-phosphate *(2)* (0.1 mmole) [1] was treated with 0.1 mmole of uridine 2′(3′)-phosphate *(3)* in pyridine in the presence of 1.5 mmoles of dicyclohexylcarbodiimide. Subsequent treatment with Dowex-50 ($H^{\oplus}$-form) was used to decompose the *N*-phosphorylureas formed [2]. The resultant *N*,2′,5′-triacetylcytidyl-3′→5′-uridine 3′(2′)-phosphate was treated with dicyclohexylcarbodiimide in the presence of triethylamine to form the dinucleotide with the terminal 2′,3′-cyclophosphate *(4)*. Treatment of *(4)* with pancreatic ribonuclease at pH 7.0 leads to *N*,2′,5′-triacetylcytidyl-3′→5′-uridine 3′-phosphate. Subsequent removal of the ribonuclease on a column of Dowex-50X2 (pyridinium form) and final deacetylation with 7 N ammonia leads to CpUp *(1)*, which was isolated pure in 53 % yield by chromatography on DEAE-cellulose. Using the same method, ApUp and IpUp were prepared in 47 % and 44 % yields, respectively. Enzymatic degradation showed that the synthetic dinucleotides contained exclusively the C(3′)-C(5′) internucleotidic linkage.

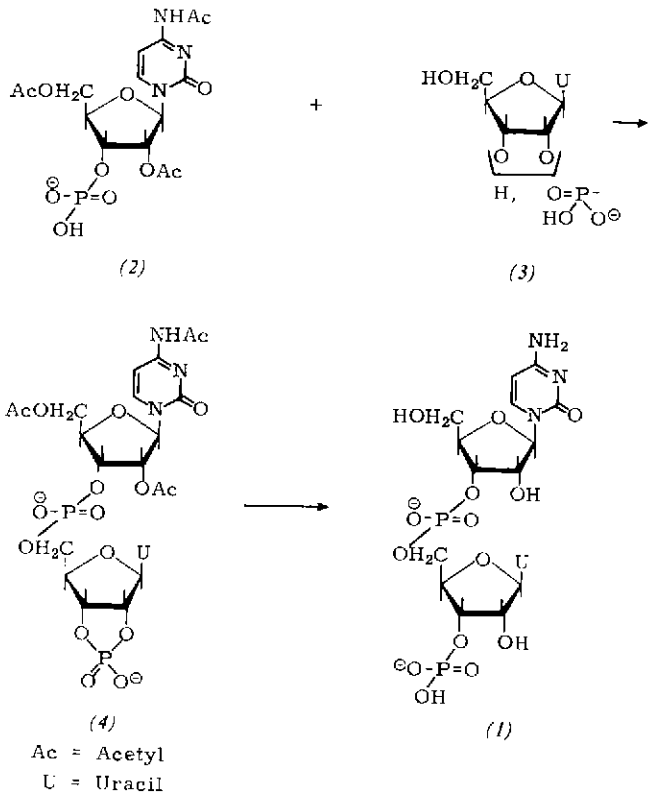
[1] *S. S. Malhotra* and *M. C. Whiting*, J. chem. Soc. (London) *1960*, 3812.

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[3] *J. Heiß*, Ph. D. Thesis, Technische Hochschule München, 1964.

[4] *E. Lippert* and *H. Prigge*, Ber. Bunsenges. physik. Chem. *67*, 6, 554 (1963).

Other workers have recently described [3] syntheses of ribodinucleotides using the tetrahydropyranyl group [4] to protect the 2′-hydroxyl group. However, removal of this acid-labile protecting group frequently leads to simultaneous isomerization of the internucleotidic linkage [3, 5].




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[2] *C. A. Dekker* and *H. G. Khorana*, J. Amer. chem. Soc. *76*, 3522 (1954).

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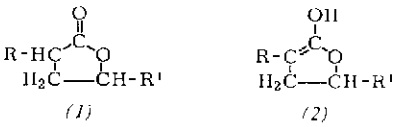
[5] *D. H. Rammler, Y. Lapidot*, and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 1989 (1963); *Y. Lapidot* and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 3852 (1963).

## Enolization of γ-Lactones

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The reaction of 2,6-dimethylphenolate with chloramine gives a doubly unsaturated ε-caprolactam which is converted with mineral acid to α-methyl-γ-acetonyl-γ-butyrolactone *(1a)* [1]. An incorrect structure was initially assigned to this compound as it was shown by the Zerewitinoff technique to contain about one active hydrogen atom. After the structure *(1a)* was confirmed, we investigated the behavior towards Zerewitinoff reagent ($CH_3MgI$) of *(1a)*, α-methyl-γ-n-propyl-γ-butyrolactone *(1b)* [derived from *(1a)* by Clemmensen reduction], and γ-butyrolactone *(1c)*. Compounds *(1a)*, *(1b)*, and *(1c)* proved to contain, respectively, 0.5, 0.4 and 0.4–0.5 active hydrogen atoms. The infrared and NMR spectra do not show OH groups, and when *(1c)* is warmed with tritiated water, its hydrogen atoms do not exchange. It is probable that $CH_3MgI$ induces the enolization *(1)* → *(2)*; this enolization and the reaction of the Grignard reagent with the C=O group probably proceed at comparable rates, thus enabling methane to be produced by reaction of the Zerewitinoff reagent with *(2)*.




*(a)*: R = $CH_3$, R' = $CH_2COCH_3$
*(b)*: R = $CH_3$, R' = $CH_2CH_2CH_3$
*(c)*: R = R' = H

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[1] *W. Theilacker, K. Ebke, L. Seidl*, and *S. Schwerin*, Angew. Chem. *75*, 208 (1963); Angew. Chem. internat. Edit. *2*, 154 (1963).

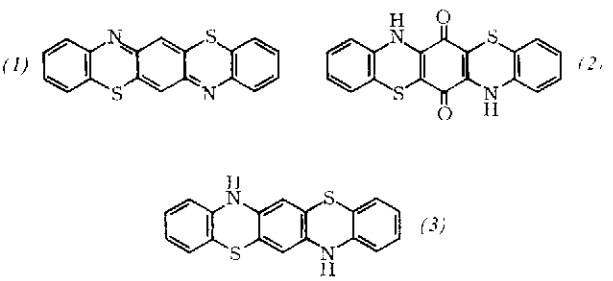
## 7,14-Dihydrotriphendithiazine Bis-S-oxides

By Dr. O. Christmann

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(Germany)

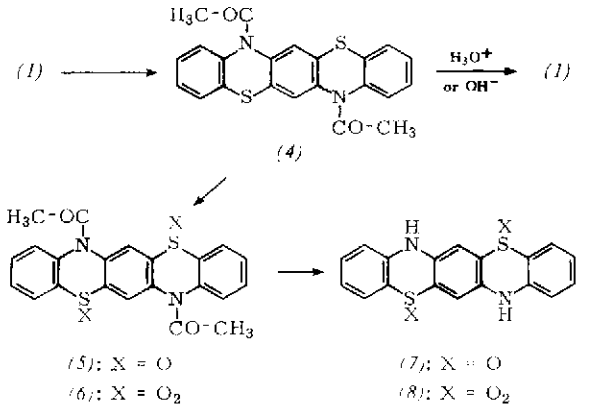
*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

Triphendithiazine *(1)* [1], 7,14-dihydro-6,13-dioxotriphendithiazine *(2)* [2, 3], and derivatives of these two parent compounds are known [1, 2], but compounds derived from 7,14-dihydrotriphendithiazine *(3)* have not yet been described. Attempts to prepare such derivatives remained without success [4].



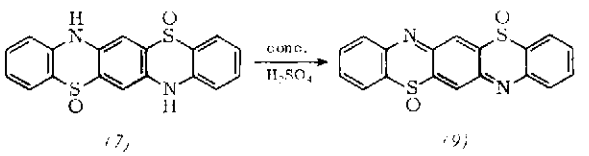

Compounds of type *(3)* are distinguished from the deeply colored quinonoid systems *(1)* and *(2)* principally by their central benzenoid ring. Although *(2)* and its derivatives can be reduced to hydroquinones, the latter are immediately reoxidized by atmospheric oxygen to the quinones [3].

By reductive acetylation of triphendithiazine *(1)* with zinc in glacial acetic acid/acetic anhydride, we succeeded in preparing 7,14-diacetyltriphendithiazine *(4)*. Deacetylation in acidic or basic media immediately reconverts *(4)* into the starting material *(1)*. Stable representatives of the benzenoid type *(3)* are accessible when *(4)* is oxidized by 30% $H_2O_2$ in glacial acetic acid to 7,14-diacetyltriphendithiazine bis-*S*-oxide *(5)* or *S*-dioxide *(6)*. Deacylation of the *S*-oxides *(5)* or *(6)* with NaOH/*N*-methylpyrrolidone affords orange alkali salts and hence, lemon-yellow 7,14-dihydrotriphendithiazine bis-*S*-oxide *(7)* or *S*-dioxide *(8)*, respectively. Compounds *(7)* and *(8)* are highly stable and extremely insoluble in organic solvents, and have properties reminescent of quinacridone.



(5): X = O
(6): X = O$_2$
(7): X = O
(8): X = O$_2$

Compounds (7) and (8) are distinguishable by their behavior in sulfuric acid: whereas (8) may be reprecipitated unchanged from concentrated sulfuric acid, (7) is successively changed into a dark-blue sulfate and a violet compound. All



(7) (9)

the observations made so far suggest that the benzenoid system (7) is converted into the energetically more favorable quinonoid form (9).

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[1] Brit. Pat. 698200 (Febr. 20th, 1951), Imperial Chemical Industries, inventors: *R. J. Fielden* and *D. G. Wilkinson*; Chem. Abstr. *48*, 7313 (1954).

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[3] *K. Fries*, *W. Pense*, and *O. Peeters*, Ber. dtsch. chem. Ges. *61*, 1398 (1928).

[4] *K. J. Farrington* and *W. K. Warburton*, Austral. J. Chem. *10*, 502 (1957).

## Hydrogen Fluoride Glasses

By Dr. J. Schröder

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Laboratorium Aachen (Germany)

Stable glass phases have been found in many systems of metal fluorides and hydrogen fluoride within extensive ranges of concentration. We have succeeded in preparing transparent stable glasses from hydrogen fluoride and the following metal fluorides, which may be added alone or in admixture in any desired proportions (cf. Table 1): Fluorides of the metals of the second and third main and auxiliary groups of the periodic table, of the lanthanides and some actinides, as well as $ZrF_4$, $HfF_4$, $PbF_2$, and $BiF_3$. All other solid metal fluorides can be added to these glasses in limited amounts. Large proportions of phosphates can also be incorporated into the glasses. Pyroceramic materials may be obtained by addition of certain transition metal fluorides or by heat treatment.

Compared with other compounds containing HF, the binding forces of the HF in the glasses are remarkably strong, probably owing to the formation of very strong hydrogen bonds. The glass phases are stable over large ranges of composition; mixtures of only one metal fluoride and less than 20 mole-% HF give stable glasses with scarcely any tendency towards devitrification or cristallization.

Table 1. Composition of various hydrogen fluoride glasses

| Glass No. | Metal fluoride | [mole-%] | HF [mole-%] | Glass No. | Metal fluoride | [mole-%] | HF [mole-%] |
|---|---|---|---|---|---|---|---|
| 1 | $MgF_2$ | 76 | 24 | 15 | $MgF_2$ | 11 | 44 |
| 2 | $CaF_2$ | 81 | 19 | | $BaF_2$ | 6 | |
| 3 | $SrF_2$ | 74 | 26 | | $LaF_3$ | 11 | |
| 4 | $BaF_2$ | 67 | 33 | | $GaF_3$ | 22 | |
| 5 | $PbF_2$ | 42 | 58 | | $ThF_4$ | 6 | |
| 6 | $YF_3$ | 64 | 36 | 16 | $LaF_3$ | 31 | 38 |
| 7 | $LaF_3$ | 84 | 16 | | $GaF_3$ | 31 | |
| 8 | $LaF_3$ | 67 | 33 | 17 | $GaF_3$ | 20 | 60 |
| 9 | $AlF_3$ | 63 | 37 | | $ThF_4$ | 20 | |
| 10 | $GaF_3$ | 57 | 43 | 18 | $MgF_2$ | 35 | 30 |
| 11 | $BiF_3$ | 70 | 30 | | $PbF_2$ | 35 | |
| 12 | $ZrF_4$ | 53 | 47 | 19 | $MgF_2$ | 18 | 28 |
| 13 | $ThF_4$ | 45 | 55 | | $SrF_2$ | 4 | |
| 14 | $ThF_4$ | 12 | 88 | | $BaF_2$ | 28 | |
| | | | | | $PbF_2$ | 4 | |
| | | | | | $LaF_3$ | 4 | |
| | | | | | $BiF_3$ | 14 | |

Most of the hydrogen fluoride glasses are non-toxic. Nearly all are moisture-resistant under normal conditions, and many have been exposed to boiling water for some hours without showing the slightest chemical attack or loss in weight.

The refractive index of some hydrogen fluoride glasses and the relative dispersion are extremely low, *e.g.* $n_d < 1.27$. The glasses are transparent from 2000 Å to 5 $\mu$ except for a small absorption band at 2.8 $\mu$. Their thermal expansion coefficients are rather high and can be controlled by changing the composition. We have succeeded in preparing strong leak-proof seals between hydrogen fluoride glasses and magnesium, aluminum, and several alloys of these metals.

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## Reactions of Halides of Group IV Elements with Trifluoroacetic Acid [1]

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Some trifluoroacetates, mainly of metals which form basic oxides, have been prepared by *F. Swarts* [2] and later by *G. H. Cady* [3]. We obtained some new compounds by the reaction of the tetrachlorides of Group IV elements with anhydrous trifluoroacetic acid (Table 1).

Table 1. Preparation of trifluoroacetates.

| Metal chloride | Conditions | Product | Yield [%] |
|---|---|---|---|
| $SiCl_4$ | 70 °C, 250 h benzene | $Si(OCOCF_3)_4$ water-clear liquid, b.p. 25 °C/$10^{-3}$ mm | 25 |
| $TiCl_4$ | 70 °C, 250 h homogeneous phase | $3\,TiO(OCOCF_3)_2 \cdot 2\,CF_3COOH$ white crystals | 100 |
| $ZrCl_4$ | 40 °C, 4 h heterogeneous phase | $Zr(OCOCF_3)_4$ white crystals | 100 |
| $ThCl_4$ | 70 °C, 24 h heterogeneous phase | $Th(OCOCF_3)_4$ white crystals | 100 |

Germanium and tin tetrachloride do not react with trifluoroacetic acid, probably because of insufficient polarization of the metal-chlorine bond.

$SiCl_4$ does not react quantitatively. It gives partially acylated by-products which could not be separated by distillation. $Ti(OCOCF_3)_4$ could not be obtained. Obviously the formation of $TiO(OCOCF_3)_2$ is preferred which crystallizes from the solution as $3TiO(OCOCF_3)_2 \cdot 2CF_3COOH$ *(1)*. In addition, $(CF_3CO)_2O$ is formed, which reacts further with the hydrochloric acid formed simultaneously to give trifluoroacetyl chloride:

$$TiCl_4 + 4\,CF_3COOH \rightarrow TiO(OCOCF_3)_2 + (CF_3CO)_2O + 4\,HCl$$
$$(CF_3CO)_2O + HCl \rightarrow CF_3COCl + CF_3COOH$$

On heating in high vacuum at 60 °C, *(1)* looses trifluoroacetic acid and yields $TiO(OCOCF_3)_2$ *(2)*, which sublimes at 180 °C in high vacuum. It follows from the infrared spectrum that the compound has a markedly salt-like character, as have $Zr(OCOCF_3)_4$ and $Th(OCOCF_3)_4$. In $Si(OCOCF_3)_4$ on the other hand, the bonds are mainly covalent.

The reaction of $TiOCl_2$ with trifluoroacetic acid, also yields *(1)* and from it *(2)*. The latter forms an etherate $TiO(OCOCF_3)_2 \cdot C_2H_5OC_2H_5$ *(3)*. When *(1)* is reacted with ether, trifluoroacetic acid is replaced with the formation of *(3)* and the ether adduct of trifluoroacetic acid $3\,CF_3COOH \cdot 2\,C_2H_5OC_2H_5$, which can also be obtained directly from trifluoroacetic acid and ether [4].

The products of the exothermic thermal decomposition in high vacuum are shown in Table 2.

Table 2. Thermal decomposition of trifluoroacetates.

| Compound | Decomposition temperature [°C] | Decomposition products |
|---|---|---|
| $TiO(OCOCF_3)_2$ | 240 | $(CF_3CO)_2O$ |
| $TiO(OCOCF_3)_2$ | 272 | $CO_2$, $COF_2$, $(CF_3CO)_2O$, $CF_3COF$, CO |
| $Zr(OCOCF_3)_4$ | 280 | $CO_2$, $COF_2$, $(CF_3CO)_2O$, $CF_3COF$, CO |
| $Th(OCOCF_3)_4$ | 272 | $CO_2$, $COF_2$, $(CF_3CO)_2O$, $CF_3COF$, CO |

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[1] First Communication on Reactions of Metal Halides with Perfluoromonocarboxylic acids.

[2] *F. Swarts*, Bull. Acad. roy Belgique Classe Sci. *8*, 343 (1922); Bull. Soc. chim. Belgique *48*, 176 (1939).

[3] *R. Hara* and *G. H. Cady*, J. Amer. chem. Soc. *76*, 4285 (1954); *G. S. Fujioka* and *G. H. Cady*, ibid. *79*, 2451 (1957).

[4] *M. Hauptschein* and *A. Grosse*, J. Amer. chem. Soc. *73*, 4139 (1951).

## Triethylstannylboranes

By Priv.-Doz. Dr. H. Nöth and
cand.-chem. K.-H. Hermannsdörfer

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der Universität München (Germany)

Dimethylamino groups on the boron atom stabilize the B–Si bond in silylboranes [1]; analogous stabilization occurs in organostannylboranes [2], described here for the first time. When triethylstannyl-lithium is reacted with equivalent amounts of dimethylaminochloroboranes in ether, LiCl is eliminated and yellow to brown liquids are formed from which colorless stannylboranes can be isolated by high-vaccum distillation. The following are examples of compounds so prepared:

$[(CH_3)_2N]_2B{-}Sn(C_2H_5)_3$, *(1)*, b.p. 32–35 °C/*ca.* $10^{-3}$ mm;
$[(CH_3)_2N]ClB{-}Sn(C_2H_5)_3$, *(2)*, b.p. 26–28 °C/*ca.* $10^{-3}$ mm;
$(CH_3)_2NB[Sn(C_2H_5)_3]_2$, *(3)*, b.p. 91–93 °C/*ca.* $10^{-3}$ mm.

The rapid hydrolysis according to

$$(1) + 3\,H_2O \rightarrow 2\,(CH_3)_2NH + B(OH)_3 + HSn(C_2H_5)_3$$

and the reaction with halogens (X = Br, I)

$$(1) + X_2 \rightarrow [(CH_3)_2N]_2BX + XSn(C_2H_5)_3$$

as well as other data (molecular weight, elemental analysis, infrared spectrum, dipole moment) prove the presence of covalent B–Sn bonds. HCl attacks the B–N bond before the B–Sn bond.

The stannylboranes are less stable than the analogous silylboranes. Compound *(1)* decomposes at about 100 °C into $B_2[N(CH_3)_2]_4$ and $Sn_2(C_2H_5)_6$; from *(3)* one obtains $B_4[N(CH_3)_2]_6$, $Sn_2(C_2H_5)_6$ and further products. Compound *(2)* decomposes slowly even at room temperature.

So far, no definite B–Sn compound has been obtained from the reaction between $(C_2H_5)_3SnLi$ and $(C_6H_5)_2BCl$ or $(C_4H_9)_2BCl$. The prediction that organogermanyl- and organoplumbyl-dimethylaminoboranes would be stable appears to be correct; their synthesis is under investigation.

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[1] *H. Nöth* and *G. Höllerer*, Angew. Chem. *74*, 718 (1962); Angew. Chem. internat. Edit. *1*, 551 (1962).

[2] *M. J. Newlands* and *B. Guy* have recently prepared a β-triphenylstannyl-1,3-dimethylbenzo-1,3,2-diazaborolidine and the analogous germanyl compound (personal communication).

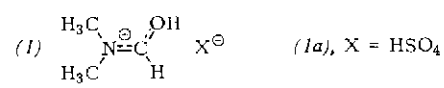
## Dimethylformamide-onium Salts

By Dr. H. Machatzke and Dr. E. Siegel

Wissenschaftliches Hauptlaboratorium
der Farbenfabriken Bayer AG., Leverkusen (Germany)

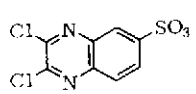
*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

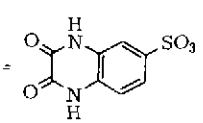
In concentrated sulfuric acid, dimethylformamide is protonated at the oxygen atom *(1a)* [1].



*(1a)*, X = $HSO_4$

Salts of dimethylformamide were previously unknown as isolable chemical entities. We found that 2,3-dichloroquinoxaline-6-sulfonic acid and 2,3-dihydroxyquinoxaline-6-sulfonic acid both form stable, readily crystallizable onium salts [*(1b)* and *(1c)*, respectively] with dimethylformamide.

*(1b)*, X = 


*(1c)*, X = 


To prepare these compounds, 2,3-dichloroquinoxaline-6-sulfonyl chloride [2] or 2,3-dihydroxyquinoxaline-6-sulfonyl chloride [3] is dissolved in absolute dimethylformamide; on addition of one mole of water, a considerable amount of heat is evolved and colorless crystals of *(1b)*, m.p. 130–131 °C, 85 % yield, or *(1c)*, m.p. 232–234 °C (decomp.), 95 % yield, rapidly separate. Compound *(1c)* crystallizes with one molecule of water of crystallization, *(1b)* is free from chloride ions. The formation, properties and reactions of these compounds indicate that they are salt-like, and exclude isomeric *O*-acyl derivatives of dimethylformamide such as Vilsmeyer adducts [4]. The compounds *(1b)* and *(1c)* dissolve very readily in water with liberation of one mole of acid; they are insoluble in ether. Compound *(1b)* can be recrys-

tallized from absolute ethanol, chloroform, dimethylformamide and acetone and can be precipitated from solution in thionyl chloride with ether.

Compounds *(1b)* and *(1c)* react instantaneously with NaI in absolute dimethylformamide to give the sparingly soluble sodium salts of the parent quinoxalinesulfonic acids. On addition of aniline to a solution of *(1b)* in acetone, anilinium 2,3-dichloroquinoxalinesulfonate precipitates immediately. Mercaptobenzthiazole reacts with *(1b)* in acetone to form 2-chloro-3-(2'-mercaptobenzthiazolyl)quinoxalinesulfonic acid.

The infrared spectra of *(1b)* and *(1c)* show a strong absorption at 1680 $cm^{-1}$, *i.e.* in the region of the C=N vibration [5].

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[1] *G. Fraenkel* and *C. Franconi*, J. Amer. chem. Soc. *82*, 4478 (1960).

[2] Belg. Pat. 613586 (Febr. 7th, 1961) (p. 16), inventors: *E. Siegel* and *K. Sasse*, Farbenfabriken Bayer; Belg. Pat. 617695 (May 16th, 1961) (p. 12), CIBA.

[3] From 2,3-dihydroxyquinoxaline and chlorosulfonic acid at 70 °C and treatment of the reaction mixture with ice; m.p. > 300 °C (decomp.).

[4] *H. Bredereck, R. Gompper, K. Klemm*, and *H. Rempfer*, Chem. Ber. *92*, 837 (1959).

[5] *H. H. Bosshard* and *H. Zollinger*, Helv. chim. Acta *42*, 1659 (1959).

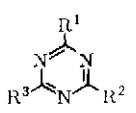
## Synthesis of Halogenoalkyldichloro-s-triazines and Bis(halogenoalkyl)chloro-s-triazines

By Dr. H. Herlinger

Wissenschaftliches Hauptlaboratorium
der Farbenfabriken Bayer AG., Leverkusen (Germany)

*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

Mixed trimerization of trichloroacetonitrile with aliphatic or aromatic nitriles (molar ratio 2:1) affords triazine derivatives in high yields [1]; however it was not hitherto possible to convert trichloroacetonitrile with cyanogen chloride in molar ratios of 1:2 or 2:1 into the triazines *(2)* and *(3)* in good yields [2]. Since the trimerization of cyanogen chloride and of trichloroacetonitrile alone yields cyanuryl chloride *(1)* and tris(trichloromethyl)-*s*-triazine *(4)*, respectively, it was to be expected that their mixed trimerization would yield a mixture of the triazines *(1)–(4)*.



*(1)*: $R^1 = R^2 = R^3 = Cl$
*(2)*: $R^1 = R^2 = Cl$; $R^3 = CCl_3$
*(3)*: $R^1 = Cl$; $R^2 = R^3 = CCl_3$
*(4)*: $R^1 = R^2 = R^3 = CCl_3$

When, however, hydrogen chloride is passed into a mixture of trichloroacetonitrile and cyanogen chloride in a molar ratio of 2:1 at −25 °C, 2,4-bis(trichloromethyl)-6-chloro-*s*-triazine *(3)* is formed in 90 % yield, together with small amounts of *(4)*; the mixture can be separated by distillation [*(3)* b.p. 164–168 °C/12 mm, m.p. 55–56 °C, *(4)* b.p. 176–178 °C/12 mm, m.p. 96 °C]. At a molar ratio of 1:2, large amounts of *(1)* are formed, together with 2-trichloromethyl-4,6-dichloro-*s*-triazine *(2)*. The reaction products can be separated by distillation or by crystallization from petroleum ether [*(1)* b.p. 198 °C, m.p. 146 °C, *(2)* b.p. 142–146 °C/12 mm, m.p. 115–116 °C]. At a molar ratio of 1:1.6, *(2)* and *(3)* are formed in 51 and 33 % yield respectively. The infrared spectra lend themselves to quantitative determination of the triazines *(1)–(4)* in the reaction mixture. The solubility in petroleum ether increases from *(1)* to *(4)*. As in the case of cyanuryl chloride *(1)*, the chlorine atoms of *(2)* and *(3)* can be replaced selectively by nucleophilic agents, *e.g.* aliphatic and aromatic amines, alcohols, phenols, and thiols. Other α,α-dihalogeno nitriles, such as α,α,β-trichloropropionitrile [3] also undergo mixed trimerization with cyanogen chloride.

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German version: Angew. Chem. 76, 437 (1964)

[1] German Patent 682391 (Dec. 17th, 1937) IG. Farben, inventor: *K. Dachlauer*; Chem. Zbl. *1939*, II, 4355.

[2] *Ch. J. Grundmann, G. Weise*, and *S. Seide*, Liebigs Ann. Chem. *577*, 77 (1952).

[3] Belg. Pat. 611822 (Dec. 21st, 1961) Farbenfabriken Bayer, inventors: *H. Herlinger, O. Bayer*, and *U. Unterstenhöfer*.

## The Reaction of Benzotriazinones with Isocyanates

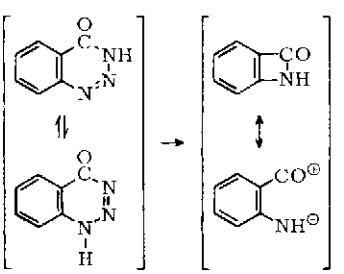
By Dr. H. Herlinger

Wissenschaftliches Hauptlaboratorium
der Farbenfabriken Bayer AG., Leverkusen (Germany)

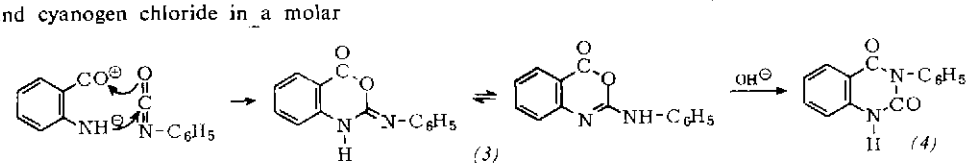
*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

Thermal decomposition of benzotriazinone *(1)* yields first the unstable lactam of anthranilic acid *(2)*; this compound is a strong acylating agent. When benzotriazinone and phenylisocyanate are heated together, they react immediately at 140–160 °C, undergoing cycloaddition to form the tautomeric heterocycle 2-phenyliminobenzo-3,1-oxyzine-4-one *(3)*, m.p. 191 °C, in 80 % yield.

The structure of the tautomers was proved by their rearrangement in aqueous-alcoholic NaOH to 3-phenylquinazoline-2,4-dione *(4)*. The melting point and infrared spectrum of *(3)* agreed with the figures shown by a product prepared from *N*-phenyl-*N'*-(2-carboxyphenyl)thiourea with mercuric oxide [1]. When benzotriazinone was treated with *m*-chlorophenyl isocyanate under the same conditions as with phenyl isocyanate, it gave 2-(*m*-chlorophenylimino)-benzo-3,1-oxazine-4-one, m.p. 214 °C, in 80 % yield. In the reaction with methyl isocyanate, the primary product rearranged immediately to 3-methylquinazoline-2,4-dione.



*(1)* *(2)*



*(3)* *(4)*

Received, March 4th, 1964 [Z 686/512 IE]
Publication deferred until now at the author's request
German version: Angew. Chem. 76, 437 (1964)

[1] *G. Doleschall* and *K. Lempert*, Tetrahedron Letters *1963*, 1195.

## Tetrachlorodiazocyclopentadiene from Hexachlorocyclopentadiene

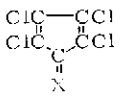
By Dr. H. Disselnkötter

Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG., Leverkusen (Germany)

*Dedicated to Professor H. Meerwein on the occasion of his 85th birthday*

Hexachlorocyclopentadiene reacts with hydrazine hydrate or with substituted hydrazines in lower alcohols to form the intensely red hydrazones *(1a)–(1c)* of tetrachlorocyclopentadienone [1]. To prepare *(1a)*, 300 g (6 moles) of hydrazine hydrate were added dropwise to a boiling solution of 545 g (2 moles) of hexachlorocyclopentadiene in 1500 ml of methanol within 30 minutes. After boiling for further 30 min the mixture was cooled to 40 °C and poured into 15 l of water. The crystals formed were filtered off with suction, pressed and washed with petroleum ether. On drying *in vacuo*, 340 g of crude product were obtained. Recrystallization from benzene gave 210 g of *(1a)* (yield 45 %). Compounds *(1b)* and *(1c)* were obtained by dropwise addition of a three-fold molar excess of the appropriate hydrazine to a cold solution of hexachlorocyclopentadiene in ethanol, stirring for a few hours and processing as described for *(1a)*.

Previously, only aryl-substituted hydrazones such as *(1c)* had been prepared (by coupling of diazonium salts with tetrachlorocyclopentadiene) [2].



*(1)*

| | X | M.p. [°C] | Yield [%] |
|---|---|---|---|
| *(a)* | $N-NH_2$ | 176 (from benzene) | 45 |
| *(b)* | $N-N(CH_3)_2$ | 89 (from petroleum ether) | 70 |
| *(c)* | $N-NHC_6H_5$ | 136 (from cyclohexane) | 69 |

Compound *(1a)* is insoluble in hydrochloric acid and does not form azines either with an excess of hexachlorocyclopentadiene or with carbonyl compounds. An aqueous hypochlorite solution oxidizes *(1a)* in ethyl acetate/methanol (2:1 by vol.) smoothly to tetrachlorodiazocyclopentadiene *(1d)*, X = $N_2$, m.p. 103 °C (decomp.), bright yellow needles. The yield after crystallization from methanol is 60 %. Compound *(1d)* is thus more readily obtained than tetrabromodiazocyclopentadiene [3]. Like diazocyclopentadiene, *(1d)* reacts with compounds of trivalent phosphorus [4]. In cyclohexane at 20 °C, it forms the addition compounds *(1e)*, X = $N-N=P(C_6H_5)_3$, m.p. 132 °C (decomp.), and *(1f)*, X = $N-N=P[N(CH_3)_2]_3$, m.p. 113 °C, in yields of 76 and 98 %, respectively.

A solution of *(1d)* in acetic acid is fairly stable up to about 80 °C; above 100 °C, nitrogen is split off rapidly. With chloral at 100–120 °C a crystalline product (b.p. 80–85 °C/0.1 mm, m.p. 62 °C, yield after distillation and crystallization from methanol: 48 %) is formed with additional liberation of carbon monoxide. According to its NMR spectrum it appears to be 5-trichloromethyl-1,2,3,5-tetrachlorocyclopenta-1,3-diene or the 1,2,4,5-tetrachloro compound.

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Publication deferred until now at the author's request
German version: Angew. Chem. 76, 431 (1964)

[1] Compound *(1a)* has also been prepared independently by *A. Hausweiler* (personal communication).

[2] *A. Roedig* and *L. Hörnig*, Chem. Ber. *88*, 2003 (1955).

[3] *D. J. Cram* and *R. D. Partos*, J. Amer. chem. Soc. *85*, 1273 (1963); *W. v. E. Doering* and *C. H. De Puy*, ibid. *75*, 5955 (1953).

[4] *F. Ramirez* and *St. Levy*, J. org. Chemistry *23*, 2036 (1958).

## The Reactions of Hydrazine and Alkyl-Substituted Hydrazines with Pyrimidines

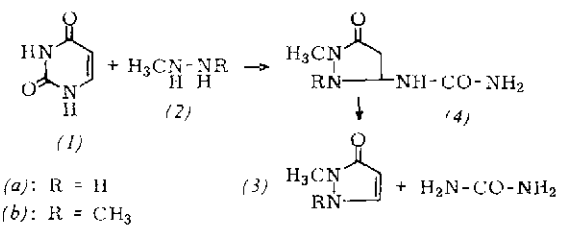
By Doz. Dr. F. Lingens and Dipl.-Chem. Helga Schneider-Bernlöhr

Biochemische Abteilung im Chemischen Institut der Universität Tübingen (Germany)

The reaction of a pyrimidine with hydrazine yields a pyrazolone and urea [1]. In an analogous manner, uracil *(1)* and a 5- to 8-fold excess of monomethylhydrazine *(2a)* react (80 °C, 15 h) to form 1-methylpyrazol-5-one *(3a)*, m.p. 104–108 °C, 30 % yield, and urea. Under the same conditions *(1)* and 1,2-dimethylhydrazine *(2b)* are converted in 30 % yield into 1,2-dimethylpyrazol-5-one *(3b)*, m.p. of picrate 162 °C, and urea. Compounds *(3a)* and *(3b)* were isolated by distillation in a high vacuum.

Compounds *(3a)* and *(3b)* can also be prepared by dropwise addition of ethyl propiolate to a stirred and cooled solution of *(2a)* or *(2b)*. After stirring at 20 °C for 6 hours, the mixture is neutralized and extracted with ethyl acetate. The yields of *(3a)* or *(3b)* are 65 %.

When uracil *(1)* is reacted under mild conditions (6 h, 80 °C) with 10 % solutions of *(2a)* or *(2b)*, the following intermediary products, which are stable at pH 7 to 10, can be isolated: 1-methyl-3-ureidopyrazolid-5-one *(4a)*, m.p. 140 °C, 30 % yield, and 1,2-dimethyl-3-ureidopyrazolid-5-one *(4b)*, m.p. 165 °C, 60 % yield. Isomeric open-chain structures, *e.g.* $H_2N\ CO\ NH-CH=CH\ CO\ N(CH_3)-NHR$, could be excluded on the basis of NMR and ultraviolet spectra.



*(1)* + *(2)* → *(4)*

*(a)*: R = H
*(b)*: R = $CH_3$

*(3)* + $H_2N-CO-NH_2$

The pyrazolones *(3a)* and *(3b)* were obtained in 30 % yield from *(4a)* and *(4b)* by decomposing with 2 N HCl, neutralizing, and extracting with ethyl acetate.

Thymine reacted considerably more slowly with the hydrazines; on reaction with *(2a)*, only 1,4-dimethylpyrazol-5-one (m.p. 130–132 °C) and urea were isolated. Cytosine reacted with *(2a)* to give a pyrazolone hydrazone (m.p. of picrate 153 °C). No reaction occurred with *(2b)*. Ribonucleic acid is attacked by *(2b)* preferentially at the uracil residues. Hydrazine and alkyl-substituted hydrazines cause mutations in *Escherichia coli* [2] and *Salmonella typhimurium* [3].

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[1] *R. Fosse, A. Hieulle*, and *L. W. Bass*, C. r. hebd. Séances Acad. Sci. *178*, 811 (1924).

[2] *F. Lingens*, Z. Naturforsch. *19b*, 151 (1964).

[3] *F. Lingens, H. Kraus*, and *S. Lingens*, Hoppe-Seylers Z. physiol. Chem., in the press.

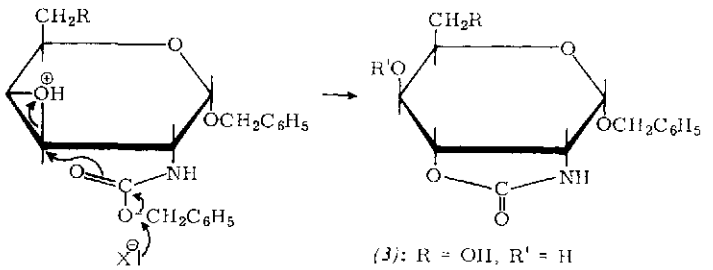
## A New Synthesis of Oxazolidones and the Preparation of 2,6-Diamino-2,6-dideoxy-D-gulose

By Dr. P. H. Gross, Dr. K. Brendel, and Prof. Dr. H. K. Zimmerman

Department of Chemistry, University of the Pacific, Stockton, Cal. (U.S.A.)

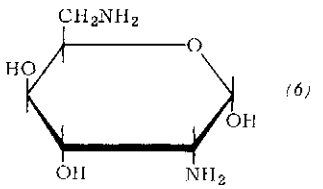
When benzyl-*N*-Cbo-3-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucosamine [1] (m.p. 137 °C; $[\alpha]_D^{20} = +99°$, c = 1 in pyridine) is treated with potassium acetate in acetic acid/acetic anhydride, benzyl-*N*-Cbo-3,6-di-*O*-acetyl-4-*O*-mesyl-α-D-glucosamine

(m.p. 85 °C, $[\alpha]_D^{20} = +102°$; c = 1 in pyridine) is obtained in 84 % yield. On hydrolysis with KOH in water/dioxan, the latter compound affords benzyl-*N*-Cbo-3,4-anhydro-α-D-galactosamine *(1)* (m.p. 158 °C; $[\alpha]_D^{20} = +71°$, c = 1 in pyridine) in 86 % yield. Mesylation of *(1)* yields the 6-mesyl derivative *(2)* (m.p. 124 °C; $[\alpha]_D^{20} = -64°$, c = 1 in pyridine) in 92 % yield. Compound *(2)* is obtained more simply in 98 % yield from benzyl-*N*-Cbo-3-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucosamine and sodium isopropoxide in dioxan/isopropanol at 0 °C. Its preparation by both these routes excludes the possibility of the formation of 4,6- and 3,6-anhydro sugars.



*(1)*: R = OH
*(2)*: R = $OSO_2CH_3$

*(3)*: R = OH, R' = H
*(4)*: R = $OSO_2CH_3$, R' = $COCH_3$
*(5)*: R = $N_3$, R' = $COCH_3$



*(6)*

The preparation of these new *N*-Cbo-amino-sugar epoxides has revealed stereospecifically interesting routes to the gulosamine series by way of oxazolidones. When heated in 50 % acetic acid, *(1)* yields benzyl-α-D-gulopyranosido-[2,3-*d*]oxazolid-2'-one *(3)* (m.p. 114 °C; $[\alpha]_D^{20} = +65°$, c = 1 in pyridine) in 90 % yield. On successive alkaline hydrolysis, acetylation, and acidic hydrolysis, *(3)* yields D-gulosamine hydrochloride [2]. When boiled with acetic acid and subsequently acetylated, *(2)* is converted quantitatively into benzyl-4-*O*-acetyl-6-*O*-mesyl-α-D-gulopyranosido[2,3-*d*]oxazolid-2'-one *(4)* (m.p. 177 °C; $[\alpha]_D^{20} = +72°$, c = 1 in pyridine). On treatment with sodium azide in dimethylsulfoxide, *(4)* yields the 6-azido compound *(5)*, which can be converted by catalytic hydrogenation and hydrolysis into 2,6-diamino-2,6-dideoxy-D-gulose dihydrochloride *(6)*, which mutarotates: $[\alpha]_D^{20} = +35°$ after 10 min and $-10°$ after 36 h, c = 2.7 in water. The infrared spectrum of *(6)* coincides almost completely with that of gulosamine hydrochloride [2] and contains band displacements only between 730 and 960 $cm^{-1}$, as compared with the corresponding glucose derivative.

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German version: Angew. Chem. 76, 377 (1964)

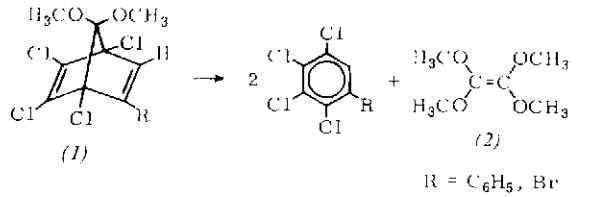
[1] *P. H. Gross* and *H. K. Zimmerman*, Liebigs Ann. Chem., in the press.
[2] *R. Kuhn* and *W. Bister*, Liebigs Ann. Chem. *617*, 92 (1958).
[3] *H. Wiedmann* and *H. K. Zimmerman*, Liebigs Ann. Chem. *641*, 138 (1961).

## Carbocyclic and Heterocyclic Four-Membered Rings from Tetramethoxyethylene by Cycloaddition

By Dr. R. W. Hoffmann and cand. chem. H. Häuser

Organisch-Chemisches Institut
der Universität Heidelberg (Germany)

Tetramethoxyethylene *(2)* is readily obtained by subjecting 7,7-dimethoxybicyclo[2,2,1]heptadiene derivatives *(1)* to thermal decomposition [1].

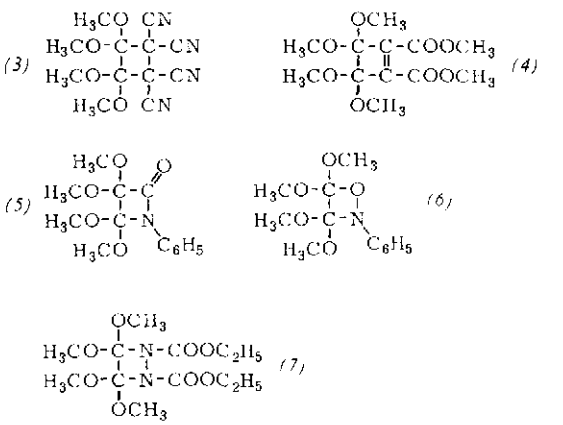


*(1)*

*(2)*

R = $C_6H_5$, Br

Being a double ketene acetal, *(2)* exhibits high reactivity. For example, it adds on ethanol or water spontaneously. It is readily alkylated even with $CCl_4$. Cycloadditions take place at 40–80 °C. Thus, the cyclobutane derivative *(3)*, m.p. 179 °C, is formed from tetracyanoethylene in 63 % yield [2]; with methyl acetylenedicarboxylate one obtains the addition product *(4)*, b.p. 150 °C/0.01 mm, in 97 % yield (characterized as the dicarhoxylic acid, m.p. 134 °C).



*(3)* *(4)*

*(5)* *(6)*



*(7)*

Addition of tetramethoxyethylene *(2)* onto double bonds between elements of the first main group leads smoothly to heterocyclic four-membered rings. Thus, phenyl isocyanate gave *(5)*, b.p. 132 °C/0.01 mm, in 76 % yield; reaction of *(2)* with nitrosobenzene or azodicarboxylic ester resulted in quantitative formation of the addition products *(6)*, m.p. 83 °C, and *(7)*, m.p. 111 °C. Addition onto nascent sulfene was not successful [3].

Received, March 6th, 1964 [Z 691/516 IE]
German version: Angew. Chem. 76, 346 (1964)

[1] *R. W. Hoffmann* and *H. Häuser*, Tetrahedron Letters *1964*, 197; *D. M. Lemal*, *E. P. Gosselink*, and *A. Ault*, ibid. *1964*, 579.
[2] The structure of the adducts was confirmed by analysis, molecular-weight determination, infrared and NMR spectra.
[3] For literature on sulfenes cf. *J. F. King* and *T. Durst*, J. Amer. chem. Soc. *86*, 287 (1964).

## Tricyanomethanido Metal Complexes Containing Carbon Monoxide and Nitric Oxide

By Priv.-Doz. Dr. W. Beck, Dipl.-Chem. R. E. Nitzschmann, and Dipl.-Chem. G. Neumair

Anorganisch-Chemisches Laboratorium der Technischen Hochschule München (Germany)

Potassium tricyanomethanide, $K[C(CN)_3]$, has become readily accessible by a new method of preparation [1]. Two-fold reaction of pentacarbonylmanganese halides [2], $Mn(CO)_5X$ (X = Cl, Br, I), with potassium or silver cyanomethanide in tetrahydrofuran gave tricyanomethanidopentacarbonylmanganese, $Mn(CO)_5C(CN)_3$, in the form of yellow needles, stable in air for prolonged periods, sparingly soluble in tetrahydrofuran and insoluble in petroleum ether. To prepare this substance, $Mn(CO)_5I$ is shaken in tetrahydrofuran with a slight excess of silver tricyanomethanide for 10 hours at 20 °C under exclusion of light and air.

On heating with phosphines or phosphite in tetrahydrofuran, $Mn(CO)_5C(CN)_3$ reacts with substitution of one mole of CO:

$$Mn(CO)_5C(CN)_3 + L \rightarrow Mn(CO)_4LC(CN)_3 + CO \quad (1)$$

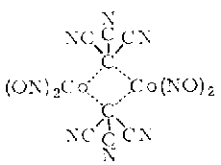
$L = P(C_6H_5)_3$, $P(C_6H_{11})_3$, $P(OC_6H_5)_3$

The infrared spectra of the yellow compounds *(1)* show two CO stretching vibrations in the region of 1850–2000 $cm^{-1}$ in addition to the CN absorption at 2200 $cm^{-1}$. The occurrence of only two CO frequencies indicates a *trans*-configuration of the $C(CN)_3$ and phosphine ligands.

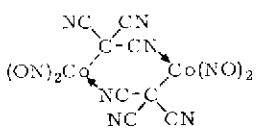
Whereas tetracarbonyliron halides do not form tricyanomethanido complexes with potassium or silver tricyanomethanide, $C_5H_5Fe(CO)_2C(CN)_3$ (decomposition point 110 °C) is obtained in the form of light brown crystals when $C_5H_5Fe(CO)_2I$ [3] is reacted with $Ag[C(CN)_3]$ in methanol. Analogous reactions of nitrosylmetal halides, such as $[Co(NO)_2Cl]_2$ [4] and $[Ni(NO)I]_n$ [5], with $K[C(CN)_3]$ in methanol lead to the formation of the tricyanomethanido compounds $[Co(NO)_2C(CN)_3]_n$ and $[Ni(NO)C(CN)_3]_n$.

Light brown, crystalline $[Co(NO)_2C(CN)_3]_n$ reacts with phosphines to give $Co(NO)_2PR_3C(CN)_3$ ($R = C_6H_5$, $C_6H_{11}$); when the blue compound $[Ni(NO)C(CN)_3]_n$ is reacted with phosphines, the compounds $[Ni(NO)PR_3C(CN)_3]_2$ and $Ni(NO)(PR_3)_2C(CN)_3$ can be isolated. These nitrosyltricyanomethanides of cobalt and nickel which contain phosphine have a structure analogous to that of the corresponding nitrosyl halide complexes [6].

In $[Co(NO)_2C(CN)_3]_n$ and $[Ni(NO)PR_3C(CN)_3]_2$ the presence of tricyanomethanide bridges must be assumed by analogy with the nitrosyl halide complexes [6]. For the cobalt complex with n = 2, for instance, the structures *(2)* and *(3)* may be envisaged.



*(2)*



*(3)*

In addition to the intense CN absorption at about 2200 $cm^{-1}$, these compounds exhibit a further CN band which is displaced towards shorter wavelengths by about 50 $cm^{-1}$. This CN absorption indicates the occurrence of $C-C\equiv N$ bridges [structure *(3)*].

Received, March 9th, 1964 [Z 690/515 IE]
German version: Angew. Chem. 76, 346 (1964)

[1] *S. Trofimenko, E. L. Little*, jr., and *H. F. Mower*, J. org. Chemistry *27*, 433 (1962).

[2] Preparation: *G. Wagner*, Ph. D. Thesis, Technische Hochschule München, 1958.

[3] *T. S. Piper* and *G. Wilkinson*, J. inorg. nuclear Chem. *2*, 38 (1956).

[4] *W. Hieber* and *R. Marin*, Z. anorg. allg. Chem. *240*, 241 (1939); *W. Hieber* and *W. Beck*, Z. Naturforsch. *13b*, 194 (1958).

[5] *W. Hieber* and *R. Nast*, Z. anorg. allg. Chem. *244*, 23 (1940).

[6] *W. Hieber* and *K. Heinicke*, Z. anorg. allg. Chem. *316*, 305 (1962); *W. Hieber* and *I. Bauer*, ibid. *321*, 107 (1963).

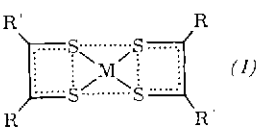
## Bis-Dithione Complexes of Transition Metals

By Priv.-Doz. Dr. G. N. Schrauzer, Dr. V. Mayweg, Dipl.-Chem. H. W. Finck, cand.-chem. U. Müller-Westerhoff, and cand.-chem. W. Heinrich

Institut für Anorganische Chemie
der Universität München (Germany)

The reactive α,β-dithiodiketones, which normally do not exist as free monomers, form stable complexes of type *(1)* with transition metals. Bis-dithiobenzilnickel, the first representative of this new class of compounds, is obtained *e.g.* by the reaction of diphenylacetylene with nickel sulfides [1,2] or by the action of $H_2S$/HCl on benzoin in the presence of nickel chloride [3]. Analogous complexes are formed by the reaction of disubstituted alkynes with metal carbonyls in the presence of sulfur. These methods give, however, only low yields and are not sufficiently general. We wish to report the following method: Acyloins are reacted in inert solvents (*e.g.* xylene) by heating with $P_2S_5$ to give phosphorothioic esters of the dithioacyloins. Frequently these react directly with metal salt solutions to yield the complexes *(1)*. In this way we have prepared bis-dithione complexes of V, Cr, Mo, W, Re, Fe, Co, Ni, Ru, Os, Pt (Table 1).

Bis-dithiobenzil complexes of transition metals with an even number of electrons are diamagnetic. The corresponding compounds of vanadium and rhenium are paramagnetic and exhibit E.P.R. signals with fine structure. The dithiobenzil complexes listed in Table 1 are stable to air even at elevated temperatures. On heating they decompose into the metal sulfide, sulfur, 2-phenylthionaphthene and in some cases also into tetraphenylthiophene. Most complexes are resistant to concentrated non-oxidizing acids. They have very similar infrared and ultraviolet spectra and must be planar by analogy with bis-ditbiobenzilnickel. The highest occupied molecular orbital is spread over the whole molecule and the corresponding lowest antibinding molecular orbital lies only 1.7–1.8 eV above it. All complexes thus show an allowed electronic transition in the near infrared ($\lambda_{max}$ = 700–800 mμ, ε *ca.* 20000). On account of the low excitation energy the complexes are readily reduced taking up one or two electrons. The salts of the mono- and dianions were isolated and are dia- or paramagnetic depending on the number of electrons. Attempts to obtain the uncharged manganese compound of dithiobenzil have so far been unsuccessful. The compound is polar and decomposes in acidic media.



*(1)*

Table 1. Complexes of the type *(1)*.

| M | R | R' | M.p. [°C] | Color | |
|---|---|---|---|---|---|
| | | | | solution | solid |
| Ni | $C_6H_5$ | $C_6H_5$ | 293 (decomp.) | green | green |
| Co | $C_6H_5$ | $C_6H_5$ | ≈360 (decomp.) | (insol.) | black |
| Fe | $C_6H_5$ | $C_6H_5$ | 295 (decomp.) | green | black |
| V | $C_6H_5$ | $C_6H_5$ | 210 (decomp.) | violet | black |
| Re | $C_6H_5$ | $C_6H_5$ | ≈340 (decomp.) | green | green |
| Pt | $C_6H_5$ | $C_6H_5$ | 310 | red | red |
| Os | $C_6H_5$ | $C_6H_5$ | 190 (decomp.) | red | red |
| Ru | $C_6H_5$ | $C_6H_5$ | 225 | green | blue |
| Cr | $C_6H_5$ | $C_6H_5$ | 241 | blue | violet |
| Mo | $C_6H_5$ | $C_6H_5$ | ≈360 (decomp.) | green | green |
| W | $C_6H_5$ | $C_6H_5$ | ≈360 (decomp.) | blue-green | black |
| Ni | $C_6H_5$ | H | 175 | green | green |
| Ni | $CH_3$ | $CH_3$ | ≈256 (decomp.) | blue-violet | blue-violet |
| Ni | $C_2H_5$ | $C_2H_5$ | 112 (decomp.) | blue | blue |
| Ni | n-$C_3H_7$ | n-$C_3H_7$ | 52–54 (decomp.) | blue | blue |
| Ni | p-$ClC_6H_4$ | p-$ClC_6H_4$ | 335 (decomp.) | green | black |
| Pt | p-$ClC_6H_4$ | p-$ClC_6H_4$ | >340 | red | deep blue |

Received, March 9th, 1964 [Z 688/514 IE]
German version: Angew. Chem. 76, 345 (1964)

[1] *G. N. Schrauzer* and *V. Mayweg*, J. Amer. chem. Soc. *84*, 3221 (1962).

[2] *G. N. Schrauzer* and *V. Mayweg*, Z. Naturforsch. *19b*, 192 (1964).

[3] *G. N. Schrauzer* and *H. W. Finck*, Angew. Chem. *76*, 143 (1964); Angew. Chem. internat. Edit. *3*, 133 (1964).

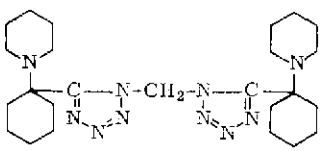
## The Synthesis of 1,1-Diisonitrilomethane

By Doz. Dr. R. Neidlein

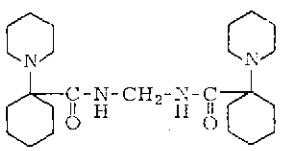
Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg/Lahn (Germany)

Compounds with more than one isonitrile group at one carbon atom were previously unknown. Bis(formylamino)-methane *(1)* [1] was used as starting material for the preparation of 1,1-diisonitrilomethane *(2)*. When 0.05 mole of *(1)* was treated with 0.1 mole of phosgene at *ca.* −60 °C in the presence of 35 ml of triethylamine, two molecules of water were eliminated [2] to give 1,1-diisonitrilomethane, which was extracted with methylene dichloride. The product is stable for 10–20 min at *ca.* 30 °C in solution; on evaporation of the solvent, it rapidly polymerizes with considerable evolution of heat to give a black mass. If the cold methylene

*(1)* $O{=}C(H)-N(H)-CH_2-N(H)-C(H){=}O \longrightarrow C{\equiv}N-CH_2-N{\equiv}C$ *(2)*



*(3)*



*(4)*

dichloride extract is immediately treated with equimolar amounts of *N*-cyclohexenylpiperidine and hydrazoic acid in benzene [3], the bis-tetrazole derivative *(3)* (m.p. 243–244 °C) is formed and may be isolated by removal of the solvent. A further derivative, *N,N'*-bis-(1-piperidinocyclohexylcarbonyl)methylenediamine *(4)* (m.p. 106–107 °C), was obtained by *Ugi*'s method [3].

Received, March 31st, 1964 [Z 718/544 IE]
German version: Angew. Chem. *76*, 440 (1964)

[1] *P. Knudsen*, Ber. dtsch. chem. Ges. *47*, 2700 (1914).

[2] *I. Ugi, W. Betz, U. Fetzer*, and *K. Offermann*, Chem. Ber. *94*, 2814 (1961).

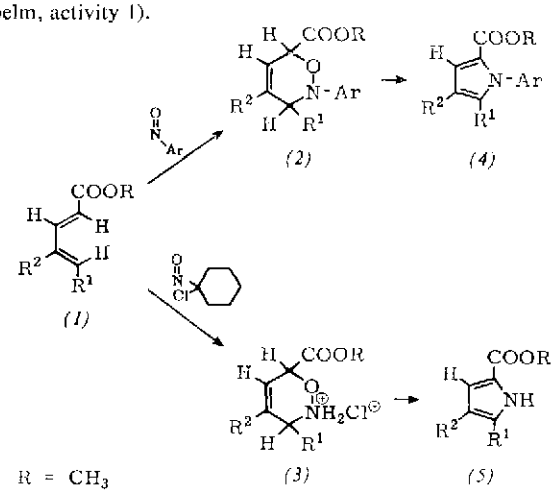
[3] *I. Ugi*, Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962).

## A New Synthesis of Pyrrole-2-carboxylic Acid Derivatives

By Prof. Dr. G. Kresze and Dipl.-Chem. J. Firl

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der Technischen Hochschule München (Germany)

Diene syntheses involving butadienecarboxylic esters *(1)* and nitrosobenzenes in $CH_2Cl_2$ afford 1,2-oxazine derivatives *(2)* as residues after removal of the solvent by vacuum distillation. The reaction of *(1)* with 1-chloro-1-nitrosocyclohexane in ethanol produces the hydrochlorides *(3)* (cf. Table 1). Compounds of types *(2)* and *(3)* which contain an acidic hydrogen on C-6 can be converted by dehydration into the pyrrole-2-carboxylic acid derivatives *(4)* and *(5)*; the dehydration is effected by bases, but most effectively simply by chromatography with an anhydrous non-polar solvent (benzene, carbon tetrachloride) on an approximately tenfold quantity of neutral aluminum oxide (from Messrs. Woelm, activity I).



*(1)* *(2)* *(3)* *(4)* *(5)*

R = $CH_3$

The products are formed directly in high purity. The crude products of the diene syntheses may be employed for the dehydration without further purification. Table 1 gives a list of the pyrrolecarboxylic acid derivatives synthetized so far by this route; the range of application and mechanism of the reaction will be discussed in greater detail elsewhere.

Table 1. Substituents and properties of compounds *(2)*–*(5)*.

| Compound | $R^1$ | $R^2$ | Ar | M.p. [°C] | Yield [%] | Compound | M.p. [°C] | Yield [%] [a] |
|---|---|---|---|---|---|---|---|---|
| *(2a)* | $CH_3$ | H | $C_6H_5$ | 58 [b] | 93 | *(4a)* | 39 [c] | 76 |
| *(2b)* | $CH_3$ | H | *p*-$ClC_6H_4$ | 63 [b] | 92 | *(4b)* | 83 [b] | 79 |
| *(2c)* | H | H | *p*-$ClC_6H_4$ | 74 [b] | 83 | *(4c)* | 90 [b] | 80 |
| *(2d)* | $C_6H_5$ | H | *p*-$ClC_6H_4$ | 85 (decomp.)[b] | 55 [d] | *(4d)* | 145 [b] | 77 |
| *(2e)* | $CH_3$ | Br | *p*-$ClC_6H_4$ | [e] | 74 | *(4e)* | 89 [b] | 55 |
| *(3a)* | H | H | | [f] | 92 | *(5a)* | 74 [c] | 85 |
| *(3b)* | $CH_3$ | H | | [f] | 72 | *(5b)* | 101 [c] | 88 |

[a] Calculated on the basis of the initial adducts; in the case of *(4e)*, based on *(1)*.
[b] From hexane.
[c] Sublimes.
[d] Together with 35 % of the isomeric adduct.
[e] Pyrrole synthetized from the crude product.
[f] Hydrochlorides were converted into the free bases, which were employed without further purification.

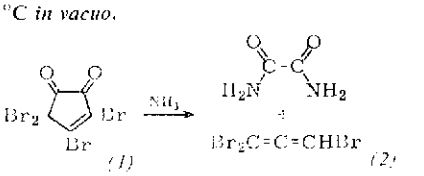
Received, March 9th, 1964 [Z 704/530 IE]
German version: Angew. Chem. *76*, 439 (1964)

## Tribromoallene and Perbromoallene

By Prof. Dr. A. Roedig, Dipl.-Chem. N. Detzer, and Dr. H. J. Friedrich

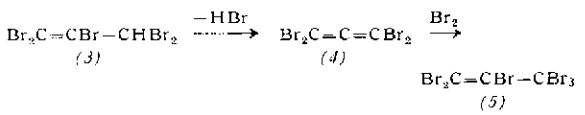
Chemisches Institut der Universität Würzburg (Germany)

Tetrabromocyclopent-1-ene-3,4-dione *(1)* is split by liquid $NH_3$ in propane at −75 °C into oxamide and tribromoallene *(2)*, the latter being isolated in 75 % yield after removal of the solvent at −70 °C *in vacuo*.

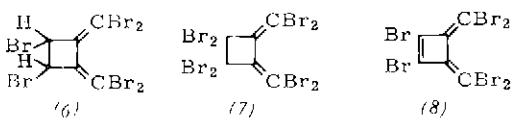


*(1)* *(2)*

Tribromoallene *(2)* is rapidly brominated in $CCl_4$ at room temperature to give pentabromopropene *(3)*, which can be smoothly dehydrobrominated by the method reported for the dehydrochlorination of 3-*H*-pentachloro-1-propene [1], to give perbromoallene *(4)* (80 % yield). The addition of bromine onto *(4)* gives perbromopropene *(5)*.



The infrared spectra of *(2)* and *(4)* as liquid films, show characteristic allene vibration bands at 5.14 and 5.12 μ, respectively. Perbromoallene *(4)* shows less, and tribromoallene *(2)* very much less tendency to dimerize than does perchloroallene [1]. In $CCl_4$ at 40 °C, the allene vibration band of *(4)* disappears in 45 min while the allene band of *(2)* disappears in 90 hours. The dimer of *(2)*, which is formed in 50 % yield, can also be prepared by treatment of *(1)* with NaOH [2]. Contrary to reports in the literature [3] it is a hexabromo-1,2-dimethylenecyclobutane of structure *(6)* (m.p. 137 °C). The dimerization of *(4)* gives perbromo-1,2-dimethylenecyclobutane *(7)* (m.p. 131 °C) which can be smoothly debrominated with Al turnings in ether to give perbromo-1,2-dimethylenecyclobutene *(8)* (m.p. 165 °C).



The ultraviolet spectra of *(6)*, *(7)*, and *(8)* in n-heptane are very similar to those of the corresponding chloro compounds [1,4]. The structure *(7)* was confirmed by Raman spectroscopy [5].

The structure *(6)* with protons on the ring was deduced from the NMR spectrum, which excludes cyclic and open-chain structures with olefinic protons. The $^1H$ signal of *(6)* at $\tau$ = 5.46 ppm (in $CCl_4$ with tetramethylsilane as standard) corresponds to that of cyclobutyl bromide ($\tau$ = 5.53 ppm) and is significantly different from that of 1,2-dibromoethylene ($\tau$ = 3.00 ppm). The $\tau$-value calculated for the $^1H$ resonance in *(6)* by the method of *Primas*, *Arndt*, and *Ernst* [6], is 5.49 ppm while that calculated for olefinic protons is 2.95 ppm.

Received, March 16th, 1964 [Z 697/522 IE]
German version: Angew. Chem. 76, 379 (1964)

[1] *A. Roedig, G. Märkl*, and *B. Heinrich*, Angew. Chem. *75*, 88 (1963); Angew. Chem. internat. Edit. *2*, 47 (1963); *A. Roedig, F. Bischoff, B. Heinrich*, and *G. Märkl*, Liebigs Ann. Chem. *670*, 8 (1963).

[2] *C. A. Theurer*, Liebigs Ann. Chem. *245*, 348 (1888).

[3] *F. J. Moore* and *R. M. Thomas*, Amer. Chem. J. *39*, 974 (1917); *T. van der Linden*, Recueil Trav. chim. Pays-Bas *57*, 401 (1938).

[4] See also *A. Roedig* and *F. Bischoff*, Naturwissenschaften *49*, 448 (1962).

[5] *J. Brandmüller* and *E. Ziegler*, Z. analyt. Chem. *200*, 299 (1964).

[6] *H. Primas, R. Arndt*, and *R. Ernst*, International Meeting on Molecular Spectroscopy, Bologna 1959.

## Pentafluoro-orthotelluric Acid, $HOTeF_5$

By Doz. Dr. A. Engelbrecht and F. Sladky

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der Universität Innsbruck (Austria)

On heating $BaTeO_4$ with $HSO_3F$ (molar ratio 1:10) for 3 hours to 160 °C, a mixture of volatile tellurium compounds is obtained instead of the unknown $TeO_2F_2$, the formation of which would be expected by analogy with $SeO_2F_2$ [1]. The main constituent isolated from the crude fraction distilling between 58 and 65 °C was a compound of the composition $HTeOF_5$ (yield 25 %), which turned out to be a fluoro acid of hexavalent tellurium (molecular weight determined from the vapour density at 20 °C: 243.5; calculated: 239.6; m.p. 40 ± 1 °C; b.p. 60 ± 1 °C; density of the liquid at 40 °C: 2.626 g/cm³; vapour pressure at 0 °C: 40.2 mm).

The colorless compound solidifies to a glassy-crystalline mass; above 40 °C it is a mobile, strongly refractive liquid. It does not attack glass, mercury, and polyethylene at room temperature. As cock grease we used "halocarbon oil" [2].

The aqueous solution immediately displays a strong acid reaction. Qualitative measurements of the conductivity of such solutions showed that $HOTeF_5$ rapidly hydrolyses to telluric and hydrofluoric acid. It has not been possible to precipitate a sparingly soluble compound of the anion $OTeF_5^-$ from aqueous solutions.

HCl, HF, or $CO_2$ are liberated, when $HOTeF_5$ is condensed on solid KCl, KF, or $K_2CO_3$. In the reaction with KCl the weight increase corresponded to the formation of $KOTeF_5$ with a yield of about 95 %.

The infrared spectrum of $HOTeF_5$ displays a very sharp OH-band at 3670 $cm^{-1}$.

Formally the compound corresponds to the hydroxofluoro anions of elements of groups 4 and 5 of the periodic system [3]. Since, however, the group number of tellurium is 6, $HOTeF_5$ is not a hydroxofluoro anion but a strong, volatile acid. Its stability is undoubtedly due to the attainment of an octahedral configuration by the hexavalent tellurium, with the 5 fluoride ions and the OH ion as ligands.

Received, March 19th, 1964 [Z 698/526 IE]
German version: Angew. Chem. 76, 379 (1964)

[1] *A. Engelbrecht* and *B. Stoll*, Z. anorg. allg. Chem. *292*, 20 (1957).

[2] Product of Halocarbon Products Corp., Hackensack, N.Y. (U.S.A.).

[3] *L. Kolditz* and *H. Preiss*, Z. anorg. allg. Chem. *325*, 263 (1963), where further references are given.

## Aliphatic Nitrile Oxides [1]

By Prof. Dr. G. Zinner and H. Günther

Institut für Pharmazie und Lebensmittelchemie
der Universitäten Marburg und Münster (Germany)

By elimination of HCl from hydroxamic chlorides *(1)* in inert solvents at about −15 °C, several aliphatic nitrile oxides *(2)* were prepared and isolated. Their infrared spectra displayed a clearly defined absorption band at 4.40 μ; as is to be expected, they dimerize to furoxans *(3)* at room temperature. They undergo addition reactions, *e.g.* with mercaptans [to give *(4)*], with amines [to *(5)*], and with hydrazines [to *(6)*], as well as cycloadditions, *e.g.* with diphenylketene [to *(7)*] and with butadiene [to *(8)* and *(9)*].

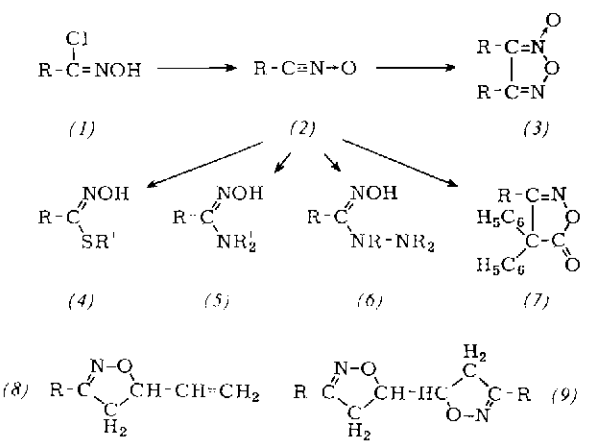


Table 1. Substituents and melting points of compounds *(1)*–*(9)*.

| R | Melting points [°C] | | | | |
|---|---|---|---|---|---|
| | *(1)* | *(2)* | *(3)* | *(4)* | *(5)* |
| $CH_3$ | –3 [2] | –5 | –13 [3] | 55 [a] | 92 [b] |
| $(CH_3)_3C$ | 33 | 18 | 67 | 74 [c] | 139 [b] |
| $(C_2H_5)_2CH$ | 17 | –33 | –2 | 77 [c] | 57 [b] |

| R | *(6)* | *(7)* | *(8)* | *(9)* |
|---|---|---|---|---|
| $CH_3$ | 64 | | | |
| $(CH_3)_3C$ | | 138 | –3 | 177 |

[a] R' = n-$C_4H_9$; [b] $R_2 = (CH_2)_5$; [c] R = $C_6H_5$–$CH_2$.

Received, March 23rd, 1964 [Z 703/535 IE]
German version: Angew. Chem. 76, 440 (1964)

[1] Communication No. 17 on Hydroxylamine Derivatives. Communication No. 16: *G. Zinner* and *W. Ritter*, Arch. Pharmaz. *296*, 681 (1963).

[2] Cf. also *O. Piloty* and *H. Steinbock*, Ber. dtsch. chem. Ges. *35*, 3101 (1902).

[3] *R. Scholl*, Ber. dtsch. chem. Ges. *23*, 3490 (1890), gives: b.p. 106.5–107.5 °C/14 mm and b.p. 223 °C/726 mm.

## Phosphacyanines, a New Class of Compounds Containing Trivalent Phosphorus

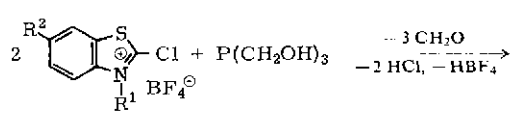
By Prof. Dr. K. Dimroth and Dr. P. Hoffmann

Chemisches Institut
der Universität Marburg/Lahn (Germany)

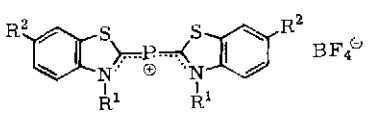
*Dedicated to Professor H. Meerwein on the occasion of his 85th birthday*

A solution 0.02 mole of *N*-ethyl-2-chlorobenzothiazolium fluoroborate *(1)*, $R^1 = C_2H_5$, $R^2 = H$, and 0.01 mole of tris-(hydroxymethyl)phosphine *(2)* in 10 ml of *N,N*-dimethylformamide (DMF) was treated at 0 °C under nitrogen with 0.03 mole of diisopropylethylamine dissolved in 10 ml of DMF and yielded orange-red crystals of *(3b)*, with elimination of formaldehyde.

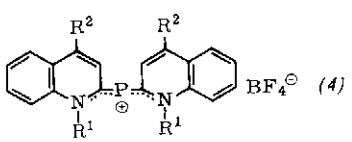
We obtained analogous compounds from variously substituted 2-chlorobenzothiazolium salts and 2-chloroquinolinium salts; it appears therefore that phosphacyanines *(3)*



*(1)* *(2)*



*(3)*



*(4)*

or *(4)* (*i.e.* analogues of the azacyanines) have been formed (yields: 40–50 %). Some of their properties are listed in Table 1.

Table 1. Properties of compounds *(3a)*–*(3d)*, *(4a)*, and *(4b)*.

| Compound | $R^1$ | $R^2$ | M.p. [°C] | $\lambda_{max}$ [mμ] | ε · 10⁻⁴ |
|---|---|---|---|---|---|
| *(3a)* | $CH_3$ | H | 225–230 | 472 | 4.37 |
| *(3b)* | $C_2H_5$ | H | 214–220 | 472 | 4.37 |
| *(3c)* | $CH_3$ | $OCH_3$ | 208–220 | 485 | 4.34 |
| *(3d)* | $C_2H_5$ | $OCH_3$ | 215–223 | 485 | 4.34 |
| *(4a)* | $C_2H_5$ | H | 126 (decomp.) | 592 | 4.27 |
| *(4b)* | $C_2H_5$ | $CH_3$ | 178–185 | 587 | 4.11 |

Oxidation of *(3a)*–*(3d)*, *(4a)*, and *(4b)* by alkaline hydrogen peroxide affords 2-benzothiazolones or 2-quinolones, together with phosphoric acid, in quantitative yields.

The NMR-spectra are compatible with the cyanine structure; the chemical shift of the phosphorus resonance (–26.05 ppm), however, is unexpectedly large and without parallel [*]. The excellent agreement of the electron spectra with those of the analogous aza- and methinecyanines supports the constitution proposed.

Received, March 24th, 1964 [Z 706/528 IE]
Publication deferred until now at the authors' request
German version: Angew. Chem. 76, 433 (1964)

[*] We wish to thank Dr. *E. Fluck*, Heidelberg, for determining the phosphorus NMR spectra, and for their interpretation.

## Arylcyanophenols and 2,4,6-Tricyanophenol

By Prof. Dr. K. Dimroth and Dr. K. J. Kraft

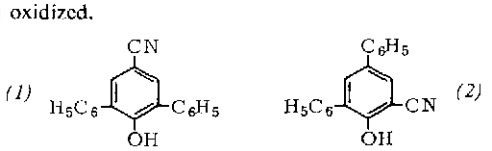
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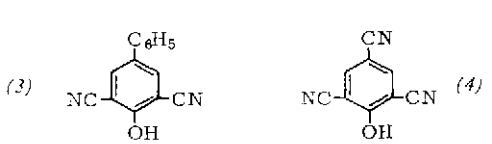
*Dedicated to Professor H. Meerwein on the occasion of his 85th birthday*

The observation that 4-cyano-2,6-diphenylphenol *(1)* can be dehydrogenated to a stable, green phenoxyl radical [1] prompted us to prepare further arylcyanophenols. 2-Cyano-4,6-diphenylphenol *(2)* was obtained from 2,4-diphenylanisole by bromination, conversion into the corresponding organolithium compound, carboxylation, preparation of the amide, dehydration, and demethylation with pyridine/HCl [2]. Compound *(2)* can be dehydrogenated to a red, stable phenoxyl radical.

2,6-Dicyano-4-phenylphenol *(3)* was prepared from 4-hydroxydiphenyl by condensation with formaldehyde to give 2,6-bishydroxymethyl-4-phenylphenol, methylation, oxidation to the dicarboxylic acid, conversion into the diamide, dehydration, and demethylation. Phenol *(3)* is oxidized with lead tetraacetate in glacial acetic acid to give a blue radical which has not yet been closely investigated.

Finally, we have prepared 2,4,6-tricyanophenol *(4)* by conversion of methoxytrimesic acid into the triamide, dehydration, and demethylation. Like picric acid, *(4)* is a strong acid ($pK_c = 1.0$ at 20 °C and ionic strength $\mu = 0.02$); it has not yet been oxidized.





The half-wave potentials were measured polarographically in acetonitrile/water (9:1) containing 0.01 M $N(CH_3)_4OH$ and $N(CH_3)_4Cl$ with a rotating graphite electrode and a silver/

silver chloride reference electrode [3]. The potentials increase considerably with increasing cyanation (Table 1).

Table 1. Half-wave potentials.

| Compound | M.p. [°C] | $E^1/_2$ [mV] | Color of radical |
|---|---|---|---|
| 2,4,6-Triphenylphenol [4] | 149–150 | + 211 | red |
| 4-Cyano-2,6-diphenylphenol | 165–166.5 | + 549 | green |
| 2-Cyano-4,6-diphenylphenol | 138–139 | + 593 | red |
| 2,6-Dicyano-4-phenylphenol | 215 (decomp.) | > + 800 | blue |
| 2,4,6-Tricyanophenol | 185 (decomp.) | — | — |

These results show that for stabilization phenoxyl radicals need not necessarily have bulky substituents at the 2-, 4-, and 6-positions. All the radicals were characterized by ESR measurements [5].

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[1] *D. Schminke*, Ph. D. Thesis, Universität Marburg, 1961.

[2] The preliminary stages were investigated by *K. Schromm*, Marburg.

[3] *F. W. Steuber*, Ph. D. Thesis, Universität Marburg, 1963; *F. W. Steuber* and *K. Dimroth*, Tagung für moderne elektrochemische Analysenmethoden, Eisenach, April 1964.

[4] *K. Dimroth*, *F. Kalk*, *R. Sell*, and *K. Schlömer*, Liebigs Ann. Chem. *624*, 51 (1959).

[5] *F. Bär*, Marburg.

## The Constitution of the Dimer of 2,4,6-Triphenylphenoxyl

By Prof. Dr. K. Dimroth and Dipl.-Chem. A. Berndt

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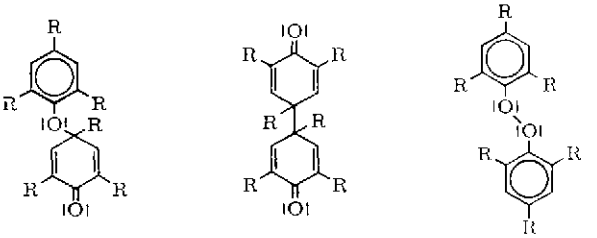
*Dedicated to Professor H. Meerwein on the occasion of his 85th birthday*

2,4,6-Triphenylphenol is readily dehydrogenated to a red free radical, which is perfectly stable towards oxygen [1] and which crystallizes as a colorless dimer. In solution, the dimer dissociates partly into 2,4,6-triphenylphenoxyl radicals (dissociation constant in benzene: $4\times10^{-5}$ at 20 °C, heat of dissociation: *ca.* 10 kcal/mole). Equilibrium between the colorless dimer and red monomer is reached so quickly that solutions of the former may be readily and without retardation redox-titrated, *e.g.* by using a solution of hydroquinone.

Introduction of large substituents (bromine or one or two phenyl groups) into the central nucleus of triphenylphenol displaces the position of equilibrium considerably in favor of the dimer and reduces the speed with which this equilibrium is attained. These observations cast some doubt on the validity of formula *(1)* for the dimer. Although the infrared spectrum of the dimer has a doublet at 1665 and 1642 $cm^{-1}$, which may be ascribed to the C=O vibrations of a quinol [2], the result would also agree with the presence of a diquinol *(2)*. A band at 958 $cm^{-1}$, *i.e.* in the region of –O–O– absorption, suggests a diphenyl peroxide structure *(3)* [3].

Formulation of the dimer as an ion pair [4] is incorrect, since neither the anion nor the cation [5] absorb in the region of the doublet.

By reaction of 2,4,6-triphenylbenzenediazonium fluoroborate with $CH_3{}^{18}OH$ [*] and cleavage of the resulting methyl ether with pyridinium chloride, we obtained [$^{18}$O]-2,4,6-triphenylphenol. Oxidation of this gave the dimer containing *ca.* 55 atom-% of $^{18}$O. The displacement of the infrared absorption bands (Table 1) demonstrates conclusively that the



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

doublet at 1665 and 1642 $cm^{-1}$ originates from a C=O vibration. The peroxide structure *(3)* is thus eliminated, all the more so as the band at 958 $cm^{-1}$ is not significantly displaced. The occurrence of a shift in the ether region excludes structure *(2)*.

Table 1. Characteristic absorption bands of dimeric [$^{16}$O]- and [$^{18}$O]-2,4,6-triphenylphenoxyl *(1)* (approximately 55 atom-% $^{18}$O) in $CCl_4$.

| $\tilde{\nu}$[$^{16}$O]-*(1)* [$cm^{-1}$] | $\tilde{\nu}$[$^{16}$O]-*(1)* + $\tilde{\nu}$[$^{18}$O]-*(1)* [$cm^{-1}$] | | $\Delta\tilde{\nu}$ [$cm^{-1}$] |
|---|---|---|---|
| 1665 | 1665 | 1620 | 45 |
| 1642 | 1642 | 1597 | 45 |
| 1201 | 1185 | | 16 |
| 958 | 956 | | 2 |

The quinol structure *(1)* is thus demonstrated. The *o*-quinol structure is not disproved by the above experiments, but seems less likely. Scission of the C–O bond of *(1)* in solution to form the radical, *i.e.* dissociation of the dimer *(1)*, requires only a very small energy of activation.

The present results are confirmed by an X-ray analysis of dimeric 3-bromo-2,4,6-triphenylphenoxyl; this work shows in addition that the product in question is a *p*-quinol derivative [6].

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[1] *K. Dimroth*, *F. Kalk*, *R. Sell*, and *K. Schlömer*, Liebigs Ann. Chem. *624*, 51 (1959).

[2] *E. Müller*, *K. Ley*, and *G. Schlechte*, Chem. Ber. *90*, 2660 (1957).

[3] *St. Goldschmidt* and *Ch. Steigerwald*, Liebigs Ann. Chem. *438*, 202 (1924).

[4] *E. Müller*, *K. Ley*, and *W. Schmidhuber*, Chem. Ber. *89*, 1738 (1956).

[5] *W. Umbach*, Ph. D. Thesis, Universität Marburg, 1962.

[6] *R. Allmann*, personal communication.

[*] We wish to thank Prof. *D. Samuel*, Rehovoth, Israel, for the labelled methanol.

## Complexes of Organotin Compounds with Aluminum Halides

By Priv.-Doz. Dr. W. P. Neumann,
Dipl.-Chem. R. Schick [1], and Dr. R. Köster

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Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

In carrying out alkylations on tin, *Köster* [2] obtained in 1955 the crystalline complexes *(3)* and *(7)*. Up to then, only compounds of organotin halides with Lewis bases were known [3]. In preparing starting materials such as tin tetraalkyls, we came again across these complexes [4, 5].

Solutions of these compounds (0.1 mole/l) in benzene and nitrobenzene at 35 °C displayed relatively high conductivities: in the case of *(3)* we obtained $33\times10^{-4}$ and $86\times10^{-1}$ mho/cm²; for *(7)* we found $0.3\times10^{-4}$ and $2.9\times10^{-1}$ mho/cm². This suggests the formulae $[R_3Sn]^+[AlCl_4]^-$ for *(3)* and $[R_2SnCl]^+[AlCl_4]^-$ for *(7)*, at least as equilibrium states [6].

On heating equimolar amounts of organotin halide and aluminum halide to 90–100 °C (clear melt) for a short period, followed by cooling and recrystallization from benzene, we obtained the colorless compounds listed in Table 1, mostly in the form of well-shaped crystal needles. As these substances are extremely sensitive to moisture, careful exclusion of air (argon) is essential.

Table 1. Melting points and cryoscopic data of compounds *(1)–(9)*.

| Compound | M.p. [°C] | Mean particle weight [a] per formula weight at a concentration [mole/l] of | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0.01 | 0.02 | 0.04 | 0.06 | 0.08 | 0.10 |
| *(1)*, $(CH_3)_3SnCl\cdot AlCl_3$ | 91 | 1.04 | 1.40 | — | — | — | — |
| *(2)*, $(CH_3)_3SnBr\cdot AlBr_3$ | 111 | — | — | — | — | — | — |
| *(3)*, $(C_2H_5)_3SnCl\cdot AlCl_3$ | 23 | 1.09 | 1.52 | 2.48 | 3.50 | 4.51 | 5.52 |
| *(4)*, $(C_2H_5)_3SnBr\cdot AlBr_3$ | 49 | 0.95 | 1.03 | 1.31 | — | — | — |
| *(5)*, $(i\text{-}C_4H_9)_3SnCl\cdot AlCl_3$ | 90 | 0.92 | 0.98 | 1.15 | 1.37 | 1.63 | — |
| *(6)*, $(CH_3)_2SnBr_2\cdot AlBr_3$ | 73 | 0.91 | 0.93 | 0.97 | — | — | — |
| *(7)*, $(C_2H_5)_2SnCl_2\cdot AlCl_3$ | 84 | 0.92 | 0.94 | 1.00 | 1.06 | — | — |
| *(8)*, $(C_2H_5)_2SnBr_2\cdot AlBr_3$ | 72 | 0.94 | 0.96 | 0.98 | — | — | — |
| *(9)*, $(n\text{-}C_4H_9)_2SnCl_2\cdot AlCl_3$ | 55 | — | 0.96 | 1.01 | 1.05 | — | — |

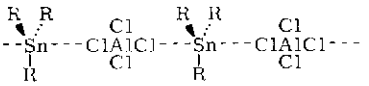
[a] Determined cryoscopically in benzene.

When *(3)* and *(7)* are subjected to mild alcoholysis no gas is evolved; the compounds do therefore not contain alkyl groups bound to aluminum. Prolonged heating of *(3)* on the other hand leads to the formation of a small amount of $(C_2H_5)AlCl_2$.

Trialkyltin halide is a stronger complexing agent than dialkyltin halide. Thus, heating of *(7)* with an equimolar amount of $(C_2H_5)_3SnCl$ causes displacement of $(C_2H_5)_2SnCl_2$ which can be distilled off at a vacuum of 11 mm Hg, leaving *(3)* behind. A complex of $(C_2H_5)SnCl_3$ with $AlCl_3$ could not be isolated. At 90 °C, $C_2H_5Cl$ is rapidly given off by the mixture, leaving $SnCl_2$ behind. In contradiction with other reports [6], we did not observe the formation of stable complexes between tin tetraalkyls and $AlCl_3$.

The mean particle weight of the dialkyltin dihalide complexes *(6)–(9)* in benzene undergoes little change with the concentration; they dissociate to a slight extent (Table 1). The symmetrical Sn–C vibration in the infrared spectrum of dimethyltin dibromide at 514 $cm^{-1}$ splits into two absorptions of approximately half the intensity, occurring at 508 and 521 $cm^{-1}$, when the complex *(6)* is formed (suspension in nujol).

The mean particle weight of the trialkyltin halide complexes *(1)* and *(3)–(5)* in benzene, on the other hand, is very sensitive to changes in concentration (Table 1); association takes place. In the infrared spectrum of *(2)* the symmetrical Sn–C vibration at 512 $cm^{-1}$ weakens (as compared with the asymmetric vibration at 543 $cm^{-1}$) when the concentration in benzene is increased and disappears in the solid state (suspension in nujol). Thus, in the polymer, the $(CH_3)_3Sn$ group is completely or at least nearly planar: there is penta-coordination around the tin atom:



On the basis of the results of particle-weight determinations this probably applies also to the trialkyltin halide complexes *(1)* and *(3)–(5)*. Analogous structures have been proved or assumed for trialkyltin acylates [7], amides [8] and fluoro salts [9].

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[1] Cf. *R. Schick*, Diploma Thesis, Universität Gießen, 1962.

[2] *R. Köster*, quoted in [5] and in *H. Zeiss*: Organometallic Chemistry. Reinhold, New York 1960, p. 247.

[3] Summary cf. *R. K. Ingham*, *S. D. Rosenberg*, and *H. Gilman*, Chem. Reviews *60*, 459 (1960).

[4] *W. P. Neumann*, Liebigs Ann. Chem. *653*, 157 (1962).

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

[6] *O. A. Osipov* and *O. E. Kashireninov*, Zh. obshchei Khim. *32*, 1717 (1962), mixed ethyltin chlorides with $AlCl_3$ in benzene and concluded from physical data (without isolating any substance) that 1:1-complexes are present; they assumed hexa-coordination around the tin atom. The solutions in benzene are reported to possess no conductivity.

[7] *M. J. Janssen*, *J. G. A. Luijten*, and *G. J. M. van der Kerk*, Recueil Trav. chim. Pays-Bas *82*, 90 (1963), where further references are given; *R. Okawara* and *M. Ohara*, Bull. chem. Soc. Japan *36*, 623 (1963).

[8] *M. J. Janssen*, *J. G. A. Luijten*, and *G. J. M. van der Kerk*, J. organometal. Chem. *1*, 286 (1964), where further references are given.

[9] *B. J. Hathaway* and *D. E. Webster*, Proc. chem. Soc. (London) *1963*, 14; *H. C. Clark* and *R. J. O'Brien*, ibid. *1963*, 113; Inorg. Chem. *2*, 1020 (1963).

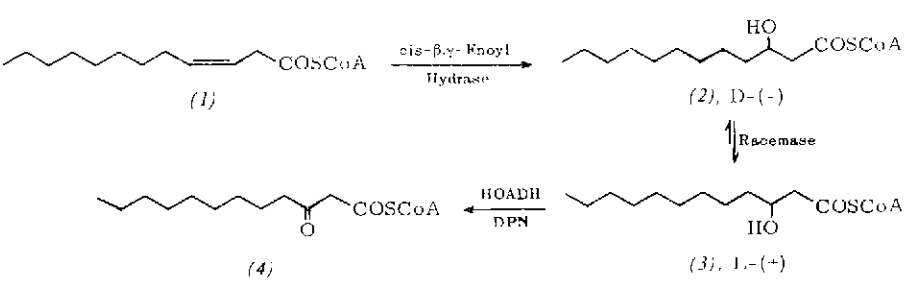
## The Metabolism of cis-β,γ-Enoyl-Coenzyme A Compounds

By Doz. Dr. W. Stoffel, Dipl.-Chem. R. Ditzer, and Dipl.-Chem. H. Caesar

Physiologisch-Chemisches Institut der Universität Köln (Germany)

Coenzyme A derivatives of cis-β,γ- or cis-α,β-unsaturated fatty acids are formed in the course of the β-oxidation of mono- and polyunsaturated fatty acids with cis-olefinic double bonds. We have investigated the further metabolism of the cis-β,γ-enoyl-CoA compounds, using *cis*-3-dodecenoyl-CoA *(1)* as an example. This compound is formed in the β-oxidation of oleic acid.

Contrary to earlier reports [1–3] crotonase does not hydrate *(1)*. Instead, a cis-β,γ-enoyl hydrase isolated from liver mitochondria catalyses this reaction. The product is D-(−)-β-hydroxylauroyl-CoA *(2)*. It is racemized by a racemase isolated from mitochondria to L-(+)-β-hydroxylauroyl-CoA *(3)* which is dehydrogenated by β-hydroxyacyl dehydrogenase (HOADH) [specific for the L-(+)-form] to β-ketolauroyl-CoA *(4)* and so removed from the equilibrium.



The following observations confirm this course of reaction:

1. Reduced pyridine nucleotide (DPNH) is formed only in presence of cis-β,γ-enoyl hydrase, racemase and HOADH. D-(−)-β-Hydroxylauroyl-CoA *(2)* is dehydrogenated to *(4)* only in presence of racemase and HOADH.

2. After incubation of 35 μmoles of [5-$^{14}$C]-cis-3-dodecenoyl-CoA *(1)* with cis-β,γ-enoyl hydrase and racemase, 3.0 mg of methyl rac.β-hydroxylaurate (m.p. 27 °C) were isolated by saponification, esterification and gas-chromatographic separation. The optical rotation of methyl D-(−)- or L-(+)-β-hydroxylaurate ($[\alpha]_D^{20} = \pm 19.5°$; c = 1 in $CHCl_3$)did not change in the blank under the conditions of isolation.

Through these reactions the unsaturated fatty acids are connected with the metabolic cycle of the saturated fatty acids [4], so that our knowledge of the β-oxidation of all the fatty acids occurring in the animal kingdom is thereby complete.

Received, March 25th, 1964 [Z 717/542 IE]
German version: Angew. Chem. 76, 440 (1964)

[1] *J. R. Stern* and *A. Del Campillo*, J. biol. Chemistry *218*, 985 (1956).

[2] *S. J. Wakil* and *H. R. Mahler*, J. biol. Chemistry *207*, 215 (1954).

[3] *D. E. Green* in: Progress in the Chemistry of Fats and other Lipids. Pergamon Press, London 1963, p. 102.

[4] *W. Seubert*, *G. Greull*, and *F. Lynen*, Angew. Chem. *69*, 359 (1957).

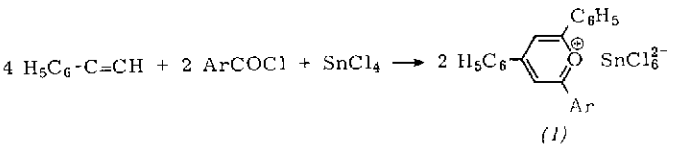
## New Syntheses of Pyrylium Salts

By Dr. Richard Schmidt

Institut für Organische Chemie
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der Technischen Hochschule Stuttgart (Germany)

*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

By reacting phenylacetylene with aromatic acid chlorides in the presence of Lewis acids, pyrylium salts *(1)* could be obtained in good yields:



*(1)*

The reactions went best with excess acid chloride acting as both reactant and diluent at 5 to +15 °C. The pyrylium salts prepared are shown in Table 1.

Table 1. Properties of the pyrylium salts *(1)*.

| | Ar | Hexachlorostannate | | Perchlorate | | |
|---|---|---|---|---|---|---|
| | | m.p. [°C] (decomp.) | yield [%] | m.p. [°C] | λmax [mμ] | log εmax |
| *(1a)* | Phenyl | 290–298 | 73 | 287–290 (288–290 [1]) | 360 408 [2] | |
| *(1b)* | *o*-Chlorophenyl | 294–298 | 72 | 209 | 314 | 3.90 |
| *(1c)* | *p*-Chlorophenyl | 290–294 | 81 | 200–202 | 320 | 3.98 |
| *(1d)* | *p*-Tolyl | 273–277 | 55 | 230–232 (224 [3]) | 325 415 | 4.09 2.89 |

$SnCl_4$ has been the most suitable Lewis acid. The hexachlorostannates could be converted to perchlorates with perchloric acid in dimethylformamide/water. The pyrylium salts are yellow and fluoresce strongly in solution. The ultraviolet spectra were taken in methanol. By comparison of *(1a)* with authentic 2,4,6-triphenylpyrylium perchlorate [1] and by conversion of *(1a)* to 2,4,6-triphenylpyridine [4] the course of the reaction was clarified.

Received, March 31st, 1964 [Z 711/537 IE]
German version: Angew. Chem. 76, 437 (1964)

[1] *C. G. LeFèvre* and *R. J. W. LeFèvre*, J. chem. Soc. (London) *1932*, 2894.

[2] *R. Wizinger*, *S. Losinger*, and *P. Ulrich*, Helv. chim. Acta *39*, 5 (1956).

[3] *K. Dimroth*, *G. Neubauer*, *H. Möllenkamp*, and *G. Oosterloo*, Chem. Ber. *90*, 1668 (1957).

[4] *W. Dilthey*, J. prakt. Chem. (2) *94*, 53 (1916).

# CONFERENCE REPORTS

## Colloquium in Honor of G. Scheibe

On the occasion of Prof. *G. Scheibe*'s 70th birthday a colloquium was held in Munich (Germany) on November 29th and 30th, 1963. The following is a selection from the papers read.

### Influence of Heavy Atoms on the Polarization of Triplet/Singlet Phosphorescence of Organic Compounds

*F. Dörr*, *H. Gropper*, and *N. Mika*, München (Germany)

The triplet/singlet phosphorescence of organic molecules in isotropic solid solution, when excited with linearly polarized light, is itself partially polarized. On theoretical grounds, a degree of polarization $\rho = 0.5$ is to be expected in the plane perpendicular to the electric vector of the exciting light source, if the absorbing and the emitting transition moments in the molecule are parallel. If they are perpendicular to each other, $\rho = 0.33$ [1]. The π–π absorption transitions of planar molecules are all polarized in the plane of the molecule. For numerous aromatic hydrocarbons, the triplet/singlet phosphorescence consists essentially of only one intense component, which is polarized perpendicularly to the plane of the molecule [2]. However, halogeno substituents, *e.g.* in naphthalene, intensify other components of the phosphorescence that are polarized in the plane of the molecule. The resulting intensification of emission is known as the heavy atom effect [3]. The superimposition of differently polarized components is also manifest in the degree of polarization, which becomes increasingly positive with increasing atomic number of the substituting element [4]. A similar influence has now been observed in the series fluorene, dibenzofuran, carbazole, and dibenzothiophene, in which $\rho$ rises from −0.32 to +0.04.

The theory of triplet/singlet transitions [5] provides selection rules for the mixing of singlet and triplet states via

[1] *W. L. Lewschin*, Z. Physik *32*, 307 (1925).

[2] *H. Gropper* and *F. Dörr*, Ber. Bunsenges. physik. Chem. *67*, 46, 193, 202 (1963).

[3] *D. S. McClure*, *N. W. Blake*, and *P. L. Hanst*, J. chem. Physics *22*, 255 (1954).

[4] *F. Dörr*, *H. Gropper*, and *N. Mika*, Z. Naturforsch. *18a*, 1025 (1963).

[5] *D. S. McClure*, J. chem. Physics *17*, 665 (1949); *20*, 682 (1952).

the different components of the spin orbit operator {LS}. On the assumption that for the compounds under examination, only the lowest triplet state $T_0$ of the symmetry $^3L_a$ or $^3L_b$ is noticeably influenced by spin orbit coupling, the following combinations result as the most probable ones. (Coordinates: x = longitudinal axis, z = transverse axis, y = normal to plane of molecule).

1. If $T_0 \equiv {}^3L_a$ (z-symmetry), the following states mix:

(a) via $\{LS\}_x$, an $S(\sigma,\pi^*)$-state; polarization along y;

(b) via $\{LS\}_y$, an $S_x$-state (probably $^1L_b$); polarization along x.

2. If $T_0 \equiv {}^3L_b$ (x-symmetry), the following states mix:

(a) via $\{LS\}_y$, an $S_z$-state (probably $^1L_a$); polarization along z;

(b) via $\{LS\}_z$, an $S(\sigma,\pi^*)$-state; polarization along y.

## The Boltzmann Occupation of the Energy Terms of Atoms and Molecules

*H. Krempl*, München (Germany)

It is known from Boltzmann statistics that

(a) for absorption, the cross-sectional area of a band represented by the extinction coefficient $E_A$ obeys the law

$$E_A = \log I_0/I = \varepsilon_A \cdot c \cdot \exp(-U_a/kT) \cdot d \qquad \text{and}$$

(b) for emission, the intensity $E_E$ of any line obeys the law

$$E_E = \varepsilon_E \cdot c \cdot \exp(-U_a/kT) \cdot d \ ,$$

where c is the concentration of the materials concerned, d is the thickness of the layer, and $U_a$ is the appropriate height of the term above the ground state. $\varepsilon_A$ and $\varepsilon_E$ are atomic and molecular constants, respectively (transition probability functions).

Both these laws were examined over a wide range of temperature (a) for the first band of benzene, $\lambda$ = 2700 Å, over the range of −176 to +100 °C; (b) for the atoms and ions of C, Mg, Al, Zn, Pb over the range of 8000 to 40000 °C, by means of spectrochemical thermoanalysis in an electrically heated plasma.

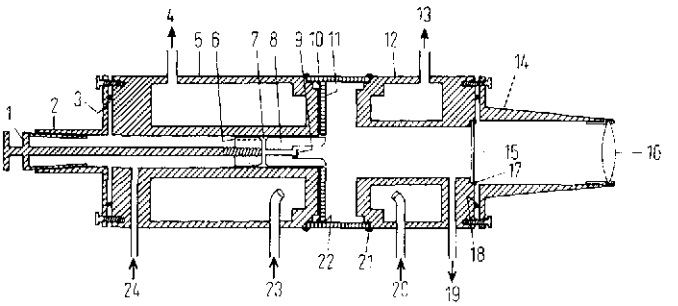
At moderate concentrations, *i.e.* as long as Beer's law holds (a) or in optically thin plasmas (b), the law predicted statistically by Boltzmann proved to be valid.

For initial terms close to the ionization limit, a lower degree of occupation was observed in the case of emission than is to be expected theoretically; this may be ascribed to the action of the surrounding plasma fields on the undisturbed term system.

## The Hollow Cathode as a Light Source for Emission Spectrography in the Vacuum Ultraviolet Region

*G. Milazzo*, Rome (Italy)

The hollow cathode (Fig. 1) is based on the principle of cathode sputtering and is superior as a light source to arc and spark discharges mainly for two reasons. Through cooling and by its mode of construction, the Doppler and Stark effects are largely avoided, so that background-free spectra with very sharply defined lines are obtained. By combining the hollow cathode with a vacuum spectrograph, spectra of nonmetals (*e.g.* Br, I) and metalloids (*e.g.* Si, Ge, As) can be measured in the vacuum ultraviolet region simply and with great accuracy. (An atlas of the spectra of several elements in the vacuum ultraviolet region is under preparation, in collaboration with the Vatican Astronomical Observatory.) Where possible, the cathode itself is made from the material under examination. Alternatively (Cl, Br), it suffices to introduce the sample into a carrier material (Al, Mg). In this very simple way it is possible to employ spectroanalytical methods for non-metals also, which have their analytically most sensitive lines in the vacuum ultraviolet region. In this way, iodine can be detected with certainty down to $10^{-8}$ g. Traces of oxygen can be detected indirectly by means of the CO spectrum.




1: contact and adjustment pivot of the hollow cathode
2: standard tapered joint
3; 18: O-rings
4; 13; 20; 23: outlet and inlet tubes for coolant
5: cathode block
6; 7: gas channels
8: actual hollow cathode
10; 11: Pyrex glass insulation
12: anode block
14: joint for connecting to spectrograph
15: LiF window
16: LiF lens
17; 21; 22: vacuum sealing wax
19; 24: outlet and inlet for carrier gas

## Photochemistry and Spectroscopy of Acridines

*V. Zanker, F. Mader*, and *W. Körber*, München (Germany)

Earlier investigations [6] of the photochemical behavior of acridine proved that the same end products, *viz.* the sparingly soluble dimer 9,9′-diacridanyl and, presumably, the more soluble 9,10-dihydro derivative acridan, occur in H-containing solvents, both in the presence and absence of $O_2$. Our investigations showed in addition that on photolysis in ethanol saturated with nitrogen, acridine (conc. $> 5\times10^{-4}$ M) forms a colorless product, (purified by recrystallization from dimethyl sulfoxide) m.p. 262 °C under nitrogen. This substance exhibits a split acridan band in the ultraviolet – an indication of substitution at C-9 – and a weak band at 360 mμ, which is characteristic for diacridanyls. Its infrared spectrum is identical with that of synthetic 9,9′-diacridanyl prepared from acridine with Na/Hg. The results of its elemental analysis also correspond to the formula of diacridanyl. The mass spectrum yields fragments of mass number 180. This shows that the 9,9′-bond is the weakest one and that the compound dissociates into acridinium ions. By analogy to *N,N′*-dimethyl-9,9′-diacridanyl, the molecular weight of which (388) can be determined as a result of its superior solubility, and the mass spectrum of which yields ostensibly similar fragments with mass number 194, it must be assumed that the photochemical reduction product obtained from acridine is 9,9′-diacridanyl (mol. wt. 360).

At acridine concentrations of $< 5\times10^{-4}$ M in H-containing solvents, a "soluble acridan" is formed as photochemical product and could be isolated from dioxan and cyclohexane. The ultraviolet spectra again point to acridans substituted at C-9 (split acridan band), and the elemental analyses and molecular weights tally with 9-dioxanylacridan and 9-cyclohexylacridan, respectively. The conclusion is that acridans substituted at C-9 are formed from acridine also in other H-containing solvents. On the basis of these results, we explain the reaction in terms of radicals, the primary reaction consisting of hydrogen transfer from the solvent with the formation of a 9-acridanyl radical. It was possible to prove spectroscopically the presence in solutions containing oxygen, of an $O_2$-adduct, probably diacridanyl peroxide, and its stable decomposition product, acridone. The spectra of some acridans and diacridanyls were analysed by fluorescence and fluorescence polarization. The characteristic acridan band devoid of fine structure at 300 mμ is a superimposition of the

$^1L_b$-band upon the $^1L_a$-band. The splitting of the acridine band in the 9-substituted derivatives is to be explained by a bathochromic shift of the $^1L_b$-band.

The preband, occurring at about 360 mμ with the diacridanyls is markedly influenced by temperature and disappears almost completely at −183 °C. This implies the existence of two different conformations of diacridanyl, the conformer richer in energy absorbing at the longer wave length (at 360 mμ). In the frozen state, the diacridanyls undergo an interesting photolysis involving splitting of the 9,9'-bond and electron detachment, acridinium cations being formed. On melting the solution, diacridanyl is reformed.

## Studies of the Tetrahydrate of Hydrogen Bromide $H_9O_4^{\oplus}Br^{\ominus}$

*H. Zimmermann, J. Rudolph*, and *G. Henning*, München (Germany)

At low temperatures, hydrogen bromide forms a crystalline tetrahydrate, m.p. −56 °C [7]. Its infrared spectrum was examined at −170 °C. In contrast to that of the corresponding acid solutions at room temperature, it exhibits a fine structure [8]. In particular, the long-wave infrared spectrum shows groups of sharply defined bands, for which it was possible to set up a term series for the vibrational states. This term system indicates that the substance is present in the form $H_9O_4^+Br^-$. The $H_9O_4^+$ complex consists of a pyramid-shaped $H_3O^+$ ion that is linked to three further water molecules by exceptionally strong hydrogen bonds. This complex has therefore a structure similar to that of the $H_9O_4^+$ ion, which is present in aqueous solutions of acids, according to *Wicke, Eigen*, and *Ackermann* [9].

From the infrared spectra of the tetrahydrate of hydrogen bromide, it appears probable that the proton in the hydrogen bonds under discussion moves in an asymmetrical potential field with two minima. At low temperatures, it is fixed in the lower potential trough. Proton mobility therefore is very low, and the conductivity at −180 °C amounts to $K < 10^{-9}$ mho · cm$^{-1}$. The conductivity varies with temperature and shows a sharp point of inflection at −90 °C. A discontinuous change in the properties of the substance at −90 °C can be similarly proved in the wide-band nuclear resonance spectrum, but not in the infrared spectrum. [VB 780/136 IE]

German version: Angew. Chem. *76*, 305 (1964)

[6] Cf., for example, *V. Zanker* and *P. Schmidt*, Z. physik. Chem. NF *17*, 11 (1958); *A. Kellmann*, J. Chim. physique *57*, 1 (1960); *M. Giurgea, V. Topa*, and *S. Haragea*, ibid. *58*, 705 (1961).

[7] *S. U. Pickering*, Phil. Mag. V, *35*, 111 (1893).

[8] Cf. *Th. Ackermann*, Z. physik. Chem. N.F. *27*, 269 (1961).

[9] *E. Wicke, M. Eigen*, and *Th. Ackermann*, Z. physik. Chem. N.F. *1*, 340 (1954).

## Chemical Reactions with (n, γ), β⁻, and Fission Recoil Atoms

*F. Baumgärtner*, München (Germany)

Recoil atoms resulting from nuclear reactions are capable of forming new molecules. Nuclear reactions thus represent a means for synthetizing molecules independently of preparative chemical methods. Thus, by β-disintegration of the parent substances, it was possible to prepare the hitherto unknown compounds dicyclopentadienylrhodium *(1)*, dienzene technetium(I) *(2)*, and cyclopentadienyltricarbonyltechnetium *(3)*. These substances were purified by sublimation. *(2)* is a stable Tc cation, which has also been synthetized macroscopic amounts.

$$^{105}Ru(C_5H_5)_2 \xrightarrow{\beta^-} {}^{105}Rh(C_5H_5)_2 \qquad (1)$$

$$^{99}Mo(C_6H_6)_2 \xrightarrow{\beta^-} {}^{99m}Tc(C_6H_6)_2^+ \qquad (2)$$

$$(C_5H_5)_2{}^{99}Mo_2(CO)_6 \xrightarrow{\beta^-} (C_5H_5){}^{99}Tc(CO)_3 \qquad (3)$$

To extend the range of syntheses with recoil atoms, *i.e.* in order to be independent of specific parent substances, we used two-phase mixtures of uranium oxide and the target material. In the uranium phase, energy-rich recoil atoms were produced by nuclear fission and some of these, *e.g.* $^{105}Ru$, $^{131}I$, $^{99}Mo$, react with the target compound. The following radioactive molecules have been prepared via uranium fission:

$$U(n,f) + Fe(C_5H_5)_2 \rightarrow Ru(C_5H_5)_2$$
$$U(n,f) + Fe(C_5H_5)_2 \rightarrow C_5H_5FeC_5H_4I$$
$$U(n,f) + Cr(CO)_6 \rightarrow Mo(CO)_6$$
$$U(n,f) + Cr(C_6H_6)_2 \rightarrow Mo(C_6H_6)_2$$
$$U(n,f) + Cr(C_6H_6)_2 \rightarrow Tc(C_6H_6)_2^+$$
$$U(n,f) + C_6H_5{-}X \rightarrow C_6H_5{-}I \quad (X = Cl, Br, \text{or } I)$$

According to the last equation, organically bound halogen may be substituted very selectively by fission iodine. Between 500 and 4 °K the yields of these recoil syntheses are independent of the temperature.

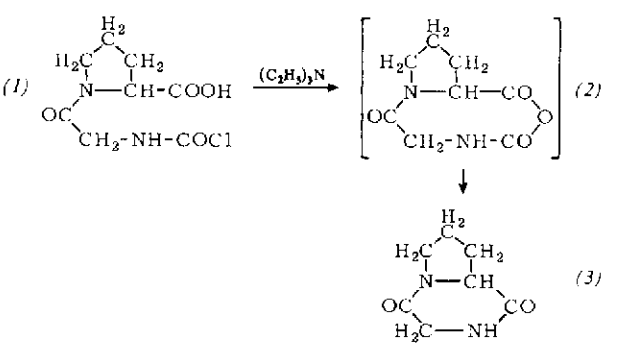
[Chemische Gesellschaft Heidelberg (Germany), January 14th, 1964] [VB 790/131 IE]

German version: Angew. Chem. *76*, 307 (1964)

## Chemical Synthesis of Polypeptides and the Hydrodynamic Properties of Their Solutions

*G. Spach*, Strasbourg (France)

Condensation of the tripeptide L-alanylglycylglycine with dicyclohexylcarbodiimide or ethyl metaphosphate yields only products with a degree of polymerization < 6. In order to obtain high molecular-weight copolypeptides with the amino acids in a regular order, a new synthesis depending on internal anhydride formation was considered. In a preliminary investigation, the carbamyl chloride *(1)* was synthetized by the action of phosgene on glycyl-L-proline. The substituted diketopiperazine *(3)* containing an intramolecular peptide link was formed from *(1)* with the stoichiometric quantity of triethylamine. The intermediate anhydride *(2)* was not isolated and is probably of low stability [1].




Examination of dilute solutions of the homopolypeptides polybenzyl-L-glutamate and polycarbobenzoxy-L-lysine in dimethylformamide showed that the molecules exist in the form of a helix of type $3.0_{10}$, with three monomers per turn, while in the solid state they assume an α-helix configuration with 3.6 monomers per turn [2].

Polybenzyl-DL-glutamate exists in both the A and B forms depending on the polymerization solvent. The A form appears

[1] *A. Brack*, Thèse 3e cycle Université de Strasbourg, 1963.

[2] *G. Spach, L. Freund, M. Daune*, and *H. Benoit*, J. molecular Biol. *7*, 468 (1963).

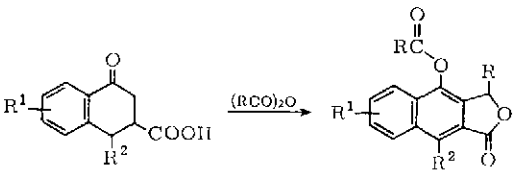
to be a flexible chain of rod-like units of about 100 Å length each; it is probably a block-copolymer in which sequences of D and L residues alternate. The rigid molecules of the B form can be considered in a first-stage model as a mixture of polybenzyl-L- and -D-glutamate.

[GDCh-Ortsverband Marburg/Lahn (Germany)
January 24th, 1964] [VB 797/137 IE]
German version: Angew. Chem. 76, 381 (1964)

## A New Synthesis of Hydroxyphthalides

*A. Sieglitz*, München (Germany)

1-Oxotetralin-3-carboxylic acids *(1)* react with carboxylic anhydrides to yield acyloxyphthalides *(2)*.



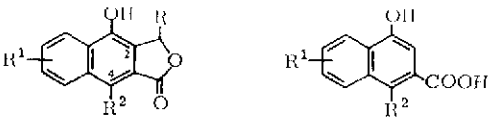
*(1)* *(2)*

The reaction was carried out with numerous derivatives of *(1)*, including 3-oxo-1,2,3,10*b*-tetrahydrofluoranthene-1-carboxylic acid [1] and 1-oxo-4,5-methylene-1,2,3,4-tetrahydrophenanthrene-3-carboxylic acid [2], and gives positive results with numerous anhydrides of aliphatic, aromatic, alkylaromatic, and heterocyclic carboxylic acids.

[1] *A. Sieglitz, H. Tröster*, and *P. Böhme*, Chem. Ber. *95*, 3013 (1962).

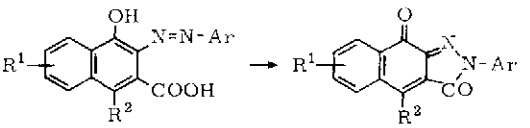
[2] *A. Sieglitz* and *W. Schidlo*, Chem. Ber. *96*, 1098 (1963).

The acyloxyphthalides *(2)* are hydrolysed under mild conditions to the free hydroxyphthalides *(3)*. More vigorous attack opens the lactone ring, producing 1-hydroxynaphthalene-3-carboxylic acids *(4)* and aldehydes R CHO [3].



*(3)* *(4)*

Hydroxyphthalides with a free 4-position *(3)*, $R^2$=H, couple with diazonium compounds in this position. Those with a substituted 4-position ($R^2$=$CH_3$,$C_6H_5$) and hydroxyphthalides derived from 3-oxo-1,2,3,10*b*-tetrahydrofluoranthene-1-carboxylic acid undergo coupling in the 2-position,



*(5)* *(6)*

with simultaneous elimination of the aldehyde RCHO. The azo dyes *(5)* thus obtained (also accessible from *(4)* when the 4-position is substituted) are readily dehydrated to form *o*-quinonoid indazolone dyes *(6)*.

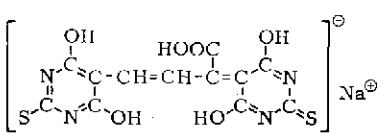
[GDCh-Ortsverband Berlin (Germany),
February 10th, 1964] [VB 796/135 IE]
German version: Angew. Chem. 76, 384 (1964)

[3] *H. Schmid, Th. M. Meijer*, and *A. Ebnöther*, Helv. chim. Acta *33*, 595 (1950).

# SELECTED ABSTRACTS

**The role of formylpyruvic acid** in forming the dyestuff of the Warren reaction has been clarified by *R. Kuhn* and *R. Lutz*. The Warren reaction is used for colorimetric determination of free sialic acids. Formylpyruvic acid was thought to occur as an intermediate in this reaction, but neither it nor the dyestuff were known in the free state.

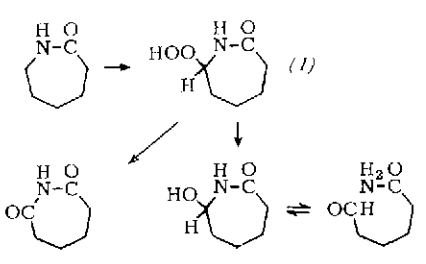
*(1)*



*Kuhn* and *Lutz* synthetized ethyl ethoxymethylenepyruvate *(2)*, b.p. 135–138 °C/11 mm, in 23 % yield from ethyl pyruvate and triethyl orthoformate. Claisen saponification of *(2)* gave red-brown flakes of the sodium salt of formylpyruvic acid; when an aqueous solution of this salt was heated with 2-thiobarbituric acid, it became deep red. Tiny blue crystals separated out of the red solution (45 % yield). This blue dyestuff *(1)* has the same absorption spectrum as the dyestuff of the Warren reaction ($\lambda_{max}$ = 550 mμ, $\varepsilon_{max}$ = $1.34\times10^5$ in cyclohexanone). / Biochem. Z. *338*, 554 (1964) / –De. [Rd 838/219 IE]

**Separation of the geometric isomers of cobalt complexes** has been achieved by *H. Seiler, C. Biebricher*, and *H. Erlenmeyer* using thin-layer chromatography. For complexes of the type [Co $en_2Cl_2$]X (X = Cl, $NO_3$, or CNS; en = ethylene diamine), a suitable mobile phase is a chloride-free, methanolic acetate buffer. The *trans*-complex always migrates further than the *cis*-complex, independently of their solubilities; apparently the polarity and water content of the mobile phase are very important. *cis*-Isomers are generally more labile than the *trans*-isomers, and partial isomerization always occurs. However, even the geometrically isomeric nitro complexes which are very poorly separable by fractional crystallizatio owing to the close similarity of their physical and chemic properties, can be satisfactorily separated by thin-lay chromatography. The mobile phase suitable for this separation is an ammonium acetate buffer in a mixture of methanol and ethanol. / Helv. chim. Acta *46*, 2636 (1963) / –Ko. [Rd 848/233 IE]

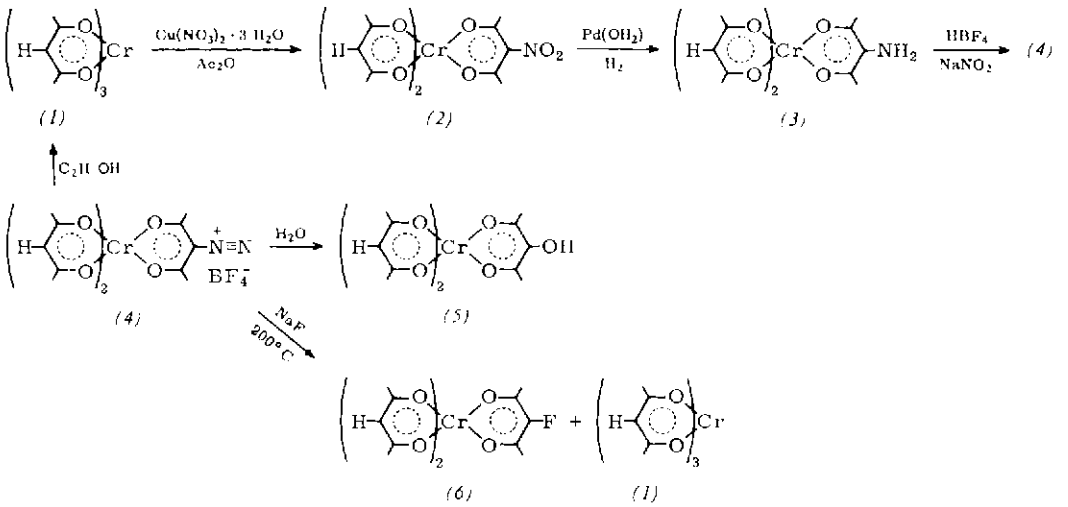
**Caprolactam hydroperoxide,** the first representative of a new type of peroxide, was prepared by *A. Rieche* and *W. Schön*. A caprolactam melt takes up oxygen at 75 °C to give the hydroperoxide *(1)* in very low yield. Pure, crystalline *(1)* melts at 139 °C with vigorous frothing. Co(II) and Fe(II) salts catalyse the conversion of *(1)* into adipimide *(2)* which is also obtained on oxidation of caprolactam at 100 °C. On



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

hydrogenation, *(1)* forms ω-formylpentanoamide *(3)*. Caprolactam hydroperoxide disturbs the polymerization of caprolactam in the same manner as air. / Z. Chem. *3*, 451 (1963) / –Kr. [Rd 842/220 IE]

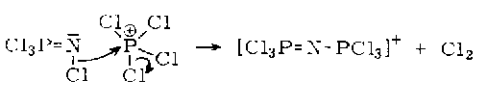
**The reaction of phosphorus pentachloride with hydroxylammonium chloride** in tetrachloroethane was studied by *M. Becke-Goehring, W. Gehrmann,* and *W. Goetze*. Mixtures of the three substances were heated to 100 °C for a desired reaction time, rapidly cooled to 50 °C and examined 2 hours later. $PCl_5$ and $(NH_3OH)Cl$ (in a molar ratio of 1:1-2) gave $P_2NOCl_5$ *(1)* in good yield after a reaction time of 1 hour.



When the reaction time was only 15 min (with a molar ratio $PCl_5$:$(NH_3OH)Cl$ of 1:1–1.5) colorless crystals of the tetrachloroethane adduct of *(2)* were formed in addition to *(1)*. At a molar ratio $PCl_5$:$(NH_3OH)Cl$ greater than 1.5:1, *(3)* was also formed in addition to a small amount of *(1)* and *(2)*. With 100 % excess $PCl_5$, only *(1)* and *(3)* were found. Obviously, *(1)* and *(3)* are secondary products of *(2)*.

$$H_2NOH + PCl_5 \rightarrow Cl_3P{=}NOH + 2\,HCl$$

$$Cl_3P{=}N{-}OH + PCl_5 \rightarrow Cl_3P{=}N{-}Cl + HCl + OPCl_3$$



$$[Cl_3P{=}N{-}PCl_3]Cl \qquad [Cl_3P{=}N{-}PCl_3][PCl_6]$$
$$(2) \qquad (3)$$

$$[Cl_3P{=}N{-}PCl_3]^+ + (H_3NOH)Cl \rightarrow Cl_3P{=}N{-}P(O)Cl_2 + Cl_2 + (NH_4)^+$$
$$(1)$$

The corresponding reaction of $C_6H_5PCl_2$, $PCl_5$, and $(NH_3OH)Cl$ led to $[C_6H_5P(Cl_2){=}N{-}P(Cl_2)C_6H_5]Cl$ and $[C_6H_5P(Cl_2){=}N{-}P(Cl_2)C_6H_5]PCl_6$. / Z. anorg. allg. Chem. *326*, 127 (1963) / –Kr. [Rd 843/221 IE]

**A stable chelate diazonium salt** has been prepared by *J. P. Collman* and *M. Yamada* and has been employed to confirm the aromatic character of 1,3-diketone/metal complexes. Chromium(III) acetylacetonate *(1)* was nitrated by less than a molar quantity of cupric nitrate in acetic anhydride. The resulting mixture of mononitrochromium(III) acetylacetonate *(2)* and the corresponding dinitro and trinitro derivatives was separable by chromatography, *(2)*, m.p. 178–180 °C, being obtained in 64.5 % yield. Hydrogenation of *(2)* with $H_2/Pd(OH)_2$ gave aminochromium(III) acetylacetonate *(3)*, m.p. 221.5–223 °C, in 69 % yield. Compound *(3)* has the properties of an aromatic amine; mineral acids effect a color change and yield salts, while acetic anhydride causes acetylation. Treatment of an aqueous solution of the fluoroborate of *(3)* with sodium nitrite in the cold affords the diazonium salt *(4)* as a purple-red precipitate; because of its sensitivity towards water, this must be isolated without delay (yield: 55 %). At room temperature in a dry atmosphere *(4)* is stable and decomposes at 165–167 °C. With water, the hydroxy chelate *(5)* is formed, which was isolated as the dodecahydrate. Alcohol reduces *(4)* to chromium(III) acetylacetonate *(1)*. Distillation of a mixture of *(4)* and NaF at 200 °C *in vacuo* yields fluorochromium(III) acetylacetonate *(6)* in 6 % yield, in addition to unsubstituted *(1)*. / J. org. Chemistry *28*, 3017 (1963) / –Ko. [Rd 852/222 IE]

**The reaction between phosphorus pentoxide and hydrogen peroxide** is described by *P. W. Schenk* and *K. Dommain*. Commercial $P_2O_5$ consists mainly of the "M" form, which crystallizes in a molecular lattice ($P_4O_{10}$ with the urotropine structure). Absolute $H_2O_2$ was obtained from commercial 35 % $H_2O_2$ by evaporation and fractional condensation. In large quantities $P_2O_5$ and $H_2O_2$ react explosively with evolution of oxygen.

On mixing the two components in liquid $NH_3$, no reaction occurs even after 8 days, but the components react on evaporation of the $NH_3$. When small quantities of $P_2O_5$ are dusted into well-cooled $H_2O_2$, the nature of the reaction products depends on the amount of water available. With over 90 % $H_2O_2$, only peroxomonophosphate plus di- and triphosphate were found; with dilute $H_2O_2$, tetrametaphosphate also resulted. Tetrametaphosphate is decomposed by $H_2O_2$ in the presence of acids. / Z. anorg. allg. Chem. *326*, 139 (1963) / –Kr. [Rd 841/237 IE]

**The crystal structure of potassium methoxide** has been investigated by *E. Weiss*. The X-ray powder pattern of $KOCH_3$ indicates it to be tetragonal with a = 3.95 Å, c = 8.77 Å, Z = 2, space group $P4/nmm\text{-}D^4_{7h}$, $\rho_{calc.}$ = 1.70 ± 0.006 g/cm$^{-3}$, $\rho_{exp.}$ = 1.2–1.5. Each oxygen atom is surrounded by five $K^+$ ions and a methyl group in the form of a distorted octahedron. The compound has a double-layer structure in which the $KOCH_3$ units are perpendicular to the plane, and the methyl groups alternate on the sides of the plane. The arrangement of O and K here is very similar to that in KOC≡COK. / Helv. chim. Acta *46*, 2051 (1963) / –Mn. [Rd 854/239 IE]

**The preparation and rate of decomposition of thiosulfuric acid** have been reported by *Max Schmidt* and *M. Wieber*. Free thiosulfuric acid is obtained in 93 % yield by double decomposition of ice-cold aqueous $Na_2S_2O_3$ and HCl solutions in a reaction capillary. The acid is stable in acetone at –70 °C. Up to 5 % $H_2S_2O_3$ solutions are obtainable. To measure the

rate of decomposition, the length and diameter of the reaction capillary were varied to alter the duration of retention therein. To stop its decomposition, the reaction solution was injected into NaOH solution. The mixture was then acidified with glacial acetic acid and samples with and without formalin (which combines with $SO_3^{2-}$ resulting from the decomposition) were titrated with iodine. The difference between the titres indicates the amount of thiosulfuric acid. Decomposition intervals of 1–50 sec can be measured. In 2–3 M solution at room temperature *ca.* 10 % is decomposed after 10 sec and *ca.* 25 % after 40 sec. Naturally no conclusions can be drawn from the decomposition curve concerning the decomposition mechanism. / Z. anorg. allgem. Chem. *326*, 174 (1963) / –Jg. [Rd 833/238 IE]

**Free thio acids of phosphorus and arsenic** have been prepared by *Max Schmidt* and *M. Wieber* by double decomposition of the corresponding salts with HCl. Ice-cold solutions of the salts were injected together with 2N HCl into a reaction capillary, and 0.1 sec later the jet was lead into acetone at –70 °C. Thus, starting from $Na_3PS_4$, 96 % yields of $H_3PS_4$ were obtained. $H_3PS_4$ decomposes irreversibly into $H_2S$ and $P_2S_5$, well below room temperature. Since $H_3PS_4$ is the least stable of the thiophosphoric acids, the acids $H_3PO_xS_y$ can be prepared similarly. On attempting to obtain $H_3AsS_4$ analogously, the latter decomposed in the reaction capillary within 0.1 sec; however, $H_3AsO_2S_2$ and $H_3AsO_3S$ (94 % yield) were isolated in this way. / Z. anorg. allgem. Chem. *326*, 182 (1963) / –Jg. [Rd 834/240 IE]

# BOOK REVIEWS

**Medizinische Biochemie** (Medical Biochemistry). By *S. M. Rapoport*. A text-book for students and doctors. VEB Verlag Volk und Gesundheit, Berlin 1962. 1st Edit,. XVI, 992 pp., 189 ill., 146 tab., linen DM 53.– (about $ 13.25).

*S. M. Rapoport*, director of the Physiologisch-chemisches Institut of the Humboldt University in Berlin, presents a text-book of medical biochemistry which surpasses the better known student text-books in scope and volume. It can justifiably claim to be the first Chemical Biology written in German and specifically designed to suit the requirements of medical students.

The traditional division into descriptive and dynamic sections has been abandoned and, instead, descriptions of compounds, physical chemistry, and methodological information are interlinked in a skilful and stimulating manner. The book starts with a discussion of the original primitive biological environment of water and electrolytes and progresses via a discourse on proteins and nucleic acids to masterful chapters dealing with the thermodynamics and kinetics of biological reactions, catalysis, and enzyme activity, culminating relatively quickly (on p. 162) in the description of a first synthesis of the unit of life, with a discussion of the structure and function of the cell. An essay on *Oparin*'s hypothesis concerning the origin of life and biological evolution follows.

The second large section, entitled "Intermediary Metabolism", begins – the reviewer finds especially successfully – with a chapter on the methods employed in classical and modern biochemistry. It is a matter of experience that students find difficulty in grasping the complicated interplay of the reactions of intermediary metabolism. Schemes and diagrams only enable the reaction sequences and cycles which they illustrate to be committed more easily to memory, whereas an indication of the method which led to any particular discovery provides an intimate approach to the material. Another welcome feature is that examination questions are included at the end of each section, and important reviews and journals are named at the end of the book.

A considerable amount of space – 400 pages in all – is occupied by the sections on functional biochemistry, general metabolism, and nutrition. These include interesting chapters on tumor metabolism, the biochemical effects of ionizing radiation, and immunochemistry; however, not surprisingly, these are not all of the same brilliance as the first sections of the volume. Instead of these chapters, it would have been better to include a description of photosynthesis, but unfortunately this subject, together with those of plant and bacterial metabolism, has been purposely omitted.

If one disregards this unfulfilled preference, and also the fact that the author, a fervid Marxist, has deemed it necessary to include a series of quotations from *Friedrich Engels* in his scientific text, this volume can be recommended as the most modern and the best "large" German-language text-book of biochemistry available at present.

*Herbert Fischer* [NB 134/71 IE]

**Bodenphysik und Bodenkolloidik** (Soil Physics and Soil Colloid Science). By *J. di Gleria, A. Klimes-Szmik*, and *M. Dvaracsek*. VEB Gustav Fischer Verlag, Jena 1962. 1st edit., 795 pp., 265 illustrs., 255 tables, cloth, DM 124.60 (about $31.–).

The book is divided into nine parts: introductions to physical chemistry and colloid science; the mineral and organic constituents of soils; the physical chemistry and colloid science of soils; soil structure; water and air in the soil; soil heat; and soil cultivation and improvement.

The authors have industriously collected together many important and many more unimportant research results. This applies both to the text and to the 543 literature references. Unfortunately, the authors appear to be unaware of many of the basically important advances made in the last twenty years in the knowledge of the physico-chemical and colloidal behavior of soil constituents, in the light of which they could have compiled their material much more critically and intelligibly. The volume is also unsuitable as a textbook owing to its size. Nevertheless it can be of use in many ways to the research worker in the field of soil science. Perhaps it was from this point of view that the publishers set the price so high. The presentation is thoroughly pleasing with regard to both the print and the illustrations.

*U. Hofmann* [NB 144/73 IE]

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# Biosynthesis, Structure, and Biological Action of the Lipids of the Tubercle Bacillus [*]

BY PROF. DR. E. LEDERER

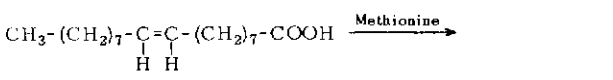
INSTITUT DE CHIMIE DES SUBSTANCES NATURELLES, GIF-SUR-YVETTE, AND LABORATOIRE DE CHIMIE BIOLOGIQUE, FACULTÉ DES SCIENCES, PARIS (FRANCE)

*The extensive studies of R. J. Anderson between 1926 and 1946 and the subsequent work of Stenhagen, Polgar, and Cason, and of the author's laboratory have demonstrated the astonishing abilities of the tubercle bacillus in synthetizing lipids. Numerous branched-chain fatty acids, glycolipids, peptidolipids, and peptidoglycolipids have been isolated, and their structures more or less elucidated. Such work is of interest not only to natural-product chemists, and biochemists, but especially to biologists and pathologists who are concerned with the harmful effects caused by the tubercle bacillus. The present article discusses chiefly three points: 1. The biogenesis of the branched-chain fatty acids. – 2. The structures of several glyco-, peptido-, and peptidoglycolipids. – 3. Adjuvant activity and immunization by the lipids of the tubercle bacillus.*

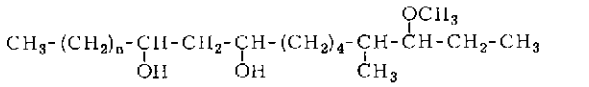
## I. Biogenesis of Branched-Chain Fatty Acids

### a) Substances with Methyl Side-Chains

The most important compounds with one methyl side-chain which are produced by the tubercle bacillus are tuberculostearic acid *(1)* and phthiocerol *(2)*. *Bloch* and coworkers [2] have shown that tuberculostearic acid *(1)* is formed from oleic acid by *C*-methylation in the presence of methionine.




*(1)*




*(2)*, n = 20 or 22

These studies, which were carried out on *Mycobacterium phlei*, were confirmed at Gif by *Gastambide-Odier* using the human strain $H_{37}R_a$ [3]. *Tanaka* and *Umezawa* [4] also investigated the biosynthesis of a methyl branched-chain fatty acid from the antibiotic variotin, and similarly established *C*-methylation of an unsaturated precursor. The mechanism of this *C*-methylation in the presence of methionine has yet to be explained.

It was known from the work of *Hofmann* [5] that, in *Lactobacilli*, lactobacillic acid *(3)* is formed from vaccenic acid in the presence of methionine. This suggested the possibility that an isomeric cyclopropanecarboxylic acid *(4)* might be a precursor in the biosynthesis of tuberculostearic acid. This acid *(4)* was synthetized at Gif by *Noble* and *Sarda* [6] from oleic acid and $^{14}CH_2I_2$. However, no conversion of *(4)* into tuberculostearic acid could be established [6] on incubation of the labelled cyclopropanecarboxylic acid with *M. phlei*.

[*] From a plenary lecture presented at the general meeting of the Gesellschaft Deutscher Chemik. r on September 10th, 1963 at Heidelberg (Germany). See [1] for earlier surveys of this topic.

[1a] *R. J. Anderson*, Progr. Chem. org. nat. Prod. *3*, 145 (1939); Harvey Lectures *35*, 271 (1939); Chem. Reviews *29*, 225 (1941); Yale J. Biol. Med. *15*, 311 (1943).

[1b] *J. Asselineau* and *E. Lederer*, Progr. Chem. org. nat. Prod. *10*, 170–270 (1953).

[1c] *J. Asselineau:* Les Lipides Bactériens. Hermann, Paris 1962.

[1d] *E. Lederer*, Angew. Chem. *72*, 372 (1960).

[1e] *J. Asselineau* and *E. Lederer* in *K. Bloch:* Lipide Metabolism. Wiley, London 1960, pp. 336–406.

[1f] *E. Lederer*, Pure and appl. Chem. *2*, 587 (1961).

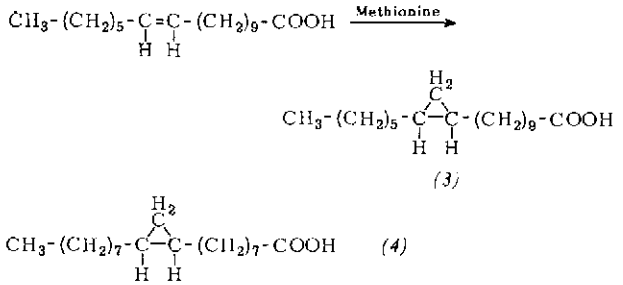
[2] *J. W. Lennarz, G. Scheuerbrandt*, and *K. Bloch*, J. biol. Chemistry *237*, 664 (1962).

[3] *M. Gastambide-Odier* and *E. Lederer*, unpublished work.

[4] *N. Tanaka* and *H. Umezawa*, J. Antibiotics, Ser. A, *15*, 189 (1962).

[5] *K. Hofmann* and *T. Y. Liu*, Biochim. biophysica Acta *37*, 364 (1960).

[6] *R. Noble, P. Sarda*, and *E. Lederer*, unpublished work.

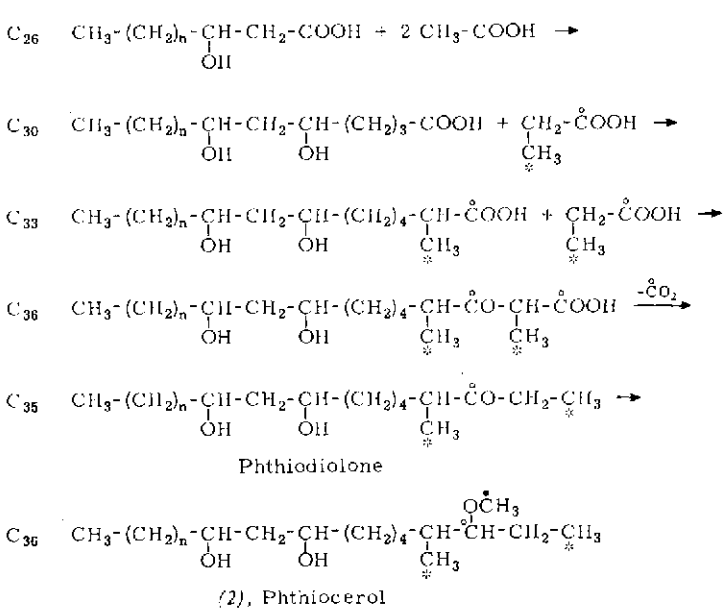


*(3)*



*(4)*

The biosynthetic route to phthiocerol *(2)* has recently been established by *Gastambide-Odier* [7]; it was found that the methyl group of methionine is incorporated only into the methoxy group of phthiocerol. The branched moiety of the carbon chain originates from propionic acid. Thus the Scheme 1 proposed earlier [1f] is probably correct. Phthiodiolone, which also appears in Scheme 1, is frequently associated with phtbiocerol.



Scheme 1. Biosynthesis of phthiocerol.

n = 20 or 22

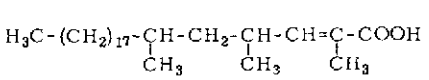
*C = carbon atom derived from sodium [3-$^{14}$C]propionate

°C = carbon atom derived from sodium [1-$^{14}$C]propionate

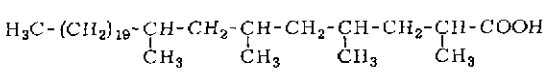
•C = carbon atom derived from [*Me*-$^{14}$C]methionine.

These results indicate again how dangerous it is to draw inferences about biogenetic reactions on grounds of structural analogy. Nature is much more imaginative than the "paper chemist".

The tubercle bacillus also uses propionic acid to huild up compounds with several methyl side-chains. There are two series of acids in this category: the α,β-unsaturated, dextrorotatory phthienoic acids *(5)* and the saturated, laevorotatory mycocerosic acids *(6)*.



*(5)*



*(6)*

[7] *M. Gastambide-Odier, J. M. Delaumény,* and *E. Lederer,* Chem. and Ind. *1963,* 1285.

The former appear only in virulent strains, and their biosynthesis has therefore not been studied very closely. The mycocerosic acids *(6)* are more easily available.

Preliminary experiments, performed a few years ago with *Grisebach,* using [*Me*-$^{3}$H,*carboxy*-$^{14}$C]propionic acid showed clearly that propionic acid is incorporated [8a]. In more recent experiments stress was laid on extreme purity of the $C_{32}$-mycocerosic acid; repeated gas chromatography of its methyl ester yielded this compound in homogeneous form, its purity being checked by mass spectrometry. The radioactive $C_{32}$-mycocerosic acid which was obtained by incubation of $H_{37}R_a$-bacilli with [1-$^{14}$C]propionic acid was then decarboxylated; 22 % of the radioactivity appeared as $CO_2$. Incorporation of 4 molecules of propionic acid would have given a value of 25 % [8b]. A radioactive $C_{26}$-mycocerosic acid was also obtained in this experiment.

It is perhaps superfluous to add that the incorporation of propionic acid into the branched-chain macrolides of streptomycetes has already been demonstrated by *Grisebach* and *Achenbach* [9], by *Kaneda* et al. [10] for erythromycin, by *Birch* et al. [11] for methymycin, by *Ollis* et al. [12] for ε-pyrromycinone, and by *Grisebach* and *Achenbach* [13] and by *Gilner* and *Srinivasan* [14] for magnamycin.

### b) Substances with Long Side-Chains

Prominent members of this group are the mycolic acids, *i.e.* "acids which have a long aliphatic side-chain in the α-position and a hydroxyl group in the β-position" [15].

To date, three types of mycolic acids have been isolated from acid-resistant bacteria:

1. From diphtheria bacilli (*Corynebacterium diphtheriae*) corynomycolic acid *(7)* [16] and corynomycolenic acid *(8)* [17] with 32 carbon atoms.

2. From *Nocardia* species, the nocardic acids *(9)* [18] with approximately 50 carbon atoms.

3. From mycobacteria, the mycolic acids *(10)* and *(11)* with 84–88 carbon atoms [1a–f, 15].

[8a] *M. Gastambide-Odier, H. Grisebach,* and *E. Lederer,* unpublished work.

[8b] *M. Gastambide-Odier, J. M. Delaumény,* and *E. Lederer,* Biochim. biophysica Acta *70,* 670 (1963).

[9] *H. Grisebach* and *H. Achenbach,* Z. Naturforsch. *17b,* 634 (1962).

[10] *T. Kaneda, C. Butte, S. B. Taubman,* and *J. W. Corcoran,* J. biol. Chemistry *237,* 322 (1962).

[11] *A. J. Birch, E. Pride, R. W. Rickards,* and *P. J. Thomson,* Chem. and Ind. *1960,* 1245.

[12] *W. D. Ollis, I. O. Sutherland, R. C. Codner, J. J. Gordon,* and *G. A. Miller,* Proc. chem. Soc. (London) *1960,* 347.

[13] *H. Grisebach* and *H. Achenbach,* Z. Naturforsch. *17b,* 6 (1962).

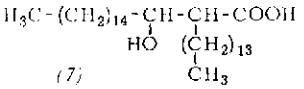
[14] *D. Gilner* and *P. R. Srinivasan,* Biochem. biophys. Res. Commun. *8,* 299 (1962).

[15] *J. Asselineau* and *E. Lederer,* Biochim. biophysica Acta *7,* 126 (1951).

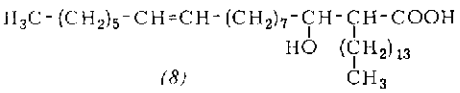
[16] *E. Lederer* and *J. Pudles,* Bull. Soc. Chim. biol. *33,* 1003 (1951).

[17] *J. Pudles* and *E. Lederer,* Biochim. biophysica Acta *11,* 163 (1953); Bull. Soc. chim. France *1954,* 919.

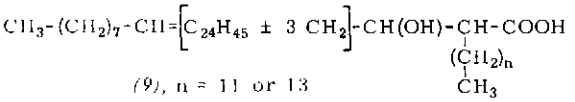
[18] *G. Michel, C. Bordet,* and *E. Lederer,* C. R. hebd. Séances Acad. Sci. *250,* 3518 (1960).



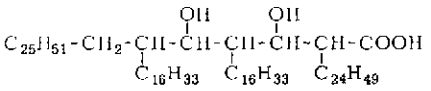
(7)



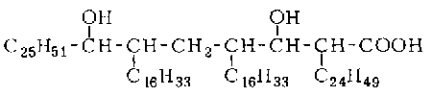
(8)



(9), n = 11 or 13



(10)



(11)

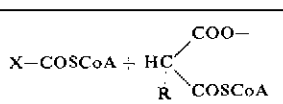
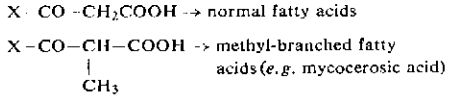
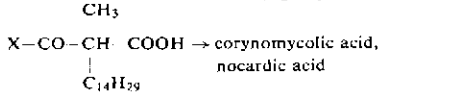
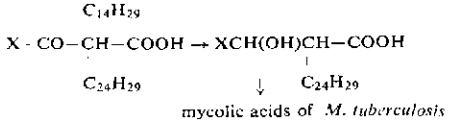
*Biosynthesis of the Mycolic Acids*

It was shown in experiments in collaboration with *Gastambide-Odier*, that incubation of live diphtheria bacilli with [1-$^{14}$C]palmitic acidy ields radioactive corynomycolic acid which, as expected, is labelled exclusively in carbon atoms 1 and 3. This demonstrates the direct condensation of two molecules of palmitic acid to the $C_{32}$-corynomycolic acid *(7)* [19]. It has not yet been shown whether this reaction scheme is also valid for the nocardic acids *(9)* and the mycolic acids *(10)* and *(11)* of mycobacteria. However, it can be assumed that the nocardic acids are built up from three molecules of long-chain fatty acids, and the mycolic acids from four molecules (*e.g.* $2\times C_{26} + 2\times C_{18} - C_{88}$). We have already published detailed reviews on this problem [1b -f].

Formulae *(10)* and *(11)* for the mycolic acids from *M. tuberculosis*, derived from the degradative studies of *Asselineau* [1c, 20] and from biogenetic considerations are only to be regarded as ideal cases; many structural variations are certainly possible.

Table 1 gives a generalized summary of the different possible fatty-acid syntheses, which probably all depend ultimately on the condensation of an acyl coenzyme A with a malonyl coenzyme A. Apparently the only variation is in the nature of this malonyl-CoA derivative.

Table 1. The biosynthesis of fatty acids in bacteria.

| |  |
|---|---|
| R = H | X-CO-$CH_2$COOH → normal fatty acids |
| R = $CH_3$ |  methyl-branched fatty acids (*e.g.* mycocerosic acid) |
| R = $C_{14}H_{29}$ |  corynomycolic acid, nocardic acid |
| R = $C_{24}H_{29}$ |  mycolic acids of *M. tuberculosis* |

[19] *M. Gastambide-Odier* and *E. Lederer*, Nature (London) *184*, 1563 (1959); Biochem. Z. *333*, 285 (1960).

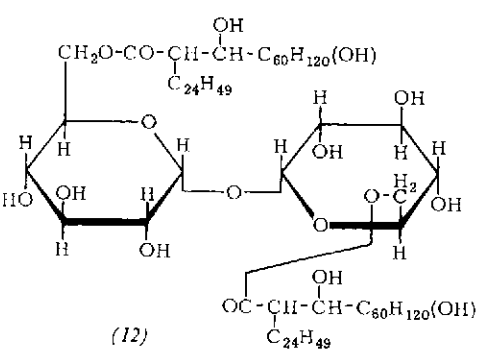
[20] *J. Asselineau*, Bull. Soc. chim. France *1960*, 135.

## II. Structures of Glycolipids, Peptidolipids, and Peptidoglycolipids

### a) Glycolipids

*Cord-Factor*

In 1960 we reported [1d] in detail upon the elucidation of the structure, the synthesis, and the biological activity of the cord factor [21a]. Formula *(12)* shows the structure of this trehalose 6,6′-dimycolate. Since then this formula has been confirmed chiefly by Japanese investigators; they also showed that in different strains the $C_{88}$-mycolic acid may be replaced by "shorter" mycolic acids (*e.g.* $C_{68}H_{136}O_4$) [21b].



(12)

The cord factors of *M. phlei* and *M. smegmatis* contain mycolic acids with two carboxyl groups (approx. $C_{67}H_{134}O_6$) [21c], while active cord-factor preparations containing dibasic mycolic acids of approximate formula $C_{84}H_{164}O_6$ have been isolated from *M. avium* [22].

Japanese authors [23] have recently isolated a diarabinose mycolate and a D-arabinose 5-*O*-mycolate from the "strongly bound" lipids of tubercle bacilli.

[21a] Elucidation of the structure of the cord factor: *H. Noll, H. Bloch, J. Asselineau*, and *E. Lederer*, Biochim. biophysica Acta *20*, 299 (1956). – Syntheses: *T. Gendre* and *E. Lederer*, Bull. Soc. Chim. France *1956*, 1478; *J. Polonsky, G. Ferréol, R. Toubiana*, and *E. Lederer*, ibid. *1956*, 1471; *G. Brochéré-Ferréol* and *J. Polonsky*, ibid. *1958*, 714. – Review articles: *H. Noll*, Adv. Tuberc. Res. *7*, 149 (1956); *E. Lederer*, Festschrift Arthur Stoll, Birkhäuser, Basel 1957, p. 384.

[21b] *J. Azuma* and *Y. Yamamura*, J. Biochemistry (Tokyo) *52*, 82 (1962).

[21c] *J. Azuma, T. Nagasuga*, and *Y. Yamamura*, J. Biochemistry (Tokyo) *52*, 92 (1962).

[22] *A. M. Miquel, H. Ginsburg*, and *J. Asselineau*, Bull. Soc. Chim. biol. *45*, 715 (1963).

[23] *J. Azuma* and *Y. Yamamura*, J. Biochemistry (Tokyo) *52*, 142, 200 (1962); *53*, 275 (1963).

*Mycosides A and B*

The mycosides are "type-specific glycolipids from mycobacteria" [24]. The following three types are known at present [25]:

Mycoside A: characteristic of the so-called atypical photochromogenic strains (*M. kansasii*).

Mycoside B: characteristic of bovine strains.

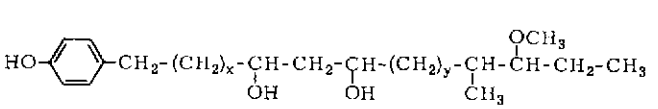
Mycoside C: characteristic of avian and related strains. The first two groups are glycolipids; the 'C' mycosides are peptidoglycolipids and will be considered further below.

Mycoside A: the exact structure of this compound is not yet known; it is certainly very closely related to mycoside B, whose structure has recently been determined by *Demarteau-Ginsburg* [27].

Mycoside B: *Smith* et al. [26] showed this substance (m.p. 25 °C, $[\alpha]_D = -22°$) to be a glycolipid containing one molecule of 2-*O*-methylrhamnose and two molecules of mycocerosic acid in combination with an "aromatic analogue of phthiocerol".

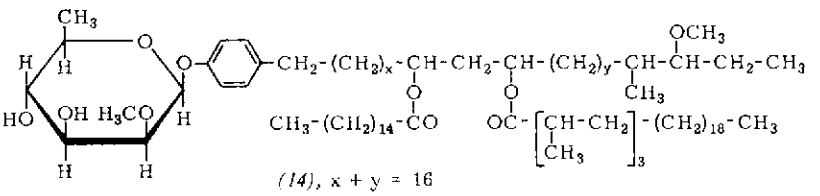
The mycoside B which we analyzed contained one molecule of normal fatty acid (mainly palmitic acid) and one molecule of mycocerosic acid (mainly the $C_{29}$-mycocerosic acid). The sugar was identified as 2-*O*-methyl-D-rhamnose [27]. Elementary analysis and mass spectrometry of the "aromatic analogue of phthiocerol", which we call "phenol-glycol B", gave the formula $C_{32}H_{58}O_4$. Ultraviolet, infrared, and nuclear magnetic resonance measurements showed the presence of a *p*-phenol; mass spectrometry of the methyl ether of the phenol showed further that this substance contained the fragment $CH_3O{-}C_6H_4{-}CH_2$. The presence of a methoxy group as well as a probably secondary β-glycol grouping indicates a close similarity to phthiocerol; this was demonstrated by the mass spectrum. Peaks at mass numbers 73 and 101 tally with the mass spectrum of phthiocerol for the groups $-CH(OCH_3){-}CH_2{-}CH_3$ (m/e = 73) and $-CH(CH_3){-}CH(OCH_3){-}CH_2{-}CH_3$ (m/e = 101).

Both ends of the aliphatic chain of "phenol-glycol B" are thus defined, and it can be assigned the formula *(13)*.



x + y = 16 *(13)*

In mycoside B, the sugar is bound by a β-glycosidic linkage to the phenolic hydroxyl group of "phenol-glycol B". The two fatty acids are present as esters of the aliphatic hydroxyl groups. Mycoside B thus has the formula *(14)* [27].



*(14)*, x + y = 16

*Phospholipids*

The work of *Anderson* [1a] showed *inter alia* that the phospholipids of mycobacteria have low nitrogen contents, and contain inositol and D-mannose. A "mann-inositose" formed from two molecules of D-mannose and one molecule of *myo*-inositol was characterized [1a]. Recent work at Gif by *Vilkas*, in part with *Ballou*, has shown that the main types of nitrogen-free phospholipids occurring in human strains, in BCG [*] and in *M. phlei* are as follows [28]:

1. A sugar-free phosphoinositide in which, as in all other such compounds of plant or animal origin, the phosphoric acid is bound to the L-1-hydroxyl group of the *myo*-inositol.

2. A mono-α-D-mannopyranoside of a phosphoinositide; according to synthetic work of *Angyal* and *Shelton* [29] the mannose is bound to the D-1-hydroxyl of the *myo*-inositol.

3. A di-α-D-mannopyranoside of a phosphoinositide; according to *Vilkas*, an α-(1→6)-D-mannobiose is present [30].

4. A pentamannoside of a phosphoinositide [31, 32].

The presence of the trimannoside postulated by us earlier [1f] could not be confirmed recently.

The amino acids, chiefly L-ornithine, which were often found in phospholipids in earlier work [33], probably originate from contaminations by peptidolipids [34]. *Houtsmuller* and *Van Deenen* [35] have, however, recently isolated a phosphatidylglycerol from *M. cereus* which contains ornithine bound in an ester linkage (see also [36]).

**b) Peptidolipids**

The peptidolipids and peptidoglycolipids described below are remarkable for several reasons:

1. They represent a new form of fat-soluble peptide derivative.

[*] BCG = *Bacillus Calmette-Guérin.*

[24] *D. W. Smith, H. M. Randall, A. P. MacLennan*, and *E. Lederer*, Nature (London) *186*, 887 (1960).

[25] *D. W. Smith, H. M. Randall, A. P. MacLennan, R. K. Putney*, and *S. V. Rao*, J. Bacteriol. *79*, 217 (1960).

[26] *D. W. Smith, H. M. Rundall, M. Gastambide-Odier*, and *A. L. Koevoet*, Ann. N.Y. Acad. Sci. *69*, 145 (1957).

[27] *H. Demarteau-Ginsburg* and *E. Lederer*, Biochim. biophysica Acta *70*, 442 (1963).

[28] *C. E. Ballou, E. Vilkas*, and *E. Lederer*, J. biol. Chemistry *238*, 69 (1963).

[29] *S.J.Angyal* and *B.Shelton*, Proc. chem. Soc. (London) *1963*, 57.

[30] *E. Vilkas* and *E. Lederer*, Bull.Soc.Chim.biol.*42*, 1013 (1960).

[31] *S. Nojima*, J. Biochemistry (Tokyo) *46*, 607 (1959).

[32] *M. C. Pangborn*, Fed. Proc. *17*, 1133 (1958).

[33] *T. Gendre* and *E. Lederer*, Ann. Acad. Sci. fennicae, Ser. A II, *60*, 313 (1955).

[34] *F. Paul* and *E. Vilkas*, C. R. hebd. Séances Acad. Sci. *254*, 3915 (1962).

[35] *U. M.T. Houtsmuller* and *L. L. M. Van Deenen*, Biochim. biophysica Acta *70*, 211 (1963).

[36] *M. A. Lanéelle, G. Lanéelle*, and *J. Asselineau*, Biochim. biophysica Acta *70*, 99 (1963).

2. Almost without exception they contain one or more D-amino acids.

3. They occasionally contain types of amino acids which occur very seldom in nature.

4. Some of them have interesting biological properties.

The study of these well-defined compounds is also of interest in view of more recent theories [37] that a lipid-soluble stage is involved in protein synthesis.

Fortuitin ($C_{53}H_{95}N_7O_{11} \pm 2CH_2$, m. p. 199–202 °C, $[\alpha]_D = -72°$) was isolated from *M. fortuitum*; it contains a mixture of homologous fatty acids (chiefly palmitic acid) which are bound by amide links to a heptapeptide, $Val_3$, $Thr_2$, $Ala_1$, $Pro_1$ [38].

Fortuitin is the only compound in this group known at present, that contains only L-amino acids.

The presence of a methoxy group, the neutral reaction of fortuitin, and its positive hydroxamate reaction indicate that the peptide chain is esterified by methanol; the NMR spectrum of fortuitin does in fact show a signal at 3.64 ppm which could indicate a methoxycarbonyl group.

$$CH_3(CH_2)_nCO\text{-}Val\text{-}Val\text{-}Val\text{-}\overbrace{Thr\text{-}Thr}^{Ac}\text{-}Ala\text{-}Pro\text{-}OCH_3$$

*(15)*, n = 16, 18, 20

Partial hydrolysis by chemical and enzymatic means has finally led to the formula *(15)* for fortuitin [39], in which a molecule of acetic acid esterifies the hydroxyl group of one of the threonine molecules.

Peptidolipin NA: In 1958 we described, with *Guinand* and *Michel* [40], a mixture of peptidolipids which was isolated from *Nocardia asteroides*; recently *Guinand* and *Michel* [41] succeeded in separating a pure compound from this mixture by counter-current distribution. The name peptidolipin NA was proposed; the substance (m. p. 232–233 °C; $[\alpha]_D = +42°$; $C_{47}H_{83}N_7O_{12}$) contains a fatty acid which is bound by an amide link to a heptapeptide L-$Thr_2$, L-$Ala_1$, D-$Ala_1$, L-$Val_1$, D-*allo*-$Ileu_1$, L-$Pro_1$.

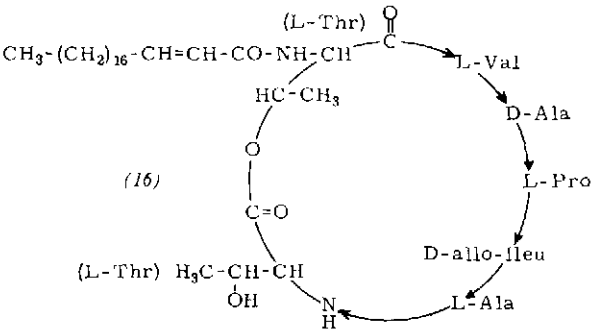
D-*allo*-Isoleucine, found in peptidolipin NA by *Ikawa* and *Snell* [42], has up till now only been isolated from actinomycin $C_3$ by *Brockmann* et al. [43].

The fatty acid obtained by vigorous acidic hydrolysis of peptidolipin NA has been demonstrated to be homogeneous by gas chromatography, and identified as *trans*-2-eicosenoic acid [44].

Partial acidic hydrolysis yields an *N*-acyl-L-threonine, free L-threonine, and a hexapeptide L-Thr-L-Val-D-Ala-L-Pro-D-*allo*-Ileu-L-Ala.

Since peptidolipin NA has no free carboxyl group, gives a positive hydroxylamine reaction, and on reduction with $LiAlH_4$ gives threoninol [45], we assume that it has a cyclic structure in which the carboxyl group of one threonine molecule is esterified with the hydroxyl group of the second.

Careful hydrolysis with acid opens the ring at the ester linkage, and a substance is obtained which still contains the fatty acid, as well as all seven amino acids. A *C*-terminal threonine is then found in this compound.




Formula *(16)* explains satisfactorily all the reactions of peptidolipin NA [44] [*]. It is reminiscent of the structures of several antibiotics, *e.g.* etamycin [46] and telomycin [47], actinomycin [48], staphylomycin [49] and ostreogrycin [50]; all of these have a lactone ring containing 5–7 amino acids, in which an *N*-acylated molecule of threonine closes the ring.

Peptidolipids from *M. paratuberculosis*. *Lanéelle* and *Asselineau* [51] isolated a mixture of peptidolipids from *M. paratuberculosis (M. johnei)*; the main fraction appears to be the n-eicosamide of a tetrapeptide containing one molecule each of D- and L-phenylalanine and two molecules of L-alanine; the *C*-carboxyl group of the peptide chain is again esterified with methanol.

### c) Peptidoglycolipids

*The Mycosides C*

Two representatives of this group have been examined in detail, *viz.* mycoside $C_2$ (m.p. 200 °C; $[\alpha]_D = -34°$; $C_{89}H_{153}N_5O_{21} \pm 3\ CH_2$) from *M. avium* [52], and

[37] *R. W. Hendler*, Nature (London) *193*, 821 (1962).

[38] *E. Vilkas*, *A. M. Miquel*, and *E. Lederer*, Biochim. biophysica Acta *59*, 731 (1962).

[39] *P. Jollès*, *E. Vilkas*, and *E. Lederer*, unpublished work.

[40] *M. Guinand*, *G. Michel*, and *E. Lederer*, C. R. hebd. Séances Acad. Sci. *246*, 848 (1958).

[41] *M. Guinand* and *G. Michel*, C. R. hebd. Séances Acad. Sci. *256*, 1621 (1963).

[42] *M. Ikawa* and *E. E. Snell*, Biochim. biophysica Acta *60*, 186 (1962).

[43] *H. Brockmann*, *N. Grubhofer*, *W. Kass*, and *H. Kalbe*, Chem. Ber. *84*, 260 (1951).

[44] *M. Guinand*, *G. Michel*, and *E. Lederer*, unpublished work.

[45] Not alaninol as was stated erroneously in a previous communication [41].

[*] Recent experiments seem to indicate that *trans*-2-eicosenoic acid is formed during hydrolysis of peptidolipin NA with strong acid by a β-elimination from 3-hydroxyeicosanoic acid; the hydroxyl group of this acid is most probably esterified with the carboxyl group of the *C*-terminal threonine. Both threonine molecules would then have their hydroxyl groups free, and formula *(16)* for peptidolipin NA would have to be modified.

[46] *J. C. Sheehan*, *H. G. Zachau*, and *W. B. Lawson*, J. Amer. chem. Soc. *80*, 3349 (1958).

[47] *J. Sheehan* et al., J. Amer. chem. Soc. *85*, 2868 (1963).

[48] *H. Brockmann* and *P. Boldt*, Naturwissenschaften *50*, 19 (1963).

[49] *H. Vanderhaeghe* and *G. Parmentier*, J. Amer. chem. Soc. *82*, 4414 (1960).

[50] *Lord Todd*, Symposium International de Chimie Organique, Brussels, June 1963.

[51] *G. Lanéelle* and *J. Asselineau*, Biochim. biophysica Acta *59*, 731 (1962).

[52] *M. Chapat*, *G. Michel*, and *E. Lederer*, Biochim. biophysica Acta *78*, 329 (1963).

mycoside $C_m$ (m.p. 198–200 °C; $[\alpha]_D$ = −31 °; $C_{108}H_{185}N_7O_{28}$ ± 3 $CH_2$) from *M. marianum* [53].

Both compounds have the following properties:

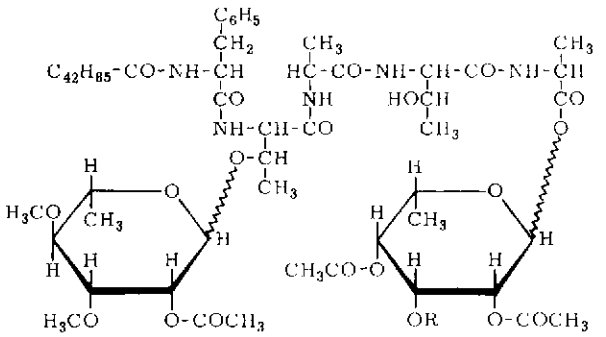
1. The lipid portion is bound by an amide link to the amino group of a molecule of D-phenylalanine; the latter is the *N*-terminal amino acid of an oligopeptide.

2. The peptide moiety has the structure D-Phe-(D-*allo*-Thr-D-Ala)$_n$, where n = 2 for mycoside $C_2$ and n = 3 for mycoside $C_m$. It is noteworthy that only D-amino acids are present; moreover, this is the first time that D-*allo*-threonine has been found in nature [54].

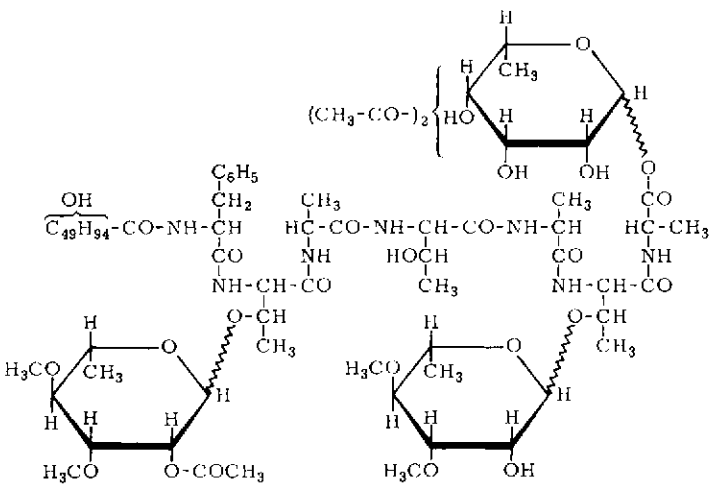
3. The *C*-terminal carboxyl group of a molecule of D-alanine is bound by an ester link to the reducing hydroxyl of a deoxysugar. This linkage is readily hydrolysed by hydroxylamine with liberation of the sugar. Sodium borohydride reduces the linkage to form the corresponding deoxyhexitol; this establishes that the carboxyl group of the amino acid is bound to the reducing hydroxyl group of the deoxysugar.

4. One or two molecules of deoxysugar are bound to the hydroxyl group of one or two molecules of D-*allo*-threonine.

5. Two to three molecules of acetic acid esterify the remaining free hydroxyl groups of the sugar in these mycosides.



*(17)*, Mycoside $C_2$, R = H, $CH_3$



*(18)*, Mycoside $C_m$

With *Chaput* and *Michel* [53], the formulae *(17)* and *(18)* were proposed for the two mycosides [*]; mycoside $C_2$ is actually a mixture of two peptidoglycolipids, one of which has 6-deoxy-L-talose at the end of the peptide chain, and the other 3-*O*-methyl-6-deoxy-L-talose. Further details of the structure determination are to be found in the complete reports [52,53].

It is remarkable that three different methods are used here by nature to make a sugar fat-soluble: reduction of the hydroxymethyl group in position 6 to a methyl group, *O*-methylation, and *O*-acetylation.

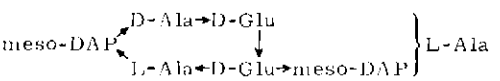
### *Wax D*

All mycobacterial strains contain 2–8 % of a glycolipid fraction which can be extracted with chloroform and which is insoluble in boiling acetone [1b–f]. The main components of these so-called wax D fractions of bovine, avian, and saprophytic strains are glycolipids which contain no amino acids and in which the mycolic acids are esterified by a polysaccharide containing arabinose, galactose, and mannose. The wax D fractions of human strains of *M. tuberculosis* also contain a peptide portion and amino sugars bound to the polysaccharide. The peptide component is especially interesting as it appears to be necessary for the immunological adjuvant activity [**] of the wax D fractions.

This peptide portion contains the typical "cell-wall amino acids" of mycobacteria, namely *meso*-α,α'-diaminopimelic acid (*meso*-DAP), D-glutamic acid, and D- and L-alanine [55]. In most cases the proportions are almost exactly *meso*-$DAP_2$, D-$Glu_2$, D-$Ala_1$, L-$Ala_2$ [56]. These seven amino acid molecules form a heptapeptide for which two tentative structures, *(19)* or *(20)*, have been considered [57].

meso-DAP-D-Ala-D-Glu-D-Glu-L-Ala-meso-DAP-L-Ala

*(19)*



*(20)*

The linkage binding the heptapeptide to the polysaccharide is resistant to reduction with sodium borohydride and to 0.01 N NaOH; this behavior appears to rule out an ester bond. In fact, the heptapeptide is clearly joined by the carboxyl group of one *meso*-DAP to the amino group of galactosamine by an amide link; the amino sugar is bound to arabinose by a glycosidic linkage.

[*] The formula of the lipid fragment is derived only from the elemental analysis of the intact mycoside by subtraction of the amino acids and sugars. The material is actually a complex mixture.

[**] An adjuvant is a substance which, when applied together with an antigen, stimulates the formation of antibodies (see below).


[53] *M. Chaput, G. Michel,* and *E. Lederer,* Biochim. biophysica Acta *63,* 310 (1962).

[54] *M. Ikawa, E. E. Snell,* and *E. Lederer,* Nature (London) *188,* 558 (1960).

[55] *C.S.Cummins* and *H.Harris,* J.gen.Microbiol. *18,* 173 (1958).

[56] *J. Asselineau, H. Buc, P. Jollès,* and *E. Lederer,* Bull. Soc. Chim. biol. *40,* 1953 (1958).

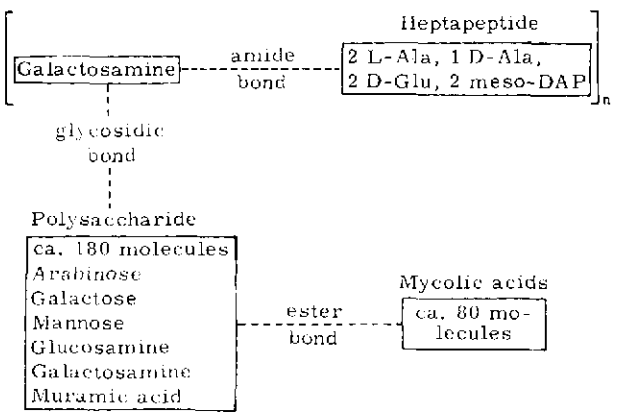
[57] *P. Jollès, H. Nguyen-Trung-Luong-Cros,* and *E. Lederer,* Biochim. biophysica Acta *43,* 559 (1960).

Resolution of wax D from human strains into several distinctly different fractions was recently achieved by ultracentrifugation in ether [58]:

1. a "light" fraction (6–10 % of the wax D), which remained soluble in ether, is free from amino acids and shows no adjuvant activity, and

2. several "heavy" fractions which sedimented after 15–150 minutes. All the "heavy" fractions contained the amino acids already mentioned, in the rough proportion *meso*-$DAP_2$, $Glu_2$, $Ala_3$. In one fraction one Glu is replaced by Gly.

The presence of muramic acid (3-*O*-lactyl-D-glucosamine) was first established in these fractions which had been purified by ultracentrifugation; this again indicates the biochemical analogy between wax D and the cell wall [59].




*(21)*, n = 1, 2, 3

All our results concerning the wax D of human strains seem to indicate that one, two, or three molecules of heptapeptide are bound to the polysaccharide through galactosamine. Formula *(21)* shows a hypothetical structure.

From the results of the ultracentrifugation of the water-soluble fraction of the wax D, the molecular weight of the peptide-containing mucopolysaccharide is about 35000. As the wax D contains about 25 % mucopolysaccharide, the minimum molecular weight of the intact wax D is approximately 140000. Ultracentrifugation of ether solutions of wax D from bovine, avian, and saprophytic strains has yielded similar fractions, but with the difference that the "heavy" fraction is normally obtained only in small amount, the major part remaining in the ether. These soluble fractions contain no amino acids and are inactive as adjuvants [59, 60].

Several "heavy" fractions from *M. avium* and *M. phlei* contain a peptide portion which is very similar to that of the wax D from human strains; these fractions also have adjuvant activity.

The wax D of the so-called "atypical photochromogenic" strains (*M. kansasii*) occupy a special position; they behave exactly like the wax D of human strains on ultracentrifugation in ether: they are almost entirely sedimented, and contain the typical heptapeptide and amino sugars; they are active as adjuvants [59, 60].

[58] *P. Jollès, D. Samour,* and *E. Lederer,* Arch. Biochem. Biophysics, Suppl. *1*, 283 (1962).

[59] *P. Jollès, D. Samour,* and *E. Lederer,* Biochim. biophysica Acta *78*, 342 (1963).

[60] *R. G. White, P. Jollès, D. Samour,* and *E. Lederer,* Immunology *7*, 158 (1964).

## III. Biological Activity

Table 2 gives a summary of the biological activities of the lipid fractions from the tubercle bacillus.

Only older data are available concerning the development of the tubercle; these were reviewed in 1960 [1d].

Table 2. Relationships between the biological activity and the chemical constitution of the lipids from tubercle bacilli.

| Biological action | Chemical constitution of the lipid |
|---|---|
| Formations of tubercles | Branched-chain fatty acids (phthienoic acids, mycocerosic acids, mycolic acids and their esters) |
| Loss of weight, haemorrhage, death | Cord factor (trehalose 6,6'-dimycolate) |
| Adjuvant action, granuloma, delayed hypersensitivity | Wax D (peptidoglycolipids) |
| Immunization | Phosphoglycolipids (?) |

During recent years we have been chiefly interested in adjuvant activity and immunization.

### a) Adjuvant Activity

It is known, mainly from the work of *Freund* [61], that killed tubercle bacilli suspended in paraffin oil exhibit an adjuvant effect; injection of an animal with the bacterial suspension together with an antigen, leads to a marked rise in antibody formation. *White, Bernstock, Johns,* and *Lederer* [62] demonstrated that the wax D fractions are responsible for this activity and that only the wax D of human strains, *i.e.* only those in which the three amino acids Ala, Glu, and *meso*-α,α'-diaminopimelic acid occur, are active.

Since then wax D fractions have been purified further and it has been found, as already mentioned, that wax D of non-human strains also contains a small amount of peptidoglycolipid, which is chemically very similar to the main fraction of the wax D of human strains [59].

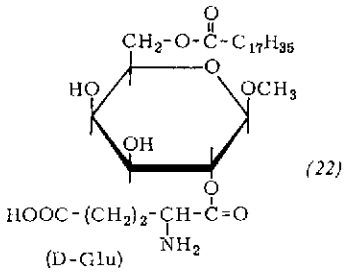
The biological experiments of *White* at London Hospital have shown that only the fractions containing the heptapeptide $DAP_2$, D-$Glu_2$, $Ala_3$ exhibit adjuvant activity. This activity appears to be proportional to the amount of the heptapeptide present in the wax D [62a]. The following substances are inactive: the water-soluble portion of the wax D, mycolic acids, the waxes A, B, and C, fortuitin, peptidolipin NA, mycosides $C_2$ and $C_m$, a synthetic galactolipid *(22)*, methyl 6-*O*-stearyl-2-

[61] *J. Freund,* Adv. Tuberc. Res. *7*, 130 (1956).

[62] *R. G. White, L. Bernstock, R. G. S. Johns,* and *E. Lederer,* Immunology *1*, 54 (1958).

[62a] *R. G. White,* unpublished work.

D-glutamyl-β-D-galactopyranoside [63], and the distearylamide of dimethyl *meso*-α,α'-diaminopimelate.




(22)

According to *White*, the adjuvant activity always parallels the formation of a granuloma at the point of injection, and the delayed hypersensitivity typical of tuberculosis [*].

It should be noted further that the adjuvant activity of the wax D lasts much longer than that brought about by the endotoxins of Gram-negative bacteria [65].

We are currently working with *Bricas* [66] on the use of enzymes in the stereospecific preparation of peptides of *meso*-α,α'-diaminopimelic acid; such peptides will have to be linked to mycolic esters of sugars, in order to obtain synthetic adjuvants.

### b) Immunization

Most authors seem to agree that neither tuberculin, nor other proteins or polysaccharides of the tubercle bacillus are able to immunize animals against experimental tuberculosis.

On the other hand, there are some reports that more or less purified lipid fractions have this property. Thus, over 30 years ago, *Boquet* and *Nègre* [67], at the Pasteur Institute in Paris, prepared a methanol extract of *M. tuberculosis* which they called "antigène méthylique" and with which they were able to immunize animals against tuberculosis. These results were confirmed and extended in 1956 by *Weiss* and *Dubos* [68]. Since then we also have been interested in this fraction, whose immunogenic activity was tested on mice by *H. Bloch*. For some time the activity appeared to be concentrated in an ether-insoluble phosphatide fraction, and we thought we had obtained a pure fraction analysing as phosphatidylinositotrimannoside [11]; this, however, has not been confirmed, so that the immunizing substance (or substances) in "antigène méthylique" have still to be identified.

There are also reports on the immunizing activity of so-called PmKo [69], a lipid fraction which is chemically very closely related to the wax D we have described. According to *Crowle* [70] three out of four such PmKo preparations were active; the same author also found wax B to be active, a behavior which hitherto had not been observed.

*Larson, Ribi* et al. [71] found that cell walls of *M. tuberculosis* (BCG) have no immunizing activity when the bacilli are broken up in water, but only when this is done in paraffin oil. The explanation for this finding is not yet clear.

On the other hand, it is probable *a priori*, that a strong immunity, comparable to that brought about by BCG, can only be produced by the application of two or more antigens. Indications of such duality are seen in the work of *Williams* and *Dubos* [72].

The problem is, moreover, complicated by the simultaneous appearance of "non-specific resistance", which can also be brought about by the endotoxins of Gram-negative bacteria.

*The present work was supported by the Fondation Waksmann pour le Développement des Recherches Microbiologiques en France, and by Grant AI-02838 of the National Institute of Allergy and Infectious Diseases (U.S. Public Health Service). The supply of isotopes was made possible by a grant of the Commissariat à l'Energie Atomique (Saclay).*

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German version: Angew. Chem. 76, 241 (1964)
Translated by Express Translation Service, London

[63] *M. Černy, J. Moron*, and *E. Lederer*, Bull. Soc. Chim. biol. *45*, 601 (1963).

[*] From experiments of *Raffel* [64], this activity was previously attributed to glycosyl esters of mycolic acid in general; *White* has not been able to confirm this in his work.

[64] *S. Raffel, J. Asselineau*, and *E. Lederer:* Experimental Tuberculosis, A Ciba Foundation Symposium, Churchill, London 1955, p. 174.

[65] *J. Munoz*, J. Immunol. *90*, 132 (1963).

[66] *E. Bricas, C. Nicot*, and *E. Lederer*, Bull. Soc. Chim. biol. *44*, 1115 (1962); *C. Nicot* and *E. Bricas*, C. R. hebd. Séances Acad. Sci. *256*, 1391 (1963).

[67] *A. Boquet* and *L. Nègre*, C. R. Séances Soc. Biol. Filiales *86*, 581 (1922); *L. Nègre:* Les Lipoides dans le Bacille Tuberculeux et la Tuberculose, Masson, Paris 1950.

[68] *D. W. Weiss* and *R. J. Dubos*, J. exp. Med. *103*, 73 (1956).

[69] *N. Choucroun*, Amer. Rev. Tuberc. *56*, 203 (1947).

[70] *A. J. Crowle*, Proc. Soc. exp. Biol. Med. *109*, 969 (1962).

[71] *C. L. Larson, E. Ribi, W. C. Wicht, R. H. List*, and *G. Goode*, Nature (London) *198*, 1214 (1963).

[72] *C. A. Williams* and *R. J. Dubos*, J. exp. Med. *110*, 981 (1959).

# New Methods of Preparative Organic Chemistry IV [*]

## Syntheses with Nascent Quinones

BY PROF. DR. H. W. WANZLICK

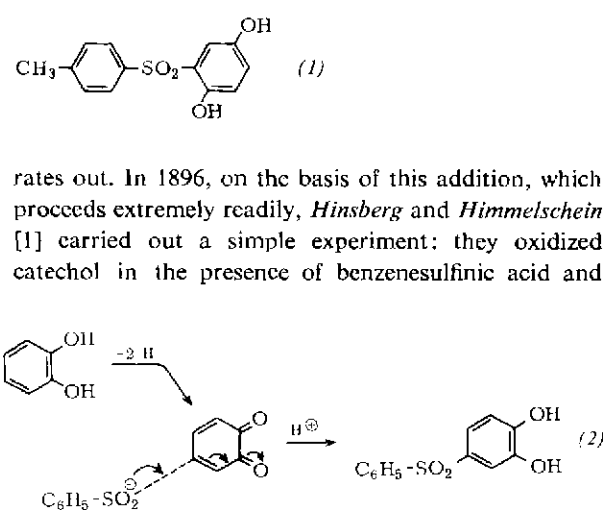
FROM WORK CARRIED OUT IN COLLABORATION WITH DIPL.-ING. M. LEHMANN-HORCHLER, DR. S. MOHRMANN, DIPL.-ING. R. GRITZKY, DIPL.-ING. H. HEIDEPRIEM, AND DIPL.-CHEM. B. PANKOW

ORGANISCH-CHEMISCHES INSTITUT DER TECHNISCHEN UNIVERSITÄT BERLIN (GERMANY)

*If catechol or other hydroquinones are dehydrogenated in the presence of a nucleophilic reagent, the latter reacts, usually by Michael addition, with the quinone formed in situ. The wide range of possible variations offered by this synthetic method is comprehensively described in the present paper. Procedures are given for carrying out typical reactions.*

### 1. Introduction

*Demonstration Experiment*: A solution of 3 g of sodium *p*-toluenesulfinate in 50 ml of water and 10 ml of acetic acid is poured into a solution of 1 g of *p*-benzoquinone in 10 ml of acetic acid and 50 ml of water. The mixture is decolorized within a few seconds and purely white 2,5-dihydroxyphenyl *p*-tolyl sulfone *(1)* immediately separates out. In 1896, on the basis of this addition, which proceeds extremely readily, *Hinsberg* and *Himmelschein* [1] carried out a simple experiment: they oxidized catechol in the presence of benzenesulfinic acid and



obtained the sulfone *(2)*. Their clear conception of this experiment, which is given here in its modern formulation, is shown by their own words [1]:

"Benzenesulfinic acid combines with quinones and iminoquinones, and reacts rapidly at normal temperatures to yield hydroxy or amino derivatives of sulfones [2]. If benzenesulfinic acid is present at the moment of formation of a quinone (or iminoquinone) of low stability, the former is converted into the corresponding sulfone, and is thus prevented from reacting further..... the formation of a hydroxy or amino sulfone indicates that the quinone was present in the oxidation mixture, even if only for a short time."

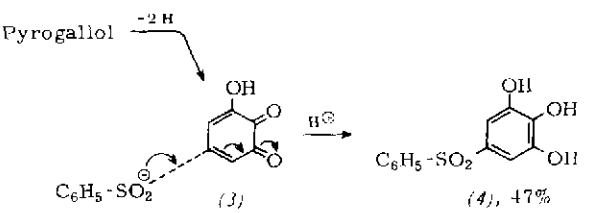
This analytical conception contains a synthetical principle, an account of which is given below. The syntheses in question have the following point in common: dehydrogenation of catechol or another quinone former in the presence of a nucleophilic reagent yields a product which is (normally) formed by Michael addition of the nucleophile onto the quinone produced *in situ*.

### 2. Simple Examples

#### a) Additions of Sulfinic Acids, Sulfite, and Thiourea

In the course of work on the mechanism of the formation of purpurogallin, *Horner* et al. studied the dehydrogenation of pyrogallol in the presence of benzenesulfinic acid to form the sulfone *(4)* [3,4].

The sulfinic acid adds onto the 3-hydroxy-*o*-benzoquinone *(3)* formed *in situ*; *(3)* has never been isolated.



Dehydrogenation of alizarin *(5)* in the presence of *p*-toluenesulfinic acid leads via the *o*-quinone *(6)* to the sulfone *(7)* [5]. Sulfite can also add onto *(6)* to form the sulfonic acid *(8)*.

[*] The papers of the previous three series are collected in three volumes published in English by Academic Press, New York, London.

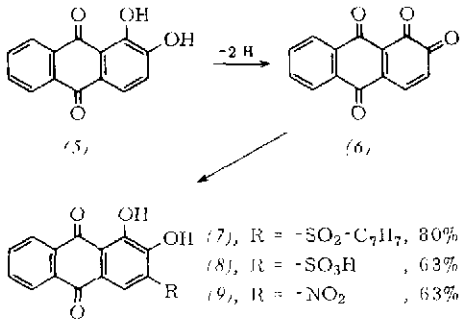
[1] *O. Hinsberg* and *A. Himmelschein*, Ber. dtsch. chem. Ges. *29*, 2023 (1896).

[2] *O. Hinsberg*, Ber. dtsch. chem. Ges. *27*, 3259 (1894); *28*, 1315 (1895).

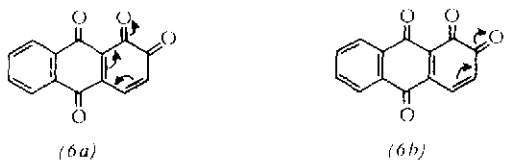
[3] *L. Horner* and *W. Dürckheimer*, Z. Naturforsch. *14b*, 743, 744 (1959).

[4] *L. Horner* and *S. Göwecke*, Chem. Ber. *94*, 1267 (1961); *L. Horner, K. H. Weber*, and *W. Dürckheimer*, ibid. *94*, 2881 (1961).

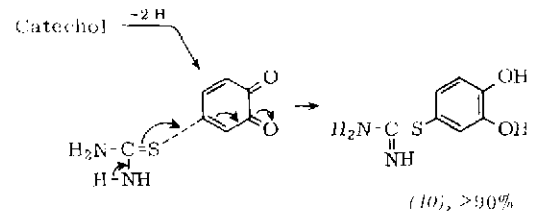
[5] *H. Heidepriem*, Ph. D. Thesis, Technische Universität Berlin, 1964.




The addition in the 3-position is remarkable. It means that polarization of the diquinone *(6)*, which is so far only known in solution [6], in the direction indicated in *(6a)* predominates over the expected polarization *(6b)*.




The addition of thiourea onto nascent *o*-benzoquinone proceeds satisfactorily [7] to yield *S*-(3,4-dihydroxyphenyl)isothiourea *(10)*.



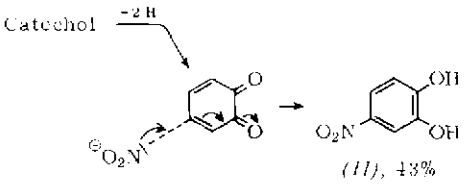

*Procedure:*

A solution of 65 g of potassium hexacyanoferrate(III) and 100 g of crystalline sodium acetate in 230 ml of water is rapidly added dropwise to a mechanically stirred solution of 13 g of catechol and 7.6 g of thiourea in 100 ml of water. The reaction product begins to separate out even during the dropwise addition. Further 100 g of crystalline sodium acetate are added, and the mixture is stirred for another hour, filtered by suction, and washed with a little water. The crude product is purified by dissolving it in dilute hydrochloric acid and stirring the clarified solution into a concentrated sodium acetate solution. The acetate of *S*-(3,4-dihydroxyphenyl)isothiourea *(10)* is obtained in over 90 % yield. M.p. ca. 180 °C (decomp.).

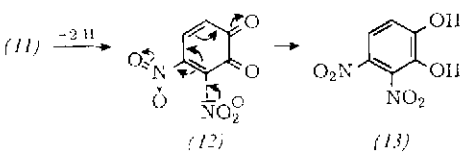
### b) Nitrite Addition

In 1878, *Benedikt* [8] discovered an unusual route to 4-nitrocatechol *(11)* by treatment of pyrocatechol with nitrous acid. A more recent, improved procedure [9] gives yields of up to 37 %. Increase in the quantity of nitrite used leads to 3,4-dinitrocatechol *(13)* as the principal product [9]. Nothing was previously known of the mechanism of the reaction.

On the basis of the idea that the reaction might proceed via *o*-benzoquinone as an intermediate, the nitrous acid playing the double role of dehydrogenating agent and nucleophilic reagent, we developed a new, simple procedure in which catechol is dehydrogenated with $K_3Fe(CN)_6$ in the presence of sodium nitrite [10].




Preliminary experiments showed that repeated dehydrogenation of *(11)* in the presence of nitrite leads to *(13)* [5]. The electron-attracting effects of the carbonyl and nitro groups indicated in *(12)* must be jointly responsible for the entry of the second nitro group [11] at position 3.




*Procedure:*

A solution of 20 g of potassium hexacyanoferrate(III) and 17 g of crystalline sodium acetate in 100 ml of water is added to a solution of 3.3 g of catechol, 2.1 g of sodium nitrite, and 2.2 g of crystalline sodium acetate in 50 ml of water. The resulting dark red mixture is filtered after 5 minutes and extracted with 200 ml of ether in several portions. The extract is dried with sodium sulfate, the ether is distilled off, and the brownish residue is pressed out on porous tile to yield about 2 g (43 %) of practically pure 4-nitrocatechol *(11)*. This may be completely purified by recrystallization from water or by sublimation *in vacuo*. M.p. 174 °C.

Dehydrogenation of alizarin *(5)* in the presence of nitrite yields alizarin orange *(9)* [5].

### c) Amine Addition

Since the groups introduced into the phenols in Sections 2a) and 2b) increase their oxidation potentials [12], it is easy to find conditions under which the reaction can be stopped after completion of the first dehydrogenation-addition process. On the other hand, if substituents which decrease the oxidation potential [12] are introduced, then secondary reactions become inavoidable. The formation of 4,5-dianilino-*o*-benzo-

[6] *O. Dimroth* and *E. Schultze*, Liebigs Ann. Chem. *411*, 345 (1916).

[7] *H.-W. Wanzlick*, Angew. Chem. *72*, 581 (1960).

[8] *R. Benedikt*, Ber. dtsch. chem. Ges. *11*, 362 (1878).

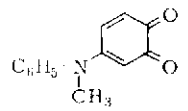
[9] *D. H. Rosenblatt*, *J. Epstein*, and *M. Levitch*, J. Amer. chem. Soc. *75*, 3277 (1953).

[10] *R. Gritzky*, Diploma Thesis, Technische Universität Berlin, 1960.

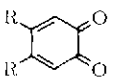
[11] Compare this with the formation of 2,3-dicyanohydroquinone (*J. Thiele* and *J. Meisenheimer*, Ber. dtsch. chem. Ges. *33*, 675 (1900)]. The participation of the carbonyl group at C-9 in promoting the polarization in *(6a)* should also be taken into consideration in the additions of alizarinquinone *(6)*.

[12] *L. F. Fieser* and *M. Fieser:* Organic Chemistry. 2nd Edit., Heath, Boston 1950, p. 755.

quinone *(15)* during the dehydrogenation of catechol in the presence of aniline has long been known [13]. The widely adaptable synthesis which involves the series of steps D–A–D A–D [14] is the subject of recent patents [15]. *Horner* and *Lang* [16] added secondary amines onto *o*-quinones produced *in situ* and obtained *inter alia* the aminoquinones *(14)*, *(16)*, and *(17)*.



*(14)*, 84%



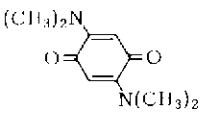
*(15)*, R = $C_6H_5$-NH-
*(16)*, R = $(CH_3)_2N$-, 53%
*(17)*, R = $(CH_2)_2N$-, 72%

*N*-Methylaniline adds on only once. The steps in the formation of *(14)* are therefore D–A–D [14].

*Procedure:*

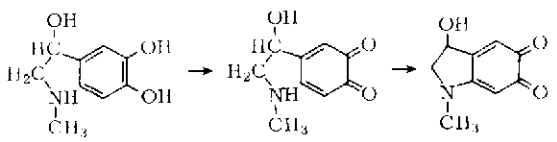
Catechol (0.55 g) is dissolved in 100 ml of acetone, and 7 g of silver oxide and 10 g of calcined sodium sulfate are added. The solution is cooled to 0 °C, treated with 2 ml of dimethylamine from a well-cooled pipet, and shaken. Processing after 10 minutes gives *(16)*, m.p. 149 °C (decomp.), in 53 % yield.

Cu(II)-catalysed autoxidation of hydroquinone in the presence of dimethylamine leads quantitatively to *(18)* [17].



*(18)*, 100%

Intramolecular amine additions are also possible and have been known for some time. The formation of adrenochrome *(21)* has been studied particularly thoroughly and might also be mentioned and formulated at this point [18].



*(19)* *(20)* *(21)*, 60%

Dehydrogenation of epinephrine *(19)* initially gives rise to *(20)*, which can be detected for a short time [19]. Subsequent A–D steps [14] lead to the formation of adrenochrome *(21)*.

[13] *F. Kehrmann* and *M. Cordone*, Ber. dtsch. chem. Ges. *46*, 3009 (1913).

[14] D = Dehydrogenation, A = Addition.

[15] J. R. Geigy AG., see Chem. Zbl. *1960*, 6926; *1962*, 9520.

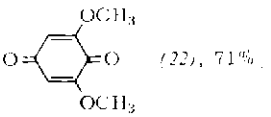
[16] *L. Horner* and *H. Lang*, Chem. Ber. *89*, 2768 (1956).

[17] *A. N. Grinev*, *I. A. Saitzev*, *N. K. Venevzeva*, and *A. P. Terentyev*, Zh. obshchei Khim. *30*, *(92)*, 1914 (1960); Chem. Zbl. *1961*, 13166; cf. *R. Baltzly* and *E. Lorz*, J. Amer. chem. Soc. *70*, 861 (1948); *A. H. Crosby* and *R. E. Lutz*, ibid. *78*, 1233 (1956).

[18] Review: *R. A. Heacock*, Chem. Reviews *59*, 181 (1959); see also *R. A. Heacock*, *O. Hutzinger*, *B. D. Scott*, *J. W. Daly*, and *B. Witkop*, J. Amer. chem. Soc. *85*, 1825 (1963).

### d) Additions of Water and Alcohols

Only one example can be given here for the addition of water and alcohols onto nascent quinones. *Horner* and *Göwecke* dehydrogenated catechol in methanolic mineral acid solution and obtained products, *e.g. (22)* from 3-methoxycatechol, which are formed by way of hemiketals [20].



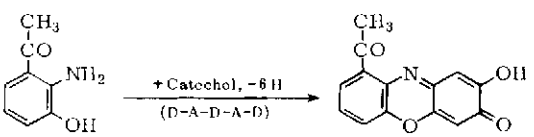
*(22)*, 71%

If isolated *o*-quinones are used as such in this reaction, methoxylation only occurs in particular cases and in considerably poorer yields.

## 3. Bifunctional Addends

The initial product of the reaction of an amine with *o*-benzoquinone is the monoaminoquinone of type *(14)*. If the amine contains another nucleophilic group in a favorable position, intramolecular secondary reactions take place.

In work on insect pigments, *Butenandt* et al. [21, 22] were able to show that dehydrogenation of catechol in the presence of the *o*-aminophenol *(23)* yields 5-acetyl-3-hydroxy-2-phenoxazone *(24)* [23].




*(23)* *(24)*, 43%

*Procedure:*

A suspension of 200 mg of 2-amino-3-hydroxyacetophenone hydrochloride, 200 mg of catechol, and 2.1 g of powdered potassium hexacyanoferrate(III) is prepared in 5 ml of acetic acid dried over copper sulfate, and the mixture is shaken in an atmosphere of carbon dioxide at room temperature. Separation of the product starts right at the beginning of the reaction and is brought to completion by controlled addition of water. Compound *(24)* is obtained in 43 % yield, m.p. > 400 °C.

A fundamentally similar combination takes place when *o*-aminophenols are dehydrogenated alone; the products are 3-amino-2-phenoxazones. Important syntheses of natural products may be quoted in this connection: in particular those of *Brockmann* et al. in the series of

[19] *A. Kodja* and *S. Bouchilloux*, C. R. Séances Soc. Biol. Filiales *153*, 1407 (1959); Chem. Zbl. *1960*, 15436.

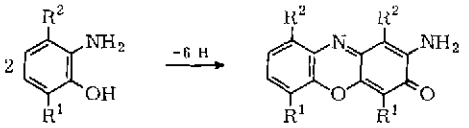
[20] For details of the mechanism, see *L. Horner* and *S. Göwecke*, Chem. Ber. *94*, 1291 (1961).

[21] *A. Butenandt*, Angew. Chem. *69*, 16 (1957).

[22] *A. Butenandt*, Verhandl. Ges. dtsch. Naturforscher, Ärzte *1959*, 152.

[23] *A. Butenandt*, *E. Biekert*, and *G. Neubert*, Liebigs Ann. Chem. *602*, 72 (1957).

actinomycins [24,25] and those of *Butenandt* et al. in the field of ommochromes [21,22]. The dehydrogenation of 2-amino-3-hydroxyacetophenone *(23)* proceeds smoothly to yield 3-amino-4,5-diacetyl-2-phenoxazone *(25)* [26]. 3-Hydroxykynurenine *(26)* yields *(27)*, which can be converted into the ommochrome xanthommatin [26,27].



*(23)*, $R^1$ = H, $R^2$ = CO-$CH_3$ — *(25)*, 80%

*(26)*, $R^1$ = H, $R^2$ = CO-$CH_2$-CH($NH_2$)COOH — *(27)*, 90%

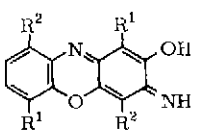
*(28)*, $R^1$ = $CH_3$, $R^2$ = $COOCH_3$ — *(29)*, 67%

*(30)*, $R^1$ = $CH_3$, $R^2$ = CO-NH-$CH_2$-$COOCH_3$ — *(31)*, >90%

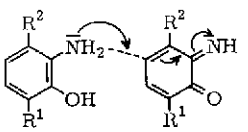
*(32)*, $R^1$ = H, $R^2$ = COOH — *(33)*, 50%

Dehydrogenation of *(28)* yields *(29)*, *i.e.* the chromophore of the actinomycins [28], and actinocylbis(glycine methyl ester) *(31)* is obtained from *(30)* [28]. These results finally led to the total synthesis of actinomycin $C_3$ by a similar method [24].

There is no doubt that these syntheses largely correspond to the course of the biosynthesis [28,28a], as is also true of the biogenesis of cinnabaric acid *(33)* and similar natural products [29]. The dehydrogenation of *(32)*, which results in the formation of *(33)*, was carried out even before the discovery of the natural product [30]. One prerequisite for the smooth occurrence of these phenoxazone syntheses is the "correct" combination of the aminophenol with the iminoquinone formed from it *in situ*; compounds of type *(34)* do not occur at all, or are only present as by-products.

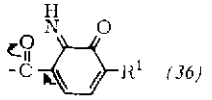


*(34)*



*(35)*

The strongly nucleophilic character of the amino group and the extreme proneness of the group C=C-C=N- to undergo addition reactions (greater than that of the system C=C-C=O [31]) must be assumed to determine the direction of the primary addition to give preferentially *(35)*. Since, in the syntheses considered in the present paper, the residue $R^2$ contains a carbonyl group attached directly to the ring, it is possible that the

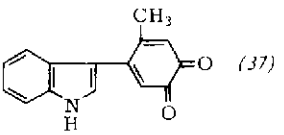


*(36)*

primary addition formulated in *(35)* is further promoted by polarization in the sense shown in *(36)* (cf. *(12)* and [11]).

## 4. C-C Bonding

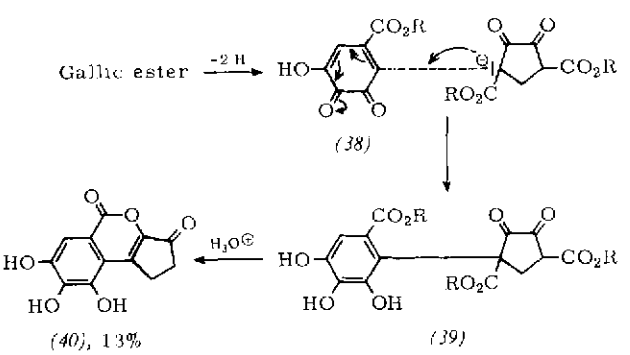
In the course of their investigations on the formation of melanins, *Bu'Lock* and *Harley-Mason* [32] dehydrogenated 4-methylcatechol in the presence of indole and obtained *(37)*.



*(37)*

To our knowledge, this is the first case of intentional formation of a C–C bond via a nascent quinone.

We found the conditions (D–A [14]) particularly simple in the synthesis of brevifolin *(40)* [34], a tannin constituent discovered and identified by *Schmidt* and *Bernauer* [33]. Gallic ester is dehydrogenated in the presence of cyclopentane-1,2-dione-3,5-dicarboxylic ester; Michael addition of this CH-acidic compound onto the *o*-quinone *(38)* which occurs as an intermediate (but which has not yet been isolated) yields *(39)*, which is converted into *(40)* simply by treatment with acid.



*(40)*, 13% — *(39)* — *(38)*

If the coreactant contains an active methylene group, the primary adduct is readily dehydrogenated further. Pyrocatechol and isopropylidene malonate (Meldrum's acid) *(41)* yield *(42a,b)*; it is the quinone-methide form *(42b)* that occurs in red crystals [10]. The mesomeric anion corresponding to the tautomers *(42a,b)* is intensely

[24] *H. Brockmann* and *H. Lackner*, Naturwissenschaften *47*, 230 (1960); *48*, 555 (1961); cf. Angew. Chem. *72*, 533, 939 (1960).

[25] *H. Brockmann*, Progr. Chem. org. nat. Prod. *18*, 1 (1960).

[26] *A. Butenandt*, *U. Schiedt*, and *E. Biekert*, Liebigs Ann. Chem. *588*, 106 (1964), where earlier literature on the dehydrogenation of *o*-aminophenols is cited.

[27] *A. Butenandt*, *U. Schiedt*, *E. Biekert*, and *R. J. T. Cromartie*, Liebigs Ann. Chem. *590*, 75 (1954).

[28] *H. Brockmann* and *H. Muxfeldt*, Chem. Ber. *91*, 1242 (1958).

[28a] *A. Butenandt* and *W. Schäfer* in [52].

[29] *J. Gripenberg*, Acta chem. scand. *12*, 603 (1958).

[30] *A. Butenandt*, *J. Keck*, and *G. Neubert*, Liebigs Ann. Chem. *602*, 61 (1957).

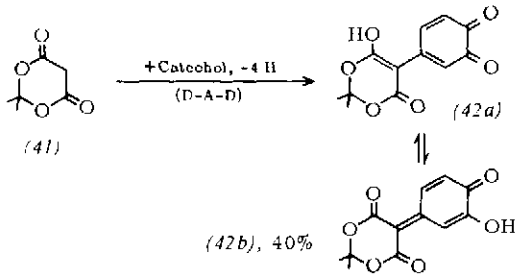
[31] Cf. *C. Schroeder*, *S. Preis*, and *K. P. Link*, Tetrahedron Letters *1960*, No. 13, 23, where further references are given.

[32] *J. D. Bu'Lock* and *J. Harley-Mason*, J. chem. Soc. (London) *1951*, 703.

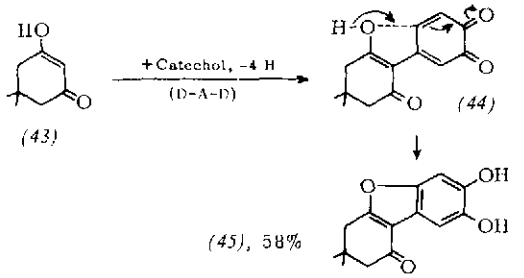
[33] *O. Th. Schmidt* and *K. Bernauer*, Liebigs Ann. Chem. *588*, 211 (1954); *K. Bernauer* and *O. Th. Schmidt*, ibid. *591*, 153 (1955).

[34] *H.-W. Wanzlick*, Chem. Ber. *92*, 3006 (1959).

blue, and aqueous solutions of the alkaline salts are stable for some time.



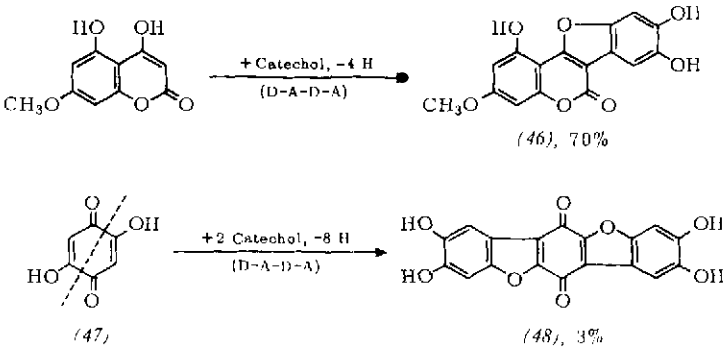

If *(41)* is replaced by dimedone *(43)*, the corresponding product *(44)* cannot be isolated (but can be observed for a short time in solution, see below). A subsequent spontaneous intramolecular addition leads to the formation of the cumarone derivative *(45)* [35,36].




*Procedure:*

A solution of 3 g of potassium hexacyanoferrate(III) in 30 ml of water is added in two portions to a solution of 1 g of catechol, 2 g of dimedone, and 12 g of sodium bicarbonate in 150 ml of water. The resulting blue color is visible for a few seconds. The cumarone derivative *(45)*, m.p. ca. 280 °C (decomp.), precipitates out immediately.

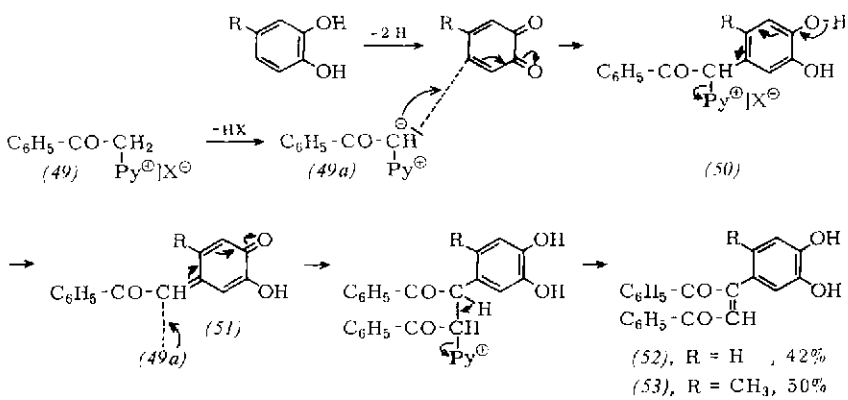
This new synthesis of 5,6-dihydroxycumarone derivatives of type *(45)* is very adaptable. Thus, wedelolactone *(46)* [35], which was isolated and whose structure was elucidated by *Govindachari* et al. [37], and thelephoric acid *(48)* [5], the constitution of which was first recognized and which was synthetized by a classical method by *Gripenberg* [38], can be prepared without appreciable difficulty.




The 2,5-dihydroxy-*p*-benzoquinone *(47)* used in the synthesis of thelephoric acid functions as a double 1,3-dicarbonyl system in the sense indicated.

The strong tendency of pyridinium salts of type *(49)* to undergo addition and condensation reactions is known from the comprehensive investigations of *Kröhnke* et al. [39]. Additions onto quinones introduced as such gave remarkable results [40]. It was therefore natural to attempt similar syntheses with nascent quinones.

If catechol is dehydrogenated in the presence of *(49)*, the product is the dibenzoylethylene derivative *(52)*. The reason for this surprising result is as follows: addition of *(49)* or *(49a)* onto *o*-quinone formed *in situ* initially yields *(50)*. This readily splits off pyridine and so, as a potential quinone methide *(51)*, can add on another molecule of *(49a)* as shown. Further elimination of pyridine finally leads to *(52)*.




*Procedure:*

A solution of 3.29 g of potassium hexacyanoferrate(III) in 100 ml of water is added to a solution of 0.62 g of 4-methylcatechol, 2,78 g of phenacylpyridinium bromide, and 10 g of

[35] *H.-W. Wanzlick, R. Gritzky*, and *H. Heidepriem*, Chem. Ber. *96*, 305 (1963).

[36] *B. Eistert* and *F. Geiss* [Tetrahedron *7*, 1 (1959)], have shown that Meldrum's acid *(41)* and dimedone *(43)* exhibit differences in their tendencies towards enolization: only *(43)* enolizes. The difference between the reactions mentioned above is therefore understandable.

[37] *T. R. Govindachari, K. Nagarajan, B. R. Pai*, and *P. C. Parthasarathy*, J. chem. Soc. (London) *1956*, 629; *1957*, 545, 548.

[38] *J. Gripenberg*, Tetrahedron *10*, 135 (1960).

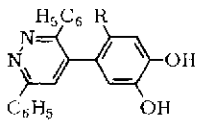
[39] *F. Kröhnke*, Angew. Chem. *75*, 181 (1963), where references to earlier reviews are given; Angew. Chem. internat. Edit. *2*, 225 (1963).

[40] *F. Kröhnke* and *H. Schmeiß*, Ber. dtsch. chem. Ges. *70*, 1728 (1937); *K. Pfleghar*, Ph. D. Thesis, Universität Gießen, 1962; cf. *F. Kröhnke* and *W. Zecher*, Angew. Chem. *74*, 811 (1962); Angew. Chem. internat. Edit. *1*, 626 (1962).

[41] *B. Pankow*, Ph. D. Thesis, Technische Universität Berlin, 1964.

crystalline sodium acetate in 200 ml of water and 100 ml of acetone. After 12 hours, the reaction mixture is extracted with ether and worked up in the usual manner. Yield: about 50 % of *(53)*, m.p. 175 °C.

By altering the experimental conditions, it is possible to isolate the salt *(50)*, R = $CH_3$, initially formed. Further reaction of this with *(49)* in acetate-buffered solution leads smoothly to *(53)*, confirming the reaction sequence formulated above. Compounds *(52)* and *(53)* react readily with hydrazine to form pyridazines *(54)*. The fact that *(50)* can be isolated opens up a route to further syntheses, which will be reported elsewhere [41].



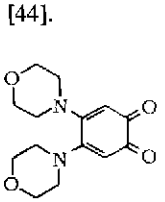
*(54)*, R = H or $CH_3$

Other reactions proceeding with the formation of a C–C linkage will be discussed in the next Section. The dimerization of *o*-quinones [42] and the formation of purpurogallin [3,4] (cf. also [43]) can only be referred to.

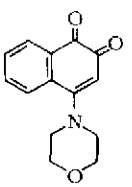
Hydroquinones can be used as starting materials in syntheses with nascent quinones. However, in special cases it is also possible to produce the hydroquinones *in situ*, *e.g.* by hydroxylation of phenols.

## 5. Special Cases

Model investigations on the oxidation of tyrosinase led *Brackman* and *Havinga* to remarkable and preparatively valuable results [44]. The Cu(II)-catalysed autoxidation of phenols in the presence of secondary amines proceeds smoothly to yield aminoquinones. Phenol itself condenses with morpholine to give *(55)*, and the corresponding reaction with β-naphthol yields *(56)*. Many other examples are quoted in the original publications [44].



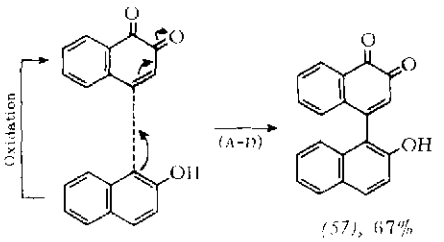
*(55)*, 64%



*(56)*, 84%

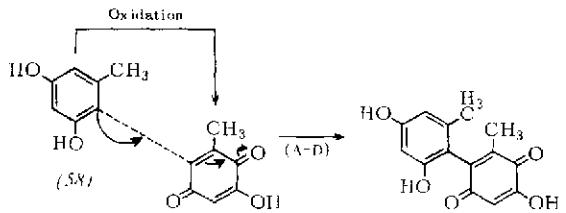
The course of these reactions is clear: *o*-hydroxylation of the phenols, dehydrogenation of the resulting catechol derivatives to *o*-quinones, and single or double addition of amines onto the latter (cf. Section 2c).

The oxidation of β-naphthol with $H_2O_2$ catalysed by molybdate, leads to the formation of *(57)* [45]. This product results from the addition of the naphthol onto the β-naphthoquinone initially formed.




*(57)*, 67%

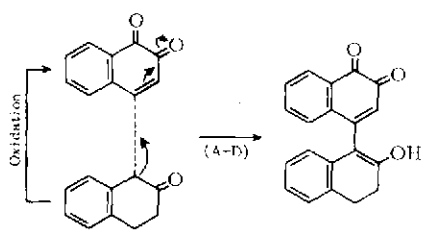
In the autoxidation of resorcinols, which was studied in detail by *Musso* et al. in the course of work on orcein and litmus dyestuffs [46], biphenyl derivatives are formed, partly by Michael addition of the resorcinols onto quinones which are formed as intermediates. An example of this is the formation via *(59)* of *(60)* in the oxidation of orcinol *(58)* [47,48]. The process largely corresponds to the oxidation of β-naphthol to *(57)*.




*(58)* *(59)* *(60)*

These processes are closely related to the reactions which lead to the characteristic "blue color of β-tetralone" [49]. It was shown [50], that autoxidation of β-tetralone *(61)* in alkaline solution yields the dyestuff *(62)* as red crystals; the mesomeric anion is deep indigo blue; cf. *(42)* and *(44)*.

The reaction mechanism was proved by the addition of labeled and normal β-naphthoquinones, and the constitution of the dyestuff *(62)* was determined by dehydrogenation to *(57)*.




*(61)* *(62)*

## 6. Biochemical Examples

Nowadays, many biosyntheses are known to pass through quinoid intermediates. The present knowledge of the formation of melanin and humic acid was recently reviewed by

[42] Cf. *L. Horner* and *W. Dürckheimer*, Chem. Ber. *95*, 1219 (1962), where references to earlier literature are given.

[43] *H. Musso*, Angew. Chem. *75*, 965 (1963); Angew. Chem. internat. Edit. *2*, 723 (1963).

[44] *W. Brackman* and *E. Havinga*, Recueil Trav. chim. Pays-Bas *74*, 937, 1021, 1070, 1100, 1107 (1955).

[45] *I. D. Raacke-Fels*, *C. H. Wang*, *R. K. Robins*, and *B. E. Christensen*, J. org. Chemistry *15*, 627 (1950); *A. R. Bader*, J. Amer. chem. Soc. *73*, 3731 (1951).

[46] *H. Musso* et al., Angew. Chem. *73*, 665 (1961).

[47] *U. v. Gizycki*, Ph. D. Thesis, Universität Marburg 1963.

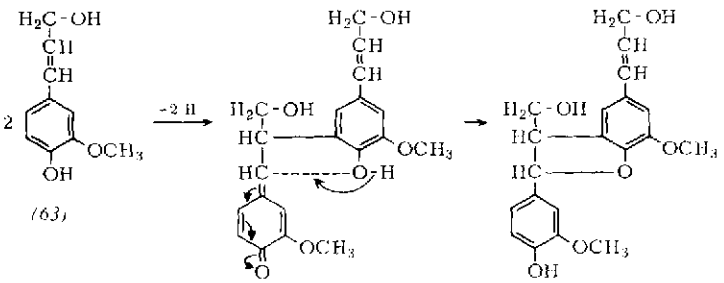
[48] *H. Musso*, Angew. Chem. *75*, 965 (1963); Angew. Chem. internat. Edit. *2*, 723 (1963).

[49] *F. Straus* and *A. Rohrbacher*, Ber. dtsch. chem. Ges. *54*, 46 (1921).

[50] *H.-W. Wanzlick*, *M. Lehmann-Horchler*, and *S. Mohrmann*, Chem. Ber. *90*, 2521 (1957).

*Thomson* [51]. The function of nascent quinones in the pupation of insects (sclerotization), which is compared with tanning by quinones (cf. [53]), is also dealt with in this article. Other examples, with references, may be found in reviews by *Musso* [48] and *van Tamelen* [54]. The biological significance of the phenoxazone syntheses discussed in Section 3 and the model experiments on the formation of melanins (Section 4) have already been referred to [32].

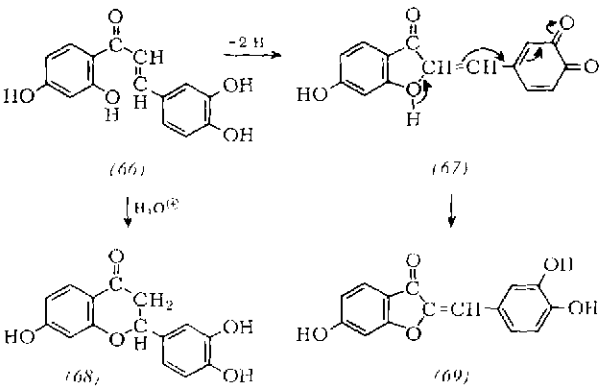
The investigations of *Freudenberg* et al. on the biosynthesis of lignin have brought to light the importance of quinone methide structures which occur there as intermediates [55]. One example of this is the condensation of two coniferyl alcohol units *(63)* with the elimination of hydrogen to form *inter alia* dehydrodiconiferyl alcohol *(65)*, a reaction which can also be carried out *in vitro* [56]. One-electron oxidation of the phenol group in *(63)* and dimerization of the mesomeric free radical produced yields the quinone methide *(64)* which is then converted into *(65)* by intramolecular addition.



*(63)* *(64)* *(65)*

The formation of lignin also involves intermolecular additions onto quinone methides, in which water, acids, phenols, alcohols, and carbohydrates participate competitively as nucleophilic reagents [55].

In the formation of aurones from chalcones, which is exemplified here by the conversion of butein *(66)* into sulfuretin *(69)* [57], intervention of *o*-quinonoid intermediates is indicated by two findings: 1. all the naturally occurring aurones known to date [58] (including bractein [59], which has only recently been isolated) contain a catechyl group; 2. The formation of aurones, which proceeds extremely easily even *in vitro*, is blocked by even partial methylation in the catechol residue, as was shown by *Geissman* et al. [57]

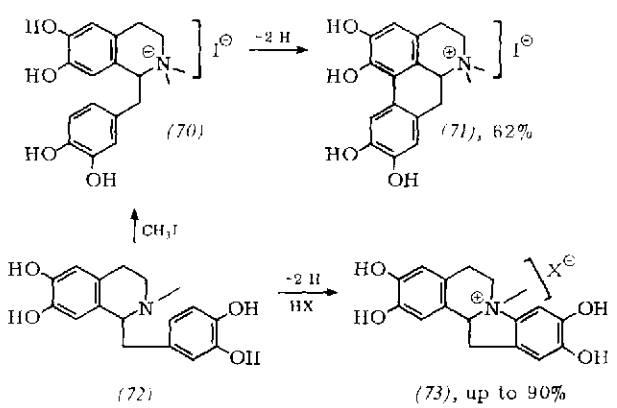


*(66)* *(67)* *(68)* *(69)*

The strong tendency of quinonoid systems to undergo additions is shown by the fact that the reaction *(66)* -> *(69)* proceeds readily *in vitro* and requires no catalyst, whilst the conversion of butein *(66)* into the flavanone butin *(68)* requires the usual treatment with hot mineral acid [60]. The polarization of the double bond initially present in the chalcone is not only reversed in the reaction leading to *(67)* but is also considerably intensified.

## 7. Concluding Remarks

The reactions discussed here offer rewarding exercises to the theoretical chemist. Even the addition mechanism, which is generally accepted nowadays, and which has been used in the present article, does not appear to have yet been rigorously proved. It is also reasonable to ask whether all the reactions discussed here pass through the quinone stage after all, since it is known that a semiquinone (which is often detectable [61]) may be formed initially in the dehydrogenation of a hydroquinone. The work of *Franck* et al. on biogenetic-type syntheses of alkaloids [62] may be mentioned at this point. The dehydrogenation of



*(70)* *(71)*, 62% *(72)* *(73)*, up to 90%

[51] *R. H. Thomson* in [52].

[52] Recent Progress in the Chemistry of Natural and Synthetic Colouring Matters. Academic Press, New York 1962.

[53] Cf. *P. Karlson*, Angew. Chem. *75*, 261 (1963); Angew. Chem. internat. Edit. *2*, 175 (1963).

[54] *E. E. van Tamelen*, Progr. Chem. org. nat. Prod. *19*, 242 (1961), particularly p. 281 et seq.

[55] *K. Freudenberg*, Progr. Chem. org. nat. Prod. *20*, 41 (1962), where further references are given.

[56] *K. Freudenberg* and *H. H. Hübner*, Chem. Ber. *85*, 1181 (1952); see also *K. Freudenberg*, *G. Grion*, and *J. M. Harkin*, Angew. Chem. *70*, 743 (1958).

[57] *M. Shimokoriyama* and *T. A. Geissman*, J. org. Chemistry *25*, 1956 (1960).

[58] *W. Karrer:* Konstitution und Vorkommen der organischen Pflanzenstoffe. Birkhäuser, Basel 1958; *T. A. Geissman:* The Chemistry of Flavonoid Compounds. Pergamon Press, London 1962.

[59] *R. Hänsel*, *L. Langhammer*, and *A. G. Albrecht*, Tetrahedron Letters *1962*, 599.

[60] *A. Göschke* and *J. Tambor*, Ber. dtsch. chem. Ges. *45*, 186 (1912).

[61] Cf. *H. Diebler*, *M. Eigen*, and *P. Matthies*, Z. Elektrochem. *65*, 634 (1961), where further references are given.

[62] *B. Franck*, *G. Blaschke*, and *G. Schlingloff*, Angew. Chem. *75*, 957 (1963), where further references are given; Angew. Chem. internat. Edit. *3*, 192 (1964).

laudanosoline methiodide *(70)*, for example, which leads smoothly to aporphine *(71)* [63] may be justifiably assumed [64] to be a free-radical reaction.

On the other hand, the dehydrogenation of laudanosoline *(72)*, in which the nitrogen is not quaternized, proceeds smoothly with the formation of the dibenzotetrahydropyrrocoline derivative *(73)*, whose trimethyl ether occurs in nature as cryptaustoline [65]; it is certainly justified to include this reaction among the quinone additions [66, 67].

*We are sincerely grateful to all those who have helped us in word and in deed, with encouragement and criticism, and to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and to Schering A.G.*

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German version: Angew. Chem. *76*, 313 (1964)
Translated by Express Translation Service, London

[63] *B. Franck*, *G. Blaschke*, and *G. Schlingloff*, Tetrahedron Letters *1962*, 439.

[64] *B. Franck* and *G. Schlingloff*, Liebigs Ann. Chem. *659*, 123 (1962).

[65] *J. Ewing*, *G. K. Hughes*, *E. Ritchie*, and *W. C. Taylor*, Nature (London) *169*, 618 (1952); Austral. J. Chem. *6*, 78 (1953).

[66] *R. Robinson* and *S. Sugasawa*, J. chem. Soc. (London) *1932*, 789.

[67] *C. Schöpf* and *K. Thierfelder*, Liebigs Ann. Chem. *497*, 22 (1932).

# New Reactive Dyes

BY DR. K. G. KLEB

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DER FARBENFABRIKEN BAYER AG. LEVERKUSEN (GERMANY)

AND DR. E. SIEGEL AND DR. K. SASSE

WISSENSCHAFTLICHES HAUPTLABORATORIUM
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*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

*Two new groups of reactive dyestuffs have been developed. One group (Levafix® dyes) comprises compounds which contain $-SO_2NH-CH_2-CH_2-OSO_3H$ or $-CH_2-N(alkyl)-CH_2-CH_2-OSO_3H$ as reactive groups. The dyes of this group react with cellulose fibers to form cellulose ethers, e.g. $R-SO_2NH-CH_2-CH_2-O$-cellulose. The substances in the second group (Levafix-E® dyes) consist of the amides formed from 2,3-dichloroquinoxaline-6-carboxylic acid and dyestuffs containing primary or secondary amino groups.*

## Introduction

The development of new reactive dyes requires solutions to problems which fall essentially into two categories:

1. The discovery of reactive systems which are suitable for incorporation into dyestuffs and which react efficiently with the substrate to be dyed under the conditions of textile dyeworks.

2. The combination of the reactive systems with dyestuffs, either already known or new, to give reactive dyes of high fastness.

The first problem is the more difficult one, since the reactive group both prescribes the type of dyestuff and largely determines the properties and scope of application of the dyes obtained with it.

Our work has led to two groups of dyestuffs:

(a) the Levafix dyes containing the reactive group

$-SO_2-NH-CH_2-CH_2-OSO_3H$ or $-CH_2-\underset{R}{N}-CH_2-CH_2-OSO_3H$,

and

(b) the Levafix-E dyes containing 2,3-dichloroquinoxaline-6-carboxylic acid bound as its amide as the reactive group.

### 1. Reactive Dyes with Sulfatoalkyl Groups Activated by Neighboring Groups [*]

In 1940, *H. Schweitzer* and *O. Bayer* described dyes containing *N*-(β- or γ-chloroalkyl)sulfonamido groups which imparted colors to wool [1] more wash-fast than comparable deyings. The action of alkalies on *N*-(β-chloroalkyl)sulfonamides *(1)* readily produces *N,N*-ethylenesulfonamides *(2)* [2], which react with primary or secondary amines – probably also with the amino groups in wool – to effect alkylation to form *(3)* [3].

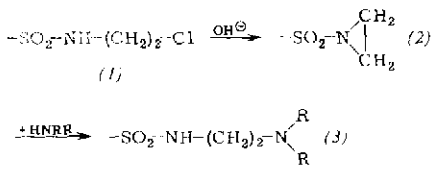
[*] Based on work by *K. G. Kleb*.

[1] *H. Schweitzer* and *O. Bayer*, German Patent 743766 (April 19th, 1940); cf. *O. Bayer*, Angew. Chem. *73*, 343 (1961).

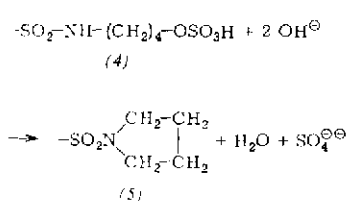
[2] *J. Nelles* and *E. Tietze*, German Patent 698597 (Feb. 8th, 1939).

[3] *J. Nelles*, *E. Tietze*, and *O. Bayer*, German Patent 695331 (April 29th, 1939).

*N*-Alkylsulfonamides with sulfato groups *(4)* in the δ- or ε-position were used in order to make the dyes originally water-soluble and then to attach them to the



textile substrate in an insoluble form produced by the action of alkalies and heat during the dyeing; the reaction leads to sulfonylpyrrolidines *(5)* or sulfonylpiperidines, respectively, by intramolecular alkylation [4].

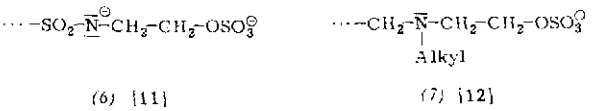


Recently several research groups studied the applicability of sulfatoalkyl groups to dyes which could react with cellulose by alkylation. As a result it was found that the reactivity of the sulfatoalkyl groups was enhanced by the introduction of the hetero-atoms O, S, or N in the γ- or even better in the β-position to the sulfato group. By themselves, alkyl hydrogen sulfates can be used as alkylating agents only under drastic conditions.

The effectiveness of the hetero-atoms and of their derivatives varies widely. Aryloxy groups [5] have only a weak action, but with hydroxyl [6], alkylthio [7], and dialkylamino groups [7,8], and with sulfonamide anions [9] as "activators", it is possible to raise the reactivity of the sulfatoalkyl group to the level required for practical application as a reactive group in textile dyeing. Carboxamide groups in the β-position are not suitable as "activators", since they react to form oxazoline derivatives by intramolecular alkylation [10].

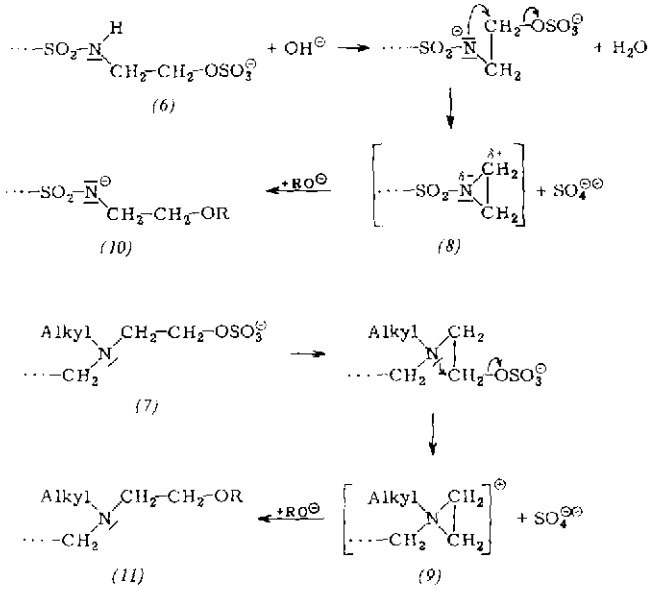
### a) Reaction Mechanism

Sulfonamide anions *(6)* or aliphatically bonded tertiary amino groups *(7)* serve to activate the sulfatoalkyl groups in the Levafix dyes.



*(6)* [11] *(7)* [12]

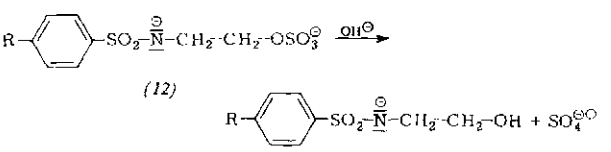
Their action can be explained by a neighboring-group effect [13]. Both groups contain a strongly nucleophilic nitrogen atom. The nitrogen atom participates in the reaction by means of an initial nucleophilic attack on the α-carbon atom, with displacement of the sulfato group, to form the reactive, cyclic intermediates *(8)* or *(9)*. In the second step, these react with external nucleophilic partners to give the stable products *(10)* and *(11)*, respectively.



The reaction sequence indicated may be considered as certain for compounds of type *(7)* by analogy with numerous other mechanisms [14].

A proof for the mode of reaction of *(6)* by direct detection of the *N,N*-ethylenesulfonamide *(8)* has not yet been achieved. Confirmation was therefore sought in other ways:

α) The reaction *(12)* → *(13)* is slowed down by electron-attracting substituents R and accelerated by electron-donating substituents. Thus, the reaction rate (Fig. 1)



*(12)* *(13)*

varies in the same direction and to about the same extent as the pK-value (Table 1) for the dissociation of the sulfonamido group [15].

Since the kinetic measurements were undertaken in 0.1 N NaOH, in which the sulfonamido group is fully

[4] *F. Nadler, E. Tietze,* and *O. Bayer,* German Patent Application J-65961, (Nov. 15th, 1939); French Patent 976047 (March 26th, 1942).

[5] *J. D. Guthrie,* U.S.-Patent 2741532 (Apr. 30th, 1952).

[6] Belgian Patent 596945 (Nov. 10th, 1960, German Priority Nov. 14th, 1959), BASF; Belgian Patent 585006 (Nov. 25th, 1959, Germany Priority Dec. 9th, 1958), BASF.

[7] Belgian Patent 573466 (Dec. 1st, 1958, German Priority Jan. 28th, 1958), Bayer.

[8] German Patent 1108176 (May 7th, 1957), BASF; German Patent 1061009 (March 15th, 1957), BASF.

[9] Belgian Patent 560033 (Aug. 13th, 1957), Swiss Priority Aug. 14th, 1956), CIBA; German Patent 1091259 (Dec. 14th, 1957, British Priority Dec. 14th, 1956), ICI; Belgian Patent 565997 (March 24th, 1958, Swiss. Priority March 25th, 1957), CIBA; Belgian Patent 569439 (July 15th, 1958, German Priority July 15th, 1957), Bayer.

[10] *P. Rehländer,* Ber. dtsch. chem. Ges. *27,* 2157 (1894).

[11] *K. G. Kleb,* Belgian Patent 569439 (July 15th, 1958).

[12] *K. Wedemeyer, D. Delfs,* and *W. Kruckenberg,* Belgian Patent 573466 (Dec. 1st, 1958).

[13] *S. Winstein* and *E. Grunwald,* J. Amer. chem. Soc. *70,* 828 (1948); cf. *W. Lwowsky,* Angew. Chem. *70,* 483 (1958).

[14] *J. Hine:* Physical Organic Chemistry. McGraw-Hill, New York 1956, pp. 123–124.

[15] Investigations by *E. Grigat.*

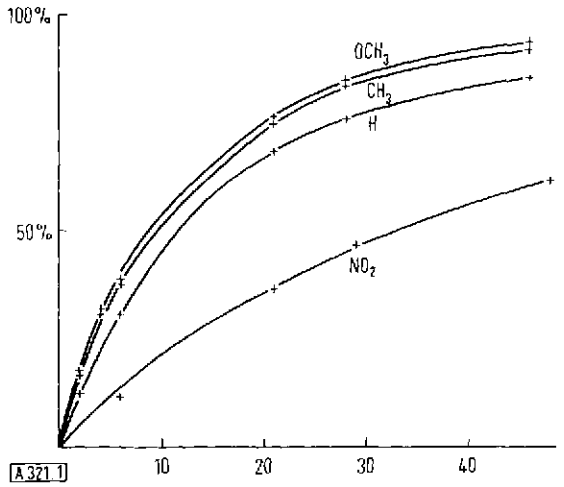
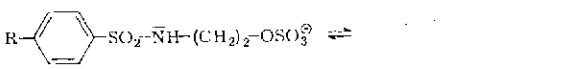



Fig. 1. Rate of the hydrolysis *(12)* → *(13)* in 0.1 N NaOH at 50 °C in relation to the substituent R.
Ordinate: conversion [%]
Abscissa: time [hours]

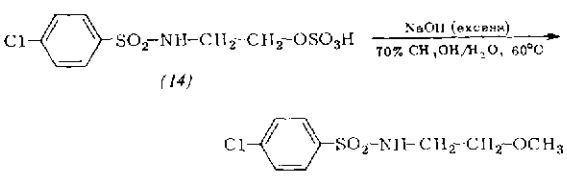
dissociated, the results can only be satisfactorily explained by the hypothesis of a neighboring-group effect. If the basicity and nucleophilicity of the sulfonamide nitrogen atom are assumed to be comparable, then the reactivity of the group *(12)* must be higher, the more basic the nitrogen atom of the sulfonamide group is or, in other words, the greater its pK value is. Thus, although electron-release by the substituent R inhibits dissociation of the sulfonamido group, it assists the hydrolysis – complete dissociation being assumed – by raising the electron density at the nitrogen atom.

Table 1. pK-Values for the dissociation



| R | pK |
|---|---|
| $NO_2$ | 9.85 |
| H | 10 55 |
| $CH_3$ | 11.0 |
| $OCH_3$ | 11.05 |

β) At 60 °C in the presence of excess sodium hydroxide, *N*-(β'-sulfatoethyl)-4-chlorobenzenesulfonamide *(14)* reacts in 70 % aqueous methanol by a first order process (half-life: 373 min) to give *N*-(β-methoxyethyl)-4-chlorobenzenesulfonamide *(15)*.

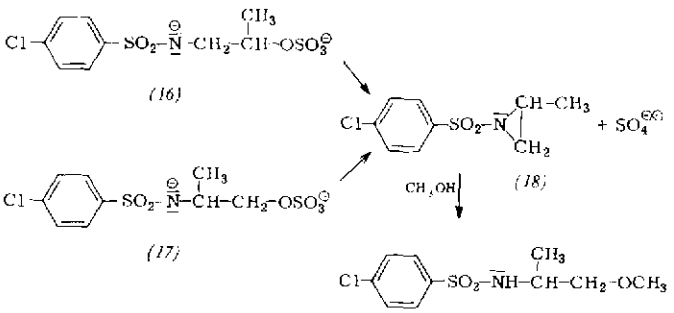



*(14)*

*(15)*, m. p. 61–62°C

If this reaction proceeds according to a normal $S_N2$ mechanism, then under equivalent conditions, the formation of two isomeric *N*-methoxypropylamides would be expected from the two isomeric *N*-sulfatopropyl-4-chlorobenzenesulfonamides *(16)* and *(17)*, with constitutions corresponding to those of the starting materials. In fact, however, *(16)* and *(17)* react to give a single *N*-methoxypropylamide, which from its nuclear magnetic resonance and infrared spectra possesses the constitution of *N*-(methoxyprop-2-yl)-*p*-chlorobenzenesulfonamide *(19)* [16].

In agreement with the data of *Winstein* and *Grunwald* [17] concerning the influence of a β-methyl group upon reactions activated by neighboring groups, *(17)* reacts about 20 times faster (half-life: 18.5 min) than *(14)*. On the other hand, the reaction of *(16)* (half-life: 138 min) proceeds more slowly than expected [17a], probably because of steric effects caused by the sulfonamide anion.




*(16)*

*(17)*

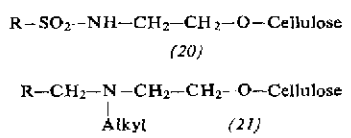
*(18)*

*(19)*, m. p. 68–69°C

These findings lead to the conclusion that a common intermediate *(18)* is formed in the first, rate-determining step of the reaction of both the isomeric *N*-(β-sulfatopropyl)sulfonamides *(16)* and *(17)*. After attack by an external nucleophilic reagent upon the carbon atom of the $CH_2$ group which is the more positive of the two ring-carbon atoms owing to the influence of the methyl group, the faster subsequent reaction leads to the end-product *(19)*.

### b) Reactions during the Dyeing Process

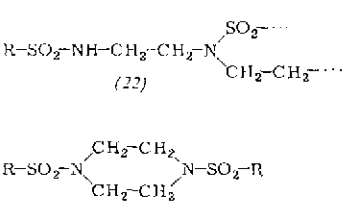
Sulfatoalkyl groups activated by neighboring groups can react with several nucleophiles during the dyeing process. The preferred reaction occurs with the hydroxyl groups of cellulose (or their anions); as a result, the β-substituted ethyl ethers of cellulose *(20)* and *(21)* are formed.



*(20)*

*(21)*

The accompanying alkylation reactions of the reactive groups with each other can lead to the formation of the products *(22)* and *(23)* from compounds of type *(6)*.

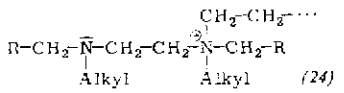


*(22)*

*(23)*

[16] Measurement and discussion of the spectra by *H. Walz*.
[17] *S. Winstein* and *E. Grunwald*, J. Amer. chem. Soc. *70*, 830 (1948).
[17a] *S. Winstein* and *E. Grunwald*, J. Amer. chem. Soc. *70*, 832–833 (1948).

Quaternary ammonium compounds *(24)* may be formed from compounds of type *(7)*.



*(24)*

These reactions are desired, when they cause dyestuff molecules to become indirectly bound firmly to the fiber, *i.e.* by interspersion of other dyestuff molecules as bridges.

The alcohols *(25)* and *(26)* may appear as a result of hydrolysis owing to the presence of water and hydroxide ions during the dyeing process.



*(25)* *(26)*

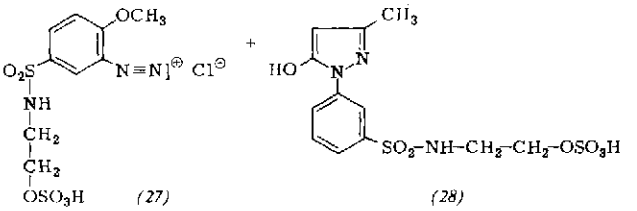
### c) Constitution of the Dyes

The Levafix dyes are combinations of a chromophoric molecule with two or more reactive groups of formulae *(6)* and *(7)*. Representatives of the azo, anthraquinone, vat, or phthalocyanine series, for example, serve as the fundamental dyeing substances. Reactive groups of type *(6)* are bound to the dye-substance either directly through the sulfonamido group or by a bridge, *e.g.* a benzene ring. Reactive groups of type *(7)* are preferably combined with large dyestuff molecules, such as those found among the vat dyes, which have hydrophilic groups (*e.g.* sulfonamido groups) attached to improve their solubility.

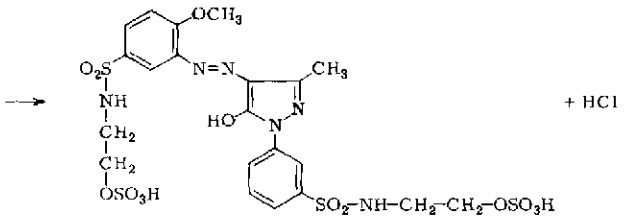
The substantivity of most dyes is reduced by replacing nuclearly bound sulfonic acid groups with reactive groups of type *(6)* or with sulfonamide links. This is especially true when all the sulfonic acid groups of this type have been replaced. This effect is applied to make dyes with very low substantivity. Starting from chromogens with low affinity for the fiber, only reactive groups are used as solubility-conferring constituents of the dyes, with the exclusion of additional ionizing groups, such as nuclearly bound sulfo or carboxyl groups. In the Levafix dyes, the reactive sulfatoalkyl groups must therefore fulfil the additional function of conferring solubility in water. In general, the solubility required for application is attained with two reactive groups per dyestuff molecule; more than two groups are necessary for large dyestuff molecules or for those which associate readily.

### d) Synthesis of the Dyes

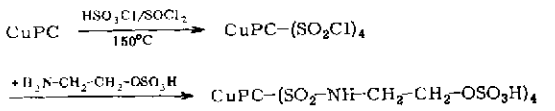
The reactive group *(6)* is prepared from 2-aminoethanol (ethanolamine) by reaction of the amino group with a sulfonyl chloride and by esterification of the hydroxyl group with sulfuric acid, in whichever sequence is desired. The sulfonyl chlorides of dyestuff intermediates or of ready-made dye-substances can be used as starting material. In the first case, intermediates with reactive groups are obtained, *e.g. (27)* and *(28)*, which can then be transformed into dyes, *e.g.* by coupling.



*(27)* *(28)*

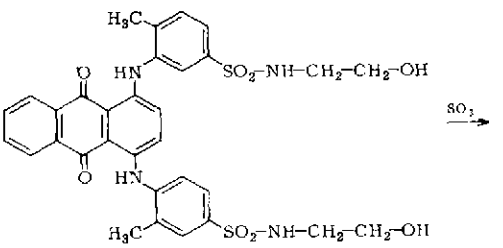


In the second case, the finished dye is prepared directly by reaction with 2-aminoethyl hydrogen sulfate.

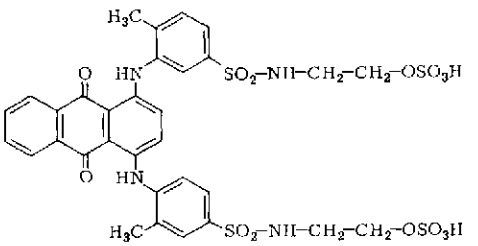


CuPC = copper phthalocyanine

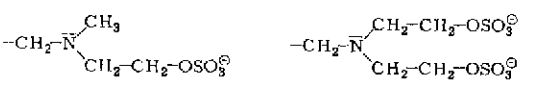
In the case of a dyestuff which must be prepared under conditions which decompose the reactive group, it is advisable to prepare the dyestuff with $-SO_2-NH-CH_2-CH_2-OH$ groups *(29)* first and then to convert this into the reactive group by sulfatation, *e.g.* with concentrated sulfuric acid or pyridine/$SO_3$.



*(29)*



Dyestuffs with the reactive group *(7)* are prepared according to similar methods, starting from amino alcohols with functional groups which allow combination with the chromogens. Here the number of variations is greater, since the bridging group to the dyestuff can be altered at will, and since the alkyl group attached to the activating nitrogen atom can differ. The systems *(7a)* and *(7b)* have probved to be useful.



*(7a)* *(7b)*

### e) Application

As a result of their low substantivity [*], the Levafix dyes are suitable only for dyeing processes in which substantivity is unnecessary or even undesirable. They are therefore used in calico printing and in pad dyeing of native or regenerated cellulose, where they are applied from concentrated solutions or printing pastes containing alkali (*e.g.* soda, potash, or caustic soda) and an auxiliary (*e.g.* urea). The yields of fixed dyestuff are very high (90 % or more) when the dyeing is carried out at 100–120 °C in steam boilers or at 130–150 °C by dry-heat treatment, provided several reactive groups and no additional groups conferring solubility in water are present in the dyestuff molecule. Heavy contamination does not occur in the baths used to elute the alkali, auxiliaries, and unreacted dye from the fiber in the washing process which follows that of dyeing. Since it possesses no or only low substantivity, unreacted dye does not run onto unprinted portions of the fabric or onto portions colored by other dyes.

The Levafix dyes can be combined not only with one another, but also with dyes of other classes, *e.g.* Naphthol-AS combinations, vat dyes, sulfuric esters of leuco vat dyes, pigment dyes, and aniline black. Emphasis is laid upon the good wash-fastness of the colors on printed or dyed fabrics, which is due to the stable dye-fiber bonds.

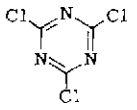
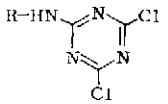
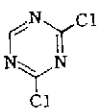
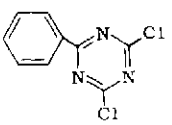
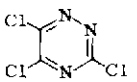
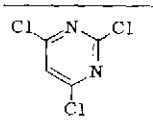
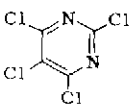
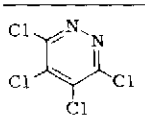
## 2. Reactive Dyes with 2,3-Dichloroquinoxaline as Reactive Group [**]

Levafix dyes with an aliphatic reactive group are little suited for application from dilute dye liquors, or for the cold pad-batch process which is continually gaining in importance [18]. In order to be useful for dyeing, a reactive dye must not display too great substantivity but must have a reactivity towards cellulose which is as high as possible; in addition, the reactive group should be able to align itself sterically on the surface of the cellulose in such a way as to favor nucleophilic substitution by a hydroxyl group of the cellulose.

These requirements are fulfilled by quasi-aromatic heterocyclic nitrogen compounds with mobile chlorine atoms of the kind existing in cyanuryl chloride or tetrachloropyrimidine. As a result of the formation of hydrogen bonds between the hydroxyl groups of the cellulose and the heterocyclic nitrogen atoms, which have a high electron density, the chlorine atoms become aligned on the cellulose surface in a sterically favorable way. Moreover they possess very good reactivity at the optimum dyeing temperatures.

In the search for new reactive dyes, the greatest outcome was therefore promised by examination of heterocyclic nitrogen compounds with mobile chlorine atoms. Hitherto, it is almost exclusively chlorotriazines and chlorodiazines that have been described; these are the reactive groups that are closest to cyanuryl chloride (Table 2). The most mobile chlorine atom of these compounds is caused to react with the amino group of a dyestuff molecule; the remaining halogen atoms are available for reaction with the fiber [18–20].

Table 2. Heterocyclic nitrogen compounds with mobile chlorine atoms used as reactive groups in reactive dyes.

| Reactive group | Trade name of the dye | Reference |
|---|---|---|
|  | Procion® (ICI) | [21] |
|  | Cibacron® (Ciba)<br>Procion-H® (ICI) | [22] |
|  | | [23] |
|  | | [24] |
|  | | [25] |
|  | | [26] |
|  | Reacton® (Geigy)<br>Drimaren® (Sandoz) | [27]<br>[28] |
|  | | [29] |

[*] The percentage of the total dyestuff which is attached to the cellulose in equilibrium at pH 7 is used as a measure of substantivity.

[**] Based on work by *E. Siegel* and *K. Sasse*.


[18] *H. Zollinger*, Angew. Chem. *73*, 125 (1961).

[19] *J. Wegmann*, Textil-Praxis *1960*, 829.

[20] *H. Ackermann* and *P. Dussy*, Melliand Textilber. *42*, 1167 (1961).

[21] German Published Patent Application 1041461 (Nov. 29th, 1954), ICI; German Published Patent Application 1062367 (Nov. 29th, 1954), ICI.

[22] German Published Patent Application 1076242 (Jan. 27th, 1956), CIBA; Belgian Patent 559944 (Aug. 10th, 1956), CIBA.

[23] Belgian Patent 592148 (June 23rd, 1959), CIBA.

[24] German Published Patent Application 1067404 (Oct. 12th, 1957), BASF.

[25] Belgian Patent 607999 (Sept. 8th, 1960), Sandoz.

[26] German Published Patent Application 1088460 (Sept. 4th, 1956), ICI; French Patent 1194043 (April 5th, 1957), BASF; Belgian Patent 572994 (Nov. 21st, 1957), Sandoz; Belgian Patent 572973 (Nov. 22nd, 1957), Bayer.

[27] German Published Patent Application 1109807 (May 23rd, 1958), Geigy.

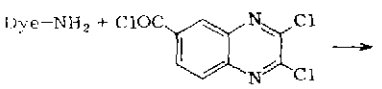
[28] Belgian Patent 573300 (Nov. 29th, 1957), Sandoz; Belgian Patent 578742 (May 28th, 1958), Sandoz.

[29] Belgian Patent 604068 (May 23rd, 1960), CIBA.

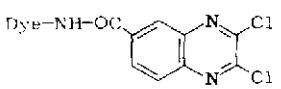
### a) Synthesis of New Reactive Groups

We studied heterocyclic nitrogen compounds possessing fused-rings and mobile chlorine atoms. Hitherto these substances had scarcely been examined. Since it was to be expected that polynuclear fused systems would lead to sparingly soluble dyestuffs of low molecular color strength, we first studied 2,3-dichloroquinoxaline, which had previously been investigated by *Sasse* and *Wegler*[30]. This substance is not suitable on its own as a reactive group, since difficulties are encountered in its selective attachment to a molecule of an amino dyestuff with preservation of one of the mobile chlorine atoms, and since the remaining chlorine atom is too strongly deactivated after introduction of the substituted amino group into the molecule.

On the other hand, we obtained valuable reactive dyestuffs *(31)* when we linked 2,3-dichloroquinoxaline to amino dyestuffs by way of a chlorocarbonyl or chlorosulfonyl group bound to the benzene ring. Since the reactivity of the chlorine atom in the chlorocarbonyl or chlorosulfonyl group is greater than that of the chlorine atoms in the heterocyclic nucleus, selective acylation of primary or secondary amino groups is achieved with preservation of the chlorine atoms in positions 2 and 3.

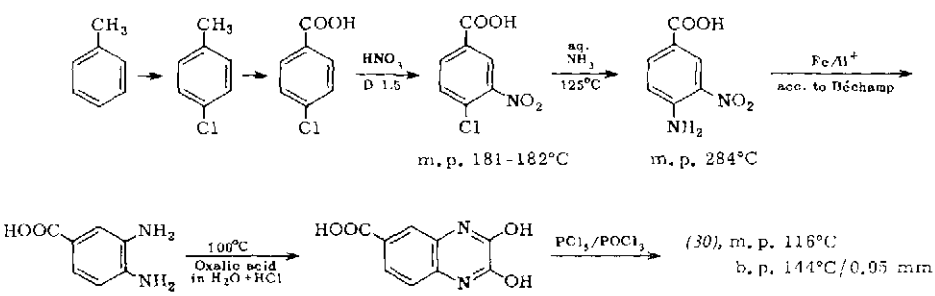


*(30)*



*(31)*

6-Chlorocarbonyl-2,3-dichloroquinoxaline *(30)* is readily accessible technically in the way indicated in Scheme 1.



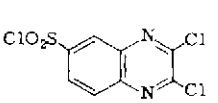
Scheme 1. Synthesis of 6-chlorocarbonyl-2,3-dichloroquinoxaline.

Compound *(30)* can be distilled *in vacuo* [31]. It is colorless and has the typical odor of carbonyl chlorides. The substance is only slowly hydrolysed by water, but reacts smoothly at 40–70 °C with aminoazo or aminoanthraquinone dyes as well as with phthalocyanine dyes or dyestuff precursors containing amino groups in aqueous solution, by acylation of the amino groups with the chlorocarbonyl group.

We then looked for further useful reactive components in other fused bicyclic systems such as 1,4-dichlorophthalazine, 2,4-dichloroquinazoline, 2-chlorobenzoxazole, 2-chlorobenzothiazole, and 2-chlorobenzimidazole as well as in the 2,3-dichloroquinoxaline series.

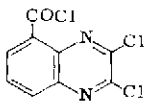
### α) Quinoxaline Derivatives

Among the chloroquinoxaline derivatives *(32)* to *(37)*, 6-chlorocarbonyl-2(3)-monochloroquinoxaline *(34)* affords the best reactive dyestuffs; 6-chlorosulfonyl-2,3-dichloroquinoxaline *(32)* is not quite so well suited for the construction of reactive dyes as the carbonyl chlorides *(30)* and *(34)*, since the substantivity of azo dyes with a sulfonamido group in the molecule is lower than that of azo dyes with a carboxamido group.



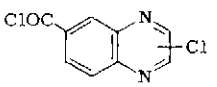
*(32)*

m. p. 86–87 °C



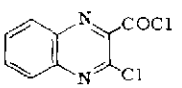
*(33)*

m. p. 113–114 °C



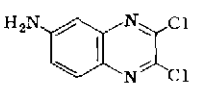
*(34)*

m. p. 113–115 °C
b. p. 138–139 °C/0.28 mm

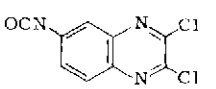


*(35)*

m. p. 122–123 °C



*(36)*



*(37)*

The connection of 2,3-dichloroquinoxaline to the dyestuff through a carboxamido or sulfonamido group has an activating influence on the chlorine atoms in the quinoxaline nucleus. Model experiments showed that this influence of substituents in the 6-position is very marked and that the activating effect increases with increasing electron-attracting character of the substituent (*i.e.* increasingly positive value of its Hammett σ-constant). The influence of substituents in the aniline nucleus of *2,3-dichloroquinoxaline-6-carboxanilide (38)* is less strong, but clearly present, and is opposed to the course of the Hammett constants in an unusual way. The anilide *(38)* can be considered as a model for dyestuffs based on 2,3-dichloroquinoxaline-6-carboxylic acid. It is known from studies of the dichlorotriazine dyes that dyestuffs with the same reactive group often differ in reactivity by a factor of 10 or more (Table 3) [32,33].

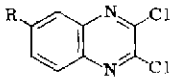
[30] *K. Sasse, R. Wegler, G. Unterstenhöfer,* and *F. Grewe,* Angew. Chem. *72,* 973 (1960).

[31] French Patent 1193734 (Jan. 11th, 1957), Geigy.

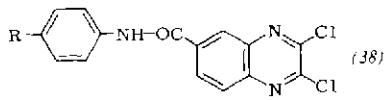
[32] *H. H. Sumner* and *T. Vickerstaff,* Melliand Textilber. *42,* 1161 (1961).

[33] *C. Preston* and *A. S. Fern,* Chimia *15,* 177 (1961).

Table 3. Pseudo-monomolecular reaction rate constants for hydrolysis of the first chlorine atom of 2,3-dichloroquinoxaline derivatives, at 22 °C and pH 13 in aqueous dioxan. Measurements were made with solutions of the heterocyclic chloro compounds ($10^{-3}$ mole) and sodium hydroxide ($2\times10^{-2}$ mole) in 100 ml of dioxan/water (60:40). The chloride ion released was titrated according to the method of *Volhard*.



| R | $k\cdot10^3$ [min$^{-1}$] | R | $k\cdot10^3$ [min$^{-1}$] |
|---|---|---|---|
| $CH_3O-$ | 11.4 | $C_6H_5NH-OC-$ | 390 |
| $C_6H_5CO-HN-$ | 15.2 | Cl— | 2600 |
| H— | 52 | $O_2N-$ | >300000 |
| $CH_3-$ | 285 | | |

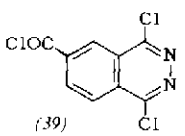


*(38)*

| R | $k\cdot10^3$ [min$^{-1}$] | R | $k\cdot10^3$ [min$^{-1}$] |
|---|---|---|---|
| $O_2N-$ | 172 | H— | 390 |
| Cl— | 250 | $CH_3O-$ | 460 |
| $CH_3-$ | 345 | | |

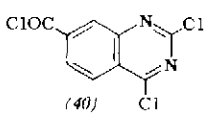
### γ) Phthalazine and Quinazoline Derivatives

Introduction of a chlorocarbonyl group into the 6-position of 1,4-dichlorophthalazine also transforms this substance, which otherwise reacts slower ($k_{OH^-}$ = 0.012 min$^{-1}$) than 2,3-dichloroquinoxaline ($k_{OH^-}$ = 0.052 min$^{-1}$), into a useful reactive component *(39)* [34]. On the other hand, a chlorocarbonyl or carboxamido group in the 7-position *(40)* activates the chlorine atoms of 2,4-dichloroquinazoline, which is already very reactive as such ($k_{OH^-} > 1$ min$^{-1}$), so strongly that selective acylation of a dyestuff containing an amino group by the chlorocarbonyl group is hardly possible, and the reactive dyes formed are rapidly hydrolysed.



*(39)*

m. p. 124–126 °C

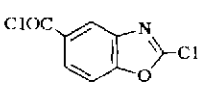


*(40)*

m. p. 65–68 °C
b. p. 150–153 °C/0.13 mm

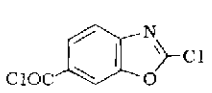
### γ) Benzoxazole and Benzothiazole Derivatives

We also obtained very useful reactive dyes from the 2-chlorobenzoxazole and 2-chlorobenzothiazole derivatives *(41)* to *(44)* [34]. The 2-chlorobenzoxazole dyes are very reactive, but the colorings obtained from them are not so resistant to boiling as those obtained from the 2,3-dichloroquinoxaline dyes.



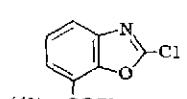
*(41)*

m. p. 78–79 °C



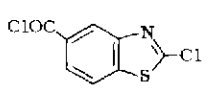
*(42)*

m. p. 109–110 °C



*(43)*

m. p. 111–112 °C



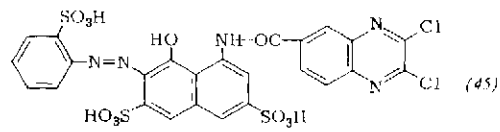
*(44)*

m. p. 134–136 °C

[34] *E. Siegel* and *K. Sasse*, Belgian Patent 613586 (Febr. 7th, 1961), 614375 (Febr. 24th, 1961), 614896 (March 9th, 1961), Bayer.

### b) Synthesis of the 2,3-Dichloroquinoxaline Dyes

Many of the azo, anthraquinone, and phthalocyanine dyestuffs, and their intermediates frequently used in reactive dyes and having a primary or secondary amino group in the molecule can be acylated with 6-chlorocarbonyl-2,3-dichloroquinoxaline. For example, the red reactive dye *(45)* is obtained by stirring a suspension of



*(45)*

finely powdered 6-chlorocarbonyl-2,3-dichloroquinoxaline into an aqueous solution of an equimolar quantity of the disodium salt of 1-amino-8-hydroxynaphthalene-3,6-disulfonic acid at 40 °C and pH 4–6, and finally coupling the acylation product with diazotized 1-aminobenzene-2-sulfonic acid at pH 7–8.

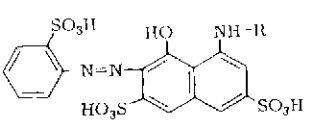
Since the relatively large 2,3-dichloroquinoxaline nucleus markedly diminishes the solubility of the dyestuffs in water, sometimes more groups which confer solubility in water must be present than are required in the corresponding dichlorotriazine dyes.

Monoazo dyestuffs, such as are obtained by coupling diazotized anilinesulfonic acids with 1-phenylpyrazolones, are the basis of brilliant greenish-yellow shades; clear orange and red shades are produced by the dyes, *e.g. (45)*, obtained by coupling diazotized anilinesulfonic acids with hydroxynaphthalenesulfonic acids, especially aminohydroxynaphthalenesulfonic acids. Derivatives of 1-amino-4-phenylaminoanthraquinone-2-sulfonic acid which contain amino groups are the basis of brilliant blues. Dyes with a turquoise tint contain copper or nickel phthalocyaninesulfonic acids as chromogens. Copper, chromium, and cobalt complexes of mono- and bisazo dyestuffs afford violet, navy-blue, brown, grey, and black shades. The 2,3-dichloroquinoxaline dyes are known in the trade by the name Lefafix-E® dyes [34].

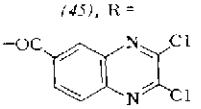
### c) Coloring Properties of the 2,3-Dichloroquinoxaline Dyes

An ideal reactive dye should react with cellulose as quickly and as fully as possible and moreover be stable to hydrolysis in alkaline aqueous media. These requirements are not readily compatible with one another, yet the 2,3-dichloroquinoxaline dyes fulfil them surprisingly well.

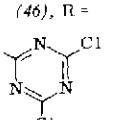
The dyeing properties of the new reactive dyes may be illustrated by the example of the dye *(45)*. We have



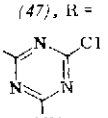
*(45)*, R =



*(46)*, R =



*(47)*, R =



chosen for comparison the dichlorotriazine dye *(46)* and the monochlorotriazine dye *(47)*.

The optimum temperature for dyeing from dilute liquors is a measure of the reactivity of the reactive groups: for *(46)*, this is 25 °C; for *(45)*, 40 °C; and for *(47)*, 80 °C. The 2,3-dichloroquinoxaline dyes therefore come next to the very reactive dichlorotriazine dyes. This is also shown by their behavior in the cold pad-batch process [35]:

Figure 2 presents the proportion of dye which reacts at room temperature with the cellulose fabric as a function of time. Mercerized poplin was steeped in a solution containing $10^{-2}$ mole/l of pure dye in each case, together with the acid-binding agent and additives specified; the excess moisture was squeezed out between rubber rollers, and the cloth was rolled up and left standing at room temperature for different periods of time for the dye to react with the cellulose. Finally, the unfixed portion of the dye was washed out and estimated colorimetrically.

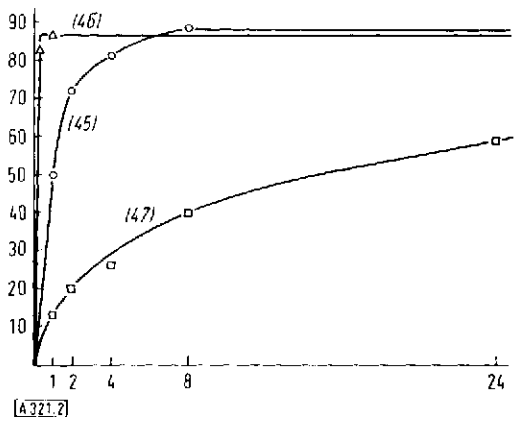



Fig. 2. Dye fixed to mercerized poplin as a function of time. The figures beside the curves indicate the identity of the dyes.

In the case of *(45)* and *(46)*, 20 g/l of soda and 100 g/l of urea were added; in the case of *(47)*, 30 ml/l of 32% caustic soda and 10 g/l of sodium sulfate were used instead.

Ordinate: amount of dye fixed [% of the total quantity]
Abscissa: time [hours]

The reaction rate is greatest for the dichlorotriazine dye *(46)*: it reached its maximum degree of fixation of 87% after only 15–20 minutes, while the 2,3-dichloroquinoxaline dye *(45)* reached its maximum (88%) only after 6–8 hours. On the other hand, the monochlorotriazine dye *(47)* had not reacted fully even after 24 hours, and its degree of fixation at that time lies considerably below the values for *(45)* and *(46)*.

Although the 2,3-dichloroquinoxaline dye *(45)* reacts with cellulose rapidly and in very high yield, its rate of hydrolysis in the alkaline dye solution ("padding liquor") is considerably smaller than that of the monochlorotriazine dye and very much smaller than that of the dichlorotriazine dye (Fig. 3) [35]. This stability to hydrolysis in the alkaline padding liquor is important for the cold pad-batch process, since the intensity of the color must not drop markedly during the padding.

The dye solutions used in the cold pad-batch process were allowed to stand at room temperature for 0, 2, or 6 hours after the addition of alkali and then padded onto the mercerized poplin, which was then laid aside for 24 hours. Moreover, an intermediate value was measured for the dye *(46)* 10 minutes after the addition of alkali. The degrees of fixation obtained in the case of immediate padding correspond to the maximum yields in Figure 2. The greater the slope of the curve in Figure 3, the more rapidly the dye is hydrolysed.

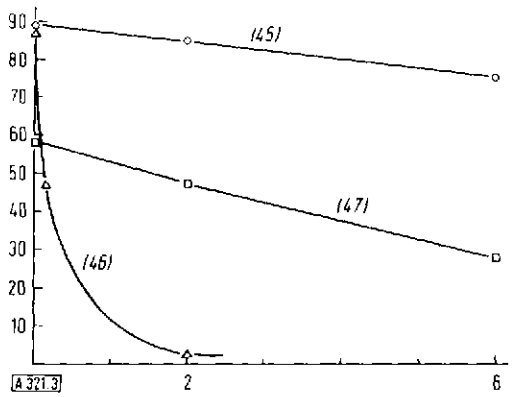



Fig. 3. Stability to hydrolysis of the dyes *(45)* to *(47)* in alkaline aqueous solution. For details see text.
Ordinate: amount of dye fixed [% of the total quantity]
Abscissa: time after addition of alkali [hours]

High reactivity towards cellulose with the greatest possible stability to hydrolysis is desired not only in dyeing, but also in calico printing; there has lately been a great demand for reactive dyes with good stability towards the alkaline printing paste and the ability to fix out in very short steaming times of 30–60 seconds. Although the very reactive dichlorotriazine dyes fulfil the second requirement, they are not sufficiently stable in the alkaline printing paste [32]. At the present time, the dichloroquinoxaline dyes are the only ones which have the ability to react completely within a steaming time of 30 seconds and to keep for over three weeks in the alkaline printing paste. Although the 2,3-dichloroquinoxaline dyes do not quite reach the standard of wet-fastness shown by the "Indanthrene"® fast reactive dyes based on sulfatoethyl groups activated by neighboring groups (see above), they are comparable in their degree of fastness to the dichlorotriazine dyes.

### d) Studies of the Dyeing Mechanism

The measurements of *Hildebrand* [36] provided information about the reactivities of the 2,3-dichloroquinoxaline dye *(45)* and the dichlorotriazine dye *(46)* towards water and towards sorbitol (as a model for cellulose [33]). He determined the rate constants for the pseudo-monomolecular reaction by working up the reaction mixtures after different times; the analysis procedure involved paper chromatographic separation, elution, and colorimetric estimation of the products.

As Table 4 shows, the ratio $k_{sorbitol}/k_{H_2O}$ is less favorable for the dichloroquinoxaline dye *(45)* than for the dichlorotriazine dye *(46)*. The fact that *(45)* nevertheless attained just as high a degree of fixation as *(46)* (Fig. 2) is connected with the rate of diffusion during the heterogeneous reaction with cellulose: the dichloro-

[35] Measurements by *W. Beckmann* and *K. Greiner*.

[36] *W. Beckmann, D. Hildebrand*, and *H. Pesenecker*, Melliand Textilber. *43*, 1304 (1962).

Table 4. Rate constants for the pseudo-monomolecular reactions of the dyes *(45)* and *(46)* with water and with sorbitol (50 g of sorbitol/l) at pH 10 and 25 °C.

| Dye | $k_{sorbitol}$ [$min^{-1} \cdot mole^{-1}$] | $k_{H_2O}$ [$min^{-1}$] | $\frac{k_{sorbitol}}{k_{H_2O}}$ |
|---|---|---|---|
| *(45)* | 0.42 | $1.8 \times 10^{-4}$ | 2340 |
| *(46)* | 12.40 | $33 \times 10^{-4}$ | 3760 |

triazine dye is partly hydrolysed within the time necessary for its diffusion into the fiber [half-life period of diffusion: 12 min; of hydrolysis: 30 min for *(46)*, 550 min for *(45)*]. Moreover, the 2,3-dichloroquinoxaline dye has greater substantivity than the dichlorotriazine dye, which is attributed to the greater expansiveness and substantivity of the dichloroquinoxaline system [37].

The elemental analysis of cotton fabric dyed by different methods with 2,3-dichloroquinoxaline red *(45)* showed that only one of the two chlorine atoms reacts with the cellulose during the cold pad-batch process at 25 °C and in the case of exhaustion dyeing at 40 °C. Under more energetic conditions of fixing, *e.g.* with steam at 103 °C or on baking at 140 °C ("thermofixing"), the second chlorine atom also enters into reaction with the cellulose or water, so that thereafter only about 15 % of the chlorine content corresponding to the second chlorine atom is still detectable.

[37] Measurements by *W. Beckmann.*

*The studies described and the preparative work leading to the Levafix dyes were carried out in the ZW-Laboratorium der Farbenfabriken Bayer under the direction of Dr. D. Delfs. Those notably concerned with the development of the Levafix-E dyes were Drs. R. Pütter, J. Singer, W. Wolf, H. Jäger, and K. Gerlach of the Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer as well as Drs. K. Greiner, H. Gutjar, and M. Söll of the Anwendungstechnische Abteilung der Farbenfabriken Bayer. We thank Professor Otto Bayer for his intensive support of this work.*

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German version: Angew. Chem. 76, 423 (1964)

# Acrolein Polymers

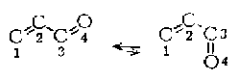
BY PROF. DR. R. C. SCHULZ [1]

ORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT MAINZ (GERMANY)

*The unsaturated aldehyde acrolein is a suitable source for different types of high polymers. If it is regarded as a 1,3-diene analogous to butadiene, then all the known modes of its polymerization can be systematically described and further possibilities predicted. A survey is given on this basis of the results obtained during the past decade. It is shown that acrolein is one of the few monomers which contain two polymerizable groups of differing reactivities. This fact allows the formation from acrolein of new homopolymers, copolymers, and graft copolymers, a scope which is not encountered with many other monomers.*

## 1. The Structure of the Monomer

As an α,β-unsaturated aldehyde, acrolein *(1)* contains a conjugated double-bond system, and can thus be considered as a 1,3-diene. This comparison is expressed by the numbering in the formulae shown below. The analogy between acrolein and butadiene and that between methacrolein and isoprene is obvious.



*(1a)* *(1b)*

It therefore follows that various polymers may be built up from acrolein. In contrast to butadiene, the two double bonds in acrolein possess unequal reactivities, so that additional variations are possible.

According to recent measurements [2, 2a], the bond lengths and angles in acrolein are as follows:

| | | | |
|---|---|---|---|
| C=C | 1.36 ± 0.02 Å | ∢ $C_1C_2C_3$ | 120 ± 3 ° |
| C–C | 1.46 ± 0.03 Å | ∢ $C_2C_3O$ | 120 ± 3 ° |
| C=O | 1.21 ± 0.02 Å | | |

The (C-2)–(C-3) bond is said to exhibit 37 [3] or 55 % [4] double bond character. Owing to the resultant restriction of free rotation, geometrical isomerism is a possibility. *Wagner* et al. [5] found that at room temperature about 95 % of the *s-trans* isomer *(1a)* is present at equilibrium. This form is more stable than the isomeric structure *(1b)* by 2.5 kcal/mole [2a].

[1] Communication No. 30 on Acrolein Polymers. Presented at the Macromolecular Colloquium at Mainz University, May 30th, 1963, and at the Forschungsinstitut für Pigmente und Lacke in Stuttgart (Germany), Jan. 21st, 1964. – Communication No. 29: Makromolekulare Chem. *72*, 198 (1964).

[2] *H. Mackle* and *L. E. Sutton*, Trans. Faraday Soc. *47*, 691 (1951); *J. Fine* et al., J. chem. Physics *23*, 601 (1955); *R. Wagner* et al., ibid. *26*, 634 (1957); *J. M. Hollas*, Spectrochim. Acta *19*, 1425 (1963).

[2a] For further details and references on monomeric acrolein, see *C. W. Smith:* Acrolein. Wiley, New York 1962.

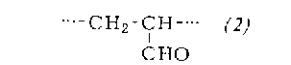
[3] *C. A. Coulson*, Trans. Faraday Soc. *42*, 106 (1946).

[4] *O. Polansky*, Mh. Chem. *88*, 107 (1957).

[5] *R. Wagner* et al., J. chem. Physics *26*, 634 (1957).

## 2. Polymerization of the Vinyl Group (1,2-Polymerization)

Our initial investigations were aimed at the construction of macromolecules with aldehyde side-groups *(2)* [6].



*(2)*

At that time polymers of this type were unknown. In view of literature reports describing the difficulties encountered in work with acrolein, we first investigated polymethacrolein [7], which in contrast to polyacrolein is soluble in numerous organic solvents. The following descriptions deal however only with acrolein and its polymers.

### a) Free-Radical Homopolymerization

High and reproducible yields can be obtained by polymerizations of acrolein initiated with water-soluble redox systems [8]. The polymers formed are produced almost exclusively by polymerization of the vinyl group [9].

Only certain combinations of oxidizing and reducing agents can be used with acrolein [10]. Systems composed of potassium peroxydisulfate and ferrous ammonium sulfate, sodium thiosulfate, or silver nitrate were found to be particularly effective. Redox systems recommended for the polymerization of acrylonitrile, such as $K_2S_2O_8/Na_2S_2O_4$ or $K_2S_2O_8/Na_2S_2O_5$ cannot be utilized with acrolein [11].

The best procedure is to add the acrolein to an aqueous solution of the oxidizing agent and then to add the reducing agent drop by drop to the resulting mixture. Acidic conditions must be maintained in the medium during the entire polymerization since competitive condensation reactions take place even at pH $\approx$ 8, leading to polyacroleins of a different type.

The polymerizations initiated by redox systems proceed by a free-radical chain mechanism [12]. The mechanisms of the redox reactions themselves can vary appreciably and are influenced by the presence of the monomers in a very complex manner [13].

Monomeric acrolein dissolves in water to the extent of 20 % [2a]. Since the polymer is insoluble, the polymerization always involves precipitation. Nevertheless, kinetic studies showed the same dependence of the overall rate of reaction on the concentration of the redox system as in other vinyl polymerizations performed under similar conditions [10].

Polymerizations in suspension and emulsion were also studied [14, 14a]. For this purpose, the adduct of polyacrolein and sodium hydrogen sulfite or sulfur dioxide proved a particularly effective emulsifying agent (see Section 5). Kinetics of the emulsion polymerization showed an anomalous relationship between the overall rate and the concentration of the emulsifying agent, but this was traced back to the water-solubility of the monomer [15].

Polymerization can also be carried out in organic media using azoisobutyronitrile as catalyst, but this technique offers no advantage since here, too, the polymer precipitates out and has properties quite similar to those of the product obtained by emulsion polymerization. No polymer is initially precipitated on polymerization in dimethylformamide, but at conversions beyond 15 %, the charge sets to a gel. The overall rate of reaction indicates that even in the initial stage of polymerization the reaction proceeds, at least partly, in a gel or microgel structure [16, 17].

During the storage of unstabilized acrolein or during distillation, polymerization sets in without any addition of catalyst [18] and can be recognized by the formation of turbidity in the liquid and separation of an insoluble powder. Neither this spontaneous nor the radical-catalysed bulk polymerization is recommended as a method for the preparation of polyacrolein, since the yields and properties of the polymer are difficult to reproduce. At elevated temperatures, the free-radical catalysed polymerization may proceed explosively. The heat of polymerization of acrolein is 19.1 kcal/mole [19].

### b) Free-Radical Copolymerization

Studies of the copolymerization of two monomers provide information about their relative reactivities, and in addition lead to polymers exhibiting novel properties. Both criteria determined the choice of vinyl and acrylic compounds used for copolymerization with acrolein.

A pair of monomers is characterized by the copolymerization parameters $r_1$ and $r_2$. These are obtained from the composition of the copolymers resulting from various monomer mixtures [20], according to the equation:

$$\frac{m_1}{m_2} = \frac{[M_1]}{[M_2]} \cdot \frac{r_1[M_1] + [M_2]}{[M_1] + r_2[M_2]} \qquad (a)$$

where [M] are the molar fractions of the monomers in the monomer mixture, and m the molar fractions of the monomer units in the resulting copolymer.

[6] *W. Kern* and *R. C. Schulz*, Angew. Chem. *69*, 153 (1957).

[7] *C. Rauh*, Angew. Chem. *69*, 162 (1957).

[8] *R. C. Schulz*, Makromolekulare Chem. *17*, 62 (1955).

[9] *R. C. Schulz*, Kunststoffe *47*, 303 (1957).

[10] *R. C. Schulz*, *H. Cherdron*, and *W. Kern*, Makromolekulare Chem. *24*, 141 (1957).

[11] For a comprehensive review of literature and patents on redox systems, cf. *H. Logemann* in *Houben-Weyl-Müller:* Methoden der organischen Chemie. 4th Edit., Thieme, Stuttgart 1961, Vol. 14/1, pp. 263–297.

[12] *W. Kern*, Makromolekulare Chem. *1*, 249 (1947/1948); *R. G. R. Bacon*, Trans. Faraday Soc. *42*, 140 (1946); *J. C. Bevington:* Radical Polymerization. Academic Press, London 1961.

[13] *R. Kerber* et al., Makromolekulare Chem. *50*, 220 (1961); *68*, 100 (1963).

[14] *H. Cherdron*, *R. C. Schulz*, and *W. Kern*, Makromolekulare Chem. *32*, 197 (1959).

[14a] French Pat. 1325213 (May 5th, 1962), inventor: *F. J. Welch*.

[15] *H. Cherdron*, Kunststoffe *50*, 568 (1960).

[16] *R. C. Schulz*, *S. Suzuki*, *H. Cherdron*, and *W. Kern*, Makromolekulare Chem. *53*, 145 (1962).

[17] According to U.S. Patent 2657192 (Jan. 25th, 1951), inventors: *H. C. Miller* and *H. S. Rothrock*, soluble polyacroleins and copolymers are formed when the polymerization is carried out in the presence of alcohol.

[18] *J. Redtenbacher*, Liebigs Ann. Chem. *47*, 113 (1843).

[19] *R. M. Joshi*, Makromolekulare Chem. *55*, 48 (1962).

[20] *L. Küchler:* Polymerisationskinetik. Springer-Verlag, Berlin 1951.

Table 1. Monomer reactivities, Q ratios, and e values for acrolein (index 1) [21,22].

| Comonomer $M_2$ | Polymerization medium | $r_1$ | $r_2$ | $Q_1$ | $e_1$ |
|---|---|---|---|---|---|
| Acrylonitrile | DMF [a] | 1.60 ± 0.04 | 0.52 ± 0.02 | 0.69 | 0.67 |
| Methacrylonitrile | Dioxan | 0.72 ± 0.06 | 1.20 ± 0.08 | 0.64 | 0.56 |
| Acrylamide | DMF | 1.69 ± 0.1 | 0.21 ± 0.02 | 0.99 | 0.05 |
| Acrylonitrile | $H_2O$ | 1.09 ± 0.05 | 0.77 ± 0.1 | 0.47 | 0.69 |
| Acrylamide | $H_2O$ | 2.0 ± 0.05 | 0.76 ± 0.02 | — | — |
| Vinyl acetate | $H_2O$ | 2.3 ± 0.1 | 0.1 ± 0.05 | 0.2 | 0.69 |
| Methyl acrylate | $H_2O$ | 0 | 7.7 ± 0.2 | — | — |
| 2-Vinylpyridine | DMF | 4 | 0 | — | — |

[a] DMF = Dimethylformamide.

The copolymerizations carried out [21,22] and the parameters found are shown in Table 1. Although all the copolymers precipitated out in aqueous systems, homogeneous reaction took place in dimethylformamide and in dioxan up to conversions of about 20 %.

After precipitation and drying, most copolymers containing more than 20 mole-% of acrolein units are insoluble in organic solvents; only those based on acrolein/methacrylonitrile or acrolein/methacrolein are readily soluble, even at acrolein contents of 70 mole-%.

Rather surprisingly, the parameters for a particular pair of monomers (*e.g.* acrolein/acrylonitrile or acrolein/acrylamide) are influenced by the nature of the reaction medium [22]. The same effect has recently been described for other pairs of monomers (acrylonitrile/ethyl acrylate; itaconic anhydride/styrene) [23,24]. To explain this behavior, it is necessary to assume that concentration changes occur during the reaction when the copolymer is precipitated, so that the monomer ratios in the liquid and solid phases differ appreciably from each other and from the originally selected composition. Factors which govern the validity of Equation (a) are thereby invalidated.

In contrast, the Q and e values [*] for acrolein, calculated from the parameters of different homogeneous copolymerizations, are in good agreement, even when different solvents are used (lines 1 and 2 in Table 1). These values should therefore be the most reliable ones.

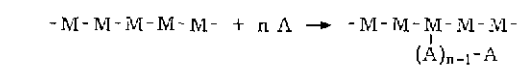
By application of statistical techniques, the most probable arrangements and the number of successive identical monomer units (lengths of sequences) can be calculated from the copolymerization parameters. Since spectroscopic measurements [25,26] provide an alternative source of information concerning the number of isolated acrolein monomer units, study of the copolymers made an important contribution to the elucidation of the structure of the homopolymer.

Copolymerizations of acrolein with styrene, acrylonitrile, methyl methacrylate, vinyl acetate, methyl acrylate, and allyl alcohol were carried out [17,27], with practical applications in mind. It was hoped that the acrylonitrile/acrolein copolymers would yield a material with improved fiber characteristics.

It may be of practical interest that the copolymers show the chemical properties, typical of polyacroleins, even at relatively low acrolein contents (see Section 5). For example, acrylonitrile/acrolein copolymers dissolve in aqueous sulfur dioxide solutions [28] to give solutions from which films can be cast or fibers spun by wet spinning [28a].

### c) Graft Copolymerization

Graft copolymerization is particularly easy to initiate with γ-irradiation. If a thin film of poly(methyl methacrylate) is dipped into a methanolic solution of acrolein, the monomer diffuses into the polymer. On subsequent irradiation, branches of acrolein units are grafted onto the polymethacrylate chains [29].



M = methyl methacrylate; A = acrolein.

The acrolein that has diffused into the polymer polymerizes much more rapidly than acrolein does on irradiation in bulk.

Separation of the polymeric components by extraction is impossible which indicates that graft copolymerization has indeed occurred. Moreover, the products are entirely insoluble in all solvents. The polyacrolein chains grafted on contain aldehyde groups which can undergo the same chemical reactions as those in homopolymers (see Section 5). The aldehyde groups can be detected, for example, by the coloration they give with fuchsin-sulfurous acid (Schiff reagent).

The conditions prevailing during the diffusion of monomer can be selected in such a way that only a thin surface layer is grafted on. In this way, plates are formed whose interiors consist of unchanged soluble poly(methyl methacrylate), while their surface layers are insoluble and exhibit the properties of a polymeric aldehyde. The thickness of this layer can be rendered visible by dyeing.

An alternative method for the preparation of surface graft copolymers is described in Section 5.

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[21] *R. C. Schulz, H. Cherdron,* and *W. Kern,* Makromolekulare Chem. *28*, 197 (1958).

[22] *R. C. Schulz, E. Kaiser,* and *W. Kern,* Makromolekulare Chem. *58*, 160 (1962).

[*] These values indicate, respectively, the reactivity and charge of the monomer in the transition state. They are calculated from the following equations:

$r_1 = (Q_1/Q_2) \exp[-e_1(e_1-e_2)]$

$r_2 = (Q_2/Q_1) \exp[-e_2(e_2-e_1)]$

*C. C. Price,* J. Polymer Sci. *3*, 772 (1948).

[23] *J. Brandrup,* Faserforschung u. Textiltechn. *12*, 133, 208 (1961).

[24] *J. Dougas* and *R. Guile,* J. Polymer Sci. *55*, 297 (1961).

[25] *R. C. Schulz, H. Cherdron,* and *W. Kern,* Makromolekulare Chem. *29*, 190 (1959).

[26] *E. Kaiser,* Makromolekulare Chem., in the press.

[27] German Pat. 855162 (1944), inventors: *H. Wolz* and *W. Bock*; U.S. Patent 2416536 (1942), inventors: *H.T. Neher* and *C. F. Woodward*; U.S. Patent 2891037 (1959), inventor: *K. H. Reinhard.*

[28] German Pat. 1019825; U.S. Patent 3036978 (1958), inventors: *W. Kern, R. C. Schulz,* and *H. Cherdron.*

[28a] German Published Pat. Applcn. 1104183 (1959); Belg. Pat. 593116 (July 18th, 1960), inventors: *W. Gältner* and *P. Schlack.*

[29] *A. Henglein, W. Schnabel,* and *R. C. Schulz,* Makromolekulare Chem. *31*, 181 (1959).

## 3. Polymerization of the Carbonyl Group (3,4-Polymerization)

The C=O double bond of acrolein can also undergo polymerization, but ionic catalysts are the only effective agents for initiating this process.

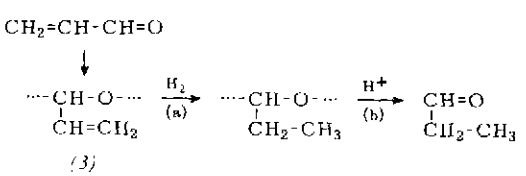
It has long been known [30] that, under the influence of bases, acrolein is converted into oily or solid products which differ in solubility and fusibility from the spontaneously formed "disacryl" polymer [18] and the free-radical polymers. The formation of oligomers was interpreted as a Michael reaction [31]. The structure of the higher molecular-weight products was not clarified; polycondensation reactions were postulated [31a].

Suitable catalysts for this type of polymerization include sodium hydroxide [31, 31a], potassium carbonate [31a], sulfur dioxide [32], thiourea [33], oxides of copper, silver, mercury, and lead [34], as well as alkali-metal and alkaline-earth nitrites [35], sulfuric acid/diethyl ether [8, 9], boron trifluoride/diethyl ether [8, 9], boron trifluoride [35a], and metallic sodium [35b].

On the basis of earlier observations [8], we used specially purified acrolein and selected typical anionic polymerization catalysts, *e.g.* sodium naphthalene, triphenylmethylsodium, n-butyl-lithium, sodamide, or metallic sodium [36]. Provided that oxygen and moisture are carefully excluded, reproducible polymerization reactions can be obtained between +30 and −60 °C. The solvent influences the rate of polymerization and the properties of the resulting polymer.

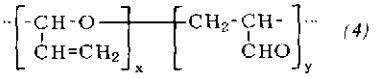
Infrared spectra show that the polyacroleins thus obtained must differ entirely from the redox polymers. They contain only few aldehyde groups, as indicated by their nitrogen content after reaction with phenylhydrazine. On the other hand, they take up as much as 0.7 molecule of hydrogen per acrolein unit on catalytic hydrogenation [Reaction (a)].

The hydrogenated polymers produce propionaldehyde on hydrolysis with acid (Reaction (b)]. Accordingly, the polyacroleins produced with the aid of strongly anionic catalysts have been formed mainly by polymerization in the 3,4-positions, and consist mainly of chains of the unit *(3)*.



*(3)*

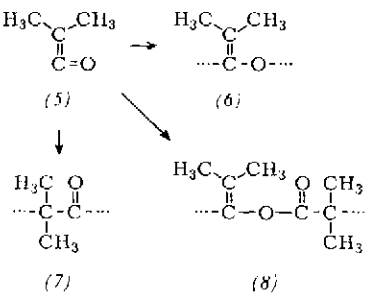
However, unit *(2)* also occurs in these polymers. The content of double bonds and carbonyl groups depends on the catalyst and the reaction conditions, and the x:y ratio in structure *(4)* can vary within wide limits.



*(4)*

Polymers possessing this structure represent a peculiar type of copolymer, since the monomeric units are isomeric.

A similar case is the ionic polymerization of dimethylketene *(5)* described by *Natta* et al. [37]. This monomer is also an unsaturated carbonyl compound, in which either the C=C double bond *(7)* or the C=O double bond *(6)* can polymerize, as well as both *(8)* at the same time. In contrast to acrolein, the double bonds in *(5)* are cumulative.

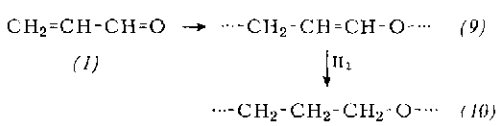


*(5)* *(6)* *(7)* *(8)*

The vinyl side-groups of polymers *(3)* or *(4)* are still capable of free-radical polymerization. Under conditions similar to those involved in the cross-linking of unsaturated polyesters, these polyacroleins can be copolymerized with, for example, styrene or methyl methacrylate, to form clear, hard, and insoluble, shaped articles. Combination of these two polymerizations involves a new principle in the preparation of copolymers [38].

## 4. 1,4-Polymerization

If acrolein is considered as a 1,3-diene, then polymerization in the 1- and 4-positions should be possible. Linear 1,4-additions would lead to polymers containing the structural unit *(9)*.



*(1)* *(9)* *(10)*

Although such structural units have formed the subject of some discussions [9, 39], they have not yet been detected in any polyacroleins. It has merely been

[30] *C. Moureu* and *C. Dufraisse*, C. R. hebd. Séances Acad. Sci. *169*, 621 (1919); *191*, 1126 (1930).

[31] *E. E. Gilbert* and *J. J. Donleavy*, J. Amer. chem. Soc. *60*, 1911 (1938).

[31a] *H. Schulz* and *H. Wagner*, Angew. Chem. *62*, 105 (1950); also patents cited there.

[32] German Pat. 1062012 (1958), inventor: *O. Schweitzer*.

[33] German Pats. 733099 (1938); 737125 (1939); 745422 (1939); 748690 (1938); inventor: *F. Köhler*.

[34] U.S. Patent 2819252 (1954), inventor: *E. C. Shokal*; French Pat. 1138853 (1955).

[35] U.S. Patent 2809185 (1954), inventors: *G. W. Hearne*, *D. S. LaFrance*, and *E. C. Shokal*.

[35a] *J. V. Andreeva*, *M. M. Koton*, and *K. A. Kovaleva*, Vysokomolek. Soed. *4*, 528 (1962).

[35b] *M. M. Koton* et al., Vysokomolek. Soed. *4*, 1537 (1962).

[36] *R. C. Schulz* and *W. Passmann*, Makromolekulare Chem. *60*, 139 (1963).

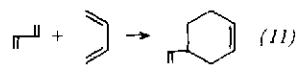
[37] *G. Natta* et al., Makromolekulare Chem. *44/46*, 546 (1961); *51*, 148 (1962).

[38] *R. C. Schulz* and *W. Passmann*, Makromolekulare Chem. *72*, 198 (1964).

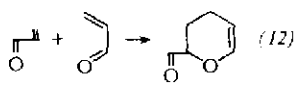
[39] *R. C. Schulz*, Angew. Chem. *73*, 777 (1961).

shown that they do not occur in the anionic polymers described above. On hydrogenation, polyethers *(10)* identical with polyoxabutane [36] would be formed.

A cyclizing 1,4-addition leading to polymers of structure *(13)* is also feasible. According to *Alder* and *Rüden* [40], acrolein can add onto dienophiles in the same way as butadiene. In the simplest case, the reaction leads to 2-formyl-$\Delta^5$-dihydropyran *(12)*, in analogy to the formation of vinylcyclohexene *(11)* [41].

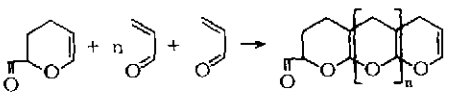


*(11)*



*(12)*

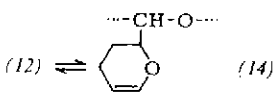
*Scherlin* et al. [42] postulated that further 1,4-additions follow the dimerization of acrolein, with possible formation of polymers *(13)*.



*(13)*

Such a sequence of reactions has not yet been established but it is possible that compounds of this type occur in the non-volatile residues obtained during the preparation of *(12)*. The same structural unit as occurs in *(13)* is formed when adjacent aldehyde groups of polyacroleins *(2)* formed by free-radical catalysts react with ring closure to give *(18)*. The difference between *(13)* and *(18)* lies in the end-groups.

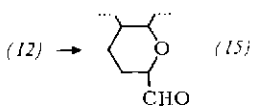
The product of dimerization of acrolein is again an unsaturated aldehyde *(12)*. It is known that this initially fluid compound becomes viscous on storage and ultimately sets to a cloudy, sticky resin. The infrared spectra of purified samples indicate that this process, which is generally designated as a "spontaneous polymerization", entails formation of a polymeric acetal *(14)* [43,44a,b].



*(12)* *(14)*

Almost complete depolymerization can be achieved by heating this material above 185 °C.

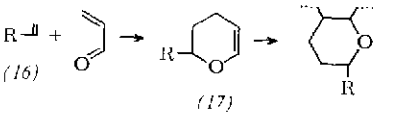
As a vinyl ether, formyldihydropyran *(12)* can be polymerized under the conditions used for cationic polymerization [44a]. The products soften without decomposing at 240–269 °C. Infrared spectra and chemical reactions indicate the structure *(15)*.



*(12)* *(15)*

On the basis of the molecular formulae of their monomeric units, *(14)* and *(15)* can be designated as polymers of acrolein, although they differ substantially from the polymers described above.

Preliminary formation of the dimer provides a further method for the preparation of acrolein copolymers [43]. Acrolein adds onto numerous vinyl and acrylic compounds *(16)* to form diene adducts, *viz.* 2-substituted dihydropyrans *(17)* [45].

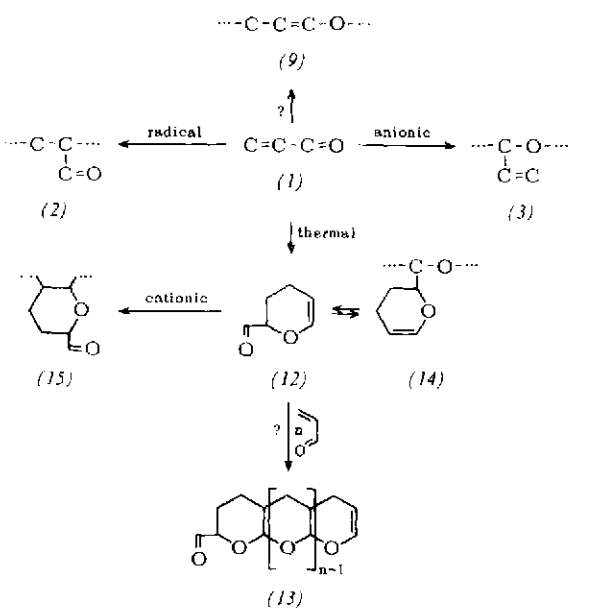


*(16)* *(17)*

The addition onto *N*-vinyl compounds proceeds particularly readily [46], *e.g.* *(16)*, R = NH–CO–OR′ or NH–CONHR′. Similarly to *(12)*, compounds of type *(17)* can be considered as cyclic vinyl ethers and are capable of polymerization. The resulting polymers represent a novel type of 1:1 copolymers of acrolein and the unsaturated compound *(16)*.

Dihydropyran [*(17)*, R=H] can also undergo polymerization [47a,b]. Since the monomer decomposes on heating to form acrolein and ethylene [48], polydihydropyran may be regarded as a 1:1 copolymer of these two substances.

The reactions leading to polymers from acrolein discussed in Sections 2–4 are listed in Scheme 1. This




*(9)* *(1)* *(2)* *(3)* *(15)* *(12)* *(14)* *(13)*

Scheme 1. Acrolein polymers.

[40] *K. Alder* and *E. Rüden*, Chem. Ber. *74*, 920 (1941).

[41] *F. Hofmann*, Angew. Chem. *25*, 1465 (1912); *J. C. Hillyer* and *J. V. Smith*, Ind. Engng. Chem. *45*, 1133 (1953).

[42] *S. M. Sherlin* et al., Zh. obshch. Khim. *8*, 22 (1938); Chem. Zbl. *1939*, I, 1971.

[43] *K. Meyersen*, unpublished work.

[44a] *S. Potnis*, *K. Shohara*, *R. C. Schulz*, and *W. Kern*, Makromolekulare Chem. *63*, 78 (1963).

[44b] *H. Ohse*, *H. Cherdron*, and *F. Korte*, Makromolekulare Chem., in the press.

[45] For a review cf. *C. W. Smith*, [2a], pp. 211 et seq.

[46] *R. C. Schulz* and *H. Hartmann*, Chem. Ber. *95*, 2735 (1962).

[47a] *S. Kamio*, unpublished work.

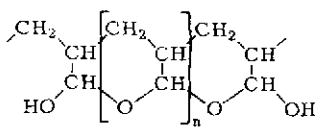
[47b] *E. A. Sapozhnikova* et al., Fiz. i. Khim. Prirodn. i. Sintetich Polimerov *1962* (1), 167; Chem. Abstr. *1963*, 15389a; *R. D. Kimbrough* et al., J. Polymer Sci. B *2*, 82 (1964).

makes it clear that acrolein occupies a special place among monomers, since the choice of polymerization conditions determines the propagation mechanism and hence the chemical structure of the units making up the chain. With most other vinyl and acrylic compounds, the catalysts influence merely the molecular weight, the degree of branching, the end-groups, or the tacticity. The physical and chemical properties of polyacroleins thus depend far more strongly on the conditions of their preparation than do those of other polymers. The various types of copolymers further increase the number of possible variations. This multiplicity of structural units naturally makes characterization and elucidation of the structure of the polymer more difficult, and may explain the frequently contradictory reports concerning the properties of polyacroleins. The differences in properties reported are not simply a consequence of varying molecular weights but are mostly produced by differences in chemical composition.

The uses of acrolein in polycondensation reactions are beyond the scope of this work (see *e.g.* [31a, 49, 50]).

## 5. Chemical Reactions of Polyacroleins

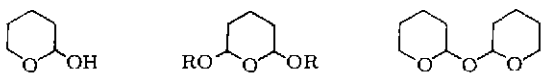
Polyacroleins obtained with the aid of redox systems in aqueous media are chemically very uniform in nature. They are characterized by great chemical reactivity, since every monomer unit contains an aldehyde group, although most of these are present not in the free form but as an aldehyde hydrate ether [51]. Without going into details about the elucidation of the structure, physical and chemical investigations [9, 52–54] have shown reliably that formula *(18)* (n = 0, 1, or 2) represents the most frequently occurring structural unit.



*(18)*, n = 0, 1, 2

Sequences of 2–4 monomer units form fused tetrahydropyran rings along the main carbon chain with a degree of polymerization of 100 to 20000. These are separated by 10–20 mole-% of isolated units with free aldehyde groups. Side reactions during polymerization give rise to branched structures, C–C double bonds, and keto groups, but these almost certainly do not amount to more than 8–10 mole-%. Cross-links, if any, can be formed only through hydrate ether groups which can easily be split.

The reactions of redox polymers of acrolein have been described in several papers [9, 51, 55–57]. Some reactions of low molecular-weight model compounds, *e.g. (19)* to *(21)*, were also studied [54]. These comparisons gave an indication of the optimum experimental conditions, possible side reactions, intermediates, and limitations to the reaction with polyacrolein. They also supplied reference substances for the assignment of infrared bands.



*(19)* *(20)* *(21)*

It was thus shown that the structural unit in *(18)* (like those of corresponding model compounds) often gave the reactions of an aldehyde group, but not invariably. This behavior explains the differences in the maximum yields obtainable in reactions with polyacroleins.

Table 2 gives a list of the most important reactions of polyacroleins together with the maximum degrees of conversion. Details can be found in the original publications cited in the Table.

All the reactions can be explained by assuming structure *(18)* for the polymer, and can be grouped into four types:

a) Reactions in which all the pyran rings are opened, and each monomer unit produces the corresponding aldehyde derivative. In these reactions, polyacrolein behaves like a polymeric monaldehyde, *i.e.* each monomer unit reacts independently of its neighbors. Practically complete conversion is achieved. Consequently, the principal use of these reactions is for quantitative determination of the aldehyde groups. Examples: formation of oximes, phenylhydrazones, oxidation, reduction.

b) Reactions in which two aldehyde groups participate. The pyran rings favor such reactions, polyacrolein behaving like a polymeric dicarbonyl compound; this mode of reaction is even more highly developed in poly(methyl vinyl ketone) [58]. For statistical reasons, conversion is limited to a maximum of 86 mole-% [58a]. Example: the Cannizzaro disproportionation reaction.

c) Reactions which occur only in the hemiacetal-like hydroxyl groups, without opening of the pyran rings. Since an average of 2 hydroxyl groups are available for every 2–4 monomer units, the conversions (per aldehyde group) lie between 50 and 25 mole-%. Examples: reactions with alcohols, thiols, secondary amines, cyanoacetic esters, and other compounds possessing a reactive methylene group.


[48] *O. Bayer* in *Houben-Weyl-Müller:* Methoden der organischen Chemie. 4th Edit., Thieme, Stuttgart 1954, Vol. 7/1, p. 253.

[49] German Pat. 837289 (1951), inventor: *H. Orth*; German Pats. 802826 and 824732 (1951), inventor; *F. Köhler*; German Pat. 1112628 (1962), inventors: *R. Zimmermann* and *H. Hotze*.

[50] *F. Brown, D. E. Hudgin,* and *R. J. Kray,* J. chem. Engng. Data, *4*, 182 (1959).

[51] *R. C. Schulz* and *W. Kern,* Makromolekulare Chem. *18/19*, 4 (1956).

[52] *R. C. Schulz,* Kunststoffe *48*, 257 (1958).

[53] *R. C. Schulz, J. Kovacs,* and *W. Kern,* Makromolekulare Chem. *54*, 146 (1962).

[54] *R. C. Schulz, K. Meyersen,* and *W. Kern,* Makromolekulare Chem. *54*, 156 (1962); *59*, 123 (1962).

[55] *R. C. Schulz,* Kunststoffe/Plastics *6*, 32 (1959).

[56] *R. C. Schulz* and *I. Löflund,* Angew. Chem. *72*, 771 (1960).

[57] *R. C. Schulz,* Kolloid-Z. *182*, 99 (1962).

[58] *R. C. Schulz, H. Vielhaber,* and *W. Kern,* Kunststoffe *50*, 500 (1960).

[58a] *P. J. Flory,* J. Amer. chem. Soc. *61*, 1518 (1939); *64*, 177 (1942).

d) Reactions which proceed only in the presence of free aldehyde groups. These are practically completely suppressed by the presence of the pyran rings. This behavior explains the absence of reactions with peroxides and of radical chain-transfer reactions. Similarly, autoxidation has so far never been observed [59]. Because of its resistance to molecular oxygen, dry polyacrolein is absolutely stable, is easy to handle, and can be stored indefinitely, even in the presence of air.

Since the redox polymers are insoluble in all organic solvents [60], each reaction commences in a heterogeneous system. If possible, the experimental conditions should be so selected that the polymeric products pass into solution as the reaction proceeds. The limitations imposed on the conditions by the low solubility of the polymer and the high viscosities of the solutions obtained are often the cause of failure to achieve the maximum conversions mentioned above.

Table 2. Chemical reactions with redox polymers of acrolein.

| Reaction | Reagent or catalyst | Monomer unit determined | Degree of conversion [a] | Ref. |
|---|---|---|---|---|
| Reduction | $KBH_4$ | $-CH_2-CH-$ <br> $CH_2OH$ [b] | >90 | [53, 61] |
| Oxidation | $H_2O_2$; $CH_3-COOOH$ | $-CH_2-CH-$ <br> $COOH$ | >90 | [62] |
| Oxime formation | $NH_2OH$ | $-CH_2-CH-$ <br> $CH=NOH$ | ≈90 | [63, 64] |
| Hydrazone formation | $R-NH-NH_2$ | $-CH_2-CH-$ <br> $CH=N-NHR$ [c] | 70–90 [d] | [65] |
| | $R-C(=O)-NH-NH_2$ | $-CH_2-CH-$ <br> $CH=N-NH-CO-R$ | [d] | [72] |
| Disproportionation | NaOH | $-CH_2-CH-CH_2-CH-$ <br> $HOH_2C$ $COOH$ | 60–70 | [66] |
| Acetal formation | R–OH or HO–R–OH | $-CH_2-CH-$ <br> $CH$ <br> $O$ $OR$ | 30–40 [d] | [67] |
| Mercaptal formation | R–SH | $-CH_2-CH-$ <br> $CH$ <br> $O$ $SR$ | 35–45 [d] | [68] |
| Formation of Schiff bases | $R-NH_2$ | $-CH_2-CH-$ <br> $CH=N-R$ [e] | 30–50 | [54, 65] |
| Knoevenagel condensation | $R^1-CH_2-R^2$ | $-CH_2-CH-$ <br> $CH=CR^1R^2$ <br> $-CH_2-CH-$ <br> $CH$ [e] <br> $O$ $CHR^1R^2$ | 20–50 [d] | [54, 69] |
| Autoxidation | $O_2$ | no reaction up to 120 °C | – | [59] |
| Bisulfite adducts | $H_2O + SO_2$; $NaHSO_3$ | *(22)* ⇌ *(23)* + $SO_2$ [g] | [f] | [55, 59, 71, 73] |
| Color reactions | | | [f] | [59] |
| Aldol condensation | $CH_2O$ | $CH_2OH$ <br> $-CH_2-C-$ <br> $CH_2OH$ | ≈90 | [70] |

[a] Defined as the number of reacted monomer units per 100 monomer units. Calculated from the composition of the polymeric reaction products or their derivatives, as determined by analysis. It was assumed in this calculation that polyacrolein has the ideal composition $(C_3H_4O)_n$ and that besides the reacted monomer units, only acrolein units occur.

[b] For esterifications, xanthations, and etherifications of the polyallyl alcohols, see [53] and [61].

[c] For conversion to polymeric formazans, and the oxidation of the latter to tetrazolium salts and complex formation, see [65].

[d] The maximum conversion depends on R.

[e] For discussions of further structures, see [54] and [69].

[f] The degree of conversion could not be determined.

[g] For reactions with the bisulfite addition compounds, see [56, 57, 71, 73].


[59] *R. C. Schulz, I. Löflund,* and *W. Kern,* Makromolekulare Chem. *32,* 209 (1959).

[60] *R. Hank,* Makromolekulare Chem. *52,* 108 (1962); *R. C. Schulz, J. Kovacs,* and *W. Kern,* ibid. *52,* 236 (1962).

[61] *R. C. Schulz* and *P. Elzer,* Makromolekulare Chem. *42,* 205 (1961).

[62] *R. C. Schulz, I. Löflund,* and *W. Kern,* Makromolekulare Chem. *28,* 58 (1958).

[63] *R. C. Schulz, H. Fauth,* and *W. Kern,* Makromolekulare Chem. *20,* 161 (1956).

[64] *M. Marx* and *J. Kovacs,* unpublished work.

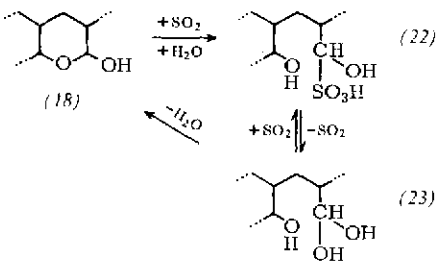
[65] *R. C. Schulz, R. Holländer,* and *W. Kern,* Makromolekulare Chem. *40,* 16 (1960).

[66] *R. C. Schulz, E. Müller,* and *W. Kern,* Naturwissenschaften *45,* 440 (1958).

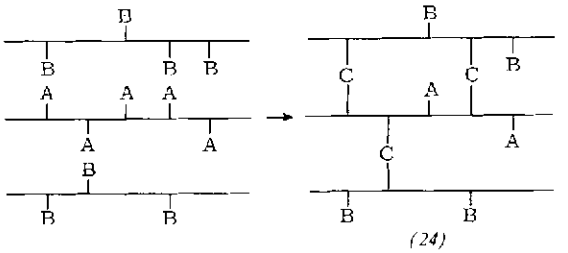
[67] *R. C. Schulz, H. Fauth,* and *W. Kern,* Makromolekulare Chem. *21,* 227 (1956).

A special place among polyacrolein reactions is occupied by the addition reactions of sulfurous acid or sodium hydrogen sulfite, yielding water-soluble derivatives of high reactivity. Most of the above reactions can also be carried out with these polyacrolein/sulfurous acid adducts.

The adduct *(22)* is in equilibrium with sulfurous acid and a hydrated form *(23)* of the polyaldehyde [59]. It cannot be isolated, so the degree of conversion cannot be determined. It is however certain that the addition of only a few molecules of sulfurous acid per macromolecule is sufficient to make polyacrolein soluble in water,




although insoluble polyacrolein is reformed on evaporation or freeze-drying of the solution. The polyacrolein/sulfurous acid adducts are strong polyelectrolytes, with the properties of wetting agents, and can be used as high molecular-weight emulsifying agents [15]. The ability of sulfur dioxide-solubilized polyacrolein to react with the reactive groups of other polymers is particularly noteworthy [56,57]. In this way "composite polymers" *(24)* are formed which are cross-linked through primary valences.




A = $CH(OH)_2$; B = OH; SH; NH; $NH_2$
C = acetal-, mercaptal-, azomethine groups.

The unreacted aldehyde groups can be identified by color tests, and are available for other reactions. Under certain conditions these composite polymers are formed only at the surface of films, fibers, thin sections, *etc.* In this way, novel surface graft copolymers are obtained by a method different from that described in Section 2c.

Most copolymers of acrolein can, like the homopolymers, undergo the reactions of Table 2. The properties of the polymeric derivatives can be varied over a wide range, according to the nature of the comonomer and the aldehyde group content.

Apart from the reactions cited above with the aldehyde or hemiacetal-like hydroxyl groups, reactions are also possible with the α-hydrogens (with respect to the CO group) of the main chain; one example of such a reaction is the aldol condensation with formaldehyde.

*The author wishes to take this opportunity to express his sincere gratitude to Professor W. Kern for introducing him to the study of this field and for many years of encouragement and advice. Thanks are also due to H. Cherdron, P. Elzer, H. Fauth, C. Gutweiler, R. Holländer, E. Kaiser, K. Kamio, J. Kovács, I. Löflund, M. Marx, E. Masuhara, K. Meyersen, M. Miething, E. Müller, R. Neeb, H. Ohse, W. Passmann, S. Potnis, R. Schaaf, K. Shohara, and S. Suzuki, who participated in the present work. All our thanks are also due to Degussa, Frankfurt/Main, who advanced generous financial support for this work.*

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Translated by Express Translation Service, London

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[69] *R. C. Schulz, K. Meyersen,* and *W. Kern,* Makromolekulare Chem. *53*, 58 (1962).

[70] *R. C. Schulz, J. Kovacs,* and *W. Kern,* Makromolekulare Chem. *67*, 187 (1963).

[71] German Pat. 1016020 (1955), inventors: *W. Kern* and *R. C. Schulz*; German Pat. 1019825 (1956), inventors: *O. Schweitzer, W. Kern, R. C. Schulz,* and *R. Holländer*; German Pat. 1083051 (1958), inventors: *W. Kern, R. Schulz,* and *I. Löflund.*

[72] With Girard reagent T, the conversion is 25–30 mole-%; the reaction of polyacrolein with hydrazides of amino acids has been described by *Th. Kauffmann* and *F. P. Boettcher,* Liebigs Ann. Chem. *625*, 123 (1959).

[73] German Published Patent Application 1156649 (Oct. 28th, 1961), Agfa AG., inventors: *W. Himmelmann, H. Ulrich,* and *H. Meckl.*

# A New Method for the Determination of Fluorine

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*A new, particularly simple and reliable method of quantitative fluorine analysis is described; it is based on the conversion of insoluble silver oxide into soluble silver fluoride by fluorosilicic acid released from the sample by Willard-Winter-Tananaev steam distillation, the silver fluoride then being determined volumetrically according to Volhard.*

In contrast to the ease of analysis for the majority of the elements, quantitative determination of fluorine demands meticulous attention to details in executing individual operations. Several methods [1] give excellent results if extreme care is exercised, and if the analyst has acquired the necessary routine. However, at present there is no procedure which is entirely satisfactory with respect to simplicity and reliability of the analytical technique. A first step in this direction has undoubtedly been taken with the introduction of steam distillation of fluorine as fluorosilicic acid, a generally applicable technique developed independently by *Willard* and *Winter* [2], and by *Tananaev* [3]. However, the methods recommended for the subsequent analytical determination of fluorine – usually precipitation of lead chloride fluoride or bromide fluoride, or thorium fluoride – are not normally simple to conduct.

We have now succeeded in simplifying the second step in such a way that even an unskilled operator can conduct fluorine determinations with rapidity and high accuracy. In our procedure fluorosilicic acid is liberated from the fluorine-containing material and used to dissolve silver oxide.

$$SiF_6^{2-} + 2\,H^+ + 3\,Ag_2O + (n-1)\,H_2O \rightarrow 6\,F^- + 6\,Ag^+ + SiO_2 \cdot n\,H_2O$$

The amount of silver equivalent to the fluorine in the solution may then be determined according to *Volhard*. The determination of fluorine is thus simply reduced to a volumetric determination of silver. The solubility of silver oxide ($Ag_2O + H_2O \rightarrow 2\,AgOH$) can only be neglected if 1 mole of silver nitrate per val $F^-$ is added to the distilled solution of fluorosilicic acid prior to the addition of the silver oxide. Standard silver nitrate and thiocyanate solutions are therefore required.

For the volatilization of fluorosilicic acid [4], the silicic acid/phosphoric acid procedure [5] was preferred, since phosphoric acid does not form a soluble silver salt, in contrast to sulfuric or perchloric acid, which have also been recommended for the Willard-Winter-Tananaev distillation. The solution of the sample was heated to 240 °C in an electrical heating mantle. The steam was superheated to 220–240 °C in a quartz coil by internal electric heating before entering the sample vessel. Recirculation of the water – considered essential by *Pietzka* and *Ehrlich* [6] – thus proved unnecessary. The amount of distillate normally required for 1 val $F^-$ is 100–150 ml. Details of the apparatus are shown in Figure 1.

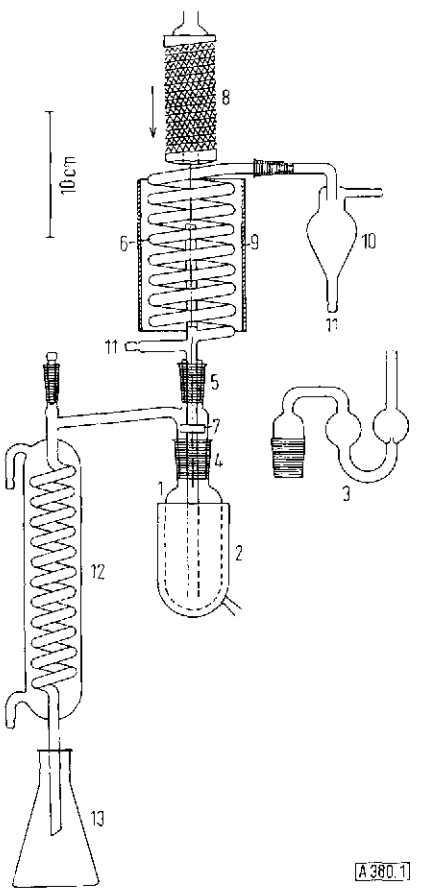



Fig. 1. Apparatus for distilling fluorosilicic acid by means of superheated steam. 1: sample vessel, 2: electrical heating mantle, 3: ball-tube adapter, 4: ground joint with Teflon sleeve, 5: ground joint with Teflon stopper, 6: quartz coil, 7: Teflon disc, 8: heating coil (removed from quartz coil), 9: heat insulation (asbestos cylinder, shown in section), 10: drip catch, 11: steam outlet, 12: condenser, 13: receiver.

[1] For recent reviews of methods for determining fluorine see: *G. W. Busch, R. C. Carter,* and *F. E. McKenna* in *C. J. Rodden:* Analytical Chemistry of the Manhattan Project. McGraw-Hill, New York 1950, pp. 226–248. – *F. E. McKenna,* Nucleonics *8*, 24, 40, 51 (1951). – *P. J. Elving, C. A. Horton,* and *H. H. Willard* in *J. H. Simons:* Fluorine Chemistry. Academic Press, New York 1954, Vol. II, pp. 51–211.

[2] *H. H. Willard* and *O. B. Winter,* Ind. Engng. Chem., analyt. Edit. *5*, 7 (1933).

[3] *I. Tananaev,* Zhur. Prikl. Khim. *5*, 834 (1932).

[4] Proof that it is actually $H_2SiF_6$ that distills over was provided by determining the atomic ratio *Si*:F in the distillate.

[5] *E. Rinck,* Bull. Soc. Chim. France (5) *15*, 305 (1948).

[6] *G. Pietzka* and *P. Ehrlich,* Angew. Chem. *65*, 131 (1953).

Volatile acids which form soluble silver salts must be rendered involatile or destroyed prior to the distillation. Sulfuric acid distils over at the high temperature employed but can be bound by adding barium phosphate prior to distillation. If large amounts of chlorine, bromine, or iodine are present, the addition of silver phosphate to the sample solution is advantageous. Nitrate is the most difficult ion to remove. We finally succeeded in preventing the formation of nitric acid by fusing any samples containing nitrate or nitrite with ammonium sulfate.

Naturally, the procedure is limited to the scope of the Willard-Winter-Tananaev distillation, and the interferences associated with this method must be taken into account. Metal ions ($Ca^{2+}$, $Pb^{2+}$, $Th^{4+}$, $Al^{3+}$, $Sb^{5+}$) which form insoluble salts or complexes with fluoride ion hardly affect the rate of distillation under the conditions given above. Boric acid steam-distils over with the fluorosilicic acid, but does not interfere. Substances containing difficultly or non-hydrolysable fluorine (*e.g.* sulfanuric fluoride, organic fluorine compounds) must be decomposed in a suitable manner.

## Examples

### a) *Analysis of Lead Chloride Fluoride*

For the determination of fluorine in PbFCl, samples of 0.2–0.5 g, *ca.* 1 g of silicon dioxide powder, and 0.75 g of silver phosphate are placed in a 100 ml pyrex flask (1 in Fig. 1), and 20 ml of 85 % phosphoric acid are added. The flask is preheated for a few minutes using the electrical heating mantle, which is provided with a control for maintaining an inner temperature of 240 °C [7]. Steam is then introduced, and finally the quartz spiral is heated by means of the heating coil of a large hair-dryer in order to superheat the steam to 220–240 °C. The volume of liquid in the sample flask remains essentially constant under these conditions. If steam is passed through the sample at a rate corresponding to ca. 250 g of water per hour, the distillate is no longer acidic after distillation of 100–150 ml. To the solution of fluorosilicic acid in the receiver are then added 10.0 ml of 0.1 N silver nitrate and 0.5 g of silver oxide. The solution is boiled briefly and cooled again and filtered through a sintered glass funnel, and the filtrate is then titrated according to *Volhard*. Table 1 gives a list of the results of analyses on 5 samples of PbClF.

Table 1. Analysis of five samples of PbClF.

| PbFCl [mg] | 0.1 N KSCN [ml] | F found [mg] | F calc. [mg] | Deviation [%] |
|---|---|---|---|---|
| 491.0 | 18.50 | 35.20 | 35.60 | −1.1 |
| 268.3 | 10.30 | 19.60 | 19.50 | +0.5 |
| 251.3 | 9.55 | 18.15 | 18.20 | −0.3 |
| 216.0 | 8.30 | 15.75 | 15.65 | +0.6 |
| 313.7 | 11.90 | 22.60 | 22.70 | −0.5 |

[7] If no degradations need to be carried out in the sample flask, the heating mantle can be replaced by a vacuum mantle. Also an aluminum block can be used for heating instead of the electrical heating mantle.

### b) *Analysis of a Mixture of Sodium Fluoride and Potassium Nitrate*

The sample is mixed with 0.7 g of ammonium sulfate per val $NO_3^-$ and heated with 2–3 ml of 1 N NaOH in the distillation flask, after the ball tube (3 in Fig. 1) has been attached. Heating is continued until the mixture melts. Any silicon tetrafluoride resulting from attack of ammonium fluoride on the glass is absorbed by the alkali. After cooling, the contents of the ball tube are rinsed into the flask, and silicon dioxide powder, phosphoric acid, and 1.2 g of precipitated barium phosphate are added. Before introducing the superheated steam, the volume of the solution must be reduced to the original volume of the 85 % phosphoric acid added by heating with the heating mantle. The reliability of the procedure is shown by the five examples set out in Table 2.

Table 2. Analysis of five samples of NaF + $KNO_3$ (≈1:1).

| NaF [mg] | 0.1 N KSCN [ml] | F found [mg] | F calc. [mg] | Deviation [%] |
|---|---|---|---|---|
| 46.5 | 11.00 | 20.90 | 21.00 | −0.5 |
| 64.0 | 15.28 | 29.00 | 28.95 | +0.15 |
| 54.0 | 12.95 | 24.6 | 24.4 | +0.9 |
| 63.9 | 15.15 | 28.8 | 28.9 | −0.4 |
| 42.1 | 10.1 | 19.2 | 19.1 | |

Figure 2 shows a graph of the relative error of the fluorine determination on 100 samples, most of which contained 1–6 mg-at. of fluorine plus varying amounts

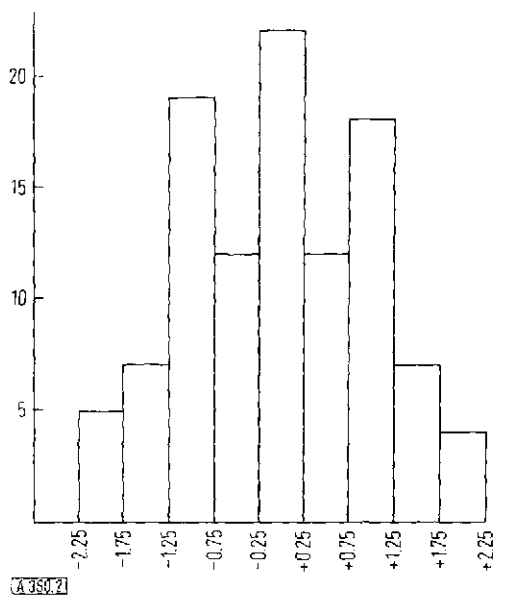



Fig. 2. Relative errors in 100 determinations of fluorine by the silver fluoride method.
Ordinate: Number of analyses.
Abscissa: Relative error [%].

of $Cl^-$, $Br^-$, $I^-$, $NO_3^-$, $SO_4^{2-}$, $Ca^{2+}$, $Pb^{2+}$, $Th^{4+}$, or $B(OH)_3$. The symmetrical distribution of deviations indicates that the procedure does not involve any systematic error. The mean error is found to be ±1.0 %. This also includes the general errors associated with volumetric determinations, *i.e.* inaccuracies of weighing, reading, *etc.*

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# Equilibrium and Nonequilibrium in the Glycolysis System [*]

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*Dedicated in gratitude and admiration to Otto Warburg on the occasion of his 80th birthday*

*The relationship between the metabolic throughput within the network of energy-furnishing metabolism and the deviation of its composite reacting units from equilibrium is discussed. Measurements have been made of the steady-state relaxation times, and, following a suggestion by Alberty, their application is described. The results confirm and extend the concepts of intracellular redox relationships which the authors' research group outlined five years ago in this journal. The maximum difference between the redox potentials of the lactate/pyruvate and of the DPN/DPNH systems was calculated to be 2 mV. Deviations of the α-glycerophosphate/dihydroxyacetone phosphate system measured in vivo are correlated with the rate of flow in the glycerophosphate cycle.*

## 1. Ordering of Nonequilibria

(The principle of opposing changes of potential differences)

The phenomenon of continuous nonequilibrium in living matter is an old problem in the philosophy of nature. A quantitative exploration was started by *Liebig*'s "law of minimum" and by *Blackman*'s concept of the "limiting factor". Especially *Blackman*'s statement "...the rate of a process is limited by the pace of the slowest factor" [1] as well as consecutively coined terms like "rate-limiting reaction" [2,3] "master reaction" [4,5], "pace-maker" [6], "bottle-neck", etc. not only describe but also require a formal and quantitative arrangement of nonequilibria within the living material.

The main point in this connection may well be illustrated by comparing wild and controlled streaming of a river. Figure 1a represents an uncontrolled waterway, in which the total gradient is distributed approximately equally among the various section along the flow line. The same flow may be tamed by constructing flood gates; the river is thus divided into reservoir – or backwater – and waterfall sections (Fig. 1b). The greater cross-sectional area of the water in the dammed up zone offers less resistance to flow and thus compensates for the minute gradients existing in the river before the dam.

*Michaelis* used a similar model (locks regulating a waterway) in describing redox pathways [7]. From the organizational point of view, the ordering of nonequilibria produced by regulation of the waterway has three effects: it facilitates control of the levels and of the rate of flow

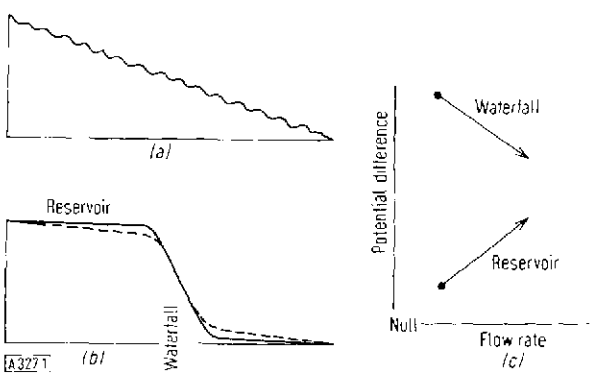



Fig. 1. Schematic representation of (a) an unregulated waterway, (b) a regulated stream, and (c) the changes in the potential gradient at increasing rates of flow (throughput).

and it concentrates the capacity of the system to do useful work. To regulate the rate of flow of water or, more generally spoken, to regulate the *throughput* of matter within the system, the "flood gate" need only be raised or lowered.

As the throughput increases, the gradients undergo a characteristic change, as shown by the dashed lines in Figure 1b. The rate-controlling factor, *i.e.* the potential drop at the "flood gate", decreases, while at the same time the potential difference between the two ends of the reservoir increases. This is indicated graphically in Figure 1c. This *principle of opposing changes in potential differences* is always encountered when a waterway (or a metabolic chain) is subdivided by "flood gates" (or limiting steps). It can help us in locating such limiting steps and their controlling factors.

[*] This article is based in part on the manuscripts of lectures presented to the meetings of the Gesellschaft für Physiologische Chemie in Berlin, autumn 1959, and the Belgian Society for Biological Chemistry in Louvain, spring 1962. The work described was supported by the special Program on "Experimental Cell Research" of the Deutsche Forschungsgemeinschaft.

[1] *F. F. Blackman*, Ann. Bot. (London) *19*, 281 (1905).

[2] *A. Pütter*, Z. allg. Physiol. *16*, 574 (1914).

[3] *H. Holzer* in: Biologie und Wirkung der Fermente, 4. Colloquium der Gesellschaft für physiologische Chemie. Springer, Berlin–Göttingen–Heidelberg 1953, in particular p. 89.

[4] *A. C. Burton*, J. cell. comp. Physiol. *9*, 1 (1936); *14*, 327 (1939).

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[6] *H. A. Krebs* and *H. L. Kornberg*, Ergebn. Physiol., biol. Chem. exp. Pharmakol. *49*, 212 (1957).

[7] *L. Michaelis*: Oxydations-Reduktionspotentiale mit besonderer Berücksichtigung ihrer physiologischen Bedeutung. 2nd Edit. Springer, Berlin–Göttingen–Heidelberg 1933.

## 2. An Example

(Metabolic patterns of skeletal muscle)

Tissues in which the metabolic rate can change considerably and at short notice as a function of the activity of the system provide a fairly simple object on which to test the above principle. Voluntary skeletal muscle is an example. In it, the rate of energy-releasing metabolism can increase by several orders of magnitude, especially in the Embden-Meyerhof glycolytic reaction chain (Fig. 2). Recently, *Hohorst* et al. [8,9] studied the changes in the metabolite pattern of the Embden-Meyerhof pathway of rat abdominal wall muscle when the latter went into tetanic contraction. Figure 3 shows some of these measurements. If we want to interpret them via the model of the regulated river, we must first calculate *ratios of the "levels"* (see [40a]) *of the metabolites* [10, 11] and compare these ratios with the known (apparent) equilibrium constants. By convention, the levels of the reaction products are placed in the numerators of the ratios. Equilibrium constants are also presented in the Figure. These can be found without difficulty for most pairs of metabolites, since they belong to two-component reactions [12] (see [*] on p. 431). However, a special assumption

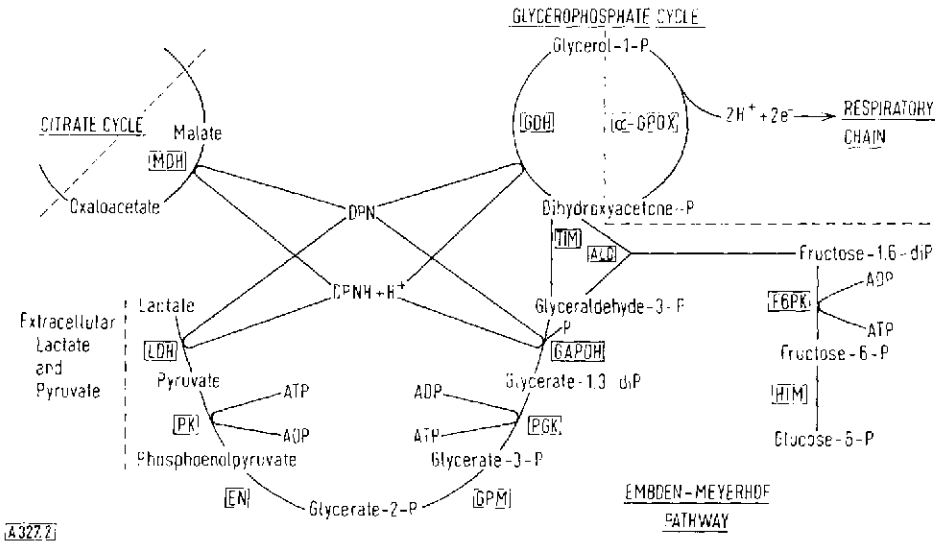



Fig. 2. Schematic diagram of the interrelationships in carbohydrate metabolism [*]

[*] The following abbreviations are used in this paper:

| | |
|---|---|
| ALD | = aldolase |
| ADP | = adenosine diphosphate |
| ATP | = adenosine triphosphate |
| DAP | = dihydroxyacetone phosphate |
| DPN | = diphosphopyridine nucleotide |
| DPNH | = reduced DPN |
| EN | = enolase |
| FDP | = fructose-1,6-diphosphate |
| F6P | = fructose-6-phosphate |
| F6PK | = phosphohexokinase (6-phosphofructokinase) |
| GAP | = glyceraldehyde-3-phosphate |
| GAPDH | = phosphoglyceraldehyde dehydrogenase |
| GDH | = glycerol-1-phosphate dehydrogenase |
| α-GP | = glycerol-1-phosphate (α-glycerophosphate) |
| G6P | = glucose-6-phosphate |
| GPM | = phosphoglyceric mutase |
| α-GPOX | = glycerol-1-phosphate oxidase |
| HIM | = phosphohexose isomerase |
| Lac | = lactate |
| LDH | = lactic dehydrogenase |
| MDH | = malic dehydrogenase |
| P | = inorganic phosphate |
| PEP | = phosphoenolpyruvate |
| PGK | = phosphoglycerokinase (ATP phosphoglyceric transphosphorylase) |
| PGA | = phosphoglyceric acid (glycerate phosphate) |
| PK | = pyruvate phosphokinase |
| Pyr | = pyruvate |
| TIM | = triosephosphate isomerase |

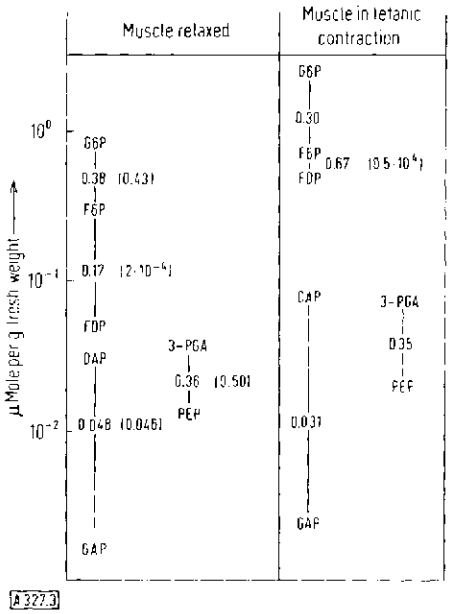



Fig. 3. Metabolite levels in rat abdominal muscle [8,9].
For the analytical method, see [11]. Ratios calculated from metabolite levels are included between metabolite pairs, while (apparent) equilibrium constants [16] are in parentheses. In the case of phosphohexokinase ratios [see Equation (a), p. 428], the [ATP]/[ADP] ratio was calculated from the levels of creatine phosphate (CP) and Creatine (C):
$[ATP]/[ADP] = 10 \times \{CP\}/\{C\}$.
$[FDP]/[F6P] = Kapp \times [ATP]/[ADP] = 10 \times 10^{3} \times \{CP\}/\{C\}$.


[8] *H. J. Hohorst, M. Reim,* and *H. Bartels,* Biochem. biophys. Res. Commun. *7*, 137, 142 (1962).

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[10] *Th. Bücher* and *M. Klingenberg,* Angew. Chem. *70*, 552 (1958).

[11] *H. J. Hohorst, F. H. Kreutz,* and *Th. Bücher,* Biochem. Z. *332*, 18 (1959).

[12] *Th. Bücher,* Pure appl. Chem. *6*, 209 (1963).

must be made for the pair F6P/FDP (see legend to Fig. 3), since it is part of a four-partner reaction.

Comparison of the ratios of the steady-state metabolite levels with the equilibrium constants reveals two facts:

1. The ratios can be classified into two categories: the first contains ratios which are of the same order of magnitude as the equilibrium constants; here the difference of potentials is small. In the second case (F6P/FDP), there is considerable difference between the two; there exists a considerable drop of potential.

2. As a consequence of the transition from the quiescent to the active state of the muscle, ratios of the first category show a decrease, while those of the second category show an increase (F6P/FDP by a factor of 4).

Employing the concepts developed in Section 1, it is obvious that the following reaction which is catalysed by the enzyme phosphofructokinase (see also Figure 2):

Fructose-6-phosphate + ATP
$\Downarrow\Uparrow$ F 6 PK (a)
Fructose-1,6-diphosphate + ADP

is a limiting step. We can attribute the other metabolite pairs to the sections with a low gradient of the chemical potential.

In a somewhat similar fashion, *Holzer* and *Holldorf* [13] defined "rate-controlling reactions" and "equilibrium reactions" (hexose monophosphate isomerase, aldolase, triose phosphate isomerase, alcohol dehydrogenase) for the fermentation process in yeast. *Hess* [14] divides the complete sequence of metabolites of glycolysis in Ehrlich ascites tumors into three groups of "quasi-equilibrium intermediates", separated or controlled by "quasi-irreversible" reactions: phosphohexokinase, phosphoglyceric kinase, and pyruvic phosphokinase. His values and those of *Mann* et al. [15], who also performed pioneer work on the dynamics of the *metabolite pattern*, are shown in Table 1.

Table 1. Ratios of metabolite levels in various cells. Apparent equilibrium constants $K_{app}$ [16] are given in parentheses in the first column.

| | Yeast [15] | Ascites tumor [14] | Skeletal muscle [7] Rest | Work |
|---|---|---|---|---|
| G6P/F6P (0.43) | 0.33 | 0.23 | 0.38 | 0.30 |
| 3-PGA/2-PGA (0.17) | 0.45 | 0.43 | 0.12 | 0.30 |
| 2-PGA/PEP (3.0) | | 1.6 | 3.0 | |

## 3. Limiting Steps

(Energetics and Definitions)

It has already been mentioned that organization of a system into "low-gradient" sections with an intervening potential drop "concentrates" its ability to do useful work: metabolic "power-plants" can only be located within a range involving a drastic drop of potential. At the same time, it should be kept in mind that the production of a maximum amount of useful work destroys the nonequilibrium and thus removes the possibility of control. The variability and controllability of a system require that at least one unidirectional step (nonequilibrium) is involved [17].

However, an ideally functioning power plant can also act as an *indirect* controlling factor in the system, for the resistance it offers depends upon the output it produces. Since it is coupled to the process which utilizes the free energy of the system, the controlling nonequilibrium is shifted towards the energy-consuming process. Such relationships are of fundamental importance in the control of energy-supplying metabolism via the cyclic participation of phosphate. In this sense, the "cross-over" theorem of *Chance* [18] may be regarded as a special case of the principle outlined above of opposing directions of changes in the potential gradients that is applicable to the region of *indirect* controlling factors.

The phosphofructokinase reaction, the limiting step in the section of the Embden-Meyerhof pathway treated in Figure 3, is not a power plant, *i.e.* it does not produce energy for the cycle. It is thus a *direct* controlling step. As such, it transforms a considerable quantity of free energy into heat. This is analogous to the problem of maintaining pressure in a leaky vessel. Maintenance of a steady nonequilibrium in such a chain of reactions is accompanied by a continuous transformation of free energy into heat [19, 20]. The *work* per unit of time per unit of volume required, which is represented by L in Equation (1), is proportional to the *metabolic throughput* $V_{st}$ (molarity per unit of time) and to the potential difference (*deviation from equilibrium* [*]).

$$L = V_{st} RT \ln \frac{\Gamma}{K_{app}} \qquad (1)$$

where $K_{app}$ = the thermodynamic equilibrium constant, see Equation (2), and $\Gamma$ = "mass-action ratio" of nonequilibrium, see Equation (4).

The continuous loss of free energy is small in those parts of the reaction chain where the potential differences and hence the deviations from equilibrium are small, but is large in the phosphofructokinase reaction. This is the energy price which the system must pay for its ability to vary its throughput.

Equation (1) follows from the thermodynamic definition of *equilibrium* and *nonequilibrium*. It is known that at equilibrium, the work which the system is capable of

[13] *H. Holzer* and *A. Holldorf* in *W. Ruhland:* Handbuch der Pflanzenphysiologie. Springer, Berlin–Göttingen–Heidelberg 1906, Vol. XII/1.

[14] *B. Hess* in *P. Karlson:* Funktionelle und morphologische Organisation der Zelle. Springer, Berlin-Göttingen-Heidelberg 1963.

[15] *P. F. E. Mann, W. E. Trevelyan,* and *J. S. Harrison* in: Recent Studies in Yeast and their Significance in Industry. Society of Chemical Industry, London 1958, in particular p. 68.

[16] *K. Burton,* Ergebn. Physiol., biol. Chem. exp. Pharmakol. *49,* 275 (1957).

[17] *H. Mittelstaedt:* Regelungsvorgänge in der Biologie, Beihefte zur Regelungstechnik. R. Oldenbourg, München 1956.

[*] $\ln \Gamma/K_{app}$ is approximated by $\Gamma/K_{app}-1$ in the neighborhood of $\Gamma/K_{app}=1$. Terms like $\Gamma/K_{app}-1$ may serve also as expressions for the *deviation* of the "mass-action ratio" from equilibrium in the treatment of the "small-deviation" sections of the metabolic pathway.

[18] *B. Chance* and *G. R. Williams,* Adv. Enzymol. *17,* 65 (1956).

[19] *W. Kuhn,* Ergebn. Enzymol. *5,* 1 (1936); Angew. Chem. *48,* 215 (1936).

[20] *L. v. Bertalanffy:* Biophysik des Fließgleichgewichts. Sammlung Vieweg, Braunschweig 1953.

doing is zero, while the entropy reaches a maximum ($dS = 0$). In this sense, equilibrium is a static condition. The observed concentrations or, to be exact, the activities of the reaction partners obey the law of mass action.

$$K_{app} = \frac{[P][Q]\cdots}{[A][B]\cdots} \qquad (2)$$

Nonequilibria can be "stationary", "nonstationary", or "steady" [*]. The stationary-state nonequilibrium is also called "flow-equilibrium" [20a].

## 4. Pacemakers

*Krebs* and *Kornberg* [6] wrote the following about the pacemaker reaction: "There is a general principle which may guide the search for pacemakers. As pacemakers are reactions of variable rate, the level of substrate concentration of the pacemaker must vary inversely with the rate: it must increase when the reaction rate decreases." In view of this definition, can the phosphohexokinase reaction be classified as a pacemaker reaction? It can be seen in Figure 3 that the metabolite levels of both F6P and FDP increase with the flow rate. Thus, the change produced is opposite to that required by *Krebs* and *Kornberg* for a "pacemaker". Actually, this phenomenon is caused by other limiting reactions taking place upstream from the metabolic sequence in question, *viz.* by the phosphorylase reaction and the glucokinase reaction. In particular, activation of phosphorylase causes the instantaneous discharge of glucose phosphates from the glycogen reservoir [21–23]. This can also be seen in Figure 3.

The above facts also explain why the phosphofructokinase reaction has been omitted from consideration in so many articles on regulation of glycolysis.

Although we cannot enter here into a detailed discussion of some recent findings concerning the functions and mechanism of this reaction [10,24–27], it is worthwhile calling attention to the advantages of analyzing processes in terms of relative rather than absolute changes in metabolite levels.

## 5. Metabolite Patterns at Rest and during Activity

(The principle of functional readiness)

In principle, a single controlling step is sufficient for control of any metabolic chain [4,5]. However, as has just been discussed, glycolysis in muscle involves *several* limiting reactions. Since we are dealing with a biological system, it is permissible to inquire about the purpose of this greater complexity.

Our problem may be considered in terms of the need for reversibility of the metabolic flow. Since the free energy is stored in standardized quantities as "high-energy" phosphate compounds and since chemical potential is consumed in this form, energetically practicable sections must be present, just as series of locks are usually needed between the higher and lower levels of a canal.

Another aspect of the problem which has received even less attention [12,27] is "functional readiness". In the metabolic organization, the entry of new substrate molecules into the glycolytic pathway is controlled by the pathway's output. The existence of this coupling means that, after disappearance of intermediate metabolites, the flow through the pathway can be restored to a steady state only after a long induction period. In fermentation research, this well-known phenomenon is called "Angärung". However, in rapidly responding tissues, such as skeletal muscle, the power output and consequently the metabolic throughput may change within a fraction of a second. Here not only well-filled energy reservoirs are required, but also a preparation of the metabolite pattern at rest counteracting any depletion of intermediate levels.

In the two sections of Figure 3, the throughput differs by at least a factor of 100. In view of this, any changes observed in the pattern of the metabolite levels, and especially any changes in their relative proportions, must be considered as relatively small. This phenomenon becomes meaningful when considered in terms of physiological requirements for functional readiness. *Functional readiness* produced by *homeostasis of cellular metabolite ratios* necessitates the interaction of several controlling reactions. Approximately one-third of the metabolite levels is controlled by these reactions. As is shown impressively in Figure 3, the other two-thirds of the levels approach (and are controlled by) equilibrium. It is with this second fraction of metabolite levels that we shall deal in the following sections.

[*] The term "stationary state" applies to a compound in a reaction sequence where there is a continuous and constant supply of substrate from an infinite reservoir, while "steady state" applies to a compound during a prolonged period of transition. In a muscle at rest the metabolites are in a "stationary state". After stimulation for reversible contraction the metabolites can be considered to be in the "steady state" [20a].


[20a] *R. Estabrook*, personal communication.

[21] *C. F. Cori* in *O. H. Gaebler:* Enzymes, Units of Biochemical Structure and Function. Henry Ford Hospital International Symposium. Academic Press, New York 1956, p. 573.

[22] *C. F. Cori:* Currents in Biochemical Research. Interscience, New York 1956, p. 198.

[23] *W. H. Danforth, E. Helmreich,* and *C. F. Cori,* Proc. nat. Acad. Sci. USA *48*, 1191 (1962).

[24] *H. A. Lardy* and *R. E. Parks* jr. in *O. H. Gaebler:* Enzymes, Units of Biological Structure and Function. Henry Ford Hospital International Symposium. Academic Press, New York 1956, p. 584.

[25] *T. E. Mansour* and *J. M. Mansour,* J. biol. Chemistry *237*, 629 (1962).

[26] *J. V. Passonneau* and *H. O. Lowry,* Biochem. biophys. Res. Commun. *7*, 10 (1962).

[27] *Th. Bücher* in: 7. Symposium der Deutschen Gesellschaft für Endokrinologie. Springer, Berlin–Göttingen–Heidelberg 1961, p. 129.

## 6. Metabolic Throughput and Deviation from Equilibrium

Let us imagine that one of the reacting units in a metabolic pathway (*i.e.* the reactants and the catalytic agent) were momentarily separated from the rest of the active pathway. Just before the separation our reaction, as a link in a metabolic chain, is *deviated from equilibrium* to a certain extent, which is a function of the throughput within the pathway. The isolated reaction would then immediately tend to attain a state of equilibrium. The initial rate (molarity per unit of time) of this relaxation process would be equal to the throughput mentioned.

As an example, let us assume that the enolase reaction system

$$\text{2-Phosphoglycerate} \underset{}{\overset{\text{Enolase}}{\rightleftharpoons}} \text{Phosphoenolpyruvate} + H_2O \qquad \text{(b)}$$

has been isolated from the metabolic sequence of the working muscle, shown in Figures 2 and 3 (*i.e.* we isolate the metabolite, the enzyme, and the activating $Mg^{2+}$).

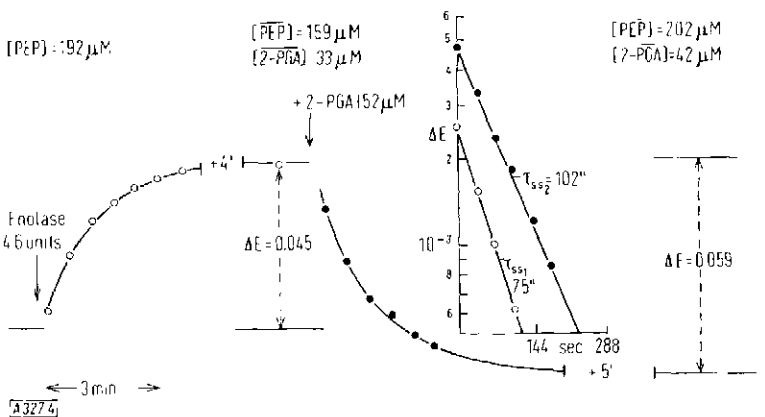



Fig. 4. Attainment of the equilibrium
2-Phosphoglycerate ⇌ Phosphoenolpyruvate
in the enolase reaction. The reaction starts (on the left) following addition of 4.6 units [34a] of enolase from rabbit muscle [34]. Extinction registered at 240 mµ (light path: 1 cm) on a Beckmann DKI instrument. 100 mM imidazole buffer, 0.8 mM $MgSO_4$, pH 6.8, 37 °C. In addition a *semi-logarithmic* plot of the measurements (o and •) is shown, applying corrections for the dilution on addition of substrate. ΔE = Change in extinction.

As *Warburg* and *Christian* have shown [28], the reaction proceeds to equilibrium by a first-order process. Therefore, the reaction rate is always proportional to the deviation $\Delta[A]_t$ of the substrate concentration from the equilibrium value:

$$\frac{d(\Delta[A])}{dt} = k\Delta[A]_t \qquad (3)$$

$$\text{or } \Delta[A]_t = \Delta[A]_o\, e^{-kt}$$

where [A], [P] = arbitrary concentrations of substrate and product and $[\bar{A}]$, $[\bar{P}]$ = concentrations at apparent equilibrium

$\Delta[A] = [A]-[\bar{A}]$ = deviation of the substrate concentration from equilibrium [28a] as in: $\Gamma = ([P] - \Delta[A])/([\bar{A}] + \Delta[A])$ (4)

[28] *O. Warburg* and *W. Christian*, Biochem. Z. *310*, 384 (1941).

With $K_{app} = [\bar{P}]/[\bar{A}]$ we obtain:

$$\Delta[A] = \frac{[A]}{1 + \frac{1}{K_{app}}}\left(1 - \frac{\Gamma}{K_{app}}\right)$$

*or*

$$\Delta[A] = -\frac{[\bar{A}]}{1 + \frac{1}{\Gamma}}\left(\frac{K_{app}}{\Gamma} - 1\right)$$

*or* (4)

$$\Delta[A] = \frac{[P]}{1 + K_{app}}\left(\frac{K_{app}}{\Gamma} - 1\right)$$

*or*

$$\Delta[A] = \frac{[\bar{P}]}{1 + \Gamma}\left(1 - \frac{\Gamma}{K_{app}}\right)$$

In the first part of the enolase experiment (left part of Fig. 4, open circles) this type of kinetics appears straight on from the start (addition of enzyme). If equilibrium is again disturbed by addition of a small amount of metabolite to the system, then the process of relaxation is repeated (full circles in Fig. 4).

The relaxation time [30a] $\tau_{ss}$, the reciprocal of the constant k of the monomolecular reaction

$$\tau_{ss} = \frac{1}{k} \qquad (5)$$

is the time during which the deviation decreases to the e-th part of the initial value. This is also evident from the semi-logarithmic plot in Fig. 4.

Employing the concept developed at the beginning of this Section we replace $\Delta[A]_t$ in Equation (3) by $\Delta[A]_{st}$,

[28a] In a previous article [29], we designated the ratio of concentrations in the mass action equilibrium with Q and in the nonequilibrium with Q. We shall now use $K_{app}$ for the former and the symbol Γ, which has been previously introduced by *W. Kuhn* [19], for the latter. This is done to avoid confusion with the efficient system of notation, developed by *Cleland* for enzyme kinetics [30]. In that system, [Q] is the concentration of a second product, see Equation (14).

[29] *H. Schimassek, B. Kadenbach, W. Rüßmann*, and *Th. Bücher* in *G. Weber:* Advances in Enzyme Regulation. Pergamon Press, London 1963, Vol. 1, p. 103.

[30] *W. W. Cleland*, Biochim. biophysica Acta *67*, 104 (1963).

[30a] The relaxation time $\tau_{ss}$ is understood to be the relaxation time of the enzymic steady state, defined from the point of view of enzyme kinetics. In this case, the notation of *Hammes* and *Alberty* [31] has been used.

the deviation of any reaction in the stationary or even in the steady state of a metabolic sequence, and $-\frac{d(\Delta[A])}{dt}$ by its metabolic throughput $V_{st}$. This yields

$$V_{st} = k\,\Delta[A]_{st} = -\frac{\Delta[A]_{st}}{\tau_{ss}} \quad \text{[molarity per unit of time]} \qquad (6)$$

from which it can be seen that there is a simple relationship between the deviation and the metabolic throughput. This relationship is due to the pioneering work of *Alberty* and his research group [32], who pointed out that Equation (6) is analogous to Ohm's law:

*current = potential/resistance*

In conformity with the relaxation concept itself, Equation (6) is valid only for small deviations from equilibrium. However, it still may be used in practice because fortunately a large number of enzymatically catalysed reactions approach first-order kinetics, even at quite large deviations from equilibrium. Processes which obey this relationship include not only the enolase reaction, which we have used as an example, but also such reactions as the complicated test system of phosphoglyceric kinase [33] (see also Fig. 9).

## 7. $\tau_{ss}$ of the Two-Partner Reaction [*]

(Enolase system)

In conformance with the method of *Hammes* and *Alberty* [31], we can derive the relaxation of an enzymatic reaction from the general equation for the rate of reaction. This general equation is obtained from the Michealis-Haldane theory by assuming steady-state concentrations of the intermediate enzyme-substrate or enzyme-product complexes. We shall use the nomenclature developed by *Cleland* [30], see Equations (1)- (3).

$$-\frac{d[A]}{dt} = \frac{\frac{V_1}{K_a}[A] - \frac{V_2}{K_p}[P]}{1 + \frac{[A]}{K_a} + \frac{[P]}{K_p}} \qquad (7)$$

$K_a$, $K_b$ = Michaelis constants

$V_1$, $V_2$ = maximum velocities of forward and back reactions.

From Equation (4) $[A] = [A] + \Delta[A]$ and $[P] = [P] - \Delta[A]$. When $\Delta[A] \ll [A]$, $[P]$, it follows that

$$-\frac{d\Delta[A]}{dt} = \Delta[A]\,\frac{\frac{V_1}{K_a} + \frac{V_2}{K_p}}{1 + \frac{[A]}{K_a} + \frac{[P]}{K_p}} \qquad (8)$$

Since it also applies that

$$-\frac{d\Delta[A]}{dt} = \frac{\Delta[A]}{\tau_{ss}} \qquad (3)$$

it is also valid that

$$\tau_{ss} = \frac{1 + \frac{[A]}{K_a} + \frac{[P]}{K_p}}{\frac{V_1}{K_a} + \frac{V_2}{K_p}} \qquad (9)$$

By using the "Haldane-Alberty relationship" [32]

$$\frac{V_1 \cdot K_p}{V_2 \cdot K_a} = K_{app} = \frac{[P]}{[A]} \qquad (7a)$$

we obtain

$$\tau_{ss} \cdot V_1 = [P]\,\frac{1 + \frac{V_1}{V_2}}{K_{app} + 1} + \frac{K_{app} K_a}{K_{app} + 1} \qquad (10)$$

Figure 5 summarizes the relaxation measurements made with the enzyme enolase (crystallized from rabbit muscle [34]). Values measured in the experiment discussed above (Fig. 4) are marked with a "plus"

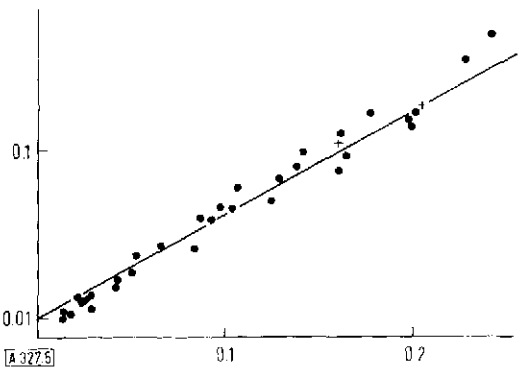



Fig. 5. Enolase reaction: Relaxation time×units of enzyme per unit volume (ordinate) versus equilibrium concentration of phosphoenolpyruvate (abscissa). The "plus" signs mark the values obtained in the experiments represented in Figure 4. Constants for the regression line, see text [Equation (11)].

Ordinate: $\tau_{ss} \cdot V_1$ [mmole/l].

Abscissa: [PEP] [mmole/l].

sign. It can be seen that the relaxation time is a function of the enzymatic acitivty used (established from the rate of the forward reaction $V_1$ [enzyme units [34a] per ml]) and of the metabolite concentrations at equilibrium. By analogy to Equation (10), the regression line is given by Equation (11):

$$\tau_{ss} \cdot V_1 = 0.0056\,[\overline{PEP}] + 0.01 \quad [\mu\text{mole/l}] \qquad (11)$$

where $V_1$ = enzyme units per ml [34a].

To apply these relationships according to the concept outlined in Section 6 and according to the measurements on muscle described in Section 2, we can convert Equations (4) to

$$\Delta[A]_{st} = \frac{[P]}{1 + K_{app}}\left(\frac{K_{app}}{\Gamma} - 1\right) \text{ etc.} \qquad (4a)$$

In this equation, $\Gamma$ is the "mass-action ratio" in steady-state nonequilibrium [see Equations (1) and (4)]. The factor $\Delta[A]_{st}$

[*] Reaction involving a single substrate and a single product, see [12].

[31] *G. G. Hammes* and *R. A. Alberty*, J. Amer. chem. Soc. *82*, 1564 (1960).

[32] *R. A. Alberty*, J. Amer. chem. Soc. *75*, 1928 (1953).

[33] *Th. Bücher*, Biochim. biophysica Acta *1*, 292 (1947).

[34] *R. Czok* and *Th. Bücher*, Adv. Protein Chem. *15*, 315 (1960).

[34a] One enzyme unit corresponds to the conversion of one µmole of substrate per hour in a standard test [35] at the temperature of the relaxation experiment.

has already been defined in connection with Equation (6). We can substitute the relationship given in Equation (4a) for $\Delta[A]_{st}$ in Equation (6), and obtain:

$$V_{st} = \frac{1}{\tau_{ss}} \frac{[\bar{P}]\,(K_{app} - \Gamma)}{K_{app}\,\Gamma + K_{app}} \qquad (6a)$$

To obtain the relaxation time of the tissue enzyme, the value measured *in vitro* is divided by the ratio [enzyme units in tissue]/[enzyme units in the relaxation experiment] (see also [34a]). To obtain these data, the

$$(\tau_{ss})_{tissue} = \frac{(\tau_{ss} \cdot V_1)_{exp.}}{(V_1)_{tissue}} \qquad (12)$$

enolase localized in the muscle is exhaustively extracted and tested under the same conditions (30000 units/g fresh weight at 37 °C) as described for obtaining $V_1$ in the relaxation experiment (4–10 units/ml). Thus, we dare to assume that the enzyme molecule behaves in the same way in a dilute, homogeneous solution as it does in its cellular environment where it is present at a concentration which is many hundred times higher. With this assumption we obtain

$$V_{st} = \frac{(V_1)_{tissue}}{(\tau_{ss} V_1)_{exp.}} \cdot \frac{[\bar{P}](K_{app} - \Gamma)}{K_{app}\,\Gamma + K_{app}} \qquad (13)$$

It is with this assumption that the relationships between the rate of flow in glycolysis in rat abdominal wall muscle at work (see Fig. 3) and the deviation of the enolase reaction from equilibrium are presented in Figure 6 for different equilibrium concentrations of phosphoenolpyruvate. Actually the glycolytic throughput ($V_{st}$) determined *indirectly* from the diagram (Fig. 6) using the deviations ($\Gamma/K_{app}$) measured in the organ (about 0.8, see Table 1) is of the same order of magnitude as the *directly* measured glycolytic throughput (formation of lactate *in situ*): about 5 mmoles per gram of fresh tissue per hour.

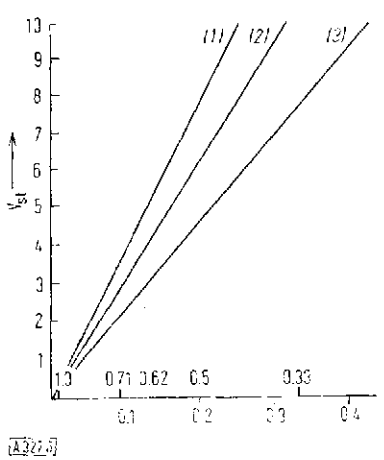



Fig. 6. Relationship between the rate of flow (current density) of glycolysis in muscle (ordinate) and the nonequilibrium of the enolase reaction (abscissa) [Equation (13)].
$(V_1)_{tissue}$ = $30 \times 10^3$ units per g fresh weight; 37 °C
$(\tau_{ss} \cdot V_1)_{exp.}$ obtained from Figure 5.
Curve (1): [P] = 56 mμmole/g fresh weight.
Curve (2): [P] = 28 mμmole/g fresh weight.
Curve (3): [P] = 14 mμmole/g fresh weight.
Ordinate: $V_{st}$ [mmole/h/g fresh weight].
Abscissa: upper scale: $\Gamma/K_{app}$.
lower scale: $[(K_{app}/\Gamma) \quad 1]/[1 + K_{app}]$

## 8. Four-Partner Reaction [*] Near Equilibrium

(Lactate/pyruvate and the extramitochondrial DPNH/DPN system)

The treatment of symmetrical four-component reactions

$$A + B \rightleftharpoons P + Q$$

is considerably more difficult than that of two-component reactions. However, such processes are important, because the action of coupling nucleotides in intermediary metabolism usually takes place via four-component reactions. Therefore, four-component reactions provide information on the state of the coupling nucleotide systems. This information sometimes cannot be obtained in any other way [10, 11, 36]. From the definition of equilibrium, the potential difference between two opposing compounds (*e.g.* lactate and pyruvate, see Equation (c) below) is numerically equal (but of opposite sign) to that of the other pair (*e.g.* DPNH and DPN). Thus the redox potential of the DPNH/DPN system can be calculated from the concentration ratios of the appropriate pair of metabolites if the deviation from equilibrium may be neglected.

Five years ago, we used our own observations and those made by the groups of *Lynen* and *Holzer* [36] to derive some conclusions, applicable to cell physiology, about the redox state of the *extramitochondrial* pyridine nucleotides in the liver [10]. Our evidence that equilibrium is a sufficient approximation for the treatment of the lactic dehydrogenase system was based on the good

$$\text{Pyruvate} + \text{DPNH} + \text{H}^{\oplus} \underset{\text{Lactic dehydrogenase}}{\rightleftharpoons} \text{Lactate} + \text{DPN} \qquad (c)$$

agreement between redox potentials of three DPN-specific extramitochondrial substrate pairs in resting liver [11]. In the meantime, *Hohorst* et al. have shown that this agreement between the redox potentials continues even if the absolute values change, either by cutting off the blood supply (ischemia) [37] or by the influence of the diet or the endocrine situation [38].

*Schimassek* has been able to obtain new evidence by continuing his perfusion experiments on rat liver, using a synthetic medium (see note [a] in Table 3) in a closed-circuit, extracorporeal circulation [39,40]. The possibility of loss of the nascent lactate into metabolizing regions outside the liver is excluded under these conditions. Since there are no opportunities worth men-

[*] A (symmetrical) four-partner reaction involves two substrates and two products.

[35] *Th. Bücher, D. Pette,* and *W. Luh* in *Hoppe-Seyler-Thierfelder:* Handbuch der physiologisch-chemischen Analyse. Springer, Berlin–Göttingen–Heidelberg, in the press.

[36] *H. Holzer, G. Schulze,* and *F. Lynen,* Biochem. Z. *328,* 252 (1956).

[37] *H. J. Hohorst, F. H. Kreutz,* and *M. Reim,* Biochem. biophys. Res. Commun. *4,* 159 (1961).

[38] *H. J. Hohorst, F. H. Kreutz, M. Reim,* and *H. Hübener,* Biochem. biophys. Res. Commun. *4,* 163 (1961); *E. Kirsten, R. Kirsten, H. J. Hohorst,* and *Th. Bücher,* ibid. *4,* 169 (1961).

[39] *H. Schimassek,* Life Sciences *1,* 629, 635 (1962).

[40] *H. Schimassek,* Biochem. Z. *336,* 460, 468 (1963).

tioning for utilizing lactate in the region of the liver parenchyma without the participation of lactic dehydrogenase, the lactate/pyruvate system is thus on a blind alley.

When in the perfusion changes occur of oxygen supply (Fig. 7), or when lactate is added [40], the observed adaptability of the system is indicative of its dynamic characteristics. In this case, the isolated organ produces roughly the same concentrations and redox ratios as those found in blood plasma, even though the volume of the perfusion system is considerably larger (100 ml as compared to 10–15 ml of blood).

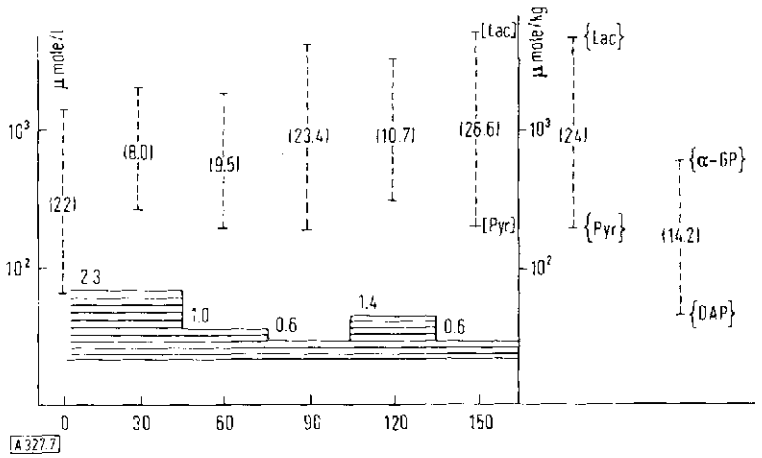



Fig. 7. Perfusion of isolated rat liver with synthetic "blood" (see note [a] in Table 3) in a closed circuit [39,40]. Ordinate: Concentrations of lactate (above) and pyruvate (below) in the medium at various rates of perfusion. Concentration ratios in parentheses. At rates of flow < 1, the oxygen consumption of the tissue (200 µatom/g/h) is not completely accounted for. The high quotient at the start of the experiment is a result of the ischemia of the organ during its transfer to the artificial circuit.

The metabolite levels (see [40a]) in the perfused liver at the end of the experiment are shown on the right: $(\{\alpha\text{-GP}\}/\{\text{DAP}\}) \times (\{\text{Pyruvate}\}/\{\text{Lactate}\}) = 0.59$ (cf. Table 4).

The figures above the profile diagram at the bottom of the section on the left indicate the rates of flow in ml/min per g of liver.

Ordinate: Concentration [µmole/l] or level [µmole/kg fresh weight]. Abscissa: Time [min].

Furthermore, it follows from these experiments that there is agreement between the levels [40a] of metabolites found in the cells by tissue analysis and the concentrations measured in the perfusion fluid

Table 2. Perfusion of isolated liver in closed system. Metabolite levels in the tissue (corrected for the content of medium and interstitial fluid) and in the medium after three hours' perfusion under standard conditions [40].

| | Cellular [*] level [11] [mmole/kg] | Concentration[*] in medium [mmole/liter] |
|---|---|---|
| Lactate | 3.5 | 3.5 |
| Pyruvate | 0.37 | 0.33 |
| Lactate/Pyruvate | 9.5 | 10.5 |

[*] See also [40a].

[40a] The term "level" is used to express analytical data in the form of moles (millimoles, micromoles) per gramm of fresh weight of whole tissue ("Gewebsgehalt" [11,37]) or of the intracellular tissue fraction ("Zellulargehalt", corrected for the extracellular space). The term "concentration" has the meaning of moles per liter of cellular or extracellular water (thermodynamic concentration). { } indicate levels, [ ] indicate concentrations.

(Table 2). *Lynen*'s postulate [41] "that the calculation of absolute concentrations from analytical data is meaningless if the cell structure is destroyed to obtain them" does not hold in this case. On the contrary, the conditions described in *Schimassek*'s system permit completely objective and meaningul correlation of the absolute levels of metabolites with *cellular concentrations* which can be evaluated thermodynamically.

Thus, the redox potential calculated from cellular levels is thermodynamically valid, and *Schimassek*'s experiments deserve special consideration because of the fundamental significance of the redox potential in the extramitochondrial DPNH/DPN system. In the section which follows we shall present further (kinetic) evidence to show that the lactate/pyruvate system is a useful indicator of this potential.

In studies, of which we were unaware when writing previous papers, *Huckabee* [42] demonstrated the following in man and in animal experiments: it is the lactate/pyruvate ratio and not the change in the lactate level of plasma which is relevant for detection of an oxygen deficiency in cells. He was able to produce large fluctuations in the lactate level without affecting the lactate/pyruvate ratio by injecting either the metabolites or bicarbonate and by hyperventilation. This offers a close analogy to the perfusion experiments described above.

Table 3. Effect of various perfusion conditions on the lactate/pyruvate ratio in the liver and in perfusion medium [40].

| Perfusion conditions | Organ $\frac{\{\text{Lactate}\}}{\{\text{Pyruvate}\}}$ | Medium $\frac{[\text{Lactate}]}{[\text{Pyruvate}]}$ |
|---|---|---|
| Homologous blood | 9.6 | 8.0 |
| Synthetic medium [a] | | |
| Control | 10 | 10 |
| Reduced perfusion rate | 25 | 26 |
| Addition of prednisolone (perfusion rate normal) | 17.7 | 18.2 |

[a] Tyrode solution, serum albumin, cattle erythrocytes [39].

This aspect is expanded in Table 3. The Table demonstrates the effects of regulatory mechanisms on the redox potential in the extramitochondrial, DPN-specific area

[41] *F. Lynen* in: Proceedings of the International Symposium on Enzyme Chemistry, Tokyo and Kyoto 1957. Pergamon Press, London 1958, in particular p. 28.

[42] *W. Huckabee*, J. clin. Invest. *37*, 244, 255, 264 (1958).

in an extracorporeal system, as has already been partially done by *Hohorst* et al. [38] in animal experiments.

The agreement between the redox potentials in tissue and plasma leads us to conclude that the interstitial fluid and blood plasma are to a certain extent, "*common-level reservoires*" of the *extramitochondrial* lactic dehydrogenase system of the cells of an organ and, in the final analysis, of any organ [10] (Fig. 8). *Klingenberg* [43] recently

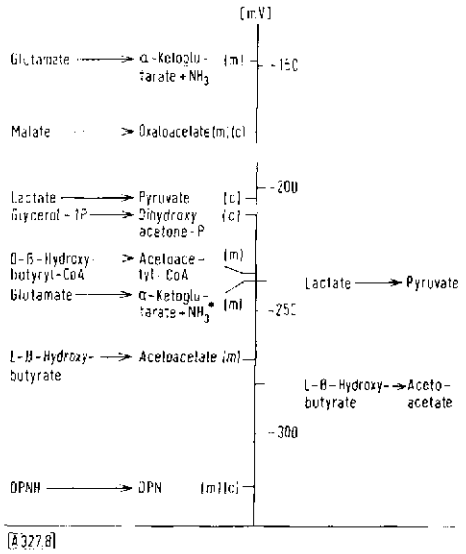



Fig. 8. On the coordination of cellular redox potentials by the blood plasma. Left: Mid-potentials [43a] of cellular redox systems at pH 7 and 37 °C. Right: Potentials ("1st" potentials [10]) of the redox systems in blood plasma. The systems of the extramitochondrial region (marked with (c), c-region [10, 52]) of cells (left) are coupled via the lactate/pyruvate system (right). The homeostasis of this potential forms the basis for the redox variation in DPN-dependent systems in the extramitochondrial region. Analogous discussions of the mitochondrial (m)-systems for the β-hydroxybutyrate/acetoacetate pair in plasma can be found in [43] and [44–46].
*$[NH_3]$ in mmole/l.

extended this hypothesis to the coupling of *mitochondrial* compartments with the β-hydroxybutyrate/acetoacetate system (see also [45, 46]).

## 9. The Deviation $K_{app}/\Gamma$-1 of the Four-Partner Reaction

(Indicator error at the indirect determination of the DPN/DPNH-potential)

As the experiment represented in Fig. 9 shows, measurement of the relaxation times in a four-component reaction does not involve much greater difficulties in the optical assay than the measurement of two-component reactions. The difficulties mentioned above with regard to the evaluation of results arise from the much more complicated enzyme mechanisms and the larger number of reactants.

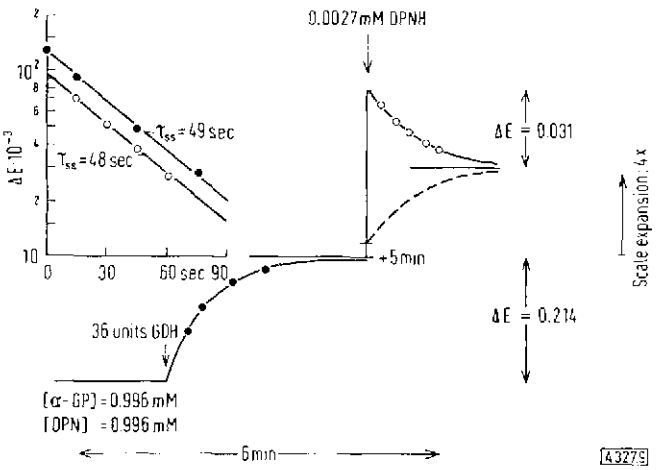



Fig. 9. Attainment of the equilibrium and relaxation (after addition of DPNH) of the glycerophosphate dehydrogenase reaction

$$\text{Dihydroxyacetone phosphate} + \text{DPNH} + \text{H}^+ \;\underset{\text{GDH}}{\rightleftarrows}\; \text{L-Glycerol-1-phosphate} + \text{DPN} \qquad \text{(d)}$$

measured by an optical assay. The reaction starts (on the left) on addition of 36 units/ml of GDH from rabbit muscle [34]. Measurements were made at 334 mμ (light path: 4 cm) on an Eppendorf Photometer. Scale expanded 4× before addition of a small amount of DPNH. $KH_2PO_4$/$K_2HPO_4$ buffer, ionic strength $\mu$ = 200 mM, pH 6.88, 37 °C. The dashed curve indicates the decrease in the concentration of dihydroxyacetone phosphate; this was calculated on the assumption that $\Delta DAP = \Delta DPNH$.

The special case in which one of the metabolite concentrations remains constant and the concentrations of two other reactants are adjusted in such a way that they are large in comparison to the deviation $\Delta[A]_t$ (see Equa-

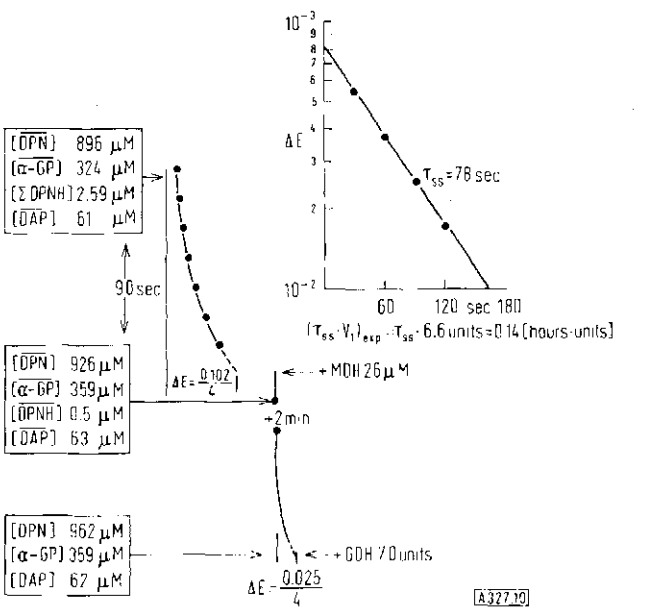



Fig. 10. Relaxation of the glycerophosphate dehydrogenase reaction after addition of enough malic dehydrogenase (as DPNH binding protein) to buffer the DPNH. The reaction starts (at the bottom) on addition of 7 units of enzyme per ml in accordance with Figure 9. Measurements at 334 mμ (light path: 2 cm) with an Eppendorf Photometer [46b]; Scale expansion 4×; K phosphate buffer, ionic strength $\mu$ = 60 mM; 0.7 mM EDTA; pH 7.2; 25 °C. Addition of 26 μmoles/l of malic dehydrogenase ($36 \times 10^3$ g/mole) results in an unspecific increase in the extinction. [ΣDPNH] = free DPNH + DPNH linked to MDH.

[43] *M. Klingenberg* and *H. v. Häfen*, Biochem. Z. *337*, 120 (1963).

[43a] *M. Klingenberg* and *Th. Bücher*, Annual Rev. Biochem. *29*, 669 (1960).

[44] *P. Borst* in: Proceedings of the Fifth International Congress of Biochemistry, Moscow 1961. Pergamon Press, London 1963, Vol. II, in particular p. 233.

[45] *P. Borst* in *Th. Bücher:* Redoxfunktionen cytoplasmatischer Strukturen, Symposium, Vienna 1962. Wiener Medizinische Akademie für Ärztliche Fortbildung. Vienna 1962, in particular p. 189.

[46] *P. Borst* in *P. Karlson:* Funktionelle und Morphologische Organisation der Zelle. Springer, Berlin–Göttingen–Heidelberg 1963.

tion (3) on p. 430) is feasible from the experimental standpoint. It is also justified from the standpoint of cell physiology, provided steady-state metabolism exists in the tissues. Such an arrangement, in which the numerical values were chosen in conformity with cellular ratios, is presented in Figure 10.

The departure from equilibrium is produced by addition of a DPNH-binding protein (dialysed malic dehydrogenase [46a] in a buffering concentration). The MDH protein binds 1 mole of DPNH per $36\times10^3$g. The dissociation constant was determined by fluorimetric titration with DPNH in the presence of DPN, α-GP, and DAP.

$$K_{DPNH\text{-}MDH} = \frac{[MDH]\,[DPNH]}{[\overline{MDH-DPNH}]} = 3\ [\mu mole/l]$$

Titration also showed that the rate at which the MDH-DPNH complex is formed does not produce any appreciable error in the results. The reaction was followed at 334 mμ, roughly at an isosbestic point [47]. Relaxation times measured at 25 °C and based on one enzyme unit per ml were roughly identical for lactic and glycerophosphate dehydrogenases from rabbit muscle [34, 46b]. In a large number of experiments, they ranged from 0.12 to 0.25 h/unit/ml. There was interference due to the superposition of a small but constant background decrease in extinction of unknown cause on the observed variation in extinction. With the large scale expansion required, accurate determination of the absolute values was thus difficult.

If, in analogy to Equation (4), we set up an equation for the symmetrical four-component reaction:

$$\Gamma = \frac{[P]\,[Q]}{[A]\,[B]} = \frac{([P]-\Delta[B])([Q]-\Delta[B])}{([\overline{A}]+\Delta[B])([\overline{B}]+\Delta[B])} \qquad (14)$$

then, assuming that [A] = const. (A = DPNH)

$$\Gamma = K_{app}\,\frac{1-\dfrac{\Delta[B]}{[\overline{P}]}\cdot\dfrac{\Delta[B]}{[\overline{Q}]}+\dfrac{(\Delta[B])^2}{[\overline{P}]\,[\overline{Q}]}}{1+\dfrac{\Delta[B]}{[\overline{B}]}} \qquad (15)$$

If we also assume

$$\frac{\Delta[B]}{[\overline{P}]} \ll 1 \text{ and } \frac{\Delta[B]}{[\overline{Q}]} \ll 1$$

(where B = pyruvate or dihydroxyacetone phosphate), then Equation (15) can be simplified to

$$\frac{\Delta[B]}{[\overline{B}]} = \frac{K_{app}}{\Gamma} - 1 \qquad (16)$$

By using Equations (6), (12), and (16), we obtain

$$\left(\frac{V_{st}}{V_1}\right)_{tissue} = \frac{[\overline{B}]_{st}}{(\tau_{ss}\cdot V_1)_{exp}}\left(\frac{K_{app}}{\Gamma} - 1\right) \qquad (17)$$

which is analogous to Equation (13).

Equation (17), obtained by making these simplifying assumptions, is evaluated in Figure 11 as a function of the relaxation times mentioned above of the DPN-specific dehydrogenases. The relationship between the rate of flow $V_{st}$ and the maximum enzymatic activity $V_1$ of the tissue is plotted on the ordinate. Thus, the curve can be used for evaluating the relationships existing in various tissues. However, it should be kept in mind that $(\tau_{ss}\cdot V_1)_{exp}$ was measured only with glycerophosphate and lactic dehydrogenases from skeletal muscle of rabbit.

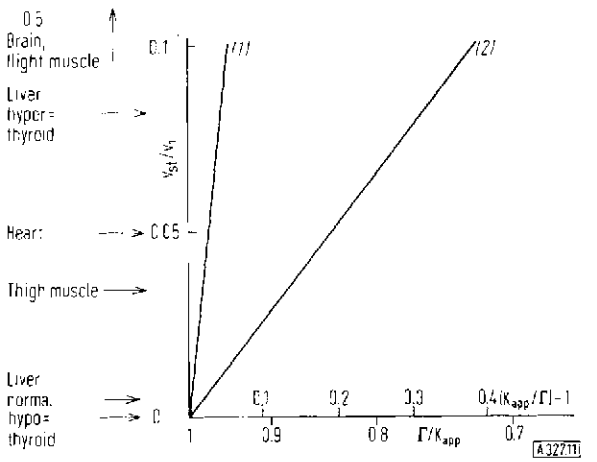



Fig. 11. Relationships between the rate of flow and the deviation of the mass-action ratio $K_{app}/\Gamma$-1 in the lactic dehydrogenase reaction (1) and in the glycerophosphate dehydrogenase reaction (2) [Equation (17)].

Curve (1): $[\overline{B}] = 0.3$ mmole/l.

Curve (2): $[\overline{B}] = 0.04$ mmole/l.

$(\tau_{ss}\cdot V_1)exp = 0.15$ mmole/l.

Ordinate: $Vst/V_1$.

Abscissa: upper scale: $(K_{app}/\Gamma)-1$.
lower scale: $\Gamma/K_{app}$.

The arrows on the ordinate indicate the proportions of the enzymatic activity of α-GPOX and GDH (cf. Table 5, Column 5) in rat tissues and in the flight muscle of the locust.

The straight line with the greater slope (Curve 1), corresponding to a pyruvate concentration of 0.3 mmole/l, is the one pertinent to the discussion of the lactic dehydrogenase system, which follows below, whereas the discussion of the glycerophosphate system is given in the last paragraph.

The activity of the lactic dehydrogenase extracted from 1 g of rat liver (fresh weight) and tested *in vitro*, was 30–40 mmole/h at 37 °C. This is the maximum value which can be assigned to $(V_1)_{tissue}$. The minimum value was calculated to be 1.7 mmole/g fresh weight/h, using the value for lactate formation in the organ at the onset of ischemia (Table 4, Column 7). The actual value of $(V_1)_{tissue}$ is probably closer to the upper limit.

As far as the metabolic throughput $V_{st}$ (lactate → pyruvate) is concerned, it can be stated that it must be considerably less than the maximum respiration value in the organ. The maximum respiratory value in rat liver is $0.6\times10^{-3}$ atoms of oxygen per g fresh weight per hour. This value also agrees with the conversion of energy-rich phosphate ($2\times10^{-3}$ atoms/g fresh weight/h) estimated from the ischemia experiments.

The ratio of the maximum value of the metabolic throughput to the minimum $(V_1)_{tissue}$, *i.e.* the upper

[46a] We wish to thank Dr. *H. U. Bergmeyer* of C. F. Boehringer u. Soehne GmbH., Biochemical Division, Tutzing (Germany), for the malic dehydrogenase.

[46b] *G. Beisenherz, H. J. Boltze, Th. Bücher, R. Czok, K. H. Garbade, E. Meyer-Arendt*, and *G. Pfleiderer*, Z. Naturforsch. *8b*, 555 (1953).

[47] *A. Pfleiderer* and *E. Hohnholz*, Biochem. Z. *331*, 245 (1959).

limiting value, is

$$\left(\frac{V_{st}}{V_1}\right)_{max} = \frac{0.6}{1.7} = 0.35. \quad (18)$$

From Fig. 11, Curve 1, this corresponds to a maximum mass-action ratio deviation of 15 % (see also [*] on p. 428).

$$\left(\frac{\Gamma}{K_{app}}\right)_{pyr.-lac.} = 0.85. \quad (19)$$

Since $\tau_{ss}$ is independent of the direction of the deviation, the calculated value of 15 % is valid for both the forward and the reverse reaction. The deviation from the mass-action ratio is proportional to the potential difference

$$\Delta E = -\frac{RT}{2F} \ln \frac{\Gamma}{K_{app}} = 2 \text{ mV}.$$

Our calculation gives a maximum value for the deviation of the redox potential of the DPNH/DPN system from that of the lactate/pyruvate system at the site where the lactic dehydrogenase is operative. Even under extreme conditions, the actual physiological deviation is considerably smaller since the actual rates of flow are very likely to be smaller and, above all, since the actual $(V_1)_{tissue}$ must be assumed to be considerably larger than the value used in the calculation.

These calculations close the ring of evidence around the status of the lactate/pyruvate system in the liver with regard to its use as an indicator for the redox potential of the extramitochondrial DPN/DPNH system. They also show that the indicator error can be neglected.

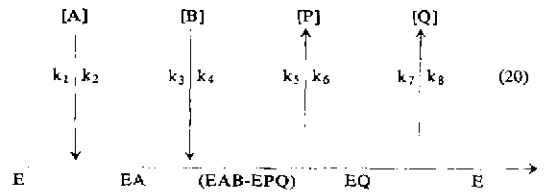
## 10. Glycerophosphate Dehydrogenase

($\tau_{ss}$, calculated and experimental)

Enzymatic catalysis of the reaction $A + B \rightleftharpoons P + Q$ can proceed via several conceivable mechanisms. These were discussed by *Bloomfield* et al. [48] and *Cleland* [30]. As far as the mechanism of the reaction catalysed by glycerophosphate dehydrogenase (von Euler-Baranowski enzyme, see also Fig. 2, top right) is concerned, it can

Dihydroxyacetone phosphate + DPNH + H$^+$
⇅ GDH (d)
L-Glycerol-1-phosphate + DPN

be deduced from fluorimetric titrations that DPNH and DPN react directly with the protein of the enzyme. Our mechanism, which was selected only for approximate calculations, is characterized by the formation of "central complexes". To simplify the calculations and for the sake of greater lucidity, we used an ordered sequence for the formation of transitory complexes, according to the following scheme which was introduced by *Cleland* ("ordered BiBi") [*]:



(20)

By using the method of *King* and *Altmann* (cited in [30]), the following equation for the steady-state reaction rate can be derived from this scheme:

$$-\frac{d[A]}{dt} = \frac{(k_1k_3k_5k_7[A][B] - k_2k_4k_6k_8[P][Q])\,E_t}{k_2(k_4 + k_5)k_7 + k_1(k_4 + k_5)k_7[A] + k_2(k_4 + k_5)k_8[Q] + k_3k_5k_7[B] + k_2k_4k_6[P] + k_1k_3(k_5 + k_7)[A][B] + (k_2 + k_4)k_6k_8[P][Q] + k_1k_4k_6[A][P] + k_1k_3k_6[A][B][P] + k_3k_5k_8[B][Q] + k_3k_6k_8[B][P][Q]} \quad (21)$$

In the nomenclature of *Cleland*, it may be represented in the following manner (see [30], especially p. 127):

$$\frac{d[A]}{dt} = \frac{V_1V_2\left([A][B] - \frac{[P][Q]}{K_{app}}\right)}{K_{ia}K_bV_2 + K_bV_2[A] + K_aV_2[B] + V_2[A][B] + \frac{K_qV_1[P]}{K_{app}} + \frac{K_pV_1[Q]}{K_{app}} + \frac{V_1[P][Q]}{K_{app}} + \frac{K_qV_1[A][P]}{K_{ia}K_{app}} + \frac{K_aV_2[B][Q]}{K_{iq}} + \frac{V_2[A][B][P]}{K_{ip}} + \frac{V_1[B][P][Q]}{K_{ib}K_{app}}} \quad (22)$$

$K_a$ etc. = Michaelis constants (*e. g.* [B] saturating, [P] and [Q] at zero concentration)
$V_1$ = maximum velocity ([A] and [B] saturating, [P] and [Q] at zero concentration)
$V_2$ in analogy to $V_1$ for the reverse reaction
$K_{ia}$ etc. = inhibition constants (dissociation constants of EA etc.)
All constants are in [µmole/l].

The value of $\tau_{ss}$ was obtained by applying a modification of the method of *Hammes* and *Alberty*, which is analogous to that used for the two-component reaction (see page 431). Assuming that $\Delta A \ll [\bar{A}], [\bar{B}], [\bar{P}], [\bar{Q}]$ and applying the very useful "Haldane" relationships given by *Cleland* (see [30], page 128), we obtain:

$$\tau_{ss} \cdot V_1 = \frac{K_{ia} \cdot K_b + K_b[\bar{A}] + K_a[\bar{B}] + [\bar{A}][\bar{B}] + \frac{K_a}{K_{iq}}[\bar{B}][\bar{Q}] + \frac{1}{K_{ip}}[A][\bar{B}][\bar{P}]}{[\bar{A}] + [\bar{B}] + \frac{[\bar{P}] + [\bar{Q}]}{K_{app}}} + \frac{V_1}{V_2K_{app}}\left(\frac{(K_q[\bar{P}] + K_p[\bar{Q}] + [\bar{P}][\bar{Q}] + \frac{K_q}{K_{ia}}[\bar{A}][\bar{P}] + \frac{1}{K_{ib}}[B][\bar{P}][\bar{Q}])}{[\bar{A}] + [\bar{B}] + \frac{[\bar{P}] + [\bar{Q}]}{K_{eq}}}\right) \quad (23)$$

[*] This graphic description of the reaction sequence should be read from left to right. The enzyme is represented by the horizontal line. The free substrates (A, B,...) and products (P, Q,...) lie above it and the transitory complexes beneath. The central complexes (EAB) and (EPQ) are characterized by the fact that they do not participate in bimolecular reactions with substrates or products, but can only undergo (monomolecular) cleavage or isomerization.

[48] *V. Bloomfield, L. Peller*, and *R. A. Alberty*, J. Amer. chem. Soc. *84*, 4365, 4367, 4375 (1962).

If $[\overline{P}]$, $[\overline{Q}]$, and $[\overline{A}]$, $[\overline{B}]$ are constant, then $\tau_{ss} \cdot V_1$ can be expressed as a function of $[\overline{B}]$:

$$\tau_{ss} \cdot V_1 = \frac{\alpha[\overline{B}]^2 + \beta[\overline{B}] + \gamma}{[\overline{B}]^2 + \delta[\overline{B}] + \tau_i} \text{ [µmole/l]} \qquad (24)$$

If we substitute the kinetic constants obtained in the approximation experiments using the method of *Florini* and *Vestling* [48a] and by fluorimetric titration (see Table 4), and if we consider that the terms containing $K_{ib}$ and $K_{ip}$ are sufficiently small to be neglected, then, when

$[\overline{B}] = [\overline{DAP}]$ $\qquad$ $[\overline{P}] = [\alpha\text{-}\overline{GP}] = 200$ µmole/l
$[\overline{A}] \cdot [\overline{B}] = 4$(µmole/l)$^2$ $\qquad$ $[\overline{Q}] = [\overline{DPN}] = 500$ µmole/l

$$\tau_{ss} \cdot V_1 = \frac{350\,[\overline{DAP}]^2 + 117\,[\overline{DAP}] + 80 \times 10^3}{[\overline{DAP}]^2 + 2.7 \times 10^{-2}\,[\overline{DAP}] + 4} \text{ [µmole/l].} \qquad (25)$$

It can be seen that the relaxation time increases with decreasing equilibrium concentrations of $[\overline{DAP}]$. The graph of the function resembles a hyperbola.

Table 4. Kinetic constants.

| Measured by the method of | |
|---|---|
| *Florini* and *Vestling* | Fluorimetry |
| $V_1$ = 3.8 nmole/l/h | $K_{ia}$ = 0.01 µmole/l |
| $V_2$ = 0.8 mmole/l/h | $K_{iq}$ = 2.8 µmole/l |
| $K_a$ = 2 µmole/l | |
| $K_q$ = 30 µmole/l | |
| $K_p$ = 530 µmole/l | |
| $K_q$ = 980 µmole/l | |

25 °C, 50 mmole/l of triethanolamine/HCl buffer, 5 mmole/l of EDTA, pH 7.5, $K_{app} = 2.5 \times 10^4$

Our measurements (Fig. 12) on the relationship between $\tau_{ss} \cdot V_1$ and the equilibrium concentration of dihydroxyacetone phosphate are in agreement with the theory cited above insofar as there is a large variation in $\tau_{ss} \cdot V_1$ in the range of low $[\overline{DPA}]$ concentrations. The shape of the curve also resembles that described by Equation (20). However, the numerical values of $\tau_{ss} \cdot V_1$ calculated from Equation (20) are much higher than the experimental values.

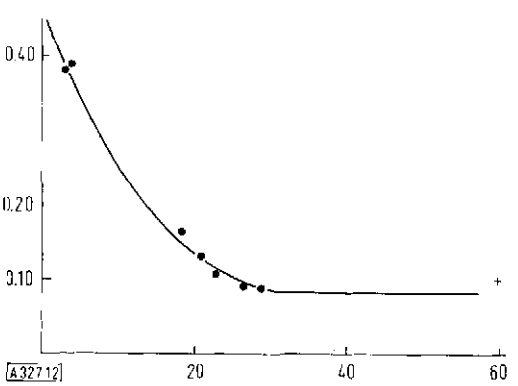



Fig. 12. Glycerophosphate dehydrogenase reaction.
Relaxation time×enzyme units per unit volume (ordinate) versus equilibrium concentration of dihydroxyacetone phosphate (abscissa).
Experiments of the type indicated in Figure 9 ($[\overline{DAP}] \times [\overline{DPNH}]$ approximately constant), but at pH 7.2 with an ionic strength $\mu = 0.1$ mM. The "plus" sign corresponds to the experiment reproduced in Figure 10.
Ordinate: $\tau_{ss} \cdot V_1$ [mmole/l].
Abscissa: $[\overline{DAP}]$ [µmole/l].

[48a] *R. Florini* and *C. S. Vestling*, Biochim. biophysica Acta *25*, 755 (1957).

In view of these discrepancies, it would be advisable, at the present state of the theory, to measure relaxation times directly and not to calculate them by using Michaelis constants (cf. [14]). The adoption of $\tau_{ss}$ as a parameter in mathematical models should prove to be advantageous for the same reason.

## 11. The Glycerophosphate Cycle

The glycerophosphate/dihydroxyacetone phosphate system cannot be treated in the same manner as the lactate/pyruvate system (see Section 9) without introducing some further considerations. First, the cellular activity of GDH is lower by at least one order of magnitude (Table 5, Column 3) than that of LDH (except in the flight muscles of insects [49,50,52]). Second, in conformance with Equation (17), $V_{st}/V_1$ is a function of $[\overline{B}]$. However, $[\overline{B}]$, the metabolite concentration, in the glycerophosphate system is considerably lower than that in the lactate system.

Third, the glycerophosphate system is not isolated in a "blind alley", but oscillates between and is coupled with two different redox systems. In the glycerophosphate cycle (Fig. 2, top right), it is coupled to the extramitochondrial DPNH/DPN system via extramitochondrial glycerophosphate dehydrogenase; in the same cycle, it is coupled to the respiratory cycle via glycerophosphate oxidase (the Meyerhof-Green enzyme). The *mitochondrial reaction*, which is unidirectional under aerobic conditions, is the *controlling reaction*.

Another fact that is also of functional importance is the redox potential of the extramitochondrial DPNH/DPN system, which is considerably more positive (about 80 mV [10,43a–46]) than the mid-potential (Fig. 8). This is indicated by the potential of the lactate/pyruvate system (see Sections 8 and 9).

We have already discussed in previous articles the differences between the redox potentials of the lactate and glycerophosphate systems, in connection with the glycerophosphate cycle [10,49,50]. In order to make use of the more extensive information now available, we have marked the ratios found in various tissues (see Table 5, Column 5) for the activities of glycerophosphate oxidase and glycerophosphate dehydrogenase by arrows at the ordinate of Figure 11 ($V_{st}/V_1$). We assume here that $V_{st}$ is proportional to the activity level of the controlling mitochondrial enzyme and that $(V_1)_{tissue}$ is proportional to the activity level of the extramitochondrial enzyme.

[49] *E. Zebe*, *A. Delbrück*, and *Th. Bücher*, Biochem. Z. *331*, 254 (1959); Ber. Physiol. *189*, 115 (1957).

[50] *Th. Bücher*, "Redoxbeziehungen des α-Glycerophosphats", S.-Ber.Ges. Beförderung ges. Naturwiss. Marburg *85*, 383 (1963).

[51] *Y. P. Lee* and *H. A. Lardy*, Fed. Proc. *20*, 224 (1961); *Y. P. Lee*, *A. E. Takemori*, and *H. A. Lardy*, J. biol. Chemistry *234*, 305 (1959) [51a].

[51a] Inadvertently the second paper in ref. [51] was not quoted in our previous publications [12] and [29].

[52] *A. Delbrück*, *E. Zebe*, and *Th. Bücher*, Biochem. Z. *331*, 273 (1959).

Table 5. On the cellular state of the lactate/pyruvate and glycerophosphate/dihydroxyacetone phosphate systems: Levels of enzyme activity in some mammalian tissues (columns 2–5), ratios of metabolite levels (column 6), and rates of flow measured *in vivo* (columns 7 and 8). The activities were measured in tissue extracts and isolated mitochondria under standard conditions (25 °C). At 37 °C, the enzyme values would be 2–2.5 times higher. The metabolic throughput was calculated from metabolite changes in ischemia experiments.

| 1 | 2 | 3 | 4 | 5 | 6 [l] | 7 | 8 |
|---|---|---|---|---|---|---|---|
| Organ | LDH [a] | GDH [a] | α-GPOX [b] | $\frac{\text{α-GPOX}}{\text{GDH}} \times 10^3$ | $\frac{\{\text{α-GP}\}\{\text{Pyr}\}}{\{\text{DAP}\}\{\text{Lac}\}}$ | Metabolic throughput *in vivo* lactate formation | glycerophosphate formation |
| | [μmole/h/g fresh weight] | | | | | [μmole/h/g fresh weight] | |
| Brain (rat) [m] | 1700 | 74 | 36 | 49 | 0.11 [c]<br>(0.17) [k] | | |
| Heart (rat) | 26000 | 236 | 13 | 5.6 | 0.11 [d]<br>(0.2) [k] | | |
| Heart (dog) | 18000 | 670 | 34 [a] | 5.1 | 0.1 [e] | 240 [e] | 36 |
| Skeletal muscle (rat) | 30000 | 2600 | 90 | 3.5 | 0.23 [f]<br>(0.46) [k] | 9200 [f] | 640 |
| Liver, | | | | | | | |
| hyperthyreoid | 24000 [h] | 2200 [h] | 190 [i] | 8.6 | 0.3 [g] | | |
| normal | 14000 | 2300 | 15 [i] | 0.6 | 0.7 [g] | 1700 [f] | 190 |
| hypothyreoid | 16000 [h] | 2800 [h] | 1 [i] | 0.04 | 0.9 [g] | | |

[a] From unpublished measurements of *D. Pette*.
[b] From unpublished measurements of *B. Kadenbach*.
[c] From measurements of *W. Wesemann* and *H. J. Hohorst* [9].
[d] From measurements of *Th. Bücher* and *G. Hermann* [10].
[e] From measurements of *M. Klarwein* et al. [58].
[f] From measurements of *H. J. Hohorst* et al. [8,9,21].
[g] From measurements of *H. Schimassek* [29].
[h] From unpublished measurements of *H. Mitzkat* and *G. Rassner*, cf. [60]. The significance of the deviation from normal values was not statistically confirmed.
[i] From measurements of *B. Kadenbach* and *H. Brandau* [59].
[k] Ratios in parentheses are based on the plasma value [Lac]/[Pyr] = 10.
[l] $[\overline{\text{α-GP}}]\cdot[\overline{\text{Pyr}}]/[\overline{\text{DAP}}]\cdot[\overline{\text{Lac}}] = 0.8$.
[m] Compare also [53].

Curve 2 of Figure 11 describes the system under consideration. Sections of the abscissa corresponding to the arrows opposite the ordinate would lead us to anticipate considerable deviations of $\Gamma/K_{app}$ -1 in some cases. That such deviations do indeed exist and that their interpretation can be correlated with the chain of reasoning presented here, will now be shown using liver as an example [29].

*Lardy* and coworkers discovered that the cellular activity of mitochondrial glycerophosphate oxidase is governed by the inductive action of the thyroid hormone [51]. The hormone does not affect the activity of the extramitochondrial enzyme. In fact, the ratio α-GPOX/GDH can be varied over a range of two orders of magnitude by feeding or withdrawing the thyroid hormone (Table 5, bottom of Column 5).

In order to demonstrate deviations in the metabolite ratio {α-GP}/{DAP}, we may use the {Lac}/{Pyr} ratio as an indicator for the redox potential of the extramitochondrial DPNH/DPN system (see Section 9). When the two DPN-specific systems are at equilibrium

Lactate + Dihydroxyacetone phosphate
⇅ LDH + GDH + DPN/DPNH (e)
Pyruvate + Glycerol-1-phosphate

then we have in our ionic medium

$$\frac{[\overline{\text{α-GP}}]\,[\overline{\text{Pyr}}]}{[\overline{\text{DAP}}]\,[\overline{\text{Lac}}]} = 0.8 \qquad (26)$$

and, therefore,

$$\frac{\Gamma}{K_{app}} \approx \frac{1}{0.8}\,\frac{\{\text{α-GP}\}\,\{\text{Pyr}\}}{\{\text{DAP}\}\,\{\text{Lac}\}} \qquad (27)$$

If the measured values given at the bottom of Column 6 in Table 5 are inserted, $\Gamma/K_{app}$ in the hypothyroid state becomes 1.1, in the normal state 0.8, and in the hyperthyroid state 0.4. Sections of the abscissa corresponding to the arrows on the ordinate in Figure 11 represent smaller deviations. Thus, for the hypothyroid state, we obtain from the graph: $\Gamma/K_{app} = 0.76$.

At the present state of these techniques, exact numerical agreement between the values predicted by reconstruction experiments and those measured in the organ could only be accidental. However, even an agreement between mere trends, which can be seen from examination of Figure 11 and Table 5, is already convincing evidence for the existence of the glycerophosphate cycle *in vivo* in rat liver. Besides, it should be noted that with the characterization and localization of the enzymes (see review in [50]) and with the measurement of the ratios listed in Table 5, we have gathered all the evidence which could be obtained *in vitro* to contribute to a demonstration of the existence of the glycerophosphate cycle. Irrespective of whether the results are positive [53–56] or negative [57], reconstruction experiments with homogenate fractions or isolated mitochondria


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[55] *P. Borst*, Biochim. biophysica Acta *57*, 256 (1962).
[56] *B. Sacktor* and *A. Dick*, J. biol. Chemistry *237*, 3259 (1962).
[57] *R. Hedman, E. M. Suranyi, R. Luft*, and *L. Ernster*, Biochem. biophys. Res. Commun. *8*, 314 (1962).
[58] *M. Klarwein, W. Lamprecht*, and *E. Lohmann*, Hoppe-Seylers Z. physiol. Chem. *328*, 41 (1962).
[59] *B. Kadenbach, H. Brandau*, and *Th. Bücher*, Enzymologia biol. clin., in the press.
[60] *J. R. Tata, L. Ernster, O. Lindberg, E. Arrhenius, S. Pedersen*, and *R. Hedman*, Biochem. J. *86*, 408 (1963).

and GDH cannot yield more significant data than those obtained from the measurement of kinetic constants of the enzymes.

As shown by the data and discussion of this Section, the α-glycerophosphate/dihydroxyacetone phosphate system departs considerably from equilibrium even at low rates of flow. Exact agreement between the redox potentials for the lactate/pyruvate and α-glycerophosphate/dihydroxyacetone phosphate systems are not to be anticipated even if the liver is in a normal state. In this respect, we have to correct our previous statements [10,11].

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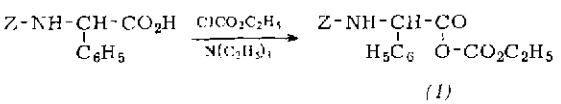
# COMMUNICATIONS

## Synthesis of 6-[(D-α-Amino-α-phenylacetyl)amino]-penicillanic Acid Using β-Dicarbonyl Compounds as Amino-Protecting Groups

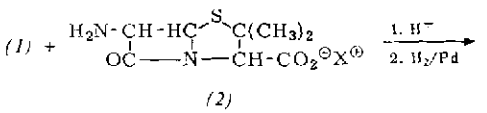
By Prof. Dr. E. Dane [1] and Dipl.-Chem. T. Dockner

Institut für Organische Chemie
der Universität München (Germany)

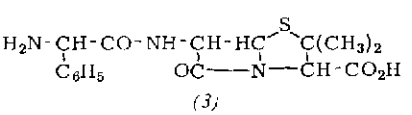
*Doyle* et al. [2] prepared 6-[(D-α-amino-α-phenylacetyl)-amino]penicillanic acid [ampicillin, *(3)*], in the following way:



*(1)*



*(2)*



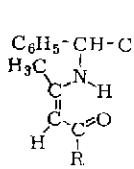
*(3)*

Z = $C_6H_5CH_2O$-CO- $X^{\oplus}$ = $Na^{\oplus}$

The catalytic hydrogenation required for removal of the protecting group does, however, not proceed satisfactorily because of the S-content of the compound.

We have found that it is also possible to use β-dicarbonyl compounds as amino-protecting groups in the synthesis of *(3)* [3].

D-α-Amino-α-phenylacetic acid dissolved in methanolic KOH reacts with benzoylacetone, acetylacetone, and ethyl acetoacetate to give the potassium salts *(4a)* to *(4c)*. The formation of *(4a)* requires heating at 60 °C for some hours. The reaction with acetylacetone takes some hours at room temperature, acetoacetic ester reacts when the solution is warmed briefly.



| | R | Decomp. temp. [°C] | Yield [%] |
|---|---|---|---|
| *(4a)* | $C_6H_5$ | 231–234 | 95 |
| *(4b)* | $CH_3$ | 222–224 | 80 |
| *(4c)* | $CO_2C_2H_5$ | 229–233 | 84 |

The potassium salts *(4a)–(4c)* were treated with pivaloyl chloride in tetrahydrofuran at −5 to −10 °C [*(4a)*, *(4b)* in suspension, *(4c)* in solution] giving the corresponding mixed anhydrides. To the anhydride solution was added a solution in chloroform of the triethylammonium salt *(2)*, $X^{\oplus}$ = $[HN(C_2H_5)_3]^{\oplus}$. The oily products remaining after evaporation were taken up in $NaHCO_3$ solution. The pH was gradually brought to 2 by addition of 1 N HCl with stirring. This precipitated the compound formed from *(4a)*, 6-[α-(benzoylacetonylamino) - α - phenylacetylamino]penicillanic acid, m.p. 138–147 °C, yield 63 %. The protecting group was split off by passing $CO_2$ into a solution of the compound in chloroform covered with water. We did not isolate the *N*-protected compounds from *(4b)* and *(4c)*. The protecting groups were split off in the acid solution. After extraction with ether, the pH of the aqueous phase was adjusted to 5 with $NaHCO_3$ solution. The solution was then concentrated by evaporation, and *(3)* crystallized out at 4 °C. The yield based on *(2)*, $X^{\ominus}$ = $H^{\oplus}$, was 50–60 %. Microbiological tests showed that the compound obtained from *(4c)* had the characteristic activity against *E. coli*.

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German version: Angew. Chem. 76, 342 (1964)

[1] We wish to thank the Fonds der Chemischen Industrie and Farbenfabriken Bayer A.G. for supporting this work.

[2] *F. P. Doyle, G. R. Fosker, J. H. C. Nayler*, and *H. Smith*, J. chem. Soc. (London) *1962*, 1440.

[3] *E. Dane, F. Drees, P. Konrad*, and *T. Dockner*, Angew. Chem. *74*, 873 (1962); Angew. Chem. internat. Edit. *1*, 658 (1962); German Patent 1143516 (April 27th, 1961) and foreign patents, Farbenfabriken Bayer A.G., inventors: *E. Dane, F. Drees*, and *P. Konrad*.

## Selective Hydrolysis of Pyrophosphate Bonds in Polynucleotides

By Dr. H. Schaller

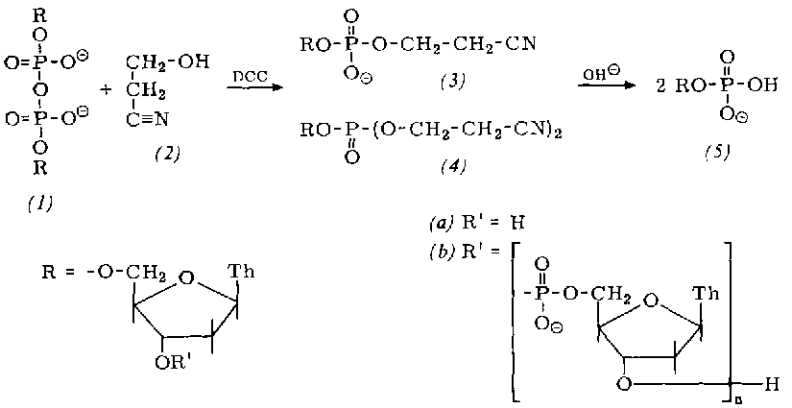
Institute for Enzyme Research, University of Wisconsin, Madison, Wis. (U.S.A.) and Max-Planck-Institut für Virusforschung, Tübingen (Germany)

Dinucleoside pyrophosphates *(1a)* can be split to 2 moles of mononucleotide *(5a)* by reaction with dicyclohexylcarbodiimide (DCC) and 2-cyanoethanol *(2)* and alkaline hydrolysis of the phosphoric acid di- and tri-esters, *(3a)* and *(4a)*, formed [1].

This method is also suitable for the selective hydrolysis of pyrophosphate bonds in polynucleotides *(1b)*, as they are found at the end of a polymerization with DCC [2] or similar reagents. The doubly esterified phosphate groups in the polynucleotide chain are partly also esterified, but are recovered unchanged on treatment with alkali, since the β-elimination of the cyanoethyl group from the triester proceeds very rapidly [1].

To a polymerization mixture of thymidylic acid (2 mmoles) with DCC (4 mmoles) in dimethylformamide (0.9 ml) and pyridine (0.1 ml), 20 mmoles of *(2)* and 5 mmoles of DCC

were added after the end of the reaction. After 3 days the mixture was worked up in the usual way [3] and treated in addition with $NH_3$ for 10 hours at 25 °C. By chromatography on DEAE-cellulose, polythymidylic acid *(5b)*, n = 1–10, was obtained in the same yield and purity as in the procedure with acetic anhydride/pyridine [3].



*(1)* *(2)* *(3)* *(4)* *(5)*

*(a)* R' = H

*(b)* R' =



Received, February 28th, 1964 [Z 715/540 IE]
German version: Angew. Chem. *76*, 439 (1964)

[1] *H. Schaller* and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 3828 (1963).

[2] *H. G. Khorana*: Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest. Wiley, New York 1961. Chapter 5.

[3] *H. G. Khorana, J. P. Viszolyi*, and *R. K. Ralph*, J. Amer. chem. Soc. *84*, 414 (1962).

## Determination of the Magnetic Susceptibility of Organic Compounds from Proton Resonance

By Dr. H. J. Friedrich

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The magnetic susceptibility effect observed in proton resonance in small cyclindrical tubes causes a shift of the resonance signal, relative to an external standard, which is proportional to the volume susceptibility of the medium [1]:

$$\Delta H/H = c \cdot \Delta\chi_v$$

Previous c-values taken from the literature (*e.g.* 2.60 [2]; 2.79 [3]; 1.57 [4]) have usually been vitiated by influences of the medium, such as magnetic anisotropy effects, van der Waals interaction, and electrical polarization effects.

Our determinations on tetramethylsilane in 35 diamagnetic media yielded the value 2.09 ± 0.1 for c, which is in agreement with the theoretical value $2\pi/3 = 2.094$. Corresponding measurements in paramagnetic media (solutions of diphenylpicrylhydrazyl) yielded c = 2.07 ± 0.1.

The method [5] was applied to the determination of the magnetic susceptibilities and spin densities of novel radicals [6] recently prepared by *Hünig* (cf. Table). We measured the shift of the $^1$H-signal of acetonitrile (10 %) in nitromethane, after the addition of about 5 mg radical/ml, at 20 °C, by means of a Varian-A60-NMR-spectrometer. The observed paramagnetism corresponds to that for monomeric radicals with a single unpaired electron ($\chi_{p,\,theor.} = 1280 \times 10^{-6}$).

| $[R{:}X{:}X{:}R]^{\oplus}\,Y^{\ominus}$ | $\chi_{mol} \times 10^6$ | $\chi_{dia} \times 10^6$ (calc.) | $\chi_{para} \times 10^6$ | spins/g $\times 10^{-21}$ |
|---|---|---|---|---|
| R = *N*-ethylquinol-2-yl, X = N, Y = $ClO_4$ | 1021 | −250 | 1271 | 1.3 |
| R = *N*-ethylbenzthiazol-2-yl, X = N, Y = $BF_4$ | 988 | −240 | 1228 | 1.3 |
| R = *N*,*N*-diethylbenzimidazol-2-yl, X = N, Y = $BF_4$ | 1009 | −270 | 1279 | 1.3 |
| R = *N*-ethylpyrid-2-yl, X = N, Y = $ClO_4$ | 1074 | −200 | 1274 | 1.7 |
| R = 2,3-dimethylindolizin-1-yl, X = CH, Y = $ClO_4$ | 1010 | −240 | 1250 | 1.4 |
| R = 1,2-dimethylindolizin-3-yl, X = CH, Y = $ClO_4$ | 998 | −240 | 1238 | 1.4 |

Received, March 11th, 1964 [Z 720/551 IE]
German version: Angew. Chem. *76*, 496 (1964)

[1] Cf. *C. A. Reilly*, Analytic. Chem. *30*, 842 (1958).

[2] *A. A. Bothner-By* and *R. E. Glick*, J. chem. Physics *26*, 1647 (1957).

[3] *D. F. Evans*, Proc. chem. Soc. (London) *1958*, 115.

[4] *H. P. Fritz* and *K. E. Schwarzhans*, J. organometallic Chem. *1*, 208 (1964).

[5] *H. J. Friedrich*, Z. Naturforsch., in the press. See this paper for further literature references.

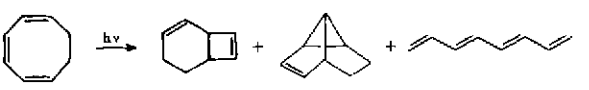
[6] *S. Hünig* et al., Liebigs Ann. Chem., in the press; Tetrahedron Letters *1964*, 181.

## Photolysis of Bicyclo[4,2,0]octa-2,4-diene, Cycloocta-1,3,5-triene and Cycloocta-1,3,6-triene

By Dr. W. R. Roth and Dipl.-Chem. B. Peltzer

Institut für Organische Chemie
der Universität Köln (Germany)

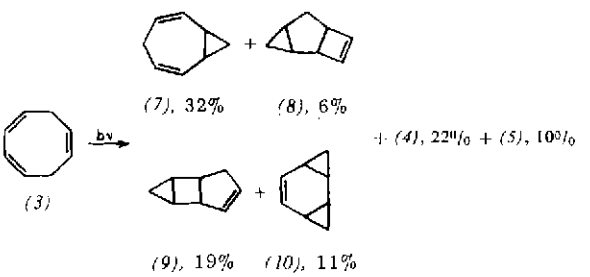
Bicyclo[4,2,0]octa-2,4-diene *(1)*, cycloocta-1,3,5-triene *(2)*, and cycloocta-1,3,6-triene *(3)*, which are in equilibrium at 200 °C [1], were photolysed (high-pressure mercury lamp, quartz apparatus) at room temperature in methanol solution and in the gas phase. Compound *(1)* was thereby isomerized to *(2)* in 40 % yield, the remainder was decomposed into benzene and ethylene. Compound *(2)* formed 68 % of bicyclo[4,2,0]octa-2,7-diene *(4)* [2] and 32 % of tricyclo-[3,2,1,$0^{2,8}$]-3-octene *(5)*. All-*trans*-octatetraene *(6)* was formed as an intermediary product and reacted further to produce *(4)* and *(5)* presumably with re-formation of *(2)*.



*(2)* *(4)* *(5)* *(6)*

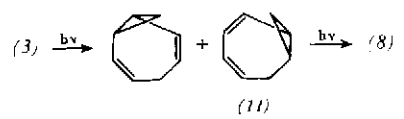
The structures of *(4)* and *(5)* were deduced from the infrared and NMR-spectra, from the products of hydrogenation, *viz.* bicyclo[4,2,0]octane and bicyclo[3,2,1]octane, and from thermal reactions: *(4)* was converted at 200 °C into an

equilibrium mixture of *(1)*, *(2)* and *(3)*; compound *(5)* was rearranged, with a 1,5-homodienyl hydrogen shift [3], into bicyclo[3,3,0]octa-2,7-diene. The photolysis of *(3)* gave rise to *(4)*, *(5)*, and *(7)–(10)*.




The formation of *(4)* and *(5)* in 22 and 10 % yields indicates that they originate from *(2)* which occurs as an intermediary product. This assumption could be supported by photolysis of 5,8-dideuterocycloocta-1,3,6-triene *(3a)*. Its product of isomerisation *(4a)* showed a distribution of deuterium which corresponds to an isomerization *(3)* → *(2)*, by way of a 1,5-hydrogen shift [4].

Compound *(7)* was formed, on the other hand, without hydrogen shift: The product *(7a)* which was obtained on photolysis of *(3a)*, carries deuterium only at C-4 and C-8. It is suggested that its formation is due to a rearrangement of the santonine type [5]. The 1,2-homotropilidene *(11)*, which would also be expected, is converted to *(8)* under the conditions of experiment.




Open-chain 1,3,6-trienes can be isomerized in the same way. Thus 5,5-dimethylhepta-1,3,6-triene is readily rearranged on irradiation into a mixture of *cis*- and *trans*-3,3-dimethyl-1,2-divinylcyclopropane [6].

The structure of *(10)* was deduced from infrared and NMR spectra. The formation of *(10)* is the first example of a photochemically induced Diels-Alder reaction.

Received, March 12th, 1964 [Z 693/534 IE]
German version: Angew. Chem. *76*, 378 (1964)

[1] *A. C. Cope* et al., J. Amer. chem. Soc. *74*, 4867 (1952); *W. R. Roth*, Liebigs Ann. Chem. *671*, 25 (1964).

[2] *O. L. Chapman:* Advances in Photochemistry. Interscience, New York 1963. Bd. I, p. 390.

[3] *D. L. Glass, J. Zirner*, and *S. Weinstein*, Proc. chem. Soc. (London) *1963*, 276; *W. R. Roth*, Liebigs Ann. Chem. *671*, 10 (1964).

[4] *K. J. Crowley*, Proc. chem. Soc. (London) *1964*, 17.

[5] *D. Arigoni* et al., Helv. chim. Acta *40*, 1732 (1957); *D. H. R. Barton*, ibid. *42*, 2604 (1959).

[6] Experiments in collaboration with *P. Fuss*.

## Diastereomeric Secalonic Acids [1]

By Prof. Dr. B. Franck [*] and Dipl.-Chem. E. M. Gottschalk

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der Universität Göttingen (Germany)

Secalonic acid, the pale yellow main pigment of ergot (*Claviceps purpurea*), was originally isolated by *Kraft* [2] and has since been investigated by several groups of workers [1,3–6]. We found that the crystalline secalonic acid obtained from a number of ergot varieties consists of a mixture of two diastereomers. Thus, secalonic acid derived from German and Austrian cultured ergot and from Spanish wild ergot could be separated chromatographically into secalonic acid A ($R_F$ = 0.42) and secalonic acid B ($R_F$ = 0.64) [7,8]. On the other hand, secalonic acid from a strongly pigmented Canadian wild ergot contained only the slow-moving component A. The mass spectra of secalonic acids A and B show the same molecular peaks (at M = 638) and the same fragmentation. Both acids have identical chemical formulae, ultraviolet spectra, functional groups, and exhibit the same reactions on degradation with alkali, but have different melting points $R_F$- values, and optical rotations (cf. Table 1). They are therefore diastereomers.

Table 1. Properties of the diastereomeric secalonic acids A and B, $C_{32}H_{30}O_{14}$ (mol. wt. 638.6).

| | A | B |
|---|---|---|
| M. p. [°C] (from $CHCl_3$) | 246–247 (decomp.) | 254–256 (decomp.) |
| $[\alpha]_D^{20}$ ($CHCl_3$) | −76 ° | −196 ° |
| $[\alpha]_D^{20}$ (pyridine) | −177 ° | +194 ° |

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German version: Angew. Chem. *76*, 438 (1964)

[*] Present address: Institut für Organische Chemie der Universität Kiel (Germany).

[1] Communication No. VI on Ergot Pigments. – Communication No. V: *B. Franck* and *G. Baumann*, Chem. Ber. *96*, 3209 (1963).

[2] *F. Kraft*, Arch. Pharmaz. *244*, 336 (1906).

[3] *A. Stoll, J. Renz*, and *A. Brack*, Helv. chim. Acta *35*, 2022 (1952).

[4] *B. Franck*, Planta med. *8*, 420 (1960).

[5] *B. Franck, O. W. Thiele*, and *T. Reschke*, Chem. Ber. *95*, 1328 (1962).

[6] *J. W. Apsimon, A. J. Corran, N. G. Creasey, W. Marlow, W. B. Whalley*, and *K. Y. Sim*, Proc. chem. Soc. (London) *1963*, 313.

[7] Thin-layer and column chromatography with a 9:1 mixture of chloroform and methyl propyl ketone on Kieselgel G [E. Merck, Darmstadt (Germany)] impregnated with 6.3 % of oxalic acid.

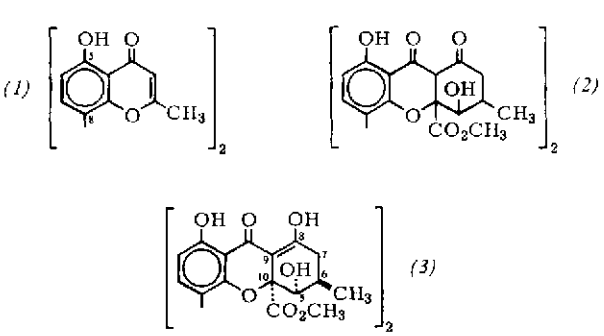
[8] Chrysergonic acid, which was isolated by *A. Stoll* et al. [3] and whose structure was recently investigated [6], was found as already suggested by its low rotation ($[\alpha]_D^{20}$ = −3 ° in pyridine) [3] – to be a 2:1 mixture of secalonic acids A and B.

## The Structure of Secalonic Acids A and B [1]

By Prof. Dr. B. Franck, Dipl.-Chem. E. M. Gottschalk, cand. chem. U. Ohnsorge, and Dipl.-Chem. G. Baumann

Organisch-Chemisches Institut der Universität Göttingen and Institut für Organische Chemie der Universität Kiel (Germany)

The diastereomeric secalonic acids A and B [1] were shown by degradation [1,2], spectra [1–3], and synthesis of *(1)* [3] to be symmetrical derivatives of a new type of natural product skeleton, *viz.* 5,5′-dihydroxy-8,8′-bichromonyl *(1)*. Moreover, they contain four hydroxy groups, two *C*-methyl, and two methoxycarbonyl groups [2]. *Whalley* et al. [4] recently suggested an arrangement of the substituents according to Formula *(2)*. We were able to obtain an independent confirmation of the structure of ring C in our pure, diastereomeric secalonic acids A and B by means of mass spectrometry, ring C being split off as methyl cresotinate, and by degradation with ozone to α-hydroxy-β-methylglutaric acid and methylsuccinic acid. In contrast to *(2)*, however, the β-dicarbonyl system in the secalonic acids is enolized to the vinylogous carboxylic acid *(3)* [5].




(The rings are labelled as A, B, and C from left to right.)

The relative and absolute configurations of the three centers of asymmetry at C-10, C-5, and C-6 of secalonic acid A shown in *(3)* were established as follows: The methylsuccinic acid formed by ozonolysis of secalonic acid A is dextrorotatory and has the *(R)*-configuration. It therefore follows that the center of asymmetry at C-6 of this secalonic acid – which carries the methyl group – has the absolute configuration shown in *(3)*. Since the proton on C-5 in *(3)* has a doublet at $\tau = 4.36$ with $J = 9$ cps in its NMR spectrum in pyridine, it is in *trans*-diaxial orientation relative to the methine proton on C-6. This proves that the hydroxy group is *trans*-diequatorial relative to the methyl group. The configuration of the methoxycarbonyl group follows from the mass spectrum and the optical rotatory dispersion of secalonic acids A and B. The opposite Cotton effect curves [5a] with unusually high peak values for secalonic acid A ($[\alpha]^{22}_{246} = 133000°$) and secalonic acid B ($[\alpha]^{23}_{246} = -115000°$) in chloroform show [6] that the two diastereomers differ in their configuration at one ring linkage, namely at the angular methoxycarbonyl group. In secalonic acid A *(3)*, the methoxycarbonyl group must be in the less stable position, *viz. cis*-quasiaxial relative to the neighboring hydroxy group, because it is split off more readily in mass spectroscopy [7] (the M - $COOCH_3$ fragment from *(3)* is 2.7 times more intense relative to the molecular peak than that from secalonic acid B).

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German version: Angew. Chem. *76*, 438 (1964)

[1] Communication No. VII on Ergot Pigments. – Communication No. VI: *B. Franck* and *E. M. Gottschalk*, Angew. Chem. *76*, 438 (1964); Angew. Chem. internat. Edit. *3*, 441 (1964).

[2] *B. Franck, O. W. Thiele*, and *T. Reschke*, Chem. Ber. *95*, 1328 (1962).

[3] *B. Franck* and *G. Baumann*, Chem. Ber. *96*, 3209 (1963).

[4] *J. W. Apsimon, A. J. Corran, N. G. Creasy, W. Marlow, W. B. Whalley*, and *K. Y. Sim*, Proc. chem. Soc. (London) *1963*, 313.

[5] Stable reaction products which are epimeric at C-9, as discussed by *W. B. Whalley* et al. [4], cannot therefore exist.

[5a] Measured by Prof. *S. Shibata*, Tokyo.

[6] See *C. Djerassi:* Optical Rotatory Dispersion. McGraw-Hill, New York 1960, p. 64; *H. G. Leemann* and *S. Fahbri*, Helv. chim. Acta *42*, 2696 (1959).

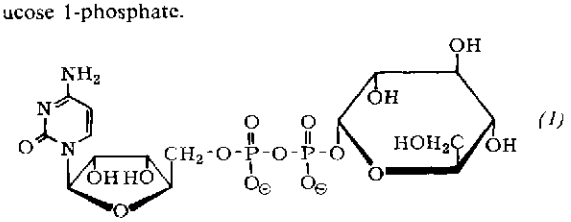
[7] See *K. Biemann:* Mass Spectrometry. McGraw-Hill, New York 1962, p. 144.

## Enzymatic Reactions on Ion-Exchange Thin-Layer Plates

By Dr. K. Randerath and Dr. Erika Randerath

John Collins Warren Laboratories, Huntington Memorial Hospital of Harvard University
and
Biochemical Research Department, Massachusetts General Hospital and Harvard Medical School [*]

Mono- and oligonucleotides may be separated by anion-exchange thin-layer chromatography on cellulose impregnated with polyethyleneimine [1]. We found that enzymatic reactions may be performed directly on the ion-exchange layer. As an example, we quote the degradation of cytidine diphosphate glucose *(1)* to cytidine 5'-monophosphate and glucose 1-phosphate.



*(1)*

snake-venom phosphodiesterase ↓ pH 7.8, 45–60 min, 23°C.

cytidine 5'-monophosphate + glucose 1-phosphate

A buffered solution of the enzyme is applied to the substance spot and covered with paraffined film (Parafilm®). The degradation products are separated by thin-layer chromatography, compared with known compounds and estimated quantitatively after elution. The monophosphates can be degraded further to cytidine, orthophosphate and glucose if, after pretreatment with phosphodiesterase, a solution of prostate phosphomonoesterase is added to the substance spot:

cytidine 5'-monophosphate + glucose 1-phosphate

$$\xrightarrow[\text{pH 5–6, 60 min, 23 °C.}]{\text{prostate phosphomonoesterase}} \text{cytidine} + 2\,H_3PO_4 + \text{glucose}$$

Suitable substrates for the phosphodiesterase reaction are, in addition to nucleotide sugars, other diesters of pyrophosphoric acid, *e.g.* diphosphopyridine nucleotide as well as oligonucleotides with a free terminal 3'-hydroxy group. Oligonucleotides with a free, terminal 5'-hydroxy group may be degraded with spleen phosphodiesterase, and nucleoside 2',3'-cyclophosphates with ribonuclease on ion-exchange layers. The layer has no influence on the specificity of the enzymes investigated.

The method is suitable not only for the analysis of traces of nucleotides (quantities $< 10^{-9}$ mole), but also as a sensitive detection procedure in enzyme fractionations.

Received, March 20th, 1964 [Z 700/525 IE]
German version: Angew. Chem. *76*, 494 (1964)

[*] Address: Massachusetts General Hospital, Boston 02114 (U.S.A.).

[1] *K. Randerath*, Angew. Chem. *74*, 780 (1962); Angew. Chem. internat. Edit. *1*, 553 (1962); *G. Weimann* and *K. Randerath*, Experientia *19*, 49 (1963); *K. Randerath*, Biochim. biophysica Acta *61*, 852 (1962).

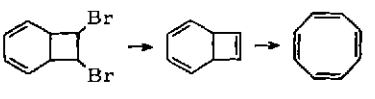
## Bicyclo[4,2,0]octa-2,4,7-triene

By Prof. Dr. Emanuel Vogel, Dr. H. Kiefer, and Dr. W. R. Roth

Institut für Organische Chemie der Universität Köln (Germany)

*Dedicated to Prof. H. Meerwein on the occasion of his 85th birthday*

*Huisgen* and *Mietzsch* [1] recently presented convincing kinetic evidence for the existence of valence tautomerism between cyclooctatetraene *(3)* and bicyclo[4,2,0]octa-2,4,7-triene *(2)*. We have now shown that bicyclo[4,2,0]octa-2,4,7-triene is produced in good yield when 7,8-dibromobicyclo-[4.2.0]-octa-2,4-diene ("cyclooctatetraene dibromide") *(1)* [2] is dehalogenated with disodium phenanthrene in dimethyl ether at −78 °C [3]. The purest sample of *(2)* prepared so far contained 95 % of the bicyclic compound; the impurity was solely *(3)*, which was obviously produced during the work-up (distillation at −20 °C) [4].



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

The chemical evidence for the structure *(2)* is based on its catalytic hydrogenation to bicyclo[4,2,0]octane together with its ready isomerization to *(3)*. Compound *(2)* reacts with maleic anhydride at 0 °C to give the known adduct of *(3)*. Bromination of *(2)* gives mainly tetrabromides [5]. The structure *(2)* is in complete agreement with the spectroscopic data. The NMR spectrum shows the expected signals from the four olefinic protons on the six-membered ring (multiplet centered at 4.37 $\tau$), the two protons on the double bond in the four-membered ring (singlet at 4.12 $\tau$), and the two aliphatic, doubly allylic protons (symmetrical multiplet centered at 6.68 $\tau$). The presence of the cyclobutene ring is

further deduced from the characteristic –C–H and –C=C– stretching vibrations (at 3112 and 1552 $cm^{-1}$ respectively) in the infrared spectrum determined at –20 °C [6]. The ultraviolet maxima at 273 mμ (ε = 3100) and 277 mμ (ε = 3000) correspond to those of other cyclohexadienes fused onto three- and four-membered rings [7].

The activation parameters, $E_a$ = 18.7 ± 0.8 kcal/mole and $A = 9.1 \times 10^{11}$ $sec^{-1}$, for the rearrangement of bicyclo[4,2,0]-octa-2,4,7-triene *(2)* to cyclooctatetraene *(3)*, were derived by means of the Arrhenius equation from the rate constants determined between 0 and –20 °C (5 °C intervals) by NMR spectroscopy. The half-life of *(2)* in this rearrangement at 0 °C is 14 min. We intend to determine the enthalpy of the rearrangement in order to obtain an independent estimate of the equilibrium concentration of the bicyclic isomer.

Received, March 23rd, 1964 [Z 701/531 IE]
German version: Angew. Chem. 76, 432 (1964)

[1] According to *R. Huisgen* and *F. Mietzsch*, Angew. Chem. 76, 36 (1964); Angew. Chem. internat. Edit. 3, 83 (1964), the equilibrium concentration of *(2)* is of the order of 0.01%.

[2] Attempts to convert *(1)* into *(2)* by dehalogenation with NaI are described by *R. E. Benson* and *T. L. Cairns*, J. Amer. chem. Soc. 72, 5355 (1950).

[3] Cf. *N. D. Scott, J. F. Walker*, and *V. L. Hansley*, J. Amer. chem. Soc. 58, 2442 (1936); *H. Günsten* and *L. Horner*, Angew. Chem. 74, 586 (1962); Angew. Chem. internat. Edit. 1, 455 (1962).

[4] According to *E. Migirdicyan* and *S. Leach*, Bull. Soc. Chim. Belges 71, 845 (1962), and *G. J. Fonken*, Chem. and Ind. 1963, 1625, low-temperature ultraviolet irradiation of *(3)* also gives rise to *(2)*, but it could not be isolated.

[5] Cf. *V. Georgian, G. Georgian*, and *A. V. Robertson*, Tetrahedron 19, 1219 (1963); *C. D. Nenitzescu* et al., Chem. Ber. 97, 372 (1964).

[6] Determined by *W. Lüttke* and *A. de Meijere*.

[7] *A. Eschenmoser* et al., Helv. chim. Acta 46, 2893 (1963), where further references are given.

## Proof of a Norcaradiene-Cycloheptatriene Valence Tautomerism by NMR Spectroscopy

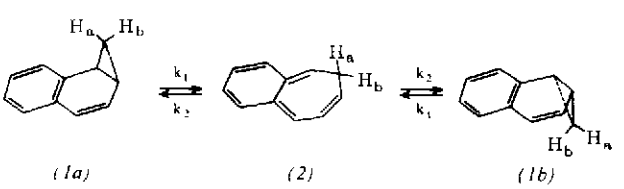
By Prof. Dr. Emanuel Vogel, cand. chem. D. Wendisch and Dr. W. R. Roth

Institut für Organische Chemie
der Universität Köln (Germany)

*Dedicated to Prof. H. Meerwein on the occasion of his 85th birthday*

The height of the energy barrier separating norcaradiene and cycloheptatriene is unknown and the assumption of a valence tautomerism between these two isomers is thus hypothetical [1]. In the case of benzonorcaradiene, the energy barrier has been determined from the temperature dependence of the NMR spectrum.

Benzonorcaradiene *(1)* is produced [2] by the addition of methylene onto naphthalene; its NMR spectrum shows, in addition to the signals due to the four aromatic protons, a doublet at 3.83 τ (two olefinic protons), a multiplet at 7.83 τ (benzyl proton), a complex multiplet at 8.33 τ (allyl proton) and multiplets at 8.70 and 10.35 τ, assigned to the two methylene protons.




*(1a)* *(2)* *(1b)*

On heating, the methylene signals first lose their fine structure; they then broaden until at 180 °C, they merge to a uniform flat absorption band which lies midway (9.54 τ) between the original signals. Further rise in temperature increases the sharpness of this new band. The other signals retain their positions.

These changes in the spectrum are completely reversible and can be explained by an equilibrium between the antipodes *(1a)* and *(1b)*, which is rapidly attained. As the protons $H_a$ and $H_b$ formally change places during this process, the positions of the NMR signals of $H_a$ and $H_b$ depend on the rate of the inversion *(1a)* ⇌ *(1b)*.

According to *Gutowsky* and *Holm* [3], the rate constant for such a proton exchange is given by the equation

$$k = \pi (\delta - \Delta) / \sqrt{2}$$

where $\delta$ is the chemical shift of the two protons at infinitely small rate of exchange, and $\Delta$ is the frequency interval between their signals at the temperature of observation; the rate constants for the isomerization *(1a)* ⇌ *(1b)* between 150 and 180 °C were determined in this way. Evaluation according to the Arrhenius equation gave the activation parameters $E_a$ = 19.4 kcal/mole and $A = 6.2 \times 10^{11}$ $sec^{-1}$ [4]. The isomerization *(1a)* ⇌ *(1b)* is considered to be a consequence of a norcaradiene-cycloheptatriene equilibrium which reveals its existence in the interconvertibility of the antipodes *(1a)* and *(1b)* [5]. With the assumption that $k_2 \gg k_1$ (the concentration of *(2)* remains below that detectable by NMR spectroscopy), the energy barrier for the norcaradiene-cycloheptatriene rearrangement *(1)* ⇌ *(2)* is 19.4 kcal/mole and the frequency factor $A = 1.2 \times 10^{12}$ $sec^{-1}$.

Received, March 23rd, 1964 [Z 702/523 IE]
German version: Angew. Chem. 76, 432 (1964)

[1] For the synthesis of stable norcaradienes, see: *E. Vogel, W. Wiedemann, H. Kiefer*, and *W. F. Harrison*, Tetrahedron Letters 1963, 673; *R. Darms, T. Threlfall, M. Pesaro*, and *A. Eschenmoser*, Helv. chim. Acta 46, 2893 (1963).

[2] *W. v. E. Doering* and *M. J. Goldstein*, Tetrahedron 5, 53 (1959).

[3] *H. S. Gutowsky* and *C. H. Holm*, J. chem. Physics 25, 1228 (1956).

[4] Spin-spin interaction was not considered, although strictly speaking the above treatment is valid only if (for k = 0) coupling constants and line-widths are equal to zero; see *S. Alexander*, J. chem. Physics 37, 967 (1962).

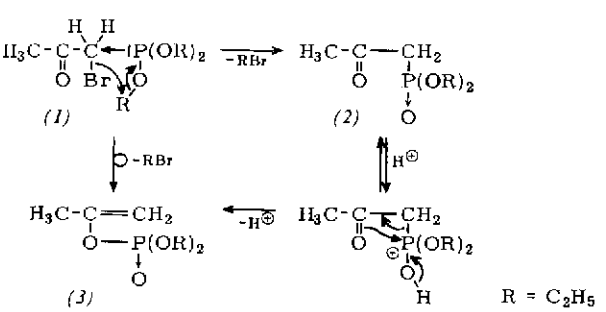
[5] Substitution of an H-atom of the $CH_2$ group in *(1)* by another group should not significantly affect the rate of isomerization to the corresponding cycloheptatriene *(2)*. However, with such substituted benzonorcaradienes, the equilibrium concentrations of *(1a)* and *(1b)* will in general by very different since the two forms are now exo-endo isomers; the inversion of the three-membered ring can then no longer be observed by NMR spectroscopy. Thus, the NMR spectrum of benzonorcaradiene-carboxylic ester is not temperature-dependent.

## Phosphonic Ester/Enol Phosphate Rearrangement

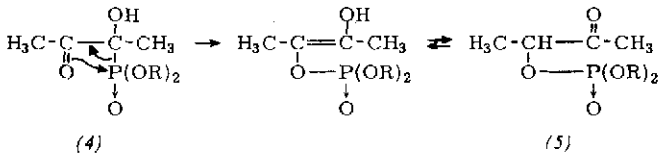
By Dr. H. Machleidt and Dr. G. U. Strehlke

Organisch-Chemisches Institut der Universität Bonn (Germany)

The reaction of bromoacetone *(1)* with triethyl phosphite at 140–170 °C gives rise to compounds *(2)* and *(3)* [1], in the approximate ratio of 1:1. On prolonged heating, this propor-



tion changes and is displaced in favor of *(3)*. It is probable that *(3)* is partly formed by way of *(2)* [2]. This view is supported by the observation that *(2)* rearranges to an extent of 50 % into *(3)* at 170 °C in the presence of 2 % $H_3PO_4$ during 13 h. In the presence of 0.5 % $H_3PO_4$ the extent of rearrangement amounts to 12 %, and is less than 1 % in the absence of acids. Rearrangement of *(2)* into *(3)* occurs also in a 2 % solution of $H_3PO_4$ in nitrobenzene or mesitylene at 170 °C.



*(4)* *(5)*

R = $C_2H_5$

The process is an intramolecular rearrangement and not an intermolecular transphosphorylation, as shown by the fact that added 2-butanone [3 moles per mole of *(2)*] is without influence on the reaction. It is possible that the facile rearrangement *(4)* → *(5)* [3] proceeds similarly.

Received, March 23rd, 1964 [Z 723/548 IE]
German version: Angew. Chem. *76*, 494 (1964)

[1] *N. Kreuzkamp* and *H. Kayser*, Chem. Ber. *89*, 1614 (1956); *A. N. Pudovik* and *V. P. Avery' Anava*, Zhur. obsh. Khim. *26*, 1426 (1956); Chem. Abstr. *50*, 14512 (1956).

[2] *F. Cramer*, Angew. Chem. *72*, 239 (1960).

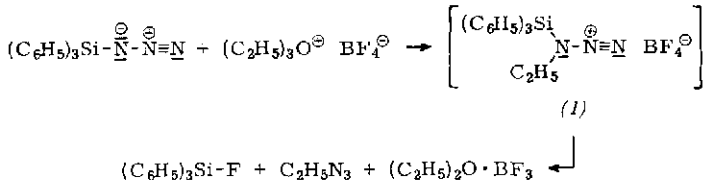
[3] *V. A. Kukhtin*, *V. S. Abramov*, and *K. M. Orekhova*, Doklady Akad. Nauk SSSR *128*, 1198 (1959); Chem. Abstr. *54*, 7536 (1960).

## The Reaction of Triphenylsilyl Azide with Triethyloxonium Tetrafluoroborate [1]

By Dr. N. Wiberg and cand. chem. K. H. Schmid

Institut für Anorganische Chemie
der Universität München (Germany)

The action of stoichiometric quantities of "ethyl cations" in the form of triethyloxonium tetrafluoroborate on triphenylsilyl azide in methylene chloride at 20 °C did not lead to the expected *N*-diazonium salt *(1)*. The latter is probably formed as an intermediate, but being a strong silylating agent, it removes a fluoride anion from the tetrafluoroborate to form triphenylfluorosilane *(2)*.

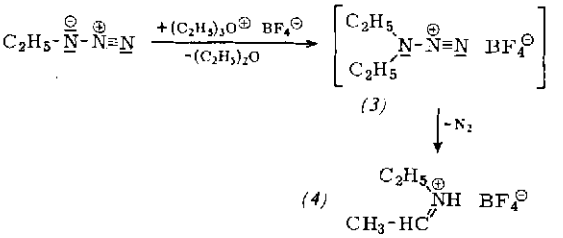


*(1)*

*(2)*

Excess triethyloxonium tetrafluoroborate decomposes the ethyl azide formed, with evolution of nitrogen [2].

working rapidly, however, *N*-ethyl-*N*-ethylideneammonium tetraphenylborate (m.p. 131 °C), which is resistant to hydrolysis, can be precipitated from water with $NaB(C_6H_5)_4$ [3].



*(3)* *(4)*

Since no nitrogen is evolved during the reaction of stoichiometric amounts of triphenylsilylazide and triethyloxonium tetrafluoroborate *(1)* must be more stable than *(3)* – obviously owing to the influence of its triphenylsilyl group.

Received, March 31st, 1964 [Z 713/539 IE]
German version: Angew. Chem. *76*, 381 (1964)

[1] Communication No. 3 on Silyl Azides. – Communication No. 2: *N. Wiberg*, *F. Raschig*, and *R. Sustmann*, Angew. Chem. *74*, 716 (1962); Angew. Chem. internat. Edit. *1*, 551 (1962).

[2] The reaction of n-butyl azide with alkyl cations proceeds similarly, according to *W. Pritzkow* and *G. Pohl*, J. prakt. Chem. *20*, 132 (1963).

[3] The hydrophobic property of tetraphenylborate gives rise to immonium salts of this anion which are resistant to hydrolysis. Tetrafluoroborate and hexachloroantimonate [*J. Goubeau*, *E. Allenstein*, and *A. Schmidt*, Chem. Ber. *97*, 884 (1964)] do not display this property. We found that immonium tetraphenylborates are readily obtained from substituted ammonium tetraphenylborates $R_2NH_2^{\oplus}B(C_6H_5)_4^{\ominus}$ and ketones (aldehydes). For example, a solution of $(CH_3)_2NH_2^{\oplus}B(C_6H_5)_4^{\ominus}$ in acetone deposites crystalline $(CH_3)_2C{=}N(CH_3)_2^{\oplus}$ $B(C_6H_5)_4^{\ominus}$, m.p. 278–280 °C (decomp.), in the course of a few days.

## The Reaction of Silyl Azides with Antimony Pentachloride [1]

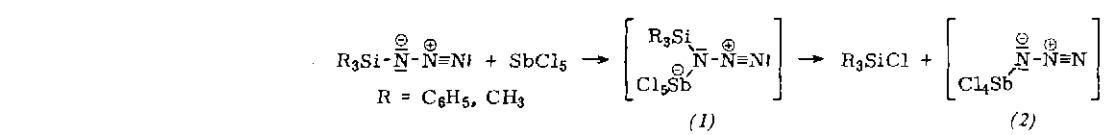
By Dr. N. Wiberg and cand. chem. K. H. Schmid

Institut für Anorganische Chemie
der Universität München (Germany)

The reaction of antimony pentachloride with triphenylsilyl azide or trimethylsilyl azide in a molar ratio of 1:1 does not stop at the stage of the addition product *(1)* [2]; instead, *(1)* decomposes instantaneously with silylation of a chloride ion from the antimony [1].

The tetrachloroantimony azide *(2)* produced thereby forms yellow crystals on sublimation *in vacuo* at 80–90 °C and melts with gradual decomposition at 126–127 °C to give a red-orange liquid. On heating further, the azide explodes. In the infrared spectrum of *(2)*, $\tilde{\nu}_{as}(N_3)$ is at 2140 $cm^{-1}$ and $\tilde{\nu}_s(N_3)$ at 1180 $cm^{-1}$.

Cryoscopic molecular-weight determinations in benzene indicated that *(2)* has twice the expected molecular weight.

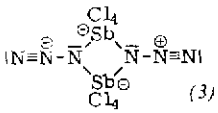


*(1)* *(2)*

*N*-Ethyl-*N*-ethylideneammonium tetrafluoroborate *(4)* is thereby formed as colorless, extremely thin platelets, m.p. 140–142 °C, with $\tilde{\nu}_{C=N}$ at 1720 $cm^{-1}$. It is insoluble in common organic solvents and is hydrolysed by water. By

A plausible explanation for this lies in the dimerization via nitrogen bridges *(3)*, by means of which the strongly acidic, pentavalent antimony attains the favored coordination number of 6 [3].

As expected, as a derivative of $SbCl_6$, *(3)* is more resistant to hydrolysis than $SbCl_5$: it remains dissolved in water for a short time without decomposing.



*(3)*

Received, March 31st, 1964 [Z 716/541 IE]
German version: Angew. Chem. 76, 380 (1964)

[1] Communication No. 4 on Silyl Azides. – Communication No. 3: *N. Wiberg* and *K. H. Schmid*, Angew. Chem. *76*, 381 (1964); Angew. Chem. internat. Edit. *3*, 444 (1964).

[2] *J. Goubeau, E. Allenstein*, and *A. Schmidt* recently prepared $CH_3N_3SbCl_5$ [Chem. Ber. *97*, 884 (1964)].

[3] *P. L. Paetzold*, Z. anorg. allg. Chem. *326*, 47 (1963), observed similar results with dichloroboron azide $Cl_2BN_3$: the compound is trimeric.

## The Crystal Structure of Rubidium and Cesium Hexachloro-, -bromo-, and -iodorhenates(IV)

By Priv.-Doz. Dr. H. J. Berthold
and cand. chem. G. Jakobson

Institut für Anorganische Chemie und Kernchemie
der Universität Mainz (Germany)

All rubidium and cesium hexachloro-, -bromo-, and iodorhenates(IV) crystallize with the antifluorite structure of $K_2PtCl_6$ (space group $O_h^5$–Fm3m). The lattice constants (together with our values for $K_2ReCl_6$ [1–3] and $K_2ReBr_6$ [2,4]) are [5]:

| M | $M_2ReCl_6$ | $M_2ReBr_6$ | $M_2ReI_6$ |
|---|---|---|---|
| K | 9.840 ± 0.005 Å | 10.382 ± 0.005 Å | – |
| Rb | 9.974 ± 0.005 | 10.485 ± 0.01 | 11.31 ± 0.02 |
| Cs | 10.260 ± 0.005 | 10.685 ± 0.01 | 11.44 ± 0.02 |

The values for $K_2ReCl_6$ and $K_2ReBr_6$ were obtained by using film and counter diffractometer techniques. The other values were obtained by evaluation of asymmetric powder patterns (camera diameter 57.3 mm). The accuracy of the data is limited by the easily occurring partial hydrolysis of the sparingly soluble substances during their preparation or recrystallization, resulting in the inclusion of hydroxide or oxide ions in the lattice.

The compounds were prepared by boiling $Re_2O_7$ and Rb or Cs halide in concentrated solutions of the corresponding hydrohalic acids. After boiling off the halogen liberated by reduction of the rhenium the mixture was concentrated and, after crystallizing out, the complex salt was filtered off. It was freed from alkali-metal halide (and iodine) by extraction and then recrystallized from the appropriate concentrated hydrohalic acid. The iodo compound could not be recrystallized because of its poor solubility.

$Rb_2ReCl_6$ and $Cs_2ReCl_6$ like $K_2ReCl_6$ are green-yellow, $Rb_2ReBr_6$ and $Cs_2ReBr_6$ are red (somewhat lighter than the dark red $K_2ReBr_6$), while $Rb_2ReI_6$ and $Cs_2ReI_6$ are deep black like $K_2ReI_6$.

Received, April 9th, 1964 [Z 719/550 IE]
German version: Angew. Chem. 76, 497 (1964)

[1] *B. Aminoff*, Z. Kristallogr. A *94*, 246 (1936); *C. M. Nelson, G. E. Boyd*, and *Wm. T. Smith*, J. Amer. chem. Soc. *76*, 348 (1954).

[2] *J. Dalziel, N. S. Gill, R. S. Nyholm*, and *R. D. Peacock*, J. chem. Soc. (London) *1958*, 4012.

[3] *H. G. Smith* and *G. E. Bacon*, Rome Abstracts S 2.19, Supplement to Acta crystallogr. *16* (1963).

[4] *D. H. Templeton* and *C. H. Dauben*, J. Amer. chem. Soc. *73*, 4492 (1951).

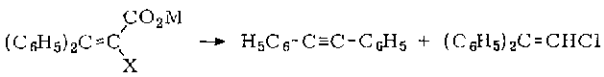
[5] The structure of $K_2ReI_6$ is not yet known.

## Aryl Rearrangements in the Thermolysis of β-Arylated α-Halogenoacrylates [*]

By Doz. Dr. G. Köbrich and Dipl.-Chem. H. Fröhlich

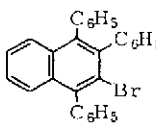
Organisch-Chemisches Institut
der Universität Heidelberg (Germany)

Extending research on the thermolysis of *o*-halogenobenzoates [1], we have investigated the decarboxylation of β-arylated α-halogenoacrylates *(1)* with respect to their capacity to undergo α-elimination. Dry heating of *(1a)* *(1c)* yields primarily tolane *(2)* [*(1a)*: 88 %; *(1b)*: 52 %; *(1c)*: 35 %]; *(1c)* also gave *ca.* 1 % 1,2,4-triphenyl-3-bromonaphthalene *(4)*, identified by comparison with a sample independently obtained by diene synthesis from diphenylisobenzofuran and β-bromostyrene.



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

*a*: M = K, X = Cl
*b*: M = Ag, X = Cl
*c*: M = Ag, X = Br
*d*: M = Ag, X = H

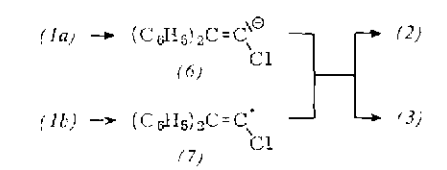


*(4)*, m.p. 245 °C

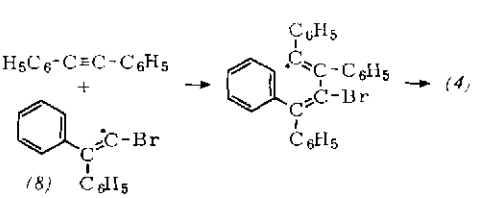
Additionally, *(1b)* and *(1c)* yield polymeric products, which are also formed (besides 21 % phenylacetylene and 3.4 % diphenyldiacetylene, $H_5C_6{-}C{\equiv}C{-}C{\equiv}C{-}C_6H_5$) in the decomposition of silver α-chloro-β-phenylacrylate.

The decomposition temperatures [*(1a)*: 325 °C; *(1b)*: 220–270 °C] are lowered to 150–190 °C by using dimethylsulfoxide (DMSO) as solvent. Under these conditions tolane and 1,1-diphenyl-2-halogenoethylene *(3)* are obtained. The proportions are influenced by the cation, which points to a different mechanism of decomposition: *(1a)* gives rise to 72 % *(3)* and 19 % *(2)*, yet *(1b)* gives 11 % *(3)* and 62 % *(2)* together with 1,1-diphenylethylene *(5)* and benzophenone in small quantities. The latter is formed from *(5)* under the reaction conditions, as was shown by a control experiment. From silver α-chloro-β,β-bis-(*p*-anisyl)acrylate [*(1b)*, *p*-$CH_3OC_6H_4$ instead of $C_6H_5$] the corresponding acetylene *(2)* is formed in 76.5 % yield; a halogenoethylene [corresponding to *(3)*] was not detectable. Styrene is polymerised during decomposition of the silver salt, but not of the potassium salt.

We conclude from this and further findings [2] that decarboxylation of the potassium salt *(1a)* gives the carbanion *(6)*, while the silver salt *(1b)* gives the radical *(7)*. Both rearrange without solvent to tolane by Cl elimination and phenyl migration. The radical *(8)* arising correspondingly from *(1c)* adds partly to the tolane already formed and cyclizes with loss of hydrogen to give the naphthalene derivative *(4)* [3].



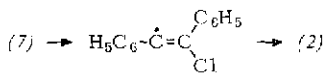
*(6)* *(7)*



*(8)*

DMSO [4] is capable of capturing the major part of *(6)* before the elimination by protonating it to the halogenoethylene *(3)*; however, it seems to lack in saturating the radical *(7)* in corresponding amounts.

The equally conceivable phenyl rearrangement (before halogen abstraction)



can be excluded on the grounds that dry decomposition of the chlorine-free silver salt *(1d)* yields solely *(5)* (39 %) and *ca.* 1 % benzophenone and that after thermolysis of *(1b)* in DMSO no chlorostilbene is detectable.

The step *(6)* → *(2)* has a parallel in the base-initiated Fritsch-Buttenberg-Wiechell rearrangement [5]. The thermolysis of the potassium salt *(1a)* represents the only method so far of achieving this isomerisation in a non-alkaline milieu. A radical-induced aryl migration of olefines [corresponding to *(7)* → *(2)*] was hitherto unknown. Further investigations with respect to the possible appearance of an olefine carbene are in progress.

Received, April 13th, 1964 [Z 722/547 IE]
German version: Angew. Chem. *76*, 495 (1964)

[*] Communication No. 1V: On the Existence of C-Atoms with Halogen and Alkali Metal Substituents. – Communication No. III: *G. Köbrich* and *K. Flory*, Tetrahedron Letters *1964*, 1137.

[1] *G. Köbrich*, Chem. Ber. *92*, 2985 (1959); *96*, 2544 (1963); Liebigs Ann. Chem. *664*, 88 (1963).

[2] *G. Köbrich, H. Fröhlich*, and *W. Drischel*, unpublished work.

[3] See similar cyclizations by *O. Blum*, Ber. dtsch. chem. Ges. *62*, 881 (1929); *L. I. Smith* and *H. H. Hoehn*, J. Amer. chem. Soc. *63*, 1184 (1941); *E. H. Braye, W. Hübel*, and *I. Caplier*, ibid. *83*, 4406 (1961).

[4] *E. J. Corey* and *M. Chaykovsky*, J. Amer. chem. Soc. *84*, 866 (1962).

[5] Review: *G. Köbrich*, Angew. Chem. *76* (1964), in the press; Angew. Chem. internat. Edit. *3* (1964), in the press.

## Preparation of Fluorinated Si–N Compounds Using $SiF_4$ [1]

By Prof. Dr. U. Wannagat and Dr. H. Bürger

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der Technischen Hochschule Graz (Austria)

$SiCl_4$ (and analogously higher silicon halides) reacts with (a) $NH_3$, (b) $RNH_2$, (c) pyridine (= Py), or (d) $(R_3Si)_2NH$ to give (a) $[Si(NH)_2]_x$, (b) $Cl_3SiNHR$, (c) $SiCl_4Py_2$, and (d) $Cl_3SiNHSiR_3$. With the same reactants $SiF_4$ yields only the adducts (a) $SiF_4(NH_3)_2$ *(1)*, (b) $SiF_4(NH_2R)_2$ [2], and (c) $SiF_4Py_2$. It does not react with $(R_3Si)_2NH$ up to 120 °C. However, it reacts vigorously with silyl-substituted alkali-metal amides (R = $CH_3$) at −78 °C:

$$2\ (C_2H_5)_3SiNHLi + 3\ SiF_4 \rightarrow Li_2SiF_6 + (C_2H_5)_3Si{-}NH{-}SiF_3 \qquad (2)$$

or

$$2\ (R_3Si)_2NNa + 3\ SiF_4 \rightarrow Na_2SiF_6 + (R_3Si)_2N{-}SiF_3 \qquad (3)$$

At room temperature *(3)* reacts further:

$$(R_3Si)_2N{-}SiF_3 + NaN(SiR_3)_2 \rightarrow NaF + (R_3Si)_2N{-}SiF_2{-}N(SiR_3)_2 \qquad (4)$$

In contrast with $SiF_4$, the solid crystalline $F_4Si(NH_3)_2$ *(1)*, the oldest known Si–N compound [3], reacts vigorously with hexamethyldisilazane at 100 °C in solution or suspension essentially according to:

$$F_4Si(NH_3)_2 + 2\ R_3Si{-}NH{-}SiR_3 \rightarrow 2\ NH_3 + 2\ R_3SiF + R_3Si{-}NH{-}SiF_2{-}NH{-}SiR_3 \qquad (5)$$

With $F_4Si(NH_2R)_2$ instead of *(1)*, $R_3SiNHR$ and $(R_3Si)_2NR$ are formed as well; apparently the $NH_3$ is not only displaced by $(R_3Si)_2NH$ from its coordinate bond with $SiF_4$.

On heating cyclosilazanes $[-R_2Si{-}NH{-}]_{3\ or\ 4}$ finely mixed with $F_4Si(NH_3)_2$, a mixture of linear silazanes $F{-}[SiR_2{-}NH]_n{-}SiR_2F$ with $n = 0$, 1 *(6)*, 2, and 3 is formed. Further products are $[-F_2Si{-}NH{-}]_x$ and $NH_3$. 1,3-Difluorotetramethyldisilazane *(6)*, $F{-}SiR_2{-}NH{-}SiR_2{-}F$, is much less reactive than its 1,3-dichloro analogue [4]; the other newly prepared F/Si/N compounds are also remarkable for their thermal and hydrolytic stability.

| Compound | B.p. [°C/mm] | $n_D^{20}$ | δ [*] [cps] | $J(H\text{-}^{19}F)$ [cps] |
|---|---|---|---|---|
| *(2)* | 144/738 | 1.3876 | −16.5 | 0.75 |
| *(3)* | 133/748 | 1.3760 | | |
| *(4)* | 72–73/0.2 | 1.4511 | −12.8 | |
| *(5)* | 175/740 | 1.4017 | − 5.1 | 0.9 |
| *(6)* | 118/745 | 1.3741 | −10.2 | 5.8 |

[*] Chemical shift at 60 Mcps against tetramethylsilane as standard.

Received, April 15th, 1964 [Z 721/552 IE]
German version: Angew. Chem. *76*, 497 (1964)

[1] Communication No. 44 on SiN Compounds. – Communication No. 43: Mh. Chem., in the press.

[2] Prepared for the first time in the course of the present investigation.

[3] *J. Davy*, Philos. Trans. *1812*, I, 352.

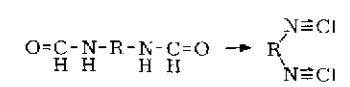
[4] *U. Wannagat, E. Bogusch*, and *P. Geymayer*, Mh. Chem., in the press.

## 1,4-Dipolar Cycloaddition onto Diisonitriles

By Doz. Dr. R. Neidlein

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der Universität Marburg/Lahn (Germany)

With the exception of 1,1-diisonitrilomethane [1], 1,4-diisonitrilobenzene [2], and xanthocilline [3], diisonitriles have previously not been described. By passing equimolar quantities of phosgen [4] into a suspension of *N,N'*-bisformyldiamines *(1)* in methylene chloride/triethylamine (250:35) at −10 to −30 °C diisonitriles *(2)* are obtained:

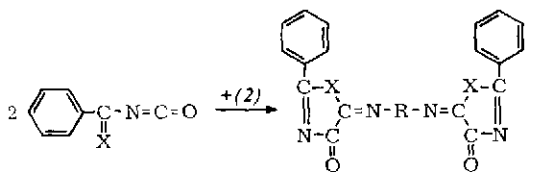


*(1)* *(2)*

| *(2)*, R | M.p. [°C] (decomp.) | Yield [%] |
|---|---|---|
| *m*-Phenylene | 106–107 | 83 |
| *p*-Phenylene | 165–166 | 75 |
| 1,4-Cyclohexylene | 108–109 | 96 |

In anhydrous ether/benzene (1:1), diisonitriles react at room temperature with 1,4-dipolar compounds, *e.g.* benzoyl isocyanate *(3)*, to yield heterocyclics *(4)*.

Equimolar quantities of thiobenzoyl isocyanate *(5)*, obtained from 2-phenyltbiazoline-4,5-dione [5] by elimination of



(3), X = O
(5), X = S

(4), X = O; R = *p*-phenylene
75 %, m.p. 174–175 °C (decomp.)
(6), X = S; R = 1,4-cyclohexylene
92 %, m.p. 213–214 °C (decomp.)

carbon monoxide in boiling xylene, react with diisonitriles in xylene at ca. 150 °C to yield derivatives, *e.g. (6)*, of *N,N'*-bis-(4-oxothiazolinylidene)diamines.

Received, April 16th, 1964 [Z 724/549 IE]
German version: Angew. Chem. *76*, 500 (1964)

[1] *R. Neidlein*, Angew. Chem. *76*, 440 (1964); Angew. Chem. internat. Edit. *3*, 382 (1964).

[2] *R. C. A. New* and *L. E. Sutton*, J. chem. Soc. (London) *1932*, 1415.

[3] *I. Hagedorn* and *H. Tönjes*, Pharmazie *11*, 409 (1956); *12*, 570 (1957).

[4] *I. Ugi, W. Betz, U. Fetzer*, and *K. Opfermann*, Chem. Ber. *94*, 2814 (1961).

[5] *J. Goerdeler* and *H. Horstmann*, Chem. Ber. *93*, 671 (1960).

## Preparation of Polymethylene by the Reaction of Diazomethane with Diborane

By Dr. G. H. Dorion, S. E. Polchlopek [*], and E. H. Sheers

American Cyanamid Company, Stamford, Conn. (U.S.A.)

We have synthetized polymethylene at room temperature by addition of 1 mmole of diborane in 0.8 ml of anhydrous tetrahydrofuran[1] to a solution of 16 mmole of diazomethane in 80 ml of ether. An almost quantitative yield was obtained. The polymer was highly crystalline when studied by microscopy, melted at 136 °C, and was estimated by infrared spectroscopy to contain less than 1.0 methyl group per 1000 methylene groups. A typical sample contained 1.02 % boron and had a molecular weight (ebulliometry, toluene) greater than 20000.

The significance of this rather simple room-temperature synthesis is that it affords a highly linear polymer. Polyethylenes show $CH_3$:$CH_2$ group ratios of 2:1000 to 33:1000 [2].

Received, April 13th, 1964 [Z 725/543 IE]
German version: Angew. Chem. *76*, 495 (1964)

[*] Present address: Barnes Engineering Co., Stamford, Conn. (U.S.A.).

[1] *H. C. Brown:* Hydroboration. Benjamin, New York 1962, p. 94.

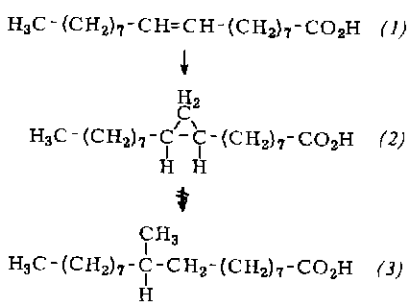
[2] *A. H. Willbourn*, J. Polymer Sci. *34*, 569 (1959).

# CONFERENCE REPORTS

## Federation of European Biochemical Societies

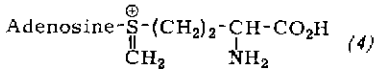
The first meeting of this federation, which was founded in January 1964, took place in London from March 23rd to 25th, 1964. The agenda included colloquia on "The Biochemistry of Chloroplasts" and on "Inborn Errors of Metabolism", a symposium on "The Structure and Activity of Enzymes", and 139 short papers.

The program on the first day included the Jubilee Lecture of the British Biochemical Society. *E. Lederer*, Gif-Sur-Yvette (France), spoke on the origin and function of some methyl groups in branched-chain fatty acids. In general, the methyl groups are derived by direct *C*-methylation of preformed molecules, or from propionic acid, isoleucine, or mevalonic acid. During the biosynthesis of tuberculostearic acid *(3)*



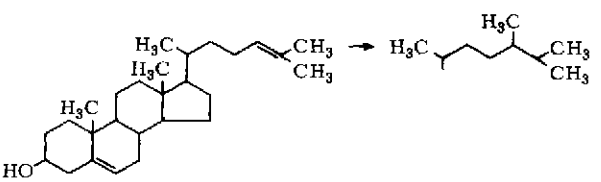
*(1)*
*(2)*
*(3)*

from the corresponding unsaturated acid *(1)*, the possible occurrence of a cyclopropane type intermediate *(2)* was envisaged. However, the bacillus was unable to convert a synthetic sample of this compound into tuberculostearic acid. Cyclopropanecarboxylic acids may be biosynthetized from an unsaturated acid and *S*-adenosylmethionine. When the methyl group of the methionine used is fully deuterated, two of the deuterium atoms are retained in the cyclopropane ring, suggesting the conversion of active methionine into a methylene-donating molecule *(4)*



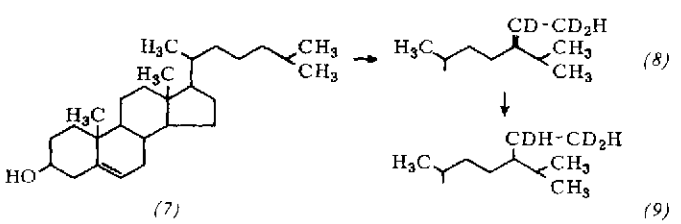
*(4)*

Similarly, methylation of C-24 in desmosterol *(5)* to give ergosterol *(6)* proceeds with retention of only 2 hydrogen atoms.



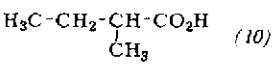
*(5)* *(6)*

The ethylation of cholesterol *(7)* that occurs at C-24 to give β-sitosterol *(9)* appears to be in fact a form of double methylation. Biological deutereomethylation gave an intermediate *(8)* which was isolated and which on ozonization gave acetaldehyde deuterated on both carbon atoms.

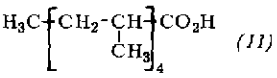


*(7)* *(8)* *(9)*

In *Ascaris lumbricoides*, condensation of acetate and propionate moities gives a branched fatty acid *(10)*, and in the preen



*(10)*



*(11)*

gland of the goose, the long chain fatty acid *(11)* is built up entirely from propionic acid units.

The methyl group of coenzyme Q is known to be derived from mevalonic acid: this methyl group may play an important part in oxidative phosphorylation via a quinone methide.

In the symposium, *F. M. Richards*, New Haven, Conn. (U.S.A.) listed some chemical modifications made at specific sites in ribonuclease in order to study the contribution made by its various constituent amino acids to the activity of the whole molecule. Thus, dinitrophenylation of lysine 41 results in complete loss of enzymatic activity; this in turn affects the reactivity of lysine 7 towards fluorodinitrobenzene. Mutually exclusive carboxymethylation of histidines 12 or 119 with iodoacetic acid also results in marked loss of ribonuclease activity. It was noted as illustrative of the effect of the tertiary structure on the chemical reactivity of constituent amino acids that three of the tyrosine residues do not ionize in the usual pH range, only 4 out of 6 of these residues react with iodine, and methionines 13, 29, 30, and 79 do not react with iodoacetic acid.

During recombination of the terminal peptide containing 20 amino acids (S-peptide) with the protein part of the molecule (S-protein) to give ribonuclease-S, residues 3–13 in the peptide are crucial for enzymatic activity in the newly formed complex. Recombination with S-protein of an S-peptide in which methionine 13 has been oxidized to the sulfone gives a catalytically active complex. However $\Delta S$ for this reaction is −100 e.u. compared with −150 e.u. when the recombination is carried out with unoxidized S-peptide. It was pointed out that this methionine is adjacent to position 12 which is implicated in the enzymatic activity of the molecule and yet it can be changed by 50 e.u. (conformational entropy) without changing the enzyme's activity.

*S. Moore*, New York (U.S.A.) gave evidence that the dimer of ribonuclease which is enzymatically active and which is obtained by lyophilization of a 50 % acetic acid solution of ribonuclease consists of a head-to-tail fit of two partially uncurled molecules. By carboxymethylation of the dimer with 2 moles of iodoacetic acid, he obtained a new dimer consisting of 1 molecule of a hitherto inaccessible ribonuclease which is carboxymethylated at positions 12 and 119, and one molecule of active ribonuclease.

Substances which inhibit enzymatic hydrolysis of cytidine 2′,3′-phosphate and protect the enzyme against alkylation were reported by *A. P. Mathias*, London (England). In general, there is good agreement between the $K_i$ values obtained for each compound in both reactions. The pH activity curves in organic solvents, the variation with pH of the rate of hydrolysis of cytidine 2′,3′-phosphates, and the results of spectrophotometric and kinetic examinations of the inhibition of ribonuclease by $Zn^{2+}$ ions all imply that there are two histidines in the active site. It was suggested that a protonated imidazole group interacts with the 2′-oxygen of the substrate and another imidazole in its basic form is hydrogen-bonded to the attacking water molecule. This view was contested by *H. Witzel*, Marburg (Germany) in the resulting discussion and in a short paper. This worker postulated that the binding of the enzyme to the substrate involves only the phosphate group in dianionic form, the two concomitant positive charges being supplied by a triprotonated diimidazole system and the ε-ammonium group of lysine 41.

One-hundredfold purification of an enzyme from pig pancreas which catalyses the reactivation by oxygen of reduced ribonuclease was described by *P. Venetianer*, Budapest (Hungary). This enzyme requires a thermostable dialysable cofactor which can be replaced by dehydroascorbic acid.

Amino acid sequences for beef chymotrypsinogen arrived at by *B. Keil*, Prague (Czechoslovakia), and *B. S. Hartley*, Cambridge (England), differ, but both are in agreement over the relative positions of all five disulfide bridges. Serine 195 and histidine 57 probably constitute the active site. The catalytic activity also depends on the *N*-terminal isoleucine as was shown by *B. Labouesse*, Orsay (France). *J. Kraut*, La Jolla (U.S.A.), and *D. M. Blow*, Cambridge (England), reported progress on X-ray crystallographic analyses of chymotrypsinogen and α-chymotrypsin, respectively. Both agree that neither of these molecules contains an α-helix. *R. A. Oosterbaan*, Rijswijk (Holland), described the incubation of chymotrypsin with its substrate (*N*-acetyltyrosine ethyl ester) in the presence of $H_2^{18}O$. Subsequent acetylation of the protein and isolation of the tetrapeptide Gly-Asp(Ac)-Ser-Gly showed that it contained no $^{18}O$. Thus it appears that ring structures involving serine and a neighboring aspartic acid are not involved in the active site.

*J. I. Harris*, Cambridge (England), compared some aspects of the structure and mode of action of yeast and muscle glyceraldehyde-3-phosphate dehydrogenases (GAPDH). Inactivation of GAPDH by iodosobenzoate is due to formation of an intra-chain S–S bridge between two cysteines in the "active-center" peptide. Yeast alcohol dehydrogenase contains four identical polypeptide chains each with a molecular weight of 36 000. Treatment of the enzyme with [1-$^{14}$C]iodoacetic acid leads to complete loss of its activity, and the resulting *S*-carboxymethylcysteines occur in the same sequence of amino acids in the enzyme protein. Some peptide sequences in dehydrogenases are the same as some in haemoglobin.

*M. F. Perutz*, Cambridge (England), described the isolation of a new form of reduced haemoglobin from horse which, when subjected to two-dimensional X-ray crystallographic analysis, showed an increase of 7 Å in the distance between its reactive SH groups (loaded with Hg) compared to the oxidized form. Hence the difference between horse oxyhaemoglobin and human reduced haemoglobin is not a species difference but is due to a large change in the shape of the molecule on uptake of oxygen. In a short paper, *D. Labie*, Paris (France), described a new normal human haemoglobin, haemoglobin $A_4$.

In the colloquium on the biochemistry of chloroplasts, the isolation of these particles in mixtures of hexane and carbon tetrachloride was described by *R. Leech*, London (England). High-speed centrifugation between sucrose densities of 1.29 and 1.36 gave particles which were morphologically closer to those in the leaf than chloroplasts isolated by aqueous methods. However, some lipids, *e.g.* carotenoids and plastoquinones, had been removed; this presumably accounts for the fact that these particles did not give the Hill reaction.

[VB 814/143 IE]

German version: Angew. Chem. *76*, 503 (1964)

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## Reactions of Compounds with Electropositive Chlorine

*K. Dehnicke* [1], Stuttgart (Germany)

*Reactions with ClF:* $SbCl_5$ reacts with ClF at 5 °C to form $SbCl_4F$. Infrared and Raman spectra show that the compound occurs undissociated as trigonal bipyramids in the molten state and as ions $[SbCl_4]^+ + F^-$ in the solid state [2]. The force constant of $[SbCl_4]^+$ corresponds with that of the isoelectronic $SnCl_4$. – $AsCl_3$ reacts with ClF as follows:

$$2\ AsCl_3 + 6\ ClF = [AsCl_4]^+[AsF_6]^- + 4\ Cl_2.$$

[1] In collaboration with *K.-U. Meyer*, *J. Weidlein*, *J. Strähle*, and *U. Müller*.

[2] *Cf. L. Kolditz*, Z. anorg. allg. Chem. *289*, 128 (1957).

The vibration spectrum demonstrates that the ionic form is present exclusively [3]. The force constant of $[AsCl_4]^+$ is somewhat higher than that of the isoelectronic $GeCl_4$.

*Reactions with $Cl_2O$:* Oxide chloride syntheses with $Cl_2O$ are already familiar. $ZrOCl_2$ has now been prepared at −15 °C in $CCl_4$:

$$ZrCl_4 + Cl_2O \rightarrow ZrOCl_2 + 2\,Cl_2.$$

According to the infrared spectrum, $ZrOCl_2$ is a zirconyl tetrachloro-oxozirconate $[ZrO]^{2+}[ZrOCl_4]^{2-}$ with a chain-form anion polymerized via the oxygen atoms.

*Reactions with $ClNO_3$:* By the method of *Schmeisser* [4], the anhydrous nitrates $Co(NO_3)_2$ ($\mu$ = 4.85 B.M.) and $Mn(NO_3)_2$ ($\mu$ = 5.48 B.M.) result from $CoCl_2$ and $MnCl_2$ with chlorine nitrate. $Co(NO_3)_2$ forms a solvate with $N_2O_4$, which according to spectral and magnetochemical data is a nitrosyl trinitratocobaltate $NO^+[Co(ONO_2)_3]^-$ ($\mu$ = 5.19 B.M.) with the nitrato group as a bidentate ligand.

From the chloride fluorides $SbCl_4F$ and $[AsCl_4]^+[AsF_6]^-$ the complex nitrates $[Sb(ONO_2)_4]^+F^-$ and $[As(ONO_2)_4]^+[AsF_6]^-$ are obtained with chlorine nitrate. $SbF_3Cl_2$ yields an unstable $SbF_3(ONO_2)_2$, which is stabilized by rearrangement at 40 °C:

$$SbF_3(ONO_2)_2 \rightarrow NO_2^+\,[SbOF_3(ONO_2)]^-.$$

Thermal decompositon of the fluoride nitrates leads to the formation of definite oxide fluorides, *e.g.*

$$[As(ONO_2)_4]^+[AsF_6]^- \rightarrow 2\,AsOF_3 + 4\,NO_2 + O_2.$$

*Reactions with $ClN_3$:* $SbCl_5$ reacts with chlorine azide to form $SbCl_4N_3$, which splits off $N_2$ and $Cl_2$ and is thereby converted into polymeric $SbNCl_2$. An unstable chloride azide $VCl_4N_3$ is formed from $VCl_4$ and $ClN_3$. In solution it splits off $N_2$ spontaneously:

$$VCl_4N_3 \rightarrow [Cl_4V{-}\bar{\underline{N}}] + N_2$$

The radical is stabilized by anionotropy yielding an *N*-chlorovanadium imide:

$$[Cl_4V{-}\bar{\underline{N}}] \rightarrow Cl_3V{=}N{-}Cl.$$

This compound is monomeric, sublimes readily and melts at 132 °C in a sealed tube. The V–N double bond absorbs in the infrared at 1110 $cm^{-1}$.

[Inorganic Chemistry Colloquium, Technische Hochschule Aachen (Germany), February 18th, 1964] [VB 798/140 IE]

German version: Angew. Chem. *76*, 385 (1964)

## Recent Investigations of Inorganic Nitrogen-Halogen Compounds

*J. Jander* and *V. Engelhardt*, München (Germany)

When $I_2$ disproportionates in excess liquid $NH_3$ a red N-I compound precipitates [5]. The tensimetric analysis of its degradation shows a nitrogen:iodine ratio of 2:1, *i.e.* $NH_2I{\cdot}NH_3$. Chemical evidence for this formula includes:

1. $NH_2I{\cdot}NH_3$ is converted into a black compound with a nitrogen:iodine ratio of 1:1 ($NH_2I$) by careful removal of $NH_3$ at −90 °C.

2. $NH_2I{\cdot}NH_3$ results also from ammonolysis of ICl, IBr, $INO_3$, pyridine, or $IClO_4$·pyridine in liquid $NH_3$ at −75 °C, *e.g.*

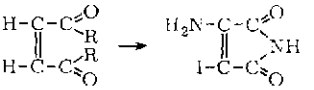
$$ICl + 3\,NH_3 \rightarrow NH_2I{\cdot}NH_3 + NH_4Cl$$

3. $NH_2I{\cdot}NH_3$ corresponds in color completely with the sparingly soluble $(CH_3)_2NI{\cdot}NH_3$ formed from $(CH_3)_2NI$ and liquid $NH_3$ at −75 °C.

4. $NH_2I{\cdot}NH_3$ is also formed when pale yellow, saturated solutions of $NI_3{\cdot}3\,NH_3$ in liquid $NH_3$, which contain dissolved $NH_2I$ (as shown by the Equation), are cooled with liquid air:

$$NI_3{\cdot}3\,NH_3 \rightleftharpoons NHI_2 + NH_2I + 2\,NH_3 \rightleftharpoons 3\,NHI_2 + NH_3$$

5. $NH_2I{\cdot}NH_3$ in liquid $NH_3$ has the properties of an iodinating agent, *e.g.*



The infrared spectrum of the solid red substance at −90 °C displays band groups at 3000 $cm^{-1}$ (N–H stretching vibrations), 1600 $cm^{-1}$ (N–H–N bending vibrations) and 1100 $cm^{-1}$ ($H_2N$–H rocking vibrations) which are typical of compounds containing $NH_3$ and $NH_2$. The black $NH_2I$ shows the two bands in the NH stretching region to be expected. On pumping off more $NH_3$ *in vacuo* at higher temperature a black substance with only one NH stretching band is obtained and at the same time the intensities of the bands at 1600 and 1100 $cm^{-1}$ decrease considerably. These changes are to be expected for the transition $NH_2I \rightarrow NHI_2$. The end product of the decomposition *in vacuo* is a black substance which displays no absorption in the three frequency regions mentioned. This is $NI_3$ which can be decomposed and removed without hazard in high vacuum at room temperature.

[GDCh-Ortsverband Braunschweig (Germany), February 19th, 1964] [VB 802/138 IE]

German version: Angew. Chem. *76*, 386 (1964)

## The Biological Utilization of Lactose

*K. Wallenfels*, Freiburg/Breisgau (Germany)

1. As far as we know, lactose occurs in the free form only in milk. It may be considered, therefore, as a product of the evolution of mammals. Its controlled use as a carbon source for *Coli* bacteria appears then as a consequence of the process of adaptation of a symbiont to its host. One can assume that lactose is utilized by the higher organism according to the same principles as by bacteria.

2. The utilization of lactose by *Coli* bacteria is controlled genetically and determined by the constitution of the lac-region in the chromosome of the bacterial cell. This region consists of the sections i o z y A, of which z, y, A represent structural genes [2] and cause the synthesis of enzymatically active proteins. Until now, only the products of the z- and A-genes, β-galactosidase and galactoside transacetylase, have been isolated and crystallized. The locus i controls the synthesis of the repressor. Suitable galactosides (inducers) abolish repression of the o-, z-, y-, and A-activities and therefore induce the enzyme synthesis. By changes in structure, inducers can be inactivated or even converted into very active inhibitors of the induction.

3. (with *H. V. Rickenberg* and *B. Müller-Hill*): Each product of a gene of the lac-region has its own specificity for galactosides of different chemical constitution. All specificities are relative, but markedly different from each other, *i.e.* good inducers can be, for example, no or poor substrates for galactosidase or transacetylase. The combined action of these relative specificities leads to an extremely high specificity of the lac-system, since only very few compounds are simultaneously substrates for all activities.

4. (with *H. Sund*, *K. Weber*, *B. Müller-Hill*, *Ch. Streffer*, and *R. Weil*): The product investigated in the greatest detail hitherto of the lac-region of the *Coli* chromosome is the β-galactosidase (molecular weight: 520000). It may be split by different methods into 4 large sub-units (mol.wt. 130000). Treatment with performic acid yields 12 smaller sub-units (mol.wt. 43000). The sulfur balance shows the presence of 84–88 half cystine residues, 46 reacting as free SH-groups in the denatured state. Twelve free SH-groups per molecule of galactosidase can be alkylated or mercurated, without the activity decreasing. Further substitution of 6–8 SH-groups leads to complete inactivation.

[3] Cf. *L. Kolditz*, Z. anorg. allg. Chem. *280*, 313 (1955).

[4] *M. Schmeisser* and *K. Brändle*, Angew. Chem. *73*, 388 (1961).

[5] *J. Jander*, *U. Engelhardt*, and *G. Weber*, Angew. Chem. *74*, 75 (1962); Angew. Chem. internat. Edit. *1*, 46 (1962).

5. (with *P. Schädel, E. Schillinger*, and *W. Hengstenberg*): The specificity of β-galactosidase is largely known. Both the structure of the aglycone as well as that of the glycone determine the substrate quality. The β-linked galactoside residue is up to now the optimal glycone structure. Substitution at one of the hydroxyl groups, replacement of an OH-group by H, or epimerisation decrease the cleavability considerably. With the aglycone, a strong electronic influence on cleavability is shown: nitrophenyl is better than phenyl and this is better than alkyl. Replacement of the glycosidic oxygen by sulfur so reduces the cleavability, that thiogalactosides with an unsuitable aglycone are practically not cleaved. Nitrophenyl thiogalactoside, however, is cleaved. Further nitro groups increase the cleavability considerably. 2,4,6-Trinitrophenyl β-D-thiogalactoside is the second best substrate after *o*-nitrophenyl galactoside. It is slowly hydrolysed non-enzymatically at pH 7.6 to picric acid and thiogalactose, whereas enzymatic fission at the same pH yields only galactose and thiopicric acid. Enzymatic cleavage proceeds therefore in the manner expected for a proton-catalysed reaction.

6. (with *G. Kurz*): By enzymatic oxidation of the liberated galactose with DPN and galactose dehydrogenase (*Ps. saccharophila*), it can be shown that the direct product of the enzymatic hydrolysis of lactose is β-galactose.

7. (with *K. Herrmann*): In the biochemical utilization of lactose, phosphorylation by galactokinase to α-galactose 1-phosphate follows hydrolysis. The substrate of this enzyme is α-galactose. When it was investigated, whether in the case of galactose utilization the speed of mutarotation can likewise be regulated enzymatically, a high aldose-1-epimerase activity (A-1-E) was discovered in *Coli* bacteria. The enzyme accompanies β-galactosidase in the purification up to high degrees of purity and can be separated by recrystallization.

8. (with *G. Seeler* and *K. Herrmann*): Estimations of A-1-E activity in different *E. coli* mutants ($i^-z^+y^+$; $i^-z^+y^-$; $i^+z^+y^+$ with and without methyl thiogalactoside as inducer of the lac-region) show that the enzyme is determined not in the lac-region of the *E.coli* chromosome and probably also not in the gal-region.

[GDCh-Ortsverband Frankfurt/Main (Germany), January 30th, 1964, and Institut Pasteur, Paris (France), February 15th 1964],

[VB 800/139 IE]

German version: Angew. Chem. *76*, 383 (1964)

# SELECTED ABSTRACTS

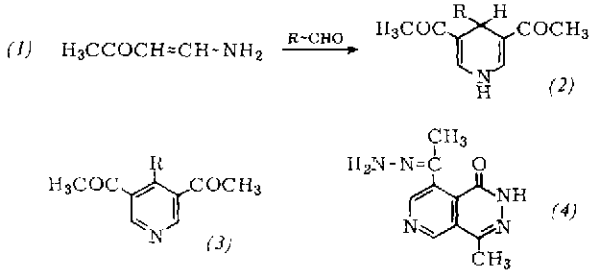
**The synthesis of polyunsaturated fatty acids in microorganisms** has been investigated by *J. Erwin* and *K. Bloch*. *Euglena gracilis* produces large amounts of linolenic acid in light but only traces of other polyunsaturated acids. About 85 % of the α-linolenic acid is contained in the chloroplast lipids of the green cells. Cells grown in the dark and many colorless mutants of *Euglena* synthetize only small amounts of α-linolenic acid, although the cells' content of $C_{20}$, $C_{22}$ and $C_{24}$ polyene acids is considerably increased. In [$^{14}$C]acetate media with and without Hill-reaction inhibitors, cell growth was stimulated by brief illumination. Incorporation of acetate into unsaturated acids was reduced by Hill-reaction inhibitors, but its incorporation into saturated acids was unaffected. / Biochem. Z. *338*, 496 (1963) / – De. [Rd 837/229 IE]

**A new synthesis of secondary and tertiary amines** was discovered by *K. A. Schellenberg*. Primary or secondary amines were treated with carbonyl compounds and $NaNH_4$ in a neutral aqueous solution at 0 °C. The Schiff bases or tertiary immonium salts produced as intermediates were presumably reduced by the $BH_4^{\ominus}$. A typical example is the reaction of $N^2$-carbobenzoxy-L-lysine with acetone and $NaBH_4$. Subsequent treatment with methanolic HBr leads to esterification and hydrolysis of the protecting groups. $N^6$-Isopropyl-lysine methyl ester dihydrobromide is produced in 53 % yield, m.p. 156.5–157.5 °C. In an analogous manner $N^2$,$N^6$-diisopropyl-lysine methyl ester hydrobromide (m.p. 186.5–188.5 °C) is formed from L-lysine hydrochloride in 4 % yield. Further examples: *N*-isopropylbutylamine, m.p. 197–197.8 °C, yield 63 %; *N*-ethylpiperidine, m.p. 225 to 227 °C, yield 53 %. / J. org. Chemistry *28*, 3259 (1963) / – Kr. [Rd 845/231 IE]

**Chinese iatrochemists in the middle ages prepared mixtures of steroid hormones** for medical purposes as *L. Gwei-Djeu* and *J. Needham* have been able to show by translations of old manuscripts from the 10th to 16th centuries. One manuscript describes the addition of bean juice from the soap bean tree *Gleditschia sinensis* to large quantities of urine. This juice contains saponins, and a precipitate was thus obtained from which the steroid conjugates were extracted with hot water. The Chinese chemists sublimated the residue from the extraction in small earthenware vessels under accurately controlled conditions. They obtained white, relatively pure, crystalline substances, which, emulsified in milk fat, were used in the treatment of hypogenitalism. / Nature (London) *200*, 1047 (1963) / –Sch. [Rd 861/230 IE]

**Hapten-binding antibodies** were obtained *in vitro* by *P. Haux, P. W. Jungblut*, and *F. Turba* by refolding of rabbit γ-globulin, in which about 5 sulfur bridges had been reduced with mercaptoethanol. On reduction, the γ-globulin unfolds. The reduced but reducing-agent-free rabbit γ-globulin was brought into contact with dinitrophenylated human albumin, which was absorbed on low-capacity DEAE-cellulose, and then oxidized with $O_2$ in tris buffer (at pH 7.0). Part of the γ-globulin refolded. The proteins were separated from the DEAE-cellulose with a solution of tris buffer and NaCl (pH 9.5) with addition of ε-DNP-lysine as dissociating hapten. The specific refolded γ-globulin was obtained from the eluate by chromatography. The "antibody" thus produced bound about 2 moles of the hapten, ε-DNP-lysine, per mole. Before refolding, the binding capacity was only about 5 % of this value. Refolded and normal γ-globulin had the same sedimentation constant. / Biochem. Z. *338*, 393 (1963 / – De. [Rd 839/228 IE]

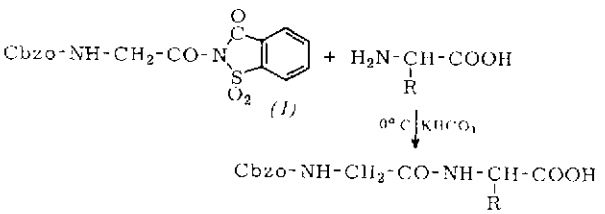
**Syntheses of pyridine derivatives from aminobutenone and aldehydes** were reported by *F. Micheel* and *H. Dralle*. 1-Amino-1-buten-3-one *(1)* or 1-methoxy-1-buten-3-one (in the presence of $NH_3$) react with aldehydes in the presence of $H^+$ ions (glacial acetic acid) exothermically to form 3,5-diacetyl-1,4-dihydropyridine derivatives *(2)* (yields 33–57 %). On dehydrogenation with $NO_2$ and $CrO_3$, the latter give the pyridine derivatives *(3)* (yields 25–88 %).




*(a)*: R = H; *(b)*: R = $CH_3$; *(c)*: R = $C_6H_5$; *(d)*: R = $COOC_2H_5$

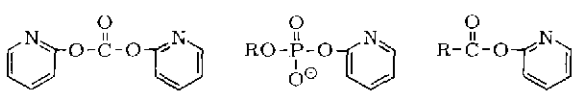
Oxidation of *(3a)* with $HNO_3$ gives pyridine-3,5-dicarboxylic acid; oxidation of *(3b)* and *(3d)* yields pyridine-3,4,5-tricarboxylic acid. Compound *(3d)* is converted into *(4)* with hydrazine hydrate. / Liebigs Ann. Chem. *670*, 57 (1963)/ –Ma. [Rd 899/249 IE]

**A new method of peptide synthesis using amino acid derivatives of saccharin** (*o*-sulfobenzoic imide) has been described by *F. Micheel* and *M. Lorenz*. *N*-Carbobenzoxy- (Cbzo) amino acids, whose carboxyl group is activated by condensation with saccharin, react with amino acids in tetrahydrofuran/water. The saccharin derivates are obtained from the *N*-Cbzo-amino acid and pseudosaccharin chloride by a reaction involving rearrangement in methylene chlorid at 0 °C. The *N*-Cbzo-glycine derivative *(1)*, m.p. 156–158 °C corr. (decomp.), is formed in 91 % yield. Compound *(1)* is also obtained from *N*-Cbzo-glycine and saccharin in the presence of dicyclohexylcarbodiimide in tetrahydrofuran (91 %). Examples of dipeptides and saccharin derivatives: *N*-Cbzo-glycyl-DL-phenylalanylsaccharin, m.p. 154–155 °C corr., 70 %; *N*-Cbzo-glycylglycine, m.p. 178 °C corr., 86 %; *N*-Cbzo-glycyl-L-phenylalanine, m.p. 125–126 °C corr., 93 %; *N*-Cbzo-glycyl-L-glutamic acid, m.p. 161–162 °C corr., 77.2 %.



Advantages of this method: protection of the carboxyl group of the free amino acid is not necessary, high yields, ease of separation of the saccharin, no racemization during peptide synthesis. / Tetrahedron Letters *1963*, 2119 / –Ma. [Rd 853/223 IE]

**Transacylations using α-hydroxypyridyl phosphates and carboxylates** are described by *W. Kampe*. Di-α-pyridyl carbonate *(1)* yields α-pyridyl monohydrogen phosphates *(2)*, while carboxylic acids or their amine salts yield α-pyridyl carboxylates *(3)* in very good yields. The esters *(2)* react with phosphoric acids to give pyrophosphates, with alcohols to give diesters, and with amines to give phosphoramides (yields: 70–90 %). The esters *(3)* undergo transesterification with alcohols in the presence of catalytic quantities of alkoxide or sodium α-pyridoxide, sometimes very rapidly, in 75–90 % yields. This catalysis with base probably depends on an equilibrium between α-pyridoxide anions and alcohol molecules. Furthermore, *(3)* reacts easily with amines, the



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

reaction rates at room temperature depending on the consitution of the reactant. / Tetrahedron Letters *1963*, 2133 / –Ma. [Rd 856/224 IE]

**Aldehyde hemihydrates** were obtained by *D. L. Klass, W. N. Jensen, J. S. Blair*, and *T. W. Martinek* by dry distillation of a mixture of the barium salts of higher fatty acids and barium formate. Using barium dodecanoate they obtained, besides the aldehyde hemihydrate, n-dodecanal, *n*-dodecanal-*n*-dodecanol hemiacetal, and n-dodecanol. Aldehyde hemihydrates are also formed from the aldehydes and stoichiometric quantities of water. The structures of the adducts

$H_3C-(CH_2)_n-CHOH-O-CHOH-(CH_2)_n-CH_3$

n = 5, m. p. 54 – 59 °C (decomp.)

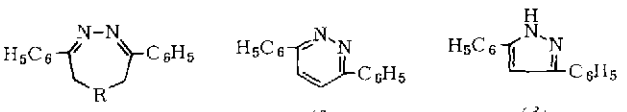
n = 8, m. p. 58.5 – 63 °C (decomp.)

n = 10, m. p. 56 – 60 °C (decomp.)

(α,α'-dihydroxy ethers) were proved by infrared spectroscopy./ J. org. Chemistry *28*, 3029 (1963) / –Kr. [Rd 844/227 IE]

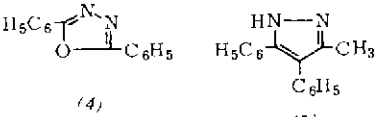
**Inorganic salts have been used as the stationary phase** in gas chromatography by *J. A. Favre* and *L. R. Kallenbach*. Of 44 salts tested with a 1:1:1 mixture of *o*-, *m*-, and *p*-terphenyl, the most effective were potassium antimonate, carbonate, borate, and phosphate. The salts are suitable for the separation of very high-boiling organic substances, with operating temperatures of up to 500 °C; the maximum is about 300 °C with organic liquid phases. Retention times are of the order of a few minutes. The resolving power of a given potassium salt can be very much increased by the addition of a few per cent of KOH. The salts were applied to the support, Chromosorb P, in aqueous solution. Separation of higher polyphenyls was also investigated; for hexaphenyls, for example, lithium chloride is a very suitable stationary phase. / Analytic. Chem. *36*, 63 (1964) / –Jg. [Rd 835/232 IE]

**Ring contractions by desulfurization leading to pyridazines and pyrazoles** are described by *J. D. London* and *L. B. Young*. 2,7-Dihydro-3,6-diphenyl-1,4,5-thiadiazepine *(1a)* is converted by halogenation-dehalogenation with *N*-bromosuccinimide in $CCl_4$, by treatment with $SO_2Cl_2$ in $CH_2Cl_2$ followed by NaI in acetone, or with bromine in acetic acid (in each case under reflux) into 3,6-diphenylpyridazine *(2)*, m.p. 222 °C (yields: 83, 65, or 40 %, respectively). Compound *(2)* is also formed in 80 % yield by thermolysis in boiling ethylene glycol. The dioxide *(1b)* also undergoes thermal decomposition in boiling ethanol or acetic acid to yield 80 and 90 % *(2)*, respectively. The monoxide *(1c)*, on the other



*(1a)*: R = S
*(1b)*: R = $SO_2$
*(1c)*: R = SO

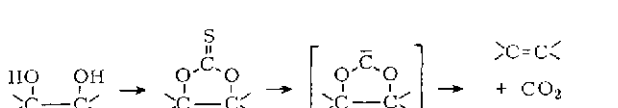
*(2)* *(3)*



*(4)* *(5)*

hand, is converted in hot acetic acid into 3,5-diphenylpyrazole *(3)*, m.p. 199 °C. When heated with hydrogen peroxide in acetic acid, *(1a)* yields 2,5-diphenyl-1,3,4-oxadiazole *(4)*, m.p. 138 °C, and *(3)* yields 1,2-dibenzoylhydrazine. Isomerization of *(1b)* with ethanolic $NaOC_2H_5$ leads to a sulfinic acid, which loses sulfur dioxide on melting to yield 3-methyl-4,5-diphenylpyrazole *(5)*. / J. chem. Soc. (London) *1963*, 5496 / –Ma. [Rd 858/225 IE]

**A new stereospecific synthesis of olefins from 1,2-diols** has been found by *E. J. Corey* and *R. A. E. Winter*. A 1,2-diol is converted, *e.g.* by means of thiocarbonyldiimidazole in boiling toluene or xylene (30 min), into the cyclic thiocarbonate *(1)*. When heated with an excess of a desulfurizing agent, *e.g.* trimethyl or triethyl phosphite (70–80 h reflux under nitrogen), *(1)* splits off $CO_2$ and S by specifically *cis*-elimination. Even highly substituted olefins are obtainable



*(1)* *(2)*

without difficulty. The reaction probably proceeds via the carbene *(2)*. Examples: *meso*-hydrobenzoin (→ thiocarbonate) → *cis*-stilbene (92 % yield); (±)-hydrobenzoin → *trans*-stilbene (87 %); *cis*-1,2-cyclohexanediol → *cis*-cyclodecene (84 %); *trans*-1,2-cyclohexanediol → *trans*-cyclodecene (81 %). / J. Amer. chem. Soc. *85*, 2677 (1963) / –Ma. [Rd 860/226 IE]

**Chemotaxonomie der Pflanzen – Eine Übersicht über die Verbreitung und die systematische Bedeutung der Pflanzenstoffe** (Plant Chemotaxonomy – A Survey of the Distribution of Plant Constituents and Their Significance for Botanical Classification). By *R. Hegnauer*. Birkhäuser Verlag, Basel and Stuttgart. Vol. I (1962): Thallophyta, Bryophyta, Pteridophyta, and Gymnospermae. Chemical Series, Vol. 14, 1st edit. 517 pp., numerous illustrs. and tables, cloth, DM 96.– (about $ 24.–). Vol. II (1963): Monocotyledoneae. Chemical Series, Vol. 16, 1st edit. 540 pp., several illustrs., numerous tables, cloth, DM 98.– (about $ 24.50).

In this work, planned to be completed in about five volumes, *R. Hegnauer*, Professor of Pharmacognosy at the University of Leiden (Holland), has undertaken to collect all the data known on phytochemical materials and to classify them according to the criteria of botanical systematics. The subject matter in these books is presented according to a single general scheme: within each family a description of the botanical characteristics and distribution of the various species and their systematic classification is followed by a description of their morphology, and finally by a detailed description of their phytochemical characteristics. Extensive literature references are given, and finally views are expounded on the significance of the constituents referred to for the classification of plants.

It is immediately apparent that while there are many structural peculiarities in the phytochemical spectra of some genera or families, only the most painstaking investigation of enough well-defined plant material would give a safe basis for a taxonomic evaluation. Many chemical investigations of plants, though useful in themselves, are useless for the purposes of systematics, because only too often the chemists have not taken the trouble to characterize their starting materials adequately. It is also obvious from this work how restricted these chemical investigations have been to date: although there are multitudinous publications referring to economically and medicinally important plants, there are whole families of plants which have never been investigated phytochemically at all.

The work is written and organized with extreme care. Printing and other errors are few. The reviewer has noticed the following: *Cedrus deodora* instead of *C. deodara*; phenoxazim instead of phenoxazine (p. 171): *Whally* for *Whalley*; telephoric acid is not a dibenzylbenzoquinone derivative, but a diphenylbenzoquinone derivative; the term isoprenoid should not be used in connection with cortisalin (p. 112); in the formula for cycasin, the representation with a pentavalent nitrogen should be replaced by the modern azoxy representation; *Missiorny* should be *Misiorny* (p. 381); in the formula for maltol, the two substituents have been interchanged; *Dietrich* should read *Dietsche* (p. 475), *Clatriau* should be *Clautriau* (p. 57); the structure of belladin given (p. 69) is not quite correct; the isoquinuclidin formula (p. 152) has an H missing; on p. 484 the reference should be to 1,8-dihydroxy-2-acetylnaphthalene or 2-acetylplumbagin and not to 1,8-dioxy-2-acetoxynaphthalene; also it would be preferable if the accepted prefix "hydroxy" were used consistently in place of the no longer official "oxy" nomenclature.

In many of the organic structural formulae, especially in the alicyclic field, there is a general neglect of stereochemistry; also some formulae are represented in such a way as to insinuate configurations, *e.g.* in the ephedrine formula, which in reality indicates ψ-ephedrine. The importance of configuration and stereoselectivity in the enzymatic synthesis of various compounds is so clearly recognized nowadays that a more thorough treatment of this aspect of structural chemistry is greatly to be desired in later volumes.

These minor objections should in no way be taken to belittle the magnificent performance of the author. The work presents a number of views that will be extremely useful to the scientist interested in phytochemistry. Through its clear exposure of the gaps in existing knowledge, it will stimulate research and open new horizons in plant chemistry.

*C. H. Eugster* [NB 138/72 IE]

**Chemie in nichtwäßrigen ionisierenden Lösungsmitteln** (Chemistry in Nonaqueous Ionizing Solvents). A series of monographs edited by *G. Jander*, *H. Spandau*, and *C. C. Addison*. Vol. I. The Chemistry of Anhydrous Liquid Ammonia. Part 2: Organic Reactions in Liquid Ammonia. By *H. Smith*. Verlag Friedr. Vieweg & Sohn, Braunschweig, 1963. 1st edit., XV, 363 pp., cloth DM 55.20 (about $14.00).

This book is the first of a series of monographs dealing with the chemistry of nonaqueous solvents which are written partly in German and partly – like the present volume – in English. This part deals with organic reactions in anhydrous liquid ammonia, whereas inorganic reactions in this solvent are to be discussed in Part 1, which will be in German but is not due to be published for some time yet. On account of this, the general problems relating to liquid ammonia and solutions of alkali and alkaline-earth metals in this solvent are discussed only briefly or not at all in Part 2. Yet it is precisely these solutions which play a very important part in certain reductions carried out in organic chemistry; in fact, they may be regarded as the most important portion of the book. Section H, which deals with these reductions, is the best chapter of the book with regard to both its concise presentation and its theoretical treatment. This conciseness is lacking in the other sections, which are mainly compilations, particularly in the introductory sections A and B: on the 'Formation of ammoniates' and 'Solubilities'. However, this is not the fault of the author since there are only unrelated observations to be found scattered widely throughout the literature and these can only be reviewed; incidentally, this remark applies not only to the subject matter of these two chapters. More coherent relationships occur apart from in section H also in section D (ionic reactions in liquid ammonia), although this subject might have been treated somewhat more fully. Greater clarity of the theoretical aspects would also be desirable for the sub-section on nucleophilic aromatic substitutions which is appended in section J. Other themes dealt with include the 'Properties of solutions of organic substances' (section C), 'Amonolytic reactions' (E), 'Electrolysis' (F), and 'Oxidation reactions' (G).

The book serves mainly as an efficient guide to the literature (1388 references). It cannot serve as a laboratory manual, for no practical hints are given, not even for reactions of a general nature.

*W. Hückel* [NB 139/68 IE]

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# Complexes of Tetradentate Ligands Containing Phosphorus and Arsenic [*]

BY DR. L. M. VENANZI

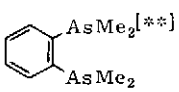
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*The effect of ligand shape on coordination numbers and geometry of coordination compounds has been studied using two tetradentate ligands containing phosphorus and arsenic. These tend to form five-coordinate complexes with trigonal bipyramidal structure [Fe(II), Co(I), Co(II), Rh(I), Ni(II), Pd(II), Pt(II)], but can also form six-coordinate complexes with octahedral structure [Fe(II), Ru(II), Os(II), Co(III), Rh(III), Pd(IV), Pt(IV)]. The magnetic properties and the stereochemistry of the complexes are explained by ligand field theory which predicts that, for metal ions with $d^6$-electronic configuration, a low overall field strength should favor the formation of five-coordinate paramagnetic complexes while a high overall field strength should favor the formation of six-coordinate diamagnetic complexes. – This work provides further indication that the tendency of polydentate ligands to use all the potential donor atoms is not as pronounced as is generally believed. This is shown by the isolation of chromium(III) complexes in which the tetradentate ligands are, in fact, acting as tridentate, and by the isolation of mercury(II) complexes where only two of the four donor atoms of the polydentate ligand are actually bonded to the central metal atom.*

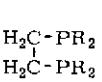
## 1. Introduction

One of the most fruitful developments which has taken place in recent years in the field of coordination chemistry has been the investigation of the complexing properties of polydentate ligands. Most of these have been either polyamines or aminopolycarboxylic acids [1]. Recently, however, polydentate ligands containing phosphorus(III) and arsenic(III) have attracted increasing attention.

Most of the studies reported to date in the coordination chemistry of the heavy Group V donors [1a] have been carried out using bidentate ligands such as *o*-phenylenebis(dimethylarsine) or, for short, DAS *(1)* [2] and 1,2-disubstituted phosphinoethanes or DP *(2)* [3]. However, tridentate ligands such as bis-(3-dimethylarsinopropyl)arsine *(3)* [4] are being increasingly used and

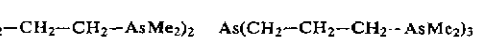


DAS *(1)*



DP *(2)*

some complexes of tris-(3-dimethylarsinopropyl)arsine *(4)* have been described [5].



*(3)* *(4)*

The chemistry of complexes of the heavy Group V donors has many interesting aspects:

1. *The formation of stable complexes with the platinum metals.* Numerous complexes of P(III) and As(III) as donors with these elements are known; any attempt to

[*] Adapted from a Plenary Lecture at the General Meeting of the Gesellschaft Deutscher Chemiker on Sept. 10th, 1963 in Heidelberg (Germany).

[1] *S. Chaberek* and *A. E. Martell:* Organic Sequestering Agents. Wiley, New York 1959.

[1a] The heavy Group V donors, in this context, are phosphorus(III), arsenic(III), and antimony(III). Antimony(III) forms coordination compounds which are similar to those of arsenic(III), although the complexes of antimony(III) are less stable. As no polydentate ligands containing Sb(III) have yet been reported, only those of P(III) and As(III) will be discussed.

[2] *T. M. Dunn, R. S. Nyholm,* and *S. Yamada,* J. chem. Soc. (London) *1962*, 1564, and previous references quoted therein.

[**] Throughout this article, Me = $CH_3$, Ph = $C_6H_5$.

[3] *J. Chatt* and *R. G. Hayter,* J. chem. Soc. (London) *1961*, 773.

[4] *G. A. Barclay, R. S. Nyholm,* and *R. V. Parish,* J. chem. Soc. (London) *1961*, 4433.

[5] *G. A. Barclay* and *A. K. Barnard,* J. chem. Soc. (London) *1961*, 4269.

enumerate even only the main types would go beyond the scope of this introduction.

2. *The stabilization of low oxidation states.* Numerous complexes of metals in their low oxidation states have been prepared; a representative selection is shown in Table 1 [6]. The thermal stability of most of these complexes is fairly high, but their resistance towards oxidation by air is often lower than that of the corresponding metal carbonyls.

Table 1. Complexes of Group VB donors with metals in low oxidation states.

| Complex | M or L | Ref. |
|---|---|---|
| $[M(DP)_3]$ | V, Cr, Mo, W | [6a] |
| $[M(DP)_2]$ | Fe, Co | [6a] |
| | Ni, Pd | [6b] |
| | Pt | [6c] |
| $[M(CO)_2(DAS)_2]$ | Cr, Mo, W | [6d] |
| $[Fe(CO)(DAS)_2]$ | | [6e] |
| $[Co_2(CO)_4(Ph_3P)_4]$ | | [6f] |
| $[NiL_4]$ | $PF_3$, $PCl_3$ | [6g] |
| | $MePCl_2$ | [6h] |
| $[RhCl\{(PhO)_3P\}_3]$ | | [6i] |
| $[Re(CO)_4(Ph_3P)_2]Cl$ | | [6j] |

3. *The formation of low-spin complexes.* Practically all the complexes of the heavy Group V donors are of low-spin type. Ligands containing these donors cause spin pairing more easily than aromatic nitrogen heterocycles. The magnetic properties of some phosphine and arsine complexes and of the corresponding *o*-phenanthroline or 2,2′-bipyridyl complexes are shown in Table 2 [7].

Table 2. Comparison of the magnetic properties of phosphine and arsine complexes with those of the corresponding complexes with *o*-phenanthroline (phen) or dipyridyl (dpy).

| Complex | Magnetic properties | Ref. |
|---|---|---|
| $[Ni(DAS)_3](ClO_4)_2$ | diamagnetic | [7a] |
| $[Ni(phen)_3](ClO_4)_2$ | $\mu_{eff.} = 3.10$ B.M. | [7b] |
| $[Co(DAS)_3](ClO_4)_2$ | $\mu_{eff.} = 1.92$ B.M. | [7b] |
| $[Co(dipy)_3](ClO_4)_2$ | $\mu_{eff.} = 4.85$ B.M. | [7b] |
| $[FeBr_2(DAS)_2]$ | diamagnetic | [7c] |
| $[FeBr_2(phen)_2]$ | $\mu_{eff.} = 4.9$ B.M | [7d] |

4. *The formation of complexes with unusual coordination numbers.* Coordination numbers of 3, 5, 7, and 8 have been observed in complexes of the heavy Group V donors. A list of some of these compounds is given in Table 3 [8]. Although unusual coordination numbers have been observed with other ligands, there is often a difference in the number of bonds found in the complexes formed by, say, nitrogen donors, and those found in the complexes formed by heavy Group VB donors.

Table 3. Complexes with Group VB donors exhibiting unusual coordination numbers.

| Complex | M | Ref. |
|---|---|---|
| $[MCl_4(DAS)_2]$ | Ti, V, Zr, Hf | [8a] |
| $[MoI(CO)_2(DAS)_2]I$ | | [8b] |
| $[Mn(CO)_4(Ph_3P)]$ | | [8c] |
| $[M(DP)_2]$ | Fe, Co | [8d] |
| $[M\{(p\text{-}Cl\text{—}C_6H_4)_3P\}_3]$ | Pd | [8e] |
| | Pt | [8f] |
| $[NiCl(DAS)_2](ClO_4)$ | | [8g] |
| $[CuCl\{(PhO)_3P\}_2]$ | | [8h] |
| $[AgI(Me_2PhP)_2]$ | | [8i] |
| $[AuI_2(DAS)_2](ClO_4)$ | | [8j] |

## 2. Bonding

The unusual coordinating properties of P(III) and As(III) can be attributed to the large degree of covalence of the metal-ligand bond. This covalence is associated with a) the high polarizability of the donor atoms [9], which use hybrid orbitals of the $sp^3$-type for $\sigma$-bond formation, and b) the contribution from $\pi$-bond formation involving transfer of charge from filled d-orbitals of the metal atom to empty d-orbitals of the donor atom [10], as shown in Figure 1.

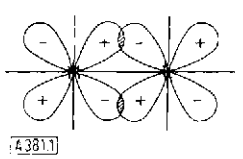



Fig. 1. Schematic representation of $\pi$-bond formation between filled metal d-orbitals and empty ligand d-orbitals.

As most of the platinum-metal atoms or ions are rich in d-electrons, they should be capable of forming strong $\pi$-bonds and therefore strong metal-ligand bonds, thus


[6a] *J. Chatt* and *H. R. Watson*, J. chem. Soc. (London) *1962*, 2545.

[6b] *J. Chatt*, *F. A. Hart*, and *H. R. Watson*, J. chem. Soc. (London) *1962*, 2537.

[6c] *J. Chatt* and *G. A. Rowe*, Nature (London) *191*, 1191 (1961).

[6d] *H. L. Nigam*, *R. S. Nyholm*, and *M. H. B. Stiddard*, J. chem. Soc. (London) *1960*, 1803.

[6e] *H. Nigam*, *R. S. Nyholm*, and *D. V. Ramana Rao*, J. chem. Soc. (London) *1959*, 1397.

[6f] *W. Hieber* and *W. Freyter*, Chem. Ber. *91*, 1230 (1958).

[6g] *G. Wilkinson*, J. Amer. chem. Soc. *73*, 5501 (1951).

[6h] *D. L. Quin*, J. Amer. chem. Soc. *79*, 3681 (1957).

[6i] *L. Vallarino*, J. chem. Soc. (London) *1957*, 2473.

[6j] *W. Hieber* and *L. Schuster*, Z. anorg. allg. Chem. *287*, 214 (1956).

[7a] *R. S. Nyholm*, J. chem. Soc. (London) *1950*, 2061.

[7b] *F. H. Burstall* and *R. S. Nyholm*, J. chem. Soc. (London) *1952*, 3570.

[7c] *R. S. Nyholm*, J. chem. Soc. (London) *1950*, 851.

[7d] *F. Basolo* and *F. P. Dwyer*, J. Amer. chem. Soc. *76*, 1454 (1954).

[8a] *R. J. H. Clark*, *J. Lewis*, and *R. S. Nyholm*, J. chem. Soc. (London) *1962*, 2460.

[8b] *H. L. Nigam*, *R. S. Nyholm*, and *M. H. B. Stiddard*, J. chem. Soc. (London) *1960*, 1806.

[8c] *W. Hieber* and *W. Fryer*, Chem. Ber. *92*, 1765 (1959).

[8d] See ref. [6a].

[8e] *L. Malatesta* and *M. Angoletta*, J. chem. Soc. (London) *1957*, 1186.

[8f] *L. Malatesta* and *C. Cariello*, J. chem. Soc. (London) *1958*, 2323.

[8g] *C. M. Harris*, *R. S. Nyholm*, and *D. J. Phillips*, J. chem. Soc. (London) *1960*, 4379.

[8h] *A. E. Arbuzov* and *V. M. Zoroastrova*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1952*, 809.

[8i] *R. C. Cass*, *G. E. Coates*, and *R. G. Hayter*, J. chem. Soc. (London) *1955*, 4007.

[8j] *C. M. Harris* and *R. S. Nyholm*, J. chem. Soc. (London) *1957*, 63.

[9] *R. W. Parry* and *R. N. Keller* in *J. C. Bailar*: The Chemistry of the Coordination Compounds. Reinhold, New York 1956, p. 119.

[10] *J. Chatt* and *R. G. Wilkins*, J. chem. Soc. (London) *1952*, 273.

accounting for the stability of the complexes. Furthermore, since strong covalent bonding in transition metal complexes induces spin pairing [11], it is to be expected that the complexes of the heavy Group V donors should be of low-spin type.

The stabilization of low oxidation states can also be explained in terms of $d_\pi$-$d_\pi$ bonding [12]. In this respect, phosphines and arsines are similar to carbon monoxide [13]: the latter acts as an electron acceptor by using its $\pi^*$-levels, while the former use their empty d-orbitals.

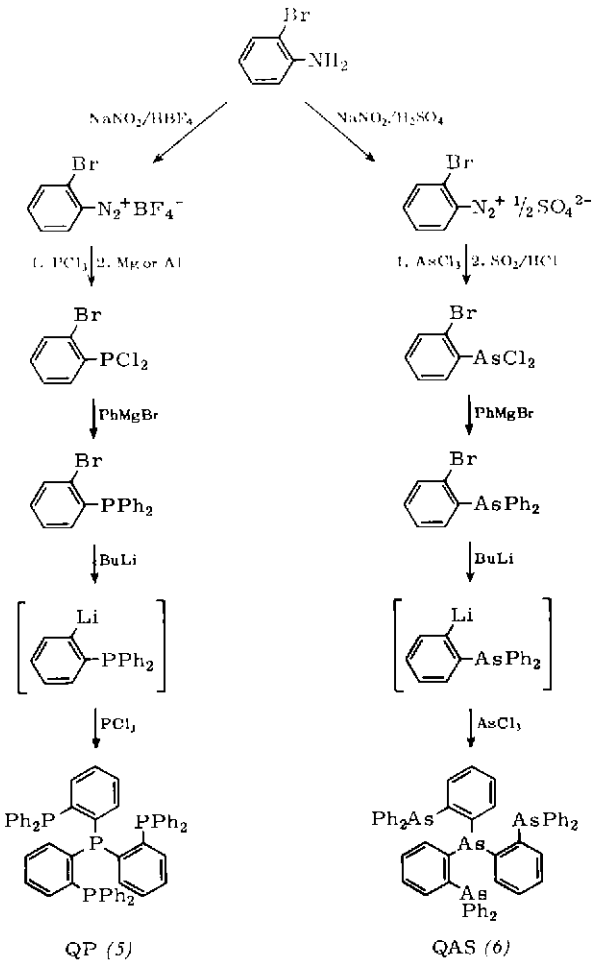
Finally, although unusual coordination numbers could arise as a result of a variety of factors, it is probable that strong $\sigma$-bonding is the most important one in the formation of complexes with unusually high coordination numbers: strong mixing of metal and ligand orbitals would favor the use of all the available empty low-energy metal orbitals. On the other hand, $\pi$-bonding may be responsible for the formation of complexes with unusually low coordination numbers: hybridization of the filled (n-1)d- and empty np-orbitals of the metal ion would give better overlap with the ligand orbitals and would prevent the use of some of the metal's p-orbitals for $\sigma$-bonding.

The above considerations are certainly an over-simplification of the problem, but they provide useful working hypotheses, particularly in the chemistry of the later transition elements.

## 3. Tetradentate Ligands

In recent years, we have managed to prepare two tetradentate ligands, one containing phosphorus, *viz.* tris-(*o*-diphenylphosphinophenyl)phosphine or QP *(5)* [14], and the other containing arsenic, *viz.* tris-(*o*-diphenylarsinophenyl)arsine or QAS *(6)* [15].

These complexing agents were prepared as indicated in Scheme 1. The use of aryl-substituted compounds was dictated by practical considerations: they are easier to synthetize than the corresponding alkyl derivatives and the free ligands, once obtained, are stable in air. The complexes of these ligands proved to be of great interest.




QP *(5)* QAS *(6)*

Scheme 1. Synthesis of the tetradentate ligands QP *(5)* and QAS *(6)*.

These compounds may be easily prepared by the following routes:

$$Na_2[MX_4] + QAS \rightarrow [MX(QAS)]X + 2\,NaX;$$
(M = Pd(II) or Pt(II); X = Cl, Br, or I)

$$MX_2 + QP + NaClO_4 \rightarrow [MX(QP)](ClO_4) + NaX;$$
(M = Fe(II), Co(II), or Ni(II); X = Cl, Br, or I)

$$[Rh_2Cl_2(CO)_4] + 2\,QAS \rightarrow 2[RhCl(QAS)] + 4\,CO;$$

$$4\,[CoX(QP)]X + 5\,N_2H_4 \rightarrow 4\,[CoX(QP)] + 4\,N_2H_4{\cdot}HCl + N_2;$$
(X = Cl or Br)

A small selection of complexes of this type is shown in Table 4 [16]. The complexes of doubly charged metal ions dissociate as 1:1-electrolytes in nitrobenzene,

### a) Five-Coordinate Complexes

The largest class of compounds is of the type $[M^{n+}X(Q)]^{(n-1)+}$ (X = halogen; Q = QP or QAS).

Table 4. Colors, decomposition points (D.p.), molar conductances ($\Lambda_M$), and magnetic moments ($\mu_{eff.}$) of five-coordinate complexes of QP and QAS.

| Complex | Color | D.p. [°C] | $\Lambda_M$ [*] [mho] | $\mu_{eff.}$ [B.M.] | Ref. |
|---|---|---|---|---|---|
| [FeCl(QP)] ($ClO_4$) | blue-black | 282—284 | 27.2 | 2.85 | [16a] |
| [FeCl(QP)] [$BPh_4$] | dark blue | 258—261 | 16.0 | 2.84 | [16a] |
| [CoCl(QP)] ($ClO_4$) | black | 264—266 | 28.9 | 1.91 | [16a] |
| [CoCl(QP)] [$BPh_4$] | dark-blue | 203—207 | 18.6 | 1.88 | [16a] |
| [CoCl(QP)] | dark-blue | 243—247 | 0 | diamag. | [16a] |
| [CoBr(QP)] | blue-black | 234—236 | 0 | diamag. | [16a] |
| [NiCl(QAS)] ($ClO_4$) | dark blue | 321—322 | 23.9 | diamag. | [16b] |
| [NiI(QAS)] I | blue-black | 330—331 | 24.4 | diamag. | [16b] |
| [RhCl(QAS)] | deep red | > 330 | 0.3 | diamag. | [16c] |
| [RhI(QAS)] | deep red | > 330 | 0.1 | diamag. | [16c] |
| [PdCl(QAS)]($ClO_4$) | dark red-purple | 315—316 | 25.2 | diamag. | [16d] |
| [PdI(QP)] [$BPh_4$] | red-purple | 257—260 | 18.7 | diamag. | [14] |
| [PtCl(QP)] [$BPh_4$] | yellow | 309—312 | 18.6 | diamag. | [14] |
| [PtI(QAS)] [$BPh_4$] | red | 278—279 | 20.7 | diamag. | [16f] |

[*] In $10^{-3}$ M solution in nitrobenzene at 20 °C.


[11] *R. N. Keller* and *R. W. Parry* in *J. C. Bailar:* The Chemistry of the Co-ordination Compounds. Reinhold, New York 1959, p. 157.

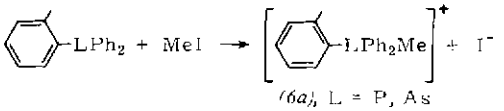
[12] *L. M. Venanzi:* Chimica Inorganica. Fondazione Donegani, Accademia Nazionale dei Lincei 1961, p. 415 (in English).

[13] *L. E. Orgel:* An Introduction to Transition Metal Chemistry. Methuen, London 1960, p. 135.

[14] *J. G. Hartley, L. M. Venanzi,* and *D. C. Goodall,* J. chem. Soc. (London) *1963,* 3930.

[15] *T. E. W. Howell, S. A. J. Pratt,* and *L. M. Venanzi,* J. chem. Soc. (London) *1961,* 3167.

whereas those of singly charged metal ions are non-electrolytes in the same solvent (see Table 4). Thus if all the donor atoms of the polydentate ligands are bonded to the central metal atom, these complexes have a coordination number of five. This has been shown to be invariably the case as follows: tertiary phosphorus or arsenic derivatives react readily with methyl iodide to give a quaternary compound [17], but coordinated tertiary phos-

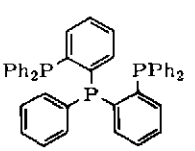


*(6a)*, L = P, As

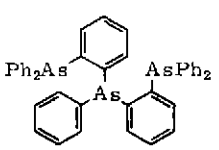
phines and arsines do not undergo this reaction unless the complexes are appreciably dissociated in solution. The test for the presence of uncoordinated P(III) or As(III) can be carried out very simply by dissolving the complex in nitrobenzene and measuring any changes in conductivity occurring upon addition of methyl iodide when the formation of a quaternary salt leads to an increase in the number of ions.

None of the complexes of the type $[M^{n+}X(Q)]^{(n-1)+}$ (X = halogen; Q = QP or QAS) reacts with methyl iodide; thus, all the donor atoms of the polydentate ligand must be coordinated to the central metal atom, *i.e.* all the complexes of this type are five-coordinate.

Further evidence for the unusual nature of these complexes is provided by their colors, which differ from those of complexes with similar ligands and more common coordination numbers, the general trend being a shift towards the red as compared with the corresponding four-coordinate complexes. This can be seen by comparing the spectra of the complexes of QP and QAS with those of the two tridentate ligands bis-(*o*-diphenylphosphinophenyl)phenylphosphine or TP *(7)* and bis-(*o*-diphenylarsinophenyl)phenylarsine or TAS



TP *(7)*



TAS *(8)*

*(8)* of the type [MI(T)] $(ClO_4)$ (M = Pd or Pt; T = TP or TAS), which have a four-coordinate square-planar structure [14, 16d, 16f] (see Fig. 2).

The magnetic susceptibilities of the five-coordinate complexes also show some unexpected features, *e.g.* they indicate the presence of two unpaired electrons in the iron(II) complexes, instead of the more usual four unpaired electrons or the diamagnetism exhibited by

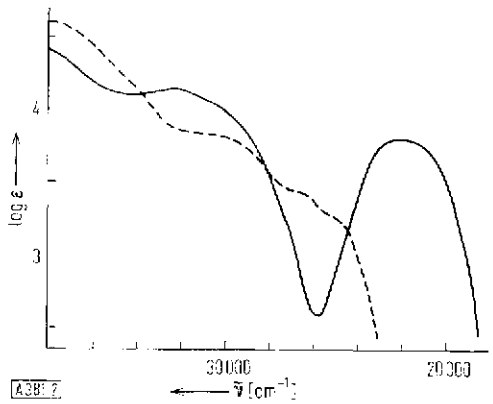
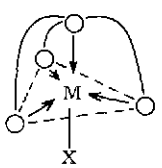


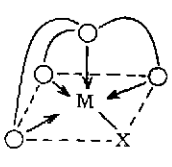

Fig. 2. The visible and ultraviolet spectra of [PtI(QAS)] $(ClO_4)$ (——) and [PtI(TAS)] $(ClO_4)$ (– – –) in methanol.

the complexes of this ion. A low magnetic moment is also observed in the cobalt(II) complexes, corresponding to the presence of one unpaired electron, instead of the more common three unpaired electrons (see Table 4).

The geometrical arrangement of the five ligands around the central metal atom can be either trigonal bipyramidal *(9)* or square pyramidal *(10)*:




*(9)*




*(10)*

X-ray structural investigation of [PtI(QAS)][$BPh_4$], showed that the coordination around its platinum atom is trigonal bipyramidal *(9)* [18].

Spectral studies have shown that this geometry prevails in all the complexes of the type $[M^{n+}X(Q)]^{(n-1)+}$. Thus, on replacement of the arsenic ligand by the phosphorus analogue or of the iodide ion by another anion in the platinum complexes, the pattern of the

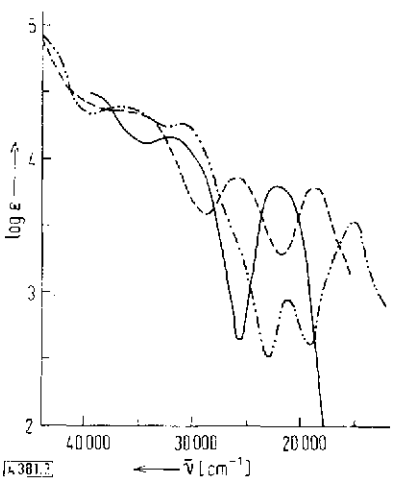



Fig. 3. The visible and ultraviolet spectra of [PtI(QAS)] $(ClO_4)$ (——), [PdI(QAS)] $(ClO_4)$ (– – –), and [NiI(QAS)] $(ClO_4)$ (— · · — · · —) in dichloromethane.

[16a] *J. G. Hartley* and *L. M. Venanzi*, unpublished observation.

[16b] *G. Dyer, J. G. Hartley*, and *L. M. Venanzi*, unpublished observations.

[16c] *R. J. Mawby* and *L. M. Venanzi*, Experientia, Suppl. IX, 240 (1964).

[16d] *C. A. Savage* and *L. M. Venanzi*, J. chem. Soc. (London) *1962*, 1548.

[16f] *J. A. Brewster, C. A. Savage*, and *L. M. Venanzi*, J. chem. Soc. (London) *1961*, 3699.

[17] *F. G. Mann* and *J. Watson*, J. org. Chemistry *13*, 502 (1948).

[18] *G. A. Mair, H. M. Powell*, and *L. M. Venanzi*, Proc. chem. Soc. (London) *1961*, 170.

absorption bands in the visible and ultraviolet spectra remains unchanged but the absorption maxima shift as predicted by ligand field theory [14, 16f]. In addition, replacement of the platinum by another metal atom results only in the band-shifts predicted by the ligand field theory [16a] (see Fig. 3).

The magnetic susceptibility of the complexes can also be accounted for in terms of the ligand field theory. The d-energy-level splitting for trigonal bipyramidal fields was worked out by *Ballhausen* and *Jørgensen* from group-theoretical considerations [19], but the effect of a field of this symmetry can be visualized in a simpler, more intuitive manner. If an electron is placed successively in each of the five d-orbitals arranged with their origin at the centre of a trigonal bipyramid (see Fig. 4), it will be

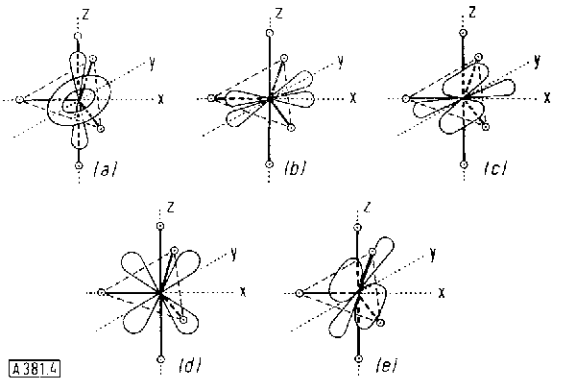



Fig. 4. The directional properties of d-orbitals relative to the ligands in a trigonal bipyramidal complex:
(a) $d_{z^2}$; (b) $d_{x^2-y^2}$; (c) $d_{xy}$; (d) $d_{xz}$; (e) $d_{yz}$.

seen that the electrostatic repulsions experienced by the electron will be of three types:

1. strong, when the electron is in the $d_{z^2}$ orbital;

2. medium, when the electron is in the $d_{x^2-y^2}$ or $d_{xy}$ orbitals;

3. weak, when the electron is in the $d_{xz}$ or $d_{yz}$ orbitals.

It is found that the interaction between the field of the ligands and the electron in the $d_{x^2-y^2}$ orbital is equal to that with the electron in the $d_{xy}$ orbital, and that the interaction between the external field and the electron in the $d_{xz}$ orbital is equal to that with the $d_{yz}$ orbital, although it is not possible to infer this from the diagrams shown in Figure 4. Thus, the presence of a trigonal bipyramidal field splits the five-fold degenerate d levels into three sets of orbitals. The sets with higher energy will be those where greater repulsion occurs, giving the following order of energies for the d-orbitals:

$$d_{z^2} > d_{x^2-y^2} = d_{xy} > d_{xz} = d_{yz}$$

If the magnitude of the interaction for the three groups of orbitals is taken into consideration, and if the energy of the orbitals in a spherical field is taken as the zero point for the energy scale, then the d-level splitting shown in Fig. 5 is obtained.

This splitting explains the magnetic susceptibility of the complexes: those of the $d^6$ ions show two unpaired

[19] *C. J. Ballhausen* and *C. K. Jørgensen*, Kgl. danske Vidensk. Selsk., mat.-fysiske Medd. *29*, No. 4 (1954).

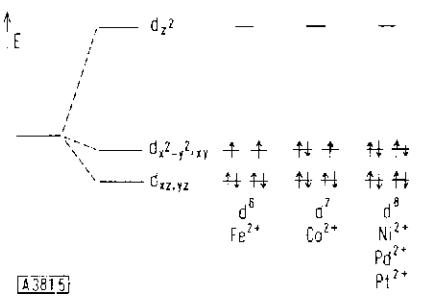
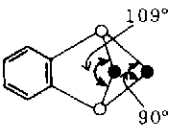



Fig. 5. Crystal field splitting and orbital occupancy in trigonal bipyramidal complexes $[M^{n+}X(Q)]^{(n-1)+}$.

electrons, those of $d^7$ ions show one unpaired electron, and those of the $d^8$ ions are diamagnetic.

The frequent occurrence of trigonal bipyramidal structures in the complexes of the tetratertiary phosphine QP *(5)* and of the corresponding arsine QAS *(6)* must be due to a large extent to the steric requirements of these ligands. After coordination, the bonds about the apical donor atom will be tetrahedral, so that the positions of the three terminal donor atoms will lie around a three-fold axis of symmetry. Given a metal ion of suitable size, the above arrangement of donor atoms could give rise to tetrahedral coordination around the central metal atom. For complexes of QP and QAS with transition metals, however, it is found that the donor-donor distances are too short for the formation of tetrahedral complexes, but are just right for the formation of trigonal bipyramidal complexes. This geometry not only preserves the trigonal symmetry of the three terminal donor atoms, but also, for a given donor-donor separation, allows a longer metal-donor bond length than does tetrahedral geometry, as shown in *(11)*.



*(11)*

Although five-coordinate complexes of many transition metal ions have been reported, the use of QP and QAS has allowed, for the first time, the preparation and the systematic study of a whole series of complexes with trigonal bipyramidal structures.

### b) Six-Coordinate Complexes

The two tetradentate ligands QP and QAS can also form six-coordinate complexes. Their preparation is often quite simple; some of the methods used are shown below.

$$[M^{n+}X(Q)]X_{(n-1)} + X_2 \rightarrow [M^{(n+2)+}X_2(Q)]X_n$$
(M = Rh, Pd, or Pt; X = Cl or Br; Q = QP or QAS)

$$Na_2[MX_5(NO)] + QAS \rightarrow [MX_2(QAS)] + 2\,NaX + NOX$$
(M = Ru or Os; X = Cl or Br)

$$[FeCl(QP)]Cl + 2\,NaX \rightarrow [MX_2(QP)] + 2\,NaCl$$
(X = $MeCO_2$, NCS, $NO_2$, or CN)

A selection of the compounds prepared to date is shown in Table 5 [20]. Conductivity measurements have shown that two of the anions are bonded to the central metal

Table 5. Colors, decomposition points (D.p.), molar conductances ($\Lambda_M$), and magnetic moments ($\mu_{eff.}$) of six-coordinate complexes of QP and QAS.

| Complex | Color | D.p. [°C] | $\Lambda_M$ [*] [mho] | $\mu_{eff.}$ [B.M.] | Ref. |
|---|---|---|---|---|---|
| $[ReCl_2(QAS)]$ | orange | 278–279 | 1.3 | 0.83 | [20a] |
| $[Fe(SCN)_2(QP)]$ | red | 314–317 | 0 | diamag. | [20b] |
| $[Fe(NO_2)_2(QP)]$ | yellow | 342–346 | 0 | diamag. | [20b] |
| $[RuCl_2(QAS)]$ | pale yellow | > 380 | 0 | diamag. | [20c] |
| $[Ru(NO_3)_2(QAS)]$ | yellow | 355–360 | 0 | diamag. | [20c] |
| $[OsCl_2(QAS)]$ | pale yellow | > 380 | 0 | diamag. | [14] |
| $[OsCl_2(QP)]$ | yellow-white | > 380 | 0 | diamag. | [14] |
| $[CoCl_2(QP)]Cl$ | red-brown | 296–301 | 18.3 | diamag. | [20a] |
| $[RhCl_2(QAS)](ClO_4)$ | yellow | 265–270 | 20.4 | diamag. | [16c] |
| $[RhI_2(QAS)]I$ | orange | 250–254 | 19.0 | diamag. | [16c] |
| $[PdCl_2(QAS)]Cl_2$ | yellow | 306–310 | 44.2 | diamag. | [14] |
| $[PtCl_2(QAS)]Cl_2$ | pale-yellow | 324–328 | 45.1 | diamag. | [14] |

[*] In $10^{-3}$ M solution in nitrobenzene at 20 °C.

atom (see Table 5) and, as the complexes do not react with methyl iodide, it is inferred that they are six-coordinate.

In view of the rather rigid steric requirements of the ligands, it was of interest to establish the geometry of the metal-ligand bonds in the six-coordinate complexes. An X-ray study of $[RuBr_2(QAS)]$ indicated a slightly distorted octahedron of donor atoms around the Ruthenium atom (see Fig. 6) [18]. Comparison of the visible and ultraviolet spectra of complexes of the type $[M^{(n+2)+}X_2(Q)]X_n$ showed that they are all of similar structure.

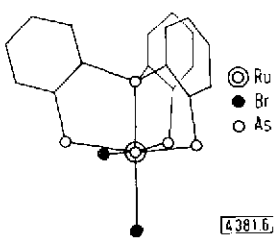



Fig. 6. Schematic representation of the geometry of the $[RuBr_2(QAS)]$ molecule.

Complexes of the above type are very resistant to oxidation. Although this may be expected for the derivatives of cobalt(III) and rhodium(III), it is somewhat surprising to find that this is also true of those of ruthenium(II) and osmium(II) in view of the observations of *Nyholm* et al. that $[RuCl_2(DAS)]$ and $[OsCl_2(DAS)]$ are oxidized by chlorine to $[RuCl_2(DAS)]^+$ and $[OsCl_2(DAS)]^+$ [22a, b] and that the osmium compound can be oxidized further to $[OsCl_2(DAS)]^{2+}$ [22b]. Even more surprising is the observation that $[ReCl_2(QAS)]$ remains unchanged in the presence of excess chlorine at room temperature, which suggests that the stabilization of the low oxidation states in these complexes is kinetic rather than thermodynamic.

The chelating agents QP and QAS do not always act as tetradentate ligands; for example, with chromium(III), tridentate complexes of the type $[CrX_3(QP)]$ may be prepared as follows [23]:

$$CrCl_3 + QP \rightarrow [CrCl_3(QP)]$$
$$[CrCl_3(QP)] + 3\ NaX \rightarrow [CrX_3(QP)] + 3\ NaCl$$
$$(X = Br, I, \text{ or } SCN)$$

These complexes are non-electrolytes in nitrobenzene (see Table 6), and react with methyl iodide. Their

Table 6. Colors, decomposition points (D.p.), and molar conductances ($\Lambda M$) of complexes of chromium(III) with QP and TP [23].

| Complex | Color | D.p. [°C] | $\Lambda M$ [*] [mho] |
|---|---|---|---|
| $[CrCl_3(QP)]$ | dark blue | 350–375 | 1.22 |
| $[CrBr_3(QP)]$ | dark blue | > 400 | 1.35 |
| $[CrI_3(QP)]$ | black | > 400 | 1.82 |
| $[Cr(SCN)_3(QP)]$ | dark purple | > 400 | 1.64 |
| $[CrCl_3(TP)]$ | dark blue | 360–370 | 1.13 |

[*] In $10^{-3}$ M solution in nitrobenzene at 18 °C.

limiting conductances after quaternization with MeI indicate that only three of the donor atoms of the organic ligand are coordinated to the chromium atom. Confirmation of this hypothesis is provided by comparison of the visible and ultraviolet spectra of the complexes of the tetradentate ligand QP with those of the closely related tridentate ligand TP *(7)*. TP complexes of the type $[CrX_3(TP)]$ are also non-electrolytes in nitrobenzene, but do not react with methyl iodide. The spectra of the two series of complexes are practically identical (see Fig. 7); this confirms that, in the chromium(III) complexes, the tetradentate ligand QP is in fact acting as a tridentate ligand.

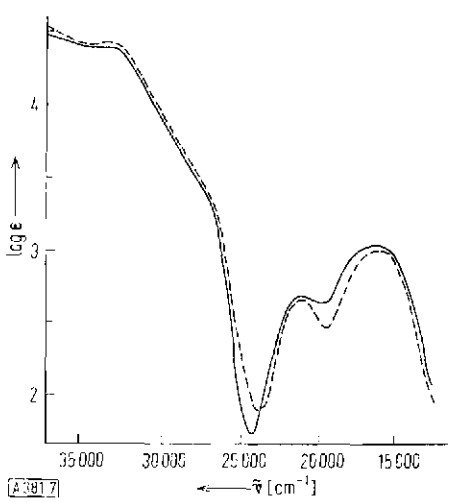



Fig. 7. The visible and ultraviolet spectra of $[CrCl_3(QP)]$ (——) and $[CrCl_3(TP)]$ (– – –) in dichloromethane.

[20a] *R. J. Mawby* and *L. M. Venanzi*, J. chem. Soc. (London) *1962*, 4447.

[20b] *J. G. Hartley* and *L. M. Venanzi*, unpublished observations.

[20c] *J. G. Hartley* and *L. M. Venanzi*, J. chem. Soc. (London) *1962*, 182.

[21] *R. H. B. Mais*, *H. M. Powell*, and *L. M. Venanzi*, Chem. and Ind. *1963*, 1204.

[22a] *R. S. Nyholm* and *G. J. Sutton*, J. chem. Soc. (London) *1958*, 567.

[22b] *R. S. Nyholm* and *G. J. Sutton*, J. chem. Soc. (London) *1958*, 572.

[23] *D. C. Goodall* and *L. M. Venanzi*, unpublished observations.

This behavior can be rationalized by comparing the energy of a chromium-halogen bond with that of a chromium-phosphorus bond; the former is known to be a strong bond because it has, in addition to σ-character, a contribution from dative π-bonding of the type $M \xleftarrow{\pi} X$, whereas the latter bond is fairly weak because chromium(III), which is a $d^3$ ion, cannot form strong dative π-bonds of the type $M \xrightarrow{\pi} L$.

### c) Mercury(II) Complexes

The mercury(II) complexes are of the type $[HgX_2(Q)]$ (X = Cl, Br, or I; Q = QP or QAS) (see Table 7) and are prepared by reaction of the ligands with the appropriate mercury halides [24]. They are non-electrolytes in nitrobenzene and react with methyl iodide, indicating that they contain uncoordinated tertiary phosphorus or arsenic. Confirmation of this was obtained by an X-ray study of $[HgBr_2(QAS)]$ which showed that here the QAS

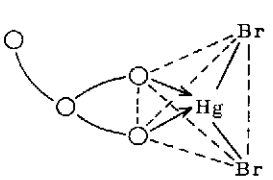
Table 7. Colors, decomposition points (D.p.) and molar conductances ($\Lambda_M$) of complexes of mercury(II) with QP and QAS [24].

| Complex | Color | D.p. [°C] | $\Lambda_M$ [*] [mho] |
|---|---|---|---|
| $[HgCl_2(QAS)]$ | colorless | 273–274 | 1.0 |
| $[HgCl_2(QP)]$ | colorless | 313–315 | 3.8 |
| $[HgBr_2(QAS)]$ | colorless | 255–258 | 1.7 |
| $[HgBr_2(QP)]$ | colorless | 279–282 | 4.1 |
| $[HgI_2(QAS)]$ | very pale yellow | 224–225 | 2.0 |
| $[HgI_2(QP)]$ | very pale yellow | 253–255 | 7.8 |
| $[Hg(SCN)_2(QAS)]$ | colorless | 238–240 | 1.5 |
| $[Hg(SCN)_2(QP)]$ | colorless | 214–215 | 3.9 |

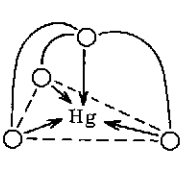
[*] In $10^{-3}$M solution in nitrobenzene at 18 °C.

was acting only as a bidentate ligand, using only two of its terminal donor atoms *(12)* [25]. It is presumed that the compounds of the other halides have similar structures.

Mercury(II) is a $d^{10}$ ion and tends to form four-coordinate complexes because any increase in coordination number places electrons in antibonding orbitals. These complexes have a tetrahedral arrangement of bonds [26]. As mentioned above, the two tetradentate ligands cannot use all four donor atoms to give tetrahedral complexes with transition metal ions. The mercury(II) ion is larger than most transition metal ions and a complex of the type $[Hg(Q)]^{2+}$, if it were formed at all, would have trigonal pyramidal coordination at the mercury atom *(13)*. Thus, it is not surprising to find that this geometry is not preferred in the presence of strongly coordinating anionic ligands.




*(12)*




*(13)*

[24] *G. Dyer, D. C. Goodall,* and *L. M. Venanzi,* unpublished observations.

[25] *R. H. B. Mais* and *H. M. Powell,* unpublished observations.

[26] *A. F. Wells:* Structural Inorganic Chemistry. Oxford University Press, 1962, p. 892.

It is interesting to note that the reactions of mercury(II) perchlorate with QP and with QAS give compounds of the type $[Hg(Q)](ClO_4)_2$, which are 1:2-electrolytes in nitrobenzene, which do not react with methyl iodide, and which contain ionic perchlorate, as shown by infrared spectra [24]. These compounds may well contain four-coordinate mercury with a trigonal pyramidal structure *(13)* owing to the weak coordinating properties of the anion.

### d) Iron(II) Complexes

The behavior of the iron(II) complexes with QP is of great interest. This ion gives five-coordinate complexes with a trigonal bipyramidal structure and two unpaired electrons (see Table 4) and also six-coordinate, diamagnetic complexes with an octahedral structure (see Table 5).

These stereochemical and magnetic differences can be explained in a similar way to those observed in the complexes of $d^8$ ions. The complexes of nickel(II) are normally six-coordinate and have two unpaired electrons, but many diamagnetic, four-coordinate compounds with square-planar structures are known. These differences have been associated with the effect of field asymmetry on the total energy of the complex. This relationship is shown in Figure 8 [27]. A similar diagram

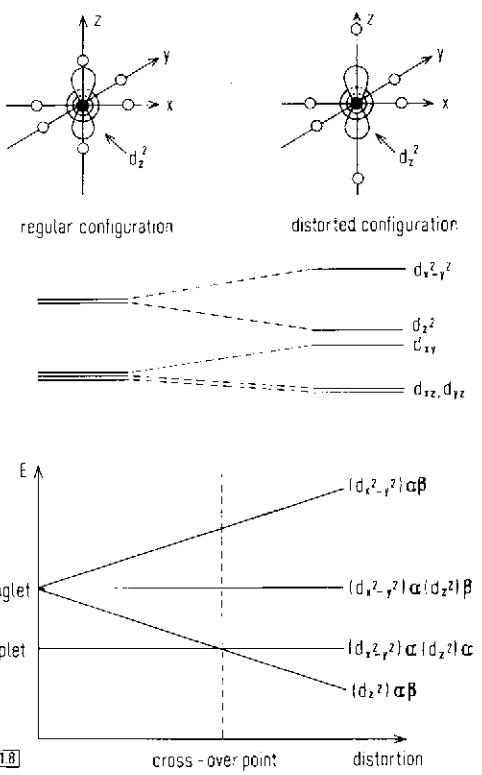



Fig. 8. The effect of distortion on the energy levels of octahedral complexes of $d^8$ metal ions.

can be constructed for the trigonal bipyramidal complexes of iron(II). The postulated distortion and a qualitative energy level diagram are shown in Figure 9.

Thus, when the overall field strength is large, one is on the right-hand side of the cross-over point and one obtains diamagnetic, octahedral complexes; when

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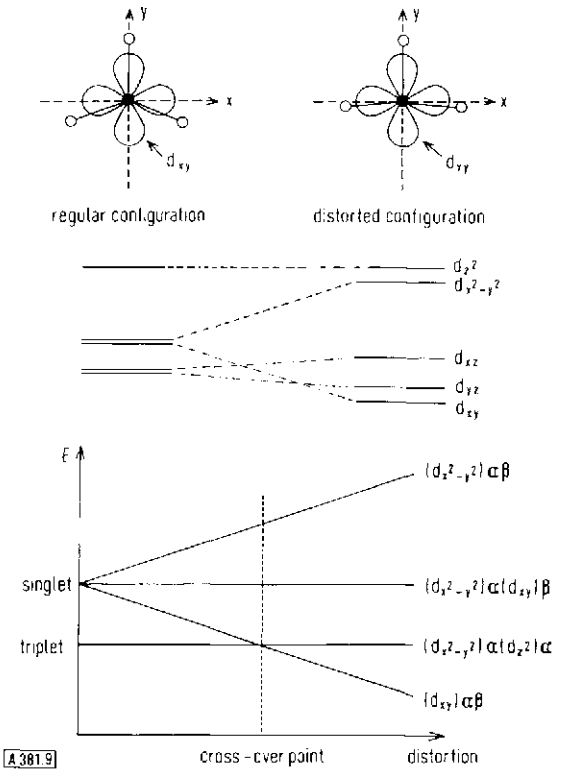



Fig. 9. The effect of distortion on the energy levels of trigonal bipyramidal complexes of $d^6$ metal ions.

the overall field strength is low one is on the left-hand side of the cross-over point and one obtains paramagnetic complexes.

This also explains the diamagnetism and octahedral structure of the QP and QAS complexes of ruthenium(II), osmium(II), and the other $d^6$ ions of higher charge, as the crystal field splitting increases with the charge on the transition metal ion, and also on passing from the first to the second and third transition series. Similar behavior is also observed in the $d^8$ complexes referred to above, where the compounds of palladium(II) and platinum(II) are almost always square-planar.

### 4. Conclusion

Ligands such as QP and QAS provide an interesting example of the interplay of electronic and steric factors in determining coordination numbers. Although these ligands tend to favor the formation of trigonal bipyramidal complexes, crystal field effects can force six-coordinate structures to occur.

Our work provides a further indication that the tendency of polydentate ligands to attach themselves to metal atoms or ions using all their donor atoms is not as pronounced as is generally believed.

A comparison between the complexing properties of QP and QAS and of similar nitrogenous ligands would be of great interest. A number of complexes of $N(CH_2CH_2NH_2)_3$ are known, but none of them appears to be five-coordinate. As the tetradentate ligand $As(CH_2CH_2CH_2AsMe_2)_3$ does not appear to form five-coordinate complexes either, it is likely that the frequent occurrence of five-coordination in complexes of QP and QAS is mainly due to the rather stringent steric requirements of these ligands.

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# The Chemistry of New Heat-Resistant Films and Fibers

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*This survey is principally concerned with papers published since 1959 on hydrocarbon polymers, aliphatic poly(terephthalamide) fibers, poly(hydroxybenzoic acid) films, poly(oxadiazole) fibers, poly(benzimidazole) films, poly(phenyltriazole) films, poly(pyromellitimide) films, and fibers from cyclized poly(acrylonitrile). All these materials have extremely high melting points and satisfactory in-use characteristics at high temperatures.*

## I. Thermal Stability and Polymer Structure

### 1. Introduction

Extreme conditions in space, *i.e.* oxidizing or reducing "atmospheres", high temperatures, magnetic belts, or radiation fluxes, demand new and heat-resistant materials. Most of the polymers, fibers, films, and elastomers [1] known today have valuable properties below 300 °C. Space flights [2] require materials which are

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[1] This review does not include information about commercial plastics which may be considered as forerunners of the polymers, films, and fibers discussed here.

[2] *R. Bartholmew, G. R. Eykamp,* and *W. E. Gibbs,* Rubber Chem. Technol. *32,* 1587 (1959).

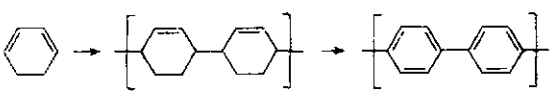
thermally stable for 400 hours at up to 350 °C, or 80 hours at up to 550 °C.

Great advances have been made since about 1959 in the preparation of high-melting polymers. *Wittbecker* and *Morgan* [3] reported the interfacial polymerization technique [3, 4], and cyclopolymerization [5, 6] as well as intramolecular cyclization [7–10] of high molecular-weight compounds were developed. This new phase of polymer chemistry [1, 11] is reviewed here, with particular regard to film- and fiber-forming polymers and to the relationship between structure and heat-resistance [11a].

## 2. Poly-(*p*-phenylene), Polyacene, and Graphite

The melting points of *p*-phenylenes increase from *p*-terphenyl to *p*-sexiphenyl (Fig. 1) [12]. It has therefore been suggested that poly-(*p*-phenylene) would be infusible and stable up to 800 or 900 °C, whereas poly-(*m*-phenylene) would melt at a lower temperature [12a, b].

*Marvel* et al. [13, 14] prepared linear polycyclohexene *(1)*, m.p. 170 °C, with a molecular weight of 5000 to 10000, from 1,3-cyclohexadiene with coordination catalysts. Dehydrogenation with chloranil gave black,



*(1)* *(2)*

incompletely aromatized poly-(*p*-phenylene) *(2)*. *Kovacic* [9b] prepared the same polymer by low-temperature polymerization of benzene with metal halide catalysts. It is infusible, decomposes at 530 °C, and is insoluble in the conventional solvents. It is therefore unsuitable for the preparation of shaped objects, since fibers and films are either melt-spun or cast from solutions.

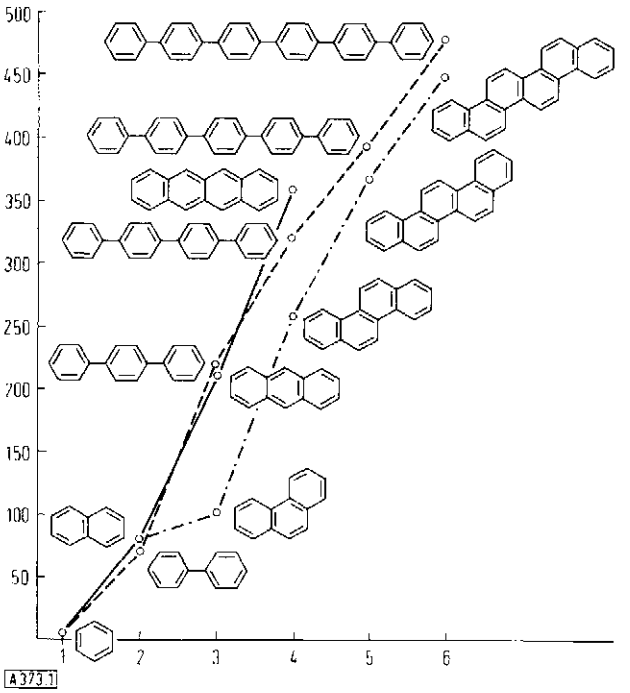
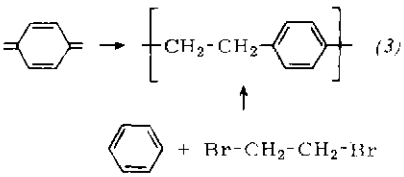



Figure 1. Melting points of polycyclic aromatics [12].
(— · · —) linearly fused
(— · — · —) angularly fused
(— — — —) not fused
Ordinate: melting point [°C]
Abscissa: number of rings

Molecular models show that poly-(*p*-phenylene) is a rigid linear polymer, and that fibers and films would be unusually brittle and almost inextensible, since the molecule cannot become bent or coiled.

The insertion of two methylene groups after every phenylene group gives the much more flexible poly-(*p*-xylylene) *(3)*. *Auspos* et al. [15], *Schaefgen* [16], and *Errede* [17] prepared this polymer by pyrolysis of *p*-xylene, as an insoluble, crystalline material which does not melt below 520 °C, and which yields optically anisotropic films.




*(3)*

*Farthing* [18] and *Vansheidt* et al. [19] used the Wurtz reaction to prepare a poly-(*p*-xylylene) which melts at 395 to 405 °C, and which is soluble in diphenyl, α-bromonaphthalene, and benzyl benzoate.

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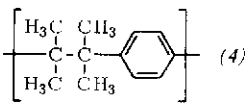
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[18] *A. C. Farthing*, J. chem. Soc. (London) *1953*, 3261.

[19] *A. A. Vansheidt, E. P. Melnikova, L. V. Kukhareva*, and *M. G. Krakovyak*, Zhur. priklad. Khim. *31*, 1898 (1958).

Thus the insertion of $-CH_2CH_2$-groups in the poly-(*p*-phenylene) chain provides solubility, and hence the possibility of preparing films and possibly fibers; however it lowers the melting point and thermal stability. The insertion of two ispropylidene groups after each phenylene group *(4)* gives a crystalline polymer with improved chain flexibility, but the melting point is even lower (300 °C). *Korshak* et al. [20] have synthetized such compounds by treating diisopropylbenzene with t-butyl peroxide.

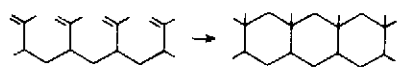


*(4)*

Films of poly-(*m*-xylylene) [21] (m.p. 60 °C) and poly-(*o*-xylylene) [22] (m.p. 110 °C) [22a] are also low-melting.

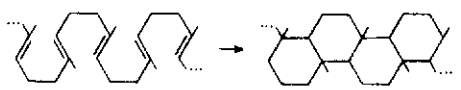
The thermal stability of graphite is very high. *Gulbrandson* [22b] has shown that carbon is even more fireproof under the conditions encountered in space than certain metals; thus in theory it should burn three times as rapidly as tungsten, but in practice it burns twelve times more slowly. This, and the increase in melting points of linearly and angularly fused polycyclic aromatics (Fig. 1), indicate that the as yet unknown linear polyacene and the angular polyphene should be as infusible and heat-resistant as graphite. "Ladder polymers", which resemble graphite in their structure, should also be stable and high-melting.

The cyclization of 1,2-polyisoprene *(5)* gives nearly quantitatively linear polycycloisoprene *(6)* with molecular weights of 15000 to 30000, which is soluble and can therefore be cast into films (m.p. 180 °C) [23, 24].



*(5)* *(6)*

The cyclization of 1,4-polyisoprene *(7)* yields segmented angular polycycloisoprene *(8)*, m.p. 80 °C [25, 26].



*(7)* *(8)*

However, aromatization of the linear or angular polycycloisoprene does not give polyacene or polyphene, but only fragments of the dimensions of pentacene or phenanthrene.

[20] *V. V. Korshak, S. L. Sosin,* and *M. V. Chistyakova,* Vysokommolekularnye Ssoedineniya *1*, 937 (1959).

[21] *F. R. Dammont,* Polymer Letters *1*, 339 (1963).

[22] *L. A. Errede,* J. Polymer Sci. *69*, 253 (1961).

[22a] Chemical Week, May 11th, 1963, p. 60.

[22b] *L. A. Errede,* J. Polymer Sci. *49*, 253 (1961).

[23] *R. Angelo,* Polymer Preprints *4*, No. 1, 32 (1963).

[24] *N. G. Gaylord, I. Kossler, M. Stolka,* and *J. Vodehnal,* J. Amer. chem. Soc. *85*, 641 (1963).

[25] *F. T. Wallenberger,* Mh. Chem. *93*, 74 (1962).

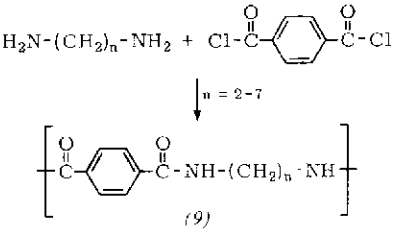
[26] *W. F. Watson, D. F. Lee,* and *J. Scanlan,* Proc. Roy. Soc. Ser. A *273*, 345 (1963).

## II. Polyphenylene-Like Polymers

### 1. Polyamide Fibers

#### a) *Aliphatic Poly(terephthalamides)*

High-melting poly(terephthalamides) *(9)* with molecular weights of 15800 to 31000 have been prepared by *Shashoua* and *Eareckson* [27] from short-chain primary and secondary aliphatic diamines and terephthalyl dichloride. These polymers can be regarded structurally as poly-(*p*-phenylenes) with inserted $-CO-NH-(CH_2)_n-NH-CO$-groups. They are prepared by interfacial polymerization [3, 4], in which the acid chloride is reacted with the diamine in water at room temperature. Since the reaction takes place at the phase boundary, vigorous stirring must be maintained [28].



*(9)*

The melting points of the poly(terephthalamides) synthetized from primary and secondary amines alternate (Fig. 2) in a similar manner as the melting points of aliphatic polyamides [29].

Poly(terephthalamides) derived from primary amines are soluble only in sulfuric and trifluoroacetic acids.

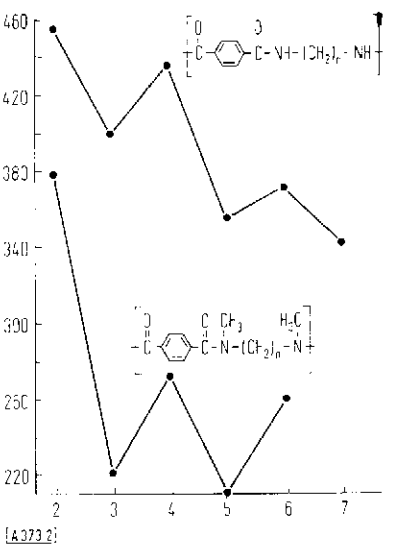



Figure 2. Melting points of secondary and tertiary aliphatic poly(terephthalamides) [27].
Ordinate: melting point [°C]
Abscissa: number of methylene groups in the aliphatic diamine.

[27] *V. E. Shashoua* and *W. M. Eareckson,* J. Polymer Sci. *40*, 343 (1959).

[28] *P. W. Morgan* and *S. L. Kwolek,* J. chem. Educat. *36*, 182, 530 (1959).

[29] *D. D. Coffman, G. F. Berchet, W. R. Peterson,* and *E. W. Spanagle,* J. Polymer Sci. *2*, 306 (1947).

[29a] *W. O. Statton,* Ann. N.Y. Acad. Sci. *83*, 27 (1959).

Their properties are determined by the ease of formation of hydrogen bonds, and by the rigidity of the *p*-phenylene unit. Complete *N*-methylation changes the solubility characteristics and lowers the melting point (Fig. 2), since hydrogen bonding is no longer possible in secondary terephthalamides.

Primary terephthalamide polymers are spun from trifluoroacetic acid. The fibers are strong (2 to 5 g/den) and have elongations of 10 to 40 % [27]. The initial modulus alternates and indicates a chain rigidity varying between 40 and 90 g/den [27] (Fig. 3). This alternation of the fiber properties indicates that members

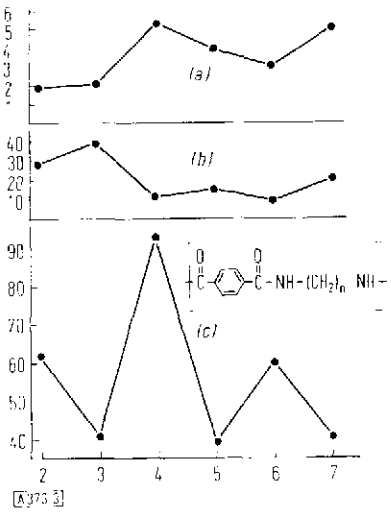
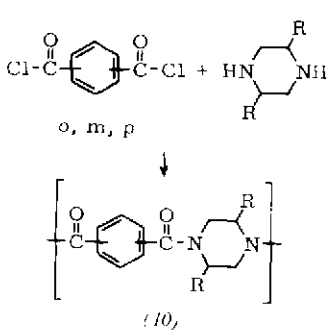



Fig. 3. Tenacity (a), elongation (b), and modulus at 1 % elongation (c) of aliphatic poly(terephthalamides) [27].

Ordinates: (a) tenacity [g/den]
(b) elongation [%]
(c) initial modulus [g/den]
Abscissa: number of methylene groups in the aliphatic diamine

with an odd number of C-atoms and with low moduli, have a less extended structure than those with an even number of C-atoms. X-ray diagrams [29a] show that members with an odd number of C-atoms possess only longitudinal lattice order. Freshly drawn poly(terephthalamide) fibers take up 8 to 20 % of water at a relative humidity of 90 %, and so lie between nylon 6-6 (7 %) and cotton (25 %).

Poly(ethyleneterephthalamide) and poly(tetramethyleneterephthalamide) fibers are among the highest-melting fibers known, with melting points of 455 and 436 °C respectively. Rigid, inflexible, cyclic diamines such as piperazine also give thermally stable poly(phthalamides), poly(isophthalamides), and poly(terephthalamides) [30].




*(10)*

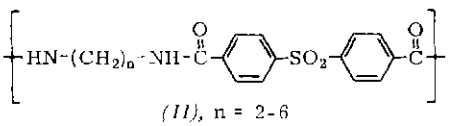
[30] *M. Katz*, J. Polymer Sci. *40*, 337 (1959).

Polyamides based on 2,5-dimethylpiperazine and phthalic, isopthalic, or terephthalic acids decompose at 467, 474, and 438 °C respectively. Fibers from these polymers have not been reported.

Aromatic polyamides have been prepared from *m*- or *p*-phenylenediamine by interfacial polymerization [30a]. They were found to melt above 360 °C. The thermally most stable aromatic polyamide [30b] was prepared from 4,4′-diaminostilbene-2,2′-disulfonic acid. It shows a weight loss of only 5.1 % after 74 hours of exposure to air at 300 °C.

b) *Aliphatic Poly-(4,4′-sulfonyldibenzamides)*

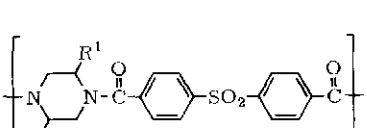
*Stephens* [31] prepared high-melting polyamides of the type *(11)* by interfacial polymerization [3, 4] of 4,4′-sulfonyldibenzoyl dichloride and certain aliphatic diamines or piperazines.



*(11)*, n = 2-6

The melting points of the polymers based on aliphatic diamines are moderately high, and exhibit the usual alternation: with ethylenediamine m.p. 380 °C, with trimethylenediamine m.p. 298 °C, with tetramethylenediamine m.p. 358 °C. These polymers are lower-melting than the corresponding terephthalamides, owing to the greater flexibility of the dicarboxylic acid components. However, this disadvantage is to some extent offset by an increase in the solubility in polar solvents; this property is attributable to the polar $SO_2$ groups [32].

The use of piperazine as the diamine component increases the melting point, since piperazine is much less flexible than the aliphatic diamines. At the same time, the polymer retains the favorable soluhility characteristics due to the $SO_2$ group. *Stephens* [31] has investigated fibers from two of these very high-melting polyamides: the polyamide *(12)* from 4,4′-sulfonyldibenzoic acid and 2,5-dimethylpiperazine, which has a water absorption of



*(12)*, $R^1 = R^2 = CH_3$
*(13)*, $R^1 = H$, $R^2 = CH_3$

11.6 %, and the related polyamide *(13)* from 2-methylpiperazine. Both fibers can be spun from *N,N*-dimethylformamide and from formic acid. Their properties are shown in Table 1.

[30a] *H. F. Mark*, *S. M. Atlas*, and *N. Ogata*, J. Polymer Sci. *61* S 49 (1962).

[30b] *R. A. Dine-Hart*, *B. J. C. Moore*, and *W. W. Wright*, J. Polymer Sci. B *2*, 369 (1964).

[31] *W. C. Stephens*, J. Polymer Sci. *40*, 359 (1959).

[32] *C. F. Horn*, Makromolekulare Chem. *30*, 123 (1959).

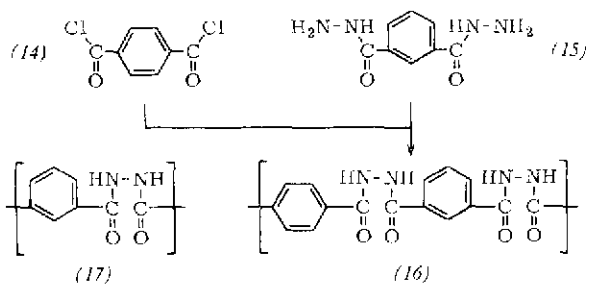
Table 1. Properties of fibers from the poly-(4,4'-sulfonyldibenzamides) *(12)* and *(13)* [31].

| | *(12)* | *(13)* |
|---|---|---|
| Draw ratio | 1:3.25 | 1:3 |
| Draw temperature [°C] | 325 | 290 |
| Tenacity [g/den] | 2.5 | 3.0 |
| Elongation [%] | 20 | 25 |
| Initial modulus [a] [g/den] | 45 | 40 |
| Dry tenacity [b] [g/den] | 2.7 | 2.6 |
| Dry elongation [b] [%] | 13 | 18 |
| Dry initial modulus [a, b] [g/den] | 42 | 30 |
| Zero-strength temperature [c] [°C] | 340 | 355 |

[a] At 1 % elongation
[b] At 150 °C.
[c] Temperature at which the fiber will break under a load of 0.1 g/den.

c) *Aromatic Polyhydrazides*

*Frazer* and *Wallenberger* [33, 34] have recently reported the preparation of 24 high molecular-weight aromatic and heteroaromatic polyhydrazides with melting points between 320 °C and >400 °C. These were synthetized from equimolar proportions of aromatic diacid chlorides *(14)* and aromatic dihydrazides *(15)* in hexamethylphosphoramide.

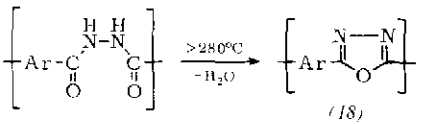


*(14)* *(15)* *(17)* *(16)*

These aromatic polyhydrazides may be regarded as polyamides with hydrazine as the diamine component. They differ from aliphatic polyhydrazides [33a] in their melting points and solubilities: aliphatic polyhydrazides melt between 200 and 300 °C and are insoluble in dimethyl sulfoxide, while aromatic polyhydrazides are normally soluble in dimethyl sulfoxide, and can thus be used for the production of fibers.

An interesting example of the close relationship between polymer structure and solubility [33] is provided by poly-(terephthalic/isophthalic dihydrazide): the regular compound *(16)* is soluble in dimethyl sulfoxide, whereas random copolymers with more than 65 % of *p*-phenylene units, as well as poly(terephthalic dihydrazide), are insoluble.

The highest-melting aromatic polyhydrazides are poly-(terephthalic dihydrazide) (>400 °C) and the alternating poly(terephthalic/isophthalic dihydrazide) (375 °C) [33, 34]. However, these temperatures are neither true melting points nor true decomposition points, since polyhydrazides liberate one molecule of water per hydrazide group at and above 280 °C to give quantitative yields of high molecular-weight poly-[2,5-(1,3,4-oxadiazoles)] *(18)*, which are even more heat-resistant (see below).



*(18)*

Polyhydrazide fibers have been spun [33] from polymers with structures *(16)* and *(17)*. Useful solvents were *N,N*-dimethylformamide and dimethyl sulfoxide. The properties of the fibers are shown in Table 2.

Table 2. Properties of fibers from the aromatic polyhydrazides *(16)* and *(17)* [33a].

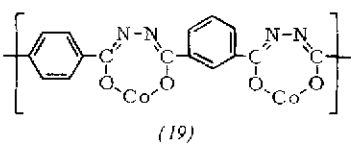
| | *(16)* | *(17)* |
|---|---|---|
| Tenacity [g/den] | 5.2 | 6.0 |
| Elongation [%] | 14 | 8 |
| Initial modulus [a] [g/den] | 115 | 151 |
| Knot tenacity [g/den] | 2.1 | 1.0 |
| Knot initial modulus [a] [g/den] | 50 | 90 |
| Fiber-stick temperature [°C] | 320 | 335 |
| Moisture regain [%] | 4.5 | 4.3 |
| Density [g/cm³] | 1.443 | 1.452 |

[a] At 1 % elongation.

The high chain rigidity (modulus of elasticity) is attributable to the *p*-phenylene group, as in the case of the terephthalamides. A poly(isophthalic dihydrazide) fiber prepared for comparison had a lower modulus, *i.e.* a lower rigidity than the poly(isophthalic/terephthalic dihydrazide) *(16)*.

The hydrazide group is known to enolize. According to *Frazer* and *Wallenberger* [33], the color of polyhydrazides changes from white to yellow in the presence of bases. This color change is most pronounced with aromatic polyhydrazides, and particularly with poly(terephthalic hydrazide), owing to the extended conjugation and the resonance interaction with the adjacent benzene rings. Poly-(*N,N'*-dimethylterephthalic dihydrazide) [33] does not undergo this color change.

Aromatic polyhydrazides give polymeric chelates with mono- and divalent metal salts ($Ni^{2+}$, $Ca^{2+}$, $Ag^{+}$, $Pb^{2+}$) in basic media; these chelates contain one metal ion per hydrazide linkage [33b, 34]. Very tough fibers of polyhydrazide chelates *(19)* with metal ions ($Cr^{3+}$, $Co^{2+}$, $Ag^{+}$)



*(19)*

*Chelate Fiber* [33b]
Color: bright yellow.
Tenacity: 1.0 g/den
Elongation: 96 %
Modulus: 38 g/den

were prepared by passing the polyhydrazide fiber through solutions of the salts in dimethylformamide. The melting points of the chelate fibers are not higher than those of the normal polyhydrazide fibers [33b, 34], possibly because chelation was incomplete.

d) *Aromatic Polyoxamides*

Since none of the polyamides and polyhydrazides mentioned can be obtained with a sufficiently high

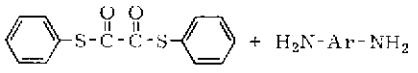
[33] *A. H. Frazer* and *F. T. Wallenberger*, J. Polymer Sci. A *2*, 1147 (1964).

[33a] *A. H. Frazer* and *F. T. Wallenberger*, J. Polymer Sci. A *2*, 1137 (1964).

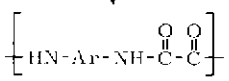
[33b] *A. H. Frazer* and *F. T. Wallenberger*, J. Polymer Sci. A *2*, 1825 (1964).

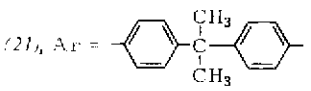
[34] *A. H. Frazer* and *F. T. Wallenberger*, 14th Delaware Science Symposium, Wilmington, Delaware (Feb. 1963); cf. Chem. Engng. News *41*, March 11th, 1963, p. 40.

molecular weight for fiber formation by melt polymerization, *Hall* and *Berge* [35] tried to prepare polyoxamides by reacting aromatic diamines with diphenyldithiol oxalate *(20)* [36] in tetramethylene sulfone at 130 to 200 °C.

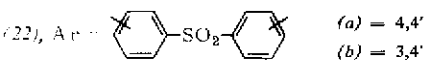


*(20)*





*(21)*, Ar =



*(22)*, Ar =



*(a)* = 4,4'
*(b)* = 3,4'

The polyoxamide from 2,2-di-(4-aminophenyl)propane *(21)* melts above 400 °C, has an intrinsic viscosity of 0.60, and gives perfectly clear, tough, and flexible films from dichloroacetic acid or *N*-methylpyrrolidone solutions. The polyamide from oxalic acid and 4,4'-diaminodiphenyl sulfone *(22a)* also melts above 400 °C, while the polyoxamide from 3,3'-diaminodiphenyl sulfone *(22b)* melts at 375 °C and is less rigid.

## 2. Polyester Films

### a) *Structure and Properties*

In a recent survey, *Wilfong* [37] showed that only very few polyesters have melting points above 380 °C. High melting points are generally attributed to a dipole interaction, strong intermolecular forces, molecular symmetry, or close packing of linear chains. High rigidity is primarily introduced by the *p*-phenylene unit of terephthalic acid, hydroquinone, or 4,4'-diphenylenedicarboxylic acid (cf. [38]). Owing to the absence of hydrogen bonds, polyesters melt at appreciably lower temperatures than the corresponding polyamides (Fig. 4).

Alternation of the melting points [37,40] is attributed to structural differences, since the X-ray repeat period of high-melting polyesters with an even number of C-atoms is equal to one chemical repeat unit, while that of low-melting polyesters with an odd number of C-atoms corresponds to two chemical repeat units.

Even polyesters with rigid structures [41], such as poly(ethylene 1,5-naphthalenedicarboxylate), m.p. 226 °C,

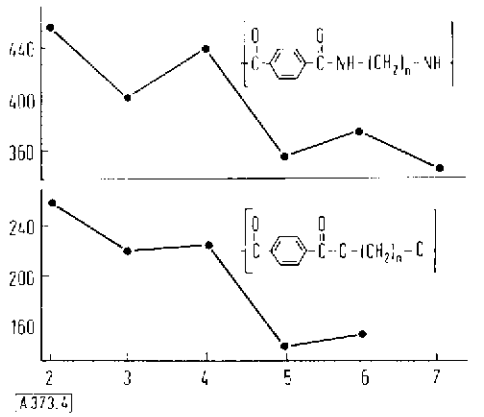
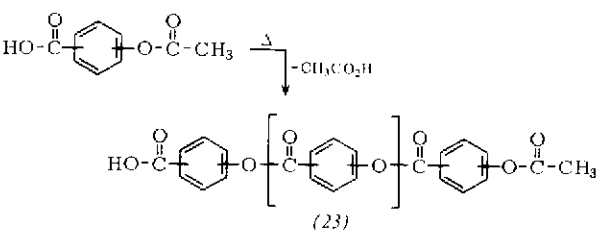



Fig. 4. Melting points of polyamides [27] and comparable polyesters [38].
Ordinate: melting point [°C]
Abscissa: number of methylene groups in the diamine and glycol.

poly(ethylene 2,6-naphthalenedicarboxylate), m.p. 255 °C, and poly(ethylene 2,7-naphthalenedicarboxylate), m.p. 260 °C, do not have particularly high melting points. Only some of the completely aromatic [42] polyesters melt above 380 °C. Poly(hydroquinone isophthalate), m.p. 385 °C [42], poly(hydroquinone terephthalate), m.p. >400 °C [42], 500 °C [39], and similar compounds [42 44] have very high melting points, surprisingly high melt viscosities, and are soluble [39], so that it might be possible to spin them into fibers.

### b) *Poly(hydroxybenzoic acids)*

Films of poly-(*p*-hydroxybenzoic acid) are as tough as some commercial polycarbonates, and melt at 380 to 450 °C [45]. They are prepared by the autocondensation of *p*-acetoxybenzoic acid. High molecular-weight poly-(*m*-hydroxybenzoic acid) and copolymers of *m*- and *p*-hydroxybenzoic acids have been prepared by a two-stage, Mg-catalyzed melt polymerization at 200 °C, followed by polymerization in the solid phase at about 300 °C [46].



*(23)*

Some of these polyesters *(23)* were reported to have molecular weights of up to 20000 [46]. They are crystalline and stable to oxidation, but sensitive to hydrolysis. The film pressing temperatures [46] (usually 10 to 15 °C above the melting point) and the flow points [46] (at which the films begin to elongate spontaneously) of

[35] *H. K. Hall* and *J. W. Berge*, Polymer Letters *1*, 277 (1963).
[36] *H. O. Jones* and *H. S. Tasker*, J. chem. Soc. (London) *95*, 1904 (1909).
[37] *R. E. Wilfong*, J. Polymer Sci. *54*, 385 (1961).
[38] *O. B. Edgar* and *R. Hill*, J. Polymer Sci. *8*, 1 (1951).
[39] *V. V. Korshak* and *Z. V. Vinovgradova*, Vyssokomolekularnye Ssoedineniya *1*, 834 (1959).
[40] *C. S. Fuller* and *W. O. Baker*, J. chem. Educat. *20*, 3 (1943).
[41] Brit. Pat. 604073 (1948), I.C.I.
[42] French Pat. 1163702 (1958), I.C.I.
[43] *A. Conix*, Ind. Engng. Chem. *51*, 147 (1959).
[44] *V. V. Korshak* and *Z. V. Vinovgradova*, Vyssokomolekularnye Ssoedineniya *1*, 1482 (1959).
[45] *J. R. Caldwell*, U.S.-Pat. 2600376 (1952), Eastman Kodak Co.
[46] *R. Gilkey* and *J. R. Caldwell*, J. appl. Polymer Sci. *2*, 198 (1959).

the copolymers increase with increasing content of the *p*-isomers (Table 3). At least 60 % of the *p*-isomer are required to achieve very high-melting films with a flow point of 300 °C. The melting points of the two homopolymers are given [46] as 200 °C (*meta*) and above 450 °C (*para*).

Table 3. Properties of films from poly(hydroxybenzoic acids).

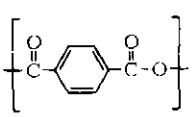
| | Isomer ratio *m*:*p* | | | |
|---|---|---|---|---|
| | 100:0 | 55:45 | 40:60 | 0:100 |
| *Fiber-press temperature* [°C] | 215 | 285 | 385 | — |
| Flow point [°C] | 154 | 221 | 300 | 400 |
| Tenacity [psi] | 11050 [a] | 9400 [a] | 10700 | — |
| Elongation [%] | 34 [a] | 16 [a] | 6 | — |
| Modulus [$10^5$ psi] | 2.8[a] | 2.7 [a] | 3.2 | — |

[a] Average values.

Films of hydroxybenzoic acid copolymers are tough, moderately extensible, and stiff (Table 3), and thus resemble films of poly-[2,2-di-(*p*-hydroxyphenyl)propane carbonate] [47], which are reported to posses a tear strength of 9000 to 10000 psi, an elongation at break of 60–100 %, and an initial modulus of $3.5\times10^5$ psi. Since increasing quantities of the *p*-isomer raise not only the melting point, but also the initial modulus (as a measure of stiffness) and reduce the extensibility (Table 3) there is also a resemblance between the mutual relationships of these copolymers and those of the poly-(terephthalic/isophthalic dihydrazides) as shown in Table 2 [33a].

c) *Poly(terephthalic anhydride)*

Little is known about film- or fiber-forming aromatic polyanhydrides with very high melting points. *Yoda* [48] recently reported on 24 polyanhydrides, of which only two melt above 300 °C: poly(terephthalic anhydride)



*(24)*

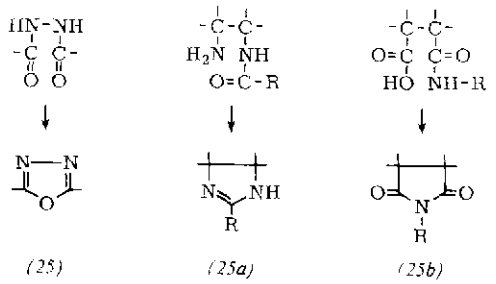
*(24)* (m.p. 400 °C) and poly(bis-*p*-carboxyphenylmethane anhydride) (m.p. 325 °C). Poly(terephthalic anhydride) [49] in particular should be of great interest in the film and fiber fields, since it is resistant to hydrochloric acid, nitric acid, and even to aqua regia [50].

## III. Structural Analogues of Polyphenylene and Polyacene

### 1. Synthesis of Heteroaromatic Polymers

A new development in polymer chemistry was due to the intramolecular cyclization of polymers. This led to film- and fiber-forming hetero-aromatic polymers.

The cyclization of a diacylhydrazine to form 1,3,4-oxadiazole *(25)* [51], the cyclodehydration of a β- (or *o*-) aminoacid amide [52a] to give imidazole *(25a)*, and the reaction of a carboxamide group with a β- (or *o*-) carboxyl group [52b] to give the imide group *(25b)* are well known.

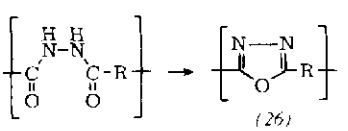


*(25)* *(25a)* *(25b)*

The same reactions were used for the cyclization of polyhydrazides [53, 54] and poly(aminobenzamides) [10], and for the cyclodehydration of poly(amide acids) [9c, 56a, b]. High molecular-weight poly-(1,3,4-oxadiazoles) [53] and their fibers [54], poly(benzimidazoles) [10] and their films [55b], and poly(pyromellitimide) films [9, 56c] were obtained. The structure of the "prepolymers" can be chosen in such a manner that the resulting film or fiber possesses the thermal stability of poly-(*p*-phenylene), in addition to the flexibility which is lacking in the latter. Polymers and fibers were also prepared by cyclization of poly(acrylonitrile) [57] which may be regarded as heteroaromatic analogues of polyacene.

### 2. Poly(oxadiazole) Fibers

Thirteen aliphatic and aromatic polyhydrazides [33, 33a] have been converted into high molecular-weight poly-(1,3,4-oxadiazoles) *(26)* by thermal cyclodehydration at 170 to 280 °C [53].



*(26)*

[47] *R. J. Thompson* and *K. B. Goldbaum*, Modern Plastics *35*, 131 (1958).

[48] *N. Yoda*, J. Polymer Sci. A *1*, 1323 (1963).

[49] *A. Conix*, J. Polymer Sci. *29*, 343 (1958).

[50] *F. Henglein* and *H. Turrasch*, Kunststoffe *6*, 5 (1959).

[51] *R. Stolle*, Ber. dtsch. chem. Ges. *32*, 796 (1899).

[52a] *R. Walther* and *T. V. Tulawski*, J. prakt. Chem. *59*, 249 (1899).

[52b] *W. R. Roderick* and *P. L. Bhatia*, J. org. Chemistry *28*, 2018 (1963).

[53] *A. H. Frazer*, *W. Sweeny*, and *F. T. Wallenberger*, J. Polymer Sci., in the press.

[54] *A. H. Frazer* and *F. T. Wallenberger*, J. Polymer Sci., in the press.

[55] *R. Phillips* and *W. W. Wright*, J. Polymer Sci. B *2*, 47 (1964).

[55a] *H. Vogel* and *C. S. Marvel*, J. Polymer Sci. *50*, 511 (1961).

[55b] *H. Vogel* and *C. S. Marvel*, J. Polymer Sci. A *1*, 1531 (1963).

[55c] *M. R. Lilyquist* and *J. R. Holsten*, Polymer Preprints *4*, No. 1, pp. 6–14 (1963).

[55d] *H. H. Levine*, *C. B. Delano*, and *K. J. Kjoller*, Polymer Preprints *5*, No. 1, 160 (1964).

[56] *W. M. W. Edwards* and *J. M. Robinson*, U.S.-Pat. 2710853 (1955); 2867609 (1959), duPont.

[56a] *W. F. Gresham* and *M. A. Naylor*, U.S.-Pat. 2731447 (1956), duPont.

[56b] E. I. duPont de Nemours & Co, Inc., Austral. Pat. Appl. 58424 (1960); Brit. Pat. 903271.

[56c] *L. E. Amborski*, Polymer Preprints *4*, No. 1, pp. 175–182 (1963).

[56d] *E. Heine*, Du Pont Magazine, March 1963, pp. 26–29.

[57] *R. C. Houtz*, Textile Res. J. *20*, 786 (1950).

Figure 5 represents a thermogravimetric analysis of the cyclization of the polyhydrazide *(16)* from isophthalic dihydrazide and terephthaloyl dichloride. The initial weight loss is due to the loss of surface water (25 to 240 °C). The weight loss at higher temperatures (280 to

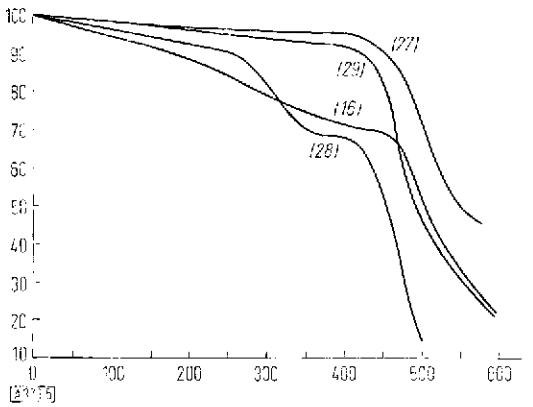
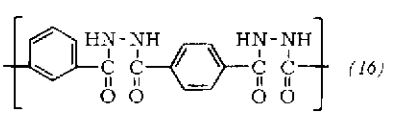
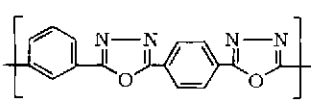


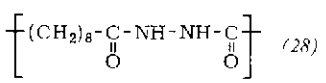

Fig. 5. Thermogravimetric analysis of componnds *(16)*, *(27)*, *(28)*, and *(29)* [53].
Ordinate: weight retention [%]
Abscissa: temperature [°C]

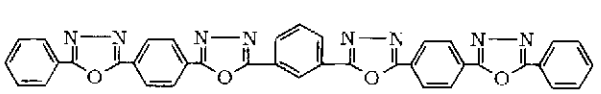
350 °C) corresponds to the conversion of the polyhydrazide to poly-(1,3,4-oxadiazole) *(27)* (calculated water loss: 11.11 %). In the cyclization of poly(octanedicarboxylic dihydrazide) *(28)* (Fig. 5) the surface water is given off between 25 and 225 °C, while the water of reaction is liberated between 250 and 350 °C. Completion of the formation of poly(octamethylene-1,3,4-oxadiazole) is indicated by constant weight.

Poly-(1,3,4-oxadiazoles) give the expected analytical results, and have a high inherent viscosity in $H_2SO_4$ [$\eta$ – 0.6 for *(27)*] and high X-ray crystallinity. The infrared and ultraviolet spectra also indicate that cyclization is complete. Films could be pressed from aliphatic poly(oxadiazoles) melting below 350 °C, while very high-melting or infusible poly(oxadiazoles) could not be


*(16)*


*(27)*


*(28)*


*(29)*

made into films or fibers. Poly(oxadiazoles), like the nine-membered model compound *(29)*, are also resistant to oxidation, and decompose between 450 and 500 °C [57a].

[57a] *F. T. Wallenberger*, unpublished work.

The thermal cyclodehydration of a fiber from poly(isophthalic/terephthalic hydrazide) *(27)* yields a polyoxadiazole fiber with outstanding thermal stability, namely poly-[*m*/*p*-phenylene-2,5-(1,3,4-oxadiazole)] *(27)* [54].

The reaction proceeds at 280 °C in a muffle furnace under positive nitrogen pressure, and is complete in 48 to 72 hours, as shown by elementary analysis. The fiber is stable to prolonged heating at 400 °C. Other properties are shown in Table 4.

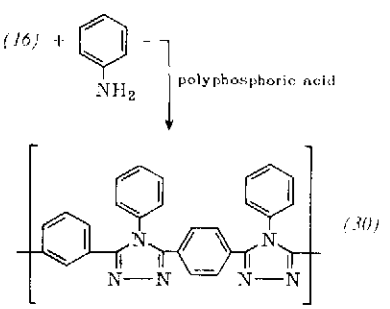
Table 4. Properties of fibers from the poly-(1,3,4-oxadiazole) *(27)* [54]

| | |
|---|---|
| *Straight* | |
| Denier | 3.0 |
| Tenacity [g/den] | 2.6 |
| Elongation [%] | 3.1 |
| Modulus [g/den] | 124 |
| *Loop* | |
| Denier | 3.9 |
| Tenacity [g/den] | 1.8 |
| Elongation [%] | 2.8 |
| *Knot* | |
| Denier | 3.0 |
| Tenacity [g/den] | 2.3 |
| Elongation [%] | 2.8 |
| Modulus [g/den] | 79 |
| X-ray crystallinity (amount/perfection) | low/low |
| X-ray orientation [degrees] | 31–38 |
| Oxygen content [%] | |
| calculated | 11.10 |
| found | 12.10 |

*Huisgen* et al. [57b] have recently shown that the oxadiazole ring is spectrally and electronically equivalent to a *p*-phenylene structure. Poly-(1,3,4-oxadiazole) can therefore be regarded as a pseudo-polyphenylene.

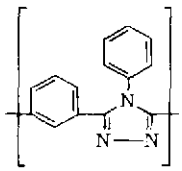
### 3. Poly(phenylenetriazole) Films

The treatment of polyhydrazides with aniline and polyphosphoric acid yields high molecular-weight poly-(phenylenetriazoles) *(30)*–*(32)* [55c]. Reaction of the polyhydrazide *(16)* proceeds in solution at 250 to 265 °C. *Lilyquist* and *Holsten* [55c] claim that the reaction is homogeneous throughout. The final viscosity depends on the molecular weight of the prepolymer.

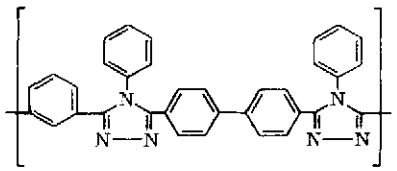



Poly-(*m*-phenylene-4-phenyltriazole) *(31)* and alternating poly(*m*/*p*-phenylene-4-phenyltriazole) *(30)* are soluble in strongly polar solvents such as formic acid [55c]. Poly-(*m*-phenylene/*p*,*p'*-diphenylene-4-phenyltriazole) *(32)*, on the other hand, is insoluble, probably owing to the greater stiffnes of the *p*-diphenylene group.

[57b] *J. Sauer*, *R. Huisgen*, and *H. J. Sturm*, Tetrahedron *11*, 214 (1960).



(31)



(32)

Formic acid can also be used as a solvent for the casting or spinning of films or fibers from poly-(*m*/*p*-phenylene-4-phenyltriazole). The fibers can be drawn over hot surfaces (250 °C), remaining amorphous and unoriented. The films were tough, and had excellent strength and dimensional stability at high temperatures (cf. Table 5). The thermal stability is notable particularly after annealing at 290 °C: the breaking temperature with a load of 0.1 g/den is 423 °C.

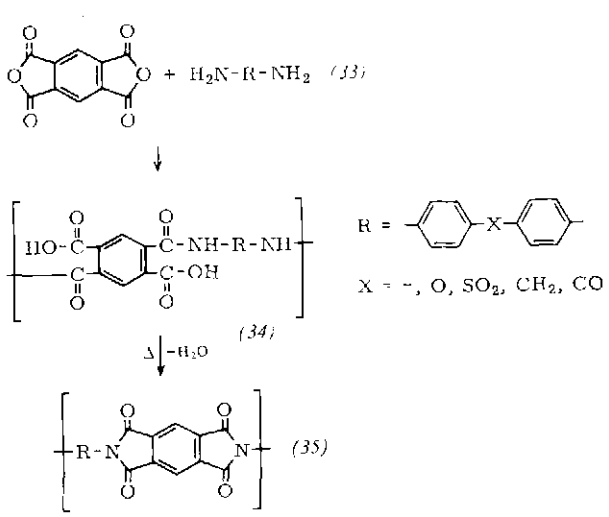
Table 5. Properties of films from the poly-(*m*/*p*-phenylene-4-phenyltriazole) *(30)* [55c].

| | |
|---|---|
| Tensile strength [psi] | 9200 |
| Elongation [%] | 13.0 |
| Tensile modulus [psi] | 135000 |
| Film-stick temperature [°C] | 310–320 |
| Zero-strength temperature [a] [°C] | 423 |
| Glass-transition temperature [°C] | 280 |

[a] Temperature at which the film will break under a load of 20 psi.

### 4. Poly(pyromellitimide) Films

Poly(pyromellitimide) films are stable up to 800 °C, highly resistant to oxidation, extremely tough [56, 56a-c], and exhibit excellent flame and radiation resistances. They are prepared [58, 58a, f] from pyromellitic anhydride *(33)*, which reacts under mild conditions in dimethylformamide or dimethylacetamide with aromatic diamines, in the molar ratio of 1:1, to form poly(pyromellitamic acid) *(34)*. Films cast from this solution underwent cyclodehydration on heating to yield the insoluble, infusible polyimide *(35)*.



(33)

(34)

(35)

The poly(pyromellitimide) that is derived from 4,4'-diaminodiphenyl ether gives films with the best combination of mechanical, electrical, and thermal properties [58, 58c]. Polyimides based on alipbatic diamines have a lower thermal stability than aromatic poly(pyromellitimides) [56, 58e, d].

H-film derived from such a poly(pyromellitimide) *(35)* [58e] with high thermal stability and very good electrical properties resembles a ®Mylar polyester film at room temperature (Table 6), but substantially retains its strength and rigidity at much higher temperatures [56a, 58b, c]. After 1000 hours in air at 300 °C, it still retains more than half of its original tensile strength [56d]. The breaking temperature of 815 °C is unusually high. H-film does not become very brittle at low temperatures, and retains 50 % of its extensibility at room temperature even in liquid helium (4 °K) [58c].

Table 6. Properties of H-film and films from ® Mylar polyester (polyethyleneterephthalate) [56c].

| | H-film | ® Mylar |
|---|---|---|
| Tensile strength [$10^3$ psi] | | |
| at 23 °C | 25 | 23 |
| 200 °C | 15 | 7 |
| 500 °C | 5 | – |
| Modulus [$10^3$ psi] | | |
| at 23 °C | 400 | 500 |
| 200 °C | 250 | 50 |
| Elongation [%] | | |
| at 23 °C | 90 | 100 |
| 200 °C | 90 | 125 |
| Melting point [°C] | None | 200 |
| Zero-strength temperature [a] [°C] | 815 | 250 |

[a] Temperature at which the film will break under a load of 20 psi.

### 5. Poly(benzimidazole) Films

Aliphatic and aromatic poly(benzimidazoles) *(37)* have been synthetized by *Brinker* and *Robinson* [10] and by *Vogel* and *Marvel* [55a, b]. Fully aromatic polymers with high thermal stability have been prepared by reacting aromatic tetramines with diphenyl esters of aromatic dicarboxylic acids in a melt polymerization. The reaction proceeds in two stages: initially at 220 to 260 °C, and then below 400 °C. The poly(amino amide) *(36)*, which is undoubtedly an intermediate, has not been isolated. Reactivity, polymer solubility and crystallinity of poly(benzimidazoles) are dependent upon the polymerization temperature [55d]. Mixed aliphatic-aromatic


[58] *J. I. Jones, F. W. Ochynski,* and *F. A. Rackley,* Chem. and Ind. *1962,* 1686.

[58a] *G. M. Bower* and *L. W. Frost,* J. Polymer Sci. A *1,* 3135 (1963).

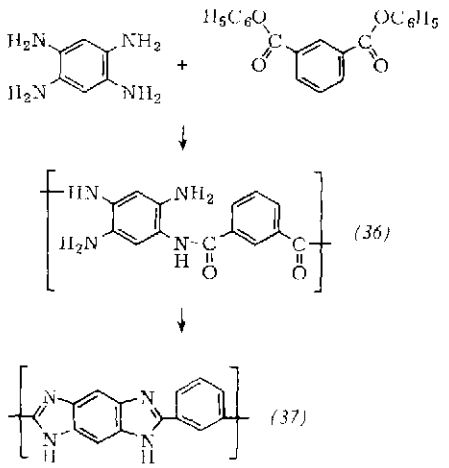
[58b] *L. E. Amborski,* Ind. Engng. Chem. Prod. Res. Develop. *2,* 189 (1963).

[58c] *W. E. Tatum, L. E. Amborski, C. W. Gerow, J. Heathcock,* and *R. S. Malluck,* Electrical Insulation Conference, Sept. 17th, 1963, Chicago, Ill., AIEE Document T-153-3.

[58d] *S. I. Nishizaki* and *A. Fukami,* J. chem. Soc. Japan, ind. Chem. Sect. *66,* 382 (1963).

[58e] *C. S. Sroog, S. V. Abramo, C. E. Berr, W. M. Edwards, A. L. Endrey,* and *K. L. Oliver,* Polymer Preprints *5,* No. 1, 132 (1964).

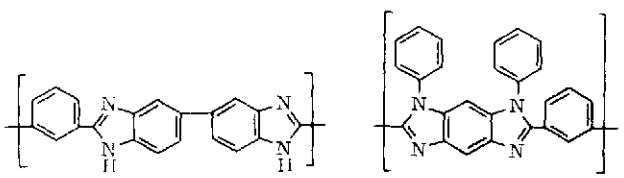
poly(benzimidazoles) (aliphatic dicarboxylic acids) are stable up to 470 °C. Poly(benzimidazoles) from isophthalic acid and 1,2,4,5-tetraaminobenzene or 3,3'-diaminobenzidine begin to volatilize at 600 °C losing about



(36)

(37)

30 % of their weight at 900 °C. *Vogel* and *Marvel* [55a] succeeded in producing films from certain poly(benzimidazoles). The properties of a film of poly-[2,2'-(*m*-phenylene)-5,5'-dibenzimidazole] *(38)* are shown in Table 7. The thermal stability of *(38)* in the presence of oxygen is equivalent to that of a copolymer from tetrafluorocthylene and hexafluoropropylene [55].



(38) (39)

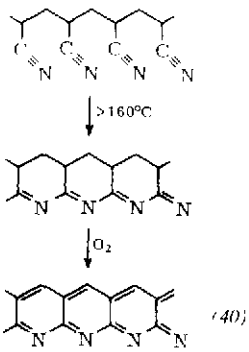
Table 7. Properties of films from the poly(benzimidazole) *(38)* [55a].

| | 25 °C | 200 °C |
|---|---|---|
| Tensile strength [g/den] | 0.7 | 0.5 |
| Elongation [%] | 7 | 9 |
| Modulus [g/den] | 35 | 15 |

A polymer prepared from 1,3-dianilino-4,6-diaminobenzene and diphenyl isophthalate *(39)* [55b] was less stable (decomposition temperature: 400 °C) than the unsubstituted compound *(37)* (decomposition temperature: 600 °C). Poly(benzimidazoles) are soluble in dimethyl sulfoxide and formic acid, and can therefore be cast into films [55].

### 6. Fireproof Fiber from Cyclized Poly(acrylonitrile)

A method of preparing black, fireproof textile fibers (Fiber AF) from cyclized poly(acrylonitrile) fibers has been described by *Vosburgh* [59]. Orlon fibers or fabrics are heated in air above 160 °C. The product is probably a double-chain polymer *(40)* ("ladder" structure) [57, 59–61].



(40)

The logarithm of the reaction time is inversely proportional to the reaction temperature. *Vosburgh* found that the most important process variables were heating time and temperature, fabric structure, and reaction atmosphere. The reaction is exothermic and is accompanied by severe shrinkage. The optimum oxygen concentration is 15 to 20 %. Fiber AF is fireproof, and withstands thermal radiation 100 times more intense than the limiting radiation flux for conventional textile fabrics. It gradually loses its tensile strength on prolonged exposure to high temperatures. At 900 °C, it is completely consumed in 3 hours. Other properties are shown in Table 8. The fiber is suitable for the fabrication of fireproof clothing, and for fabrics which do not demand high abrasion resistance.

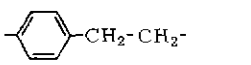
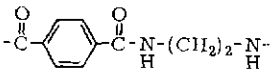
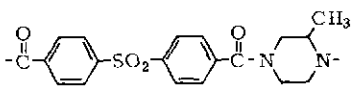
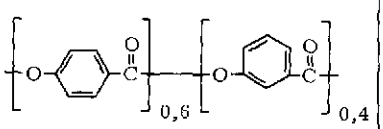
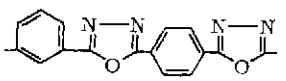
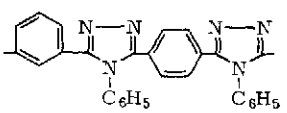
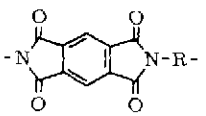
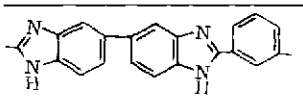
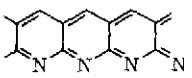
Table 8. Properties of AF-fiber and normal poly(acrylonitrile) fiber [59].

| | Poly(acrylonitrile) fiber | AF-fiber [e] 2h, 285 °C | AF-fiber [e] 4h, 285 °C |
|---|---|---|---|
| *Fabric* | | | |
| Weight [oz/square yard] | 6.03 | 10.42 | 13.00 |
| Pick count | 70×46 | 80×61 | 80×64 |
| Tongue tear strength [lb] | — | 10.5 | 11.0 |
| Crease angle [°] | 67 | 75 | 66 |
| Fireproof | No | Yes | Not quite |
| *Yarn (Warp/Ends)* | | | |
| Denier | 400 | 524 | 551 |
| Tenacity [g/den] | 4.1 | 1.0 | 1.5 |
| Elongation [%] | 15.2 | 6.4 | 7.5 |
| Loop tenacity [g/den] | 3.7 | 0.9 | 1.1 |
| Loop elongation [%] | 13.2 | 2.5 | 4.3 |
| Knot tenacity [g/den] | 2.5 | 0.9 | 1.3 |
| Knot elongation [%] | 8.7 | 3.5 | 4.7 |
| Initial modulus [a] [g/den] | 60 | 25 | 26 |
| Recovery after 3 % elongation | | | |
| Tensile recovery [%] | 50 | 75 | 75 |
| Work recovery [%] | 25 | 48 | 36 |
| Abrasion [b] | 450 | 11 | 16 |
| Impact strength [g·cm/den·cm] | 2.85 | 0.19 | 0.26 |
| Twist failure [c] | 25 | 10.5 | 11.5 |
| Flex life [c] | 2000 | 9–11 | 200 |
| Zero-strength temperature [d] [°C] | 155 | 300 | — |

[a] At 1 % elongation.
[b] Yarn on yarn.
[c] Under a load of 0.1 g/den.
[d] Temperature at which fiber will break under a load of 0.2 g/den.
[e] Polyacrylonitrile fiber was heated (time and temperature as stated) and scoured.


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Table 9. Heat-resistant fibers and films.

| Structure | Melting point [a] | Zero-strength temp. [b] | Form | Tenacity | Elongation | Initial modulus [c] | Reference |
|---|---|---|---|---|---|---|---|
|  | 405 °C | 300 °C | Film | – | ≦600 % [d] | – | [17, 19] |
|  | 455 °C | 380 °C | Fiber | 1.8 g/den | 26 % | 62 g/den | [3, 27] |
|  | >380 °C | 355 °C | Fiber | 3.0 g/den | 25 % | 40 g/den | [3, 31] |
|  | 385 °C | >300 °C | Film | $1.1\times10^4$ psi | 6 % | $3.2\times10^5$ psi | [45, 48] |
|  | >450 °C | >400 °C | Fiber | 2.6 g/den | 3 % | 124 g/den | [53, 54] |
|  | >500 °C | 423 °C | Film | $0.9\times10^4$ psi | 13 % | $1.3\times10^5$ psi | [55c] |
|  | >900 °C | 815 °C | Film | $2.5\times10^4$ psi | 90 % | $4.0\times10^5$ psi | [56c] |
|  | >500 °C | – | Film | 0.7 g/den | 7 % | 35 g/den | [10, 55a, b] |
|  | >900 °C | >400 °C | Fiber | 1.0 g/den | 6 % | 25 g/den | [57, 59] |

[a] Temperature, at which polymer leaves a molten trail on hot bar.
[b] Temperature, at which fiber breaks under 0.1 g/den load, or film under 20 psi.
[c] At 1 % elongation.
[d] With plasticizer.

## IV. Conclusion

The properties of the high-melting fibers and films are listed in Table 9.

It is hoped that the present study, relating polymer structure with in-use properties of films and fibers, will encourage further technical development in the field of heat-resistant polymers, films, fibers, and elastomers.

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# Amides of the Alkali and the Alkaline Earth Metals

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*Following preparative work, the behavior of amides towards excess ammonia (ammoniate formation) and on removal of ammonia (degradation to imides) was studied particularly with regard to the solid state (crystal structure) and the transition to the liquid phase (melting point). Energy relationships are discussed on the basis of enthalpies of formation. Studies on ternary amides and imides are still in the initial stage. – Emphasis is laid here on the establishment of parallels between amides and hydroxides as well as between the aquo and ammono systems, and also on the differences between the amides with their dipolar $NH_2^-$ anion, and the halides. The results, although still incomplete, permit a survey to be given of experimental data with the aid of information obtained from the pertinent literature.*

## 1. Preparation of the Amides

Two principal methods are available for the preparation of the amides of *alkali metals*: reaction of the metal with (a) liquid or (b) gaseous ammonia.

The purest products are obtained by the long-established reaction of metals with *liquid* ammonia [2]. The alkali metals dissolve in ammonia to give the familiar intensely blue solutions. The rate of formation of the metal amide and hydrogen is slow, particularly with the lighter alkali metals. It increases appreciably with rising temperature and with increasing atomic weight of the alkali metal [3, 4]. Acceleration of the reaction by catalysts, *e.g.* iron oxide or platinized platinum, is also possible.

Lithium and sodium amides are most readily obtained by sealing the solution of the alkali metal together with the catalyst in a pressure tube, taking care to exclude air and moisture, and allowing the mixture to stand at room temperature until the deep-blue solution is fully decolorized. With potassium, rubidium, and cesium, the reaction is complete after a few hours, even at low temperatures, and it is possible to work at normal pressure, so that the hydrogen formed can escape [5]. The second method depends on the reaction of the molten metal with *gaseous* ammonia, *e.g.* at 400 °C for $LiNH_2$ or 300 °C for $NaNH_2$. With lithium, higher temperatures must be avoided as the decomposition pressure becomes too high and degradation to the imide occurs. It is advantageous to allow the very mobile molten reaction product to drain away into a cooler zone of the apparatus [6].

In addition, numerous reactions are known in organic chemistry in which alkali amides are formed as by-products. Mention may be made of the hydrogenation of conjugated double bonds by the method of *Birch* [6a], where liquid ammonia serves as solvent and often also as proton donor. Although these reactions proceed very rapidly even at low temperatures, they are mostly unsuitable for the preparation of metal amides since the organic substances are difficult to separate off. However, when the solvent and the organic compound are readily volatile, such a reaction may be preparatively useful [7]:

$$R_2NH + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[\text{n-Octane}]{\text{Na}} CH_3{-}CH{=}CH{-}CH_3 + R_2NNa$$

The following *substituted* amides have been prepared in this way: sodium diethylamide, sodium anilide, sodium *N*-ethylanilide, and sodium *N*-isopropylanilide. Little is known about the chemical and physical properties of these compounds, but studies of alkali metal methylamides have been carried out [8–10]. The latter compounds can generally be prepared from the alkali metal and methylamine, and, in the case of lithium, also from phenyl-lithium and methylamine in ether. Cesium reacts rapidly with methylamine, even at low temperatures, to form $CsNHCH_3$; the other alkali metals react too slowly under these conditions. At higher temperatures, *e.g.* 30–50 °C, only the lithium compound is obtained. Cyanides and decomposition products of the amine are formed by the other elements of this group.

The preparation of amides by sealing alkali metal dissolved in liquid ammonia in a pressure tube was also applied to the *alkaline earth metals* [11]. Products free from hydride are obtained in this way, and partial thermal decomposition is prevented; both of these side

[1] Communication No. 49 on Metal Amides and Nitrides. – Communication No. 48: *R. Juza, A. Rabenau,* and *J. Nitschke,* Z. organ. allg. Chem., in the press.

[2] *A. Joannis,* C. R. hebd. Séances Acad. Sci. *112,* 392 (1891).

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[6a] *A. J. Birch,* J. chem. Soc. (London) *1944,* 430.

[7] U.S.-Pat. 742790 (June 26th, 1952), Ethyl Corp., New York, N.Y., inventor: *A. Prior.*

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[10] *N. G. Lutly, F. W. Bergström,* and *H. S. Mosher,* J. org. Chemistry *14,* 322 (1949).

[11] *R. Juza* and *H. Schumacher,* Z. anorg. allg. Chem., in the press.

reactions can interfere during the reaction of metals with gaseous ammonia at elevated temperatures [12, 13].

Magnesium occupies a special position. In order to obtain magnesium amide by this method, the addition of a small quantity of ammonium iodide is required [14]. This substance behaves as an acid in liquid ammonia and acts as a catalyst; it also precipitates the sparingly soluble magnesium amide:

$$Mg + 2\ NH_4^+ = Mg^{2+} + 2\ NH_3 + H_2$$
$$Mg^{2+} + 4\ NH_3 = Mg(NH_2)_2 + 2\ NH_4^+.$$

By adding alkali metal amides or halides to magnesium in liquid ammonia, *Bergstrom* obtained amidometalates, *e.g.* $Mg(NHNa)_2 \cdot 2\ NH_3$. In the case of beryllium such derivatives are the only amides known at present [15]. On the other hand, the reaction of gaseous ammonia with magnesium nitride at 350 °C under a pressure of 10 atm. for 4–6 weeks results in the formation of magnesium amide [14].

The amides of the heavier metals of both groups are clearly the ones most readily obtained. Preparation of the amides of the lighter elements sometimes requires laborious methods, and special difficulties may be anticipated in the case of beryllium amide.

## 2. Properties

Irrespective of their method of preparation, all the amides of the alkali metals are colorless, crystalline substances. They are extremely *reactive* and are rapidly attacked by moisture and atmospheric oxygen. Cesium amide is the most sensitive, and oxidizes explosively with spontaneous ignition. It is noteworthy that the decomposition in air of potassium, rubidium, and cesium amides is accompanied by the formation of an intense yellow coloration typical for the peroxides of these metals. With the exception of lithium amide, all the alkali metal amides can be heated up to their melting points in nickel, copper, or silver crucibles without appreciable decomposition. The fused amides are good conductors of electricity; this confirms the salt-like character of these compounds.

The amides of the heavy alkaline earth metals are crystalline, more or less greyish-white compounds, irrespective of their method of preparation. Magnesium amide is precipitated as a whitish-grey powder in liquid ammonia, but is amorphous as indicated by X-ray studies. Its particles are so fine that excess ammonia is adsorbed. This is similar to the adsorption of water by amorphous hydroxides [14]. A white crystalline product is obtained from the reaction between magnesium nitride and ammonia. The alkaline earth amides react less vigorously with moisture or atmospheric oxygen than the alkali metal amides, and on heating they lose ammonia and are all converted into the corresponding imides. They are only slightly soluble in liquid ammonia.

Amides of the heavier alkali metals (sodium to cesium) decompose when heated above their melting points. At 335–400 °C, two possible modes exist for the thermal decomposition of sodium amide [16], depending on the total pressure in the system. If the pressure exceeds the dissociation pressure of sodium hydride, then the reaction proceeds according to the equation

$$NaNH_2 \rightarrow NaH + 0.5\ N_2 + 0.5\ H_2.$$

If, on the other hand, the total pressure is below the dissociation pressure of NaH, the following decomposition takes place:

$$NaNH_2 \rightarrow Na + 0.5\ N_2 + H_2.$$

The gaseous mixture produced always contains ammonia together with the hydrogen and nitrogen.

The solubilities of the alkali amides in liquid ammonia differ strongly. Lithium amide is very sparingly soluble, sodamide dissolves far more readily (0.114 g of $NaNH_2$/100 g of $NH_3$ at −20 °C) and potassamide is readily soluble (65.8 g of $KNH_2$/100 g of $NH_3$ at −32.4 °C) [17]. Rubidium amide is extremely soluble – several hundred grams dissolve in 100 g of liq. $NH_3$ (cf. Section 3); the solubility of cesium amide is slightly lower.

Like the hydroxides in water, metal amides behave as solvobases in the liquid-ammonia system. The numerous reactions of these ammoniacal bases described in the literature [18] involve mostly organic compounds, but inorganic neutralization reactions are also known. In considering the use in liquid ammonia of indicators normally employed in aqueous systems, primary attention should be given to the large difference in the dissociation constants of water and ammonia:

$$[NH_4^+]\,[NH_2^-]/[NH_3] = 4.5 \times 10^{-35}\ (\text{at } -50\,^\circ C)$$

The enthalpy of neutralization, $\Delta H_N$, of liquid ammonia:

$$NH_4^+ + NH_2^- \rightarrow 2\ NH_3\ (liq.);\ \Delta H_N$$

is directly related to the dissociation constant. According to van't Hoff's reaction isochore, the dissociation constant decreases with increasing enthalpy of neutralization. Values of

$$\Delta H_N = -26.1\ kcal/mole$$

were obtained by calorimetric measurements involving the reaction of dilute solutions of $KNH_2$ with strong ammonium acids such as $NH_4I$, $NH_4NO_3$, $NH_4SCN$, and $NH_4Br$ [19]. (For water, $\Delta H_N = -13.4$ kcal/mole.) Furthermore, the *proton affinity* [*] of ammonia, 209

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[19] *H. D. Mulder* and *F. C. Schmidt*, J. Amer. chem. Soc. *73*, 5575 (1951).

[*] The proton affinities were determined using the Born-Haber cycle, *e.g.* with $NH_4Cl$ [20].

[20] Cf. *T. C. Waddington*, Advances inorg. Chem. Radiochem. *1*, 205 (1959).

kcal/mole, *i.e.* the energy released when a proton becomes attached to the $NH_3$ molecule, is much greater than the proton affinity of water (182 kcal/mole) [20], so that ammonia is a solvent of pronounced basic character. For this reason, the usual indicators for aqueous systems cannot always be employed, since indicators which are weak acids are completely dissociated, while weak bases do not dissociate at all. Further difficulties are caused by poor solubilities and reaction between the indicator and the amide bases (see [18] for colors and usefulness of indicators in neutralization reactions).

## 3. Ammoniates

The reaction with liquid ammonia generally results in the formation of amides, but with heavy alkali metals ammoniates of the amides are formed [21], in analogy with the hydrate formation of alkali metal hydroxides. The relationships can be readily investigated by measuring *pressure changes*. A known amount of $NH_3$ is condensed onto the alkali metal amide, and decomposition is then conducted inside a tensioeudiometer [22] with systematic variation of the temperature. The temperature dependence of the equilibrium pressures permits calculation of the enthalpies of formation of the ammoniates by means of the van't Hoff isochore.

The simplest system is that of cesium amide and ammonia [21]. First the pressure of the liquid ammonia is measured; the value obtained lies below the saturation pressure of pure ammonia owing to dissolved $CsNH_2$. Subsequently, the dissociation pressure of the monammoniate is established. When the latter is decomposed, the $NH_3$ pressure falls to zero. The enthalpy of formation of the ammoniate $CsNH_2 \cdot NH_3$ is found to be $\Delta H_B = -10.7$ kcal/mole.

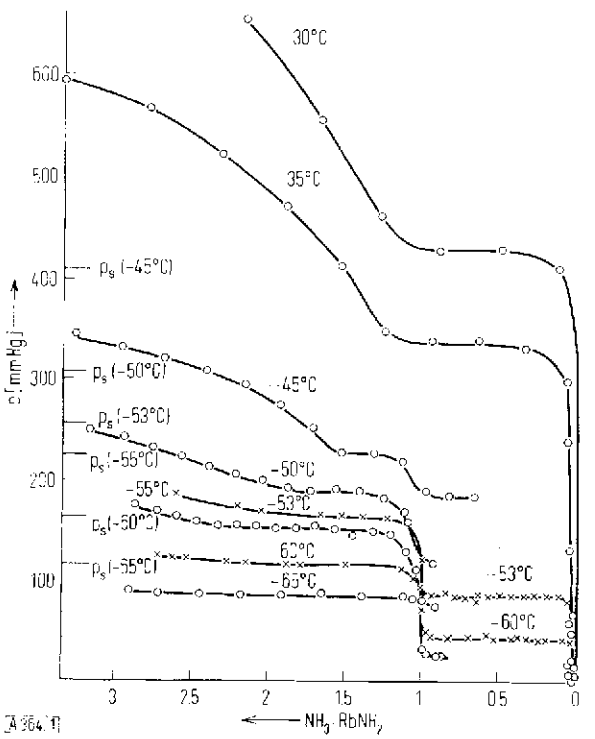



Fig. 1. Tensiometric decomposition reactions in the $RbNH_2/NH_3$ system ($p_s$ = saturation pressure of $NH_3$ at the temperature stated).

The system rubidium amide/ammonia is more complicated, in particular because of the extreme solubility of $RbNH_2$ in liquid ammonia [21]. The degradation diagram (Fig. 1) is again that of the two-phase system monoammoniate/ammonia. From the temperature coefficient of the decomposition reaction, the enthalpy of the formation of $RbNH_2 \cdot NH_3$ can be calculated as $\Delta H_B = -9.0$ kcal/mole. A cursory examination suggests that the abrupt breaks of the −30 and −35 °C curves on the right-hand side of Figure 1 are associated with the monoammoniate; in fact, they are due to a saturated solution with $RbNH_2$ as solid phase. Similar saturated solutions, with $RbNH_2 \cdot NH_3$ as the solid phase, are responsible for the breaks in curves corresponding to higher ammonia contents. The range of existence of this compound can be read off from the graph of log p versus 1/T (Fig. 2) and does not extend above −42 °C. Above this temperature, the saturated solution II with $RbNH_2$ as solid phase is present, below −42 °C $RbNH_2 \cdot NH_3$ is the solid phase of the saturated solution I.

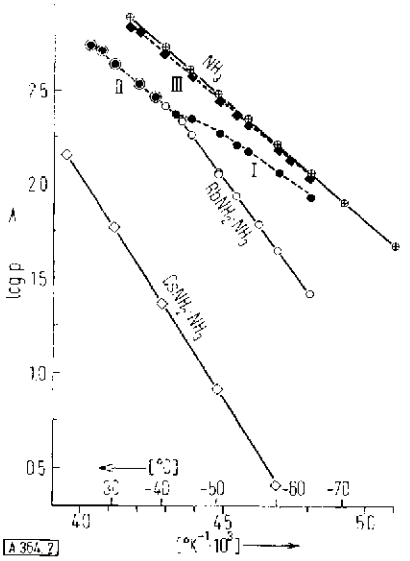



Fig. 2. Equilibrium pressures of $CsNH_2 \cdot NH_3$, $RbNH_2 \cdot NH_3$, and of their saturated solutions in liquid ammonia.

I Saturated solution in liquid ammonia with $RbNH_2 \cdot NH_3$ as the solid phase

II Saturated solution in liquid ammonia with $RbNH_2$ as the solid phase

III Decomposition pressure of $RbNH_2 \cdot NH_3$.

In the potassium amide/ammonia system [21, 23], only a diammoniate exists below −60 °C, a diammoniate and a monoammoniate coexist between −60 and −42 °C, and only the monoammoniate appears above −42 °C. The enthalpy of formation of the monoammoniate is $\Delta H_B = -7.3$ kcal/mole.

The thermal stability of the ammoniate increases from potassium to cesium, as shown by the dissociation pressures; the *enthalpies of formation* of the monoammoniates increase in the same order (see above). Consequently, sodium and lithium amides do not form ammoniates.

Similar relationships are found in the far more numerous hydrates of the alkali metal hydroxides. Here again an intermediate alkali metal hydroxide, NaOH, forms the most hydrates, and the number of water molecules attached to the hydroxides falls off in the direction to lithium and cesium hydroxides. Among the monosolvated compounds, $CsNH_2 \cdot NH_3$ and $CsOH \cdot H_2O$ have the highest thermal stabilities.

[21] *R. Juza* and *A. Mehne*, Z. anorg. allg. Chem. *299*, 41 (1959).

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The construction of the phase diagram and the elucidation of the energy relationships naturally give no information about the *constitution* of these ammoniates. Two alternative structures are possible; the $NH_3$ molecule is associated with either the metallic ion or the $NH_2^-$ ion. The first alternative involves an ion-dipole bond, the second a hydrogen bond.

Determination of crystal structures should resolve this problem. The existence of a hydrogen bond would be shown by a small N–N bond length, similar to that in solid $NH_3$ [24]; the alternative structure requires a much greater N–N bond length. However, the magnitudes of the enthalpies of formation of the monoammoniates [21] give a highly probable indication of the type of bonding of the ammonia molecules. Thus, the greatest values are found for $CsNH_2 \cdot NH_3$ and the smallest for $KNH_2 \cdot NH_3$. The same conclusions can be drawn from the equilibrium vapor pressures of these compounds. If the $NH_3$ molecule were coordinated to the cation, the opposite behavior would be expected for electrostatic reasons, *i.e.* the compound with the smallest cation would have the greatest stability. On the other hand, a hydrogen bond is weakened by the counterpolarizing effect of a small cation, and this is indeed confirmed in the series Cs, Rb, K. The same reasoning explains the absence of ammoniate formation with sodium, lithium, and alkaline earth amides.

Crystal structure determinations on hydrates of alkali metal hydroxides provided information about the way in which the water is bound in these compounds. $NaOH \cdot H_2O$ [25] crystallizes in an orthorhombic layer lattice. Hydrogen bridges between the oxygen atoms are highly developed within the layers, and the O–O distance is very small (2.64 to 2.66 Å). The layers are interlinked by weak hydrogen bonds with an O–O distance of 3.11 Å, which is even less than that found in compounds containing OH groups and free from hydrogen bonds ($\approx$ 3.3 Å). Similar relationships are found in all the hydrates of alkali metal hydroxides investigated so far [26].

In general, fluorine shows the greatest tendency towards hydrogen bonding. Hydrogen bonds to oxygen are less strong, while those to nitrogen are only weak [27]. This explains why ammoniate formation is restricted to the amides of the heavy alkali metals, why only one or two ammonia molecules are attached, and why the thermal stability of these compounds is so poor.

## 4. Crystal Structures

It is now possible to correlate the crystal structures of the alkali metal amides and to discuss the crystallochemical relationships existing among the amides themselves, and among the amides, hydroxides, hydrogen sulfides, and dihydrogen phosphides.

*Lithium amide* [6] is tetragonal, the $NH_2^-$ ions being approximately cubic close-packed (Fig. 3). The lithium ions can occupy either octahedral or tetrahedral interstices; in practice, the latter are found. In effect, two deformed zinc blende unit cells are placed on top of each other. The $NH_2^-$ ions have been displaced from their ideal positions; those with $z = 1/8$ and $7/8$ are nearer the lithium ions ($z = 0$), while the others approach $z = 1/2$.

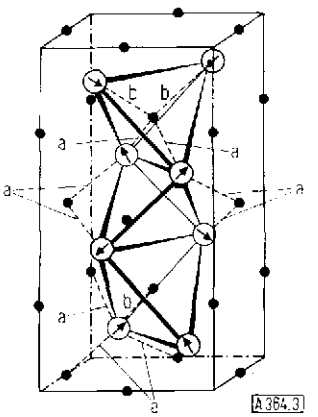



Fig. 3. Crystal structure of lithium amide. ● Li; ○ $NH_2$.

In this way, the substance acquires a slight tendency towards a layer structure. Two of the four lithium ions which surround an $NH_2^-$ ion are at a greater distance (b = 2.35 Å) than the other two (a = 2.15 Å). It is likely that the dipole of the $NH_2^-$ ion is orientated in the direction of the greater distances. This direction is indicated by the arrows in Figure 3.

It would be very interesting to determine experimentally the positions of the hydrogens here and in the low-temperature modifications of the other amides in order to obtain a reliable indication of the position of the dipoles. Appreciable difficulties are likely to be encountered in this investigation even at the preparation and handling stages.

The unit cell of *sodium amide* [28] is rhombic (Fig. 4). Here again the $NH_2^-$ ions have an approximately cubic close-packed structure. The sodium ions occupy the

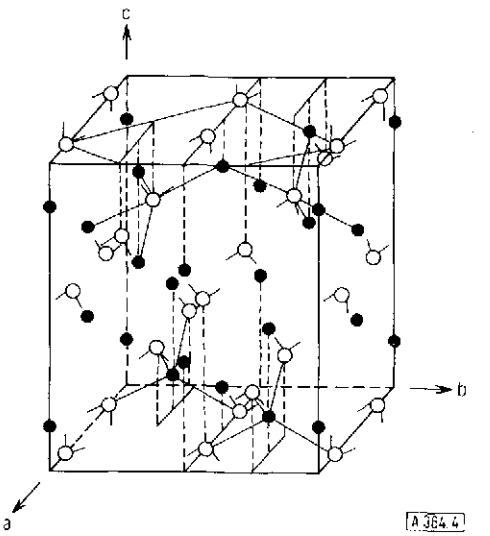



Fig. 4. Crystal structure of sodium amide. ● Na; ○ $NH_2$.

[24] *I. Olovsson* and *D. H. Templeton*, Acta crystallogr. *12*, 832 (1959).

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[27] The bond energies of the hydrogen bonds vary markedly with the lengths of the bonds. Cf. *C. A. Coulson:* Valence. 2nd Edit., Oxford University Press, 1961.

[28] *R. Juza, H. H. Weber*, and *K. Opp*, Z. anorg. allg. Chem. *284*, 73 (1956).

tetrahedral interstices, which are surrounded by $NH_2^-$ ions in a fairly strict tetrahedral arrangement. On the other hand, the $Na^+$ tetrahedra which surround the $NH_2^-$ ions are very strongly distorted, the sodium ions being removed from the positive side of the $NH_2^-$ dipole.

The structure of sodium amide has been reinvestigated and confirmed by *Zalkin* and *Templeton* [29], who calculated the orientation of the $NH_2^-$ ions in the unit cell. The H–N–H angle (104°) [30] is known from infrared measurements, and the H–H distance in $NH_2$ (1.63 Å) from proton magnetic resonance [31]. These figures give an H–N distance of 1.03 Å. The N–N distance in sodium amide is 3.81 Å, much greater than that in solid ammonia (3.38 Å) [24]; consequently no hydrogen bonding exists between the nitrogen atoms in $NaNH_2$. In Figure 4 the positions of the hydrogen atoms of the $NH_2^-$ ions are indicated by two short lines. The *structural relationship* between lithium and sodium amides can be better appreciated if only the monoclinic unit cell (indicated on the upper base in Figure 4) is used. Figure 5 gives a schematic representation of this portion of the sodamide unit cell, and also that of lithium amide and lithium hydroxide.

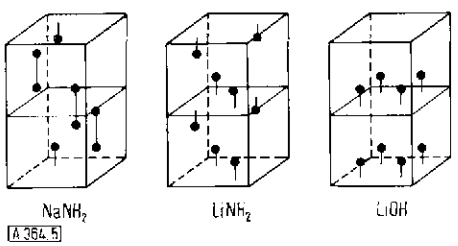



Fig. 5. Structural relationships between $NaNH_2$, $LiNH_2$, and LiOH. The anions arranged in a distorted cubic close-packed lattice are not shown.
● Cations.

The anions are always approximately cubic close-packed and are not indicated; what is shown is the position of the cations in the tetrahedral interstices. *Ernst* has demonstrated the presence of a layer lattice in lithium hydroxide [32]; the tetrahedral interstices with z = $^1/_4$ are all occupied and those with z = $^3/_4$ are all vacant. In lithium amide, as mentioned above, tetrahedral occupation of the tetrahedral interstices by lithium occurs, and a weak layer character appears owing to the displaced $NH_2^-$ ions (not shown here). In sodium amide, two superposed tetrahedral interstices are always occupied.

The picture is much simpler for the *high-temperature modifications* [21, 23, 33] with freely rotating $NH_2^-$ dipoles and quasi-spherical $NH_2^-$ ions. β-$KNH_2$ and β-$RbNH_2$ have the sodium chloride lattice (coordination number 6), and β-$CsNH_2$ crystallizes in the cesium chloride (lattice coordination number 8). The transition temperatures are low, being approximately 50, 40 and 30 °C, respectively.

The corresponding *low-temperature modifications* are much less symmetrical, but their structures are closely related to those of the high-temperature modifications.

The low-temperature modification [33] of *cesium amide* can be derived from the high-temperature form as shown in Figure 6. Below the transition temperature, relatively slight splitting of the cubic powder pattern reflections occurs due

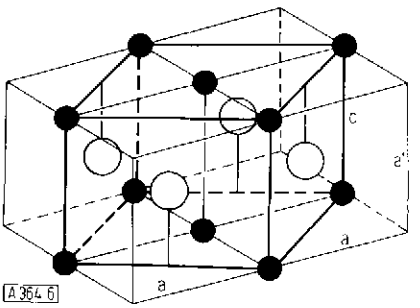



Fig. 6. Crystal structure of the low-temperature modification of cesium amide and its relation to the high-temperature modification.
● Cs; ○ $NH_2$.

to tetragonal transformation; the structure of the low-temperature modification is that of ammonium bromide, γ-$NH_4Br$. Accurate determination of the z-parameter of the $NH_2^-$ ion is not possible, but its value does not deviate markedly from z = $^1/_2$. The tetragonal deformation indicates that orientation of the $NH_2$ dipole occurs in the low-temperature modification of cesium amide; allowance for the as yet unknown positions of the hydrogens would probably reduce the degree of symmetry still further.

Investigation of the low-temperature modifications of *potassium* and *rubidium amides* [34, 34a] presented difficulties as single crystals could not at first be obtained. Crystals from the melt become opaque and polycrystalline below the transition temperature. Crystalline ammoniates are generally obtained from liquid ammonia, but after decomposition at room temperature, these also form polycrystalline $RbNH_2$. Knowledge of the $RbNH_2/NH_3$ system described above (cf. Fig. 1 and 2) showed however that $RbNH_2$ itself appears as the solid phase above −42 °C in liquid ammonia, and it was then possible to obtain single crystals by slow cooling to 15 °C of a solution saturated at + 35 °C [34a].

The unit cells of both amides are monoclinic and, according to Figure 7, are closely related to the sodium chloride lattice, *i.e.* to the high-temperature modification. The c-axis of the monoclinic unit cell is approximately equal to the edge of

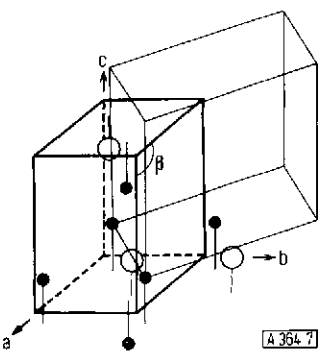



Fig. 7. Crystal structure of the low-temperature modifications of potassium and rubidium amides and their relationship to the high-temperature modifications.
● K or Rb; ○ $NH_2$.

[29] *A. Zalkin* and *D. H. Templeton*, J. physic. Chem. *60*, 821 (1956).
[30] *S. P. Mason*, J. physic. Chem. *61*, 384 (1957).
[31] *R. Freemann* and *R. E. Richards*, Trans. Faraday Soc. *52*, 802 (1956).
[32] *Th. Ernst*, Z. physik. Chem. *20*, 65 (1933).
[33] *R. Juza* and *A. Mehne*, Z. anorg. allg. Chem. *229*, 33 (1959).
[34] *R. Juza*, *H. Jacobs*, and *W. Klose*, Naturwissenschaften *49*, 35 (1962).
[34a] *H. Jacobs*, Diploma Thesis, Universität Kiel, 1962.

the cube and (a + b) is approximately equal to the face diagonal of the cube, although a is substantially greater then b. The positions x $^1/_4$ z and $\bar{x}$ $^3/_4$ $\bar{z}$ are likewise taken from the sodium chloride lattice. The axis of the $NH_2^-$ dipole is probably contained in the two planes of symmetry of the unit cell.

*Comparison* of the structures of the alkali metal amides with those of the corresponding hydroxides, hydrogen sulfides, and dihydrogen phosphides was also of interest with particular reference to the ionic sizes and dipole moments of the anions. The size of the ions increases in the order $OH^- < NH_2^- < SH^- < PH_2^-$, and it is generally assumed that the dipole moments decrease in the same order as those of the parent molecules, *i.e.* $H_2O$ (1.84 D), $NH_3$ (1.47 D), $H_2S$ (0.93 D), and $PH_3$ (0.55 D), although they cannot be determined directly. A large dipole moment and a small ionic radius indicate a low degree of symmetry, possibly associated with a layer structure. Table 1 gives a list of crystallographic data for the four types of compounds.

Table 1. Crystallographic data for the hydroxides, amides, hydrogen sulfides, and dihydrogen phosphides of the alkali metals.
(L = low-temperature modification; T = transition point; H = high-temperature modification; CN = coordination number).

| | OH | $NH_2$ | SH | $PH_2$ | |
|---|---|---|---|---|---|
| Li | tetragonal<br>CN = 4<br>P 4/nmm | tetragonal<br>CN = 4<br>I $\bar{4}$ | tetragonal<br>CN = 4<br>I $\bar{4}$ | | |
| Na | rhombic<br>CN = 5<br>C mcm | rhombic<br>CN = 4<br>F ddd | rhombohedral<br>CN = 6; α = 96,3°<br>R 3 m | | L |
| | + 292,8 °C | | + 85 °C | | T |
| | cubic<br>CN = 6<br>F m 3 m | | cubic<br>CN = 6<br>F m 3 m | | H |
| K | monoclinic<br>CN = 6; β = 103,6°<br>P $2_1$ or P $2_1$/m | monoclinic<br>CN = 6; β = 95,8°<br>P $2_1$/m or P $2_1$ | rhombohedral<br>CN = 6; α = 97,2°<br>R $\bar{3}$ m | monoclinic<br>CN = 6<br>C 2/m | L |
| | + 249 °C | + 50 °C | + 180 °C | | T |
| | cubic<br>CN = 6<br>F m 3 m | cubic<br>CN = 6<br>F m 3 m | cubic<br>CN = 6<br>F m 3 m | | H |
| Rb | monoclinic<br>CN = 6; β = 106°<br>P $2_1$ or P $2_1$/m | monoclinic<br>CN = 6; β = 97,8°<br>P $2_1$/m or P $2_1$ | rhombohedral<br>CN = 6; α = 97,2°<br>R $\bar{3}$ m | monoclinic<br>CN = 6<br>C 2/m | L |
| | + 245 °C | + 40 to 45 °C | + 130 °C | | T |
| | cubic<br>CN = 6<br>F m 3 m | cubic<br>CN = 6<br>F m 3 m | cubic<br>CN = 6<br>F m 3 m | | H |
| Cs | | tetragonal<br>CN = 8<br>P 4/nmm | | | L |
| | + 215 °C | + 30 to 35 °C | | | T |
| | | cubic<br>CN = 8<br>P m 3 m | cubic<br>CN = 8<br>P m 3 m | | H |

*Lithium hydroxide* [32] crystallizes in the tetragonal system and, as can be seen from Figure 5, has a pronounced layer lattice, whereas the layer character in lithium amide is only weakly developed. The low-temperature modification of sodium hydroxide [35], which crystallizes in a Tl I lattice, and hence is still related to the NaCl lattice, also differs appreciably from sodamide with its (2+2) coordination. Even better agreement is obtained between the amides and hydroxides of potassium and rubidium. The low-temperature modifications [36] of these compounds also form monoclinic crystals; the monoclinic distortion is stronger in the hydroxides than in the amides. No reliable indication of the identity of the space group of these amides and hydroxides can be obtained, as a determination of the position of the hydrogen atoms is required for this purpose. The high-temperature modifications of potassium and rubidium hydroxides [37] are the same as those of the amides, all possessing the NaCl structure.

Cesium hydroxide has also two enantiotropic modifications whose structures have not as yet been determined. The existence of a high-temperature modification of sodamide corresponding to that of sodium hydroxide is to be expected, although none has yet been observed, even at only a few degrees below its melting point [14].

The *hydrogen sulfides* [38–40] present a somewhat different picture, owing to the higher degrees of symmetry of these compounds due to the lowering of the dipole moments and increase in the ionic radius in the order $OH^-$, $NH_2^-$, $SH^-$. Lithium hydrogen sulfide [41] is isotypic with lithium amide, and the layer character in LiSH is again less highly developed than in LiOH. α-Sodium, α-potassium, and α-rubidium hydrogen sulfides crystallize in a weakly rhombohedrically deformed sodium chloride lattice, which is the alternative,

[35] *Th. Ernst*, Nachr. Akad. Wiss. Göttingen, math.-physik. Kl. *76*, (1946).

[36] *I. A. Ibers, I. Kumamoto*, and *R. G. Snyder*, J. chem. Physics *33*, 1164 (1960).

[37] *W. Teichert* and *W. Klemm*, Z. anorg. allg. Chem. *243*, 138 (1939).

[38] *W. Teichert* and *W. Klemm*, Z. anorg. allg. Chem. *243*, 86 (1939).

[39] *W. Teichert* and *W. Klemm*, Z. anorg. allg. Chem. *246*, 3 (1941).

[40] *C. D. West*, Z. Kristallogr., Mineralog., Petrogr., Abt. A *88*, 97 (1934).

[41] *R. Juza* and *P. Laurer*, Z. anorg. allg. Chem. *275*, 79 (1954).

frequently encountered deformed form of the NaCl lattice. Cesium hydrogen sulfide has the lattice of cesium chloride. The high-temperature modifications have exactly the same structure as the corresponding hydroxides and amides.

The structures of potassium and rubidium *dihydrogen phosphides* were recently elucidated [42] and fit readily into the series. Both compounds form crystals with the monoclinically distorted NaCl structure, but in a space group with a higher degree of symmetry than the corresponding hydroxides and amides. Both structures may also be described as approximately rhombohedral deformations of the NaCl lattice, but they have slightly different "rhombohedral angles", so that their analogy to the hydrogen sulfides is at least as pronounced as that to the amides. No high-temperature modifications of these compounds have yet been observed between 20 and 100 °C.

Calcium and strontium amides are so far the only *alkaline earth metal amides* whose structures have been determined [11]. The two substances are isotypic and form tetragonal crystals of the anatase type.

The axial ratio is exactly 2.00:1 in calcium amide, and very close to 2:1 in strontium amide. This results in an ideal position of the amide ions with $z = 0.25$. The structure (cf. Fig. 8) can be interpreted to consist of two cubic face-centered unit cells occupied by $NH_2^-$ ions. Half of the

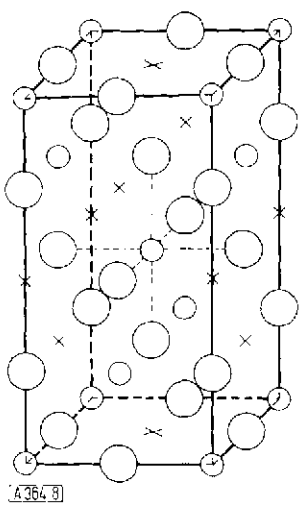



Fig. 8. Crystal structure of calcium and strontium amides.
● Ca or Sr; ○ $NH_2$; × represents lattice sites occupied by Ca in the $Ca(NH_2)_2$/CaNH solid solution.

octahedral interstices are occupied by calcium or strontium ions, *i.e.* the coordination number is 6. If the second half of the interstices indicated by crosses were also occupied, the sodium chloride lattice would result; this phenomenon will be dealt with further in Section 7 during the discussion of the thermal decomposition of these compounds.

## 5. Molecular Volumes

The comparison between the amides and hydroxides can be extended further to a discussion of their densities and molecular volumes [4, 11, 14] on the basis of known structures, allowing conclusions to be drawn about unknown structures.

In Figure 9 the molecular volumes (in the sense of *Biltz*'s volume chemistry [43]) are plotted against the molecular volumes of the alkali metal fluorides. The "standard" increase (broken line) is the rise of the molecular volume of the alkali metal fluorides, which, as is

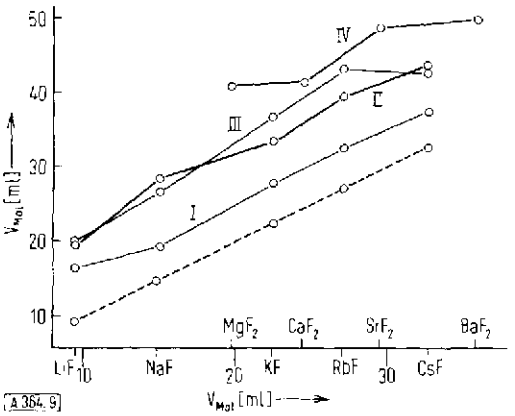



Fig. 9. Molecular volumes of the amides (II), hydroxides (I), and chlorides (III) of the alkali metals and the amides of the alkaline earth metals (IV), plotted against the molecular volumes of the corresponding fluorides.
(Broken line: Alkali fluorides *vs.* alkali fluorides).

well known, all have the same type of lattice. The corresponding curve III for the alkali metal chlorides is linear and somewhat steeper so long as they crystallize in the sodium chloride lattice. Cesium chloride with a coordination number of 6 would be very bulky, but its true coordination number of 8 leads to a smaller molecular volume. This change in coordination number thus gives rise to a break in the curve.

The molecular volume curve of the amides contains two breaks (curve II). $LiNH_2$ and $NaNH_2$, the first two amides, crystallize with a coordination number of 4. Potassium amide with a coordination number of 4 would be too bulky and no longer capable of existence. Thus a coordination number of 6 is found for both potassium and rubidium amides. For the same reason, cesium amide has a coordination number of 8.

In the hydroxides (curve I), the lithium compound has a coordination number of 5 (without allowing for the varying interatomic distances), and potassium and rubidium have a coordination number of 6.

The change in coordination number is therefore accompanied by a lowering of the molecular volume for sodium hydroxide, but no further change in coordination is observed. No information is available about the structure of cesium hydroxide.

Similar relationships are found for the alkaline earth metal amides. The abscissa in Figure 9 contains the molecular volumes of the alkaline earth fluorides; that of magnesium fluoride must be corrected for a coordination number of 6 since this compound crystallizes in the rutile lattice with a coordination number of 4. It can be concluded from Figure 9 that magnesium amide will crystallize with a coordination number of 4 [14] but it has not yet been possible to interpret its complex X-ray diagrams. Sixfold coordination has been demonstrated for both calcium and strontium amides [11], while barium amide very probably crystallizes in two modifications [44], both of which have complicated

[42] *G. Bergerhoff* and *F. Schultze-Rhonhof*, Acta crystallogr. *15*, 420 (1962).
[43] *W. Biltz*: Raumchemie der festen Stoffe. Verlag Leopold Voss, Leipzig 1934.
[44] *A. Lämmke*, Diploma Thesis, Universität Kiel, 1963.

structures and, to judge from the course of the molecular volume plot, have a coordination number of 8. A calcium fluoride structure might have been anticipated; by analogy to the anatase-type structure of calcium and strontium amides, a zirconium dioxide structure is expected for barium amide.

## 6. Enthalpies of Formation, Lattice Energies, and Melting Points

The *enthalpies of formation* [4] of the alkali metal amides were determined by calorimetric determinations of the heats of solution. The values obtained are appreciably lower than those found for the corresponding hydroxides but vary in the same way with the cation in both series of compounds; the course of this variation is completely different from that observed with the halides.

The enthalpies of formation provide no direct information on constitutional problems, but by the use of the Born-Haber cycle, permit calculation of the *lattice energies*. The proton affinity of the $NH_2^-$ ion is unknown, but this difficulty can be circumvented by precise evaluation of the relative lattice energies from experimental data; the absolute values are then obtained by equating the lattice energy of potassium chloride (167 kcal/mole) to the lattice energy of the high-temperature NaCl-lattice modification of potassium amide. For this purpose, the lattice energy of potassium chloride must be corrected for the size of the $NH_2^-$ ion ($r_{Cl^-} = 1.81$ Å; $r_{NH_2^-} = 1.73$ Å), which is spherically symmetrical in the high-temperature modification [44a]; the corrected value is found to be 172 kcal/mole. Absolute lattice energies determined in this way are listed in Figure 10. Their course is practically identical with that of the lattice energies of the alkali metal hydroxides, but deviates markedly from that of the halides.

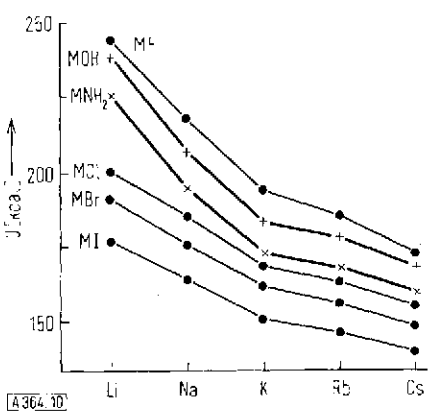



Fig. 10. Lattice energies U of the alkali metal amides, hydroxides, and halides.

The lattice energies for a given anion depend on the size of the cation and should rise from the cesium to the lithium compound, as indicated by the curve for the fluorides, the gradient being somewhat steeper at the last break, *i.e.* from the sodium to the lithium compound.

[44a] *A. Lämmke*, Universität Kiel, unpublished work.

However, the values found for the lithium halides are too low. According to *Pauling* [45, 46] and *van Arkel* [47], this is due to the fact that the distances between the lithium and halide ions in the lattices of lithium halides are larger than those calculated from the appropriate ionic radii. The cations and anions no longer come into contact inside the lattice; instead, anion-anion contact takes place and this results in a lowering of the lattice energy owing to the appearance of additional forces of repulsion. This effect is small in lithium fluoride, but increases with the size of the anion in the order LiF < LiCl < LiBr < LiI. It is also noticeable in NaBr and NaI.

No similar lowering of the lattice energy occurs in lithium hydroxide or lithium amide. These compounds crystallize with a coordination number of 4 and this lower value is responsible for the elimination of the disturbing influence of anion-anion contact. The lattice energies of these compounds are therefore higher.

The schematic energy diagram (Fig. 11) illustrates these and further energy relationships to be discussed below. Level I corresponds to isolated gaseous ions, and level VI

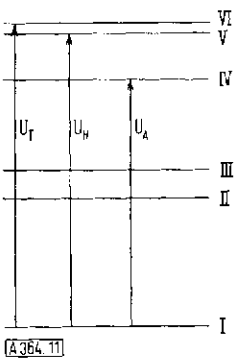



Fig. 11. Schematic representation of the energy levels of compounds with and without dipole anions.

$U_T$, $U_H$, $U_A$: Lattice energies.

I: Gaseous ions
II: Disordered melt
III: Ordered melt
IV: Anion-anion contact
V: High-temperature modification
VI: Low-temperature modification.

to the most stable modification, *e.g.* one with orientated dipoles. The transition from I to VI gives the lattice energy of this low-temperature modification: $\Delta U_{I,VI} = U_T$. In the high-temperature modification, the lattice energy $\Delta U_{I,V} = U_H$ is smaller; the lattice energy, $\Delta_{UI,IV} = U_A$, of a crystal with anion-anion contact is even smaller.

The *melting points* [3] of the alkali metal amides (in °K) are to a first approximation proportional to the enthalpies of fusion (Richards' rule). As can be seen in Figure 12, the melting points of the alkali metal hydroxides and amides are appreciably lower than those of the halides; this difference can be explained by the fact that the $OH^-$ and $NH_2^-$ ions are ion dipoles. In the solid

[45] *L. Pauling*, J. Amer. chem. Soc. *49*, 765, 781 (1927).

[46] *L. Pauling:* The Nature of the Chemical Bond. 3rd Edit., Cornell University Press, Ithaca 1959.

[47] *A. E. van Arkel*, Z. physik. Chem. *50*, 648 (1928).

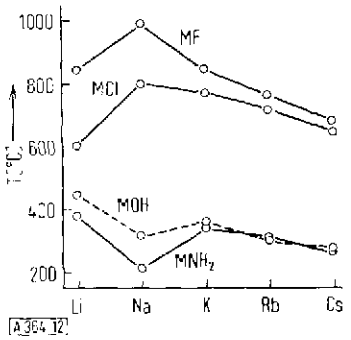



Fig. 12. Melting points of the alkali metal amides, hydroxides, chlorides, and fluorides.
(M = Metal).

state, the lattice energy is only a little higher than that of a crystal built up of dipole-free ions, since the dipole forces of the anions cannot exert their full effect; the dipoles arrange in the crystal field corresponding to the coordination polyhedron (level VI). In the molten state, the association of each cation with a dipole anion is more strongly favored (level III), resulting in lowering of the enthalpy of fusion of the amides and hydroxides to $\Delta U_{VI,III}$ and hence in lower melting points, whereas the enthalpy of fusion for a non-ordered, dipole-free liquid ($\Delta U_{VI,II}$) is greater.

The course of the melting points of the amides and hydroxides from lithium to cesium differs from that of the halides. The relatively high melting points of lithium amide and lithium hydroxide deserve special attention. At this point, it should be remembered that lattice theory predicts an increase in melting point on passing to smaller cations. Thus, the low melting points of the lithium halides are anomalous, and in order to explain it we must again turn to the theory underlying the lattice energy. Repulsion forces owing to anion-anion contact arise in the lithium halides with a coordination number of 6, and the lattice energy is reduced (level IV) with a consequent fall in their enthalpies of fusion $\Delta U_{IV,II}$ and melting points. In lithium amide and hydroxide, which have a coordination number of 4, no anion-anion contact occurs, so that their lattice energies (level VI), energies of fusion $\Delta U_{VI,III}$, and melting points are high.

The initially somewhat complicated course of the melting points of the alkali metal amides can thus be explained by considering the structural and calorimetric data, but no reliable explanation can be given for the fall in melting point from potassium to sodium amide. Attempts to discover a suspected high-temperature modification with a coordination number of 6 remained unsuccessful.

## 7. Imide Formation by Thermal Decomposition

Sodium, potassium, rubidium, and cesium form no imides, although imides are readily formed by thermal decomposition of lithium and the alkaline earth amides. Investigations concerning the formation of these compounds are made difficult by the slow rates at which pressure equilibria are attained. To explain the crystallographic changes occurring during the amide-imide transformation, the degradation products were also subjected to X-ray structural analysis. It was shown that the structures of the amides and imides were markedly similar, and that during the degradation *mixed crystals* appeared which are distinguished by the simultaneous occurrence of both $NH_2^-$ and $NH^{2-}$ ions.

Lithium amide decomposes to form lithium imide at 300–400 °C [48, 49]. Initially ammonia is given off without the formation of a new phase. The mixed crystals with the amide structure exist until 25 % of the $NH_3$ has been liberated; lithium imide then appears as a new phase on removal of more ammonia.

Table 2 shows the distribution of the ions in the lattice in schematic form. The $LiNH_2$ unit cell corresponding to two deformed zinc blende cells contains $2\times4$ anions and $2\times4$ lithium ions in the tetrahedral interstices; further tetrahedral interstices are unoccupied. In the mixed crystals derived from lithium amide, the anion lattice is predominantly occupied by $NH_2^-$ and partly by $NH^{2-}$ ions. A number of lithium ions, equivalent to the additional charge of the $NH^{2-}$ ions, leave the cation lattice and enter into the unoccupied tetrahedral interstices of the face-centered cubic anion lattice [14].

The same behavior is observed during the decomposition of calcium amide to calcium imide [11] (cf. Table 2, B). However, here the cations are in octahedral instead of tetrahedral interstices of the face-centered cubic anion lattice, and the mixed crystals are based on the imide rather than on the amide.

With the alkaline earth compounds, the transformation of the mixed crystals into the imides occurs without the appearance of a new phase but with an increase in volume. Evidently, here the filling of the interstices is more important than the replacement of the amide ions by the smaller imide ions.

The magnesium amide/magnesium imide system [14] behaves crystallographically in a different manner. Amide/imide mixed crystals are again formed on thermal degradation of the amide, but other structures appear.

Since the chemical and physical properties of the amides and hydroxides have much in common, similar relationships should exist for *oxides* and *imides*. In the ammonia system, imides correspond to oxides in the aqueous system.

The imides react with ammonia at elevated temperature to form amides. The latter are not very resistant toward air and moisture, and the imides react explosively with water. Lithium nitride and the alkaline earth nitrides are much less sensitive.

One notable difference between oxides and imides is to be found in their colors. The alkaline earth oxides are all white, but magnesium imide is pale yellow. The yellow color deepens progressively in the order MgNH $<$ CaNH $<$ SrNH $<$ BaNH, barium imide being deep ochre.

[48] *O. Ruff* and *F. Georges*, Ber. dtsch. chem. Ges. *44*, 504 (1911).
[49] *R. Juza* and *K. Opp*, Z. anorg. allg. Chem. *266*, 325 (1951).

Both oxides and imides have simple crystal structures. Lithium imide [49] crystallizes in the cubic antifluorite lattice, and is isotypic with lithium oxide. Calcium, strontium, and barium imides [13], like the corresponding oxides, crystallize in the sodium chloride lattice.

Table 2. Phases occurring on thermolysis of $LiNH_2$, $Ca(NH_2)_2$, and $LiMg(NH_2)_3$.

| Compound | Cations in | | Anions | Structure [*] |
|---|---|---|---|---|
| A. Lithium amide degradation | | | | |
| | Tetrahedral interstices | | | |
| $LiNH_2$ | $2\times$ {$Li_4$ | $\square_4$ | $(NH_2)_4$} | $\overline{LiNH_2}$ |
| $LiNH_2/Li_2NH$-mixed crystal | $2\times$ {$Li_4$ | $Li_1\square_3$ | $(NH_2)_3(NH)_1$} | $\overline{LiNH_2}$ |
| $Li_2NH$ | $Li_4$ | $Li_4$ | $(NH)_4$ | $CaF_2$ |
| B. Calcium amide degradation | | | | |
| | Octahedral interstices | | | |
| $Ca(NH_2)_2$ | $2\times$ {$Ca_2$ | $\square_2$ | $(NH_2)_4$} | Anatase ($TiO_2$) |
| $Ca(NH_2)_2/CaNH$-mixed crystal | $Ca_{3.5}$ | $\square_{0.5}$ | $(NH_2)(NH)_3$ | $\overline{NaCl}$ |
| $CaNH$ | $Ca_4$ | | $(NH)_4$ | $NaCl$ |
| C. Lithium magnesium amide degradation | | | | |
| | Tetrahedral interstices | | | |
| $LiMg(NH_2)_3$ | $Li_{4/3}$ | $Mg_{4/3}\square_{4/3}\square_4$ | $(NH_2)_4$ | $Mg(NH_2)_2$ |
| $Li_2Mg_2(NH)_3$ | $2\times$ {$Li_{8/3}$ | $Mg_{4/3}$ $Mg_{4/3}\square_{8/3}$ | $(NH)_4$} | $LiNH_2$ |
| $LiMgN$ | $Li_4$ | $Mg_4$ | $N_4$ | $CaF_2$ |

[*] $\overline{LiNH_2}$; $\overline{NaCl}$ indicate deformed lattices with a certain breadth of phase boundary. $CaF_2$ indicates the antifluorite lattice.

$\square$ indicates vacant tetrahedral or octahedral interstices in the anion lattice.

The $NH^{2-}$ ion is isoelectronic with the $O^{2-}$ ion but, like $NH_2^-$, it must be regarded as dipole ion. Neutron diffraction experiments on calcium imide [50] have shown that the protons in the crystal are probably free to rotate about the nitrogen atom. It is possible that fixation of the $NH^{2-}$ dipole occurs in magnesium imide, which has a complicated crystal structure [14].

The enthalpies of formation and lattice energies of the imides of Ca, Sr, and Ba have been calculated [51]. Since the compounds are isotypic, the oxides with their comparatively small $O^{2-}$ ions have the greatest lattice energies, the imides have lower lattice energies, and the sulfides the lowest.

## 8. Ternary Amides and Imides

Ternary amides of the alkali and alkaline earth metals have been known for a long time in addition to the binary amides and imides.

Some of the alkaline earth metals react only very slowly with liquid ammonia to form the corresponding amides. If a solution of an alkali metal amide is added, *e.g.* $KNH_2$, then the reaction

$$2\,KNH_2 + Mg \rightarrow Mg(NH_2)_2 + 2\,K$$

occurs rapidly. The alkali metal dissolved in the ammonia can be readily detected, but its quantitative separation is hardly possible since it reacts further to reform the amide. Only rarely two separate amides are the end-products; in general, ternary amidometalates are formed, *e.g.* $BeNK\cdot 2\,NH_3$, $Mg(NHK)_2\cdot 2NH_3$, $CaNK\cdot 2\,NH_3$, $SrNK\cdot 2\,NH_3$, and $BaNK\cdot 2\,NH_3$. These metathetical reactions have been the subject of some earlier papers [52–54].

These ternary compounds used to be formulated as the ammoniates of ternary nitrides or imides, *e.g.* $BeNK\cdot 2\,NH_3$, but it is probable that they are in fact ternary amides. It cannot yet be decided whether the compounds should be represented as "double amides", *e.g.* $KBe(NH_2)_3$, or as complexes, *e.g.* $K[Be(NH_2)_3]$, potassium triamidoberyllate.

In one solitary case it has been possible to confirm the formation of a ternary compound. During the preparation of the ternary nitride LiMgN [55], it was observed that LiMgN can take up ammonia; the problem was then to decide whether the ammoniate of a ternary nitride, a ternary amide, or a ternary imide, is formed. It was found that a *lithium magnesium amide* [14], written as $LiMgN\cdot 2\,NH_3$ according to the old mode of formulation, was formed from lithium and magnesium in liquid ammonia and also during the reaction of LiMgN or of a stoichiometric $Li_3N/Mg_3N_2$ mixture at higher temperatures (350 °C) and elevated pressures of ammonia (10 atmospheres). The X-ray diagram of $LiMg(NH_2)_3$ is identical with that of $Mg(NH_2)_2$ if slight differences in intensity are disregarded. From experiments with varied Li:Mg ratios it appears that $LiMg(NH_2)_3$ is the terminal member of a series of mixed crystals starting with $Mg(NH_2)_2$. The fact that lithium and magnesium can replace each other corresponds to the similarity of their ionic radii. Since magnesium amide, whose complicated structure is still

[50] *M. J. Kay* and *A. F. Andresen*, Acta crystallogr. *13*, 1087 (1960).

[51] *A. P. Altshuller*, J. chem. Physics *23*, 1561 (1955).

[52] *E. C. Franklin*, *e.g.* in J. Amer. chem. Soc. *48*, 2848 (1926).

[53] *F. W. Bergstrom*, *e.g.* in J. Amer. chem. Soc. *50*, 652 (1928).

[54] *F. W. Bergstrom* and *W. C. Fernelius*, Chem. Reviews *12*, 43 (1933); *20*, 413 (1937); *R. Levine* and *W. C. Fernelius*, ibid. 54, 449 (1954).

[55] *R. Juza* and *F. Hund*, Z. anorg. allg. Chem. *257*, 1 (1948).

unknown, assumes a coordination number of 4 according to molecular volume considerations, filling of the tetrahedral interstices is indicated in Scheme C of Table 2, but no precise information on this aspect is as yet available.

Lithium magnesium amide can be degraded isothermally, reversible pressure equilibria being established. The end-product of the thermal decomposition is a new phase with the composition $LiMgN \cdot {}^1/_2\ NH_3$, which is a *lithium magnesium imide* [56] of formula $Li_2Mg_2(NH)_3$ and which is isotypic with lithium amide. When the composition deviates from the 1:1 cation ratio, X-ray reflections due to either MgNH or $Li_2NH$ appear in addition to those of the ternary imide. Accordingly, the ternary imide phase has a limited range of stability.

As shown in Table 2, the substances discussed in Sections 7 and 8 are characterized by extraordinary mutual interchangeability of their ions. During the degradation of lithium and calcium amides, $NH_2^-$ and $NH^{2-}$ ions are found together at anionic positions and one kind of metallic ions or vacancies at the cationic sites. In the ternary compounds, the anionic positions are occupied by one kind of anion, while the cationic sites are occupied by two different metallic ions or remain empty. Occupation of the lattice sites is partly ordered and partly random.

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Translated by Express Translation Service, London

[56] *R. Juza* and *E. Eberius*, Naturwissenschaften *49*, 104 (1962).

# The Chemical Composition of the Stars [*]

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*The abundances of the elements in the atmospheres, i.e. the directly observable layers, of the stars are related to the energy production by nuclear processes in the interior of the stars and to their evolutionary states. For purposes of quantitative analysis of a given stellar spectrum, several "model atmospheres" are first calculated, assuming tentative numerical values for the effective temperature $T_e$, for the gravitational acceleration g at the surface of the star, and for the relative abundances of the more important elements. The appropriate temperature distribution is obtained from the theory of radiative equilibrium in conjunction with the quantum theory of the continuous absorption coefficient; the pressure stratification is obtained from the hydrostatic equation. Evaluation of the Fraunhofer lines requires a theory of line absorption coefficients and line widths. In conclusion, the final numerical values for $T_e$, g, and the abundances of the elements in the stellar atmosphere are determined by comparison of the calculated spectra with the measured spectrum of the star. The main sequence stars and the hot supergiants, i.e. the star population I of the spiral arms and the disk population of the Milky Way, all have the same chemical composition, which coincides with that of the interstellar medium. In the old population II stars of the galactic halo (high velocity stars, subdwarfs), on the other hand, the abundance of all the heavy elements relative to that of hydrogen is reduced by a factor of as high as 200, possibly even 500; hydrogen seems to be the original material of our Milky Way. In helium stars, almost all the hydrogen has been transformed into helium even in the atmosphere; it is likely that these are well mixed stars.*

## I. Introduction [1]

Qualitative identification of many elements in the atmospheres of the sun and the stars was made possible by the laws of spectral analysis discovered by *Kirchhoff* and *Bunsen* in 1859. In addition, the relationship discovered by *Kirchhoff* and named after him between the emission and absorption of radiation under conditions of thermodynamic equilibrium became one of the most important

[*] Adapted from the Anniversary Address at the General Meeting of the Gesellschaft Deutscher Chemiker on Sept. 11th, 1963 in Heidelberg (Germany).

[1] The following publications can serve as a further introduction to the subject matter treated here:

*O. Struve, B. Lynds*, and *H. Pillans:* Elementary Astronomy. Oxford University Press, 1959.

*S. v. Hoerner* and *K. Schaifers:* Meyers Handbuch über das Weltall. Bibliographisches Institut, Mannheim 1961.

Comprehensive reviews with extensive literature references:

*L. H. Aller:* The Abundance of the Elements. Interscience, New York 1961.

*E. M. Burbidge, G. R. Burbidge, W. A. Fowler*, and *F. Hoyle:* Synthesis of the Elements in Stars. Rev. mod. Physics *29*, 547 (1957).

*B. M. Glennon* and *W. L. Wiese:* Bibliography on Atomic Transition Probabilities. National Bureau of Standards, Washington 1962.

Handbuch der Physik. Springer, Heidelberg 1958, Vol. 51, inter alia: *E. M. Burbidge* and *G. R. Burbidge*, Stellar Evolution; *H. E.*

fundamentals for the quantitative analysis of solar and stellar spectra. However, fruitful application of these discoveries to astrophysics came only after the twenties, when quantum theory provided deeper insight into the relationships between atomic structure and spectral lines and thus led to a better understanding of the behavior and radiation of matter under cosmic conditions.

The modern theory of stellar spectra began in 1920 with *Saha*'s theory of thermal ionization. Quantitative analysis of cosmic spectra was developed in the next two decades, following the work of *K. Schwarzschild*, *Eddington*, and *Russell*. An exciting feature of this development is the fact that the abundances of the chemical elements in the various stellar atmospheres (*i.e.* in the directly observable stellar layers) can be related to recent concepts concerning the energy production in stellar interiors by nuclear processes. Hence, our data can also be applied to problems of stellar evolution, primarily in connection with the relationship between nuclear reactions and the abundance of the lighter elements. However, the heavy elements are also involved, since the arguments for abandoning the long popular "Big Bang" theory are becoming more and more convincing, and the newer theories assume the creation of the heavy elements to take place during specific phases of stellar evolution. It thus appears fitting to preface our actual subject with some remarks concerning the evolution of stars and of the Milky Way.

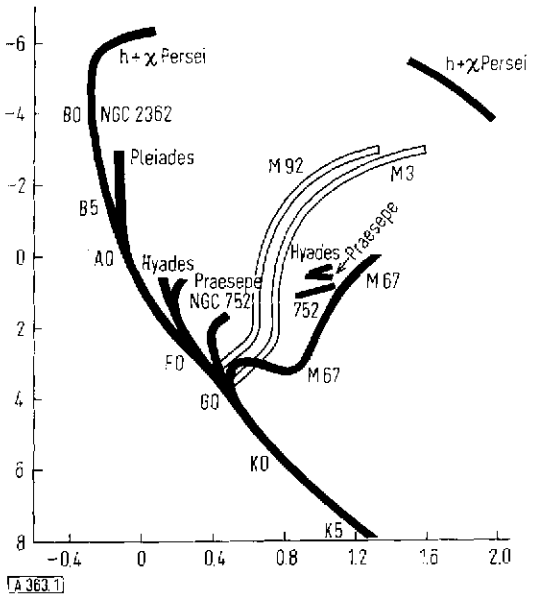



Fig. 1. Color-magnitude diagrams or Hertzsprung-Russell diagrams of the galactic star cluster h + χ Persei, NGC 2362, Pleiades, Hyades, Praesepe, NGC 752, M 67, as well as of the globular star clusters M 92 and M 3 (after [2]).

Abscissa: Color index B—V.

Ordinate: Absolute visual brightness $M_V$ (based on a distance of 10 parsec = 32.6 light years).

The spectral types S are indicated along the main sequence. The position at which the diagram of a cluster deviates towards the right from the main sequence characterizes its age. The age is only 3 million years for h + χ Persei and about 10 billion years for the oldest galactic star clusters, *e.g.* M 67 and the globular star clusters (which belong to the galactic halo).

## 1. Evolution of Stars

According to present-day concepts, the life of a star proceeds approximately as follows: Interstellar matter with a density of approx. $10^{-23}$ g/cm$^3$ gradually forms a cloud with a mass exceeding that of the sun by a factor of several hundred to thousand. This cloud then breaks up, and further localized condensation yields numerous stars, a so-called stellar association or star cluster. The evolution of these stars may be followed on the Hertzsprung-Russell diagram or its equivalent, the color-magnitude diagram (Figure 1). In such a diagram, the abscissa indicates the spectral type (color index) or temperature of the star, and the ordinate gives either its absolute brightness (based on a distance of 10 parsec = 32.6 light years) or luminosity (based on that of the sun). The changes occurring during the life-time of a star are recorded in this diagram: A young star begins on the right as a distended cool mass which heats up moving to the left during its contraction phase. Contracting stars are apparently quite unstable, like the rapidly varying T Tauri and RW Aurigae stars. The atmospheres of the latter show evidence of powerful eruptions, so-called flares, perhaps involving nuclear reactions due to high-energy particles.

At the end of a 20-million-year contraction process, a star with a mass equivalent to that of the sun is compressed to such an extent that the temperature in its interior reaches some $10^7$ °K, and the transformation of hydrogen to helium begins. In smaller stars (up to a mass slightly larger than that of the sun), this conversion proceeds by direct fusion; in heavier stars with somewhat higher central temperatures, it proceeds by the nuclear reaction cycle discovered by *Bethe* and *von Weizsäcker* in 1938:

$$^{12}C(p,\gamma)^{13}N(\beta^+\nu)^{13}C(p,\gamma)^{14}N(p,\gamma)^{15}O(\beta^+\nu)^{15}N(p,\alpha)^{12}C$$

which uses carbon and nitrogen as catalysts, so to speak. The star is now located on the main sequence of the Hertzsprung-Russell diagram. It remains there in a quasi-steady state until about 10 % of its hydrogen is fused to helium. With cooler stars (whose temperatures are, at the most, slightly higher than that of the sun), this process takes longer than the entire "history of the world" (astronomically speaking, *i.e.* about 10 billion years). On the other hand, hot stars burn their hydrogen very rapidly; *e.g.* the well-known blue stars in Orion were formed at a time at which our oldest ancestors just prepared to come down from the trees.

*Suess* and *H. C. Urey:* Die Häufigkeit der Elemente in Planeten und Meteoriten; *L. H. Aller*, The Abundances of the Elements in the Sun and Stars.

*P. W. Merrill:* Lines of the Chemical Elements in Astronomical Spectra. Carnegie Institution of Washington, 1956.

*J. L. Greenstein:* Stellar Atmospheres (Stars and Stellar Systems, Vol. VI). University of Chicago Press, 1960.

*G. Traving:* Über die Theorie der Druckverbreiterung von Spektrallinien. G. Braun, Karlsruhe 1960.

*A. Unsöld:* Physik der Sternatmosphären. 2nd Edit., Springer, Heidelberg 1955.

*V. Weidemann:* The Atmosphere of the White Dwarf van Maanen 2. Astrophys. J. *131*, 638 (1960).

*V. Weidemann:* Effektive Temperatur und Schwerebeschleunigung der Weißen Zwerge. Z. Astrophysik *57*, 87 (1963).

[2] *H. L. Johnson* and *A. R. Sandage*, Astrophys. J. *121*, 616 (1955).

At the end of this period, *i.e.* after about 10 % of its hydrogen is used up, the further development of a star depends critically on whether the burned-out matter in its interior is steadily mixed with fresh material, or whether it remains in the innermost region as a burned-out helium core. Mixing of stellar material takes place only in exceptional cases; a helium core is the rule. In the latter case, the shell in which the energy production by nuclear processes is going on in the star spreads outwards from the center; the star expands and becomes a red giant, located in the upper right portion of the Hertzsprung-Russell diagram. What happens beyond this stage has not yet been sufficiently studied. Later on the process of formation of heavy 4n-nuclei $^{12}C$, $^{16}O$, *etc.* from $^{4}He$ at even higher temperatures probably becomes the principal factor in energy supply.

The abundance distribution indicates that at some stage heavy elements may also be formed; this might occur during catastrophic processes (supernovae?) and would involve large numbers of free neutrons. During such a catastrophic process, the star gives back an appreciable portion of its material to the interstellar gas; this material has, of course, been chemically changed by the nuclear reactions. More is known about the next stage of stellar evolution; the star finally ends up as a white dwarf consisting of degenerate matter (mostly helium) of enormous density.

### 2. Evolution of the Milky Way

The evolution of stars takes place as part of the overall development of the galactic system (Figure 2). Our galaxy started – as we shall show later – as an almost spherical cloud of hydrogen, which then produced the first stars; these consisted of almost pure hydrogen.

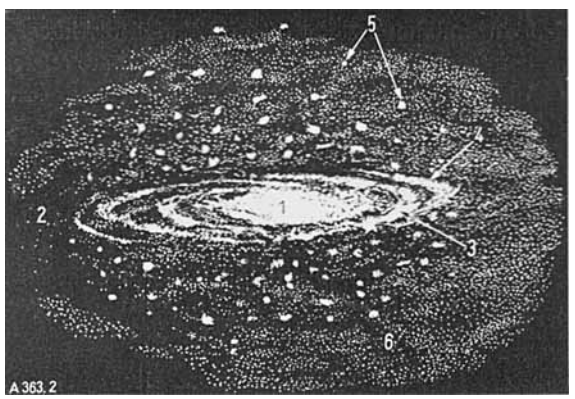



Fig. 2. Schematic diagram of the structure and population groups of the Milky Way (after [3]).
1: Nucleus; 2: disk; 3: galactic star cluster; 4: spiral arms; 5: globular star cluster; 6: halo.

These oldest stars – insofar as they still exist – constitute the Milky Way halo; they move around the galactic center in highly elliptical orbits and are recognizable as the so-called high-velocity stars and subdwarfs. The galactic disk, whose stars now execute almost circular orbits around the galactic center, was formed simultaneously with the first stellar generations, *i.e.* during a period in which more and more hydrogen was converted into helium and heavy elements; it is perpendicular to the axis of rotation of the original Milky Way. The old stars, including our sun, have all practically identical chemical compositions, namely that of the present-day interstellar gas from which they did in fact originate. Accumulations of this gas in the galactic disk later produced the spiral arms of the Milky Way. Exactly how this occurred remains a very difficult problem of magnetohydrodynamics. In these spiral arms we find *inter alia* young, bright blue stars of high mass (O and B stars), whose age cannot exceed one to ten million years, if only for reasons of energy supply.

We thus see that the various parts of our Milky Way are populated by stars of different ages and – as we would anticipate – of different chemical compositions. We speak of different star populations, of the halo population II, the disk population, and the extreme population I of the spiral arms. The classification of stellar populations by *W. Baade* was probably one of the most important discoveries of modern astronomy.

## II. Quantitative Analysis of Stellar Spectra

### 1. Observational Data; Profiles and Equivalent Widths of the Fraunhofer Lines

The spectrum of the sun can be recorded at high dispersion and a resolving power of $\lambda/\Delta\lambda \approx 10^6$. The observatories in Utrecht (Holland), Ann Arbor (Michigan, U.S.A.), Göttingen (Germany), and elsewhere have prepared photometric atlases (Figure 3), from which the intensity distribution in the lines, *i.e.* the line profiles,

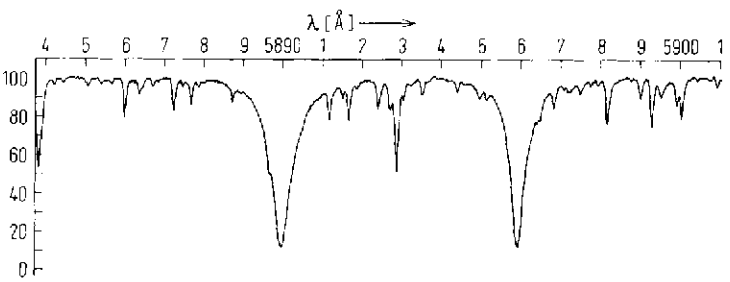



Fig. 3. Utrecht photometric atlas of the solar spectrum; sodium D-lines $\lambda$ = 5889.96 and 5895.93 Å.

can be obtained. However, while any line profile is a very sensitive function of the resolving power of the spectrograph, the energy absorbed in the line is independent thereof. It is therefore advantageous, particularly for stellar spectra of small dispersion, to measure the equivalent width $W_\lambda$ (Figure 4). The latter gives the width (in angstroms or milliangstroms) of a rectangular strip in the spectrum whose area, as a measure of the absorbed energy, is equal to that of the line profile.

The largest reflecting telescopes and spectrographs are just sufficient for obtaining suitable stellar spectra. Thanks to the cooperation of American colleagues, I was able to make use of excellent telescopes and spectrographs in American

[3] *A. Unsöld*, Naturwissenschaften *47*, 76 (1960).

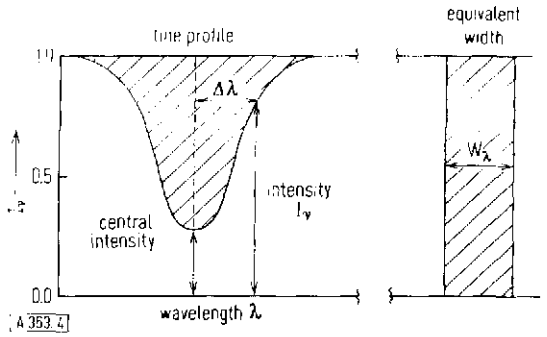



Fig. 4. Profile and equivalent width $W_\lambda$ of a Fraunhofer line.

observatories. With the 100-inch Hooker telescope of the Mount Wilson Observatory at Pasadena, Calif., one can obtain satisfactory spectra of 7th magnitude stars, *i.e.* stars just below the limit of visibility of the naked eye, in the photographic region ($\lambda$ = 3200–4900 Å) with a dispersion of 10 Å/mm and in the visual region ($\lambda$ = 4800–6800 Å) with 15 Å/mm. It is often also useful to take infrared spectra up to $\lambda \approx 8800$ Å. All the plates used are of course provided with photometric density scales so that the profiles or equivalent widths of the lines can be measured (this is best done with a directly recording microphotometer). For example, one of our recent investigations, the analysis of the A2-supergiant α Cygni (by *H. G. Groth*), is based on the measurement of some 800 lines.

## 2. Physics of Stellar Atmospheres

Measurements such as those described above serve as a basis for the determination of the parameters which characterize the atmosphere of a given star. These parameters include the effective temperature $T_e$, which is defined in conformity with the Stefan-Boltzmann radiation law, the radiant energy flux per cm² of the stellar surface being $\pi F = \sigma T_e^4$. Another essential quantity is the gravitational acceleration g (cm/sec²) at the surface of the star [4]. Last, but not least we want to determine the chemical composition of the stellar atmosphere, *i.e.* the abundance of all the elements.

It is readily appreciated that $T_e$, g, and the abundance of the elements completely determine the structure, *i.e.* the temperature and pressure distribution, of a static atmosphere. If we are dealing with stars of uniform composition, the theory of the internal constitution of the stars further requires the existence of a relationship between their mass, their luminosity, and $T_e$, *Eddington*'s well known mass-luminosity relation. If such a relationship exists, then $T_e$ and g are also related in a simple manner to the two parameters of the Hertzsprung-Russell diagram, namely $T_e$ and the luminosity L (or the absolute brightness $M_v$). For stars with the same effective temperature $T_e$, the gravitational acceleration g is related to the mass M and the radius R of the star in a simple manner. On the other hand, the luminosity L (or the absolute magnitude $M_v$) depends only on the size of the star, *i.e.* on its radius R. By using the mass-luminosity relation, we can calculate (again for stars of the same effective temperature $T_e$) the relationship between g and L (or $M_v$). Thus, $T_e$ and g determine the position of the star on the Hertzsprung-Russell diagram or – in other words – its spectral type S and its luminosity class LC. These two parameters are used in the classification of stellar spectra, for example, in the well known Morgan and Keenan classification.

However, a two-parameter classification of stellar spectra does not suffice for all stars. Apart from differences in chemical composition, we must also take into account turbulent motions, magnetic fields, rapid rotation, and possibly even further quantities, all of which must be derived from the same observational material.

The complexity of the task suggests use of a method of successive approximation. Our first question is thus: what type of spectrum (equivalent widths, intensity distribution in the continuum) would be given by an atmosphere of proposed $T_e$, g, and fixed chemical composition, according to theory? In other words, we calculate a so-called model atmosphere. We then investigate how the measured quantities (*e.g.* the $W_\lambda$ of some of the elements) and the various stages of ionization fit our calculations. Finally, the parameters are revised until as good an agreement as possible is achieved between the model atmosphere and the measured spectrum. These cumbersome calculations are greatly facilitated nowadays by electronic computers.

The temperature distribution in a stellar atmosphere is determined by the nature of the energy transfer. *K. Schwarzschild* recognized in 1905 that in stellar atmospheres energy is transported primarily by radiation; we speak of radiative equilibrium. The mathematical problem involved is simple, provided the continuous absorption coefficient $\varkappa$ is independent of frequency or can be replaced by a mean value taken over the entire spectrum – the so-called Rosseland opacity coefficient $\bar{\varkappa}$. Unfortunately, however, this approximation is mostly insufficient, and one is forced to solve an infinite system of differential or integral equations, one for each frequency; the latter are related by an integral relation expressing the constancy of the total radiative flux, *i.e.* the conservation of energy.

Several atomic processes affect the continuous absorption coefficient $\varkappa$ (Figures 5 and 6), including

1. bound-free and free-free transitions of hydrogen atoms (particularly in hot stars);

2. bound-free and free-free transitions of the negative hydrogen ions $H^-$ (in cooler stars).

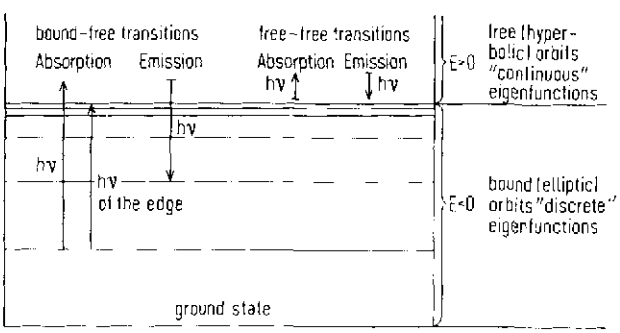



Fig. 5. Formation of continuous atomic spectra. Bound-free and free-free transitions.

[4] We can calculate the effective temperature $T_e$ for the sun directly from the solar constant, and its gravitational accelleration g from its mass and radius, and obtain $T_e$ = 5780 °K and g = $2.74 \times 10^4$ cm/sec², *i.e.* 28 times the gravitational acceleration at the earth's surface.

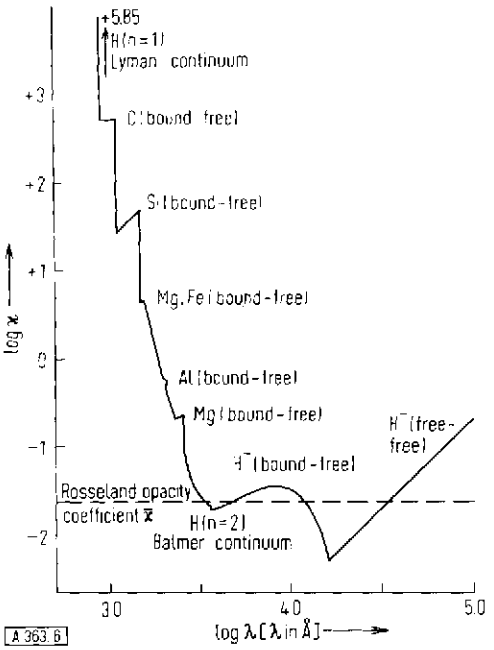



Fig. 6. Continuous absorption coefficient $\varkappa$ per gram of solar matter at $T = 5040\,^{\circ}K$ ($\Theta = 1$) and $\log P_e = 0.5$, or $P_e = 3.16$ dynes/cm² (after [5]).

In addition, smaller but still not negligible contributions are due to continuous absorption by HeI and HeII (in hot stars) and by metals (in cooler stars), and to the scattering of light by free electrons (Thomson scattering; in hot stars) and by neutral hydrogen atoms (cooler stars). Our knowledge concerning the continuous spectra of molecules in cooler stars is still rather scant.

The type of relationship existing between the elementary processes of absorption and emission is crucial for calculating the energy transfer by radiation. To start these calculations, one tries to get along with Kirchhoff's law, *i.e.* one assumes local thermodynamic equilibrium, although – strictly speaking – the existence of a radiative flux is, of course, not compatible with thermal equilibrium. In order to justify this approximation theoretically, one would have to prove that the relaxation times of all essential elementary processes are sufficiently short. So far, this has been possible only for the $H^-$-absorption prevailing in cooler stars, *e.g.* the sun. To begin with, it can be shown that despite deviation of the radiation field from Planck's formula, the electrons and heavy particles possess a Maxwellian velocity distribution, which we may then use for defining a "local temperature". Negative hydrogen ions are formed primarily by the process of "associative detachment" (*Dalgarno, Pagel*):

$$H + H^- \rightleftharpoons H_2 + e^-$$

Finally, the $H_2$ molecules, which are important despite their low concentration, are formed by three-body collisions of the many H atoms present. In this manner, local thermodynamic equilibrium is assured.

Similar theoretical treatment may also be applied to the ionization of the atoms. On the other hand, with regard to the occupation numbers of excited states (relative to the ground state), we must still content ourselves with verification of the assumption of local thermodynamic equilibrium by means of observational data.

In addition to radiative energy transfer, transport by convection plays an important role in somewhat deeper layers of cooler stellar atmospheres. Convection currents arise in the zones where the atomic hydrogen is partly ionized. If in such a hydrogen-convection zone, for example, in the solar atmosphere, a partly ionized volume element rises to cooler regions and the hydrogen recombines via the reaction $H^+ + e^- \rightarrow H$, the heat of recombination (which corresponds to about 25 kT!) is liberated, so that the temperature of the volume element remains higher than that of the surroundings. It therefore continues to rise – like a hot air balloon – and a convection current is set into motion. Incidentally, this hydrogen convection zone is essentially the cause not only of the granulation of the solar surface, but also of sunspots, of the phenomena of solar activity, and thus also of the hyperthermal phenomena (radio frequency radiation, cosmic rays) of the "disturbed sun".

A small portion of the energy flux of the sun is also emitted by the upper layers of the convection zone in the form of sonic, shock, and other waves. Slightly higher up, the dissipated energy can no longer be radiated away because the density of the matter is small. This in turn results in heating of the solar corona to the enormous temperature of about one million degrees. Similar processes probably occur to a significant degree in the outermost layers of the other cool stars.

In high temperature supergiants, *e.g.* $\alpha$ Cygni, 55 Cygni, we also encounter energy transfer through irregular oscillations of the entire star mass, a movement which in the stellar atmosphere assumes more or less the character of shock waves.

The motions in stellar atmospheres are important in our considerations, not so much because of their contribution to the energy transport as because of their direct effect on the line spectrum. We shall discuss this phenomenon later.

The calculation of the pressure distribution is much simpler than that of the temperature distribution. The increase in gas pressure $P_g$ with depth t of the stellar atmosphere can usually be computed by means of the hydrostatic equation

$$dP_g/dt = -g\rho$$

where $\rho$ is the density, and g is again the gravitational acceleration. In hot stars, we must also take the radiation pressure into account, in addition to the gas pressure. The dynamic pressure of turbulent motions is of importance in some stars. In sunspots and Ap stars, where magnetic fields of several thousand gauss exist, we must also take into account the forces generated by these fields.

For the calculation of model stellar atmospheres, extensive tables listing various data as functions of the temperature T and the electron pressure $P_e$ are of vast help. Thus, given a mixture of elements for a particular model, one is able to obtain directly from these tables the gas pressure $P_g$, the mean molecular weight $\mu$, the continuous absorption coefficients $\varkappa$ for many frequencies and their Rosseland mean value $\bar{\varkappa}$, the specific heats $c_p$ and $c_v$, as well as other thermodynamic quantities.

### 3. Quantitative Theory of Fraunhofer Lines

In practice, the problem of radiative energy transfer can be treated also for spectral lines to a considerable extent by assuming local thermodynamic equilibrium,

[5] *G. Bode*, Ph. D. Thesis, Universität Kiel 1964.

*i.e.* by applying Kirchhoff's law. An approximation, which in the limiting case reduces to local thermodynamic equilibrium, is favored precisely by the enormous variety of elementary processes possible (consider for example, the crowded energy level diagram of the iron atom). On the other hand, explicit justification of this approximation by means of kinetic calculations is so complicated that despite tremendous efforts, the calculations of theoreticians have so far produced only meager results.

If, for example, the center of the solar disk emits radiation of frequency $\nu$, its intensity $I_\nu$ in a line can be calculated by the following procedure: The emission of radiation in a layer of thickness dt, situated at a depth t, is proportional to both the Kirchoff-Planck function $B_\nu(T)$, where T is the prevailing local temperature, and the absorption coefficient, which is composed of a continuous component $\varkappa$ and of the specific line absorption coefficient $\varkappa_\nu$ for the frequency $\nu$. Up to the point where it leaves the stellar atmosphere, the intensity of the emitted radiation $(\varkappa + \varkappa_\nu)B_\nu(T)$ is reduced by an absorption factor $e^{-\tau_\nu}$, where $\tau_\nu = \int(\varkappa + \varkappa_\nu)dt$ is the so-called optical depth (for continuous absorption plus line absorption). Thus, we finally obtain an important relationship for the observed intensity distribution $I_\nu$ in a Fraunhofer absorption line:

$$I_\nu = \int_0^\infty B_\nu[T(\tau_\nu)]\, e^{-\tau_\nu} d\tau_\nu$$

This expression forms the basis for the evaluation, *e.g.* of the Utrecht photometric atlas.

The pure continuum, which is the basis of the measurements, is obtained simply by neglecting the line absorption coefficient $\varkappa_\nu$. Our formula shows that if $\varkappa$ and $\varkappa_\nu$ are the same functions of depth, then the continuum and the wings of the lines originate mainly at an optical depth of $\tau_\nu \approx 1$. On the sun, however, the concentration of the neutral metal atoms, such as FeI, TiI, decreases so rapidly with depth in the atmosphere (owing to increased ionization) that their Fraunhofer lines, which dominate the spectrum, are mainly formed at optical depths of 0.05 to 0.1 only.

Calculation of the line absorption coefficient $\varkappa_\nu$ (per atom of the element, for example) as a function of the temperature T, electron pressure $P_e$ (or gas pressure $P_g$), and the distance from the line center ($\Delta\nu$ in frequency units or $\Delta\lambda$ in wavelength units) is not quite as simple. The following effects contribute to the line absorption coefficient (Figure 7):

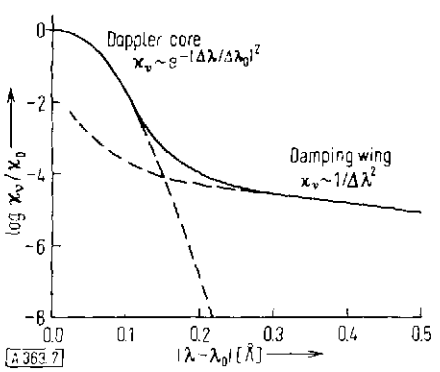



Fig. 7. Line absorption coefficient $\varkappa_\nu$ (referred to $\varkappa_0$ for the line center). Doppler core and damping wings of the sodium D-lines, calculated for T = 5700 °K and pure radiation damping.

1. The Doppler effect due to thermal velocities of particles and turbulent motions. The thermal velocities of, for example, the Fe atoms in the solar atmosphere ($T \approx 5700$ °K) amount to 1.3 km/sec, corresponding to a Doppler width $\Delta\lambda_D = 0.017$ Å in the line at $\lambda = 3860$ Å. The Doppler distribution of the line absorption coefficient, corresponding to the Maxwell velocity distribution of the atoms, is $\varkappa_\nu \sim \exp-(\Delta\lambda/\Delta\lambda_D)^2$. Turbulent motions usually give rise to similar velocities.

2. Damping. Radiation damping is always present, and in addition – at somewhat higher pressures – there is collision damping. Both effects are based on the fact that (in the language of classical theory) a sine-wave train emitted by an atom has a limited length or time of duration due to emission by the atoms themselves and possibly also to perturbations by collisions with other particles. The spectral analysis of such a wave train necessarily produces a line having a finite width in the frequency or wavelength scale. In a largely ionized gas, collisions with free electrons are an important factor; in cooler stars, line-broadening collisions with neutral H atoms usually predominate. The actual damping width is always considerably smaller than the Doppler width, but for damping in the line wings, the absorption coefficient decreases only $\sim 1/(\Delta\lambda)^2$, where $\Delta\lambda$ = distance from the line center. In effect, damping thus always predominates over the Doppler effect in the line wings (Figure 7).

The absolute magnitude of the absorption coefficient is always normalized by the quantum theoretical relationship

$$\int \varkappa_\nu d\nu = (\pi e^2/mc) \cdot N \cdot f$$

In this equation, e and m are the charge and mass of the electron, respectively, c is the velocity of light, N the number of atoms in the absorbing quantum state, and f the oscillator strength. The oscillator strengths f used here are proportional to the well-known Einstein transition probabilities. Since analysis of a spectrum thus always yields the number of atoms N only in terms of the combination N·f, the determination of exact oscillator strengths is one of the most important and complicated problems for the astrophysicist.

a) For hydrogen and HeII, the f values can be calculated exactly from quantum theoretical considerations.

b) *Bates* and *Damgaard* have developed a very useful approximation method for more or less hydrogen-like spectra (in particular, for systems with 1, 2, or 3 outer electrons).

c) For the spectra of ions and atoms with several outer electrons, so-called complex spectra, one can start by making relative measurements of line emission (*e.g.* in an electric arc or a King furnace) or absorption (King furnace) and calibrate them by measuring the absolute f values for a few selected lines of the atom or ion. The main difficulty lies in the problem of measuring directly the number of absorbing or emitting atoms. For example, a sample can be placed in a sealed quartz absorption tube in the electric furnace. Numbers of atoms have also been determined in electric arcs and in atomic beams. Most recently, direct electronic measure-

ments of the decay constants of single atomic states and hence also of transition probabilities have been accomplished. It is to be hoped that this method -- which no longer requires determination of the number of particles – will also allow measurements of transition probabilities in ionized atoms, which so far have completely eluded experimental approach.

Let us now examine the manner in which the profile or equivalent width $W_\lambda$ of a Fraunhofer line increases with the concentration of the emitting atoms N [or their product with f and with the statistical weight g of the lower atomic state, which always enters as a factor] (Figure 8). As already mentioned, in the inner part of

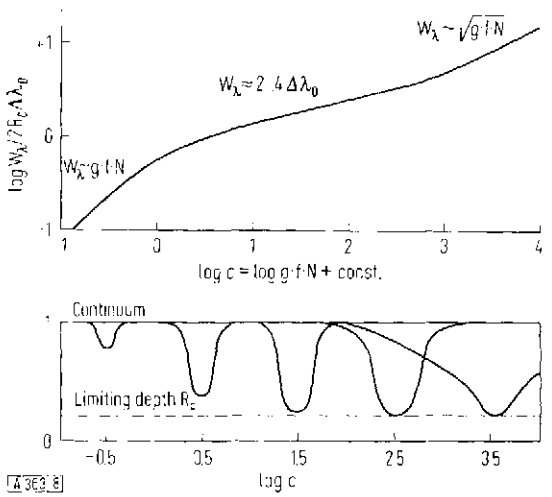



Fig. 8. Curve of growth. The equivalent width $W_\lambda$ – referred to a strip having twice the Doppler width $\Delta\lambda_D$ and a depth $R_c$ – is plotted as a function of the concentration of the absorbing atoms, *i.e.* of log (g·f·N) + const.

It was assumed that the continuous and the line absorptions depend upon depth in the atmosphere in the same way, and that the damping width is $^1/_{50}$th of the Doppler width.

The line profiles (below) illustrate the formation of the curve of growth.

the lines, the absorption coefficient is determined by the Doppler effect; further out toward the edges of the line are the damping wings, in which the damping constants $\gamma$ are determined by radiation and collision damping. Thus, we obtain the curve of growth which is very important for the evaluation of stellar spectra: Weak lines simply reflect the Doppler distribution of the absorption coefficient $\varkappa_\nu \sim \exp-(\Delta\lambda/\Delta\lambda_D)^2$ at the line center, and $W_\lambda$ is obviously proportional to g·f·N. With increasing g·f·N, the line center attains a maximum depth $R_c$. The reason for this is that the radiation received is only emitted by the uppermost layers, whose temperature (according to the theory of radiative equilibrium) approaches a certain limiting value. In addition, the line broadening by damping is not very pronounced at first; we thus obtain relatively sharp, deep lines and the curve of growth becomes rather flat.

This behavior changes only when g·f·N increases still further, *i.e.* when the line broadens into the damping wings. There the line absorption coefficient is $\varkappa_\nu \sim g \cdot f \cdot N \cdot \gamma/(\Delta\lambda)^2$. It follows that, at a fixed depth in the line (*i.e.* for $\varkappa_\nu$ = const.), the line width $\Delta\lambda$ (and thus also the equivalent width $W_\lambda$) increases proportionally with $\sqrt{g \cdot f \cdot N \cdot \gamma}$ The stronger lines of the solar spectrum, *e.g.* the sodium D-lines as well as the H- and K-lines of CaII, lie on this damping branch of the curve of growth.

The hydrogen lines are of special importance. Inasmuch as they exhibit particularly strong linear splittings in an electric field due to the Stark effect, their broadening in partly ionized gases takes place mostly through the Stark effect of the statistically distributed fields of ions. This theory, originally developed by *Holtsmark*, has recently been refined (by *Griem* and *Kolb*, in particular) by taking into account non-adiabatic effects and the collision damping of electrons, and by an improved calculation of the microfield in the plasma.

## III. Abundance of Elements in the Atmospheres of Various Stars

So far, we have tried to present the methodology of the quantitative analysis of stellar spectra, at least in crude outline; we shall now turn to the results obtained. The accuracy with which the abundance of a given element can be determined in stars of various temperatures varies, of course, from case to case; the factors determining this are the number of lines by which the element is represented in the spectrum, the region of the curve of growth in which these lines lie, and, above all, the accuracy with which the oscillator strengths are known. As a rule, it can be said that, relatively to hydrogen as the most abundant element, the abundance of helium and of the lighter non-metals, which require high ionization energies, can best be determined in hot stars; on the other hand, the more easily ionized metals are best observed in cooler stars. Careful determinations give a probable accuracy $\Delta \log N = \pm 0.3$.

In Table 1, we have collected the results of careful spectral analyses for the following main sequence O and B stars: 10 Lacertae (O9 V), $\tau$ Scorpii (B0 V), $\gamma$ Pegasi (B2.5 V). (The spectral type S and the Morgan-Keenan luminosity class LC are given in parentheses.) The effective temperature $T_e$ and the gravitational acceleration g obtained in the course of the analysis of the spectrum are also given. Table 1 contains the logarithm of the number of atoms (log N) referred, as usual, to log N = 12 for hydrogen. Helium and the lighter elements up to Si or S are represented by transitions between highly excited levels, whose f values had been calculated rather accurately (*Glennon* and *Wiese*, 1962). The heavy elements can be expected only in high stages of ionization and consequently show no lines in the accessible spectral region.

The next group of stars shown in Table 1 are the hot supergiants, $\zeta$ Persei (B1 Ib) and 55 Cygni (B3 Ia), as well as the A stars $\alpha$ Lyrae (A0 V) and $\alpha$ Cygni (A2 Ia). The He lines are extremely temperature-sensitive and weak in the last two stars; He can thus be determined only with uncertainty. Instead, the lines of the ionized and neutral metals appear in large numbers below 10000 °K. Unfortunately, the data for the ionized metals will continue to be of very limited value until a greater number of reliable absolute measurements of their oscillator strengths become available. $\alpha$ Cygni is one of the brightest supergiants; its luminosity exceeds that of the sun by a factor of about 20000.

Table 1. Abundances (log N) of the elements in various stars. The logarithms of the numbers of atoms N were referred to log N = 12 for hydrogen. For the "old" stars γ Serpentis and HD 140283, and the helium star HD 160641, log N was further reduced in such a way that the values for the heavy elements are directly comparable.

| Spectral type | O9 V | B0 V | | B2.5V | B1 Ib | B3 Ia | A0 V | A2 Ia | G2 V | | F6 IV–V | | (G)Halo subdwarf | | (O)He star |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Star | 10 Lac | τ Scorpii | | γ Peg | ζ Persei | 55 Cygni | α Lyr | α Cyg | Sun | | γ Serpentis | | HD 140283 | | HD 160641 |
| Ref. | [6] | [7] | [8,9] | [10] | [11] | [12] | [13] | [14] | [15] | [16] | [17] | | [18] | | [19] |
| $T_e$ [°K] | 37500 | 32800 | 35000 | 24000 | 27000 | ? | 9500 | 9170 | 5780 | | 6350 | | 5940 | | $\bar{T}$ = 31500 |
| log g | 4.45 | 4.45 | 4.30 | 4.0 | 3.6 | 2.90 | 4.5 | 1.13 | 4.44 | | 4.0 | | 4.6 | | |
| | | | | | | | | | | | | reduced | | reduced | |
| H | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.24 | 12.00 | 14.32 | none |
| He | 11.23 | 11.23 | 11.04 | 11.17 | 11.31 | 11.18 | 11.4 | 11.40 | | | | | | | 11.61 |
| C | 8.37 | 8.37 | 7.7 | 8.58 | 8.26 | 8.41 | | 8.03 | | 8.72 | 8.43 | 8.67 | | | 8.65 |
| N | 8.37 | 8.57 | 8.26 | 8.01 | 8.31 | 8.63 | 8.8 | 9.48 | | 7.98 | | | | | 8.76 |
| O | 8.77 | 9.12 | 8.63 | 8.63 | 9.03 | 8.98 | 9.3 | 9.44 | | 8.96 | 9.07 | 9.31 | | | 8.90 |
| Ne | 8.72 | 8.72 | 8.86 | 8.73 | 8.61 | | | | | | | | | | 9.40 |
| Na | | | | | | | 7.3 | | 6.12 | 6.30 | 6.06 | 6.30 | 3.50 | 5.82 | |
| Mg | 8.22 | 7.73 | 8.3 | 7.95 | 7.77 | | 7.7 | 7.74 | 7.27 | 7.40 | 7.50 | 7.74 | 4.96 | 7.28 | 7.60 |
| Al | 7.07 | 6.58 | 6.4 | 5.76 | 6.78 | | 5.7 | 6.62 | 6.12 | 6.20 | 6.14 | 6.38 | 3.48 | 5.80 | |
| Si | 7.75 | 7.95 | 7.63 | 7.03 | 7.97 | 7.46 | 8.2 | 7.77 | | 7.50 | 7.36 | 7.60 | 5.18 | 7.50 | 7.60 |
| S | | | | 7.80 | 7.48 | | | | | 7.30 | 7.17 | 7.41 | | | |
| Ca | | | | | | | 6.3 | 6.73 | 6.16 | 6.15 | 5.90 | 6.14 | 3.88 | 6.20 | |
| Sc | | | | | | | 3.4 | *3.19* | | 2.82 | 2.45 | 2.69 | 1.41 | 3.73 | |
| Ti | | | | | | | 4.8 | 5.35 | | 4.68 | 4.28 | 4.52 | 2.51 | 4.83 | |
| V | | | | | | | 4.0 | *3.88* | | 3.70 | 3.23 | 3.47 | | | |
| Cr | | | | | | | 5.6 | 5.77 | | 5.36 | 4.92 | 5.16 | 2.98 | 5.30 | |
| Mn | | | | | | | 5.3 | *5.57* | | 4.90 | 4.72 | 4.96 | 2.57 | 4.89 | |
| Fe | | | | | | | 6.5 | 7.78 | 6.47 | 6.57 | 6.17 | 6.41 | 4.34 | 6.66 | |
| Co | | | | | | | | 3.73 | | 4.64 | 4.21 | 4.44 | 2.44 | 4.76 | |
| Ni | | | | | | | 7.0 | 4.82 | | 5.91 | 6.41 | 6.65 | 4.23 | 6.55 | |
| Sr | | | | | | | 2.8 | 3.11 | | 2.60 | 2.43 | 2.67 | 0.11 | 2.43 | |
| Ba | | | | | | | | | | 2.10 | 2.09 | 2.33 | | | |

We have incomparably better and more comprehensive observational data for the sun (G2 V) than for any other star; moreover, $T_e$ and g are known from independent measurements. The right-hand part of the sun's column in Table 1 shows the most recent and probably most accurate analysis (only for the more important elements), due to *Goldberg, Müller,* and *Aller* [16]. Earlier, *Weidemann* achieved about the same accuracy for some of these elements. The possible errors in the absolute f values naturally do not show up. As far as the cooler stars are concerned, there is still no acceptably satisfactory method of analysis.

The abundances of elements manifested in the stars which we have considered up to now are denoted as "normal" by the astronomer. Comparison of these abundances shows no differences which exceed the limits of error. Moreover, this abundance distribution in turn agrees – as far as can be verified – with that in the interstellar gas and in the galactic nebulae (*e.g.* the Orion nebula). The stars listed in Table 1 belong partly to the population I of the spiral arms (10 Lac up to 55 Cyg and α Cyg) and partly to the population of the galactic disk (α Lyr, sun). The analyses thus confirm the hypothesis that these stars were formed from the interstellar gas, and that the composition of the latter has not changed essentially since the formation of the galactic disk.

This picture changes if we consider the high-velocity stars and subdwarfs, *i.e.* the old stars of population II. For example, the F6 IV–V star γ Serpentis moves at 80 km/sec relative to our galactic vicinity and is thus a star of "moderately high" velocity. An accurate analysis shows that this star has, just at the limit of accuracy of the measurement, less of all the heavy elements than the stars previously discussed (the abundance decreases by $\Delta \log N = 0.24$, *i.e.* by a factor of 1.7, relative to hydrogen).

In the appreciably faster subdwarf HD 140283 (size and temperature are approximately those of the sun; the Morgan-Keenan classification for "normal" stars loses meaning in this case), all recognizable heavy elements, *viz.* C, Na, Mg, Al, Si, Ca, Sc, Ti, Cr, Mn, Fe, Co, Ni, and Sr, are less abundant than in the sun by a factor of 200. Within the limits of error, no differences between the abundances of the heavier elements can be distinguished. Quite recently *Wallerstein, Greenstein, Parker,*

[6] *G. Traving*, Z. Astrophys. *41*, 215 (1957).

[7] *G. Traving*, Z. Astrophys. *36*, 1 (1955); *44*, 142 (1958).

[8] *L. H. Aller, G. Elste,* and *J. Jugaku*, Astrophys. J. Suppl. *3*, 1 (1957).

[9] *J. Jugaku*, Publ. Astron. Soc. Japan *11*, 161 (1959).

[10] *L. H. Aller* and *J. Jugaku*, Astrophys. J. Suppl. *4*, 109 (1959).

[11] *R. Cayrel*, Suppl. Ann. Astrophys. No. 6 (1958).

[12] *L. H. Aller*, Astrophys. J. *123*, 133 (1955).

[13] *K. Hunger*, Z. Astrophys. *49*, 129 (1960) and earlier papers. In the model for a temperature of 9500 °K, $T_0$ has been lowered somewhat.

[14] *H. G. Groth*, Z. Astrophys. *51*, 206, 231 (1961). Model 3a: for the first ionization stage of Mg and Cr; Model 3b: tabular values are in italics.

[15] *V. Weidemann*, Z. Astrophys. *36*, 101 (1955). $T_0$ = 3400 °K, mainly methodology.

[16] *L. Goldberg, E. A. Müller,* and *L. H. Aller*, Astrophys. J. Suppl. *5*, 1 (1960). $T_0$ = 4500 °K.

[17] *W. H. Kegel*, Z. Astrophys. *55*, 221 (1962).

[18] *B. Baschek*, Z. Astrophys. *48*, 95 (1959). See also *L. H. Aller* and *J. L. Greenstein*, Astrophys. J. Suppl. *5*, 139 (1960), table on p. 170.

[19] *L. H. Aller*, in: Colloque International d'Astrophysique, Liège (Belgium) 1953, p. 354. Radial velocity: + 100 km/sec; $M_V$ = −3. Reduced to log $N_{He\,(from\,H)}$ = 12.00 −0.60 plus log $N_{He\,(original)}$ = 11.20: together: 11.61. Concerning helium stars, cf. *A. R. Klemola*, Astrophys. J. *134*, 130 (1961).

and *Helfer* found some red giants (HD 122563, 165195, and 221170) with probably even smaller abundances of the heavy elements relative to hydrogen, and have asserted that individual differences exist in the abundances of the various elements.

Thus, the high velocity stars are those which have been formed at the very beginning of the evolution of our galactic system. The main sequence stars $\gamma$ Ser and HD 140283 have burned up only a small part of their internal hydrogen, while the red giants have already moved a bit further on the Hertzsprung-Russell diagram. The analytical data on the subdwarf HD 140283 must probably be interpreted to mean that the abundance ratios of the heavy elements in interstellar matter have changed amazingly little during the course of the evolution of our galactic system. The formation of the heavy elements must thus always have taken place under almost the same conditions. This is by no means easy to comprehend since the various groups of elements are formed by different nuclear processes.

The helium stars present completely different and highly interesting problems. Only few examples of these are known and, judging from their high radial velocities, they seem to belong to population II. Hot stars exhibit only very weak or no hydrogen lines, but show instead a very strong and complete helium spectrum. The lines for the heavy elements are more or less normal. Quantitative analysis of the star HD 160641 indicated a temperature of 30000 °K. Its abundance distribution of the elements (Table 1) can be interpreted to mean that while the star started with the normal mixture of elements (*e.g.* that of the sun), all of its hydrogen has by now been transformed to helium. A similar star, BD + 10° 2179, has recently been investigated by *Klemola*; the ratio of hydrogen to the heavy elements in its atmosphere is almost 1000 times lower than in normal stars. In this star, the relative abundances of the heavy elements are also almost normal (there is possibly less oxygen than normal). The cool and variable star R Coronae Borealis, which is very peculiar in many respects, probably also belongs to this group.

The formation of helium stars must probably be thought of as a process in which an old star with a burned-out helium core turns inside out; the dynamic causes of this anomalous evolution are still unknown.

The final stage of stellar evolution, the white dwarfs, have recently been investigated by *Greenstein* and (quantitatively) by *Weidemann*. The key to the understanding of their peculiar spectra is provided by their enormous gravitational acceleration $g \approx 10^8$ cm/sec$^2$ (for comparison, imagine having a weight of 10000 tons suddenly placed on one's legs!), as well as their large abundance of helium. Some of the stars show almost exclusively helium lines. According to *Weidemann*, the highly broadened hydrogen lines which another group of stars exhibits almost exclusively may be due to an extremely small hydrogen abundance in their atmospheres. The stellar interior must in fact be virtually devoid of hydrogen, since otherwise the star would soon explode by nuclear fusion.

So far we have discussed groups of stars whose "normal" or "anomalous" composition can be related to their evolutionary stage. In addition, there are stars which give spectra in which some element is represented unusually strongly or unusually weakly. Among the A stars there is a subsidiary sequence of "peculiar A stars" (Ap), followed by the "metallic-line stars". *Babcock* found on their surface non-uniformly distributed magnetic fields of several thousand gauss. The problem is then whether the anomalies in their spectra can be explained by assuming an anomalous structure of the atmosphere having normal element abundances, or whether large numbers of particles of very high energy, accelerated by magnetic fields, have appreciably changed the abundance of some elements by nuclear reactions? Studies at the Max-Planck-Institut für Physik in Heidelberg (Germany) have shown that high-energy $^3$He particles are formed during large solar eruptions.

The splitting of the spectral sequence in cool stars, which is probably related to the O:C:metals abundance ratio, also deserves mention. Finally, the $C_2$ bands show that there are – in cool stars, at any rate – appreciable variations in the $^{12}C$:$^{13}C$ isotope ratio. This is the only case in which reliable statements can be made concerning the cosmic abundance of isotopes.

## IV. Terminology

Color index B–V

Difference between the apparent brightnesses of a star, measured by plates or photocells sensitive in the blue (B) and in the visual (V) spectral regions. B–V increases from negative to positive values along the sequence of spectral types as the stellar temperature decreases.

Fraunhofer lines

Absorption lines in the spectra of the sun and stars.

Brightness of stars

The apparent brightness is given in magnitudes m. A difference in magnitude $m_1 - m_2 = 1.0$ corresponds to a brightness ratio $I_2/I_1 = 2.51$, or $\log I_2 - \log I_1 = 0.400$ (*Pogson*). Negative magnitudes correspond to high brightnesses, positive magnitudes to low brightnesses. The absolute brightness is based on a standard distance (from the observer) of 10 parsec = 32.6 light years.

King's furnace

Develops temperatures of up to about 3000 °K by means of resistance heating of a carbon tube.

Luminosity

Total radiation emitted by a star, usually referred to that of the sun, which is taken as unity.

Magnetohydrodynamics

Fluid motions in media with high electrical conductivities passing through magnetic fields are greatly influenced by induction currents and the forces generated by them. These forces are important in addition to the hydrodynamic forces.

Milky Way

Our Milky Way (galaxy) is similar to the well known spiral nebula in the constellation Andromeda. It consists of a flat disk which contains a central nucleus and spiral arms. Our

sun moves around the galactic nucleus in a circular orbit whose radius is approximately 30000 light years, and completes the orbit in 200 million years. The nucleus and disk are surrounded by an almost spherical halo, which contains the globular star clusters as well as the high velocity stars and subdwarfs.

Spectral Classification

The spectra of stars are arranged according to two parameters:

a) Spectral types (S) O B A F G K M which constitute a sequence in which the effective temperature decreases from left to right.

b) Luminosity classes (LC) I–V which correspond essentially to a decreasing absolute brightness; I = supergiants; V = main sequence stars. The older Harvard classification was elaborated by *Morgan* and *Keenan* to yield the MK classification generally used today.

The relatively few stars which do not fit into the two-parameter scheme are denoted as "peculiar", *e.g.* the Ap stars with strong magnetic fields.

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# A Synthetic Route to the Corrin System

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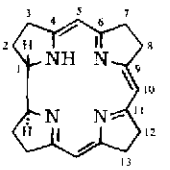
ORGANISCH-CHEMISCHES LABORATORIUM DER EIDGENÖSSISCHEN TECHNISCHEN HOCHSCHULE, ZÜRICH (SWITZERLAND)

*Dedicated to Prof. H. Meerwein on the occasion of his 85th birthday*

*The synthesis of the nickel(II) complex of (±)-1,8,8,13,13-pentamethyl-trans-corrin illustrates a synthetic route to the corrin system. Repeated use of triethyloxonium tetrafluoroborate in this synthesis demonstrates the preparative value of the trialkyloxonium salts discovered by Meerwein et al.*

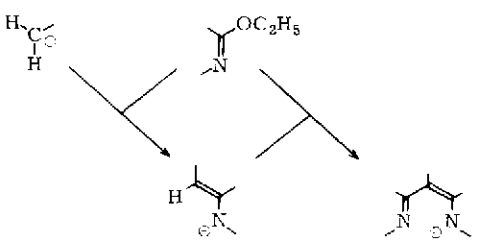
Corrin *(1)* [3] is the name given to the hypothetical parent compound of the porphyrinoid ligand system that, in the form of a cobalt complex, characterizes the vitamin $B_{12}$ structure [4]. Our knowledge of the constitution of this system stems from the now classical series of X-ray structural analyses carried out during the last 10 years by *Dorothy Crowfoot-Hodgkin* and her collaborators in Oxford (England) [5]. The consequent elaboration of the chemistry of this novel type of structure has since received additional impetus through the discovery of $B_{12}$ coenzymes [6], as manifested by the work going on at Nottingham (England) [7] and Stuttgart (Germany) [8].

This article describes the first results of investigations directed toward the development of synthetic pathways [9] to compounds with the corrin structure.



*(1)*

The concept underlying our work is patterned on a type of reaction that seems predestined for the construction of the conjugated unsaturated carbon-nitrogen chain typical of the corrin chromophore, *viz.* C→C condensation of carbanionoid carbon centers with C=N double bonds of imino ether derivatives [10] (Scheme 1). The



Scheme 1. The reaction principle used for the synthesis of the corrin chromophor.

[1] Deceased December 12th, 1963.

[2] Röntgenanalytische Abteilung des Organisch-Chemischen Laboratoriums der ETH, Zürich (Switzerland).

[3] In order to emphasize the *trans*-linking of the rings A and D as it occurs in vitamin $B_{12}$ compounds, we use the expression "*trans*-corrin" for the system shown in *(1)*. All the formulae representing compounds with chiral structures are to be taken as standing for the corresponding pair of mantiomers.

[4] *R. Bonnett:* The Chemistry of the Vitamin $B_{12}$ Group. Chem. Revs. *63*, 573 (1963).

[5] *D. Crowfoot Hodgkin, A. W. Johnson,* and *A. R. Todd:* Special Publication No. 3. The Chemical Society, London 1955, p. 109; *D. Crowfoot Hodgkin, J. Kamper, J. Lindsey, M. Mackay, J. Pickworth, H. J. Robertson, C. B. Shoemaker, J. G. White, R. J. Prosen,* and *K. N. Trueblood,* Proc. Royal Soc., Ser. A *242*, 228 (1957).

[6] *H. A. Barker, H. Weissbach,* and *R. D. Smith,* Proc. nat. Acad. Sci. USA *44*, 1093 (1958); Vitamin $B_{12}$ and Intrinsic Factor, 2nd Symposium. Enke Verlag, Stuttgart 1962; *P. Galen Lenhert,* and *D. Crowfoot Hodgkin,* Nature (London) *192*, 937 (1961).

[7] *D. Dolphin, A. W. Johnson, R. Rodrigo,* and *N. Shaw,* Pure appl. Chem. *7*, 539 (1963).

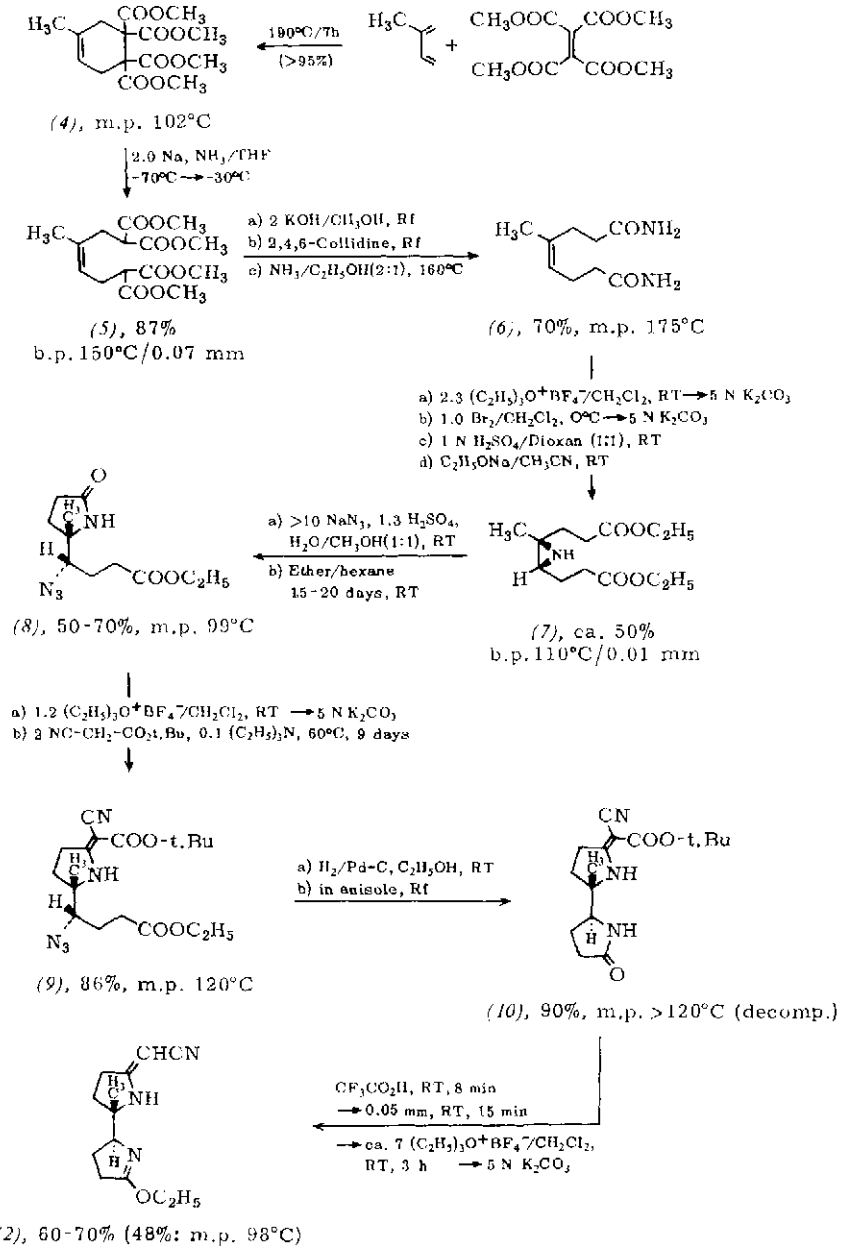
[8] *K. Bernhauer, O. Müller,* and *F. Wagner,* Angew. Chem. *75*, 1145 (1963); Angew. Chem. internat. Edit. 3, 200 (1964).

[9] Cf. also *R. Bonnett, V. M. Clark, A. Giddey,* and *A. R. Todd,* J. chem. Soc. (London) *1959*, 2087; *A. W. Johnson* in: Vitamin $B_{12}$ und Intrinsic Factor, 2nd Symposium. Enke Verlag, Stuttgart 1962, p. 1; *A. Eschenmoser,* Pure appl. Chem. *7*, 297 (1963).

[10] *S. Petersen,* Angew. Chem. *64*, 602 (1952).

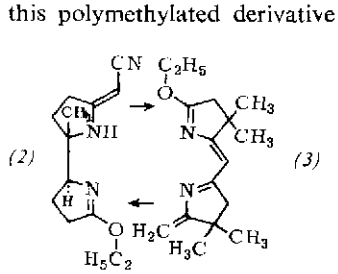
verification of such a scheme hinges on the availability of the trialkyloxonium salts discovered by *Meerwein* et al. [11] as reagents that allow a reliable conversion of amide or lactam groups into the corresponding imino ether derivatives.

the development of a synthetic route to the corrin type of structure was inspired by the substitution pattern present in natural corrin complexes; moreover, it circumvents dangers of isomerization and dehydrogenation




Scheme 2. Synthesis of compound *(2)*. In the experimental data, Rf = boiling under reflux, RT = room temperature. Melting and boiling points are uncorrected. Physical properties of the compounds are listed in Table 1 [12].

The synthetic route is illustrated by the formulae of the bicyclic intermediates *(2)* and *(3)*; their combination in the sense shown is intended to yield a derivative of (±)-1,8,8,13,13-pentamethyl-*trans*-corrin. The choice of this polymethylated derivative as the first subject for




that might well lie along the path to the unsubstituted corrin.

Scheme 2 shows a synthesis of the left-hand structure *(2)*. The monocyclic tetraester *(4)*, readily prepared by Diels-Alder addition of tetramethyl ethylenetetracarboxylate onto isoprene, is smoothly converted into the aliphatic tetraester *(5)* by a novel reductive ring-cleavage with sodium in liquid ammonia. The position and configuration of the double bond in *(5)* is unambiguously defined by the method of formation.

[11] *H. Meerwein, G. Hinz, P. Hofmann, E. Kroning*, and *E. Pfeil*, J. prakt. Chem. *147*, 17 (1937); *H. Meerwein, E. Battenberg, H. Gold, E. Pfeil*, and *G. Willfang*, ibid. *154*, 83 (1939).

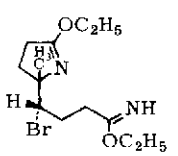
[12] With the exception of the sodium salt *(17)*, all the compounds shown in Schemes 2-4 gave correct elementary analyses.

Table 1. Physical data for the compounds shown in Scheme 2.

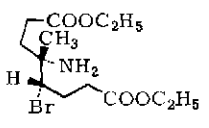
The data denote the following: mμ: maxima in the ultraviolet spectrum in ethanol; log ε values in brackets. $cm^{-1}$: characteristic bands in the infrared spectrum in $CHCl_3$. ppm: selected signals referred to $(CH_3)_4Si$ = 0 ppm from NMR spectra in $CDCl_3$, obtained with Varian A 60. s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, b = broad, no fine structure.

| Compound | |
|---|---|
| *(5)* | ppm: 3.18/3.42 (2t/$-CH\langle$; 5.13 (t/=CH—) |
| *(7)* | ppm: 0.48 (s/NH) |
| *(8)* | $cm^{-1}$: 3430(NH); 2110($N_3$); 1723/1690 (C=O)<br>ppm: 3.28 (m/$\rangle CH-N_3$) |
| *(9)* | mμ: 278 (4.32)<br>$cm^{-1}$: 3335 (NH); 2210 (C≡N); 2110 ($N_3$); 1725/1665 (C=O); 1590<br>ppm: 8.75 (b/NH); 3.35 (m/$\rangle CH-N_3$) |
| *(10)* | mμ: 278 (4.38)<br>$cm^{-1}$: 3280/3200 (NH); 2200 (C≡N); 1691/1660 (C=O); 1587<br>ppm: 8.37/9.0 (2s/2 NH); 3,7 (m/$\rangle CH\ \ N\langle$) |
| *(2)* | mμ: 266 (4.35)<br>$cm^{-1}$: 3435 (NH); 2185 (C≡N); 1645 (C=N); 1615 (C=C)<br>ppm: 4.17/1.29 (q/t/J ≈ 7/—O—$CH_2$—$CH_3$);<br>3.87/3.56 (s/=CH—/cis + trans);<br>1.08/1.13 (s/—$CH_3$/cis:trans ≈ 1:1)<br>$pK^{*}_{MCS}$ = 3,92 (Equiv.wt. 234); m/e (M) = 233 |

The crystalline diamide *(6)* is the starting material for a sequence of operations leading to sterospecific imination of the double bond to form the aziridine derivative *(7)*, without isolation of pure intermediates. Thus, first, reaction of *(6)* with triethyloxonium tetrafluoroborate yields the diimino diether, $\tilde{\nu}_{C=N}$ = 1642 $cm^{-1}$; secondly, careful bromination of the latter with one equivalent of bromine affords the monocyclic bromodiimino diether *(6a)*, $\tilde{\nu}_{C=N}$ = 1642/38 $cm^{-1}$; $\delta_{\rangle CHBr}$ = 4.1 ppm; thirdly, mild hydrolysis of *(6a)* with dilute sulfuric acid followed by treatment with sodium ethoxide yields *(7)*. The assignment of *cis*-configuration to the aziridine derivative *(7)* rests on the postulate of direct participation of the imino ether nitrogen in the bromination step, assuming that inversion occurs in the cyclization of the α-bromo amine *(6b)* formed during hydrolysis. This assignment is confirmed by the fact that *(7)* reacts with one equivalent of nitrosyl chloride/triethylamine at low temperature to split off $N_2O$, giving stereospecifically a high yield of diethyl *cis*-4-methyl-4-octenedioate [13].



*(6a)*

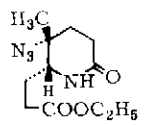


*(6b)*

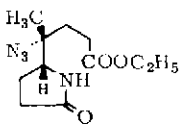
[13] We have checked that the cleavage of *N*-nitrosoaziridines to $N_2O$ and the corresponding olefins, observed by *C. L. Bumgardner, K. S. McCallum*, and *J. P. Freeman*, J. Amer. chem. Soc. *83*, 4417 (1961), and by *W. Rundel* and *E. Müller*, Chem. Ber. *96*, 2528 (1963), in the case of the unsubstituted aziridine, proceeds with retention of configuration and can therefore be used for determining the configurations of aziridines and aziridine precursors. The reaction with 1.0 mole of nitrosyl chloride/triethylamine in ether at −60 → 0 °C gave 87% *trans*-stilbene (quantitative analysis by gas chromatography) from *trans*-2,3-diphenylaziridine, and 80–86% *cis*-stilbene containing 7.5–1.7% *trans*-isomer from *cis*-2,3-diphenylaziridine.

Introduction of the second nitrogen function is achieved by proton-catalysed opening of the aziridine ring of *(7)* with azide ions. The main reaction consists in the attachment of the azide group to the secondary carbon atom; a slow cyclization step then leads to the butyrolactam derivative *(8)*. The fact that the azide group in this compound is on a secondary carbon atom is shown by the NMR spectrum: the signal at 3.28 ppm, corresponding to the tertiary hydrogen, is displaced upfield by 0.8 ppm after catalytic hydrogenation of the azide group to an amino group. The configuration of *(8)* is derived by assumption of *trans*-opening [14] of the aziridine ring. This is suggested by the entry of the azide ion at the secondary carbon atom, *i.e.* at the position corresponding to an $S_N2$-type reaction.

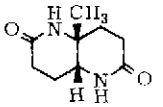
A by-product *(8a)* [$\tilde{\nu}_{C=O}$ = 1665/1728 $cm^{-1}$, $\delta_{\rangle CH-N-CO}$ = 3.25 ppm], isolated in small yield from the reaction of *(7)* with azide ions and formed by a rapid cyclization step, originates from competitive opening of the aziridine ring at the tertiary carbon atom. Compound *(8a)* can be transformed via the isomeric lactam *(8b)*, which is formed by equilibration with sodium ethoxide (K ≈ 2 in $C_2H_5OH$, 25 °C), into the same five-membered cyclic dilactam *(8d)* as is obtained by catalytic hydrogenation and subsequent cyclization of *(8)*. This relates the configuration of *(8a)* to that of *(8)*. It is noteworthy that catalytic hydrogenation carried out immediately after the azide reaction, followed by a double cyclization leads exclusively to the six-membered bicyclic dilactam *(8c)*.



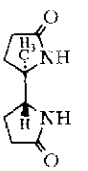
*(8a)*



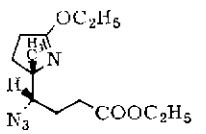
*(8b)*



*(8c)*

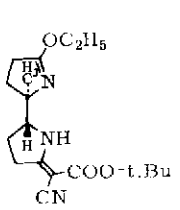


*(8d)*

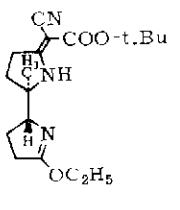


*(8e)*

The system *(2)* can be constructed from the dilactam *(8d)* by a sequence of reactions analogous to the transformations *(8)* → *(9)* and *(10)* → *(2)*, but the isomeric intermediates *(10a)* and *(10b)* must be separated by chromatography. A more convenient route is described below.



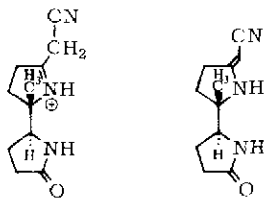
*(10a)*



*(10b)*

[14] Cf. also *F. H. Dickey, W. Fickett*, and *H. J. Lucas*, J. Amer. chem. Soc. *74*, 944 (1952); *R. Ghirandelli* and *H. J. Lucas*, ibid. *77*, 106 (1955).

The lactam group in the butyrolactam derivative *(8)* can be transformed with triethyloxonium tetrafluoroborate into the corresponding iminoether grouping *(8e)* without altering the azide function. This reaction provides, in the sense of Scheme 1, the opportunity for introducing the two-carbon chain required to complete the synthesis of *(2)*. Condensation with t-butyl cyanoacetate in the presence of catalytic amounts of triethylamine proves particularly suitable for this purpose: a uniform reaction leads to compound *(9)*, in which the arrangement of the imino and the ester groups are assumed, on the basis of infrared spectroscopic investigations on simple model systems, to be *cis*. Selective catalytic hydrogenation of the azide to the amino group proceeds readily to yield the bicyclic monolactam *(10)*. Brief treatment of *(10)* with anhydrous trifluoroacetic acid effects smooth cleavage [15] of the t-butyl ester group, together with spontaneous decarboxylation. Conversion of the lactam into the imino ether with triethyloxonium tetrafluoroborate is achieved via the immonium



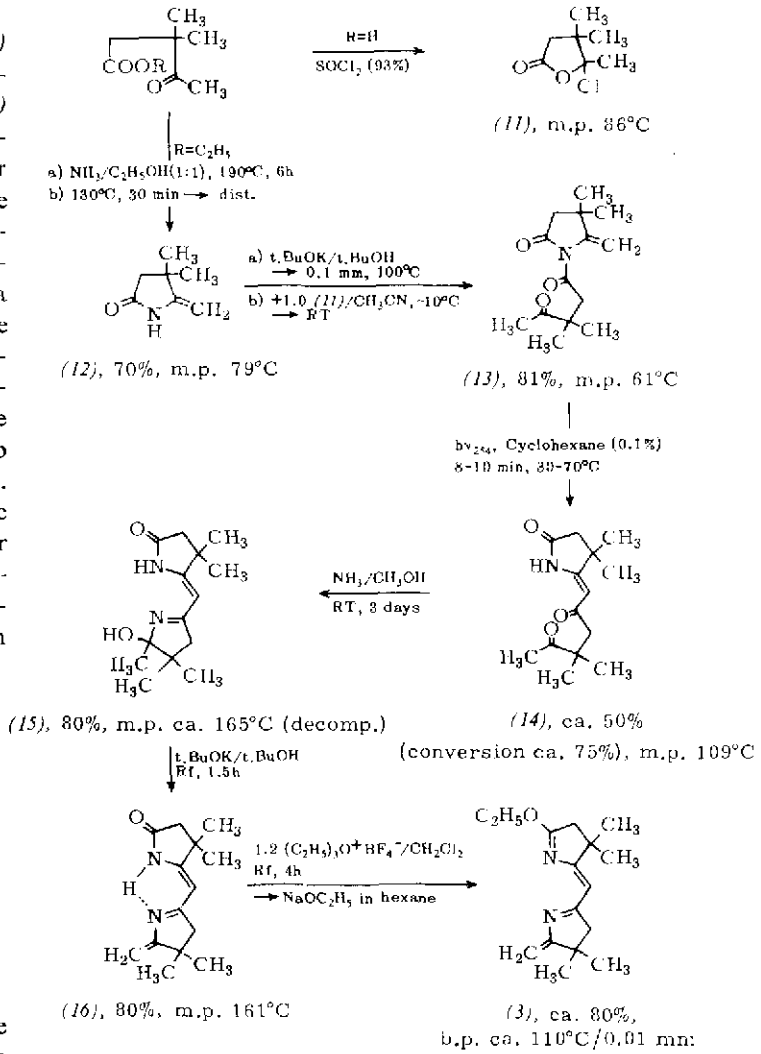
*(10c)* *(10d)*

$\lambda_{max}$ = 268 mμ
(log ε = 4.3)

salt *(10c)*; neither the neutral compound *(10d)* nor the cyano ester *(10)* can be *O*-alkylated selectively on the lactam group because of interfering side reactions in the enamine region. In practice the trifluoroacetic acid is sucked off immediately after cleavage of the ester group, and the residue (log $\varepsilon_{268\ m\mu} < 3.6$ in $CH_2Cl_2$) is alkylated directly with an excess of triethyloxonium tetrafluoroborate. The crystalline product obtained in this way gives analytical and spectroscopic data that confirm the constitution of the structural formula *(2)*; its NMR spectrum indicates, however, the presence of the two possible geometrical isomers.

Scheme 3 summarizes the reaction sequence leading to the right-hand structure *(3)*. The crucial intermediate is β,β-dimethyl-γ-methylenebutyrolactam *(12)*, which can be prepared by various methods, starting from β,β-dimethyllevulinic acid. A simple and efficient process consists in the reaction of the corresponding ethyl ester with ethanolic ammonia at elevated temperature, followed by pyrolytic elimination of ammonia. *C*-Acylation of *(12)* by the acyl residue of β,β-dimethyllevulinic acid is achieved indirectly by *N*-acylation of the potassium salt of *(12)* with the pseudo-acid chloride *(11)*, followed by a photochemically induced *N*-acyl → *C*-acyl migration *(13)* → *(14)*. This last process occurs rapidly in dilute cyclohexane solution on irradiation with a low-pressure mercury vapor lamp, but is accompanied by a photochemical change of the

[15] *H. Kappeler* and *R. Schwyzer*, Helv. chim. Acta *44*, 1136 (1961).




Scheme 3. Synthesis of compound *(3)*. In the experimental data, Rf = boiling under reflux, RT = room temperature. Melting and boiling points are uncorrected. The physical properties of the compounds shown are listed in Table 2.

Table 2. Physical data for the compounds shown in Scheme 3. For explanations see Table 1. sh = shoulder; main band = in italics.

| Compound | |
|---|---|
| *(12)* | mμ: 225 (3.94)<br>cm⁻¹: 3440 (NH); 1710/1690 (sh)/1652<br>ppm: 4.09/4.32 (2 d/J ≈ 2/ >C=CH₂)<br>Mol. wt. — 136 (ethyl acetate) |
| *(13)* | mμ: 242 (3.46)<br>cm⁻¹: 1755/1710 (C—O); 1655 (C=C)<br>ppm: 5.72/4.69 (2 d/J ≈ 2/ >C—CH₂) |
| *(14)* | mμ: 283 (4.30)<br>cm⁻¹: 3320 (NH); 1750/1705/1665 (C=O); 1595<br>ppm: 5.31 (s/=CH—); 10.5 (b/NH) |
| *(15)* | mμ: 350 (4.35); 284 (3.60)<br>cm⁻¹: 3630 (OH); 1735 (sh)/1720/1650/1595<br>ppm: 2.35 (s/—CH₂—); 2.56 (q/J ≈ 16/ —CH₂—)<br>4.95 (s/=CH—) |
| *(16)* | mμ: 251 (3.77); 260 (3.79); 272 (3.77);<br>*319* (4.13); 337/357/375 (sh)/4.0/3.9/3.7)<br>cm⁻¹: 3190 (NH); 1730 (sh)/1720/1645/1632/1594<br>ppm: 1.21/1.34 (2s/4—CH₃); 2.39/2.60 (2s/2—CH₂—);<br>4.50/5.02/5.07 (3s/=CH—/=CH₂)<br>Mol. wt. = 225 (ethyl acetate) |
| *(3)* | mμ: 304 (4.21/Cyclohexane)<br>cm⁻¹: 1580 (—N=C—OC₂H₅), 1625<br>ppm: 1.19/1.26 (2s/4 CH₃); 1.39/4.40<br>(t/q/J ≈ 7/—O—CH₂—CH₃); 2.47/3.01<br>(2s/2 —CH₂—); 4.54/5.09/5.83 (3s/=CH—/=CH₂) |

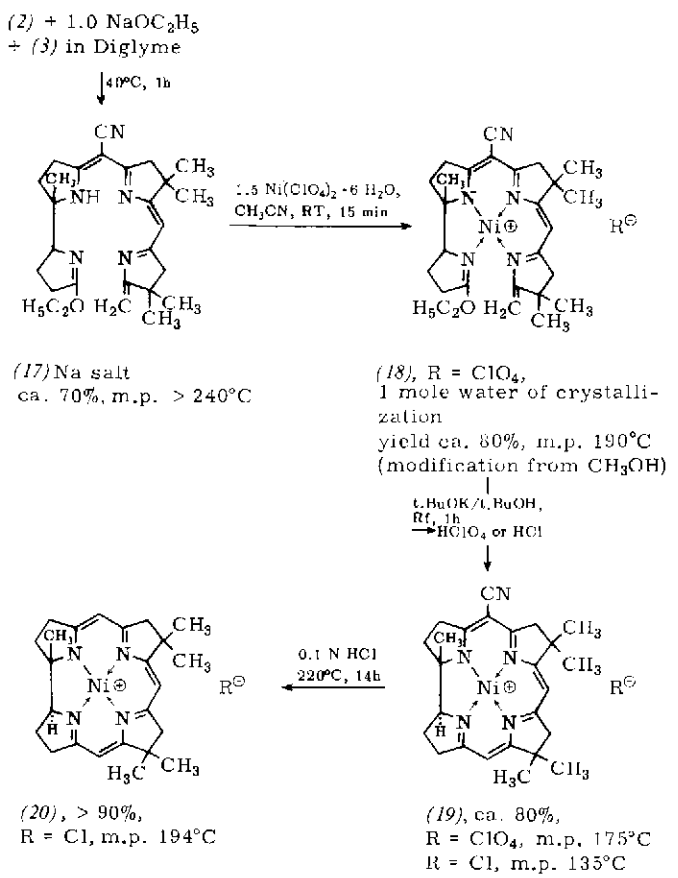
reaction product at about half its rate of formation; it is therefore best carried out in a continuous flow system [16].

Replacement of both carbonyl oxygens in *(14)* by nitrogen is achieved with methanolic ammonia. The initial product is compound *(15)*; its tertiary hydroxyl group can be eliminated either pyrolytically or by treatment with potassium t-butoxide. The constitution of *(16)* follows clearly from its NMR spectrum. The configuration shown is deduced from an infrared band at about 3190 $cm^{-1}$, whose position, shape, and intensity are independent of concentration (0.03–5 % solution in $CCl_4$); the band is assigned to an intramolecularly associated NH group. This internal hydrogen bond presumably contributes to the success of the subsequent reaction with triethyloxonium tetrafluoroborate, which results in a practically exclusive *O*-alkylation. With this formation of the sensitive iminoether derivative *(3)* the synthesis of the right-hand half of the corrin system is complete.

Scheme 4 shows a solution of the crucial problem of the present work, *i.e.* the combination of the two components *(2)* and *(3)* to the corrin system. Starting with the sodium salt of component *(2)* in diglyme, specific C → C condensation of the β-aminocrotonitrile system of *(2)* with the conjugated – and hence more reactive – iminoether grouping of component *(3)* is achieved; under suitable conditions the sodium salt of the condensation product *(17)* crystallizes out directly from the reaction mixture in good yield. The free condensation product is very labile and has not been obtained in crystalline form. The configurational details of formula *(17)* remain hypothetical, but the constitution is well founded on spectroscopic data, particularly on the NMR spectrum, which contains all the signals required by formula *(17)* with respect to both position and intensity. The same characteristic signals, particularly those of the three vinyl protons and of the iminoether ethoxyl group, are observed in the spectrum of the beautifully crystalline diamagnetic nickel(II) complex *(18)*, obtained by reaction of the sodium salt *(17)* with nickel(II) perchlorate in acetonitrile. The planoid structure of the ligand system in this complex now satisfies the geometrical requirements for the final ring closure to the macrocyclic corrin ligand, *i.e.* the two condensing centers are fixed close to each other. Ring closure of *(18)* can be achieved in high yield by treatment with potas-

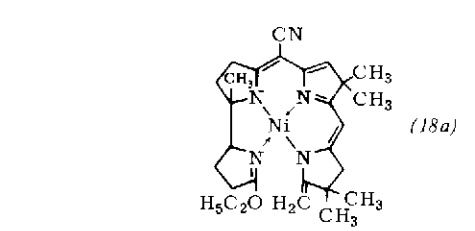
Table 3. Physical data for the compounds shown in Scheme 4. sh = shoulder; main band = in italics.

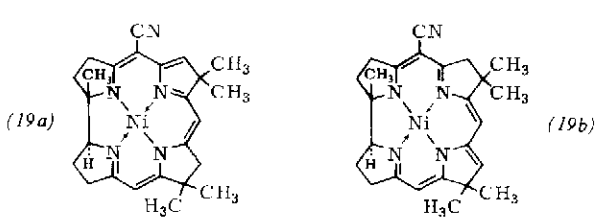
| Compound | |
|---|---|
| *(17)* Na Salt | mμ: 271 (sh/4.36); *279* (4.40); 288/302/374 (sh/4.3/4.0/4.3); *388* (4.35); 406/432/454 (sh/4.3/4.0/3.5)<br>$cm^{-1}$: 2170 (C≡N); 1640/1588/1527/1492<br>$pK^{*}_{MCS}$ = 12/5.8/3.5 (Equiv. wt. = 485)<br>ppm (liberated): 4.59/5.17/5.73 (3s/ = CH—/=$CH_2$) |
| *(18)*, $ClO_4^- \cdot H_2O$ | mμ: 249 (4.27); 259/276 (sh/4.2/4.1); *303* (4.09); 362 (3.61); *427* (4.11); ca. 510 (2.9); [cf. Fig 1]<br>C<br>$cm^{-1}$: 2205 (C≡N); 1633 (—N=C—$OC_2H_5$); 1585/1530/1478<br>ppm: 4.61/5.06 (2 d/J ≈ 2/ =$CH_2$); 5.70 (s/ = CH-) |
| *(19)* $ClO_4^-$ | mμ: 240 (sh/4.23); 271 (3.91); *302* (4.34); 315/325 (sh/4.2/4.0); *440* (4.23) [cf. Fig. 1]<br>$cm^{-1}$: 2210 (C≡N); 1638/1615/*1592*/1565/*1508*/1490<br>NMR spectrum of the Chloride: Fig. 2 |
| *(20)* $Cl^-$ | mμ: 242 (4.13); 251/265/274 (sh/4.0/3.8/3.9); *302* (4.27); *316* (4.27); 388 (sh/3.8); *428* (4.04); 447 (sh/3.9)<br>$cm^{-1}$: 1630, 1588, 1560, 1506<br>ppm: 6.03 (s/ =CH—); 6.1–6.25 (m/2 =CH—) |




Scheme 4. Combination of compounds *(2)* and *(3)* to the corrin system. In the experimental data, **Rf** = boiling under reflux, **RT** = room temperature. Melting and boiling points are uncorrected. The physical properties of the compounds are listed in Table 3 [12].

[16] The acyl substituent on the ring migrates to only a very small extent; in one experiment, the corresponding isomeric rearrangement product was isolated in about 1 % yield.



sium t-butoxide. The strong base undoubtedly evokes intermediate formation of a neutral complex, *e.g. (18a)*, by deprotonation of the singly positively charged complex ion *(18)*. In this intermediate, the nucleophilic reactivity of the exocyclic methylene group is greater than in *(18)* and the nickel-nitrogen bonds may be shorter. Indeed, a neutral deprotonated corrin complex ($C_{25}H_{29}N_5Ni \cdot H_2O$; m.p. $> 300\,^{\circ}C$; mol. wt. in $CH_2Cl_2$ –468; $\delta_{=CH-}$ = 5.27/5.06/4.93 (3s) ppm) can be isolated by avoiding acidic conditions during isolation. This complex has the structure *(19a)* or *(19b)*. On protonation with acids, crystalline salts of the orange-yellow, diamagnetic complex ion *(19)* are formed.

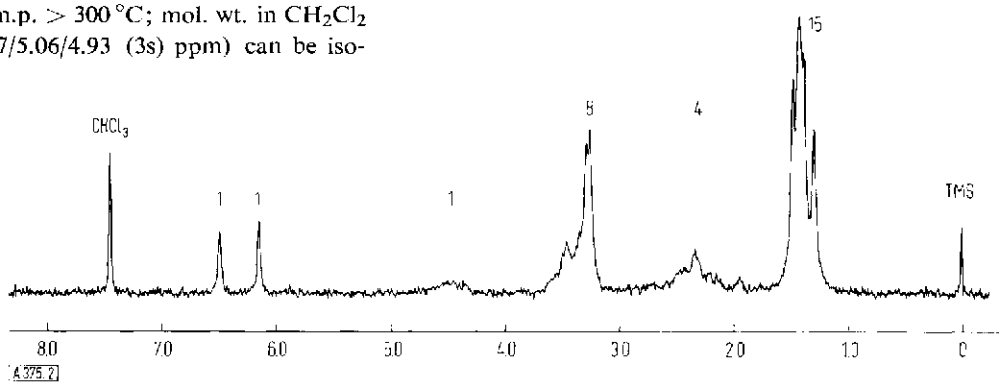



Fig. 2. NMR spectrum of compound *(19)*, R = Cl. TMS = tetramethylsilane. The numbers above the curve indicate the number of protons associated with each signal.
Abscissa: $\delta$ [ppm].

That ring closure of the open complex *(18)* does lead to the nickel(II) complex of 1,8,8,13,13-pentamethyl-5-cyano-*trans*-corrin *(19)* is supported by analytical data and by the following spectroscopic observations:

a) The ultraviolet spectrum of *(19)*, R = $ClO_4$, shows the expected bathochromic displacement of the main band at long wavelength with respect to that of the precorrinoid complex *(18)*; see Fig. 1.

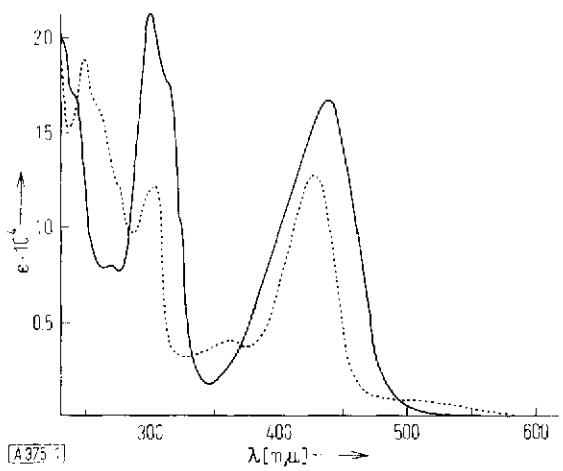



Fig. 1. Ultraviolet spectra of compounds *(18)*, R = $ClO_4$ (. . . .), and *(19)*, R = $ClO_4$ (——), in ethanol.

b) The infrared spectrum of *(19)*, R = $ClO_4$, does not show the iminoether C=N band at about 1640 $cm^{-1}$ that is present in the spectrum of *(18)*. Two intense bands appear in the C=C/C=N region at 1592 and 1508 $cm^{-1}$; two such bands characterize the same region of the infrared spectra of cobyrinic acid derivatives [17].

[17] Heptamethyl dicyanocobyrinate [cf. *F. Wagner* and *K. Bernhauer* in: Vitamin $B_{12}$ Coenzymes (Conference), New York Academy of Sciences, 1963] exhibits two prominent peaks at 1500 and 1580 $cm^{-1}$ in chloroform (experiments by Dr. *R. Keese*).

c) Comparison of the NMR spectra of *(18)* and *(19)*, R = Cl, shows the disappearance of the iminoether ethoxy and exocyclic methylidene groups, which participate in the cyclization (Fig. 2). All signals observed in the NMR spectrum of *(19)* (Fig. 2) correspond in position, structure, and intensity to the constitution shown [18].

The nickel(II)-corrin complex *(19)* is rather inert to hydrolysis, even under vigorous conditions (conc. HCl/Rf/4 h; dilute $NaOH/C_2H_5OH$/Rf/7 h); a preparative method for the hydrolysis of the cyanide group with simultaneous decarboxylation to form the nickel(II) complex of 1,8,8,13,13-pentamethyl-*trans*-corrin *(20)*, R = Cl, consists in heating *(19)* for several hours in 0.1 N hydrochloric acid at 220 °C.

The constitution of the synthetic corrin complexes is confirmed by three-dimensional X-ray analysis of the nickel(II)-1,8,8,13,13-pentamethyl-5-cyano-*trans*-corrin chloride *(19)*, R = Cl. The air-dried crystals obtained from ethyl acetate/methanol are triclinic (a = 11.10, b = 12.31, c = 10.69 Å; $\alpha = 103.9\,^{\circ}$, $\beta = 96.0\,^{\circ}$, $\gamma = 77.9\,^{\circ}$; density = 1.364 g/$cm^3$; space group $P\bar{1}$; Z = 2). The X-ray molecular weight of 566 (calc. for $C_{25}H_{30}N_5NiCl$

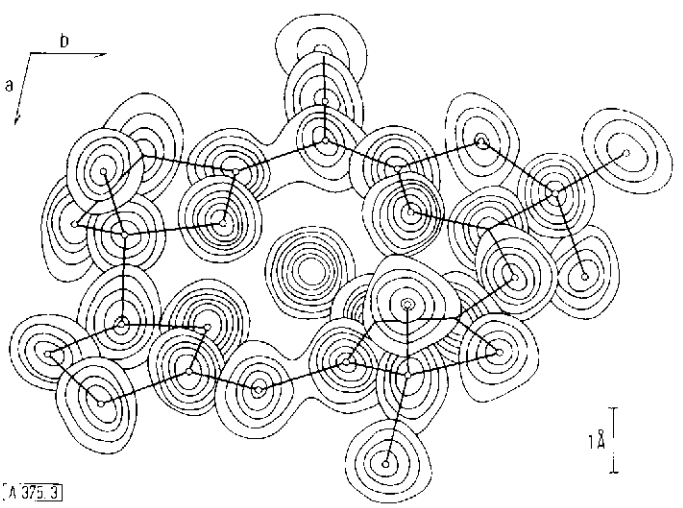



Fig. 3. X-ray analysis of nickel(II)-1,8,8,13,13-pentamethyl-5-cyano-*trans*-corrin chloride *(19)*, R = Cl.
Second electron density synthesis.

[18] $\delta_{=CH}$ of heptamethyl aquocyanocobyrinate perchlorate in deuterochloroform: 6.4 ppm (experiments by Dr. *R. Keese*).

– 494.7) indicates the presence of solvent of crystallization; the NMR spectrum of the air-dried crystals in deuterochloroform shows the presence of methanol and water. The intensities of the X-ray reflections were measured with the linear diffractometer of *Arndt* and *Phillips* [19] and converted to relative $F^2$ values. The position of the nickel atom was obtained from a three-dimensional Patterson function. The result of the second electron-density synthesis is summarized in Figure 3; it is in significant agreement with the structural formula *(19)* and, in particular, confirms the *trans*-linkage of rings A and D. Since only weak indications of the solvent molecules are present in the electron density syntheses, it seems probable that they are largely disordered in the crystal. Discussion of bond lengths and bond angles is premature, since further calculations are in progress.

The results described in this paper indicate the general direction of a route, along which the synthesis of corrin complexes with other metal ions, as well as with simpler or more complex substituents, can be attempted. With these possibilities a broader basis for studying corrin chemistry is in prospect.

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# Quantum Chemistry of the Crystal Surface

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  2. Energy spectra for crystal models with localized bonds
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    a) When the change of the potential function inside the crystal is sufficiently large
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## Introduction

The study of the chemical bond in solids is steadily gaining in importance [1,2]. One can expect special properties of chemical bonds to prevail at surfaces, for on one hand, free valences are available [3], and on the other, the type of bonding and hence also the arrangement of the atoms at the surface are different from those in the bulk of the crystal [4–6]. These phenomena are important not only in solid state physics but also for an understanding of the properties of materials which are involved in chemisorption and catalysis.

The quantum chemistry of surfaces is concerned with the possible states of energy of electron systems which exist on the surface of a finite crystal, as well as with the wave functions which describe the state of these electrons. From these relationships, quantum chemistry can be used to derive conclusions as to the electron distribution in the surface layers. Both a free surface and one containing adsorbed material perturb the ideal lattice periodicity. Since such perturbances bear a formal resemblance to defects within the crystal lattice, the theories evolved for the latter may be applied to surface phenomena. However, it must be noted that these theories were developed primarily for semiconductors and presuppose knowledge of the energy spectrum of a finite crystal [7–10].

One-electron approximations are particularly graphic and readily understood, although they have considerable disadvantages in quantitative computations. In the one-electron approximation it is assumed that certain definite states can be ascribed to the electrons. The

[1] *W. B. Pearson* and *G. H. Wolff*, Discuss. Faraday Soc. *18*, 142 (1959).

[2] *Chr. K. Jørgensen*, Symposium on Local Properties of Perfect Crystals, Geneva 1962.

[3] *P. Handler:* Semiconductor Surface Physics. University of Pennsylvania Press, Philadelphia 1957, p. 23; Semiconductor Surfaces. Pergamon Press, Oxford 1960, p. 1.

[4] *R. E. Schlier* and *H. E. Farnsworth*, J. chem. Physics *30*, 917 (1959).

[5] *D. Haneman*, J. physic. Chem. Solids *14*, 162 (1960).

[6] *D. Haneman*, Physic. Rev. *121*, 1093 (1961).

[7] *P. Agrain* and *C. Dugles*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *56*, 363 (1952).

[8] *K. Hauffe* and *H. J. Engell*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *56*, 366 (1952).

[9] *F. F. Volkenshteyn*, Advances Catalysis Related Subjects *9*, 807 (1959).

[10] *K. Hauffe*, Advances Catalysis Related Subjects *7*, 213 (1955).

total energy of the electron system can then be expressed as the sum of the energies of the occupied states. The wave functions which describe the states of the individual electrons in the crystal can be designated as "molecular orbitals", in analogy to the terminology of quantum chemistry. It is frequently assumed that the molecular orbitals can be approximated by linear combinations of atomic orbitals, *i.e.* as linear combinations of the wave functions which describe the electron states in the single atoms (LCAO-method [*]).

If an atomic orbital, localized at an atom $\alpha$, is designated as $\chi_{\alpha i}$, then the molecular orbital assumes the following form (according to the molecular orbital method in the MO-LCAO approximation)

$$\Psi_j = \sum_{\alpha i} c_{j;\alpha i} \cdot \chi_{\alpha i}$$

where $c_{j;\alpha i}$ are the coefficients whose squares yield the probability of finding the electron with the atomic orbital $\chi_{\alpha i}$ in the state corresponding to the j-th molecular orbital. In general, we can conceive of several atomic orbitals pertaining to a single atom and can index them with subscript i. The probability that an electron will be found in the vicinity of an atom $\alpha$ is then $\sum_i c_{j;\alpha i}^2$; this probability is also designated as the electron density. The coefficients $c_{j;\alpha i}$ which, in the simplest version (the Hückel approximation), determine the solution of the quantum-mechanical problem, must satisfy the system of equations

$$(\alpha_{\alpha i} - E_j)c_{j;\alpha i} + \sum_{\gamma k} \beta_{\alpha i;\gamma k} \cdot c_{j;\gamma k} = 0$$

where $E_j$ is the electron energy; $\alpha_{\alpha i}$ is the so-called Coulomb integral, which is a measure of the energy of an electron localized at an isolated atomic orbital; $\beta_{\alpha i;\gamma k}$ is the resonance integral, which is a measure of the overlap, and hence of a possible bond between the orbitals $\chi_{\alpha i}$ and $\chi_{\alpha k}$ of the atoms $\alpha$ and $\gamma$.

The above system of equations can only be solved for definite values of energy $E_j$. The ensemble of these energies is designated as the spectrum of allowed energies. If the crystal is considered to be an assembly of unit cells, then the atoms may be indexed by the cell number (p) and by the number of the atom ($\gamma$) within the cell. The expression for the molecular orbitals can then be written in the following form:

$$\Psi_j = \sum_{p\gamma;i} c_{j;p\gamma;i} \cdot \chi_{p\gamma;i}$$

From the periodicity of the infinite crystal it follows that the expression

$$|c_{j;p\gamma;i}|^2 = |c_{j;1\gamma;i}|^2$$

must be valid, *i.e.* that equivalent lattice sites must ha vethe same electron residence probabilities (or electron densities). Since an infinite crystal contains an infinitely large number of unit cells, the probability of the occurrence of an electron in a single unit cell is infinitely small.

This approximation is justified only when the bonding of the electrons to the individual atoms is relatively strong. The great advantage of this approximation is that the theoretical results can be easily and graphically interpreted by means of chemical concepts and may then be compared with experimental data from organic or inorganic chemistry.

The objective of quantum chemistry of surfaces is therefore to find the allowed energy levels of the one-electron states for a given arrangement of the atomic nuclei in the finite crystal, as well as to determine the pertinent one-electron wave functions, *i.e.* the "molecular" orbitals.

[*] LCAO = linear combination of atomic orbitals.

## 1. Electron States in a Finite Crystal

Two kinds of states can be distinguished in a finite crystal:

a) Volume States: The energies of these states are virtually identical with those in an infinite crystal. The electrons are distributed uniformly throughout the crystal so that the effect of the surface on their energy is small. The probability of occurrence of an electron in any unit cell of a large crystal is again very low, and at large distances from the surface, it is constant for equivalent atomic orbitals.

b) Surface States: The energies of these states are determined primarily by the conditions in the neighborhood of the surface, for the probability of finding the electrons in these states at large distances from the surface is negligibly low. Nevertheless, the probability of finding an electron in the crystal's surface layers has a finite value. Such surface states [11] have been computed for various models, using the simplified one-electron approximation methods [12–14]. It has been found that surface states with diametrically different properties are possible.

### 1. Volume States

Let us consider briefly some properties of volume states which are of importance for the understanding of the nature of the surface states.

Let us imagine that a crystal is formed from single atoms which are originally at an infinite distance away from each other and which then approach to within lattice dimensions; the process of crystal formation will produce fundamental changes in the original discrete electronic energy levels of the isolated atoms. The originally discrete levels are broadened into energy bands because of overlap of the atomic orbitals. If the interaction between the atoms or ions of the crystal is sufficiently strong, these bands will overlap or even cross (Fig. 1). When, for any reasons (*e.g.* of symmetry),

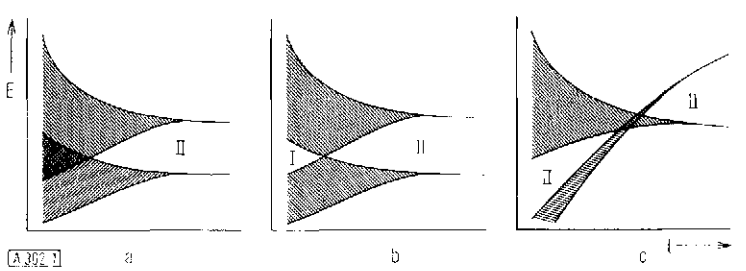



Fig. 1. Allowed energy bands of molecular orbitals.
a: overlapping of bands; b: crossing of bands;
c: overlapping of bands predominantly via a change of the Coulomb potential during crystal formation;
Abscissa: a parameter characteristic of the spacing between the electrons;
Ordinate: energy;
I: gap of the first kind;
II: gap of the second kind.


[11] *I. Tamm*, Physik. Z. Sowjetunion *1*, 733 (1932).
[12] *I. M. Lifshits* and *I. J. Pekar*, Usp. fiz. Nauk *56*, 531 (1955).
[13] *J. Koutecký*, J. physic. Chem. Solids *14*, 233 (1960).
[14] *J. Koutecký*, Physica Status Solidi *1*, 554 (1961).

the wave functions corresponding to the various atomic orbitals cannot interact, then the bands overlap and give rise to states which, although of different type, have the same energies (Fig. 1a). In such a case, the molecular orbitals may be represented as linear combinations of atomic orbitals of only one kind. The molecular orbitals will then have the form

$$\Psi_{j\,(i)} = \sum_{p,\gamma} c_{j;\,p\gamma;\,i} \cdot \chi_{p\gamma,\,i}$$

(No summation over the index i).

On the other hand, when interaction between the wave functions is possible, then the bands cross at a definite distance between atomic nuclei (Fig. 1b). Any further decrease in the atomic spacing again results in a gap between the bands. The width, position, and even the nature of the bands after such a crossing are quite different from those before the crossing at larger interatomic distances. The crossing is often an indication of localized bonds between the atoms of the crystal, the energies of the bonding and antibonding states of this localized bond being allocated to the two bands. The positions of the bands can change not only because of interaction between the orbitals – *i.e.*, for instance, because of the formation of a chemical bond – but also because of changes occurring in the Coulomb potential of an electron in a given atomic orbital during the mutual approach of the atoms (Fig. 1c).

Let us consider, for instance, a crystal composed of two different atoms, A and B. Let us suppose that the highest one-electron energy level of a free atom A partly occupied by electrons is situated lower than the corresponding level of the free atom B. The crystal may then be considered as being composed of ions, formed by transition of all the electrons from the highest partly filled level of the A atom to the highest partly occupied level of the B atom. As the ions A and B approach each other, their energies are reduced by electrostatic attraction; this manifests itself as a shift of the highest occupied band of the B ion. Thus, at small interionic distances, we find this band at a level lower than that of the empty band associated with the originally partly occupied degenerate levels of the free atom A.

The transition of an electron from the highest occupied band (which arises from the energy level of the B atom) to the empty band (which arises from the degenerate level of atom A) is equivalent to the creation of a neutral atom in a lattice composed of monovalent ions.

The gaps between the allowed energy levels of the volume states can be differentiated into gaps of the first and of the second kind. Gaps of the first kind are caused by localized bonding, although the localization need not be complete. The energy bands separated by a gap of the first kind correspond to molecular orbitals of the bonding and antibonding states. Gaps of the second kind separate bands whose molecular orbitals are produced by different atomic orbitals; in this case, there need not be any correspondence between the energy sequence of the molecular orbitals and those of the atomic orbitals in the isolated atoms; ionic crystals stand out especially in this respect.

Crystals in which there is a gap between the energy bands of the bonding and antibonding states and in which the bonding states are fully occupied (in accordance with the Pauli principle) while the antibonding states are empty are insulators or semiconductors. In the terminology of solid state physics, the highest completely filled energy band is designated as the "valence band", and the first empty band as the "conduction band". Thus, insulators and semiconductors are substances which have large or small gaps, respectively, between the valence and conduction bands.

Metals exhibit considerable broadening of the bands and correspondingly strong overlapping, but the resulting complex band is not fully occupied. The kind of gap prevailing within a given substance can be determined either by investigation of the wave functions the energies of which produce the above bands separated by the gap, or else from chemical and physical informations about properties of the bonds in the crystal. To gain a clearer understanding of the phenomena involved, we shall now proceed to examine a simple model.

## 2. Energy Spectra Corresponding to Models of Crystals with Localized Bonds

Even a simplified model, such as that of a chain of mutually interacting atoms, provides an insight into most of the typical crystal properties.

We shall consider only two atomic orbitals for each atom and shall use these to form the molecular orbitals [15–17] (Fig. 2). The first of these atomic orbitals is spherically symmetrical (the s orbital), while the second one is antisymmetrical [*] with respect to a plane

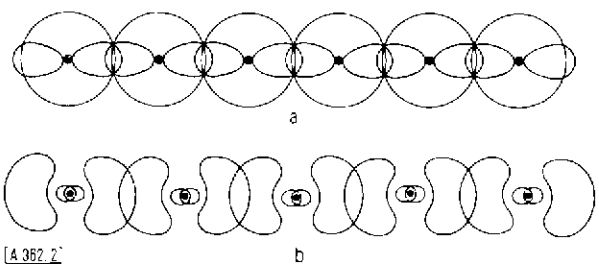



Fig. 2. Linear atomic chain.

a: Atomic 2s and 2p orbitals whose linear combination according to the MO-LCAO method results in molecular orbitals;

b: 2sp hybrids which cause localized bonds at small interatomic distances.

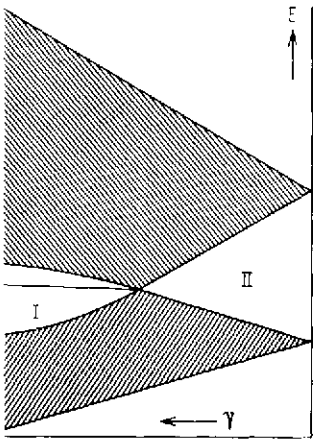
passing through the atom and orthogonal to the atomic chain (the 2p orbital). The remaining 2p atomic orbitals are neglected. If the interatomic distance is very large, then two discrete energy levels can be distinguished; one of these corresponds to the 2s and the other to the 2p state. As the atoms approach each other, these levels give rise to bands, mostly via the separate interactions of s orbitals with each other and of p orbitals with each other. In addition, interaction between the s and p orbitals is also present and results in intermingling of 2p orbitals in the 2s orbitals and vice versa. It is only at small interionic distances that we can use the concept of a localized bond, *i.e.* we can say that 2sp hybrids (Fig. 2b) are formed between the atoms.

It is convenient to take the sp hybrids into account when the interaction between the hybrids of the same atom is smaller than that between the sp hybrids of two

[15] *E.T. Goodwin*, Proc. Cambridge philos. Soc. *35*, 232 (1939).
[16] *K. Artmann*, Z. Physik *131*, 244 (1952).
[17] *J. Koutecký* and *M. Tomášek*, J. physic. Chem. Solids *14*, 241 (1960).

[*] The notation "antisymmetrical" means that the sign of the atomic orbital considered is changed by reflection in a plane.

neighboring atoms. At a given interatomic distance, the formation of sp-hybridized bonds within an infinitely long atomic chain manifests itself via the crossing of the bands and formation of a new gap (see Fig. 3). The

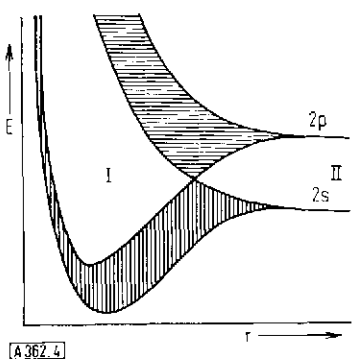



A 362. 3

Fig. 3. The band diagram of a linear atomic chain (Fig. 2) as a function of the interatomic distance.

γ: A parameter which is an approximately exponential function of the interatomic distance r [$\gamma \sim \exp(-kr)$]. The energy level of the Shockley surface state is shown in gap I.

energy gap II present at large interatomic distances results mainly from the difference in the energies of the 2s and 2p atomic orbitals. The gap present at small interatomic distances is caused by localized bonding. For a concrete example, see the energy states of diamond as a function of the interatomic distances (Fig. 4 [18]).




A 362. 4

Fig. 4. The band diagram of diamond as a function of the distance r between the carbon atoms [18].

The gap II present at large spacings between the carbon atoms is caused by the energy difference between the 2s and 2p atomic orbitals. The gap I present at smaller interatomic spacings is caused by localized bonding between hybrid $sp^3$ orbitals.

### 3. Surface States

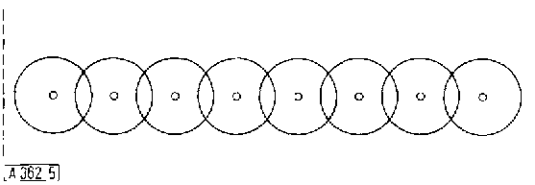
a) *When the Change of the Potential Function inside the Crystal is Sufficiently Large.*

Let us consider a simple case in which we may restrict ourselves to a single band of those volume states which are generated by atomic orbitals of a single kind. We are thus dealing with the wave function of the form

$$\Psi_j = \sum_p c_{j;p} \cdot \chi_p$$

(Indices other than those for the unit cell are superfluous). Index p is summated from $-\infty$ to $+\infty$ in the case of an infinite chain and from 1 to $+\infty$ in the case of a finite chain.

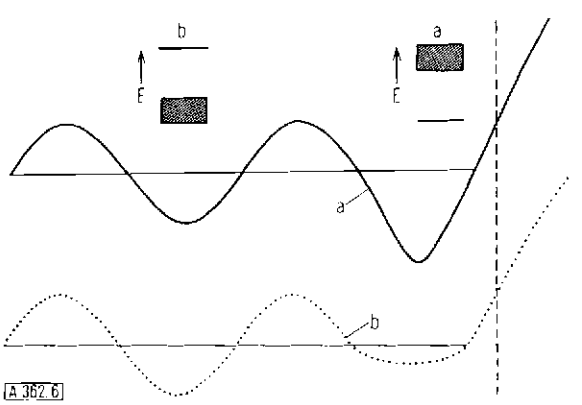
Our model is a linear atomic chain with uniform interatomic distances, in which a spherically symmetrical s-type atomic orbital is considered for each atom (Fig. 5). We thus obtain a single band of allowed volume state energies. In a real crystal, this assumption is justified to some extent when the bands of allowed volume state energies are quite far apart and are separated by wide gaps of the second kind.



A 362. 5

Fig. 5. The simplest model of a finite linear atomic chain: the atomic orbitals are combined into molecular orbitals.

The existence of the crystal surface may be related to a perturbance of the ideal periodicity of the potential function inside the crystal (Fig. 6). One measure of this perturbance of the potential is the Coulomb integral difference $(\alpha_i - \alpha)$, where $\alpha_i$ is the Coulomb integral for the i-th atom and $\alpha$ is the integral corresponding to the atom in an ideal infinite chain. When this perturbance encompasses only the surface atoms, the surface states described by *Tamm* [11] are obtained; these are characterized by an exponential decrease of the electron density with increasing distance from the surface. While this is a monotonic function, other surface states (discussed below) do not decrease monotonically. In the case of Tamm states, the potential drop at the crystal surface must be large enough [11,16,19] to force the electron to stay in the deep potential well near the




A 362. 6

Fig. 6. Tamm surface states. Schematic representation of the potential and the corresponding one-electron energies for the model shown in Fig. 5 as a function of the distance from the surface. a: Decrease, and b: rise of the potential in the region of surface atoms (perpendicular dashed line: the crystal boundary).

[18] *G. E. Kimball*, J. chem. Physics *3*, 560 (1935).

[19] *E. T. Goodwin*, Proc. Cambridge philos. Soc. *35*, 221 (1939).

surface atom and to prevent it from delocalization, the behavior favored from the energy point of view. When the potential drop at the surface is large enough, the energy level of the localized state lies below the band of allowed volume state energies (Fig. 6a). Tamm surface states also appear in the case of a rise in potential at the crystal surface (Fig. 6b), although here they are not favored because they lie above the band of allowed volume state energies. Inside the crystal, the electrons in volume states are delocalized and can avoid this unfavorable region, and have thus lower energies than electrons in surface states.

When $\alpha_j = \alpha\,(j \neq 1)$, the condition for the existence of Tamm surface states can be expressed in terms of Coulomb integrals as $|\alpha_1 - \alpha| > \beta$, where $\beta$ is the resonance integral between two neighboring atomic orbitals. The exponential decrease of the probability of finding an electron at the p-th atom is given by the equation:

$$\left|c_p/c_{p-1}\right|^2 = \left|(\alpha_1-\alpha)/\beta\right|^2 .$$

The energy of the Tamm state is

$$E = \alpha_1 + \beta^2/(\alpha_1-\alpha) .$$

If we proceed from a finite atomic chain to a semi-infinite [*] crystal, then all the qualitative deductions remain the same as those for the one-dimensional case, but the discrete energy levels corresponding to the surface states spread out into bands (Fig. 7). The number of Tamm surface states equals the number of surface atoms.

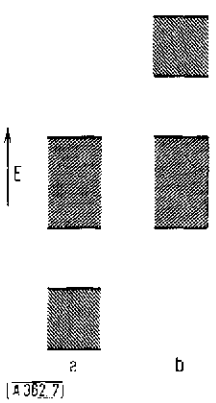



Fig. 7. Molecular orbital energies for a cubic crystal bounded by a single plane; it is assumed that only one atomic orbital of each atom may be used in the construction of the molecular orbital (the volume state bands are hatched from the upper right to the lower left, the surface state bands from the upper left to the lower right). a: Decrease and b: rise of the potential in the region of surface atoms.

If the perturbance of the potential reaches even deeper beneath the crystal surface, then states may exist having the maximum electron residence probability not only at the surface cells, but also in cells located below the surface [20]. In brief, one can say that the Tamm surface states are occasioned by local changes of potential at and immediately below the crystal surface. The mere existence of a surface is not sufficient for their occurrence.

[*] The term semi-infinite implies that the crystal is bounded by one plane and thus occupies only a half-space.

[20] *J. Koutecký*, Physic. Rev. *108*. 13 (1957).

b) *When There are Strong Bonds between the Surface Atoms and Those of the Second Layer*

Let us again consider linear atomic chains, but let us now assume that the bonds between the atoms at the surface and those immediately below them are stronger than the bonds in the bulk of the crystal [20,21]. A stronger bond indicates an electron with lower energy, *i.e.* an electron localized in a bonding state between the two atoms. Localization of the electron in an antibonding state (relative to the stronger bond) is, on the other hand, not favored. In accordance with this concept, two localized states are obtained when the strengthening of the bond between the first and the second atoms is sufficiently great: one lies below and the other above the band of allowed volume state energies (Fig. 8).

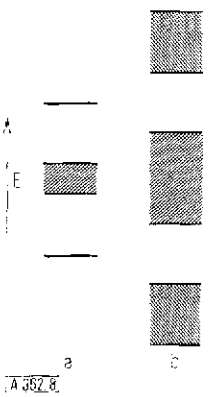



Fig. 8. One-electron energies of a semi-infinite crystal with a strengthened bond, a: between the surface atom and that immediately below it, b: between the first and second surface layers of a semi-infinite crystal (similar spectra are obtained in the case of chemisorption when the surface is completely occupied). The band marking is the same as in Fig. 7.

The strength of the bonds between the surface atoms and those in the second layer is not identical with the bond strengths prevailing in the bulk of the crystal. In the MO-LCAO approximation, this bond strength is expressed in terms of the difference between the resonance integrals $\beta_{1,2}$ and $\beta$ (for two neighboring atomic orbitals inside the crystal). The condition for the existence of such a surface state is:

$$\beta_{1,2}^2 > 2\,\beta^2 .$$

If the increase in bond strength of more than two atomic layers is sufficiently large, several localized states are obtained in a gap of the second kind, both below and above the band of allowed volume state energies.

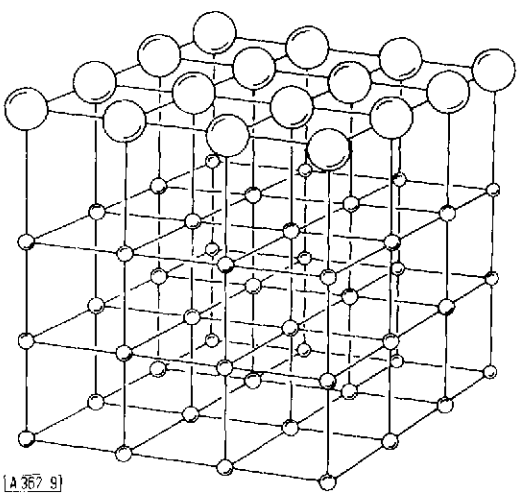
If both the Coulomb potential of the surface layer and the bond strength between the atoms of the surface layers are changed, then we have an intermediate case. The drop in the Coulomb potential facilitates the occurrence of localized bonding surface states and prevents antibonding surface states. The opposite result is obtained if the Coulomb potential increases. The shift of the energy of the localized state may then be of such magnitude as to render the surface state energy identical with some volume state energy, thus leaving no basis for the independent existence of a surface state, in which case the latter disappears.

[21] *T. A. Hoffmann*, Acta physica Acad. Sci. hung. *3*, 195 (1953).

## II. Chemisorption States

### 1. Tamm Chemisorption States

Changes in the Coulomb potential and bond strengths in surface layers may be caused by the mere existence of the crystal surface. The potential in the region of surface atoms can, however, also be altered by adsorption of ions [7,8,10]. When the surface is fully occupied (formation of a monolayer), its symmetry need not be disturbed by the adsorption. If homopolar bonds are formed between the chemisorbed particles and the surface atoms [22–24] and if the surface is fully occupied, the chemisorption can also be thought of as an incorporation of the chemisorbed particles into the crystal; the bond strengths which deviate from those prevailing in the bulk of the crystal may be ascribed to the bonds formed between the chemisorbed particles and the atoms at the crystal boundary. For the above representations to hold, the chemisorbed particles must form – at least approximately – a two-dimensional network with a symmetry identical to that of the crystal surface (Fig. 9). In effect we are dealing with a perfect



[A 367 9]

Fig. 9. Chemisorption model at full coverage and preserved symmetry of the surface.

analogy to a crystal with an altered bond strength between the atoms of the surface and those in the second layer (cf. Sect. I.3b). Thus, localization of electrons in surface states may be compared with the localization of electrons in strong chemisorption bonds.

In chemisorption, bonding states may occur whose energies lie below the band of allowed volume state energies. In addition, there is a band corresponding to the antibonding states of the chemisorption bond and lying above the band of allowed volume state energies (Fig. 8). The condition for the existence of these states is again substantially greater strength of the chemisorption bond relative to the strength of the bonding of the atoms inside the crystal. If this condition is not satisfied, then the electrons participating in the chemisorption bond cannot be definitely assigned to any specific localized state. Instead, all the electrons of the crystal will participate to the same extent in the chemisorption bond, and the chemisorbed particles will appear only as an extension of the crystal itself. This chemisorption bond has a metallic character. Just as for surface states, differences between the electronegativity of the chemisorbed and of the crystal atoms may result in shifts in the localized chemisorption bands within the crystal. This shift may even lead to the disappearance of these bands, as these are merged into a volume state band.

If the surface is only incompletely covered [24–27], we are dealing with perturbed symmetry of the crystal surface. Thus, the chemisorbed layer can no longer be formally regarded as an extension of the crystal. However, the essential conclusions derived above remain valid even in this case. Because of the analogy between Tamm surface states and the localized surface states prevailing in the case of a strong chemisorption bond, these latter states are called Tamm chemisorption states.

### 2. Shockley Chemisorption States

As already mentioned, the gaps between the bands in the band diagram of allowed volume state energies may result from the existence of localized bonds between atoms of the unit cell. When the crystal surface intersects localized bonds (or at least bonds which are stronger than others), we find Shockley surface states [28–31]. These lie in gaps of the first kind. If the gap is of the second kind, then surface formation results in no localized surface states at all. Shockley surface states are thus localized free valences present in the surface of a crystal with localized bonds [13,14,32].

The formation of Shockley surface states may be explained more lucidly by means of the simple model of a linear atomic chain [17,33]. We shall consider only one 2s and one 2p orbital for each atom. In the case of the 2p orbital, the axis of maximum electron density (Fig. 2a) coincides with the chain axis. If localized bonds occur in this chain between sp hybrids and if the chain is then broken (Fig. 2b), then one of these localized sp bonds is also broken. We then have a state in which the electron is localized in the vicinity of the surface, predominantly in the sp hybrid of the broken bond. In this state, the probability of finding the electron in the sp hybrid which is oriented towards the chain break is significantly higher than that of finding it in the oppositely oriented sp hybrid of the same atom. The probability of its occurrence in the latter hybrid may even be negligibly low. This occurs when the interaction between two sp orbitals not forming a bond between two neighboring atoms is negligible. In addition, for sp orbitals of the same orientation, the amplitude of the wave function decreases with increasing distance from the chain break (Fig. 10).

Mere cleavage of the bond between the surface atoms is sufficient to create a Shockley surface state. On the other hand, change in the Coulomb potential within a finite crystal can cause the Shockley surface state to disappear. As already stated, Shockley surface states always lie in the gap between the bands of allowed


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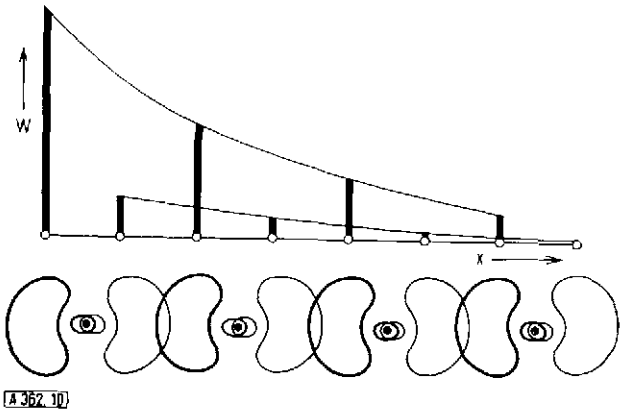



Fig. 10. Schematic representation of the wave function for Shockley surface states. W: The probability of finding the electron in a 2sp hybrid orbital; x: distance from the surface.

volume state energies. Specifically, they are usually found in not too wide gaps. Variation of the potential within the crystal causes a shift of the energy level of the surface state, which may then merge with the upper or lower volume state band.

When a surface atom possessing localized bonds interrupted by a crystal surface interacts with a molecule of a surrounding gaseous phase, chemisorption states of the Shockley type may be formed. These surface states, which correspond to the bonding and antibonding states of the chemisorption bond, are localized only if the chemisorption bond is not too strong. These states are called "Shockley chemisorption states" because they can be derived from the Shockley surface states.

If the strength of the chemisorption bond is of the same magnitude as that prevailing in the bulk of the crystal, then the bands of allowed volume state energies overlap the energies of the chemisorption states, and the latter are then no longer localized. When the chemisorption bond is very strong, then Tamm chemisorption state energy bands may appear below the lowest or above the uppermost band. The differences in the electronegativities of the participating atoms are also of major importance in this connection.

Shockley surface states may also appear when the crystal possesses both strong and weak bonds [32–36]. Let us consider as model an atomic chain of which it is sufficient for our purposes to take into account only a single atomic orbital, which is symmetrical with respect to the plane passing through the atom and perpendicular to the chain. The spacings between the atoms alternate in length so that a stronger bond always succeeds a weaker one in the chain. If we now form a semi-infinite chain by breaking a stronger bond, a Shockley surface state will be produced in the gap between the allowed energy bands of the atomic chain. No Shockley states would arise from the breaking of a weaker bond.

The difference in bond strength resulting from the varying bond lengths is expressed in the MO-LCAO approximation as the difference in the resonance integrals. Thus, bonds with resonance integrals $\beta$ and $\beta'$ alternate in the chain. If a $\beta$ bond is interrupted by the surface, then the condition for the existence of a Shockley surface state is

$$|\beta/\beta'| > 1$$

The energy is then given by the relationship $E = \alpha$, where $\alpha$ is the Coulomb integral of an isolated atomic orbital.

The molecular orbital for the Shockley surface state may be written in the form

$$\Psi = \sum_p c_{p;1} \cdot \chi_{p;1}$$

since $c_{p;2} = 0$. The unit cell contains two atoms.

The above model is only a mental exercise since we have not considered the possibility of change in the interatomic distances on transition from the infinite to the semi-infinite chain. If the surface atom is assigned the number 1 and the atoms succeeding it (in the direction of the crystal center) are numbered consecutively higher as the distance from the chain break increases, then the probability of finding an electron in the orbitals of even-numbered atoms is zero, provided we consider only interactions between neighboring atomic orbitals. In this case, an analogy can be drawn between the Shockley surface states and the non-bonding molecular orbitals familiar fron the theory of conjugated hydrocarbons [37].

According to the MO-LCAO theory of conjugated hydrocarbons, molecular orbitals occur in "alternant" [*] hydrocarbons containing an odd number of atoms in the conjugated system which possess the following two characteristics:

a) The energy of these molecular orbitals corresponds to that of a $p_z$-localized electron. No strengthening or weakening of the bonds between the atoms of the conjugated system is required for the electron to be in this state; hence, this state is called a non-bonding one (as distinguished from bonding and antibonding states).

b) Only for one atomic class is the residence probability of one electron greater than zero. The non-bonding orbital system is associated with the phenomenon that hydrocarbons with an odd number of carbon atoms are free radicals if each carbon atom contributes one electron to the conjugated $\pi$-electron system.

Thus, here Shockley surface states form an expression for the free radical properties of a surface in which free valences are present. It can be shown that the energy bands of the Shockley surface states are only half-filled with electrons, since the number of electrons equals the number of atomic orbitals.

We should emphasize here that results which agree qualitatively are obtained with other models using the one-electron approximation. For example, *Kronig* and *Penney* [38–43] employed a model with a constant linear potential along the interatomic bond, while the atoms themselves represented very narrow and deep potential wells. Here, too, Tamm and Shockley surface states can be differentiated. Their properties

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[*] The term "alternant" implies that two classes of atoms are formed in such a way that every second neighbor of an atom belongs to the same class.

[38] *R. L. Kronig* and *W. G. Penney,* Proc. Roy. Soc. (London) *A 130,* 499 (1931).

[39] *P. Phariseau,* Physica (Utrecht) *26,* 737 (1960).

[40] *P. Phariseau,* Physica (Utrecht) *26,* 1192 (1960).

[41] *T. B. Grimley* and *B. W. Holland,* Proc. physic. Soc. *78,* 217 (1961).

[42] *J. Koutecký,* Czechoslov. J. Physics *B 12,* 177 (1962).

[43] *J. Koutecký* and *M. Tomášek,* Czechoslov. J. Physics *B 12,* 48 (1962).

are similar to those of states calculated by the MO-LCAO method. We may thus conclude that, provided a one-electron approximation is used, the results are qualitatively independent of the particular model employed.

## III. Surface States in Semi-Infinite Diamond-Type Crystals

### 1. Boundary Formed by the (111) Plane [44]

So far we have represented the properties of the main types of surface states by means of simplified models. However, complex spectra of allowed volume state energies may give rise to various combinations of and transitions between surface or chemisorption states.

Diamond is a real crystal with distinct localized bonds. The (111) plane intersects one of the localized bonds formed by $sp^3$ hybrid orbitals of each surface atom (Fig. 11); each surface atom is bound (by three bonds) to three atoms of the second layer. Let us then set up a

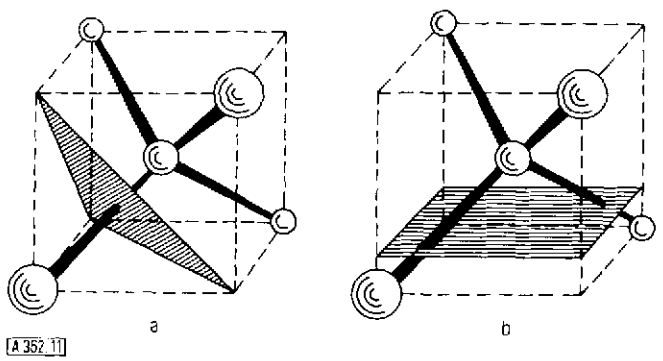



Fig. 11. Position of the $2sp^3$ orbitals of boundary atoms in diamond a: Crystal bounded by the (111) plane, b: by the (100) plane.

simple model, in which we consider the mutual interaction between such $sp^3$ hybrids of the adjacent atoms whose maximum electron density coincides with the line interconnecting them. We shall also consider the interaction between the $sp^3$ hybrids of one and the same atom (this allows shifting of an electron from one bond to another). Such a simplified model neglects a number of other interactions between various atomic hybrid orbitals, even though these undoubtedly are also of considerable importance with diamond and attain even greater importance in the case of the related silicon and germanium crystals.

We thus consider the resonance integrals $\gamma$ between the $sp^3$ hybrids of neighboring carbon atoms and the resonance integrals $\gamma'$ between $sp^3$ hybrids of one carbon atom. The relationship $\gamma'/\gamma = 0.25$ seems to be valid for diamond. This model yields two bands of allowed volume state energies (Fig. 12): one of the bands corresponds to the bonding states, the other to the antibonding states, with regard to the localized bond between the $sp^3$ hybrids of neighboring carbon atoms. The finite width of these bands is caused by the interaction between the $sp^3$ hybrids of the same atom. If this interaction were absent, the energy spectrum of diamond would consist of two discrete lines corresponding to the bonding and antibonding orbitals localized on bonds between neighboring carbon atoms.

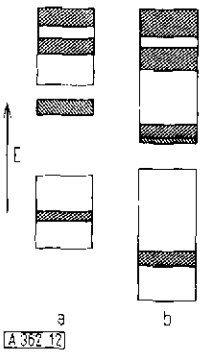



Fig. 12. One-electron energies of a diamond-type crystal bounded by the (111) plane. The bands of the surface states are hatched from the upper left to the lower right when they do not overlap with the bands of volume states. In the case of overlap, they are hatched from the upper right to the lower left). a: Weak and b: strong interaction between the $sp^3$ hybrids of the same atom.

This type of interaction also entails a complex structure of the single bands. In this case, the valence band as well as the conduction band consist of partial bands corresponding to the various possible interactions between the $sp^3$ hybrids of the same carbon atom. These partial bands overlap, since interaction between the states corresponding to them is forbidden for reasons of symmetry.

The band of Shockley surface states whose properties are due to the existence of free surface bonds is found in the gap of the first kind present between the valence and conduction bands. The Shockley band is only half-filled. An electron in a state of this energy band is localized mostly in that $sp^3$ hybrid of the surface atom which is oriented outward from the crystal surface.

Here again the typical alternating probability of occurrence of the electrons in the hybridized orbitals is encountered. The probability that an electron existing in this Shockley state will be found in the remaining $sp^3$ hybrids of the surface atoms is very small. Furthermore, in the above model, the same probability with those $sp^3$ hybrids of the second layer atoms which are oriented inward into the crystal is in fact zero.

However, additional surface states are made possible by the complex volume band structure of the valence and conduction bands. The electrons present in these states are preferentially localized in those $sp^3$ hybrids which form the bonds between the first and second atomic layers. The probability that an electron present in this state will reside in an $sp^3$ hybrid which belongs to a second-layer carbon atom and is oriented inward into the bulk of the crystal is again zero. Thus, these states again reflect the specific bond conditions between the layers of atoms near the surface. Their existence demonstrates the fact that the bonds between the first and second layers differ in character from those between the second and third layers, etc.

Interaction between an $sp^3$ hybrid of a surface atom and the atomic orbital of a chemisorbed atom may lead

[44] *J. Koutecký* and *M. Tomdšek*, Physic. Rev. *120*, 1212 (1960).

[45] *J. Koutecký*, Surface Science, in the press.

to localized chemisorption states (Fig. 13) [45]. If this interaction is significantly weaker than that between $sp^3$ hybrids of neighboring atoms inside the crystal, then Shockley bonding and antibonding states arise in the gap between the valence and conduction bands

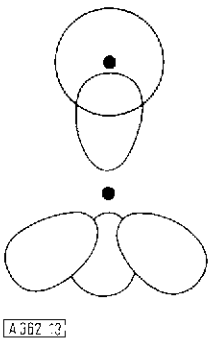


Fig. 13. Model of chemisorption at the (111) diamond surface. The atomic $sp^3$ orbitals of a surface atom of a diamond crystal and the atomic s orbital of the chemisorbed atom are shown schematically. The chemisorption bond arises from the overlap between an s and an $sp^3$ atomic orbital.

(Fig. 14a). In contrast, when the interaction is very strong, the energy levels of localized chemisorption states may be below the valence band or above the conduction band (Fig. 14b). These energy bands are of the Tamm type.

In addition, the model also yields chemisorption bands whose localized surface states fall within the conduction and valence bands of the volume states. These surface states characterize the bonding conditions between the first and second layers below the surface.

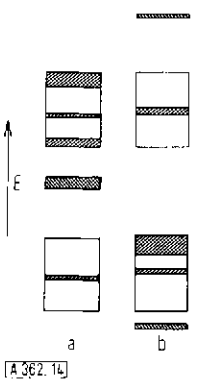



Fig. 14 Allowed one-electron energies for chemisorption at the (111) diamond surface in accordance with the model of Fig. 13. a: Weak and b: strong chemisorption bond. (The band marking is the same as in Fig. 12).

If we assume a large difference between the energy of that surface atom $sp^3$ hybrid which is oriented toward the vacuum and the energy of the $sp^3$ hybrids in the bulk of the crystal, then we obtain Tamm surface states. Such a change in energy leads to the formation of bands situated below the valence band or below (according to the sign of this energy change) the conduction band of the volume state (Fig. 15). In addition, the bands of the surface states lie within the bands of the volume states.

A small change in the energy of a vacuum-directed $sp^3$ hybrid of a surface atom (relative to an atom in the bulk of the crystal) causes only a shift of the band of the Shockley surface states.

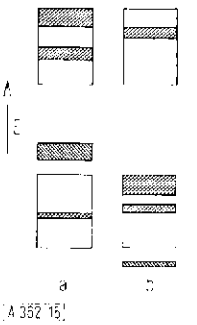



Fig. 15. Allowed one-electron energies for a: a small and b: a large change in the potential of the outward-directed $sp^3$ hybrid of a surface atom of the (111) diamond plane. (The band marking is the same as in Fig. 12).

### 2. Boundary Formed by the (100) Plane [46]

The (100) plane cuts through two bonds of each surface carbon atom in the crystal (Fig. 11). Interaction between these two free $sp^3$ hybrids produces rehybridization of the hybrid orbitals. The spectrum of allowed surface state energies (Fig. 16) exhibits a band I between the

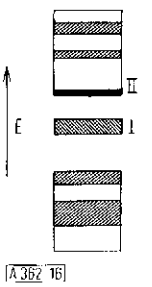



Fig. 16. Allowed one-electron energies in a diamond crystal bounded by the (100) plane. (The band marking is the same as in Fig. 12).

valence and conduction bands. This band is situated at a lower level than that of the semi-infinite diamond crystal bounded by the (111) plane, and is fully occupied. In addition, there is also a band II situated in the vicinity of the lower edge of the conduction band. In our model, band II degenerates to a single energy level and is empty in the ground state. There are no free valences here, only a lone electron pair belonging to the surface atom. Thus, while the (111) surface is characterized by a polyradical, the (100) surface is characterized by lone electron pairs which tend to form donor-acceptor bonds with gas molecules. Naturally other valence states, permitting other bonds, may arise by excitation.

## IV. Electronic States in Crystals Containing Heterogenous Atomic Species

Our discussion thus far was concerned with crystals composed of atoms of the same kind. The problem then arises whether the results derived will still hold when atoms of various kinds are present in the unit cell, or whether the presence of two kinds of atoms will not result in a new kind of surface state.

[46] *J. Koutecký*, Czechoslov. J. Physics *B 12*, 184 (1962).

The simple model of a chain whose unit cell contains two different atoms A and B was studied by means of the MO-LCAO method [47,48]. It was found that the volume states form two energy bands separated by a gap of the second kind. A finite chain is again produced by bond rupture. Let an atom of species A then be situated at the surface and that of species B below it. The atomic orbitals of atoms A and B will then be characterized by differing Coulomb integrals $\alpha_A$ and $\alpha_B$, where $\omega = \alpha_A - \alpha_B$ is the gap width between the two energy bands of volume states. It turns out that the fact that the chain is finite, *i.e.* that the bond is ruptured at the surface, is not sufficient to produce Shockley surface states. As for a chain of identical atoms, bond alternation and the formation of a finite crystal by rupture of the stronger bond is the prerequisite for the appearance of Shockley surface states. The condition for Tamm surface states – a sufficiently large change of the Coulomb potential in the vicinity of a surface atom – is qualitatively similar to the requirements imposed on a chain of identical atoms.

The condition for the existence of Tamm surface states is

$$\delta^2 + \delta\omega/2 > \beta$$

where the variation of the Coulomb integral of a surface atom is expressed by

$$\delta = \alpha_1 - \alpha_A$$

$\beta$ being the resonance integral. The occurrence of Tamm surface states is facilitated by an increase in the potential difference between the surface atom and its neighbors.

However, here we encounter not only the surface states already discussed, but also some characteristic new phenomena. We can, for instance, stipulate that the potential of an electron localized in the orbital of the atom A shall be smaller than that in the orbital of atom B. Thus, if the surface causes a rise in the potential near the surface atom A, then the latter acquires greater similarity to the B atoms within the chain than it has to an identically situated A atom. Within the gap between the energy bands of the volume state, we then find one surface state energy level which is characteristic of chains containing various atomic species. A similar result is obtained when the potential of an electron localized in the orbital of atom A is intrinsically higher than the corresponding potential of a B atom, but is reduced because of surface formation. Here again, the A atom at the surface acquires greater similarity to a B atom than it has to the A atoms within the chain. The condition for the existence of this surface state is $\delta\omega < 0$.

## V. Concluding Remarks

From the above arguments it can be seen that it is possible for an electron to become localized in various states near the surface, depending on the physical and chemical causes of this localization. Surface atoms generally exhibit properties different from those of free atoms or of atoms bound in the crystal bulk. The nature of the surface states, especially the extent of localization, is an indication of the extent to which the properties of the atoms within the crystal have been retained by the surface atoms.

In spite of the variety of the surface states, there are still some common characteristics among them, so that a theory accounting for all the phenomena may be developed.

Knowledge of the degree of filling of the one-electron energy spectra is a prerequisite for obtaining some information about the effect of the surface states on surface behavior. *Volkenshteyn*'s concept [9] of the occurrence of a chemisorption bond at the surface of ionic crystals might serve as an example. According to it, a localized state of the Tamm type arises during chemisorption. The pertinent wave function may be formed by linear combination of the orbitals of excited atoms. In addition, linear combination of the same atomic orbitals produces also the conduction band of the volume state of an ionic crystal. This chemisoption surface state may localize either a single electron provided by the chemisorbed atom (weak bond) or two electrons (strong bond). Another model used in the theory of chemisorption and catalysis is the concept already mentioned of ionosorption [10].

No fixed free surface valences have thus far been considered in the chemisorption theory. We have seen, however, for an ideal diamond surface created by the (111) plane, that the Shockley state band in the gap between the conduction and valence bands is only half-filled; this phenomenon is a characteristic indication of the existence of fixed free valences at the surface. The surface state corresponding to these valences can easily disappear when a bond formed with a chemisorbed substance is stronger. This is in agreement with the fact that the concentration of surface states on impure germanium surfaces is very low.

As shown by the examples, the present-day theories of chemisorption and catalysis are tailored to special cases. Quantum chemistry shows that multifarious states may exist at surfaces; electrons may be localized in these states and this localization explains the vast differences in surface properties observed. Thus, three basic problems remain to be solved by the quantum chemistry of surfaces:

1. The theoretical basis for surface states in electrically conducting and in salt-like crystals remains to be worked out. First steps have already been taken in this direction [49,50]. These classes of substances do not lend themselves too readily to interpretation by the MO-LCAO method, since the latter yields only crude and not entirely reliable approximations.

[47] *A. T. Amos* and *S. G. Davison*, Physica (Utrecht), in the press.

[48] *J. Koutecký*, unpublished work.

[49] *E. Antončik*, J. physic. Chem. Solids *21*, 137 (1961).

[50] *D. A. Dowden* and *D. Wells*: Actes du II-ème congrès international de catalyse 1960. Ed. Technip, Paris 1961, p. 1499.

2. A semiquantitative calculation of the surface states should be executed for at least a few simple substances; this will allow quantitative predictions to be made about the strengths of bonds between surface atoms or of the chemisorption bonds. In order to achieve this aim it will of course be necessary to take into account the small changes in volume states due to surface formation, for their total effect is not negligible [51].

3. The qualitative and quantitative theoretical results should be utilized in surface chemisorption, in semiconductor electrochemistry [52], and in the clarification of the effect of surfaces on semiconductor properties. Quantum chemistry can be used not only to explain the properties of pure surfaces but also of surface compounds, that is, the problems of real surfaces.

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[52] *H. Gerischer:* Advances in Electrochemistry and Electrochemical Engineering I. Interscience Publishers, New York 1961, p. 139.

# COMMUNICATIONS

## Synthesis of Alkynylamines by Nucleophilic Substitution of Halogenoalkynes [*]

By Dr. H. G. Viehe and M. Reinstein

Union Carbide European Research Associates, Brussels (Belgium)

We recently reported [1] the synthesis of diethyl(phenylethynyl)amine *(1)*, the first representative of this class of compounds. Fluorophenylacetylene was formulated as a hypothetical intermediate in the reaction

$$C_6H_5-CH=CClF \xrightarrow[86\,\%]{2\ LiN(C_2H_5)_2} C_6H_5-C\equiv C-N(C_2H_5)_2 \quad (1)$$

because the occurrence of chlorophenylacetylene was unlikely according to the literature [2].

However, we have now obtained dimethyl(phenylethynyl)amine *(2)* in 87 % yield by condensation of chlorophenylacetylene with lithium dimethylamide in ether in a molar ratio of 1.1:1; the temperature during addition of the alkyne was −80 °C; the reaction mixture was then allowed to warm up to room temperature, the total reaction time being one hour.

$$C_6H_5-C\equiv C-Cl \xrightarrow[87\,\%]{LiN(CH_3)_2} C_6H_5-C\equiv C-N(CH_3)_2 \quad (2)$$

The ease of substitution of the chlorine may be due to the activating phenyl residue [3,4]. This is reconcilable with the fact that t-butylchloroacetylene does not react with lithium dimethylamide under the same conditions. On the other hand, t-butylethynyldimethylamine *(3)* is readily formed from t-butylfluoroacetylene [5] and lithium dimethylamide. It is more advantageous in practice not to use t-butylfluoroacetylene as such, but instead to treat its "dihydrobromide", *i.e.* 1,2-dibromo-1-t-butyl-2-fluoroethane, with excess amide (molar ratio 1:4, ether as solvent, temperature of addition −80 °C followed by warming to room temperature, reaction time about 1 hour).

$$(CH_3)_3C-CHBr-CHBrF \xrightarrow{LiN(CH_3)_2} [(CH_3)_3C-C\equiv C-F] \quad \text{(not isolated)}$$

$$\xrightarrow[\text{overall } 48\,\%]{LiN(CH_3)_2} (CH_3)_3C-C\equiv C-N(CH_3)_2 \quad (3)$$

t-Butylethynyldimethylamine *(3)* is also formed in 44 % yield from t-butylchloroacetylene when the latter is heated with trimethylamine for 60 hours at 135 °C.

$$(CH_3)_3C-C\equiv C-Cl \xrightarrow[44\,\%]{N(CH_3)_3} (3)$$

Starting from 1,1-dichloro-2-fluoroethylene and lithium diethylamide in a molar ratio of 1:3.3 in ether (addition temperature −80 °C followed by warming to room temperature, reaction time 1.5 hours) bisdiethylaminoacetylene *(4)* is obtained.

$$Cl_2C=CHF \xrightarrow[57\,\%]{LiN(C_2H_5)_2} (C_2H_5)_2N-C\equiv C-N(C_2H_5)_2 \quad (4)$$

The reaction products were isolated and characterized by elementary analysis, infrared spectra, and hydration to the corresponding amides.

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[*] Communication No. 6 on Heterosubstituted Acetylenes. Communication No. 5: [1].

[1] *H. G. Viehe*, Angew. Chem. *75*, 638 (1963); Angew. Chem. internat. Edit. *2*, 477 (1963).

[2] *V. Wolf* and *F. Kowitz*, Liebigs Ann. Chem. *638*, 33 (1960).

[3] *H. G. Viehe* and *E. Franchimont*, Chem. Ber. *95*, 319 (1962); *H. G. Viehe*, Chem. Ber. *92*, 3064 (1962); see also: *J. F. Arens*, Recueil Trav. chim. Pays-Bas *82*, 183 (1963).

[4] *G. R. Ziegler*, *C. A. Welch*, *C. E. Orzech*, *S. Kikkawa*, and *S. I. Miller*, J. Amer. chem. Soc. *85*, 1648 (1963).

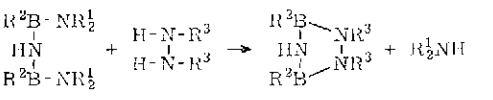
[5] This synthesis and properties of this compound will be reported separately.

## 1,3,4-Triaza-2,5-diborolidines

By Dr. K. Niedenzu, Dr. P. Fritz, and Dr. H. Jenne

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Recently, *Nöth* and *Regnet* [1] described the first derivative of 1,3,4-triaza-2,5-diborolidine. This five-membered boron-nitrogen heterocycle was obtained by aminolysis of 1,2,4,5-tetraza-3,6-diborine. We have now found that hydrazinolysis of bis(aminoboryl)amines *(1)* [2] also affords triazadiborolidines.



*(1)* *(2)*

For instance, when stoichiometric amounts of *N,N'*-dimethylhydrazine and bis(dimethylaminophenylboryl)amine are refluxed in ether for 1 h, 3,4-dimethyl-2,5-diphenyl-1,3,4-

triaza-2,5-diborolidine *(2)*, $R^2 = C_6H_5$, $R^3 = CH_3$, b.p. 180–182 °C/3 mm, m.p. 106–108 °C (sealed tube, uncorrected), precipitates out on cooling. Concentration of the mother liquor yields a second crop of crystals; the overall yield is about 85 %.

1,3,4-Triaza-2,5-diborolidines appear to be stable to heat. For example, when *(2)*, $R^2 = C_6H_5$, $R^3 = CH_3$, is heated to 225 °C *in vacuo*, no signs of decomposition are found. This behavior seems to indicate the existence of resonance stabilization of the ring by participation of BN double bonds.



This assumption is supported by the presence of a peak in the infrared spectrum of *(2)* near 1400 $cm^{-1}$; this region is normally assigned to BN double bonds [3]. In addition, the chemical reactions of *(2)*, *e.g.* with metal carbonyls, indicate a strong similarity between triazadiborolidines and the cyclopentadiene system.

However, the heterocycle *(2)* is not stable to hydrolysis. Traces of moisture first attack the B–N–B bridge to yield 3,4-dimethyl-2,5-diphenyl-1,3,4-oxodiaza-2,5-diborine, m.p. 202–204 °C [4]; this is followed by ring cleavage to afford dihydroxyphenylborane and *N,N'*-dimethylhydrazine.

Received, April 2nd and 27th, 1964 [Z 730/556 IE]
German version: Angew. Chem. *76*, 535 (1964)

[1] *H. Nöth* and *W. Regnet*, Z. Naturf. *18b*, 1138 (1963).

[2] *H. Jenne* and *K. Niedenzu*, Inorg. Chem. *3*, 68 (1964).

[3] *G. M. Wyman*, *K. Niedenzu*, and *J. W. Dawson*, J. chem. Soc. (London) *1962*, 4068.

[4] A melting point of 204 °C is given by [1].

## Diethylselenothiophosphinic Acid Derivatives

By Doz. Dr. W. Kuchen and Dipl.-Chem. B. Knop

Institut für Anorganische Chemie und Electrochemie der Technischen Hochschule Aachen (Germany)

Sodium diethylselenothiophosphinate *(1a)* has been obtained both in the fused state according to the equation:

$$(C_2H_5)_2P(S)-P(S)(C_2H_5)_2 + Na_2Se + Se \xrightarrow[2\ h]{\approx 200\ ^\circ C} 2\ (C_2H_5)_2P(S)SeNa \qquad (1a)$$

and in absolute alcohol by the reaction:

$$(C_2H_5)_2P(S)Cl + NaSeH \xrightarrow{0\ ^\circ C} (C_2H_5)_2P(S)SeNa + HCl \qquad (1a)$$

It was isolated as its crystalline dihydrate $(C_2H_5)_2P(S)SeNa \cdot 2H_2O$ *(1b)*, m.p. 124–125 °C. This is isomorphous with $(C_2H_5)_2P(S)SNa \cdot 2H_2O$ [1], which also melts at 124–125 °C.

Aqueous solutions of diethylselenothiophosphinic acid $(C_2H_5)_2P(S)SeH$ *(2)* were obtained from *(1b)* using a strongly acidic cation exchanger (*Ionenaustauscher I, from* E. Merck, Darmstadt, Germany). The acid gradually decomposes on standing for a few hours at room temperature in diffuse daylight, its solutions turning yellow.

The anion *(3)* derived from the thiol form of *(2)* according to the equilibrium

$$(C_2H_5)_2P(S)Se^{\ominus} \rightleftharpoons (C_2H_5)_2P(Se)S^{\ominus} \qquad (3)$$

is presumably practically the only species present in aqueous solutions of *(1b)* and *(2)* [2]. Hence the intensely yellow, crystalline product, m.p. 56.5 °C, which is formed in water by the reaction:

$$2\ (C_2H_5)_2P(S)SeNa \cdot 2\ H_2O + KI_3 \rightarrow (C_2H_5)_2P(Se)-S-S-P(Se)(C_2H_5)_2 + 2\ NaI + KI \qquad (1b)$$

is most probably bis(diethylselenophosphoryl)disulfane, especially since the infrared spectrum of the yellow compound in the KBr region is practically the same as that of $(C_2H_5)_2P(S)-S-S-P(S)(C_2H_5)_2$ [1].

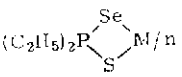
Diethylselenothiophosphinic esters, *e.g.* $(C_2H_5)_2P(S)SeC_2H_5$, b.p. 135 °C/10 mm, $n_D^{20} = 1.5854$, and $(C_2H_5)_2P(S)Se\text{-}n\text{-}C_3H_7$, b.p. 86–87 °C/0.06 mm, $n_D^{20} = 1.5738$, were obtained smoothly by refluxing *(1b)* with alkyl bromides.

$$(C_2H_5)_2P(S)SeNa \cdot 2\ H_2O + RBr \rightarrow (C_2H_5)_2P(S)SeR + NaBr \qquad (1b)$$

The structures proposed for the esters are supported by the separation of diethylphosphinothioic bromide from the products of the reaction of any one of them with 1 mole of bromine, the main reaction probably being the following:

$$(C_2H_5)_2P(S)SeR + Br_2 \rightarrow (C_2H_5)P(S)Br + RSeBr.$$

Compound *(1b)* reacts with metals to form non-electrolytic inner complexes of the type:



*e.g.* bis(diethylselenothiophosphinato)zinc(II), m.p. 157 °C; -cadmium(II), m.p. 160 °C; -nickel(II), olive-green, decomp. >142 °C; -lead(II), green-yellow, m.p. 132 °C; orange-red tris(diethylselenothiophosphinato)bismuth(III), m.p. 94 °C. The zinc and cadmium complexes, like the corresponding dialkyldithiophosphinato complexes *(4)* of these two metals, are associated in benzene [3]. The thermal and chemical stabilities [3] of the compounds *(4)* are not attained by their seleno analogues.

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German version: Angew. Chem. *76*, 496 (1964)

[1] *W. Kuchen*, *K. Strolenberg*, and *J. Metten*, Chem. Ber. *96* 1733 (1963).

[2] According to *M. J. Kabachnik*, *T. A. Mastrukova*, *A. E. Shipov*, and *T. A. Melentyeva*, Tetrahedron *9*, 10 (1960), the analogous acid $(C_2H_5)_2P(S)OH$ occurs in aqueous alcoholic solutions almost completely in the thiono form. The negative charge is thus, as would be expected, located almost exclusively at the more electronegative atom.

[3] *W. Kuchen* and *J. Metten*, Angew Chem. *72*, 584 (1960); *W. Kuchen*, *J. Metten*, and *A. Judat*, Chem. Ber., in the press.

## Benzo[a]quinolizinium Salts from 3,4-Dihydroxyphenethylamine Hydrobromide and Acetoacetaldehyde, a Possibly Biogenetic-Type Cyclization

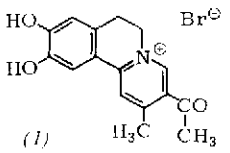
By Prof. Dr. H. J. Teuber and Dipl.-Chem. D. Laudien

Institut für Organische Chemie der Universität Frankfurt/Main (Germany)

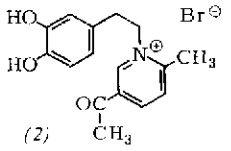
3,4-Dihydroxyphenethylamine (dopamine) hydrobromide reacts in hot glacial acetic acid with 2 moles of either acetoacetaldehyde dimethylacetal or 1-methoxy-1-buten-3-one, analogously to tryptamine [1], to yield 40 % of the benzo[*a*]quinolizinium salt *(1)* and 31 % of the pyridinium salt *(2)* [2]. In aqueous solution at 20 °C, only about 13 % of *(1)* is obtained. Product *(1)* can be separated from *(2)* as a red anhydro base $C_{16}H_{15}NO_3$.

Pure *(1)* was characterized as its oxime, 2,4-dinitrophenylhydrazone, and diacetyl derivative as well as by the mono-

methyl ether formed on reaction with methyl iodide. On reduction with sodium borohydride, *(1)* is converted into the corresponding bright yellow secondary alcohol.



*(1)*



*(2)*

The 60 Mc proton resonance spectrum [3] of the anhydro base of *(1)* in trifluoroacetic acid ($\delta = 0$ for tetramethylsilane) shows 4 one-proton singlets at $\delta = 9.1$, 8.2, 7.7, and 7.1. They correspond to the isolated protons of the pyridine and benzene rings and prove that double ring closure has occurred.

This novel synthesis leads in one step beyond the isoquinoline ring closure [4] obtained hitherto with monocarbonyl compounds to the ring system of protoemetine [5] with side chains in the "natural" positions.

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German version: Angew. Chem. *76*, 534 (1964)

[1] *H. J. Teuber* and *U. Hochmuth*, Tetrahedron Letters *1964*, 325.

[2] *H. J. Teuber, G. Wenzel*, and *U. Hochmuth*, Chem. Ber. *96*, 1119 (1963).

[3] We wish to thank Dr. *P. Pfaender* for measuring and interpreting the NMR spectra.

[4] *C. Schöpf* and *H. Bayerle*, Liebigs Ann. Chem. *513*, 190 (1934).

[5] *H.-G. Boit:* Ergebnisse der Alkaloid-Chemie bis 1960. Akademie Verlag, Berlin 1961, p. 372.

## Structure and Properties of Trihalogenogermane Etherates

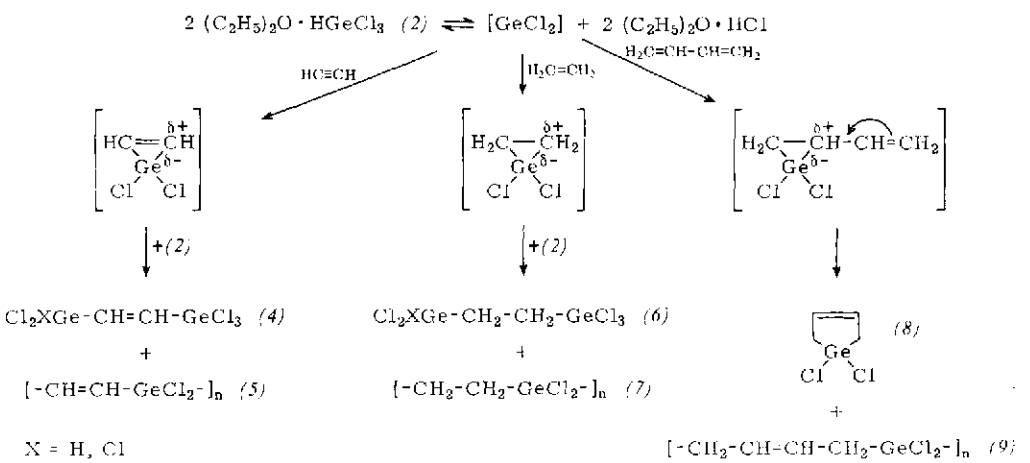
By Dr. O. M. Nefedov, cand. chem. S. P. Kolesnikov, and Dipl.-Chem. V. I. Sheichenko

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$HGeCl_3$ *(1)* associates with diethyl ether to forme an etherat $2(C_2H_5)_2O \cdot HGeCl_3$ *(2)*, a bright yellow oil which is insoluble in excess diethyl ether, but which dissolves *(1)*. The infrared spectrum of *(2)* does not contain a Ge–H band, which would be expected to occur between 2000 and 2200 $cm^{-1}$. The NMR spectrum of *(2)* [60 Mc, tetramethylsilane as internal standard] shows only the signals of the $CH_2$ and $CH_3$ groups of the ether ($\delta = -1$ to $-4$ ppm) plus a singlet at $\delta = -14.7$ to $-14.5$ ppm. Comparison of this figure with the values for $HGeCl_3$ ($-7.6$ ppm) and dilute hydrochloric acid ($-16.6$ ppm) shows that the H–Ge bond in $HGeCl_3$ is strongly polarized, hence the proton attaches itself to the lone electron pairs of the ether's oxygen atoms.

Other similar etherates are formed by *(1)*, *e.g.* with di-n-butyl ether and with tetrahydrofuran ($\delta_{Ge-H} = -14.2$ ppm); the etherate with tetrahydrofuran is soluble in tetrahydrofuran and diethyl ether. After standing for 1–2 days, *(2)* dissolves in ether. At the same time, a new NMR signal appears at about $-11$ ppm, because the etherate has partly decomposed into $C_2H_5OH$ and $C_2H_5GeCl_3$. Etherates of other trihalogenogermanes, *e.g.* $HGeI_2Cl$, are formed when $GeI_2$ is dissolved in strong hydrochloric acid/ether $[2(C_2H_5)_2O \cdot HGeI_2Cl$ *(3)*, $\delta_{Ge-H} = -12.1$ ppm]. $2(C_2H_5)_2O \cdot HSnCl_3$ ($\delta_{Sn-H} = -11.8$ ppm) is formed from $SnCl_2$ under the same conditions. The etherates of trihalogenogermanes differ strongly in their chemical behavior from the trihalogenogermanes themselves: the etherates act as sources of $GeHal_2$, *i.e.* germanium analogues of dihalogenocarbenes [1]. The reaction diagram shows the reactions of *(2)* with acetylene, ethylene, and butadiene (ca. 20 °C, normal pressure). The other etherates *(3)* react analogously. Compounds *(4)* and *(6)* react with $CH_3MgBr$ to yield the hexamethyl derivatives, and *(8)* gives rise to the dimethyl derivative. Yields: *(4)* 50–60 %; *(5)* 20–30 %; *(6)* 50–60 %; *(7)* 20–25 %; *(8)* 60–65 %; *(9)* ca. 30 %. Both RMgHal and RLi cause *(2)*, *(3)*, $GeI_2$, other etherates of *(1)*, and also the complex compound formed from *(1)* and pyridine to undergo telomerization of the $GeCl_2$ or of the $GeR_2$ formed from it – a property characteristic of carbenes and their analogues; $R-[GeR_2]_n-R$ (n usually $\geq 2$) and small quantities of cyclopolymers $[-GeR_2-]_n$ with n = 4 or 6 are formed.

Like $HGeCl_3$ and the stable compounds $GeHal_2$ and $SnHal_2$ [2], the etherates of $HGeHal_3$ are strong reducing agents, being oxidized to $GeHal_4$ or $SnHal_4$. For example, *(1)* and

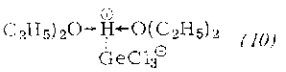



*(2)* reduce $ArN_3$ to $ArN_2NH_2$, and $ArNO_2$ to $ArNH_2$. Cautious evaporation of the etherate *(2)* leaves a residue of $GeCl_2$ (probably polymeric $[GeCl_2]_n$) in 50–60 % yield as an amorphous or finely crystalline bright yellow to red powder. This is soluble in acetone but insoluble in diethyl ether and hydrocarbons, and decomposes at 140 °C. Atmospheric moisture hydrolyses it to GeO; it reacts with benzyl chloride to form $H_5C_6-CH_2-GeCl_3$.

The structure *(10)* proposed for the etherate *(2)* explains the ease of formation of $GeCl_2$ by the dissociation:

$$GeCl_3^{\ominus} \rightleftharpoons GeCl_2 + Cl^{\ominus}$$

and also its greater reactivity, compared with that of the stable compounds $GeI_2$ and $SnHal_2$ [3].



*(10)*

$HCCl_3$ scarcely reacts with diethyl ether ($\Delta\delta_{C-H} \approx 0.5$ ppm), and $HSiCl_3$ not at all ($\Delta\delta_{Si-H} = 0$ ppm). The difference in behavior of $HGeCl_3$ and $HSiCl_3$ can probably

be explained by the difference in direction of their polarizations ($H^{\delta+}Ge^{\delta-}Cl_3$ and $H^{\delta-}Si^{\delta+}Cl_3$ [4]).

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[1] *O. M. Nefedov* and *S. P. Kolesnikov*, Izv. Akad. Nauk SSSR, Otdel Khim. Nauk *1963*, 2068; *O. M. Nefedov, S. P. Kolesnikov, A. S. Chachaturov*, and *A. D. Petrov*, Dokl. Akad. Nauk SSSR *154*, 1389 (1964).

[2] *O. Dimroth* et al., Ber. dtsch. chem. Ges. *40*, 2376 (1907); *43*, 2757 (1910); *50*, 1534 (1917).

[3] *M. E. Volpin* et al., Tetrahedron *18*, 107 (1962); Izv. Akad. Nauk SSSR, Otdel Khim. Nauk *1963*, 2067.

[4] *C. Eaborn:* Organosilicon Compounds. Butterworths, London 1960.

## Compounds Containing the Si—N—B Linkage [1]

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*Geymayer, Rochow*, and *Wannagat* [2] recently prepared the compounds $[(R_3Si)_2N]_2BF$ *(1)*, $(R_3SiNBCl)_3$ *(2)*, and $[R_3SiNBN(SiR_3)_2]_2$ *(3)*, where R = $CH_3$. We have also obtained *(1)* and *(3)* by somewhat different synthetic methods, and have prepared $[(CH_3)_3Si]_2NBF_2$ *(4)* by two different types of reaction.

$BF_3$ was passed through a solution of $[(CH_3)_3Si]_2NLi$ [3] in pentane/hexane; subsequent distillation at reduced pressure afforded good yields of *(1)*, m.p. 18 °C, b.p. 63 °C/0.5 mm. Its structure was confirmed by elementary analysis, infrared and $^1H$—NMR spectra (dioxane as internal standard; $\delta = 0.21$ ppm relative to low field of tetramethylsilane); mol. wt. found 350, calc. 348. The reverse order of mixing of the reactants did not result in the formation of *(4)*, even at −78 °C. However, when *(1)* was heated with $BF_3$ at 95 °C for several hours, good yields of *(4)*, m.p. −37.6 °C, b.p. 21 °C/5.2 mm, were

$$\underset{(1)}{[(CH_3)_3Si]_2N-B(F)-N[Si(CH_3)_3]_2} + BF_3 \rightarrow 2\,\underset{(4)}{[(CH_3)_3Si]_2NBF_2} \quad (a)$$

obtained. Compound *(4)* is a colorless liquid. Its structure was confirmed by elementary analysis, and infrared and mass spectra.

Solutions of $[(CH_3)_3Si]_3N$ [4] in pentane do not react with $BF_3$ at room temperature. However, on heating the reactants in the absence of solvent at 130 °C for several hours, large amounts of *(4)* were obtained.

$$[(CH_3)_3Si]_3N + BF_3 \rightarrow \underset{(4)}{[(CH_3)_3Si]_2NBF_2} + (CH_3)_3SiF \quad (b)$$

When *(4)* was heated in a sealed tube at 200 °C for several hours, no $BF_3$ was evolved. This indicates that reaction (a) is not reversible. Instead, $(CH_3)_3SiF$ was eliminated from *(4)*, and it appears that the *B*-fluoroborazine analogous to *(2)* was produced.

When *(1)* was heated at 200 °C for 36 h in a sealed tube, $(CH_3)_3SiF$ was eliminated, and ca. 75 % of *(3)* were obtained.

$$2\,\underset{(1)}{[(CH_3)_3Si]_2N-B(F)-N[Si(CH_3)_3]_2} \longrightarrow \underset{(3)}{[(CH_3)_3Si]_2N-B\langle N(Si(CH_3)_3)-B-N(Si(CH_3)_3)\rangle B-N[Si(CH_3)_3]_2} + 2\,(CH_3)_3SiF \quad (c)$$

The structure of *(3)*, m.p. 208 °C, was confirmed by elementary analysis, and infrared and $^1H$—NMR spectra (dioxane as internal standard; $\delta[(CH_3)_3Si]_2N$ − 0.19 ppm and $\delta(CH_3)_3SiN$ = 0.15 ppm relative to low field of TMS); mol. wt. found 520, 511, calc. 517. The NMR signals were in the ratio 1.96:1. The NMR data indicate that the nitrogen atoms of the ring system are less effective in withdrawing electrons from the protons than the exocyclic nitrogen atoms. This suggests that delocalization of the lone pairs of electrons on the nitrogens in the ring is not extensive. A similar conclusion, based on different experimental evidence, has been reached regarding electron delocalization in the ring system of $[t\text{-}C_4H_9(H)NBN(t\text{-}C_4H_9)]_2$ the only other dimeric borazine derivative known [5].

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[1] This work was supported by the Advanced Research Projects Agency, Office of the U.S. Secretary of Defense.

[2] *P. Geymayer, E. G. Rochow*, and *U. Wannagat*, Angew. Chem. *76*, 499 (1964); Angew. Chem. internat. Edit. *3*, (1964), in the press.

[3] *U. Wannagat* and *H. Niederprüm*, Angew. Chem. *71*, 574 (1959).

[4] *V. J. Goubeau* and *J. Jiménez-Barberá*, Z. anorg. allg. Chem. *303*, 217 (1960).

[5] *M. F. Lappert* and *M. K. Majumdar*, Proc. chem. Soc. (London) *1963*, 88.

## Iron Carbonyl Complexes of the Dimers of Cyclooctatetraene and Bullvalene

By Priv.-Doz. Dr. G. N. Schrauzer and Dipl.-Chem. P. Glockner

Institut für Anorganische Chemie
der Universität München (Germany)

and by Dipl.-Ing. R. Merényi

Union Carbide European Research Associates,
Brussels (Belgium)

Light-induced addition of cyclooctatetraene onto cyclooctatetraeneiron tricarbonyl [1] leads to two isomeric complexes, *viz.* $C_{16}H_{16}Fe(CO)_3$ *(1)*, m.p. 118 °C, and $C_{16}H_{16}Fe(CO)_3$ *(2)*, m.p. 172 °C (decomp.).

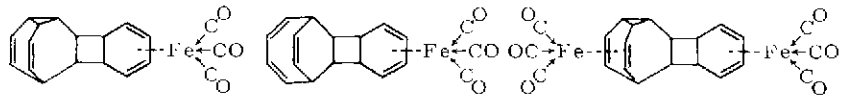
Compound *(1)* is also formed directly by the reaction of $Fe_2(CO)_9$ with the dimer of cyclooctatetraene $C_{16}H_{16}$ *(3)*, m.p. 76 °C [2]. *(1)* is a π-complex whose organic ligand undergoes fast and reversible valence isomerization; its NMR spectrum is strongly temperature-dependent. However, the structure of *(2)* does not "fluctuate".

The reaction of *(3)* with $Fe(CO)_5$ at 160–170 °C gives besides *(1)*, another $C_{16}H_{16}Fe(CO)_3$ isomer *(4)*, m.p. 175–180 °C (decomp.), a binuclear complex $C_{16}H_{16}Fe_2(CO)_6$ *(5)*, m.p. 191 °C, and a trinuclear complex $C_{16}H_{16}Fe_3(CO)_9$ *(6)*, m.p. 170 °C (decomp.) [3].

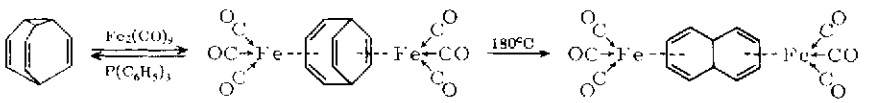
Complex *(5)* is also formed by the reaction of *(1)* with $Fe(CO)_5$ at 180 °C, as well as by heating *(6)* in a sealed glass tube to 180 °C. The complicated NMR spectra of *(4)*, *(5)*, and *(6)* are not temperature-dependent; thus, the reversible valence isomerization of the parent hydrocarbon is suppressed by complex formation. The structures of *(4)* and *(6)* are still unknown [4]. The proposed structure for *(5)* is not in contradiction to its NMR spectrum.

The reaction of tricyclo[3,3,2,$0^{4,6}$]deca-2,7,9-triene (bullvalene) *(7)* [2,5] with $Fe_2(CO)_9$ in boiling benzene affords the complex $C_{10}H_{10}Fe_2(CO)_6$ *(8)*, m.p. 120 °C; when heated to 140 °C in the presence of excess triphenylphosphine, *(8)* decomposes into bullvalene *(7)* and $Fe(CO)_3 \cdot 2P(C_6H_5)_3$; at 180 °C in an autoclave, it is transformed into the known complex 9,10-dihydronaphthalenediiron hexacarbonyl *(9)*, m.p. 195–197 °C (decomp.) [6]. The NMR spectra of *(8)*

and *(9)* support the proposed structures; unlike to that of bullvalene *(7)*, they are not temperature-dependent. Thus, it is possible to stabilize the intermediates of the transformation of bullvalene into naphthalene [2] as *(8)* and *(9)* by complex formation, although these intermediates were



*(1)* *(2)* *(5)*



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

not isolated in their non-complexed form. This transformation is favored by the presence of the $Fe(CO)_3$ groups and takes place at a much lower temperature than with free bullvalene; bullvalene *(7)* therefore loses its "fluctuating" structure on $\pi$-complex formation.

Received, April 27th, 1964 [Z 729/555 IE]
German version: Angew. Chem. *76*, 498 (1964)

[1] *G. N. Schrauzer* and *S. Eichler*, Angew. Chem. *74*, 585 (1962); Angew. Chem. internat. Edit. *1*, 454 (1962).

[2] *G. Schröder*, Angew. Chem. *75*, 722 (1963); Angew. Chem. internat. Edit. *2*, 481 (1963).

[3] Complex *(6)* is also formed on irradiation of *(1)* and *(2)* in the presence of $Fe(CO)_5$ and was originally considered as a binuclear complex $C_{10}H_{10}Fe_2(CO)_6$. Recent osmometric molecular-weight determinations in $C_6H_6$ and $CHCl_3$ confirmed the formula $C_{16}H_{16}Fe_3(CO)_9$.

[4] An X-ray study is in progress (*M. R. Truter* et al., University of Leeds, England).

[5] *W. v. E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963); Tetrahedron *19*, 715 (1963).

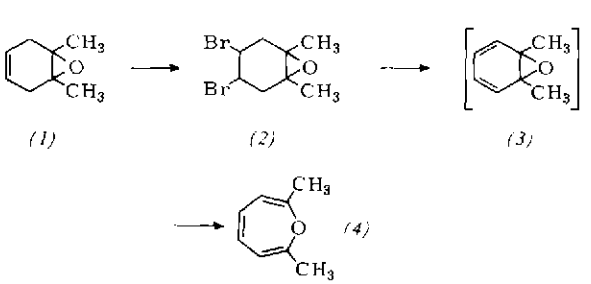
[6] *E. Weiss*, *W. Hübel*, and *R. Merényi*, Chem. Ber. *95*, 1155 (1962).

## Synthesis of an Oxepin Derivative

By Prof. Dr. E. Vogel, Dipl.-Chem. R. Schubart, and Dr. W. A. Böll

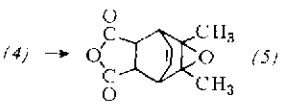
Institut für Organische Chemie der Universität Köln (Germany)

Oxepins are of theoretical interest on account of their cyclic 8-$\pi$-electron system, and several attempts at their synthesis have been made [1]. 2,7-Dimethyloxepin *(4)* is the first simple representative [2] of this class of compounds to be prepared. It is obtained in 60 % yield as a stable yellow liquid, b.p. 51 °C/14 mm, $n_D^{20} = 1.5045$, when the dibromo compound *(2)*, m.p. 85–86 °C (derived from the unsaturated epoxide *(1)* [3]) is dehydrobrominated with potassium t-butoxide in ether at 0 °C. The epoxide *(3)* is a likely intermediate.



*(1)* *(2)* *(3)* *(4)*

The proof of the structure of *(4)* is based mainly on its NMR spectrum, which has a singlet at 8.1 $\tau$ (6 methyl protons) and two multiplets centered at 4.1 and 4.7 $\tau$ (two protons each). The olefinic region in the NMR spectrum is similar to that of 1,6-dimethylcycloheptatriene [4]. In the infrared spectrum a band at 1660 $cm^{-1}$ (C=C), typical of enolic ethers, appears. The yellow color of *(4)* is due to the long-wave end of a broad ultraviolet absorption band with $\lambda_{max} = 297$ m$\mu$ (log $\varepsilon$ = 3.25). On standing for some time with maleic anhydride, *(4)* reacts to form the adduct *(5)*, m.p. 235 °C (decomp.), derived from *(3)* [5].



*(4)* → *(5)*

The synthesis of *(4)* instigated reinvestigation of the dehydrobromination of 1,2-epoxy-4,5-dibromocyclohexane [1b, 1c]. Previously only phenol had been isolated from this reaction. When 1,5-diazabicyclo[3,4,0]non-5-ene [6] is used as dehydrohalogenating agent, a yellow elimination product, b.p. 27 °C/14 mm, was obtained in good yield in 95 % purity; it is assumed to be oxepin. The product began to rearrange into phenol above 70 °C, and its catalytic hydrogenation yielded mainly oxepane. Maleic anhydride added onto it fairly rapidly, even at 20 °C; the adduct melts at 264 °C (decomp.). Finally, the NMR spectrum shows absorptions only in the olefinic range (three multiplets with relative intensities of 1 : 1 : 1, centered at 3,9 $\tau$, 4.4 $\tau$, and 4.7 $\tau$) which suggest that the product is actually oxepin [7].

Received, May 4th, 1964 [Z 732/561 IE]
German version: Angew. Chem. *76*, 535 (1964)

[1a] *S. Olsen* and *R. Bredoch*, Chem. Ber. *91*, 1589 (1958); [b] *J. Ferry*, Diploma Thesis, Technische Hochschule Karlsruhe, 1958; [c] *J. Meinwald* and *H. Nozaki*, J. Amer. chem. Soc. *80*, 3132 (1958); [d] *J. Meinwald*, *D. W. Dicker*, and *N. Danieli*, ibid. *82*, 4087 (1960); [e] *E. E. Schweizer* and *W. E. Parham*, ibid. *82*, 4085 (1960).

[2] 3-Benzoxepin and some of its derivatives were described by *K. Dimroth* et al., Angew. Chem. *69*, 95 (1957); Chem. Ber. *90*, 1623 (1957); Angew. Chem. *73*, 436 (1961); 1-Benzoxepin was recently obtained in our laboratories (unpublished).

[3] *W. Hückel* and *U. Wörffel*, Chem. Ber. *88*, 338 (1955).

[4] Unpublished experiments with *H. D. Roth*.

[5] The kinetic and thermodynamic relationship between oxepins and the valence-bond isomeric aromatic oxides has still to be investigated.

[6] *E. Truscheit* and *K. Eiter*, Liebigs Ann. Chem. *658*, 65 (1962).

[7] Note added in proof (May 25th): Oxepin has now been prepared in pure form, b.p. 38 °C/30 mm, $n_D^{25} = 1.5162$, broad ultraviolet absorption band with $\lambda_{max} = 271$ m$\mu$ (log $\varepsilon$ = 3.15), in cyclohexane. The compound appears to exist in equilibrium with its valence tautomer benzene epoxide.

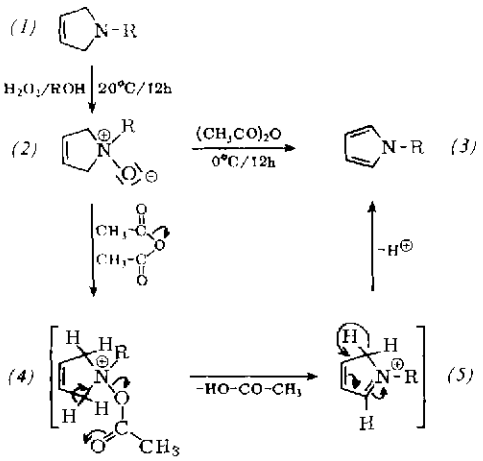
## A New Synthesis of N-Alkylpyrroles

By Dr. R. Kreher and cand. chem. H. Pawelczyk

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

*N*-Alkylpyrroles *(3)* are formed in 50–60 % yield by the action of acetic anhydride at 0 °C [1] on *N*-alkyl-$\Delta^3$-pyrroline-*N*-oxides *(2)*, which are in turn obtained in almost quanti-

tative yields by oxidation of *N*-alkyl-$\Delta^3$-pyrrolines *(1)* [2] with 30 % hydrogen peroxide.



*(a)*: R = $C_6H_5$-$CH_2$-$CH_2$-
*(b)*: R = $C_6H_5$-$CH_2$-
*(c)*: R = n-$C_4H_9$-

To account for the formation of the pyrrole derivatives, we assume that, by analogy to the Polonovski reaction [3], the *N*-oxide is acetylated by the acetic anhydride at the oxygen. The intermediate *(4)*, which cannot be isolated, loses a molecule of acetic acid with formation of a pyrroleninium cation *(5)*, which is converted with loss of a proton into the mesomerically stabilized pyrrole system [4].

Received, May 6th, 1964 [Z 734/560 IE]
German version: Angew. Chem. *76*, 536 (1964)

[1] Thermal decomposition of the *N*-oxides *(2)* at 120–140 °C occurs differently in part (cf. *H. Pawelczyk*, Diploma Thesis, Technische Hochschule Darmstadt, 1964).

[2] We succeeded in preparing *N*-alkyl-$\Delta^3$-pyrrolines *(1)* from *cis*-1,4-dichloro-2-butene and primary amines, and in characterizing them by analysis of their picrates; cf. the preparation of *N*-phenyl-$\Delta^3$-pyrroline according to *G. Wittig* and *H. Sommer* [Liebigs Ann. Chem. *594*, 10 (1955)] and *J. M. Bobbitt, L. H. Amundsen*, and *R. I. Steiner* [J. org. Chemistry *25*, 2230 (1960)].

[3] *R. Huisgen, F. Bayerlein*, and *W. Heydkamp*, Chem. Ber. *92*, 3223 (1959).

[4] The removal of the acetoxy group together with a hydrogen atom from the alkyl group, occurs only to a very small extent in the reaction of *N*-benzyl-$\Delta^3$-pyrroline-*N*-oxides *(2b)*, in which the $\alpha$-hydrogen atoms of the benzyl residue are activated by the phenyl group; this side-reaction leads, after hydrolysis, to benzaldehyde and $\Delta^3$-pyrroline.

## New Modifications of $Nb_2O_5$ [*]

By Prof. Dr. H. Schäfer, Dr. F. Schulte, and Dr. R. Gruehn

Anorganisch-chemisches Institut der Universität Münster (Germany)

$Nb_2O_5$ migrates towards the coldest part of a temperature gradient during the endothermic equilibrium reaction [1]

$$Nb_2O_5\,(s) + 3\,NbX_5\,(g) \rightleftharpoons 5\,NbOX_3\,(g) \qquad (X = Cl, Br, \text{or } I).$$

By variation of temperature and pressure, especially in the system X = Cl, three new modifications, *viz.* P-, B-, and N-$Nb_2O_5$ [2,3], result as well-formed crystals besides the forms known earlier, *viz.* H-$Nb_2O_5$ and M-$Nb_2O_5$. The transport conditions were for example 850→750 °C, $p(NbOCl_3)$ ≈ 5 atm. To ensure that the Nb was present to a very high extent in the oxidation state 5, chlorine was filled into the reaction tube (1 atm at room temperature).

All the $Nb_2O_5$ modifications transported in this way were colorless, with the exception of the B-form, which was obtained under these conditions with a pale blue color and a composition corresponding to $NbO_{2.496}$ [4]. These new Modifications are mostly formed simultaneously, but usually apart from each other and in such large crystals that they can be easily isolated.

P-$Nb_2O_5$ forms colorless prisms or plates; it contains < 0.01 % Cl.

Its d-values [**] [Å] (estimated intensities in brackets) are: 6.37 (5); 3.85 (10); 3.54 (4); 3.18 (7); 3.10 (7); 2.76 (2); 2.70 (7); 2.66 (7); 2.31 (4); 2.29 (2); 2.12 (4); 2.09 (2); 1.99 (2); 1.95 (5); 1.93 (2); 1.87 (3); 1.77 (2); 1.75 (5); 1.74 (6).

On annealing amorphous $Nb_2O_5 \cdot nH_2O$ containing 8 % HCl X-ray crystalline P-$Nb_2O_5$ (+ T-$Nb_2O_5$) resulted.

B-$Nb_2O_5$ can be separated as pale blue or colorless plates which are often over 5 mm in size and contain < 0.01 % Cl.

Its d-values [Å] (estimated intensities in brackets) are: 6.15 (5); 3.63 (10); 3.31 (10); 3.07 (10); 2.96 (10); 2.73 (1); 2.68 (6); 2.50 (6); 2.44 (6); 2.34 (3); 2.26 (1); 2.22 (3); 2.19 (2); 2.16 (2); 2.05 (3); 1.91 (6); 1.88 (2); 1.82 (1); 1.80 (7).

*Laves* et al. [5] have also meanwhile, obtained the B-modification using the same transport method.

B-$Nb_2O_5$ (+ T-$Nb_2O_5$) was obtained from $NbO_2$ crystals with a small iodine content by igniting them in air; no macroscopically recognizable B-crystals resulted, however.

N-$Nb_2O_5$ occurs as colorless crystalline needles with 0.1 % Cl. The product contained appreciable amounts of $SiO_2$, but whether this is included in the lattice is not yet known.

Its d-valnes [Å] (estimated intensities in brackets) are: 7.17 (2); 6.89 (2); 4.78 (3); 4.73 (3); 3.73 (10); 3.58 (10); 3.56 (10); 3.33 (1); 3.16 (3); 2.87 (1); 2.77 (9); 2.67 (1); 2.53 (1); 2.50 (1); 2.43 (1); 2.39 (1); 2.37 (1); 2.30 (7).

Nothing is yet known about the thermodynamic stability of the new modifications. The T-modification [6] and its precursor [7], designated by us as TT-$Nb_2O_5$, were also obtainable by transport, but not yet as perfect crystals.

We will gladly respond to requests for prints of Guinier photographs, crystal photographs, and limited samples of substances.

Received, May 11th, 1964 [Z 735/568 IE]
German version: Angew. Chem. *76*, 536 (1964)

[*] Contributions to the Chemistry of Niobium and Tantalum, Part 40. – Part 39: *H. Schäfer, R. Gruehn, F. Schulte*, and *W. Mertin*, lecture delivered at Bordeaux 1964, in the press.

[**] d = interplanar spacing.

[1] *H. Schäfer:* Chemische Transportreaktionen. Verlag Chemie, Weinheim 1962, p. 109; *H. Schäfer* and *M. Hüesker*, Z. anorg. allg. Chem. *317*, 321 (1962).

[2] Systematic nomenclature ($\alpha,\beta,\gamma\cdots$) seems to be inopportune since new modifications are still being found.

[3] *F. Schulte*, Ph. D. Thesis, Universität Münster, 1962; *H. Schäfer* and *R. Gruehn*, experimental work with *M. Rönspiess*, unpublished.

[4] Special analytical method: *R. Gruehn*, Ph. D. Thesis, Universität Münster, 1962.

[5] *F. Laves, R. Moser*, and *W. Petter*, Naturwissenschaften, in the press.

[6] *G. Brauer*, Z. anorg. allg. Chem. *248*, 9 (1941).

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

## Synthesis and Reactions of Benzodioxolone-N,N-diethylimidinium Chloride

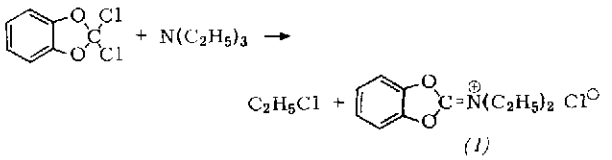
By Doz. Dr. H. Gross and Dipl.-Chem. J. Rusche

Institut für Organische Chemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

*Dedicated to Professor H. Bredereck on the occasion of his 60th birthday*

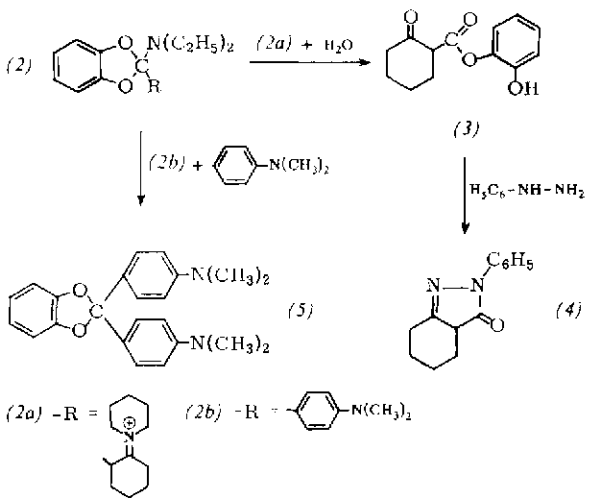
Benzodioxolone-*N*,*N*-diethylimidinium chloride *(1)*, the postulated primary product of the interaction of triethylamine and catechol dichloromethylene ether [1], has now been iso-

lated in pure form by heating the reactants for 3 h at 130 °C and recrystallizing the product from acetonitrile/ether. Its polar character follows from its high melting point (decomp.



*(1)*

above 176 °C) and its behavior towards polar and non-polar solvents. Its infrared spectrum features a strong band at 1730 $cm^{-1}$, which is attributable to the C=N bond [2, 3]. On treatment with *N*-cyclohexenylpiperidine, *(1)* yields presumably first *(2a)*, which is hydrolysed smoothly to *o*-hydroxyphenyl cyclohexanone-2-carboxylate *(3)*, m.p. 98–99 °C; yield: 71 % [4]. Alkaline hydrolysis of *(3)* gave cyclohexanone, carbon dioxide, and catechol; treatment of *(3)* with phenylhydrazine gave the expected 2-phenyl-4,5-tetramethylenepyrazol-3-one *(4)*. *N*-Cyclopentenylpiperidine reacted similarly with *(1)* to give *o*-hydroxyphenyl cyclopentanone-2-carboxylate, m.p. 153–154.5 °C, in 76 % yield. Neither



*(2b)* nor a hydrolysis product thereof could be isolated from the reaction of *(1)* with dimethylaniline; nascent *(2b)* immediately reacts further with dimethylaniline to form the *o*-phenyleneketal of Michler's ketone *(5)*, m.p. 156–158 °C, in 65 % yield; this could be hydrolysed almost quantitatively to the ketone.

Received, May 12th, 1964 [Z 733/558 IE]
German version: Angew. Chem. *76*, 534 (1964)

[1] *H. Gross, J. Rusche,* and *H. Bornowski,* Liebigs Ann. Chem., in the press.

[2] Cf. *H. Bosshard* and *H. Zollinger,* Helv. chim. Acta *42*, 1666 (1959).

[3] Spectrum determined by Dr. *G. Kretschmar.*

[4] All yields based on *O,O'*-dichloromethylenecatechol.

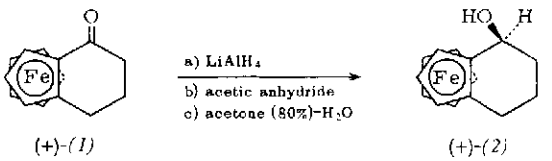
## The Absolute Configuration of 1,2-(α-Oxotetramethylene)ferrocene

By Doz. Dr. K. Schögl and cand. chem. H. Falk

Organisch-Chemisches Institut der Universität Wien (Austria)

Ferrocene derivatives with at least two different substituents on one ring are asymmetric and can thus be resolved into optical antipodes [1–3]. We have now succeeded in ascertaining the absolute configuration of (+)-1,2-(α-oxotetramethylene)ferrocene, *i.e.* (+)-*(1)*.

The latter ($[\alpha]_D = +510°$ in ethanol, *i.e.* 87 % optical purity) was reduced with $LiAlH_4$ to a mixture of the epimeric *endo*- and *exo*-alcohols. The mixture of acetates obtained therefrom could be hydrolysed stereoselectively with aqueous acetone (owing to neighboring group effect of the iron) [4] to the dextrorotatory *exo*-alcohol *(2)* ($[\alpha]_D = +113°$ in ethanol). The reaction of (+)-*(2)* with racemic α-phenylbutyric anhydride in pyridine according to *Horeau* [5] liberated α-phenylbutyric acid which was optically active ($\alpha_D = -0.79°$, l = 1 dm, in 2 ml of benzene) on account of the asymmetric esterification. Since 550 mg of (+)-*(2)* yielded 230 mg (= 27 %) of the phenylbutyrate *(3)* (isolated by preparative




(+)-*(1)* (+)-*(2)*

thin-layer chromatography, identified by infrared spectroscopy), the optical yield amounted to 20 %. As expected, saponification of *(3)* then yielded an excess of the (+)-acid. The asymmetric carbon atom in (+)-*(2)* thus has the (*S*)-configuration [5], which determines the absolute configuration of (+)-*(2)* to be (*R*)-1,2-(α-oxotetramethylene)ferrocene [6]. Also the absolute configurations of all optically active ferrocenes derived from *(1)* have thereby been established [7].

Since other methods for determining the configurations of the ketone *(1)* and of the alcohol *(2)*, *e.g.* asymmetric Meerwein-Ponndorf reduction or *Prelog*'s method [8], proved to be unsuitable, we checked *Horeau*'s method with several examples, including ( )-α-methylbenzyl alcohol, quinine, quinidine, and cinchonidine, in which an aromatic ring system is also present next to the asymmetric carbon atom, before applying it to the ferrocene derivative *(2)*. Correct results with very satisfactory chemical and optical yields were invariably obtained regarding the configuration of the carbon atom in question.

The result of this chemical determination of the configuration of *(2)* – and with it of *(1)* – corresponds with the absolute configuration of (+)-*(1)* postulated by us earlier [7] on the basis of the octant rule [8].

Received, May 13th, 1964 [Z 738/564 IE]
German version: Angew. Chem. *76*, 570 (1964)

[1] *J. B. Thomson,* Tetrahedron Letters *1959*, No. 6, 26.

[2] *L. Westman* and *K. L. Rinehart,* Acta chem. scand. *16*, 1199 (1962).

[3] *K. Schlögl* and *M. Fried,* Mh. Chem. *95*, 558 (1964).

[4] *E. A. Hill* and *J. H. Richards,* J. Amer. chem. Soc. *83*, 4216 (1961).

[5] *A. Horeau,* Tetrahedron Letters *1961*, 506; *1962*, 956.

[6] For the (*R*),(*S*)-nomenclature of ferrocene derivatives see [7].

[7] *K. Schlögl* and *M. Fried,* Tetrahedron Letters *1963*, 1473; *K. Schlögl, M. Fried,* and *H. Falk,* Mh. Chem. *95*, 576 (1964).

[8] *E. L. Eliel:* Stereochemistry of Carbon Compounds. McGraw-Hill, New York 1962.

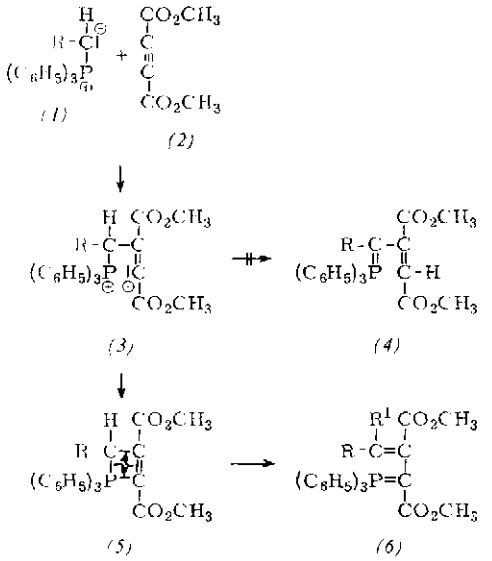
## The Reaction of Alkylidenetriphenylphosphoranes with Acetylenedicarboxylic Esters

By Prof. Dr. H. J. Bestmann and Dipl.-Chem. O. Rothe

Institut für Organische Chemie der Technischen Hochschule München (Germany)

A recent communication [1] on the reaction of triphenylphosphineimines with acetylenedicarboxylic esters prompts us to publish some results of our experiments on the reaction of alkylidenetriphenylphosphoranes *(1)* and dimethyl acetylenedicarboxylate *(2)*.

The reaction of *(1)* with *(2)* proceeds extremely readily. The product is not that of a Michael addition *(4)* [2], but an ylide *(6)*, which is very stable. It is assumed that the betaine *(3)* initially formed rearranges to *(6)* via *(5)*.



| | R′ | R¹ | M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| *(6a)* | $CH_3$ | H | 174—176 | 77 |
| *(6b)* | $CH_3(CH_2)_2$— | H | 133—137 | 47 |
| *(6c)* | $C_6H_5$ | H | 182—184 | 72 |
| *(6d)* | $C_6H_5$—CH=CH— | H | 173—178 | 48 |
| *(6e)* | $C_6H_5$ | $CH_3$ | 213—216 | 60 |
| *(6f)* | $C_6H_5$ | $C_6H_5$ | | |

The structure *(6)* was derived:

a) By degradation reactions: Hydrolysis of *(6c)* led to benzylidenesuccinic acid and triphenylphosphine oxide; oxidative cleavage gave benzaldehyde.

b) From infrared spectra: The spectra of all the compounds *(6)* contain two carbonyl bands, one of which appears at 6.15–6.20 μ; this is characteristic of alkylidenephosphoranes with an ester group at the carbon atom of the C=P double bond [3].

c) From NMR spectra: The signal of the olefinic proton at 4.4 τ in the NMR spectrum of *(6a)* is split into a quadruplet (J = 3.9 cps). For the methyl group, two doublets appear at 8.4 τ and 8.25 τ (J = 3.9 cps); one can be assigned to the *cis*- and one to the *trans*-form.

Starting from *(2)* and α-methylbenzylidenetriphenylphosphorane, $(C_6H_5)_3P{=}C(C_6H_5)(CH_3)$, which cannot undergo Michael addition to give *(4)*, we obtained a compound *(6e)* whose constitution has been established by oxidative cleavage to acetophenone and by its infrared spectrum. These findings support the supposition [1] that the yellow compound formed from diphenylmethylenetriphenylphosphorane, $(C_6H_5)_3P{=}C(C_6H_5)_2$, and *(2)* is *(6f)*.

Received, May 19th, 1964 [Z 737/559 IE]
German version: Angew. Chem. 76, 569 (1964)

[1] *G. W. Brown, R. C. Cookson, I. D. R. Stevens, T. C. W. Mak,* and *J. Trotter,* Proc. chem. Soc. (London) *1964*, 87.

[2] *S. Trippett,* J. chem. Soc. (London) *1962*, 4733.

[3] *H. J. Bestmann* and *H. Schulz,* Chem. Ber. *95*, 2921 (1962).

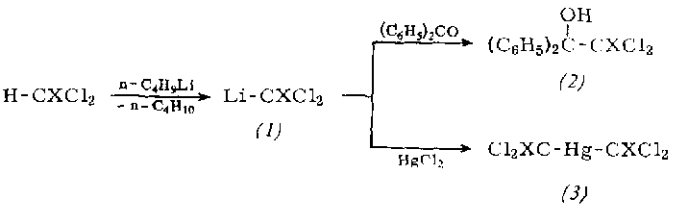
## Dichloromethyl-lithium and Trichloromethyl-lithium [*]

By Doz. Dr. G. Köbrich, Dipl.-Chem. K. Flory, and W. Drischel

Organisch-Chemisches Institut der Universität Heidelberg (Germany)

We have obtained solutions of the title compounds *(1a)* and *(1b)* by treating respectively methylene dichloride and chloroform with n-butyl-lithium in tetrahydrofuran/ether/petroleum ether (4:1:1) [1] at ca. −110 °C.

These compounds react with benzophenone to give good yields of the known alcohols *(2)*; with mercuric chloride, they give respectively bisdichloromethylmercury *(3a)* [97 % yield, m.p. 154–155 °C (decomp.)] and bistrichloromethylmercury *(3b)* [91 % yield, m.p. 146.5–148.5 °C (decomp.)].



*(a)* X = H; *(b)* X = Cl

The following experiments give an indication of the stability of the organo-lithium compounds *(1)*: if *(1b)* is allowed to warm up in the above solvent mixture to −60 °C during 12 min and is kept at this temperature for further 25 min, treatment with $HgCl_2$ gives 50 % *(3b)*. Unlike *(1b)*, *(1a)* can be prepared in tetrahydrofuran at −65 °C; reaction with $HgCl_2$ after 30 min gives 91 % *(3a)* and, even after 11 h, the yield of *(3a)* is still ca. 75 %.

The greater stability of *(1a)* relative to *(1b)* thus established is unexpected since the inductive effect of an additional α-halogen atom should stabilize the carbanionoid state further; it is, however, consistent with the assumption [2] that α-elimination of LiCl occurs more readily from *(1b)* than from *(1a)* since the carbene produced from the former (dichlorocarbene) is more stable than that formed from the latter (chlorocarbene [3]). Further investigations of the organo-lithium compounds *(1)* and related substances are in progress.

Received, May 20th, 1964 [Z 739/566 IE]
German version: Angew. Chem. 76, 536 (1964)

[*] Part V: On the Existence of Carbon Atoms with Halogen and Alkali-Metal Substituents. — Part IV: *G. Köbrich* and *H. Fröhlich*, Angew. Chem. 76, 495 (1964); Angew. Chem. internat. Edit. *3*, 445 (1964).

[1] *G. Köbrich* and *H. Trapp,* Z. Naturforsch. *18b*, 1125 (1963); *G. Köbrich, H. Trapp,* and *I. Hornke,* Tetrahedron Letters *1964*, 1131; *G. Köbrich* and *K. Flory,* ibid. *1964*, 1137.

[2] *J. Hine,* J. Amer. chem. Soc. *72*, 2438 (1950).

[3] *G. L. Closs* and *L. E. Closs,* J. Amer. chem. Soc. *82*, 5723 (1960).

## Alkyl(Aryl)dialkylaminotrifluorophosphoranes and -fluorophosphines [*]

By Dr. R. Schmutzler

University Chemical Laboratory, Cambridge (England)

We have found that, like chlorophosphines $R_nPCl_{3-n}$ [1], several dialkylaminochlorophosphines $RPClNR_2'$ react with Group V trifluorides in accordance with the following equation:

$$3\,RPClNR_2' + 3\,MF_3 \rightarrow 3\,RPF_3NR_2' + 2\,M + MCl_3$$
(M = As or Sb)

$CH_3PF_3N(CH_3)_2$ *(1)*, b.p. 85 °C, $C_6H_5PF_3N(CH_3)_2$ *(2)*, b.p. 88 °C/6.5 mm, and $C_6H_5PF_3N(C_2H_5)_2$ *(3)*, b.p. 81–82 °C/2 mm, were readily accessible by this route. Compound *(2)* and several other aryldialkylaminotrifluorophosphoranes were previously prepared in a three-step reaction [2].

The $^{19}F$-NMR spectra (Table 1) of *(1)–(3)* consist of a pair of doublets (a) and a double triplet (b), the doubling arising from P–F spin-spin splitting. An intensity ratio a:b = 2:1 was found. These data are consistent with trigonal-bipyramidal geometry, as in trifluorophosphoranes $R_2PF_3$, with a fluorine atom in each apical position and one occupying an equatorial site. The phosphorus-fluorine coupling constants $J_{P-F}$ and the chemical shifts $\delta_F$ are consistently larger for

Table 1. Chemical shifts $\delta$ [ppm] and spin-spin coupling constants $J_{P,F}$ [cps] for *(1)*–*(5)*.

| | *(1)* | *(2)* | *(3)* | *(4)* | *(5)* |
|---|---|---|---|---|---|
| $^{19}$F-NMR spectra [a] | | | | | |
| $\delta_{Fa}$ [b] | 27.6 | 40.6 | 43.5 | | |
| $\delta_{Fb}$ | 69.0 | 68.5 | 66.5 | | |
| $J_{P-Fa}$ | 808 | 818 | 823 | | |
| $J_{P-Fb}$ | 965 | 959 | 966 | | |
| $J_{Fa-Fb}$ | 53 | 54 | 55–56 | | |
| $\delta_F$ | | | | 117.9 | 128.5 |
| $J_{P-F}$ | | | | 920 | 989 |
| $^{31}$P-NMR spectra [c] | | | | | |
| $\delta_P$ | | | | −168.9 | −159.8 |
| $J_{P-F}$ | | | | 917 | 985 |

[a] $CFCl_3$ as internal standard.
[b] $F_a$: F atom at apex, $F_b$: F atom at base of trigonal bipyramid.
[c] 85 % $H_3PO_4$ as external standard.

equatorial than for apical fluorine atoms both in dialkylaminotrifluorophosphoranes $RPF_3NR'_2$ and in other trifluorophosphoranes $R_2PF_3$ [3]. Thus, there is sufficient evidence that the stereochemical conclusions put forward for $R_2PF_3$ also hold for *(1)*–*(3)*.

Fluorination of $RPClN(CH_3)_2$ with NaF in tetramethylene sulfone (as a polar medium, preventing oxidation-reduction reactions) led to $CH_3PFN(CH_3)_2$ *(4)*, b.p. 85–86 °C, and $C_6H_5PFN(CH_3)_2$ *(5)*, b.p. 88–90 °C/15 mm.

Both *(4)* and *(5)* are distinguished by very large negative chemical shifts in their $^{31}$P-NMR spectra, which are indicative of fluorides of trivalent phosphorus (cf. for instance: $[(CH_3)_2N]_2PF$, $\delta_P$ = −151.4 ppm; $C_6H_5PFN(CH_3)_2$, $\delta_P$ = −159.8 ppm; $ClCH_2PF_2$, $\delta_P$ = −201.8 ppm; $C_6H_5PF_2$, $\delta_P$ = −208.3 ppm; based on 85 % $H_3PO_4$ as an external standard).

Received, May 21st, 1964 [Z 742/567 IE]
German version: Angew. Chem. 76, 570 (1964)

[*] Phosphorus-Fluorine Chemistry, Part IX. – Part VIII: J. chem. Soc. (London) *1964*, in the press.

[1] *I. P. Komkov, S. Z. Ivin, K. W. Karawanov*, and *L. Je. Smirnov*, Zhur. obshch. Khim. *32*, 301 (1962); *R. Schmutzler*, Chem. and Ind. *1962*, 1868; Inorg. Chem. *3*, 410 (1964).

[2] *Zh. M. Ivanova* and *A. V. Kirsanov*, Zhur. obshch. Khim. *32*, 2592 (1962).

[3] *E. L. Muetterties, W. Mahler*, and *R. Schmutzler*, Inorg. Chem. *2*, 613 (1963); *E. L. Muetterties, K. J. Packer, W. Mahler*, and *R. Schmutzler*, Inorg. Chem. *3* (1964), in the press.

## Addition of Secondary N-Trimethylsilylamides onto Aldehydes [1]

By Prof. Dr. L. Birkofer and Dipl.-Chem. H. Dickopp

Institut für Organische Chemie der Universität
Köln (Germany)

Secondary *N*-trimethylsilylamides such as *N*-trimethylsilyl-*N*-methylformamide, *N*-trimethylsilyl-*N*-methylacetamide, or *N*-trimethylsilyl-2-pyrrolidone react without a catalyst with aliphatic or aromatic aldehydes to give the *N*-alkyl-*N*-(α-trimethylsiloxyalkyl)amides *(1)*–*(6)* in 80–90 % yield. To our knowledge, the reaction of free secondary amides has previously been achieved only with formaldehyde to give *N*-hydroxymethyl derivatives [2].

*N*-Trimethylsilyl-*N*-methylformamide reacts exothermally with aldehydes at room temperature; the other silylamides react only when heated. The products *(1)*–*(6)* may be purified by vacuum distillation. They are colorless, oily liquids which are relatively insensitive to water and alcohol at room temperature. However, they are hydrolysed in the presence of $H^+$ ions, and the intermediate hydroxy compounds decompose to the corresponding amides and aldehydes.

$$R^1{-}CHO + R^2{-}CO{-}N{-}R^3 \xrightarrow[Si(CH_3)_3]{} R^1{-}CH{-}O{-}Si(CH_3)_3 \quad R^2{-}CO{-}N{-}R^3$$

*(1)*–*(6)*

| | $R^1$ | $R^2$ | $R^3$ | B.p. [°C/mm] | $n_D^{20}$ |
|---|---|---|---|---|---|
| *(1)* | $C_6H_5$– | H– | $CH_3$– | 156–157/12 | 1.4973 |
| *(2)* | $C_6H_5$– | $CH_3$– | $CH_3$– | 154.8–155/12 | 1.4941 |
| *(3)* | *p*-$CH_3OC_6H_4$– | $CH_3$– | $CH_3$– | 125–126/0.02 | 1.5012 |
| *(4)* | $CH_3{-}CH_2{-}CH_2$– | H– | $CH_3$– | 109.8–110/12 | 1.4357 |
| *(5)* | $CH_3{-}CH_2$– | $CH_3$– | $CH_3$– | 97.8–98/12 | 1.4324 |
| *(6)* | $C_6H_5$– | $-(CH_2)_3$– | | 174.5–175.5/12 | 1.5056 |

The structures *(1)*–*(6)* were established by analysis and NMR and infrared spectra.

The mechanism of formation is assumed to be an addition of Si–N onto the carbonyl double bond, for which a cyclic transition state is probable because of the availability of the silicon 3d-orbitals, into which an electron pair from the carbonyl oxygen can be donated. The reaction appears to be generally applicable. Thus, *N*-trimethylsilyl-*N*-alkylamides react with epoxides in the presence of basic catalysts to give *N*-alkyl-*N*-(β-trimethylsiloxy)alkylamides.

Received, June 8th, 1964 [Z 750/583 IE]
German version: Angew. Chem. 76, 648 (1964)

[1] Organosilicon Compounds, Part 26. – Part 25: *L. Birkofer, A. Ritter*, and *F. Bentz*, Chem. Ber., in the press.

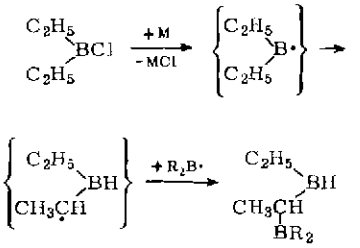
[2] *H. Böhme, A. Dick*, and *G. Driesen*, Chem. Ber. *94*, 1879 (1961).

## Stable Free Radicals with B-N and Al-N Bonds

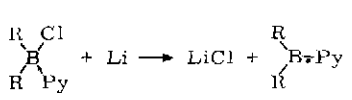
By Dr. R. Köster, Dr. G. Benedikt, and Dr. H. W. Schrötter

Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

On dehalogenation of alkylchloroboranes (*e.g.* $R_2BCl$, $RBCl_2$, or *B*-chloroborolanes) with alkali metals (*e.g.* K/Na alloys), compounds containing B–H bonds are obtained (*e.g.* 1-diethylborylalkyldiboranes or 2-borolanylborolanes [1]), which originate from the extremely unstable primary dialkylboryl or borolanyl radicals as a result of hydrogen migration and subsequent combination (*e.g.* with another boryl or borolanyl radical). Thus, for example:



The intermediate free radicals may be trapped in the form of stable compounds if the dehalogenation is carried out in the presence of a suitable base (*e.g.* pyridine, quinoline, or isoquinoline). Intensely colored free radicals can be produced in high yield from the resultant addition compounds. Lithium in suitable solvents (*e.g.* diethyl ether or tetrahydrofuran) has proved particularly valuable for effecting dehalogenation.



R = $C_2H_5$, $C_6H_5$

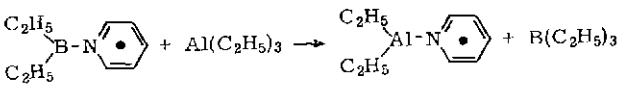
In ether, the diethylborylpyridine radical is deep-green. After storage for several days at room temperature, the compound separates out as a dark-blue precipitate. Both the solid and its

solution (*e.g.* in diethyl ether) give a strong ESR signal (g = 2.003). With low concentrations of the compound (approximately $10^{-3}$ mole/l), the signal (total width ca. 28 Gauss) shows hyperfine structure (ca. 50 lines), which could not however be fully resolved on further diluting or on cooling to ca. −70 °C.

Interaction of the unpaired electron with the atomic nuclei of the pyridine ring alone would theoretically give rise to 54 lines. With the resolution attained (smallest interlinear distance ca. 0.3 Gauss), these could certainly not all be observed because of overlapping. The unpaired electron may therefore also interact with the boron nucleus (nuclear spin = 3/2 for $^{11}B$), the number of hyperfine structural lines being then increased to 216.

The diethylborylquinoline radical (g = 2.003) is yellow, the corresponding isoquinoline radical (obtainable analogously by reduction with lithium in tetrahydrofuran) is red. The diphenylborylpyridine radical (unresolved ESR signal, g = 2.003), which is isoelectronic with the triphenylmethyl radical, is deep-blue to violet in tetrahydrofuran and can be prepared in the solid state in 86 % yield; cryoscopic molecular-weight determinations in benzene indicated about 1.1 times the simple formula weight. The B—N radicals react with triphenylmethyl with simultaneous decolorization. They are also extremely sensitive towards oxygen.

The corresponding Al—N radicals are formed analogously by dehalogenation. Starting from diethylaluminum chloride pyridinate, a red-violet compound (ESR signal, g = 2.003) is obtained with lithium in ether at 0 °C. The Al—N radical is also accessible by an exchange reaction of the corresponding boron radical with triethylaluminum.



Received, June 8th, 1964 [Z 754/581 IE]
German version: Angew. Chem. 76, 649 (1964)

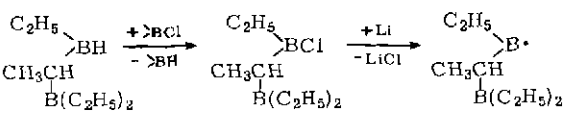
1] *R. Köster* and *G. Benedikt*, Angew. Chem. 75, 346 (1963); Angew. Chem. internat. Edit. 2, 219 (1963).

## The Formation of Organic Carboranes

By Dr. R. Köster and Dr. G. Benedikt

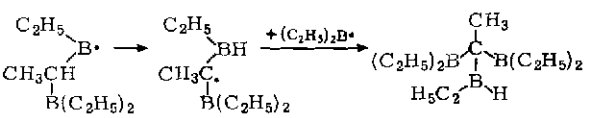
Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany)

The B-H compounds of type *(1)* derived from alkylboranes by way of free radicals [1] may be subjected to H/Cl exchange [2] and then dehalogenated further by means of lithium (*e.g.* in tetrahydrofuran) according to the reaction sequence:



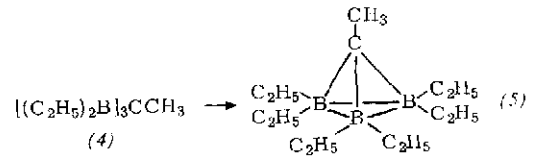
*(1)* *(2)*

As a result of migration of the α-hydrogen of the ethylidene group to the boron atom, *(2)* gives rise to radicals, from which tris(ethylboryl)alkanes *(3)* may be formed by combination with a dialkylboryl radical.



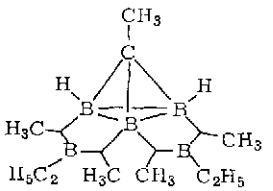
*(2)* *(3)*

Starting from these or from the homologous compound 1,1,1-tris(diethylboryl)ethane *(4)* — formed analogously by H/R exchange [2] — organoboron compounds with the carborane structure are obtained *(5)* [3].



*(4)* *(5)*

It can be demonstrated by mass spectrometry [5] that the reaction mixture contains *inter alia* a compound of molecular formula $C_{14}H_{31}B_5$ [4]. Its structure *(6)* follows from its mode of preparation, its infrared spectrum, its $^{11}B$ nuclear magnetic resonance spectrum (3 signals at δ = −3.4, −9.2, and −25.4 ppm, referred to δ = 0 for $^{11}B$ in $Ca[B(C_2H_5)_4]_2$), and its chemical degradation (BH content by alcoholysis, reaction with ethylene, transalkylation with aluminum trialkyl, followed by deuterolysis → $D_3CCH_3$, $D_2CHCH_3$ together with $DCH_2CH_3$).

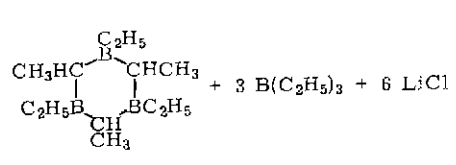


*(6)*

The mixtures also contain compounds with four and six boron atoms.

Preparation of $C_{14}H_{31}B_5$ *(6)*: 200 g of diethylchloroborane are added dropwise with cooling to 13.8 g of lithium chips in 300 ml of tetrahydrofuran. After all the metal has been consumed, the LiCl is filtered off, and the solvent and the triethylborane are removed under reduced pressure (15 mm). Subsequent vacuum distillation affords 50.5 g of a colorless liquid, b.p. 30—100 °C/$10^{-3}$ mm, and 15.7 g of a non-volatile viscous residue. Fractionation yields 14 g of a liquid, b.p. 40—60 °C/$10^{-3}$ mm, consisting principally of $C_{14}H_{31}B_5$ (intensive absorption band, with $\tilde{\nu}_{max}$ (BH) = 2570 $cm^{-1}$); mass-groups found in the mass-spectrometric analysis: 252—254, 224—226, 117—119. A second fraction (9 g), b.p. 60 to 85 °C/$10^{-3}$ mm, contains, in addition to a little $C_{14}H_{31}B_5$, boron compounds of higher molecular weight; mass-groups found: 318—321, 303—308, 291—294, 263—266.

If the nascent BH compounds formed during the dehalogenation (*e.g.* of diethylchloroborane by lithium) are removed by means of ethylene as ethylboranes (hydroboration), no C—$CH_3$ groups are formed. The organoboron compounds then contain, apart from ethyl groups, only ethylidene groups. The main product (over 50 % yield) is 1,3,5-triethyl-2,4,6-trimethyl-1,3,5-triboracyclohexane *(7)*, b.p. 70—71 °C/0.01 mm.



*(7)*

The $^{11}B$ nuclear magnetic resonance spectrum of this compound exhibits only a single broad signal (width ca. 37 ppm), with δ = −99.8 ppm. This position thus corresponds to the $^{11}B$ signal of the trialkylboranes and to those of other known organoboron heterocyclics.

Received, June 8th, 1964 [Z 755/582 IE]
German version: Angew. Chem. 76, 650 (1964)

[1] *R. Köster, G. Benedikt*, and *H. W. Schrötter*, Angew. Chem. 76, 649 (1964); Angew. Chem. internat. Edit. 3, 514 (1964).

[2] *R. Köster*, Angew. Chem. 73, 66 (1961).

[3] *R. Köster* and *G. W. Rotermund*, Tetrahedron Letters *1964*, 1667.

[4] The molecular formula was obtained using a high-resolution mass spectrometer.

[5] *D. Henneberg*, Lecture at the Symposium on "Modern Methods of Organic Analysis", Eindhoven (Holland), May 1964; to be published in Z. analyt. Chem.

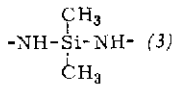
## Equilibriation of Cyclic Silazanes and Isolation of a Linear Polysilazane

By Dr. G. Redl and Prof. Dr. E. G. Rochow

Department of Chemistry, Harvard University, Cambridge, Mass. (U.S.A.).

Hexamethylcyclotrisilazane *(1)* and octamethylcyclotetrasilazane *(2)* can be polymerized by heating them with ammonium halides [1]. Ammonia is split off and a crosslinked polymer containing tertiary nitrogen atoms is obtained. We wished to study the kinetics of this reaction by measuring the rate of evolution of ammonia volumetrically in a closed system. It was found that under these circumstances hardly any evolution of ammonia was observable, and the polymer obtained was less crosslinked than that obtained in the open system.

The extent of crosslinking was estimated from NMR spectra. The spectra of the cyclic silazanes *(1)* and *(2)* consist of a single peak at $\delta = 0.06$ ppm due to the methyl protons. The azo-proton peak is extremely broad and can hardly be detected. The spectra of the crosslinked polymers contain several peaks because of the different methyl proton environments. A peak at $\delta = 0.09$ ppm is assigned to methyl protons attached to a silicon atom between secondary nitrogen atoms *(3)*. In a perfectly linear polymer, only this peak should be present.



*(3)*

The product obtained by heating *(1)* with $NH_4Br$ at 130 to 140 °C under 4 atm of ammonia for 80 h was an equilibrium mixture containing approximately 55 % *(1)* and 20 % *(2)*. After removal of all the volatile products by distillation, a colorless viscous residue (20 %) was obtained which was shown to be a linear silazane polymer with an average molecular weight of 1200.

The proton resonance spectrum of this polymer had only a single methyl proton peak at $\delta = 0.09$ ppm and a broad but well-defined azo-proton peak at $\delta = 0.50$ ppm. Integration of the peaks could be carried out only approximately because of slight overlap, but the methyl-proton peak area was found to be 6.0–6.5 times larger than that of the azo-protons. The intensity of the NH stretching and deformation bands at 3399 and 1159 $cm^{-1}$ in the infrared spectrum of *(1)* [2] is unchanged in that of the polymer. This is further evidence for the linear structure of the new polymer since the intensity of these bands is strongly reduced in the infrared spectrum of the crosslinked polysilazane.

It was found that, although $NH_4Br$ is slightly soluble in liquid or molten cyclic silazanes at 140 °C and atmospheric pressure, it is insoluble in the reaction mixture under 4 atm of ammonia, and that the reaction proceeds in exactly the same way with omission of the $NH_4Br$. However, when an inert gas (nitrogen) was used instead of ammonia, no reaction was observed. The catalyst must therefore be ammonia or some ion derived from it. We believe that the reaction is similar to the base-catalysed polymerization of cyclic siloxanes [3], with $NH_2^-$ ions acting as chain initiators, and that the chains are terminated by reaction with $NH_4^+$ ions. The linear polymer then would have the structure:
$NH_2\text{-}SiMe_2\text{-}(NH\text{-}SiMe_2\text{-})_nNH_2$.

The compositon calculated with $n = 15.2$ (corresponding to an average molecular weight of 1200) agrees well with its analysis.

Received, June 3rd, 1964 [Z 760/570 IE]
German version: Angew. Chem. 76, 650 (1964)

[1] *C. R. Krüger* and *E. G. Rochow*, Angew. Chem. *74*, 588 (1962); Angew. Chem. internat. Edit. *1*, 458 (1962).

[2] *H. Kriegsmann*, Z. anorg. allg. Chem. *303*, 219 (1960).

[3] *W. T. Grubb* and *R. T. Osthoff*, J. Amer. chem. Soc. *77*, 1405 (1955).

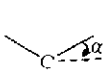
# CONFERENCE REPORTS

## Modern Problems of Stereochemistry

On February 29th, 1964 the annual meeting of the Schweizerische Chemiker-Verband took place in Bern (Switzerland).

*A. Dreiding* (Zürich) chose for his opening paper two subjects of current importance: conformational analysis and stereoelectronics. In the first part of his account he dealt with the methods of calculating intramolecular strains. For the four types of intramolecular interaction the following expressions give satisfactory results:

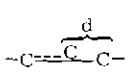
*Bayer strain* (deformation of bond angles)



$E = K \cdot \alpha^2$

*Bond strain* (change of bond length)

(to be ignored in calculations owing to the steep rise in potential)



$E = k \cdot d^x$

*Pitzer strain* (torsion of staggered arrangement)



$E = 1.40\,(1 + \cos 3\,\omega)$

*Prelog strain* (intramolecular van der Waals forces)



$E = 10^4 \times e^{-4.6r} - \frac{49}{r^6}$

With these equations the energy contents of the conformations of simple molecules, *e.g.* cyclohexane, can be calculated with the aid of electronic computers [1]. These calculations lead to qualitatively satisfactory results, which, however, are not yet sufficiently quantitative in most cases owing to the inexactness of the primary equations.

Newer results of conformational analysis in simple ring compounds were dealt with in detail and the growing importance of the molecular topological approach was alluded to [*]. In the case of cyclohexane, the twist form (symmetry $D_2$) is second in stability to the "rigid" chair form. It has the lowest energy content of all "mobile" conformations, the boat (symmetry $C_{2v}$) being the transition form between two twist forms.

The findings of conformational analysis stimulated the synthesis of the hydrocarbon "twistane" *(2)* (an isomer of

[1] *J. B. Hendrickson*, J. Amer. chem. Soc. *83*, 4537 (1961).

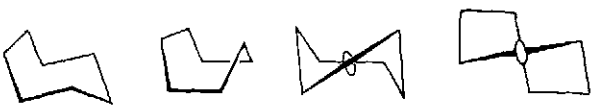
[*] By this term the speaker apparently understands a purely geometrical approach, not at all as closely related to the current concept of topology in mathematics as the use of the same name by *Wassermann* for a somewhat different concept in chemistry [J. Amer. chem. Soc. *83*, 3789 (1961)] (Abstractor's note).

adamantane). It consists of four fused six-membered rings, all of which are in the twist form [2].



(1) (2)

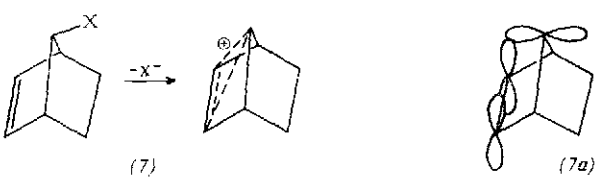
First results have recently been obtained in the conformational analysis of the saturated seven-membered ring. As in the case of the six-membered ring there are two forms, chair *(3)* and boat *(4)*; in contrast to the situation in the six-membered ring, however, both forms of the seven-membered ring are flexible (flexomers) and can assume a large number of conformations, of which the twist boat *(6)* and the twist chair *(5)* are the most stable ones. The twist chair is more stable than the twist boat by about 2.5 kcal/mole and is thus the most stable conformation of cycloheptane [1].



(3) (4) (5) (6)

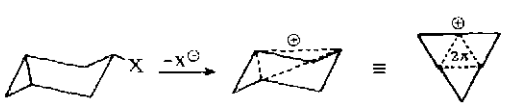
A new branch of stereochemistry is *stereoelectronics*. This concept collects together those phenomena which result from the interaction of electron orbitals suitably arranged sterically. It was illustrated by two examples, *homoaromaticity* and *valence tautomerism*.

Anti-7-norbornenyl derivatives *(7)* solvolyse up to $10^{11}$ times faster than the corresponding saturated compounds. Because of their favorable steric position *(7a)* the π-electrons of the double bond can delocalize the positive charge of an incipient C-7 carbonium ion.



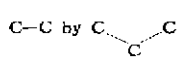
(7) (7a)

A similar delocalization of charge is possible when the double bond is replaced by a cyclopropane ring *(8)*.

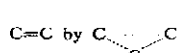


(8)

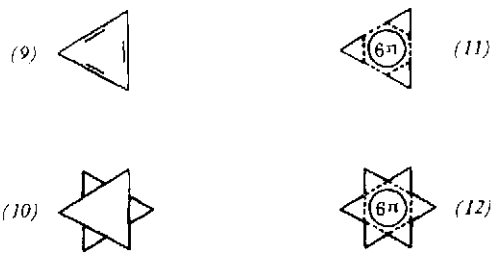
Systems that can be regarded [like the symmetrical cation *(8)*] as being formed from aromatic compounds through replacement of the groupings



and



are termed, after *Winstein* [3], homoaromatic; *(8)* is accordingly the trishomocyclopropenyl cation. By synthesis of the hydrocarbons cyclonona-1,4,7-triene *(9)* [4] and tetracyclo[9,1,0,$0^{3,5}$,$0^{7,9}$]dodecane *(10)* [5] it could however be shown that "homoaromatic" delocalization of the electrons with formation of trishomobenzene *(11)* or hexakishomobenzene *(12)* [*] does not occur in these systems.

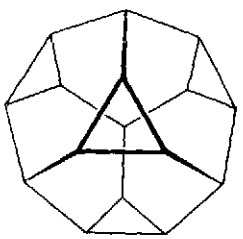



(9) (11)

(10) (12)

*Valence tautomerism* as a stereoelectronic problem was illustrated by Cope's rearrangement. This takes place only when sterically specific interactions of the electron orbitals of the participating bonds are possible.

The speaker ended his paper with a reference to his own work, not yet concluded, on the synthesis of a spheroidal polycyclic system "chemophane" *(13)*, for which interesting properties may be expected because of the possible homoaromatic delocalization of the bonds.



(13)

*R. F. Zürcher* (Ciba AG, Basel) gave a paper on "Determination of configuration and conformation by means of proton spin resonance". The speaker illustrated the principles of such investigations by examples drawn from the steroids, in which structure and configuration often can be determined only from the position of the proton signals of the two angular methyl groups. Substituents on the basic skeleton alter the magnetic shielding of the methyl protons and shift their signals. This "additional chemical shift" Δδ is characteristic for the type and the position of the substituent in the molecule [6]. Substituents in equivalent positions relative to a methyl group shift the signal of this methyl group to about the same extent. With several substituents the effect is approximately additive.

An alteration in the configuration of the basic skeleton also leads to an additional chemical shift. For example, the difference between *trans*-fusion of rings A and B (in 5α-steroids) and *cis*-fusion (in 5β-steroids) is noticeable in the NMR spectrum by the different positions of the C-19 methyl signals. The methyl group C-19 is axial to both rings in the first case, but equatorial to ring A in the second.

By use of Karplus' equation, which gives for vicinal protons the relationship between the angle of torsion ω and the coupling constant J, information about the conformation of steroids can be obtained in some special cases, *viz.* when the proximity of substituents leads to substantial alterations in the chemical shifts of certain protons, so that the splitting of their signals can be estimated. It was found in this manner, for example, that ring C in 11β-bromo-12-keto steroids is practically not deformed.

[2] *H. W. Whitelock* Jr., J. Amer. chem. Soc. *84*, 3412 (1962).

[3] *S. Winstein* and *J. Sonnenberg*, J. Amer. chem. Soc. *83*, 3244 (1961).

[4] [a] *P. R. Radlick* and *S. Winstein*, J. Amer. chem. Soc. *85*, 344 (1963); [b] *K. G. Untch*, J. Amer. chem. Soc. *85*, 345 (1963).

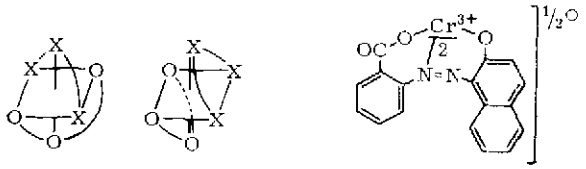
[5] [a] *R. S. Boikes* and *S. Winstein*, J. Amer. chem. Soc. *85*, 343 (1963); [b] *W. R. Roth*, Angew. Chem. *75*, 682 (1963); Angew. Chem. internat. Edit. *2*, 556 (1963).

[*] Termed hexahomobenzene in the original publication.

[6] *R. F. Zürcher*, Helv. chim. Acta *44*, 1380, 1755 (1961).

*G. Schetty* (Geigy AG, Basel) reported on the steric configuration of 1:2 metal-dye complexes [7].

*o,o'*-Disubstituted azo dyes and the trivalent metals Cr and Co form 2:1 complexes, in which a dye molecule occupies three of the six coordination sites.



*(14)* *(15)* *(16)*

With octahedral coordination of the ligands two basically different arrangements of the dye molecules in the complex result, namely:

1. the "Drew-Pfitzner" arrangement with the dye molecules perpendicular to each other *(14)*,

2. the "Pfeiffer" or "sandwich" arrangement in which the two dye molecules lie parallel to each other *(15)*. In this rraangement five forms are possible [*].

The azo dye obtained from anthranilic acid by diazotization and coupling with β-naphthol forms with trivalent Cr a 2:1 complex *(16)*, which can be separated into four fractions by chromatography on $Al_2O_3$. This indicates that the complex has the "sandwich" arrangement. The fractions can easily be isomerized by heating in water. The ratio of isomers depends on the pH.

Systematic investigations of complexes of different azo dyes, including those with pyrazolone derivatives as coupling components, showed that the "Drew-Pfitzner" arrangement occurs as well as the "sandwich" arrangement. The type of complex formed is determined by the size of the dye molecules and particularly by the spacing of those atoms which serve as ligands in the complex.

[VB 813/145 IE]

German version: Angew. Chem. *76*, 501 (1964)

[7] *G. Schetty*, Helv. chim. Acta *46*, 1132 (1963); see also Angew. Chem. *75*, 1140 (1963); Angew. Chem. internat. Edit. *3*, 155 (1964).

[*] One symmetrical form and four enantiomeric pairs, *i.e.* a total of nine isomers, not ten as first assumed by *Pfeiffer*, Ber. dtsch. chem. Ges. *74*, 935 (1941) (Abstractor's note)

# Raman Colloquium

About 100 scientists from 9 countries took part in the symposium held in Freudenstadt (Germany) from March 10th to 13th, 1964. Recent results in Raman spectroscopy were reported in 28 lectures.

The recording of Raman spectra within frequency ranges of about 1000 $cm^{-1}$ is possible, according to *M. Delhaye* et al., within tenths of a second, if image converters or image amplifier tubes are used. In this way, cinematographs of a test sample may be taken in the course of a chemical reaction. The same authors reported on the use of lasers for exciting Raman spectra. A single laser flash sufficed to produce a complete Raman spectrum of $PBr_3$. Similarly, *B. Schrader* and *M. Stockburger* showed Raman spectra of colored crystalline powders (*p*-nitraniline and *p*-nitro-*p*-dimethylaminostilbene) with a ruby laser as source of radiation. These authors also explained new testing arrangements permitting the recording of Raman spectra even of substances with slight scattering, with a test sample of only 0.07 ml, by using low-pressure mercury arcs with a contraction, a condenser, and interference filters.

The emission of Raman lines from nitrobenzene stimulated by a ruby laser beam was treated by *G. Rivoire* and *R. Dupeyrat* who investigated, among other things, the dependence of intensity on direction and put forward quantum-mechanical equations for interpreting the stimulated emission.

For the further improvement of the photographic technique used for intensely colored substances a helium lamp was constructed by *Mecke*, *Schühly*, and *Stammreich*, and a Raman set-up, equipped with it, was described.

*J. Behringer* lectured on an expansion of the theory of the resonance Raman effect on molecules with more than two atoms. A point on the potential hyperplane in the excited state is ascribed to the equilibrium configuration of the nuclei in the ground state. The gradient of the plane at this point and the symmetry characteristics of the overlap integrals of the vibration eigenfunction determine the selection rules of the resonance Raman effect. A qualitative interpretation of the experimental results is made possible by this approach.

*H. Hacker* reported on recent resonance Raman measurements. Investigations were carried out on azobenzenes and azonaphthalenes in solution. The N–N frequency was found to lie between 1380 and 1440 $cm^{-1}$. The scattering coefficients of various Raman lines and the factors determining intensity were discussed.

Further lectures dealt with the measurement of intensities, which presents great difficulty, especially in the case of crystalline powders. *H. Moser* reported on the determination of relative scattering coefficients, independent of the apparatus used. The Raman spectra were recorded according to the pellet method of *Schrader* and *Kresze* and the intensities extrapolated from several determinations with varying pellet thickness to infinitely thin pellets. So far, such intensity measurements have been carried out on naphthalene, benzoic acid, tetracyanoethylene, $KNO_3$, $K_2SO_4$ and $KBrO_3$.

*E. Steger* reported on the determination of the scattering coefficients of inorganic anions (*e.g.* $PO_4^{3-}$, $SO_4^{2-}$, $ClO_4^-$) in aqueous solution and discussed the assumptions, on the basis of which the derivations of the bond polarizability can be calculated from these values. Relationships between changes in intensity of characteristic Raman vibrations and bond characteristics in silicon and tin compounds were discussed by *H. Kriegsmann*. *H. Gerding* and *C. C. Smitskamp* examined changes in intensity, caused by intermolecular forces, in the Raman spectra of mixtures of $POCl_3$ or $PSCl_3$ with $CCl_4$ or $GeCl_4$, in which maximum values may occur at certain mixing ratios.

*G. Matz* reported on the efficiency of Raman spectroscopy in routine application to problems of qualitative and quantitative analysis in an industrial laboratory and on an apparatus set up for such measurements. According to this report, Raman spectroscopy is frequently not inferior to other spectroscopic methods as regards rapidity and accuracy.

Complete assignment of the ground vibration spectra of symmetrical molecules is normally possible only if the Raman spectra, too, are taken into consideration. Examples for the assignment of vibrations and structural conclusions resulting therefrom were contributed in reports by *Stammreich* (*p*-benzoquinone), *Lippert*, *Moser* et al. (tetracyanoethylene), *Schrötter* and *Hoffmann* (trimeric dialkylaluminum hydrides), *Ziegler* (determination of the constitution of perchlorinated hydrocarbons $C_6Cl_8$, $C_6Cl_6$, and $C_8Cl_8$) as well as *Gerding* and *Smitskamp* ($SeO_3$).

Calculation of the force constants from completely assigned vibration spectra was treated in the lectures by *Duinker* and *Mills*, by *Sawodny*, and by *Strey*. The latter reported on computations of force constants, according to an iteration method, for the molecules $H_2O$ and $C_2H_4$ as well as their isotopic deuterium and $^{18}O$ derivatives. *Duinker* and *Mills*

worked out a new set of valence force constants from the vibrations of benzene and from the Coriolis zeta-coefficients, in which a limited number of interaction constants were considered on the basis of a hybrid orbital field of force. The resulting force constants agree closely with theoretical expectations and may be applied to halogenated benzene derivatives as well as pyridine and its deuterium derivatives, with only minor modifications. – From the ground vibrations of molecules with a known geometrical arrangement *Sawodny* computed complete series of force constants of the general valence force model, by ascribing the vibrations, regarded as uncoupled, to individual internal coordinates and thus obtaining solutions for the force constants, which are improved by gradual introduction of kinetic coupling according to the Newton method. This method yields good results if the normal vibrations are predominantly determined by single symmetry coordinates. [VB 812/144 IE]

German version: Angew. Chem. *76*, 616 (1964)

## Recent Investigations into the Structures of Noble-Metal Compounds

*K. Brodersen*, Aachen (Germany)

Iridium(III) chloride occurs as two modifications which differ in crystal form, color, and magnetic properties. Its monoclinic modification forms platelets with the lattice constants: a = 5.99 Å, b = 10.36 Å, c = 5.98 Å, and β = 109°27′. The arrangement of atoms in the unit cell corresponds to that in aluminum(III) chloride, the parameters of the chlorine atoms being slightly different.

Platinum(II) chloride crystallizes in needle-like hexagonal prisms. Its rhombohedral unit cell has dimensions a = 8.09 Å and α = 108°15′ and consists of six formula units. The lattice sites can be found from Weissenberg and precession photographs; space group: $D_{3d}^5$–C $\bar{3}$ m,

lattice sites: 6 Pt on 6 (h): x = 0.079 and z = 0.333
6 Cl on 6 (h): x = 0.583 and z = 0.825
6 Cl on 6 (f): x = 0.258.

The six platinum atoms are arranged octahedrally with Pt-Pt distances of 3.32 Å or 3.40 Å. Each platinum is surrounded nearly quadratically by four chlorine atoms with Pt-Cl distances 2.34 Å or 2.39 Å. The 12 chlorine atoms are situated in front of the 12 edges of the $Pt_6$ octahedron. Accordingly, platinum(II) chloride has a structure with $Pt_6Cl_{12}$-complexes and with weak metal-metal bonds.

[GDCh-Ortsverband Heidelberg (Germany),
May 26th, 1964] [VB 823/146 IE]

German version: Angew. Chem. *76*, (1964), in the press.

## Size of the Solvation Sheath of Poly(vinyl alcohol) in Aqueous Solutions

*S. Peter*, Hannover (Germany)

The rheological properties of aqueous solutions of poly(vinyl alcohol) with molecular weights of 20000 or 85000 and 180000 were examined at 20–50 °C and at concentrations up to about 10% by weight, using a Couette viscometer. The degree of hydrolysis of the products prepared by alkaline saponification of poly(vinyl acetate) was 98 %.

The activation energy for the flow process was determined from the temperature depence of the viscosity in the absence of forces of interaction between the dissolved particles. At low concentrations, it corresponds to the activation energy for the flow of pure water. With increasing concentration, the activation energy rises and appears to approach a limiting value of about 6.2 kcal/mole.

The effective, rheologically immobile volume proportion in the solution was determined using an expression proposed by *Franck*. With increasing dilution, the effective, rheologically immobile volume corresponding to unit weight of solute (denoted by $\varphi_{sp}$) tends to a limiting value $\varphi^0_{sp}$ which is proportional to the intrinsic viscosity $[\eta]$ (cf. Table 1).

Table 1. Limiting values $\varphi^0_{sp}$ for $c \to 0$, at 20 °C.

| Molecular weight | $\varphi^0_{sp}$ [cm³] | Immobile water [mole/mole of monomer] [a] | $[\eta]$ [cm³/g] |
|---|---|---|---|
| 20000 | 14.7 | 36 | 44.1 |
| 85000 | 27.5 | 67 | 82.5 |
| 180000 | 39.8 | 97 | 117.4 |

[a] Determined assuming the density of water in the solvation sheath to be equal to that of pure water.

The assumption that large solvation sheaths occur in aqueous solutions of poly(vinyl alcohol) is confirmed by the fact that $[\eta]$ and $\varphi^0_{sp}$ decrease with increasing temperature, whereas $[\eta]$ should increase with temperature if the solvent flows more or less freely through the poly(vinyl alcohol) coils. Thus, for polyisobutylene (mol. wt. 180000) in benzene, $[\eta]$ has a value of 35.2 cm³/g at 24 °C and 76.5 cm³/g at 60 °C; poly(vinyl alcohol) with the same molecular weight, on the other hand, gave $[\eta]$ = 119.4 cm³/g in water at 20 °C, and 99.0 cm³/g at 50 °C.

[GDCh-Ortsverband Hannover (Germany),
February 20th, 1964] [VB 806/142 IE]

German version: Angew. Chem. *76*, 441 (1964)

## Experiments with Potassium Needles

*K. Neumann*, Gießen (Germany) [1]

When potassium is sublimed onto wires of metals such as silver, gold, and platinum, moderate supersaturation leads to the formation of very fine needles with a thickness of a few hundred Å and a length up to 1 mm. With suitable illumination, their diffraction diagrams can be observed as bright lines under the microscope, and their growth can be followed. At first, their length increases exponentially with time until a maximum constant rate of growth has been attained. This exceeds the value calculated for direct condensation of the vapor on the growing tip by several powers of ten. Actually, potassium condenses on the long mantle faces and migrates from there along to the tip. Finally, the rapid lengthwise growth stops suddenly, and the needles begin instead to increase gradually in thickness, making it possible to recognize their shape: hexagonal (rarely quadratic) prisms with a roof formed from three or four (011) rhombs. The three long lateral faces are likewise (011) faces. The unimpeded growth at the tip is probably due to a spiral dislocation terminating at this position.

Observation of the rate of growth (or evaporation) as a function of the degree of supersaturation (or unsaturation) in the vapor phase also provides important information on the selfdiffusion of the K adatoms. Furthermore, the increase in vapor pressure of the needles owing to their low thickness is readily determined and from this in turn, the free surface energy of the (011) faces can be obtained, a magnitude which otherwise cannot be determined experimentally for solids. Its value is 170 ± 15 erg/cm² at 25 °C.

With about 15-fold supersaturation in the vapor phase, rapid lengthwise growth stops as a result of two-dimensional nucleus formation on the side faces. If the supersaturation is reduced after some time, the needles again increase in length, but at a slower rate, because they have meanwhile become thicker. In this manner, the thickening can be followed in the critical region in which nucleus formation on the surface is

[1] Based on work carried out by *F. Hock*, *W. Dittmar*, *H. D. Meissner*, and *A. Köhler*.

rate-determining. With a crystal temperature of 25 °C and sixteenfold supersaturation, a rate of thickening of $10^{-9}$ cm per sec was observed, corresponding to a condensation coefficient of 0.2 or the origination of about one crystallization nucleus per minute on every prism surface. The same value is derived from the nucleation theory of ideal crystals by taking a value of 167 erg/cm² for the free surface energy when calculating the atomic deposition work functions.

A critical value for the degree of unsaturation was likewise observed. If the pressure in the vapor phase decreases beyond this, rapid evaporation at the tip ceases because the side faces begin to evaporate, starting from the top edges. When the pressure is not far from that of the saturated state, these edges are protected by a diffusion stream from the neighboring roof faces, the dislocation stage of which has a slightly higher vapor pressure. According to theory, this protection may be effective down to extremely low pressures so that a critical degree of unsaturation need not necessarily occur with all needles.

[Chemisches Kolloquium der Universität Bonn (Germany), February 25th, 1964) [VB 808/141 IE]

German version: Angew. Chem. 76, 653 (1964)

# The Structure of Glass

The Fourth Interunion Conference on the Vitreous State took place in Leningrad (U.S.S.R.) from March 16th to 21st, 1964. It was again held under the patronage of the Nestor of Soviet glass science, Prof. *A. A. Lebedev* and was organized by the U.S.S.R. Academy of Sciences, the Grebenstshikov Institute of Silicate Chemistry, the Leningrad Chemical Mendeleev Society, and the State Optical Institute in Leningrad. Most of the lectures dealt with investigations into the microheterogeneities in glass. While during the Third Conference on the structure of glass the main topic of discussion was the contrast between the crystallite and the network theories, during this year's session the crystallite theory was acknowledged by most participants.

*E. A. Poray-Koshits*, Leningrad (U.S.S.R.), reported on crystallochemical aspects of the structure of inorganic glasses. The properties of quartz glass, whose structure corresponds most closely with the concepts of the network theory, can be described satisfactorily in terms of the vitron theory (*Tilton*). $Si_2O_7$ groups with Si–O–Si angles of 143 ± 17° and interatomic distances of 1.60 Å for Si–O and 3.0 Å for Si···Si, are supposed to be the basic units. He then compared results of electron-optical investigations with those of small-angle X-ray scattering on multicomponent glasses; both methods lead to the concept of a microheterogeneous structure.

*V. A. Florinskaya*, Leningrad (U.S.S.R.), investigated the structure of glass by various physical methods, *e.g.* infrared spectroscopy and electron microscopy. Investigations of the system $Li_2O$–$SiO_2$ have shown that above 20 mole-% $Li_2O$, segregation phenomena decrease, but increase again with $Li_2O$ contents exceeding 33 mole-% (glasses with less than 20 mole-% $Li_2O$ were not examined). This is consistent with the results of *Vogel* and coworkers. In the melt, inhomogeneities are already present in the form of extremely stable silicates. On cooling a melt, several new structural units become superimposed on each other. The microheterogeneous character of glass is determined by the most stable compounds. Microheterogeneities often have dimensions of 100 Å and exhibit higher order than their surroundings. By studying the variation of crystal equilibria with temperature it was shown that the crystallization times required for equilibrium to be reached at room temperature and at very high temperatures amounted to about 30 years.

*O. K. Botvinkin*, Moscow (U.S.S.R.), gave an account of the diversity in glass structures. Although there are examples to be found which conform to each of the various concepts of glass structure, the properties of most complex glasses can only be understood in terms of a microheterogeneous structure. In an experiment to study the canal system in leached out borosilicate glasses, the pores were filled with a liquid organic resin which was then solidified; the $SiO_2$ framework was then dissolved away. *Botvinkin* proposed that in future studies, special attention should be given to nucleation and crystallization in combination with the formation of ion clusters and segregation phenomena.

*A. A. Appen*, Leningrad (U.S.S.R.), considered glass formation as the overlapping of bilateral processes. The attainment of diverse equilibria in glasses, is important *e.g.* in the processes:

$$\text{association} \rightleftharpoons \text{dissociation}$$

or

$$\text{dissolution} \rightleftharpoons \text{crystallization.}$$

*Appen* suggested that the fundamental investigations of *Lebedev* and *Stocharov* into states of equilibrium by refractive-index and viscosity measurements be taken up again. As a supporter of the network theory even for complex glasses, he was of the opinion that experimentally detectable microheterogeneities probably result from insufficient homogenization of the melt and should be regarded as defects in glass. *D. A. Goganov* and *E. A. Poray-Koshits*, Leningrad (U.S.S.R.), investigated sodium borosilicate glasses by X-ray scattering methods using small angles of incidence to surfaces which had been subjected beforehand to different thermal treatments. Droplet-shaped regions of phase separations with uniform dimensions or volumes are formed. *N. S. Andreyev* and *V. J. Averyanov*, Leningrad (U.S.S.R.), also observed phase separation with sodium silicate glasses in the metastable liquation region. These results were obtained from light scattering and electron-optical investigations. *V. J. Averyanov* and *E. A. Poray-Koshits*, Leningrad (U.S.S.R.), investigated the segregation of $Li_2O$–$SiO_2$ glasses with increasing $Li_2O$ content by electron microscopy. The dimensions of the regions of segregation reach a maximum and then – above 29 mole-% – a minimum, as found by *W. Vogel* and *H. G. Byhan*.

According to *A. B. Shatilov*, Leningrad (U.S.S.R.), an accuracy of ± 10 % is attainable in the determination of the size of microheterogeneities in glass by X-ray small-angle scattering. Regions 0.25 μ in diameter can be detected by infrared scattering. The results are dependent on the wavelength of the radiation. Microliquation of $K_2O$–$SrO$–$SiO_2$ melts and $K_2O$–$BaO$–$SiO_2$ melts has been studied by *F. I. Galakhov*, Leningrad (U.S.S.R.). Secondary segregation processes occur in these glasses which lead to a three-phase glass. Two different droplet-shaped microphases are embedded in a homogeneous base glass. Hence further evidence for the occurrence of secondary segregation phenomena has been obtained.

According to *N. M. Weisfeld* and *V. I. Shelyubski*, Moscow (U.S.S.R.), unambiguous results can be obtained with Class 2 electron microscopes (resolving power 20–30 Å) only for the identification of structural elements larger than 500 Å (all samples were prepared as replicas in the presence of air). Direct specimen irradiation, vacuum preparation, and decoration techniques have not been used hitherto.

*Aniuta Winter-Klein*, Paris (France), dealt with glass formation from the viewpoint of the arrangement of electrons in the atoms. Compounds of elements with 4p electrons in the outer

shell are the best glass formers. The derivation of further regularities of vitrification was attempted by consideration of the electron configurations of the elements. Within the four characteristic temperature ranges of glass (1. glass as a highly viscous liquid, 2. glass as a supercooled liquid, 3. glass in the state of transformation, 4. glass as a solid), the physical properties undergo various profound changes.

*P. J. Bray*, Providence, R.I. (U.S.A.), investigated the structures of vitreous and crystalline boric acid, of lithium borate glasses, of lead silicate glasses, of glasses of the systems $NaF-B_2O_3$ and $CaO-Al_2O_3-B_2O_3$, and of phosphate glasses by NMR measurements. Even small amounts of $Li_2O$ suffice to convert boron ions (coordination number = 3) into a state of tetrahedral coordination. The change in coordination (from coordination number $> 4$ to $= 4$) of lead ions in binary silicate glass in the region of higher PbO concentrations was definitely detected. The proportion of boron ions with a coordination number of 4 can be found in the system $CaO-Al_2O_3-B_2O_3$ (Cabal glass). Even small amounts of fluorine in the system $NaF-B_2O_3$ cause 3-coordinate boron ions ($[BO_3]$ planar triangles) to be converted into 4-coordinate ($[BO_4]$ tetrahedra) ions. With phosphate glasses, similarity between the structural elements in the glass and in the corresponding crystalline compounds was demonstrated.

*O. L. Anderson*, Murray Hill, N.J. (U.S.A.), divided the lattice properties of glasses into three classes: 1. properties corresponding to those of a single crystal, 2. properties like those of a liquid, and 3. properties similar to those of common solids, but not like those of single crystals, which are simple functions of pressure, volume, and temperature and dependent on heat pretreatment. These three classes of properties were derived using a linear-chain model of a dynamic lattice under the assumption that non-harmonic forces exist between the atoms of the chains, which are assumed to be diatomic, with small disturbances of the vibrational energies.

*R. D. Maurer*, Corning, N.Y. (U.S.A.), investigated the effect of temperature and time on the growth of crystal nuclei in glass by small-angle scattering of X-rays. The differences in the refractive indices were measured and calculated for scatterings of various strengths.

The mobility of ions in glass was ascertained by *K. Kühne*, Berlin (Germany), from electrical-potential measurements. Measurements on electrical potential cells consisting of two different glasses allowed conclusions to be drawn concerning defects due to bubble formation at the metal-glass interface on melting-in a metal.

*W. Vogel*, Jena (Germany), reported on the microheterogeneous structure of glasses in the system $Li_2O-SiO_2$. Electron microscopy of direct samples or replicas revealed a segregation maximum in the range from 0 to 33 mole-% $Li_2O$. Although extensively microheterogeneous structures are present in the middle ranges, glasses with about 33 mole-% $Li_2O$ are homogeneous in the sense of an infinitely large drop. Special hydrofluoric-acid treatment isolated either drop-like regions or the glass phase encompassing the drop-like regions and thus permitted separate examination of these microphases. The composition of the drops approaches that of lithium disilicate; at 16–17 mole-% $LiO_2$, secondary segregation into $SiO_2$ and a metasilicate phase occurs.

The dependence of the turbidity of optical glass on heat treatment was investigated by *H. Besen*, Jena (Germany). On slow cooling of fluorosilicate glasses, turbidity occurs which gives rise to characteristic color effects due to Rayleigh scattering at submicroscopic droplets. The droplets result from phase separation. The color effects were produced during systematic thermal-treatment experiments and were investigated by measuring the spectral transmittance of specimens 100 mm thick. Samples heated at 950 °C and cooled at a constant rate in order to remove their turbidity were used as specific, reproducible starting material. The very sharply defined region of turbidity for each glass examined was determined by annealing for 24 hours while cooling. Annealing for various times at the turbidity maximum during cooling or reheating showed that turbidity developed about seven times faster during reheating than during cooling [1].

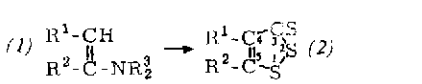
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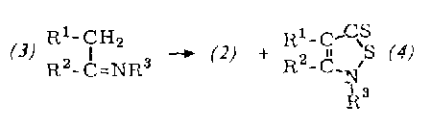
German version: Angew. Chem. *76*, 538 (1964)

[1] For a theoretical structural interpretation cf. *H. Rötger*, Silikattechnik *15*, 71 (1964).

# SELECTED ABSTRACTS

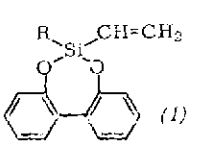
**The synthesis of trithiones from enamines, carbon disulfide and sulfur** is described by *R. Mayer, Peter Wittig, J. Fabian*, and *H. Heitmüller*. Trithiones *(2)* are formed exothermically at room temperature in 30–60% yield by reacting enamines *(1)*, $CS_2$ and sulfur in a polar solvent, such as dimethylformamide. Mono- or 4,5-disubstituted derivatives are obtained according to the type of enamine used. The amine which is split off is bound as the ammonium salt of dithiocarbamic acid. The enamines of cyclic ketones react particularly well.





The reactions of enamines of substituted acetaldehydes are of special preparative value, since they lead to trithiones substituted only in the 4-position. Trithione itself is made from the enamine of acetaldehyde. The syntheses probably proceed by nucleophilic addition of the β-carbon atom of the enamine to a $CS_2$ double bond, followed by sulfuration and cyclization. Ketimines *(3)* react with $CS_2/S$ to give trithiones and 1,2-thiazoline-5-thiones *(4)*, a new heterocyclic system. Anils give *(4)* exclusively. / Chem. Ber. *97*, 654 (1964) / –Ma. [Rd 898/248 IE]

**New types of cyclic silicon compounds** were synthetized by *R. M. Ismail*. Vinyltrichlorosilane, or organovinyldichlorosilanes, react with 2,2'-dihydroxydiphenyl and aliphatic or aromatic hydroxy compounds to give compounds of type *(1)* in 60–87% yield. They show high thermal stability and are suitable comonomers in the production of heat-resistant plastics.



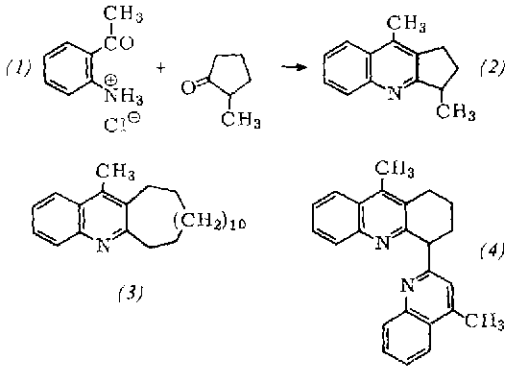
*(1)*

Examples:

*(1)*, R = $OC_8H_{17}$, b.p. 203–204 °C/1.8 mm
R = $OC_{12}H_{25}$, b.p. 225–230 °C/0.7 mm
R = $OC_6H_5$, b.p. 172–174 °C/1 mm
R = $OC_6H_4(p)Cl$, b.p. 185–187 °C/0.7 mm

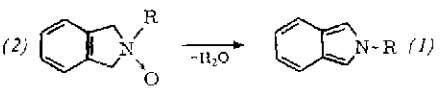
Z. Naturforsch. *18b*, 1124 (1963) / –Ma. [Rd 902/252 IE]

**An improvement of the Friedländer synthesis** was achieved by *G. Kempter, P. Andratschke, D. Heilmann, H. Krausmann,* and *M. Mietasch.* Friedländer synthesized substituted quinolines by condensing *o*-aminobenzaldehyde with compounds containing a $-CO-CH_2-$ group. The authors replaced the difficultly available and unstable *o*-aminobenzaldehyde with the easily obtainable *o*-aminoacetophenone hydrochloride *(1)*. By reacting *(1)* with cyclanones – in the



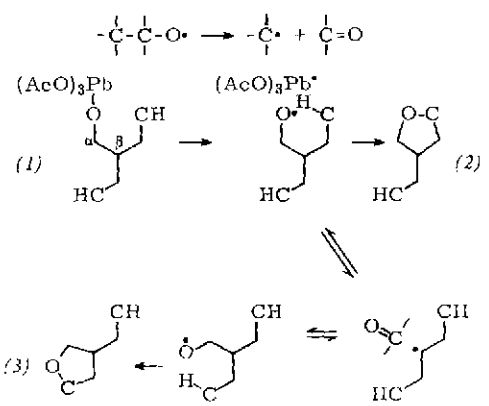
absence of solvents – one obtains, for example, *(2)*, b.p. 119 °C/4.5 mm, in 65 % yield, or *(3)*, m.p. 62.5–64 °C, in 75 % yield. Both $-CO-CH_2-$ groups of 2-acetylcyclohexanone can take part in the reaction. With 2 moles of *(1)* it forms *(4)*, m.p. 85–86 °C, in 32 % yield. / Chem. Ber. *97*, 16 (1964) / –Kr. [Rd 894/247 IE]

**A new synthesis of *N*-alkylisoindoles** *(1)* by pyrolysis of *N*-oxides of *N*-alkylisoindolines *(2)* was discovered by *J. Thesing, W. Schäfer,* and *D. Melchior. N*-Methyl-, *N*-ethyl-, and *N*-butylisoindole were obtained as the oxalates or trinitrobenzoates in 40–65 yield. If the alkyl group is adjacent to a conjugated system, as in *N*-(β-phenethyl)isoindoline *N*-oxide, the yield falls to 8–11 %, with simultaneous production of

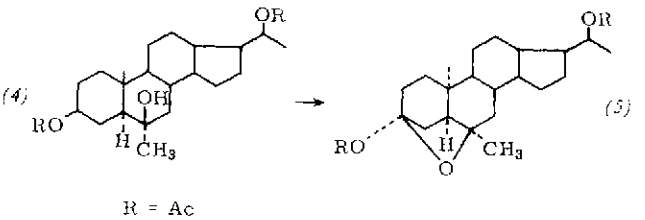


44 % *N*-hydroxyindoline and styrene. The yield of *N*-(β-phenethyl)isoindole is raised to 38 % if the *N*-oxide is decomposed in refluxing butanolic potassium hydroxide solution. / Liebigs Ann. Chem. *671*, 119 (1964) / –W. [Rd 892/245 IE]

**A homolytic hydrogen transfer in a cyclohexane ring** is reported by *K. Heusler* and *J. Kalvoda.* The fragmentation of alkoxyl radicals into a CO-compound and a C-radical can be reversible. For example, two isomeric tetrahydrofuran derivatives, *(2)* and *(3)*, which differ in the configuration at the α- and β-carbon atoms, are formed from the Pb derivative *(1)* of a secondary alcohol. It is assumed that there is an intermediate stage in which the asymmetry of the α- and β-positions is eliminated. The indicated C-atoms are part of a steroidal skeleton.

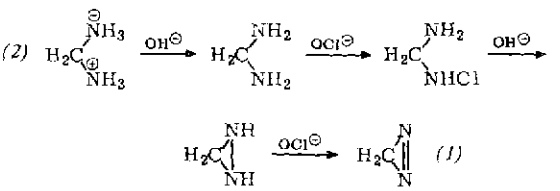


The tertiary steroidal alcohol 3β,20β-diacetoxy-6α-methyl-6β-hydroxy-5α-pregnane *(4)* undergoes a homolytic fission of the 5,6-bond with lead tetraacetate. This is followed by a transannular homolytic 1,5-hydrogen transfer, rotation of ring A around the (C-9)–(C-10) bond, and recyclization to



a pregnane *(5)*, m.p. 112–114 °C. The 6β,19-oxide is formed as a by-product. The carbon atom 10 of *(5)* is epimerized. The course of the reaction was followed by specific deuteration. / Helv. chim. Acta *46*, 2732 (1963) / –Ma. [Rd 900/250 IE]

**A simple synthesis of cyclodiazomethane** was achieved by *R. Ohme* and *E. Schmitz.* Cyclodiazomethane *(1)*, the parent compound of the diazirines, is formed when methylenediammonium salts *(2)* are added with stirring to a solution of NaOCl at 0–5 °C. Compound *(1)* is carried away in a stream of nitrogen, washed with strong sodium hydroxide solution, dried over soda lime and absorbed in absolute ether at



–50 °C. The melting point of *(1)* (from ethanol/water) is 134–136 °C; the compound is formed in 26 % yield. Cyclodiazomethane is explosive and should never be handled in an undiluted form. / Chem. Ber. *97*, 297 (1964) / –Kr. [Rd 893/246 IE]

**Reactions of sulfides in molten salts** were studied by *M. Feld, S. Sundermeyer,* and *O. Glemser.* They dissolved 20–30 % by weight of $K_2S$ in a LiCl/KCl eutectic melt and at 380–400 °C passed in phosgene. Carbonyl disulfide was formed in 75 % yield according to the reaction

$$COCl_2 + K_2S \rightarrow COS + 2\,KCl$$

The remainder of the $COCl_2$ was converted into $CO_2$. On passing in trimethylchlorosilane hexamethyldisilthiane, $(CH_3)_3Si-S-Si(CH_3)_3$, was formed in 81 % yield based on reacted chlorosilane. / Chem. Ber. *97*, 620 (1964) / –Kr. [Rd 897/253 IE]

**Hexaalkylplumbosiloxanes** were synthetized for the first time by *H. Schmidbaur* and *H. Hussek.* The hexamethyl derivative is formed even at room temperature in ether according to the reaction

$$(CH_3)_3SiONa + (CH_3)_3PbBr \rightarrow NaBr + (CH_3)_3SiOPb(CH_3)_3$$

in 76 % yield (b.p. 172 °C/720 mm in a dry, inert atmosphere). Both trimethyltriethyl derivatives and the hexaethyl derivative were analogously prepared. The alkylplumbosiloxanes are colorless, very mobile liquids of intolerable odor and high toxicity. In the presence of $O_2$ they explode at about 140 °C with evolution of black clouds (Pb). They react very rapidly with agents containing active protons but also with acid anhydrides and halides. Anhydrous $AlCl_3$ reacts explosively under normal conditions but at very low temperatures $(CH_3)_3PbCl$ as well as some $(CH_3)_3SiCl$ and AlOCl can be isolated. / J. organometallic Chem. *1*, 257 (1964) / –Kr. [Rd 895/255 IE]

**The properties of alkylstannosiloxanes, alkylsiloxanes and alkylstannoxanes** were compared by *H. Schmidbaur* and *H. Hussek*. They prepared, for example, hexamethylstannosiloxane (m.p. −59 °C, b.p. 141 °C/720 mm) in 78 % yield according to the reaction

$(CH_3)_3SiOLi + ClSn(CH_3)_3 \rightarrow LiCl + (CH_3)_3Si{-}O{-}Sn(CH_3)_3$

The simplest distannosiloxane (b.p. 77 °C/1 mm) is formed in 86 % yield according to the reaction

$2\ (CH_3)_3SnOLi + Cl_2Si(CH_3)_2 \rightarrow 2\ LiCl + [(CH_3)_3SnO]_2Si(CH_3)_2$

The analogous stannodisiloxane was also prepared.

The alkylstannosiloxanes are colorless, highly toxic compounds mostly with an unpleasant odour. They are thermally not so stable as the alkylsiloxanes and -stannoxanes. The majority of the compounds decompose above 150 °C into siloxanes and stannoxanes. The alkylstannosiloxanes exist in monomeric form; they are very reactive towards electrophilic and nucleophilic agents. In this respect they resemble the (even more reactive) alkylstannoxanes. The NMR spectra show the gradual change of the bond properties in siloxanes, stannosiloxanes and stannoxanes. / J. organometallic Chem. *1*, 244 (1964) / −Kr. [Rd 896/254 IE]

# BOOK REVIEWS

**Vitamin-Bestimmungen. Erprobte Methoden** (Determination of Vitamins. Approved Methods). By *R. Strohecker* and *H. M. Henning*. Published for E. Merck AG., Darmstadt by Verlag Chemie, GmbH., Weinheim/Bergstr. 1963. 1st edit., 365 pp., 42 illustr., 8 color plates, linen, DM 42.– (about $ 10.50) [*].

This comprehensive, excellently produced and illustrated book by two experienced analysts provides a collection of reliable methods for estimating the 15 most important vitamins, applicable primarily to pharmaceuticals and concentrates, but also to foods and animal feedstuffs. Almost all the currently known chemical, physico-chemical, and microbiological methods of liberation, extraction, separation, and assay are used and described in a readily intelligible manner. The relevant literature could not be completely reviewed, but on the other hand, the reader is familiarized with valuable analytical information as yet unpublished elsewhere, *e.g.* the extensive use of thin-layer chromatographic procedures, which also provide simple tests for the specificity of the reactions.

The authors very correctly emphasize that there are no generally applicable analytical methods. The appropriate combination of procedures for extraction, purification, and determination must be selected critically and adapted to the specific properties and composition of each individual sample, even in the case of relatively simple pharmaceutical preparations. In this regard, thorough study of the introductory chapter, which provides a wealth of basic information and guidance, is indispensible.

The proposed methods have proved their reliability in the reviewer's laboratory, where the details of the methods were sometimes altered in a few points. For colorimetric measurements, we generally use a reagent blank rather than an empty cuvette. The vitamin D determination by direct spectrophotometry or colorimetric measurement gives correct values only with pure crystalline vitamin D, and gives high results for all other forms of the vitamin owing to interfering impurities. It is also useful to dissolve materials for separation by thin-layer chromatography either in the mobile phase or in one of its components in order not to influence the separation by the presence of an extra solvent. Although it is stated that relatively large errors are inherent in several methods, more details would occasionally be desirable.

This valuable book is recommended to all engaged in the analysis of vitamins. *B. Schmidli* [NB 181/75 IE]

**Kurzes Lehrbuch der Biochemie für Mediziner und Naturwissenschaftler** (Concise Textbook of Biochemistry for Medical and Science Students). By *P. Karlson*. Georg Thieme Verlag, Stuttgart 1962. 3rd edit., XVI, 360 pp., 63 illustrations, linen DM 31.– (about $ 8.00).

In recent years it has become clear that a modern introduction to biochemistry is necessary, not only for medical students, but for all scientists. *Karlson*'s book, now appearing in its third edition, fulfils this need.

The arrangement of the first edition is unchanged except for a new chapter, twelve pages long, in which mineral metabolism, physico-chemical aspects of water as a solvent, osmosis and active transport, are discussed.

It seems desirable, even in a book for beginners, to consider basic physico-chemical concepts, such as equilibria, in an introductory chapter. There should be also fuller discussion about the fundamentals of macromolecular chemistry, so that problems of molecular biology can be understood in the further course of studies. The reviewer has observed again and again that even those students, whose grasp of the subject is not very great, approach the physico-chemical fundamentals of biochemistry with enthusiasm.

The manner in which the author has mastered the wealth of material, so that the most recent developments are discussed without noticeable omission, fascinates the reader throughout the book. Naturally, the reader's knowledge of organic chemistry is assumed.

Mistakes or misprints have been almost eliminated in this edition. A trivial mistake: diesterase cleaves the O–P bond (p. 121).

The book will keep its important place in biochemical teaching.

*F. Cramer* [NB 180/78 IE]

**Altamira und die Urgeschichte der chemischen Technologie.** (Altamira and the Prehistory of Chemical Technology). By *E. Pietsch*. German Museum – Transactions and Reports – Volume 31, No. 1. R. Oldenbourg Verlag, Munich, 1963. 1st Edit., 68 pp., 35 illustr., 12 color plates, 1 chronological table, brochure DM 4.80 (about $ 1.25).

This brochure reports a veritable masterpiece accomplished for the German Museum by the author and his assistants. It consisted of a reproduction, faithful almost even to the very materials used, of a section 9.5 m by 4.6 m from the ceiling in the "Cave of Bulls" at altamira in Spain. This portion shows a typical selection of the masterly animal portraits created by our ancestors in the period from the Aurignacian to the Magdalenian culture phases 30000 to 10000 years ago, in younger Palaeolithic times. Since the roof of the cave, for obvious reasons, could not be touched, it had to be photographed by stereophotography for mensuration. The resulting plan served as basis for a plaster of Paris pattern which was given a plasticine skin in order to reproduce the fine structure in all details. From this pattern a mold was made in silicone rubber which was itself supported in a bed of plaster of Paris. The reproduction of the roof was finally cast in this mold and, in order to reproduce the limestone in the cave as faithfully as possible, a mixture of chalk from Solnhofen and white cement (Dyckerhoff) was used. Only iron oxide pigments and charcoal were used for painting, just as in the original. The fixative for the paint had to be Mowilith [*] instead of the natural calcium bicarbonate contained in the moisture on the roof. Even the illumination in the exhibition room has been arranged to approximate the tallow lamps of the Palaeolithic period.

[*] An English edition will appear by the end of 1964.

[*] Mowilith is the German trade name for synthetic drying oils containing polymerized vinyl and acetylenic compounds.

Accompanying the brochure is a condensed survey giving the development of technology from the preparation of flint cells 600000 years ago to the development of the art of tanning and pottery and up to the beginning of the Bronze Age (4000 B.C.).

The text is supplemented by a host of instructive illustrations. Only with the colored plates of the animal pictures would one have wished for something more impressive.

*U. Hofmann* [NB 179/74 IE]

**Enzyme im Blutplasma** (Enzymes in Blood Plasma). By *B. Hess*. Biochemistry and the Clinic – Monographs edited by *G. Weitzel* and *N. Zöllner*. Georg Thieme Verlag, Stuttgart 1962. 1st. edit., VIII, 142 pp., 33 illust., 13 tables, stiff covers DM 29.70 (about $ 7.50).

The measurement of enzyme activities in serum has acquired great interest in clinical diagnosis within the last decade. *Hess* gives an excellent summary of the results to date in this field in a text intended primarily for the orientation of the clinician. However, the biochemist also receives a very lucid survey of the vast possibilities for applying enzyme assays in clinical practice. The most important items are selected from the glut of literature available and presented in concise form, so that the book provides at the same time a valuable approach to the literature. The value of this undertaking is all the greater, because the non-specialist is no longer able to survey the literature in this field on his own, and a similar concentrated exposition of recent information does not exist in the German language. The book contains about 600 references, unfortunately quoted without titles, as is usual in the series "Biochemistry and the Clinic."

The book deals with fundamentals (systematics of plasma enzymes; identification methods; isozymes, enzyme patterns; mechanism of enzyme liberation; origin, synthesis, and breakdown of plasma enzymes; *etc.*), and then with the pathology and clinical implications of serum enzymes, arranged according to disease groups. The last section deals summarily with questions of method: theoretical bases of activity tests, definitions of units, assay conditions. The author's clear, concise style has resulted in a presentation, which remains fluently readable, despite the large number of facts communicated in relatively small space, so that the outsider is presented with a valuable survey; at the same time, the expert finds an abundance of information on details of clinical enzyme diagnostics. *D. Busch* [NB 177/79 IE]

**Synthetic Methods of Organic Chemistry.** By *W. Theilheimer*. Yearbook 1963. Vol. 17 (with a key to the subject index, etc. in German). Verlag S. Karger AG., Basel-New York 1963. 1st Edit., XVI, 507 pp., clothbound DM 150.–.

When leafing through Volume 17 of "Synthetic Methods", one again finds a wealth of original reactions, many of which can be applied more generally. The whole field of organic chemistry is covered by 955 examplex. The syntheses extend over numerous types of compounds, including the carbon compounds of hetero-elements (particularly phosphorus, sulfur, and boron). Reagents and methods (photochemical reactions, for instance) are classified seperately and also cover a wide field. Chemists working on synthetic problems can again find constant help in this selection. This presupposes, however, adeptness in the use of the logically arranged subject index, although the extensive list of terms included gives a great deal of information. Because this yearbook is so valuable, an additional punched card index should be issued at least every five years to facilitate literature screening.

Once again the binding and print are excellent.

*S. Hünig* [NB 137/69 IE]

**Grundlagen der Arzneimittelforschung und der synthetischen Arzneimittel** (Fundamentals of Drug Research and of Synthetic Drugs). By *J. Büchi*. Chemical Series Volume 15. Textbooks and Monographs from the Realms of the Exact Sciences. Birkhäuser Verlag, Basel, Stuttgart 1963. 1st edit., 744 pp., numerous figs., tables, and formulae, linen DM 96.– (about $ 24.00).

Drug research, in the author's opinion, includes all fields which are involved in the development of new pharmaceuticals. These include problems in the chemical and physicochemical fields, such as the synthesis, analytical characterization, and conversion of drugs into a suitable form for administration. In addition, there is pharmacological testing on animals and also clinical evaluation. The aims of systematic drug research include appraisal of the relationships between the pharmacological action and chemical constitution or physico-chemical properties of drugs as well as their mode of action and their biochemical transformations in organisms.

Of a book that, according to the introduction, is intended "to provide the basic principles of this field of knowledge for students and professionals who wish to be trained or informed in some branch or other of drug research" one can scarcely demand that all the aspects mentioned should be treated exhaustively; this would ask too much of a single author. The same is true of one reviewer. The chemist will be primarily interested in the chapters dealing with preparative and analytical problems, which constitute about one-third of the volume. The work contains no information on syntheses, but the structural formulae of very many substances are given; they serve as examples of the connections between chemical variation and parallelism or modification of activity, which are organized into more or less firm rules. One must admire the author's familiarity with the literature and one is amazed at the predictions to which the principle of chemical similarity can occasionally lead. Of course, most of the rules are the result of postexperimental interpretation, and for most of them, contrary examples are also indicated or are not difficult to find. The purely pharmaceutical chapters, *e.g.* that on the influence on activity of different modes of application or that on the conversion of drug substances into drug forms, are valuable and illustrated with many examples. The characterization of chemical analytical testing methods is also comprehensive and thorough.

The reading of the book, the title of which is somewhat unhappily chosen, will no doubt be stimulating to any chemist interested in pharmaceuticals, but an uncritical reader may possibly be led to believe that new drugs will very soon be developed "by constructive planning" on the basis of theoretical speculations. Up to now, the discovery of new kinds of drugs has been due, at all events, quite predominantly to empiricism, *i.e.* either to schematic pharmacological testing of innumerable chemical compounds or to chance observations, which were then developed systematically with due regard to all previous experiences.

*H. Böhme* [NB 178/76 IE]

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# Intramolecular Free-Radical Reactions

BY DR. K. HEUSLER AND DR. J. KALVODA

CIBA AG., BASEL (SWITZERLAND)

*In the present article an attempt is made to summarize the steric requirements and the influence of neighboring groups which determine the course of intramolecular radical reactions. Steroids are used as substrates for these reactions, since here the spatial arrangement of the ring members and the distances between substituents are largely fixed. Furthermore, intramolecular free-radical reactions are of practical importance in steroid chemistry in connection with substitution at non-activated carbon atoms. Almost all the reactions discussed begin with the formation of an oxygen radical by oxidation of an alcohol with lead tetraacetate or by homolysis of the corresponding hypoiodite.*

## A. Introduction

Although a large number of free-radical reactions is known, the steric requirements for the attack of free radicals on saturated compounds, the nature and geometry of the transition state, the influence of neighboring functional groups and the reaction medium on the course of the reaction have been far less thoroughly studied than for heterolytic reactions. For example, the free-radical substitution at a carbon atom, corresponding to an $S_N2$ reaction, has not yet been detected with certainty [1], and the cases in which neighboring groups are definitely known to participate in homolytic reactions are very few [2].

Knowledge regarding the course of free-radical reactions in solution is mainly derived from investigations on bimolecular homolytic processes, frequently chain reactions, and has been reviewed by *Walling* [3]. It is the aim of the present survey to point out certain new aspects of free-radical reactions in solution – particularly stereochemical problems, the influence of neighboring groups, and new possibilities of substitution reactions – the understanding of which is important for the preparative use of such reactions.

For our investigations, we have chosen *intramolecular* free-radical reactions, since these are particularly well suited to the study of the steric requirements and the influence of neighboring groups. Moreover, reactions whose intermolecular analogues are unfavorable owing to entropy considerations, can gain importance in intramolecular processes.

The relative positions of reaction centers are very easily assigned in the case of fused-ring cyclohexane derivatives, since the spatial arrangement of the ring members and the distances between substituents are fixed in these compounds. Furthermore, hydroxylated cyclohexanes with known configurations and conformations, which can be used to obtain oxy-radicals, are readily available. Examples are found particularly among alicyclic natural products, such as steroids or terpenoids, whose skeletons exhibit considerable rigidity owing to the fused rings. Fortunately, intramolecular free-radical reactions have

[1] It is, however, not impossible that the reactions described by *R. A. Ogg* and *M. Polanyi*, Trans. Faraday Soc. *31*, 482 (1935), *R. A. Herrmann* and *R. M. Noyes*, J. Amer. chem. Soc. *78*, 5764 (1956), *J. N. Pitts*, *R. S. Tolberg*, and *T. W. Martin*, ibid. *79*, 6370, (1957), *J. N. Pitts*, *D. D. Thompson*, and *R. W. Woolfolk*, ibid. *80*, 66 (1958), and *J. E. Bujake*, *M. W. T. Pratt*, and *R. M. Noyes*, ibid. *83*, 1547 (1961), are substitutions of this type.

[2a] *J. E. Leffler*, *R. D. Faulkner*, and *C. C. Petropoulos*, J. Amer. chem. Soc. *80*, 5435 (1958).

[2b] *J. C. Martin* and *E. H. Drew*, J. Amer. chem. Soc. *83*, 1232 (1961).

[2c] *W. G. Bentrude* and *J. C. Martin*, J. Amer. chem. Soc. *84*, 1561 (1962); Chem. and Ind. *1959*, 192.

[2d] *R. H. Thompson* and *A. G. Wylie*, Proc. chem. Soc. (London) *1963*, 65.

[2e] *De Los F. De Tar* and *A. Hlynsky*, J. Amer. chem. Soc. *77*, 4411 (1955).

[2f] *G. W. Griffin* and *E. J. O'Connel*, J. Amer. chem. Soc. *84*, 4148 (1962).

[2g] *D. L. Tuleen*, *W. G. Bentrude*, and *J. C. Martin*, J. Amer. chem. Soc. *85*, 1938 (1963).

[3] *Ch. Walling*: Free Radicals in Solution. Wiley, New York 1957.

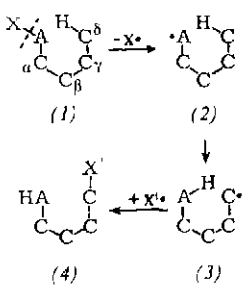
also achieved practical importance [4] in steroid chemistry, and this has been decisive in promoting more thorough investigations.

In the following parts of this paper we shall be concerned mainly with intramolecular reactions initiated by the formation of an *oxy-radical*, and only in this connection shall we examine the reactions of nitrogen and carbon radicals in any detail. Carbenes and nitrenes, which may be regarded as diradicals, will not be considered.

We shall begin by discussing the attack of an oxy-radical on a carbon-hydrogen bond, *i.e.* the abstraction of hydrogen, laying particular emphasis on the spatial requirements of these reactions. Two types of intramolecular free-radical reactions, namely the oxidation of monohydric alcohols with lead tetraacetate [5] and the hypoiodite reaction [6], will then be examined in greater detail. Finally, in this connection, steric effects, participation of neighboring groups, and fragmentation reactions are discussed.

## B. The Intramolecular Abstraction of Hydrogen

Intramolecular abstraction of hydrogen corresponds to the transfer of a hydrogen atom to an attacking free radical in the same molecule, and hence to a hydrogen shift. The most frequently observed intramolecular hydrogen transfers are 1,5-shifts. They can be generally represented by Scheme 1 [7].



Scheme 1. Free-radical induced intramolecular 1,5-hydrogen shifts.

The reaction is initiated by thermal or photolytic homolysis of the A–X bond in *(1)*, and this is followed by the hydrogen shift from C-δ to A. The resulting carbon radical *(3)* finally reacts with a free radical X'•, which may be identical with X•. Besides certain hydrogen transfers from carbon to carbon [8] [*(2)* → *(3)*, A = C], it is in particular the Hoffmann-Löffler-Freytag reaction [9] (A = N) which, being initiated by the homolysis of *N*-chlorides, proceeds according to this Scheme. The most important reactions of this type are those in which A is an oxygen atom [10]. Oxygen radicals may be produced by conventional methods [11], *e.g.* by the photolysis of nitrites [12] (A = O; X = NO) or by cleavage of hypochlorites [13] (A = O; X = Cl).

Two further methods have recently been described for the production of oxygen radicals, namely the oxidation of monohydric alcohols with lead tetraacetate [5] and the cleavage of alkyl hypoiodites [6]. The advantage of these methods over the photolysis of nitrites and hypochlorites is that the unstable product *(1)* does not have to be formed and isolated in a separate step from the alcohol *(1)*, A = O, X = H. Instead, the cleavable product *(1)*, A = O, X = $Pb(OAc)_3$ or I, is produced from the alcohol in the same solution in which the oxy-radical is generated.

The following general rules apply to intramolecular hydrogen abstractions:

1. The most favorable transition state for the hydrogen transfer is that of a 6-membered ring in the chair form. Consequently, hydrogen is preferentially abstracted from the δ-carbon atom. The steric requirements for this reaction are more important than the energetic ones; thus, for example, hydrogen on a non-activated δ-carbon atom is removed in preference to a more weakly bonded hydrogen in the ε-position [12, 14a]. In the formation of bridged systems, the reaction centers can also assume positions which favor abstraction of hydrogen from the ε-carbon atom [9, 14b]. Hydrogen shifts corresponding to 1,2- and 1,3-hydride shifts observed with (carbonium and) oxonium ions [15] do not occur with oxy-radicals.

[4a] See also *K. Schaffner, D. Arigoni,* and *O. Jeger,* Experientia *16,* 169 (1960).

[4b] *Th. B. Windholz* and *M. Windholz,* Angew. Chem. *76,* 249 (1964); Angew. Chem. internat. Edit. *3,* 353 (1964).

[5] *G. Cainelli, M. Lj. Mihailović, D. Arigoni,* and *O. Jeger,* Helv. chim. Acta *42,* 1124 (1959), and subsequent publications.

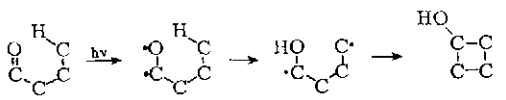
[6] *Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner,* and *A. Wettstein,* Experientia *17,* 475 (1961), and subsequent publications.

[7] This principle was formulated for the first time by *D. H. R. Barton, J. M. Beaton, L. E. Geller,* and *M. M. Pechet,* J. Amer. chem. Soc. *82,* 2640 (1960).

[8] *De Los F. De Tar* and *E. I. Relyea,* J. Amer. chem. Soc. *78,* 4302 (1956); *C. A. Grob* and *H. Kammüller,* Helv. chim. Acta *40,* 2139 (1957), where previous publications are quoted.

[9] *M. E. Wolff,* Chem. Reviews *63,* 55 (1963).

[10] As has recently been shown, the hydrogen transfer occurs in a similar 6-membered cyclic transition state, even if the oxygen radical is formed not by homolysis of an O-X bond, but by photochemical excitation of a C=O group. The reaction probably proceeds in *two* stages. – *N. C. Yang, A. Morduchowitz,* and *D. H.*



*Yang,* J. Amer. chem. Soc. *85,* 1017 (1963); *I. Orban, K. Schaffner,* and *O. Jeger,* J. Amer. chem. Soc. *85,* 3033 (1963).

[11] See review by *P. Gray* and *A. Williams,* Chem. Reviews *59,* 239 (1959).

[12] *A. L. Nussbaum* and *C. H. Robinson,* Tetrahedron *17,* 35 (1962).

[13a] *M. Akhtar* and *D. H. R. Barton,* J. Amer. chem. Soc. *83,* 2213 (1961).

[13b] *Ch. Walling* and *A. Padwa,* J. Amer. chem. Soc. *83,* 2207 (1961); *85,* 1597 (1963).

[13c] *F. D. Greene, M. L. Savitz, H. H. Lau, F. D. Osterholtz,* and *W. N. Smith,* J. Amer. chem. Soc. *83,* 2196 (1961); *F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith,* and *P. M. Zanet,* J. org. Chemistry *28,* 55 (1963).

[13d] *E. L. Jenner,* J. org. Chemistry *27,* 1031 (1962).

[13e] *L. Deniville, R. Forst,* and *J. P. Sassoules,* C. R. hebd. Séances Acad. Sci. *255,* 1953 (1962).

[13f] *J. S. Mills* and *V. Petrow,* Chem. and Ind. *1961,* 946.

[14a] See discussion by *M. Szwarc* and *J. H. Brinks* in: Theoretical Organic Chemistry. Butterworths, London 1959, p. 262.

[14b] *H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni,* and *O. Jeger,* Experientia *16,* 530 (1960); Helv. chim. Acta *45,* 753 (1962).

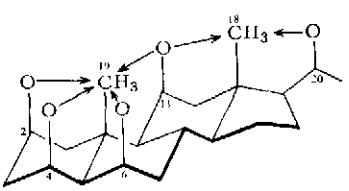
[15] *A. G. Davies:* Organic Peroxides. Butterworths, London 1961, pp. 143 et seq.

2. As expected, the reactivity of the hydrogen atoms decreases in the order tertiary > secondary > primary [16]. For example, if two δ-carbon atoms at the same distance from the radical center carry a tertiary and a secondary hydrogen atom respectively, the tertiary hydrogen will be preferentially attacked.

Formulae *(5)–(10)* illustrate these general rules and demonstrate the importance of steric requirements for successful intramolecular radical reactions.

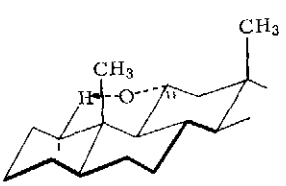
Certain assertions can also be made regarding the favorable distance between the O-radical and the hydrogen atom for the intramolecular abstraction of hydrogen and regarding the orientation of the C–H bond attacked with respect to the attacking oxy-radical [for references, see under formulae *(5)* to *(10)*]. Since the conformations of the methyl groups in steroids of the type *(5)* in the transition state cannot be ascertained, the internuclear distances between the oxygen atoms and the carbon atoms carrying hydrogen were determined from Dreiding models of the compounds *(5)* to *(10)*. These values are greater than the internuclear distance between the oxygen radical and the hydrogen to be abstracted in the starting material which, for a C–O distance of 2.6 Å and for normal bond angles, is at least 2.1 Å. This minimum distance is realized when the C–O and the C–H bonds lie in the same plane. For the reactions indicated by arrows in formulae *(5)–(10)*, Dreiding models give values of 2.5 to 2.7 Å for the C O distances, corresponding very closely to the O–O distances in compounds of the type O–H···O, *i.e.* in compounds with hydrogen bridges [27]. For intramolecular hydrogen bridges between C–H groups and oxygen atoms, the C–O distances have been found to be 2.6 to 3.0 Å [28].

The distance between the 20-oxygen atom and the 18-carbon in *(5)* can be reduced to about 2.0 Å, depending on the configuration of the side chain. The distances marked in the formulae can be varied to some extent by changes in the basic skeleton, *e.g.* by the introduction of trigonal centers or the formation of bridged systems.



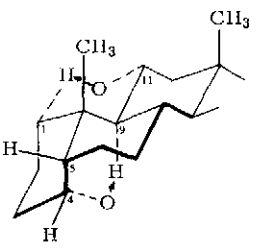
*(5)*

2β-Hydroxysteroids [17]
4β-Hydroxysteroids [18]
6β-Hydroxysteroids [19]
11β-Hydroxysteroids [20]
20β-Hydroxysteroids [21]



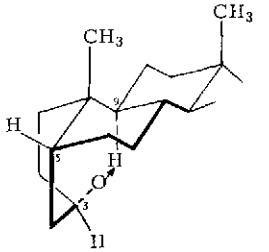
*(6)*

11α-Hydroxy-5β-steroids [22]



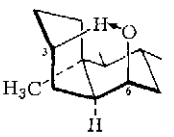
*(7)*

11α-Hydroxy-5β-steroids [22]
4α-Hydroxy-5β-steroids [23]



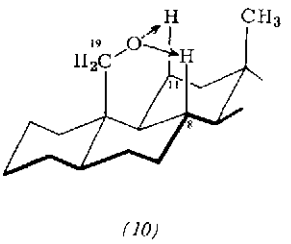
*(8)*

3α-Hydroxy-5β-steroids [24]



*(9)*

6β-Hydroxy-10α-steroids [25]



*(10)*

19-Hydroxysteroids [26]

[16] *C. H. Leigh* and *M. Szwarc*, J. chem. Physics *20*, 846 (1952).

[17] Nitrite photolysis: [a] *R. Kwok* and *M. E. Wolff*, Chem. and Ind. *1962*, 1194; Lead tetraacetate and hypoiodite reactions: [b] *K. Heusler, J. Kalvoda, P. Wieland, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *45*, 2575 (1962); [c] *P. N. Rao* and *J. C. Uroda*, Naturwissenschaften *50*, 548 (1963).

[18] Hypoiodite reaction: [a] cf. [17b]; Lead tetraacetate: [b] *K. Heusler, J. Kalvoda, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 352 (1963).

[19] Lead tetraacetate: [a] *A. Bowers, R. Vilotti, J. A. Edwards, E. Denot*, and *O. Halpern*, J. Amer. chem. Soc. *84*, 3204 (1962); [b] *A. Bowers, E. Denot, L. C. Ibañez, M. E. Cabezas*, and *H. J. Ringold*, J. org. Chemistry *27*, 1862 (1962); [c] *A. Bowers, L. C. Ibañez, M. E. Cabezas*, and *H. J. Ringold*, Chem. and Ind. *1960*, 1299; [d] *B. Berkoz, E. Denot*, and *A. Bowers*, Steroids *1*, 251 (1963); [e] *J. F. Bagli, P. F. Morand*, and *R. Gaudry*, J. org. Chemistry *28*, 1207 (1963); – Hypoiodite reaction: [f] *K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *45*, 2161 (1962); see also [6]; [g] *H. Ueberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 344 (1963); [h] *K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner*, and *A. Wettstein*, Experientia *18*, 464 (1962); [i] *J. Kalvoda, K. Heusler, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 1017 (1963); [k] cf. [19e]; – Hypochlorite photolysis: [l] cf. [13a] and [13f]; – Nitrite photolysis: [m] *D. H. R. Barton, J. M. Beaton, L. E. Geller*, and *M. M. Pechet*, J. Amer. chem. Soc. *83*, 4076 (1961); [n] *D. H. R. Barton* and *M. Akhtar*, J. Amer. chem. Soc. *84*, 1496 (1962); [o] *R. Gardi* and *C. Pedrali*, Gazz. chim. ital. *91*, 1420 (1961); [p] *T. Jen* and *M. E. Wolff*, J. med. pharm. Chem. *5*, 876 (1962).

[20] Lead tetraacetate: [a] cf. [18b] and *G. B. Spero, J. L. Thompson, W. P. Schneider*, and *F. Kagan*, J. org. Chemistry *28*, 2225 (1963); – Hypoiodite reaction: [b] cf. [6]; [c] *J. Kalvoda, K. Heusler, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *46*, 618 (1963); – Nitrite photolysis: [d] *D. H. R. Barton* and *J. M. Beaton*, J. Amer. chem. Soc. *83*, 750, 4083 (1961); *84*, 199 (1962); [e] *M. Akhtar, D. H. R. Barton, J. H. Beaton*, and *A. G. Hortmann*, J. Amer. chem. Soc. *85*, 1512 (1963); [f] *H. Reimann, A. S. Caponaggi, T. Strauss, E. P. Oliveto*, and *D. H. R. Barton*, J. Amer. chem. Soc. *83*, 4481 (1961).

[21] Lead tetraacetate: [a] cf. [5]; [b] *G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailović, D. Arigoni*, and *O. Jeger*, Helv. chim. Acta *44*, 518 (1961); [c] *K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner*, and *A. Wettstein*; *G. Cainelli, D. Arigoni*, and *O. Jeger*, Experientia *16*, 21 (1960); Helv. chim. Acta *44*, 502 (1961); [d] *Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner*, and *A. Wettstein*, Helv. chim. Acta *45*, 1317 (1962); [e] *L. Velluz, G. Muller, R. Bardoneschi*, and *A. Pottevin*, C. r. hebd. Séances Acad. Sci. *250*, 725 (1960); – Hypochlorite reaction: [f] cf. [13]; – Hypoiodite reaction: [g] cf. [6]; [h] cf. [21d]; – Nitrite photolysis: [i] *D. H. R. Barton, J. M. Beaton, L. E. Geller*, and *M. M. Pechet*, J. Amer. chem. Soc. *82*, 2640 (1960); *83*, 4076 (1961); [k] *A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian*, and *D. H. R. Barton*, Tetrahedron *18*, 373 (1962); J. Amer. chem. Soc. *82*, 2973 (1960).

[22] Lead tetraacetate: [a] *J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailović, K. Schaffner*, and *A. Wettstein*, Helv. chim. Acta *44*, 186 (1961); *D. Bertin* and *J. Perronnet*, C. r. hebd. Séances Acad. Sci. *257*, 1946 (1963); – Hypoiodite reaction: [b] *Ch. Meystre* and *J. Kalvoda, G. Anner* and *A. Wettstein*, Helv. chim. Acta *46*, 2844 (1963).

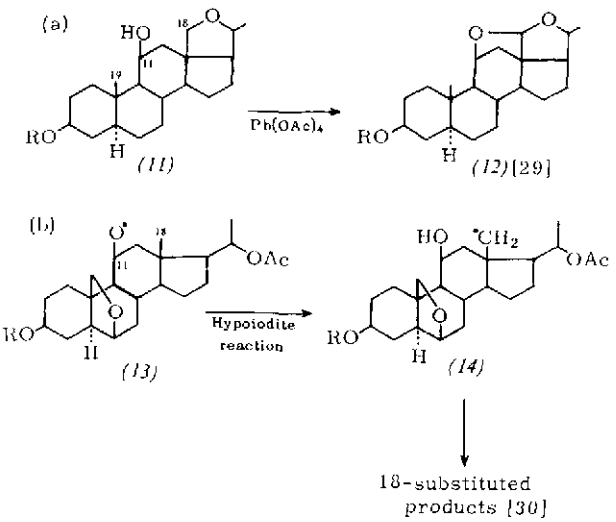
[23] Lead tetraacetate: [a] cf. [18b]; – Hypoiodite reaction: [b] *K. Heusler* and *J. Kalvoda*, Helv. chim. Acta *46*, 2020 (1963).

[24] Lead tetraacetate: [a] cf. [14b]; [b] *A. Bowers* and *E. Denot*, J. Amer. chem. Soc. *82*, 4956 (1960).

[25] Lead tetraacetate: *K. Heusler* and *J. Kalvoda*, Tetrahedron Letters *1963*, 1001; Helv. chim. Acta *46*, 2732 (1963).

[26] Lead tetraacetate and hypoiodite reaction: unpublished work from the laboratories of ETH Zürich and CIBA AG, Basel.

Thus the distance between 11β-O and C-18 in *(11)* and *(13)* is 2.65 Å, but the distance between 11β-O and C-19 is 2.5 Å in *(11)* and 2.9 Å in *(13)*. It is now interesting

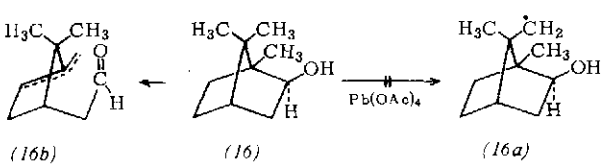



to compare the reactions of *(11)* and *(13)*: A C–H bond on an oxygen-bearing C-atom is weaker than a C–H bond in a $CH_3$ group. This appears to be the deciding factor when the C···O distance is less than 2.70 Å, since despite the shorter distance between 11β–O and C-19, compound *(11)* yields predominantly the 11β,18-ether *(12)*. In compound *(13)*, on the other hand, the distance to the oxygen-bearing C-19 is too great (2.9 Å) compared with the distance to the unsubstituted C-18 (2.65 Å), so that the latter is substituted, although the reaction in this position is less favored energetically.

Finally, no intramolecular abstraction of hydrogen occurs after the production of the O-radical *(15)* by means of the hypoiodite reaction [31, 32]. In this case the distance between




the 6β-oxygen and C-19 is over 3 Å, owing to the deformation of ring B caused by the cyclopropane ring. The distance be-



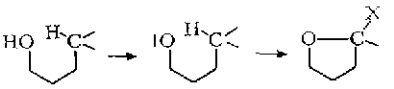

tween the methyl groups and the oxygen atom in *(16)* [33] is also greater than 3 Å, so that here again the oxygen radical fails to attack the methyl group.

It can be concluded from these experiments that the activation energy for the intramolecular abstraction of hydrogen reaches a minimum in fixed systems with an O···C distance of 2.5 to 2.7 Å in the starting material, but that for distances exceeding 2.8 Å, the rate of this reaction becomes smaller than those of intermolecular hydrogen abstraction or fragmentation reactions. Intramolecular reactions in compounds in which the O···C distance is 2.5 to 2.7 Å are so much more rapid than intermolecular free-radical reactions, that they can even be carried out in solvents, such as cyclohexane, which are readily susceptible to free-radical attack.

The experiments referred to also give some indications regarding the geometry of the transition state in the hydrogen shift. Although the reactions on the angular methyl groups indicated in *(5)* do not yield accurate conclusions, owing to the free rotation of these groups, the hydrogen transfers illustrated in *(6)*, *(7)*, and *(9)* are significant. The fact that these reactions, in which all reacting centers are fixed as constituents of a six-membered chair-like ring, proceed with good yield, confirms the general rule regarding the geometry of the transition state [34]. The linearity of the C, H, and O atoms taking part in the reaction, which was postulated for himolecular hydrogen transfers (from C to halogen) [35], is practically impossible in these cases.

### C. The Hypoiodite Reaction

The term "hypoiodite reaction" is used here to denote the homolytic cleavage of alkyl hypoiodites *(17)*, which leads to an intramolecular substitution on non-activated carbon atoms. The end-products of the reaction are generally tetrahydrofuran derivatives *(18)*.




Alkyl hypoiodites have never yet been isolated in the pure state, but are readily prepared in solution by the action of *N*-iodosuccinimide or acyl hypoiodites, *e.g.* acetyl hypoiodite, on alcohols [6]. Acetyl hypoiodite can be obtained from silver acetate, mercury(II) acetate, or particularly advantageously, from lead tetraacetate and iodine in non-polar solvents such as cyclohexane. Alkyl hypoiodites prepared in this way decompose homolytically above 60 °C into iodine atoms and oxy-radicals. This decomposition is accelerated by iodine atoms. An adequate concentration of iodine atoms is ob-

[27] *L. Pauling:* The Nature of the Chemical Bond. 3rd Edit., Cornell University Press, Ithaca 1960.

[28] *D. J. Sutor*, J. chem. Soc. (London) *1963*, 1105.

[29] *P. F. Beal* and *J. E. Pike*, Chem. and Ind. *1960*, 1505.

[30] Unpublished work.

[31] Unpublished work by Dr. *Ch. Meystre*.

[32] *K. Tanabe*, *R. Takasaki*, *K. Sakai*, *R. Hayashi*, and *Y. Morisawa*, Chem. pharmac. Bull. (Tokyo) *10*, 1126 (1962); *J. Tadanier*, J. org. Chemistry *28*, 1744 (1963); *R. M. Moriarty* and *T. D. D'Silva*, ibid. *28*, 2445 (1963), and *P. B. Sollman*, ibid. *28*, 3559 (1963), obtained a 3α,5α-cyclo-6β,19-ether by the action of lead tetraacetate on a 3α,5α-cyclo-6β-hydroxysteroid. For the significance of this lead tetraacetate oxidation, cf. the discussion in Section F.

[33] *R. E. Partch*, J. org. Chemistry *28*, 276 (1963).

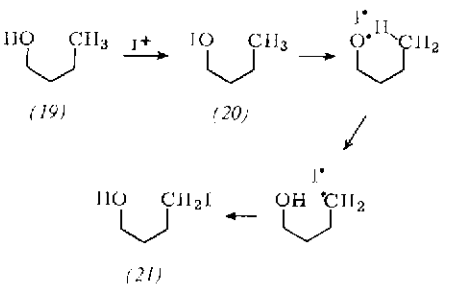
[34] A transition state of this type has already been discussed in a different context: [a] cf. [21b]; [b] *E. J. Corey* and *W. R. Hertler*, J. Amer. chem. Soc. *82*, 1657 (1960); [c] cf. [13a] and [13b]; [d] cf. [12].

[35] *D. J. Wilson* and *H. S. Johnston*, J. Amer. chem. Soc. *79*, 29 (1957).

tained, *e.g.* by irradiation of dissolved iodine with light of a wavelength between 500 and 550 mμ, *i.e.* in the region of the principal absorption band of iodine (522 mμ in saturated hydrocarbons, and 512 mμ in halogenated hydrocarbons [36]). For this reason, the reaction proceeds well in non-polar solvents, in which iodine is normally soluble, while in aromatic solvents, such as benzene, in which charge-transfer complexes are formed with iodine, the concentration of free iodine atoms formed on irradiation is not sufficiently large. Although the photolysis of nitrites is similar in many respects, the hypoiodite reaction [36a] exhibits special characteristics connected with the method of preparation of the alkyl hypoiodites, and with the bulk and the oxidation potential of the iodine atoms. Since the course of the reaction also depends on the degree of substitution of the attacked center, substitutions on methyl, methylene, and methine groups will be treated separately.

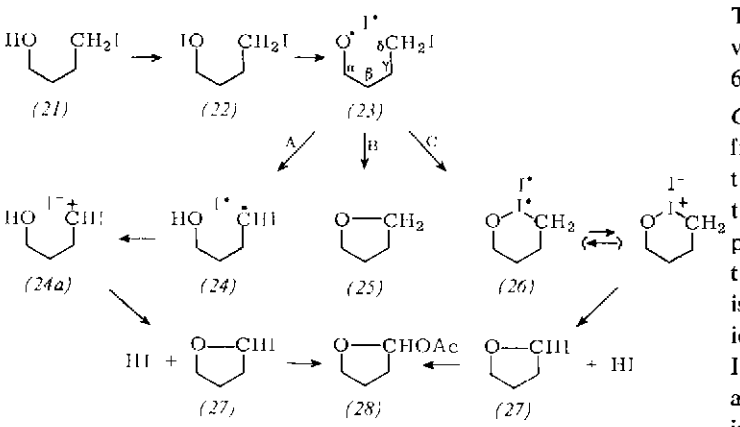
### 1. Substitution on Methyl Groups

The first stages of the hypoiodite reaction with alcohols in which the δ-carbon is a methyl group *(19)* correspond exactly to the general scheme *(1)* → *(4)*. In the same manner as the hypoiodite *(20)* formes from *(19)*



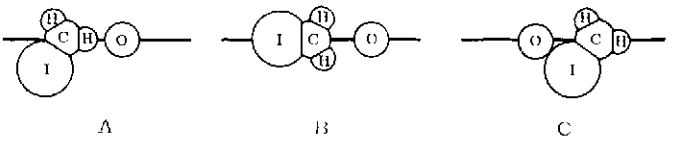
*(19)* *(20)* *(21)*

in the reaction mixture, the resulting alcohol *(21)* is converted to a hypoiodite *(22)*, and this undergoes homolysis to yield *(23)*.



*(21)* *(22)* *(23)* *(24a)* *(24)* *(25)* *(26)* *(27)* *(28)* *(27)*

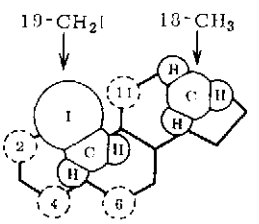
Subsequent reactions are determined by the steric arrangement of the reaction centers in *(23)*, if the C(α)–O and the γ,δ-bonds are fixed. There are three possible orientations, A, B, and C, for the oxygen atom with respect to the $CH_2I$ group, which arise by rotation of the $CH_2I$ group about the γ,δ-bond [37].



A B C

In Case A, the oxygen, hydrogen, and carbon lie in a straight line when projected on a plane perpendicular to the C(α)–O bond. This orientation definitely favors the abstraction of hydrogen. In Case B, the hydrogens are turned around, and the oxygen, carbon, and iodine are now situated in a straight line when projected. This position fulfils the requirement for a replacement of the iodine by oxygen with reversal of the configuration. Finally, in Case C, the arrangement is suitable neither for a hydrogen abstraction nor for a substitution. In this case, an interaction probably arises between the oxygen radical and the iodine atom.

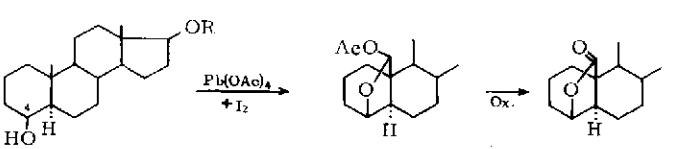
These three possibilities can be easily realized in the steroid series, for example in the substitution at the 19-methyl group. A 19-iodomethyl group, formed according to *(19)* → *(21)* by the attack of a neighboring oxygen radical, is fixed between the axial 2β- and 11β-hydrogen atoms *(29)*, so that the power of free rotation is lost.



*(29)*

The three orientations A, B, and C can be experimentally verified by the introduction of oxygen atoms in the 4β-, 6β-, and 2β-positions [37].

*Case A*: This corresponds to the intermediate product from a 4β-hydroxysteroid [18a] which, by normal abstraction of hydrogen, yields the C-radical *(24)*. Since substitution by a second iodine atom in the 19-position is not possible in steroids owing to steric factors, electrons are transferred to the iodine atom, and the iodo ether *(27)* is formed through a carbonium ion (stabilized by the iodine atom on C-19) by elimination of hydrogen iodide. If the reaction is carried out in the presence of lead tetraacetate or mercury (II) acetate, the hemiacetal acetate is formed. Acid oxidation of *(27)* and *(28)* with chromium trioxide yields the corresponding lactone. This reaction sequence is illustrated by the example *(30)* → *(31)* [17b] and in the 20-hydroxy series by *(32)* → *(35)* [21d].



*(30)* *(31)*, ca. 78%

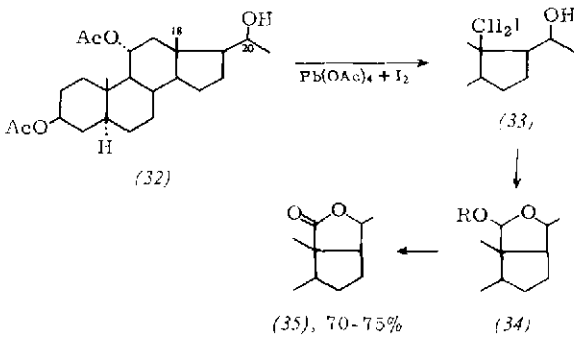
[36] *H. Tsubomura* and *R. P. Lang*, J. Amer. chem. Soc. *83*, 2085 (1961).

[36a] The homolytic cleavage of *N*-iodoamides, which leads to γ-iodoamides and, by intramolecular substitution via an iminolactone, to γ-lactones [*D. H. R. Barton* and *A. J. L. Beckwith*, Proc. chem. Soc. (London) *1963*, 335], is an interesting extension of the hypoiodite reaction and a parallel to the Löffler-Freytag reaction [9].

[37] Review: *J. Kalvoda*, *K. Heusler*, *P. Wieland*, *G. Anner*, and *A. Wettstein*, Gazz. chim. ital. *93*, 140 (1963).

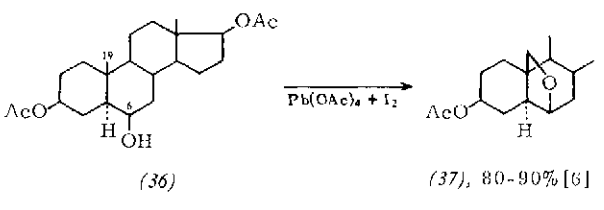
Thus a *double* substitution of the methyl group takes place. However, iodosuccinimide, silver acetate and mercury(II) acetate in the presence of iodine also yield *singly* substituted products, *i.e.* 4β,19- and 18,20-ethers respectively, since the hypoiodite is more slowly formed from the alcohol with these reagents than with lead tetraacetate and iodine, so that the ether *(25)* is formed from part of the iodohydrin *(21)* by an ionic reaction, before a hypoiodite is formed again.

Using a 20-hydroxysteroid as starting material, the iodohydrin intermediate *(33)* can be isolated under suitable conditions.

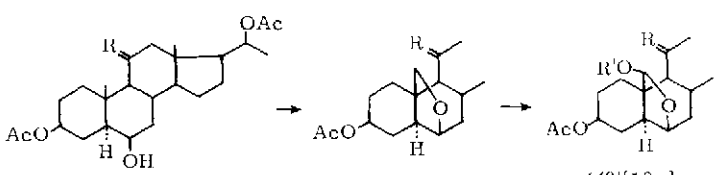



*(32)* *(33)* *(34)* *(35)*, 70-75%

*Case B*: This case merits special attention, since a second hydrogen abstraction does not occur, although a hypoiodite is again formed, at least in part, from the iodohydrin intermediate of type *(21)*. This appears to be one of the few cases of homolytic substitution at carbon by attack of an oxygen radical with displacement of an iodine atom [38] ($S_H2$ reaction [39]). This reaction only occurs when the "linear" arrangement B of the O, C, and I atoms prevails, as it is found in 6β-hydroxy-19-iodides. The transition state for the $S_H2$ reaction thus appears to correspond substantially to that of the bimolecular nucleophilic substitution ($S_N2$). The sensitivity of this reaction to steric effects is shown by the examples *(36)* → *(37)* and *(38)* → *(40)*.

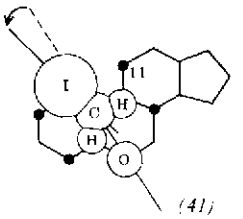



*(36)* *(37)*, 80-90% [6]



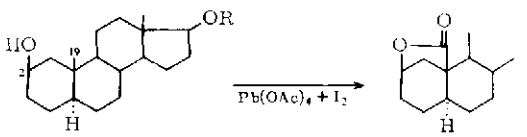

*(38)* *(39)*, R = H, OAc or O, yield ca. 60% *(40)* [19e], yield ca. 7%

At the same time, these examples prove that the iodohydrin intermediate *(21)* does again form an oxygen radical *(23)* through a hypoiodite *(22)*. Thus on introduction of an 11-substituent, the pseudo-linearity of 6β-O, C-19, and I is somewhat disturbed on steric grounds, and, as indicated in *(41)*, the orientation of the reaction centers approaches Type A. In fact, mixtures of singly *(39)* and doubly *(40)* substituted products are obtained with lead tetraacetate and iodine.




*(41)*

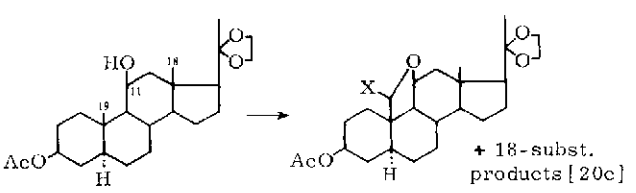
*Case C*: Here the oxygen radical appears to attack the most closely positioned iodine atom; the iodo ether *(27)* is formed through an intermediate *(26)* of the iodonium type [40], and the methyl group is doubly substituted, as in Case A. This reaction course has been observed with 2β-hydroxysteroids (the crude product was converted directly to the lactone by mild oxidation).



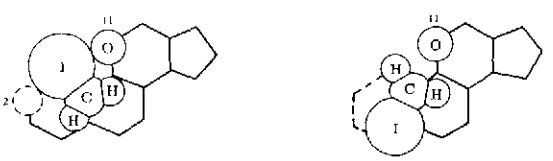

*(42)* yield 54% [18b] (no 2β,19-ether)

The mode of reaction of 11β-hydroxysteroids, *e.g. (43)* and *(45)*, is of interest in this connection, although these do not yield uniform products owing to the simultaneous attack on C-18 and C-19.

In compounds of the 5α-series, the spatial arrangement of the 11β-oxygen atom in the intermediate product, with respect to the $CH_2I$ group on C-10, which has a fixed conformation, is analogous to that of the 2β-oxygen atom in *(42)* [cf. *(43a)*]. Nevertheless, 11β,19-ethers (in addition to 18-substituted compounds) are found in this case besides the hemiacetals expected from the Type C orientation.




*(43)* *(44)*, X = H, OAc




*(43a)*, 5α-H(A/B-trans) *(45a)*, 5β-H(A/B-cis)

The formation of the 11β,19-oxido compound *(44)*, X = H, with no substituents in the 19-position could be due

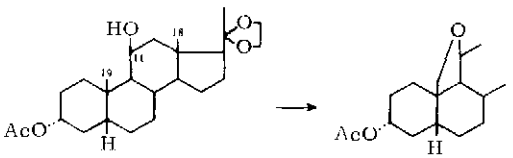
[38] This reaction is energetically favorable: the dissociation energy of a C–I bond is 49–55 kcal/mole, while ca. 77 kcal/mole are liberated in the formation of a C–O bond. *E. W. R. Steacie:* Atomic and Free Radical Reactions. Reinhold Publishing Corp. New York 1954; *P. Gray*, Trans. Faraday Soc. *52*, 344 (1956).

[39] For nomenclature, see *E. L. Eliel* in *M. J. Newman:* Steric Effects in Organic Chemistry. Wiley, New York 1956, p. 143; see also [1].

[40] See [2a] and *J. E. Leffler* and *J. S. West*, J. org. Chemistry *27*, 4191 (1962).

to steric hindrance of the formation of the second hypoiodite: the ether would then be formed in an ionic reaction from the corresponding iodohydrin.

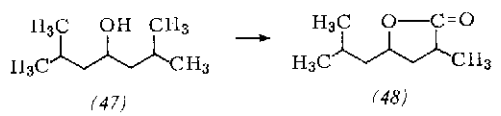
In the 11β-hydroxysteroids of the 5β-series *(45)*, the $CH_2I$ group in the intermediate product is not fixed. The iodine atom can rotate freely above ring A, which is folded downwards [cf. *(45a)*]. The principal product is the 11β,19-ether *(46)*. It appears that the $S_H2$ reaction



*(45)* *(46)*[20c]

gains in importance in this case. This would mean that the $CH_2I$ group preferentially assumes the "linear" arrangement B.

However, intermolecular $S_H2$ reactions of this type do not occur [41]. Preliminary experiments with the aliphatic alcohol *(47)* show that the "double" substitution of one of the four methyl groups is preferred in this case, although the "linear" arrangement B could be realized. After oxidation of the reaction mixture with chromium(VI) oxide the lactone

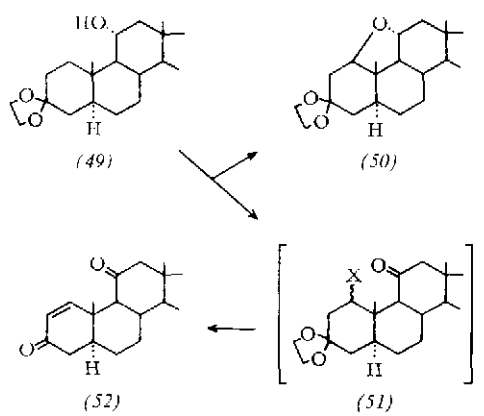


*(47)* *(48)*

*(48)* can be isolated (as a mixture of the two stereoisomers) as the principal product (ca. 37 %) by preparative gas chromatography [42].

## 2. Substitutions on Methylene and Methine Groups

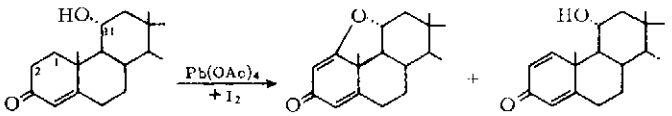
Substitutions on secondary and tertiary carbon atoms by the hypoiodite reaction are less numerous. The abstraction of secondary hydrogen atoms was investigated for 11α-hydroxy- and 19-hydroxysteroids [cf. *(6)*, *(7)*, and *(10)*]. The course of the hypoiodite reaction with 11α-hydroxysteroids depends on the nature of the substituent on C-3. For example, the principal product from a 3,3-ethylenedioxy-11α-hydroxy compound *(49)*



*(49)* *(50)* *(52)* *(51)*

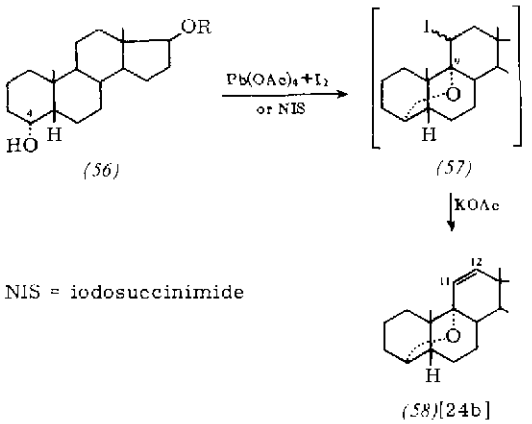
is the saturated 1,11α-ether *(50)*. 1-Iodo- or 1-acyloxy-11-oxosteroids *(51)* occur as by-products; on acid and base hydrolysis they are probably converted to 3,11-dioxo-$\Delta^1$-steroids *(52)*, but these were not isolated in pure form.

This behavior differs from that of the 3-oxo-11α-hydroxysteroids, *e.g.* *(53)*, the hypoiodite reactions of which yield 1,2-unsaturated 1,11α-ethers *(54)* as the principal products, together with the corresponding 1-dehydro compounds *(55)*.



*(53)* *(54)* *(55)*[22b]

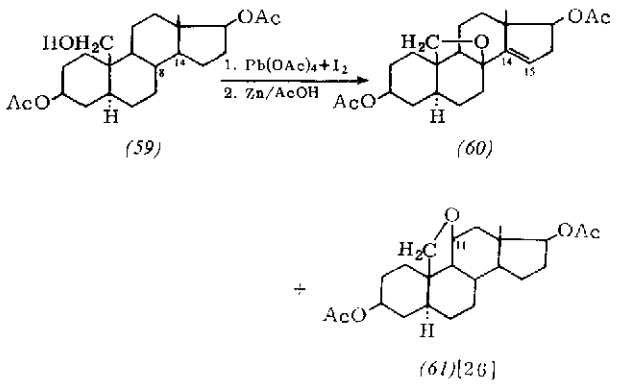
In 4α-hydroxysteroids of the 5β-H series (A/B-cis) *(56)*, the 7α- and 9α-hydrogen atoms are equidistant from the 4α-oxy-radical; of these two atoms, the latter is almost exclusively attacked.



*(56)* *(57)* *(58)*[24b]

NIS = iodosuccinimide

In the 19-hydroxysteroids, *e.g.* *(59)*, on the other hand, both the tertiary 8β- and the 11β-hydrogen are attacked, probably because the approach of the oxygen radical to



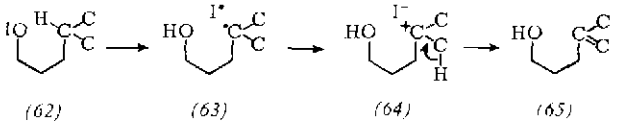
*(59)* *(60)* *(61)*[26]

the 8β-hydrogen atom is more difficult than to the 11β-hydrogen atom owing to steric factors. The first stages of the radical chain-reaction are the same in substitution on a methylene or methine group as in the attack on a methyl group. However, in the substitution at a tertiary carbon atom, the iodination of the C-radical *(63)* by an iodine atom is impossible or very difficult for steric

[41] *L. H. Slaugh*, J. Amer. chem. Soc. *83*, 2734 (1961).

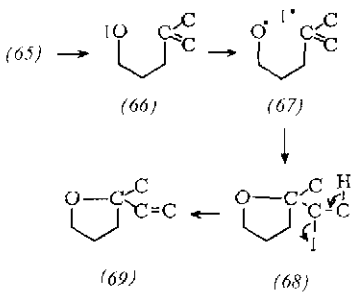
[42] Unpublished work. The constitution of *(48)* follows from the infrared, NMR, and mass spectra.

reasons. Therefore, an electron displacement, *i.e.* an oxidation to the carbonium ion *(64)*, occurs as in the conversion *(24)* → *(27)*. The ion pair *(64)* corresponding to the radical pair *(63)* is stabilized by release of a



*(62)* *(63)* *(64)* *(65)*

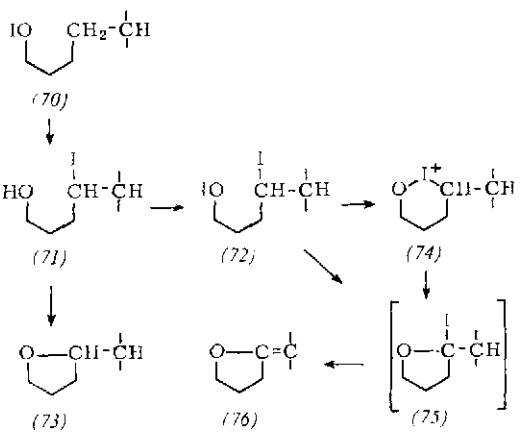
proton to form *(65)*. The double bond in the intermediate of type *(65)* is situated in the 9,11-position in the reaction *(56)* → *(57)*, and in the 8,14-position in the reaction *(59)* → *(60)*. Since *(65)* is again an alcohol, a hypoiodite is formed once more and, on homolysis, the O-radical and an iodine atom are added to the double bond *(68)*. Hydrogen iodide is finally split off by the action of a base and the allyl ether *(69)* is formed.



*(65)* *(66)* *(67)* *(69)* *(68)*

The iodo ether intermediate of type *(68)* was not isolated, but its formation was indirectly verified in the case of the 4α,9α-ether. Thus, if the crude product of the hypoiodite reaction is oxidized with chromium trioxide/silver chromate, instead of the potassium acetate treatment, a 4α,9α-oxido-11-ketone is obtained [23b].

In the formation of the 1,11α-ethers *(50)* und *(54)*, the reaction does not appear to proceed through the 1,2-olefin of type *(65)* which has been isolated in some cases as a by-product [cf. *e.g.* *(55)*], since the hypoiodite reaction with an 11α-hydroxy-$\Delta^1$-3-oxosteroid yields a complex mixture, containing no $\Delta^1$-1,11α-ether. Nevertheless, it must be assumed that an iodohydrin of type *(71)* [analogous to *(21)*] is also formed initially.



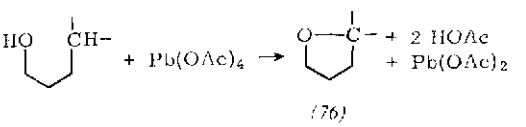
*(70)* *(71)* *(72)* *(74)* *(73)* *(76)* *(75)*

Since the formation of the second hypoiodite *(71)* → *(72)* is difficult owing to steric factors, part of the iodohydrin *(71)* can undergo an ionic reaction, eliminating HI, to form the saturated ether *(73)*.

Depending on the configuration of the 1-iodine atom and the conformation of ring A in the iodohydrin of type *(71)* formed from *(53)*, a spatial arrangement of oxygen and iodine similar to that in Case A or C in the attack on a methyl group (cf. above) is possible, so that after the second hypoiodite formation, the enol ether *(76)* is finally produced. From the ketal *(49)*, the ether *(50)* could be formed directly through a carbonium ion in the 1-position, as in the substitution of tertiary hydrogen atoms, since the approach of the iodine atom is sterically hindered.

## D. The Oxidation of Monohydric Alcohols with Lead Tetraacetate [5]

The oxidation of monohydric alcohols to tetrahydrofuran derivatives *(76)*, is stoichiometrically a simple oxidation. However, the course of the reaction is



*(76)*

divided into three stages, namely the formation of a lead alkoxide from the alcohol and lead tetraacetate, the formation of the oxy-radical, and the formation of the ether.

### 1. Lead Alkoxide Formation

Since the homolytic cleavage of an O–H bond is almost impossible owing to the high bond energy [43], it must be assumed that a readily cleavable derivative is first formed in the lead tetraacetate reaction. It is reasonable to assume that this initial product is a lead alkoxide, although such a compound has never been isolated [44]. In the exchange of an acyloxy group on the tetravalent lead for an alkoxy group, the equilibrium

$$ROH + Pb(OAcyl)_4 \rightleftharpoons RO-Pb(OAcyl)_3 + HOAcyl$$

is displaced to the left on the addition of acid [44]. This exchange should proceed in the same manner and at roughly the same rate as the exchange of acyl groups on tetravalent lead [45a]. On the other hand, it also depends on the steric effect in the alcohol part. Tertiary [21b, 25] or strongly hindered secondary alcohols [18b] react only slowly.

### 2. Cleavage of the Pb–O Bond in Oxygen Compounds of Tetravalent Lead

Both heterolytic and homolytic cleavages of Pb–O bonds are known [45b]. The cleavage of glycols in polar media at low temperatures should mainly proceed

[43] The bond energy of a O–H bond is ca. 102 kcal/mole; see *T. L. Cottrell:* The Strengths of Chemical Bonds. Butterworths, London 1954.

[44] *R. Criegee, L. Kraft,* and *B. Rank,* Liebigs Ann. Chem. *507*, 159 (1933), isolated a crystalline product of the formula $Pb(OAc)_2(OH)(OCH_3)$ from lead tetraacetate and incompletely anhydrous methanol, and referred to the different rates of cleavage of glycols in benzene and acetic acid.

[45a] *E. A. Evans, J. L. Huston,* and *T. H. Norris,* J. Amer. chem. Soc. *74*, 4985 (1952).

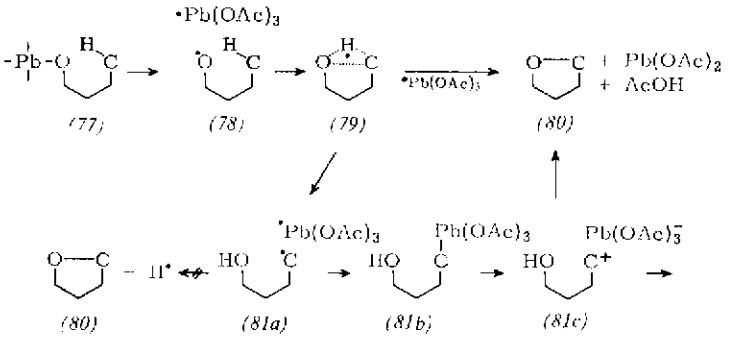
[45b] According to infrared measurements the Pb–O bonds in lead(IV) acylates exhibit ionic character. Nevertheless we shall use the terms homolysis and heterolysis of the Pb–O bond although in fact a single or double electron transfer from oxygen to lead is involved.

heterolytically [46], while in methylation with lead tetraacetate [47] in non-polar solvents at elevated temperatures, methyl radicals are formed by decarboxylation of the acetoxy-radicals produced by homolysis of the lead(IV) salt. The homolysis of lead(IV) acylates of primary, secondary, and tertiary carboxylic acids can also be carried out photolytically [48a]. At very low temperatures, the carbon radicals produced by decarboxylation can be detected directly by ESR measurements [48b].

The cleavage of the Pb–O (alkyl) bond in lead alkoxides of the type $(RCOO)_3Pb-OR'$ appears to be similar to, but considerably easier to effect than, the cleavage of a Pb–O–(Ac) bond in lead tetraacylates: the alkoxylead triacetates are thermally decomposed at temperatures as low as 70 to 80 °C (boiling benzene or cyclohexane), while lead tetraacetate (in the absence of a "catalyst" [47]) is only decomposed above 140 °C. The fact that the above-mentioned lead alkoxides can also be decomposed by irradiation at low temperatures to yield tetrahydrofuran derivatives [49] also indicates a homolytic cleavage of the R'O–Pb bond. The fragmentation reactions summarized in Section F particularly show that the cleavage of the R'O Pb bond yields products with the character of an alkoxy-radical (R'O·). The heterolytic decomposition into $R'O^+$ and $Pb(OAc)_3^-$ repeatedly discussed in connection with the oxidation of monohydric alcohols with lead tetraacetate, is not compatible with the experiments described below [50].

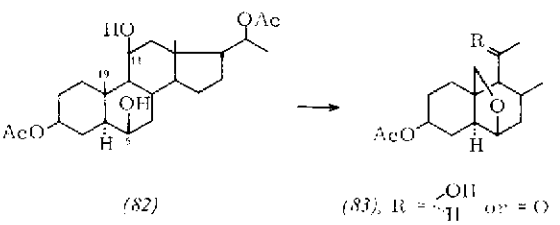
### 3. Ether Formation

The steric requirements for the tetrahydrofuran formation from alcohols with lead tetraacetate are substantially the same as for the abstraction of hydrogen in the homolysis of nitrites, hypochlorites and hypoiodites, and have been discussed in detail in Section B. Thus the cleavage of the lead alkoxide *(77)* again leads, through the oxy-radical *(78)* [51], to a transition state *(79)* which can undergo hydrogen abstraction *(81a)*. However, the direct formation of an ether from *(81a)* by ejection of a hydrogen atom is energetically unfavorable. There must therefore be another route available for the ring-closure to form *(80)*.



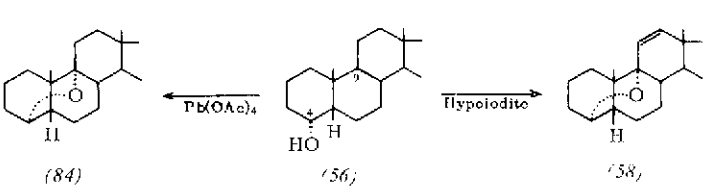

Nothing can be said at present regarding the importance of the transition state symbolized by formula *(79)*. In particular, it is not known whether, and to what extent, the indicated bond between oxygen and carbon in *(79)* exhibits bond character; however, it does not appear to be impossible that the three bonding electrons which are available for the three dotted bonds are approximately symmetrically distributed in certain cases. It is interesting to note that even the degree of conformational mobility of the reaction centers in the starting material yields information about the course of the reaction.

If the relative positions of the oxygen radical and the δ-carbon atom in *(78)* are fixed, direct oxidation of *(79)* to the ether *(80)* occurs – probably with the aid of a lead triacetate radical – without the intervention of a free carbonium ion as an intermediate. This was demonstrated for the example of a 6β,11β-dihydroxysteroid *(82)* [52], in which lead tetraacetate predominantly attacks the 6β-oxygen owing to steric factors. Although the C-19




methyl group is equidistant from the 6β- and 11β-oxygen atoms, the only product of the reaction is the 6β,19-ether *(83)*; an intermediate of the type *(81)* is therefore unlikely.

The behavior of 4α-hydroxy-5β-steroids *(56)* is particularly interesting in this connection. Whereas lead acetate yields only the saturated 4α,9α-ether *(84)* [18b], a $\Delta^{11}$-4α,9α-ether *(58)* is formed in the hypoiodite reaction, which proceeds through an intermediate 9-carbonium ion (cf. Section C. 2).




[46] *R. Criegee*, Angew. Chem. *70*, 173 (1958). The formation of aldehydes [*V. M. Micović* and *M. Lj. Mihailović*, Recueil Trav. chim. Pays-Bas *71*, 970 (1952)] and ketones (cf. [18b, 20a, 24h]) from primary and secondary alcohols by means of lead tetraacetate should also be classified as heterolytic reaction.

[47] *L. F. Fieser* and *F. C. Chang*, J. Amer. chem. Soc. *64*, 2043 (1942); *L. F. Fieser*, *R. C. Clapp*, and *W. H. Daudt*, ibid. *64*, 2052 (1942); *L. F. Fieser* and *A. E. Oxford*, ibid. *64*, 2060 (1942); *D. H. Hey*, *C. J. M. Stirling*, and *G. H. Williams*, J. chem. Soc. (London) *1954*, 2747; *1955*, 3963.

[48a] *V. Franzen* and *R. Edens*, Angew. Chem. *73*, 579 (1961), have investigated the decomposition of lead(IV) salts on irradiation with ultraviolet leight.

[48b] *K. Heusler*, *H. Labhart*, and *H. Loeliger*, unpublished work.

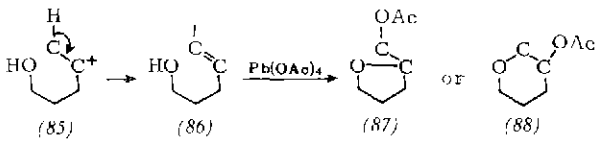
[49] *J. Kalvoda* and *K. Heusler*, Chem. and Ind. *1963*, 1431.

[50] In this connection, it should be mentioned that in no case to date has it been possible to isolate rearrangement products which might have been expected if an alkoxy cation occurred as an intermediate in the lead tetraacetate oxidation. It is particularly significant that, in the reaction of lead tetraacetate with 3β-hydroxycholestane, which does not contain a hydrogen atom in the δ-position relative to the hydroxy group favorably situated for abstraction, practically pure starting product is recovered together with a little 3-ketone, even after prolonged reaction.

[51] This statement does not imply that free oxy-radicals are produced. It seems probable that the lead atom remains somehow associated with the reaction complex during the transition *(77)* → *(80)*. Cf. the discussion in Section F.

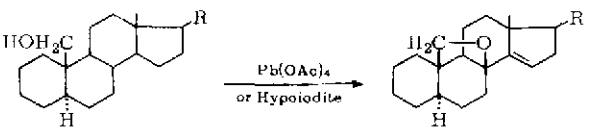
[52] Unpublished results.

However, when the centers in *(78)* are not fixed (especially in aliphatic compounds), the reaction leads to a radical pair *(81a)*, which is transformed into the ion pair *(81c)*, either by direct electron transfer or via the organolead compound *(81b)* [53a]. In addition to the formation of the ether *(80)*, a proton may be eliminated from *(81c)* with formation of a double bond *(86)*; a newly formed oxy-radical can finally add to this double bond to form the 5- or 6-membered cyclic ethers *(87)* and *(88)* [53b–e].



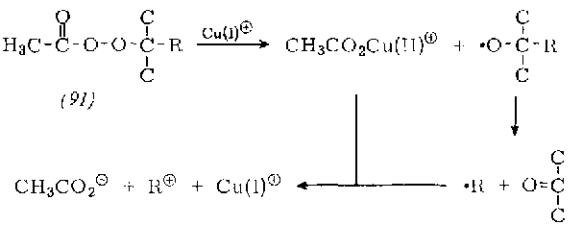

*(85)* *(86)* *(87)* *(88)*

It can be seen from the oxidation of 19-hydroxysteroids *(89)* that the ability to rotate freely about *one* C–C bond is sufficient for the formation of a carbonium ion as an intermediate. In this case unsaturated ethers *(90)* are formed, not only in the hypoiodite reaction, but also with lead tetraacetate.



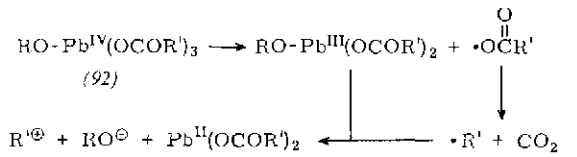

*(89)* *(90)*[26]

The cleavage of a lead alkoxide such as $R'O-Pb(OCOR)_3$ may be compared to the copper-catalysed decomposition of a peroxyester [54]. In the cleavage of peroxyacetates *(91)* in the presence of copper salts, the only products which have so far been observed are acetate ions and derivatives of alkoxy-radicals.




*(91)*

It is quite possible that the carbonium ions formed in the oxidation of free radicals with lead triacetate behave in a similar manner to those from the oxidation with copper ions. In the copper-catalysed decomposition of peroxyesters, the alternative mode of cleavage into an alkoxide-copper complex and acyloxy-radicals has not so far been observed [54]. However the alternative cleavage of the lead alkoxides *(92)* may possibly occur in the treatment of alcohols with lead salts of tertiary carboxylic acids. In any case, no 6β,19-ether



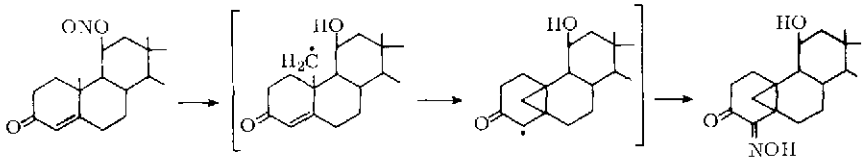
*(92)*

is formed in the reaction of lead tetrapivalate with a 6β-hydroxysteroid, although the lead(IV) salt is completely decomposed on heating. However, this result could also be explained by steric hindrance in the formation of the lead alkoxide. The copper-catalysed decomposition of tertiary peroxyesters has not as yet been described.

Other peculiarities of the lead tetraacetate oxidation of monohydric alcohols will be discussed in Section F.

## E. Participation of Neighboring Groups

In most of the examples described so far, the abstraction of hydrogen by an oxy-radical is followed by a direct



*(93)* *(94)*

substitution (*e.g.* by NO or iodine) on the carbon atom from which the hydrogen has been removed. This Section will deal with reactions in which this is not the case. Reactions of this kind always involve the addition of a carbon-free radical to unsaturated systems, namely C=C, C=O, and C≡N.

The participation of a neighboring double bond [*(93)* → *(94)*] has been described by *Barton* [20d].

The conversion to the dienone *(99)*, observed by *Barton* [55] in the photolysis of the nitrite *(95)*, can also be formally interpreted as the addition of a carbon-free radical *(96)* to an unsaturated system, followed by fragmentation to form a carbonyl compound [*(97)* → *(98)*].

[53a] The carbonium ion character of this intermediate is strongly supported by the results of the oxidation of 4,4-dimethylpentan-1-ol with lead tetraacetate which produces in addition to the 3,3-dimethyltetrahydropyrane (3–4%) 1–2% of 2-methyl-2-ethyltetrahydrofuran formed by rearrangement of the neopentyl-type carbonium ion generated as an intermediate. Private communication from Prof. *M. Lj. Mihailović*, Beograd, Yugoslavia; cf. also communication at the XXXIV International Congress for Industrial Chemistry, Beograd, September 22nd–29th, 1963.

[53b] *O. Jeger*, IUPAC-Congress, Montreal (Canada), August 1961.

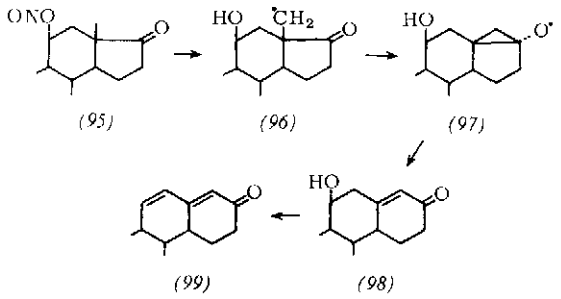
[53c] *D. Hauser*, Ph. D. Thesis, ETH Zürich, 1964.

[53d] *V. M. Mićović, R. I. Mamuzić, D. Jeremić*, and *M. Lj. Mihailović*, Tetrahedron Letters *1963*, 2091.

[53e] The reaction *(86)* → *(87)* was recently observed during the oxidation of a bicyclic unsaturated alcohol with lead tetraacetate Private communication from Prof. *R. M. Moriarty*, Washington, D.C., Tetrahedron Letters *1964*, in press.

[54] *J. K. Kochi*, J. Amer. chem. Soc. *85*, 1958 (1963); Tetrahedron *18*, 483 (1962); *Ch. Walling* and *A. Zavitsas*, J. Amer. chem. Soc. *85*, 2084 (1963); See also *G. Sosnovski* and *S.-O. Lawesson*, Angew. Chem. *76*, 218 (1964); Angew. Chem. internat. Edit. *3*, 269 (1964).

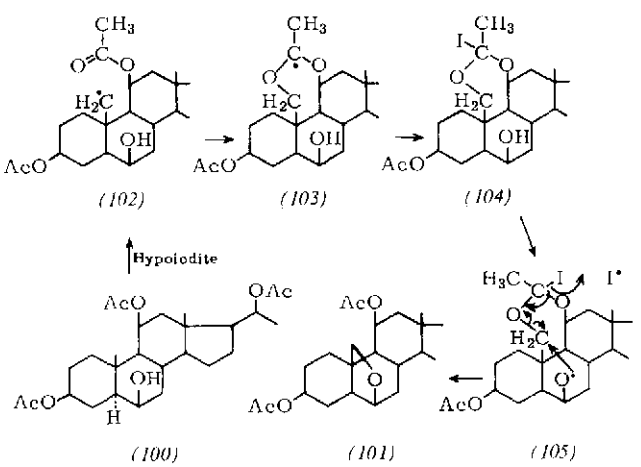
[55] *H. Reimann, A. S. Caponaggi, T. Strauss, E. P. Oliveto*, and *D. H. R. Barton*, J. Amer. chem. Soc. *83*, 4481 (1961).



(95) (96) (97) (99) (98)

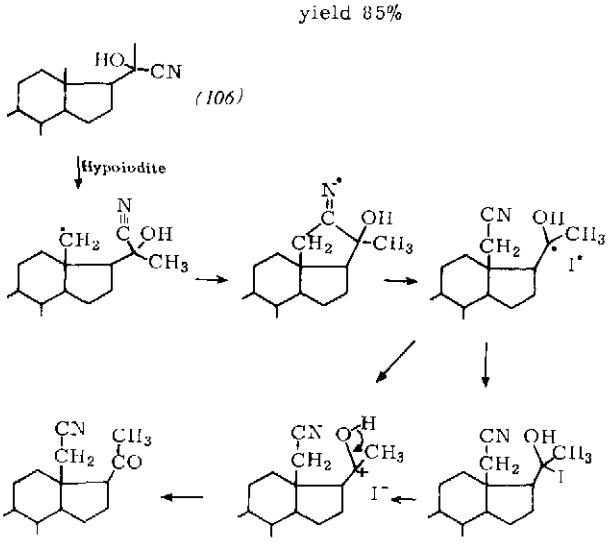
Ester carbonyl groups can also combine with carbon-free radicals. Evidence for this is found in the hypoiodite reaction of 6β-hydroxy-11β-acetoxysteroids. As described in Section C.1 (Case B), the hypoiodite reaction of a 6β-hydroxysteroid with a substituent in the 11-position should in part lead to the formation of hemiacetal-like compounds, with double substitution on the C-19 methyl group. However the 11β-acetoxy compound *(100)* yields only the simple 6β,19-ether *(101)* [52].

The angular substituent is so strongly hindered by the 11β-acetoxy group (as shown by a molecular model) that the formation of a 19-iodide is practically excluded. The course of the reaction can be best explained by assuming the intermediate addition of the initially formed carbon radical *(102)* to the acetate carbonyl group *(103)* [56]. The arrangement of



(102) (103) (104) (100) (101) (105)

yield 85%



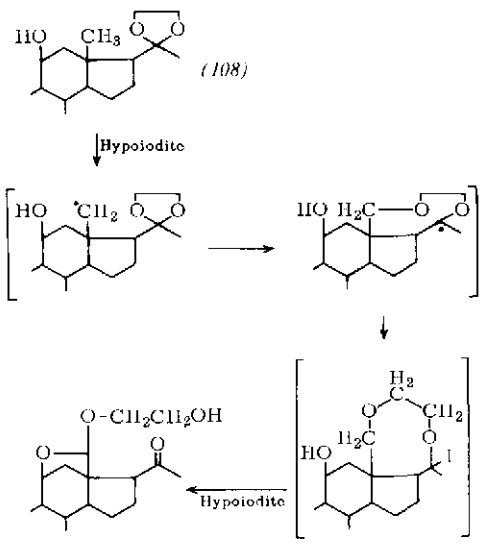
(106) (107)

[56] Similar addition products have been postulated by *J. C. Martin* and *E. H. Drew* [2b] to explain the cleavage of peroxides induced by cyclohexene.

the reactive centers (·O → C–O) in the intermediate *(105)* again favors a homolytic substitution ($S_H2$). Preliminary results with 4β-hydroxy-11β-acetoxysteroids appear to confirm the existence of this intermediate in the hypoiodite reaction (but not in the lead tetraacetate reaction) [52].

Finally, let us turn our attention to the remarkable case of the participation of a C≡N group [57]. The hypoiodite reaction with 20-hydroxy-20-cyanosteroids *(106)* yields 18-cyano-20-ketones *(107)* [6].

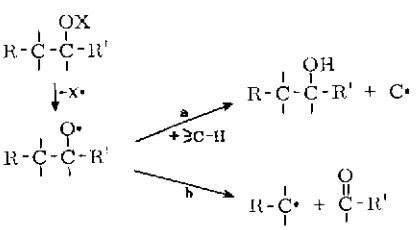
The participation of a neighboring ketal group was observed with an 11β-hydroxy-20-ethylenedioxysteroid *(108)* [20c], but an ionic mechanism cannot be definitely excluded in this case.



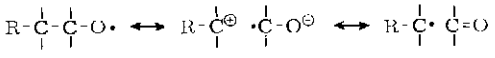
(108)

## F. Fragmentation Reactions

So far, we have discussed only the reactions of oxy-radicals which commence with an (intramolecular) abstraction of hydrogen (a) and have given no attention to the carbonyl-forming fragmentations (b), which are also energetically favored [11].



The rate $k_b$ of the cleavage reaction increases with the stability of the product of cleavage, R–$\dot{C}$– [58, 59]. Besides this, other factors must play a part: the stability of the ketone formed, the decrease in strain by ejection of bulky groups [59], polar structures in the transition



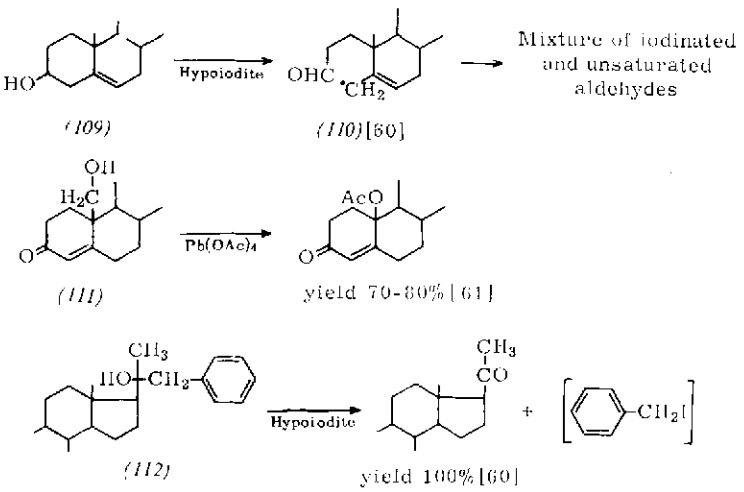
[57] *J. Kalvoda, K. Heusler, Ch. Meystre, G. Anner,* and *A. Wettstein,* IUPAC-Congress, London, July 1963.

[58] *J. K. Kochi,* J. Amer. chem. Soc. *84,* 1193 (1962).

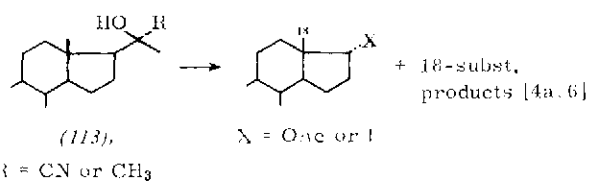
[59] *Ch. Walling* and *A. Padwa,* J. Amer. chem. Soc. *85,* 1593 (1963).

state stabilized by polarizing groups in R, entropy factors in the resonance stabilization of the radical formed by cleavage (*e.g.* R = benzyl), and, in cyclic compounds (particularly with small rings), the decrease in strain as a result of ring opening.

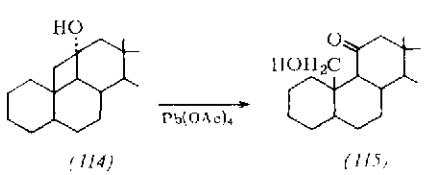
These factors also determine the outcome of the competition between intramolecular hydrogen abstraction and fragmentation. Particularly when the cleavage gives rise to an allyl or benzyl radical or to a radical adjacent to an oxygen function (especially a hydroxy, acyloxy or ketal group), the hydrogen abstraction can be entirely suppressed. This is exemplified by the reactions of *(109)*, *(111)* and *(112)*.




With tertiary 20-hydroxysteroids *(113)*, in contrast to the reaction of secondary 20-hydroxysteroids, the hydrogen abstraction from C-18 is distinctly suppressed in favor of the fragmentation, although the carbon radical formed is not appreciably stabilized. This is true of both the reaction with lead tetraacetate and the hypoiodite reaction.

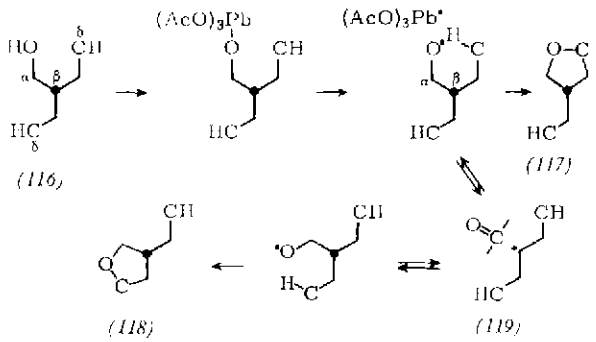



The influence of ring strain on the ease of fragmentation is shown by the reaction *(114)* → *(115)*, investigated by *Jeger* et al. [61].

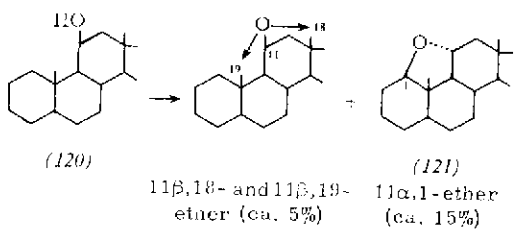



Fragmentation reactions are by no means restricted to tertiary alkoxy-radicals, but have also been observed with secondary alkoxy-radicals, particularly in the photolysis of nitrites [12] and in the oxidation with lead tetraacetate [61].

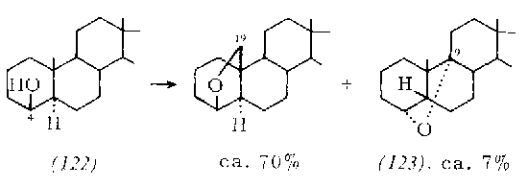
The peculiar character of the fragmentations in the lead tetraacetate reaction deserves special mention: In the oxidation of various steroid alcohols which exhibit exclusively hydrogen abstraction in the hypoiodite reaction, a novel mode of reaction, namely a *reversible* fragmentation, is observed. This is recognized from the fact that a sterically homogeneous alcohol *(116)* with




two δ-CH groups, and in which all C–C bonds lie in a rigid, polycyclic system and are therefore fixed in their orientation, yields two isomeric ethers *(117)* and *(118)*. These differ from the starting material in the stereochemistry of the α- or of the α- and β-carbon atoms. The isomerization is possible owing to the fact that the centers α and β in the (hypothetical) cleavage product *(119)* are trigonal [62]. An inversion on the α-carbon atom *(121)* takes place with 11β-hydroxysteroids *(120)* [18b, 62a].




The configurations of the α- and β-carbon atoms *(123)* are found to change with 4β-hydroxy-5α-steroids *(122)* [18b].



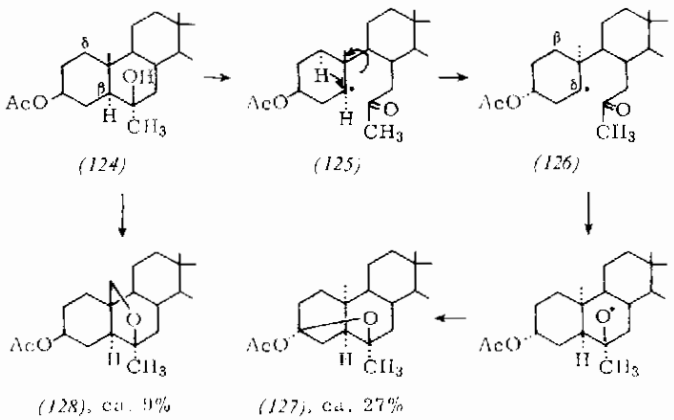

The example of a 6α-methyl-6β-hydroxysteroid *(124)* [25] shows that the bond between C-α and C-β is completely broken. The recombination in this case does not occur with C-β, but with a new C-radical *(126)*, which is formed by a homolytic hydrogen shift *(125)* from a δ-carbon atom to C-β.

[60] Unpublished work; see also *F. A. Braude* and *O. H. Wheeler*, J. chem. Soc. (London) *1955*, 320 (in particular p. 326).

[61] *M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailović, K. Schaffner, D. Arigoni*, and *O. Jeger*, Helv. chim. Acta *45*, 2674 (1962).

[62] See also *M. C. R. Symons*, Nature (London) *198*, 1196 (1963); *E. L. Eliel:* Stereochemistry of Carbon Compounds, McGraw Hill, New York 1962, pp. 380 et seq.

[62a] *G. B. Spero, J. L. Thompson, W. P. Schneider*, and *F. Kagan*, J. org. Chemistry *28*, 2225 (1963).



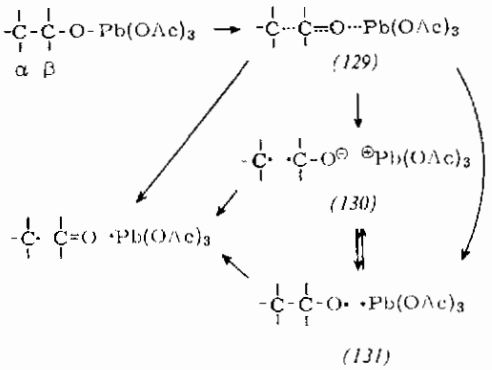
(124) (125) (126)

(128), ca. 9% (127), ca. 27%

The fact that, in the β,δ-hydrogen shift [63], the hydrogen atom from C-1 is displaced and not that from C-3, which is probably more weakly bound, indicates that the homolytic hydrogen shift in the ring is coupled with etherification of the 6-oxygen to C-3 *(127)* and occurs only when the hydrogen atom at position 3 already lies within bonding distance of the 6β-oxygen atom.

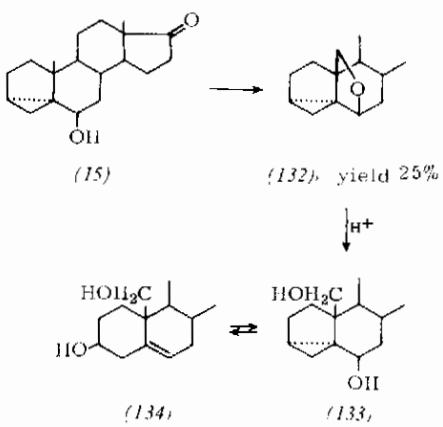
Finally, we shall attempt to explain why the reversible cleavage is principally observed in the oxidation with lead tetraacetate. Hydrogen abstraction (a) and fragmentation (b) are unimolecular processes, and the ratio of the reaction rates $k_a/k_b$ should therefore be independent of the solvent [64]. This has been confirmed by the investigation of the reaction *(124)* → *(128)* in benzene and in cyclohexane [25]. On the other hand, if the hypoiodite and hypochlorite as well as the lead tetraacetate reaction proceed through the same free oxy-radical, the ratio $k_a/k_b$ should also be independent of the method of production of this radical. This is obviously not the case, as is shown by a comparison of the hypoiodite and lead tetraacetate reactions with the starting materials *(124)* and *(122)* [or *(30)*]. The change in the ratio $k_a/k_b$ in the oxidation with lead tetraacetate can be caused by a retardation of the abstraction reaction ($k_a$) or an acceleration of the fragmentation reaction ($k_b$). Considering the strong dependence of the rate $k_a$ on the geometry of the transition state as discussed in Section B, it appears to be possible that the lead tetraacetate reaction gives rise to an intermediate product or transition state *(129)* which differs in the geometry of its basic skeleton from that of the free oxy-radical formed in the photolysis of hypoiodites and nitrites [65]. This could be due to an appreciable contribution from structures, possibly with polar character, in which the α,β-bond is already distinctly stretched.

An intermediate product of type *(130)*, in which the carbonyl group has a ketyl character [66], could also explain the isomerization and recyclization. A structure of type *(131)* would finally lead to hydrogen abstraction and ether formation. The elongation of the α,β-bond could slow down the hydrogen abstraction by increasing the O–C distance (which, even in alcohols with a C O



(129) (130) (131)

distance of 2.5 to 2.7 Å in the ground state, can lead to mixtures of abstraction and fragmentation products). On the other hand, in cases where the O–C distance in the ground state is too large for a hydrogen abstraction, the elongation could cause acceleration of this reaction to the point where it becomes observable, particularly when the fragmentation is energetically unfavorable owing to structural factors. An example of this might be the oxidation of 3,5-cyclo-6β-hydroxysteroids as mentioned in Section B [Formula *(15)*]. Thus, despite the considerable O–C distance of more than 3 Å, the 6β,19-ether *(132)* [23, 67] is formed with lead tetraacetate [68] but only in benzene, and not in cyclohexane, where the intermolecular hydrogen abstraction predominates [69].



(15) (132), yield 25%

(134) (133)

[63] The hydrogen shift can be regarded as a 1,3- or as a 1,5-migration. For homolytic 1,5-shifts, see [8]; however, 1,3-shifts are also known: cf. *O. A. Reutov*, Record of Chemical Progress (Kresge Hooker Sci. Library) *22*, 1 (1961); *O. A. Reutov* and *T. N.* Shatkina, Tetrahedron *18*, 305 (1962).

[64] *Ch. Walling* and *P. Wagner*, J. Amer. chem. Soc. *85*, 2333 (1963).

[65] The occurrence of free NO radicals (and hence also more or less free oxy-radicals) has been definitely established in the photolysis of nitrites [*M. Akhtar* and *M. M. Pechet*, J. Amer. chem. Soc. *86*, 265 (1964)].

[66] Ketyl-containing complexes are also discussed in a different connection by *Ch. Walling* [59] and by *V. Franzen*, Liebigs Ann. Chem. *633*, 1 (1960).

[67] The structure and stereochemistry of *(132)* was established by a synthesis of *(133)* from authentic *(134)*.

[68] Cf. [31]. Since *(15)* is a secondary alcohol and the cyclopropyl radical expected in the fragmentation is not stabilized, the fragmentation must be slower in this case. In the example *(16)* mentioned at the beginning, the fragmentation to the tertiary carbon radical with opening of the strained ring system is energetically favored.

[69] The hydrogen atoms in benzene are about 670 times less reactive towards the attack of alkoxy radicals at 135 °C than those in cyclohexane: *A. L. Williams*, *E. A. Oberright*, and *J. W. Brooks*, J. Amer. chem. Soc. *78*, 1190 (1956). Cyclohexyl ethers are sometimes formed as by-products in oxidations of alcohols with lead tetraacetate in cyclohexane as solvent [14b].

## G. Closing Remarks

The intramolecular substitution reactions of oxy-radicals may be summarized as follows:

In the photolysis of *nitrites* and *hypochlorites* only ligand transfers have been observed as primary processes (formation of 1,5-nitroso alcohols or 1,5-chlorohydrins).

In the *hypoiodite reaction*, the principal process besides the ligand transfer (formation of 1,5-iodohydrins, which can then undergo intramolecular solvolysis, in the same way as the chlorohydrins, to yield tetrahydrofuran derivatives) is the oxidation of carbon radicals to carbonium ions. In contrast to the photolysis of nitrites and hypochlorites, in which only a single intramolecular substitution is possible, the same carbon atom may be doubly substituted in the hypoiodite reaction. The reason for this difference is that the hypoiodites are prepared from alcohols and split homolytically *in situ*, so that both the initially formed (monoiodinated) alcohols and the regenerated starting material can react further. The yields in the hypoiodite reaction are therefore generally higher than those of the analogous photolyses of nitrites or hypochlorites.

The course of the reaction can be influenced by special steric relationships. If the reaction centers are suitably situated, the hypoiodite reaction can lead to a homolytic substitution of iodine on the carbon by an oxy-radical.

The action of *lead tetraacetate* on alcohols leads directly to high yields of tetrahydrofuran derivatives, without the formation of a "free carbonium ion", when all the participating centers are fixed in the arrangement which favors hydrogen abstraction. In the lead tetraacetate oxidation of alcohols in which the hydroxy groups and the attacked C–H bond are not fixed, acetoxylated or unsaturated 5- or 6-membered cyclic ethers can be formed through intermediates with a carbonium character.

Easily cleavable derivatives of homoallyl and homobenzyl alcohols are not suitable as starting materials for intramolecular substitution reactions, since in such cases the carbonyl-forming fragmentation competes successfully with the intramolecular hydrogen abstraction. This side reaction occurs in general when the carbon radical produced is stabilized. In the presence of acylates of tri- and tetravalent lead, the carbonyl-forming fragmentation may be reversible.

The course of the intramolecular free-radical reactions can be changed by the addition of intermediately formed carbon radicals onto neighboring unsaturated systems such as C–C, C=O, or C≡N groups.

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# Valence Compounds of the Inert Gases

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## Introduction

Ever since the discovery of the inert gases [1] in the period from 1892 to 1897 [2] by *Ramsay* and *Lord Rayleigh* [3], various workers have attempted to prepare compounds of these elements. No genuine valence compounds were obtained until 1962, although substances which might be termed "compounds" in a wider sense of the word have been known for some time.

For example, the charged particle $He_2^+$ is thermodynamically stable against decomposition into the components $He + He^+$. The energy of dissociation of $He_2^+$ is 108.4 kcal/mole [4], the normal value of the free enthalpy of decomposition thus being strongly positive. Molecules like HHe and $He_2$ are spectroscopically known in activated states. Their electronic ground states, however, are instable, *i.e.* they contain terms of repulsion [6]; this has been confirmed by theoretical considerations [5].

[1] Cf. Gmelins Handbuch der Anorganischen Chemie. 8th Edit. Springer, Heidelberg 1926, System No. 1.

[2] Helium was detected as early as 1868 in the solar spectrum; cf. [1].

[3] Radon was first recognized to be an inert gas by *Soddy* and *Rutherford*; the various emanations were characterized from 1899 onward, cf. [1].

[4] *F. L. Arnot* and *M. B. M. Ewen*, Proc. Roy. Soc. (London), Ser. A *171*, 106 (1939).

[5] See, for example, *C. A. Coulson:* Valence. Clarendon Press Oxford 1952.

[6] Further data on molecules of this kind are to be found in *Landolt-Börnstein:* Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik. Springer, Berlin 1951, Vol. I, parts 2 and 3.

"Compounds" in the form of volatile molecules may be formed by a spark discharge in inert gases (almost always He) in the presence of certain metals, *e.g.* Hg [7] but these are detectable only by spectroscopy. Substances such as $WHe_2$ [8] and $Pt_{3.3}He$ [9] have been obtained in the solid state. However, in these cases the helium appears to be merely adsorbed on the highly divided metals. It is significant that the Debye X-ray pattern of $Pt_{3.3}He$ closely resembles that of colloidal platinum [9, 10].

Inert gas clathrates [11] are the substances which most closely resemble conventional chemical compounds. The inert gas hydrates [12, 13], which were first described in 1896, form members of this group; these have the remarkable composition $G_{5.75} \cdot H_2O$ (G = Ar, Kr Xe, or Rn, but not He or Ne!) governed by their crystal structure [14]. In addition, double hydrates $R \cdot 2\,G \cdot 17\,H_2O$ [15], *e.g.* with $R = CH_3COOH$, $CH_2Cl_2$, $CHCl_3$, or $CCl_4$, of argon, krypton, and xenon are known. Mention may also be made of the interesting inclusion compounds of hydroquinone, $G \cdot 3C_6H_4(OH)_2$ (G = Ar, Kr, or Xe), which are usually a little deficient in inert gas, *e.g.* 0.88 Xe [16].

"Compound formation" in all these clathrates is governed only by van der Waals forces, the neutral inert gas atoms lying in the interstices of these cage structures.

## I. Early Experiments

Numerous attempts have been made to prepare genuine inert gas compounds [1], although many were probably never published; of those reported, experiments which might have led to the formation of halides are particularly interesting.

According to *Ruff* [17], fluorine does not react with argon and krypton when subjected to an electrical discharge; *Yost* [18] stated that attempts to obtain chlorides or fluorides of xenon from a mixture of both gases by excitation with ultraviolet irradiation or electric sparks were unsuccessful. Postulates concerning the existence of krypton chloride or bromide [19] could not be confirmed.

The range of interhalogen compounds, examples of which – ICl and $ICl_3$ – were known as early as 1814 [22], has grown markedly since the discovery of $IF_5$ [20] in 1902 and that of $BrF_3$ [21] in 1905/1906. After the preparation in 1931 of $IF_7$ [23], $BrF_5$ [24], and $ClF_3$ [25], it became clear that xenon, radon, and perhaps even krypton might be able to form fluorides.

This explains why the experiments mentioned above were carried out just after 1931. *Yost* [18], despite his lack of success, emphasized that the non-existence of xenon fluorides had by no means been proved.

In addition to these experimental results, the success of the concept of "filled shells" in the electronic configuration of the inert gases [26] contributed considerably to the general assumption that compounds of this kind could not exist.

Attempts were made to calculate the heats of formation of such compounds. By applying the Born-Haber cycle, it was shown [27], that a hypothetical neon(I) chloride $Ne^+Cl^-$ made up of ions and crystallizing in the NaCl lattice would be thermodynamically unstable and would decompose into its elements. However, it is quite clear that this compound, made up of two non-metals, would not be salt-like in structure, and would not be isotypical with NaCl. If compound formation were to occur at all, neon should form a dichloride $NeCl_2$, or perhaps $NeCl_4$, and even more probably $NeF_2$ or $NeF_4$. Finally, the interhalogen compounds mentioned above show that the existence of neon halides is particularly improbable.

The heats of formation of the halides of the heavy inert gases Xe and Rn cannot be calculated with sufficient reliability to allow a prognosis regarding their possible existence, even though the Born-Haber cycle can be used – despite its fundamental drawbacks – to calculate the heats of formation of covalent halides of light elements such as $CCl_4$ or $CF_4$ [28].

## II. The Discovery of the First Inert Gas Fluorides

The first inert gas fluoride, xenon difluoride $XeF_2$, was prepared in Germany in the last week of July, 1962 [29]. The first corresponding experiment in the United States was carried out on August 2nd, 1962 [30], and resulted in the preparation of xenon tetrafluoride

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[8] *E. H. Boomer*, Proc. Roy. Soc. (London), Ser. A *109*, 198 (1925).

[9] *H. Damianovich*, Proc. 8th Amer. Sci. Congr. *7*, 137 (1942); cited after [10].

[10] *N. V. Sidgewick*: The Chemical Elements. Clarendon Press, Oxford 1950, Vol. I.

[11] *H. M. Powell*, J. chem. Soc. (London) *1948*, 61; a good review of clathrate compounds is given by *L. Mandelcorn*, Chem. Reviews *59*, 827 (1959).

[12] *P. Villard*, C. R. hebd. Séances Acad. Sci. *123*, 377 (1896).

[13] *R. de Forcrand*, C. R. hebd. Séances Acad. Sci. *176*, 355 (1923); *181*, 15 (1925).

[14] *M. v. Stackelberg* et al., Z. Elektrochem., Ber. Bunsenges. physikal. Chem. *58*, 25 (1954); *W. F. Claussen*, J. chem. Physics *19*, 1425 (1951).

[15] See also *J. G. Waller*, Nature (London) *186*, 429 (1960); *M. Godchot, G. Cauquil*, and *R. Calas*, C. R. hebd. Séances Acad. Sci. *202*, 759 (1936); *B. A. Nikitin*, Ber. Akad. Wiss. UdSSR *24*, 562 (1939).

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[17] *O. Ruff* and *W. Menzel*, Z. anorg. allg. Chem. *213*, 206 (1933).

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[22] *L. J. Gay-Lussac*, Ann. Chimie [1] *91*, 48 (1814).

[23] *O. Ruff* and *R. Keim*, Z. anorg. allg. Chem. *193*, 176 (1930).

[24] *O. Ruff* and *W. Menzel*, Z. anorg. allg. Chem. *202*, 49 (1931).

[25] *O. Ruff* and *H. Krug*, Z. anorg. allg. Chem. *190*, 270 (1930).

[26] *W. Kossel*, Ann. Physik [4] *49*, 229 (1916).

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[29] *R. Hoppe, W. Dähne, H. Mattauch*, and *K. M. Rödder*, Angew. Chem. *74*, 903 (1962); Angew. Chem. internat. Edit. *1*, 599 (1962). The results on $XeF_2$ were obtained in July but were submitted for publication only on October 8th, 1962, since it seemed necessary to confirm the chemical analysis by a mass-spectroscopic investigation. The American authors published their results on August 20th, 1962.

[30] See *H. H. Claassen, J. G. Malm*, and *H. Selig* in: Noble-Gas Compounds. The University of Chicago Press, Chicago 1963, p. 31.

$XeF_4$ during the following few days [31 31b]. This independent and practically coincident work represents the starting point of modern developments in this field. The excellent and numerous American experiments were initiated by *Bartlett* [32].

In his initial attempts to prepare $PtF_5$, *Bartlett* had obtained a by-product thought to be $PtOF_4$ [33] but subsequently shown to be a new type of complex, $O_2^+[PtF_6]^-$ [34]. Since the ionization potentials of oxygen (12.2 eV) and xenon (12.13 eV) are very similar, a prepartion of $Xe[PtF_6]$ was attempted and met with success [32]. Publication of these results stimulated the work subsequently carried out at National Argonne Laboratories.

Our research group in Münster had already deliberated upon the possibility of formation and the properties of xenon fluorides in 1949/1950 [35], and, from 1951 onwards, we were convinced that $XeF_4$ and $XeF_2$ must be thermodynamically stable to decomposition into their elements.

The enthalpy of formation of $IF_5$ was determined by *Woolf* [36] in 1951. Using his value and the value previously obtained for $TeF_6$ [37], it was possible to calculate the mean thermochemical bond energies of $Te^{VI}$-F and $I^{V}$-F. Extrapolation of these values demonstrated that the bond energy of $Xe^{IV}$-F is probably greater than 20 kcal/val, and hence over half the dissociation energy of the $F_2$ molecule: $XeF_4$ would thus be stable [43].

Projected experimental investigations at Münster University encountered the major difficulty that at first xenon of adequate purity and, up to 1963, cylinders containing compressed fluorine were not obtainable in Germany. Judging from the experiments of *Ruff* and *Yost*, the high-pressure synthesis originally appeared to be the most promising method [35]. Model experiments carried out for the preparation of compounds with extremely anomalous valencies such as $K_2Au^{IV}F_6$ [38, 39], $K_2AgF^{IV}_6$ [39], and $KHg^{III}F_4$ [40, 41] by direct fluorination at a fluorine pressure of 1 atm, can merely be mentioned in passing.

The first krypton fluoride $KrF_4$ was prepared by *von Grosse*, also in 1962; this compound is unstable under normal conditions [42].

## III. The Preparation of Inert Gas Compounds

Several limiting cases can be distinguished. The first group consists of compounds which are thermodynamically stable under normal conditions and do not decompose into their components or into other compounds. Fluorides are the only known compounds of this type. The reaction

Inert gas + fluorine = inert gas fluoride

is therefore so to speak "exothermic" and takes place when sufficient excitation energy is supplied to the mixture of the elements, *e.g.* thermally by electric discharge or by exposure to ultraviolet light or $\gamma$- or $\beta$-rays. Sometimes unstable fluorides (*e.g.* $KrF_4$) are also obtained in this way.

A second group of inert gas compounds can be obtained from these fluorides under more or less mild conditions. This long-established method of preparation leads mostly but not invariably (*e.g.* $XeOF_4$) to compounds which are thermodynamically unstable, and decompose into their components or other substances.

Methods of preparation in which the starting point is the inert gas and a fluorine compound, rather than fluorine itself, naturally deserve special attention. A few examples of such methods have been described.

## IV. Xenon Difluoride $XeF_2$

Xenon difluoride $XeF_2$ was first obtained by subjecting xenon/fluorine mixtures to electric spark discharges ($Xe:F_2$ = 1:1 to 1:3, generally 1:2; $p_{tot.}$ = 700–800 mm, room temperature, cold finger at −78 °C) [43]. $XeF_2$ is also formed as the primary product in the high-pressure synthesis of $XeF_4$ [44], during pumping of an $Xe/F_2$ mixture ($Xe:F_2$ = 1:4) through a zone heated to 400 °C [45], and on irradiating xenon and fluorine with $\gamma$-rays below −35 °C [45a]; above this temperature $XeF_4$ is also formed.

Photosynthesis of $XeF_2$ [46] can be carried out in nickel vessels fitted with sapphire windows; quartz is attacked during the reaction ($\lambda$ = 2500–3500 Å; the maximum of the continuous absorption of gaseous fluorine in the ultraviolet region occurs at 2900 Å).

It must be assumed that the initial reaction is dissociation of the $F_2$ molecule into F atoms [47], which then form XeF as an intermediate according to the equation

$$F + Xe + F_2 = XeF + F_2,$$

or the equation

$$F + Xe + Xe = XeF + Xe.$$

The existence of XeF as an intermediate was confirmed by other authors [47a]. The formation of $XeF_2$ can then be pictured according to the reactions

$$XeF + F = XeF_2$$

and

$$XeF + XeF = XeF_2 + Xe \text{ [47]}.$$


[31] *H. H. Hyman* (Editor): Noble-Gas Compounds. The University of Chicago Press, Chicago 1963.

[31a] *C. L. Chernick, H. H. Claassen* et al., Science (Washington) *138*, 136 (1962).

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[32] *N. Bartlett*, Proc. chem. Soc. (London) *1962*, 218.

[33] *N. Bartlett* and *D. H. Lohmann*, Proc. chem. Soc. (London) *1960*, 14.

[34] *N. Bartlett* and *D. H. Lohmann*, Proc. chem. Soc. (London) *1962*, 115.

[35] Cf. *R. Hoppe* et al. [31], p. 98.

[36] *A. A. Woolf*, J. chem. Soc. (London) *1951*, 231.

[37] *D. M. Yost* and *W. H. Claussen*, J. Amer. chem. Soc. *55*, 885 (1933).

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[41] *R. Hoppe* and *H. Mattauch*, unpublished work (Münster 1961).

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[43] *R. Hoppe, H. Mattauch, K. M. Rödder,* and *W. Dähne*, Z. anorg. allg. Chem. *324*, 214 (1963).

[44] *M. H. Studier* and *E. N. Sloth*, J. physical Chem. *67*, 925 (1963).

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[45a] *D. R. MacKenzie* and *R. H. Wiswall* [31], p. 81; see also *D. R. MacKenzie* and *R. H. Wiswall*, Inorg. Chem. *2*, 1064 (1963).

[46] *J. L. Weeks, C. L. Chernick,* and *M. S. Matheson*, J. Amer. chem. Soc. *84*, 4612 (1962).

[47] *J. L. Weeks* and *M. S. Matheson* [31], p. 89.

[47a] *W. E. Falconer* and *J. R. Morton* [31], p. 245.

It is of interest to note that $XeF_2$ can be prepared even without the use of elementary fluorine. It is formed together with organic products by the action of electrical discharges on mixtures of xenon and carbon tetrafluoride [48] ($Xe:CF_4 = 1:1$), and also when xenon is heated in the presence of $CF_3OF$ ($CF_3OF:Xe = 2.2:1$; 250 atm, 500 °C) and $SO_3F_2$ ($SO_3F_2:Xe = 2.2:1$; 150 atm, 450 °C) [49].

Xenon difluoride is a colorless substance which forms magnificently lustrous crystals [29] of characteristic odor [43]. It forms tetragonal crystals with a = 4.315 Å and c = 6.990 Å, with two linear F–Xe–F structural units (Xe–F = 2.00 Å) per unit cell [50–53].

Neutron diffraction data [52] and X-ray structural analysis [51] indicate the space group $D_{4h}^{17}$–I4/mmm with 2Xe in 2(a), 4F in 4(e) and $z_F = 0.2837$ [neutron diffraction] or, less reliably, 0.306 [X-ray analysis]. The given parameter indicates a Xe–F distance of 1.98$_3$ Å [or 2.14 Å, a value not taken into consideration in this paper]. As a result of precession of the rigid $XeF_2$ dumb-bell molecules about [001] (7°) or vibrations normal to the molecular axis, the actual Xe–F distance is probably 2.00 ± 0.01 Å. This distance is in accordance with the distance I–Cl in the isoelectronic $ICl_2^-$ group (I–Cl = 2.36 Å), taking into consideration the differences between Cl and F, *etc.*, although according to *Smith* [45], the bonding relationships in $XeF_2$ are appreciably different from those in the structural unit $ICl_2^-$. The infrared spectrum of $XeF_2$ [52a] exhibits no Q branch due to the asymmetric stretched vibrational band, showing that the $XeF_2$ molecule is also linear.

The unexpectedly high melting point of xenon difluoride (140 °C) [54] is noteworthy, as are its low vapor pressure (3.8 mm at 25 °C) [54] and its large heat of sublimation ($\Delta H_{subl}$ = 12.3 kcal/mole [55]).

According to calculations performed by *Jortner* [56], only about 2 kcal/mole of the heat of sublimation can be ascribed to dispersion forces. Approximately 11 kcal/mole are thus due to electrostatic interchange effects between adjacent molecules. The linear $XeF_2$ units are considered by *Jortner* to have an appreciable polarity, and the effective charge of the F atoms [57] may be as much as −0.5 to 0.7 units, in agreement with spectroscopic findings [45].

$XeF_2$ is diamagnetic [43]. $\chi_{mol} = -50\times10^{-6}$, the expected value, but, in contrast to $XeF_4$, its susceptibility is not significantly dependent on the temperature [43]. The nuclear magnetic resonance of the F atoms in $XeF_2$ has also been measured (cf. page 545).

Xenon difluoride is decomposed by water. At 0 °C a yellow solution is first formed at the surface, but the color disappears when the ice melts, and complete evolution of xenon occurs at slightly higher temperatures [55a]. At lower temperatures, the xenon is not always completely liberated [43]. Decomposition also takes place with alcohol or with water containing ammonia or hydrazinium hydroxide. A violent reaction accompanied by ignition occurs with methanol [43].

$XeF_2$ is remarkably soluble in anhydrous hydrogen fluoride (*e.g.* 7.82 moles of $XeF_2$ in 1000 g of HF at 12.25 °C). The conductivity of such solutions is not higher than that of pure HF, so that apparently no dissociation or any other reaction takes place [55b].

The heat of formation estimated from spectroscopic data is $\Delta H_{250}^{\circ}(XeF_2, gas) = -19.4$ kcal/mole [69]; $XeF_2$ is thus thermodynamically stable. It may be stored without decomposition in glass or quartz vessels, provided moisture is excluded.

Double fluorides with $SbF_5$ and $TaF_5$ are discussed on p. 543.

## V. Xenon Tetrafluoride

Colorless crystals of xenon tetrafluoride $XeF_4$ were first prepared by heating a mixture of the approximate composition $Xe + 5\ F_2$ under pressure in a nickel vessel [31, 31a].

The compound is also formed when a mixture of xenon and fluorine is passed through a red-hot nickel tube [58], as well as by the action of electric discharges on similar mixtures of the gases at −78 °C [59].

$XeF_4$ is thermodynamically stable, (cf. p. 544) and can be stored in glass vessels at room temperature; samples kept at −25 °C exhibit no decomposition or reaction with the glass after long periods [58]. Its specific heat has been measured as a function of temperature: $C_p$ = 28.334 cal/deg/mole at 298 °K. The molecular lattice (5 atoms, 6 degrees of freedom) leads to an expected value of 30 cal/deg/mole [60a]. Its melting point of 114 °C [61] is astoundingly high, while its low vapor pressure (3 mm at 25 °C) [61] and large heat of sublimation ($\Delta H_{subl}$ = 15.3 kcal/mole [55]) are due, as for $XeF_2$, to an appreciable polarity of the Xe–F bond, possibly $Xe^{+2.0}(F^{-0.5})_4$. $XeF_4$ crystallizes in the monoclinic system [50, 51, 62–66] in the space group $C_{2h}^5$-$P2_1n$.

With regard to the structural parameters of $XeF_4$, the reader is referred to the original literature cited. Two molecules are contained in the unit cell. The structure contains well-defined, planar, practically square $XeF_4$ units with an Xe–F distance

[48] *D. E. Milligan* and *D. R. Sears*, J. Amer. chem. Soc. *85*, 823 (1963).

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[50] *S. Siegel* and *E. Gebert*, J. Amer. chem. Soc. *85*, 240 (1963).

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[52] *H. A. Levy* and *P. A. Agron* [31], p. 221.

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[55a] *J. G. Malm, B. D. Holt*, and *R. W. Bane* [31], p. 167.

[55b] *H. H. Hyman* and *L. A. Quartermann* [31], p. 275.

[55c] *S. M. Williamson* and *C. W. Koch* [31], p. 158.

[56] *J. Jortner, E. G. Wilson*, and *St. A. Rice* [31], p. 358.

[57] *J. C. Hindman* and *A. Svirmickas* [31], p. 251.

[58] *J. H. Holloway* and *R. D. Peacock*, Proc. chem. Soc. (London) *1962*, 389.

[59] *A. D. Kirshenbaum, L. V. Streng, A. G. Streng*, and *A. v. Grosse*, J. Amer. chem. Soc. *85*, 360 (1963).

[60] *A. G. Streng, A. D. Kirshenbaum, L. V. Streng*, and *A. v. Grosse* [31], p. 73.

[60a] *W. V. Johnston, D. Pilipovich*, and *D. E. Sheehan* [31], p. 139.

[61] *C. L. Chernick* [31], p. 35.

[62] *J. A. Ibers* and *W. C. Hamilton*, Science (Washington) *139*, 106 (1963).

[63] *W. C. Hamilton* and *J. A. Ibers* [31], p. 195.

[64] *D. H. Templeton, A. Zalkin, J. D. Forrester*, and *S. M. Williamson*, J. Amer. chem. Soc. *85*, 242 (1963).

[65] *D. H. Templeton, A. Zalkin, J. D. Forrester*, and *S. M. Williamson* [31], p. 203.

[66] *J. H. Burns, P. A. Agron*, and *H. A. Levy* [31], p. 211.

of $1.96_5 \pm 0.02_2$ Å: this bond is thus slightly shorter than that in $XeF_2$. The gaseous molecule also has the square structure [67].

$XeF_4$ is diamagnetic, and below 0 °C its susceptibility varies with temperature in agreement with measurements of the nuclear magnetic resonance of the fluorine [68].

$XeF_4$ is hydrolysed in water, $XeO_3$ or the corresponding oxoxenates being obtained by disproportionation (cf. p. 543) [55c].

$XeF_4$ dissolves in anhydrous HF to the extent of 0.18 moles per 1000 g at 20 °C, and 0.73 moles at 60 °C. As with $XeF_2$, the conductivity of the HF remains unaltered, and no indication of any other reactions between the solvent and the solute has been obtained [55b].

$XeF_4$ reacts with $SF_4$ to form $SF_6$, with complete reduction to Xe, and $XeF_6$ is formed with $O_2F_2$ [60]. It is noteworthy that $XeF_4$ reacts neither with $BF_3$ nor with NaF or KF up to 200 °C [68a, 81].

## VI. Higher Fluorides and Oxide Fluorides of Xenon

Xenon hexafluoride $XeF_6$ occurs under equilibrium conditions in the $Xe/F_2$ system at 250 °C and represents the highest stable fluoride of xenon [69]; it was prepared as such by heating mixtures of $Xe/F_2$ (Xe:Fe = 1:4 to 1:20; $p_{tot}$ = 25–250 atm, T = 250–500 °C and higher) [70–73], and also by the action of electric discharges [60] on such mixtures (Xe:Fe = 1:3) at −78 °C. It is also formed when $XeF_4$ reacts with $O_2F_2$ [60].

$XeF_6$ forms colorless crystals at room temperature, and melts at 46 °C to form a pale yellow liquid, b.p. 87 °C. The gas is yellow-green.

The vapor pressure of solid $XeF_6$ is given to be 6–7 mm at 0 °C [60, 70, 71] and 30 mm at 25 °C [70]. Its heat of sublimation is about 9.1 kcal/mole [60, 61]. The strongest, unusually broad absorption band of $XeF_6$ in the infrared spectrum occurs at 610 $cm^{-1}$; a second, weaker band of normal width appears at 520 $cm^{-1}$ [75].

$XeF_6$ is a stable compound: $\Delta H^{\circ}_{298}$ ($XeF_6$, gas) = −79 kcal/mole [74]. At room temperature, it hardly attacks glass and quartz, but in the molten state reacts rapidly with both, with initial formation of $XeOF_4$, and finally of an explosive solid, presumably $XeO_3$ [76].

The solubility of the compound in anhydrous hydrogen fluoride is high (3.16 moles of $XeF_6$/1000 g of HF at 15.8 °C, and 19.4 at 30.2 °C). Its solutions exhibit appreciable molar conductivity [0.024 moles of $XeF_6$/l: 147 mho/cm²] and, like liquid $XeF_6$, are pale yellow, becoming colorless on cooling. Nuclear magnetic resonance studies also indicate marked changes in the character of $XeF_6$ on dissolution, *e.g.* in the sense of a dissociation [55b].

The Yugoslavian research group has also reported that $XeF_8$ is formed in traces as a by-product in the high-pressure synthesis of $XeF_6$ (Xe:$F_2$ = 1:16) at 620 °C and 200 atm as a yellow compound which remains undecomposed only at very low temperatures (77 °K). Details have not yet been given [77, 78].

Three oxide fluorides are known, *viz.* $XeOF_4$, $XeO_2F_2$, and $XeOF_2$.

$XeOF_4$ is the initial product of the reaction of $XeF_6$ (at 50 °C) with quartz vessels, and is also formed during the hydrolysis of $XeF_6$ with the calculated quantity of water [76]. It is a colorless liquid which sets at −28 °C [76, 79]; its vapor pressure (8 mm at 0 °C and 29 mm at 23 °C) is approximately equal to that of $XeF_6$ [76].

The strongest infrared absorption band of $XeOF_4$ occurs at 608 $cm^{-1}$ and thus overlaps that of $XeF_6$. On the other hand, $XeOF_4$ shows practically no absorption at 520 $cm^{-1}$ [75].

$XeO_2F_2$ is formed as a further intermediate during the hydrolysis of $XeF_6$ to $XeO_3$ [80].

A colorless compound, m.p. 90 °C, b.p. ca. 115 °C, which according to *Peacock* is formed from Xe and $F_2$ in the presence of $O_2$ or air is regarded as $XeOF_2$ [81]. Oxide fluorides are also formed during the reaction of Xe with $O_2F_2$ at 300–400 °C as stable, colorless products of overall composition $Xe_{1.2}O_{1.1}F_{3.0}$ or under the influence of electric discharge ($XeOF_2$) [60].

In conclusion, it may be mentioned that the existence of $XeF_5$ is suspected [69] (this would be extremely surprising) and that an X-ray structural analysis carried out on the so-called "dense" modification of $XeF_4$ suggests that this is actually an adduct $XeF_2 \cdot XeF_4$ and not $XeF_4$ [82–84]. Since no confirmatory analytical data are available, the validity of this interpretation remains an open question.

## VII. Fluorine Compounds of Krypton

The first krypton fluoride prepared was krypton tetrafluoride $KrF_4$, which was obtained in the form of colorless, transparent crystals from the elements under the influence of an electric discharge at 84–86 °K and 7–12 mm total pressure [42, 60].

This substance decomposes into its elements at room temperature but can be sublimed at −40 to −30 °C, or even at 0 °C if the process is carried out rapidly. Its sublimation point was determined by extrapolation to be about 70 °C; its heat of sublimation is 8.8 kcal/mole [60].

[67] *R. K. Bohn, K. Katada, J. V. Martinez,* and *S. H. Bauer* [31], p. 238.

[68] *J. Slivnik, B. Brčić, B. Volavšek, A. Šmalc, B. Frlec, R. Zemljič, A. Anžur,* and *Z. Veksli,* Croat. chem. Acta *34,* 188 (1962).

[68a] *N. Bartlett,* Chem. Engng. News *41,* No. 5, p. 36 (1963).

[69] *B. Weinstock, E. E. Weaver,* and *C. P. Knop* [31], p. 50.

[70] *J. G. Malm, I. Sheft,* and *C. L. Chernick,* J. Amer. chem. Soc. *85,* 110 (1963).

[71] *E. E. Weaver, B. Weinstock,* and *C. P. Knop,* J. Amer. chem. Soc. *85,* 111 (1963).

[72] *F. B. Dudley, G. Gard,* and *G. H. Cady,* Inorg. Chem. *2,* 228 (1963).

[73] *J. Slivnik* et al., Croat. chem. Acta *34,* 253 (1962).

[74] *L. Stein* and *P. L. Plurien* [31], p. 144.

[75] *D. F. Smith* [31] p. 39.

[76] *C. L. Chernick, H. H. Claassen, J. G. Malm,* and *P. L. Plurien* [31], p. 106.

[77] *J. Slivnik, B. Volavšek, J. Marsel, V. Vršćaj, A. Šmalc, B. Frlec,* and *A. Zemljič* [31], p. 64.

[78] *J. Slivnik, B. Volavšek, J. Marsel, V. Vršćaj, A. Šmalc, B. Frlec,* and *A. Zemljič,* Croat. chem. Acta *35,* 81 (1963).

[79] *D. F. Smith,* Science (Washington) *140,* 899 (1963).

[80] *M. H. Studier* and *E. N. Sloth* [31], p. 47.

[81] *A. J. Edwards, J. H. Holloway,* and *R. D. Peacock,* Proc. chem. Soc. (London) *1963,* 275.

[82] *J. H. Burns,* J. physical Chem. *67,* 536 (1963).

[83] *J. H. Burns, R. D. Ellison,* and *H. A. Levy,* J. physical Chem. *69,* 1569 (1963).

[84] *J. H. Burns, R. D. Ellison,* and *H. A. Levy* [31], p. 226.

Mixtures of Kr and $F_2$ do not react when excited by exposure to ultraviolet light, by heating to 400–500 °C (nickel vessels), or on irradiation with a beam of electrons at −130 °C [46, 60, 45a].

Recently, krypton difluoride $KrF_2$, whose formation in minute amounts had previously been deduced from spectroscopic observations [85,86], was prepared from a mixture of Kr and $F_2$ at −150 °C in a beam of electrons, being obtained in the form of a colorless substance which sublimed unchanged at lower temperatures (p ≈ 2 mm at −40 °C) but which decomposes into its elements at room temperature [87].

A colorless substance which is obtained in small quantities from $Kr/F_2$ mixtures under the influence of an electric discharge at −130 °C decomposes rapidly at room temperature but can be maintained unchanged at 77 °K, and is presumably also $KrF_2$ [43, 88].

No well-defined fluorides of other inert gases have so far been prepared, although the formation of radon fluorides has been claimed [31a, 89].

## VIII. Fluorine Compounds of Higher Order

The first inert gas compound in the narrower sense of the word, $Xe[PtF_6]$, was obtained by *Bartlett* in the summer of 1962 [32]. This compound is formed on reaction of gaseous $PtF_6$ and Xe as an orange solid insoluble in carbon tetrachloride. Its vapor pressure is negligible at room temperature but it is possible to sublime the substance *in vacuo*. It decomposes with water:

$$XePtF_6 + 3\,H_2O = Xe + {}^1/_2\,O_2 + PtO_2 + 6\,HF$$

This compound is analogous to the $O_2^+[PtF_6]^-$ previously prepared [34]. Further investigations of this class of compounds by *Bartlett* et al. have so far resulted in no clarification of their structures, but rather introduced new complications [90]:

Xe and $PtF_6$ interact at room temperature to form red products whose composition lies between the limiting forms $Xe[PtF_6]$ and $Xe[PtF_6]_2$. Xenon tetrafluoride is evolved when the platinum-rich products, *e.g.* $Xe[PtF_6]_{1.8}$, are heated. The brick-red diamagnetic (!) residue left after thermal decomposition has the composition $XePt_2F_{10}$. Analogous deep-red substances are obtained with rhodium and have compositions close to $XeRhF_6$. Krypton forms no compounds with either $PtF_6$ or $RhF_6$.

According to *Peacock*, xenon tetrafluoride is reduced by tantalum pentafluoride, and also by antimony pentafluoride, with formation of addition compounds of $XeF_2$ [81]. The straw-yellow adduct $XeF_2 \cdot 2\,SbF_5$ melts at 63 °C and can be sublimed unchanged *in vacuo*.

[85] *J. J. Turner* and *G. C. Pimentel* [31], p. 101.

[86] *J. J. Turner* and *G. C. Pimentel*, Science (Washington) *140*, 974 (1963).

[87] *D. R. MacKenzie*, Science (Washington) *141*, 1171 (1964).

[88] *R. Hoppe*, *K. M. Rödder*, *Ch. Hebecker*, and *I. Siddiqi*, unpublished work (1963–1964), cf. [43].

[89] *P. R. Fields*, *L. Stein*, and *M. H. Zirin* [31], p. 113; J. Amer. chem. Soc. *84*, 4164 (1962).

[90] *N. Bartlett* and *N. K. Jha* [31], p. 23.

## IX. Oxygen Compounds of Xenon

No oxides of xenon have so far been obtained from the elements. However, oxides or their derivatives are formed when xenon fluorides reacts with water or alkaline or acid solutions.

a) Xenon difluoride is decomposed by water [55c] or aqueous solutions above 0 °C, giving oxygen and elementary xenon. An intermediate yellow coloration is observed at the surface at 0 °C. Derivatives of "hypoxenic acid" $Xe(OH)_2$ have not yet been prepared.

(b) Xenon tetrafluoride reacts with water with initial formation of a brilliant canary-yellow color at the surface of the colorless $XeF_4$ crystals [55c].

The yellow solid formed in this way is of unknown composition and decomposes rapidly between −5 and +5 °C in NaOH solution, but somewhat more slowly in pure water or 9 M $H_2SO_4$, and after 20 minutes in 3 M $H_2SO_4$. Bubbles of gas are generated during the decomposition; the supernatant liquid remains colorless.

The overall reaction proceeds according to the equation:

$$6\,XeF_4 + 12\,H_2O = 4\,Xe + 3\,O_2 + 2\,XeO_3 + 24\,HF$$

The form in which $XeO_3$ is present in the solution has not yet been elucidated. Compounds such as $Xe(OH)_6$ [91], $H_4XeO_6$ [55c], and $H_2XeO_4$ [92] have been proposed.

According to a different source [55a], formation of the yellow substance during the hydrolysis of $XeF_4$ with NaOH is not transient, but a pale-yellow solution is formed which retains its color for several days.

No matter what the composition of the yellow substance may be, evaporation of the solution yields colorless xenon trioxide $XeO_3$ [93–96]. This strongly endothermic compound ($\Delta H^\circ_{298}$ ($XeO_3$, solid) = +96 kcal/mole) [97] detonates readily.

The crystal structure of $XeO_3$ has been elucidated by X-ray studies on single crystals [98]. $XeO_3$ crystallizes in the rhombic system, with a = 6.163 Å, b = 8.115 Å, and c = 5.234 Å, in the space group $D_2^4$–$P2_12_12$, with 4 molecules per unit cell. Its structure is closely related to that of $HIO_3$ [99–101]. The structural group $XeO_3$ is present in the crystal as a closed "shallow" pyramidal group; the Xe–O distances are 1.74 to 1.77 Å, and the O–Xe–O angles lie between 100 and 108°; the corresponding values for $HIO_3$ are 1.78–1.90 Å and 94 to 100°. With regard to the individual parameters of the occupied point sites, reference should be made to the original literature [98].

[91] *F. B. Dudley*, *G. Gard*, and *G. H. Cady*, Inorg. Chem. *2*, 228 (1963).

[92] *M. Kilpatrick* [31], p. 155.

[93] *S. M. Williamson* and *C. W. Koch*, Science (Washington) *139*, 1046 (1963).

[94] *D. H. Templeton*, *A. Zalkin*, *J. D. Forrester*, and *S. M. Williamson*, J. Amer. chem. Soc. *85*, 817 (1963).

[95] *D. F. Smith*, J. Amer. chem. Soc. *85*, 816 (1963).

[96] *N. Bartlett* and *P. R. Rao*, Science (Washington) *139*, 506 (1963). These authors gave the composition $XeO_2 \cdot 2H_2O$ for their substance, which exploded violently at 40 °C.

[97] *St. R. Gunn* [31], p. 149.

[98] *D. H. Templeton*, *A. Zalkin*, *J. D. Forrester*, and *S. M. Williamson* [31], p. 229.

[99] *A. F. Wells*, Acta crystallogr. *2*, 128 (1949).

[100] *M. T. Rogers* and *L. Helmholz*, J. Amer. chem. Soc. *63*, 278 (1941).

[101] *J. A. Ibers*, Acta crystallogr. *9*, 225 (1956).

Oxoxenates(VI) of the alkali metals have been described, but their compositions have not yet been established [102]. Barium xenate $Ba_3XeO_6$ was recently prepared as a white precipitate, which is sparingly soluble in water; its thermal decomposition into BaO, Xe, and $O_2$ commences at 125 °C and is complete at 250 °C [102].

The thermal stabilities of alkali metal xenates are said to be higher [102]. Xe(VI) solutions oxidize acidified bromide and iodide solutions to $Br_2$ and $I_2$, respectively [103].

(c) Xenon hexafluoride forms perxenates in alkaline solutions by disproportionation. These perxenates have the general formula $M^I_{2n}XeO_{4+n}$ and, in general, contain water of crystallization [92, 55a]. Analytical data for the substances obtained from NaOH indicate compositions lying between the limiting formulae $Na_4XeO_6 \cdot 2\,H_2O$ and $Na_6XeO_7 \cdot H_2O$ [55a]. The existence of heavy metal perxenates has also been claimed [104]. Xe(VIII) solutions, which slowly decompose into Xe(VI) solutions and oxygen, have been studied in somewhat greater detail [105]. Recently, $Na_4XeO_6 \cdot 8H_2O$ was isolated and its structure determined: the perxenate anion $[XeO_6]^{4-}$ is an almost regular octahedron. The Xe–O distance of 1.875 Å is longer by 0.12 Å than that in $XeO_3$. Correspondingly, the I–O bond length of 1.93 Å in the $[IO_5]^{5-}$ anion is greater by 0.11 Å than that in the $IO_3^-$ anion (1.81 Å). The $[XeO_6]^{4-}$ anion is isoelectronic with the long familiar $IO_6^{5-}$ ion; it is likely that all the 5s and 5p as well as the 5d orbitals participate in the bonds in both ions [105a].

Recently, barium kryptate, apparently $BaKrO_4$, was prepared from $KrF_4$, as a colorless compound with no tendency to decompose up to 0 °C [106].

## X. Thermochemistry and Bonding Relationships

According to the investigations carried out so far, the following compounds are formed exothermically:

Xenon difluoride $XeF_2$. The enthalpy of formation was determined from spectroscopic measurements and estimated to be $\Delta H^\circ_{298}(XeF_2, \text{solid}) = -20$ kcal/mole [69].

Xenon tetrafluoride $XeF_4$. Two calorimetric determinations have so far been reported. In one, the reaction

$$XeF_4 + 4\,I^- = 2\,I_2 + Xe + 4\,F^-$$

was utilized, although a small portion of the $XeF_4$ reacts [107] according to

$$XeF_4 + 2\,H_2O = Xe + O_2 + 4\,HF.$$

In the other, gaseous $XeF_4$ was reduced with $H_2$ to Xe and gaseous HF [74]. $\Delta H^\circ_{298}$ ($XeF_4$, solid) was found to be −60 kcal/mole [107], whence it follows that $\Delta H^\circ_{298}$ ($XeF_4$, gas) = −48 kcal/mole, with $\Delta H_{subl}$ ($XeF_4$) = 12 kcal/mole; in the other estimation $\Delta H^\circ_{298}$ ($XeF_4$, gas) = −55 kcal/mole [74]. The entropy at 298.16 °K is 35.0 ± 1.0 e.u. Consequently, the free enthalpy of formation $\Delta F^\circ$ = −29.4 kcal/mole, with $\Delta H^\circ_{298}$ ($XeF_4$, solid) = −60 kcal/mole.

Xenon hexafluoride $XeF_6$. Reduction of gaseous $XeF_6$ with $H_2$ to Xe and gaseous HF was also utilized here. A calorimetric value of $\Delta H^\circ_{298}$ ($XeF_6$, gas) = −79 kcal/mole was found [74].

These thermochemical values for the xenon fluorides were as expected [43]. The values listed in Table 1 were obtained by calculating the mean thermochemical bond energy E(Xe–F) from the enthalpies of formation, and comparing it with the corresponding values for halogen fluorides [108, 109].

Table 1. Mean thermochemical bond energies for halogen fluorides, halogen chlorides, and inert gas fluorides.

| Halogen fluorides | | | | | Halogen chlorides | | | Inert gas fluorides | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | III | V | VII | | I | III | | II | IV | VI |
| F | 36.7 | | | | | | | | | | |
| Cl | 60.7 | 40.9 | | | Cl | 58.0 | | Ar | | | |
| Br | 63.4 | 49.6 | 48.4 | | Br | 55.9 | | Kr | ≈16 | ≈16 | |
| I | 73.9 | (69) | 63.9 | 55.1 | I | 57.9 | (40?) | Xe | ≈30 (46?) | 30–≈32 | 31.5 |

The results listed in this table lead to the following conclusions.

1. Thermochemically, $XeF_4$ and $XeF_6$ closely resemble the corresponding bromine compounds $BrF_3$ and $BrF_5$ (diagonal relationship), insofar as their respective bond energies are roughly equal: the bond energies of the bromine compounds are about 16 kcal/mole higher than those of the xenon compounds.

2. The bond energy of $XeF_2$ is probably greater than the value derived from the enthalpy of formation estimated from spectroscopic data. A value of 40–45 kcal/mole is to be expected.

If a parallel is now drawn analogously between $KrF_2$ and ClF and between $KrF_4$ and $ClF_3$, then it can be estimated tentatively that the bond energies in both $KrF_2$ and $KrF_4$ are about 16 kcal/mole. However, at least 18.3 kcal per F atom [= 1/2 $D_0(F_2)$] are required to obtain an "exothermal" compound, so that these compounds lie at the border of thermodynamic instability, as is actually observed in practice.

Comparison of the bond energies of ICl and $ICl_3$ with those of IF and $IF_3$ on the one hand and those of $XeF_2$ and $XeF_4$

[102] *A. D. Kirshenbaum* and *A. v. Grosse*, Science (Washington) *142*, 580 (1963).

[103] *C. W. Koch* and *S. M. Williamson* [31], p. 181.

[104] *D. M. Gruen* [31], p. 174.

[105] *E. H. Appelman* [31], p. 185.

[105a] *W. C. Hamilton, J. A. Ibers*, and *D. R. MacKenzie*, Science (Washington) *141*, 532 (1963).

[106] *A. G. Streng* and *A. v. Grosse*, Science (Washington) *143*, 242 (1964).

[107] *St. R. Gunn* and *S. M. Williamson* [31], p. 133.

[108] The values used were taken from *E. H. Wiebenga* et al., Advances inorg. Chem. Radiochem. *3*, 133 (1961).

[109] National Bureau of Standards Circular No. 50.

on the other hand shows that all xenon chlorides are probably unstable; $XeCl_2$ is the one most likely to be capable of "preparation", analogously to $KrF_2$ and $KrF_4$, but it has not so far been obtained.

Finally, the enthalpy of formation of solid xenon trioxide $XeO_3$ was determined as $\Delta H^{\circ}_{298}$ ($XeO_3$, solid) = 96 + 2 kcal/mole [97]. This value fits conveniently into the series $Sb_2O_3$, $TeO_2$, $I_2O_5$ when the values for the latter are converted for their formation from gaseous atoms.

The nature of the bonds in inert gas compounds has been the subject of much discussion. Let us recall that $Te^0$, $I^I$, $Xe^{II}$, and $Te^{II}$, $I^{III}$, $Xe^{IV}$ represent an isoelectronic series. The bonds in the xenon fluorides (*e.g.* in $XeF_2$) are almost certainly neither purely covalent (*i.e.* F–Xe–F) nor purely ionic (*i.e.* $F^-Xe^{2+}F^-$). If an ionic structure (*e.g.* $I^{3+}Cl_3^-$) is taken for a start and the true nature of the bonds is then approached by superimposing covalent bonds, it becomes clear that since the discovery of compounds such as ICl, $ICl_3$, $IF_5$, and $IF_7$, no fundamental objections could be raised against the existence of inert gas compounds (as had been previously because of the "filled" electron configurations of the inert gases).

Despite numerous theoretical calculations [75, 110–121], spectroscopic investigations, and measurements either of the nuclear magnetic resonance of the fluorine atoms or of the Mössbauer effect, no quantitative description of the character of the bonds in, for example, the xenon fluorides has yet been made. On the basis of theoretical calculations, it can be taken as certain that [owing to the unusually high heats of sublimation of $XeF_2$, $XeF_4$, and $XeF_6$, as well as from the extent of the chemical shift in their F–NMR spectra, which lies between the limiting values for $F_2$ (purely covalent bond) and $F^-$ in HF (practically pure ionic bond)] the effective charge per fluorine atom in $XeF_2$ and $XeF_4$ is about −0.5. The effective charge on the xenon atom is therefore about +1 in $XeF_2$ or +2 in $XeF_4$. It becomes clear that $XeF_2$ cannot therefore be strictly compared with the $ICl_2^-$ ion, although the latter is also linear, because the bond character of $ICl_2^-$ can be described quite well by resonance between the two limiting forms Cl–I $Cl^-$ and $Cl^-$ I–Cl.

It is also certain that there are no pure σ-bonds, although a certain π-bond character is present. In addition an increasing number of authors postulate that the 5d-orbitals of xenon also participate in the bond.

It should be remembered that detailed interpretation of chemical shifts in nuclear magnetic resonance measurements is difficult, and that uncertainties always remain in any interpretations.

## XI. Conclusions

From our present knowledge, several reasons can be proposed to explain the failures of earlier attempts to prepare inert gas compounds, and why it was widely assumed that compounds of this type could not exist:

a) Firstly, before 1950 experimental difficulties were encountered.

Above all, fluorine-resistant "greases" (for example Hostaflon of appropriate softening point) became available only after 1950. All earlier authors experienced appreciable difficulties in this respect.

b) In addition, successful application of the concept of the special stability of completed electron shells (*e.g.* in carbonyls and complex compounds of the transition metals, particularly for the interpretation of their magnetic behavior caused the fact to be overlooked that the well-known and long-established interhalogen compounds were necessarily close neighbors of possible valence compounds of the inert gases.

c) Finally, the view was widely held that any possible inert gas compounds would be thermodynamically unstable and would tend to decompose into their elements so that they could only be prepared and handled with particular experimental skill.

The following-up of a chance observation by *Bartlett* led in a remarkable fashion to the preparation of $XePtF_6$ and stimulated the high-pressure synthesis of $XeF_4$, whereas the determination of the heat of formation of $IF_5$ led our research team in Münster to the assurance that $XeF_4$ and $XeF_2$ must be exothermal compounds and initiated, although with some delay, experiments resulting in the preparation of $XeF_2$. Starting from different observations independently and at the same time, a new field of inorganic chemistry was opened up which in reality presents no particular experimental difficulties. Inert gas compounds readily fit the periodic system (with the inert gases considered as Group 8 elements). Severe limitations are placed upon the range of thermodinamically stable compounds only by the fact that no other nonmetal has such a low dissociation energy and at the same time such a high mean thermochemical bond energy as fluorine.

The formation of $XeO_3$, of salts of corresponding acids, and of double fluorides, shows that although there are probably not very numerous stable binary compounds of the inert gases, a number of additional derivatives may become accessible by using sufficiently mild conditions, *e.g.* by working in solution. Preparation of helium, neon, and even argon compounds is nevertheless unlikely.

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[112] *R. J. Gillespie* [31], p. 333.
[113] *J. Hinze* and *K. S. Pitzer* [31], p. 340.
[114] *L. L. Lohr* and *W. N. Lipscomb* [31], p. 347.
[115] *E. A. Boudreaux* [31], p. 354.
[116] *J. Jortner, E. G. Wilson,* and *St. A. Rice* [31], p. 358.
[117] *J. H. Waters* and *H. B. Gray,* J. Amer. chem. Soc. *85*, 825 (1963).
[118] *J. Jortner, St. A. Rice,* and *E. G. Wilson,* J. chem. Physics *38*, 2302 (1963).
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# The Preparation of Catena Compounds by Directed Synthesis [1]

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Six years ago [2] we discussed some of the principles involved in the synthesis of catena compounds, a new class of substances consisting of rings, which are not chemically combined but which are held together like the links of a chain *(1)*, and began some experimental work on such systems [2, 3].

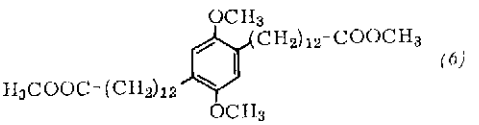


*(1)*

As the reactions we envisaged were of statistical character, only very poor yields were to be expected. Our experimental results [3] were even more disappointing than expected although they gave valuable information about the behavior and morphology of long-chain and macrocyclic compounds in solution.

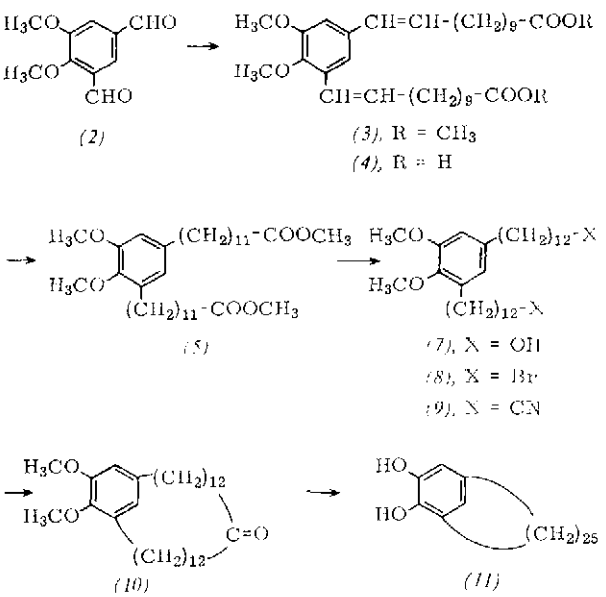
On the other hand, *Wasserman* [4] claimed to have obtained yields of approximately 1 % (relative to the entire mixture isolated) using one of these methods. Later on he modified this statement to a claim [5] of having obtained by chromatography yields that were several powers of ten less than those previously reported, namely a few milligrams of an oil which was thought to be a catenane. The new principle of the directed synthesis which we have now applied proved successful. By steric control it avoids the extra-annular ring closures which always occur predominantly in statistical cyclization methods.

4,5-Dimethoxyisophthalaldehyde *(2)* [6] was converted into the dicarboxylic ester *(3)* by Wittig reaction with an excess of 10-methoxycarbonyldecylidenetriphenylphosphorane [7]. Hydrolysis gave the crystalline dicarboxylic acid *(4)* (m.p. 67–71 °C, after sintering) in 52–58 % yield based on *(2)*. Catalytic hydrogenation and esterification of *(4)* gave *(5)*. Surprisingly, this ester could not be cyclized by the acyloin ring closure method of *Hansley*, *Prelog*, and *Stoll*, but remained unchanged, whereas the dicarboxylic ester *(6)* of a hydroquinone ether was cyclized readily.



*(6)*

The diester *(5)* was therefore reduced to the diol *(7)* with $LiAlH_4$, and *(7)* was converted into the dinitrile *(9)* via the dibromide *(8)*. The cyclic β-imino nitrile obtained from *(9)* by ring closure according to the method of *Ziegler* was hydrolysed and remethylated to give the ketone *(10)*, m.p. 45–47 °C. Reduction of *(10)* using the method of *Huang-Minlon* [8] and subsequent demethylation afforded 3,5-pentacosamethylenecatechol *(11)*, m.p. 100–102 °C.



*(2)*; *(3)*, R = $CH_3$; *(4)*, R = H; *(5)*; *(7)*, X = OH; *(8)*, X = Br; *(9)*, X = CN; *(10)*; *(11)*

Ketal formation from the *ansa*-catechol derivative *(11)* with 1,25-dichloropentacosan-13-one *(12)* according to the method of *Salmi* [9] yielded the 1,3-benzo[*d*]dioxole derivative *(13)*, m.p. 48–50 °C.

We obtained the ketone *(12)* from 13-chlorotridecanoyl chloride by ketene dimerisation [10] with triethylamine. $Cl-(CH_2)_{12}-COCl \rightarrow Cl-(CH_2)_{12}-CO-(CH_2)_{12}-Cl$ *(12)*

Nitration of *(13)* with copper nitrate in acetic anhydride [11] afforded the nitro compound *(14)*, which on catalytic hydrogenation gave the amine *(15)*, m.p. 56–57.5 °C. Cyclization of *(15)* with potassium carbonate in amyl alcohol by the method of *Lüttringhaus* and *Simon* [12] in

[1] Part of the Habilitation Thesis of *G. Schill*, communicated in part at the Conference of University Chemistry Teachers at Freiburg/Brsg. on April 28th, 1964.

[2] *A. Lüttringhaus*, *F. Cramer*, *H. Prinzbach*, and *F. M. Henglein*, Liebigs Ann. Chem. *613*, 185 (1958).

[3] *G. Schill*, Ph. D. Thesis, Universität Freiburg 1959; further work with *H. Preugschas*, *J. Winterhalter*, and *R. Vollrath*, unpublished.

[4] *E. Wasserman*, J. Amer. chem. Soc. *82*, 4433 (1960).

[5] *E. Wasserman*, Sci. American *207*, No. 5, 94 (1962).

[6] *J. Koetschet* and *P. Koetschet*, Helv. chim. Acta *13*, 482 (1930); *C. Favre*, ibid. *36*, 712 (1953).

[7] *L. D. Bergelson* and *M. M. Schemjakin*, Angew. Chem. *76*, 113 (1964); Angew. Chem. internat. Edit. *3*, 250 (1964).

[8] *Huang-Minlon*, J. Amer. chem. Soc. *68*, 2487 (1946).

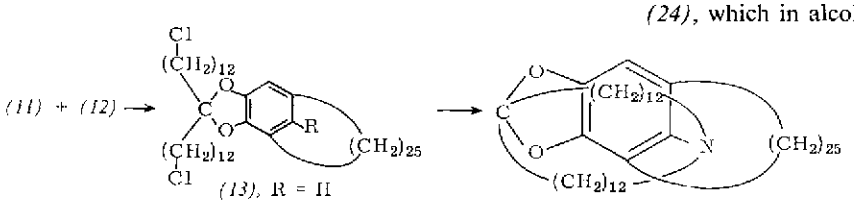
[9] *J. C. Sauer*, J. Amer. chem. Soc. *69*, 2444 (1947).

[10] *E. J. Salmi*, Ber. dtsch. chem. Ges. *71*, 1803 (1938).

[11] *J. B. Menke*, Rec. Trav. Chim. Pays-Bas *44*, 146, 269 (1925).

[12] *A. Lüttringhaus* and *H. Simon*, Liebigs Ann. Chem. *557*, 120 (1947).

the presence of alkali iodide gave a 29.7 % yield [based on *(14)*] of crystalline 2,2,*N*,*N*-bisdodecamethylene-4,6-pentacosamethylene-5-amino-1,3-benzo[*d*]dioxole *(16)*, m.p. 121–125 °C, which is linked intra-annularly and in which the chains of the double ansa-system are situated on opposite sides of the benzene ring.

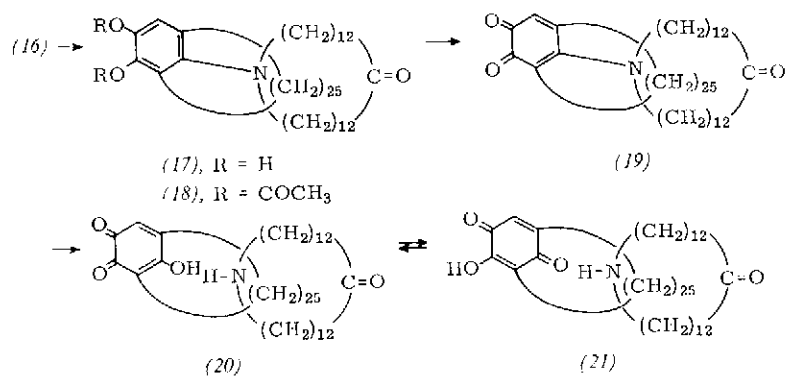


*(13)*, R = H
*(14)*, R = $NO_2$
*(15)*, R = $NH_2$

*(16)*

Formation of the isomer of *(16)* with extra-annular attachment of the rings (both chains of the double ansa-system on the same side of the benzene ring) can be excluded. In *(13)*, the chain derived from *(12)* which becomes attached to the benzene ring is fixed at right angles to the plane of the ring on account of the tetrahedral structure of the aliphatic carbon. The side reaction which would lead to an isomer of *(16)* is suppressed for this reason and on account of the chain-length of 12 methylene groups.

Cleavage of the ketal linkage in *(16)* with HBr in acetic acid gave the intra-annularly linked catechol derivative *(17)* which was characterized as its crystalline diacetate *(18)*, m.p. 104–106 °C. Dehydrogenation of *(17)* with ferric sulfate gave the amino-*o*-quinone *(19)*. Hydrolysis of *(19)* with acid afforded the desired catena compound *(20)*, which rearranged to the tautomer *(21)*. The reactions leading from *(16)* to *(21)* are nearly quantitative.



*(17)*, R = H
*(18)*, R = $COCH_3$

*(19)*

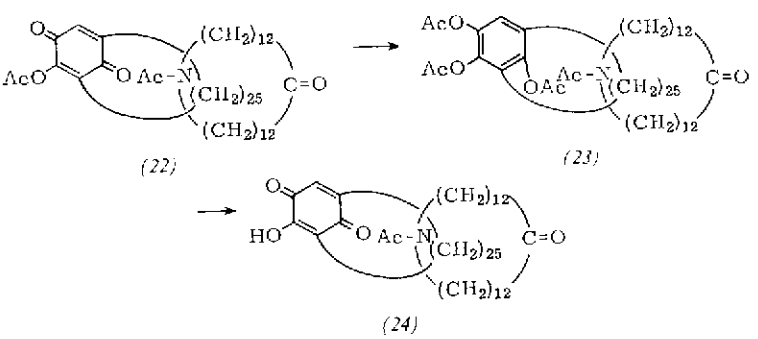
*(20)*

*(21)*

Acetylation of *(21)* with acetic anhydride/sodium acetate gave the *O*,*N*-diacetate *(22)*, which was characterized by analysis and its infrared spectrum, which showed the carbonyl band of the *O*-acetyl group at 1779 $cm^{-1}$, that of the keto group at 1717 $cm^{-1}$, and the coinciding carbonyl bands of the quinone and of the *N*-acetyl group at approximately 1650 $cm^{-1}$.

Reductive acetylation of *(22)* gave the tetraacetate *(23)* which was also identified by analysis and infrared spectroscopy. It showed the band of the *O*-acetyl group at 1786 $cm^{-1}$, that of the keto group at 1715 $cm^{-1}$, and that of the *N*-acetyl group at 1650 $cm^{-1}$. Molecular-weight determination by isothermal distillation [13] gave the figures 960 and 995, which are in good agreement with the value of 1022.5, calculated for the combined weight of the two chemically unconnected parts of the molecule.

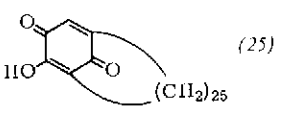
Alkaline hydrolysis of the tetraacetate *(23)* followed by dehydrogenation yielded the *catena*-hydroxy-*p*-quinone *(24)*, which in alcoholic solution gave alkali salts with the mauve color characteristic of 2-hydroxy-3,5-dialkylbenzoquinones [14]. C, H, and N determinations of *(24)* gave the expected values; its infrared spectrum showed the expected carbonyl bands. The ultraviolet spectrum of *(24)* had maxima ($\lambda_{max}$ = 266 mμ, log ε = 3.97; 406 mμ, log ε = 2.87 in alcohol) similar to those of the "simple" hydroxyquinone *(25)*,



*(22)*

*(23)*

*(24)*



*(25)*

m.p. 64–67 °C ($\lambda_{max}$ = 269 mμ, log ε = 4.02; 413 mμ, log ε = 2.90 in alcohol).

The catena compound *(24)* was homogeneous on paper chromatograms, except for a very small amount of impurity which remained at the start. The hydroxyquinone *(25)*, which would have been formed from the isomer of *(16)* with extra-annular linking of the rings during the reaction sequence quoted, could not be detected.

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German version: Angew. Chem. 76, 567 (1964)

[13] *H. Hoyer*, Angew. Chem. *73*, 465 (1961).
[14] *W. Flaig* and *J. C. Saalfeld*, Liebigs Ann. Chem. *618*, 117 (1958).

# The Modes of Reaction of Ambident Cations

BY PROF. DR. S. HÜNIG

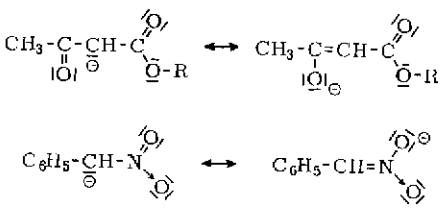
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*Dedicated in gratitude and admiration to Prof. Hans Meerwein on the occasion of his 85th birthday*

*The effect of the nature of the coreactants and the reaction conditions on the ability of certain mesomeric cations to react with nucleophilic reagents to form isomeric products has been studied. The structures of the products isolated are determined by competition between a kinetically controlled but reversible reaction and a thermodynamically controlled reaction.*

## 1. Comparison of Ambident Anions and Cations

The mesomeric anions derived from β-dicarbonyl compounds and nitroalkanes, *e.g. (1)* and *(2)*, can react with electrophiles at either the oxygen or the carbon atom.



*(1)*



*(2)*

This ambident character [1] is of great significance from both the preparative [2] and theoretical [3] points of view. Systematic investigations carried out over the past few years have revealed that the relative proportions of products resulting from the two possible reaction paths depend on numerous, frequently still unclarified factors. One of the principal difficulties encountered in their elucidation is that the electrophilic partner of these anions becomes available as a free cation only in the case of the solvated proton, with which the anion simply undergoes association. All other reagents (*e.g.* methyl iodide) must react by substitution. Consequently, the result of the reaction is governed in a complicated manner by both the ambident anion and the electrophilic reagent. In addition, the cation associated with the anion frequently exerts a decisive effect [4], which is also dependent upon the solvent used.

The reaction between ambident cations and nucleophilic reagents might be expected to proceed in a more straightforward manner. In the following, such cations will comprise mainly types *(3)* and *(4)*, derived from amides and esters of carboxylic acids.

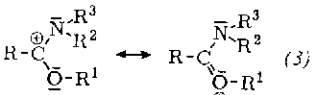
[1] *N. Kornblum* et al., J. Amer. chem. Soc. *77*, 6269 (1955).

[2] Cf., for example, *H. Henecka:* Chemie der β-Dicarbonylverbindungen. Springer, Berlin 1950.

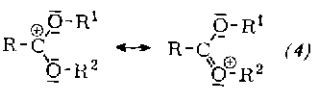
[3] Cf., for example, *J. Hine:* Physical Organic Chemistry. McGraw-Hill, New York 1962, pp. 233–244.

[4] *N. Kornblum* and *P. Pink*, Tetrahedron Letters *1963*, Suppl. I, 17; *H. E. Zaugg* et al., J. org. Chemistry *26*, 644 (1961); β-Diketones: *H. Stetter*, Angew. Chem. *67*, 769 (1955).

Even when they are strongly electrophilic, these cations can be conveniently isolated if the anions are stable complexes (*e.g.* $BF_4^{\ominus}$, $SbCl_6^{\ominus}$, or $ClO_4^{\ominus}$) and if the solvent is only slightly nucleophilic (*e.g.* $CH_2Cl_2$). This principle was developed and used with great success by *Meerwein* [5], and has been employed for the preparation of most of the complex cations described here.



*(3)*



*(4)*

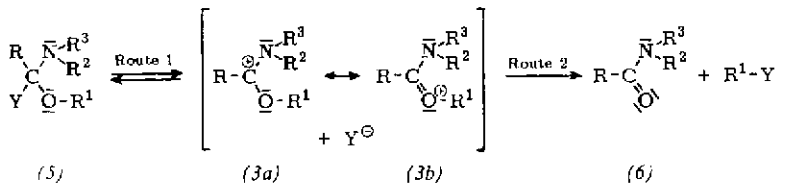
Numerous anions may be used as the attacking nucleophile (*e.g.* $Cl^{\ominus}$, $C_2H_5O^{\ominus}$), but uncharged bases can also be used (*e.g.* $C_2H_5OH$, $HNR_2$). These entities can attack *(3)* or *(4)* at two points (see below). The reaction invariably begins with an addition to the lone pair of electrons on the nucleophile. The influence of the nucleophile on the formation of products with ambident cations should therefore be more straightforward than that of an electrophile with ambident anions. Since the effect due to the complex anion can be neglected, it should be possible to recognize the factors which essentially govern the result of the reaction.

## 2. General Reaction Scheme

The ambident cation *(3)* is used as an illustration, since the reactions with *(4)* proceed in an analogous manner. The nucleophile $Y^{\ominus}$ rapidly adds on at the position of lowest electron density, *i.e.* at the carbon atom in *(3)*, to form *(5)* (Route 1). If the energy released on formation of the new bond is large, *(5)* can be considered as a kinetically controlled product. On the other hand, if an equilibrium *(5)* ⇌ *(3)* is set up, then $Y^{\ominus}$ effects slow dealkylation of *(3)* (Route 2) to form the thermodynamically stable compound *(6)* and $R^1$–Y [6].

[5] *H. Meerwein* et al., Angew. Chem. *67*, 374 (1955).

[6] Cf., for example, analogous considerations by *S. Winstein* and *E. M. Kosower*, J. Amer. chem. Soc. *81*, 4399 (1959); *J. Miller*, J. Amer. chem. Soc. *85*, 1628 (1963).



(5) (3a) (3b) (6)

The relative importance of reaction routes 1 and 2 is essentially dependent on
the nature of the nucleophilic reagent,
the stability of the ambident cation,
the temperature and duration of the reaction, and
the solvent.

These factors influence the energy profile of the overall reaction (Fig. 1) [6]:

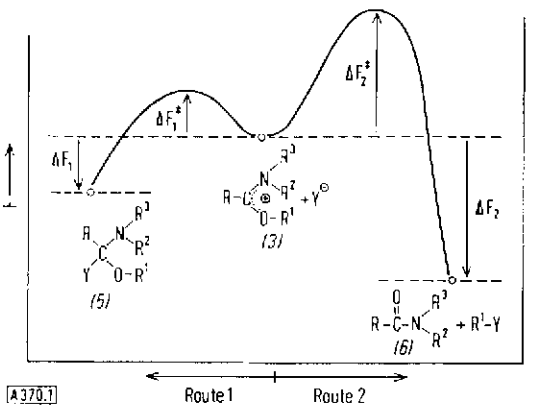



Fig. 1. General energy profile of the system (5) ⇄ (3) → (6); schematic.

a) The primary ratio of the reaction products from (3) is mainly determined by the ratio of the free activation energies $\Delta F_1^{+}$ and $\Delta F_2^{+}$ associated with Routes 1 and 2. Since only Route 1 corresponds to a simple association of ions, $\Delta F_1^{+}$ is always less than $\Delta F_2^{+}$. Moreover, it may be assumed that $\Delta F_1^{+}$ is small, and variations in the ratio $\Delta F_1^{+}/\Delta F_2^{+}$ due to changes in the reaction conditions and the nature of the nucleophile can, to a first approximation, be ignored, except for steric factors.

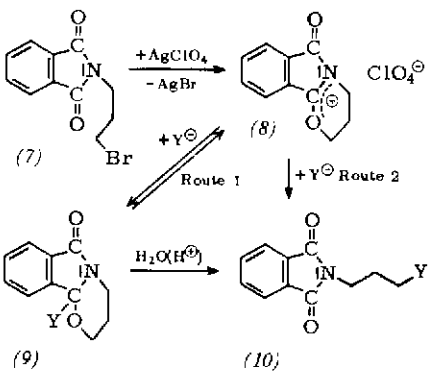
b) The position of the equilibrium between (3) and (5) in Route 1 depends on the difference in energy $\Delta F_1$ between (3) and (5), *i.e.* on their relative positions in the energy diagram.

c) Since the transformation (3) → (6) results in release of the mesomeric energy of the amide as well as the energy of charge neutralization, (6) must be the thermodynamically stable product, *i.e.* $\Delta F_2 > \Delta F_1$. Both $\Delta F_2$ and $\Delta F_2^{+}$ may assumed to be so large that the reaction (3) → (6) can be regarded as irreversible. The energy profile shown in Figure 1 is repeated in subsequent illustrations in order to show the changes more clearly.

## 3. The Influence of the Nucleophile on the Course of the Reaction

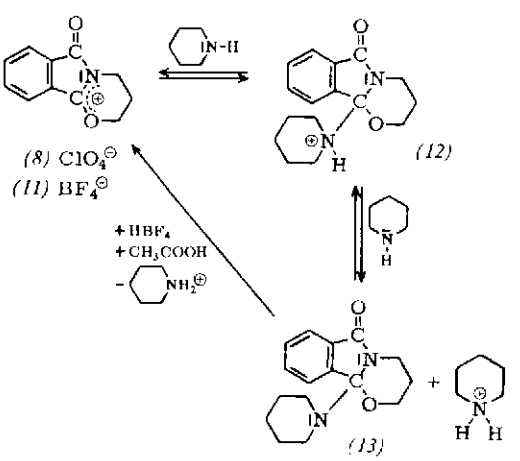
So far, investigations into the above factors have involved exclusively the nature of the nucleophilic reagent.

A compound particularly suitable for study is the strong electrophile *N,O*-trimethylenephthalimidium perchlorate (8), which is formed smoothly from (7) and silver perchlorate [7].




| | Route 1 | Route 2 |
|---|---|---|
| $Y = O_2N{-}CH_2^{\ominus}$ | Piperidine | Pyridine |
| $CN^{\ominus}$ | $C_2H_5OH$ | $I^{\ominus}$ |
| $C_2H_5O^{\ominus}$ | $H_2O$ | $C_6H_5SO_2^{\ominus}$ |

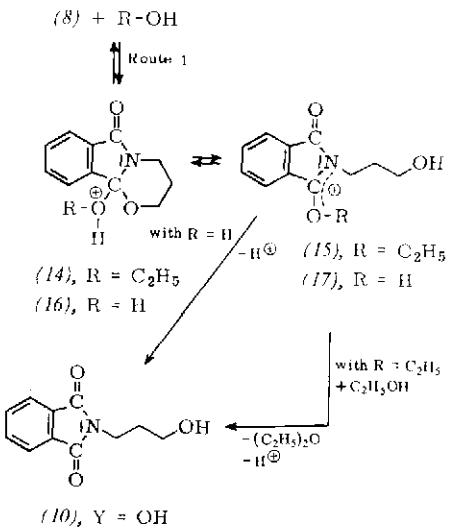
This energy-rich tricyclic compound (8) reacts with nucleophiles to form (9) or (10) according to whether Route 1 or Route 2 is followed. The differences in the infrared and ultraviolet spectra of the two products permit unambiguous assignment of their structures [7]. Whereas the phthalimide derivative (10) represents the stable end-product, the adducts (9) are readily hydrolysed to form γ-hydroxypropylphthalimide (10), Y = OH. The reactions of (8) with piperidine, ethanol, and water occupy a special position, since here the adduct (9) can be formed only by release of a proton. The synthesis of (13) therefore requires the use of excess piperidine. Water rapidly transforms (13) into γ-hydroxypropylphthalimide (10), Y = OH. Undoubtedly, the first step of the reaction entails protonation of the base (13) to




[7] *L. Geldern*, Ph. D. Thesis, Universität Marburg, 1962; *S. Hünig* and *L. Geldern*, J. prakt. Chem., in the press.

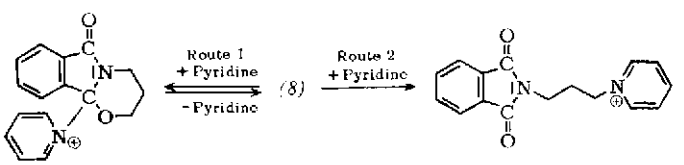
give *(12)*, which is in equilibrium with the ambident cation *(8)*. The rapid hydrolysis of the latter to form γ-hydroxypropylphthalimide has already been mentioned. Exclusion of a nucleophilic solvent should prevent this last step. The fluoroborate *(11)* of the ambident cation can in fact be obtained from *(13)* and excess fluoroboric acid in glacial acetic acid, *i.e.* the reaction sequence *(8)* → *(12)* → *(13)* can be completely reversed.

The reaction of the cation *(8)* with alcohol also leads to γ-hydroxypropylphthalimide *(10)*, Y = OH, when water is carefully excluded; diethyl ether is formed at the same time. This result excludes Route 2. Instead, Route 1 must result in the formation of adduct *(14)*, which undergoes prototropy to form *(15)*, an open-chain,




ambident phthalimidium cation. This substance is then dealkylated by excess ethanol to form *(10)* and diethyl ether, by analogy with Route 2. Water probably reacts in the same way with the ambident cation *(8)* by Route 1 [*(8)* → *(16)* → *(17)* → *(10)*]. Although this problem can be resolved only by the use of $H_2{}^{18}O$, findings with related cations support this course of reaction [*(21)* → *(20)*; *(71)* → *(76)*].

No similar stabilization of the adduct formed by Route 1 occurs during the reaction of *(8)* with pyridine. Here, the adduct *(18)*, which has not been isolated, is still positively charged. The small gain in bonding energy rapidly drives the reaction forward with formation, via *(8)*, of the more stable phthalimide derivative *(19)*.




In the case of the iodide ion, which is a good leaving group [8], it is doubtful whether the reaction with *(8)* results in formation of a covalent bond in the sense of *(9)* at all. When the components are mixed in acetonitrile, an intense red color develops, similar to that of

[8] *J. Mathieu, A. Allais*, and *J. Valls*, Angew. Chem. *72*, 71 (1960).

quaternary, aromatic-heterocyclic iodides [9]. Thus, at least an internal ion pair associated with a charge-transfer band [10] is initially formed. Since the solution is almost instantaneously decolorized again, only the γ-iodopropylphthalimide *(10)*, Y = I, formed by Route 2, can be isolated.

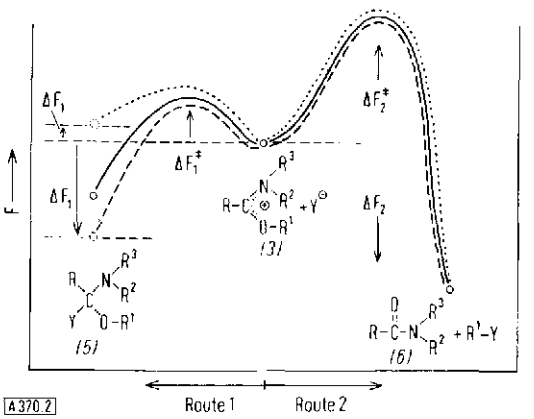
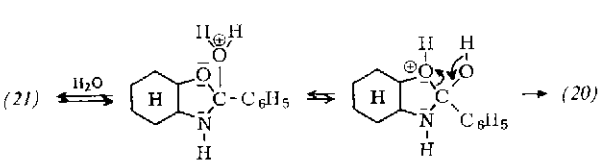



Fig. 2. The influence of the nucleophile on the position of *(5)* in the energy profile (schematic).
..... Y = *e.g.* $I^{\ominus}$
----- Y = *e.g.* $CN^{\ominus}$
——— General curve (cf. Fig. 1).

These examples show that the effect of the nucleophile on the course of the reaction depends predominantly on the position of *(5)* in the energy diagram, *i.e.* on the magnitude of $\Delta F_1$ (Fig. 2). Since the small free activation energy $\Delta F_1{}^{+}$ changes only slightly with the nature of the nucleophile, the product formed by Route 1 can be isolated only for low energy levels of *(5)*, *i.e.* for large values of $\Delta F_1$. Naturally, the nucleophile also produces changes in $\Delta F_2{}^{+}$ and $\Delta F_2$, but to a first approximation this effect can be neglected.

The same reasoning may explain the similar behavior of nucleophilic reagents towards a large number of ambident cations. Table 1 contains characteristic examples; only ambident cations which have been isolated are listed. The arrows show the possible points of attack for reactions by Routes 1 and 2, while the outer columns contain the products isolated.

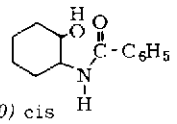
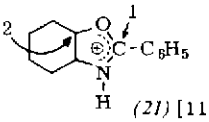
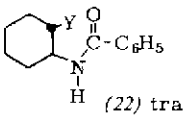
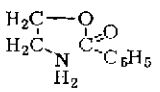
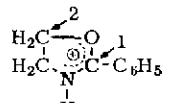
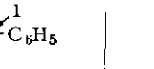
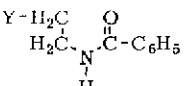
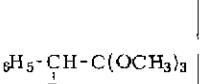
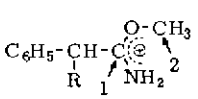
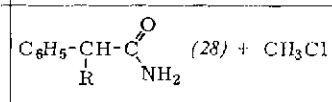
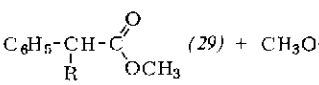
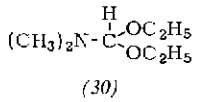
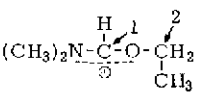
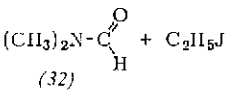
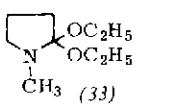
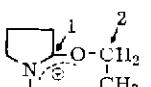
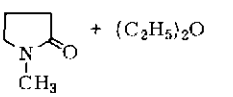
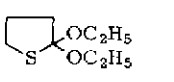
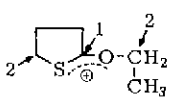
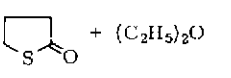
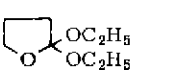
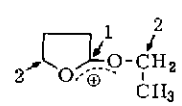
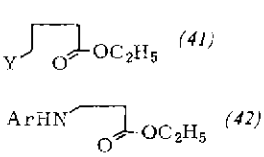
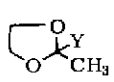
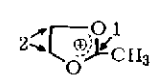
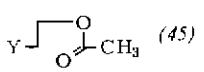
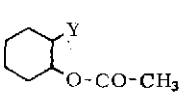
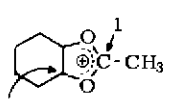
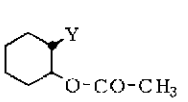
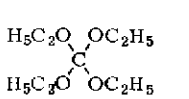
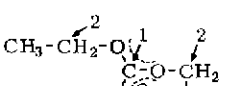
Examination of Table 1 reveals that here again the kinetically controlled products of Route 1 can be isolated only where strongly nucleophilic reagents such as $C_2H_5O^{\ominus}$ and $CN^{\ominus}$ are used. The only exception is that of $H_2O$ in *(21)*. Here the stereochemistry of the product *(20)* shows that the cleavage of the ring is introduced by the conversion of the kinetic adduct *(51)* into *(52)* by prototropy [11].




[9] *H. Decker*, Ber. dtsch. chem. Ges. *37*, 2938 (1904); *A. Hantzsch*, ibid. *28*, 683 (1895); *E. M. Kosower*, J. Amer. chem. Soc. *80*, 3253 (1958).

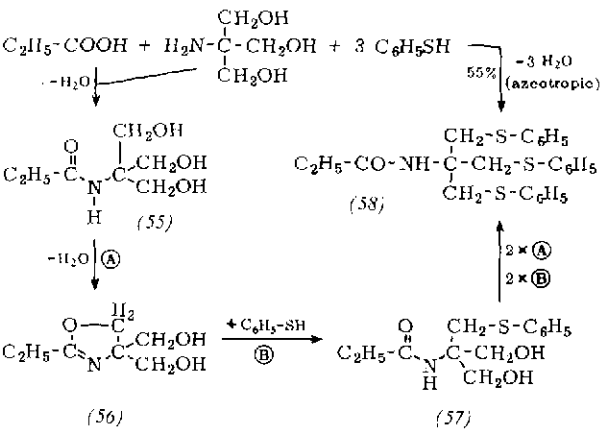
[10] Cf. *G. Briegleb:* Elektronen-Donator-Acceptor-Komplexe. Springer, Berlin 1961, p. 4.

Table 1. Products of the reaction of ambident cations with nucleophilic reagents.

| Route 1 | Nucleophile Y | Ambident Cation | Nucleophile Y | Route 2 |
|---|---|---|---|---|
|  *(20)* cis | $H_2O$ |  *(21)* [11] | $CH_3COO^{\ominus}$<br>$Tos^{\ominus}$<br>$Cl^{\ominus}$ |  *(22)* trans |
|  *(23)* | $H_2O$ [12]<br>$(OH^{\ominus})$ |  *(24)* | $HCl/C_2H_5OH$ [12]<br>  [13]<br>$p\text{-}NO_2\text{-}C_6H_4\text{-}COO^{\ominus}$ [13] |  *(25)* |
|  *(26)* | $CH_3OH$ |  *(27)* [14] | $Cl^{\ominus}$<br>$CH_3OH$ |  *(28)* + $CH_3Cl$<br>  *(29)* + $CH_3OCH_3$ |
|  *(30)* | $C_2H_5O^{\ominus}$ |  *(31)* [15] | $I^{\ominus}$ |  *(32)* + $C_2H_5J$ |
|  *(33)* | $C_2H_5O^{\ominus}$ |  *(34)* [16] | $C_2H_5OH$ |  *(35)* |
|  *(36)* | $C_2H_5O^{\ominus}$ |  *(37)* [16] | $C_2H_5OH$ |  *(38)* |
|  *(39)* | $C_2H_5O^{\ominus}$<br>$C_2H_5OH$<br>$NR_3$ |  *(40)* [16, 17] | $C_2H_5OH$<br>$Cl^{\ominus}$; $Br^{\ominus}$<br>$I^{\ominus}$; $CH_3COO^{\ominus}$<br>$C_6H_5O^{\ominus}$; $ArNH_2$ |  *(41)*, *(42)* |
|  *(43)* | $C_2H_5O^{\ominus}$<br>$CN^{\ominus}$ |  *(44)* [13] | $Cl^{\ominus}$; $Br^{\ominus}$; $I^{\ominus}$<br>$C_2H_5OH$; $H_2O$<br>$(CH_3)_3N$ |  *(45)* |
|  *(46)* cis | $CH_3COOH$<br>$H_2O$ |  *(47)* [19] | $CH_3COO^{\ominus}$<br>$Tos^{\ominus}$<br>$Cl^{\ominus}$; $Br^{\ominus}$ |  *(48)* trans |
|  *(49)* | $C_2H_5O^{\ominus}$ |  *(50)* | | |

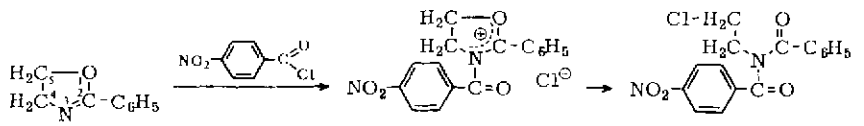
Results obtained with *N*-alkyloxazolinium salts have shown that the hydrolysis of oxazolines to esters of aminoethanol [*(24)* → *(23)*] can be interpreted as proceeding by Route 1 [20]. Thus it is doubtful whether the hydrolytic cleavage of the ion *(44)* to form *(45)* [18] proceeds by Route 2.

The ambident character of the oxazolinium ions was observed by *Gabriel* and *Heymann* [12] as long ago as 1890. An explanation for this repeatedly confirmed behavior [21] was first given by *Fry* [13] in 1950 when he postulated a reversible nucleophilic attack at C-2 and an irreversible attack at C-5, but made no comment on the nature of the nucleophilic reagent. The opening of the 2-phenyloxazoline ring by acid chlorides was explained in the same way, the intermediate ion, *e.g. (53)*, which resembles the phthalimidium ion *(8)*, reacting by Route 2, *e.g.* to form *(54)* [14]. The attack of thiocarboxylic acids [22] [*(24)* → *(25)*] can be used in the synthesis of optically active cysteine starting from optically active 5-carboxy-2-phenyloxazoline [23]. Since



*(55)* *(58)* *(56)* *(57)*

factory yields are often obtained during the preparation of orthoesters [14] from imino ether hydrochlorides and alcohols by the method of *Pinner* [25]. This reaction is

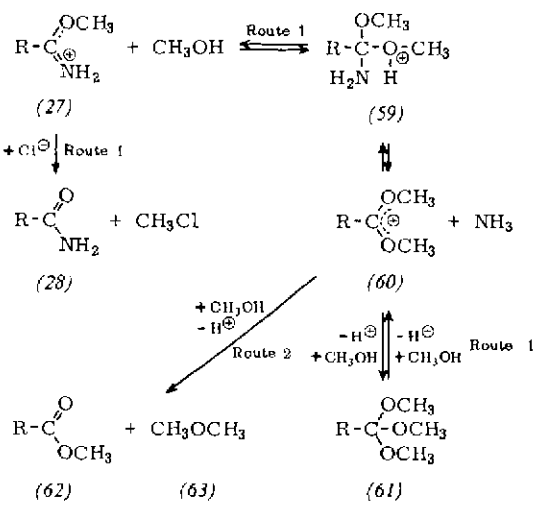


*(53)* *(54)*

thiophenols also open the oxazoline ring at the bond between O-1 and C-5 [24a], β-acylaminothioaryl ethers, *e.g. (58)*, can be obtained from carboxylic acids, β-amino alcohols, and thiophenols in a single-stage synthesis [24b].

The amide *(55)* initially formed undergoes ring closure to form the basic oxazoline *(56)* which then reacts as a cation with the thiophenoxide ion to form the thioether *(57)*. The steps A + B twice repeated finally lead to the product *(58)*.

Oxazolines may be regarded as cyclic imino ethers; accordingly the cations of imino ethers also exhibit ambident characteristics and it is not surprising that unsatisfactory yields are often obtained during the preparation of orthoesters [14] from imino ether hydrochlorides and alcohols by the method of *Pinner* [25]. This reaction is always accompanied by the well-known Pinner cleavage [26], which proceeds by Route 2 to form an amide and an alkyl chloride [*(27)* → *(28)*]. The primary adduct *(59)* formed by Route 1 is stabilized in the form of the ambident carboxonium ion *(60)*.



*(27)* *(59)* *(28)* *(60)* *(62)* *(63)* *(61)*

In the presence of ammonia as a base, it is possible to isolate the orthoester *(61)* as the kinetically controlled product from the reaction with alcohol. However, the ammonium ion formed catalyses the attainment of the equilibrium *(61)* ⇌ *(60)* so strongly that the concurrent reaction to form the thermodynamically stable products, *viz.* the carboxylic ester *(62)* and the ether *(63)*, cannot be prevented. This hypothesis is based on

[11] *S. Winstein* and *R. Boschan*, J. Amer. chem. Soc. *72*, 4669 (1950).

[12] *S. Gabriel* and *Th. Heymann*, Ber. dtsch. chem. Ges. *23*, 2495 (1890); *A. A. Goldberg* and *W. Kelly*, J. chem. Soc. (London) *1948*, 1919.

[13] *E. M. Fry*, J. org. Chemistry *15*, 802 (1950).

[14] Cf. *S. M. McElvain* and *B. E. Tate*, J. Amer. chem. Soc. *73*, 2233 (1951).

[15] *H. Meerwein*, *W. Florian*, *N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[16] *H. Meerwein*, *P. Borner*, *O. Fuchs*, *H. J. Sasse*, *H. Schrodt*, and *J. Spille*, Chem. Ber. *89*, 2060 (1956).

[17] *K. Wunderlich*, Ph. D. Thesis, Universität Marburg, 1957.

[18] *H. Meerwein*, *K. Bodenbenner*, *P. Borner*, *F. Kunert*, and *K. Wunderlich*, Liebigs Ann. Chem. *632*, 38 (1960).

[19] *C. B. Anderson*, *E. C. Friedrich*, and *S. Winstein*, Tetrahedron Letters *1963*, 2037.

[20] *P. Allen, Jr.* and *J. Ginos*, J. org. Chemistry *28*, 2759 (1963); see this publication for further references regarding hydrolysis of oxazolines and *O,N*-acyl migration in 2-amino alcohols.

[21] Cf., for example, *N. J. Leonard*, *K. Conrow*, and *R. R. Sauers*, J. Amer. chem. Soc. *80*, 5185 (1958); *H. W. Heine*, J. Amer. chem. Soc. *79*, 907 (1957).

[22] *M. Svoboda*, *J. Silcher*, *J. Farkas*, and *M. Pankova*, Chem. Listy *49*, 135 (1955); *J. M. Nys* and *M. J. Libeer*, US.-Pat. 2823207 (1958).

[23] *E. M. Fry*, J. org. Chemistry *15*, 438 (1950).

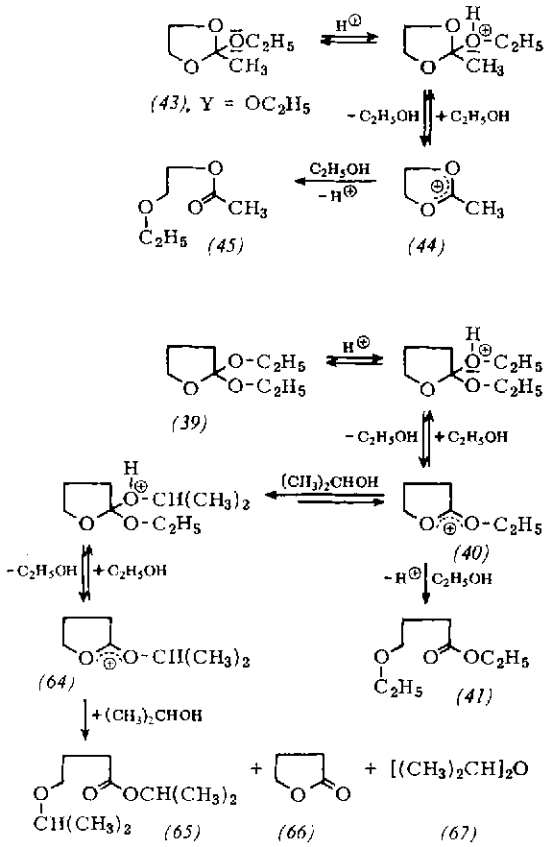
[24] *H. L. Wehrmeister*, J. org. Chemistry *28*, 2587, 2589 (1963).

[25] Cf. *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., Thieme, Stuttgart 1952, Vol. VIII, p. 539.

[26] See [25], p. 700, and [14]. – This reaction is suitable for the direct preparation of labile alkyl chlorides from imide chlorides and alcohols; *H. Eilingsfeld*, *M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960); Chem. Ber. *96*, 2671 (1963).

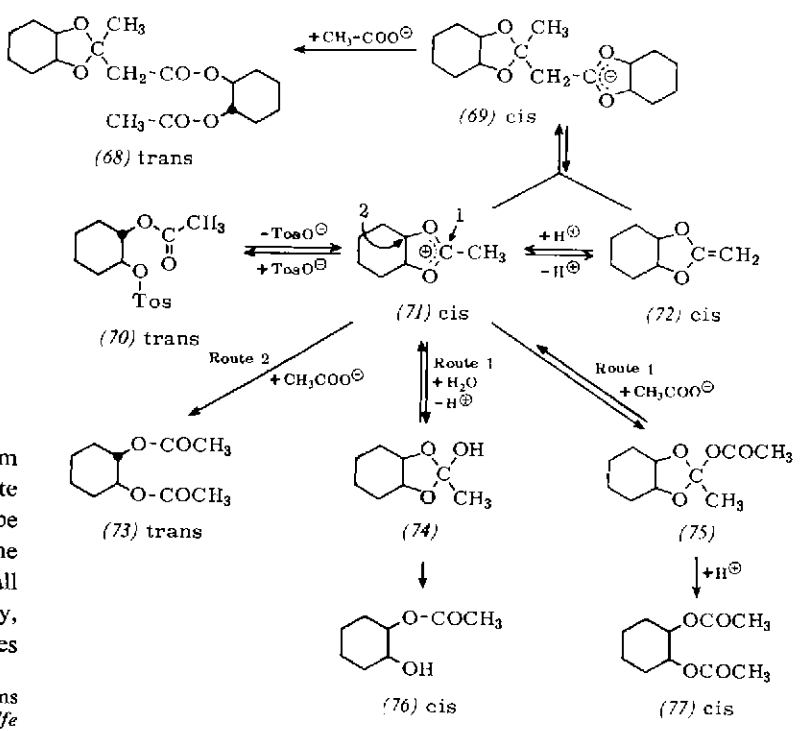
the argument advanced by *McElvain* [28] and was confirmed by investigations carried out by *Meerwein* (see below).

Apart from the hydrolysis products *(20)* and *(23)*, so far only thermodynamically controlled products, *e.g.* *(22)*, *(25)*, *(28)*, *(29)*, *(54)*, and *(58)*, have been isolated from reactions involving ambident cations, *e.g.* *(21)*, *(24)*, and *(27)*. Synthesis of peralkylated imino ether cations, *e.g.* *(31)* and *(34)*, finally enabled *Meerwein* et al. [17, 18] to isolate highly reactive amide acetals *(30)* and lactam acetals *(33)* as the kinetically controlled products obtained by Route 1 from the reaction with alkoxide [29]. As expected, the analogous thiocarboxonium salts [16–18], *e.g.* *(37)* or *(40)*, *(44)*, *(47)*, *(50)*,



are converted into orthoesters. While with the lactam acetals the reversible character of the reaction by Route 1 is apparent from the low conductivity [16], it can be detected with the orthoesters *(39)* and *(43)* by the irreversible rearrangement induced by acid or small quantities of boron trifluoride [16, 18]. Undoubtedly, the cations *(40)* and *(44)* are formed as intermediates en route to the alkoxycarboxylates *(41)* and *(45)*. This is confirmed by the rapid interchange of the alkoxy groups; for example, the difficultly soluble fluoroborate of the cation *(64)* can be isolated with isopropanol, being then "dealkylated" by Route 2 to form *(65)*, *(66)*, and *(67)*. The assumption of a reversible and an irreversible mode of reaction with nucleophiles, which has particularly been emphasized by *Meerwein* [16], simultaneously explains the long-known decomposition of orthoesters into esters and ethers [27] [cf. *(61)* → *(62)* and *(63)*]. The cations *(34)*, *(37)*, and *(40)* show the effect of the hetero-atom. Only in the last case is the five-membered ring opened with ethanol, but even here, as with *(64)*, a side-reaction involving substitution of the side-chain, *i.e.* the formation of butyrolactone and diethyl ether, must be assumed.

The isolation of carboxonium ions of this type supports the views of *Winstein* and *Boschan* [11], who postulated the existence of the intermediate ion *(71)* from the stereochemistry of the solvolysis of *(70)* in acetic acid/water with formation of *(73)* and *(76)*. The kinetically controlled adduct *(75)* expected in acetic acid cannot be isolated in the reaction between the ketene acetal *(72)* and glacial acetic acid [30]. Nevertheless, it must be present in equilibrium, since in the presence of a strong acid it is possible to isolate the *cis*-diacetate *(77)*, the formation of which can be attributed to an acid-catalysed rearrangement of *(75)* [11]. The cation *(71)*, recently isolated as the fluoroborate by the same group of workers [19], does in fact exhibit the expected properties. Furthermore, it was found that *(71)* reacts with acetate ions in glacial acetic acid to form about 50 % of the dimer *(68)*.



Evidently, *(71)* has been partly deprotonated to form the ketene acetal *(72)*, which then undergoes nucleophilic addition onto excess *(71)* to form *(69)*. Finally, *(68)* is formed from *(69)* and acetate.

Similarly, the ambident cation *(80)* must be assumed to be an intermediate in the solvolysis of the isomeric *p*-toluene-

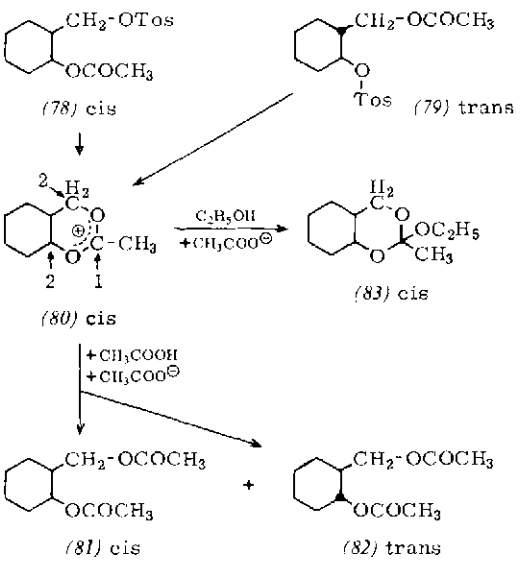
[27] The fast, acid-catalysed hydrolysis of orthoesters also gains from the formation of the carboxonium ion. Cf. *R. H. DeWolfe* and *J. L. Jensen*, J. Amer. chem. Soc. *85*, 3264 (1963). – According to *J. Hine*, J. Amer. chem. Soc. *85*, 3239 (1963), the behavior of acetals and orthoesters is determined by an increase in the heat of formation through double-bond no-bond resonance.

[28] *S. M. McElvain* and *C. L. Stevens*, J. Amer. chem. Soc. *69*, 2663 (1947).

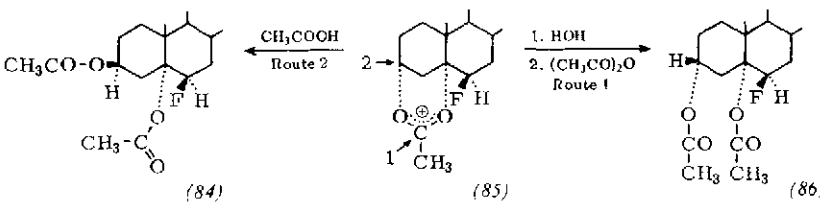
[29] *N,N*-Dialkylamide acetals from imide chlorides: Cf. *H. Eilingsfeld*, *M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960); Chem. Ber. *96*, 2671 (1963); *Z. Arnold*, Collect. czechoslov. chem. Commun. *26*, 723 (1961); *H. H. Bossard*, *E. Jenny*, and *H. Zollinger*, Helv. chim. Acta *44*, 1204 (1961).

[30] This presumably explains the basic properties of orthoesters in the presence of acetic anhydride, which were observed by *F. Kröhnke* and *W. Weiß*, Liebigs Ann. Chem. *669*, 52 (1963).

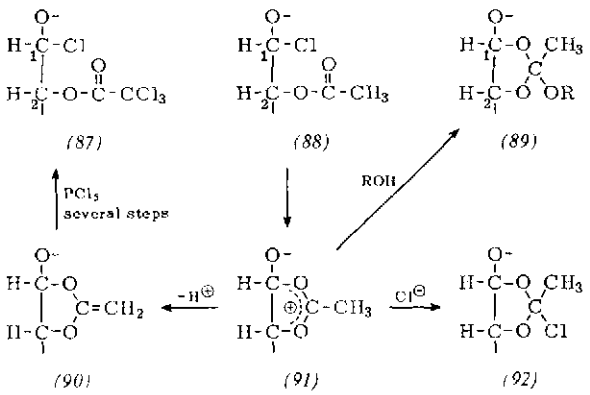
sulfonates *(78)* and *(79)* [31]. Ethanolysis in the presence of sodium acetate therefore stops at the labile orthoester stage (Route 1). In glacial acetic acid/sodium acetate, on the other hand, a mixture of the stable diacetates *(81)* and *(82)*, formed by Route 2, is isolated.



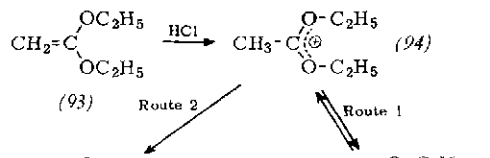

Carboxonium ions and products therefrom can be expected to be formed during the acylation of 1,2- and 1,3-glycols. Thus, the ambident cation *(85)* was recently isolated in the cholestane series. This reacts with acetic acid to form the 3β,5α-di-*O*-acetate *(84)*, while hydrolysis and subsequent esterification produce the isomeric 3α,5α-diacetoxy derivative *(8b)* [32].

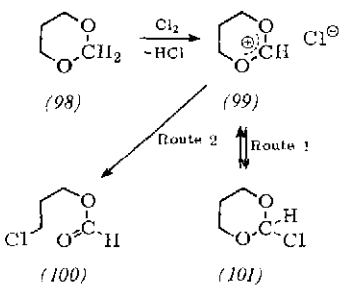



The results of this mode of reaction have been known much longer in the chemistry of carbohydrates [33]. Here, extra isomers were observed during the normal synthesis of glycosides from peracetylated α-halogeno sugars *(88)*, silver carbonate and an alcohol; as early as 1930, these were recognized by *Freudenberg* [34] as orthoesters *(89)*. This author even succeeded in isolating the extremely reactive isomeric hepta-*O*-acetyl-α-maltosyl chloride containing the grouping *(92)*. It is not known why the orthoester chloride can be isolated in this particular case [35]. *Freudenberg* considered the possibility of intermediate formation of ketene acetals *(90)*, which could serve as the preliminary stage in the formation of 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl chloride from penta-*O*-acetylglucose and phosphorus pentachloride [36], for it is otherwise difficult to explain.




Since halide ion is a better leaving group than acetate, reactions in which α-halogeno-α,α-dialkoxy compounds, *e.g. (97)*, *(101)*, *(105)*, should normally lead to the thermodynamically stable products via the intermediate carboxonium ion *(94)*, *(99)*, *(103)*. This is true of the addition of HCl onto ketene acetals, *e.g. (93)* → *(95)* + *(96)* [37], and also for the halogenation of acetals, *e.g. (98)* → *(100)* [38]. The suggested course




[31] *Ö. Kovács, G. Schneider*, and *L. K. Láng*, Proc. chem. Soc. (London) *1963*, 374; *L. J. Dolby, C. N. Lieske, D. R. Rosencrantz*, and *M. J. Schwarz*, J. Amer. chem. Soc. *85*, 47 (1963).

[32] *I. W. Blunt, M. P. Hartshorn*, and *D. N. Kiok*, Chem. and Ind. *1963*, 1955. The fluorine-free carboxonium ion had been postulated earlier: *P. A. Plattner* and *W. Lang*, Helv. chim. Acta *27*, 1872 (1944); *P. A. Plattner, A. Fürst, F. Koller*, and *W. Lang*, ibid. *31*, 1455 (1948).

[33] Cf. *E. Pascu*, Advances Carbohydrate Chem. *1*, 77 (1945); *R. V. Lemieux*, ibid. *9*, 1 (1954); *L. J. Haynes* and *F. H. Newth*, ibid. *10*, 207 (1955).

[34] *K. Freudenberg* and *H. Scholz*, Ber. dtsch. chem. Ges. *63*, 1969 (1930).

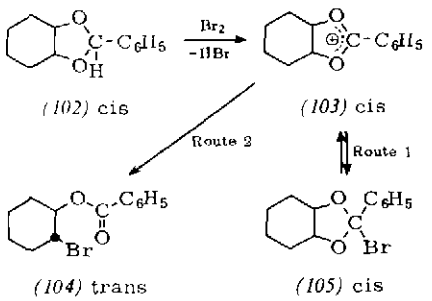
[35] According to *B. Helferich* and *H. Jochinke*, Ber. dtsch. chem. Ges. *74*, 719 (1941), the analogous 2,5,6-tri-*O*-acetyl-3-*O*-mesyl-α-D-glucosyl bromide exists. In view of the low reactivity, however, it seems doubtful whether this compound really has the structure of an orthoester halide.

[36] *P. Brigl*, Hoppe-Seylers Z. physiol. Chem. *116*, 1 (1921).

[37] *S. M. McElvain* and *D. Kundiger*, J. Amer. chem. Soc. *64*, 254 (1942); *S. M. McElvain* and *M. J. Curry*, ibid. *70*, 3781 (1948); for the assumption of carboxonium ions, see [41].

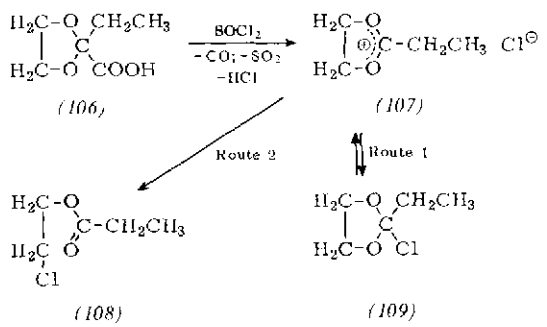
[38] *L. A. Cort* and *R. G. Pearson*, J. chem. Soc. (London, *1960*, 1682, where intermediate *(99)* is mentioned. Cf. the analogous result obtained by *H. Baganz* and *L. Domaschke*, Chem. Ber. *91*, 653 (1958), in the chlorination of 1,3-dioxolane.

of the reaction is confirmed by the formation of *trans*-2-bromocyclohexyl benzoates during the free-radical bromination of *O,O'*-benzylidenecyclohexane-*cis*-1,2-diol *(102)* [39]. For the same reasons, the halogen



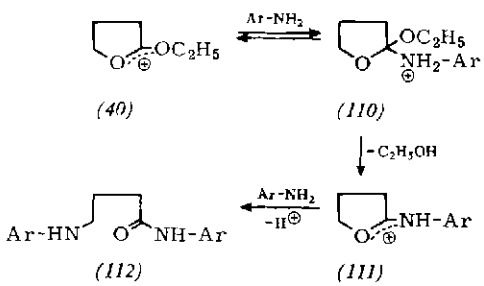

*(102)* cis *(103)* cis *(104)* trans *(105)* cis

compound obtained from the carboxylic acid *(106)* and thionyl chloride, which is stable towards cold water, has the structure *(108)* [41] and not *(109)* [40].




*(106)* *(107)* *(108)* *(109)*

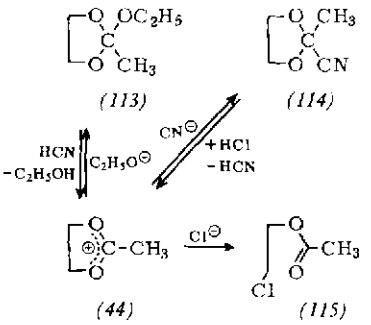
A variant of the reaction scheme is provided by the attack of excess aromatic amines on the carboxonium ion *(40)*. Here the kinetically controlled primary adduct




*(40)* *(110)* *(112)* *(111)*

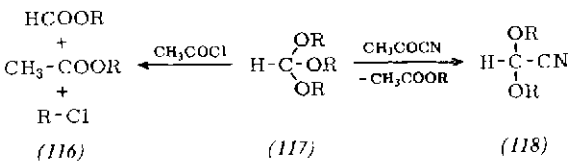
*(110)* is stabilized by forming the imino ether cation *(111)*, which is then split open by Route 2 to form the γ-arylaminobutyric arylamide *(112)* [17].

The following example gives a particularly clear illustration of the effect of the nucleophilic component on the course of the reaction: As shown in Table 1, the carboxonium ion *(44)* adds on cyanide and alkoxide ions by Route 1 to form the unstable compounds *(113)* and *(114)* [18]. Even hydrocyanic acid is able to split off alcohol from the orthoester *(113)* to reform the ambident ion *(44)*, which is immediately trapped in the form of *(114)* [42]. The proton-active hydrogen chloride




*(113)* *(114)* *(44)* *(115)*

again displaces hydrogen cyanide from *(114)* so that the ion *(44)* can now react to form the stable β-chloroethyl acetate *(115)*. This explains why the orthoformate *(117)* reacts directly with acetyl chloride to form the stable products *(116)* [43], whereas acetyl cyanide produces α,α-dialkoxyacetonitrile *(118)* by Route 1 [44].




*(116)* *(117)* *(118)*

## 4. The Effect of the Ambident Cation on the Course of the Reaction

As shown in Figure 1, the effect of the ambident cation in system *(3)* is determined by its energy content as compared with those of the two possible reaction products *(5)* and *(6)* [45]. If *(3)* is very rich in energy, $\Delta F_1$ becomes so large, even when a weak nucleophile is used, that isolation of a kinetically controlled product formed by Route 1 becomes possible (Fig. 3). If, on the

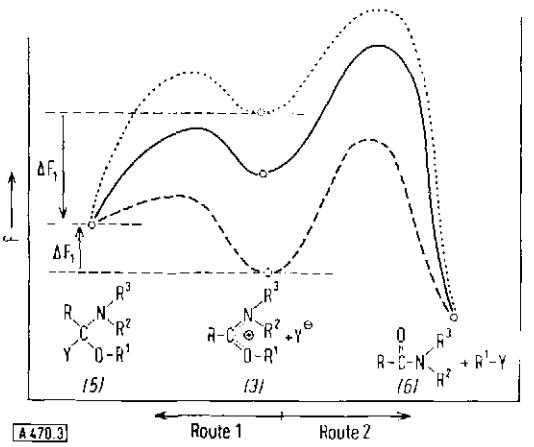



Fig. 3. Effect of the ambident cation on the position of *(3)* in the energy profile diagram.
—— General curve (Fig. 1);
..... *(3)* rich in energy;
- - - - - *(3)* poor in energy.

[39] *A. Rieche, E. Schmitz, W. Schade*, and *E. Beyer*, Chem. Ber. *94*, 2926 (1961).

[40] *E. Vogel* and *H. Schinz*, Helv. chim. Acta *33*, 116 (1950).

[41] *S. M. McElvain* and *A. N. Bolstad*, J. Amer. chem. Soc. *73*, 1988 (1951).

[42] *I. G. Erickson*, J. Amer. chem. Soc. *73*, 1338 (1951).

[43] *H. Post*, J. org. Chemistry *1*, 231 (1937).

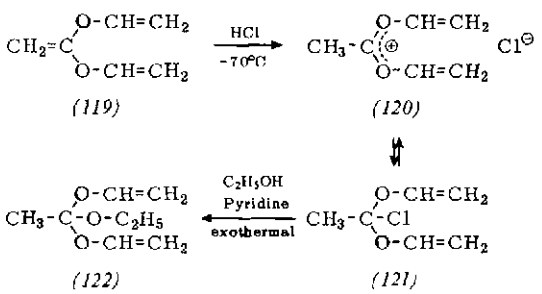
[44] *H. Böhme* and *R. Neidlein*, Chem. Ber. *95*, 1859 (1962).

[45] Strictly speaking, the energy content of *(3)* is that of the system $Cat^{\oplus}$ + $Y^{\ominus}$. Since, however, the nucleophile remains constant, this energy depends practically only on the energy of dissociation of *(5)* (Cat-Y), which in turn is determined solely by the nature of $Cat^{\oplus}$.

other hand, *(3)* is strongly stabilized by mesomerism, so that $\Delta F_1$ is very small or, in extreme cases, has its sign reversed, then even strongly nucleophilic reagents lead only to the thermodynamically stable *(6)* via Route 2 (Fig. 3). Examples of both alternatives are known.

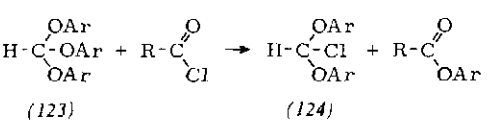
### a) Energy-Rich Ambident Cation

As described above, the addition of HCl onto ketene acetals produces ambident cations which do not add on the weakly nucleophilic $Cl^{\ominus}$ ion to form the kinetically controlled α-chloro-α,α-dialkoxy compound [*(93)* → *(97)*]. However, this metastable adduct can be isolated when divinylketene acetal *(119)* is used [41].



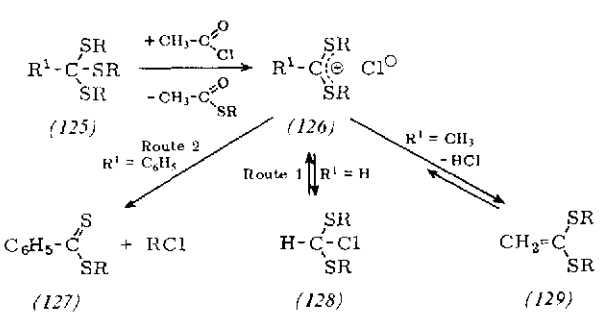
*(119)* *(120)* *(122)* *(121)*

Owing to the *O*-vinyl mesomerism (= strengthened O–C vinyl bond) the ambident cation *(120)* is so rich in energy that it adds on chloride ions to form *(121)*. The constitution of this compound follows from its vigorous reaction with alcohol containing pyridine to form mixed orthoesters *(122)* [41]. Analogously, it is possible to obtain the distillable, readily hydrolyzable compound diphenoxymethyl chloride (formyl chloride diphenylacetal) *(124)* from phenyl orthoformate *(123)* and acyl chloride [44].



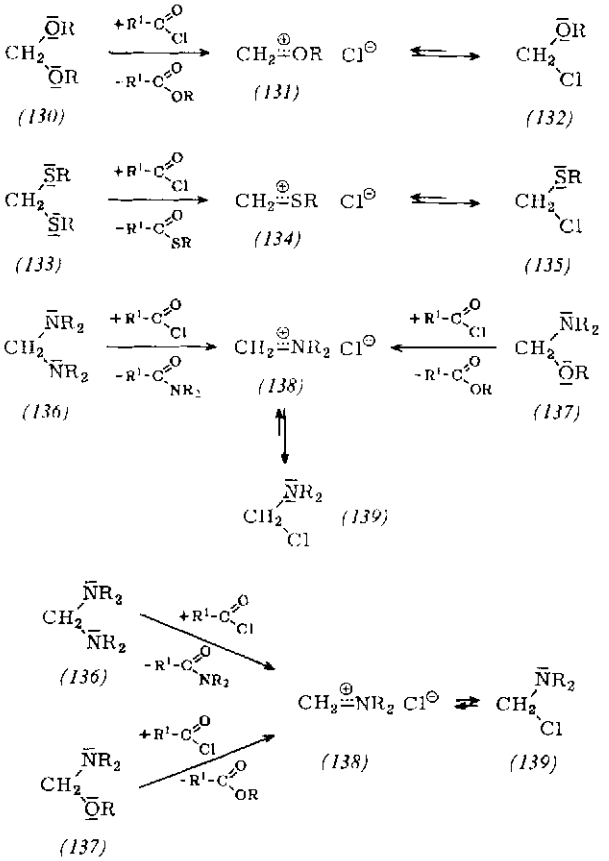
*(123)* *(124)*

The extent to which the reaction is affected by the substituent on the carbon atom of the ambident cation is shown by the cleavage of trithio-orthoesters *(125)* with acid chlorides [46]. Here the dithiocarboxonium ion *(126)* must be an intermediate, but it forms the unstable, rapidly hydrolysed formyl chloride mercaptal *(128)* only when $R^1 = H$. In *(126)*, $R^1 = C_6H_5$, the ambident ion evidently contains so little energy that only the stable products *(127)* can be isolated. Finally, when $R^1 = CH_3$, the ion *(125)* loses a proton to form the ketene mercaptal *(129)*.



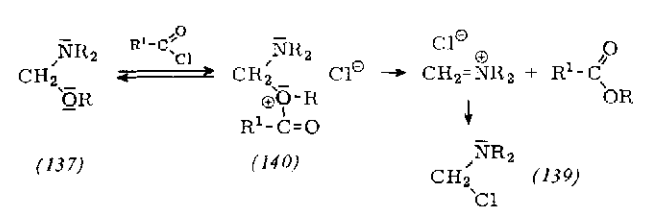
*(125)* *(126)* *(127)* *(128)* *(129)*

Cations in which the positive charge is distributed between only one hetero-atom and the carbon atom are naturally much richer in energy. For this reason, they are able to take up even the weakly nucleophilic chloride and bromide ions exclusively by Route 1 to form the labile adduct. This postulate is confirmed without exception by the numerous reactions of acetal-like compounds with hydrogen halides or with inorganic or organic acid chlorides. Examples are the reactions of acyl chlorides with formaldehyde acetal *(130)* [43], mercaptal *(133)* [46], aminal *(136)* [47], and α-aminomethyl ethers *(137)* [47]. α-Chloro ethers *(132)* [43],



*(130)* *(131)* *(132)* *(133)* *(134)* *(135)* *(136)* *(138)* *(137)* *(139)*

α-chloro thioethers *(135)* [46], and α-chloroamines *(139)* [47] are formed. The reaction must always begin with reversible addition of the acid chloride, the adduct then decomposing exothermically to form the ambident cation. This explains why, in the case of the aminoethyl ether *(137)*, the reaction proceeds via the adduct *(140)*, as is shown by the predominant formation of α-chloroamines *(139)* [47,48].



*(137)* *(140)* *(139)*

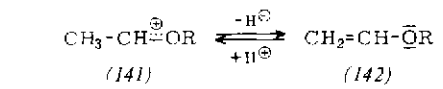
[46] *H. Böhme* and *J. Roehr*, Liebigs Ann. Chem. *648*, 21 (1961).

[47] *H. Böhme* and *K. Hartke*, Chem. Ber. *93*, 1305 (1960).

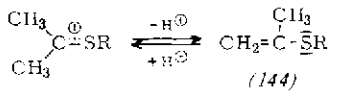
[48] *H. Meerwein*, Angew. Chem. *67*, 374 (1955).

Since α-chloroamines *(139)* are sparingly soluble in nonpolar solvents, it may be assumed that they are in equilibrium with their ions *(138)*. Both *(138)* [47] and *(131)* [48] have been isolated with complex anions.

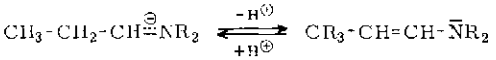
It should be noted that the reactions proceed smoothly only with derivatives of formaldehyde, tertiary aldehydes, or corresponding ketones. In other cases the energy-rich ions are stabilized even more readily than the carboxonium derivatives mentioned above, with loss of a proton [*(71)* → *(72)*; *(126)* → *(129)*]. The electrophilic character of the cations *(141)* [48], *(143)* [47], and *(145)* [49] then changes to nucleophilic character [*(142)*, *(144)*, and *(146)*], so that these partners, which are interrelated by addition or subtraction of a proton, often undergo aldol-type condensations. This explains



*(141)* *(142)*

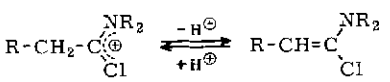


*(143)* *(144)*



*(145)* *(146)*

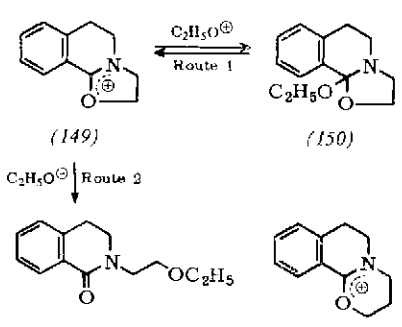
the favored position of formaldehyde in the Mannich reaction, which proceeds via *(138)* [50], and also the limitation of the Vilsmeier reaction to formylamines. If in the latter reaction, the intermediate *(147)* contains an alkyl group, partial deprotonation again occurs and hence dimerization of both partners takes place [29].



*(147)* *(148)*

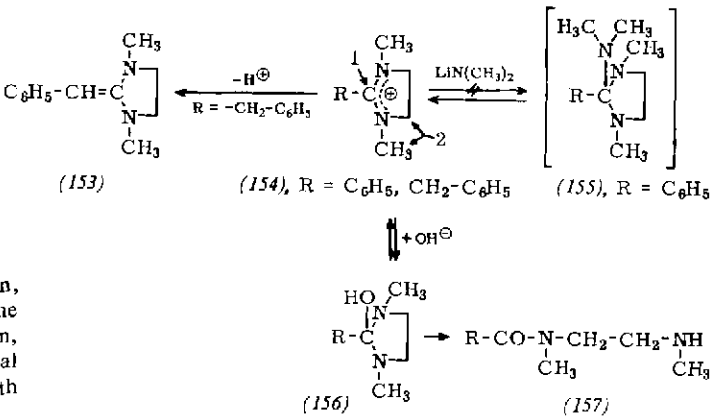
### b) Low-Energy Ambident Cation

Although simple trialkylimino ether cations, *e.g. (31)* and *(34)* in Table 1, add on alkoxide ions smoothly to form the corresponding amide acetals, *e.g. (30)* and *(33)* in Table 1, the ion *(149)* yields only the stable ether *(151)* [51]. Neither the transition to the less strained dihydrooxazine system *(152)* [52] nor the use of cyanide ions [53] or of a lower temperature alters the course of the reaction [52]. Since the perchlorates of the ambident cations *(149)* and *(152)* can be recrystallized unchanged from water, these ions are so stable that it is impossible to isolate them in the form of the amide acetal, *e.g. (150)*.



*(149)* *(150)* *(151)* *(152)*

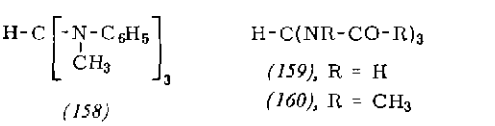
By comparison with all the ambident cations discussed so far, the amidinium ions have appreciably less energy, as is manifest in the unusual basicity of the amidines. Nevertheless, it is surprising that the amidinium ion itself *(154)* is not attacked by lithium dimethylamide in boiling ether [55]. Trisdialkylaminomethanes such as *(155)* cannot be isolated, in agreement with other attempts of synthesis [56, 57], because the resonance energy of the amidinium ions is too great.



*(153)* *(154)*, R = $C_6H_5$, $CH_2$-$C_6H_5$ *(155)*, R = $C_6H_5$ *(156)* *(157)*

If R contains a methyl group, then the cation can again react by loss of a proton, but only with alkoxide as the base [55, 57]. Ketene aminals, *e.g. (153)*, are formed. The occurrence of reversible addition onto *(154)* by Route 1 is shown by the exothermic reaction of the ketene aminal *(153)* with water. Here the ion *(154)* must be an intermediate; the adduct of this ion with hydroxyl ions *(156)*, even if present in very small concentrations, initiates opening of the ring to give *(157)*. The question whether the decomposition of the ion on fusion of the iodide *(154)* involves dealkylation (Route 2), as with other ammonium ions [58], remains to be resolved.

If the energy content of the amidinium ion is increased by weakening the basicity of the nitrogen atom, trisaminomethanes, *e.g. (158)* [59], *(159)* [60], and *(160)* [61], can be prepared [55].



*(158)* *(159)*, R = H *(160)*, R = $CH_3$

[49] Cf. *G. Opitz, H. Hellmann*, and *H. W. Schubert*, Liebigs Ann. Chem. *623*, 112, 117 (1959).

[50] Cf. *H. Hellmann* and *G. Opitz:* α-Aminoalkylierung. Verlag Chemie, Weinheim/Bergstr. 1960, p. 4 et seq.

[51] *W. Schneider* and *B. Müller*, Chem. Ber. *93*, 1579 (1960).

[52] Unpublished work together with Dr. *L. Geldern*; cf. [8].

[53] Unpublished work together with Dr. *Th. Eicher*.

[54] *A. Rieche* and *E. Schmitz*, Chem. Ber. *89*, 1254 (1956); *E. Schmitz*, ibid. *91*, 1133 (1958).

[55] *H. Böhme* and *F. Soldan*, Chem. Ber. *94*, 3109 (1961).

[56] Cf. the references given in [55].

[57] *H. Baganz* and *L. Domaschke*, Chem. Ber. *95*, 2095 (1962).

[58] *J. H. Brewster* and *E. Eliel:* Organic Reactions. Wiley, New York 1953, Vol. VII, p. 99.

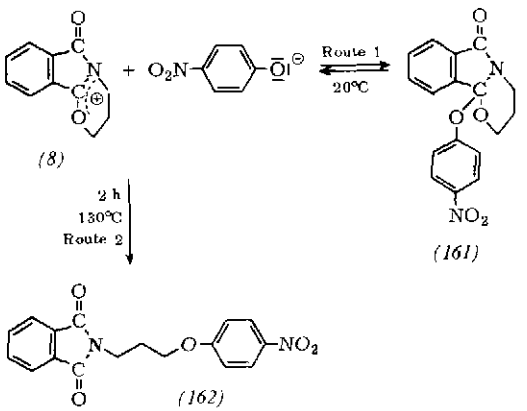
[59] *D. H. Clemens* and *W. D. Emmons*, J. Amer. chem. Soc. *83*, 2588 (1961).

[60] *H. Bredereck, R. Gompper, H. Rempfer, K. Klemm*, and *H. Keck*, Chem. Ber. *92*, 329 (1959).

[61] *A. Pinner*, Ber. dtsch. chem. Ges. *16*, 1659 (1883).

## 5. Influence of Temperature on the Course of Reaction

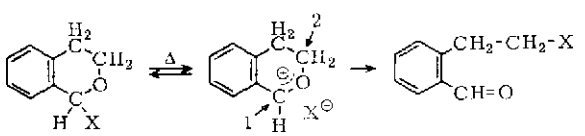
With suitable co-reactants, the isolated kinetically controlled product can be cleaved again by increasing the temperature to such an extent that a "rearrangement" with formation of the stable end-product occurs.




(8) (161) (162)

For example, the phthalimidium ion *(8)* combines instantaneously with the yellow *p*-nitrophenoxide ion in acetonitrile to form the colorless adduct *(161)*, from which the nitrophenoxy group can be easily split off by hydrolysis. If *(161)* is heated for about 2 hours at 130 °C, then the ether *(162)*, which is resistant to hydrolysis and which has the typical phthalimide structure, is obtained in quantitative yield [8].

The same process occurs during the thermal rearrangement of the 1-halogenoisochromanes *(163)* [54], which are very sensitive to hydrolysis. The ambident cation *(164)* formed as an intermediate takes up halide ion



*(163)* *(164)* *(165)*, X = Cl, Br

by Route 2 to form the stable *o*-halogenoethylbenzaldehyde *(165)*. In agreement with this mechanism, the optimum reaction temperature is appreciably higher (180 °C) for *(163)*, X = Cl, than for *(163)*, X = Br, (130 °C).

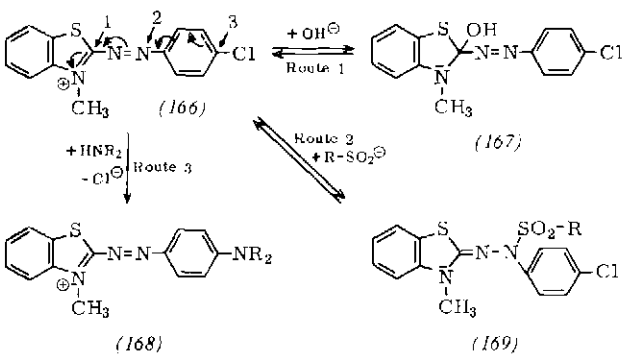
## 6. Effect of Solvent on the Course of Reaction

The ionizing effect of the solvent plays a decisive part in solvolysis reactions. This is also true for compounds which ionize to form ambident cations. A study of the solvent effect when solvolysis is excluded, *i.e.* the rate of rearrangement of the kinetically controlled product to form the thermodynamically controlled product, does not appear to have been undertaken so far. Experiments in this direction are being carried out at present in our laboratory.

## 7. Concluding Remarks

The examples given so far have all involved cations with a three-atom mesomeric system containing two points of attack for nucleophilic reagents. However, ambident behavior by a compound is not confined to a mesomeric three-atom system, and hence to two points of attack, nor to cations, nor indeed to ions. The sole criterion is the existence of an electron system which can be attacked at several points and in which reaction at one point eliminates the potential reactivity at the other sites. This general principle will now be illustrated by several examples.

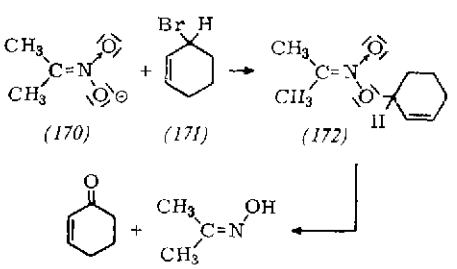
a) Heterocyclic quaternary azo salts of type *(166)* have three sites capable of being attacked by nucleophilic reagents, corresponding to the mesomerism indicated by bent arrows [62]. Hydroxide ions add on reversibly to form a pseudo-base *(167)* [62], while sulfinate ions are




*(166)* *(167)* *(168)* *(169)*

also taken up reversibly by the azo group to form *(169)* [62]. On the other hand, amines react irreversibly by additive substitution [63] in the phenyl nucleus to form colored salts of type *(168)* [62,64]. Apart from steric factors, the course of the reaction is influenced primarily by the gain in bonding energy.

b) As mentioned above, reactions of ambident anions often take place in heterogeneous phase, so that their course is difficult to follow [5]. The reaction of the ambident 2-nitropropane anion *(170)* with carbonium ions of different energy contents [65] is a favorable exception.



*(170)* *(171)* *(172)*

[62] *W. Kniese*, Ph. D. Thesis, Universität Marburg, 1963.

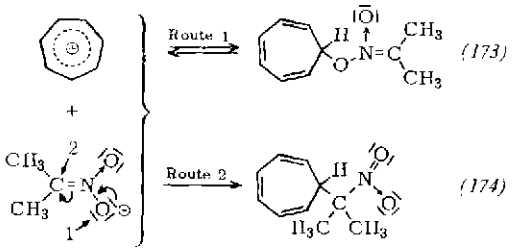
[63] Cf. *J. Sauer* and *R. Huisgen*, Angew. Chem. *72*, 294 (1960).

[64] *S. Gabriel* and *T. Heymann*, Ber. dtsch. chem. Ges. *23*, 2493 (1890); *Th. Wagner-Jauregg* and *M. Roth*, Chem. Ber. *93*, 3036 (1960); *L. J. Bellamy*: The Infrared Spectra of Complex Molecules. Methuen, London 1958, pp. 179, 209, 162, 205.

[65] *M. Bersohn*, J. Amer. chem. Soc. *83*, 2136 (1961).

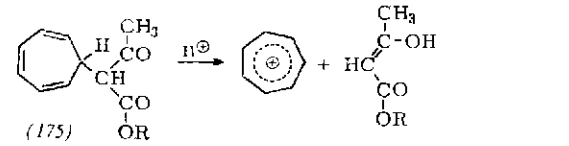
If the highly reactive carbonium ion obtained from 3-bromocyclohexene *(171)* is used, the reaction takes place irreversibly at the position of highest electron density [66], *viz.* at the oxygen atom. The primary product *(172)* decomposes by a conventional redox reaction.

With the tropylium ion, however, which is low in energy, *O*-alkylation proceeds reversibly to form *(173)*, so that the thermodynamically more stable *C*-alkylated product *(174)* can be formed [65].

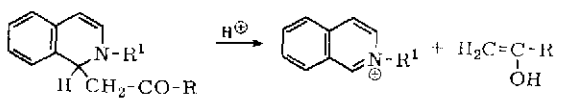



*(173)* *(174)*

It should be noted that even *C*-alkylated products of type *(175)* [67] or *(176)* [68] are readily cleaved again



*(175)*

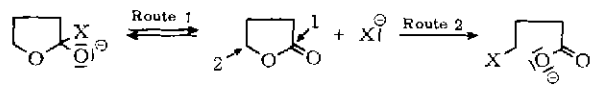


*(176)*

on protonation, if the ambident cation is strongly stabilized by mesomerism. The reactions correspond to a Grob fragmentation [69].

As to ambident neutral compounds, these must be differentiated according to their nucleophilic or electrophilic character.

c) A typical example of an electrophilic ambident neutral compound is γ-butyrolactone *(178)*. The ring is opened between the γ-carbon atom and the lactone oxygen by numerous nucleophiles under more or less drastic conditions [70].

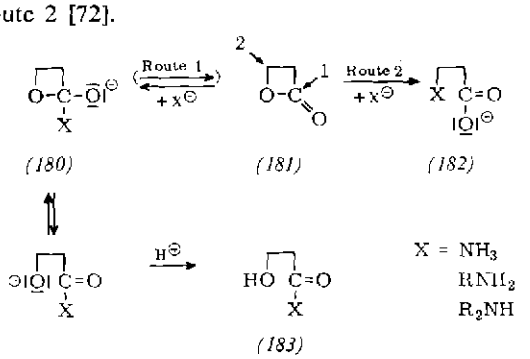



*(177)* *(178)* *(179)*

| | | | |
|---|---|---|---|
| $X = C_2H_5O^{\ominus}$ | $CH_3S^{\ominus}$ | $CN^{\ominus}$ | $(NH_2)_2\overset{\oplus}{C}\text{-SH}$ |
| $C_6H_5O^{\ominus}$ | $CH_3\text{-}C(=O)\text{-}S^{\ominus}$ | $R\text{-}SO_2NH^{\ominus}$ | HCl |
| $S_2^{2\ominus}$ | $SO_3^{2\ominus}$ | $H_2N\text{-}R$ | HBr |
| | | $P(OR)_3$ | $SOCl_2$ |

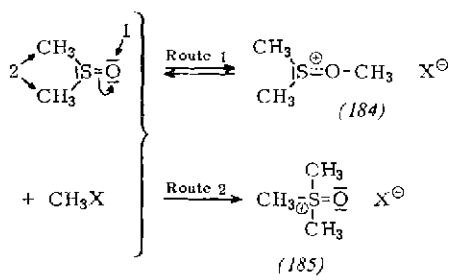
The labile adduct *(177)*, which was isolated with X = $SCH_3$ [71], generally cannot become stabilized, so that the ring eventually opens to form *(179)*. If proton rearrangement is possible, as in the reaction with primary amines in alcohol, then γ-hydroxybutyramides are formed from *(177)*. Butyrolactams are formed [70] only at higher temperatures and in the absence of solvent. The greater ring strain of β-propiolactone *(181)* permits it to be attacked in accordance with Route 2 by almost all the nucleophilic reagents mentioned for butyrolactone (generally even at room temperature) to form β-substituted propionic acids *(182)*. Only alkoxide ions add on by Route 1 to form β-hydroxypropionates *(183)*, X = OR.

Ammonia and primary or secondary amines, whose primary adducts *(180)* can themselves become stabilized by prototropy, lead to β-hydroxypropionamides and also to β-aminopropionic acids. With tertiary amines, on the other hand, the adduct *(180)* cannot become stabilized, so that only betaines of β-alanine are formed by Route 2 [72].




*(180)* *(181)* *(182)* *(183)*

d) Dimethyl sulfoxide is an example of a nucleophilic neutral ambident compound [73]. Kinetically controlled alkylation results in attack on its oxygen atom. The instability of *(184)* is shown not only by its rapid hydrolysis but also by the retro-alkylation of $X^{\ominus}$, depending




*(184)* *(185)*

on its nucleophilic character: $I^{\ominus} > NO_3^{\ominus} > Tos^{\ominus}$. This explains why, under the same conditions, methyl *p*-bromobenzenesulfonate forms 94 % of the *O*-sulfonium salt *(184)*, whereas methyl iodide forms 93 % of the *S*-methylsulfonium salt *(185)* [73, 74]. Only in the latter reaction can the reversible nature of Route 1 become effective, the thermodynamically stable end-product *(185)* being formed.

[66] Cf. the methylation of tautomeric compounds with diazomethane: *F. Arndt, B. Eistert, R. Gompper,* and *W. Walter,* Chem. Ber. *94*, 2125 (1961).

[67] *K. Conrow,* J. Amer. chem. Soc. *81*, 5461 (1959).

[68] *F. Kröhnke* and *I. Vogt,* Liebigs Ann. Chem. *600*, 211 (1956).

[69] Cf. *C. A. Grob* in: Theoretical Organic Chemistry (Kekulé Symposium). Butterworths, London 1959, p. 114.

[70] *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., Thieme, Stuttgart 1963, Vol. VI/2, pp. 777 et seq.

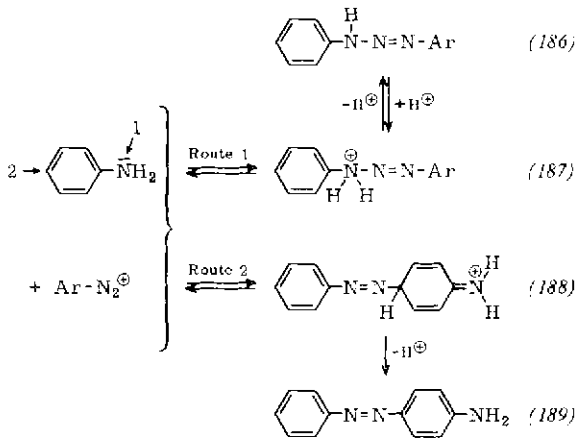
[71] *H. Plieninger,* Chem. Ber. *83*, 265 (1950).

[72] *H. Kröper* in [70], p. 527; *H. E. Zaugg* in: Organic Reactions. Wiley, New York 1954, Vol. VIII, p. 305.

[73] *S. Winstein* and *St. G. Smith,* Tetrahedron *3*, 317 (1958).

[74] Cf. *R. Kuhn* and *H. Trischmann,* Liebigs Ann. Chem. *611*, 117 (1958).

Aromatic amines also appear to be ambident, in the sense that they react with electrophilic reagents, *e.g.* diazonium ions, both at the $NH_2$ group and in the aromatic ring. However, here both primary reaction products *(187)* and *(188)* must be stabilized by deprotonation. Since this sequence of reactions is reversible with the diazoamino compound *(186)*, the kinetically controlled product can be converted into the azo compound *(189)*. All migrations of *N*-substituents into the aromatic ring should be considered on this basis, provided cleavage with reformation of aromatic amine occurs.




*(186)* *(187)* *(188)* *(189)*

*Some aspects of the above work are related to experimental work carried out by Drs. L. Geldern, W. Kniese, and T. Eicher, to whom thanks are due for their contributions. I am also indebted to the Fonds der Chemischen Industrie and to the Badische Anilin- und Sodafabrik, Ludwigshafen, for financial support of this work.*

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# Relations between Structure and Reactivity of Ambifunctional Nucleophilic Compounds

BY DOZENT DR. R. GOMPPER

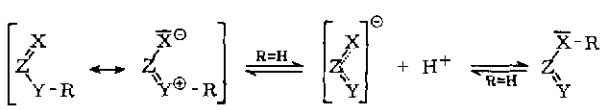
INSTITUT FÜR ORGANISCHE CHEMIE UND ORGANISCH-CHEMISCHE TECHNOLOGIE DER TECHNISCHEN HOCHSCHULE STUTTGART (GERMANY)

*Dedicated to Professor Hellmut Bredereck on the occasion of his 60th birthday*

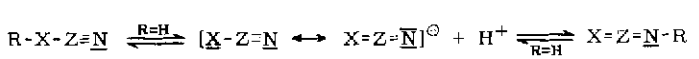
*Theoretical considerations and recent experimental results have added greatly to our knowledge of the structures and reactivities of ambifunctional nucleophilic compounds during the last few years. In the present work an attempt is made to present a survey of the theories which have been developed to explain the behavior of these compounds towards electrophilic reagents, and to formulate rules which may serve as guides for carrying out new reactions.*

## A. Introduction

The investigation of the structure and reactivity of tautomerizable compounds [general formulae *(1)* or *(3)* and *(4)* or *(6)*, R = H] belongs to the classical field of organic chemical research. However, while the problem of tautomerism [*(1)* ⇌ *(3)* and *(4)* ⇌ *(6)*] may now be regarded as being largely settled (cf. [1–4],




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




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

among others), the same cannot be said of the alkylation and acylation of *(1)* and *(3)* and of *(2)* and *(5)*. In the systems *(1)*, *(3)*, *(2)*, and *(5)*, partly also in *(4)* and *(6)*, resonance interaction occurs between atoms X and Y or X and N. Compounds of this type therefore differ in many respects from normal difunctional substances. *Kornblum* [5] has termed anions of formula *(2)* "ambident anions"; by analogy with the nomenclature used by *Pfrommer* [6], we generally speak of "ambifunctional nucleophilic compounds". In this context, "ambifunctional" refers to systems containing two centers

[1] *H. A. Staab:* Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim/Bergstr. 1959, pp. 642–650.

[2] *W. Hückel:* Theoretische Grundlagen der organischen Chemie. Akademische Verlagsgesellschaft, Leipzig 1961, Vol. 1, pp. 274–321.

[3] *H. Henecka:* Chemie der β-Dicarbonylverbindungen. Springer, Berlin, Göttingen, Heidelberg 1950.

[4] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Cornell University Press, Ithaca, N.Y. 1953, pp. 530–572.

[5] *N. Kornblum, R. A. Smiley, R. K. Blackwood,* and *D. C. Iffland,* J. Amer. chem. Soc. *77*, 6269 (1955).

[6] *J. F. Pfrommer,* Chemiker-Ztg. *81*, 457 (1957).

susceptible to electrophilic or nucleophilic attack, but in which only one of these centers can take part in one transition state (ambifunctional electrophilic compounds are not considered in the present work).

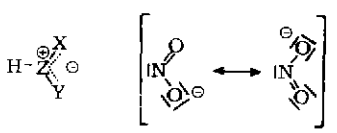
Table 1 gives a survey of the most important ambifunctional nucleophilic compounds. The need to differentiate between two types A and B arises from

Table 1. Ambifunctional nucleophilic systems.

| A | B |
|---|---|
| Allyl anions | Nitrite ions |
| Enols [*] | Oximes [*] |
| Enthiols [*] | Hydrazones |
| Enamines | Sulfinic acids [*] |
| Carboxylic and carbonic acid derivatives [*] | Sulfinic acid amides |
| Thiocarboxylic acids [*] | Triazines [*] |
| Carboxylic and carbonic acid amides [*] | Anions of the azoalkanes |
| Thioamides [*] | |
| Amidines [*] | Anions of phosphorous acid diesters and thiophosphorous acid diesters |
| Anions of the nitroalkanes | |
| Nitramines [*] and nitramides [*] | |
| Nitrosamines [*] | |
| Cyanate ions | Cyanide ions |
| Thiocyanate ions | Sulfoxides |
| Cyanamides [*] | |
| Anions of the alkyl cyanides | |
| Diazoalkanes [*] | |
| Fulminate ions | |
| Anions of the sulfoxides | |
| Phosphoric acid amides [*] | |
| Thiophosphoric acid [*] and its amides [*] | |

[*] And their anions.

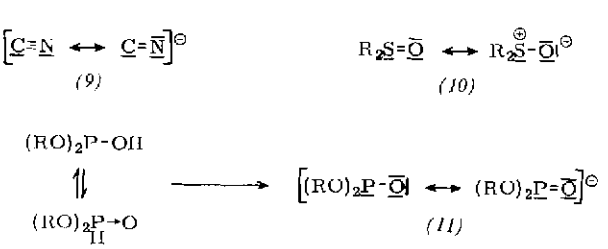
the fact that compounds with Z = N, S, or P can react, not only through the terminal atoms X and Y of *(1)*, *(2)*, and *(5)*, but also through the central atom Z. However, the free electron pair on Z does not take part in the resonance in the sense of formulae *(1)* and *(2)* [cf. for example, the nitrite anion *(7)*].



*(8)* *(7)*

Therefore, if X and Y are different, compounds of type B have three possibilities of reaction, and a third resonance form *(8)* must be formally considered in addition to *(1)* and *(3)*.

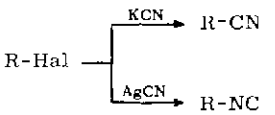
In group B, the cyanide ions *(9)*, the anions *(11)* of the phosphorous acid diesters, and the sulfoxides *(10)* are special cases, in which the resonance systems embrace only two atoms.



*(9)* *(10)* *(11)*

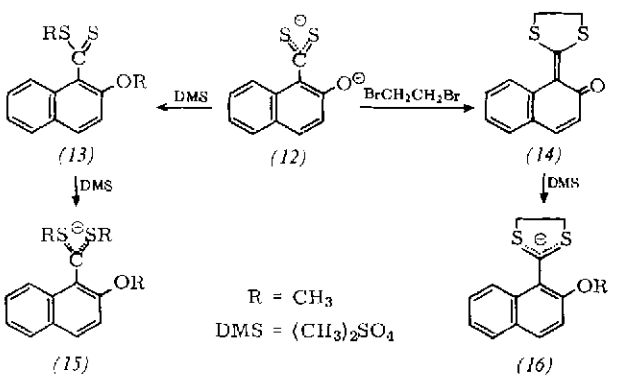
Before we examine the laws underlying the reactions of ambifunctional nucleophilic compounds, let us first recall the factors which affect the course of the reaction:

1. *Nature of the cation (for anions)*



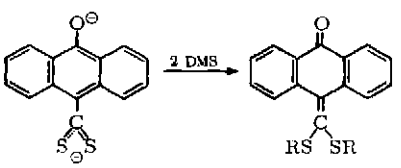

It has long been known (cf. [7]) that alkyl halides react with alkali metal cyanides to form nitriles, with, at most, traces of isonitrile, whereas with silver cyanide, at least below 100 °C, the formation of isonitrile is predominant.

2. *Nature of the resonance system and the degree of resonance*




*(13)* *(12)* *(14)* *(15)* *(16)*

Methylation of the disodium salt *(12)* of 2-hydroxynaphthalene-1-dithiocarboxylic acid leads to the formation of the methoxydithioester *(13)* [8]. The same reaction in the anthracene series yields the quinone methide derivative *(18)*. The greater nucleophilic character of the sulfur in *(17)* is explained by the




*(17)* *(18)*

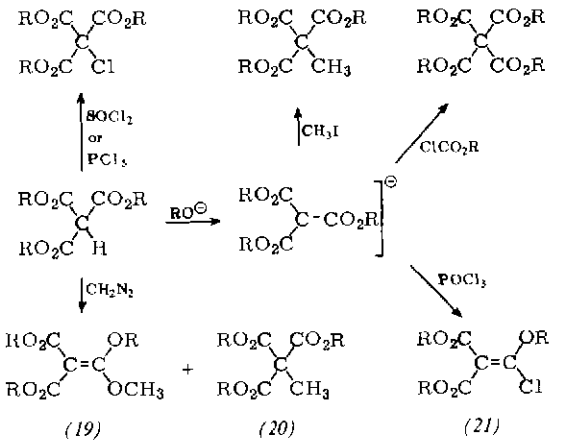
weaker aromatic character of anthracene. If the dithioester *(13)* is heated with dimethyl sulfate, the dithiocarboxonium salt *(15)* is formed. A related product *(16)* results from the analogous reaction of the quinone methide derivative *(14)*, but in this case owing to electrophilic attack on the oxygen atom. Thus the nucleophilic reactivity of the oxygen and sulfur depends very strongly on the resonance system in which they are incorporated.

[7] *Houben-Weyl:* Methoden der organischen Chemie. Thieme, Stuttgart 1952, Vol. 8, pp. 290, 352.

[8] *R. Gompper* and *R. Schmidt*, Angew. Chem. *74*, 780 (1962); Angew. Chem. internat. Edit. *1*, 596 (1962); *R. Schmidt*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1962.

3. *Nature of the electrophilic reagent*

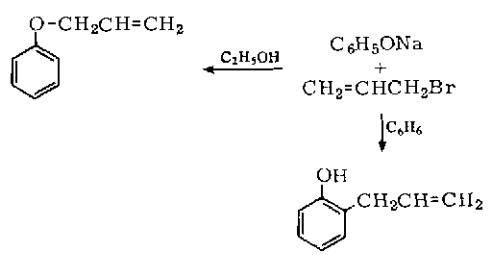
Alkylation and acylation of the alkali metal salts of carboxylic acid esters generally proceed by *C*-substitution. This is also apparent in the reactions of sodium methanetricarboxylic acid ester with methyl iodide [9] or chlorocarbonic acid ester [9]. Only on reacting



*(19)* *(20)* *(21)*

methanetricarboxylic acid ester with diazomethane, *O*-methylation to the ketene acetal *(19)* [yield 80 %, together with 20 % of *(20)*] has been observed [10] (the only other example so far of the conversion of a carboxylic acid derivative to a ketene acetal was the reaction of 7-nitrofluorene-1,9-dicarboxylic acid anhydride with diazomethane [11]). Whereas the action of $PCl_5$ [12] or $SOCl_2$ [13] on a methanetricarboxylic acid ester yields only a chloromethanetricarboxylic acid ester, the ketene acetal derivative *(21)* is formed in good yield by the reaction of its potassium salt with $POCl_3$ [12] (salts of other carboxylic acid esters undergo similar reactions).

4. *Nature of the solvent*



The reaction of sodium phenoxide with allyl bromide is a most impressive example of the solvent effect; according to *Claisen* [14], it leads to the formation of allyl phenyl ether in ethanol or acetone, but to *o*-allylphenol in benzene.

[9] *R. Scholl* and *W. Egerer*, Liebigs Ann. Chem. *397*, 358, 361 (1913).

[10] *F. Arndt* and *C. Martius*, Liebigs Ann. Chem. *499*, 228 (1932).

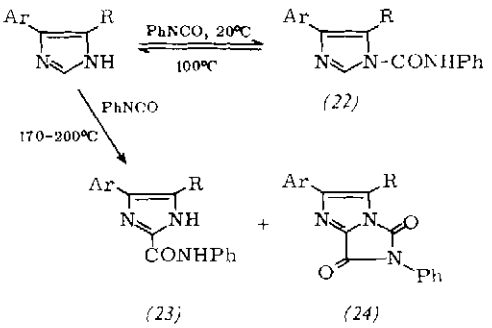
[11] *R. Kuhn* and *U. Breyer*, Chem. Ber. *95*, 111 (1962).

[12] *R. Gompper* and *H. Hiller*, unpublished work.

[13] *F. Adickes*, *W. Brunnert*, and *O. Lücker*, J. prakt. Chem. *130*, 163 (1931).

[14] *L. Claisen*, *F. Kremers*, *F. Roth*, and *E. Tietze*, Liebigs Ann. Chem. *442*, 210 (1925).

5. *Reaction temperature*



*(22)* *(23)* *(24)*

The reaction of imidazoles with phenyl isocyanate at 20 °C yields ureas *(22)* [15, 16], which regenerate isocyanate on heating. However, if 4,5-disubstituted imidazoles are heated to boiling with excess phenyl isocyanate [16], imidazole-2-carboxylic acid anilides *(23)* and imidazohydantoins *(24)* are formed.

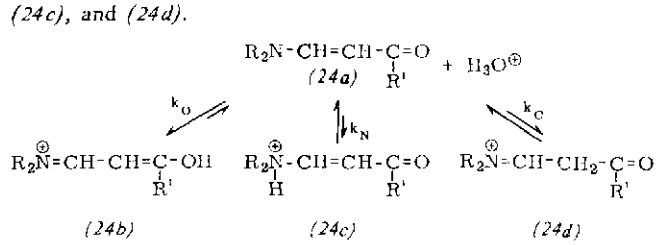
## B. Theoretical Foundations

In all attempts to explain the reactions of ambifunctional nucleophilic compounds with electrophilic reagents (for a review and discussion of earlier literature, see [17]), it is necessary to differentiate between kinetically and thermodynamically controlled reactions.

### I. Thermodynamically Controlled Reactions

Since in equilibrium reactions the logarithm of the equilibrium constant K is proportional to the change in free energy $\Delta F$, the end product to be expected is the compound most stable under the prevailing conditions, independently of the reaction mechanism. The stability is determined by the bond energy and the resonance energy. However, since in many cases these two quantities cannot be determined with sufficient accuracy, conclusions drawn on this basis are generally only of value for the reaction of *(1)* or *(3)* to form onium salts.

An example is the protonation of α,β-unsaturated β-aminocarbonyl compounds *(24a)* [17a], which can form *(24b)*, *(24c)*, and *(24d)*.



*(24b)* *(24c)* *(24d)*

The greatest number of limiting structures can be given for *(24b)*, so that *O*-protonation should predominate. The infrared spectra of solid salts of *(24a)* do indeed point to the

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[17a] *H. E. A. Kramer* and *R. Gompper*, Tetrahedron Letters *1963*, 969.

structure *(24b)*. NMR spectra [17a] show that the principal constituent of aqueous solutions is also *(24b)*. However, *N*- and *C*-protonation was also observed to a lesser extent [*(24b)* is not only the most stable of the three salts, it is also the one most rapidly formed].

Thus if equilibrium (a), whose constant $K_H$ is a measure of the affinity of Y and X for hydrogen, *i.e.* of their

(a) $H-X + Y^{\ominus} \rightleftharpoons H-Y + X^{\ominus}$

"hydrogen basicity", is set in parallel with equilibrium (b), whose constant $K_Z$ corresponds, *e.g.*, to the "carbon" [17b–20], "halogen", "sulfur" [21] and "nitrogen basicities", then it should be possible on the

(b) $Z-X + Y^{\ominus} \rightleftharpoons Z-Y + X^{\ominus}$

$Z = R_3C$, RCO, Hal, RS, $RSO_2$, $RN_2$, NO
$Y = R_3C$, $R_2N$, RO, RS

basis of the hydrogen basicity, to predict the course of the thermodynamically controlled reactions of Y, *i.e.* in our case of *(1)* to *(6)*. Although the analogy between (a) and (b) can only be formal (*e.g.* affinities for $Ag^{\oplus}$ are significantly different from affinities for $H^{\oplus}$ [22]), the resulting predictions are nevertheless fulfilled in the majority of cases (the respective reactions with formaldehyde may be regarded as models of thermodynamically controlled reactions). On extending the range of the acids and bases considered, the following rule for the stability of the end product is established [23]: "Hard", *i.e.* difficultly polarizable, acids combine particularly firmly with "hard" bases. "Soft", *i.e.* easily polarizable, acids form particularly strong bonds with "soft" bases.

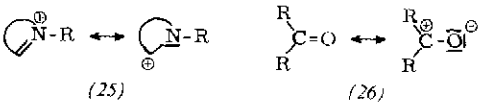
It might also have been expected that the position of the tautomeric equilibrium between *(1)*, *(3)*, and *(8)*, and between *(4)* and *(6)* would yield information as to the likely products of thermodynamically controlled reactions. The picture is however influenced by solvent and chelation effects, so that correct conclusions can be drawn only in exceptional cases.

When should thermodynamic control be expected? This question is more difficult to answer than that of the reaction product. However a few rules of thumb can be stated. Thermodynamically controlled reactions are always to be expected when the temperature is so high that the products of kinetically controlled reactions can decompose again to yield the starting materials or otherwise rearrange. The temperature threshold is particularly low when:

a) stable cations are used or relatively stable cations occur as intermediates, or

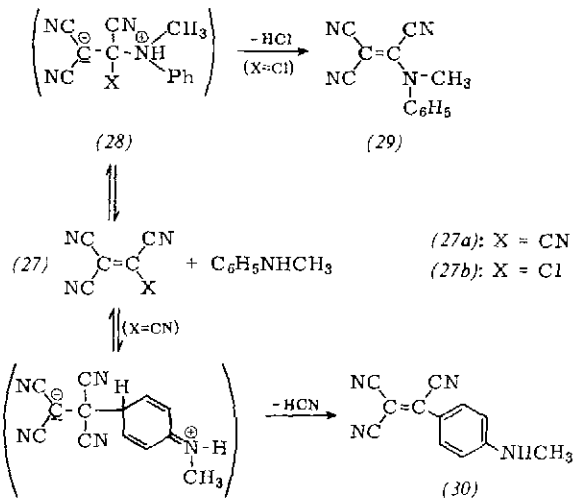
b) electrophilic reagents with multiple bonds are added.

The stable cations include, for example, the triarylcarbonium ions, the carbonium-immonium ions of the Mannich reaction, and the aryldiazonium ions. Electrophilic reagents with multiple bonds include aldehydes and ketones, carboxylic acids and their derivatives, and quaternary salts of *N*-heterocyclics. However, no sharp boundary can be drawn between the two groups. Thus, a glance at the resonance structures of the quaternary cyclimmonium salts *(25)* or the carbonyl compounds *(26)* shows that these compounds can also be regarded as very stable carbonium ions.



*(25)* *(26)*

The reagents included under (a) and (b) can be further subdivided according to their reactivity, *i.e.* their "electrophilicity". The less reactive they are, the greater in general is the tendency towards thermodynamically controlled reactions at a given temperature. This is illustrated by the reactions of *N*-methylaniline with tetracyanoethylene *(27a)* and tricyanovinyl chloride *(27b)*. With *(27a)*, the product is *N*-methyl-*p*-tricyanovinylaniline *(30)* [24], while the more reactive *(27b)* yields *N*-methyl-*N*-tricyanovinylaniline *(29)* [25]. Whereas $Cl^{\ominus}$ is rapidly liberated from the adduct *(28)*, $CN^{\ominus}$




remains bound owing to its stronger nucleophilic character. Thus in the case of *(27a)*, the formation of *(28)* is reversible, so that the thermodynamically controlled reaction to form *(30)* becomes possible.

## II. Kinetically Controlled Reactions

The "dynamic basicity" of compounds with free electron pairs is termed "nucleophilicity", and is measured by the rate constant of the reaction. The main problem in predicting the course of kinetically controlled reactions of ambifunctional nucleophilic compounds is to determine the nature of the factors on which the nucleophilicity depends. If the ease with which an atom of a nucleophilic group makes electrons available for bond-

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ing corresponded to the tendency of this atom to take part in nucleophilic substitutions, the basicity would provide a convenient expedient for the determination of the nucleophilicity. However, all attempts to demonstrate such a relationship have shown (cf. [26–30]) that it exists, at best, in series of similar compounds (alcohols, amines). Thus no direct parallel exists between basicity as a thermodynamic and nucleophilicity as a kinetic quantity.

However, the attempt to derive the nucleophilicity from a property of the atom which is independent of the type of compound ("sulfur is more nucleophilic than nitrogen") was also unsuccessful. Not only do the bonding conditions have a great influence, but the nucleophilicity is found to depend very strongly on the electrophilic reagent (alkylating agents [31–33], carboxylic acid derivatives [34–37], arylating agents [38–42], phosphorus compounds [43–46], and disulfides [47]; for other examples cf. [33, 35]).

The solvent also plays an important part (cf. [48]). Particularly impressive is the finding [49] that the "normal" order of nucleophilicity observed in water $I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ is reversed in the case of tetraalkylammonium halides in acetone, *i.e.* chlorides become more nucleophilic than iodides. Thus it appears that the more weakly solvated is an atom in an anion or even in a molecule, the more strongly nucleophilic it becomes. Strong solvation probably creates a sheath of solvent, which wards off the electrophilic attack in many cases.

*Streitwieser* [28] has assumed that nucleophilicity is determined by the energy of solvation of the base, the strength of its bond with a 2p-orbital of the carbon, its steric effect, and the electronegativity and polarizability of the reacting atom. *Edwards* and *Pearson* [33] have named the basicity, the polarizability and the α-effect (presence of free electron pairs on the atom adjacent to the nucleophilic center) as the most important factors. Surprisingly, electrostatic attraction is only rarely mentioned. Only *Hudson* [50, 51] centers his interpretation of nucleophilic reactivity around this factor. That an essential function must be assigned to the electrostatic attraction between the reactants (cf. also [52]) is clearly shown by, among other things, the difference in the orders of nucleophilicity observed with non-polar alkylating agents and polar acylating agents. The discovery [37] that anions react more rapidly with the acetylimidazolium cation than with *p*-nitrophenyl acetate, and only slowly or not at all with the acetyl phosphate anion, is very informative (for the effect of electrostatic interactions on the saponification of esters, cf. [53]). The calculated gain in energy when the two hydrogen atoms or a hydride ion and a proton approach each other [54–57] points in the same direction (cf. kinetic investigations [58]).

Good agreement with epxerimental results is obtained if it is assumed that the polarizability and the electrostatic attraction together constitute the phenomenon of nucleophilicity, the relative contributions of the two effects varying from one case to another.

Polarizability gives rise to the London and Van der Waals dispersion forces which lead to stabilization of the transition state [52, 59–62] (however, a clear distinction between London forces and polar forces is not always quite simple [61, 63]. The α-effect is probably related to the polarizability and electrostatic attraction. It is certainly not fortuitous, on the one hand, that it is associated with a particularly high polarizability of the nucleophilic reactant, and on the other, that it makes its appearance mainly with polar electrophilic reagents [36].

These considerations lead to the following basic principles for the behavior of ambifunctional nucleophilic compounds towards electrophilic reagents:

1. Owing to Coulomb attracting forces, a polar electrophilic reagent combines preferentially with the atom of an ambifunctional nucleophilic compound which bears


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the highest electron density. The rate of this reaction increases with the difference in the charges of the positively and negatively charged centers, while reactions with other nucleophilic centers are suppressed in a similar measure.

2. If the electrophilic reagent carries no significant positive charge, or none at all, a covalent bond is preferentially formed to the most easily polarizable atom of the ambifunctional system.

*Birch* and *Dewar* [64] had already reached a similar conclusion. These authors worked on the assumption that, in the collision, an electrophilic reagent perferentially strikes the atom bearing the largest negative charge in a nucleophilic system. If it is also assumed that, for example in the reaction of an enolate anion, the transition state resulting from an attack on the C atom is poorer in energy than that resulting from an attack on the O atom, then it follows from the collision theory that *O*-substitution should predominate with energy-rich electrophilic reagents, and *C*-substitution with energy-deficient reagents. This can be verified by several examples [3]. *Brändström* [65] has criticized and improved upon this theory.

## Alkylation of Metal Nitrites

Some of the strongest evidence for the basic principles advanced above are the results obtained by *Kornblum* [5, 66] in his investigations on the action of alkyl halides on metal nitrites. These results can be summarized (Table 2) by saying that the course of the reaction – formation of alkyl nitrite or nitroalkane – depends on whether the transition state possesses a stronger or weaker $S_N2$ character, *i.e.* on whether, in the extreme case, the reaction is truly $S_N2$ or $S_N1$. In the first case the product is predominantly or exclusively nitroalkane, and in the second the alkyl nitrite. A strong $S_N1$ character results from the ability of the alkyl halide to dissociate into ions; this dissociation occurs more readily as the carbonium ion formed becomes more stable (*e.g.* $p\text{-}CH_3OC_6H_4CH_2^{\oplus} > p\text{-}O_2NC_6H_4CH_2^{\ominus}$), and as the halide anion is more readily detached. For this reason, the $S_N1$ character is more pronounced in the reaction with silver nitrite (association of $Hal^{\ominus}$ with $Ag^{\oplus}$ to form AgHal) than in the reaction with sodium nitrite; a suitable model for the $S_N2$ scheme is the reaction of α-halogenocarboxylic acid esters with sodium nitrite in dimethylformamide [67], which gives the α-nitroesters in high yields:

$$R\text{–}CH(Hal)\text{–}CO_2R' + NaNO_2 \xrightarrow[\text{(DMF)}]{} R\text{–}CH(NO)_2\text{–}CO_2R' + NaHal.$$

In the nitrite anion *(7)*, the negative charge is distributed over the two oxygen atoms. In agreement with the above principles, the greater the positive charge on the C atom of the alkylating agent in the transition state, the greater is the yield of alkyl nitrite (the extent to which the course of the reaction is affected by the arrangement of the atoms in crystalline $AgNO_2$ – Ag lies closer to the N-atom and Na to the O-atom [68] – must remain unsettled for the present). The fact that the molecular refractions of the alkyl nitrites are greater than those of the nitroalkanes [69] is an indication of the greater polarizability of the N-atom, which determines the course of the $S_N2$-type reaction.

*Kornblum* [5] has concluded that alkylation of ambifunctional anions always occurs on the atom with the greatest electron density when the $S_N1$ character is dominant. In reactions with a strong $S_N2$ character, on the other hand, the alkylation should occur on that atom of the mesomeric anion which the electronegativity scale shows to have the lower electron density. Even if this formulation remains unsatisfactory insofar as it gives no explanation of the course of the $S_N2$ reactions (no conclusion on the electron density can be drawn, strictly speaking, from electronegativity), it can nevertheless explain the alkylation of, *e.g.* the cyanide, thiocyanate, cyanate, amide, thioamide, and nitrosamine anions. It agrees only in part with the results obtained with enolate and phenoxide anions, and largely fails with the anions of the nitroalkanes, oximes, and enthiols. However, its chief drawback is that it is valid only for anions and alkylating agents.

Table 2. Reaction of benzyl bromides with silver nitrite.

$$p\text{-}R\text{–}C_6H_4\text{–}CH_2Br + AgNO_2 \xrightarrow[\text{(ether)}]{0\,^{\circ}C} Ar\text{–}CH_2\text{–}ONO + Ar\text{–}CH_2\text{–}NO_2$$

| R | Half-time of the reaction [min] | Yield [%] | |
|---|---|---|---|
| | | Nitrite | Nitroalkane |
| $O_2N$ | 180 | 16 | 84 |
| H | 16 | 30 | 70 |
| $CH_3$ | 1 | 48 | 52 |
| $CH_3O$ | very small | 61 | 39 |

## Cation and Solvent Effects

It only remains to be settled whether cation and solvent effects can also be explained with the aid of the principles discussed above. In reactions of ambifunctional anions, the reactants include not only the electrophilic reagent, but also the cations and the solvent molecules. Thus in nonpolar solvents, the electrostatic attraction originating from an anion takes effect mainly on the cation. This is why, in organic solvents such as benzene, even strong electrolytes are associated in ion pairs or higher aggregates (cf. [70]).

The degree of proximity or the strength of "bonding" [71] in the ion pair depend on the negative and positive charge densities of the two ions, on the concentration, and on the ability of the solvent to sol-


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vate ions [48,70,72–74]. Owing to the electrostatic orientation of the ions, it is to be expected that the atom of the mesomeric anion system which has the greatest electron density will lie nearest to the cation (cf. [75], among others). The electron density depends on the resonance of the system and on the radii of atoms taking part in the resonance. Apart from certain exceptions [76], the result of the interaction between anions and cations is a reduced reactivity of ion pairs and similar aggregates as compared with the free ions [49,17b,77–90]. Deviations which are often observed with $Li^{\oplus}$ are associated with the solvation of $Li^{\oplus}$, which may simulate a larger ionic radius [91]; as expected, ion pairs of Li salts are particularly unreactive (cf. [92,93] among others).

As an example of the cation and concentration effects, consider the reaction of methyl iodide with lithium, sodium, potassium, and bis-piperidinium salts of 3-hydroxybenzofuran-2-carboxylic acid ester, which is strictly of second order [94]. The rates of the ionic and ion pair reactions increase with increasing radius of the cation; however, the ionic reaction is favored in dilute solutions and the ion pair reaction in concentrated solutions.

Anions have an effect on solvent molecules similar to that on cations. The solute-solvent interaction is determined by ion-dipole and dipole-dipole attraction, $\pi$-complex formation, and hydrogen bonding [48,95].

Most anions are much more weakly solvated in aprotic dipolar solvents [48] (*e.g.* dimethylformamide, dimethylsulfoxide, actone, acetonitrile, nitrobenzene) than in protonic; the reverse is true of polarizable, charged transition states [96]. Solvation of anions in protonic solvents depends primarily on ion-dipole interactions and on the formation of strong hydrogen bridges (*e.g.* [97–99]), an effect which is most pronounced with small anions. The ion-dipole interaction also plays a part in dipolar aprotic solvents. It is overlaid, particularly with large anions, by attraction due to mutual polarization.

As a result of the anion-solvent interaction, the electron-rich center in the ambifunctional anion is shielded by solvent molecules; this result is particularly important in protonic solvents, and *Kornblum* [100] has coined the name "selective solvation" to describe it. As in the occurrence of ion pairs, it leads to a shielding of the atoms with higher electron density against attack by electrophilic reagents. This explains, *e.g.*, the above-mentioned reversal of the order of nucleophilicity of the halide anions in changing from water to acetone as the solvent.

The shielding of the atom with the highest electron density by cations and solvent molecules affects not only the "specific" reactivity of this atom, but also, as a result of the demands on the free electron pair, the reactivity of the whole resonance system. The reactivity of the shielded anion therefore approaches that of the free compound, and consequently the substitution, even on the center which is not blocked, requires a greater activation energy.

*Brändström* [65,84] has tried to explain the alkylation of β-dicarbonyl compounds in a somewhat different form, but one which nevertheless, in its essence, corresponds to the view expounded above. Starting from the observation that the alkali metal salts of β-dicarbonyl compounds partly exhibit the properties of covalent compounds rather than those of the salts (cf. also [101]), the formation of chelate-alkali metal compounds such as *(31)* and that of β-dicarbonyl compounds fixed in the *trans*-configuration of the type *(33)* are assumed (Solv = solvent molecule) (cf. [102]). On addition of alkyl halide (RX), this occupies one coordination site; the *C*-alkylation is then induced in *(32)* and *(34)* by polarization of the C-Hal bond by the metal ion, and proceeds as a multi-center process. Since *(33)* is less stable than *(31)*, free enolate ions are formed relatively readily in this case; if these satisfy the condition of high charge density on the oxygen, they are then alkylated to form enol ethers. *Brändström* has quoted numerous examples in support of his theory (cf. also [103]). However, he leaves undecided, among other things, the question of the *O*-acylation of sodium acetoacetate with carboxylic acid chlorides in ether suspension.


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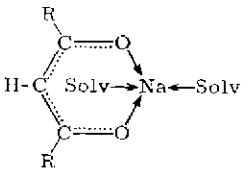
[100] *N. Kornblum, P. J. Berrigan,* and *W. J. Le Noble,* J. Amer. chem. Soc. *82,* 1257 (1960).

[101] *D. G. Hill, J. Burkus, S. M. Luck,* and *Ch. R. Hauser,* J. Amer. chem. Soc. *81,* 2787 (1959).

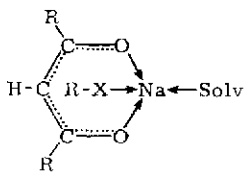
[102] *N. V. Sidgwick* and *F. M. Brewer,* J. chem. Soc. (London) *1925,* 2379.

[103] *H. D. Zook* and *W. L. Gumby,* J. Amer. chem. Soc. *82,* 1386 (1960).

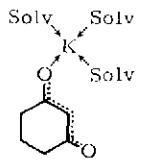
*Nesmeyanov* [104] has examined the cation effect from similar aspects, with the "double reactivity and tautomerism" of enols as an example.



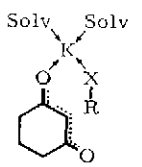
*(31)*



*(32)*



*(33)*

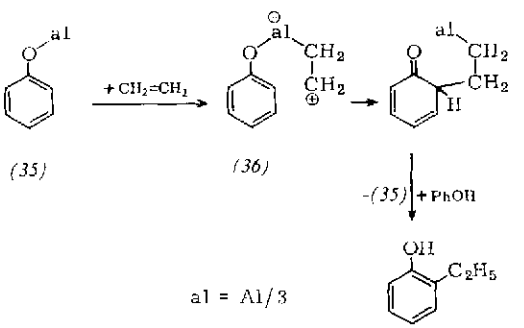


*(34)*

Investigations on the alkylation of metal salts of the phenol and dihydroresorcinol series have played an important part in the development of the theory of the cation and solvent effects. These will therefore be discussed below, together with a few other results.

## Alkylation of Metal Phenoxides

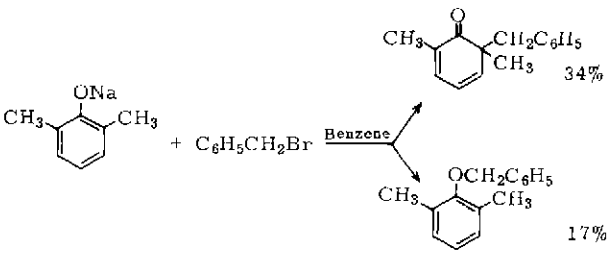
As an example of the action of chelation in organic reactions [105], let us examine the *o*-alkylation of phenols with olefins, with aluminum phenoxide as catalyst [106–108], for which the following mechanism is assumed: The olefin, *e.g.* ethylene, reacts with *(35)*



*(35)* *(36)*

to form the complex *(36)*, in which the electrophilic attack of the ethylene is directed towards the *o*-position. The reaction ends with the reformation of *(35)* by proton exchange with excess phenol.

According to *Claisen* [14], the reaction of metal phenoxides with particularly reactive alkyl halides (allyl bromide, benzyl bromide) in non-polar solvents (benzene, toluene, etc.) yields *o*-alkylphenols. More recent investigations [109–122] have confirmed that, apart from a few exceptions [119,123], in addition to *O*-alkylation, *o*-substitution occurs practically exclusively. Moreover, certain preparative improvements have been discovered and the range of application of the reaction has been extended. Thus, for example, it is advantageous to prepare the sodium phenoxide in toluene, in which the reaction is also carried out, with sodium hydride [110]; the yields of *o*-benzylphenols are between 80 and 90 %. The use of *o,o'*-dimethylphenols permits the synthesis of dienones [111–117]:



Dienones are also formed with α-naphthol, β-naphthols [122] and anthrone, even when methyl iodide is used.

Particular theoretical significance is attached to *Kornblum*'s discovery [118] that only *C*-alkylation occurs in completely heterogeneous reactions, and only *O*-alkylation in homogeneous reactions (on the question of the "heterogeneity factor", see also [94,103,112,117, 121,122,124,125]). The preparative result (Scheme 1), that only 19 % of *p*-(t-octyl)-*o*-allylphenol is formed in the heterogeneous reaction in ether while 96 % of *p*-t-octylphenyl allyl ether is formed in the homogeneous reaction in ethylene glycol dimethyl ether (EGDE), appears at first to contradict this statement. However,

[104] *A. N. Nesmeyanov* and *M. I. Kabachnik*, Zh. obshch. Khim. *25*, 37 (1955); Chem. Abstr. *50*, 1577 (1956).

[105] *H. L. Finkbeiner* and *M. Stiles*, J. Amer. chem. Soc. *85*, 616 (1963).

[106] *R. Stroh, R. Seydel*, and *W. Hahn*, Angew. Chem. *69*, 699 (1957).

[107] *A. J. Kolka, J. P. Napolitano, A. H. Filby*, and *G. G. Ecke*, J. org. Chemistry *22*, 642 (1957).

[108] *K. C. Dewhirst* and *F. F. Rust*, J. org. Chemistry *28*, 798 (1963).

[109] *V. A. Zagorevsky*, Zh. obshch. Khim. *27* (89), 3055 (1957); Chem. Zbl. *1959*, 4451; Zh. obshch. Khim. *28*, (90) 488 (1958); Chem. Zbl. *1959*, 6784.

[110] *F. M. Elkobaisi* and *W. J. Hickinbottom*, J. chem. Soc. (London) *1958*, 2431.

[111] *D. Y. Curtin* and *R. J. Crawford*, Chem. and Ind. *1956*, 313; J. Amer. chem. Soc. *79*, 3156 (1957).

[112] *D. Y. Curtin, R. J. Crawford*, and *M. Wilhelm*, J. Amer. chem. Soc. *80*, 1391 (1958).

[113] *D. Y. Curtin* and *M. Wilhelm*, J. org. Chemistry *23*, 9 (1958).

[114] *D. Y. Curtin* and *R. R. Fraser*, Chem. and Ind. *1957*, 1358; J. Amer. chem. Soc. *80*, 6016 (1958).

[115] *T. L. Brown, T. Y. Curtin*, and *R. R. Fraser*, J. Amer. chem. Soc. *80*, 4339 (1958).

[116] *D. Y. Curtin, R. C. Tuites*, and *D. H. Dybvig*, J. org. Chemistry *25*, 155 (1960).

[117] *D. Y. Curtin* and *D. H. Dybvig*, J. Amer. chem. Soc. *84*, 225 (1962).

[118] *N. Kornblum* and *A. P. Lurie*, J. Amer. chem. Soc. *81*, 2705 (1959).

[119] *N. Kornblum* and *R. Seltzer*, J. Amer. chem. Soc. *83*, 3668 (1961).

[120] *T. Nozoe, S. Ito*, and *T. Tezuka*, Chem. and Ind. *1960*, 1088.

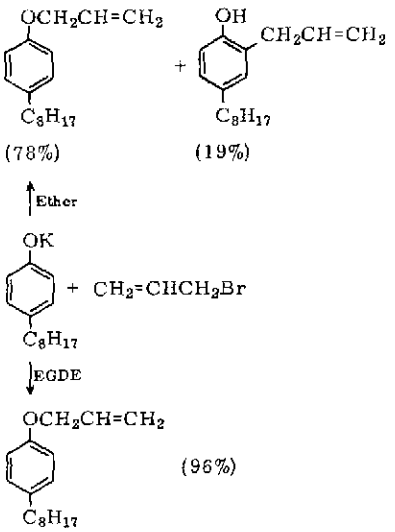
[121] *F. Kalberer* and *H. Schmid*, Helv. chim. Acta *40*, 780 (1957).

[122] *E. Wenkert, R. D. Youssefyeh, R. G. Lewis*, J. Amer. chem. Soc. *82*, 4675 (1960).

[123] *D. S. Tarbell* and *J. F. Kincaid*, J. Amer. chem. Soc. *62*, 728 (1940); cf. [111].

[124] *R. Barner* and *H. Schmid*, Helv. chim. Acta *43*, 1393 (1960).

[125] *H. F. Zougg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers*, and *R. W. De Net*, J. org. Chemistry *26*, 644 (1961).




Scheme 1. Homogeneous and heterogeneous alkylation of potassium *p*-t-octylphenoxide.

if the course of the reaction of potassium *p*-t-octylphenoxide with allyl chloride is followed, taking into account that the reaction mixture becomes homogeneous after 50–60 % conversion; it becomes clear that only the dissolved portion of the phenoxide is *O*-alkylated. This portion obviously increases as the reaction proceeds.

Table 3. „Heterogeneous" reaction of allyl chloride with potassium *p*-t-octylphenoxide in toluene at 25 °C.

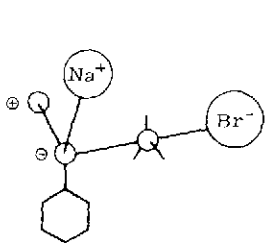
| Conversion [%] | *O*-allylation [%] | *C*-allylation [%] |
|---|---|---|
| 10 | 1 | 99 |
| 22 | 11 | 89 |
| 34 | 44 | 56 |
| 100 | 81 | 19 |

Since *o*-alkylation of the phenoxide requires a considerably greater activation energy than the *O*-alkylation, owing to the removal of the aromaticity in the transition state, it is to be expected that the former is possible only when the ions are particularly strongly bound together. As can be seen from Table 3, this type of bonding is exhibited by metal phenoxides only in the crystalline state, but not by ion pairs in solution.

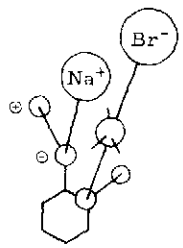
It should be pointed out that, under conditions (ether as solvent) in which the Na salt of 2,6-dimethylphenol reacts with allyl bromide to the extent of 55 % (C–R/O–R = 0.5), no reaction occurs with the Li salt [112].

The reaction mechanism which thus suggests itself for the Claisen *o*-alkylation of the phenols [118] corresponds to *Brändström*'s views [65], expressed in formula *(34)* (cf. also [126]): *O*-Alkylation requires the linear transition state *(37)*. In a non-polar solvent, however, the halide ion may be poorly solvated, and furthermore, the electrostatic equilibrium between cations and anions in the crystal is disturbed by withdrawal of the negative charge from the oxygen. These difficulties do not occur in the *C*-alkylation with the transition state *(38)*. The outgoing halide anion can be solvated by ion pair formation with the sodium ion, and, in addition, the reduction of the negative charge on the oxygen is compensated for by the transfer of a sodium ion to the halide ion so that, unlike in *(37)*, Coulomb repulsion forces occur between the sodium ions.

In the *O*-alkylation in homogeneous solution, which contains relatively unstable (since non-chelated) ion pairs or dissociated ions, the deciding factor is that, as a result of the aromatic character of the ring, the limiting structure *(39a)* is more important then the

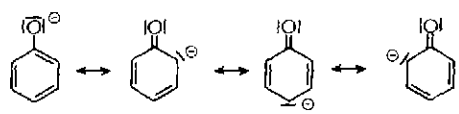



*(37)*




*(38)*

limiting structures *(39b)* to *(39d)*. The oxygen is therefore more nucleophilic than the *o*- and *p*-C-atoms.



*(39a)* *(39b)* *(39c)* *(39d)*

The picture given by the transition state *(38)* does not quite tally, inasmuch as it gives the impression that a bond is first formed between th *o*-C and the allyl-C, and only subsequently does the $Na^+$ ion promote liberation of the halide ion. However, the Claisen *o*-alkylation proceeds preferentially with those alkyl halides which tend towards $S_N1$-type reactions (cf. [127, 128]). The observation that sodium 2,6-dimethylphenoxide with methyl *p*-bromobenzenesulfonate [114] and sodium β-naphthoxide with dimethyl sulfate [122], in contrast to the reactions with methyl iodide, yield only the methyl ethers, also supports *Brändström*'s assertion [65] that the *C*-alkylation must be induced by polarization of the C-Hal bond of the alkylating agent by the metal cation. This agrees with the fact that, in the alkylation of metal β-naphthoxides, the proportion of the *C*-substitution product increases with the reactivity of the halide and with the electropositive character of the metal [117].

The material available [117, 118, 120, 129] on reactions with typical carbonium ion formers (trityl chloride, benzhydryl chloride) is too sparse to lead to definite conclusions. In this case, *p*-alkylation appears to occur in addition to *O*-alkylation and *o*-*C*-alkylation (for the formation of *o*-tropylphenol from sodium phenoxide and tropylium bromide [120], cf. [129a]).

[126] *C. K. Ingold*, Annual Rep. Progr. Chem. *1926*, 142.

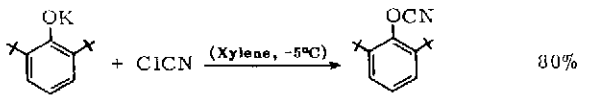
[127] *A. Streitwieser, Jr.*, Chem. Reviews *56*, 610 (1956).

[128] *S. Winstein, A. Fainberg*, and *E. Grunwald*, J. Amer. chem. Soc. *79*, 4146 (1957).

[129] *M. Busch* and *R. Knoll*, Ber. dtsch. chem. Ges. *60*, 2249 (1927).

[129a] *Ch. Jutz* and *F. Voithenleitner*, Chem. Ber. *97*, 31 (1964).

While the solvent-dependence of the reaction of sodium 2,6-dimethylphenoxide with perchloryl fluoride [130] is the same as in alkylation, no corresponding influence is known in the reaction of metal phenoxides with acid halides. The *O*-acylation appears to have precedence under all circumstances. Sodium 2,6-di-t-butylphenoxide reacts with benzoyl chloride to form 4-hydroxy-3,5-di-t-butylbenzophenone (24 %) and its enol benzoate [131] (on the question of steric hindrance, cf. [132]), but it yields phenyl urethane with phenyl isocyanate. Potassium 2,5-di-t-butylphenoxide reacts with cyanogen chloride to form 2,6-di-t-butylphenyl cyanate [133].

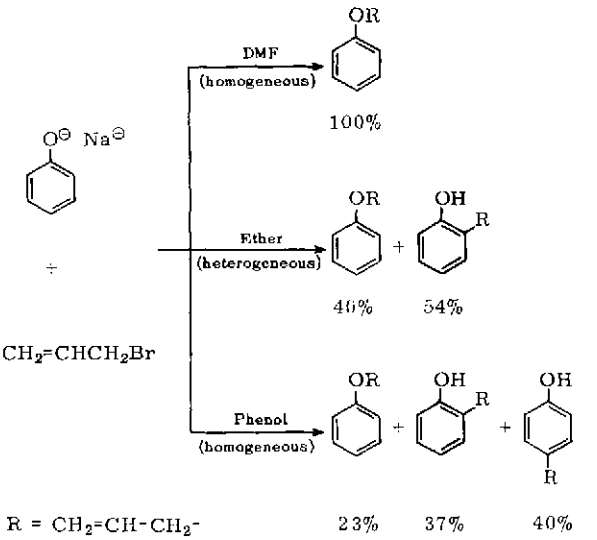



Thus it appears that the strongly polar acylating agents are capable of overcoming the insufficient solvation of the outgoing halide anion. This may be assumed to be due to the strong electrostatic attraction between the carbonyl or cyanide carbon atom and the phenoxide oxygen.

It should be noted that, in non-polar solvents, alkali metal salts of β-dicarbonyl compounds are also *O*-acylated by carboxylic acid chlorides [65].

So far, the solvent has been examined in connection with the Claisen *o*-alkylation only from the point of view of the heterogeneous or homogeneous reaction. However, what is the nature of its influence when separately solvated ions are present? The answer to this question, and hence a further possibility of verifying the theoretical considerations discussed here, is given by investigations of *Stetter* [134], *Zook* [103, 135], *Zaugg* [125, 136, 137], *H. Schmid* [121, 124], *Kotlyarevskii* [138], and particularly *Kornblum* [139–141] (cf. also [142–144]).

The great importance of the "selective solvation" of the atom with the greatest electron density is shown by the fact that even the little favored *C*-alkylation of phenols can be forced [139, 140] (Scheme 2). It should be remembered that *O*- and *C*-alkylations in protonic solvents are $S_N2$ processes.




Scheme 2. *O*- and *C*-alkylation of sodium phenoxide.

As shown by Table 4, the selective solvation becomes more evident as the tendency of the solvent towards H-bonding is increased; however, the acidity of the solvent is not a reliable measure of this effect. Finally, it is remarkable that, with sodium β-naphthoxide, which has a greater "carbanion activity" than the phenoxide, *C*-alkylation is possible even in more weakly H-bonded solvents, and the same result can be achieved with tetrahydrofuran, in which H-bonding is impossible. In the non-polar tetrahydrofuran, however, the transition state *(38)* is favored; correspondingly, exclusive *O*-substitution is again found in the polar dimethylformamide or dimethyl sulfoxide.

Table 4. Reaction of sodium phenoxide with allyl bromide at 27 ° [139].

| Solvent | *O*-allylation [%] | *C*-allylation [%] |
|---|---|---|
| Methanol | 100 | 0 |
| tert-Butanol | 100 | 0 |
| Water | 51 | 38 |
| Phenol | 23 | 77 |
| 2,2,3,3-tetrafluoropropanol | 58 [*] | 37 [*] |
| 2,2,2-trifluoroethanol | 37 | 42 |

[*] With allyl chloride.

The selective solvation in the reaction of phenols with acid chlorides in aqueous alkali [145] is unable to prevent the exclusive *O*-acylation. Also, in the amination of potassium phenoxide in water with hydroxylamine-*O*-sulfonic acid, *O*-phenylhydroxylamine is formed [146].

$$C_6H_5\text{-}O^{\ominus}\ K^{\oplus} + H_2N\text{-}O\text{-}SO_3H \xrightarrow[100°C]{(H_2O)} C_6H_5\text{-}O\text{-}NH_2 \quad 15\%$$

[130] *A. S. Kende* and *P. MacGregor*, J. Amer. chem. Soc. *83*, 4197 (1961).

[131] *T. H. Coffield, A. H. Filbey, G. G. Ecke*, and *A. J. Kolka*, J. Amer. chem. Soc. *79*, 5019 (1957).

[132] *L. A. Cohen* and *W. M. Jones*, J. Amer. chem. Soc. *84*, 1625 (1962).

[133] *R. Stroh* and *H. Gerber*, Angew. Chem. *72*, 1000 (1960).

[134] *H. Stetter* and *W. Dierichs*, Chem. Ber. *85*, 61 (1952); *H. Stetter* et al., Angew. Chem. *67*, 769 (1955).

[135] *H. D. Zook* and *T. J. Russo*, J. Amer. chem. Soc. *82*, 1258 (1960).

[136] *H. E. Zaugg*, J. Amer. chem. Soc. *82*, 2903 (1960); *83*, 837 (1961).

[137] *H. E. Zaugg, B. W. Horrom*, and *S. Borgwardt*, J. Amer. chem. Soc. *82*, 2895 (1960).

[138] *I. L. Kotyarevskii* et al., Tr. Vost.-Sibirsk. Filiala, Akad. Nauk S.S.S.R., Ser. Khim. *4*, 26, 32 (1956); Chem. Abstr. *51*, 14593, 14594 (1957); Izvest. Sibir. Otdel. Akad. Nauk S.S.S.R. *6*, 54 (1958); Chem. Zbl. *1959*, 13136.

[139] *N. Kornblum, P. J. Berrigan*, and *W. J. Le Noble*, J. Amer. chem. Soc. *82*, 1257 (1960); *85*, 1141 (1963).

[140] *N. Kornblum, R. Seltzer*, and *P. Haberfield*, J. Amer. chem. Soc. *85*, 1148 (1963).

[141] *W. J. Le Noble*, J. Amer. chem. Soc. *85*, 1470 (1963).

[142] *K.-W. Rosenmund* and *H. Bach*, Chem. Ber. *94*, 2394 (1961).

[143] *S. I. Savyalov, V. I. Gunar, G. N. Pershin*, and *S. N. Milovanova*, Dokl. Akad. Nauk S.S.S.R. *1960*, 1241; Chem. Abstr. *55*, 437 (1961).

[144] *N. A. Semenov* and *R. Kh. Freidlina*, Dokl. Akad. Nauk S.S.S.R. *1960*, 1576; Chem. Abstr. *55*, 9334 (1961).

[145] *Houben-Weyl:* Methoden der organischen Chemie. Thieme, Stuttgart 1952, Vol. 8, p. 543.

[146] *C. L. Bumgardner* and *R. L. Lilly*, Chem. and Ind. *1962*, 559.

## C. Summary

The ideas developed in Section B of the course of the reactions of ambifunctional compounds with electrophilic reagents can be summarized in the following rules:

I. Thermodynamically controlled reactions

a) Thermodynamic control of electrophilic substitution is always observed when the temperature is so high that the products of kinetically controlled reaction steps can decompose to give the starting components or otherwise rearrange.

The temperature threshold is particularly low when

α) stable cations are used or relatively stable cations occur as intermediates, or

β) electrophilic reagents with multiple bonds are added.

b) The cationic residue of the electrophilic agent is generally bonded to the atom of the ambifunctional compound which has the greatest hydrogen basicity (C > N > O > S).

II. Kinetically controlled reactions

a.α) Strongly polar electrophilic reagents preferentially attack the atom of the ambifunctional system which exhibits the greatest electron density.

a.β) Weakly polar electrophilic reagents favor the most easily polarizable atom of the ambifunctional system.

b) Ambifunctional compounds of type *(1)* or *(3)* always add electrophilic reagents in such a way as to maintain maximum resonance in the transition state.

c) For the reactions of ambifunctional anions of type *(2)* and *(5)* with weakly polar electrophilic reagents it holds, in addition to a.β), that

α) the nucleophilicity of the atoms of the first short period of the periodic system decreases with increasing atomic number: C > N > O > F;

β) the nucleophilicity of the atoms of the higher periods is always greater than that of atoms of the first short period;

γ) the graduation of the nucleophilicity given by rules c.α) and c.β) is displaced in favor of the atom which carries the negative charge when one resonance structure contributes particularly heavily.

d.α) The atoms with the greatest electron density are shielded against the attack of nucleophilic reagents by cations and polar solvents. Solvents which can form hydrogen bridges are particularly effective.

d.β) Cations and, in part, solvent molecules which are particularly firmly bound to an atom of an ambifunctional anion give rise to multi-center processes in which the electrophilic reagent is directed towards the "other" atom of the anion or into the *o*-position.

Owing to the variety of compounds listed in Table 1 and to the immense number of possible combinations of reactants, solvents, catalysts, and temperature conditions, "ad-hoc assumptions" cannot be entirely avoided in the discussion of special reactions. However, a glance at the great body of facts shows that the rules given here provide a useful basis for preparative and theoretical investigations. It should be mentioned that the reactions of ambifunctional electrophilic reagents can be regarded from similar points of view.

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# The Phenomenon of Phototropy [*]

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*Dedicated to Professor Gustav Kortüm on the occasion of his 60th birthday*

*A short survey of the present status of our knowledge in the field of "phototropy" is presented. The laws which govern this phenomenon are described, taking parafuchsin and N,N'-dimethyl-1,4-diaminoanthraquinone as examples. Phototropy and thermotropy are related. The acceleration of the regression of phototropically induced states by irradiation with light is discussed in some detail. An understanding of phototropy promises insight into the mechanisms of photochemical reactions and into the prerequisites for the preparation of light-fast dyes.*

## I. Introduction

The general Scheme (a) is assumed [1] for photochemical reactions.

$$A \rightleftharpoons A^* \rightarrow X \rightarrow B \qquad (a)$$

A = starting material; A* = optically excited A
X = a non-isolable intermediate
B = the first well-defined product capable of detection.

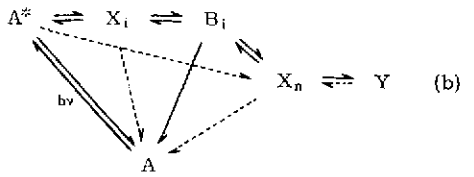
*Marckwaldt* observed that reversible color changes occurred with certain substances on exposure to light [2] and designated this phenomenon as phototropy.

[*] Reported in part at the II. International Dyestuff Symposium in Schloß Elmau (Germany), April 1964.

[1] *O. Kling, E. Nikolaiski,* and *H. L. Schläfer,* Ber. Bunsenges. physik. Chem. 67, 883 (1963).

[2] *W. Marckwald,* Z. physik. Chem. 30, 140 (1899).

For this case, Scheme (a) must be extended into Scheme (b)




Y = the photochemical end-product (the indices $i$ and $n$ indicate that various phototropic states B and different intermediate states X can occur).

The term phototropy [**] may be defined as follows:

*Phototropy is a reversible process which is produced by light absorption and leads to a quantum-mechanically stable but thermodynamically unstable state.*

The limitation "quantum-mechanically stable" is intended to indicate that because of the short life of the optically excited states A*, the simplest case of phototropy in the original sense of the word, *viz.* the optical transition $A \rightleftharpoons A^*$, is excluded. In the same way, transitions into quantum-mechanically metastable states with longer life-times are excluded. This means that fluorescence and phosphorescence are not included among phototropic phenomena. The limitation "thermodynamically unstable" was chosen to differentiate phototropy from photochemical reactions in general. A phototropic process is represented by the transitions

$$A \rightarrow A^* \rightarrow X_i \rightarrow B_i \rightarrow A$$

in Scheme (b). In many examples of phototropy, photochemical reactions with formation of Y compete with the reversible reaction leading from $B_i$ back to A; in these the equilibrium lies well towards Y, *i.e.* favors the thermodynamically stable or metastable states. It follows that "irreversible" photochemical reactions can emanate from phototropic states B. As a result, phototropic processes are also of interest in industrial technology.

The occurrence of this phenomenon of phototropy makes it possible to investigate the mechanism of the photochemical reactions which cause fading when dyes are exposed to light. Phototropic dyes in which the reverse reaction to reform A is slow are usually considered to be fugitive and undesirable. On the other hand, short-lived phototropic states may even enhance the light-fastness of dyes by stepwise transformation of their excitation energies. Fluorescence is associated with a relatively long life of A* (cf. the high dipol moments of A*), and many fluorescent dyestuffs are fugitive. Thus, when A* is chemically reactive, shortening of its life-time is desirable. Insofar as phototropy reduces the life-time of A*, and B does not give rise to additional "irreversible" transitions to Y, it may under certain conditions enhance light-fastness.

The definition of phototropy cannot be very precise. In particular, close distinction between $X_i$ and $B_i$ in Scheme (b) cannot be made. As in Scheme (a), the sensitivity of the method of measurement adopted will determine whether a substance is recognized as phototropic or not. The life-time of B again plays a decisive part. Phototropic reactions with life-times of milliseconds can be detected by means of flash spectroscopy [3a]; at the other extreme, reactions with half-lives of several days are known [3b].

Two examples will serve to illustrate the most important phototropic phenomena.

## II. The Phototropy of Parafuchsin

Following the work of *Frankenburger*, *Hammerschmidt*, *Heyde*, and *Zimmermann* [8–10], the old IG-Farbenindustrie works in Ludwigshafen developed an ultraviolet dosimeter. This instrument was based on the phototropic behavior of triphenylmethane dyes; changes in the dyestuff solutions were measured by comparison with suitable filters under standard conditions. Such dosimeters were successfully used for some years to measure atmospheric ultraviolet radiation [4]. *Lifschitz* [5] and *Holmes* [6,6a] proposed the reaction scheme *(1)* ⇌ *(2)* for the phototropy of alcoholic

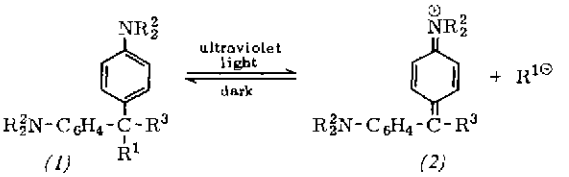



Table 1. Substituents of compounds *(1)* and *(2)*.

| $R^1$ | $R^2$ | $R^3$ | Compound |
|---|---|---|---|
| CN | H | $p$-$C_6H_4$—$NR^2_2$ | Pararosaniline; Parafuchsin (pararosaniline hydrochloride) |
| OH, CN | $CH_3$ | $C_6H_5$; $p$-$C_6H_4$—$NR^2_2$ | Crystal violet; Malachite green |
| CN | $CH_3$ | 4-$C_{10}H_6$-1-NH-$C_6H_5$ | Victoria blue (for T > 35 °C) |

solutions of triphenylmethane dyes, for ions were detected by conductivity and e.m.f. measurements on exposed and unexposed solutions [5,7].

[**] In biology, the term "phototropism" denotes "growth movement under the effect of light". For this reason, it would be better to designate the reversbile photochemical changes as photochromism, an expression common in German terminology. Nevertheless, in the present article, the English term "phototropy" is used throughout. Phototropic and photochromic processes are thus synonymous. It is also possible to use the term "phototropy" in the generic sense, and to limit "photochromism" to the sub-group involving visible color changes.


[3a] For example: *R. Livingston* and *V. A. Ryan*, J. Amer. chem. Soc. *75*, 2176 (1953).

[3b] *H. Waibel*, Melliand Textilber. *36*, 737 (1955).

[4] *H. Israel-Köhler*, Meteorol. Z. *54*, 138 (1937); *L. Schulz*, ibid. *52*, 266 (1935); *F. W. P. Götz*, ibid. *54*, 189 (1937); *H. Ungeheuer*, Bioklim. Beiblätter 66 (1935).

[5] *S. Lifschitz* and *Ch. L. Joffé*, Z. physik. Chem. *97*, 426 (1921); *S. Lifschitz* and *G. Girbes*, Ber. dtsch. chem. Ges. *61*, 1463 (1928); *S. Lifschitz*, ibid. *52*, 1919 (1919); *58*, 2434 (1925).

[6] *E. O. Holmes*, J. Amer. chem. Soc. *44*, 1002 (1922).

[6a] *L. Harris*, *J. Kaminsky*, and *R. G. Simard*, J. Amer. chem. Soc. *57*, 1151 (1935).

[7] *V. de Gaouck* and *R. J. W. Le Fèvre*, J. chem. Soc. (London) *1939*, 1457.

According to *Frankenburger, Weyde, Robl, Heyde,* and *Zimmermann* [8–10], the phototropic quantum yield of crystal violet in alcohol is equal to 1, and this value was subsequently found for malachite green as well [6a]. This means that the direct transitions A* → A can be neglected, and that the phototropic transitions A* → B are by far the predominant ones. Addition of water prevents the dark reaction B → A* [11,12]; addition of potassium cyanide accelerates it, but at the same time promotes formation of Y in photochemical reactions [11]. While the forward light reaction A → A* → B is only very slightly temperature-dependent between −6 and +40 °C, the reverse dark reaction B → A is accelerated by a rise in temperature (about fivefold for a temperature increment of 10 °C [11]). The establishment of a stationary concentration of *(2)* depends on the rates of the forward (light) reaction A → B and of the back (dark) reaction B → A, and may take up to one hour, depending on the concentration of dyestuff and the light intensity [8].

Unlike leuco-cyanides, the leuco-sulfites of triphenylmethane dyes are phototropic in aqueous media, and can be used in concentrated solutions [13], *e.g.* parafuchsin leuco-sulfite was used in the dosimeter in the following concentrations [13,14]: $1.235\times10^{-3}$ mole parafuchsin/l; $7.6\times10^{-4}$ mole $K_2S_2O_5$/l; $5.21\times10^{-3}$ mole HCl/l; 1.34 mole KCl/l.

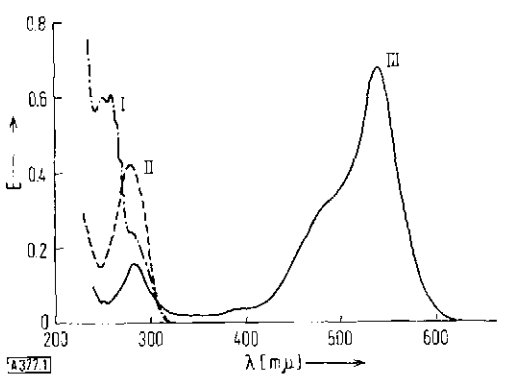



Fig. 1. Absorption spectra (E = optical density) of parafuchsin in aqueous solution at room temperature.

Curve I: c = $1.23\times10^{-3}$ M parafuchsin + $7.6\times10^{-4}$ M $K_2S_2O_5$ + $5.21\times10^{-3}$ M HCl + 1.34 M KCl (c·d = 0.2 [g·cm/l]; d = 0.5 cm).

Curve II: c = $7.6\times10^{-4}$ M $K_2S_2O_5$ + $5.21\times10^{-3}$ M HCl + 1.34 M KCl (d = 0.5 cm).

Curve III: c = $1.23\times10^{-6}$ M parafuchsin + $1.0\times10^{-3}$ M HCl + 1.34 M KCl (c·d = 0.008 g·cm/l). The absorption is due to *(2a)*.

The band at 280 mμ of Curve I corresponds to the temperature-dependent absorption of $H_2SO_3$ (see Curve II). Aqueous parafuchsin solutions without $H_2SO_3$ form insoluble products when irradiated with ultraviolet light, but not with visible light.


[8] *E. Weyde* and *W. Frankenburger*, Trans. Faraday Soc. *27*, 561 (1931).

[9] *E. Weyde, W. Frankenburger,* and *W. Zimmermann*, Naturwissenschaften *18*, 206 (1930).

[10] German Pat. 489471 (June 10th, 1927), inventors: *E. Weyde, R. Robl,* and *W. Zimmermann.*

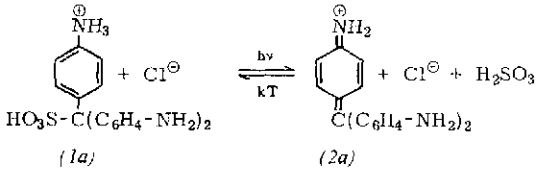
[11] *E. Weyde,* internal report of the IG-Farbenindustrie, Dec. 17th, 1931.

[12] *G. Rößler, W. Zimmermann,* and *E. Weyde,* internal report of the IG-Farbenindustrie, March 26th, 1928

[13] *E. Weyde,* internal report of the IG-Farbenindustrie, Dec. 11th, 1928.

[14] *H. Hammerschmidt* and *W. Frankenburger,* internal report of the IG-Farbenindustrie, Febr. 2nd, 1938.


In aqueous medium, the mechanism *(1a)* ⇌ *(2a)* is suggested [5,6]. Figure 1 shows the spectra of *(1a)* and *(2a)*.




The above parafuchsin solution exhibited strong thermotropic [*] properties, *i.e.* its color changed with temperature (cf. [6]). This phenomenon contributes to clarification of that of photochromism, so that description of some of its properties is pertinent.

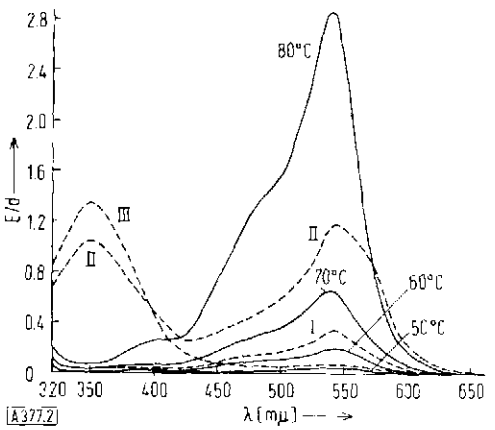



Fig. 2. Thermotropy (continuous curves) and phototropy (dotted curves) of an aqueous parafuchsin solution.

c = $1.23\times10^{-4}$ M parafuchsin + $7.51\times10^{-3}$ M $K_2S_2O_5$ + $5.21\times10^{-3}$ M HCl + 1.34 M KCl.

Curves I, II, and III after short, medium, and long (345 sec) periods of ultraviolet irradiation, respectively.

Figure 2 shows the growth of the absorption band of the quinonoid form *(2a)* of parafuchsin with increasing temperature. The absorption band (maximum at 540 mμ) appears also after brief exposure of *(1a)* to ultraviolet radiation. A further, unidentified absorption band (maximum at about 350 mμ) [**] appears on prolonged irradiation. Reaction Scheme *(b)* should therefore be extended to include further phototropic B-stages, which may be designated as $B_1$, $B_2$, $B_3$, *etc.* In the present case, $B_1$ absorbs at 540 mμ, $B_2$ at 350 mμ.

When unirradiated, heated solutions of *(1a)* are cooled, a new equilibrium concentration of *(2a)* is set up (Curve I in Fig. 3). The rate at which equilibrium is established rises with increasing concentration of $H_2SO_3$, the latter being determined by the amount of $K_2S_2O_5$ added. After brief exposure to light, the intensity of the band due to *(2a)* falls to the value determined by the respective temperature, at a rate similar to that found after heating. The long half-lives for the formation of the phototropically induced states $B_1$ by the

[*] In German, the term "thermochromism" and in English, the term "thermotropy" are generally used.

[**] The shoulder at 570 mμ of the 540 mμ band appears at the site of the parafuchsin absorption in conc. HCl without addition of $H_2SO_3$.

reverse reaction therefore obey general kinetic laws, as is shown by comparison with the thermotropic behavior. The formation of the second phototropic stage $B_2$ by the back reaction proceeds much slower (several hours, cf. Curve IV in Fig. 3). After prolonged irradiation, the dark-phase reverse reaction to reform *(1a)* therefore proceeds via two steps of different rates.

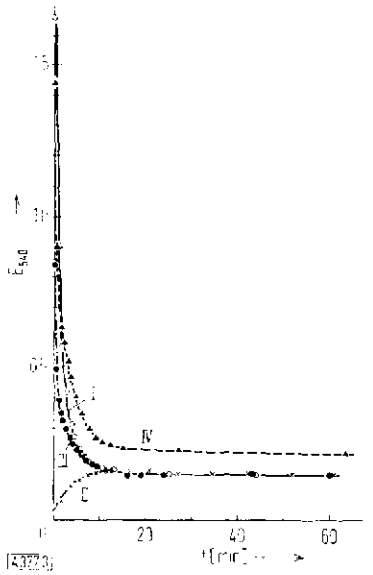



Fig. 3. Thermotropy and phototropy of a parafuchsin solution (solution as in Fig. 1); rate of attainment of equilibrium *(1a)* ⇌ *(1b)*.

Thermotropy: Curve I: quenching from 80 to 50 °C;
Curve II: heating from 20 to 50 °C.

Phototropy: Curve III: dark reverse reaction at 50 °C after ultraviolet irradiation;
Curve IV: dark reverse reaction at 50 °C after ultraviolet irradiation for a longer period than with Curve III.

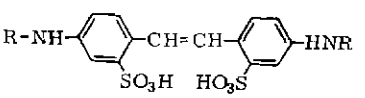
Phototropic and thermotropic processes in parafuchsin are thus closely allied. In the first case, a shift to the right of the equilibrium A ⇌ B [*(1a)* ⇌ *(2a)*] is produced by exposure to light, in the second, the same shift is produced by a rise in temperature. The dark-phase reverse reaction of *(2a)* proceeds in a kinetically similar fashion in both cases.

Thermodynamically unstable states induced by phototropy may be stable in other regions of temperature. This explains why many substances, *e.g.* spiropyrans [18, 19] and dianthrone [20, 21], exhibit both phototropic and thermotropic behavior [15–22]. *Stobbe*'s postulate that both phenomena must always appear together seems unfounded and is not mandatory [16]. Where thermotropism has been demonstrated, phototropy may be regarded as temporary partial "heating" of individual molecules. For this reason, *Holmes* termed this phenomenon "cold heat" [6].

Acceleration of the dark reaction by rise in temperature has frequently been demonstrated, but the light reaction is understandably little affected by temperature. For this reason, certain substances have a critical temperature at which the dark (back) reaction is as fast as the light (forward) reaction, *i.e.* no phototropy is observed above these threshold temperatures [17,22].

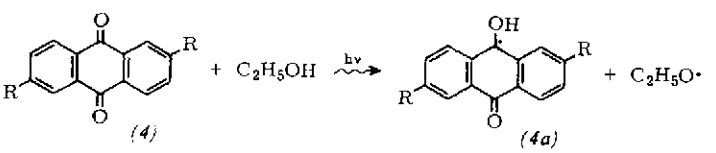
## III. Phototropy of Carbonyl Compounds, Particularly Anthraquinone Dyestuffs

Phototropy has been observed in numerous classes of chemical compounds [17,23–24b]. It is noteworthy that most phototropic organic substances contain carbonyl groups, *e.g.* quinoquinoline hydrochloride [5], 2,3,6,7-tetrachloro-1-oxodihydronaphthalene [5,25], acetanilides [26], fulgides [27], anthraquinone derivatives, thioindigo [28,29], and aminocamphor derivatives [30]. For stilbene derivatives *(3)*, phototropy is known only where R = X–CO– but not where R = H [17,30].




*(3)*

Anthraquinone and its derivatives may serve here as typical examples of carbonyl compounds. *Bellard* and *Cooper* [31] were able to show that on illumination in the presence of disodium anthraquinone-2,6-disulfonate *(4)*, R = $-SO_3Na$, ethyl alcohol is oxidized to acet-




*(4)* *(4a)*

[15] *A. Senier* et al., J. chem. Soc. (London) *95*, 441, 1943 (1909); *99*, 2081 (1911); *101*, 1950 (1912); *105*, 1917, 2462 (1914); *107*, 452, 1168 (1915); *113*, 28 (1918).

[16] *H. Stobbe* and *H. Mallison*, Ber. dtsch. chem. Ges. *46*, 1226 (1913); *H. Stobbe*, Liebigs Ann. Chem. *359*, 1 (1908).

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[18] *G. Kortüm* and *G. Bayer*, Z. physik. Chem. *33*, 1 (1962).

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[21] *W. G. Nielsen* and *G. K. Frenkel*, J. chem. Physics *21*, 1619 (1953); *Y. Hirshberg* and *E. Fischer*, J. chem. Soc. (London) *1953*, 629.

[22] *A. Senier*, *F. G. Sheppard*, and *R. Clarke*, J. chem. Soc. (London) *101*, 1950 (1912).

[23] *S. E. Sheppard*, Chem. Reviews *4*, 319 (1927).

[24] *S. S. Bhatnagar*, *P. L. Kapur*, and *S. U. Hashmi*, J. Indian chem. Soc. *15*, 573 (1938); *G. H. Brown*, Wright Air Development Center Techn. Rep. 59–436.

[24a] *G. H. Brown* and *W. G. Shaw*, Rev. pure appl. Chem. *11*, 2 (1961).

[24b] *H. S. A. Gilmour* in *D. Fox*, *M. M. Labes*, and *A. Weissberger:* Physics and Chemistry of Organic Solid State. Interscience Publishers, New York-London 1963.

[25] *F. Weigert*, Z. Elektrochem. angew. physik. Chem. *24*, 222 (1918).

[26] *H. Stobbe*, Ber. dtsch. chem. Ges. *46*, 1226 (1913).

[27] *H. Stobbe*, Liebigs Ann. Chem. *359*, 1 (1908); *A. Hänel*, Naturwissenschaften *37*, 90 (1950).

[28] *W. R. Brode* and *G. M. Wyman*, J. Res. nat. Bur. Standards *47*, 170 (1951).

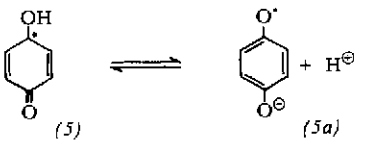
[29] *G. M. Wyman* and *W. R. Brode*, J. Amer. chem. Soc. *73*, 1487 (1951).

[30] *H. Stobbe* and *H. Mallison*, Ber. dtsch. chem. Ges. *46*, 1226 (1913); *B. K. Singh* and *B. Bhaduri*, Trans. Faraday Soc. *27*, 478 (1931).

[31] *S. L. Bollard* and *H. R. Cooper*, Proc. Roy. Soc. (London) Ser. A *225*, 416 (1954).

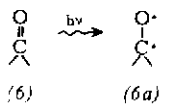
aldehyde and acetic acid. The formation of semiquinone radicals *(4a)* by dehydrogenation of the alcohol is proposed.

*Bridge* and *Porter* were able to detect these semiquinone radicals *(5)* and, in alkaline media, also semiquinone radical ions *(5a)* by flash spectroscopy; both had half-lives of the order of milliseconds [32].



*(5)* *(5a)*

*Dörr* [33] and *Bridge* [34] suggested that the primary step *(6)* ⇌ *(6a)* during excitation of the keto group represents an $n \rightarrow \pi$ transition of a non-bonding n electron from the oxygen's lone electron pairs into an antibonding $\pi$ state. A long time ago, *Schenk* postulated



*(6)* *(6a)*

such diradicals during the primary photochemical reaction of quinones, and termed them phototropically isomeric diradicals [35]. Semiquinone radicals as the primary products in the photoreaction of ketones were also found by *Bäckström* [35a].

$n \rightarrow \pi$ transitions of this type can also be influenced by substituents [33, 34, 36]. Electron donors such as amino or hydroxyl groups impart negative character to the ring system and inhibit the transfer of a free electron from the carbonyl oxygen. In addition, these substituents displace the much more intense $\pi \rightarrow \pi$ bands toward longer wavelengths [33, 34], so that irradiation by light may produce a reduction in the proportion of $n \rightarrow \pi$ transitions. The differences in the action of various anthraquinone derivatives on the photo-oxidation of alcohols are explained in this way. While anthraquinone and its sodium 2-sulfonate, disodium 2,6-disulfonate, and 1-methyl and 1-chloro derivatives are active, the disodium 1,5-disulfonate as well as 2,6-dihydroxyanthraquinone, 2-aminoanthraquinone, and anthracene are inactive [32]. Accordingly, flash spectroscopy showed radicals only in the active group of substances. *Schwab* and *Dörr* [36] similarly found radicals in 2-methyl- and 1-chloroanthraquinone (only a few for 1-hydroxyanthraquinone) but none in 2-amino-, 1-amino-, and 1,5-diaminoanthraquinone. *Dörr* pointed out the parallel occurrence of fiber damage with the appearance of these radicals [36a].

Numerous general properties of phototropic substances can be demonstrated using a solution of anthraquinone in dioxane. On exposure to light, a pale-yellow substance is formed, with an absorption maximum at 373 mμ (Fig. 4), which slowly disappears again in the dark (Fig. 5). This phototropically induced absorption band is substantially similar to the absorption band of the leuco-form (Fig. 4). The reverse reaction in the dark

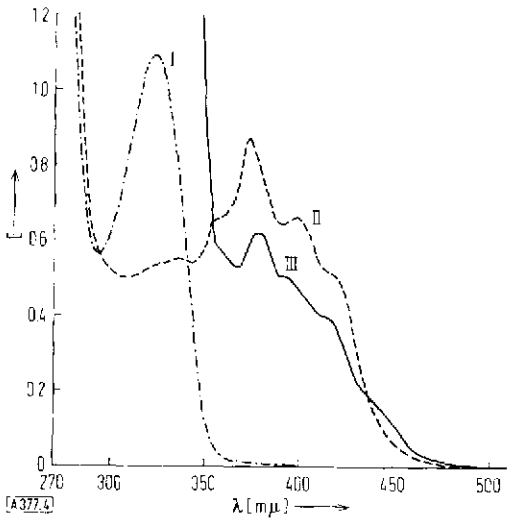



Fig. 4. Absorption spectra of anthraquinone solutions at room temperature.
Curve I: solution in dioxane under nitrogen.
Curve II: solution I, irradiated with ultraviolet light for 360 sec.
Curve III: ether extract of an anthraquinone vat.

depends on the oxygen content of the solution. As in many phototropic reactions, the reverse process is accelerated with rising temperature (Fig. 5). A second photo-product is formed from the primary photo-product of the reaction, being characterized by its substantially slower reverse reaction. For this reason, the plot of the concentration of the primary product (the leuco-form), against the time of irradiation passes through a maximum.

When intermittent irradiation is used, a "stationary" terminal value is slowly established, which falls off only slightly during the dark reaction. Under these conditions of irradiation, the kinetics of the photo-

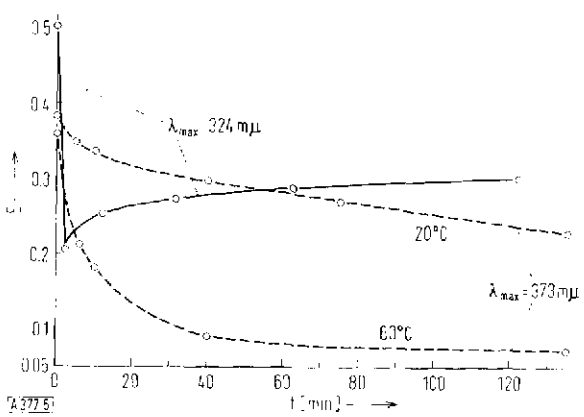



Fig. 5. Changes in extinctions of anthraquinone solutions in dioxane with time during and after ultraviolet irradiation (Hg lamp S 81, Quarzlampengesellschaft Hanau, Germany).
$\lambda_{max}$ = 324 mμ: disappearance of an anthraquinone band on irradiation and reformation of the band in the dark at 30 °C (the dark period begins at the minimum).
$\lambda_{max}$ = 373 mμ: temperature dependence of the dark reverse reaction after 4 min of continuous irradiation.


[32] *N. K. Bridge* and *G. Porter*, Proc. Roy. Soc. (London) Ser. A *244*, 259, 276 (1958).

[33] *F. Dörr*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 950 (1957); *64*, 581 (1960).

[34] *N. K. Bridge*, J. Soc. Dyers Colourists *76*, 486 (1960).

[35] *G. O. Schenk*, Naturwissenschaften *35*, 28 (1948); *40*, 205, 229 (1953); *41*, 452 (1954); Z. Nautrforsch. *3b*, 59 (1948); *G. O. Schenck* and *R. Wolgast*, Naturwissenschaften *48*, 737 (1961).

[35a] *H. L. S. Bäckström*, Z. physik. Chem. *25*, 99 (1934).

[36] *O. Schwab* and *F. Dörr*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 870 (1962); *O. Schwab*, Ph. D. Thesis, Technische Hochschule München, 1962.

[36a] *F. Dörr*, Chimia *15*, 63 (1961).

chemical reaction depend on the duration of the light and dark periods. Light-fastness is therefore a function of the irradiation conditions. Figure 6 shows the behavior of 2-aminoanthraquinone as an example. The

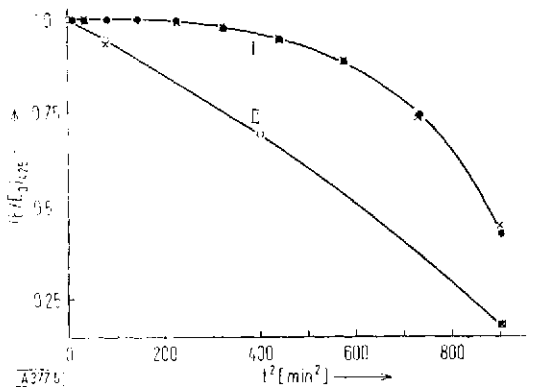



Fig. 6. 2-Aminoanthraquinone in dioxane at 30 °C. Disappearance of the long-wave extinction maximum (425 mμ) on intermittent ultraviolet irradiation (dark period = 2 min).
Curves I and II: light intervals 3 and 10 min.

importance of the dark reaction is well-known from the assimilation of $CO_2$ by plants. The promotion of plant growth by intermittent illumination may be as efficient as that obtained with continuous exposure to light [36b].

The influence of substituents and the surrounding medium on the light reaction can be readily demonstrated using the aminoanthraquinone derivatives. When the primary step leads to the formation of a phototropic diradical as formulated by *Dörr* and *Bridge*, inhibition of the photochemical reaction is to be expected if there is hydrogen bonding at the lone electron pair of the carbonyl oxygen [34]. In dioxane, the light reaction of 2-aminoanthraquinone does indeed proceed more rapidly than that of 1-aminoanthraquinone, but the rates become equally slow when 20 % water is added to the dioxane. The *N*-benzoylamino derivatives behave in the same way as the free amines (cf. Fig. 7).

Since it often happens in solution that the activated electron rapidly attains the potential minimum of the excited state, phototropy might be expected to be in-

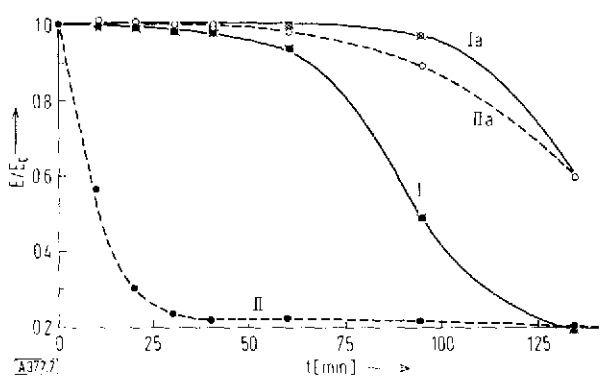
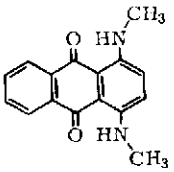



Fig. 7. Disappearance of the long-wave extinction maxima for *N*-benzoyl-1- and -2-aminoanthraquinones in dioxane (I and II) and in a 4:1 dioxane/water mixture (Ia and IIa) *vs.* ultraviolet irradiation time.

[36b] *A. Zeller* and *H. F. Oberländer*, Naturwissenschaften *50*, 712 (1963); *V. Warburg*, Biochem. Z. *100*, 230 (1919); *R. Emerson* and *W. Arnold*, J. gen. Physiol. *15*, 391 (1932); *P. Möckel*, Naturwissenschaften *48*, 435 (1961).

dependent of the wavelength of the irradiation absorbed. However, *N,N'*-dimethyl-1,4-diaminoanthraquinone *(7)* is an exception. *Dörr* suspected that only




*(7)*

irradiation in the n → π band wavelengths (which are normally at about 250–350 mμ) leads to photochemical reactions. Figure 8 shows the long-wave absorption band (maxima at 595 and 640 mμ) and the long-wave shoulder of the ultraviolet band of *(7)*. No evidence of

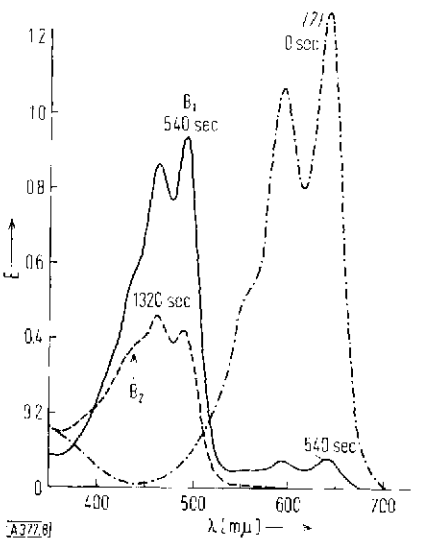
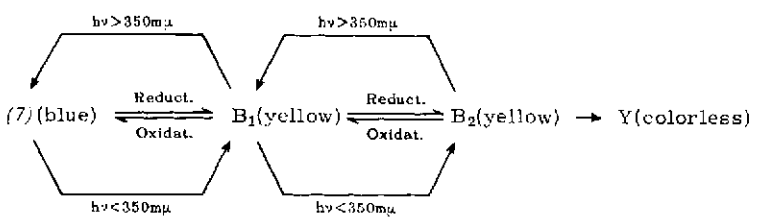



Fig. 8. Absorption band of *N,N'*-dimethyl-1,4-diaminoanthraquinone and phototropically induced bands $B_1$ and $B_2$ after 0, 540, and 1320 sec of ultraviolet irradiation in absolute ethanol.

a photochemical reaction was found on irradiation of *(7)* for 20 min at the long-wave absorption band (using a mercury immersion lamp with a ferric sulfate ultraviolet filter which absorbs strongly below 400 mμ). The reaction proceeded immediately on removal of the filter.

Irradiation of *N,N'*-dimethyl-1,4-diaminoanthraquinone in the absence of oxygen obeys the following complex reaction scheme:




$B_1$ is formed on irradiation with ultraviolett light, and $B_2$ appears after prolonged exposure (cf. Fig. 8). In the dark, *(7)* is reformed after some hours, the rate depending on the temperature and the amount of oxygen present. $B_1$ is identical with the first reduction product obtained with zinc dust in glacial acetic acid and is soluble in water, alcohol, and most organic solvents. On

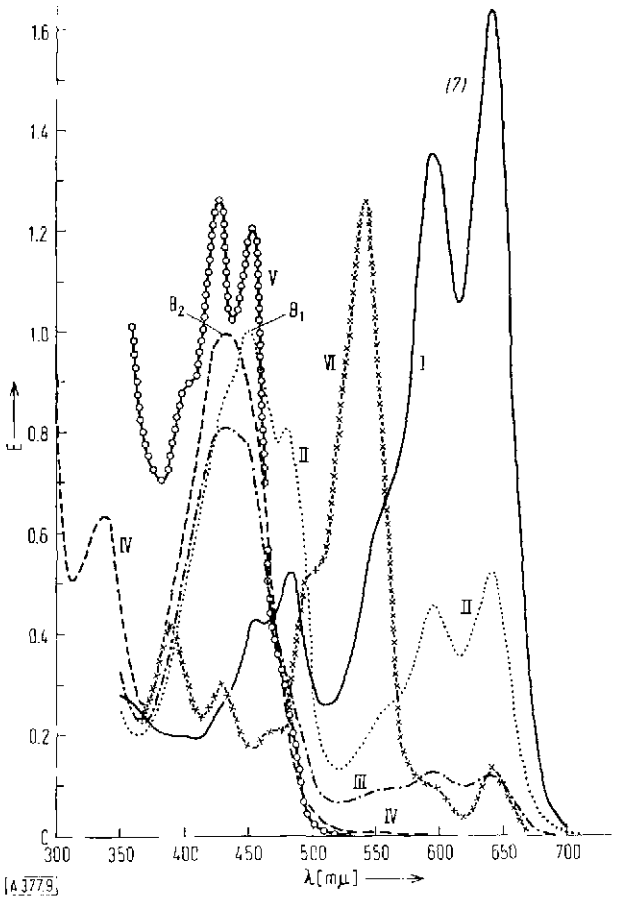



Fig. 9. Reduction products ($B_1$ and $B_2$, semiquinone, and the leuco-form) of *N,N'*-dimethyl-1,4-diaminoanthraquinone *(7)*. (The ordinate scale for Curves V and VI is arbitrary.)

Curves I—IV: Reduction of *(7)* with Zn/glacial acetic acid in glacial acetic acid.

Curve V: Leuco-form of *(7)* in glacial acetic acid (reducing agent: NaOH and dithionite).

Curve VI: Spectrum of the semiquinone radical *(7)*-H•. Compound *(7)* was electrolysed for 90 minutes in acetone/$NaClO_4$.

prolonged reduction or heating of the reaction solution, $B_2$ is formed (Fig. 9). In air, $B_1$ is rapidly, and $B_2$ slowly, oxidized back to the original dye *(7)*. When illuminated, $B_2$ is fairly quickly transformed back into *(7)* via $B_1$ (Fig. 10), but on prolonged irradiation with ultraviolet light, decomposition of *(7)* takes place.

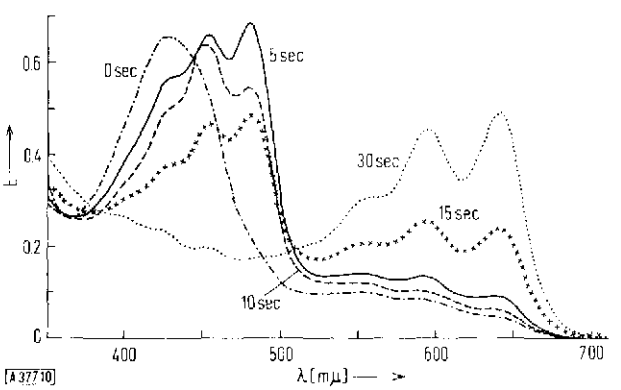



Fig. 10. The reaction $B_2 \rightarrow$ *(7)* in ultraviolet light. $B_2$ was obtained by reduction with Zn/glacial acetic acid in glacial acetic acid at room temperature.

Figure 11 shows the chronological steps involving $B_2$, $B_1$, and *(7)* when $B_2$ is irradiated.

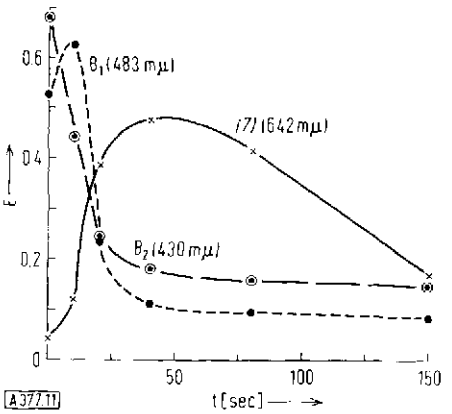



Fig. 11. The reaction $B_2 \rightarrow$ *(7)* accelerated by ultraviolet irradiation; in ethanol. $B_2$ was obtained by reduction with Zn/glacial acetic acid. The extinctions for $B_2$, $B_1$, and *(7)* were recorded for each respective maximum (cf. Fig. 8).

It is clear that the reverse reaction leading to reformation of *(7)* proceeds via the yellow stage $B_1$. When $B_2$ is illuminated with visible light only, *(7)* is reformed quantitatively and does not decompose, but in the absence of an ultraviolet filter *(7)* is formed again first and is then transformed into $B_1$ and the other stages by the ultraviolet light.

An interesting photochemical cycle is thereby established: the reduced stages $B_1$ and $B_2$ are oxidized to *(7)* by light of long wavelength, and are reduced again by light of short wavelength, part being transformed into a colorless substance Y, which has not yet been closely examined. Formation of phthalic acid as end-product via the diimine of *(7)* has occasionally been postulated. According to *Quinkert*, saturated cyclic ketones split to give high yields of carboxylic acids [37] on exposure to ultraviolet light.

The same reactions take place in dioxane, tetrahydrofuran, and dimethylformamide, but at different rates. An example of the effect of the medium on the rate of the light reaction of *(7)* is shown in Figure 12; in one experiment *(7)* was dissolved in alcohol and in the other dyed onto polyamide (on polyester the reaction is even slower than on polyamide).

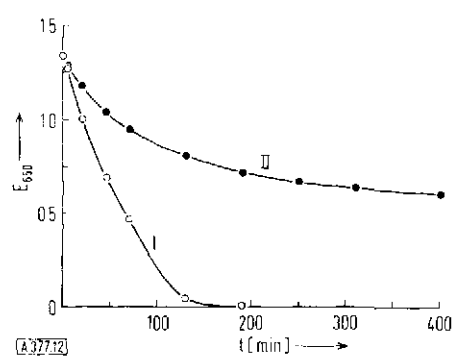
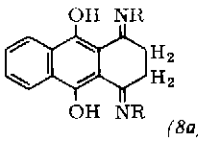



Fig. 12. Fading of *N,N'*-dimethyl-1,4-diaminoanthraquinone on ultraviolet irradiation.

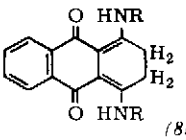
Curve I: *(7)* in ethanol.
Curve II: *(7)* dyed on polyamide.

[37] *G. Quinkert, B. Wegemund,* and *E. Blanke,* Tetrahedron Letters *1962*, 221.

Work on the interpretation of the nature of the intermediates $B_1$ and $B_2$ is not yet complete [*]. In contrast to the photochemical products of anthraquinone, this product is not the leuco-form of *(7)*, whose absorption spectrum is shown in Figure 9, Curve V. Structures *(8a)* or *(8b)* were proposed for the leuco-form of anthraquinone derivatives with proton-donating substituents at the 1- and 4-positions [39–41].

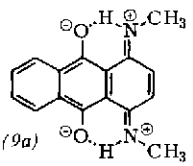


*(8a)*

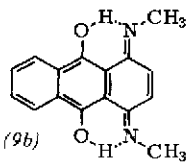


*(8b)*

With the aid of the polarographic half-wave potentials of *(7)* in a 0.1 M LiCl solution in 30 % water/70 % ethanol, it was shown that in the first stage of the reaction, one electron and one proton are taken up. On electrolysis under the same conditions in ethanol, *(7)* exhibits a spectrum identical with that of $B_1$, whereas on electrolysis in aprotic solvents such as acetone or acetonitrile, it gives rise to a long-lived free radical whose electron resonance spectrum exhibits a simple band (half-width ~ 12 gauss) with no fine structure. This radical has an absorption band with a simple maximum at 540 mμ (Curve VI of Fig. 9). According to *Dörr* and *Schwab* [36], its spectrum is similar to that of 1-chloroanthraquinone. It is probable that a semiquinone radical *(7)*-H· is involved, which reacts further in protonic solvents to form $B_1$. *Moran* and *Stonehill* postulated the formation of anthranone from the photoreactions of anthraquinone derivatives [38]. In the case of 1,4-bis-*N*-benzoylaminohydroquinone, *Coffey* [39] prefers the oxanthrone form to the anthrahydroquinone form, in contrast to the results with anthraquinone [42]. 1,4-Diamino-1-(*N*-methylamino)anthraquinone and 2-(*N*-methylamino)anthraquinone behave similarly on exposure to light. In these derivatives, as well as in *(7)*, the enolic forms *(9a)* or *(9b)* participate, so that their related behaviors, which differ



*(9a)*



*(9b)*

from that of anthroquinone, become plausible. *Couper* [43] concluded that successive decomposition of the methylamino groups occurs in *(7)* dyed on acetate. In our method, such reactions occurred to only a very slight extent. The same author found a yellow substance in solutions in ethyl acetate after the latter had been exposed to light, but this could not be detected on acetate fibers. *Couper* had previously suggested that a reduction step was involved and that the effect of light on the fiber and the solution leads to different decomposition products.

The results obtained with *(7)* may be summarized briefly as follows: the compound is stable in visible light but phototropic on exposure to ultraviolet light. When oxygen is excluded, *(7)* is ultimately reduced in two stages to a stable colorless substance. The "damage" caused by ultraviolet irradiation when *(7)* is transformed into $B_1$ and $B_2$ can generally be reversed by irradiation in its absorption band in the visible region, or the reverse reaction (oxidation) can be speeded up. This behavior was also observed in, for example, 2,2,6,7-tetrachloro-1-oxodihydronaphthalene, fulgides, stilbenes [44], anils [44], spiranes [45], *etc.* [24a, 25, 46 to 49].

Cellulose nitrate films undergo yellowing – presumably because of traces of impurities they contain – when irradiated by short-wavelength light ($\lambda < 300$ mμ), but are bleached again [50] by radiation of longer wavelength (300 mμ $< \lambda <$ 450 mμ). Aminoazo dyestuffs dyed on acetate are reported to exhibit the rare phenomenon of phototropy produced by longer-wavelength radiation ($\lambda = 400$ mμ); shorter-wavelength energy ($\lambda = 350$ mμ) has no effect, even though light of both spectral regions is absorbed to approximately the same extent [50]. It is probably not incorrect to assume a similar dependence on the wavelength of the radiation to explain the "irreversible" decolorization of dyes by light, although little information on this topic has so far been reported. As early as 1919, *Perrin* collected these observations in a general reaction scheme [50a]:

$$A_1 + h\nu_1 \rightleftharpoons A_2 + h\nu_2$$

The above behavior therefore effectively amounts to phototropically induced secondary phototropy, which may enhance the fastness of dyestuffs. For the frequency $\nu_1$ of most primary phototropy effects studied so far, $\nu_1 > \nu_2$. The absorption band induced by primary phototropy has generally a longer wavelength than that of the original compound. Our observations of a short-wave induced band of *N,N'*-dimethyl-1,4-diaminoanthraquinone *(7)* represent a rare exception. *Hirshberg* [19] found that for spiropyrans, $\nu_2$ does not lie in the region of the induced absorption band of long wavelength, but in the region of the long-wave ultraviolet band used as the source of radiation.

## IV. Phototropy of Miscellaneous Compounds

Several hundred phototropic substances have now been discovered, but indications of the type of structures necessary for phototropy are not yet available. So far, the mechanism of phototropy has been completely explained for only a few compounds. Early purely chemical investigations on phototropic solids brought little information and failed largely because the phototropically induced substance is present in only small amounts.

[*] It seemed more important to us to demonstrate the basic principles of phototropy with the aid of model experiments.


[38] *J. J. Moran* and *H. J. Stonehill*, J. chem. Soc. (London) *1957* 788.

[39] *S. Coffey*, Chem. and Ind. *1953*, 1068.

[40] *K. Zahn* and *P. Ochwat*, Liebigs Ann. Chem. *462*, 72 (1928).

[41] *S. M. Bloom* and *R. F. Hutton*, Tetrahedron Letters *1963*, 1993.

[42] *K. H. Meyer*, Liebigs Ann. Chem. *379*, 37 (1911).

[43] *M. Couper*, Textile Res. J. *21*, 720 (1951).

[44] *S. E. Sheppard*, Chem. Reviews *4*, 319 (1927).

[45] *O. Chandé* and *P. Rumpf*, C. R. hebd. Séances Acad. Sci. *236*, 697 (1953); *J. L. Masse*, ibid. *238*, 1320 (1954); *E. Berman, R. E. Fox*, and *F. D. Thomson*, J. Amer. chem. Soc. *81*, 5605 (1959).

[46] *H. Stobbe*, Liebigs Ann. Chem. *359*, 1 (1908); *380*, 1 (1911); Z. Elektrochem. angew. physik. Chem. *14*, 473 (1908); Ber. dtsch. chem. Ges. *46*, 226 (1913).

[47] *F. G. Brikwede*, J. opt. Soc. America *14*, 312 (1927).

[48] *M. Padoa* and *L. Santi*, Atti Accad. naz. Lincei, Mem., Cl. Sci. fisiche, mat. natur., Sez. II *21*, 188 (1912); Sez I, *25*, 808 (1916).

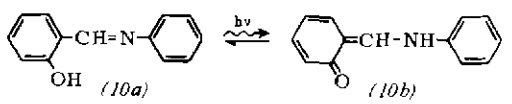
[49] *W. C. Clerk* and *G. F. Lothian*, Trans. Faraday Soc. *54*, 1790 (1958).

[50] *L. W. Mechel* and *H. Stauffer*, Helv. chim. Acta *24*, 151 (1941).

[50a] *J. Perrin*, Ann. Physique *10*, 133 (1919); *11*, 108 (1919).

In addition to transformations into quinonoid structures, *e.g.* in triphenylmethane dyes and camphor derivatives [51], we have mentioned induced reduction and oxidation processes. Phototropically induced isomerizations have also often been reported. Phototropic transformations from the more stable *trans*- into the less stable *cis*-form were studied by *Brode* and *Wyman* using thioindigo and hydroxyazo dyes [52]. Other phototropic *trans-cis* transformations were studied by *Klotz* and *Horowitz* [53] and by *Hartley* [53a]. The back reactions in these *trans-cis* rearrangements are kinetically of first order with respect to the phototropic substances [50, 53], while the back reactions of other phototropic systems may be of second order [53b].

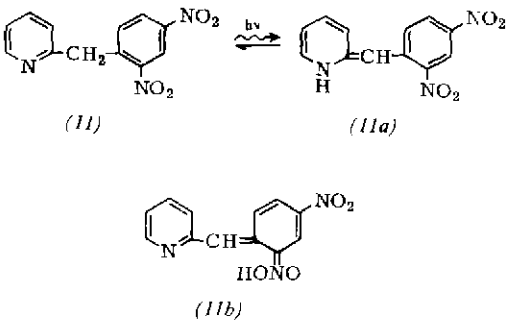
In model experiments designed to interpret the mechanism of vision, *Yoshizawa* and *Wald* [53c] found a phototropic reaction of rhodopsin to form *all-trans*-vitamin A-aldehyde + opsin. Secondary phototropy can cause 11-*cis*-vitamin A-aldehyde and opsin to be reformed, and these then recombine to form rhodopsin. *Gaouck* and *Le Fèvre* proposed the reaction scheme *(10a)* ⇌ *(10b)* [7] for the phototropy of anils, which occurs only in their solid form and which is considered



*(10a)* *(10b)*

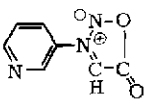
to involve exchange of protons between adjacent molecules. The two forms appear isomorphous on X-ray analysis. If the hydroxyl group in *(10a)* is methylated, phototropy is no longer observed. *Cohen*, *Hirshberg*, and *Schmidt* [54, 54a] observed phototropy of anils in "rigid solvents" and therefore suspect intramolecular proton transitions. In polar solvents, the phototropically induced form *(10b)* occurs in the dark, but in paraffin oil it appears only on exposure to radiation.

For 2-(2′,4′-dinitrobenzyl)pyridine *(11)*, a phototropic mechanism to form *(11a)* or *(11b)* is proposed [55]: *(11)* adsorbed on NaCl exhibits the same phototropic changes into *(11a)* or *(11b)*, but *(11)* adsorbed on MgO does not [55a].



*(11)* *(11a)* *(11b)*

In the case of spiranes [45] and spiropyrans [56, 57], the formation of phototropically induced isomers by opening of the ring has been reported. Phototropically induced free radicals from anthraquinone derivatives have been mentioned above; free radicals have been detected by electron-spin resonance in the phototropic reactions of solid *N*-3′-pyridylsydnone *(12)* [58, 59] and


*(12)*

of an imidazole derivative [60]. Oxygen-free methanolic solutions of chlorophyll also exhibit phototropy with the formation of free radicals [61] [*]. Formation of radicals is also postulated on exposure of malachite green leuco-cyanide in cyclohexane to light [62]. According to *Feichtmayr* and *Scheibe* [63], naphthoxy-radicals arise by phototropy of 2,3,6,7-tetrachloro-1-oxodihydronaphthalene. Phototropically induced free radicals or triplet states have been detected by their paramagnetism [64], but they do not always arise [58].

Some substances are phototropic only in the crystalline state or in the form of a particular modification, *e.g.* 2,3,6,7-tetrachloro-1-oxodihydronaphthalene [65]. Where pleochroism is present, *i.e.* where the absorption depends on the crystal's orientation, phototropic behavior may also be anisotropic and apparently reinforces the pleochroism.

[51] *B. K. Singh* and *B. Bhaduri*, Trans. Faraday Soc. *27*, 478 (1931).

[52] *W. R. Brode* and *G. M. Wyman*, J. Res. nat. Bur. Standards *47*, 170 (1951); *G. M. Wyman* and *W. R. Brode*, J. Amer. chem. Soc. *73*, 1487 (1951); *W. R. Brode*, *J. H. Gould*, and *G. M. Wyman*, ibid. *74*, 4641 (1952).

[53] *M. Horowitz* and *I. M. Klotz*, J. Amer. chem. Soc. *77*, 5011 (1955).

[53a] *G. S. Hartley*, J. chem. Soc. (London) *1938*, 633.

[53b] *M. Padoa* and *T. Minganti*, Chem. Abstr. *8*, 1368 (1914).

[53c] *T. Yoshizawa* and *G. Wald*, Nature (London) *197*, 1279 (1963).

[54] *M. D. Cohen*, *Y. Hirshberg*, and *G. M. J. Schmidt* in *M. Hadzi*: Hydrogen Bonding. Pergamon Press, London-New York 1959.

[54a] *G. N. Lewis* and *D. Lipkin*, J. Amer. chem. Soc. *64*, 2801 (1942).

[55] *R. Hardionk*, *H. S. Mosher*, and *P. Passailaigue*, Trans. Faraday Soc. *56*, 44 (1960); *W. C. Clark* and *G. F. Lothian*, ibid. *54*, 1795 (1958).

[55a] *G. Kortüm*, *M. Kortüm-Seiler*, and *D. S. Bailey*, J. physic. Chem. *66*, 2439 (1962).

[56] *Y. Hirshberg* and *E. Fischer*, J. chem. Soc. (London) *1954*, 297, 3129.

[57] *Y. Hirshberg*, J. Amer. chem. Soc. *78*, 2304 (1956).

[58] *H. S. Gutowsky* and *R. L. Rutledge*, J. chem. Physics *29*, 1183 (1958).

[59] *T. Mill*, *A. van Roggen*, and *C. F. Wahlig*, J. chem. Physics *35*, 1139 (1961).

[60] *T. Hayaski*, *K. Maeda*, *S. Shida*, and *K. Nakada*, J. chem. Physics *32*, 1568 (1960).

[61] *R. L. Livingston* and *V. A. Ryan*, J. Amer. chem. Soc. *75*, 2176 (1953); *R. L. Livingston*, *G. Porter*, and *M. Windsor*, Nature (London) *173*, 485 (1954); *E. W. Abrahamson* and *H. J. Linschitz*, J. chem. Physics *23*, 2198 (1955).

[*] Phototropy can play a role in biochemistry (cf. the postulates concerning the mechanism of vision. During natural growth processes, hydrogen bonds must be opened and closed. Keto-enol tautomerism of the anils [7] indicates that phototropy may be capable of effecting this (cf. also [61a]).

[61a] *R. Robert*, J. Soc. Dyers Colourists *65*, 699 (1949).

[62] *E. O. Holmes*, J. physic. Chem. *61*, 434 (1957).

[63] *F. Feichtmayr* and *G. Scheibe*, Z. Naturforsch. *13b*, 51 (1958); J. physic. Chem. *66*, 2449 (1962).

[64] *G. Kortüm*, Angew. Chem. *70*, 14 (1958); *G. Kortüm*, *W. Theilacker*, and *G. Littmann*, Z. Naturforsch. *12a*, 401 (1957).

[65] *F. Weigert*, Z. Elektrochem. angew. physik. Chem. *24*, 222 (1918); *H. Stobbe*, Liebigs Ann Chem. *359*, 1 (1908).

The first inorganic substance found to be phototropic was lithopone ZnS, which exhibits this phenomenon in the presence of moisture and oxygen; generally, such substances are solids [66]. Solutions of certain inorganic substances also exhibit phototropy [67].

Sensitized phototropy was observed in aqueous potassium ferrocyanide solutions to which phenolphthalein had been added. Here reversible color changes take place on exposure to light [68]. It is noteworthy that, as for phosphorescence, traces of activators may be responsible for the manifestation of phototropy by inorganic substances [67]. An example of this type in organic chemistry is acetanilide-*p*-disulfoxide, in which phototropy appears only in the presence of 0.1–1.0 % 1-acetanilide-*p*-disulfide [69].

Vat dyes can acquire phototropic properties by aftertreatment on the fiber, *e.g.* after impregnation [70]. The dark reverse reactions of phototropic dyes on dyed fibers may take several days to reach completion [70].

Phototropy thus plays a part both in the light-fastness of dyes and in biochemical processes. *Hirshberg* [19] has recommended the use of phototropic dyes with short-wave induced primary phototropy that is extinguished by long-wave induced secondary phototropy as high-speed memory elements for computers. Phototropic dyes have also been proposed as light filters which adapt themselves to match any given light intensity [24b], and phototropically formed dyestuff radicals may be employed as polymerization initiators [71].

The known behavior of phototropic systems can be summarized by the qualitative energy diagram shown in Figure 13; kT with an arrow pointing downwards denotes an exothermic process, one pointing upwards an endothermic process or one requiring an activation energy. On absorption of light by a species A, an activated quantum-mechanically unstable or metastable

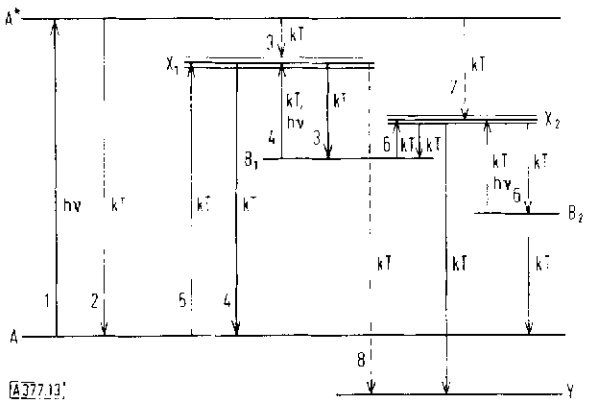



Fig. 13. Qualitative energy diagram for phototropic and photochemical processes.

state A* is produced (Process 1); A* can return to state A by giving off thermal energy (Process 2). If phototropy is involved, transformation into a quantum-mechanically stable but thermodynamically unstable state $B_1$ occurs via an intermediate state X (Process 3). Little is known about the positions and number of the intermediate states $X_1$ and $X_2$. The phototropically induced state $B_1$ can be transformed back into state A (Process 4) either thermally by using an activation energy, or by secondary phototropy using light energy. Here again the reaction proceeds via a largely unknown state $X_1$. At high temperatures, more molecules with adequate thermal energy kT are available, so that the reverse reaction $B_1 \rightarrow X_1 \rightarrow A$ (Process 4) is accelerated.

Again, at high temperatures, more molecules with higher thermal energies are available in the starting state A and thus more molecules can attain the state $B_1$ via $X_1$ by thermal means. The thermal equilibrium $A \rightleftharpoons B_1$ is consequently displaced towards $B_1$. When $B_1$ can be identified optically, this process is described as thermotropy or thermochromism (Process 5). Under certain conditions, adsorption causes the state $B_1$ to become energetically more favorable than state A; such a process is termed metachromatism [72]. Sometimes various unstable states $B_2$, $B_3$, *etc.*, can exist; $B_2$ may then be reached via $B_1$ (Process 6) or directly via A* (Process 7). Transformation of $B_2$ back into A may occur directly via $X_2$ or via $B_1$ and $X_1$. In addition to the phototropic and thermotropic states $B_1$, $B_2$, *etc.*, an end-product Y, which is energetically more favorable than A, may be formed directly by photochemical reactions from all the intermediate states. Naturally, here too normal, thermally activated chemical reactions leading to Y via any of the intermediate states X (Paths 5–8) are possible. The fact that the light-induced deterioration of dyes frequently occurs with rather low quantum yields probably means that here the intermediate state X in the reaction A* →X→Y is energetically higher than A*. A physical interpretation of this phenomenon would be that, although the excited molecule is high in energy, the more polar structures, which are necessary for the reaction with neighboring molecules, are in a rather deep potential well owing to Coulomb forces.

The relative positions of the levels in the above purely qualitative and heuristic energy scheme (Fig. 13) can of course vary from system to system. We found the energy difference between A and $B_1$ for parafuchsin-$H_2SO_3$ to be about 30 kcal/mole. For the activation $A \rightarrow A^*$ in the absorption maximum, a value $h\nu \cdot N_L$ = 105 kcal/mole is required, so that the transformation $A^* \rightarrow X_1 \rightarrow B_1$ liberates about 75 kcal/mole.

For the phototropic *cis-trans* rearrangement of 4-(*p*-dimethylaminobenzazo)phenylmercury(II) acetate, $\Delta F$ was found to be 22.5 kcal/mole, and $\Delta H$ = 19.6 kcal/mole [53]. $\Delta H$ for the phototropy of a 2,4,5-triphenylimidazole derivative was given as 5 kcal/mole, and the

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[70] *H. Waibel*, Melliand Textilber. *36*, 737 (1955).

[71] U.S.-Pat. 2875047 and 3097096, inventor: *G. Oster*.

[72] *J. A. Bergeson* and *M. Singer*, J. biophysic. biochem. Cytol. *4*, 433 (1958); *P. Ehrlich*, Ph. D. Thesis, Universität Leipzig, 1877; *G. Kortüm*, *J. Vogel*, and *W. Braun*, Angew. Chem. *70*, 651 (1958); *G. Kortüm* and *J. Vogel*, Chem. Ber. *93*, 706 (1960).

activation energy for $B_1 \rightarrow X_1$ as 14 kcal/mole [73]. The activation energy for the dark reverse reaction of salicylidene-*m*-toluidine was found to be 25 kcal/mole [73], and that for the phototropic *cis-trans* rearrangement of the methinecyanines was 8 kcal/mole [74].

## V. Closing Remarks

In 1899, in the first publication dealing with phototropy, *Marckwald* concluded that "the action of light described here is a purely physical phenomenon; my reason for describing it is to encourage, physicists to investigate the matter further". In 1929, *Chalkley* [17] declined to differentiate between purely physical or chemical explanations for phototropy.

Today it is clear that phototropy mostly represents transformations into thermodynamically unstable, chemically still partly unknown states of molecules. Owing to the revolution in physico-chemical techniques, the study of phototropy has recently received great impetus and may substantially help to clarify the reaction mechanisms of photochemical processes. Its general laws are today fairly well understood; what is still lacking is a larger amount of evidence to help to explain the dependence of the mechanism on chemical constitution. Just as the list of stable atomic nuclei has been complemented by unstable nuclei, photochemistry will enrich the number of thermodynamically stable compounds with thermodynamically unstable species. In 1964, it is therefore reasonable to alter *Marckwald*'s words as follows: "My reason for describing this phenomenon is to encourage chemists to investigate the matter further".

*The authors wish to express their thanks to their colleagues, particularly Mr. W. Ditter, for assistance with the measurements and their evaluation, to Dr. Beck (Ludwigshafen), who carried out the polarographic measurements, and to Dr. Schlag (Ludwigshafen) for the electron spin resonance studies.*

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German version: Angew. Chem. 76, 463 (1964)
Translated by Express Translation Service, London

[73] *G. Lindemann*, Z. wiss. Photogr., Photophysik Photochem. *50*, 347 (1955).

[74] *G. Scheibe, E. Günther*, and *F. Dörr*, S.-B. bayer. Akad. Wiss. Jan. 15th, 1954; *G. Scheibe, E. Günther*, and *F. Baumgärtner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *60*, 570 (1956); *G. Dobmeier*, Ph. D. Thesis, Technische Hochschule München, 1957.

# COMMUNICATIONS

## On the Existence of a Tungsten Carbonyl Carbene Complex

By Prof. Dr. E. O. Fischer and Dipl.-Chem. A. Maasböl

Institut für Anorganische Chemie der Universität München (Germany)

When $W(CO)_6$ is treated with $LiC_6H_5$ in ether under nitrogen, nucleophilic addition takes place without elimination of CO to yield an orange-yellow, water-soluble, diamagnetic anion, which can be precipitated as its tetramethylammonium salt. This orange, finely crystalline derivative has the composition $[N(CH_3)_4][W(CO)_5COC_6H_5]$ and melts at 102.5 °C (decomp.). The anion can be protonated by acids. On attempting to isolate the free "hydride" resulting from acidification by extraction with ether, only $W(CO)_6$ and benzaldehyde were found after removal of solvent from the extract. In dilute solution, the protonated product can be methylated in good yields using diazomethane. After chromatography and sublimation *in vacuo* at 45–50 °C, orange-red, diamagnetic crystals, m.p. 59 °C, which are very soluble in organic media, can be isolated. Analysis and molecular-weight determinations indicate that their composition is $W(CO)_5(COC_6H_5)(CH_3)$.

Yellow diamagnetic crystals of $[N(CH_3)_4][W(CO)_5COCH_3]$ m.p. 143 °C, can be obtained in an analogous manner by addition of $LiCH_3$ to $W(CO)_6$ in ether and precipitation of the salt from aqueous solution. On protonation and subsequent methylation with $CH_2N_2$, the anion gives yellow, diamagnetic, volatile $W(CO)_5(COCH_3)(CH_3)$ *(1)*, m.p. 52 °C.

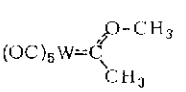
The nature of the bonding of the methyl group introduced into the complex *(1)* by $CH_2N_2$ could not be settled by infrared spectroscopy. The spectrum of $W(CO)_5(COCH_3)(CH_3)$, the compound which has so far been more thoroughly investigated, shows two strong, somewhat broadened bands at 1252 and 1167 $cm^{-1}$ (Nujol/Hostaflon). While the band at 1252 $cm^{-1}$ can be attributed quite plausibly to a C–O single bond, that at 1167 $cm^{-1}$ may be due to either a C O bond or a $CH_3$–W group, as a comparison with the spectrum of $C_5H_5W(CO)_3CH_3$ [1] shows, in which the $\delta(CH_3-W)$ vibration appears at 1179 $cm^{-1}$ [2].

More reliable information on the structure of *(1)* was obtained from comparison of the proton magnetic resonance spectra [3] of $W(CO)_5(COCH_3)(CH_3)$, $C_5H_5W(CO)_3CH_3$, and $C_5H_5W(CO)_3COCH_3$ [4].

| Compound | Chemical shift τ referred to $C_6H_6$ (relative to TMS at τ = 2.88) [ ] = relative intensities Concn.: 1 mmole/ml $C_6H_6$ | |
|---|---|---|
| *(1)* $W(CO)_5(COCH_3)(CH_3)$ | 6.17[3] | 7.69[3] |
| *(2)* $C_5H_5W(CO)_3COCH_3$ | 5.23[5] | 7.50[3] |
| *(3)* $C_5H_5W(CO)_3CH_3$ | 5.45[5] | 9.55[3] |

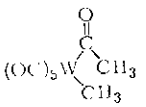
We assign the peak at τ = 7.69 for *(1)* to the methyl group introduced by $LiCH_3$ addition. If it is assumed that this is present as a W–$COCH_3$ grouping, the value agrees well with that of the peak for the acetyl group bound to tungsten in *(2)* [τ = 7.50]. The fact that the other $CH_3$ proton peak for compound *(1)* occurs at τ = 6.17 and that of a $CH_3$ group bound directly to tungsten only appears at much higher fields, *e.g.* τ = 9.55 for *(3)*, leads to the conclusion that no $CH_3$–W grouping is present in *(1)*.

We believe therefore that a structure such as



may be assumed for $W(CO)_5(COCH_3)(CH_3)$. This corresponds to a "methoxymethylcarbene" bound to $W(CO)_5$ and

would thus represent the first transition-metal complex of a carbene. X-ray investigations currently in progress are expected to show that the alternative structure



does not occur. We are of this opinion because of the evidence already cited and also because of the absence of any characteristic >C=O vibrations in the infrared spectrum between 1500 and 1800 $cm^{-1}$.

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[1] *E. O. Fischer, W. Hafner,* and *H. O. Stahl,* Z. anorg. allg. Chem. *282,* 47 (1955); *T. S. Piper* and *G. Wilkinson,* J. inorg. nucl. Chem. *3,* 104 (1956).

[2] We wish to thank Doz. *H. P. Fritz* for numerous discussions.

[3] We wish to thank Dipl.-Chem. *C. G. Kreiter* for measurement of the NMR spectra and for many discussions.

[4] *K. Fichtel,* Ph. D. Thesis, Universität München, 1961.

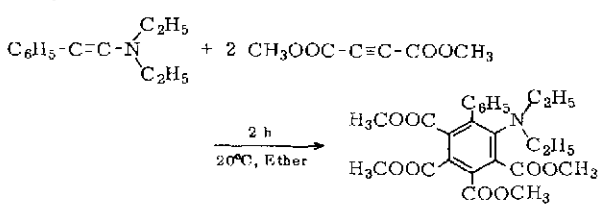
## Addition Reactions of Alkynylamines [1]

By Dr. H. G. Viehe, Dr. R. Fuks, and M. Reinstein [1a]

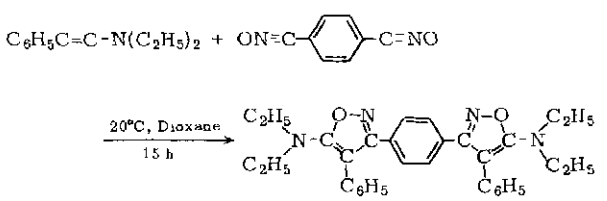
Union Carbide European Research Associates,
Brussels (Belgium)

Many compounds react with alkynylamines [2] by addition to their nitrogen-polarized triple bond, mostly under very mild conditions. Examples are given in the following equations. The tendency of alkynylamines (which can be considered as intramolecular anhydrides of carboxamides) to combine with water is so strong that they promise to become dehydrating agents of general importance. For example, the formation of anhydrides from carboxylic acids occurs more rapidly with alkynylamines than with dicyclohexylcarbodiimide or ethoxyacetylene.

1. Cycloadditions

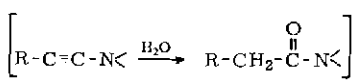


m.p. 140°C, yield ca. 80%

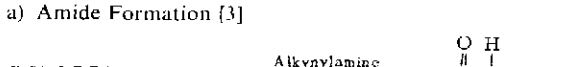


m.p. 228°C, yield 91%[4]

2. Dehydration Reactions



a) Amide Formation [3]

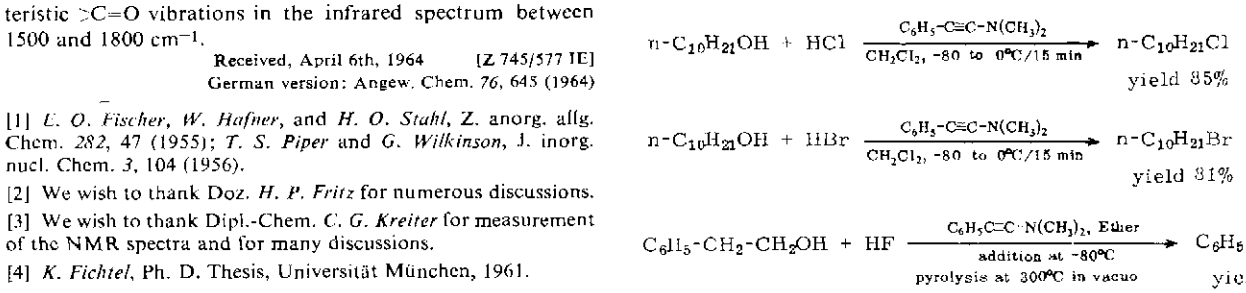


b) Carboxylic Anhydride Formation

The table gives yields [%] after 5 min at 10 °C in benzene. The data were obtained by titration of the residual free acid, the figure in brackets is yield of isolated anhydride.

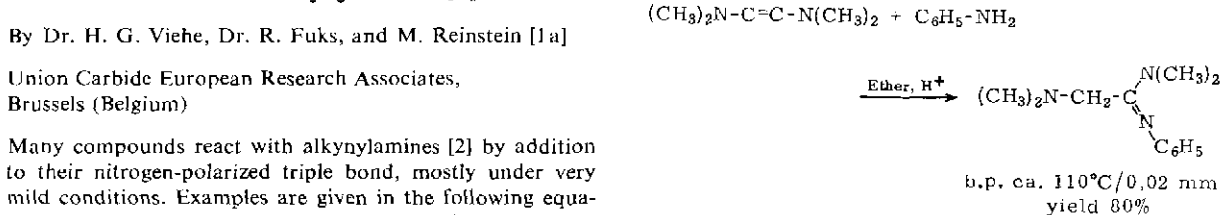
| | $C_6H_5C{\equiv}C{-}N(CH_3)_2$ | $(CH_3)_3C{-}C{\equiv}C{-}N(CH_3)_2$ |
|---|---|---|
| n-$C_3H_7COOH$ | 96 | 93 |
| $C_6H_5COOH$ | 98 | 97 (95) |
| | $C_6H_{11}{-}N{=}C{=}N{-}C_6H_{11}$ | $H{-}C{\equiv}C{-}OC_2H_5$ |
| n-$C_3H_7COOH$ | 70 | 0 |
| $C_6H_5COOH$ | 63 | 0 |

c) Conversion of Alcohols to Alkyl Halides

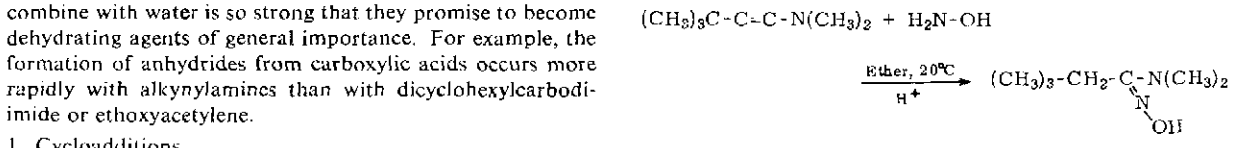


3. Addition of Amines

a) Amidine Formation

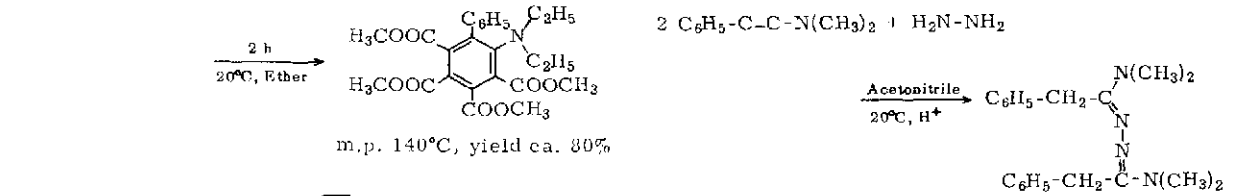


b) Amidoxime Formation



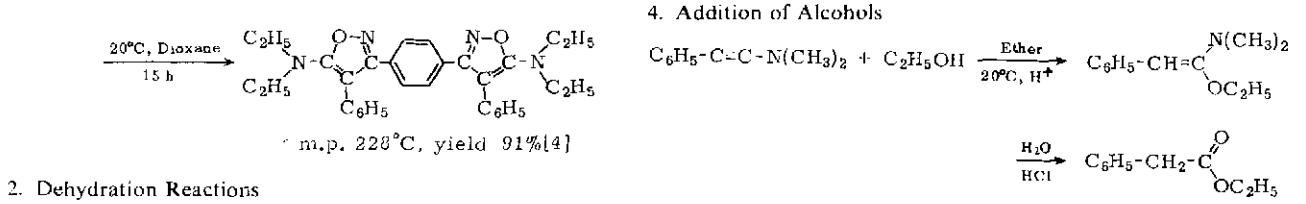
m.p. 114°C
yield 73%

c) Amide Hydrazone Formation



m.p. 147–148°C
yield 50%

4. Addition of Alcohols



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[1] Heterosubstituted Acetylenes, Part 8. – Part 7: *H. G. Viehe, S. I. Miller,* and *J. I. Dickstein,* Angew. Chem. *76,* 537 (1964); Angew. Chem. internat. Edit. *3,* 582 (1964).

[1a] Responsible for experimental work.

[2] *H. G. Viehe* and *M. Reinstein,* Angew. Chem. *76,* 537 (1964); Angew. Chem. internat. Edit. *3,* 506 (1964).

[3] *R. Buijle* and *H. G. Viehe,* Angew. Chem. *76,* 572 (1964); Angew. Chem. internat. Edit. *3,* 582 (1964).

[4] We are indebted to Dr. *F. Eloy* for carrying out this experiment.

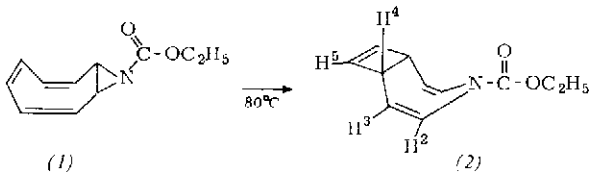
## The Rearrangement of 9-Azabicyclo[6,1,0]-nonatriene to 4-Azabicyclo[5,2,0]nonatriene

By Dr. S. Masamune and N. T. Castellucci

Mellon Institute, Pittsburgh, Pennsylvania (U.S.A.)

We have investigated the thermal rearrangement of the adduct of ethoxycarbonylnitrene onto cyclooctatetraene.

The generation of ethoxycarbonylnitrene, $C_2H_5OCON$, from *N*-(*p*-nitrobenzenesulfonoxy)urethane and triethylamine [1] in cyclooctatetraene afforded this adduct *(1)* in 35–40 % yield. The NMR spectrum of *(1)* is very similar to that of cyclooctatetraene epoxide [2] and shows a singlet at $\tau = 6.90$ (two allylic protons), a multiplet at $\tau$ -- 3.95–4.15 (six olefinic protons), and signals for an ethyl group. This spectrum and the elemental analysis support the assignment of structure *(1)* to this adduct.




*(1)* *(2)*

Although cyclooctatetraene epoxide is stable at 120 °C for a few hours, adduct *(1)* rearranged readily within 30 minutes at 80 °C to afford an isomer *(2)*, b.p. 65–67 °C/0.07 mm, $\lambda_{max} = 228$ mμ ($\varepsilon = 1.23 \times 10^4$) in isooctane, $\lambda_{max} = 5.81$, 6.02 μ, in chloroform. The NMR spectrum of this isomer exhibited signals at $\tau = 6.23$ (H-4) [*], 4.83 [*] and 5.00 (H-3) [*], 3.77 (sharp singlet, H-5), 3.08 [*] and 3.25 (H-2) [*] in addition to a typical ethyl-group absorption. The spectral evidence permits us to assign structure *(2)* to the rearranged compound. The coupling constants [J(H-4)–(H-5) = 0, J(H-2) (H-3) = 10.5 cps] are in agreement with the stereochemistry expected for this molecule.

The valence-bond rearrangement of *(1)* to *(2)* presents a striking contrast to the thermal behavior of cyclooctatetraene [4], its epoxide [3], and its carbene adducts [5].

Received, May 8th, 1964 [Z 740/565 IE]
German version: Angew. Chem. *76*, 569 (1964)

[1] *W. Lwowski, T. J. Maricich*, and *T. W. Mattingly*, J. Amer. chem. Soc. *85*, 1200 (1963). – We were able to trap an unstable intermediate, m.p. 55 °C, in the formation of the nitrene. This intermediate was characterized by its analysis and spectra as the triethylamine salt of *N*-(*p*-nitrobenzenesulfonoxy)urethane. This salt is very unstable and readily generates the nitrene and triethylamine sulfonate at room temperature.

[2] *A. C. Cope, P. T. Moore*, and *W. R. Moore*, J. Amer. chem. Soc. *80*, 5505 (1958).

[3] *G. Büchi* and *E. M. Burgess*, J. Amer. chem. Soc. *84*, 3104 (1962).

[*] These peaks showed fine splittings.

[4] *R. Huisgen* and *F. Mietzsch*, Angew. Chem. *76*, 36 (1964); Angew. Chem. internat. Edit. *3*, 83 (1964).

[5] *E. Vogel*, Angew. Chem. *74*, 829 (1962); Angew. Chem. internat. Edit. *2*, 1 (1963); *E. Vogel, W. Wiedemann, H. Kiefer*, and *W. F. Harrison*, Tetrahedron Letters *1963*, 673; *T. J. Katz* and *P. J. Garratt*, J. Amer. chem. Soc. *85*, 2852 (1963); *K. F. Bangert* and *V. Boekelheide*, ibid. *86*, 905 (1964).

## Peptide Syntheses with Alkynylamines [1]

By Dr. R. Buijle and Dr. H. G. Viehe

Union Carbide European Research Associates, Brussels (Belgium)

Alkynylamines are excellent dehydrating agents [2]. One of the reactions which can be readily carried out with these reagents is the synthesis of amides from amines and carboxylic acids. As the following examples show, peptides are obtained in almost quantitative yield by this method.

1. A solution of 1 g of dimethylaminophenylacetylene or dimethylamino-t-butylacetylene in 25 ml of tetrahydrofuran is added at 35–40 °C over 1 h to a solution of 1.27 g of bis-carbobenzoxy-L-cystine and 0.8 g of dimethyl-L-aspartate in 30 ml of tetrahydrofuran. Dimethyl bis-carbobenzoxy-L-cystinyl-bis-L-aspartate, m.p. 82 °C from ether/petroleum ether, is formed in 99 % yield (1.95 g).

2. Under identical conditions, the reaction of 1.50 g of γ-methylcarbobenzoxy-L-glutamate with 0.80 g of dimethyl-L-aspartate gives 2.1 g (97 %) of the corresponding peptide.

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German version: Angew. Chem. *76*, 572 (1964)

[1] Heterosubstituted Acetylenes, Part 9. – Part 8: [2].

[2] *H. G. Viehe, R. Fuks*, and *M. Reinstein*, Angew. Chem. *76*, 571 (1964); Angew. Chem. internat. Edit. *3*, 581 (1964).

## Alkynylamines from Halogenoalkynes and Tertiary Amines

By Dr. H. G. Viehe [1]

Union Carbide European Research Associates, Brussels (Belgium)

and Prof. S. I. Miller and J. I. Dickstein

Illinois Institute of Technology, Chicago, Ill. (U.S.A.)

Until recently, alkynylamines (amino acetylenes) were almost unknown but some have now become readily accessible [3] either via nucleophilic substitution of halogen at the acetylenic triple bond [1] or by elimination of hydrogen halide from suitable halogenated amines [2].

Following the synthesis of dimethylamino-t-butylacetylene *(1)* from t-butylchloroacetylene and trimethylamine, it appeared desirable to determine the structure of the *N*-phenylethynylammonium salts *(2)* [4] obtained in 35 % yield on treating triethylene diamine with phenylhalogenoacetylenes in benzene at room temperature, by analogy to the reaction of halogenoacetylenes with triphenylphosphine [4,5].

$$(CH_3)_3C\text{-}C{\equiv}C\text{-}Cl + 2\ N(CH_3)_3 \longrightarrow (CH_3)_3C\text{-}C{\equiv}C\text{-}N(CH_3)_2 + (CH_3)_4N^{\oplus}Cl^{\ominus}$$

*(1)*

$$C_6H_5\text{-}C{\equiv}C\text{-}Cl + 2\ N\langle\rangle N \longrightarrow C_6H_5\text{-}C{\equiv}C\text{-}N\langle\rangle N\ {}^{\oplus}N\langle\rangle N \quad Cl^{\ominus}$$

*(2)*

$$\xrightarrow{H_2O} C_6H_5\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}N\langle\rangle N\ {}^{\oplus}N\langle\rangle N \quad Cl^{\ominus}$$

*(3)*

The salt *(2)* which separates out slowly from the benzene solution of the components is very hygroscopic; its triple bond apparently becomes hydrated with formation of *(3)*, for its infrared spectrum subsequently shows an amide band at 6.12 μ. The elemental composition and molecular weight of *(3)* indicate combination of 2 moles of triethylene diamine with 1 mole of phenylchloroacetylene. The NMR spectrum of *(3)* shows a ratio of 5 phenyl protons (–2.6 ppm in relation to $H_2O$) to about 26 alkyl protons (ca. 2 at 0.45 ppm, ca. 16 at 1.1–1.2 ppm, ca. 2 at 1.85 ppm, and ca. 6 at 2.2 ppm).

Quaternary alkynylammonium salts appear to be unstable (like quaternary cyanoammonium salts) and to undergo Hofmann degradation with loss of alkane to yield alkynylamines;

the latter are only weakly basic owing to the electron attraction of the triple bond. The quaternary *N*-alkynylammonium salt which is presumably initially formed from triethylene diamine and phenylchloroacetylene can condense in a subsequent reaction with a further mole of tertiary amine [6] to form *(2)*.

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[1] Heterosubstituted Acetylenes, Part 7. – Part 6: *H. G. Viehe* and *M. Reinstein*, Angew. Chem. 76, 537 (1964); Angew. Chem. internat. Edit. 3, 506 (1964).

[2] *H. G. Viehe*, Patent Applications.

[3] Cf. references cited in [1], and *V. I. Ivanik*, Zh. obsh. Khim. (U.S.S.R.) 33, 1697 (1963); *V. Wolf* and *F. Kowitz*, Liebigs Ann. Chem. 638, 33 (1960).

[4] *H. G. Viehe* and *E. Franchimont*, Chem. Ber. 95, 319 (1962).

[5] *G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa*, and *S. I. Miller*, J. Amer. chem. Soc. 85, 1648 (1963); *C. E. Orzech, C. A. Welch, G. R. Ziegler, J. I. Dickstein*, and *S. I. Miller*, ibid. 84, 2020 (1962); *A. K. Kuriakose* and *S. I. Miller*, Tetrahedron Letters 1962, 905.

[6] Cf. also: *S. D. Ross, J. J. Bruno*, and *R. C. Peterson*, J. Amer. chem. Soc. 85, 3999 (1963).

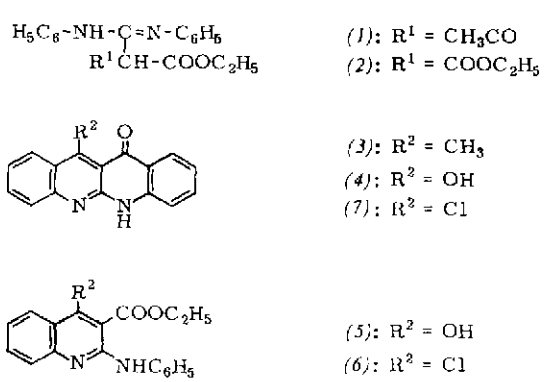
## A New Synthesis of Dibenzo[b,g]-[1,8]-naphthyridones

By Dr. A. K. Mallams [*]

Department of Chemistry, University of the Witwatersrand, Johannesburg (South Africa)

*Dziewoński* and *Dymek* [1] isolated the dibenzo[*b,g*]-[1,8]naphthyridone *(4)* from the mixture of compounds obtained by heating acetanilide with diphenylurea. The present new synthesis gave excellent yields of dibenzo[*b,g*]-[1,8]naphthyridones without any by-products.

When 2 g of ethyl α-(*N,N'*-diphenylguanyl)acetoacetate *(1)* [2] were heated with 20 g of polyphosphoric acid at 140 °C for 1 h, a 94 % yield of 11-methyldibenzo[*b,g*]-[1,8]naphthyrid-12(5*H*)-one *(3)* was obtained as yellow needles from aqueous acetic acid, m.p. 304–308 °C (decomp.). The use of smaller amounts of polyphosphoric acid gave lower yields of *(3)*. The latter was insoluble in hot dilute alkali but soluble in hot mineral acids. Ethanolic solutions of *(3)* exhibit yellow-green fluorescence.



*(1)*: $R^1 = CH_3CO$
*(2)*: $R^1 = COOC_2H_5$

*(3)*: $R^2 = CH_3$
*(4)*: $R^2 = OH$
*(7)*: $R^2 = Cl$

*(5)*: $R^2 = OH$
*(6)*: $R^2 = Cl$

When 2 g of ethyl *N,N'*-diphenylguanylmalonate *(2)* [2,3] were heated with 20 g of polyphosphoric acid at 140 °C for 1 h, a quantitative yield of 11-hydroxydibenzo[*b,g*]-[1,8]-naphthyrid-12(5*H*)-one *(4)* was obtained as yellow needles from acetic acid, m.p. > 400 °C. Smaller amounts of polyphosphoric acid (10 g) resulted in lower yields of *(4)*. When the reaction was stopped after 20 min by pouring the reaction mixture into 80 ml of cold water, the insoluble product *(4)* was obtained in 20 % yield. Neutralization of the acidic filtrate gave a 35 % yield of ethyl 4-hydroxy-2-phenylaminoquinoline-3-carboxylate *(5)* as pale yellow needles from dilute ethanol, m.p. 185–187 °C.

Treatment of 0.2 g of *(5)* with 2 g of polyphosphoric acid at 140 °C for 1 h afforded a quantitative yield of *(4)*.

Ethyl 4-chloro-2-phenylaminoquinoline-3-carboxylate *(6)* was prepared in 94 % yield by refluxing 0.1 g of *(5)* with 2 ml of redistilled phosphorus oxychloride for 10 min; colorless needles from dilute ethanol, m.p. 62–63 °C.

11-Chlorodibenzol[*b,g*]-1,8]naphthyrid-12(5*H*)-one *(7)* was obtained analogously in 65 % yield on refluxing 0.1 g of *(4)* with 6 ml of redistilled phosphorus oxychloride for 3 h; pale yellow needles from ethanol, m.p. > 400 °C.

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German version: Angew. Chem. 76, 646 (1964)

[*] Present address: Organic Research Division, African Explosives and Chemical Industries, Modderfontein, Transvaal, South Africa. The author wishes to thank the Sir Ernest Oppenheimer Memorial Trust for the award of a research fellowship.

[1] *K. Dziewoński* and *W. Dymek*, Roczniki Chem. 20, 38 (1946).

[2] *W. Traube* and *A. Eyme*, Ber. dtsch. chem. Ges. 32, 3176 (1899).

[3] *V. E. Tishchenko* and *N. V. Koshkin*, Zh. obshch. Khim. 4, 1021 (1934).

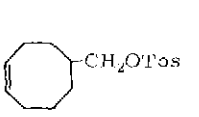
## Bicyclo[3,3,1]nonan-2-ol from 4-Cyclooctenylmethyl Toluenesulfonate

By Doz. Dr. M. Hanack and Dipl.-Chem. W. Kaiser

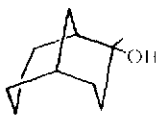
Chemisches Institut der Universität Tübingen (Germany)

2-Acetoxybicyclo[3,2,1]octane is formed by acetolysis of 3-cycloheptenylmethyl *p*-bromobenzenesulfonate [1]. 4-Cyclooctenylmethyl derivatives also give rise to bicyclic reaction products by transanular participation of the double bond during solvolysis.

4-Cyclooctenylmethanol (m.p. of *p*-nitrobenzoate 52–53 °C) is readily obtained from 4-cyclooctenecarboxylic acid [2]. The alcohol was converted into the tosylate *(1)* (Tos = $SO_2C_6H_4CH_3$), m.p. 29–30 °C, which was solvolysed at 60 °C for 48 hours in glacial acetic acid plus sodium acetate. The acetate obtained was reduced with $LiAlH_4$ to give some unidentified hydrocarbons and 60 % of an alcohol fraction which consisted predominantly of bicyclo[3,3,1]nonan-2-ol *(2)* [3]. Oxidation of the alcohol gave bicyclo[3,3,1]nonan-2-one [3,4] plus 18 % of another ketone, presumably bicyclo-[4,2,1]nonan-2-one. The participation of the double bond is



*(1)*



*(2)*

also shown by the rate of acetolysis of *(1)*. The reaction proceeds fifty times as fast as acetolysis of cyclooctanylmethyl toluenesulfonate.

Received, May 29th, 1964 [Z 744/576 IE]
German version: Angew. Chem. 76, 572 (1964)

[1] *G. LeNy*, Séances Acad. Sci. 251, 1526 (1960); cf. also *S. Winstein* and *P. Carter*, J. Amer. chem. Soc. 83, 4485 (1961).

[2] *G. Stork* and *H. K. Landesman*, J. Amer. chem. Soc. 85, 5129 (1963).

[3] *H. Meerwein, F. Kiel, G. Klosgen*, and *E. Schoh*, J. prakt. Chem. [2] 104, 161 (1922).

[4] *J. P. Ferris* and *N. C. Miller*, J. Amer. chem. Soc. 85, 1325 (1963).

## Conversion of Succinyl Dichloride into γ-Chlorocaproic Acid

By Dr. H. Reinheckel

Institut für Fettchemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

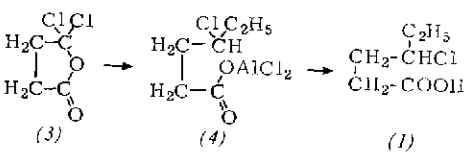
The dichlorides of higher α,ω-dicarboxylic acids are alkylated by $Al_2(C_2H_5)_3Cl_3$ to give diketones [1], by analogy to the reaction of the ω-carbonyl chlorides of carboxylic esters or of normal acyl chlorides. However, succinyl dichloride reacts in a different manner, as it yields only traces of octane-3,6-dione *(2)*, being mainly converted into γ-chlorocaproic acid *(1)*. This product is formed by alkylation and reduction of one carbonyl group, the second carbonyl group remaining unchanged.

The yield of *(1)* depends on the reaction conditions. Ethane is evolved as a by-product; ethylene is formed only in small amounts.

$$ClCO-(CH_2)_2-COCl \rightarrow \underset{\underset{Cl}{|}}{C_2H_5-CH-(CH_2)_2-COOH} + C_2H_5-CO-(CH_2)_2-CO-C_2H_5$$

*(1)*, 50–75 % *(2)*, 3–5 %

The reaction must start from the unsymmetrical cyclic form of succinyl dichloride, *viz.* γ,γ-dichloro-γ-butyrolactone *(3)*. One of the two carboxyl groups is converted into the aluminum salt *(4)* which cannot react further, even in the presence of a large excess of the ethylaluminum compound.



*(3)* *(4)* *(1)*

Under the same conditions, γ-chlorocaproyl chloride reacts in the normal way to give 6-chloro-3-octanone.

Reducing properties of ethylaluminum compounds other than dialkylaluminum hydrides are known only for triisobutylaluminum [2]. Triethylaluminium only rarely shows any reducing effects [2, 3]. Halogenated hydrocarbons [4] or ketones [5] can be reduced by triethylaluminum and, to a small extent, by diethylaluminum chloride. The reaction described here is, as far as we are aware, the first example of the reducing effect of $Al_2(C_2H_5)_3Cl_3$ on organic compounds in stoichiometric proportions.

Received, June 1st, 1964 [Z 743/575 IE]
German version: Angew. Chem. *76*, 646 (1964)

[1] *H. Bertsch* and *H. Reinheckel*, Fette, Seifen, Anstrichmittel *64*, 881 (1962).

[2] *K. Ziegler, K. Schneider*, and *J. Schneider*, Liebigs Ann. Chem. *623*, 9 (1959).

[3] *H. Meerwein, G. Hinz, H. Majert*, and *H. Sönke*, J. prakt. Chem. [2] *147*, 226 (1937).

[4] *H. Reinheckel*, Angew. Chem. *75*, 1206 (1963); Angew. Chem. internat. Edit. *3*, 65 (1964).

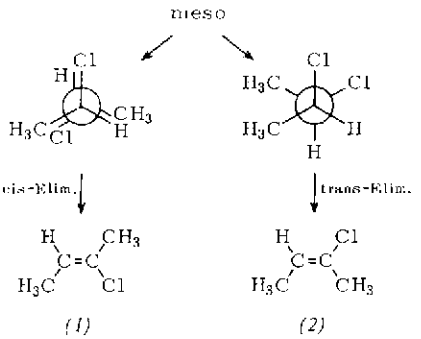
[5] *S. Pasynkiewicz, W. Dahlig*, and *T. Wojnarowski*, Roczniki Chem. [Ann. Soc. chim. Polonorum] *38*, 67 (1964).

## Elimination of HCl from Gaseous 2,3-Dichlorobutane on $CaCl_2$, CaO, and $Al_2O_3$ [1, 2]

By Priv.-Doz. Dr. H. Noller, Dipl.-Phys. H. Hantsche, and Dr. P. Andréu

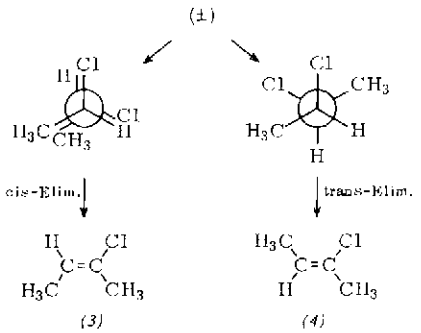
Physikalisch-Chemisches Institut der Universität München (Germany)

Compounds incorporating two asymmetric carbon atoms offer a possibility of deciding whether the atoms eliminated in elimination reactions are removed from *cis*- or *trans*-positions. In the elimination of HCl from 2,3-dichlorobutane, *cis*-elimination must give rise to *trans*-2-chloro-2-butene *(1)* from the *meso*-form, *trans*-elimination to *cis*-2-chloro-2-butene *(2)*.




*(1)* *(2)*

With the (±)-form, *i.e.* the racemate, *cis*-elimination yields the *cis*-olefins *(3)*, while *trans*-elimination yields the *trans*-olefin *(4)*.




*(3)* *(4)*

By varying the time of contact with the catalyst, it could be demonstrated that the above olefins are primary products, *i.e.* they do not arise by isomerizations under the experimental conditions.

Surprisingly, on $CaCl_2$ or CaO, the *meso*- and (±)-forms both afford the same ratio of *trans*-: *cis*-olefin (cf. Table).

| Catalyst | *trans*-2-Chloro-2-butene: *cis*-2-chloro-2-butene | | Temp. [°C] |
|---|---|---|---|
| | from *meso*-form | from (±)-form | |
| $CaCl_2$ | 4.4 | 4.4 | 188 |
| CaO | 1.95 | 2.0 | 217 |
| $Al_2O_3$ (basic) | 1.2 | 3.3 | 216 |
| $Al_2O_3$ (acidic) | 0.52 | 21 | 177 |

This agreement between the *meso*- and (±)-forms is maintained over the entire temperature range (170–350 °C) examined. With increasing temperature, there is merely a diminishing preponderance of the *trans*-olefin.

These results can be accounted for if a two-stage mechanism is envisaged. The carbonium ion formed as an intermediate possesses free rotation, a fact that was hardly to be predicted. Its lifetime is apparently longer than the time required for several rotations.

With $Al_2O_3$, on the other hand, the elimination proceeds in part stereospecifically (cf. Table), *i.e.* surprisingly in favor of *trans*-elimination. The lifetime of the carbonium ion relative to the time required per rotation is thus smaller on $Al_2O_3$ than on CaO or $CaCl_2$, being apparently of the order of magnitude of one rotation on $Al_2O_3$, so that the initial configuration retains an influence on the nature of the products. With increasing temperature, the stereospecificity diminishes.

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German version: Angew. Chem. 76, 645 (1964)

[1] Mechanism of Contact Eliminations, Part 7. – Part 6: *P. Andréu, M. Heunisch, E. Schmitz*, and *H. Noller*, Z. Naturforschg. in the press.

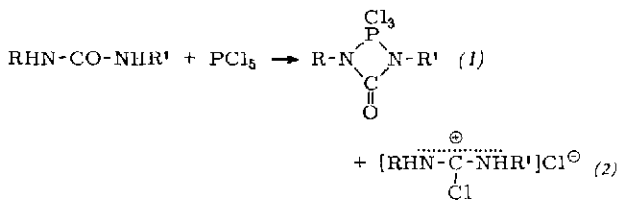
[2] This work was supported financially and materially by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

## 2-Phospha-1,3-diazetidinones, a New Class of Compounds

By Dr. H. Ulrich and Dr. A. A. R. Sayigh

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The reaction of 1,3-disubstituted ureas with phosphorus pentachloride yields in addition to the known chloroformamidine hydrochlorides *(2)* [1] 1,3-disubstituted trichloro-2-phospha-1,3-diazetidinones *(1)*. The distribution of the reaction products depends predominantly on the nature of the substituents and to a minor degree on the polarity of the solvent. Primary alkyl groups favor attack on the nitrogen with formation of *(1)*; secondary alkyl groups react almost exclusively on the oxygen with formation of *(2)*. Similar results have been observed by us in the reaction of 1,3-disubstituted ureas with phosgene [2].



*(1a)* R = R' = $CH_3$; b.p. 78–79 °C/1.5 mm; Yield: 71.9 %

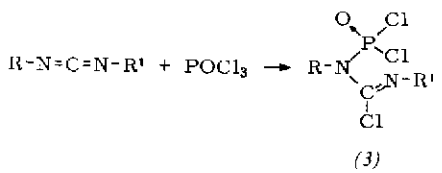
*(1b)* R = R' = $(CH_2)_3CH_3$; b.p. 105–108 °C/0.3 mm; Yield: 71 %

*(1c)* R = $C_6H_5$, R' = $(CH_2)_3CH_3$; non-distillable oil

The reaction proceeds on mild warming of the components in carbon tetrachloride and is accompanied by vigorous evolution of HCl.

The structures of the trichloro-2-phospha-1,3-diazetidinones obtained were elucidated by elementary analysis and infrared and NMR spectroscopy.

The carbonyl absorption at 5.6 μ is in agreement with the strained four-membered ring structure postulated. The isomeric compounds *(3)*, which were obtained from *N,N'*-dialkylcarbodiimides and phosphorus oxychloride, show as expected a C=N absorption at 6.0 μ.

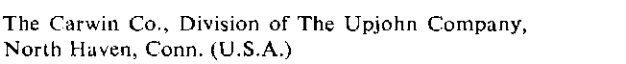


*(3)*

In the $^1$H-NMR spectrum (Varian A 60) of *(2b)* and *(2c)*, the $CH_2$ group next to the nitrogen is not only coupled with the neighboring methylene group, but also with the phosphorus nucleus. The chemical shifts for the pairs of triplets of equal intensity in carbon tetrachloride are 192 cps [3.2 ppm; $J_{PH}$ = 28 cps] for *(1b)* and 215 cps [3.6 ppm; $J_{PH}$ = 34 cps] for *(1c)*, relative to tetramethylsilane.

In the dimethyl derivative *(1a)*, two pairs of doublets at 198 cps [3.3 ppm; $J_{PH}$ = 20 cps] and 173 cps [2.9 ppm; $J_{PH}$ = 21 cps] were observed; these are presumably due to geometrical isomers, *i.e.* the methyl groups are respectively either both above or alternately above and below the plane of the four-membered ring. Geometrically isomeric phosphazene dimers were already reported by *Trippett* [3].

When the 2-phospha-1,3-diazetidinones are heated above 100 °C in an inert solvent, disproportionation occurs as expected with formation of trichlorophosphazene *(4)* and isocyanate ($\nu_{N=C=O}$ = 4.42 μ). The cleavage products thus obtained react with each other to form a carbodiimide *(5)* ($\nu_{N=C-N}$ = 4.7 μ) and phosphorus oxychloride [4]:



Received, June 5th, 1964 [Z 758/572 IE]
German version: Angew. Chem. 76, 647 (1964)

[1] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960).

[2] *H. Ulrich, J. N. Tilley*, and *A. A. R. Sayigh:* Abstracts A, XIXth International Congress of Pure and Applied Chemistry. London 1963, p. 251.

[3] *S. Trippet*, J. chem. Soc. (London) *1962*, 4731.

[4] *H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *74*, 900 (1962); Angew. Chem. internat. Edit. *1*, 595 (1962); J. chem. Soc. (London) *1963*, 5558.

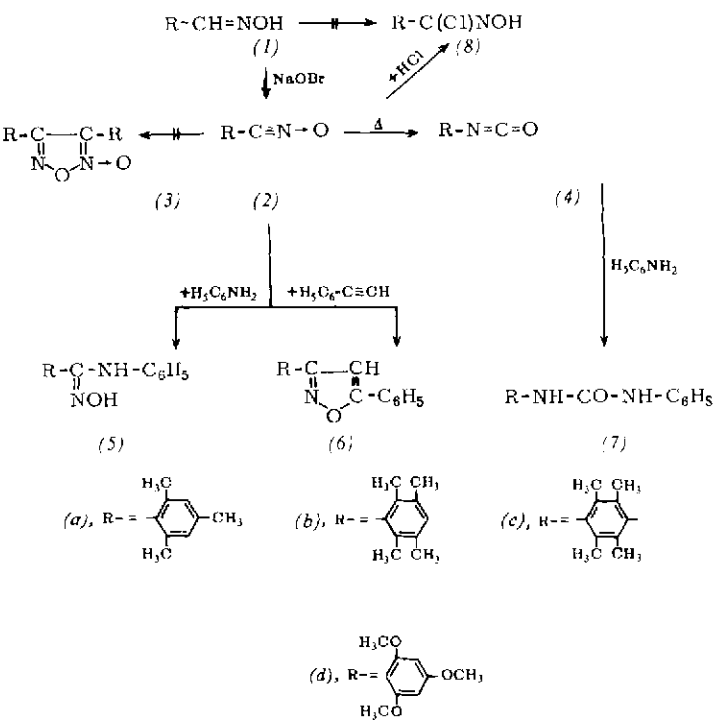
## Stable Aromatic Nitrile Oxides [1,2]

By Prof. Dr. Ch. Grundmann and Judith M. Dean

Mellon Institute, Pittsburgh, Pa. (U.S.A.)

All the aromatic nitrile oxides *(2)* known so far are unstable and dimerize within hours or days to the corresponding furoxans *(3)* [3].

However, studies of Stuart-Briegleb models indicate the possibility of substituting the *o,o'*-positions with substituents of critical spatial requirements in order to block the dimerization to furoxans without impairing the ability of the nitrile oxide function to add onto other unhindered systems. The preparation of the nitrile oxides *(2a)–(2d)* has confirmed our anticipations. Compound *(2c)* is the first known individual bifunctional nitrile oxide [4]. All four preparations *(2a)–(2d)* are crystalline compounds which are stable at room temperature as well in solution as in the solid state. Their dimerization to furoxans cannot be enforced; on prolonged heating above 120 °C, *(2a)* and *(2b)* rearrange slowly to the corresponding isocyanates *(4)*, which were characterized by their reaction with aniline to give substituted phenylureas *(7)*. *(2a)–(2d)* react very easily with aniline or phenylacetylene to form hydroxamanilides *(5)* or 5-phenylisoxazoles *(6)*. Hydrogen chloride adds onto *(2a)–(2d)* to yield hydroxamyl chlorides *(8)*.



The usual route for the synthesis of nitrile oxides, *viz.* chlorination of the oximes *(1)* to afford the hydroxamyl chlorides *(8)*, followed by dehydrohalogenation of *(8)* with base, was found totally unsuitable for the preparation of *(2a)–(2d)*, since chlorine always substituted simultaneously in the group R. However, the alkali salts of the oximes *(1a)–(1d)* were readily dehydrogenated with alkyli hypobromite at 0–10 °C to afford the nitrile oxides *(2a)–(2d)* in excellent yields. The melting points and yields of compounds *(2)* and *(5)–(8)* are given in Table 1.

Table 1. Melting points and yields of the nitrile oxides *(2)* and their reaction products *(5)–(8)*.

| | Compound | | | | |
|---|---|---|---|---|---|
| | | *(a)* | *(b)* | *(c)* | *(d)* |
| M.p. [°C] | *(2)* | 114 | 120 | 169–170 [*] | 160–170 [*] |
| Yield [%] | | 97 [6] | 98 [6] | 65 | 79 |
| M.p. [°C] | *(5)* | 160 | 247 | 300 [*] | 199 [*] |
| Yield [%] | | 91 | 94 | 79 | 85 |
| M.p. [°C] | *(6)* | 94 | 175 | 312 | 98 |
| Yield [%] | | 98 | 88 | 95 | 86 |
| M.p. [°C] | *(7)* | 245 | 306 | – | – |
| Yield [%] | | [5] | [5] | | |
| M.p. [°C] | *(8)* | 72 | 124–126 [*] | – | – |
| Yield [%] | | 88 | 81 | | |

[*] Melts with decomposition.

Aliphatic nitrile oxides are by far more transient than their aromatic counterparts; their most stable representative seems to be t-butylnitrile oxide [7], but even this compound dimerizes completely to the furoxan within 2–3 days [3]. To obtain really stable aliphatic nitrile oxides, even bulkier groups will be required next to the $-C\equiv N\rightarrow O$ grouping. We are at present engaged in preparing such compounds.

Received, June 5th, 1964 [Z 759/571 IE]
German version: Angew. Chem. 76, 682 (1964)

[1] Nitrile Oxides, Part II. – Part I: *Ch. Grundmann*, Angew. Chem. *75*, 450 (1963); Angew. Chem. internat. Edit. *2*, 260 (1963).

[2] This work was supported by Public Health Service Research Grant CA-07272-01 of the National Cancer Institute, Bethseda, Md (U.S.A.).

[3] For the rate of dimerization of known aromatic nitrile oxides, cf. *A. Quilico:* The Chemistry of Heterocyclic Compounds. Interscience, New York 1962, Vol. 17, p. 21, Table II.

[4] For previous unsuccessful attempts to prepare terephthalobis(nitrile oxide), cf. *R. H. Wiley* and *B. J. Wakefield*, J. org. Chemistry *25*, 546 (1960). Oxalobis(nitrile oxide) has been obtained so far only in solution [1].

[5] Not determined.

[6] For infrared spectra, see *S. Califano, R. Moccia, R. Scarpati*, and *G. Speroni*, J. chem. Physics *26*, 1777 (1957).

[7] *S. Califano, R. Scarpati*, and *G. Speroni*, Atti Accad. naz. Lincei, Rend., Cl. Sci. fisiche, mat. natur. [8] *23*, 263 (1958); Chem. Abstr. *52*, 12557 f (1958); *G. Zinner* and *H. Günther*, Angew. Chem. *76*, 440 (1964); Angew. Chem. internat. Edit. *3*, 383 (1964).

## Preparation of Anhydrous Potassium Hexathiocyanatoaluminate and Its Behavior in Liquid Ammonia

By Prof. Dr. O. Schmitz-DuMont and Dipl.-Chem. B. Ross

Anorganisch-Chemisches Institut der Universität Bonn (Germany)

When 1 mole of anhydrous aluminum chloride is added to a solution of 6 moles of potassium thiocyanate in acetonitrile, potassium chloride is precipitated. If the potassium chloride is filtered off and the filtrate evaporated to dryness *in vacuo* at room temperature with exclusion of moisture, a pale pink, crystalline thiocyanato complex $K_3[Al(SCN)_6]\cdot CH_3CN$ *(1)* is left as residue. The compound $K_3[Al(SCN)_6]$ *(2)* is obtained free from acetonitrile by heating *(1)* at 140 °C in a stream of nitrogen.

Both *(1)* and *(2)* dissolve in water to give a clear, colorless solution with an acidic reaction, and in liquid ammonia to give a bright yellow solution. On evaporation of the ammonia, a mixture of an ammonate of aluminum thiocyanate and potassium thiocyanate results. Accordingly, *(1)* and *(2)* behave like potassium hexathiocyanatotitinate(IV) [1].

The reaction of 3 moles of potassium thiocyanate with 1 mole of anhydrous aluminum chloride in acetonitrile leads to precipitation of only 2 moles of potassium chloride with formation of a solution of the complex $K[Al(SCN)_3Cl]$ *(3)*. This complex is stable only in solution. It is assumed that the complex ion still retains acetonitrile as a ligand bound to the $Al^{3+}$, *e.g.* as $[Al(SCN)_3Cl(NCCH_3)_2]^-$. The residue obtained after evaporation of the acetonitrile consists of a mixture of potassium chloride and an adduct of acetonitrile and aluminum thiocyanate. On adding this mixture to acetonitrile, it dissolves to reform complex *(3)*.

Received, June 5th, 1964 [Z 751/585 IE]
German version: Angew. Chem. 76, 647 (1964)

[1] *O. Schmitz-DuMont* and *B. Ross*, Angew. Chem. *76*, 304 (1964); Angew. Chem. internat. Edit. *3*, 315 (1964).

## A New Synthesis of Germylsilane [*]

By R. Varma and A. P. Cox

Mallinckrodt Chemical Laboratory, Harvard University, Cambridge, Mass. (U.S.A.)

Previously, silylpotassium $H_3SiK$ [1] has been used to only a limited extent in inorganic synthesis. Silylpotassium was prepared by the reaction (a) of disilane $Si_2H_6$ with a slight excess of potassium hydride in 1,2-dimethoxyethane over a period of 24 hours at room temperature. After removing volatile products – mainly monosilane, monoglyme, some hydrogen, and a very small quantity of disilane – an excess of germyl chloride was distilled in and allowed to react with the $H_3SiK$ at room temperature for 15 minutes (b). The germyl-

$$Si_2H_6 + KH \rightarrow H_3SiK + SiH_4 \quad (a)$$

$$H_3SiK + GeH_3Cl \rightarrow GeH_3SiH_3 \quad (b)$$

silane $GeH_3SiH_3$ [2] produced was purified by fractionation on a low-temperature column kept at approximately −115 °C in order to separate it from $Si_2H_6$ and $Ge_2H_6$, and was obtained in ca. 20 % yield.

Its infrared and mass spectra agree with those cited in reference [2] for $GeH_3SiH_3$. In addition, its microwave spectrum [3] strongly supports this identification.

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German version: Angew. Chem. 76, 649 (1964)

[*] Part of the research was made possible by support extended to Harvard University by the Office of Naval Research.

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[2] *E. J. Spanier* and *A. G. MacDiarmid*, Inorg. Chem. *2*, 215 (1963).

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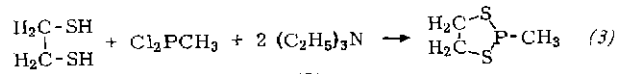
## Condensation of Methyldichlorophosphine with Dithiols

By Dr. M. Wieber, Dipl.-Chem. J. Otto, and Prof. Dr. Max Schmidt

Institut für Anorganische Chemie der Universität Marburg/Lahn (Germany)

Methyldichlorophosphine *(1)* reacts in ether in the presence of triethylamine *(2)* with dithioglycol or 3,4-dimercaptotoluene in very good yields to form 2-methyl-1,3,2-dithia-

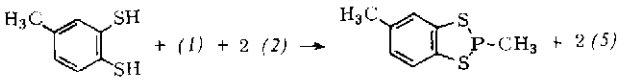
phospholane *(3)* or 2,7-dimethylbenzo[*d*]-1,3,2-dithiaphospholane *(4)*, and triethylammonium chloride *(5)*.



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

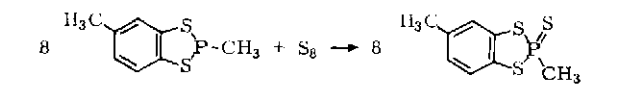
+ 2 $(C_2H_5)_3N \cdot HCl$,

*(5)*



*(4)*

Analogously, propane-1,3-dithiol produces the six-membered heterocycle 2-methyl-1,3,2-dithiaphosphane *(6)*, but only in moderate yield (ca. 30 %), the remainder forming a polymer of the same composition. All three derivatives [*(3)*, m.p. −5 °C, b.p. 90 °C/5 mm; *(4)*, b.p. 110–114 °C/2 mm; and *(6)*, b.p. 102 °C/5 mm] distil undecomposed and are oils of unpleasant odor; they are readily soluble in organic solvents, and easily hydrolysed by water. As nucleophilic reagents, they react with sulfur and selenium, yielding cyclic esters of methyltrithiophosphonic or methyldithioselenophosphonic acid, *e.g.*



*(4)* *(7)*

Thus, *(3)* and S afford 2-sulfo-2-methyl-1,3,2-dithiaphospholane, m.p. 74 °C, b.p. 132–134 °C/2 mm; *(3)* and Se form the corresponding selenophospholane, m.p. 68 °C, b.p. 148 °C/2 mm; *(4)* and S or Se yield the sulfophospholane *(7)* or selenophospholane respectively; but neither can be distilled unchanged. Finally *(6)* and S produce the corresponding sulfophosphane, m.p. 121 °C.

An attempt to oxidize *(3)* to the dithiophosphonic ester with oxygen at room temperature failed; warming led to a violent explosion.

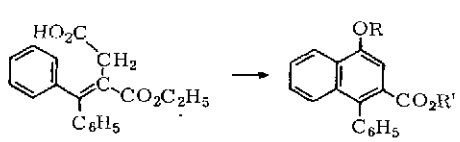
Received, June 8th, 1964 [Z 753/584 IE]
German version: Angew. Chem. 76, 648 (1964)

## The Synthesis of Fluoranthene Derivatives from Monoethyl 4,4-(*o*,*o*'-Biphenylene)itaconate

By Prof. Dr. A. Sieglitz and Dipl.-Chem. P. Böhme

Institut für Chemische Technologie der Farbstoffe und Kunststoffe, Technische Hochschule München (Germany)

Some time ago, *Borsche* [1] obtained 1-hydroxy-4-phenyl-3-naphthoic acid *(2b)* from the ester *(2a)*, which was synthetized by cyclizing monoethyl 4,4-diphenylitaconate *(1)* with acetic anhydride and sodium acetate; *(1)* was derived in turn from benzophenone by Stobbe condensation [2].

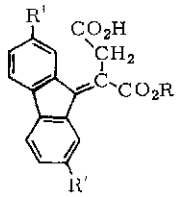


*(1)*

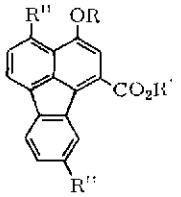
*(2a)*: R = $COCH_3$; R' = $C_2H_5$
*(2b)*: R = R' = H

Numerous derivatives of *(2b)* can be prepared by this route. 3-Hydroxyfluoranthene-1-carboxylic acid *(4a)* [3] should be accessible by a similar route from fluorenone via the monoethyl ester *(3a)* of 4,4-(*o*,*o*'-biphenylene)itaconic acid *(3b)*.

However, attempts by *Campbell* and *Fairful* [4] to close the fluoranthene ring by reaction of *(3a)* with acetic anhydride/sodium acetate, and by treatment of *(3b)* with aluminum chloride in nitrobenzene or with concentrated sulfuric acid were unsuccessful. When the ester *(3a)* was boiled with acetic anhydride/acetic acid/zinc chloride, only the anhydride of *(3b)* was formed.



*(3a)*: R = $C_2H_5$; R' = H
*(3b)*: R = R' = H
*(3c)*: R = $C_2H_5$; R' = Cl
*(3d)*: R = H; R' = Cl



*(4a)*: R = R' = R'' = H
*(4b)*: R = $COCH_3$; R' = $C_2H_5$; R'' = Cl
*(4c)*: R = R' = H; R'' = Cl

We have now found that the reaction of *(3a)* with acetic anhydride and aluminum chloride gives an uncharacterized intermediate which is converted into *(4a)* in good yield with alkali. Halogeno derivatives of *(3a)* can be cyclized with acetic anhydride/acetic acid/zinc chloride. Thus, for example, the monoethyl ester *(3c)* obtained from 2,7-dichlorofluorenone by Stobbe condensation gives, in addition to the anhydride of the dicarboxylic acid *(3d)*, the intermediate *(4b)*, which on hydrolysis yields 4,9-dichloro-3-hydroxyfluoranthene-1-carboxylic acid *(4c)*, a compound we had already prepared by another route [3].

Received, June 8th, 1964 [Z 756/586 IE]
German version: Angew. Chem. 76, 648 (1964)

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## Non-Enzymatic Reduction of Methylene Blue and 2,6-Dichlorophenolindophenol by Reduced Di- and Triphosphopyridine Nucleotides

By Dipl.-Chem. F. Wagner, Prof. Dr. J. Convit, E. Bernt, and Dr. M. Nelböck

Escuela José Vargas, Hospital Vargas, Caracas (Venezuela), and Biochemische Abteilung, C. F. Boehringer & Soehne GmbH, Tutzing (Germany)

Contrary to expectations, methylene blue (MB) is stoichiometrically decolorized to leuco-methylene blue ($MBH_2$) by the reduced di- and triphosphopyridine nucleotides DPNH and TPNH on irradiation with light without addition of enzymes. The most effective wavelengths are those between 600 and 700 mμ.

The DPN or TPN thereby formed is fully active in enzymatic reactions, *e.g.* with the DPN-dependent enzymes lactic dehydrogenase and alcohol dehydrogenase, and the TPN-dependent enzymes glutathione reductase and glucose-6-phosphate dehydrogenase.

2,6-Dichlorophenolindophenol is similarly reduced, but triphenyltetrazolium chloride is not.

The same reactions were carried out with absolutely pure DPNH and TPNH. Traces of proteins were removed by dialysis, and possible traces of enzymatic activity were destroyed by heating the coenzyme solutions at 100 °C. Any enzymatic reaction (*e.g.* of diaphorase) was thus excluded.

Flavin adenine dinucleotide ($4 \times 10^{-5}$ M) accelerates the reoxidation of $MBH_2$ to MB by atmospheric oxygen, and thus leads to a faster oxidation of DPNH. Glutathione ($10^{-4}$ M) and ferric chloride ($3 \times 10^{-5}$ and $3 \times 10^{-4}$ M) did not affect the reaction rate.

Since DPNH and TPNH do not react with MB in the absence of light, dehydrogenase substrates can be oxidized with DPN or TPN in the dark in the presence of MB. Subsequently, in the presence of light, MB is hydrogenated to $MBH_2$ by the DPNH or TPNH, and DPN or TPN is regenerated. Aeration reoxidizes the autoxidizable $MBH_2$, and the chain of processes can be repeated by renewed reaction in the dark. By this means, catalytic (instead of stoichiometric) quantities of the expensive coenzymes suffice even for preparative aerobic oxidation of, for example, glucose 6-phosphate to 6-phosphogluconate.

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## Superconductivity in $In_3SbTe_2$

By Priv.-Doz. Dr. A. Rabenau, Dr. K. Deneke, and M. M. van der Meij

Philips Zentrallaboratorium GmbH, Laboratorium Aachen (Germany) and Philips Research Laboratories, Eindhoven (Holland)

The ternary phase $In_3SbTe_2$ with the NaCl structure [1] (a = 6.13 Å), which lies on the pseudobinary section InTe–InSb, is closely related to the high-pressure phase InTe(II) [2], which also crystallizes with the NaCl structure [3] (a = 6.16 Å). This correspondence manifests itself in the physical properties: InTe(II) is a metallic conductor which becomes superconducting at ca. 3.45 °K [3,4]. We have found from resistivity measurements that $In_3SbTe_2$ is also a metallic conductor exhibiting transition to superconductivity.

The resistivity decreases linearly with temperature from $7.2\times10^{-4}$ ohm·cm at room temperature to $3.6\times10^{-4}$ ohm·cm at 4.2 °K. The very sharp transition to superconductivity points to a critical temperature of 1.06 °K.

Within the range of homogeneity of the phase $In_{1-x}Te(II)$ (where $0\leqslant x\leqslant0.18$), the value of the critical temperature varies according to the formal valence of the indium [5]. It decreases from ca. 3.45 °K for $In_{1.00}Te$ to ca. 1 °K on the tellurium-rich side ($In_{0.82}Te$), while the formal valence of the indium increases from 2.00 to 2.44. Bearing in mind that the formal valence of indium in $In_3SbTe_2$ is 2.33, we find the level of the critical temperature of the ternary phase to correspond to the situation in InTe(II).

Received, June 10th, 1964 [Z 761/587 IE]
German version: Angew. Chem. 76, 651 (1964)

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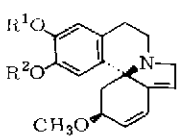
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## The Total Synthesis of Erysotrine

By Prof. A. Mondon and Dipl.-Chem. H. J. Nestler

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Although compounds incorporating the erythrinan skeleton have been accessible for some time [1–4], the synthesis of an aromatic *Erythrina* alkaloid has so far not been achieved. We have now achieved a total synthesis of erysotrine *(1)* [5,6].

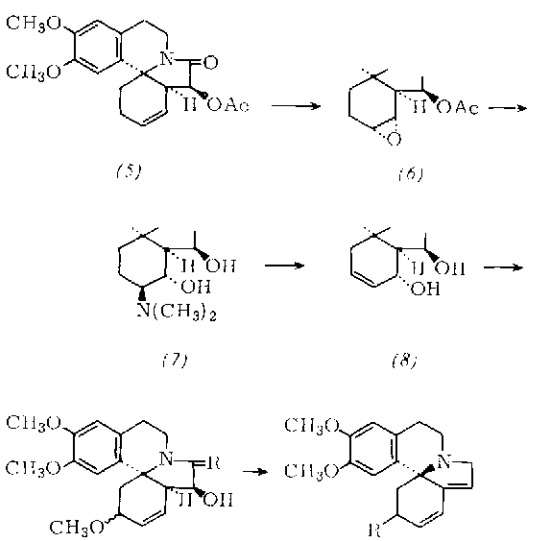


*(1)*, $R^1 = CH_3$; $R^2 = CH_3$
*(2)*, $R^1 = H$ ; $R^2 = CH_3$
*(3)*, $R^1 = CH_3$; $R^2 = H$
*(4)*, $R^1 = H$ ; $R^2 = H$

Although this compound has not yet been found in nature, it occupies a key position as the product of methylation of the phenolic alkaloids erysodine *(2)*, erysovine *(3)*, and erysopine *(4)*.

On treatment with peroxybenzoic acid, the unsaturated α-acetoxy-γ-lactam *(5)* [7] gave the α-epoxide *(6)*, which is cleaved by dimethylamine to give *(7)*. Degradation according to *Cope* via the *N*-oxide affords the unsaturated diol *(8)*, the structure of which was confirmed by its conversion into known erythrinan derivatives. Methanolic hydrochloric acid converts *(8)* into a mixture of the epimeric 3-methyl ethers *(9a)* and *(9b)*. After chromatographic separation, each methyl ether is reduced by lithium aluminohydride to the bases *(10a)* or *(10b)*, from which the two doubly unsaturated bases *(11a)* and *(11b)* are obtained by way of the mesylates. The overall yields, based on *(5)*, amounted to 1.8 and 2.4 %, respectively.

The infrared spectrum of the picrate of the base *(11a)* in chloroform is identical with that of erysotrine picrate, and thus justifies assignment of the racemic base *(11a)* to the naturally occurring 3β-series, and of *(11b)* to the 3α-series.



*(5)* *(6)* *(7)* *(8)*

*(9a)*,*(9b)*, R = O (±)-*(11a)*, R = $\alpha$-$OCH_3$
*(10a)*,*(10b)*, R = $H_2$ Picrate, m.p. 198 °C
(±)-*(11b)*, R = β-$OCH_3$
Picrate, m.p. 175 °C

Compound *(11a)* was resolved into its optical antipodes with dibenzoyl-(+)-tartaric acid. The less soluble salt yields a dextrorotatory base, whose picrate (m.p. 161 °C, $[\alpha]_D^{25} = +140°$ in ethanol, c = 0.23) is identical with erysotrine picrate obtained from natural sources [8]. After decomposition of the picrate and distillation of the free base, the synthetic erysotrine was obtained as crystals, m.p. 97 °C ([6] gives m.p. 97–98 °C).

Received, June 15th, 1964 [Z 763/588 IE]
German version: Angew. Chem. 76, 651 (1964)

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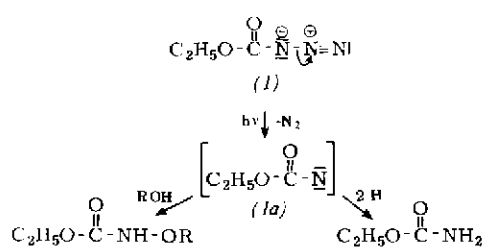
## The Photochemical Decomposition of Alkyl Azidoformates in Aliphatic Alcohols

By Dr. R. Kreher and Dipl.-Ing. G. H. Bockhorn

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

*Dedicated to Professor C. Schöpf on the occasion of his 65th birthday*

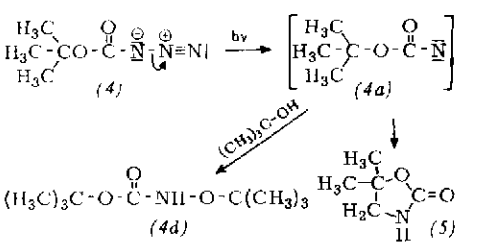
Ethyl azidoformate *(1)* loses nitrogen during its photochemical decomposition [1] in t-butanol, and reacts with the tertiary alcohol to yield ethyl *N*-t-butoxycarbamide *(2d)*, b.p. 97–98 °C/13 mm, in 60 % yield; *(2d)* is also obtained from t-butoxyamine and ethyl chloroformate in the presence of triethylamine. On photolysis in methanol, ethanol, or isopropanol, *(1)* is chiefly reduced to ethylcarbamide *(3)*, with simultaneous loss of nitrogen; according to gas chromatography, ethyl *N*-alkoxycarbamates *(2a)–(2c)* are also formed in small quantities.



*(1)*

*(1a)*

| | | | |
|---|---|---|---|
| *(2a)*, R = $CH_3$- | 28% | *(3)*, | 52% in methanol |
| *(2b)*, R = $CH_3$-$CH_2$- | 3% | | 97% in ethanol |
| *(2c)*, R = $(CH_3)_2CH$- | 10% | | 90% in isopropanol |
| *(2d)*, R = $(CH_3)_3C$- | 60% | | |



*(4)* *(4a)* *(4d)* *(5)*

The photochemical decomposition of *(1)* presumably proceeds by way of the reactive ethoxycarbonylazene *(1a)* [2]. In methanol, ethanol, and isopropanol, *(1a)* apparently dehydrogenates the solvent to give the corresponding carbonyl compound, being thereby reduced to *(3)* [3].

On photolysis of the t-butyl ester *(4)* in t-butanol, the t-butoxycarbonylazene *(4a)* initially formed reacts not only with the tertiary alcohol to yield t-butyl *N*-t-butoxycarbamide *(4d)*, m.p. 70–71 °C, in 29 % yield, but preferentially tends to undergo an intramolecular reaction to yield 60 % 5,5-dimethyloxazolid-2-one *(5)*, m.p. 80–82 °C [4]; in this reaction, the azene group is apparently inserted into a C–H bond of the t-butyl group.

Received, July 3rd, 1964 [Z 770/591 IE]
German version: Angew. Chem. 76, 681 (1964)

[1] Refluxing alcoholic solutions of *(1)* were illuminated by means of a high-pressure ultraviolet lamp [Type S 81, Quarzlampengesellschaft Hanau (Germany)]. Comparable results were obtained by using a low-pressure ultraviolet lamp (Type NK 6/20, same source) at room temperature.

[2] *K. Hafner* and *C. König*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 96 (1963); *W. Lwowski* and *T. W. Mattingly*, Tetrahedron Letters *1962*, 277; *G. Jäger*, Ph. D. Thesis, Technische Hochschule Darmstadt, 1962.

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[4] Photolysis of *(4)* in acetonitrile affords *(5)* in yields of up to 80 %.

## Determination of the Sequence of a Code Triplet

By Prof. Dr. F. Cramer, Dr. H. Küntzel, and Dr. J. H. Matthaei [*]

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Up to the present, only polyribonucleotides with a statistical distribution of their bases were available for deciphering the genetic code; hence only the overall composition of most of the code triplets could be determined [1,2]. Recently, we have indicated possibilities for further analysis of the genetic code using oligonucleotides and polynucleotides with definite base sequences [3].

An enzymatic method was used to obtain coding polynucleotides with definite 3'-terminal base sequences. As expected [4], these polynucleotides effect specific adsorption of aminoacyl-RNA onto ribosomes in a simplified cell-free system derived from *Escherichia coli* [4]. This enabled us to carry out the first determination of the base sequence of a coding triplet. This finding also demonstrates that the RNA template is read off starting from the 3'-terminal end.

The following polynucleotides were prepared using a partially purified polynucleotide phosphorylase from *Micrococcus lysodeikticus* [5]: poly-pApC 50:1 *(1)*, poly-pApU 50:1 *(2)*, poly-pApG 100:1 *(3)*, poly-pUpG 100:1 *(4)*, and poly-pCpG 100:1 *(5)*. Polynucleotides *(1)* and *(2)* were hydrolysed with pyrimidine-specific ribonuclease from pancreas, and *(3)*, *(4)*, and *(5)* with guanine-specific ribonuclease $T_1$ from takadiastase. The 3'-phosphate residues were removed from the cleavage products using bacterial alkaline phosphatase.

For the polynucleotide Ap···ApApC obtained from *(1)* the 3'-terminal nucleotide was determined as follows (this polynucleotide contains an average of 50 nucleotides per chain): Samples of the polynucleotide were labelled in the cytosine moiety with tritium, and the [$^3$H]cytosine was liberated by oxidation with periodate and subsequent treatment with cyclohexylamine [6]. Equilibrium dialysis for 6 h against water showed that all the radioactivity had been liberated in the form of dialysable nucleobase, while the remainder of the ultraviolet-absorbing material retained by the dialysis membrane. Examination of the product obtained from the treatment with periodate and amine by paper chromatography revealed cytosine and no adenine.

About 150 μμmoles of ribosomes [8] were incubated for 60 sec at 36 °C with 300 μμmoles of polynucleotide and 1 mμmole of aminoacyl-RNA in 350 μl of standard buffer [7]. The aminoacyl-RNA was charged with one labelled and 19 non-labelled amino acids; all the 20 amino acids normally occurring in proteins were tested. Each incubate was then diluted with 30 times its volume of ice-cold 0.01 M tris-HCl buffer (pH 7.2)/0.01 M magnesium acetate and centrifuged at 150000 g for 60 min. The precipitate obtained was taken up in 0.1 M triethylammonium hydrogen carbonate (pH 7.6), applied to fibre glass paper (Whatman GFA), and dried for liquid scintillation counting. Comparison of the coding properties of poly-Up···UpUpG and poly-Up···UpU indicates that *UpUpG* is the coding sequence for *leucine*. However, valine and cysteine, having also codons consisting of one guanylic and two uridylic acid residues [2], are not coded by this sequence (see Table; the values given are the mean from two experiments).

| Amino acid | Aminoacyl-RNA bound [nμmoles] | | |
|---|---|---|---|
| | without polynucleotide | with poly-Up···UpU | with poly-Up···UpUpG |
| [$^{14}$C]Val | 139 | 125 | 350 |
| [$^{35}$S]Cys | 482 | 465 | 480 |
| [$^3$H]Leu | 780 | 788 | 716 |
| [$^3$H]Phe | 64 | 174 | 70 |

Hydrolysis at pH 9 of the complex of ribosomes, polynucleotide, and aminoacyl-RNA obtained by centrifugation, and subsequent high-voltage paper electrophoresis in 2 M acetic

acid showed that no labelled amino acid is linked by a peptide bond in the complex. Electron-microscopic investigations [9] of fractionated polyuridylic acid (average chain length 750 Å) indicated that 30-S- and 50-S-subunits of the ribosomes add onto one end of this nucleic acid more than 12 times as much as onto the rest of the chain. The above observations suggest that this end is the 3'-terminal one.

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[*] We are indebted to Misses *E. Gärtner*, *K. Eckert*, and *G. Heiler* for valuable assistance.

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## Coding with Mono- and Polytrinucleotides

By Dr. J. H. Matthaei, Dr. H. Kleinkauf, and Prof. Dr. G. Schramm [*]

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Polytrinucleotides ought to act as templates in the biosynthesis of poly(amino acids) [1], whereas isolated trinucleotides lead only to a more or less specific binding of aminoacyl-RNAs onto ribosomes [1–3]. Trinucleotides which would be inactive in a homopolymer because of its tertiary structure might be active in a copolymer with a second trinucleotide [1]. We have therefore started to prepare homopolytrinucleotides by chemical synthesis and to test their coding properties. We have found that ApGpC and ApGpU are coding sequences for asparagine.

A mixture of trinucleotides was secured by complete degradation of a commercial sample of yeast RNA with pancreatic ribonuclease (RNase) followed by five extractions with phenol, threefold extraction with ether, and lyophilization. Individual mono-, di-, and trinucleotides were separated from 6.5 g of the crude mixture of degradation products by chromatography on four columns (6 cm in diameter, 2 m long) of DEAE-Sephadex (A-25 coarse) connected in series. Movable pistons fitted with a sintered-glass filter were inserted into the columns from beneath in order to keep the Sephadex together even on shrinkage. The elution was carried out upwards (against gravity) using 4×2 channels of a Durrum elastic-tubing pump, which pumped 165 l of ammonium carbonate solution (pH 8.7, concentration increasing linearly from 0.1 to 1.0 M) from one column to the next within six days. Each trinucleotide fraction contained 100 to 300 mg. They were diluted tenfold with $H_2O$ and purified and desalted in four stages by sorption on DEAE-cellulose filters of decreasing diameter (each 4 cm in height) and desorption with about 1 M ammonium hydrogen carbonate (pH 7.8). The solutions of oligonucleotides were concentrated, acidified with cellulose phosphate (P-cellulose, p.a., from Serva, Heidelberg), filtered, centrifuged, and lyophilized. The sequence of each trinucleotide was determined by high-voltage paper electrophoresis of the products obtained from it by hydrolysis either at 37 °C with 0.5 N KOH or with $T_1$-RNase.

75 mg of ApGpCp (or 60 mg of ApGpUp) were dissolved by ultrasonic agitation in 1.1 (0.9) g of ethyl tetrametaphosphate [4a] plus 0.125 (0.10) ml of anhydrous trisdimethylamino phosphate and polymerized by rotating at 60 °C for 48 h in a sealed tube [4b]. Dialysis of the products overnight gave a loss of 44 % (45 %) of the ultraviolet-absorbing material. The solution retained by the dialysis membrane was concentrated and separated on a column (3 cm in diameter, 150 cm long) of Sephadex G-75 into fractions of various chain-lengths.

The coding properties of fractions with a chain length of about 18 nucleotides was investigated using our previously published method [5]; however, for the purpose of peptide synthesis, a complete protein-synthetizing system [6], including the supernatant from 100000 g centrifugation of an almost ribonuclease-free extract of *Escherichia coli*, was used. The mixtures were incubated for 3 min at 0 °C and then for 7 min at 36 °C. Most of the experiments with poly-ApGpUp and poly-ApGpCp gave a specific increase in the incorporation of asparagine. In some experiments with poly-ApGpUp also methionine was incorporated, but this was presumably due to cleavage of the terminal nucleotide. These findings agree well with the observation that the trinucleotides ApGpC and ApGpU, which have been freed from the 3'-terminal phosphate, effect specific attachment of asparaginyl-RNA onto ribosomes following the method described in the previous communication [5].

The polynucleotide-dependent incorporation was about 20 times as high in the complete protein synthetizing system as in the simplified system for amino acid adaptation [2, 5]. The peptides presumably formed will be investigated.

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German version: Angew. Chem. 76, 717 (1964)

[*] We are indebted to Misses *F. Schürnbrand* and *K. Eckert* for valuable assistance.

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[2] *J. H. Matthaei*, Lecture at the Bunsen-Tagung, Berlin, May 1964.

[3] *M. W. Nirenberg*, recently reported similar results at the VIth International Congress of Biochemistry, New York, July 1964.

[4a] *W. Pollmann* and *G. Schramm*, Biochim. biophysica Acta *80*, 1 (1964).

[4b] *G. Schramm, H. Grötsch*, and *W. Pollmann*, Angew. Chem. *74*, 53 (1962); Angew. Chem. internat. Edit. *1*, 1 (1962).

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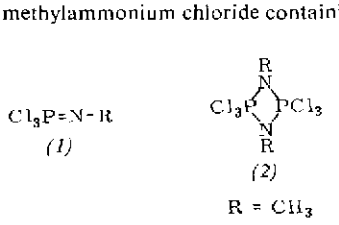
[6] *J. H. Matthaei* and *M. W. Nirenberg*, Proc. nat. Acad. Sci. USA *47*, 1580 (1961).

## A New Type of Phosphorus-Nitrogen Compound with Pentavalent Phosphorus

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Following the interaction of $PCl_5$ with amines, products of type *(1)* or *(2)* have previously been obtained [1]. Compound *(2)* is formed in the reaction of $[(CH_3)NH_3]Cl$ with $PCl_5$. If methylammonium chloride containing a few percent of water



*(1)* *(2)* R = $CH_3$ *(3)*

is employed in this reaction, in addition to *(2)*, a brown oil is obtained which slowly deposits crystals that are recrystallizable from benzene. According to analysis and molecular-weight determinations (ebullioscopically in dichloroethane), the pure compound has the formula $P_4[N(CH_3)]_6Cl_8$. The $^{31}P$-NMR-spectrum shows only one signal at +74.3 ppm (referred to 85 % phosphoric acid). The phosphorus atoms in the compound are thus pentavalent and chemically equivalent; this is shown particularly by comparison with the chemical shift of +78.2 ppm observed with *(2)*. The cage-structure *(3)* may therefore be considered for the compound. The compound is stable in sealed tubes up to 400 °C without melting.

Received, July 2nd, 1964 [Z 766/593 IE]
German version: Angew. Chem. 76, 686 (1964)

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# CONFERENCE REPORTS

## Immunochemistry

This year, the 15th Moshach Colloquium of the Gesellschaft für Physiologische Chemie (German Society for Physiological Chemistry) was held from April 22nd to 25th. It was devoted to immunochemistry. *O. Westphal*, Freiburg (Germany), who was chairman of the symposium, and *M. Heidelberger*, New Brunswick (U.S.A.), pointed out that immunochemistry deals not only with chemical and biochemical mechanisms of immunity processes. The high specificity of antibodies towards their inducing antigen often makes them ideal and as yet unsurpassed reagents for complex structures in natural products. In this context, immunochemistry is also an important branch of analytical natural-product chemistry. The many variants of serological precipitation in gels are of increasing importance, in particular for the analysis of complex protein mixtures. This was discussed by *Ö. Ouchterlony*, Göteborg (Sweden), *P. Grabar*, Paris (France), and *G. Schwick*, Marburg (Germany).

*W. T. J. Morgan*, London (England), reported on the structures of human blood-group substances of the A, B, O(H), and $Le^a$ system. The blood-group specific substances on erythrocyte surfaces are glycolipids, but little is known of their chemical structures. In many humans they also occur in secretions and body fluids. They are mucopolysaccharides containing about 20 % protein and about 80 % carbohydrate. The carbohydrate portion consists of L-fucose, D-galactose, *N*-acetyl-D-glucosamine, and *N*-acetyl-D-galactosamine. In addition, *N*-acetylneuraminic acid occurs in very variable amounts. The chemical structures responsible for the four specificities (A, B, O(H), $Le^a$) were elucidated a) by means of immunochemical methods, b) by stepwise enzymatic degradation, and c) from the structure of the oligosaccharides obtained on hydrolysis with acids (mineral acids and polystyrenesulfonic acid) and bases (*e.g.* triethanolamine). The results led to the following tentative sequences for the first five sugar units in each individual glycolipid [1]:

A substance
1) α-GalNAc-(1-3)-β-Gal-(1-3)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc
2) α-GalNAc-(1-3)-β-Gal-(1-4)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc

B substance
1) α-Gal-(1-3)-β-Gal-(1-3)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc
2) α-Gal-(1-3)-β-Gal-(1-4)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc

O(H) and $Le^a$ substances
1) β-Gal-(1-3)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc
2) β-Gal-(1-4)-β-GNAc-(1-3)-β-Gal-(1-3)-GalNAc

Each substance therefore contains at least two different serologically active carbohydrate chains. These are probably anchored to a common peptide skeleton, which itself has no serological significance. L-Fucose and neuraminic acid are presumably attached to the sugar chain as acid-labile, non-reducing groups.

Some oligosaccharides containing fucose were obtained by alkaline hydrolysis of the group-specific substances. In these, fucose is linked 1→2-glycosidically to galactose and also (very probably) 1→4-glycosidically to *N*-acetylglucosamine. These results give an indication of the positions of attachment of fucose in the total structure of the specific mucopolysaccharides. It thus appears that relatively small regions in the polysaccharide portion of the mucopolysaccharide are responsible for the characteristic serological properties of the blood-group specific substances.

*G. F. Springer*, Evanston (U.S.A.), dealt with the "relation of blood-group active substances to bacteria, higher plants, and viruses". Blood-group active substances represent a structural principle, that is widespread in nature, being encountered in the cells of the most primitive as well as the highest forms of life.

Numerous bacteria (*e.g. Escherichia coli* O 86) have high blood-group B activity. Oligosaccharides of high B-specificity were isolated from the serologically active polysaccharide of *E. coli* O 86. One is a heptasaccharide consisting of 4 galactose molecules, 1 fucose, 1 glucose, and 1 hexosamine molecule. A galactose is at the reducing end. B-specific haptenes from *E.coli* O 86 are very similar to human glucose-free blood-group substances.

Polysaccharides with high blood-group O(H) activity were found in two higher plants (*Taxus* and *Sassafras*). Neither polysaccharide contains fucose, whereas α-linked L-fucose is present in human O(H) substance and is serologically essential. In contrast, the *Taxus* polysaccharide contains 2-*O*-methylfucose, and the *Sassafras* polysaccharide 3-*O*-methylfucose. On the basis of immunochemical investigations of synthetic methyl glycosides of fucose ethers, it was concluded that the O(H)-complementary structure of the antibody (eel serum) is smaller than a monosaccharide that requires a *C*- or *O*-methyl group in an equatorial position adjacent to an ether oxygen. Enantiomorphic isomers can possess quantitatively equal activities.

Some viruses (*e.g.* influenza virus or fowl pest virus) have high blood-group A specificity. This cannot be separated from the virus and increases with its purification.

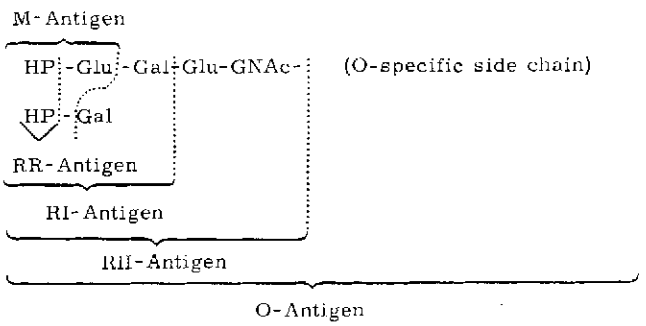
*O. Lüderitz*, Freiburg (Germany), spoke about the somatic antigens of *Salmonella* S and R forms. *Salmonella* O antigens are obtained by extraction with phenol/water as high molecular-weight, branched lipopolysaccharides, in the structures of which various monosaccharides participate in varying number and attachments. Some O antigens contain up to 8 different sugar units, and all the *Salmonella* O antigens investigated up to now contain at least the following 5 monosaccharides (basic sugars): heptose, galactose, glucose, 2-oxo-3-deoxyoctanoic acid, and glucosamine. From structural analyses it appears that oligosaccharidic structures correspond to the specificities of the O factors of an O antigen. On transformation from the morphologically smooth S forms into the morphologically rough R form, *Salmonella* germs lose their O specificity. The R mutants synthetize only a relatively unspecific R antigen that is also a lipopolysaccharide. R antigens contain only the basic sugars; they are deficiency mutants of

[1] Gal = galactose, GalN = galactosamine, G = glucose, GN = glucosamine, Ac = acetyl.

the wild form. On careful chemical degradation of O antigens, structures with R specificity could occasionally be liberated. Hence it is concluded that R antigens are the basic structures of O antigens. Accordingly, R antigens may be regarded as intermediates of O antigen synthesis, which accumulate in R cells, because an enzyme (or several enzymes) needed for the synthesis of the complete S form is (are) missing. R antigens were differentiated by means of serological methods into two R serogroups (RI and RII). In contrast to the RII mutants, the RI mutants have a polysaccharide fraction which contains the specific sugars of the S form in addition to the typical R lipopolysaccharide. In RI mutants, therefore, the S specific sugars are synthetized but not incorporated into the lipopolysaccharide. In contrast, analysis of representatives of the serotype RII showed that here the synthesis of an S-specific sugar is blocked. Two further R mutants in *Salmonellas* are the M mutants and the RR mutants. The former cannot synthetize galactose; its lipopolysaccharide consists of glucosamine, 2-oxo-3-deoxyoctanoic acid, heptose, and glucose. When grown on fructose, the RR mutant forms no glucose; its RR antigen consists essentially of poly(heptose phosphate). The following path for the biosynthesis of the O antigen was suggested.

$$RR \rightarrow M \rightarrow RI \rightarrow RII \rightarrow O$$

From the results of chemical analyses, the following tentative scheme might be derived:




"The capsulate antigen of mucoid strains of *Escherichia coli*" was the subject of the lecture by *W. F. Goebel*, New York (U.S.A.). Under certain cultural conditions, many *Enterobacteriaceae* grow in mucoid form, *i.e.* they surround themselves with a mucous layer, which consists of M antigen. Acidic polysaccharides were isolated from two strains of *E.coli* (*E. coli* K235 and *E.coli* K12 infected with T6 phage); these proved to be identical. The substance was called colanic acid. The acidic polysaccharide isolated from *E. coli* K235 was found to be antigenic in rabbits. Colanic acid consists of glucuronic acid (17.9 %), galactose (33 %), glucose (16.3 %), and fucose (32.7 %). It is presumably identical with M antigen. *K. Jann*, Freiburg (Germany), reported on "immunochemical investigations of the K antigens of *E.coli*". Coli bacteria often possess K antigens as surface antigens in addition to the somatic O antigen. These occur especially in pathogenic coli bacteria and form a kind of natural protecting wall against the defence mechanisms of higher organism (*e.g.* against phagocytosis). Chemical investigations of a large number of *E.coli* species with different K antigens showed that these bacteria frequently have acidic polysaccharides containing hexuronic acid in addition to lipopolysaccharides (O antigens). After extraction from the bacteria with phenol/water, these polysaccharides were isolated in purified form by fractionation with cetyltrimethylammonium bromide and analysed. In 4 instances it could be clearly shown by means of immunochemical methods that these were the K antigens of the bacteria concerned. These acidic polysaccharides have the following compositions:

| | |
|---|---|
| from *E.coli* 08:K42(A):– : | galacturonic acid:galactose:fucose = 1:1:1 |
| from *E.coli* 09:K30(A):H12: | glucuronic acid:galactose:mannose = 1:1:1 |
| from *E.coli* 059:K(B):H19: | galacturonic acid:glucosamine:mannose = 1:1:3 |
| from *E.coli* 0141:K85(B):H4: | glucuronic acid:glucosamine:mannose: rhamnose = 1:1:2:1 |

In order to elucidate the serologically active groups, oligosaccharides were isolated from partial hydrolysates of the acidic polysaccharides and examined for their inhibitory effect in the homologous serological system. It was shown that the serological specificity of the K antigens is mainly caused by structures containing hexuronic acid. A trisaccharide was isolated from the acidic polysaccharide of *E.coli* O8:K42(A):– and the structure galactosyl-(1-3)-galacturonic acid-(1-2)-fucose was proposed for it on the basis of chemical investigations. Analytical and serological findings permit the conclusion that this trisaccharide is the repeating structural unit of the acidic polysaccharide.

*F. A. Anderer*, Tübingen (Germany), reported on the "Chemical basis of antigenicity in globular proteins". The protein of tobacco mosaic virus (TMV) is globular; the primary structure of its subunits is known and so is the spatial arrangement of the protein in the virus. All the polypeptide chains in the virus are arranged structurally identically, so that the virus has a periodically repeating surface structure. For the determination of the serologically determinant amino-acid sequences, 20 peptides were examined which, taken as a whole, contain the entire amino acid sequence of the virus protein. Only 4 partial sequences (15–25 % of the polypeptide chain) proved to be serologically active. From the results of the serological investigations it was concluded that the specific TMV-antibodies are directed against definite regions of the protein. Since the surface structure of the TMV arises from the tertiary structure of the protein, its antigen specificity should also depend on the tertiary structure. Preliminary experiments have shown that the C-terminal hexapeptide from the virus protein forms antibodies in the rabbit which react with TMV and neutralize its infectivity.

*K. Rajewsky*, Frankfurt (Germany), spoke about "immunological studies of lactic dehydrogenases". When enzyme proteins are used as antigens, advantage is taken of two characteristic properties of the proteins: 1. their enzymatic activity, 2. their capacity to take part in immunological reactions. Enzymes are mostly inhibited by their antibodies (antienzymes). The serological reaction can be followed by measurement of the enzyme activity in the immune precipitate and in the supernatant. Such investigations with lactic dehydrogenase (LDH) were easy to perform since there is a simple assay method and also a sensitive specific stain for this enzyme. In the region of the maximum of the precipitation curve (LDH-anti LDH), enzymatic activity begins to become detectable in the supernatant. Even with excess antibody, the immune precipitates show distinct, albeit reduced, activity. The 5 LDH-isoenzymes of higher organisms were investigated by gel diffusion and immuno-electrophoresis. In two samples (heart and muscle isoenzymes), a serological relationship was established between the LDH isoenzymes of ox, pig, and man.

"Synthetic polypeptides as model antigens" was the topic of the lecture by *E. Rüde*, Freiburg (Germany), who first gave a survey of the work of *M. Sela*, Rehovoth (Israel). The main theme was the question of the relationship between chemical structure and antigenicity, *i.e.* the ability of a macromolecular substance to induce the formation of antibodies in higher organisms. Investigations of this kind were conducted with synthetic polypeptides or poly-(α-amino acids) prepared by polymerization or copolymerization of different *N*-carboxyamino acid anhydrides with basic starters. Both linear and branched poly-(α-amino acids) were synthetized by this method; some products were antigenic. It was shown that 1. the presence and 2. the steric accessibility of certain amino acids (*e.g.* tyrosine, cyclohexylalanine, or phenylalanine) or amino-acid combinations (*e.g.* lysine and glutamic acid) in the macromolecules are prerequisites for their antigenicity. The shape of the macromolecule appears to be relatively unimportant in determining antigenicity. The molecular weight can also vary within wide limits; polypeptides of suitable composition with molecular weights of only 4000 can even be antigenic.

The lecturer reported finally on work intended to evaluate the influence of sugars on the antigenicity of synthetic polypep-

tides. Serine glucoside was synthetized and incorporated into synthetic polypeptides via the corresponding *N*-carboxy-amino acid anhydride. Serine glucoside alone did not suffice to convert a non-antigenic polymer into an antigen. When introduced into an already antigenic polypeptide, however, serine glucoside conferred a new specificity on same thus acting as a determinant group. In this connection, serine-*N*-acylglucosamides were also synthetized and incorporated into polypeptides. Serine glycosides are also of interest as model substances for a possible type of linkage between carbohydrate and protein in natural glycoproteins.

*M. Eigen*, Göttingen (Germany), gave an introduction to the physical chemistry of antigen-antibody reactions.

The present theories of antibody formation were reviewed by *F. Haurowitz* (Bloomington, U.S.A.) following a survey on the chemistry of antibodies (structural analysis of $\gamma$-globulins). The importance of the so-called natural antibodies (opsonins) for the fate of infectous agents (phagocytosis, intracellular killing) was discussed by *D. Rowley* (Adelaide, Australia).

*H. Fischer*, Freiburg (Germany), pointed out that complement takes part in immunological cytolysis to a much larger extent than was previously assumed. Following a discussion of the mechanisms of complement action, *H. J. Müller-Eberhard* (La Jolla, U.S.A.) reported on the isolation of complement factors and opened new aspects for the biochemical analysis of complement and its reactions. Five out of the ten hitherto known factors of human complement were obtained in highly purified form. Three factors were characterized as $\beta$-globulins and as $\beta_{1c}$, $\beta_{1E}$, and $\beta_{1F}$ represent the third, fourth, and fifth complement components respectively. The other isolated proteins were identified as 11S-component and C'1-esterase and are assigned to the first complement component.

The cytolytic reaction of the complement begins with the adsorption of the first complement component (C'1), which by enzymatic activity causes addition of the fourth complement component ($\beta_{1E}$). In the course of the reaction, addition of the second complement component then occurs; this is only possible with the aid of the first component. After fixation of the second complement component to the cell membrane, the sensitized cell can "react" numerous molecules of the third complement component ($\beta_{1c}$). The $\beta_{1F}$ globulin and the sixth component follow the $\beta_{1c}$ in the complement reaction chain. Afterwards the cell membrane is in an irreversible condition of susceptibility to attack by the seventh and eighth components, which brings about an irreparable permeability defect. *P. Klein*, Mainz (Germany), dealt with the characterization and the reaction mechanism of the factors of the third complementary component. The third component, identical with $\beta_{1c}$, is determined by its ability of lysing the sensitized erythrocyte-$C'_{1,2,4}$($EAC'_{1,2,4}$) complex. It was shown that the factors $C'_{3a}$ and $C'_{3b}$ can be added onto $EAC'_{1,4,2}$ cells. The $EAC'_{1,4,2,3a,3b}$ cell formed can be brought to lysis by complement treated with cobra toxin or by pseudoglobulin (both free from $C'_{3a}$ and $C'_{3b}$). Chromatographic and electrophoretic methods separated the lytic principle into 3 subfactors ($C'_{3\beta}$, $C'_{3c}$, $C'_{3d}$), which are different from $C'_{3a}$ and $C'_{3b}$. The subfactors act on the $EAC'_{1,4,2,3a,3b}$ cell in a characteristic sequence.

In two special sessions *M. Hasek* (Prague, Czechoslovakia) reported on immunological tolerance, and *G. F. Springer* (Evanston, U.S.A.) gave a survey on aspects of germ-free life.

[VB 822/149 IE]

German version: Angew. Chem. 76, 721 (1964)

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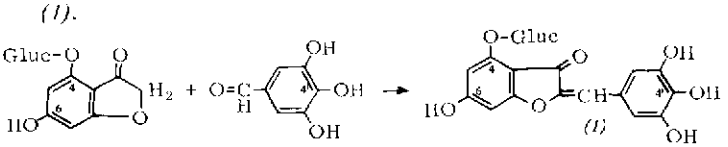
# Plant Products

The 12th Meeting of the Deutsche Gesellschaft für Arzneipflanzenforschung (German Society for Medicinal Plant Research) was held in Berlin from May 19th to 23rd, 1964. It consisted of a symposium on advances in the field of psychotropically active drugs and of individual reports on the analysis of secondary plant products.

*U. Beiss*, Göttingen (Germany), described a procedure for separating lipids. The material is subjected to preliminary purification by elution through Sephadex with $CHCl_3$/methanol/water. The lipids pass through the column while contaminants are adsorbed. Subsequently, they are chromatographed with two-dimensional development on paper impregnated with kieselgel. The solvents used are 1. tetrahydrofuran/diisobutyl ketone/water (45:9:4) and 2. diisobutyl ketone/methyl isobutyl ketone/methyl ethyl ketone/$CHCl_3$/formic acid/glacial acetic acid /water (10:8:8:100:10:10:1). In this way, a mixture of plant lipids was separated into more than 20 components.

*K. Egger*, Heidelberg (Germany), demonstrated the possibilities of partition chromatographic separations of flavones on polyamide with lipophilic eluants such as $CHCl_3$/methanol/methyl ethyl ketone (5:2:1). In the swollen state, Perlon functions as polar stationary phase. Groups of substances such as the 3-rhamnosides of myricetin, quercetin, and kaempferol, which have nearly identical $R_F$-values with dilute alcohol on Perlon, are sharply separated from each other. This led to a two-dimensional chromatographic technique on Perlon: in the one direction, with alcohol/water, separation depends largely on the type of glycosidation, and in the other direction, with $CHCl_3$/methanol/methyl ethyl ketone, it depends on the aglycone. The free aglycones, too, can be characterized in this manner.

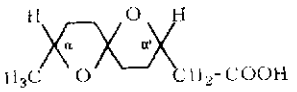
*L. Pallos*, Budapest (Hungary), elucidated the constitution of some naturally occurring aurone glycosides by synthesis. He employed *Geissmann*'s synthesis via coumaranone and benzaldehyde leading to benzylidenecoumaranone = aurone. Subsequent glycosidation yields glycoside mixtures, however. The reaction partners must therefore be glycosidated prior to the aldol condensation. Under these circumstances, alkali can no longer be employed for the condensation, but can be replaced by acetic anhydride, peracetylated substances then being obtained. These can be saponified in the cold with Na methoxide in absolute methanol. In this way it was shown that sulfurein is 6,3',4'-trihydroxyaurone 6-glucoside and that palasitrin is 6,3',4'-trihydroxyaurone 6,3'-diglucoside. For the synthesis of this latter compound, protocatechualdehyde had to be partially acetylated in the 3'-position and the 4'-hydroxy group protected with $H_3C{-}SO_2Cl$. Deacetylation and reaction with acetobromoglucose then followed. In the direct reaction, the 4'-glucoside would have been formed. It was possible to confirm that the structure of bractein is that proposed by *Hänsel (1)*.




(1)

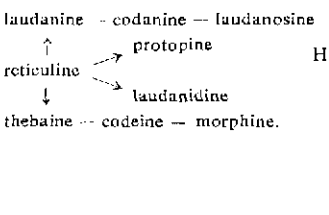
*E. Graf*, Tübingen (Germany), spoke about exogonic acid, a compound found in the resin of *Exogonium purga* (Resina Jalapae) and *Ipomea operculata* (Resina operculina). On saponification with alkali, the ether-insolubles from the resins yield acidic oligosaccharides (including purginic acid) plus a mixture of simple carboxylic acids. The crude exogonic acid which can be recovered from this mixture contains a contaminant which can be largely separated off by freezing the solution. The contaminant was identified as 4-oxocaprylic acid. After methylation with diazomethane, the remaining mixture can be fractionated by gas chromatography into five components A–E, the relative proportions of which are A:B:C:D:E = 6:1:11:41:41. A is 4-oxocaprylic acid, which had not been completely removed. The main components D

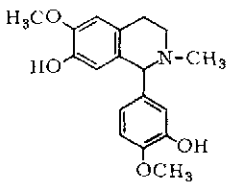
and E were taken together for structural determinations. Their reactions indicated a masked keto group (ketal). Only unbranched acids are obtained by $KMnO_4$ degradation. Finally, analytical data, including NMR-spectra, showed that exogonic acid is a derivative of oxetone, namely α-methyl-α'-carboxymethyloxetone *(2)*, a diketal with an unbranched carbon chain.



*(2)*

*E. Brochmann-Hanssen*, San Francisco, Calif. (U.S.A.), succeeded in isolating a new phenolic base from opium alkaloids and elucidating its structure. This base is apparently of great importance in the biosynthesis of the other alkaloids. Firstly, the alkaloid extract was adjusted to pH 1 and was then extracted with $CHCl_3$. The aqueous epiphase was mixed with dichloroacetic acid and again shaken with chloroform. The extract is then evaporated to dryness, and the residue subsequently dissolved in dilute sodium hydroxide and treated once more with chloroform. Only phenolic substances, including the new alkaloid, termed reticuline, remain in the aqueous phase. Reticuline can be converted into (±)-laudanosine with diazomethane, thus establishing its basic structure. The substance possesses two methoxy groups and two phenolic hydroxy groups. Comparison of its NMR-spectrum with those of some synthetically available partial methyl ethers with laudanosine structure made it possible to establish the position of the substituents, resulting in structure *(3)*. The compound is probably an intermediate in the biogenesis of the other opium alkaloids:



*(3)*

According to *T. Hartmann*, Bonn (Germany), the biogenesis of volatile amines can be formally represented as the decarboxylation of the corresponding amino acids. Additions of leucine to mycelial cultures of *Claviceps purpurea* do indeed lead to the formation of isoamylamine. However, until now, no amino acid was known which could be responsible for the abundant occurrence therein of n-hexylamine. Accurate analyses of the mycelia, which accumulate n-hexylamine, have now demonstrated the presence of an amino acid which is chromatographically identical with synthetic α-aminoheptanoic acid. The acid is readily identifiable in young mycelia. Its presence could not be demonstrated in *Secale cornutum*, however. It was not possible to show that other volatile amines arose by direct decarboxylation of amino acids. This concept should not, therefore, be generalized. For identification, the amines were treated with dinitrofluorobenzene and separated by partition chromatography on paper impregnated with paraffin oil using methanol/water (10:6) as eluant.

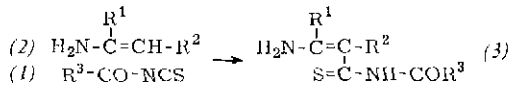
*R. Tschesche*, Bonn (Germany), spoke on the constitution of saponins, their hemolytic activity, and their ability to form complexes with sterols. An elegant method was elaborated for examining their complexing ability. The saponin is transferred to a paper strip, together with $^{14}C$-labelled cholesterol, and the paper developed with carbon tetrachloride. If a complex has been formed, the total radioactivity, or at least most of it, remains with the saponin at the start. If complex formation does not occur, however, the cholesterol is eluted by the carbon tetrachloride. In this way it was possible to determine whether there is a connection between hemolytic index and complex formation. This seems to be the case to only a very limited extent. Rather, the hemolytic index seems to depend in equal proportions on complex formation, detergent character, and protein association. [VB 826/152 IE]

German version: Angew. Chem. 76, 723 (1964)

## New Observations on Acylheterocumulenes

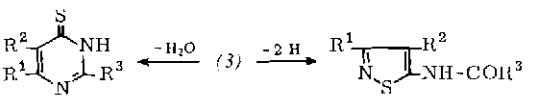
*J. Goerdeler*, Bonn (Germany)

Acyl isothiocyanates *(1)* add onto C-2 of 1-alkoxy-1-amino- or 1,1-diaminovinyl ketones *(2)* or analogously substituted acrylic esters *(2)* [1] to form compounds *(3)*. Cyclization of *(3)* can be induced by alkali or occurs spontaneously and yields 4-mercaptopyrimidines *(4)* with amino or alkoxy groups in the 6-position. Alternatively, dehydrogenative cyclization leads to 3,5-diaminoisothiazoles *(5)* or 3-alkoxy-5-aminoisothiazoles *(5)* (experiments with *U. Keuser*).



*(2)* $R^1 = H_2N$, $R^2 = H$; *(1)* $R^3 = R$, $R^3 = OR$

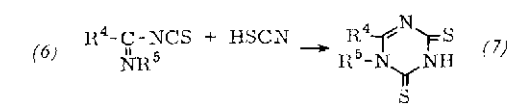
*(3)*



*(4)* *(5)*

$R^1$ = OR, $NH_2$; $R^2$ = COR, COOR

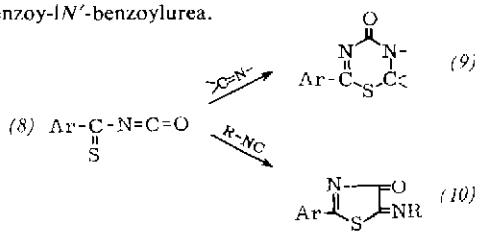
Monomeric *N*-substituted α-iminoalkyl isothiocyanates *(6)* are readily converted into dimers (α-iminoalkyltriazinedithiones) [2]. On the other hand, they are easily cyclized to 1,3,5-triazine-2,4-dithiones *(7)* by thiocyanic acid. This confirms the hypothesis of *I. Ugi* and *F. Rosendahl* [3] that an α-iminoalkyl isothiocyanate is formed as an intermediate when



*(6)* *(7)*

HSCN adds onto an isonitrile. It should be mentioned, however, that methyl and phenyl isothiocyanates do not add onto monomeric α-iminoalkyl isothiocyanates.

Thermal decomposition of 2-arylthiazoline-4,5-diones yields arylthioacyl isocyanates *(8)* [4]; phenylthioacyl isocyanate was isolated as red crystals, m.p. 16.5 °C. Additions of aromatic and heterocyclic amines onto *(8)* yield thioacylated ureas; in the aliphatic series, side reactions occur. Thiobenzoylurea can, however, be readily obtained by hydrolysis of *N*-thiobenzoyl-*N'*-benzoylurea.



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

1,4-Cycloadditions onto *(8)* with morpholinohexene, *N,N'*-dicyclohexylcarbodiimide, *N*-benzylideneaniline, and phenyl isocyanate afford thiazine or thiadiazine derivatives *(9)*; the corresponding reaction with isonitriles affords 2-aryl-4-oxo-5-alkyliminothiazolines *(10)*. Benzoyl isocyanate reacts in an analogous manner [5]. These cycloadditions are reversible and can be carried out in most cases with the precursors of the thioacyl isocyanates (experiments with *H. Schenk*).

[GDCh-Ortsverband Krefeld, Krefeld-Uerdingen (Germany), April 30th, 1964] [VB 821/150 IE]

German version: Angew. Chem. 76, 654 (1964)

[1] *J. Goerdeler* and *H. Pohland*, Chem. Ber. 96, 526 (1963).

[2] *J. Goerdeler* and *D. Weber*, Tetrahedron Letters *1964*, 799.

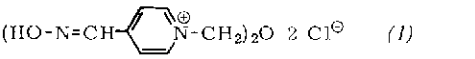
[3] *I. Ugi* and *F. Rosendahl*, Liebigs Ann. Chem. *670*, 80 (1963).

[4] *J. Goerdeler* and *H. Schenk*, Angew. Chem. *75*, 675 (1963); Angew. Chem. internat. Edit. *2*, 552 (1963).

[5] *R. Neidlein* has independently observed the same isonitrile reaction with benzoyl and thiobenzoyl isocyanates [Angew. Chem. 76, 596 (1964)].

# SELECTED ABSTRACTS

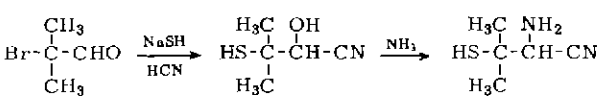
**Bis-(4-hydroxyiminomethylpyridinio)methyl ether dichloride** *(1)*, a drug which reactivates acetylcholine esterase inhibited by phosphoric esters, has been developed by *A. Lüttringhaus* and *I. Hagedorn*. According to clinical investigations carried out by *W. D. Erdmann* and *H. Engelhard*, *(1)* acts as an antidote to poisoning with esterase-blocking alkyl phosphates and has a high therapeutic index. It shows



*(1)*

considerable superiority over reference substances and, when given in greater doses, is capable of passing the blood-brain barrier. It is obtained in 95 % yield by reacting pyridine-4-carboxaldoxime with α,α'-dichlorodimethyl ether, and can be obtained in the form of the *syn*- and the *anti*-oxime, m.p. 235 °C and 220 °C, respectively. Aqueous solutions of *(1)* are stable and can be injected intramuscularly. / Arzneimittelforsch. *14*, 1, 5 (1964) / –De. [Rd 907/258 IE]

**Penicillamine nitrile** was synthetized for the first time by *I. Ugi* and *E. Böttner*. α-Bromoisobutyraldehyde was treated with NaSH and HCN in methanol. Subsequent addition of $CH_2N_2$ and 85 % phosphoric acid gave α-hydroxy-β-mercaptoisovaleronitrile *(1)* in 88 % yield; b.p. of the hydrochloride 92–94 °C/4 mm.

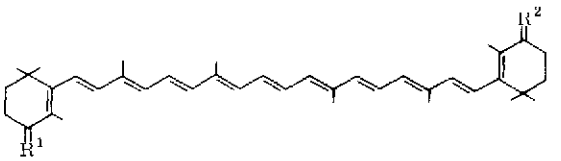


*(1)* *(2)*

Reaction of *(1)* with liquid $NH_3$ gave penicillamine nitrile (α-amino-β-mercaptoisovaleronitrile) *(2)* in 75 % yield; m.p. of the hydrochloride: 181–182 °C. Compound *(2)* reacts with aldehydes and ketones to form 4-cyano-5,5-dimethylthiazolidines. / Liebigs Ann Chem. *670*, 83 (1964) / –Ma. [Rd 901/251 IE]

**The synthesis of substituted benzoic acids, benzonitriles, and benzaldehydes** is reported by *F. Effenberger* and *R. Gleiter*. These substances can be prepared from *p*-substituted *N*-alkyl- and *N*-arylbenzamides, the starting materials being readily obtained in good yield by Friedel-Crafts reaction of isocyanates and benzene derivatives. Hydrolysis of *N*-substituted benzamides, *e.g. p*-chlorobenzanilide, with alcoholic KOH gives rise to *p*-substituted benzoic acids, *e.g. p*-chlorobenzoic acid (yield = 91 %). Von Braun degradation of *N*-substituted benzamides, *e.g. N*-cyclohexyl-*p*-toluamide, leads to nitriles, *e.g. p*-toluonitrile (yield = 100 %). Sonn-Müller aldehyde synthesis via the imidochlorides, which are reduced to Schiff bases with $SnCl_2$ and subsequently converted into aldehydes by hydrolysis with acid, was used to prepare some aromatic aldehydes, especially ones that cannot be obtained by direct formylation, *e.g. p*-fluorobenzaldehyde and 2,4-dichlorobenzaldehyde (obtained in 83 % and 61 % yield, respectively). / Chem. Ber. *97*, 480 (1964) / –Ma. [Rd 5/282 IE]

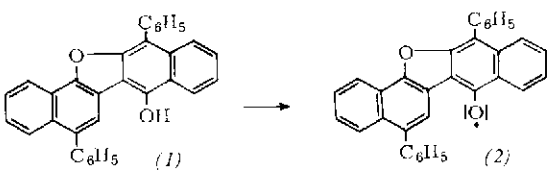
**Keto-carotenoids in crustacea** were detected by *H. Thomman* and *H. Wackernagel*. Flamingo feathers contain canthaxanthin as coloring matter; the carotenoid source is considered to be their food, particularly small crustacea such as water-fleas (*Daphnia*). β-Carotene *(1)*, echinenone *(2)*, and canthaxanthin *(3)* were isolated from various *Daphnia* species,



*(1)*: $R^1 = H_2$, $R^2 = H_2$; *(2)*: $R^1 = O$, $R^2 = H_2$; *(3)*: $R^1 = O$, $R^2 = O$

*(2)* and *(3)* in large quantities. It is presumed that water-fleas oxidize β-carotene and accumulate *(2)* and *(3)*. The astaxanthin from flamingo feathers may be derived from *(3)*. / Naturwissenschaften *51*, 87 (1964) / –De. [Rd 906/257 IE]

**5,12-Diphenyl-7-oxyldinaphtho[1,2-*b*:2',3'-*d*]furan** *(2)* a new, stable aroxyl radical has been described by *D. Schulte-Frohlinde* and *F. Erhardt*. Oxidation of *(1)* (obtained from 1-hydroxy-4-phenylnaphthalene) with $PbO_2$ in benzene yields the aroxyl radical *(2)*, which is green in solution and forms black crystals, m.p. above 192 °C, in 50 % yield. According to measurements of their paramagnetic spin resonance, the crystals contain about 15 % free radical, the solutions about 90 %. Solid *(2)* is stable to oxygen. Its degree of dissociation



*(1)* *(2)*

and its sensitivity towards oxygen lie between those of triphenylphenoxyl and tri-t-butylphenoxyl. It is somewhat superior to α,α-diphenylpicrylhydrazyl for trapping other free radicals. / Liebigs Ann. Chem. *671*, 84, 88 (1964) / –Ma. [Rd 903/256 IE]

# BOOK REVIEWS

**Newer Methods of Preparative Organic Chemistry,** Volume II, edited by *W. Foerst*, translated from the German into English by *F. K. Kirchner*. Academic Press, New York and London. 1963. XV + 417 pp. Cloth-bound S 14.50.

Some 50 years ago, the editors of the 4th edition of *Beilstein* had to acknowledge that it was impossible to encompass the whole field of organic chemistry in a handbook of reasonable timeliness. The past decade brought the same realization in the much more restricted field of preparative organic chemistry. *Houben-Weyl* mushroomed from a modest handbook of 4 volumes (4th edition, 1925) into a grandiose compendium of the size of *Beilstein* and with all its merits, but also with the inevitable disadvantage of staying hopelessly behind the rapidly advancing improvement of classical procedures and the steady development of novel techniques. Nonetheless, for generations to come, this impressive work will still remain the starting point for any systematic search for the best solution of problems in preparative organic chemistry. The referee doubts, however, if future generations will ever dare to compile another edition. Like *Beilstein*, which covers the progress of organic chemistry in series of supplements, even in this restricted field, the only possible solution providing a steady, timely source of information is the publication of specialized monographs by experts in individual fields. Long before a new edition of *Houben-Weyl* could even be visualized,

this approach has been chosen all over the world and has resulted in a large number of surveys and progress reports of this kind.

A highly successful attempt in this direction was the innovation of "Neuere Methoden der Präparativen Organischen Chemie" edited by *W. Foerst*, the first volume of which appeared during World War II as a collection of verbatim reprints of articles originally published between 1940 and 1942 in "Die Chemie". Thus, a unique combination of timeliness and competence with a minimum of time-consuming editorial work was achieved which resulted in enthusiastic acceptance of this volume everywhere. Its importance was immediately recognized by the Allies who had it translated into English and reprinted in several editions in the United States.

After the war, as editor of "Angewandte Chemie" *W. Foerst* resumed publication of this popular series and presents in the present volume authentic English translations of the fourteen articles comprising Volume II of the original German edition, which appeared in 1960.

The contributions are again written by recognized authorities in their fields. The selection of the individual chapters resulted both from the personal interest of the editor and from the availability of German specialists. A book of this kind can hardly satisfy everybody, and what is missing from this volume may reasonably be expected in future issues of this series. However, even the highly critical reader, will have to admit that all the articles are well-presented, interesting, exhaustive reports of the progress in their respective field. Contrary to Volume I, which covered also mere techniques such as chromatography and vacuum distillation, Volume II is strictly oriented towards the preparation of definite classes of compounds. However, sometimes the impression is obtained that too much has been included; procedures such as the continuous preparation of phenylsodium and the alkylation of phenols with low molecular-weight olefins under pressure which require specialized expensive equipment will rarely appeal to the average laboratory worker for the occasional preparation of a compound. The individual chapters deal mainly with the principles of various types of syntheses and with their variations and applications. Reaction mechanisms are occasionally discussed, especially where their understanding may allow the experimenter to extend the scope of the reaction or vary its conditions rationally rather than by intuition alone. Each chapter includes a generous supply of detailed preparative directions for actual examples in the style of *Houben-Weyl*; these are adequate for reproduction without recourse to the original literature. The book contains the following contributions, which have been brought up to date by the authors: Syntheses with Acetoacetaldehyde (*W. Franke, R. Kraft, K. Kossing*); Preparation of Peptides and Ureas Using Reactive Amides or Imides (*St. Goldschmidt, H. L. Krauss*); The Preparation of Long-Chain Carboxylic Acids from 1,3-Cyclohexanediones (*H. Stetter*); Ethyl 2-Cyclopentanonecarboxylate and Its Importance in Syntheses (*R. Mayer*); Ketene in Preparative Organic Chemistry (*G. Quadbeck*); Preparative and Analytical Importance of Phosphines and Related Compounds (*L. Horner, H. Hoffmann*); Reduction of Carbonyl Compounds with Complex Hydrides (*H. Hörmann*); Alkylation of Aromatic Amines (*R. Stroh, J. Ebensberger, H. Haberland, W. Hahn*); Chemical Synthesis of Intermediates of Carbohydrate Metabolism (*H. O. L. Fischer*); Amidomethylation (*H. Hellmann*); Selective Catalytic Oxidations with Noble Metal Catalysts (*K. Heyns, H. Paulsen*); Alkylation of Phenols with Alkenes (*R. Stroh, R. Seydel, W. Hahn*); Continuous Preparation of Phenylsodium (*H. Ruschig, R. Fugmann, W. Meixner*); Newer Investigations on Oxidations with Lead Tetraacetate (*R. Criegee*).

The author and subject indices compensate to a large extent the lack of systematic arrangement of the information presented. Like its predecessor, the above volume will extend the use of these extremely valuable monographs to chemists not conversant with German. The organic chemist may rightfully consider this book indispensable, but any member of the profession who is occasionally concerned with problems of organic preparations will derive ample benefits from it.

*Ch. Grundmann* [NB 182/86 IE]

**Zwischenprodukte-Tafeln.** (Intermediates Tables), by *O. Horn*. Carl Hanser Verlag, München 1963. 1st Edit., 20 tables, paperback, DM 7.80 (about $ 2.00).

The number of organic intermediates has grown enormously in the past decades. These compounds, in addition to their original application as dyestuff components, are meanwhile used in many other fields. Petrochemistry has made it possible to develop new syntheses of intermediates from cheap raw materials so that the whole field is now extremely difficult for the non-specialist to comprehend.

The present "Intermediates Tables", based on lectures by the author, render a valuable service in view of this situation. In twenty tables, the essential routes of syntheses for the manufacture of intermediates are clearly presented in the form of family trees. Starting from the raw materials methane, acetylene, olefins, benzene, toluene, xylene, naphthalene, and anthracene, the more important derivatives and their respective genetics are evolved. Thus, the entire range from classical dyestuff intermediates to modern processes of olefin chemistry is embraced. The reagents and characteristic reaction conditions are not always given for the individual process stages but could perhaps have been mentioned without any great loss in clarity.

The "Intermediates Tables" is a kind of "organic chemical technology without words" and will probably not only facilitate students' understanding of the subject but will always be of service when a survey on this complex field is sought. *W. Hahn* [NB 185/81 IE]

**Anabole Steroide** (Anabolic Steroids). By *H. L. Krüskemper*. Biochemie und Klinik, monographs edited by *G. Weitzel* and *N. Zöllner*. Georg Thieme Verlag, Stuttgart 1963. 1st edit., VIII, 166 pp., 14 illustr., 14 tables, cardboard DM 38.– (about $ 10.00).

With this monograph, the author presents a book, to which one may ascribe the highest praise because of its potential to induce the production of new works on this subject. His exhaustive survey of the abundance of experimental results is supported by 1108 literature references. After a review of the nomenclature, chemistry, and metabolism of anabolic steroids (19 pp.), their effects are described in detail (49 pp.). In a further chapter (9 pp.) the effect of anabolic steroids is compared with that of other anabolic hormones. The most important results on the problem of the structure and activity of anabolic steroids as well as on their clinical use, contraindications, and side-effects are presented in detail and in review, so that the book will be of great use equally to biochemists, experimental clinicians, and physicians. The author indicates numerous questions which still remain open. The reviewer is certain that the book deserves a mark of thanks in many future publications on this subject. *E. Gerhards* [NB 187/82 IE]

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# The Structure of the Proton and the Neutron

BY PROF. DR. H. SCHOPPER

INSTITUT FÜR EXPERIMENTELLE KERNPHYSIK DER TECHNISCHEN HOCHSCHULE UND DES KERNFORSCHUNGSZENTRUMS KARLSRUHE (GERMANY)

*A short survey is given of the present state of our knowledge of the structure of the proton and the neutron. The results so far obtained have been derived from studies of the scattering of fast electrons.*

## I. Introduction

In the exploration of the macrocosm, attempts are being made to probe ever farther into the universe. The most remote objects known at present, *e.g.* the radio source 3C/295, are some $10^{27}$ cm distant from the earth. Conversely, penetration into the microcosm has now proceeded down to dimensions of about $10^{-14}$ cm.

The ultimate aim of the exploration of space, at least as far as basic research is concerned, is an attempt to comprehend the structure and origin of the universe. In contrast, elementary particle physics attempts to elucidate the structure of matter and its constituents. Ideas concerning the origin and transformations of elementary particles are closely related to theories concerning the creation and development of the cosmos. Progress in these fields keeps demanding increasingly costly instruments: on the one hand, giant optical and radio telescopes and satellite observatories, and on the other, particle accelerators of ever increasing dimensions.

Some decisive steps in the elucidation of the structure of elementary particles have been achieved in recent years. It was shown for the first time that the fundamental building blocks of matter, the proton and the neutron, have structures of their own and are not elementary in the strict sense [1]. Although the problems and methods of elementary particle physics are far removed from those of classical chemistry, it may still be of interest to chemists to find out about the present state of our knowledge in this field. After all, chemists such as *Dalton* and *Avogadro* were the first to produce experimental evidence for the atomic structure of matter.

However, physicists soon discovered that the atoms discovered by the chemists were indivisible only with respect to chemical methods. The golden era of physics followed, with its atomic shell theory and the simultaneous development of quantum mechanics, resulting in complete understanding of the structure of atomic shells and of the forces which hold them together. However, this did not provide an answer to the question of the fundamental nature of matter, since the classical experiments of *Rutherford* demonstrated that almost the entire mass of the atom resides in its nucleus. The by no means complete studies of nuclear physics had shown that all atomic nuclei are made up of protons and neutrons, and it seemed that these particles, the nucleons, represent the ultimate building blocks of matter. Doubts were first raised when it was discovered that the free neutron was not a stable particle but had a half-life of 12 minutes, decaying into a proton, with emission of an electron and a neutrino [2]. The situation became even more complicated when, after 1945, numerous short-lived new elementary particles were discovered (mesons, K-mesons, and other strange particles) [3].

For a variety of reasons, it was suspected that all these particles too were not elementary, but had also composite structures. Detection of the structure of these elementary particles was first achieved with the help of scattering very fast electrons by protons and neutrons [1]. Although the results obtained to date are not final, one important fact has been established: in the past, penetration into new orders of magnitude of smaller dimensions, led to the discovery of new building blocks of matter (atoms, electrons, protons, neutrons); now this no longer seems to be the case. Although the study of nucleons did lead to the discovery of new particles –

[1] *R. W. Mc. Allister* and *R. Hofstadter*, Physic. Rev. *102*, 851 (1956); *M. R. Yearian* and *R. Hofstadter*, ibid. *111*, 934 (1958).

[2] *A. N. Sosnovsky* et al., Nuclear Physics *10*, 395 (1958).

[3] *W. S. C. Williams:* Introduction to Elementary Particles. Academic Press, New York 1961.

as discussed below – these were in no way more elementary than the previously known ones They are also extremely short-lived and, for this reason, certainly cannot be regarded as the ultimate, indivisible constituents of matter. The question "What is matter?" therefore seems more complicated than ever.

## II. Indirect Evidence for the Structure of Nucleons

The discovery that the neutron has a magnetic moment of $-1.91\ \mu_K$ ($\mu_K$ – Bohr magnetons; the negative sign indicates that the spin and magnetic moment have opposite directions) was initially very surprising, since in classical physics a magnetic moment was always associated with circular currents. Since the neutron is electrically neutral, generation of a magnetic moment in the absence of an electric charge seemed incomprehensible.

An anomalous magnetic moment was discovered also for the proton. The total magnetic moment of this particle is $+2.793\ \mu_K$, whereas *Dirac*'s theory implies a value of only $+1\ \mu_K$. It should be noted that the anomalous part, $1.79\ \mu_K$, with respect to its absolute value is roughly equal to the magnetic moment of the neutron. The occurrence of normal Dirac magnetic moments of electrons and protons is interpreted in terms of relativistic quantum mechanics by assuming that even when the particle is not subject to external forces, it executes microscopic vibrations which on the average generate small circular currents. Such moments do not therefore presuppose the presence of a complex structure within the particles; as in classical physics, these can be regarded as point particles.

An explanation of the anomalous moments seems possible only by postulating that protons and neutrons are not genuine elementary particles but have internal circular currents [4]. However, the carriers of this current cannot be electrons, since for a variety of reasons, which are described in any book dealing with the subject of β-decay electrons cannot exist within the atomic nucleus. No other stable carriers of electric charges are known. According to the main concept of *Yukawa*'s meson theory [5], the structure of protons and neutrons cannot be explained on the basis of stable particles, but is due to unstable particles, which circulate for extremely brief periods within the interior of protons and neutrons and which are soon recaptured. π-Mesons were the first type of particles to be considered. These exist in three differently charged states, *viz.* positive, negative, and neutral. As will be seen later, other particles may contribute to the structure of nucleons.

In the simplest case, a proton can dissociate into a $\pi^+$-meson and a neutron. Similarly, a neutron may dissociate into a π-meson and a proton. The π-mesons produced surround the "bare" nucleons in the form of a cloud (Fig. 1) [4]. Theory predicts that the mesons are generated in orbits of finite angular momentum [4], *i.e.* they rotate about the remainder of the nucleon. Circular currents are thereby formed and give rise to the anomalous magnetic moments. The opposite charges of the

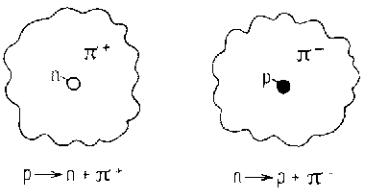



Fig. 1. Virtual dissociation of the nucleons into a meson cloud and a "bare" nucleon.

mesons in protons and neutrons explain the different signs of the anomalous moments. In addition, it has been known for some time that the nuclear forces between the nucleons and mesons are independent of the electrical charge. For this reason, the probability of meson emission is identical for protons and neutrons; this explains the approximately equal absolute values of the anomalous magnetic moments.

In addition to the intermediate states with one meson with there are likely to be others into which two or more mesons are emitted. Other "virtual" particles may appear, *e.g.* K-mesons or proton-antiproton pairs. It has not yet been possible to derive from theory a quantitative prediction of the contribution of the various virtual states to the total structure of the nucleons [4].

If this explanation of the anomalous magnetic moments is correct, then it follows directly that the nucleons must have a spatially extended distribution of electrical charge. It is to be expected that the center contains an approximately point-size bare nucleon with one or more clouds or shells of virtual particles surrounding it. Naturally, structural details cannot be derived from the magnetic moments alone, but the expected spatial extension of the structure can be at least roughly estimated from *Heisenberg*'s uncertainty principle.

The time which elapses before an emitted meson is recaptured is given by $\Delta t \cdot \Delta E = h/2\pi$. In order to determine the greatest possible time $\Delta t$, the least possible energy $\Delta E$ must be substituted in the equation. This is given by the mass m of the virtual particle at rest as $E = mc^2$. The greatest distance which a particle moving with the speed of light can cover in the time $\Delta t$ is given by the so-called Compton wavelength $\lambda/2\pi = \Delta t \cdot c = (h/2\pi)\,mc$. For a π-meson, $\lambda/2\pi = 1.4\times10^{-13}$ cm. This value gives an indication of the expected dimensions of nucleons.

## III. Investigation of the Structure of Nucleons by Electron Scattering

It is possible to determine the structures of crystals and molecules indirectly by electrons or X-ray diffraction. From the angular distribution of the diffracted electrons the spatial arrangement of the diffracting centers can be

[4] *D. R. Yennie, D. G. Ravenhall,* and *M. M. Levy,* Rev. mod. Physics *29*, 144 (1957).

[5] *H. Yukawa,* Proc. physico-math. Soc. Japan *17*, 48 (1935).

inferred. The method of electron diffraction can be applied directly to the investigation of the structure of nucleons, but the wavelength of the electrons must be of the order of $10^{-13}$ cm, since a structure can be resolved only when its details are comparable with the wavelength of the radiation used.

One additional difficulty that arises is that not only are the electrons scattered by the electrical charge of the proton, but an interaction also occurs between the magnetic moment of the electron and that of the proton. These two effects must be separated by a suitable mathematical analysis. For this purpose, a theoretical relationship between the observed scattering pattern and the spatial distribution of the scattering centers must be known [6].

The scattering cross-section for the deflection of an electron by a point proton can be readily calculated [4]. If the value of this "point scattering cross-section" is known, the scattering of a spatially extended proton can be derived by regarding the proton as being composed of numerous point charges. It is then only necessary to add together the scattering waves due to each individual center of scattering. Since coherent scattering is involved, the individual partial waves must be added with proper phases. Such a procedure is well known from X-ray diffraction. On investigating crystals one has to do with scattering centers arranged in a regular lattice, whereas in nucleons, a continuous density distribution must be expected. The conditions are therefore more akin to those encountered in X-ray diffraction by gaseous molecules or liquids.

It is expedient to derive the so-called form factor first from the measured scattering intensities instead of calculating the spatial distribution of the scattering centers directly. This form factor is a function of the recoil momentum q transferred to the scattering particle [4]. Mathematically, the form factor and the density distribution of the scattering particles behave like Fourier transforms [*].

The mathematical derivation cannot be given here; instead, the principal characteristics of the form factor are discussed with the aid of Figure 2, to enable us to interpret the experimental results later.

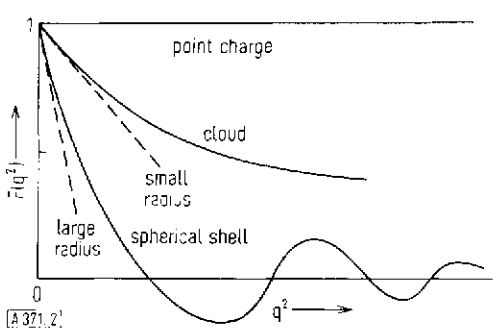



Fig. 2. Schematic representation of the form factor F as a function of the recoil momentum q for various charge distributions. A steeper slope (dotted line) corresponds to a greater mean radius.

A point charge has an associated constant form factor (Fig. 2). If the scattering centers are spread out in space, then the form factor decreases as $q^2$ increases, the slope being steeper the greater the mean radius. The tangent at $q^2 = 0$ gives directly the value of the mean radius $\bar{r}$, since $(\vartheta F/\vartheta q^2)_{q_2=0} = -\bar{r}/6$. The shape of the form factor at high q-values provides information on structural details. Thus, a diffuse distribution gives a steadily decreasing form factor, while density distributions with sharp edges or lattice-like arrangements lead to oscillations of the form factor. It can also be shown readily that the value of the form factor at $q^2 = 0$ is proportional to the total charge which it describes. Thus, the form factors shown in Figure 2 each describe an elementary charge. A density distribution composed of a diffuse cloud and a point-like nucleus is characterized by the form factor shown in Figure 3.

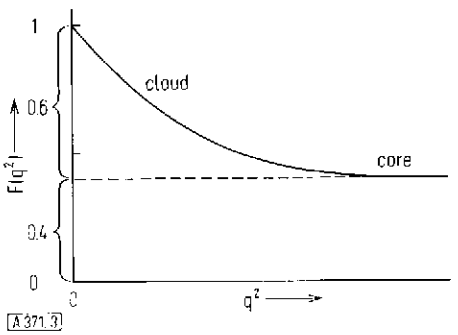



Fig. 3. Schematic representation of the form factor F as a function of the recoil momentum q for a combined charge distribution: 40 % of the charge is concentrated at a point core, and 60 % is distributed over a diffuse cloud.

Two form factors must be derived from the scattering experiments: one describing the distribution of the electrical charge, and the other the distribution of the magnetic dipole moments. Determination of both form factors is possible when the scattering is studied not only as a function of the scattering angle, but also as a function of the energy of the incident electrons. Since "electric" and "magnetic" scattering exhibits different relationships with respect to angle and energy [4], separation of the two effects is possible.

## IV. Experimental Procedure

As explained above, the electrons used must correspond to a wavelength of about $10^{-13}$ cm to be capable of resolving details of the structure of nucleons: the electrons must therefore have energies of several hundred MeV. For this reason, the structure of nucleons can be studied only with the aid of large electron accelerators.

The pioneer experiments were carried out by *Hofstadter* et al. in Stanford (U.S.A.) about seven years ago, using a linear accelerator with an initial maximum energy of about 500 MeV [1]. About two years ago, *Wilson* et al. carried out investigations at Cornell University, Ithaca (U.S.A.) using a synchrotron, *i.e.* a circular accelerator, with a maximum energy of about 1400 MeV [7]. Very

[6] *R. Hofstadter:* High-Energy Electron Scattering Tables. Stanford University Press, 1960.

[*] In X-ray diffraction terminology, this is called transformation to the reciprocal lattice.

[7] *D. M. Olson, H. F. Schopper,* and *R. R. Wilson,* Physic. Rev. Letters 6, 286 (1961); *R. M. Littauer, H. F. Schopper,* and *R. R. Wilson,* ibid. 7, 141 (1961); *K. L. Berkelman, M. Feldman, R. M. Littauer, G. Rouse,* and *R. R. Wilson,* Physic. Rev. *130*, 2061 (1963).

recently, a linear accelerator in Orsay near Paris [8], with a maximum energy of about 1000 MeV, and a synchrotron at Cambridge (U.S.A.) with 6000 MeV, have been put into operation. Fortunately, it will soon be possible to carry out similar experiments in Germany; work has just started with the DESY synchrotron in Hamburg (Germany), which has a maximum energy of 6000 MeV.

As an example of the experimental method, the set-up used at Cornell – where I had the privilege of working [7] – will be described. The arrangements employed at Cambridge and Hamburg are entirely analogous.

Figure 4 shows the arrangement in a schematic form. Straight sections are arranged between the magnets of

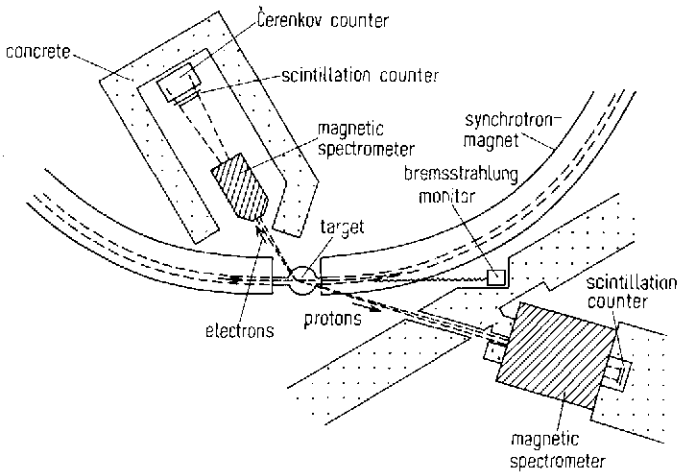



Fig. 4. Diagram of the experimental arrangement for measuring electron scattering by nucleons used at Cornell University, Ithaca, N.Y. (U.S.A.).

the synchrotron, which maintain the electrons in their circular orbit. In one of these sections, there is a scattering chamber with a hydrogen target in its center. The use of a target inside the machine has the advantage that, after a single passage through the target, any non-scattered electrons continue to orbit in the machine and will strike the target several times. Up to 100 such multiple traversals can be obtained. The scattered electrons are analyzed with a magnetic spectrometer, in order to separate elastically and inelastically scattered electrons. The electrons are detected by means of two scintillation counters and a so-called Čerenkov counter, which enables them to be differentiated from accompanying $\pi$-mesons. A second spectrometer is installed at the outside of the synchrotron for detecting protons recoiling from the scattering in coincidence with the electrons. In this way, the reliability and accuracy of the measurements can be appreciably increased.

Substances containing hydrogen (*e.g.* polyethylene) or liquid hydrogen are used as targets for the study of protons. Since, unfortunately, no pure neutron targets are available, deuterium, preferably in the liquid form, is used for the investigation of neutrons. Here however, scattering by protons naturally occurs at the same time as scattering by the neutrons. It can be shown that for high electron energies, the binding between the neutron and the proton in the deuteron can be neglected to a first approximation. Consequently, the known scattering for the proton can simply be subtracted from the scattering by the deuteron, to give the scattering due to the neutron. The magnitiude of the error introduced in this way has not yet been theoretically established; for this and several other reasons, the results for scattering by neutrons are substantially less reliable than those for protons [4].

The main difficulty encountered in carrying out the measurements is the low probability of scattering at high energies and large scattering angles. Counting rates of only a few particles per hour are obtained; thus, very long measuring times are incurred, and the elimination of systematic experimental errors is very difficult.

## V. Results and Their Interpretation

The form factors for the electric and magnetic density distributions in the proton derived from the measurements carried out to date [9] are shown in Figure 5. Certain qualitative conclusions can be drawn directly from these results without having to go into a detailed evaluation. First, it is obvious that the form factors are not constant, and consequently the proton is not a point-like particle. The slopes at $q^2 = 0$ determine the mean radii and for the electric charge distribution of the proton one obtains $r_{Ep} = 1.0\times10^{-13}$ cm, and for the magnetic moment of the proton $r_{Mp} = 1.0\times10^{-13}$ cm.

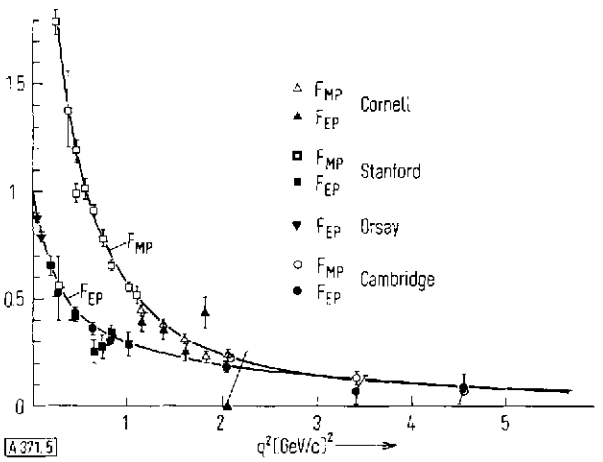



Fig. 5. Experimental form factors F of the proton as a function of the recoil momentum q. $F_{Ep}$ = form factor for the electric charge distribution; $F_{Mp}$ = form factor for the magnetic dipole moment distribution.

Surprisingly, the radii for the two distributions agree to within 10 %. Moreover, the most recent measurements at very high $q^2$ values seem to indicate that the two form factors decrease monotonically, with no indication of their reaching a constant value [9]. According to the arguments presented in Section II, this implies that the proton does not have a point nucleus.

[8] *P. Lehmann, R. Taylor,* and *R. W. Wilson,* Physic. Rev. *126,* 1183 (1962).

[9] *K. W. Chen, A. A. Cone, J. R. Dunning, S. G. Frank, N. F. Ramsey, J. Walker,* and *R. Wilson,* Physic. Rev. Letters *11,* 561 (1963).

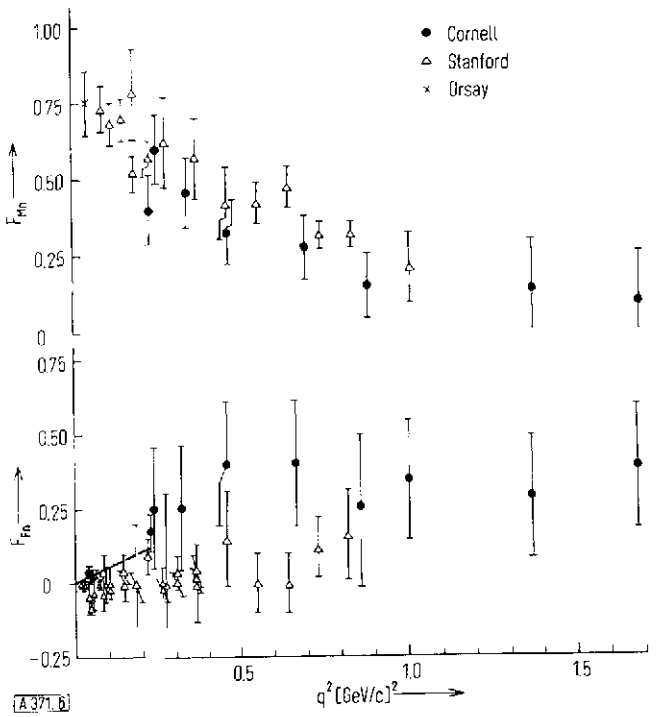



Fig. 6. Experimental form factors F of the neutron as a function of the recoil momentum q. $F_{En}$ = Form factor for the electric charge distribution; $F_{Mn}$ = Form factor for the magnetic dipole moment distribution.

The results of measurements on neutrons (see Fig. 6) [7, 8, 10] are much less reliable than those for the proton. Since the neutron has no resultant electric charge, the form factor for the distribution of electric charge begins at zero. The initial slope of the form factor, and thus the radius of the charge distribution, has been known for some time from the scattering of thermal neutrons by atomic electrons [4]. A value of $r_{En} = 0.4\times10^{-13}$ cm was found. The form factor at higher q-values is as yet uncertain since partly conflicting results have been obtained. Local deviations from electrical neutrality within the neutron are nowhere very large, as is shown by the invariably small values of the form factor. In contrast, the course of the magnetic form factor of the neutron is very similar to that of the proton. The mean radius $r_{Mn} = 1.0\times10^{-13}$ cm found agrees within experimental limits with that found for the proton.

The elucidation of additional details concerning the structure from the shape of the form factors requires complicated theoretical considerations; a final interpretation is not as yet possible. However, certain important and surprising consequences do result from such studies.

All theoretical attempts to explain the experimentally found radii of about $10^{-13}$ cm by postulating that the nucleons consist essentially of clouds of $\pi$-mesons have so far remained unsuccessful [4]. In every case, these $\pi$-mesons produce too large values for the radius. In the face of this situation, the daring idea that as yet unknown particles are responsible for the structure of the nucleons was tentatively suggested some years ago (cf. [11]). Since the radii are directly related to the mass of the particles (cf. Section II), it was possible to predict the mass of these new particles from the measured radii. A figure approximately three to four times that of the mass of the $\pi$-mesons was obtained. Particles with approximately the right mass were observed shortly afterwards in various processes, *e.g.* during the annihilation of antiprotons by protons [12]. The particle can be considered as consisting of two $\pi$-mesons. It was therefore initially designated as a dipion, but is today generally termed a $\rho$-meson. Subsequently, another particle was discovered which also contributes to the structure of the nucleons, but is composed of three mesons. It was initially called a trimeson but is now referred to as an $\omega$-meson. Both particles have extremely short lives of about $10^{-21}$ seconds. In the meantime, numerous further mesons have been discovered, which appear to form a family with those previously known [12]. The nature of the symmetry structure of this family is one of the most interesting problems facing modern elementary particle physics.

To summarize, it can be said that the structure of protons and neutrons consists of several clouds with radii of about $10^{-13}$ cm. These clouds are made up of virtual $\rho$- and $\omega$-mesons and, perhaps, of other unknown particles. The term "virtual" signifies that these particles exist in the cloud for only very brief periods, being constantly annihilated and recreated. This concept is the only one which can explain the contribution of such short-lived particles as the $\rho$- and $\omega$-mesons to the structure of the nucleons. The distribution of the electrical charges and magnetic dipole moments in the individual clouds has not yet been elucidated in detail.

The discovery of these novel mesons during the study of the structure of nucleons has led to new concepts in the interpretation of nuclear forces and of the binding of protons and neutrons inside the atomic nucleus. Further developments cannot as yet be foreseen.

The investigations carried out so far have given no indication of the existence of any ultimate, indestructible particles. Rather, on penetrating into regions of ever smaller dimensions, everything seems to resolve itself into abstractions. This result is one which must surely be of philosophical interest.

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German version: Angew. Chem. 76, 513 (1964)
Translated by Express Translation Service, London

[10] *C. de Vries, R. Hofstadter, A. Johannsons,* and *R. Herman,* Preprint from Physic. Rev.

[11] *S. Bergia, A. Stanghellini, S. Fubini,* and *C. Billi,* Physic. Rev. Letters *6*, 367 (1961); Nuovo Cimento *21*, 155 (1961).

[12] Cf. Proceedings High Energy Conference, CERN 1962. Scientifid Information Service 1962.

# Free Radicals and Free-Radical Reactions of Monovalent and Divalent Sulfur [*]

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*Organic free radicals of monovalent sulfur have not been hitherto observed in solution or in melts. Steric hindrance and resonance stabilization, which are responsible for the stability of the triarylmethyl, diphenylnitrogen, and phenoxyl radicals, are apparently insufficient to stabilize the organic free radicals of monovalent sulfur in such concentrations that they can be detected by current physical methods. – It was only in 1963 that aminopolysulfur radicals ($R_2N-S_n-S\cdot$) were detected in solution, and arylsulfur radicals ($Ar-S\cdot$) and phenylselenium radicals were isolated at ca. −180 °C. – Organically bound sulfur can be stabilized in the free-radical state if association of the radicals is prevented by fixing in a crystal lattice ("cystine radical"), by repulsion between radical ions (sulfinium salts), or by freezing-in (arylsulfur radicals).*

## I. Introduction

The discovery of aryl-substituted carbon, nitrogen, and oxygen radicals had a decisive influence on our views concerning the chemical bond, and, together with the discovery of short-lived alkyl radicals, provided a basis for discussion of free-radical reaction mechanisms. Although numerous reactions are known in the organic chemistry of silicon, phosphorus, and sulfur [**] which certainly proceed by a free-radical mechanism, no free radicals of trivalent silicon and germanium, divalent phosphorus and arsenic, or monovalent sulfur and selenium have as yet been observed. Trivalent radicals of the higher elements of Group IV have been sought in vain by *Krause*, *Schlenk*, *Gilman*, and *Selwood* [1]. Earlier evidence for the existence of trivalent tin and lead radicals, obtained by molecular-weight measurements, requires confirmation by ESR spectroscopy [2]. *Kuchen* [3] was unable to detect the formation of diphenylphosphorus radicals from tetraphenyldiphosphine, in analogy with the decomposition of tetraphenylhydrazine into diphenylnitrogen radicals. Despite many investigations [4–12], in particular by *Lecher*, *Schönberg*, *Selwood*, *Pearson*, *Dimroth*, and *Rundel*, the formation of monovalent sulfur radicals from disulfides was shown, prior to 1963, only in the case of cystine on irradiation with X-rays [13].

The factors stabilizing free radicals such as triphenylmethyl, diphenylnitrogen, and aroxyl, *i.e.* steric hindrance of dimerization and resonance of the radical, are apparently no longer sufficient in the case of the elements of the second and third periods. Owing to the greater covalent radii of these elements, the accumulation of phenyl groups or other bulky substituents does not prevent dimerization. Furthermore, resonance stabilization of the radical is more difficult, owing to the greater distance between the hetero-atom and the phenyl group [1b].

We succeeded recently in isolating several arylsulfur radicals by photolysis of aromatic disulfides or mercaptans in the gaseous state, followed by quenching at 77 °K [13a–13c]. By the same method the diphenylphosphorus [14], diphenylarsenic [15], phenylselenium

[*] Free-radical reactions of tetra- and hexavalent sulfur are not considered in this work. For a survey of these reactions, see [16], p. 326.

[**] For free-radical additions of Si and P compounds to olefins, see *F. W. Stacey* and *J. F. Harris* in: Organic Reactions. Wiley, New York 1963, Vol. XIII, pp. 209 et seq.

[1a] Review: *W. Hückel:* Theoretische Grundlagen der Organischen Chemie, 7th Edit., Akademische Verlagsgesellschaft, Leipzig 1952, Vol. I, p. 153.

[1b] Review: *H. A. Staab:* Einführung in die Theoretische Organische Chemie, 1st Edit., Verlag Chemie, Weinheim/Bergstr. 1959, p. 452.

[2] In hexamesityldiplumbane – which *M. Lesbre*, *J. Satge*, and *D. Voigt* [C. R. hebd. Séances Acad. Sci. *246*, 594 (1958)] believed to dissociate into free radicals, on the basis of molecular-weight determinations – no dissociation into free radicals could be detected by ESR spectroscopy [*E. Müller*, *F. Günter*, *K. Scheffler*, and *H. Fettel*, Chem. Ber. *91*, 2888 (1958)]. It has been also shown by magnetic measurements that the hexaryl compounds of digermane, diplumbane, and distannane, whose dissociation into free radicals had been assumed from cryoscopic measurements, are diamagnetic [*P. W. Selwood* et al., J. Amer. chem. Soc. *61*, 3168 (1939); *62*, 2765 (1940); *63*, 2509 (1941); *64*, 1727 (1942)]. *W. V. Farrar* has concluded from light-absorption measurements that diphenyl ditelluride dissociates completely in 1% solution to form phenyltellurium radicals [Research *4*, 177 (1951)]. Our own ESR measurements on diphenyl ditelluride solutions at room temperature gave no evidence of free radicals.

[3] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2871 (1958).

[4] Review of previous publications: *H. Z. Lecher*, Science (Washington) *120*, 220 (1954).

[5] *A. Schönberg*, *E. Rupp*, and *W. Gumlich*, Ber. dtsch. chem. Ges. *66*, 1932 (1933).

[6] *H. G. Cutforth* and *P. W. Selwood*, J. Amer. chem. Soc. *70*, 278 (1948).

[7] *H. P. Koch*, J. chem. Soc. (London) *1949*, 401.

[8] *A. Schönberg*, *A. Mustafa*, and *W. Askar*, Science (New York) *109*, 522 (1949).

[9] *A. Mustafa* and *M. Kamel*, Science (Washington) *118*, 411 (1953).

[10] *K. Dimroth* and *G. Oosterloo*, Angew. Chem. *70*, 165 (1958).

[11] *D. E. Pearson*, *D. Caine*, and *L. Field*, J. org. Chemistry *25*, 867 (1960).

[12] *W. Rundel*, Z. Naturforsch. *15b*, 546 (1960); Angew. Chem. *73*, 437 (1961).

[13] *Y. Kurita* and *W. Gordy*, J. chem. Physics *34*, 282 (1961).

[13a] *U. Schmidt* and *A. Müller*, Angew. Chem. *75*, 299 (1963); Angew. Chem. internat. Edit. *2*, 216 (1963).

[13b] *U. Schmidt*, *A. Müller*, and *K. Markau*, Tetrahedron Letters *17*, 1091 (1963).

[13c] *U. Schmidt*, *A. Müller*, and *K. Markau*, Chem. Ber. *97*, 405 (1964).

[14] *U. Schmidt*, *F. Geiger*, *A. Müller*, and *K. Markau*, Angew. Chem. *75*, 640 (1963); Angew. Chem. internat. Edit. *2*, 400 (1963).

[15] *U. Schmidt*, *A. Müller*, and *K. Markau*, unpublished work. Diphenylarsenic radical: $g_{\parallel} = 2{,}034$; $g_{\perp} = 2{,}004$; diphenyltellurium radical: $g_{\parallel} = 2{,}0342$; $g_{\perp} = 2{,}002$.

[13a, 13b], and phenyltellurium radicals [15] were isolated by photolysis of tetraphenyldiphosphine, diphenylarsine, diphenyl diselenide, and diphenyl ditelluride, and were characterized by ESR spectroscopy. The thermal stability can be determined from the rate of recombination on heating, which is measured optically by the fading of the free-radical color. It is greater for the diphenylarsenic and phenylselenium radicals than for the diphenylphosphorus and phenylsulfur radicals.

Since in these radicals steric hindrance of dimerization probably no longer plays an important part, their stability must be due to the weak bonding between the hetero-atoms in the dimer. The bonding between elements of the fourth period (As and Se) is weaker than between elements of the third period (P and S), owing to the greater distance between the atoms and the consequently smaller overlap of the electron orbitals.

Among the radicals mentioned, organic sulfur radicals are of particular interest, since they are assumed to be intermediates in important technical and physiological-chemical processes, *e.g.*:

α) The vulcanization of rubber has been often interpreted as proceeding via organic sulfur radicals [16]. Attempts have been made to detect the benzothiazolyl-sulfur radical, probably because of the accelerating action of benzothiazolyl mercaptan.

β) The regulating action of many disulfides on vinyl polymerization depends on a free-radical displacement on the sulfur of the disulfide by the macroradical, according to Equation (a) [17, 18]. The liberated organic sulfur radical adds onto the monomer M, with formation of a carbon radical [Equation (b)], which starts a new chain.

$$(M)_n\text{—}M\cdot + R\text{—}S\text{—}S\text{—}R \rightarrow (M)_n\text{—}M\text{—}S\text{—}R + R\text{—}S\cdot \quad (a)$$

$$R\text{—}S\cdot + M \rightarrow R\text{—}S\text{—}M\cdot \quad (b)$$

γ) The primary process in the denaturation of proteins by ionizing radiation is probably free-radical formation on the protein sulfur [19]. Numerous investigations on the action of ionizing or ultraviolet radiation on proteins containing sulfur have demonstrated the formation of sulfur radicals which are stable in the crystalline state.

## II. Free-Radical Reactions of Organic Sulfur Compounds

Although there is no compelling evidence for the formation of monovalent sulfur radicals (sulfenyl or thiyl radicals) RS· in solution [*], many free-radical reactions of mercaptans and organic disulfides are known which occur on heating, irradiating, or in the presence of free-radical formers, *e.g.*:

a) The disproportionation of a mixture of symmetrical disulfides in the molten state to form unsymmetrical disulfides, and the reverse process, can be plausibly interpreted by means of a homolytic dissociation (c) into organic sulfur radicals which react with the disulfide in a displacement reaction (d) [20].

$$R\text{—}S\text{—}S\text{—}R \rightleftarrows 2\ R\text{—}S\cdot \quad (c)$$

$$R\text{—}S\cdot + R'\text{—}S\text{—}S\text{—}R' \rightarrow R\text{—}S\text{—}S\text{—}R' + R'\text{—}S\cdot \quad (d)$$

b) The reactions of disulfides or mercaptans with phosphites and free-radical formers to form hydrocarbons and thioethers [20a, b], have been explained by *Walling* by the radical chains (e), (f), (g) and (e), (f), (h) [21]:

$$R\text{—}S\cdot + P(OR')_3 \rightarrow R\text{—}S\text{—}\dot{P}(OR')_3 \quad (e)$$

$$R\text{—}S\text{—}\dot{P}(OR')_3 \rightarrow R\cdot + S{=}P(OR')_3 \quad (f)$$

$$R\cdot + RSH \rightarrow RH + RS\cdot \quad (g)$$

$$R\cdot + R\text{—}S\text{—}S\text{—}R \rightarrow R\text{—}S\text{—}R + RS\cdot \quad (h)$$

c) In the addition of mercaptans to double bonds, which is induced by free-radical formers or by light [22] and is often used in preparative work, an organic sulfur radical adds onto the C=C bond. The resulting carbon radical dehydrogenates the mercaptan to form a sulfur radical which propagates the chain according to (i) and (k):

$$R\text{—}S\cdot + R'HC{=}CHR'' \rightarrow R'HC(SR)\text{—}\dot{C}HR'' \quad (i)$$

$$R'HC(SR)\text{—}\dot{C}HR'' + R\text{—}SH \rightarrow R'HC(SR)\text{—}CH_2R'' + R\text{—}S\cdot \quad (k)$$

d) Dehydrogenation or oxidation of mercaptans in the presence of styrene or dienes leads, after addition of an organic sulfur radical to a double bond, to co-oxidation, telomerization, or polymerization [23].

e) When a mixture of a disulfide and a hydrogen donor is heated, considerable quantities of mercaptan are formed [24] until equilibrium is attained [Equations (l) and (m)].

$$R\text{—}S\text{—}S\text{—}R \overset{h\nu}{\rightleftharpoons} 2\ R\text{—}S\cdot \quad (l)$$

$$2\ R\text{—}S\cdot + H_2\text{—}Don \rightleftharpoons 2\ R\text{—}SH + Don \quad (m)$$

[16] *C. Walling:* Free Radicals in Solution. J. Wiley, New York 1957, p. 335.

[17] See [16], pp. 156, 319.

[18] Review: *W. A. Pryor:* Mechanism of Sulfur Reactions. McGraw-Hill Book Company, New York 1962, p. 46.

[19] *W. Gordy* and *H. Shields*, Radiation Research *9*, 611 (1958); *W. Gordy* in: Symposium on Information Theory in Biology. Pergamon Press, New York 1958, p. 241.

[*] *W. Rundel* and *K. Scheffler* have observed weak ESR signals without hyperfine structure during ultraviolet irradiation of solutions of 2,4,6-tri-t-butylthiophenol [Z. Naturforsch. *18b*, 984 (1963)].

[20] See [18], p. 51.

[20a] *F. W. Hoffman, R. J. Ess, T. C. Simmons*, and *R. S. Hanzel*, J. Amer. chem. Soc. *78*, 6414 (1956).

[20b] *H. I. Jakobson, R. G. Harvey*, and *E. V. Jensen*, J. Amer. chem. Soc. *77*, 6064 (1955).

[21] *C. Walling* and *R. Rabinowitz*, J. Amer. chem. Soc. *79*, 5326 (1957). For the further reaction of the alkyl radicals formed according to Equation (f), in the presence of CO and disulfides to form thione esters, see *C. Walling, O. H. Basedow*, and *E. S. Savas*, J. Amer. chem. Soc. *82*, 2181 (1960). – Recently, the reaction of trialkyl phosphites with disulfides has been plausibly interpreted as occurring by a polar mechanism: *R. G. Harvey, H. I. Jacobson*, and *E. V. Jensen*, J. Amer. chem. Soc. *85*, 1618 (1963).

[22] Reviews: [16], p. 314 and [18], p. 75; *F. W. Stacey* and *J. F. Harris* in Organic Reactions. Wiley, New York 1963, Vol. XIII, p. 164 et seq.

[23] *E. L. Jenner* and *R. V. Lindsey jr.*, J. Amer. chem. Soc. *83*, 1911 (1961); ibid. *85*, 1969 (1963), where further references are given; *A. O. Oswald*, J. org. Chemistry *26*, 842 (1961); *A. O. Oswald, K. Griesbaum*, and *B. E. Hudson jr.*, ibid. *28*, 2355 (1963); *G. P. Scott* and *J. C. Wang*, ibid. *28*, 1314 (1963); Review: *F. W. Stacey* and *J. F. Harris* in Organic Reactions. Wiley, New York 1963, Vol. XIII, p. 185 et seq.

Characteristic reactions proceeding via organic radicals of monovalent sulfur may be summarized as follows:

α) Initiation of free-radical reactions of mercaptans and disulfides by light or free-radical formers (peroxides, azo-compounds) [*e.g.* initiation according to reactions (a), (c), (e), (i), or (l)].

β) Free-radical displacement reactions on the sulfur of mercaptans or disulfides [*e.g.* according to (a), (d), (g), (h)].

γ) Recombination of the short-lived, and so far not physically detected, organic sulfur radicals formed according to α) or β), to yield disulfides [Equations (c) or (l)].

δ) Addition of sulfur radicals to C=C bonds [*e.g.* (b), (i)].

ε) Dehydrogenation of aliphatic and hydroaromatic compounds by thermally or photolytically formed organic sulfur radicals [*e.g.* Equation (m)]. Analogous behavior is shown by the polysulfur radicals formed by fission of $S_8$ rings: they react with aliphatic and hydroaromatic compounds with dehydrogenation [25], substitution [26], or trithione formation [27a, b], and induce the Willgerodt reaction possibly by α-substitution of ketones via N–S radicals [27b, 28].

## III. Attempts to Detect Organic Sulfur Radicals

Earlier attempts have been already reported [4]. The evidence for the dissociation of disulfides into monovalent sulfur radicals, based on determinations of molecular weight, light absorption, and magnetism, has been either refuted by ESR spectroscopy [29] or is not convincing [30]. The methods are much too inaccurate to detect the expected small amounts of free radicals, but nevertheless are often quoted, even in recent textbooks and monographs. The strong thermochromism of many disulfides, which is often quoted as an argument in favor of dissociation, can be plausibly explained by thermal broadening of the absorption bands [31].

The stabilization of arylsulfur radicals by steric hindrance of dimerization appears to be possible only with very large substituents in the *ortho*-positions. Experiments with diaryl disulfides which were hexasubstituted by phenyl [10], iso-propyl [11], or t-butyl groups [12] gave no indication of dissociation into radicals. Since the phenoxyl radical has been recently shown by ESR spectroscopy [32] to occur during dehydrogenation of phenol, similar experiments with mercaptans in solution seem promising [33].

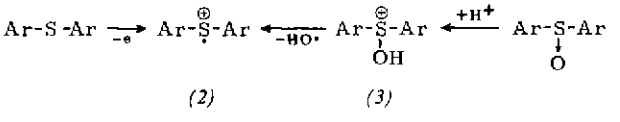
### 1. The "Cystine Radical" [13]

Irradiation of cystine crystals with X-rays produces radicals which remain stable for years in the solid state. *Gordy* has established the structure of the radical *(1)* by ESR hyperfine structural analysis of irradiated single crystals of cystine dihydrochloride. After homolytic cleavage of the S–S bond, rotation about the $C_2$–$C_3$ bond gives rise to an arrangement with widely separated radical groups, which is stable in the crystal. The free-radical state disappears immediately when the crystal is dissolved.

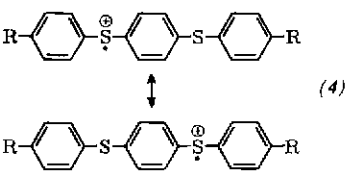
$$HOOC{-}HC(NH_2){-}CH_2{-}S\bullet \qquad (1)$$

### 2. Diarylsulfinium Salts [34, 35]

Oxidation of aromatic thioethers in concentrated sulfuric acid yields deeply colored solutions of divalent radical ions (sulfinium salts) *(2)*, some of which are stable for several days. The state of oxidation of the radical ion is between those of the thioether and the sulfoxide. The same radical ion is formed from aromatic sulfoxide on dissolution in sulfuric or polyphosphoric acid, probably by the removal of an OH radical from the cation *(3)* of the sulfoxide salt. Diarylsulfinium salts are stable only if substituted in the *p*-positions with electron-donating groups. Sulfur radical ions of the type of *Wurster*'s salt *(4)* are especially stable, and are formed even in the oxidation of nitro-substituted *p*-phenylene-dithiodiaryl ethers.



*(2)* *(3)*



*(4)*

[24] Review: [16], p. 322; *A. Schönberg* and *A. Mustafa*, J. Amer. chem. Soc. *73*, 2401 (1951) und J. chem. Soc. (London) *1949*, 889; *C. Walling* and *R. Rabinowitz*, J. Amer. chem. Soc. *81*, 1137 (1959); *Y. Schaafsma*, *A. F. Bickel*, and *A. C. Kooyman*, Tetrahedron *10*, 76 (1960).

[25] *R. Wegler*, *E. Kühle*, and *W. Schäfer* in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim/Bergstr. 1961, Vol. III, p. 1; see [18], p. 117.

[26] See [16], p. 336.

[27a] *B. Böttcher* and *A. Lüttringhaus*, Liebigs Ann. Chem. *557*, 89 (1947).

[27b] *A. Lüttringhaus*, *H. B. König*, and *B. Böttcher*, Liebigs Ann. Chem. *560*, 201 (1948).

[28] *F. Asinger* et al., Angew. Chem. *75*, 1050 (1963); Angew. Chem. internat. Edit. *2*, 220 (1963).

[29] *R. E. Davis* and *C. Perrin*, J. Amer. chem. Soc. *82*, 1590 (1960), footnote [15].

[30] For example, *G. Leandri* and *A. Tundo* explain an average deviation of 10% in the Rast molecular-weight determination for numerous disulfides by a dissociation into free radicals [Ann. Chimica *44*, 63 (1954)].

[31] *J. C. D. Brand* and *J. R. Davidson*, J. chem. Soc. (London) *1956*, 15.

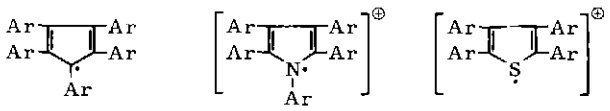
[32] *T. J. Stone* and *W. A. Waters*, Proc. Roy. Soc. (London) Ser. A *1962*, 253.

[33] In the oxidation of thiophenolates by nitroso-compounds in a flow apparatus, no S radicals could be detected by ESR spectroscopy, but anion radicals of the nitroso compound were found [*F. J. Smentowski*, J. Amer. chem. Soc. *85*, 3036 (1963)].

[34] *U. Schmidt*, *K. H. Kabitzke*, *K. Markau*, and *A. Müller*, Angew. Chem. *72*, 708 (1960).

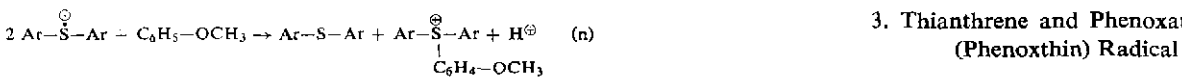
[35] *U. Schmidt*, *K. H. Kabitzke*, and *K. Markau*, Liebigs Ann. Chem. *672*, 78 (1964). Presented at the GDCh-Meeting, Heidelberg (Germany), Sept. 1963.

The tetraarylthiophenium salts *(7)* may be classified as sulfur-containing members of the series of stable five-membered cyclic radicals, such as pentaphenylcyclopentadienyl [36] *(5)* and pentaphenylpyrrolium salts [37] *(6)*. They are formed from tetraarylthiophenes in concentrated sulfuric acid.



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

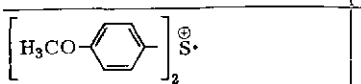
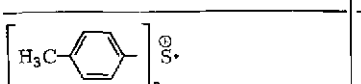
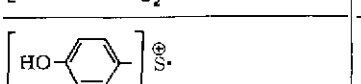
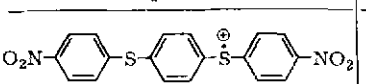
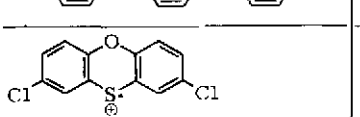
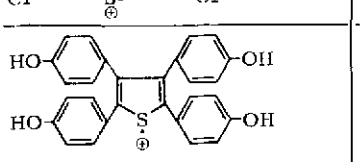
The sulfinium hexachlorostannates, which are stable in the solid state but are very sensitive to moisture, react rapidly in suspension in benzene with phenols or phenolethers to form sulfonium salts:



(n)

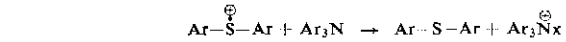
The reaction between sulfoxides and phenols or phenol ethers in concentrated acid to form sulfonium salts, which was discovered by *Smiles* [38] and which *Lüttringhaus* [39] has formulated, in the case of phenol/HCl, as passing through a sulfoxide salt, probably proceeds via a sulfur radical ion in many cases, and certainly in sulfuric acid. The radical ion is formed by removal of an OH radical from the initially produced sulfoxide salt.

Table 1. Data from the ESR spectra and colors of some sulfinium cations in $H_2SO_4$.

| Radical cation | Color | g Value | Band width [Gauss] | Number of lines |
|---|---|---|---|---|
|  | Blue-violet | 2.0078 | 10.7 | 9 |
|  | Red | 2.0091 | 12.8 | 7 |
|  | Blue | 2.0071 | 10.1 | 5 |
|  | Green | 2.0086 | 11.6 | 1 |
|  | Blue | 2.0072 | 9.3 | 3 |
|  | Red | 2.0030 | 9.6 | 5 |

Strong ESR signals were recorded with solid and dissolved sulfinium salts (cf. Table 1). The repeatedly observed fine structure of the spectra could be interpreted, *e.g.* the seven lines of the ditolylsulfinium salt by coupling of the six methyl protons. On passing from the methoxyl-substituted compounds (dianisylsulfinium salt: 9 lines; tetraanisylthiophenium salt: 13 lines) to the corresponding hydroxyl compounds, the number of lines in the spectra decreases [4,4′-dihydroxydiphenylsulfinium salt: five lines, due to coupling of the four *o*-protons; 4,4′-dihydroxy-2,2′,5,5′-tetrachlorodiphenylsulfinium salt: three lines, due to coupling of the two *o*-protons; tetra-(4-hydroxyphenyl)thiophenium salt: five lines, due to coupling of a group of four protons, probably the four *o*-protons of the phenyl groups at positions 2 and 5.

The transfer of electrons between N-and S-compounds is of interest with regard to the denaturation of proteins by radiation. For example, diarylsulfinium salts and triarylamines momentarily yield the nitrogen radical ion, which is strongly stabilized by resonance owing to its three aryl groups:

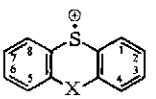


(o)

### 3. Thianthrene and Phenoxathiin (Phenoxthin) Radical Ions

High concentrations of free radicals *(8)* have been detected in the deep-blue solutions of thianthrene in concentrated sulfuric acid, by *Hirshon, Gardner,* and *Fraenkel* [40], using ESR measurements. *Wertz* and *Vivo* [41] recorded a five-line spectrum. *Shine, Davis,* and *Small* [42] as well as *Rundel* and *Scheffler* [43] deduced from the fine structure of substituted thianthrene radical ions that, in addition to the sulfur atoms, carbon atoms 2, 3, 6, and 7 possess high spin densities.

High free-radical concentrations have been also observed by ESR spectroscopy in the deep-blue solutions of chlorinated phenoxathiin *S*-oxides in sulfuric acid [44]. *Lamotte, Rassat,* and *Servoz-Gavin* [45] later recorded the ESR spectrum of the blue-violet solution of unsubstituted phenoxathiin in sulfuric acid [radical *(9)*]. However, the number of lines in the hyperfine structure cannot be established with certainty. Moreover, the spectrum is unsymmetrical and hence cannot be explained unambigously. Systematic investigation of the solutions of substituted phenoxathiin *S*-oxides yielded simpler symmetrical spectra with fine structure, which allowed conclusions to be drawn regarding the position probability of the single electron [46] (*e.g.* 1,3,4,5,6,8-hexachlorophenoxathiin radical ion: three lines, due to coupling of the two protons *para* to the free-radical sulfur).



*(8)*: X = S
*(9)*: X = O

### 4. Sulfur-Containing Oxygen and Nitrogen Radicals with High Spin Density on the Sulfur

Di-(*o*-nitrophenylsulfenyl)hydrazine *(10)* dissociates reversibly in solution above 50 °C to form *o*-nitrophenylsulfenylimine radicals *(11)* [47]. The triplet structure of the ESR

[36] *K. Ziegler* and *B. Schnell*, Liebigs Ann. Chem. *445*, 266 (1925).

[37] *R. Kuhn* and *H. Kainer*, Chem. Ber. *85*, 498 (1952).

[38] *S. Smiles* and *R. LeRossignol*, J. chem. Soc. (London) *89*, 696 (1906); *J. Goerdler* in *Houben-Weyl:* Methoden der Organischen Chemie. 4th Edit., Georg Thieme, Stuttgart 1955, Vol. IX, p. 184.

[39] *A. Lüttringhaus*, Ber. dtsch. chem. Ges. *72*, 890 (1939).

[40] *J. M. Hirshon, D. M. Gardner,* and *G. K. Fraenkel*, J. Amer. chem. Soc. *75*, 4115 (1953).

[41] *J. E. Wertz* and *J. L. Vivo*, J. chem. Physics *23*, 2193 (1955).

[42] *H. J. Shine, C. F. Davis,* and *R. J. Small*, J. chem. Physics *38*, 569 (1963).

[43] *W. Rundel* and *K. Scheffler*, Tetrahedron Letters *17*, 993 (1963).

[44] *K. H. Kabitzke*, Diploma Thesis, Universität Freiburg, 1960.

[45] *B. Lamotte, A. Rassat,* and *P. Servoz-Gavin*, C. R. hebd. Séances Acad. Sci. *225*, 1508 (1962).

[46] *U. Schmidt, K. H. Kabitzke,* and *K. Markau*, Chem. Ber. *97*, 498 (1964).

[47] *U. Schmidt, K. H. Kabitzke,* and *K. Markau*, Angew. Chem. *76*, 376 (1964); Angew. Chem. internat. Edit. *3*, 373 (1964).

spectrum shows a certain spin density on the nitrogen. However, since the equal distances between lines of equal intensity are only half as great (11 gauss) as for a comparable nitrogen radical (diphenylpicrylhydrazyl), high spin density must be assumed at an atom without nuclear spin, such as sulfur. A considerable contribution from limiting structures with free-radical sulfur *(11a)* is also indicated by the high g value (2.0076), which is within the range of the values found for sulfinium salts [$CH_3O-C_6H_4-\overset{\oplus}{S}-C_6H_4-OCH_3$: g = 2.0079] and outside that for pure N-radicals [diphenylpicrylhydrazyl: g = 2.0036]. Above about 80 °C, considerable evolution of $N_2$ occurs in toluene solution. The sulfenylimine radical *(11)* then decomposes according to Equation (r), presumably forming the arylsulfur radical – which recombines to give the disulfide *(12)* – and nitrene, which reduces the N–S radical to the sulfenamide *(13)*; compounds *(12)* and *(13)* have been detected as products. Only *(12)*, $N_2$, and $NH_3$ are formed in glacial acetic acid and in the dry decomposition of *(10)*; the $N_2$ and $NH_3$ probably result from the disproportionation of NH. When *(10)* decomposes in acrylonitrile solution, the solvent is rapidly polymerized.

$$\underset{(10)}{ArS-HN-NH-SAr} \rightleftharpoons 2\ \underset{(11)}{ArS-NH} \leftrightarrow 2\ \underset{(11a)}{Ar\overset{\oplus}{S}-\overset{\ominus}{N}H}$$

$$2\ \underset{(11)}{ArS-\dot{N}H} \rightarrow 2\ ArS\cdot + 2\ NH \qquad (r)$$

$$2\ ArS\cdot \rightarrow \underset{(12)}{ArS-SAr}$$

$$2\ ArS-\dot{N}H + 2\ NH \rightarrow 2\ ArS-NH_2 + N_2 \quad (13)$$

Aroxyls with thioether groups in the *p*-position have been studied by *Müller*, *Stegmann*, and *Scheffler* [48]. An ESR spectrum with nine lines was recorded for *p*-methylthio-*o*,*o'*-di-t-butylphenoxyl, and was explained by participation of sulfur free-radical structures. No coupling of the protons of the *p*-phenylthio group was however observed in the spectrum of the *p*-phenylthio compound, in which even stronger participation of sulfur free-radical structures should be expected (cf. the stability of the diarylsulfinium salts [34,35]).

## 5. Aminopolysulfur Radicals

By means of ESR measurements *Hodgson*, *Buckler*, and *Peters* [49] have found recently that solutions of sulfur in amines contain stable polysulfur radicals *(14)* at room temperature. These radicals probably result from the dissociation of the diaminopolysulfane *(15)*, and are possibly responsible for the catalytic action of amines in numerous reactions of sulfur [*].

$$2\ \underset{(14)}{R_2N-S_n-S\cdot} \rightleftharpoons \underset{(15)}{R_2N-S_{2n+2}-NR_2}$$

[48] *E. Müller*, *H. B. Stegmann*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 79 (1961).

[49] *W. G. Hodgson*, *S. A. Buckler*, and *G. Peters*, J. Amer. chem. Soc. *85*, 543 (1963).

[*] See, for example, [25] and *C. G. Moore* and *R. W. Saville*, J. chem. Soc. (London) *1954*, 2082; *H. Krebs*, Silicon, Sulfur, Phosphat. Colloq. Sec. Inorg. Chem. Intern. Union of pure and App. Chem. Münster (Germany), 1954, p. 107; Chem. Abstr. *52*, 5015 (1958).

## 6. Arylsulfur and Aryldisulfur Radicals

Attempts to produce monovalent organic sulfur radicals in the gaseous state by exposure of disulfides to light, followed by mixing with a hydrogen donor to detect radicals by mercaptan formation, and to determine their lifetimes by varying the distance between the zone of irradiation and the point of entry of the hydrogen donor, were successful only with aromatic disulfides [13a]. When a condenser, covered with cumol as the hydrogen donor and cooled with liquid nitrogen, was fitted past the irradiation zone, a red condensate precipitated in the photolysis of diphenyl disulfide; the red color faded on thawing. The red substance separates out on the condenser in a higher concentration when the disulfide is vaporized with accurate temperature control, and irradiated.

The red product of the photolysis of diphenyl disulfide was identified as the phenylsulfur radical by recombination to form the colorless diphenyl disulfide, by reaction with cumol to form thiophenol, and by paramagnetic resonance spectroscopy [13a–13c]. The red radical is stable at the temperature of liquid nitrogen but recombines within a few minutes even at 165 °K. The ESR signal is very strong (Fig. 1); the strong anisotropy and the high g-value indicate a phenylsulfur radical with the single electron largely localized on the sulfur atom [50].

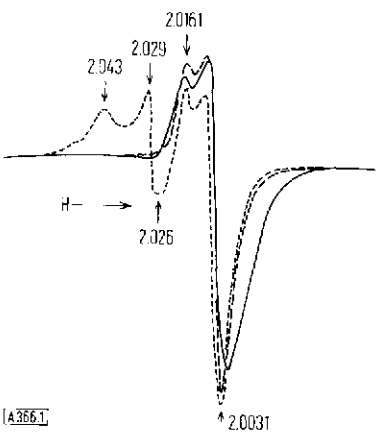



Fig. 1. ESR spectra of aromatic sulfur radicals. The measurements were recorded at 77 °K with a Varian V 4500 spectrometer with 100 kc/sec modulation. The g values were determined by measurement of the microwave frequency and of the magnetic field with a nuclear resonance probe. Frequency 9500 Mc/sec.
– – – – Phenylsulfur ($C_6H_5-S\cdot$); ——— *p*-xenylsulfur ($p$-$C_6H_5-C_6H_4-S\cdot$); ------ photolysis product of dixenyl disulfide.
Abscissa: Field strength.
Ordinate: d(absorption) d(field strength).

[50] *J. D. Michaelsen* [Ph. D. Thesis, Catholic University, Washington, 1955] has observed colored coatings on a very low-temperature condenser in the pyrolysis of aromatic disulfides. However, the free-radical nature of the colored condensate was not proved, and the results have not been published. Three weeks after the publication (March 21st, 1963) of our first communication [13a] on the isolation of the phenylsulfur radical and the detection of its free-radical nature by ESR spectroscopy, *P. J. Zandstra* and *J. D. Michaelsen* published [J. chem. Physics *39*, 933 (1963); received on April 11th, 1963] a paper describing ESR measurements on the pyrolysis products of diphenyl disulfide and β,β-dinaphthyl disulfide; the products were obtained by methods described by *Michaelsen* in his thesis. Besides a g value of 2.000, these authors found g = 2.1246 for the pyrolysis product of the disulfide. They constructed the spectrum of the phenylsulfur

A few substituted arylsulfur radicals were isolated by the same method, and the effect of the substituent on the recombination temperature was investigated [13b, 13c]. Table 2 shows that electron-donating groups, or a phenyl group in the *p*-position, stabilize the radicals and displace their light absorption towards longer wavelengths. Similarities can be recognized between the stability of the sulfur radicals and the free-radical cleavage of the corresponding disulfides by cyanoisopropyl radicals or the macroradicals in the vinyl polymerization (Table 3): with unstrained disulfides, the ease of the free-radical cleavage increases with increasing stability of the corresponding sulfur radical.

Table 2. Color and stability of monovalent organic sulfur radicals.

| Radical | Stability | Color | Color of disulfide |
|---|---|---|---|
| $C_6H_5-S\cdot$ | [a] | Red | Colorless |
| $p$-$CH_3O\ C_6H_4-S\cdot$ | [a] | Red | Colorless |
| $p$-$(CH_3)_2N-C_6H_4-S\cdot$ | [b] | Turquoise | Yellow |
| $o$-$HO-C_6H_4-S\cdot$ | [a]/[b] | Olive-green | Bright yellow |
| $p$-$ROOC-C_6H_4-S\cdot$ | [a] | Pink | Colorless |
| $p$-$C_6H_5-C_6H_4-S\cdot$ | [b] | Violet-blue | Colorless |
| α-Naphthyl-S· | [a]/[b] | Green | Bright yellow |
| $o,o',p$-$(i\text{-}C_3H_7)_3-C_6H_2-S\cdot$ | [a] | Brick-red | Colorless |

[a] The color of the radical fades in a few minutes at 165 °K.

[b] The color of the radical is still weakly present after 10 minutes at 190 °K.

Arylsulfur radicals are also formed in the photolysis of thiophenols [13c], which is not surprising in view of the large chain-transfer constants [*] [17, 18] and the numerous free-radical addition reactions [22] of the mercaptans [51]. The ESR spectrum of the prussian-blue *p*-xenylsulfur radical produced by photolysis of *p*-phenylthiophenol (*p*-xenyl mercaptan) is very similar to that of the phenylsulfur radical (Fig. 1). On photolysis of dixenyl disulfide, on the other hand, the spectrum of the xenylsulfur radical shows a second free radical signal with a high g value. It is believed that in this case homolysis of the S–C bond has also occurred, as well as cleavage of the S–S bond, giving rise to the polysulfur diradical ($\cdot S-S_n-S\cdot$) or the *p*-xenyldisulfur radical ($C_6H_5\ C_6H_4-S-S\cdot$). This view is supported by the position of the anisotropic ESR signal at higher g values (which correspond to the g value of 2.030 for the aminopolysulfane radical $R_2N-S_n-S\cdot$ [49]), by the approximately equal dissociation energies of the S–S and C–S bonds [51], and by the appearance of hydrogen sulfide [*] on reduction of the recombination product with $LiAlH_4$ [13c].

radical after mathematical elimination of a foreign radical signal, and carried out an MO calculation of the electron distribution in the phenylsulfur radical. Our own ESR measurements, repeated several times, on the phenylsulfur radical prepared by our method from diphenyl disulfide *or* thiophenol, have only given traces of a free-radical signal at the high g value of 2.1246, the maximum strength of this signal being 3% of that of the main signal. The high g value of 2.1246 published by the American authors is not, therefore, attributable to the phenylsulfur radical, but to a foreign radical which is formed in high concentrations together with the phenylsulfur radical under the drastic conditions used by *Michaelsen*. The agreement between the result of the MO calculation described by *Zandstra* and *Michaelsen* and their experimental results is probably fortuitous.

[*] The chain-transfer constant of the mercaptan or disulfide is defined as $K = v_K/v_M$, where $v_K$ = rate of reaction of the macroradical with the chain-transfer agent (disulfide or mercaptan); $v_M$ = rate of addition of the macroradical to the monomeric olefin. The greater the chain-transfer constant of a mercaptan or disulfide, the more readily will its S–H or S–S bond be cleaved homolytically by a carbon radical. For the determination of chain-transfer constants, see the standard works on polymerization kinetics.

[51] The dissociation energy of the S–H bond was at least in the aliphatic series – found to be rather greater than that of the S–S bond: $CH_3S-H = 88.8$ kcal/mole; $CH_3S-SCH_3 = 73.2$ kcl/a mole; $CH_3-SCH_3 = 73.2$ kcal/mole [*J. L. Franklin* and *H. E. Lumpkin*, J. Amer. chem. Soc. *74*, 1023 (1952)].

## IV. Free-Radical Displacement Reactions on the Sulfur of Organic Disulfides

The regulating action of disulfides on the vinyl polymerization has been already mentioned in the introduction (Section I.3). The chain-transfer constants have been measured for many disulfides [17, 18]. A simple displacement reaction on the disulfide sulfur is the reaction of triarylmethyl radicals with disulfides to form thioethers [52].

To examine the effect of substituents on the homolysis of the S–S bond, reaction (s) of the cyanoisopropyl

$$(CH_3)_2\dot{C}-CN + RS-SR \rightarrow (CH_3)_2C(CN)-SR + RS\cdot \quad (s)$$

radical with various disulfides was studied under standardized conditions [53] (see Table 3). With aromatic disulfides, free-radical displacement on the sulfur of the S–S bond is facilitated by the presence of electron donors in the *p*-position. This agrees with the fact that

Table 3. Homolytic cleavage of disulfides by cyanoisopropyl radicals or by macroradicals during styrene polymerization.

| Disulfide | Cleavage [%] by cyanoisopropyl radicals [53] [a] | K (°C) [b] of the styrene polymerization [17, 18] |
|---|---|---|
| $(C_6H_5-S-)_2$ | 11.8 | 0.14(99) |
| | | 0.06(50) |
| $(CH_3O-C_6H_4-S-)_2$ | 16.8 | 0.33(99) [c] |
| $((CH_3)_2N-C_6H_4-S-)_2$ | 31 | |
| $(ROOC-C_6H_4-S-)_2$ | 13.3 | 0.11(50) |
| $(C_6H_5-CH_2-S-)_2$ | 5.8 | 0.01(99) |
| $(n\text{-}C_4H_9-S-)_2$ | 1.2 | 0.005(99) [d] |
|  | 5.5 | |
|  lipoic acid | 12 | |

[a] The disulfides were allowed to react under standardized conditions with a tenfold excess of azo-isobutyronitrile in dioxan until the azo-compound was completely decomposed. The degree of conversion was then determined from the concentration of the unreacted disulfide.

[b] For the definition and determination of the chain-transfer constant K, see footnote [*] in opposite column.

[c] Transfer constant of di-(*p*-ethoxyphenyl) disulfide.

[d] Transfer constant of diethyl disulfide.

[*] Hydrogen sulfide can arise only from the sulfur or the polysulfides which result on heating the *p*-xenyldisulfur radical.

[52] *H. Lecher*, Ber. dtsch. chem. Ges. *48*, 524 (1915); *A. Schönberg, A. Stephenson, H. Kaltschmitt, E. Petersen*, and *H. Schulten*, ibid. *66*, 237 (1933).

[53] *U. Schmidt* and *A. Müller*, Liebigs Ann. Chem. *672*, 90 (1964).

the chain-transfer constant of dianisyl disulfide is greater than that of diphenyl disulfide. Among the aliphatic disulfides, only those with strained five- and six-membered rings react with the inert cyanoisopropyl radical [54]; the greater strain of the five-membered ring manifests itself clearly in the higher rate of reaction on free-radical attack. It should be mentioned that dibenzyl disulfide undergoes free-radical cleavage much more easily than the purely aliphatic disulfides; the chain-transfer constant is also greater than for aliphatic disulfides.

[54] *W. A. Pryor* and *P. K. Platt* [J. Amer. chem. Soc. *85*, 1496 (1963)] have recently investigated the reaction between phenyl radicals and aliphatic disulfides. As the steric hindrance of the disulfide group increases, the free-radical displacement on the sulfur is suppressed in favor of a dehydrogenation by the phenyl radical. The effect of steric hindrance of aliphatic disulfides in a free-radical displacement reaction on the sulfur also manifests itself in the smaller chain-transfer constants of branched disulfides.

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# Chromatographic Separations on Porous Gels [*]

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*Over the past few years, fractionation of mixtures of substances on the basis of differences in their molecular weights has become an important method in chemistry and biochemistry. A survey is given of the theory and practice of separations applying porous gels, and the multifarious uses of such gels are indicated.*

## 1. Introduction

Modern methods of separation, *e.g.* partition chromatography, countercurrent distribution, adsorption or ion-exchange chromatography, and electrophoresis, generally make use of differences in solubility or molecular charge. It is only comparatively recently that advantage has been taken of differences in molecular sizes [1, 1a], although zeolites [2], which have been known for some time, are in fact molecular sieves consisting of three-dimensional networks of $SiO_4$ and $AlO_4$ tetrahedra enclosing cavities (about 50 % of the volume) connected by pores. Zeolites are now produced synthetically and are used, for example, for drying gases or for separating olefins from gas mixtures; even at extreme temperatures they have specific affinities for polar substances.

The first generally applicable method for separating large from small molecules, namely dialysis through porous membranes, was derived directly from macroscopic filtration. In the meantime, dialysis techniques have been refined by the development of membranes with graduated, well-defined pore sizes. "Ultrafilters" or "membrane filters" [2a] consist of foams of cellulose derivatives or regenerates, and are used predominantly in biochemistry for the concentration and desalting of protein solutions, or in electrodialysis. In these preparations, in contrast to the zeolites, pores and cavities are identical and account for about 80 % of the volume of the filter.

The pore sizes of agar membranes have recently been determined by diffusion of proteins and viruses of various particle weights [3]. *Craig* used pretreated cellulose membranes to obtain information about the shapes of peptide and protein molecules in solution from their rates of diffusion [4]. *Synge* reported attempts to separate cytochrome c, insulin, gramicidin S, and valine by multistage electrodialysis [5]; in the course of their migration in an electric field, the ions were made to pass through membranes of increasing density, being more or less retained by these according to size. This technique may be compared with the multistage dialysis processes due to *Signer* [6] and *Craig* [7], in which the dialysate of the first unit becomes the liquid to be dialysed in the second stage, and so on. The output from the separation is poor, as regards both quality and quantity, in relation to the effort involved.

Much better separations can be achieved by the simple chromatographic process of gel filtration. This in-

[*] Extended version of lectures given at Farbwerke Hoechst, Frankfurt/Main-Hoechst (Germany), December 1962; Österreichische Gesellschaft für Physiologische Chemie, Vienna (Austria), February 1963; Kolloid-Gesellschaft, Bad Oeynhausen (Germany), October 1963.

[1] Reviews of certain aspects of gel filtration: *P. Flodin*, Ph.D. Thesis, University of Uppsala (Sweden), 1962; obtainable from A. B. Pharmacia, Uppsala (Sweden); *J. Porath*, Advances Protein Chem. *17*, 209 (1962); *B. Gelotte:* New Biochemical Separations. D. van Nostrand, London 1963; *A. Tiselius, J. Porath*, and *P. A. Albertsson*, Science (Washington) *141*, 13 (1963).

[1a] It is assumed in this paper that molecular weight is proportional to molecular size.

[2] Review: *E. A. Scheuermann*, Chemiker-Ztg. *20*, 767 (1961).

[2a] Manufacturer and literature: Membranfilter-Gesellschaft GmbH., Göttingen (Germany).

[3] *G. K. Ackers* and *R. L. Steere*, Biochim. biophysica Acta *59*, 137 (1962).

[4] *L. C. Craig* and *E. Harfenist*, Report at the 6th European Peptide Symposium, Athens (Greece) 1963; cf. Angew. Chem. *75*, 63 (1964).

[5] *R. L. M. Synge* and *M. A. Youngson*, Biochem. J. *78*, 31 P (1961).

[6] *R. Signer, H. Hänni, W. Koestler, W. Rottenberg*, and *P. v. Tavel*, Helv. chim. Acta *29*, 1894 (1946); *P. v. Tavel*, ibid. *30*, 334 (1947).

[7] *L. C. Craig* and *T. P. King*, J. Amer. chem. Soc. *77*, 6620 (1955); *78*, 4170 (1956).

volves the swelling of grains of polymeric material with solvents, the pores [7a] being filled with solvent. If the average diameter of these pores bears the correct relationship to the molecular size of the mixture to be separated, then, on loading the gel, molecules diffuse into the gel grains to a greater or lesser extent, or not at all, according to their size. For the largest particles only the solvent outside the gel is available; they are therefore the first to leave the gel packing (*e.g.* a perpendicular column) on elution, while smaller molecules penetrate for various distances into the internal phase. The substances therefore appear in the eluate of the chromatographic column in the order of decreasing molecular weights. Thus, gel filtration can be regarded as multiple dialysis, in which the gel grains act simultaneously as dialysis membranes and as receivers for the dialysate. Owing to the numerous separations repeated over the length of the column, the efficiency of gel filtration bears the same relationship to that of the dialysis process as partition chromatography does to extraction in a separating funnel (cf. [8]).

## 2. Gel Formers

Porous materials have been used in chromatography for some time, in the form of synthetic ion-exchange resins, and gel filtration effects have indeed been observed occasionally. Thus it soon became known that in ion-exchangers not only the degree of swelling, but also the capacity for large counter-ions, depends on the degree of cross-linking [9, 10]. Ions of macromolecules are eluted more rapidly than low molecular-weight ions of equal charge [11–13]. Thus, as early as 1952, *Partridge* separated amino acids, peptides, and proteins on a sulfonated polystyrene resin [14]. Even for uncharged polyalcohols, there is a qualitative relationship between the elution volume [14a] and the molecular weight on ion-exchange resins [15, 16]. Following these more casual observations, systematic attempts were soon made to find porous gels for molecular-weight chromatography, with the following requirements in mind.

The gel material must be insoluble but capable of swelling in the desired solvent; the diameters of the resulting pores must be comparable with the molecular dimensions (including the solvation sheath) of the substances to be separated.

These properties are exhibited by particles of macromolecules which have been rendered insoluble and given a porous structure by cross-linking. For optimum separation, it must be possible to vary the pore sizes accurately. Particles of highly cross-linked gels are no longer penetrable even by relatively small molecules. The gel bed [16a] should have no adsorptive properties, so that the substances to be separated can move freely according to their relative sizes. The rate of flow is governed by the size and shape of the gel particles in the column. Spherical particles are preferable to irregularly shaped particles, since even at high rates of flow the former provide a fine grain and hence promote rapid establishment of equilibrium.

In some natural materials, which exhibit gel-filtration phenomena, the macromolecules are only hydrogen-bonded. Suspensions of agar gel [17, 18] and agarose [19], can be used for fractionating macromolecules according to molecular weight. Agarose, which contains no polar groups, appears to be the most appropriate large-pored material, particularly for very high molecular and particle weights [19a]. *Hjertén* [20] has described a process for the preparation of regular spherical particles.

In gels made of natural products the degree of cross-linking is predetermined. The pore size can be adapted for particular separations by varying the quantity of swelling agent. Stiff gels correspond to high degrees of cross-linking, while the pores of less stiff gels (lower dry weight) are accessible even to large molecules [20a]. This is also recognized with homogeneous starch gels in the electrophoretic separation of proteins by *Smithies'* method [21]. Table 1 shows how much the migration of macromolecules in the electric field is affected by the three-dimensional network structure of the support [22].

Table 1. Molecular weights and relative rates of migration of proteins in a starch gel in an electric field.

| Protein | Molecular weight | Relative rate of migration | |
|---|---|---|---|
| | | on paper | in starch gel |
| β-Lipoprotein | 1300000 | 1.0 | 0.14 |
| Transferrin | 90000 | 1.0 | 0.88 |
| Hemoglobin | 60000 | 1.0 | 1.0 |

Starch grains have also been used for the chromatographic separation of amino acids and peptides [23], and of oligo- and polysaccharides [24].

In principle, it is possible to obtain cross-linked macromolecules from any polymerizable monomer by copolymerization with a bifunctional monomer. These completely synthetic materials include not only gels such as polyacrylamide [25–27] which swell in water,

[7a] The dry material is not porous, but the pores which appear on swelling are preformed by the cross-linking of the polymers.

[8] *R. L. Kisliuk*, Biochim. biophysica Acta *40*, 531 (1960).

[9] *R. Kunin* and *R. J. Meyers*, Discuss. Faraday Soc. *7*, 114 (1949).

[10] *D. K. Hale*, *D. J. Packham*, and *K. W. Pepper*, J. chem. Soc. (London) *1953*, 844.

[11] *H. Deuel*, *J. Solms*, and *L. Anyas-Weisz*, Helv. chim. Acta *33*, 2171 (1950).

[12] *R. W. Richardson*, J. chem. Soc. (London) *1951*, 910.

[13] *T. R. Kressmann*, J. physic. Chem. *56*, 118 (1952).

[14] *S. M. Partridge*, Nature (London) *169*, 496 (1952).

[14a] The term "elution volume" is applied to the quantity of eluate collected from the beginning of elution until the appearance of half the maximum concentration of the substance being eluted (cf. Fig. 1).

[15] *R. M. Wheaton* and *W. C. Baumann*, Ann. New York Acad. Sci. *57*, 159 (1953).

[16] *R. T. Clark*, Analytic. Chem. *30*, 1676 (1958).

[16a] "Gel bed" is the term used for the solvent-swollen polymer in the chromatographic column.

[17] *A. Polson*, Biochim. biophysica Acta *50*, 565 (1961).

[18] *P. Andrews*, Nature (London) *196*, 36 (1962).

[19] *S. Hjertén*, Arch. Biochem. Biophysics *99*, 466 (1962).

[19a] Cells and cell constituents can also be chromatographed.

[20] *S. Hjertén*, Biochim. biophysica Acta, in the press.

[20a] Dry agar is swollen by boiling with water and is then cooled to give a pudding-like mass which is mechanically comminuted and which does not swell further in cold water.

[21] *O. Smithies*, Biochem. J. *61*, 629 (1955).

[22] *O. Smithies*, Advances Protein Chem. *14*, 65 (1959).

[23] *B. Lindqvist* and *T. Storgårds*, Nature (London) *175*, 511 (1955).

[24] *G. H. Lathe* and *C. R. J. Ruthven*, Biochem. J. *62*, 665 (1956).

[25] *D. J. Lea* and *A. H. Sehon*, Canad. J. Chem. *40*, 159 (1962).

[26] *S. Hjertén* and *R. Mosbach*, Analytic. Biochem. *3*, 109 (1962).

[27] *S. Hjertén*, Arch. Biochem. Biophysics Suppl. *1*, 147 (1962).

but also those, *e.g.* cross-linked polystyrene, which swell in organic solvents [28,28a]. Poly(methyl methacrylate) cross-linked with ethylene bismethylacrylate forms a purely aliphatic network, which can also be prepared in the form of beads [29]. In the completely synthetic gels, the pore sizes are adjusted by variation of the ratio of monomer to cross-linking agent, or by variation of the quantity and nature [30] of the solvent present during polymerization.

A third group consists of partially synthetic gels, in which natural macromolecules are given a three-dimensional structure with the aid of cross-linking agents, *e.g.* latex cross-linked by vulcanization with sulfur. Small pieces of rubber (milled surgical gloves) swell in organic solvents and act as molecular sieves [31]. In 1954, *Deuel* and *Neukom* reported the first instance of a modified plant polysaccharide which, when swollen with water, was capable of desalting a protein solution [32].

*Porath* and *Flodin* etherified water-soluble dextran molecules with epichlorohydrin and obtained a gel which swelled only in water, and which is now known by the trade name of "Sephadex" [32a]. The size of the pores in the gel decreases as the number of hydroxy groups in the dextran replaced by ether bridges is increased. Extensive investigations on the pore structures of such dextran gels and a theoretical basis of gel filtration provided by *Porath*, *Flodin*, *Gelotte*, and *Bennich* [33–39], together with the fact that Sephadex is commercially available in several well-defined degrees of cross-linking (recently also in the bead form), have contributed to the rapid development of gel filtration into a widely used laboratory technique. Dextran gels are used in more than 95 % of all chromatographic work on gels. The present review will therefore focus attention on this material.

## 3. Theory of Gel Filtration

We have regarded gel filtration as multiple dialysis, but it can equally well be referred to as partition chromatography: the gel acts as support for the stationary solvent phase and confers on the latter the property of being only partly accessible to molecules above a certain size. Thus, a partition coefficient $K_d$, which is a function of molecular size, can be defined for the partition of every substance between the two resultant phases ("internal" and "external" solvent). This $K_d$ value is a true quotient of two concentrations only if either small molecules can diffuse unhindered (both concentrations equal; $K_d = 1$) or if large molecules are completely unable to penetrate into the solvent within the gel particles (internal concentration = 0; $K_d = 0$). However, the pore size inside the gel grains is by no means uniform, so that for intermediate molecular sizes, the $K_d$ value is a measure of the portion of the stationary phase which is available to a particular type of molecule.

$K_d$ can be calculated from the elution volume $V_e$. For molecules which are large in comparison to the pore size ($K_d = 0$), the elution volume corresponds to the solvent outside the gel particles ($V_o$), whereas for small molecules ($K_d = 1$) it also includes the volume inside the gel particle ($V_i$). Since only part of the internal solvent is accessible to molecules of intermediate size ($0 < K_d < 1$), the elution volume for these molecules is [40]

$$V_e = V_o + K_d \cdot V_i. \quad (1)$$

This gives

$$K_d = \frac{V_e - V_o}{V_i} \quad (2)$$

The external volume $V_o$ and the internal volume $V_i$ are the characteristic volumes of the gel packing. $V_o$ is obtained from the elution volume of a substance whose molecular weight is high relative to the pore size, and $V_i$ from the solvent-absorbing capacity of the dry gel. $V_i$ naturally depends on the degree of cross-linking. To determine the degree of swelling quantitatively, a weighed quantity of dry gel is swollen in excess solvent, which is then separated by centrifuging through a sintered glass plate. The solvent absorption per gram is known as the swelling power $S_r$ (solvent regain) [g of solvent/g of dry gel]. Water is the swelling agent for dextran gels, for which this generally valid theory was developed (cf. [39]); the water regain $W_r$ of these gels is normally printed on the package or container. The internal volume is then given by the simple expression

$$V_i = a \cdot W_r, \quad (3)$$

where a is the dry weight in grams of the column packing. If a is unknown, the internal volume $V_i$ can be calculated from the total volume $V_t$ and the mean specific gravity $d = (W_r + 1)a/(V_t - V_o)$ of the gel bed:

$$V_i = \frac{W_r \cdot d}{W_r + 1} (V_t - V_o) \quad (4)$$

If two substances with different molecular weights have $K_d'$ and $K_d''$ on a certain gel, then their elution volumes, according to Equation (1), are given by:

$$V_e' = V_o + K_d' V_i$$

[28] *M. F. Vaughan*, Nature (London) *188*, 55 (1960).

[28a] However, polystyrene has a strong tendency to adsorb aromatic substances, and so is not ideal for gel filtration.

[29] *H. Determann*, *G. Lüben*, and *Th. Wieland*, Makromolekulare Chem., in the press.

[30] *J. C. Moore*, Report at the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, April 1963.

[31] *P. J. Brewer*, Nature (London) *188*, 934 (1960); *190*, 625 (1961).

[32] *H. Deuel* and *Neukom*, Natur. Plant Hydrocolloids *11*, 51 (1954).

[32a] Manufacturer: AB Pharmacia, Uppsala (Sweden).

[33] *J. Porath* and *P. Flodin*, Nature (London) *183*, 1657 (1959).

[34] *J. Porath*, Clin. chim. Acta *4*, 776 (1959).

[35] *P. Flodin* and *K. Granath:* Symposium über Makromoleküle in Wiesbaden. Verlag Chemie, Weinheim 1959.

[36] *B. Gelotte*, J. Chromatogr. *3*, 330 (1960).

[37] *J. Porath*, Biochim. biophysica Acta *39*, 193 (1960).

[38] *H. Bennich*, Biochim. biophysica Acta *51*, 265 (1961).

[39] *P. Flodin*, J. Chromatogr. *5*, 103 (1961).

[40] *P. Flodin*, Ph. D. Thesis, University of Uppsala (Sweden), 1962.

and

$$V_e'' = V_o + K_d'' V_i.$$

The separation volume $V_s$ is a measure of the separating efficiency of a column:

$$V_s = V_e' - V_e'' = (K_d' - K_d'') V_i \quad (5)$$

These volumes are shown in Figure 1, the elution diagram for three substances with $K_d$ values of 0.0, 0.5, and 1.0.

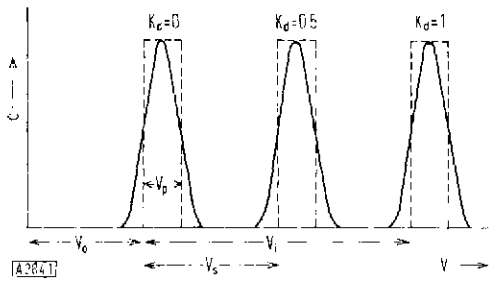



Fig. 1. Schematic elution diagram for three materials with $K_d$ values of 0.0, 0.5, and 1.0.
(- - -): theoretical shape of the bands;
(— —): experimental Gaussian distribution curves;
$V_o$ and $V_i$ = volumes of solvent outside and inside the gel;
$V_p$ = sample volume; $V_s$ = separation volume.

Every gel bed can be characterized by various parameters. Thus it is advantageous to know the size of molecules which are just unable to penetrate the gel grains, *i.e.* the "exclusion limit", and the volume relationships. Table 2 gives some data for the various types of Sephadex. The exclusion limits were determined with dextran fractions. It appears that they are considerably higher for proteins and considerably lower for nucleic acids.

Table 2. Properties of commercial Sephadex dextran gels (swelling in water; volume data based on 1 g of dry gel) [a].

| Type | Exclusion limit (molecular weight) | $W_r$ | d | $V_t$ | $V_o$ | $V_i$ |
|---|---|---|---|---|---|---|
| G-25 | 5000 | 2.5 ± 0.2 | 1.13 | 5 | 2 | 2.5 |
| G-50 | 10000 | 5.0 ± 0.3 | 1.07 | 10 | 4 | 5 |
| G-75 | 50000 | 7.5 ± 0.5 | 1.05 | 13 | 5 | 7 |
| G-100 | 100000 | 10 ± 1.0 | 1.04 | 17 | 6 | 10 |
| G-200 | 200000 | 20 ± 2.0 | 1.02 | 30 | 9 | 20 |

[a] Details of the experimental technique are to be found in the manufacturer's literature and in [39,41].

Polyacrylamide and agarose gels are prepared directly as swollen gels and are characterized by the chromatographic behavior of standard substances. Figure 2 shows the relationship between the "$R_F$ values" ($V_o/V_e$) of various substances and the absolute concentration of the gel former (which is a measure of the average pore size) for agarose gels [12]. It is possible on the basis of such a diagram, as well as from Table 2, to select for a given separation the gel with the optimum pore-size distribution.

It can be seen from Equation (5) and Figure 1 that, for small $\Delta K_d$, the internal volume $V_i$ must be large and the sample volume (volume of solvent in which the mixture is introduced into the column) must be as small as possible to achieve satisfactory separation.

[41] *H. Determann* and *B. Gelotte* in *H. M. Rauen:* Biochemisches Taschenbuch. 2nd Edit., Springer, Berlin 1964, Vol. 2.

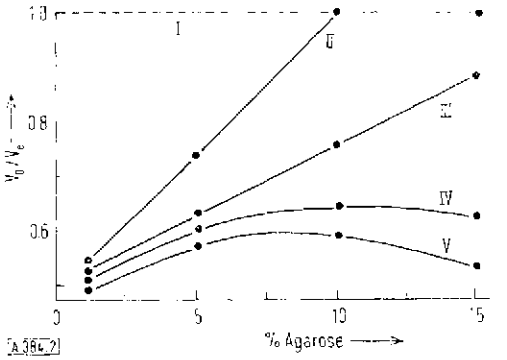



Fig. 2. Dependence of the "$R_F$ value" $V_o/V_e$ on the concentration of agarose (based on dry weight) in gel [19]. I: indian ink; II: R-phycoerythrin; III: haemoglobin; IV: cytochrome c; V: potassium dichromate.

Thus, the rules of column chromatography are valid here too: the separation is improved by long columns and sharp starting zones.

Applications of the molecular-sieve effect will be described in Section 6. If, in the separation of low and high molecular-weight substances, the difference $K_d' - K_d''$ in Equation (5) reaches its upper limit (unity), the separation volume is theoretically equal to the internal volume. The sample volume could then be made as large as $V_i$, if there was no widening of the bands as a result of diffusion. Perfectly satisfactory results are still obtained if the sample volume is 20–30 % of the total volume $V_t$ of the column. Such separations are referred to here as *gel filtration*.

Gel filtration can be carried out with relatively short columns, thus circumventing extreme dilution of the separated substances. In contrast to all other chromatographic methods, the concentration of the substances to be separated does not affect gel filtration, except at high viscosities (< 5 cp), where diffusion is limited, this leading to unsharp separations [39].

## 4. Sorption Phenomena

Behavior which differs from the gel-filtration theory is sometimes observed on highly cross-linked dextran gel packings, particularly with substances of low molecular weight. The secondary effects responsible for such deviations can be divided into two groups:

a) Certain substances are retarded on the column, owing to their structures, and largely independently of the eluent; $K_d$ is greater than expected on theoretical grounds. For example, borate and hydroxide ions are retained by complex formation; the same applies to many aromatic and heterocyclic compounds. Since this adsorption effect is completely reversible, it permits fractionation, for example, of phenols [42,43], nucleic acid constituents [44,44a], peptides containing tryptophan [45], amino acids [36,37,46], or extracts from roasted coffee [47].

[42] *A. Nilsson*, Acta chem. scand. *16*, 31 (1962).
[43] *J. B. Woof*, Nature (London) *195*, 184 (1962).
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[44a] *Th. Hohn* and *W. Pollmann*, Z. Naturforsch. *18b*, 919 (1963).
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b) Ion exchange may be observed on elution with pure water, owing to the very low carboxyl content of the dextran gels. Bases are adsorbed, and acids appear in the eluate earlier than expected, if they are introduced in very small quantities. This phenomenon may be eliminated by small additions of electrolyte to the eluent or even to the solution of the sample. These salt effects can also be used for the separation of proteins [48–50], peptides [51], or phosphoric acid derivatives [52] of roughly equal molecular weights.

Particular care must be taken in working with radioactively labelled anions such as iodide [53] or phosphate [54]. If the total concentration of ions is not high, a very small portion of these anions, which is detectable only radiochemically, may be prevented from diffusing freely by the carboxyl groups and may remain in the external volume $V_o$.

## 5. Gel Filtration

Highly cross-linked gels (with relatively small pores) are necessary for achieving quantitative separation of large molecules from low molecular-weight substances. The dextran gels Sephadex G-25 and G-50 (cf. Table 2) are mainly used for this purpose. Gel filtration is most frequently used for desalting colloid (often protein) solutions. These solutions are not appreciably diluted if the volume relationships discussed above are taken into account. Figure 3 shows the elution curves of two experiments with the same column; here the sample

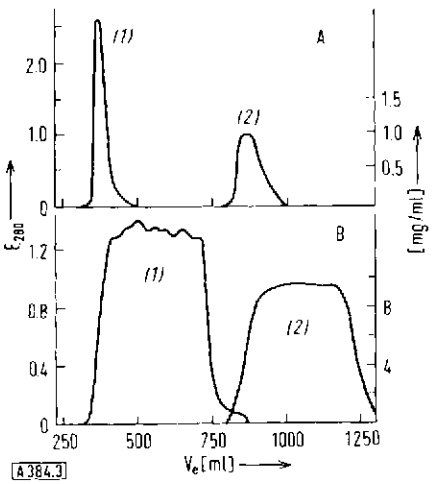



Fig. 3. Separation of haemoglobin (1) and sodium chloride (2) on a 1070 ml column containing Sephadex G-25. A: with 100 mg of haemoglobin and 100 mg of NaCl in 10 ml of water; B: with 400 mg of haemoglobin and 4 g of NaCl in 400 ml of water [39].

Left ordinate: extinction of haemoglobin at 280 mμ;
Right ordinate: mg of NaCl per ml of solution.

volumes differ by a factor of 40. Even under the extreme conditions of experiment B, the protein (zone 1) is practically completely desalted, although its solution is diluted by only 25 %. In experiment A the dilution is tenfold [39] (cf. [55]).

If another salt solution is used as eluent instead of water, the ions present in the sample solution are exchanged [39]. This may be important for desalting proteins which can be kept in solution only by electrolytes. If the second electrolyte is completely volatile, the protein can be obtained salt-free by freeze-drying after elution.

Figure 3 can be used to illustrate many of the separations to be discussed here, *e.g.* the determination of strontium in milk [56], and the desalting of virus suspensions (even under sterile conditions) [57]. The separation from macromolecules of low molecular-weight components which are not salts can be termed group separation. Thus, for example, viruses can be separated from dyestuffs, amino acids, and sugars [58], nucleic acids from nucleotides [44, 59–61] and phenol [62], and low molecular-weight antigens from antibodies [63]. The method is particularly interesting in medicine, *e.g.* for rapid determinations of polysaccharides in the presence of sugars [64, 65], of oestrogens in the urine of pregnant women [66], and of free iodide in the presence of protein-bound iodine [67–70a]. Gel filtration is the best method for separating modified protein from excess low molecular-weight reagents, *e.g.* in staining with fluorescent dyes [71–79] or in the reversible reduction of disulfide bridges [80, 80a].


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*Complex formation* between molecules of various molecular weights gives rise to special separating effects during gel filtration. For example, vasopressin and oxytocin form complexes with proteins contained in tissue extracts. These complexes can be separated from low molecular-weight components on a column of Sephadex G-25. The complex dissociates on acidification, and a further separation gives the hormone, many times concentrated, in the slowly migrating zone [81].

Vitamin $B_{12}$ can be similarly concentrated from sea-water, polysaccharide being added for complex formation [82]; it can also be isolated as a protein complex from human gastric juice [83]. The compounds formed by various pharmaceuticals [84–86c], metals [87–89], or lipids [90] with proteins have been studied on gel columns. The "radiobiuret" complex containing radioactive copper can be used with the gel filtration method for continuous microdetermination of proteins in column eluates [91]. Immunochemical investigations have also been carried out on gel columns [63, 92–95].

Particularly promising is a method for the determination of the affinity of enzymes for coenzymes, substrates, or inhibitors, as first described for the interaction of ribonuclease and 2-cytidylic acid [96]. The gel bed is equilibrated with a buffer solution containing the substrate, and the protein is then introduced into the column and eluted with the same solvent: the protein-substrate band is followed by a zone of low substrate concentration (Fig. 4). With lactic dehydrogenase, this technique can be used to determine the number of active sites on the protein with the aid of DPNH [97]. In another example, the peptide substrate of carboxypeptidase is so firmly bound to the enzyme in the absence of Zn ions that it becomes an inhibitor and

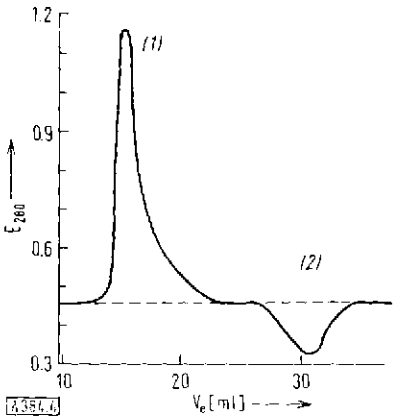



Fig. 4. Elution diagram for 3 mg of ribonuclease chromatographed in 0.1 M acetate buffer (pH 5.3) containing $9 \times 10^{-5}$ M cytidylic acid on Sephadex G-25. The enzyme-inhibitor complex passes out at (1) and is followed by a zone (2) which lacks the inhibitor [96].
Ordinate: extinction at 280 mμ.

migrates with the protein [98]. The complex from cytochrome c and cytochrome oxidase can also be isolated by gel filtration [99].

Gel filtration has proved extremely useful for the fractionation of mixtures of natural products and for purification of isolated substances. The otherwise arduous task of separating amino acids from peptide mixtures can be effected easily and quantitatively [37, 100], as can the separation of mixtures of peptides and glycopeptides [111–113] obtained by enzymatic [101–108] and chemical [109, 110] hydrolysis. Partial hydrolysates of nucleic acids [114–117] can also be fractionated, and hormones concentrated [118–122]. It is very


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convenient, particularly for incorporation experiments with radioactive amino acids, that insulin can now be isolated with ease from very small quantities of crude pancreatic extract [123, 124].

The enzymatic activities of snake venoms can be separated [125–127], and proteases [128–132a] and many other proteins, with and without enzymatic activities [25, 133–140], can be purified on gels which are only slightly cross-linked. Plasma proteins can be divided into three fractions [141 to 142b]; Figure 5 shows the effect of cross-linking on the efficiency of separation [143]. Fragments of γ-globulins have been separated on porous gels [144, 145]. A synthetic mixture of deoxyribonucleic acid and ribonucleic acid has been separated on agarose gel [61].

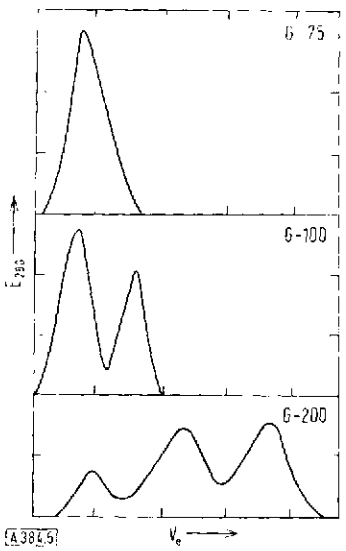



Fig. 5. Separation of about 15 ml of bovine plasma on Sephadex dextran gels of various swelling capacities under comparable conditions in 0.1 M *tris* buffer (pH 8.0; 1 M NaCl). The column volumes $V_t$ were so chosen that the external volumes $V_o$ were equal (cf. Table 2). In the experiment with Sephadex G-200 ($V_t$ = 1600 ml), the macroglobulins were found in the first band, the globulins in the second, and the albumins in the third [143].

Ordinate: extinction at 280 mμ.

## 6. Gel Chromatography

Fractionation of polymers can be achieved by the use of long columns, small sample volumes, small grain size, and slow elution, as was first shown for dextran fractions [35, 146, 147] and oligosaccharides [148]. Figure 6 shows the sharpness of the separation of oligosaccharides from glucose up to its hexamer. With chromoprotein mixtures, the progress of the separation can be seen directly from the zones on the column; the separating efficiencies of dextran gel Sephadex G-75 [149], polyacrylamide gel [26], agar gel [17], and agarose gel [19] were demonstrated in this way.

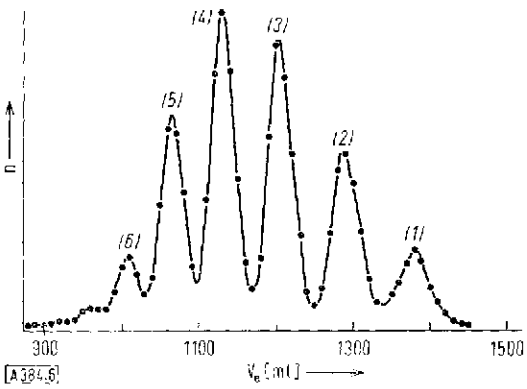



Fig. 6. Elution diagram of glucose oligomers, obtained by acetolysis of a polysaccharide followed by alkaline hydrolysis, from a Sephadex G-25 column [148]. (1) Glucose, (2) cellobiose, *etc.* up to (6) cellohexaose.

Ordinate: refractive index on a linear scale.

If a mixture is not completely separated, the sample must be passed through a longer gel bed, *e.g.* by connecting two columns in series [150]. Difficult separations can be achieved on a relatively short column if the eluate is recycled through the column in fractions, this procedure being repeated until the purification is complete. The separation can be conducted almost completely automatically if the eluate is immediately returned to the start by means of a pump; the progress of the separation can be observed with the aid of a flow photometer


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and unwanted mixed fractions removed through a multichannel valve [151]. Figure 7 shows a diagram of such an arrangement.

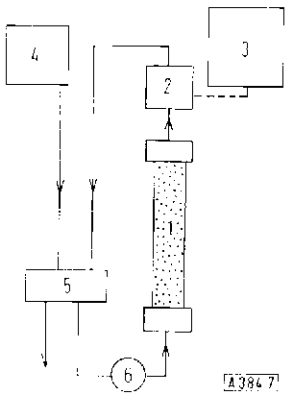



Fig. 7. Diagram of a recycling gel-chromatography apparatus.
1: Chromatographic column; 2: flow photometer; 3: recorder; 4: solvent reservoir; 5: valve; 6: recycling pump. In order to avoid compression of the gel bed, the flow passes from the bottom upwards [151].

The efficiency of gel chromatography is particularly well illustrated by the fractionation of protein associates: oligomeric serum albumins [152] are separated, as well as the enzymatically active, aggregated forms of ribonuclease, which are formed on freeze-drying of a solution of the protein in 50 % acetic acid [153].

If the elution volume is carefully recorded, gel chromatography can also be used for the estimation of molecular weights by comparison of the $K_d$ values of the unknown molecules with those of known substances. In this connection, *Porath* [154] proposed a concept which has been found to be very useful. It is based on a model involving spherical molecules of radius r and conical pores in the gel. Since the $K_d$ value of a molecule is proportional to its volume, *i.e.* to $r^3$, and its molecular weight is proportional to $r^2$ [154a], the cube root of its $K_d$ value should bear a linear relationship to the square root of its molecular weight. This is in fact the case for both polysaccharides [154] and proteins [155]. Figure 8 shows the calibration curve for proteins on Sephadex G-200. This enables the molecular weight of an unknown protein to be easily estimated from its $K_d$ value [155].

*Andrews* had previously plotted the elution volumes of various proteins from agar gel against the logarithm of their molecular weights in a single diagram and had similarly found a linear relationship over a certain range [156–156b]; he recently found the same kind of relationship for the various types of Sephadex gels [157]. The pore diameters of granulated agar gels with different degrees of swelling (cf. p. 610) have been determined experimentally from the chromatographic behavior of substances with known molecular or particle diameters [158]. Molecular-weight determinations are also possible in homogeneous gels. The substance under investigation is allowed to diffuse into a gel, and the velocity of the migrating front is compared with that of markers. The analysis can be carried out either immunologically (by precipitation [159]) or by working up individual layers [160]. Conclusions can also be drawn regarding the molecular weight of proteins from their electrophoretic behavior on gels of different densities [161].

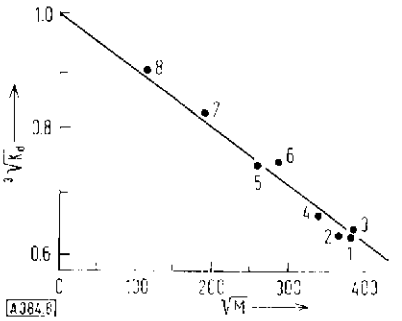



Fig. 8. $K_d$ Values and molecular weights of eight proteins chromatographed on Sephadex G-200 in 0.1 M phosphate buffer and 1 M NaCl [155].
1: Human globulin (mol. wt. 140000–150000); 2: bovine serum albumin, dimeric (mol. wt. 134000); 3: yeast aldolase (mol. wt. 147000); 4: glyceraldehyde phosphate dehydrogenase (mol. wt. 117000); 5: bovine serum albumin, monomeric (mol. wt. 67000); 6: phosphocreatin kinase (mol. wt. 81000); 7: pepsin, monomeric (mol. wt. 35000); 8: bovine ribonuclease (mol. wt. 13000).
Abscissa: $\sqrt{\text{mol. wt.}}$

## 7. Special Applications of Dextran Gels

Commercial Sephadex dextran gel has been found suitable for applications which do not correspond to gel filtration in general. For example, the huge water absorption of dry "G-25 coarse" causes considerable concentration when it is stirred into aqueous solutions of macromolecular materials and then centrifuged out [162, 163]; no change occurs in the ionic strength or pH. Sephadex acts as an inert hydrophilic support in electrophoresis in horizontal layers [164] and in vertical columns [142, 165–166a], as well as in partition chromatography of peptides [5, 167–168b], dinitrophenyl-

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amino acids [169], and soluble ribonucleic acids [170]. In comparison with cellulose used in paper chromatography, dextran gel has the advantages of greater stability and purity, as well as of higher capacity and flow rate.

The differences in solubility of proteins in saline and salt-free solutions can be used for their separation on dextran gel columns. Serum proteins, which are insoluble in the absence of salt, leave the gel bed only when sodium chloride is admixed to the eluent; other proteins appear earlier, according to size [171]. This technique can be further refined by repeated precipitation and dissolution cycles, using a salt gradient in the dextran gel [172]. Fine Sephadex G-25 powder adheres to glass plates without a bonding agent. Very small quantities of proteins [173] or protein structural units [174] can be separated by thin-layer chromatography on plates coated with Sephadex.

## 8. Gel Chromatography on Lipophilic Gels

Following the success of gel chromatography on materials which swell in water, attempts have recently been made to find suitable lipophilic gels. Here, even more than in water, particular attention must be paid to adsorption. The polystyrenes with various degrees of cross-linking used as the basis of synthetic ion-exchange resins are not very suitable, since the order of elution is often governed more by the structures of substances than by their molecular weights [28, 175].

On the other hand, separations achieved on small pieces of rubber [31] appear to be based on the molecular-sieve effect. The $K_d$ values of polyisobutene (mol. wt. 18000), pentaerythritol tetrastearate (mol. wt. 1200), squalane (mol. wt. 423), and azulene (mol. wt. 128) are related in a linear manner to the logarithm of their molecular weights. The behavior of oligomeric polystyrenes on purely aliphatic poly(methyl methacrylate) gel corresponds perfectly to the laws known for gels which swell in water. Thus, a linear relationship is again found between the cube root of the $K_d$ value and the square root of the molecular weight [29]. Similar gels should be suitable for determining the molecular-weight distribution of polymers, if it becomes possible to synthetize rigid networks with sufficiently large pores [30].

It also appeared worthwhile to convert Sephadex dextran gels into derivatives which would swell in organic solvents [176]. Sephadex G-50, medium, was suspended in benzene and acetylated with excess acetic anhydride; after careful washing, the content of acetyl groups was found by alkaline hydrolysis to be 30 % by weight, *i.e.* about 50 % of the hydroxy groups of the dextran had been esterified. The material swells, *e.g.* in methylene chloride, to about twice its original volume and acts as a molecular sieve. Figure 9 shows the result of an experiment with polystyrene fractions [177] on acetylated

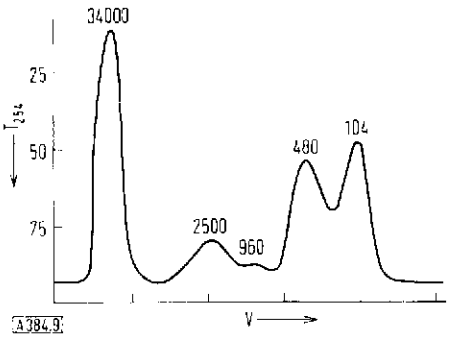



Fig. 9. Elution of five polystyrene fractions (concentration of each 2–5 mg/ml) in methylene chloride from a gel bed of acetylated Sephadex (column: 1.5 cm diameter, 120 cm length). The figures are the osmotically determined molecular weights.
Ordinate: transmission [%] at 254 mμ.
Abscissae: volume of eluate.

Sephadex [178]. It is found that, despite its lower swelling in solvents, its exclusion limit was higher than that of the poly(methyl methacrylate) gels, possibly owing to the fact that the pore size increases from the inside towards the outside.

## 9. Conclusions

The gel structure is not absolutely necessary for chromatographic separations by molecular weight. *Pedersen* observed that larger proteins dissolved in aqueous buffer pass through a glass tube filled with glass beads (diameter 20–35 μ) more rapidly than smaller proteins [152]. A similar phenomenon was described by *Vaughan*, who fractionated a polystyrene mixture in benzene on a silicate (Santocel A), with a result comparable to that obtained by conventional fractional precipitation methods [179]. Powdered plastic had no separating action, and cellulose powder was only slightly active. In the flow of blood through capillary blood vessels, the corpuscles, which only migrate in the middle, proceed at an appreciably higher speed than the plasma proteins; this effect may be compared to the fractionation of proteins on glass powder described above [152]. Thus, separations should be possible on any "rough" surface, provided the irregularities are of the correct order of magnitude. Small molecules migrate very close to the surface and so must travel greater distances than large molecules, which follow a straight path, unhindered by irregularities, in the proximity of the surface.

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*Pedersen* therefore proposed that the term "gel filtration" should be replaced by the term "exclusion chromatography" for the high molecular-weight range. Other authors disliked the name "filtration" for this chromatographic process and suggested the terms "restricted diffusion chromatography" [158] or "gel permeation chromatography" [30]. However, *Tiselius* supports the hitherto usual term "gel filtration" [180], and points out the fundamental difference between this and other chromatographic separations, namely, that the concentration in the stationary phase can, at the most, be only as great as that in the mobile phase.

Some of the difficulties in nomenclature can be avoided by agreeing to the division attempted in this summary (from practical considerations, among others) into "*gel filtration*" and "*gel chromatography*". Whatever name is given to the process, its use guarantees clean and easy separation of substances with different molecular sizes, as shown by the profusion of the applications quoted.

*I should like to thank Doz. Dr. B. Gelotte, A. B. Pharmacia, Uppsala (Sweden), for information and stimulating discussions.*

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# Electron Affinity of Organic Molecules

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*Dedicated to Dr. W. Foerst on the occasion of his 65th birthday*

*The formation of organic radical ions by direct electron exchange between a donor molecule D and an acceptor molecule A is becoming increasingly important, particularly with regard to reaction mechanisms involving intermediate radical ions. All redox processes also involve electron exchange. Finally, the knowledge of electron affinities and ionization energies of organic molecules is necessary for a quantitative theoretical interpretation of intermolecular resonance and of the semiconductor properties of crystalline organic compounds and molecular compounds.*

The electron-donating properties of organic molecules can be estimated from their ionization energies which for some organic molecules are directly measurable. However, direct experimental determination of the electron affinities of organic molecules, which govern their electron-accepting properties, was not possible until only a few years ago. This paper deals with the methods and means of determining the electron affinities of organic molecules; the discussion will be restricted to neutral molecules and will exclude consideration of radicals as electron donors and acceptors. The electron-donor and electron-acceptor properties of aromatic hydrocarbons will be treated separately in Chapter II. All the electron donors discussed this article are listed in Table 1.

The electron affinity EA of an electron-acceptor molecule A is the energy $E_j$ of the lowest unoccupied orbital of A in the ground state and is equal to the difference in energy ($E_{A^-} - E_{A + e_0^-}$) between the anion $A^-$ and the uncharged molecule $A + e_0^-$.

$$(1) \qquad E_j = -EA = E_{A^-} - E_{A + e_0^-}$$

The ionization energy I of an electron-donor molecule D is equal to the energy $E_i$ of the highest occupied orbital of D in the ground state or to the difference in energy ($E_D - E_{D^+ + e_0^-}$) between the cation $D^+ + e_0^-$ and the uncharged molecule D.

$$(2) \qquad E_i = -I = E_D - E_{D^+ + e_0^-}$$

The difference in energy between the lowest vibrational level of the ground state of the neutral molecule and the corresponding level of the ion is termed the adiabatic ionization energy, or the adiabatic electron affinity, respectively. The energy difference between the energy level of the ground state and that part of the potential curve of the ionized state to which – applying the Franck-Condon principle – transition is most likely to occur, is denoted as vertical ionization energy and vertical electron affinity, respectively.

## I. Organic Electron Acceptors (excluding Aromatic Hydrocarbons)

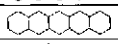
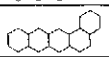
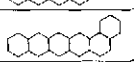
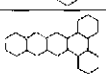
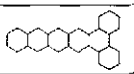
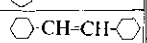
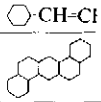
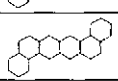
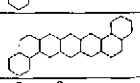
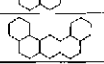
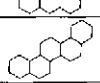
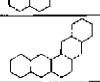
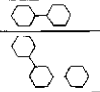
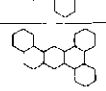
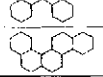
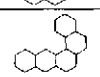
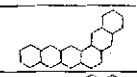
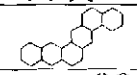
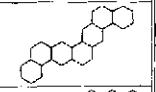
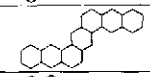
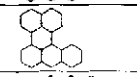
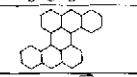
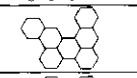
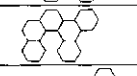
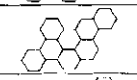
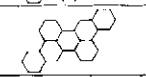
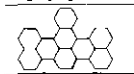
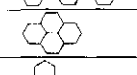
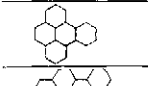
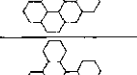
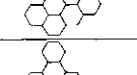
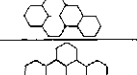
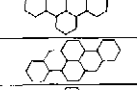
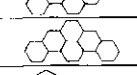
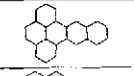
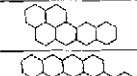
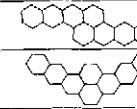
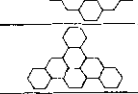
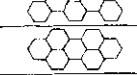
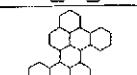
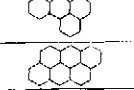
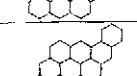
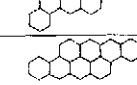
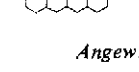
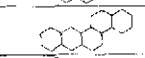
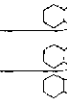
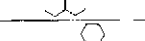
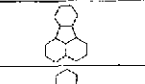
### 1. Electron Affinities Derived from the Electron Absorption Coefficient

*Lovelock* [1] determined the electron absorption coefficient $\chi$

$$(3) \qquad [e^-] = [e^-]_0 \exp(-\chi [A])$$

[1] *J. E. Lovelock* and *R. S. Lipsky*, J. Amer. chem. Soc. *82*, 431 (1960); *J. E. Lovelock*, Nature (London) *187*, 49 (1960); *188*, 401 (1960); *189*, 729 (1961).

Table 1. Electron donors discussed in the present paper. The numbering adopted here is also used in the text, in Figures 1, 2, 3, 7, 8, and 9, and in Tables 3, 5, 6, 7, and 8. Numbers 66, 85, and 87 have been omitted for technical reasons.

| No. | Name | Formula |
|---|---|---|
| 1 | Benzene |  |
| 2 | Naphthalene |  |
| 3 | Anthracene |  |
| 4 | Tetracene |  |
| 5 | Pentacene |  |
| 6 | Phenanthrene |  |
| 7 | Benz[a]anthracene |  |
| 8 | Benzo[a]tetracene |  |
| 9 | Benzo[a]pentacene |  |
| 10 | Triphenylene |  |
| 11 | Dibenz[a,c]anthracene |  |
| 12 | Dibenzo[a,c]tetracene |  |
| 13 | Dibenzo[a,c]pentacene |  |
| 14 | Chrysene |  |
| 15 | trans-Stilbene |  |
| 16 | Dibenz[a,h]anthracene |  |
| 17 | Dibenzo[a,j]tetracene |  |
| 18 | Dibenzo[a,l]pentacene |  |
| 19 | Benzo[a]phenanthrene |  |
| 20 | Dibenz[a,j]anthracene |  |
| 21 | Picene |  |
| 22 | Pentaphene |  |
| 23 | Perylene |  |
| 24 | Benzo[ghi]perylene |  |
| 25 | Coronene |  |
| 26 | Biphenyl |  |
| 27 | m-Terphenyl |  |
| 28 | Diphenylene |  |
| 29 | o-Terphenyl |  |
| 30 | Benzo[g]chrysene |  |
| 31 | Tribenz[a,c,j]anthracene |  |
| 32 | Dibenzo[g,p]chrysene |  |
| 33 | Benzo[c]chrysene |  |
| 34 | Benzo[a]tetraphene |  |
| 35 | Hexaphene |  |
| 36 | Benzo[c]pentaphene |  |
| 37 | Dibenzo[c,m]pentaphene |  |
| 38 | Naphtho[2,3-c]pentaphene |  |
| 39 | Benzo[a]perylene |  |
| 40 | Dibenzo[a,j]perylene |  |
| 41 | Dibenzo[a,n]perylene |  |
| 42 | Dibenzo[b,pqr]perylene |  |
| 43 | Tribenzo[b,k,pqr]perylene |  |
| 44 | Dibenzo[b,k]perylene |  |
| 45 | Benzo[tuv]bisanthene |  |
| 46 | Benzo[j]terrylene |  |
| 47 | Pyrene |  |
| 48 | Benzo[e]pyrene |  |
| 49 | Benzo[a]pyrene |  |
| 50 | Dibenzo[b,e]pyrene |  |
| 51 | Dibenzo[a,e]pyrene |  |
| 52 | Dibenzo[e,l]pyrene |  |
| 53 | Dibenzo[a,h]pyrene |  |
| 54 | Dibenzo[a,i]pyrene |  |
| 55 | Naphtho[2,3-e]pyrene |  |
| 56 | Naphtho[2,3-a]pyrene |  |
| 57 | Dinaphtho-[2,3-a:2',3'-h]pyrene |  |
| 58 | Dinaphtho-[2,3-a:2',3'-i]pyrene |  |
| 59 | Tribenzo[a,e,i]pyrene |  |
| 60 | Peropyrene |  |
| 61 | Dibenzo[e,p]peropyrene |  |
| 62 | Anthanthrene |  |
| 63 | Dibenz[a,j]anthanthrene |  |
| 64 | Dibenz[a,k]anthanthrene |  |
| 65 | Azulene |  |
| 67 | p-Terphenyl |  |
| 68 | Fluorene |  |
| 69 | Acenaphthylene |  |
| 70 | Acenaphthene |  |
| 71 | Benzo[c]tetraphene |  |
| 72 | Toluene |  |
| 73 | m-Xylene |  |
| 74 | Mesitylene |  |
| 75 | Durene |  |
| 76 | Pentamethylbenzene |  |
| 77 | Hexamethylbenzene |  |
| 78 | 20-Methylcholanthrene |  |
| 79 | 9,10-Dimethyl-benz[a]anthracene |  |
| 80 | Aniline |  |
| 81 | N,N-Dimethylaniline |  |
| 82 | 1-Naphthylamine |  |
| 83 | 2-Naphthylamine |  |
| 84 | Indole |  |
| 86 | N,N-Tetramethyl-p-phenylenediamine |  |
| 88 | Benzo[ghi]perylene |  |
| 89 | Tribenzo[a,e,i]pyrene |  |
| 90 | Fluoranthene |  |
| 91 | Benzo[b]fluorene |  |
| 92 | Benzo[c]fluorene |  |
| 93 | 9-Benzylidenefluorene |  |
| 94 | Benzo[ghi]fluoranthene |  |
| 95 | Benzo[b]fluoranthene |  |
| 96 | Benzo[k]fluoranthene |  |
| 97 | Rubicene |  |
| 98 | Rubrene |  |
| 99 | Phenothiazine |  |

for the capture of thermal electrons $e^-$ by a few organic molecules A. This represents the only possibility for experimental determination of the relative order of electron affinities. Under experimental conditions for which $[e^-] \gg [A]$, the absolute electron absorption coefficient $\chi$ becomes identical with the equilibrium constant $K_A$ [2]:

$$(4) \qquad K_A = \frac{g_{A^-}}{g_A \cdot g_{e^-}} e^{EA/RT} = \frac{[A^-]}{[A]\,[e^-]}$$

The electron affinity EA can be calculated from Equation (4) by setting $g_{A^-}/g_A = 2$, and hence $g_{A^-}/g_A \cdot g_{e^-} = 1$. *Lovelock* reported several electron absorption coefficients $\chi' = K'_A$ referred to chlorobenzene as standard (Table 6, Column 2). *Wentworth* and *Becker* [3] determined the absolute equilibrium constant for electron capture by anthracene. Using this value and Equation (4), they obtained a value of 0.42 eV for the electron affinity of anthracene. For a given acceptor A, and for $K'_{anthracene} = 12$ [2a], we have:

$$(5) \qquad RT \ln K_A = EA_A = RT \ln K'_A + 0.42 - RT \ln 12$$

The electron affinities of a few organic acceptors, calculated for $\chi' = K'_A$ using Equation (5) are listed in Table 5, Column 3.

### 2. Electron Affinities derived from the Electron-Transfer Energy and from the Ionization Energy of the Electron Donor

On the basis of *Mulliken*'s theory [4] of intermolecular interaction between electron-acceptor and electron-donor molecules, it is possible to derive an expression for the energy $\tilde{\nu}_{CT}$ of electron transfer from D to A in terms of the ionization energy I of the electron donor and the electron affinity EA of the acceptor [5,6]:

$$(6) \qquad \tilde{\nu}_{CT} = I - (EA - E) + \frac{C_2}{I-(EA-E)}$$

[2] $[e^-]$: Stationary electron concentration at equilibrium; $[e^-]_0$: electron concentration before approach of acceptor A to electron gas; g: number of realizable quantum states ("quantum weight"). For $e^-$, $g = 2$ ($s = \pm 1/2$); see, for example, *T. L. Hill:* Introduction to Statistical Thermodynamics, Addison-Wesley Publ. Co., Reading, Mass. (U.S.A.) 1960. Equation (3) can be written, to a good approximation, as follows: $[e^-] = [e^-]_0 - [A^-] = [e]_0(1 - \chi[A])$. Then, for the case where $[e^-] \gg [A]$ or $[A^-] \ll [e^-]_0$ we obtain:

$$(3a) \quad \chi = \frac{[A^-]}{[e^-]_0\,[A]} \approx \frac{[A^-]}{[e^-]\,[A]}$$

[2a] If $K_{ClBz}$ is the electron-capture equilibrium constant for chlorobenzene, then, for an acceptor A, we have:

$K_A/K_{ClBz} = K'_A$ and $K_{anthracene}/K_{ClBz} = 12$

and hence: (4') $K_A = (K'_A/12) \cdot K_{anthracene}$.

The change in free energy for electron capture by A is by definition $-EA = -RT \ln K_A$, and, hence, using Equation (4'), we obtain Equation (5).

[3] *E. W. Wentworth* and *R. S. Becker*, J. Amer. chem. Soc. *84*, 4263 (1962).

[4] *R. S. Mulliken*, J. Amer. chem. Soc. *72*, 600 (1950); *74*, 811 (1952); J. chem. Physics *19*, 514 (1951); J. physic. Chem. *56*, 801 (1952).

[5] *S. H. Hastings, J. L. Franklin, J. C. Schiller*, and *F. A. Matsen*, J. Amer. chem. Soc. *75*, 2900 (1953); *G. Briegleb* and *J. Czekalla*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 184 (1955); *63*, 6 (1959); Angew. Chem. *72*, 401 (1960); *R. Foster*, Nature (London) *181*, 337 (1958).

[6] For further details, see *G. Briegleb:* Electronen-Donator-Acceptor Komplexe. Springer, Berlin-Göttingen-Heidelberg, 1961.

E is predominantly the energy of the Coulomb attraction between $D^+$ and $A^-$ after the transfer of one electron from D to A. E also comprises the polarization energy [6, 7] and an energy contribution $\Delta H$ from the intermolecular bond D···A in the ground state. $C_2$ can be calculated theoretically [6].

Theoretically, Equation (6) is based on the adiabatic ionization energy. However, it is not yet certain whether the various methods for determining the ionization energy of organic molecules (*e.g.*, the electron impact and photoionization methods) yield the adiabatic or the vertical ionization energy.

It has been established that E and $C_2$ can be assumed to be nearly constant, for electron-donor/electron-acceptor complexes (EDA complexes) of the same bond type [10], so that for complexes involving one and the same acceptor, Equation (6) reduces to Equation (7).

$$(7) \qquad \tilde{\nu}_{CT} = I - C_1 + \frac{C_2}{I - C_1}$$

$C_1$ can be determined experimentally [11] by plotting $\tilde{\nu}_{CT}$ against I for the EDA complexes of a given acceptor with various donors, when Equation (7) is normalized to a standard, *e.g.* naphthalene.

The electron affinities listed in Column 4 of Table 6, were calculated from $C_1$ according to Equations (6) and (7) using the value $E \approx E_{coul} \approx -4.3$ eV for the $\pi,\pi$-complexes. It was assumed here that the average intermolecular distance for the $\pi,\pi$-complexes is nearly constant. This assumption is supported by the fact that the validity of Equations (6) and (7) has been demonstrated for a large number of EDA complexes [11]. The charge on $D^+$ and $A^-$ is shifted towards the center of the complex molecule. Because of the approximations used, electron affinities derived from $C_1$ (Table 6, Column 4) have an uncertainty of about $\pm 0.2$ eV.

In Table 2, the electron affinities calculated by *Person* [9] and by *Jortner* and *Sokolov* [12] for the halogens

Table 2. Electron affinities [eV] for halogens and iodine chloride.

| | $I_2$ | | $Br_2$ | | $Cl_2$ | | ICl | |
|---|---|---|---|---|---|---|---|---|
| $C_1$, Eqs. (6) and (7) [9] | 5.2 | | 5.1 | | 5.0 | | 4.9 | |
| EA from $C_1$ [9] | 2.0 ⊥ | 1.0 ∥ | 1.7 ⊥ | 0.8 ∥ | 1.5 ⊥ | 0.6 ∥ | 1.7 ⊥ | 0.7 ∥ |
| $EA_{vertical}$ [*] | 1.7 ± 0.5 | | 1.2 ± 0.5 | | 1.3 ± 0.4 | | 1.7 ± 0.6 | |
| EA from Eq. (25) [**] [12, 16] | 1.56 | | 1.48 | | 1.3 | | 1.43 | |

[*] Calculated theoretically from the potential curves for $Hal_2$ and $Hal^-_2$ by applying the Morse function and making use of the interatomic equilibrium distance, dissociation energy, and fundamental vibrational frequency.

[**] Relative to the iodine atom with EA = 3.23 eV [15].

[7] The valence bond energy $E_{Val}$ contributes to a slight extent to the polarization energy $E_{pol}$ and vice versa. In general, $E_{pol}$ should be equal to about 0.1 $E_{Coul.}$. Only for iodine-amine complexes does the contribution of $E_{val}$ apparently become larger [8, 8a], as a result of the relatively small intermolecular distance (about 2.3 Å). According to *Person* [9], for iodine-amine complexes $E_{val} \approx 0.25\ E_{Coul.}$. In the case of n, σ-complexes, for example, those between iodine and amines, the constants $C_1$ and $C_2$ in Equation (6) are markedly different compared to those for $\pi,\pi$- or $\pi,\sigma$-complexes. *H. Yada, J. Tanaka*, and *S. Nagakura*, Bull. chem. Soc. Japan *33*, 1660 (1960) proved this for iodine-amine complexes. See also [8a].

[8] See [6], pp. 7, 18, 76, 79, 81, 132, and 173.

[8a] *R. S. Mulliken*, Annual Rev. physic. Chem. *13*, 107 (1962)

[9] *W. B. Person*, J. chem. Physics *38*, 109 (1963).

[10] $\pi,\sigma$-; $\pi,\pi$-; n,σ-; σ,σ-complexes; for further information see [6], pp. 5 et seq.

[11] *G. Briegleb* and *J. Czekalla*, [5]; see also [6], pp. 74 et seq.

[12] *J. Jortner* and *U. Sokolov*, Nature (London) *190*, 1 (1961).

Table 3. Values of a and b [eV] from Equation (9) for electron-donor/electron-acceptor complexes.

| | Tetracyano-ethylene | Chloranil | Bromanil | 2,6-Di-chloro-*p*-benzo-quinone | Chloro-*p*-benzo-quinone | *p*-Benzo-quinone | 1,3,5-Trinitro-benzene | 2,4,6-Trinitro-toluene | *m*-Di-nitro-benzene | $I_2$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | 0.87 [*] 0.72 [**] | 0.90 | 0.93 [*] 0.97 [**] | 0.85 | 0.85 | 0.85 | 0.97 0.85 | 0.85 | 0.85 | 0.94 | 0.87 |
| b | 4.86 [*] 3.48 [**] | 4.5 | 4.94 [*] 5.27 [**] | 4.36 | 4.19 | 3.89 | 4.5 3.9 | 3.68 | 3.47 | 4.2 | 3.6 |
| | [19] [18a] | [18b, 19] | [18b] [18b] | [18] | [18] | [18] | [18c] [18] | [18] | [18] | [18c] | [8a] |

[*] For polycyclic aromatic hydrocarbons.

[**] Average values for substituted benzenes. To be precise, methoxybenzenes (a = 0.74; b = 3.64), methylbenzenes (a = 0.68); b = 3.01), and halogenobenzenes (a = 0.60; b = 2.34) [18a] would have to be distinguished.

and iodine chloride are given for comparison with those of organic acceptors. The order of these affinities seems reasonable.

X-ray studies [13] of the complexes of iodine and the other halogens with π-donors, particularly benzene, have indicated that a configuration in which the axis of the halogen molecule is vertical to the benzene plane is more probable than the alternative configuration with parallel axes. According to Equations (6) and (7) $E_\perp$ and $E_\parallel$ differ by about 1 eV [14].

At sufficiently large ionization energies (I > 7.5 eV), the third term in Equation (6) can be neglected:

$$\tilde{\nu}_{CT} = I - EA + E \qquad (8)$$

Hence, for EDA complexes between one and the same acceptor and various donors, the following approximation is often used [17].

$$\tilde{\nu}_{CT} = aI + b \qquad (9)$$

As comparison with Equation (6) shows, the term b in Equation (9) contains the electron affinity of the acceptor and the Coulomb energy E; thus, when E is nearly constant, b can be taken as a measure of the electron affinity and is therefore often referred to as the apparent electron affinity. For EDA complexes of the same bond type [10] the term a can be assumed to be constant, *i.e.*, largely independent of the acceptor. This, however, is not always true, particularly for interactions with weaker donors [18] (cf. Table 3, where the values of a and b obtained from Equation (9) are listed for a few acceptors). The values of a and b for complexes of the very strong electron-acceptors tetracyanoethylene and bromanil with polycyclic aromatic hydrocarbons differ from those obtained for their complexes with substituted benzenes [18a, 19].

Judging from the strengths of their EDA complexes with aromatic hydrocarbons, the following order of electron affinities can be derived from the b values listed in Table 3:

bromanil > tetracyanoethylene > chloranil = 1,3,5-trinitrobenzene > 2,6-dichloro-*p*-benzoquinone > chloro-*p*-benzoquinone > *p*-benzoquinone > 2,4,6-trinitrotoluene > *m*-dinitrobenzene.

This order is *not* in agreement with the relative order of electron affinities resulting from Equations (5), (7), (14), (23), and (25); see Table 6. Obviously, the constant b in Equation (9) is less suitable to determine a relative sequence of electron affinities.

From Equations (8) and (2) we obtain

$$\tilde{\nu}_{CT} = -E_i - EA + E \qquad (10)$$

As we shall see in the following, there are numerous possibilities for expressing I or $-E_i$ by means of other quantities.

### 3. Electron-Transfer Energy as a Function of the Ionization Energy of the Donor

For polycyclic aromatic hydrocarbons as donors, it follows from *Hückel*'s simple AMO theory that:

$$E_i = -I = \alpha_0 + f_H \cdot \beta \qquad (11)$$

In Equation (11), $\alpha_0$ is the Coulomb integral, β the resonance integral for two neighboring atoms (k, l), and $f_H$ is the Hückel coefficient which expresses the contribution of β to the total energy $E_i$. The electron overlap integral is assumed to be zero, and the electron repulsion is neglected.

The decrease in electron repulsion on transition from D to $D^+$ may be taken into account (by a decrease in the Coulomb attraction) in $\alpha_0$ [20]. In a simplification recently proposed by

[13] *O. Hassel*, Molecular Physics *1*, 241 (1958); *O. Hassel* and *K. O. Stromme*, Acta chem. scand. *12*, 1146 (1958).

[14] The value EA = 0.8 eV for $I_2$ quoted by *Briegleb* and *Czekalla* [5] refers to the parallel model, which was originally adopted because of symmetry considerations [4] arising from the quantum-mechanical group theory.

[15] *O. H. Pritchard*, Chem. Reviews *52*, 529 (1953).

[16] It is improbable that the values of E for EDA complexes of atomic iodine, molecular halogens, and ICl are identical. However, the order of the electron affinities calculated by *Jortner* and *Sokolov* [12] agrees – within the limits of error – with the electron affinities calculated by *Person* [9] for the vertical model.

[17] *H. McConnel, J. S. Ham*, and *J. F. Platt*, J. chem. Physics *21*, 66 (1953).

[18] *R. Foster*, Tetrahedron *10*, 96 (1960).

[18a] *E. M. Voigt*, Ph. D. Thesis, University of British Columbia, 1963.

[18b] *M. Kinoshita*, Bull. chem. Soc. Japan *35*, 1609 (1962).

[18c] See [6]; pp. 79 et seq.

[19] *H. Kuroda, M. Kubayashi, M. Kinoshita*, and *S. Takenioto*, J. chem. Physics *36*, 457 (1962).

[20] *G. W. Wheland* and *D. E. Mann*, J. chem. Physics *17*, 264 (1949) assume that the increase in α, expressed in units of β, is proportional to the positive charge (1−q)β on the carbon atom (q is the relative negative charge on the carbon).

*Ehrenson* [22], $\alpha$ can be expressed in units of $\beta$ as follows ($\alpha$,$\alpha_0$, and $\beta$ are negative; $|\alpha| < |\alpha_0|$):

$$\alpha = \alpha_0 \cdot (1 - 1/n)\omega\beta \quad (12)$$

where $\omega$ is an empirical proportionality factor and n is the number of conjugated $\pi$-electrons in the aromatic hydrocarbon.

Substituting $\alpha$ for $\alpha_0$ in Equation (11) and using Equation (12), we obtain:

$$-E_i = I = -\alpha_0 - (f_H - \frac{n-1}{n}\omega)\beta = -\alpha_0 - \varkappa\beta \quad (13)$$

When $\alpha$ = 9.878 eV, $\beta$ = −2.11 eV, and $\omega$ = 1.4 [21], Equation (13) gives satisfactory values for the ionization energy of aromatic hydrocarbons [22].

Substituting Equation (13) into Equation (10), one obtains:

$$\tilde{\nu}_{CT} = (-EA - \alpha_0 + E) - \varkappa\beta = k - \varkappa\beta \quad (14)$$

$$k = -EA - \alpha_0 + E \quad (14a)$$

This expression is based on the observation that the values of EA and E for EDA complexes of analogous donors (*e.g.* polycyclic aromatic hydrocarbons) with one and the same acceptor are nearly constant.

According to Equation (14), $\tilde{\nu}_{CT}$ should be linearly proportional to $\varkappa$. Figure 1 shows for the example of the EDA complexes of tetracyanoethylene with aromatic hydrocarbons that this requirement is satisfactorily fulfilled, considering the variability of E and $\tilde{\nu}_{CT}$ and the uncertainty in I as obtained from Equation (13). (The values of $\varkappa$ and $f_H$ in Figure 1 are listed in Columns 5 and 6 of Table 4.)

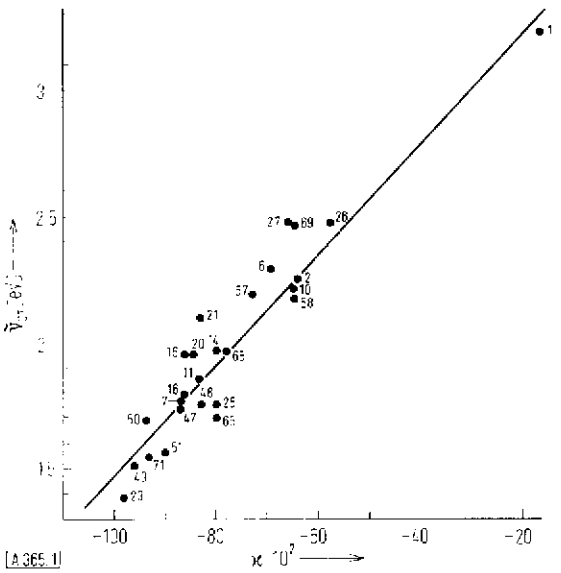



Fig. 1. Linear dependence of the electron transfer energy $\tilde{\nu}_{CT}$ on the value of $\varkappa$ obtained from Equation (14) for tetracyanoethylene-hydrocarbon complexes (the numbers refer to the hydrocarbons listed in Table 1).

The charge-transfer band maxima $\tilde{\nu}_{CT}$ for EDA complexes between the acceptors given in Table 4 and the donors listed in Column 5a of Table 6 and the corresponding $\varkappa$ values are related by the linear function represented by Equation (14). The values of $\beta$ and k calculated from this linear $\tilde{\nu}_{CT}$ *vs.* $\varkappa$ relationship, and the electron affinities derived from the k values obtained from Equation (14a) by setting E = −4.3 eV and $\alpha_0$ = −9.88 eV are listed in Table 4 for the electron acceptors tetracyanoethylene, chloranil, 2,4,7-trinitro-9-fluorenone, 1,3,5-trinitrobenzene, and iodine [23].

Table 4. Electron affinities of a few typical organic electron acceptors and of iodine, calculated from the values of k obtained according to Equations (14) and (14a) [*].

| | Tetracyanoethylene | Chloranil | 2,4,7-Trinitro-9-fluorenone | 1,3,5-Trinitrobenzene | Iodine [*] | |
|---|---|---|---|---|---|---|
| −β [eV] | 2.2 | 2.3 | 2.6 | $2.3_5$ | 1.9 | |
| k [eV] | $3.6_7$ | 4.1 | 4.6 | $4.8_6$ | $4.5_5$ | |
| EA [eV] | 1.9 | 1.5 | 1.0 | 0.7 | 1.0 (∥) | $1.9_5$ (⊥) |

[*] For $I_2$, E = −4.3 eV or E = −3.5 eV, depending on whether the parallel or vertical model is considered.

Within the limits of error (± 0.2 eV), the electron affinity values calculated using Equation (14) are in good agreement with those calculated from $C_1$ in Equation (7); compare Columns 4 and 5 of Table 6. The values of $\beta$ listed in Table 4 refer to the aromatic hydrocarbons summarized in Column 5a of Table 6 and correspond to the values quoted by *Streitwieser* [21] and *Hoijtink* [31].

## 4. Ionization Energy and Intermolecular Electron-Transfer Energy as a Function of the Electron Excitation Energy $\tilde{\nu}_0$ of Aromatic Hydrocarbons as Donors

Setting for a given molecule, in general:

$$E_i = \alpha + f\cdot\beta \quad \text{and} \quad (15a)$$

$$E_j = \alpha + f'\cdot\beta, \quad (15b)$$

we obtain for the energy difference between the highest occupied and the lowest unoccupied orbital:

$$E_j - E_i = \tilde{\nu}_0 = (f' - f)\beta \quad (16)$$

[21] *A. Streitwieser* and *P. M. Nair*, Tetrahedron *5*, 149 (1959); *A. Streitwieser*, J. Amer. chem. Soc. *82*, 4123 (1960). – *Hoijtink*'s calculations [31], based on the one-electron half-wave reduction potential of aromatic hydrocarbons (p. 626 and p. 629), in combination with *Hückel*'s equation (Equation (15b)] and *Wheland*'s f'-values [20], gave an average value of $\beta$ = −2.26 eV. See also *P. Balk*, *S. De Bruijn*, and *G. J. Hoijtink*, Recueil Trav. chim. Pays-Bas *76*, 860 (1957).

[22] *S. E. Ehrenson*, J. physic. Chem. *66*, 706 (1961).

[23] Instead of Equation (10), *Dewar* and *Lepley* [24] use

$$\tilde{\nu}_{CT} = I - EA = E_j - E_i \quad (10')$$

In other words, the energy term E is omitted. Moreover, *Dewar* and *Lepley* use *Hückel*'s simple equation [Equation (11)] for I and obtain, in place of Equation (14), a linear relationship between $\tilde{\nu}_{CT}$ and $f_H$:

$$\tilde{\nu}_{CT} = k' - f_H\beta \quad (14')$$

$$k' = -EA - \alpha_0 \quad (14a')$$

However, the simple, uncorrected Hückel equation [Equation (11)] gives less satisfactory values for the ionization energy than Equation (13) [21]. In addition, the values of k' calculated by *Dewar* and *Lepley* from Equation (14') differ by a factor of E from those obtained using Equation (14). As a result, the EA values derived from k' are 3.5–4.5 eV too high.

[24] *M. J. S. Dewar* and *A. R. Lepley*, J. Amer. chem. Soc. *83*, 4560 (1961); *M. J. S. Dewar* and *H. Rodgers*, ibid. *84*, 395 (1962); *A. R. Lepley*, ibid. *84*, 3577 (1962).

From Equations (15a), (15b), and (16), we obtain:

$$(17) \qquad E_j = \alpha + \frac{f}{f'-f} \cdot \tilde{\nu}_0$$

The data listed in Column 6 of Table 5, show that $f/(f'-f)$ is in rough approximation constant for several aromatic hydrocarbons for which f and f′ have been calculated theoretically [26]. Hence, from Equation (12), the ionization energy will be, in general:

$$(18) \qquad I = C + \gamma\tilde{\nu}_0.$$

Table 5. Corrected and uncorrected Hückel coefficients and values of x for some aromatic hydrocarbons.

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| No. [*] | f [26] Eq. (15a) | −f′ [26] Eq. (15b) | $\frac{f}{f'-f}$ | $f_H$ | −x Eq. (13) |
| 1 | 0.800 | 1.333 | 0.37 | 1.000 | 0.167 |
| 2 | 0.535 | 0.731 | 0.45 | 0.618 | 0.642 |
| 3 | 0.375 | 0.462 | 0.45 | 0.414 | 0.887 |
| 4 | 0.275 | 0.369 | 0.42 | | |
| 5 | 0.208 | 0.232 | | 0.220 | 1.117 |
| 6 | 0.526 | 0.713 | 0.40 | 0.605 | 0.696 |
| 7 | 0.406 | 0.510 | 0.44 | 0.452 | 0.870 |
| 10 | 0.584 | 0.825 | 0.42 | 0.684 | 0.648 |
| 11 | 0.444 | 0.570 | 0.43 | 0.499 | 0.838 |
| 14 | 0.460 | 0.598 | 0.44 | 0.520 | 0.802 |
| 16 | 0.423 | 0.587 | 0.42 | 0.473 | 0.864 |
| 19 | 0.497 | 0.662 | 0.42 | | |
| 20 | 0.438 | 0.561 | 0.44 | 0.491 | 0.846 |
| 21 | 0.446 | 0.574 | 0.44 | 0.501 | 0.836 |
| 22 | 0.394 | 0.49 | 0.45 | | |
| 23 | 0.320 | 0.38 | 0.46 | 0.347 | 0.983 |
| 24 | | | | 0.439 | 0.898 |
| 25 | 0.475 | 0.632 | 0.46 | 0.539 | 0.802 |
| 26 | 0.599 | 0.855 | 0.41 | 0.704 | 0.580 |
| 47 | 0.401 | 0.501 | 0.44 | 0.445 | 0.868 |
| 48 | 0.406 | 0.501 | 0.50 | 0.497 | 0.833 |
| 49 | | | | 0.371 | 0.959 |
| 50 | | | | 0.398 | 0.943 |
| 51 | | | | 0.442 | 0.899 |
| 65 | | | | 0.477 | 0.783 |
| 66 | | | | 0.662 | 0.660 |
| 67 | | | | 0.592 | 0.730 |
| 68 | | | | 0.635 | 0.649 |
| 69 | | | | 0.637 | 0.647 |
| 71 | | | | 0.405 | 0.932 |
| 87 | | | | 0.400 | 0.947 |
| 89 | | | | 0.405 | 0.945 |
| 90 | | | | 0.618 | 0.695 |
| 91 | | | | 0.520 | 0.793 |
| 92 | | | | 0.505 | 0.808 |
| 93 | | | | 0.650 | 0.680 |
| 94 | | | | 0.630 | 0.702 |
| 95 | | | | 0.600 | 0.730 |
| 96 | | | | 0.500 | 0.830 |
| 97 | | | | 0.410 | 0.937 |
| 98 | | | | 0.230 | 1.136 |

[*] The numbers refer to the hydrocarbons listed in Table 1.

Equation (18) can be fitted to experimental data only with limited accuracy, because ionization energies are known to within an accuracy of 0.1–0.2 eV for only a few aromatic hydrocarbons. Moreover, often the first excitation energy of aromatic hydrocarbons cannot be determined with great accuracy. This energy is determined a) by taking the maximum of the longest wavelength absorption band as $\tilde{\nu}_0$, and b) by basing the calculation on the 0,0-frequency $\tilde{\nu}_{00}$, provided the latter can be identified [25].

*Matsen* [26] selected for $\tilde{\nu}_0$ the frequency of the longest wavelength absorption maximum (Table 8, Column 6), as recommended by *Clar* [27], and obtained

$$(19) \qquad I = 4.39 + 0.857\ \tilde{\nu}_0\ [eV] \text{ (Fig. 2, II)}$$

*Becker* and *Wentworth* [28] based their calculation on the O,O-frequency and obtained:

$$(20) \qquad I = 5.156 + 0.775\ \tilde{\nu}_0\ [eV] \text{ (Fig. 2, III)}$$

Considering the ionization energies (which have been determined with some certainty for only relatively few aromatic hydrocarbons), cf. Table 8, Column 4, and using the $\tilde{\nu}_0$ frequencies (Table 8, Column 6), we obtain:

$$(21) \qquad I = 5.11 + 0.701\ \tilde{\nu}_0\ [eV] \text{ (Fig. 2, I)}$$

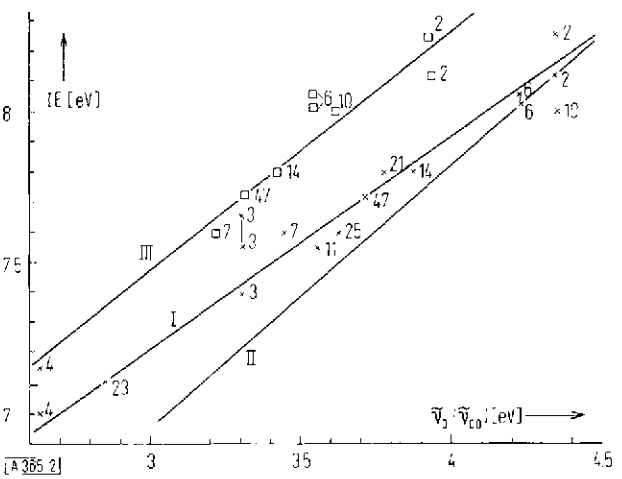



Fig. 2. Experimentally determined ionization energies $I_{exp}$ (Table 8, Column 4) of some aromatic hydrocarbons as a function of their first excitation energy $\tilde{\nu}_0$ (Table 8, Column 6); the numbers refer to the hydrocarbons listed in Table 1. Differing ionization energy values were obtained for Nos. 2, 3, 4, and 6 by various authors using different methods. I: Equation (21); II: Equation (19); III: Equation (20).

The ionization energies calculated from Equation (21) are listed in Column 5 of Table 8.

Substitution of Equation (18) into Equation (10) gives (since $I = -E_j$):

$$(22) \qquad \tilde{\nu}_{CT} = \gamma\tilde{\nu}_0 + C - EA + E$$

Considering EDA complexes of the same bond type [10] between an acceptor and analogous donors (*e.g.*, angularly condensed, unsubstituted aromatics), so that $E = -4.3$ eV [29] may be considered as nearly constant, we obtain:

$$(23) \qquad \tilde{\nu}_{CT} = \gamma\tilde{\nu}_0 + C'$$

where $C' = C - EA + E$

[25] The 0,0-frequency is the excitation energy required to raise an electron from its zero vibrational energy level in the ground state to the zero vibrational level in the excited state.

[26] See, among others, *F. A. Matsen*, J. chem. Physics *24*, 602 (1956); *G. W. Wheland*, J. Amer. chem. Soc. *63*, 2025 (1941).

[27] *E. Clar:* Aromatische Kohlenwasserstoffe, Springer, Berlin 1941.

[28] *R. S. Becker* and *W. E. Wentworth*, J. Amer. chem. Soc. *85*, 4263 (1963).

Substitution of Equations (18) and (21) into (23) reduces the latter to:

$$(23') \quad \tilde{\nu}_{CT} = 0.701\ \tilde{\nu}_0 + 0.81 - EA\ [eV] \qquad [29]$$

The calculation of electron affinities from Equation (23′) is limited by the inaccuracy in the values of I obtained from Equation (18) or (21). The uncertainties in the values of $I_{exp}$ and $\tilde{\nu}_0$ or $\tilde{\nu}_{00}$ are strongly reflected in those of the electron affinities (variations of 0.2 to 0.3 eV). The electron affinities of acceptors in EDA complexes with aromatic hydrocarbons of known excitation frequency $\tilde{\nu}_0$ can be calculated using Equation (23′) provided the values of $\tilde{\nu}_{CT}$ for the EDA complexes are known. The electron affinities of a given acceptor in EDA complexes with various donors (Table 6, Column 6a) were calculated using Equation (23′) and the average values are listed in Column 6 of Table 6.

Figure 3 shows a plot of the electron-transfer energies $\tilde{\nu}_{CT}$ *vs.* the first excitation energies $\tilde{\nu}_0$ of a series of aromatic hydrocarbons for EDA complexes of 1,3,5-trinitrobenzene, chloranil, and tetracyanoethylene. The values given in parentheses in Equations (24a)–(24c) correspond to the experimental straight lines shown in Figure 3.

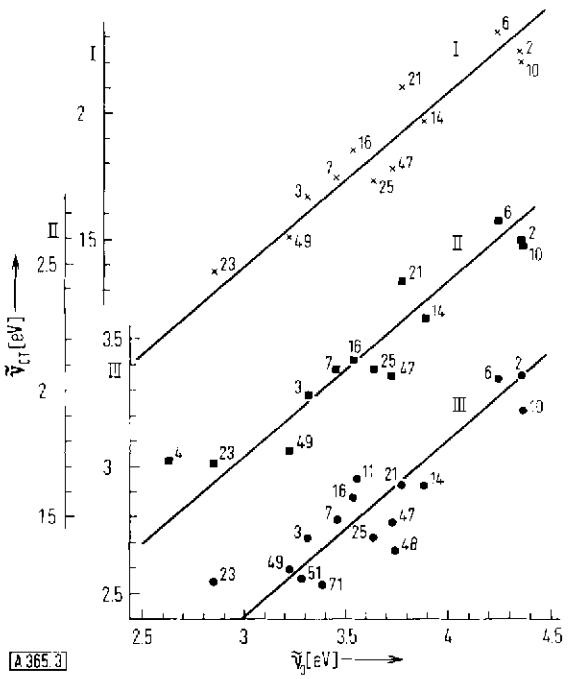



Fig. 3. Relationship between the electron transfer energy $\tilde{\nu}_{CT}$ and the first donor excitation energy $\tilde{\nu}_0$ for a few EDA complexes of the acceptors tetracyanoethylene (I), chloranil (II), and trinitrobenzene (III). The numbers refer to the hydrocarbons (donors) listed in Table 1.

(24a) Tetracyanoethylene:
(EA = 1.8 eV) $\tilde{\nu}_{CT} = 0.701\ \tilde{\nu}_0 - 0.99\ (0.72)$ [eV]

(24b) Chloranil:
(EA = 1.37 eV) $\tilde{\nu}_{CT} = 0.701\ \tilde{\nu}_0 - 0.56\ (0.37)$ [eV]

(24c) 1,3,5-Trinitrobenzene:
(EA = 0.7 eV) $\tilde{\nu}_{CT} = 0.701\ \tilde{\nu}_0 - 0.10\ (0.3)$ [eV]

[29] For halogens and XY-type interhalogen compounds, we must set E = −3.5 eV, in accordance with the vertical model (p. 619). Equation (23′) then becomes

$\tilde{\nu}_{CT} = 0.701\ \tilde{\nu}_0 + 1.61 - EA$

The deviations of the values given in parentheses from those expected from Equation (23′) fall within a range of inaccuracy of about 0.2 eV.

The averaged electron affinities calculated by different methods, *viz.* according to Equations (5), (7), (14), (23′), and (25), are collected together in Table 6, Column 8. For EDA complexes of a given acceptor (EA = const.) with analogous donors (E = const.), it follows from Equation (22) that:

$$(23'') \quad \tilde{\nu}_{CT} - \tilde{\nu}_0 = (\gamma - 1)\ \tilde{\nu}_0 + C''$$

$$(23''a) \quad C'' = C\ EA + E = 0.81\ EA$$

and from (21) that:

$$(23''') \quad \tilde{\nu}_0 - \tilde{\nu}_{CT} = 0.299\ \tilde{\nu}_0 - 0.81 + EA\ [eV]$$

Thus, although we have complexes of one and the same acceptor, *i.e.* EA = constant, $(\tilde{\nu}_0 - \tilde{\nu}_{CT})$ is not constant, as is to be anticipated if *Hückel*'s simple relationships [Equations (15a) and (15b); f = f′] were valid; instead, $(\tilde{\nu}_0 - \tilde{\nu}_{CT})$ decreases as the wavelength of the first excitation energy of the donor increases. The empirical approximate constancy of $\tilde{\nu}_0 - \tilde{\nu}_{CT}$ [6, p. 74] is valid only for aromatic hydrocarbons of nearly equal $\tilde{\nu}_0$ within the limit of accuracy (about ± 0.2 eV) of Equation (23‴).

### 5. Electron Affinities Relative to Chloranil

If we assume that for EDA complexes of the same bond type [10] and configuration [6, 13], *e.g.* π,π-complexes E may be considered to be nearly constant – an assumption that is approximately correct – then from Equation (8) we obtain the following expression for two acceptors, relative to one and the same donor:

$$(25) \quad (\tilde{\nu}_{CT})_i - (\tilde{\nu}_{CT})_k = EA_k - EA_i$$

Hence, after normalization to a given standard acceptor, Equation (25) can be used to calculate the electron affinities of other acceptors of the same type [30]. In Column 7 of Table 6, a list is given of electron affinities relative to chloranil (EA = 1.37 eV) calculated using Equation (25).

The agreement between electron affinities calculated from Equation (25) and those obtained from Equations (5), (7), (14), and (23′) in Columns 3, 4, 5, and 6 of Table 6, respectively, is satisfactory. The accuracy of the absolute electron affinity values is certainly not better than about 0.2 eV. Considering this error, their relative order should be correct.

[30] *M. Batley* and *L. E. Lyons*, Nature (London) *196*, 573 (1962) use iodine as acceptor standard. With iodine (EA = 1.8 eV) and Equation (25), they calculate the values of EA for π-acceptors (quinones, trinitrobenzene, tetracyanoethylene, *etc*). However, since it is known that EDA complexes of iodine (which is a σ-acceptor) have an entirely different configuration than the corresponding complexes of π-acceptors (trinitrobenzene, chloranil, *etc.*) [6], it is certain that the values of E [Equation (8)] for the iodine complexes are different from those for the π-acceptors (cf. the values of E given on p. 621 for the parallel and vertical model of iodine complexes with aromatic hydrocarbons). The values of E for EDA complexes of iodine with aromatic hydrocarbons are about 0.8–1.0 eV less than the values for π-acceptors. Correspondingly, the electron affinities (relative to iodine) of π-acceptors calculated by *Batley* and *Lyons* should be too high by the same amount.

Table 6. Energy data for organic electron acceptors [**].

| No. | 1<br>Acceptors | 2<br>log κ′<br>Eq. (3) | 3<br>EA [eV]<br>Eq. (5) | 4<br>EA [eV]<br>Eq. (7) | 5<br>EA [eV]<br>Eq. (14) | 5a<br>Donors<br>[*] | 6<br>EA [eV]<br>Eq. (23′) | 6a<br>Donors<br>[*] | 7<br>EA [eV]<br>Eq. (25) | 7a<br>Donors<br>[*] | 8<br>$\overline{EA}$ [eV] | 9<br>$E^{Red}_{1/2}$<br>[31, 34, 35] | 10<br>$\Delta F_{solv}$<br>[eV] | 11<br>EA [eV]<br>Eq. (28) | 12<br>EA [eV]<br>Eq. (32) | 12a<br>Donors<br>[*] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone | | | | | | 1.91 | 47 | $1.9_5$ | 47, 77 | $1.9_5$ | −0.51 | 3.63 | | 1.71 | 47 |
| 2 | Tetracyanoethylene | | | 1,7 | 1,9 | [a] | 1.53 | [d] | 2.2 | [k] | 1.80 | −0.24 | 3.51 | | 1.50 | [d] |
| 3 | 2,6-Dinitro-*p*-benzoquinone | | | | | | | | $1.7_5$ | [l] | $1.7_5$ | | | | | |
| 4 | Tetracyano-*p*-benzoquinone | | | | | | 1.66 | [e] | 1.8 | [m] | 1.7 | | | | 1.60 | [e] |
| 5 | 2,3-Dicyano-*p*-benzoquinone | | | | | | | | 1.7 | [l] | 1.7 | | | | | |
| 6 | 7,7,8,8-Tetracyano-*p*-dimethylenequinone | | | | | | | | 1.7 | 86 | 1.7 | −0.19 | 3.56 | | | |
| 7 | *o*-Bromanil | | | | | | | | 1.6 | 23 | 1.6 | | | | | |
| 8 | *o*-Chloranil | | | | | | | | $1.5_5$ | 23 | $1.5_5$ | | | | | |
| 9 | *p*-Bromanil | | | | | | | | 1.37 | 47, 77, 86 | 1.4 | 0.00 | 3.67 | | 1.19 | 47 |
| 10 | *p*-Chloranil | | | 1.4 | 1.5 | | 1.2 | [f] | 1.37 | [n] | $1.3_7$ | −0.01 | 3.65 | | 1.14 | [f] |
| 11 | *p*-Iodunil | | | | | | | | $1.3_6$ | 77.86 | $1.3_6$ | | | | | |
| 12 | Trichloro-*p*-benzoquinone | | | | | | 1.27 | 47 | 1.3 | 47.86 | 1.3 | +0.08 | 3.59 | | 1.08 | 47 |
| 13 | 2,6-Dibromo-*p*-benzoquinone | | | | | | | | 1.2 | 86 | 1.2 | | | | | |
| 14 | 2,6-Dichloro-*p*-benzoquinone | | | | | | 1.1 | 47 | 1.2 | 47,77,86 | $1.1_5$ | +0.18 | 3.64 | | 0.92 | 47 |
| 15 | 2,5-Dichloro-*p*-benzoquinone | | | | | | 1.1 | 47 | $1.1_5$ | 47,86 | 1.1 | +0.18 | 3.67 | | 0.92 | 47 |
| 16 | 2,3-Dichloro-*p*-benzoquinone | | | | | | | | 1.1 | 86 | 1.1 | | | | | |
| 17 | 1,2-Dicyano-1,2-dicarboxyethylene | | | | | | | | 1.0 | 47 | 1.0 | | | | | |
| 18 | Chloro-*p*-benzoquinone | | | | | | 0.9 | 47 | 1.0 | 47,77,86 | $0.9_5$ | +0.34 | 3.67 | | 0.72 | 47 |
| 19 | 1,8-Dihydroxy-9,10-anthraquinone | | | | | | | | 0.9 | 86 | 0.9 | | | | | |
| 20 | Phenanthrenequinone | | | | | | | | 0.7 | 86 | 0.7 | +0.66 | 3.71 | | | |
| 21 | 1,4-Naphthoquinone | | | | | | | | 0.7 | 86 | 0.7 | +0.71 | 3.66 | | | |
| 22 | Dimethylnaphthoquinone | 3.61 | 0.63 | | | | | | | | 0.6 | | | | | |
| 23 | Methyl-*p*-benzoquinone | | | | | | 0.6 | 47 | $0.6_6$ | 47,77 | $0.6_6$ | +0.58 | 3.78 | | 0.39 | 47 |
| 24 | 1,2-Naphthoquinone | | | | | | 0.6 | 47 | 0.6 | 47 | 0.6 | | | | 0.43 | 47 |
| 25 | *p*-Benzoquinone | 3.69 | 0.64 | | | | 0.46 | [g] | $0.7_7$ | [o] | 0.6 | +0.51 | 3.86 | | 0.40 | [g] |
| 26 | Duroquinone | | | | | | | | 0.6 | 77 | 0.6 | +0.84 | 3.63 | | | |
| 27 | 2,6-Dimethyl-*p*-benzoquinone | | | | | | | | 0.6 | 77 | 0.6 | | | | | |
| 28 | 1-Hydroxy-9,10-anthraquinone | | | | | | 0.5 | | 0.7 | | 0.6 | +0.77 | 3.70 | | | |
| 29 | 2,5-Dimethyl-*p*-benzoquinone | | | | | | 0.5 | 47 | $0.6_6$ | 47.86 | $0.5_8$ | −0.67 | 3.74 | | 0.30 | 47 |
| 30 | 2-Hydroxy-1,4-naphthoquinone | | | | | | 0.6 | 47 | $0.5_3$ | 47 | $0.5_7$ | | | | 0.40 | 47 |
| 31 | Cinnamaldehyde | 2.49 | 0.54 | | | | | | | | 0.5 | | | | | |
| 32 | 9,10-Anthraquinone | | | | | | | | 0.5 | 86 | 0.5 | +0.94 | 3.63 | | | |
| 33 | 2,5-Di-t-butyl-*p*-benzoquinone | | | | | | | | | | | +0.50 | | 0.91 | | |
| 34 | *p*-Xylo-1,4-benzoquinone | | | | | | | | | | | +0.67 | | 0.74 | | |
| 35 | Trimethyl-*p*-benzoquinone | | | | | | | | | | | +0.75 | | 0.66 | | |
| 36 | 2-Methyl-1,4-naphthoquinone | | | | | | | | | | | +0.77 | | 0.64 | | |
| 37 | Tetramethyl-*p*-benzoquinone | | | | | | | | | | | +0.84 | | 0.57 | | |
| 38 | 2-Amino-1,4-naphthoquinone | | | | | | | | | | | +0.92 | | 0.50 | | |
| 39 | 2,4,7-Trinitro-9-fluorenone | | | | 1.0 | [b] | 0.9 | [h] | 1.1 | [p] | 1.0 | | | | 0.88 | [h] |
| 40 | 1,3,5-Trinitrobenzene | | | 0.7 | 0.7 | [c] | 0.7 | [i] | 0.7 | [q] | 0.7 | | | | 0.50 | [s] |
| 41 | 1,4-Dinitrobenzene | | | | | | | | 0.7 | | 0.7 | | | | | |
| 42 | 1,3-Dinitrobenzene | | | | | | | | 0.3 | 86 | 0.3 | | | | | |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 43 | Nitrobenzene | 2.59 | 0.54 | | | | | | | | | 0.5 | | | | | | |
| 44 | 1,2-Dinitrobenzene | | | | | | | | | ± 0 | 86 | ± 0 | | | | | | |
| 45 | 2,4,6-Trinitrotoluene | | | | | | | | | 0.6 | 86 | 0.6 | | | | | | |
| 46 | 2,4,6-Trinitro-*m*-xylene | | | | | | | | | 0.4 | 86 | 0.4 | | | | | | |
| 47 | 2,4-Dinitrotoluene | | | | | | | | | 0.1 | 86 | 0.1 | | | | | | |
| 48 | Dinitrophenol | 3.16 | 0.59 | | | | | | | | | 0.6 | | | | | | |
| 49 | Chlorobenzene | 0.00 | 0.40 | | | | | | | | | 0.4 | | | | | | |
| 50 | Bromobenzene | 0.78 | 0.39 | | | | | | | | | 0.4 | | | | | | |
| 51 | Iodobenzene | 2.57 | 0.54 | | | | | | | $0.5_7$ | 47 | $0.5_7$ | | | | | | |
| 52 | Hexachlorobenzene | 3.00 | 0.58 | | | | | | | | | 0.6 | | | | | | |
| 53 | Azobenzene | 0.95 | 0.40 | | | | | | | | | 0.4 | | | | | | |
| 54 | 1,4-Dicyanobenzene | | | | | | | | | ± 0 | 86 | ± 0 | | | | | | |
| 55 | 1,3,5-Tricyanobenzene | | | | | | | | | 0.1 | 86 | 0.1 | | | | | | |
| 56 | 1,2,4,5-Tetracyanobenzene | | | | | | | | | 0.4 | 86 | 0.4 | | | | | | |
| 57 | Dibromopyromellitic dianhydride | | | | | | | | | $1.1_6$ | 47,77 | $1.1_6$ | $+0.32$ | | 1.09 | | | |
| 58 | 5-Hydroxy-1,4-naphthoquinone | | | | | | | | | 0.9 | 86 | 0.9 | $+0.52$ | 3.65 | | | | |
| 59 | Pyromellitic dianhydride | | | | | | | | | $0.8_5$ | 47.77 | $0.8_5$ | $+0.55$ | | 0.86 | | | |
| 60 | Diacetyl | 3.30 | 0.60 | | | | | | | | | 0.6 | | | | | | |
| 61 | Ethyl pyruvate | 3.23 | 0.60 | | | | | | | 0.6 | | 0.6 | | | | | | |
| 62 | Diethyl maleate | 3.23 | 0.60 | | | | | | | | | 0.6 | | | | | | |
| 63 | Diethyl fumarate | 3.18 | 0.59 | | | | | | | | | 0.6 | | | | | | |
| 64 | Dimethyl oxalate | 3.10 | 0.59 | | | | | | | | | 0.6 | | | | | | |
| 65 | Tetrachlorophthalic anhydride | | | 0.6 | | | | | | $0.5_6$ | [r] | $0.5_8$ | $-8.6_0$ | 3.71 | | | | |
| 66 | Maleic anhydride | | | | | | | | | $0.5_7$ | 47 | $0.5_7$ | $+0.8_4$ | | 0.84 | | | |
| 67 | Acetamide | 1.08 | 0.42 | | | | | | | | | $0.4_2$ | | | | | | |
| 68 | Acetylacetone | 0.08 | 0.34 | | | | | | | 0 | | $0.3_1$ | | | | | | |
| 69 | Ethyl acetoacetate | −0.15 | 0.32 | | | | | | | | | 0.3 | | | | | | |
| 70 | Ethyl acrylate | −1.00 | 0.25 | | | | | | | | | $0.2_5$ | | | | | | |
| 71 | Phthalic anhydride | | | | | | | | | | 47,77 | $0.1_5$ | $+1.31$ | | 0.1 | | | |
| 72 | Carbon tetrachloride | 3.84 | 0.65 | | | | | | | | | $0.6_5$ | | | | | | |
| 73 | Hexachlorobenzene | 3.00 | 0.58 | | | | | | | | | $0.5_8$ | | | | | | |
| 74 | Chloroform | 2.90 | 0.57 | | | | | | | | | $0.5_7$ | | | | | | |

[*] For key numbers to donors, see Table 1.

[**] According to *P. R. Hammond*, J. chem. Soc. (London) *1964*, 471, the following electron affinities are obtained for monosubstituted *p*-benzoquinones from the $\tilde{\nu}_{CT}$-values of the EDA-complexes with hexamethylbenzene using Equation (25): $NO_2$-benzoquinone: 1.45; CN-benzoquinone: 1.04; F-benzoquinone: 0.91; Cl-benzoquinone: 0.97; I-benzoquinone: 0.95; $CH_3$-benzoquinone: 0.75. These values correspond to those given in Table 6.

[a] No. 1, 2, 6, 7, 10, 11, 14, 16, 20, 21, 23, 25, 26, 47–49, 50, 51, 65–69, 71.

[b] No. 2, 3, 5–7, 10, 11, 14, 16, 21, 23, 25, 47–51, 65, 68, 69, 71, 89–98.

[c] No. 1–3, 6, 7, 10, 11, 14, 16, 20, 21, 23, 47, 49, 51, 69.

[d] No. 2, 3, 6, 7, 10, 14, 16, 21, 23, 25, 47, 49.

[e] No. 2, 3, 6, 10, 25, 47.

[f] No. 2–4, 6, 7, 10, 14, 16, 21, 23, 25, 47, 49.

[g] No. 2, 3, 6, 23, 47, 49.

[h] No. 2, 3, 5–7, 10, 11, 14, 16, 21, 23, 25, 47, 49–51, 71.

[i] No. 2, 3, 6, 7, 10, 14, 16, 21, 23, 25, 47–49, 71.

[k] No. 2, 3, 6, 7, 10, 14, 16, 21, 23, 25, 26, 47, 49, 72–77.

[l] No. 73–75, 77.

[m] No. 2, 3, 6, 10, 25, 26, 47, 85.

[n] No. 1–4, 6, 7, 10, 14, 16, 21, 23, 25, 26, 47, 49, 72–86, 99.

[o] No. 1–3, 6, 23, 47, 49, 72–74, 77, 80–82, 84, 99.

[p] No. 2–4, 6, 7, 10, 14, 16, 21, 23, 25, 47, 49, 68.

[q] No. 1–4, 6, 7, 10, 14, 16, 21, 23, 25, 47, 49, 72–75, 77, 79–84, 99.

[r] No. 2, 3, 6, 26, 47.

[s] No. 2, 3, 6, 7, 10, 11, 14, 16, 21, 23, 25, 47, 49, 51, 71.

### 6. Electron Affinities from Polarographic Half-Wave Reduction Potentials

The first step of reversible polarographic reduction of an electron acceptor or of reversible oxidation of an electron donor proceeds as follows:

(26a) $A_{solv} + e^- \rightleftharpoons A^-_{solv}$ : $E^{Red}_{1/2}$

(26b) $D_{solv} \rightleftharpoons D^+_{solv} + e^-$ : $E^{Ox}_{1/2}$

*Maccoll* [31] was the first to show that, for angularly condensed aromatic hydrocarbons, there is a relationship between the polarographic one-electron half-wave reduction potential, $E^{Red}_{1/2}$, and the energy of the highest unoccupied orbital, $E_i$.

The reduction potential, measured against a saturated calomel electrode, is given by the expression:

(27) $-E^{Red}_{1/2} = EA - \Delta F_{solv} - 5.07 = EA' - 5.07$ [eV] [32, 33]

*Peover* [34] measured $E^{Red}_{1/2}$ for a number of typical acceptors in acetonitrile and dimethylformamide as solvent. The half-wave potentials are largely independent of the solvent. Using EA' and $\overline{EA}$ (Table 6, Column 6) in Equation (27), it is possible to calculate the difference in solvation energy of the anion and of the neutral acceptor molecule $\Delta F_{solv}$ (Table 6, Column 10). Since $^{A^-}F_{solv} \gg {}^{A}F_{solv}$, the major part of $\Delta F_{solv}$ is represented by the solvation energy of the anion. $\Delta F_{solv} \approx {}^{A^-}F_{solv}$ is nearly constant [35]. For $^{A^-}F_{solv}$ = 3.66 eV, obtained as an average value from the values of $\Delta F_{solv}$ (Table 6, Column 10), we obtain:

(28) $EA = -E^{Red}_{1/2} + 1.41$

Figure 4 shows a plot of $\overline{EA}$ against $E^{Red}_{1/2}$ [34]; the agreement with Equation (28) is satisfactory. The straight line in Figure 4 corresponds to Equation (28').

(28') $EA = -1.04\ E^{Red}_{1/2} + 1.39$ [eV]

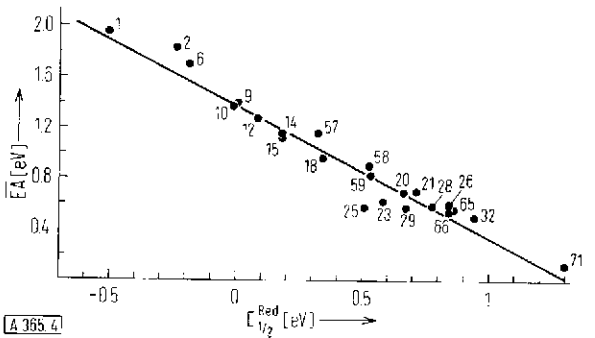



Fig. 4. Linear relationship between the electron affinity $\overline{EA}$ and the half-wave reduction potential $E^{Red}_{1/2}$ according to Equation (28'); for the numerical values and numbering of the acceptors, see Table 6.

The average value of $\Delta F_{solv}$ (= 3.66 eV) for the acceptors in Table 6 is of the correct magnitude, as indicated by comparison with the solvation energies the anions of aromatic hydrocarbons (Table 8, Columns 8 and 9). The values of $\Delta F_{solv}$ for the acceptors (Table 6) are relatively constant; this is probably due to the fact that the negative charge of the $A^-$ ion is located in certain parts of the molecule (*e.g.* $-C{=}O$, $-C{=}N$, $-NO_2$ groups), whereas in the anions of polycyclic hydrocarbons, the negative charge is dispersed over larger portions of the molecule. Therefore, in these cases $^{A^-}F_{solv}$ is not constant.

Since Equation (28) is fulfilled satisfactorily, Equation (28') can be used to estimate the electron affinities of acceptors for which only $E^{Red}_{1/2}$ has been measured. Electron affinities calculated in this manner from Equation (28') are listed for a few acceptors in Column 11 of Table 6.

According to Equations (27) and (8), there must be some relationship between $\tilde{\nu}_{CT}$ and $E^{Red}_{1/2}$ [35] when $\tilde{\nu}_{CT}$ is based on EDA complexes of different acceptors with one and the same donor:

(29) $E^{Red}_{1/2} = \tilde{\nu}_{CT} - (I + E - \Delta F_{solv} - 5.07)$

If the ionization energies of pyrene, hexamethylbenzene, and tetramethyl-*p*-phenylenediamine are taken as 7.8, 8.0, and 6.7 eV, respectively, and E = −4.3 eV is used for the Coulomb energy of the EDA complexes of the acceptors listed in Table 6 (for complexes with tetramethyl-*p*-phenylenediamine E = −3.9 eV), the following linear relationships result for the different acceptors, when $\Delta F_{solv}$ in Equation (29) is assumed to be −3.66 eV:

(30) Pyrene: $E^{Red}_{1/2} = \tilde{\nu}_{CT} - 2.09$ (2.13) [eV]

Hexamethylbenzene: $E^{Red}_{1/2} = \tilde{\nu}_{CT} - 2.29$ (2.40) [eV]

Tetramethyl-*p*-phenylenediamine: $E^{Red}_{1/2} = \tilde{\nu}_{CT} - 1.35$ ($1.36_5$) [eV]

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[31] *A. Maccoll*, Nature (London) *163*, 178 (1949); *L. E. Lyons*, ibid. *166*, 193 (1950). In addition: *A. Pullman*, *B. Pullman*, and *G. Berthier*, Bull. Soc. chim. France 591 (1950); *G. J. Hoijtink*, Recueil Trav. chim. Pays-Bas *74*, 1525 (1955); *G. J. Hoijtink*, *E. de Boer*, *P. H. van der Meij*, and *W. P. Weijland*, ibid. *75*, 487 (1956); *P. Balk*, *S. de Bruyn*, and *G. J. Hoijtink*, ibid. *76*, 860 (1957); *P. H. Given*, Nature (London) *181*, 1001 (1958); *P. H. Given* and *M. E. Peover*: Advances in Polarography. Pergamon Press, London 1960, p. 948; *M. Batley* and *L. E. Lyons*, Nature (London) *196*, 573 (1962); *M. E. Peover*, J. chem. Soc. (London) *1962*, 4540.

[32] *E. A. Matsen*, J. chem. Physics *24*, 602 (1956); *R. M. Hedges* and *F. A. Matsen*, ibid. *28*, 950 (1958); *G. J. Hoijtink* and *J. van Schooten*, Recueil Trav. chim. Pays-Bas *71*, 1089 (1952); *A. Laintinen* and *S. Warzonek*, J. Amer. chem. Soc. *64*, 1765 (1942).

[33] The electrochemical process:

$A_{solv} + Cl^-_{solv} + Hg_{liq} \rightarrow A^-_{solv} + (HgCl)_{solv}$ : $(E^{Red}_{1/2})$

can be separated into the following steps

$A_{gas} + e^- \rightarrow A^-_{gas}$ : $(-EA)$

$A_{solv} : A^-_{gas} \rightarrow A_{gas} + A^-_{solv}$ : $(\Delta F_{solv} = {}^{A}F_{solv} - {}^{A^-}F_{solv})$

$Hg_{liq} + Cl^-_{solv} \rightarrow (HgCl)_{solv} + e^-$ (in Hg)

: $(\Delta F_{Hg_2Cl_2} = \varepsilon_{Hg_2Cl_2} = 0.53$ eV)

$e^-$ (in Hg) $\rightarrow Hg_{liq} + e^-$ : (4.54 eV)

According to Equation (26a), negative values of $E^{Red}_{1/2}$ should be used for strong acceptors, and positive values for weak acceptors (the sign is sometimes given in the opposite sense). $\Delta F_{solv}$ is negative, EA is positive by convention. It is assumed that electron addition at a dropping mercury electrode according to Equation (26a) is sufficiently fast and reversible so that overvoltage phenomena and secondary reactions can be neglected. Moreover, no proton addition should take place (solvents devoid of proton activity, such as acetonitrile, dimethylformamide, or dioxane, must be used).

[34] *M. E. Peover*, Nature (London) *191*, 702 (1961); Trans. Faraday Soc. *58*, 656, 2370 (1962).

[35] *M. E. Peover*, Trans. Faraday Soc. *58*, 1656 (1962).

The numerical values refer to straight lines plotted in Figure 5 which best fit the experimental $E_{1/2}^{Red}$ and $\tilde{\nu}_{CT}$ values. Because of the uncertainty in E and the variability of $\Delta F_{solv}$, deviations are not of great importance.

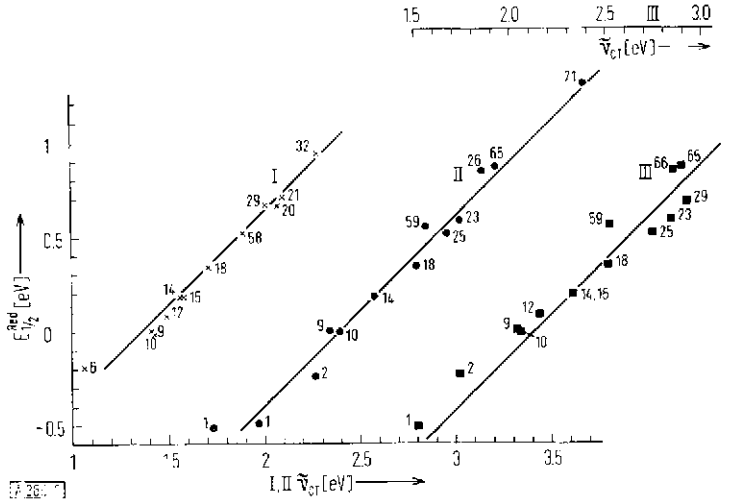



Fig. 5. Correlation between the half-wave reduction potential of the acceptor $E_{1/2}^{Red}$ [34,35] and the electron transfer energy $\tilde{\nu}_{CT}$ for donor acceptor complexes, according to Equations (29) and (30). Donors: tetramethyl-*p*-phenylenediamine (I), hexamethylbenzene (II), and pyrene (III). The numbers on the experimental points refer to acceptor numbers given in Table 6.

## 7. Electron Affinities from Polarographic Half-Wave Oxidation Potentials

According to Equation (26b), polarographic oxidation of aromatic unsubstituted and substituted hydrocarbons may be described in terms of a relationship corresponding to Equation (28) in which the first polarographic half-wave oxidation potential is a function of the ionization energy of the hydrocarbon. *Pysh* and *Yang* [36] found empirically:

(31) $I = 1.473\ E_{1/2}^{Ox} + 5.82$

From Equations (31) and (8), using E = −4.3 eV, we obtain:

(32) $EA = -\tilde{\nu}_{CT} + 1.473\ E_{1/2}^{Ox} + 1.52$

The values of $E_{1/2}^{Ox}$ [36] and $\tilde{\nu}_{CT}$ for EDA complexes between the donors listed in Column 12a and the acceptors listed in Column 1 of Table 6 have been determined experimentally. Thus, for the donors in Column 12a, the electron affinities can be calculated and averaged using Equation (32) [see Column 12]. However, the electron affinities obtained from Equation (32) are somewhat low compared to those obtained and averaged using Equations (23′) and (25) [see Table 6, Column 8].

## 8. Correlation between Electron Affinity and Electron-Transfer Energy

It follows from Equation (8) that, for complexes of one and the same donor with various acceptors, an approximately linear relationship must exist between the electron-transfer energy $\tilde{\nu}_{CT}$ and the electron affinity EA of the acceptor. Applying the ionization energies and values of E given above for pyrene, hexamethylbenzene, and tetramethyl-*p*-phenylenediamine, Equation (8) gives the following linear relationships:

(33) Pyrene: $\tilde{\nu}_{CT} = -EA + 3.51\ (3.42)$ [eV]

Hexamethylbenzene: $\tilde{\nu}_{CT} = -EA + 3.7\ (3.75)$ [eV]

Tetramethyl-*p*-phenylenediamine:
$\tilde{\nu}_{CT} = -EA + 2.8\ (2.78)$ [eV]

The straigbt lines in Figure 6 refer to the numerical values given in parentheses. In view of the relatively large inaccuracy in the EA values, the agreement between Equations (33) and (8) is satisfactory.

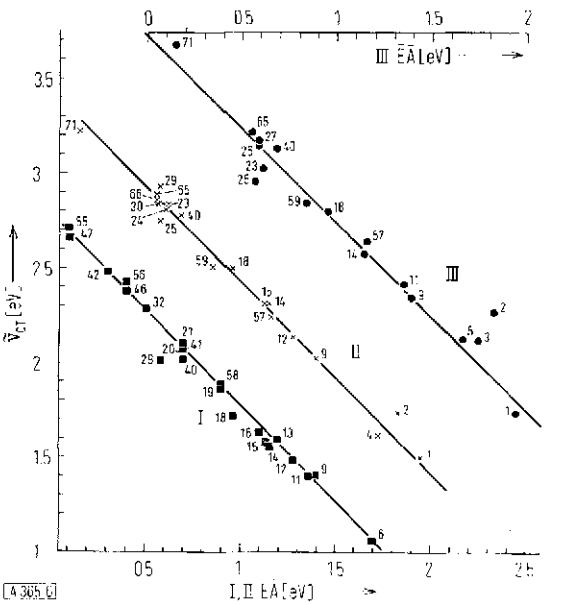



Fig. 6. Electron-transfer energy $\tilde{\nu}_{CT}$ of EDA complexes as a function of the electron affinities $\overline{EA}$ of various acceptors, according to Equation (33). Donors: tetramethyl-*p*-phenylenediamine (I), pyrene (II), and hexamethylbenzene (III). For the $\overline{EA}$ values and acceptor numbering, see Table 6.

## 9. Electron Affinity and Chemical Constitution

The relatively great inaccuracy in the electron-affinity values precludes discussion of the more refined effects induced by the structure of the compounds involved.

The strongest acceptors are 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, tetracyanoethylene, 2,6-dinitrobenzoquinone, tetracyano-*p*-benzoquinone, 2,3-dicyanobenzoquinone, and bis(dicyanomethylene)quinones. The electron affinities of unsubstituted quinones lie in the following order: 9,10-anthraquinone < 1,4-naphthoquinone ≈ 9,10-phenanthrenequinone ≈ 1,2-naphthoquinone ≈ *p*-benzoquinone < *o*-benzoquinone < 1,8-diphenoquinone.

Alkyl substituents tend to reduce the electron affinity, the effect becoming more pronounced as their number increases. Electrophilic (halogeno, CN, $NO_2$) groups

[36] *E. S. Pysh* and *N. C. Yang*, J. Amer. chem. Soc. *85*, 2124 (1963).

tend to augment the electron affinity of a compound, this effect increasing with the number of such substituents. CN and $NO_2$ tend to increase the electron affinity to a larger extent than do halogens. Cl, Br, and I do not differ appreciably in this respect. The nitroaromatics are relatively good acceptors: 2,4,7-trinitrofluorenone > 1,3,5-trinitrobenzene ≈ 1,4-dinitrobenzene > nitrobenzene > 1,3-dinitrobenzene > 1,2-dinitrobenzene. With the exception of 1,2-dinitrobenzene, the electron affinity increases with increasing number of nitro groups. Unexpectedly, the electron affinity of 1,3-dinitrobenzene is less than that of nitrobenzene. (Since the electron affinity of these two nitro compounds has been determined only once, and by two different methods, this difference may be due to the difference in the methods used.) The fact that the electron affinity of 1,2-dinitrobenzene (in contrast to that of 1,3- and 1,4-dinitrobenzene) is practically zero is consistent with steric inhibition of the mesomeric stabilization of the 1,2-dinitrobenzene anion, *i.e.*, both nitro groups cannot become coplanar with the benzene ring. Substitution by methyl generally decreases the electron affinity: 1,3,5-trinitrobenzene > 1,3,5-trinitrotoluene > 1,3,5-trinitro-*m*-xylene; also, 1,3-dinitrobenzene > 2,4-dinitrotoluene. The polycyanobenzenes are definitely poorer acceptors than the corresponding nitrobenzenes. The electron affinity of polycyanobenzenes increases with increasing number of cyano groups. Simply substituted halogenobenzenes are relatively good acceptors. An increase in the number of halogen substituents on the benzene ring does not seem to exert as strong an influence as does substitution by $NO_2$. This is exemplified by hexachlorobenzene.

Molecules with two adjacent electrophilic carbonyl groups, *e.g.* diacetyl, ethyl pyruvate, and dimethyl oxaloacetate, are relatively good electron acceptors (comparable to trinitrobenzene). The electron affinity of these compounds and that of the electrophilic -CO-C-C-CO- group, *e.g.*, in diethyl maleate and diethyl fumarate, are nearly equal.

Compounds with β-dicarbonyl groups have lower electron affinities (acetylacetone, ethyl acetoacetate).

Phthalic anhydride is practically devoid of electron-acceptor properties. It acquires such properties by electrophilic substitution (tetrachlorophthalic anhydride).

The relatively high electron affinity of $CCl_4$ is noteworthy. This is consistent with the fact that, in the presence of $CCl_4$, donors such as hexamethylbenzene show a characteristic absorption band indicative of electron-donor/electron-acceptor interaction [36a]. Carbon tetrachloride and chloroform are σ-acceptors which, despite their high electron affinity, have an EDA interaction energy that seems to be lower than that of π-acceptors with comparable electron affinities [36a].

[36a] *D. P. Stevenson* and *G. M. Coppinger*, J. Amer. chem. Soc. *84*, 149 (1962); *M. Templeton*, J. chem. Physics *37*, 161 (1962); *F. Dörr* and *G. Buttgereit*, Ber. Bunsenges. physik. Chem. *67*, 867 (1963); *R. Anderson* and *J. M. Prausnitz*, J. chem. Physics *39*, 1225 (1963).

## II. Aromatic Hydrocarbons as Electron Acceptors

### 1. Quantum-Mechanical Calculation of Electron Affinity

According to *Pople* and *Brickstock* [37], the energy of the highest occupied and that of the lowest unoccupied orbital of an aromatic hydrocarbon are:

$$E_i = -I = \alpha' + F \qquad (34a)$$

$$E_j = -EA = \alpha' - F \qquad (34b)$$

F [38] can be calculated by the semiempirical ASMOSC [42] method. The electron affinities calculated by *Pople* and *Brickstock* [37] and by *Hedges* and *Matsen* [39] from Equation (34b) are listed in Columns 3 and 4 of Table 7. $\alpha'$ was normalized by *Hedges* and *Matsen* to the ionization energy of naphthalene (8.12 eV) to $\alpha' = -3.87$ eV.

These calculations [37, 39] were carried out by *Hoyland* and *Goodman* [40] with even fewer assumptions; they also took into account the changes in electron density following removal or capture of an electron, as well as the effect of the σ-electron energy. The electron affinities calculated by these workers [40] are listed in Column 5 of Table 6.

The ω-approximation in the simplified treatment proposed by *Ehrenson* [22] gives an expression for the electron affinity corresponding to Equation (13):

$$-E_j = EA = -\alpha_0 - (f_{II} - \frac{n+1}{n}\omega)\beta = -\alpha_0 - x\beta \qquad (34')$$

As already mentioned, the ω-approximation [Equation (13)] gives satisfactory values for the ionization energies of aromatic hydrocarbons when $\alpha = -9.878$ eV, $\beta = -2.11$ eV, and $\omega = 1.4$. On the other hand, the electron affinities obtained from Equation (34) with $\omega = 1.4$ are much too high. To obtain good agreement with the electron affinities calculated from Equation (34') by *Hedges* and *Matsen* [39], *Poples* [37], and *Hoyland* and *Goodman* [40], as well as with the experimental values of *Wentworth* and *Becker* [3], the very high value of

[37] *J. A. Pople*, Trans. Faraday Soc. *49*, 375 (1953); *A. Brickstock* and *J. A. Pople*, ibid. *50*, 901 (1954); *J. A. Pople*, J. physic. Chem. *61*, 6 (1957); *C. J. Koothaan*, Rev. mod. Physics *23*, 61 (1951).

[38] $F = 2\sum_{\mu<\nu} \chi_{N\mu}\cdot\chi_{N\nu}(\beta_{\mu\nu} - \gamma_{\mu\nu}\cdot\sum_{i=1}^{N}\chi_{i\mu}\cdot\chi_{i\nu})$

$\gamma_{\mu\nu}$ = Coulomb interaction between one electron at atom μ and one electron at atom ν. $\beta_{\mu\nu}$ = resonance integral for two adjacent atoms μ and ν. N = number of occupied orbitals in the aromatic hydrocarbon. $\chi_{i\mu}$ and $\chi_{i\nu}$ = Hückel coefficients of the μ-th and ν-th atomic orbitals in the i-th molecular orbital. The x-values can be calculated with good approximation using the simple MO theory.

[39] *R. M. Hedges* and *F. A. Matsen*, J. chem. Physics *28*, 950 (1958). See also: *A. Streitwieser* and *P. M. Nair*, Tetrahedron *5*, 149 (1959); *A. Streitwieser*, J. Amer. chem. Soc. *82*, 4123 (1960); *W. F. Wolf*, Abstracts J. Amer. chem. Soc. Meeting, New York 1960.

[40] *J. R. Hoyland* and *L. Goodman*, J. chem. Physics *36*, 12, 21 (1962).

$\omega = 3.77$ must be used in Equation (34') [43,44]; similarly, a value of $\omega = 3.73$ must be used for phenanthrene, benzo[*c*]phenanthrene, and triphenylene [44]. No theoretical explanation is available for the fact that the calculations of I using Equation (13) and of EA using Equation (34') require different values of $\omega$.

In Column 6 of Table 7, a list is given of the electron affinities calculated by *Ehrenson* [22] according to the $\omega$-method, using a $\omega = 3.5$. Column 2 contains the electron affinities obtained for a few aromatic hydrocarbons by *Wentworth* and *Becker* [3] using the electron absorption coefficients determined experimentally by *Lovelock* [1].

Table 7. Electron affinities [eV] derived for aromatic hydrocarbons by various methods.

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| No. [*] | Expt. [3] | Theor. [39] | Theor. [37] | Theor. [40] | Theor. [41] |
| 1 | | −1.63 | −1.40 | −1.40 | −1.590 |
| 2 | | −0.83 | −0.14 | −0.20 | −0.246 |
| 3 | 0.42 | 0.49 | 0.64 | 0.61 | 0.147 |
| 4 | | 0.82 | | | |
| 5 | | 1.01 | | | 1.035 |
| 6 | 0.20 | | −0.06 | 0.25 | 0.014 |
| 7 | 0.46 | 0.62 | | | |
| 10 | 0.14 | −0.28 | | | −0.033 |
| 11 | | | | | 0.446 |
| 14 | 0.33 | 0.23 | | | 0.313 |
| 16 | | 0.65 | | | 0.501 |
| 17 | | 0.75 | | | |
| 19 | 0.33 | −0.14 | | | |
| 20 | | 0.75 | | | 0.463 |
| 21 | | | | | 0.442 |
| 22 | | 0.63 | | | |
| 23 | | 0.80 | | | 0.727 |
| 24 | | 0.50 | | | 0.573 |
| 25 | | 0.18 | | | 0.385 |
| 26 | | −0.78 | −0.37 | | −0.290 |
| 27 | | −0.51 | | | |
| 28 | | −0.41 | | | |
| 29 | | −0.35 | | | |
| 47 | 0.39 | 0.68 | | 0.55 | 0.417 |
| 48 | | | | | 0.410 |
| 49 | | | | | 0.676 |
| 50 | | | | | 0.683 |
| 51 | | | | | 0.590 |
| 65 | | | | 0.92 | 0.052 |

[*] For key to hydrocarbon numbers, see Table 1.


[41] *S. E. Ehrenson*, J. physic. Chem. *66*, 706, 712 (1961).

[42] Antisymmetrized Molecular Orbital Self-Consistent.

[43] *S. E. Ehrenson* [41] uses $\omega = 3.5$.

[44] *D. R. Scott* and *R. S. Becker*, J. physic. Chem. *66*, 2713 (1962).


## 2. Semiempirical Methods for Determining Electron Affinities

### a) *Electron Affinity and the Longest-Wavelength Absorption Band of the Donor*

It follows from (34) that

$$(35) \qquad (EA + I)/2 = \alpha'$$

On the basis of the electron affinities determined experimentally for a few aromatic hydrocarbons (Table 7, Column 2) and the experimental values for the first ionization energies $I_{exp}$ (Table 8, Column 4), one obtains in agreement with *Becker* and *Wentworth* [28] an average value of 8.14 eV for the sum (I + EA). From Equations (21) and (35), we obtain for $\alpha' = 4.07$:

$$(36) \qquad EA = 3.03 - 0.701\ \tilde{\nu}_0$$

The electron affinities calculated from $\tilde{\nu}_0$ (Table 8, Column 6) using Equation (36) are given in Column 2 of Table 8.

The differences between the electron affinities calculated by the ASMOSC method (Table 6, Columns 3, 4, 5, and 6), those obtained from $\tilde{\nu}_0$ (Table 8, Column 2) using Equation (36), and the few experimental EA values (Table 7, Column 2) may be considerable. The $\overline{EA}$ values obtained by averaging all EA values are given in Column 3 of Table 8.

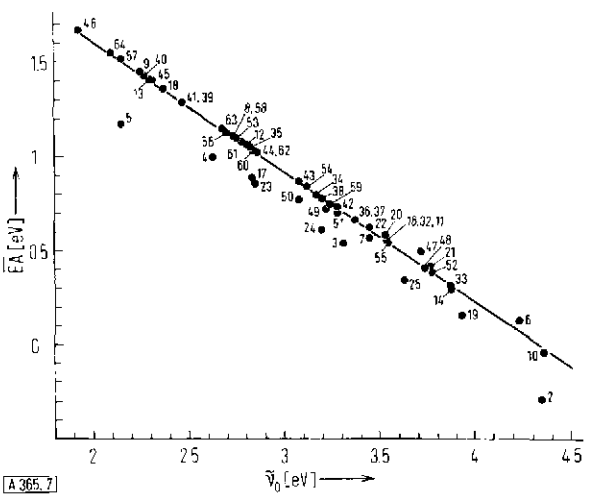



Fig. 7. Averaged electron affinities of aromatic hydrocarbons (calculated by different methods) as a function of the first excitation energy $\tilde{\nu}_0$. The straight line corresponds to Equation (37); for numerical data and key numbers to hydrocarbons, see Tables 8 and 7, respectively.

Their absolute accuracy is never better than ± 0.2 eV. Figure 7 shows a plot of these electron affinities against $\tilde{\nu}_0$ for aromatic hydrocarbons. The linear relationship

$$(37) \qquad \overline{EA} = 2.991 - 0.700\ \tilde{\nu}_0$$

obtained in this manner is in good agreement with Equation (36), which was derived directly from experimental data, and with the expression of *Becker* and *Wentworth* [28]:

$$(38) \qquad EA = 2.92 - 0.762\ \tilde{\nu}_{00}$$

It is noteworthy that the linear functions (21) and (36), which agree best with the experimental values for ionization energies and electron affinities, have the same gradient.

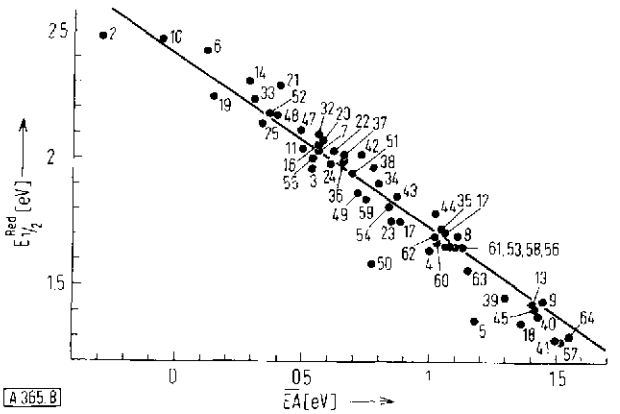



Fig. 8. Half-wave reduction potentials $E^{Red}_{1/2}$ [47] of aromatic hydrocarbons as a function of averaged electron affinities $\overline{EA}$ calculated by different methods. The solid straight line corresponds to Equation (39). For numerical data and key numbers to hydrocarbons, see Tables 8 and 1, respectively.

b) *Electron Affinity, Half-Wave Reduction Potential and Solvation Energy*

Figure 8 shows a plot of $E^{Red}_{1/2}$ (Table 8, Column 7 [45]) obtained from Equation (27) *vs.* $\overline{EA}$ (Table 8, Column 3). The $E^{Red}_{1/2}$ and EA values fit Equation (39):

(39) $$E^{Red}_{1/2} = 2.416 - 0.692\ \overline{EA}$$

It follows from Equations (39) and (27) that there is a functional relationship between $\Delta F_{solv}$ and EA. If we set

(40) $$\Delta F_{solv} = -\eta_{solv} + \delta \cdot EA$$

then from Equations (27) and (40) we obtain:

(41) $$-E^{Red}_{1/2} = EA\,(1-\delta) + \eta_{solv} - 5.07\ [eV]$$

and, by comparison with Equation (39):

$$\delta = 0.308 \text{ and } \eta_{solv} = 2.654$$

Hence:

(42) $$\Delta F_{solv} = 0.308\ EA - 2.654$$

Equation (42) can be checked by using Equation (27) to calculate $\Delta F_{solv}$ ($R^{Red}_{1/2}$ from Column 7, $\overline{EA}$ from Column 3 of Table 8).

(43) $$\Delta F_{solv} = EA - 5.07 + E^{Red}_{1/2} = EA - EA'$$

The values of $\Delta F_{solv}$ calculated using Equation (43) are listed in Column 8 of Table 8, and give rise to the following linear relationship:

(44) $$\Delta F_{solv} = 0.2714\ \overline{EA} - 2.624\ [eV]$$

which is in good agreement with Equation (42). The $\Delta F_{solv}$ values derived from Equation (44) are given in Table 8, Column 9.

The decrease in solvation energy with increasing electron affinity of aromatic hydrocarbons is possibly associated with the distribution of the negative charge over the entire molecule. The solvation energy decreases, and the increase in electron repulsion energy on transition from the neutral molecule to the anion also becomes less (*i.e.*, the electron affinity of the aromatics increases) as the range of dispersion of the negative charge over the aromatic anion increases. Also the interaction energy with the solvent molecules decreases with increasing radius of the aromatic anion.

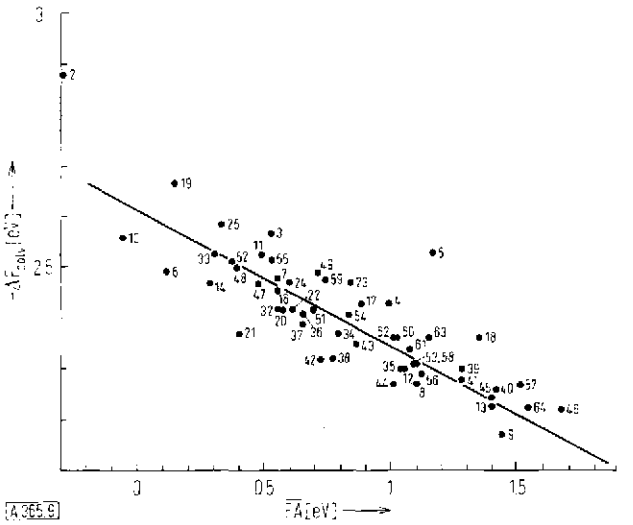



Fig. 9. Solvation energy $\Delta F_{solv}$ of aromatic hydrocarbons as a function of the electron affinity $\overline{EA}$ according to Equation (44); for numerical data and the key numbers of the aromatic hydrocarbons, see Tables 8 and 1, respectively.

Extrapolation of Equations (21) and (37) to $\tilde{\nu}_0 \rightarrow 0$ is of questionable validity because these equations have been shown to be valid only within the rather narrow range from $\tilde{\nu}_0 \approx 2.5$ to 4 eV. Extrapolation to $\tilde{\nu}_0 \rightarrow 0$ would assume I and EA to be linear functions of $\tilde{\nu}_0$ [Equations (21) and (37)] even for very low values of $\tilde{\nu}_0$; this, however, has never been proved. Though the difference (I EA) = (1.4 $\tilde{\nu}_0$ + 2.12 [eV]) [Equations (21) and (37)] decreases with decrease in the excitation energy of aromatic hydrocarbons, Equations (21) and (37) give different values, *viz.* $I_{\tilde{\nu}_0=0} = 5.11$ eV and $EA_{\tilde{\nu}_0=0} = 2.99$ eV. However, according to Hückel's theory, $\tilde{\nu}_0$ should tend to zero and I should tend to EA for infinitely large, conjugated aromatic ring systems, *e.g.* in graphite. The work function of graphite is 4.39 eV [46].

For hydrocarbons, we should expect $I_{\tilde{\nu}_0 \rightarrow 0} \neq EA$ since the electron repulsion energy of the hydrocarbon anion is greater than that of the hydrocarbon cation. Accordingly, $I_{\tilde{\nu}_0 \rightarrow 0} > EA_{\tilde{\nu}_0 \rightarrow 0}$. Finally, it should be borne in mind that Equations (21) and (37) refer to two-dimensional aromatic ring systems in the gaseous state.

### 3. Electron Affinity and Chemical Constitution [*]

a) The electron affinity increases with the number of rings fused together in a line, whereas the ionization energy decreases correspondingly (see Table 1, Nos. 1–5, 6–9, 10–13, and 14–18).

[45] *I. Bergman*, Trans. Faraday Soc. *50*, 829 (1954); *G. J. Hoijtink*, Recueil Trav. chim. Pays-Bas *73*, 355 (1954); *74*, 1525 (1955), where references to previous publications are given. The $E^{Red}_{1/2}$-values of *Bergman* must be increased by 0.5 eV in order to obtain the $E^{Red}_{1/2}$-values measured in 75% dioxane against a saturated $Hg_2Cl_2$-electrode. The $E^{Red}_{1/2}$-values measured in 75% and 96% dioxane show practically no differences.

[46] *A. Braun* and *G. Busch*, Helv. physica Acta *20*, 33 (1947).

[*] The fact that aromatic hydrocarbons are electron donors as well as electron acceptors enables them to undergo intermolecular EDA-interaction. *Wentworth* and *Chen* proved this using the spectral shift of the absorption spectra of a few polycyclic hydrocarbons on addition of hexamethylbenzene in heptane solution: J. physic. Chem. *67*, 2201 (1963).

Table 8. Energy data for aromatic hydrocarbons.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Hydrocarbon no. [*] | EA Eq. (36) | $\overline{EA}$ | $I_{exp}$ | I Eq. (21) | $\tilde{\nu}_0$ [32] | $E^{Red}_{1/2}$ [45] | $-\Delta F_{solv}$ Eq. (43) | $-\Delta F_{solv}$ Eq. (44) |
| 1 | | −1.5 | 9.24 [47] | | | | | |
| 2 | −0.01 | −0.3 | 8.26 [48]<br>8.12 [47] | 8.16 | 4.35 | 2.48 | 2.89 | 2.70 |
| 3 | 0.71 | 0.5 | 7.3 [47]<br>7.55 [48]<br>7.66 [28]<br>7.43 [50] | 7.43 | 3.31 | 1.96 | 2.61 | 2.49 |
| 4 | 1.18 | 1.0 | 7.00 [49]<br>6.96 [50] | 6.95 | 2.63 | 1.635 | 2.43 | 2.35 |
| 5 | 1.52 | 1.2 | | 6.62 | 2.15 | 1.36 | 2.51 | 2.30 |
| 6 | 0.05 | 0.1 | 8.06 [28]<br>8.03 [48]<br>8.10 [49]<br>8.03 [50] | 7.6 | 4.24 | 2.435 | 2.53 | 2.29 |
| 7 | 0.61 | $0.5_6$ | 7.6 [49]<br>7.57 [47] | 7.53 | 3.45 | 2.03 | 2.48 | 2.47 |
| 8 | 1.11 | 1.1 | | 7.03 | 2.74 | 1.69 | 2.28 | 2.32 |
| 9 | 1.45 | $1.4_5$ | | 6.69 | 2.25 | 1.445 | 2.17 | 2.23 |
| 10 | −0.02 | 0.05 | 8.0 [49]<br>8.1 [50] | 8.17 | 4.36 | 2.47 | 2.65 | 2.64 |
| 11 | 0.54 | 0.5 | 7.55 [47] | 7.6 | 3.55 | 2.04 | 2.53 | 2.49 |
| 12 | 1.06 | 1.1 | | 7.08 | 2.81 | 1.705 | 2.30 | 2.34 |
| 13 | 1.41 | 1.4 | | 6.72 | 2.30 | 1.43 | 2.23 | 2.24 |
| 14 | 0.31 | 0.3 | 7.8 [49]<br>7.81 [50] | 7.83 | 3.88 | 2.305 | 2.47 | 2.55 |
| 15 | | | 7.95 [49] | | | | | |
| 16 | 0.55 | $0.5_6$ | | 7.58 | 3.53 | 2.045 | 2.46 | 2.47 |
| 17 | 1.04 | 0.9 | | 7.09 | 2.83 | 1.75 | 2.43 | 2.38 |
| 18 | 1.36 | $1.3_6$ | | 6.77 | 2.37 | 1.35 | 2.36 | 2.26 |
| 19 | 0.27 | $0.1_5$ | | 7.86 | 3.93 | 2.245 | 2.67 | 2.58 |
| 20 | 0.55 | 0.6 | | 7.58 | 3.53 | 2.07 | 2.42 | 2.47 |
| 21 | 0.38 | 0.4 | 7.8 [49] | 7.75 | 3.77 | 2.29 | 2.37 | 2.51 |
| 22 | 0.61 | 0.6 | | 7.53 | 3.45 | 2.025 | 2.42 | 2.46 |
| 23 | 1.03 | $0.8_5$ | 7.15 [49]<br>7.07 [50] | 7.11 | 2.85 | 1.75 | 2.47 | 2.39 |
| 24 | 0.78 | 0.6 | | 7.35 | 3.20 | 1.985 | 2.47 | 2.46 |
| 25 | 0.48 | 0.3 | 7.6 [49]<br>7.63 [50] | 7.65 | 3.63 | 2.14 | 2.59 | 2.53 |
| 26 | | −0.5 | 8.4 [49] | | | | | |
| 30 | 0.43 | 0.4 | | | 3.71 | 2.15 | 2.45 | 2.52 |
| 31 | 0.52 | 0.5 | | | 3.59 | 2.07 | 2.07 | 2.49 |
| 32 | 0.56 | $0.5_6$ | | 7.58 | 3.53 | 2.09 | 2.42 | 2.47 |
| 33 | 0.31 | 0.3 | | 7.82 | 3.87 | 2.23 | 2.53 | 2.54 |
| 34 | 0.80 | 0.8 | | 7.33 | 3.17 | 1.90 | 2.37 | 2.41 |
| 35 | 1.05 | $1.0_5$ | | 7.09 | 2.82 | 1.72 | 2.30 | 2.34 |
| 36 | 0.66 | $0.6_6$ | | 7.47 | 3.37 | 1.995 | 2.41 | 2.45 |
| 37 | 0.66 | $0.6_6$ | | 7.47 | 3.37 | 2.015 | 2.39 | 2.45 |
| 38 | 0.78 | 0.8 | | 7.35 | 3.20 | 1.965 | 2.32 | 2.41 |
| 39 | 1.29 | 1.3 | | 6.84 | 2.47 | 1.465 | 2.30 | 2.27 |
| 40 | 1.43 | 1.4 | | 6.70 | 2.27 | 1.38 | 2.26 | 2.24 |
| 41 | 1.29 | 1.3 | | 6.84 | 2.47 | 1.50 | 2.28 | 2.27 |

b) A benzene ring fused on at the 1,2-positions *i.e.* onto the [*a*] side of a linear system, *e.g.* in Table 1, on passing, from No. 2 to No. 6 and from No. 3 to No. 7, from No. 4 to No. 8, and from No. 5 to No. 9, affects the electron affinity and ionization energy only slightly. A benzene ring fused on at the 3,4-positions, *i.e.* the [*c*] side, (*e.g.* on going from No. 7 to No. 11, from 8 to 12, or from 9 to 13 in Table 1) [*], at the 5,6-positions (from No. 6 to 14, from 7 to 16, from 8 to 17,

[*] With the exception of triphenylene (No. 10, Table 1), which has an extraordinarily small EA.


[47] *H. Watanabe*, J. chem. Physics *22*, 1565 (1954); *26*, 542 (1957).

[48] *M. E. Wacks* and *V. H. Dibeler*, J. chem. Physics *31*, 1557 (1959).

[49] According to Equation (7); see *G. Briegleb* and *J. Czekalla*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *63*, 6 (1959); Angew. Chem. *72*, 401 (1960).

Table 8 (continued).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Hydrocarbon no. [*] | EA Eq. (36) | $\overline{EA}$ | $I_{exp}$ | I Eq. (21) | $\tilde{\nu}_0$ [32] | $E^{Red}_{1/2}$ [45] | $-\Delta F_{solv}$ Eq. (43) | $-\Delta F_{solv}$ Eq. (44) |
| 42 | 0.73 | 0.7 | | 7.41 | 3.28 | 2.015 | 2.32 | 2.43 |
| 43 | 0.87 | 0.9 | | 7.27 | 3.08 | 1.85 | 2.35 | 2.39 |
| 44 | 1.02 | 1.0 | | 7.11 | 2.86 | 1.78 | 2.27 | 2.35 |
| 45 | 1.41 | 1.4 | | 6.73 | 2.31 | 1.415 | 2.24 | 2.24 |
| 46 | 1.67 | 1.7 | | 6.46 | 1.93 | 1.175 | 2.22 | 2.17 |
| 47 | 0.42 | 0.5 | 7.72 [48]<br>7.55 [49]<br>7.53 [50] | 7.72 | 3.72 | 2.11 | 2.47 | 2.49 |
| 48 | 0.40 | 0.4 | | 7.73 | 3.74 | 2.17 | 2.50 | 2.52 |
| 49 | 0.77 | 0.7 | | 7.37 | 3.22 | 1.86 | 2.49 | 2.43 |
| 50 | 0.87 | 0.8 | | 7.27 | 3.08 | 1.58 | (2.72) | 2.42 |
| 51 | 0.82 | 0.7 | | 7.41 | 3.23 | 1.945 | 2.42 | 2.43 |
| 52 | 0.38 | 0.4 | | 7.75 | 3.77 | 2.185 | 2.52 | 2.52 |
| 53 | 1.10 | 1.1 | | 7.04 | 2.75 | 1.65 | 2.31 | 2.33 |
| 54 | 0.84 | 0.8 | | 7.30 | 3.12 | 1.815 | 2.41 | 2.40 |
| 55 | 0.54 | 0.5 | | 7.60 | 3.55 | 2.005 | 2.52 | 2.48 |
| 56 | 1.13 | 1.1 | | 7.00 | 2.70 | 1.65 | 2.29 | 2.32 |
| 57 | 1.52 | 1.5 | | 6.62 | 2.15 | 1.28 | 2.27 | 2.21 |
| 58 | 1.11 | 1.1 | | 7.03 | 2.74 | 1.65 | 2.31 | 2.32 |
| 59 | 0.75 | 0.7 | | 7.38 | 3.24 | 1.84 | 2.48 | 2.42 |
| 60 | 1.03 | 1.0 | | 7.10 | 2.84 | 1.675 | 2.36 | 2.34 |
| 61 | 1.08 | 1.1 | | 7.06 | 2.78 | 1.65 | 2.34 | 2.33 |
| 62 | 1.02 | 1.0 | | 7.11 | 2.86 | 1.69 | 2.36 | 2.35 |
| 63 | 1.15 | $1.1_5$ | | 6.99 | 2.68 | 1.56 | 2.36 | 2.31 |
| 64 | 1.55 | $1.5_5$ | | 6.58 | 2.10 | 1.30 | 2.22 | 2.20 |
| 65 | | 0.5 | | | | | | |

[*] For key to hydrocarbon numbers, see Table 1.

and from 9 to 12), at the 7,8-positions (from No. 6 to 19, from 7 to 20, and from 11 to 31) has essentially no effect on the electron affinity and ionization energy. Accordingly, the EA and I values for tribenz[*a*,*c*,*g*]anthracene (No. 31) and dibenzo[*a*,*g*]chrysene (No. 32) compared to dibenz[*a*,*g*]anthracene (No. 20) and benzo[a]chrysene (No. 30), respectively, are practically identical.

c) Beginning with pyrene (Table 1, No. 47), an additional benzene or naphthalene ring fused on at the 1,2- and/or 6,7-positions (*i.e.* the [*a*] or [*f*] sides) has no particular effect on the electron affinity and ionization energy. This is indicated by comparison of No. 47 with Nos. 48, 52, and 55. The electron affinity of pyrene increases, and its ionization energy decreases, as a result of fusion of benzene or naphthalene rings onto sides other than the [*a*], *e.g.* at the 3,4-, 8,9-, and 9,10-positions ([*c*], [*h*], and [*i*] sides). This can be seen by comparing the electron affinity of pyrene with those of Nos. 49, 53, 54, 56, 57, and 58. Fusion onto the [*c*, *h*] sides has a greater effect on the electron affinity than [*c*, *i*] fusion (Table 1; increase in EA in going from Nos. 53 and 57 to Nos. 54 and 58, respectively).

d) Fusion of one or two benzene rings onto the [*a*] or [*a*, *g*] sides (Table 1, Nos. 39 and 40, respectively) of perylene (Table 1, No. 23) increases the electron affinity and decreases the ionization energy to the same degree as does double fusion onto the [*b*, *h*] or [*a*, *j*] sides (No. 44 or No. 41). On passing from perylene (No. 23) to benzo[*l*]perylene (No. 24) and to coronene (No. 25), the electron energy decreases and the ionization increases correspondingly.

e) The following compounds have the highest electron affinities, and, correspondingly, the lowest ionization energies: benzo[*g*]terylene (No. 46): EA = 1.4 eV; I = 6.46 eV; dibenz[*b*, *h*]anthanthrene (No. 64): EA = 1.55; I = 6.58 eV; dibenzo[*a*, *g*]perylene (No. 40): EA = 1.4; I = 6.7 eV; benzo[*a*]pentacene (No. 9): EA = 1.45; I = 6.69 eV; dibenzo-[*a*, *c*]pentacene (No. 13): EA = 1.4, I = 6.72 eV, and dibenzo-[*a*, *d*]pentacene (No. 18); EA = 1.4 eV, I = 6.77 eV.

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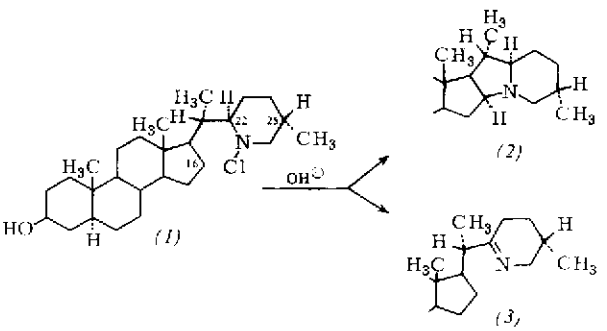
[50] From $E^{Ox}_{1/2}$, Equation (31), [36].

## An Unusual Cyclization of a Steroid N-Chloroamine [1]

By Dr. G. Adam and Dr. habil. K. Schreiber

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In an attempt to prepare the cyclic azomethine *(3)* from *(22R, 25S)-N*-chloro-22,26-imino-5α-cholestan-3β-ol *(1)* [2] by heating it for 75 min with 5 % methanolic KOH in order to eliminate hydrogen chloride, we obtained instead the *Solanum* steroid alkaloid demissidine *(2)*, m.p. 218–220 °C, $[\alpha]_D^{18} = +26.9°$ (c = 0.423 in $CHCl_3$), in 57 % yield. Careful chromatographic separation of the reaction product on $Al_2O_3$ yielded, in addition to *(2)* and 24 % dechlorinated starting material, 3.5 % of the desired $\Delta^{22(N)}$-unsaturated compound *(3)*, m.p. 190–193 °C, $[\alpha]_D^{19} = -40.6°$ (c = 0.413 in $CHCl_3$),



which has an infrared band at 1661 $cm^{-1}$. In contrast, when the *(22S, 25R)*-stereoisomer of *(1)* was dehydrochlorinated under identical conditions, it yielded the expected *(25R)*-azomethine in 60 % yield, but no solanidan [3].

In order to account for the formation of *(2)* from *(1)*, direct elimination of HCl involving participation of the non-activated C–H bond at C-16 must be assumed. This anomalous octahydropyrrocoline ring closure is likely to be due to a particularly favorable steric arrangement of the centers involved in this reaction, and to the stability of the *(22R,25S)*-solanidan skeleton once formed.

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Publication deferred until now at the author's request.
German version: Angew. Chem. *76*, 752 (1964)

[1] Solanum Alkaloids, Part 42; – Part 41: *K. Schreiber* and *G. Adam*, Chem. Ber., in the press.

[2] *G. Adam* and *K. Schreiber*, Tetrahedron, in the press.

[3] *K. Schreiber* and *G. Adam*, Tetrahedron, in the press.

## Bis(trimethylsilyl)aminohalogenoboranes [1]

By Dr. P. Geymayer, Prof. Dr. E. G. Rochow, and Prof. Dr. U. Wannagat

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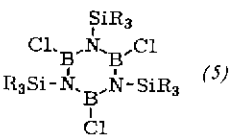
Disilazanes are cleaved at the Si–N bond by boron halides [2, 3], and are transaminated by aminoboranes [4]; both reactions lead to compounds containing the >B–NH–Si< grouping.

We have now succeeded in preparing compounds with a >B–N(Si<)$_2$ grouping.

$$X_3BO(C_2H_5)_2 + n\ NaN(SiR_3)_2 \rightarrow \underset{(1)}{} X_{3-n}B[N(SiR_3)_2]_n + n\ NaX + O(C_2H_5)_2$$

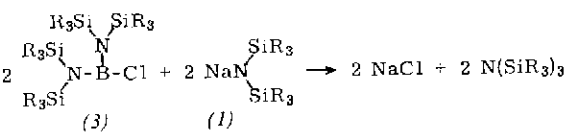
R = $CH_3$; *(2)*, X = F, n = 2; *(3)*, X = Cl, n = 2; *(4)*, X = Cl, n = 1

A solution in ether of sodium bis(trimethylsilyl)amide *(1)* [5] is added dropwise to a solution in ether of boron trihalide etherate; subsequent fractional vacuum distillation yields bis-[bis(trimethylsilyl)amino]fluoroborane *(2)*, m.p. 1 °C, b.p. 76 °C/0.2 mm, as a stable viscous liquid, which is only slowly decomposed by $CH_3OH$/HCl and which does not react further with *(1)*, even under vigorous conditions. Products obtained similarly are bis[bis(trimethylsilyl)amino]chloroborane *(3)*, m.p. 36 °C, b.p. 105 °C/11 mm, crystals that are very sensitive to hydrolysis, and bis(trimethylsilyl)aminodichloroborane *(4)*, m.p. 5–6 °C, b.p. 82 °C/11 mm, a colorless liquid which is also very sensitive to hydrolysis. The fluoro compound analogous to *(4)* could not yet be obtained. The structures proposed are supported by elementary analyses and infrared and proton magnetic resonance spectra: δ (relative to TMS) = 0.18 ppm for *(2)* with a doublet structure at high resolution, δ = 0.27 ppm for *(3)*, and δ = 0.30 ppm for *(4)*. Compound *(4)* is thermally unstable and undergoes intermolecular condensation in boiling xylene with elimination of $R_3SiCl$ to give 1,3,5-tristrimethylsilyl-2,4,6-trichloroborazole *(5)*, m.p. 140 °C, which sublimes at 95 °C/2 mm;

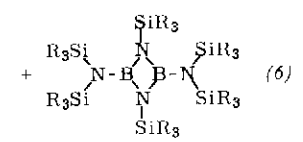


*(5)*

*(5)* has δ = 0.35 ppm and characteristic infrared peaks at 1325 and 950 $cm^{-1}$.



*(3)* *(1)*



*(6)*

Compound *(3)* does react with *(1)* under more vigorous conditions (refluxing xylene, 20 h), but instead of the expected tris[bis(trimethylsilyl)amino]boron, tris(trimethylsilyl)amine and hexakistrimethylsilyl-1,3-diaminocyclo-2,4-diboradiazetane *(6)*, m.p. 212 °C, are obtained. Compound *(6)* is a white sublimable (110 °C/0.1 mm) solid; its NMR spectrum has peaks at δ = 0.20 and 0.16 ppm in an integral ratio of 2:1 [6].

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[1] Communication No. 42 on Si–N compounds. – Communication No. 41: *U. Wannagat, F. Bogusch*, and *P. Geymayer*, Mh. Chem., in the press.

[2] *M. Becke-Goering* and *H. Krill*, Chem. Ber. *94*, 1059 (1961).

[3] *H. Nöth*, Z. Naturforsch. *16b*, 618 (1961).

[4] *H. Jenne* and *K. Niedenzu*, Inorg. Chemistry *3*, 68 (1964).

[5] *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

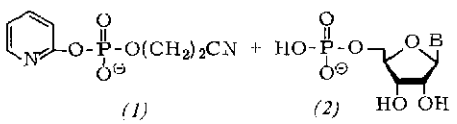
[6] Compound *(6)* has been prepared simultaneously by a different route: cf. *A. G. MacDiarmid* and *C. R. Russ*, Angew. Chem. *76*, 500 (1964); Angew. Chem. internat. Edit. *3*, 509 (1964).

## A Simple Method for Preparing Nucleoside Diphosphates [1]

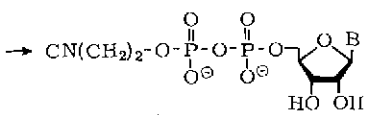
By Dr. K. H. Scheit and Dr. W. Kampe

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All the known syntheses of nucleoside diphosphates start from activated nucleoside monophosphates, *e.g.* nucleoside-5'-phosphoroimidazoles [2] or nucleoside-5'-phosphoromorpholidates [3]. The method we have discovered avoids activation of the nucleoside 5'-phosphate, a process which usually involves complications. The readily accessible 2-cyanoethyl-α-pyridyl phosphate *(1)* [4] reacts in pyridine at room temperature with monotriethylammonium salts of nucleoside 5'-phosphates *(2)* to yield unsymmetrical pyrophosphoric diesters *(3)*.



*(1)* *(2)*



*(3)*

B = uracil, cytosine, adenine

Mild alkaline hydrolysis of *(3)* at 0 °C yielded nucleoside diphosphates. The course of the reactions was followed by paper chromatography. The yields were usually 60 % based on the nucleoside 5'-phosphate used as starting material.

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German version: Angew. Chem. 76, 683 (1964)

[1] Communication No. 3 on Reactive Esters of Heterocyclic Alcohols. – Communication No. 2: *W. Kampe*, Tetrahedron Letters *1963*, 2133.

[2] *F. Cramer, H. Schaller*, and *H. A. Staab*, Chem. Ber. *94*, 1612 (1961).

[3] *J. G. Moffat* and *H. G. Khorana*, J. Amer. chem. Soc. *83*, 649 (1961).

[4] *W. Kampe*, Chem. Ber., in the press.

## Reactions with Single Crystals of Niobium Oxides [*]

By Dr. R. Gruehn, Dr. F. Schulte, and Prof. Dr. H. Schäfer

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Chemical transport [1] gives rise to various modifications of $Nb_2O_5$ [2, 3], as well as phases including Nb(IV) and Ti(IV) [4–6], as single crystals which are often several millimeters in size. We have found that some of the substances undergo transformations and redox reactions without loss of their single-crystal character (see Table).

Reactions with single crystals [3] (heated in air; experiments 21 and 23: *reduction with* $H_2/H_2O$).

| | Starting material (single crystal) | Annealing °C | Annealing h | Result (opt. and X-ray data) |
|---|---|---|---|---|
| 1 | B–$Nb_2O_5$ (blue; $Nb_2O_{2.496}$) | 860 | 80 | single cryst. B–$Nb_2O_5$ (blue [7]) |
| 2 | Product from 1 | 900 | 18 | single cryst. B–$Nb_2O_5$ (blue); colorless, polycryst. H–$NbO_{2.50}$ at the edges |
| 3 | B–$Nb_2O_5$ (blue) | 950–1000 | 4 | polycryst. H–$NbO_{2.50}$ (colorless) |
| 4 | P–$Nb_2O_5$ (blue) | 800 | 80 | single cryst. P–$NbO_{2.50}$(colorless) |
| 5 | Product from 4 | 800 | 80 | single cryst. P–$Nb_2O_5$ |
| 6 | P–$Nb_2O_5$ (colorless) | 850 | 16 | single cryst. P–$Nb_2O_5$ + polycryst. H–$Nb_2O_5$ |
| 7 | Product from 6 | 830–1000 | 80 | polycryst. H–$Nb_2O_5$ |
| 8 | N–$Nb_2O_5$ | 910 | 30 | single cryst. N–$Nb_2O_5$ |
| 9 | N–$Nb_2O_5$ | 1000 | 20 | single cryst. N–$Nb_2O_5$ + polycryst. H–$Nb_2O_5$ |
| 10 | Product from 9 | 1050–1150 | 20 | further transformn. N → H–$Nb_2O_5$ |
| 11 | M–$NbO_{2.48}$ (blue) | 830 | 12 | single cryst. M–$NbO_{2.50}$ (colorless) |
| 12 | Product from 11 | 830 | 12 | single cryst. M–$Nb_2O_5$ |
| 13 | Product from 12 | 1150 | 12 | single cryst. H–$Nb_2O_5$ |
| 14 | $NbO_{2.467}$ (II) | 650 | 4 | single cryst. $NbO_{2.50}$, X-ray pattern as for $NbO_{2.467}$ (II) |
| 15 | Product from 14 | 1150 | 150 | single cryst. $NbO_{2.50}$, X-ray pattern almost as for H–$Nb_2O_5$ |
| 16 | $NbO_{2.417}$ (I) | 650 | 50 | single cryst. $NbO_{2.50}$; diffuse X-ray pattern |
| 17 | Product from 16 | 1100 | 50 | single cryst. H–$Nb_2O_5$ |
| 18 | $NbO_{2.417}$ (II) | 650 | 4 | crystal disintegrated into similarly orientated single crystals; diffuse X-ray pattern |
| 19 | Product from 18 | 1100 | 12 | polycryst. H–$Nb_2O_5$ |
| 20 | H–$NbO_{2.49}$ (blue) | 1100 | 12 | single cryst. H–$NbO_{2.50}$ (colorless) |
| 21 | H–$NbO_{2.50}$ | 1100 | 50 | single cryst. $NbO_{2.44}$ (blue), distinctive X-ray pattern; like $NbO_{2.467}$ (II) |
| 22 | Product from 21 | 1100 | 12 | single cryst. H $NbO_{2.50}$ |
| 23 | $Nb_3O_7Cl$ (colorless) | 360–380 | 30 | single cryst. $Nb_3O_7Cl$ (blue) [8] |
| 24 | $Nb_3O_7Cl$ (deep blue) | 580 | 30 | single cryst. $Nb_3O_7Cl$ (pale blue) |
| 25 | Product from 24 | 580 | 75 | single cryst. $Nb_3O_7Cl$ (pale blue) and polycryst. B–$Nb_2O_5$ |
| 26 | $Nb_3O_7Cl$ (deep blue) | 700 | 75 | polycryst. B–$Nb_2O_5$ + P–$Nb_2O_5$ |

It was especially noteworthy that monoclinic $NbO_{2.417}$(I) could be converted into H–$Nb_2O_5$, which is also monoclinic, but that rhombic $NbO_{2.417}$(II) could not.

The transformation of P-$Nb_2O_5$ and B-$Nb_2O_5$ results in polycrystalline H-$Nb_2O_5$ without appearance of the M-form; well-ordered H-$Nb_2O_5$ is obtained from P-$Nb_2O_5$ at temperatures as low as 850 °C.

H-$Nb_2O_5$ can be reduced with $H_2/H_2O$ as a single crystal to $NbO_{2.44}$ [7] with clear alteration of the Guinier diagram. On reducing more strongly or for longer times, $NbO_2$ is formed, the phase $NbO_{2.417}$ being omitted.

The behavior of single crystals enables transformation relationships to be recognized which can yield information concerning structural relationships between allied substances.

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German version: Angew. Chem. 76, 685 (1964)

[*] Contributions to the Chemistry of Niobium and Tantalum, Part XLI. – Part XL: *H. Schäfer, F. Schulte*, and *R. Gruehn*, Angew. Chem. *76*, 536 (1964); Angew. Chem. Internat. Edit. *3*, 511 (1964).

[1] *H. Schäfer:* Chemische Transportreaktionen. Verlag Chemie, Weinheim/Bergstr. 1962.

[2] *F. Schulte*, Ph. D. Thesis, Universität Münster, 1962.

[3] For the notation and preparation of the substances cf.: *H. Schäfer, F. Schulte*, and *R. Gruehn*, Angew. Chem. *76*, 536 (1964); Angew. Chem. Internat. Edit. *3*, 511 (1964); and [5].

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

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[7] A special analytical method permits determination of these small Nb(IV) contents in single crystals with an accuracy of *e.g.* $NbO_{2.490} \pm 0.001$; cf. *R. Gruehn*, Ph. D. Thesis, Universität Münster, 1962.

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## The Course of Dehalogenation of Ethylaluminum Sesquichlorides with Sodium

By Ing. Dr. J. Dvořák and prom. Chem. V. Fic

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The production of triethylaluminum by dehalogenation of ethylaluminum sesquichlorides with sodium [1]

$$C_2H_5AlCl_2 + (C_2H_5)_2AlCl + 3\ Na \rightarrow (C_2H_5)_3Al + Al + 3\ NaCl \quad (a)$$

proceeds by a reaction more complicated than shown in Equation (a).

On adding a suspension of sodium in n-decane to a solution of ethylaluminum sesquichloride in n-decane at 120 °C with vigorous stirring under nitrogen, only ethylaluminum dichloride reacts at first. Diethylaluminum chloride, very finely dispersed sodium chloride, and metallic aluminum result.

$$2\ C_2H_5AlCl_2 + 3\ Na \rightarrow (C_2H_5)_2AlCl + 3\ NaCl + Al \quad (b)$$

Sodium chloride reacts with ethylaluminum dichloride to form a complex $Na[Al(C_2H_5)Cl_3]$, which precipitates.

$$C_2H_5AlCl_2 + NaCl \rightarrow Na[Al(C_2H_5)Cl_3] \quad (c)$$

Further additions of sodium react with this complex to give diethylaluminum chloride, sodium chloride, and aluminum.

$$2\ Na[Al(C_2H_5)Cl_3] + 3\ Na \rightarrow (C_2H_5)_2AlCl + 5\ NaCl + Al \quad (d)$$

Reactions (b)–(d) are strongly exothermic and proceed very rapidly. The dehalogenation of diethylaluminum chloride proceeds more slowly.

$$3\ (C_2H_5)_2AlCl + 3\ Na \rightarrow 2(C_2H_5)_3Al + 3\ NaCl + Al \quad (e)$$

A relative excess of sodium may be present towards the end of this reaction, since Reaction (e) takes place at the surface of the sodium, and the mixture is rather viscous owing to the separated sodium chloride and aluminum. The diffusion of diethylaluminum chloride towards the sodium surface may then be slower than the reaction of the triethylaluminum formed at the sodium surface with the sodium.

$$4\ (C_2H_5)_3Al + 3\ Na \rightarrow 3\ Na[Al(C_2H_5)_4] + Al \quad (f)$$

$Na[Al(C_2H_5)_4]$ reacts with a molecule of diethylaluminum chloride to form sodium chloride and triethylaluminum.

$$(C_2H_5)_2AlCl + Na[Al(C_2H_5)_4] \rightarrow 2\ (C_2H_5)_3Al + NaCl \quad (g)$$

The dehalogenation proceeds differently if the sesquichloride is added to a suspension of sodium in a high-boiling aliphatic hydrocarbon (n-decane; 120 °C; nitrogen atmosphere; vigorous stirring). Since the sodium is now present in excess, with each addition of sesquichloride, Reactions (b)–(f) occur successively. The product of this sequence of reactions is a mixture of the complex $Na[Al(C_2H_5)_4]$ with precipitated aluminum and sodium chloride. When more sesquichloride is added, it is dehalogenated by the $Na[Al(C_2H_5)_4]$. The $C_2H_5AlCl_2$ reacts first,

$$2\ C_2H_5AlCl_2 + Na[Al(C_2H_5)_4] \rightarrow 3(C_2H_5)_2AlCl + NaCl \quad (h)$$

and then the diethylaluminum chloride reacts according to Equation (g).

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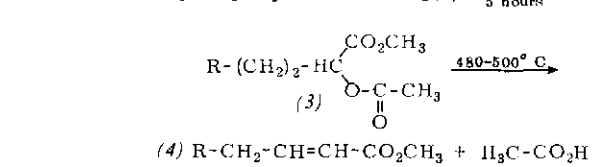
[1] *A. von Grosse* and *J. M. Mavity*, J. org. Chemistry *5*, 110 (1940); Brit. Pats. *762*, 200 (1956); *822*, 971 (1959).

## Addition of Methyl Acetoxyacetate onto Olefins by a Free-Radical Mechanism [1]

By Dr. Yu. N. Ogibin and Dr. G. Y. Nikishin

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We have succeeded in synthesizing α,β-unsaturated alkenoic esters by pyrolysis of 2-acetoxyalkanoic esters *(3)* [2], which were prepared from methyl acetoxyacetate *(1)* and α-olefins *(2)* in the presence of di-t-butyl peroxide. The molar proportions *(1)*:*(2)*:peroxide were 10:1:0.25. The table summarizes the yields and properties of the products.



| R | Yield [%] | B.p. [°C/mm] | Yield [%] [a] | B.p. [°C/mm] |
|---|---|---|---|---|
| $H_3C-(CH_2)_4-$ | 68 | 115/3 | 86 | 67–68/3 [b] |
| $H_3C-(CH_2)_5-$ | 53 | 120–121/4 | | |
| $H_3C-(CH_2)_9-$ | 66 | 182–183,5/5 | 80 | 117–118/1,5 |
| $H_3C-(CH_2)_{10}-$ | 63 | 174/4 | | |
| $H_3CO_2C-(CH_2)_8-$ | 47 | 189–190/4 | 85 | 144–145/2 |
| $HOH_2C-(CH_2)_8-$ | 40 | 165–167/2 | | |
| $H_3C-CO_2CH(CH_3)-$ | 55 | 135/3 | [c] | |
| $H_3C-CO_2CH_2-$ | 30 | 111–113/2 | | |

[a] Yields based on the ester *(3)*.
[b] 80 % *trans*- and 20 % *cis*-isomer.
[c] Pyrolysis yields a mixture of methyl hexadienoate and acetoxyhexenoate.

Received, June 15th, 1964 [Z 767/590 IE]
German version: Angew. Chem. 76, 713 (1964)

[1] Previous communications on this subject: *G. Y. Nikishin, Yu. N. Ogibin*, and *A. D. Petrov*, Dokl. Akad. Nauk USSR, Otdel. Khim. Nauk *1961*, 1397, 1463; *1963*, 1816.

[2] *R. Burns, D. T. Jones*, and *P. D. Ritchie*, J. chem. Soc. (London) *1935*, 400.

## Intermediates of the Wittig Reaction with Non-Stabilized Phosphorylides

By Dr. M. Schlosser and cand. chem. K. F. Christmann

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When freshly prepared from organolithium compounds, phosphorylides *(1)* which are not stabilized by mesomerism [R = H, alkyl, OR] immediately add onto carbonyl compounds; however, the adduct does not usually react further in the cold to form the olefin. The reaction of *(1)*, R = H, with benzaldehyde in ether does not yield any styrene at 0 °C, and on heating at 70 °C for several days, only a 30 % yield is obtained.

$(H_5C_6)_3\overset{\oplus}{P}-\overset{\ominus}{\underline{C}}H-R$ *(1)*

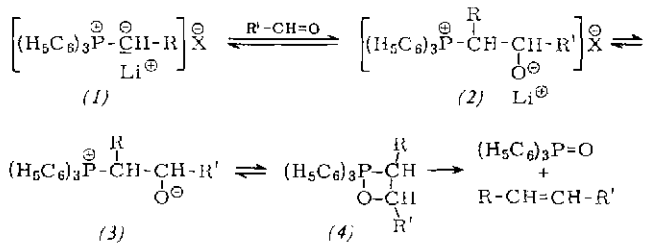
It was now found that addition of at least 1.1 equivalent of potassium t-butoxide (as its 1:1 complex with t-butanol) accelerates the Wittig reaction considerably. After 0.5 15 hours at 22 °C, the olefins were obtained in high yields (see Table).

| Phosphonium salt | Carbonyl component | Olefin | Yield [%] |
|---|---|---|---|
| $[(H_5C_6)_3P-CH_3]Br$ | Cyclohexanone | Methylenecyclohexane | 91 [b,c] |
| $[(H_5C_6)_3P-CH_3]Br$ | Benzaldehyde | Styrene | 68 [a] |
| $[(H_5C_6)_3P-CH_2CH_3]Br$ | Benzaldehyde | α-Methylstyrene | 75 [a], 100 [b] |
| $[(H_5C_6)_3P-CH(CH_3)_2]Br$ | Benzaldehyde | α,α-Dimethylstyrene | 63 [a] |
| $[(H_5C_6)_3P-(CH_2)_3CH_3]Br$ | Butyraldehyde | 4-Octene | 85 [b,c] |
| $[(H_5C_6)_3P-(CH_2)_4CH_3]Br$ | Benzaldehyde | 1-Phenyl-1-hexene | 61 [a] |
| $[(H_3C)_4P]I$ | Benzophenone | 1,1-Diphenylethylene | 60 [a] |

[a] Preparative yield; [b] Gas-chromatographic yield; [c] Could not be separated by distillation from accompanying benzene (derived from phenyl-lithium which was applied for the ylide formation).

The rate of reaction was strongly influenced by the efficiency of mixing. In the reaction leading to α-methylstyrene, yields of 67–99 % were found by gas chromatography after 20 minutes at 0 °C. In the absence of potassium t-butoxide or in the presence of less than stoichiometric proportions, *e.g.* 0.1 equivalent, only 0–5 % olefin was formed under the same conditions. Solvent-free, sublimed potassium t-butoxide was less effective than its 1:1 complex with t-butanol.

We assume that the adduct formed from the phosphorylide *(1)* and the carbonyl component does not occur as the "free" betaine *(3)*, but as a betaine-lithium ion pair *(2)* and that only the free betaine *(3)* can cyclize to the four-membered ring *(4)*. Potassium t-butoxide apparently exchanges $Li^{\oplus}$ for $K^{\oplus}$ in *(2)* and thus increases the dissociation *(2)* → *(3)*.



If the reaction *(2)* → *(3)* is really the rate-determining step in many Wittig olefinations, then it becomes plausible why polar solvents, such as tetrahydrofuran [1] or water [2], accelerate the reactions. The following observations also indicate the intermediate formation of *(2)*: the lithium compounds of β-hydroxyalkylphosphine oxides are more stable than the corresponding potassium derivatives [3]; and an adduct *(2)* or *(3)* [R = R′ = $C_6H_5$] was isolated which contained firmly bound LiBr [4].

Received, June 29th, 1964 [Z 765/597 IE]
German version: Angew. Chem. 76, 683 (1964)

[1] *G. Wittig, H. D. Weigmann*, and *M. Schlosser*, Chem. Ber. *94*, 676 (1961), where further references are given.

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## The Effect of X-Rays on the Protein Synthesis in vitro

By Prof. Dr. A. Wacker and P. Chandra

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Pyrimidines are distinctly more sensitive to X-rays than purines [1]. Thus, about 450 kr destroy 50 % cytosine, thymine, and uracil and 20 % guanine in aqueous solution, but only 8 % adenine [2]. The same sensitivity of uracil and adenine occurs in polynucleotides: 160 kr destroy 32 % of the uracil in polyuridylic acid (poly-U) and 3 % of the adenine in polyadenylic acid (poly-A). We found that this differing sensitivity toward X-rays also occurs with protein synthesis in cell-free systems [3].

As shown in the Table, the incorporation of phenylalanine (m-RNA = poly-U) falls off in dependence on the radiation dose, 50 % inhibition being obtained with about 45 kr. On the other hand, the synthesis of polylysine (m-RNA = poly-A) is inhibited by only slightly over 30 % by a dose of even 160 kr. The corresponding transfer-RNAs (t-RNAs) show radiation sensitivity opposite to that of the m-RNAs: lysine-transferring t-RNA is nearly twice as sensitive as phenylalanyl-t-RNA. This may be an indication that the anticodons AAA for phenylalanine and UUU for lysine are in fact present in the t-RNA and are necessary for cooperation with the m-RNA in protein synthesis.

Destruction of the ribose-phosphate chain in nucleic acids must also be considered [1]. As the chain length of poly-U and poly-A influences protein synthesis [4], shortening of the m-RNA would have an inhibitory effect on protein synthesis. However, it can be assumed that the ribose-phosphate chains of different nucleic acids are destroyed to about equal amounts, so that the differing sensitivity towards radiation of the incorporation of phenylalanine and lysine can be due only to the differing destruction of the bases uracil and adenine in the codons. In addition to the specific radiochemical changes of purines and pyrimidines observed

| X-ray dose [kr] | % Inhibition of synthesis of polyphenylalanine on irradiation of | | polylysine on irradiation of | |
|---|---|---|---|---|
| | m-RNS | t-RNS | m-RNS | t-RNS |
| 0 | 0 | 0 | 0 | 0 |
| 20 | 32 | 9 | 13 | 15 |
| 40 | 45 | 11 | 23 | 19 |
| 80 | 71 | 14 | 31 | 23 |
| 160 | 87 | 17 | 33 | 31 |

Cell-free extract from *Escherichia coli* B [6]. Method: [3] (without UTP and CTP). t-RNA was isolated according to [7] and was an enriched mixture of different t-RNAs. Irradiation of t-RNA after uptake of phenylalanine or lysine. X-Ray tube RT 100 [Messrs. C. H. F. Müller, Hamburg (Germany)] 100 kV, 8 mA, dose rate 30 kr/min, unfiltered. Poly-U and poly-A (Messrs. Miles & Co., Elkhart, Indiana, U.S.A.) were irradiated in aqueous solution (1 mg/ml).

after irradiation with ultraviolet light [5], this phenomenon offers a further possibility for sequence analysis of the triplets necessary for protein synthesis.

Received, July 3rd, 1964 [Z 774/620 IE]
German version: Angew. Chem. 76, 685 (1964)

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[6] *A. Wacker, M. Ishimoto, P. Chandra*, and *R. Selzer*, Z. Naturforsch. *19b*, 406 (1964).

[7] *K. S. Kirby*, Biochem. J. *64*, 605 (1956).

## 7-Dialkylaminonaphthalene-1,2-dicarboxylic Hydrazides – New Strongly Chemiluminescent Compounds

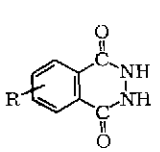
By Prof. Dr. K.-D. Gundermann and Dr. W. Horstmann [1]

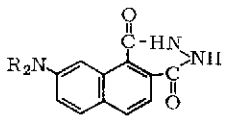
Organisch-Chemisches Institut der Bergakademie Clausthal, Technische Hochschule Clausthal (Germany)

The chemiluminescence of 3-aminophthalic hydrazide (luminol) *(1)* has hitherto been surpassed only by that of 4-diethylaminophthalic hydrazide *(2)* [2] and the 3-amino-5,6-di- and -4,5,6-trimethoxyphthalic hydrazides [3]. These compounds exhibit 1.30, 1.13, and 1.30 times the chemiluminescence of *(1)*, respectively.

On hemin-catalysed oxidation with $H_2O_2$ in aqueous alkali, the newly prepared 7-dialkylaminonaphthalene-1,2-dicarboxylic hydrazides *(3)* and *(4)*, which can be regarded as vinylogues of 3-dialkylaminophthalic hydrazides, show intense, green chemiluminescence [*] ($\lambda_{max}$ = 500 mμ) with about twice the maximum intensity and quantity of light afforded by *(1)* under optimum conditions.

Compounds *(3)* and *(4)* were made from 7-methoxynaphthalene-1,2-dicarboxylic anhydride [4] via 7-hydroxy- and 7-aminonaphthalene-1,2-dicarboxylic acid.





*(1)*, R = 3-$NH_2$
*(2)*, R = 4-$N(C_2H_5)_2$
*(3)*, R = $CH_3$
*(4)*, R = $C_2H_5$

Whereas alkali concentrations greater than 0.03 N lead to a sharp decline in the intensity and quantity of light given by *(1)* [1,5], the light yield of *(2)*, *(3)*, and *(4)* reaches a maximum at an alkalinity of ca. 0.1 N, and remains practically constant up to 1.0 N. The fluorescence spectra of *(3)* and *(4)* during the chemiluminescence reaction clearly show that, as with *(1)* [3], it is the excited 7-substituted naphthalene-1,2-dicarboxylate anions, formed from *(3)* and *(4)* in the luminous reaction, which cause the chemiluminescence.

Received, July 6th, 1964 [Z 771/600 IE]
German version: Angew. Chem. 76, 686 (1964)

[*] We wish to thank Priv.-Doz. *G. Bergman*, Clausthal, for the chemiluminescence measurements.

[1] *W. Horstmann*, Ph. D. Thesis, Universität Münster, 1964.

[2] *K.-D. Gundermann* and *M. Drawert*, Chem. Ber. *95*, 2018 (1962).

[3] *E. H. White* and *M. M. Bursey*, J. Amer. chem. Soc. *86*, 941 (1964).

[4] *L. F. Fieser* and *E. B. Hershberg*, J. Amer. chem. Soc. *58*, 2319 (1936).

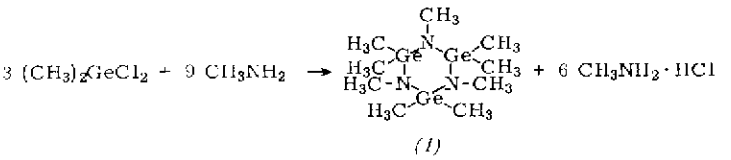
[5] *K. Weber, A. Rezek*, and *V. Vouk*, Ber. dtsch. chem. Ges. *75*, 1141 (1942).

## Synthesis and Cleavage of a Six-Membered Germanium-Nitrogen Ring

By Prof. Dr. Max Schmidt and Dr. I. Ruidisch

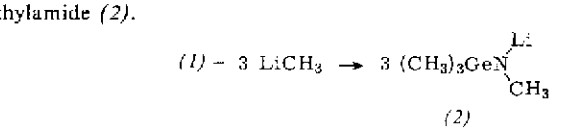
Institut für Anorganische Chemie der Universität Marburg/Lahn (Germany)

Reaction of methylamine with dimethyldichlorogermane in ether gives a 80 % yield of the trimeric dimethylgermanylmethylamine *(1)* as a colorless, viscous liquid, b.p. 80 °C/2 mm, which is readily soluble in organic solvents but is very sensitive to moisture.



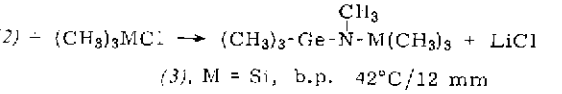
*(1)*

Compound *(1)* can be split quantitatively with methyl-lithium in ether to give a solution of lithium trimethylgermanylmethylamide *(2)*.



*(2)*

Compound *(2)* is highly reactive and with trimethylchlorosilane, -germane, -stannane, and -plumbane affords very good yields of the mixed ammonia derivatives trimethylsilyl- *(3)*, trimethylgermanyl- *(4)*, trimethylstannyl- *(5)*, and trimethylplumbyl-trimethylgermanylmethylamine *(6)*, plus LiCl. Compound *(2)* does not react with t-butyl chloride.



*(3)*, M = Si, b.p. 42 °C/12 mm
*(4)*, M = Ge, b.p. 172 °C/735 mm
*(5)*, M = Sn, b.p. 28 °C/2 mm
*(6)*, M = Pb, b.p. 49 °C/2 mm

All the new compounds are colorless liquids, readily soluble in organic solvents, and are rapidly hydrolysed to methylamine and the corresponding metaloxane. Proof for their structures is given by their NMR and infrared spectra and by elementary analyses.

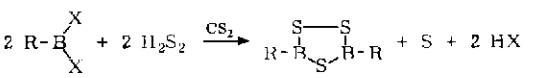
Received, July 6th, 1964 [Z 772/598 IE]
German version: Angew. Chem. 76, 686 (1964)

## 1,2,4-Trithia-3,5-diborolanes

By Prof. Dr. Max Schmidt and Dipl.-Chem. W. Siebert

Institut für Anorganische Chemie der Universität Marburg/Lahn (Germany)

Attempts to synthesize a six-membered ring containing four sulfur and two boron atoms from boron halides and hydrogen disulfide surprisingly resulted in about 60 % yields of five-membered cyclic compounds containing three sulfur and two boron atoms (1,2,4-trithia-3,5-diborolanes).



(X = Cl, Br)

*(1)*, R = Br
*(2)*, R = $C_6H_5$

It was shown by PMR-spectroscopy during the reaction that $H_2S$ (which could be formed from $H_2S_2$) does not participate in the cyclization [1].

Compounds *(1)* and *(2)* are very sensitive to protonic and many oxygen-containing solvents as well as to oxygen; they have, however, surprising thermal stability. Thus, *(1)* is a colorless liquid, b.p. 50–52 °C/1.5 mm, m.p. 17 °C, that can be maintained at 190 °C for 6 h without decomposition. Compound *(2)*, colorless plates, m.p. 110–112 °C, is also very stable at this temperature. In agreement with spectroscopic data [3] this increased stability, relative to $B_3S_3Br_3$ [2], can be explained by a sort of resonance stabilisation. The infrared and $^{11}$BMR-spectra of *(1)* and *(2)*, and corresponding experiments with silicon and aluminum halides, will be reported elsewhere.

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German version: Angew. Chem. 76, 687 (1964)

[1] *H. Schmidbaur, M. Schmidt,* and *W. Siebert,* Chem. Ber., in the press.

[2] *E. Wiberg* and *W. Sturm,* Z. Naturforsch. *8b,* 529 (1953).

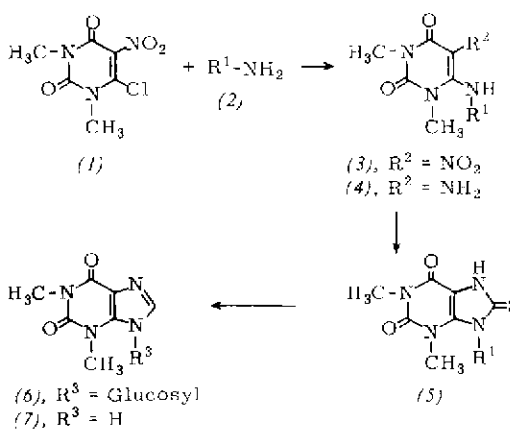
[3] Cf. *H. Noth* and *W. Regnet,* Z. Naturforsch. *18b,* 1138 (1963).

## Synthesis of the First Theophylline 9(N)-Glycoside

By Dipl.-Chem. E. Bühler and Prof. Dr. W. Pfleiderer

Institut für Organische Chemie der Technischen Hochschule Stuttgart (Germany)

Because of the shielding of N-9 in theophylline *(7)* by the 3-methyl group, alkylation and glycosidation [1–3] invariably result in substitution at N-7. In order to achieve a synthesis of a theophylline 9(N)-glycoside, we therefore treated 1,3-dimethyl-4-chloro-5-nitrouracil *(1)* [*] with 1-amino-2,3,4,6-tetra-*o*-acetyl-β-D-glucopyranose *(2)* in chloroform at room temperature to produce 1,3-dimethyl-5-nitro-4-(2,3,4,6-tetra-*o*-acetyl-β-D-glucopyranosylamino)uracil *(3)*, m.p. 164 to 166 °C, $[\alpha]_{578}^{28} = -299°$ (in $CHCl_3$), in 46 % yield.




$R^1$ = 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl.

Conversion of *(3)* into the corresponding 5-amino derivative *(4)* was accomplished by catalytic reduction with Raney nickel and hydrogen. The amine *(4)* is labile and could not be obtained pure; it was therefore immediately cyclized with $CS_2$ in pyridine to give a 10 % yield of 1,3-dimethyl-9-(2,3,4,6-tetra-*o*-acetyl-β-D-glucopyranosyl)-8-thiouric acid *(5)*, m.p. 163–166 °C, $[\alpha]_{578}^{29} = +32.8°$ in $CHCl_3$. The small yield from this cyclization and our inability to convert *(4)* directly, into *(6)* with ethyl orthoformate/acetic anhydride or dimethylformamide diethylacetal demonstrate that the close proximity of the 3-methyl group and the sugar residue oppose imidazole formation for steric reasons. Desulfuration of *(5)* with Raney nickel, and subsequent deacetylation with methanolic ammonia finally gave 9-β-D-glucopyranosyltheophylline *(6)*, m.p. 218–220 °C, $[\alpha]_{578}^{25} = -42°$ (in $H_2O$), $\lambda_{max}$ = 238 and 266 mμ, log ε = 3.97 and 3.96, in 32 % yield. Compound *(6)* is the first theophylline 9(N)-glycoside of established structure. The alleged 1,3-dimethylxanthosine mentioned in the literature [4] is a mixture of at least 5 substances; after hydrolysis of the mixture with acid no theophylline could be detected, in contrast to the claims of the author. After boiling with 1 *N* HCl for only 15 min, *(6)* gave theophylline *(7)* and glucose, which were identified by paper chromatography and mixed melting points.

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German version: Angew. Chem. 76, 713 (1964)

[1] *E. Fischer* and *B. Helferich,* Ber. dtsch. chem. Ges. *47,* 210 (1914).

[2] *J. M. Gulland, E. R. Holiday.* and *T. F. Macrae,* J. chem. Soc. (London) *1934,* 1639.

[3] *Y. Ishido* and *T. Sato,* Bull. chem. Soc. (Japan) *34,* 1347 (1961); *T. Sato, T. Simadate,* and *Y. Ishido,* J. chem. Soc. Japan, pure Chem. Sect. *81,* 1440, 1442 (1960); *T. Simadate,* ibid. *82,* 1268, 1270 (1961).

[*] We are indebted to Dr. *C. C. Cheng,* Midwest Research Institute, Kansas City, for the procedure for the preparation of *(1)*.

[4] *H. Bredereck,* Chem. Ber. *80,* 401 (1947).

## The Structure of $As_2O_5 \cdot 5/3\ H_2O$

By Prof. Dr. E. Thilo, Dr. K.-H. Jost, and Dipl.-Chem. H. Worzala

Institut für Anorganische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Adlershof (Germany)

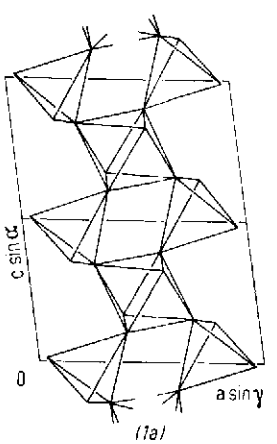
The 5/3-hydrate of arsenic(V) oxide, $As_2O_5 \cdot 5/3\ H_2O$ [1, 2], has been examined using X-rays (single crystals of the hygroscopic substance sealed in thin-walled tubes). The dimensions of the unit cell were found to be:

$a = 7.31$ Å, $\alpha = 100°$
$b = 5.73$ Å, $\beta = 98°$
$c = 4.66$ Å, $\gamma = 100°$

$\text{Density}_{pykn.} = 3.39$ g/cm³

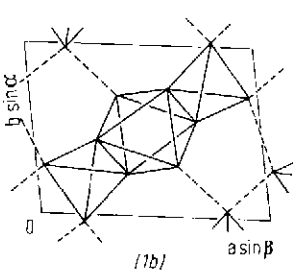
These data correspond to a cell containing 1.5 formula units (exp.: 1.45). The space group is probably $P\bar{1}$, but P1 cannot be ruled out completely. Weissenberg photographs of the zero and first layers were taken along [100], [010], and [001]; the coordinates of the arsenic atoms were ascertained from Patterson projections, and the approximate coordinates of the oxygen atoms from normal and generalized projections of the electron-density distribution. Refinement of the coordinates using difference electron-densities led for all three directions of projection to a reliability factor R = 0.13 (taking unobservable reflections into account). Accurate intensity measurements (integrated photographs) for the (hk0) reflections led to R = 0.10.

From these results it follows that $As_2O_5 \cdot 5/3\ H_2O$ is a highly polymeric compound and consists of arsenic-oxygen tetrahedra and octahedra linked to form ribbons running parallel *(1a)*. The unit cell contains two $AsO_4$ tetrahedra and one $AsO_6$ octahedron. Each $AsO_4$ tetrahedron is linked to two $AsO_6$ octahedra, and the $AsO_6$ octahedron with four tetrahedra; the ribbons are joined by hydrogen bonds [broken lines in *(1b)*].




*(1a)*

Projection in the direction of b-axis




*(1b)*

Projection in the direction of the c-axis

The mean As–O distance is 1.70 Å in the $AsO_4$ tetrahedron and 1.82 Å in the $AsO_6$ octahedron; the mean As–O As bond angle at the bridging oxygen atom is 127°, and the angle between the octahedral plane and octahedral diagonal is 87°. The length of each hydrogen bond (5 per unit cell) is between 2.53 and 2.78 Å. $As_2O_5 \cdot 5/3\ H_2O$ is therefore not a triarsenic acid $H_5As_3O_{10}$.

Received, July 10th, 1964 [Z 780/606 IE]
German version: Angew. Chem. 76, 714 (1964)

[1] *V. Auger*, C. R. hebd. Séances Acad. Sci. *146*, 585 (1908).
[2] *A. Simon* and *E. Thaler*, Z. anorg. allg. Chem. *161*, 143 (1927); *246*, 19 (1941).

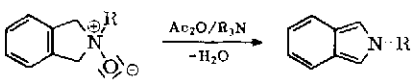
## The Preparation of N-Alkylisoindoles from N-Alkylisoindoline N-Oxides

By Dr. R. Kreher and Dipl.-Ing. J. Seubert

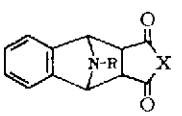
Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

*Dedicated to Prof. C. Schöpf on the occasion of his 65th birthday*

When treated with acetic anhydride/triethylamine at 0 °C, *N*-alkylisoindoline *N*-oxides *(1)*, which are obtained in good yields from *N*-alkylisoindolines and 30 % $H_2O_2$ [1], are converted into *N*-alkylisoindoles *(2)*, which can be isolated in yields of up to 75 % by distillation or crystallization. With dienophiles such as maleic anhydride [2] or *N*-phenylmaleimide, *(2)* forms the adducts *(4)* and *(5)*, respectively.




*(1)* *(2)*



*(4)*, X = >O
*(5)*, X = >N-C6H5

R = $CH_3$-$CH_2$-,
b.p. 78–82 °C/0,01 mm
R = $CH_3$-$(CH_2)_3$-,
b.p. 99–102 °C/0,01 mm
R = $C_6H_5$-$CH_2$-,
m.p. 119–120 °C

The formation of the *N*-alkylisoindoles *(2)*, which are readily accessible from *(1)* by this method, is analogous to the preparation of *N*-alkylpyrroles from *N*-alkyl-$\Delta^3$-pyrroline *N*-oxides [3]. When the decomposition of *(1)* is carried out in the melt at 120 °C instead of in acetic anhydride/triethylamine at 0 °C, an inseparable mixture of *N*-alkylisoindole and *N*-alkylisoindoline is obtained [1].

Received, July 10th, 1964 [Z 779/613 IE]
German version: Angew. Chem. 76, 682 (1964)

[1] *J. Thesing*, *W. Schäfer*, and *D. Melchior*, Liebigs Ann. Chem. *671*, 119 (1964).
[2] Cf. *G. Wittig* et al., Liebigs Ann. Chem. *572*, 1 (1951); *589*, 55 (1954).
[3] *R. Kreher* and *H. Pawelczyk*, Angew. Chem. *78*, 536 (1964); Angew. Chem. internat. Edit. *3*, 510 (1964).

## N-Sulfonylcarbodiimides

By Dr. H. Ulrich and Dr. A. A. R. Sayigh

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North Haven, Conn. (U.S.A.)

Recently, *Aumüller* [1] formulated *N*-sulfonylcarbodiimides as intermediates in the reaction of chloramine-T and cyclohexylisonitrile. Since the sulfonylcarbodiimides could not be isolated nor sufficiently characterized, *Aumüller* assumed that they are very reactive compounds which polymerize instantaneously.

We have found that *N*-sulfonylcarbodiimides can be obtained in good yield from sulfonylthioureas and either phosphorus pentachloride or preferably phosgene (see Table).

$$RSO_2NH\text{–}CS\text{–}NHR' \xrightarrow{COCl_2} RSO_2N{=}C{=}NR'$$

The structures of the sulfonylcarbodiimides were elucidated by elementary analysis and infrared spectroscopy. All the compounds showed a characteristic N=C=N– absorption at 4.58–4.6 μ, *i.e.* in the region for cumulative double-bonds. The polar sulfonyl group causes a shift of this absorption band; carbodiimides normally absorb at 4.7 μ. Small amounts of the corresponding sulfonyl isothiocyanates were obtained as by-products. In the latter compounds, the polar sulfonyl group causes a shift in the opposite direction in the infrared spectrum. Sulfonyl isothiocyanates absorb at 5.25 μ, simple isothiocyanates at 4.9 μ.

| R | R' | B.p. [°C/mm] | $n_D^{24.5}$ | Yield [%] |
|---|---|---|---|---|
| $CH_3$ | $C_2H_5$ | 98–100/0.5 | 1.4830 | 68.0 |
| $CH_3$ | n-$C_3H_7$ | 92/0.25 | 1.4812 | 73.3 |
| $CH_3$ | n-$C_4H_9$ | 103–105/0.3 | 1.4798 | 79.5 |
| $C_6H_5$ | $C_2H_5$ | 139–144/0.2 | 1.5500 | 47.6 |
| p-$CH_3C_6H_4$ | $C_2H_5$ | 147–151/0.25 | 1.5475 | 40.2 |
| $C_6H_5$ | n-$C_4H_9$ | 151–155/0.1 | 1.5380 | 40.0 |
| p-$CH_3C_6H_4$ | n-$C_4H_9$ | 159–162/0.2 | 1.5412 | 47.3 |

Surprisingly, sulfonylcarbodiimides are quite stable. Whereas aliphatic carbodiimides containing primary alkyl groups, e.g. *N,N'*-di-n-butylcarbodiimide, polymerize within a few days, aliphatic sulfonylcarbodiimides are stable. The basicity of both nitrogen atoms is presumably considerably lowered, so that sulfonylcarbodiimides are less reactive than carbodiimides in many reactions. For instance, carbodiimides react with phosgene at room temperature [2], but sulfonylcarbodiimides do not react with phosgene at all.

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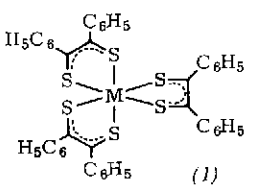
[1] *W. Aumüller*, Angew. Chem. *75*, 857 (1963); Angew. Chem. internat. Edit. *2*, 616 (1963).
[2] *H. Ulrich* and *A. A. R. Sayigh*, J. org. Chemistry *28*, 1427 (1963).

## Trisdithiobenzilmetal Complexes

By Priv.-Doz. Dr. G. N. Schrauzer, Dipl.-Chem. H. W. Finck, and Dr. V. Mayweg

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der Universität München (Germany)

We recently formulated the dithiobenzil complexes of chromium, molybdenum, tungsten, vanadium, rhenium, ruthenium, and osmium [1,2] as planar structures by analogy to the bisdithiononickel complexes; however, we have now prepared and examined larger quantities of the trisdithiobenzilmetal complexes and have thus come to the conclusion that they are in fact 6-coordinate compounds of structure *(1)*, resembling the known $CF_3$-substituted molybdenum complexes [3].




*(1)*

Our original formulation was supported mainly by the consistently low results of the C,H-analyses, and the re-

markable similarity of the infrared and ultraviolet spectra of these complexes with those of bisdithiobenzilnickel.

Received, July 13th, 1964 [Z 783/607 IE]
German version: Angew. Chem. 76, 715 (1964)

[1] *G. N. Schrauzer* and *V. Mayweg*, Z. Naturforsch. *19b*, 192 (1964).

[2] *G. N. Schrauzer, V. Mayweg, H. W. Finck, U. Müller-Westerhoff*, and *W. Heinrich*, Angew. Chem. *76*, 345 (1964); Angew. Chem. internat. Edit. *3*, 381 (1964).

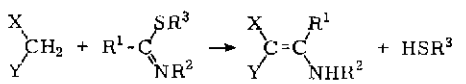
[3] *R. B. King*, Inorg. Chem. *2*, 326 (1963).

## Condensation of Active Methylene Compounds with Isothioamide Groups

By Dr. K. Hartke [*]

Instituto Central de Química, Universidad Concepción (Chile)

Enol ethers with activating groups (−CN, $-CO_2R$, $>C=O$) in the β-position react with amines to form amino olefins *(3)*. The latter are also readily obtained by condensation of compounds containing active methylene groups *(1)* with compounds *(2)* containing the group $-N=C\langle SR$ (isothioamides, isothioureas, or iminothiocarboxylic esters). The condensation takes place without a catalyst by mixing the components in a solvent, *e.g.* alcohol or ether. With compounds containing particularly reactive methylene groups, *e.g.* malonitrile or dimeric malonitrile, the reaction is frequently exothermic. In other cases the reaction mixture is allowed to stand for several hours to days at room temperature or is heated for some time on a water bath. Some compounds obtained in this way are given in the Table (structures determined by elementary analyses and infrared spectra; independent synthesis of *(3e)* [1]).



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

| (3) | X | Y | $R^1$ | $R^2$ | M. p. [°C] | Yield [%] |
|---|---|---|---|---|---|---|
| *(a)* | −CN | −CN | $-CH_3$ | Benzyl | 114–115 | 86 |
| *(b)* | −CN | $-CO_2C_2H_5$ | −H | Cyclohexyl | 116–117 | 62 |
| *(c)* | $-COCH_3$ | $-CO-CH_3$ | −H | Cyclohexyl | 87–88 | 57 |
| *(d)* | −CN | −CN | $-N(CH_3)_2$ | $-CH_3$ | 165–166 | 83 |
| *(e)* | −CN | −CN | $-SCH_3$ | $-CH_3$ | 120–121 | 85 |

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[*] Present address: Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg/Lahn (Germany).

[1] Cf. *R. Gompper* and *W. Töpfl*, Chem. Ber. *95*, 2871 (1962).

## An Explosion during the Oxidation of Tetralin with Hydrogen Peroxide in Acetone

By Dr. H. Seidl

Institut für Organische Chemie
der Universität München (Germany)

During the preparation of α-tetralone, tetralin was oxidized with 30 % $H_2O_2$ according to the method of *Treibs* et al. [1]. On subsequent evaporation of the reaction mixture *in vacuo*, as the last of the solvent distilled over, the distillation residue exploded with great violence, causing injuries and damage. Since the starch-iodide test for free $H_2O_2$ had been negative, we suspect the formation of acetone peroxides as the cause of the explosion. Other routes to α-tetralone are available[2].

Received, July 13th, 1964 [Z 785/621 IE]
German version: Angew. Chem. 76, 716 (1964)

[1] *W. Treibs, G. Franke, G. Leichsenring*, and *H. Röder*, Chem. Ber. *86*, 616 (1953).

[2] *E. L. Martin* and *L. F. Fieser* in: Organic Syntheses. Wiley, New York 1943, Coll. Vol. II, p. 569; *R. B. Wagner* and *H. D. Zook* in: Synthetic Organic Chemistry, Ketones. Wiley, New York 1953, p. 316 et seq.

## Radiochemical Hydroxylation of Phenolic Compounds

By Dr. F. Merger and Dipl.-Chem. D. Grässlin

Organisches-Chemisches Institut
der Universität Heidelberg (Germany)

We have found that gallic acid and other phenolic carboxylic acids are hydroxylated at room temperature in water by the action of $^{60}Co$ γ-rays. The hydroxylation, which can be carried out on a preparative scale, occurs with remarkable selectivity *ortho* to existing hydroxyl groups and proceeds more rapidly in the presence of oxygen than when oxygen is excluded. *m*-Dihydroxybenzoic acids are particularly easily hydroxylated between the two hydroxyl groups.

Irradiation of a 1 % aqueous solution of gallic acid saturated with oxygen (dosage rate of the $^{60}Co$ γ-ray source: $4.06\times10^5$ r/h; irradiation time: 300 h) gave 2,3,4,5-tetrahydroxybenzoic acid in 52.8 % yield with a G-value [*] of 0.22; separation of the residual gallic acid was achieved by fractional crystallization and preparative chromatography. The G-values for some other phenolic carboxylic acids are considerably higher.

Nitrophenols are hydroxylated much faster than phenolic carboxylic acids. *p*-Nitrophenol affords 4-nitrocatechol, and 4- or 5-nitropyrogallol give the hitherto unknown 1,2,3,4-tetrahydroxynitrobenzene (G = 1.41).

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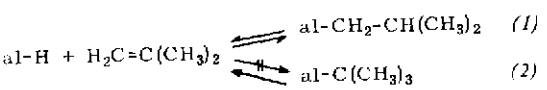
[*] The G-value indicates the number of molecules formed per 100 eV.

## t-Butylaluminum Compounds

By Dr. H. Lehmkuhl

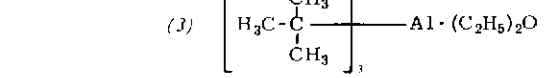
Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

The addition of al-H onto olefins occurs predominantly according to Markownikoff's rule [1,2]; the reaction of al-H with isobutene thus gives triisobutylaluminum *(1)*, but no tri-t-butylaluminum *(2)*.



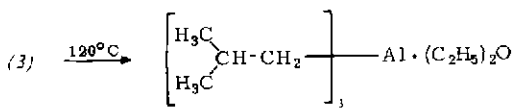
*(1)* *(2)*

It was expected [2] that *(2)* would be unstable and would rearrange to *(1) via* al-H and isobutene. Isomerization to the primary trialkylaluminum occurs with triisopropylaluminum [3]. We found, however, that *(3)*, the etherate of *(2)*, which is produced in 75 % yield by the reaction in ether of t-butylmagnesium chloride with $AlCl_3$ in a molar ratio of 3:1, is actually quite stable.



*(3)*

Compound *(3)* melts at an unusually high temperature (120–124 °C) and can be sublimed at 50 °C/$10^{-3}$ mm. On hydrolysis with $D_2O$, it gives the calculated amount of D-C(CH$_3$)$_3$, and on prolonged heating (30 h) at 120 °C it isomerizes only partly (30 %) to *(4)*.

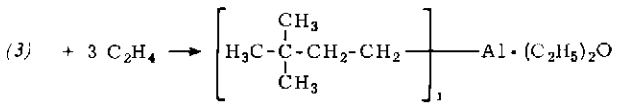


*(4)*

This isomerization is complete after heating for 24 h at 170 °C, 1 mole of isobutene and 1 mole of ethane being evolved simultaneously per mole of *(3)*. The dibutylaluminum hydride produced by the elimination of isobutene at this high temperature clearly reacts with the ether:

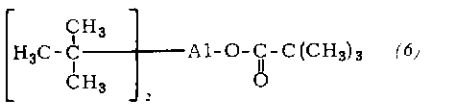
$$Bu_2AlH + (C_2H_5)_2O \rightarrow Bu_2AlOC_2H_5 + C_2H_6$$

In tri-t-butylaluminum etherate *(3)*, the bonds between the Al and the tertiary carbon atoms are considerably activated (like those in t-butyl-lithium [4]). Reaction of *(3)* with ethylene (ca. 60 atm) at 100–110 °C for 24 h gives a quantitative yield of *(5)*.



*(5)*

Under these conditions, trialkylaluminum etherates with bonds between the Al and primary carbon atoms react to only a very minor extent; triethylaluminum etherate, for example, gives only ca. 14 % tributylaluminum etherate. Propene does not add onto *(3)* and, as with other trialkylaluminum etherates [5], only one Al–C bond in *(3)* reacts with $CO_2$ at 100 °C; this reaction affords the crystalline compound *(6)*, which does not melt until 240 °C.



*(6)*

Replacement of one of the t-butyl groups in *(3)* by an alkoxy group gives ether-free di-t-butylaluminum alkoxides which no longer show abnormal reactivity towards ethylene.

Received, July 20th, 1964 [Z 790/609 IE]
German version: Angew. Chem. 76 (1964), in the press.

[1] *K. Ziegler*, Angew. Chem. *64*, 323, 324 (1952).

[2] *K. Ziegler, H. G. Gellert, K. Zosel, E. Holzkamp, J. Schneider, M. Söll*, and *W. R. Kroll*, Liebigs Ann. Chem. *629*, 121, 144 (1960).

[3] *L. J. Zakharkin* and *O. Yu. Oklobystin*, Izvest. Akad. Nauk SSSR *1958*, 1278; Chem. Abstr. *53*, 4115 (1959).

[4] *P. D. Bartlett, S. Friedman*, and *M. Stiles*, J. Amer. chem. Soc. *75*, 1771 (1953).

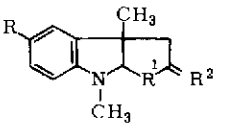
[5] *K. Ziegler, F. Krupp, K. Weyer*, and *W. Larbig*, Liebigs Ann. Chem. *629*, 251, 252 (1960).

## A New Synthesis of the Eserine Skeleton

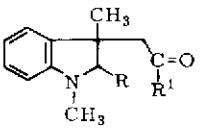
By Dr. P. Rosenmund and A. Sotiriou

Organisch-Chemisches Institut
der Universität Frankfurt/Main (Germany)

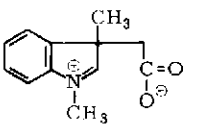
We have found that the lactone *(1)* obtained *via* 1,3-dimethyl-3-ethoxycarbonylmethylindolenine from the *N*-methylphenylhydrazone of ethyl β-formylbutyrate by hydrolysis with alcoholic KOH and acidification (overall yield for the 3 stages: 21 %) reacts quantitatively with primary amines at 50 °C in methanol as solvent to yield the corresponding lactams. Thus, methylamine yields the lactam *(2)*, which is quantitatively reduced by $LiAlH_4$ to the eserine skeleton *(3)* [eserine = *(4)*]. With equimolar amounts of dimethylamine, in addition to unchanged *(1)*, the amide *(5)* and its derivative



*(1)*, R = H, $R^1$ = O, $R^2$ = O
*(2)*, R = H, $R^1$ = N-CH$_3$, $R^2$ = O
*(3)*, R = H, $R^1$ = N-CH$_3$, $R^2$ = H$_2$
*(4)*, R = O-CO-NHCH$_3$, $R^1$ = N-CH$_3$, $R^2$ = H$_2$



*(5)*, R = OH, $R^1$ = N(CH$_3$)$_2$
*(6)*, R = N(CH$_3$)$_2$, $R^1$ = N(CH$_3$)$_2$



*(7)*

*(6)*, which is formed by interaction of *(5)* with dimethylamine, are obtained. Free carboxylic acid is not produced. It is therefore concluded that the conversion of the lactone into the lactam is initiated by a normal hydrolysis and does not involve the zwitterion *(7)*.

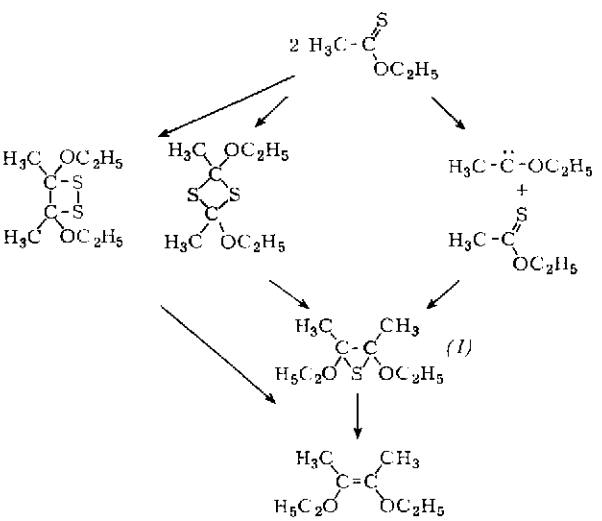
Received, July 21st, 1964 [Z 791/610 IE]
German version: Angew. Chem. 76, 787 (1964)

## Photochemical Synthesis of Endiol Ethers from Thiocarboxylic O-Esters

By Prof. Dr. Ulrich Schmidt and Dr. K. H. Kabitzke

Chemisches Laboratorium
der Universität Freiburg/Breisgau (Germany)

While searching for a reaction medium which would liberate monomolecular sulfur under mild conditions, we discovered a new photochemical process for the formation of C–C bonds. If *O*-ethyl thioacetate is irradiated with light of 254 mμ wavelength at 40 °C in the absence of solvent, 2,3-diethoxy-2-butene (b.p. 83–84 °C/80 mm, $n_D^{20}$ = 1.4161, *cis*: *trans* ≈ 2:3) is formed at 25 % conversion in 65 % yield. This compound reacts with dinitrophenylhydrazine in strongly acidic solution to give the bisdinitrophenylhydrazone of diacetyl. 3,4-Diethoxy-3-hexene (b.p. 64 66 °C/12 mm, $n_D^{20}$ = 1.4263) is formed in 60 % yield at 20 % conversion on irradiation of *O*-ethyl thiopropionate.



*(1)*

We are attempting to determine whether the dialkoxy olefins are formed by dimerization of the thiocarboxylic esters to 1,2- or 1,3-dithiacyclobutanes followed by stepwise elimination of sulfur *via* ethylene sulfides, *e.g. (1)*, or whether an ethoxycarbene is formed first and reacts with the thiocarboxylic ester to give the ethylene sulfide. A small amount of the ethylene sulfide *(1)*, m.p. 50–52 °C, $\lambda_{max}$ – 254 mμ, was isolated from an irradiation experiment.

C=S compounds with a π–π* transition at ca. 250 mμ appear to lose sulfur readily on irradiation; isocyanides are formed from isothiocyanates.

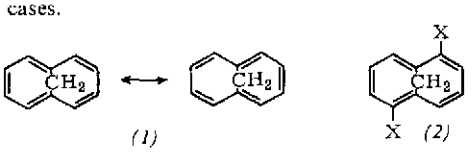
Received, May 19th, 1964; supplemented, June 22nd, 1964
Publication deferred until now at the authors' request [Z 775/605 IE]
German version: Angew. Chem. *76*, 687 (1964)

## Substitution of 1,6-Methanocyclodecapentaene

By Prof. Dr. E. Vogel and Dr. W. A. Böll

Institut für Organische Chemie
der Universität Köln (Germany)

On the basis of its NMR spectrum, we proposed that 1,6-methanocyclodecapentaene has the structure *(1)* with a delocalized system of 10 π-electrons [1]. Further investigations have shown that also the chemistry of this hydrocarbon is in accord with the concept of aromaticity. Although *(1)* formally contains five double bonds, it shows no tendency to polymerize and does not react with maleic anhydride in boiling benzene. When treated with electrophilic agents, it gives rise to mono- and disubstituted 1,6-methanocyclodecapentaenes *(2)* [2]; an addition-elimination mechanism seems to be involved at least in some cases.




*(1)* *(2)*

monosubstituted: X = Br, Cl, $COCH_3$, COOH, $NO_2$
disubstituted: X = Br, $NO_2$

Bromination of *(1)* with 1 mole of *N*-bromosuccinimide yields 90 % of a yellow monobromo derivative, b.p. 87 to 88 °C/0.05 mm; NMR: complex multiplet at 2.1–3.4 τ and an AB system at 10.5 τ (proton ratio 7:2); ultraviolet spectrum: maxima at 244 (ε = 17700), 266 (49500), 313 (6700), 395 (260), 405 (285), and 415 mμ (225) [3]. Reaction of *(1)* with 2 moles of *N*-bromosuccinimide leads to 40 % of a yellow dibromo compound, m.p. 87 °C; NMR: ABC system at 2.1–3.2 τ and a singlet at 10.3 τ (proton ratio 6:2); ultraviolet spectrum: maxima at 234 (ε = 13500), 277 (61000), 327 (8200), and 419 mμ (530). The monobromo derivative can be converted easily into the Grignard compound, which on carboxylation affords 82 % of an orange-brown carboxylic acid, m.p. 172–173 °C. Acetylation of *(1)* with acetic anhydride and $SnCl_4$ produces 82 % of an orange monoacetyl derivative, b.p. 92–94 °C/0.06 mm, which can also be converted into the carboxylic acid mentioned above by reaction with NaOBr. Nitration of *(1)* with $Cu(NO_3)_2$ in acetic anhydride leads to 53 % of a yellow mononitro product, b.p. 109–110 °C/0.04 mm, which is probably a mixture of the 2- and 3-nitro compounds, plus 4 % of a yellow-orange dinitro derivative, m.p. 113 °C.

Although the spectra of the new compounds indicate clearly that they are all substitution products of *(1)*, the position of the substituents as being at C-2 and C-7 *(2)* is supported only by the NMR spectra [4] of the dibromo and dinitro derivatives. However, X-ray structural analysis [5] of the dibromo compound has recently confirmed that the bromine atoms are in fact at C-2 and C-7.

In addition to maxima at 256 (ε = 68000), 259 (63000), and 298 mμ (6200) [1], the ultraviolet spectrum of *(1)* exhibits a long-wavelength band with 8 maxima between 350 and 400 mμ (ε = 95–185), which gives the hydrocarbon a yellow cast [6]. Low-temperature NMR spectra (down to −145 °C) give no indication of a fluctuating structure; the appearance of the spectrum remains unchanged [7]. Further evidence against the valence-bond isomeric cyclopropane structure previously considered for the hydrocarbon is the $^{13}C$–H coupling constant of the methylene hydrogen atoms (142 cps) [7]. This value is compatible with a C–$CH_2$–C bond angle of about 90 °, which is suggested by models of the molecule [8].

Received, August 5th, 1964 [Z 794/615 IE]
German version: Angew. Chem. *76*, 784 (1964)

[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964).

[2] The chemical properties of *(1)* are strikingly similar to those of *trans*-15,16-dimethyldihydropyrene [*V. Boekelheide* and *J. B. Phillips*, Proc. nat. Acad. Sci. *51*, 550 (1964)], which has a system of 14 π-electrons.

[3] The reaction of *(1)* with bromine at −10 °C also leads to the monobromo derivative, but at −75 °C a tetrabromide (addition product), m.p. 145–146 °C, is formed which gives spectra that indicate a cyclopropane structure.

[4] We wish to thank Dr. *H. Günther* and Prof. *A. A. Bothner-By* for interpretation of the NMR spectra.

[5] Personal communication from Prof. *J. D. Dunitz*, E.T.H. Zürich (Switzerland).

[6] Prof. *E. Heilbronner*, E.T.H. Zürich (Switzerland) is at present carrying out a theoretical evaluation of the spectra of *(1)* and its derivatives.

[7] We wish to thank Dr. *J. B. Lambert*, California Institute of Technology, Pasadena, Cal. (U.S.A.), for carrying out these measurements.

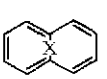
[8] *C. S. Foote*, Tetrahedron Letters *1963*, 579; *K. Mislow*, ibid. *1964*, 1415.

## Cyclodecapentaenes with a 1,6-Heteroatomic Bridge [*]

By Prof. Dr. E. Vogel, Dipl.-Chem. M. Biskup, Dipl.-Chem. W. Pretzer, and Dr. W. A. Böll

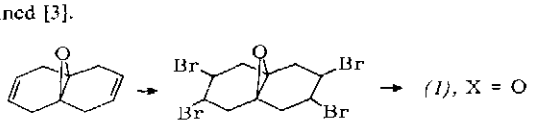
Institut für Organische Chemie
der Universität Köln (Germany)

The synthesis and properties of 1,6-methanocyclodecapentaene *(1)*, X = $CH_2$, [1] gave rise to the expectation that dehydrobromination of the tetrabromides *(3)* and *(6)* with suitable bases would lead to stable cyclodecapentaenes *(1)* bridged by an oxygen or a nitrogen atom, respectively. The analogous sulfur-bridged compound would most probably lose sulfur readily to form naphthalene.



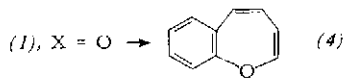

*(1)*, X = $CH_2$, O, $NCOCH_3$, (S)

The tetrabromide *(3)*, m.p. 152–154 °C, is obtained from *(2)* [2] and is probably a mixture of isomers; on dehydrobromination with potassium t-butoxide in ether at −10 °C it affords 60 % of a pale yellow, stable compound $C_{10}H_8O$, m.p. 52–53 °C. Its NMR spectrum consists only of an $A_2B_2$ system centred at 2.56 τ. The ultraviolet spectrum has maxima at 257 (ε = 74500) and 302 mμ (7100) and about sixteen maxima between 345 and 435 mμ (ε between 50 and 300). These spectra correspond to those of 1,6-methanocyclodecapentaene. This proves that the 1,6-oxygen-bridged cyclodecapentaene *(1)*, X = O, has been obtained [3].




*(2)* *(3)*

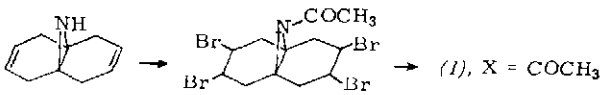
The chemical properties of *(1)*, X = O, are also in accord with the proposed structure. Treatment of the compound with acids leads to α-naphthol and other products; during chromatography on silica gel it isomerizes to 1-benzoxepin *(4)* [3], a yellow liquid, b.p. 101–102 °C/14 mm, $n_D^{20}$ = 1.6015 (yield up to 77 %). The structure of the rearrangement



*(1)*, X = O → *(4)*

product *(4)* is secured by its spectra and its catalytic hydrogenation to yield the known tetrahydro-1-benzoxepin, m.p. 30 °C [4].

The aziridine *(5)*, b.p. 76–77 °C/0.6 mm, required for the synthesis of the acetylimino-bridged compound *(1)*, X = $NCOCH_3$, was prepared from the nitrosochloride [2] of 1,4,5,8-tetrahydronaphthalene using the method of *Closs* [5]. Bromination of the *N*-acetyl derivative of *(5)*, m.p. 73–74 °C, gave the tetrabromide *(6)* as an oil, which reacted with potassium t-butoxide in tetrahydrofuran at −15 °C to form *(1)*, X = $NCOCH_3$, as pale yellow crystals, m.p. 160–161 °C,



*(5)* *(6)* → *(1)*, X = $COCH_3$

in 25–30 % yield [6]. The main evidence for structure *(1)*, X = $NCOCH_3$, is again given by the NMR spectrum of the compound; it exhibits an $A_2B_2$ system (8 protons) centred at 2.35 τ and a $CH_3$ singlet at 8.97 τ. Further support for structure *(1)*, X = $NCOCH_3$, is obtained from the ultraviolet spectrum, which has maxima at 252 (ε = 57000), 299 (5500), 387 (300), 398 (500), and 408 mμ (570) and agrees well with the ultraviolet spectra of *(1)*, X = $CH_2$, and *(1)*, X = O [7].

Received, August 5th, 1964 [Z 795/611 IE]
German version: Angew. Chem. *76*, 785 (1964)

[*] We have been prompted to publish a brief report on some of our results by the fact that our principle for synthesizing 1,6-bridged cyclodecapentaenes has meanwhile been applied by *F. Sondheimer* and *A. Shani*, J. Amer. chem. Soc. *86*, 3168 (1964).

[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964).

[2] *W. Hückel* and *H. Schlee*, Chem. Ber. *88*, 346 (1955).

[3] The results of the dehydrobromination of *(3)* inspired the synthesis of oxepins from 1,2-epoxy-4,5-dibromocyclohexanes: *E. Vogel*, *R. Schubart*, and *W. A. Böll*, Angew. Chem. *76*, 535 (1964); Angew. Chem. internat. Edit. *3*, 510 (1964). It was mentioned in this publication (footnote [2]) that we had obtained *(4)*.

[4] *G. Baddeley*, *N. H. P. Smith*, and *M. A. Vickars*, J. chem. Soc. (London) *1956*, 2455.

[5] *G. L. Closs* and *S. J. Brois*, J. Amer. chem. Soc. *82*, 6068 (1960).

[6] All of the new substances gave satisfactory results on elementary analysis.

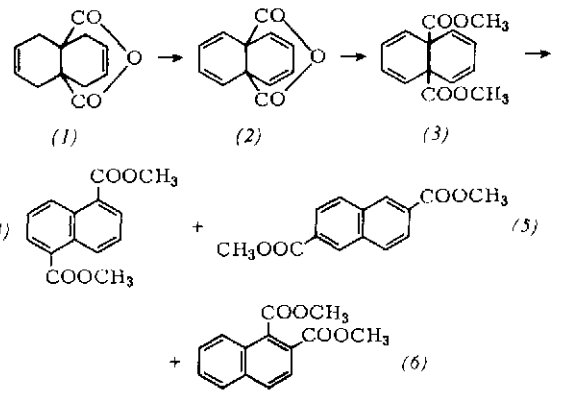
[7] We wish to thank Dr. *H. Günther* for measuring and interpreting the NMR spectra.

## Attempted Synthesis of Cyclodecapentaenes by Valence-Bond Isomerization of 9,10-Dihydronaphthalenes

By Prof. Dr. E. Vogel, Dipl.-Chem. W. Meckel, and Dr. W. Grimme

Institut für Organische Chemie
der Universität Köln (Germany)

Valence-bond isomerization of 9,10-dihydronaphthalenes represents an attractive approach to the synthesis of the hitherto unknown simple cyclodecapentaenes [1]. With the *cis*-9,10-dihydronaphthalene recently described by *van Tamelen* [2], observation of thermal isomerization to (or of establishment of an equilibrium with) cyclodecapentaene is rendered difficult by the fact that the tetraene undergoes dehydrogenation to give naphthalene even at relatively low temperatures. However, with dimethyl *cis*-9,10-dihydronaphthalene-9,10-dicarboxylate *(3)*, dehydrogenation or 1,5-hydrogen shift as reactions competing with the isomerization to a cyclodecapentaene derivative are excluded [3].



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



*(4)* + *(5)*



+ *(6)*

Dimethyl *cis*-$\Delta^{2,6}$-hexalin-9,10-dicarboxylate [4] is a suitable starting material for the synthesis of *(3)*, but attempts to convert it into *(3)* remained without success. In contrast, the corresponding anhydride *(1)* reacted smoothly with 2 moles of *N*-bromosuccinimide to give a dibromo derivative from which 25–30 % of the tetraene *(2)*, m.p. 74–75 °C, were obtained by dehydrobromination with quinoline. The structure of *(2)* was confirmed by its catalytic hydrogenation to *cis*-decalin-9,10-dicarboxylic anhydride and by its NMR spectrum, which shows only an $A_2B_2$ system centred at 4.17 τ. The maximum at 243 mμ (ε = 7900) in the ultraviolet spectrum of *(2)* corresponds to that of other known *cis*-9,10-dihydronaphthalene derivatives [2, 3]. Esterification of *(2)* with methanol led to a thermolabile dimethyl ester, m.p. 103–104 °C, whose spectra [NMR: $A_2B_2$ system centred at 4.30 τ plus singlet at 6.38 τ, proton ratio 8:6; ultraviolet absorption maximum at 258 mμ (ε = 7100)] and catalytic hydrogenation to dimethyl *cis*-decalin-9,10-dicarboxylate indicated that it was the desired compound *(3)*.

When heated at 90 °C for 2 h, *(3)* rearranges to a mixture of esters which probably consists mainly of isomeric 9,10-dihydronaphthalenedicarboxylic esters. Subsequent heating of this mixture at 150 °C, with or without Pd, produces dimethyl 1,5-, 2,6-, and 1,2-naphthalenedicarboxylates *(4)*–*(6)* and other unidentified products. While the formation of *(4)* and *(5)* is indicative of the transient occurrence of an unstable cyclodecapentaene derivative [5], the isolation of *(6)* demonstrates that there are modes of rearrangement of *(3)* other than that originally visualized.

Received, August 5th, 1964 [Z 796/612 IE]
German version: Angew. Chem. *76*, 786 (1964)

[1] For the synthesis of 1,6-bridged cyclodecapentaenes see *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964); *E. Vogel*, *M. Biskup*, *W. Pretzer*, and *W. A. Böll*, Angew. Chem. *76*, 785 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964).

[2] *E. E. van Tamelen* and *B. Pappas*, J. Amer. chem. Soc. *85*, 3296 (1963).

[3] Experiments with similar aims were recently reported by *J. J. Bloomfield* and *W. T. Quinlin*, J. Amer. chem. Soc. *86*, 2738 (1964). The 9,10-dihydronaphthalene derivative described by these authors was also known to Prof. *V. Prelog* (personal communication in 1960).

[4] *K. Alder* and *K. H. Backendorf*, Ber. dtsch. chem. Ges. *71*, 2199 (1938).

[5] In this connection cf. the interpretation of the pyrolysis of the adduct of cyclooctatetraene and dimethyl acetylenedicarboxylate: *M. Avram*, *C. D. Nenitzescu*, and *E. Marica*, Chem. Ber. *90*, 1857 (1957); *R. C. Cookson*, *J. Hudec*, and *J. Marsden*, Chem. and Ind. *1961*, 21.

# Meeting of West German Chemistry Lecturers

**April 27th–30th, 1964 in Freiburg/Breisgau (Germany)**

From the Agenda:

## Reactions of Metal-Substituted Hydrides with Halogenosilanes

*E. Amberger, H. D. Boeters,* and *Maria-Regina Kula,* Munich (Germany)

The reaction of silyl bromide with potassium dihydrogen phosphide, arsenide, or antimonide in dimethyl ether at the melting point of the ether ( 138 °C) yields the expected monosilyl derivatives of phosphine, arsine, or stibine according to Equation (1).

$$H_3SiBr + KEH_2 \rightarrow H_3SiEH_2 + KBr \qquad (1)$$

E = P, As, or Sb

Trisilylphosphine and phosphine or trisilylarsine and arsine are formed at higher temperatures [Equation (2)].

$$H_3SiEH_2 + 2\ H_3SiBr + 2\ KEH_2 \rightarrow E(SiH_3)_3 + 2\ KBr + EH_3 \qquad (2)$$

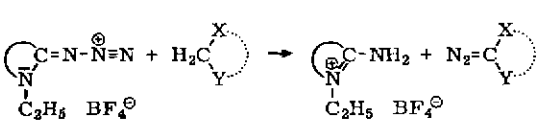
Silylstibine $H_3SiSbH_2$, on the other hand, does not form trisilylstibine according to Equation (2), but disproportionates to form silane, a polymeric antimony hydride, and hydrogen.

The first step in the formation of the trisilyl derivative is not a kind of α-elimination from the silyl bromide followed by electrophilic addition of the $SiH_2$ onto phosphorus dihydride anions, but rather a nucleophilic substitution of $PH_2$ or $AsH_2$ on the silicon. This is followed by an acid-base reaction of the resulting monosubstituted product with potassium dihydrogen phosphide or arsenide, leading to the formation of the trisilyl derivatives. Similar acid-base reactions are observed in syntheses of higher silanes by the reaction of silylpotassium with silicon halides. Trisilylstibine has been prepared by treating silyl bromide with finely divided tripotassium antimonide. The isologous carbon derivative trisilylmethane $HC(SiH_3)_3$ has been prepared by hydrogenation of $HC(SiCl_3)_3$.

## Introduction of Diazo Groups into Reactive Methylene Compounds by Azidinium Salts

*H. Balli,* Marburg/Lahn and *V. Müller,* Karlsruhe (Germany)

Diazo compounds of the type *(3)* can be prepared simply from azidinium salts *(1)* [1] and compounds with reactive methylene groups *(2)*.



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

Hitherto, the range of application of this synthesis was investigated predominantly by testing the reaction of 2-azido-3-ethylbenzothiazolium fluoroborate with C–H acidic compounds *(2)*, in which the activating groups X and Y are >CO, >C=C<, –CN, and >C=N–, generally as ring members. Multiple reaction occurs with components *(2)* containing several reaction centers.

The following diazo compounds and quinone diazides have been prepared (yield in % in parentheses): 5-diazobarbituric acid (84), 4-diazo-3-phenylisoxazol-5-one (77), 4-diazo-1-phenyl-3-methylpyrazol-5-one (96), 2-diazoindane-1,3-dione (84), 2-diazodimedone (77), ω-diazo-ω-cyanoacetophenone (88), 1-diazo-2-naphthol (21), 2,4-bisdiazoresorcinol (31), and trisdiazophloroglucinol (95).

The mechanism of the transfer reaction was discussed.

## Preparation of Helium from Lithium Deuteride by Thermonuclear Fusion

*F. Baumgärtner,* Munich (Germany)

Nuclear fusion of deuterium and tritium yields helium and a neutron with a kinetic energy of 14 MeV:

$$(1) \quad T + D \rightarrow He + n_{14\,MeV}.$$

Tritium is produced in the nuclear reaction

$$(2) \quad {}^6Li + n_{therm} \rightarrow T + He.$$

In this reaction, the triton receives an initial energy of 2.74 MeV. This is considerably higher than the energy of 0.2 MeV normally used in particle accelerators for the D–T reaction of Equation (1). Consequently, the high-energy tritons from reaction (2) appeared suitable for use in the fusion reaction (1). The sum effect of this coupled reaction is that lithium-6 and deuterium are converted into helium:

$$(1) + (2) \quad {}^6Li + D \rightarrow 2\ He + 22.4\ MeV.$$

A tube made of $^6LiD$ with walls 1 mm thick was placed in a thermal neutron field. The walls were sufficiently thick to ensure quantitative conversion of the incident neutrons according to Equation (2). Titanium or chromium probes were placed inside the tubes to detect the fast neutrons.

These elements give positively identifiable positron radiation, resulting from an (n,2n) reaction with fast neutrons with kinetic energies of 13.2 and 13.3 MeV. The thermal neutron flux present is simultaneously measured on the outside of the tube with a cobalt wire using the nuclear reaction $^{59}Co(n,\gamma)^{60}Co$.

This conversion of $^6LiD$ to helium is economically unsuitable for the production of energy, since the power density for a flux of $10^{13}$ neutrons/cm²/sec is only about 35 mW/cm³, and furthermore, the reaction is not self maintaining. However, it is advantageous to be able to convert thermal neutrons into fast neutrons (14 MeV) in this way [2], obtaining a partly higher, but above all more durable flux of fast neutrons than with simple accelerators.

## Catalytic Dehydration with Elemental Boron

*H. J. Becher, L. Marosi,* and *H. Widmann,* Stuttgart (Germany)

The catalytic properties of elemental boron (99 %, prepared by reduction of $BBr_3$ with $H_2$ at 750 °C; shown by electron microscopic and X-ray investigations to be the very finely

[1] *H. Balli* and *F. Kersting,* Liebigs Ann. Chem. *647,* 1 (1961).

[2] *F. Baumgärtner,* Radiochim. Acta *1,* 222 (1963).

crystalline α-modification; particle diameter 0.075 μ) were investigated in various decomposition reactions. Formic acid vapor is dehydrated between 200 and 300 °C. The dehydration of acetic acid vapor to acetic anhydride only becomes measurable above 350 °C, and proceeds in about 25 % yield at 500–550 °C. Alcohols are also almost exclusively dehydrated at 250–350 °C. On the other hand, α-boron has no effect on the reaction of ethylene or isopropylene with benzene at normal pressure and at temperatures of up to 550 °C.

The catalytic activity of boron in dehydrations corresponds roughly to that of γ-$Al_2O_3$, but the concurrent dehydrogenation evidently plays a less important part in the case of boron. Moreover, considerably less α-boron than $Al_2O_3$ is required for the reactions. The catalysis probably takes place on BO- or BOH-groups on the surface of the catalyst. The boron-boron arrangement must also be important, however, since finely powdered boron with a higher amorphous fraction and greater oxygen content shows weaker activity at moderate temperatures.

## Amino-Acid Sequences in Phosvitin

*H.-D. Belitz*, Berlin (Germany)

Phosvitin, the principal phosphoprotein of hen's egg yolk, with a phosphorus content of about 10 %, was cleaved with trypsin. The enzymatic hydrolysate was separated into peptides on Dowex 1X2 anion exchanger. The amino-acid sequence of a peptide containing 63 amino acid residues:

$asp_3,ser_{42},glu,gly,val,leu,his_5,lys_5,arg_4,(PO_3H_2)_{42}$

was investigated. The large peptide was broken down into smaller fragments by partial hydrolysis with HCl and by enzymatic dephosphorylation followed by cleavage with trypsin. Amino-acid and end-group analyses of the fragments gave the following partial structural formula:

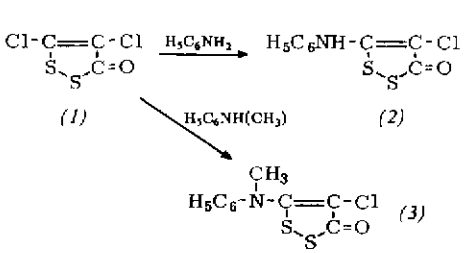
asp — $Pser_6$ — arg—asp—(Pser$_6$,lys)—(Pser$_6$,lys)— arg—(Pser$_6$,his)—
$Pser_6$ his—lys—asp—gly—val—(Pser$_3$, glu)—lys—(leu, Pser$_3$)—
his—his —arg—$Pser_6$— arg—his—lys

This indicates that phosvitin contains successions of 3–6 phosphoserine residues, separated by other, predominantly basic amino acids. The peptide investigated corresponds to about one-third of the total phosvitin molecule, which has a molecular weight of about $3\times10^4$, and contains about 170 amino-acid residues.

## Alkaline Cleavage of the 1,2-Dithiacyclopenten-3-one Ring

*F. Boberg*, Hannover (Germany)

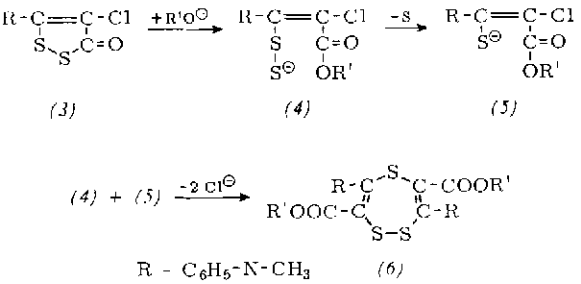
4,5-Dichloro-1,2-dithiacyclopenten-3-one *(1)* [3] reacts with aniline to form the 5-anilino compound *(2)*, which has an acidic NH group. Methylation of the *N*-sodium or *N*-potassium derivative of *(2)* leads to *(3)*, which can also be prepared directly from *(1)* and *N*-methylaniline.




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

[3] *F. Boberg* and *A. Marei*, Angew. Chem. *74*, 495 (1962).

The action of alcoholic alkali on *(3)* yields the 1,2,5-trithiacycloheptadiene derivative *(6)*. This shows that nucleophilic



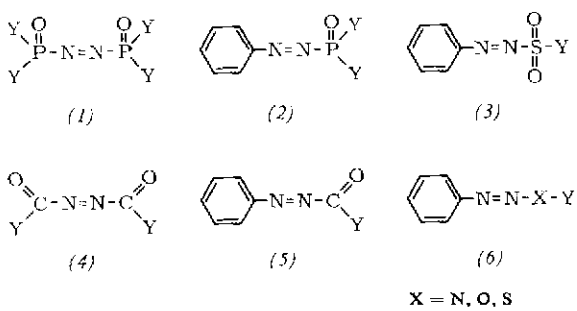

*(3)* *(4)* *(5)* *(6)*

reagents open the 1,2-dithiacyclopentenone ring at the CO–S bond. 1,2,5-Trithiacycloheptadienes with other residues R and R′ can also be prepared by this method.

## Relationships between the Color and Constitution of Azo Compounds

*H. Bock*, *E. Baltin*, *J. Kroner*, and *G. Rudolph*, Munich (Germany)

The π-electron system of azobis(phosphonic acid) derivatives *(1)* [4] is not very extensive. Their fascinating violet color led to the preparation and spectroscopic characterization of more than 60 azo compounds of types *(1)*–*(6)*.




*(1)* *(2)* *(3)* *(4)* *(5)* *(6)*

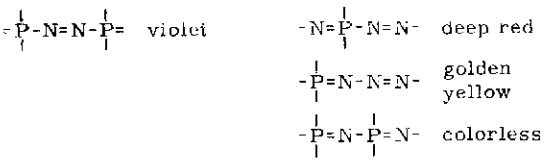
X = N, O, S

In the course of these investigations, regularities were observed, particularly for the color-determining $n\rightarrow\pi^*$ transitions, which justified the assumption of substituent-specific absorption increments. Thus, the wavelengths and intensities of the $n\rightarrow\pi^*$ maxima of unsymmetrically substituted azo compounds A–N=N–B lie, in all the compounds of types *(1)*–*(6)* studied, between those of A–N=N–A and B–N=N–B [5]. However, the mechanism of the substituent effect is not yet known, since within an LCAO/MO description, besides inductive raising of the n term and conjugative lowering of the π*-level, the $n\rightarrow\pi^*$ excitation could also be displaced toward longer wavelengths by effects of suitable d-orbitals, which are difficult to evaluate. In this connection, the following properties were discussed: the related $\pi\rightarrow\pi^*$ transitions, which, however, do not follow any analogous rules, the minute solvatochromic effects, and the different band shapes of compounds belonging to classes *(1)* to *(6)*. In the phosphorus-azo compounds *(1)* and *(2)*, inhibition of conjugation by phosphorus atoms with a coordination number of four can be verified by a linear relationship between the PO valence vibration frequency and the electronegativity of the substituents, on the basis of the similar absorption of P–O, P–S, and P–NR azo systems and the color of subsequently synthesized phosphorus-nitrogen chains [6].

[4] *H. Bock* and *G. Rudolph*, Chem. Ber. *94*, 1457 (1961).

[5] *H. Bock*, *E. Baltin*, and *G. Rudolph*, Angew. Chem. *75*, 789 (1963); Angew. Chem. internat. Edit. *2*, 484 (1963).

[6] *H. Bock* and *W. Wiegräbe*, Angew. Chem. *75*, 789 (1963); Angew. Chem. internat. Edit. *2*, 484 (1963).




These substituent effects were described here in detail for the first time but appear to be of a more general nature: according to our investigations, similar influences determine the $n \rightarrow \pi^*$ transitions of other chromophores.

## The Chemistry of $TiO_2$ Surfaces

*H.-P. Boehm* and *M. Herrmann*, Heidelberg (Germany)

Fresh cleavage surfaces of a $TiO_2$ crystal contain $Ti^{4+}$ and $O^{2-}$ ions. On access of water, the vacant coordination sites on the $Ti^{4+}$ ions are occupied by $H_2O$ molecules, each of which gives up a proton to the surface $O^{2-}$ ions. This proton transfer leads to a more uniform charge distribution. The two resulting hydroxide ions are attached in different ways and differ in chemical reactivity, as was shown by investigations on finely divided anatase.

On treatment of $TiO_2$ with alkali fluoride solutions, the hydroxide ions are exchanged for fluoride ions. The liberated hydroxide ions can be titrated, their quantity being dependent upon the specific surface area. After reaction of $TiO_2$ with thionyl chloride, the chloride content was equivalent to the amount of hydroxide ions. On shaking $TiO_2$ powder with basic solutions of aluminum chloride, one aluminum ion was adsorbed per hydroxide ion. An equivalent degree of conversion was also achieved in a few other reactions, *e.g.* neutralization with alkali. On the other hand, in other reactions, *e.g.* with unbuffered NaF solution, ammonia, or diazomethane, only half of the hydroxide ions was found to react.

$TiO_2$ surfaces are strongly polar and always adsorb some $CO_2$ on contact with air. The adsorbed carbon dioxide was detected by infrared spectroscopy and by chemical analysis. $NO_2$ is also very strongly adsorbed; nitrate ions could be detected on the surface. Furthermore, the surface of finely divided $TiO_2$ always contains organic contaminants, which must be eliminated prior to any investigation, in order to prevent reduction of the surface $Ti^{4+}$ ions. If this reduction is allowed to occur, the $TiO_2$ surface acquires strongly acidic properties, as was shown by the change in color of adsorbed dimethylaminoazobenzene.

## Formation and Properties of Alkali Disilylamides

*H. Bürger* and *H. Seyffert*, Graz (Austria)

Colorless, crystalline alkali disilylamides $MN(SiR_3')_2$ [M = Li, Na, K (m.p. 165 °C), Rb (m.p. 178 °C), or Cs (m.p. 195 °C)] are formed by metallation of $HN(SiR_3')_2$ with MX [X = alkyl, aryl, H, or $NH_2$]. Using $H^{15}N$-$[Si(CH_3)_3]_2$ it was shown that the reaction

$$HN(SiR_3')_2 + NaNH_2 \rightarrow NaN(SiR_3')_2 + NH_3 \quad [R' = CH_3]$$

is a true metallation, in contrast to the silylation of urea according to the equation

$$HN(SiR_3')_2 + H_2N{-}CO{-}NH_2 \rightarrow R_3'Si{-}NH{-}CO{-}NH{-}SiR_3' + NH_3$$

$LiN(SiR_3')_2$ and $NaN(SiR_3')_2$ can be distilled without decomposition. The compounds $MN(SiR_3)_2$ are readily soluble in aromatic hydrocarbons, but only sparingly soluble in aliphatic hydrocarbons. Their solubility increases with increasing electropositivity of M. The compounds $MN(SiR_3)_2$ react with practically all polar solvents and add on $NH_3$, pyridine, ether, tetrahydrofuran, and $HN(SiR_3')_2$, which all act as Lewis bases. In benzene, the compounds $MN(SiR_3)_2$ exist as dimers *(1)*; neither these solutions nor the fused compounds conduct electricity. On the other hand, $KN(SiR_3')_2$ forms a solution of high conductivity in liquid $NH_3$ in which metathetical reactions can occur, *e.g.* with $Ag(NH_3)_2Cl$ to form explosive $AgN(SiR_3')_2$. Spectroscopic studies have shown that the contribution of salt-like structures *(2)* increases with decreasing electronegativity of the cation.

$$[(R_3Si)_2{-}NM]_2 \longleftrightarrow 2\,[R_3\overset{\ominus}{Si}{=}\overset{\oplus}{N}{=}\overset{\ominus}{Si}R_3] + 2\,M^+$$
*(1)* *(2)*

$NaN(SiR_3')_2$ in tetrahydrofuran or ether is the most suitable reagent for the preparation of other metal disilylamides. Thus, transition metal halides gave silylamides of the elements Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd, and Hg, which are all extremely sensitive to hydrolysis.

## A New Synthesis of Oxide Iodides

*K. Dehnicke*, Stuttgart (Germany)

Gaseous ozone reacts exothermally at room temperature with metal iodides dissolved in inert solvents (cyclohexane, carbon tetrachloride). For example:

$$TiI_4 + O_3 \rightarrow TiOI_2 + O_2 + I_2$$

This reaction gives good yields of the hitherto unknown oxide iodides $TiOI_2$ and $SnOI_2$ as very hygroscopic brown solids which are amorphous to X-rays. $TiOI_2$ splits off elemental iodine at 105 °C to form TiOI. Magnetic measurements indicate that TiOI is antiferromagnetic. $SnOI_2$ disproportionates above 110 °C to $SnO_2$ and $SnI_4$.

Infrared spectra indicate that $TiOI_2$ exists as polymeric $[TiO]^{2+}_{\infty}\,2\,I^-$, with Ti O–Ti–O chains, while $SnOI_2$ has a structure with isolated complex ions (island structure). $TiOI_2$ reacts with pyridine to form an adduct of composition $TiOI_2{\cdot}3\,Py$, which may be formulated as $[TiO(Py)_3]^{2+}\,2\,I^-$. Owing to its island structure (coordination number 3), $SnOI_2$ adds on only one mole of pyridine.

## 1,4(N,O)-Cycloadditions of Azodicarboxylic Esters

*E. Fahr*, *K. H. Keil*, *F. Scheckenbach*, and *A. Jung*, Würzburg (Germany)

The formation of oxadiazolines *(1)* in the reaction of diazo compounds with azodicarboxylic esters suggests that the latter can undergo not only the known 1,2(*N*,*N*)-additions but also 1,4(*N*,*O*)-cycloadditions. This assumption was found to be confirmed in the reaction of diphenylketene with azodicarboxylic esters, which yields both a 2:1 and a 1:1 adduct.

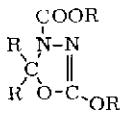
Structure *(2a)* has been discussed for the 2:1 adduct by *Ingold* and *Weaver* [6a] and by *Horner* and *Spietschka* [6b]. We were able to show, as follows, that the 2:1 adduct has the structure of the hitherto unknown bicyclic azetidinone System *(3a)* formed by 1,4(*N*,*O*)-cycloaddition of the azodicarboxylic ester: *(3a)* reacts with alcohols ($R^2OH$) to give *(4a)*, and with dilute acids to give *(4b)*. Compound *(4a)* reacts with dilute acids to give *(4b)*, and with alkalis to give *(4c)*, which is in turn converted by dilute acids into *(4d)*. The reaction of *(4d)* with diphenylacetyl chloride leads to *(4b)*, and with alkalis to benzilic acid; *(4b)* reacts with alkalis to yield *(5)*. On heating, *(3a)* irreversibly loses diphenylketene to yield the 1:1 adduct which, according to its infrared spectrum, should not be assigned the structure *(6)*, but presumably the diazetidinone structure *(7)*. The 1:1 adduct reacts with acids to give *(4d)*.

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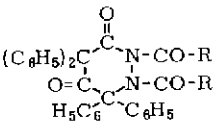
[6a] *C. K. Ingold* and *S. D. Weaver*, J. chem. Soc. (London) *127*, 378 (1925).

[6b] *L. Horner* and *E. Spietschka*, Chem. Ber. *89*, 2765 (1956).

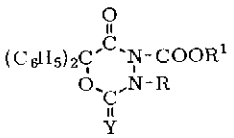
In analogy with *(3a)*, the structure of the 2:1 adduct of diphenylketene and azodibenzoyl (m. p. 161 °C) is not *(2b)* [6b], but *(3b)*. Degradation of *(3b)* yields *(5)*, among other products.

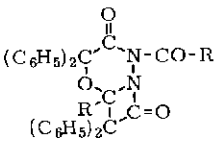


*(1)*



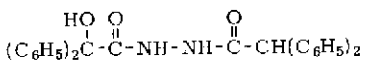
*(2a)* : R = $OR^1$
*(2b)* : R = $C_6H_5$



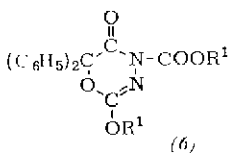


*(4a)* : R = $CO\text{-}CH(C_6H_5)_2$; Y = $OR^1$ + $OR^2$
*(4b)* : R = $CO\text{-}CH(C_6H_5)_2$; Y = O
*(4c)* : R = H; Y = $OR^1$ + $OR^2$
*(4d)* : R = H; Y = O

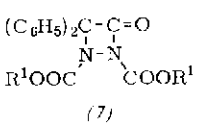
*(3a)* : R = $OR^1$
*(3b)* : R = $C_6H_5$



*(5)*



*(6)*



*(7)*

## The Relative Reactivities of Positional and Geometric Isomers of High Molecular-Weight n-Olefins

*B. Fell, F. Asinger, G. Steffan*, and *G. Hadik*, Aachen (Germany)

The following olefin reactions were studied for the nine positionally and geometrically isomeric n-undecenes, some prepared for the first time free from other isomers, as a function of the position and configuration of the double bond in the olefin molecule: addition of bromine, ionic addition of hydrogen bromide, epoxidation (Prileshayeff reaction), hydrogenation with hydrazine, and the addition of mercury(II) acetate in methanol (methoxymercuration). The rates of the first four reactions alternate in both the *cis-* and *trans-* series of n-undecenes, *i.e.* the 3- and 5-isomers in each case have higher rate constants than the 2- and 4-isomers. In the methoxymercuration reaction, on the other hand, the rate constant decreases continuously as the double bond approaches the center of the molecule; this behavior emphasizes the unique nature of this olefin reaction. Some of the reactions named were also carried out with positional and geometric isomers of n-octene. The rate constants of the isomers with internal double bonds again alternate. Thus, *cis-* and *trans*-n-3-octene react more rapidly than the respective 2- or 4-isomers.

## Amino Isocyanides

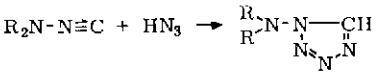
*B. Föhlisch, H. Bredereck*, and *K. Walz*, Stuttgart (Germany)

Dialkylamino isocyanides *(1)* are obtained in yields of 60–80% by the action of phosgene on *N,N*-dialkyl-*N'*-formylhydrazine in boiling methylene chloride in the presence of tertiary amines [7]. The dialkylamino isocyanides decompose at room temperature, and more rapidly on heating to form glyoxylonitrile-*N',N'*-dialkylhydrazones *(2)* and Schiff bases *(3)*.



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

The rate of decomposition can be followed spectroscopically and depends on the substituents R and on the solvent. Dialkylamino isocyanides react with $HN_3$ to form the hitherto unknown 1-dialkylaminotetrazoles *(4)*.

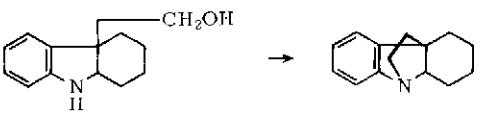


*(4)*

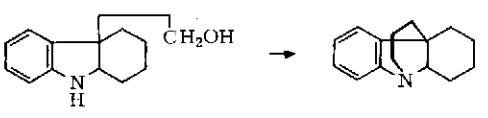
## Restricted Resonance in New Indolines with Fixed Nitrogen Torsion Angles

*H. Fritz* and *O. Fischer*, Frankfurt/Main (Germany)

The two tetracyclic indoline systems *(3)* and *(4)*, in which resonance is suppressed, have been synthesized respectively from *(1)* and from the new compound *(2)*, which was prepared by us by reduction of the corresponding acid with $LiAlH_4$.



*(1)* *(3)*



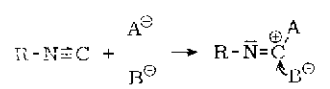
*(2)* *(4)*

These two twisted indolines enabled us to answer the question which is of theoretical interest and of importance in connection with the chromophores of alkaloids, namely what is the torsional angle at which the n-π conjugation is so greatly reduced that an aniline-type ultraviolet spectrum changes over to a benzene-type spectrum? This angle is about 65 °C, since *(4)*, in which φ = 60 °, still has an indoline spectrum, whereas *(3)*, with φ = 70 °, has a benzene-type spectrum. It is possible to test the quantitative validity of the $\cos^2\varphi$ function [*] by experimental determination of the energy contents [**] of compounds of types *(3)* and *(4)* with fixed torsional angles.

## A Contribution to the Chemistry of Isocyanides

*Ilse Hagedorn, U. Eholzer*, and *H. D. Winkelmann*, Freiburg/Brsg. (Germany)

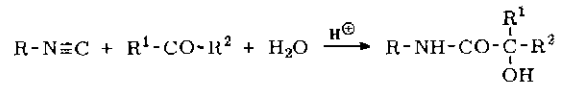
The isocyanide group reacts rapidly with protons and, in the Passerini reaction, which is catalysed by carboxylic acids, also with carbonium ions. Consequently, it is concluded that the isocyanide carbon has an exceptionally high nucleophilicity.



[7] *H. Bredereck, B. Föhlisch*, and *K. Walz*, Angew. Chem. *74*, 388 (1962); Angew. Chem. internat. Edit. *1*, 334 (1962).

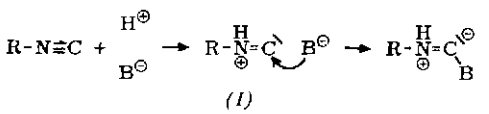
[*] The $\cos^2\varphi$ function describes the dependence of resonance energy upon the torsion angle φ in a conjugated system: $M_\varphi = M_0 \cdot \cos^2\varphi$ ($M_0$ = maximum resonance energy when the system is undistorted; $M_\varphi$ = resonance energy on distortion by an angle φ).
[**] *e.g.* through thermochemical data.

However, we found in a modified Passerini reaction that isocyanides, which are considered to be extremely sensitive to acids, react with carbonyl compounds even in the presence of molar quantities of aqueous mineral acids to form α-hydroxy amides. This reaction proceeds rapidly and in high yield, even at 0 °C.



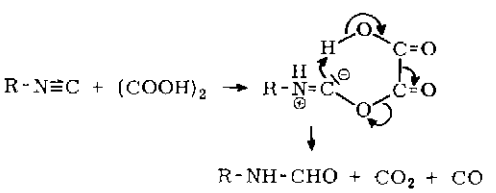
This discovery was confirmed by several examples and rules out the possibility that the isocyanide carbon has nucleophilic activity, since the protons from the mineral acid should be the preferred coreactant and should suppress the formation of C–C linkages.

The first step in any isocyanide reactions in the presence of acid is therefore assumed to be *N*-protonation, leading via an ammonium carbene *(1)* to a carbanion.

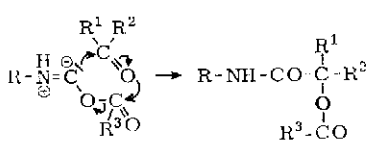


*(1)*

All the reactions of isonitriles which proceed so rapidly in the presence of acid, *e.g.* the quantitative determination of the isocyanide group with oxalic acid, may be formulated in this way.



Assuming initial *N*-protonation, the classical Passerini reaction can then be represented as follows:



Reactions of isocyanides in neutral media generally occur only on heating and are regarded as electrophilic reactions of the carbene form *(2)*, in which the electron sextet on the

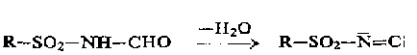


carbon atom is augmented to form an octet in the initial step. Similar behavior was observed, for example, with the β-keto isocyanide *(3)*, which is converted practically quantitatively under mild conditions into *(4)*.



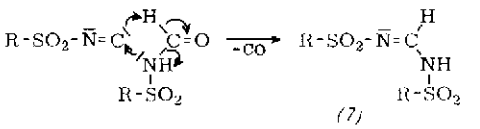
*(3)* *(4)*

This carbene character is recessive in the ground state of the isocyanide group but should be enhanced by electron-attracting groups. To test this hypothesis, an attempt was made to dehydrate *N*-formylarylsulfonamides *(5)* with $POCl_3$ in pyridine in order to obtain sulfoisocyanides *(6)*.



*(5)* *(6)*

It proved impossible to isolated *(6)* under these conditions, but in agreement with our hypothesis, *(6)* reacts spontaneously with starting material, even at 0 °C, liberating CO to give up to 90 % of *N,N'*-bisarylsulfonylformamidines *(7)*.



*(7)*

## Bonding of Dyes to Deoxyribonucleic Acid

*G. Hartmann* and *M. Liersch*, Würzburg (Germany)

The biological action of deoxyribonucleic acid (DNA) is blocked by dyes such as proflavin and actinomycin. These substances are bound by the DNA in a manner which is not yet precisely known. An intact helical structure is reported to be a prerequisite for this bonding [8,9].

We have found that DNA denaturated by heating binds proflavin and actinomycin at least as well as native DNA; the complex was isolated by gel filtration on Sephadex. By working at 4 °C and carrying out control experiments, we made certain that the denaturated DNA was not reconverted to the helical structure during the gel filtration.

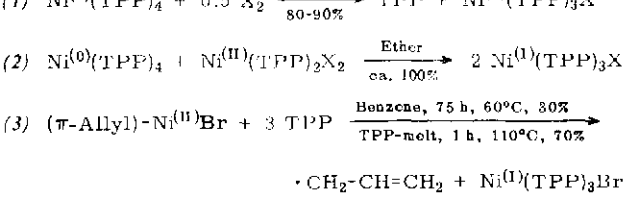
Furthermore, the maximum bonding capacity of the DNA in the presence of excess dye is not affected by denaturation. The dye complexes formed with denaturated DNA and those with DNA differ only in the somewhat higher extinction coefficients of the former, but not in the position of the absorption band.

Thus, the helical structure of DNA cannot be an essential condition for complex formation with proflavin and actinomycin.

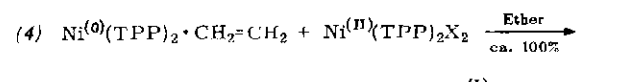
## Changes in the Coordination Numbers of Ni(0) and Ni(I) Compounds

*P. Heimbach*, Mülheim/Ruhr (Germany)

Crystalline tristriphenylphosphinylnickel(I) halides, which have not hitherto been described, can be prepared by oxidation *(1)*, disproportionation *(2)*, or reduction *(3)*



A second group of bistriphenylphosphinylnickel(I) halides (pale yellow compounds) is formed according to the equation



The ESR spectra of all the Ni(I) compounds exhibit the signal characteristic for an unpaired electron on the metal atom. Thus, the complexes are true Ni(I) compounds and do not exhibit Ni–Ni interaction. This is confirmed by the magnetic moment $\mu_B$ = 2.2 Bohr magnetons [10] obtained

[8] *L. S. Lerman*, J. molecular Biol. *3*, 18 (1961).

[9] *E. Reich*, Science (Washington) *143*, 684 (1964).

[10] I wish to thank Prof. *W. Klemm* for the measurement of the magnetic moment.

for $Ni^{(I)}[TPP]_3Cl$. This corresponds to one unpaired electron plus an additional orbital moment, which is to be expected for tetrahedral coordination of the ligands.

The molecular weights of the Ni(I) compounds, as well as of a few Ni(0) compounds which have not yet been described, were determined by cryoscopy and are shown in the Table.

| Complex | Mol. Wt. | | Solvent |
|---|---|---|---|
| | calc. | found | |
| $Ni^{(I)}(TPP)_3I$ [*] | 972.5 | 500–520 | Benzene |
| $Ni^{(I)}(TPP)_3Br$ [*] | 925.5 | 510–520 | Benzene |
| $Ni^{(I)}(TPP)_3Cl$ [*] | 881 | 510–520 | Benzene |
| $Ni^{(I)}(TPP)_2Br$ | 663.2 | 670 | Benzene |
| $Ni^{(0)}(TPP)_4$ [*] | 1108 | 510–540 | Benzene |
| $Ni^{(0)}(TPP)_4$ [*] | 1108 | 520 | Cyclohexane |
| $Ni^{(0)}(TPP)_3$ | 846 | 790 | Benzene |
| $Ni^{(0)}[P(OC_6H_5)_3]_4$ | 1300 | 1290 | Benzene |
| $Ni^{(0)}[P(OC_6H_5)_3]_2(TPP)_2$ | 1204 | 1050 | Benzene |

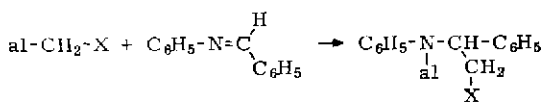
[*] Compound dissociates in solution into TPP and the corresponding complex of lower coordination number.

On reaction with excess triphenylphosphite, $Ni^{(I)}(TPP)_3Cl$ disproportionates into violet $Ni^{(II)}[P(OC_6H_5)_3]_2Cl_2$ and white $Ni(0)[P(OC_6H_5)_3]_4$.

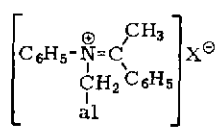
## Reactions of the Halogenomethylaluminum Compounds with Azomethines and N-Heterocycles

*H. Hoberg*, Mülheim/Ruhr (Germany)

Halogenomethylaluminum dialkyls can be prepared from dialkylaluminum halides and diazomethane and add on in the absence of electron donors to C–C multiple bonds through the al–C bond of the $X–CH_2–al$ group (al = 1/3 Al, X = halogen). Subsequent spontaneous 1,3-elimination of al–X leads to the formation of cyclopropane compounds [10a]. We have found that the al–C bond of the $X–CH_2–al$ group also adds onto the C=N bond of azomethines, even at low temperatures.

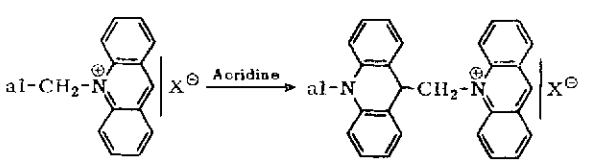


Elimination of HX from the hydrolysed product (H instead of al) with alkali hydroxide yields *N,C*-diphenylethylenimine. Intermolecular elimination of HX (without addition of base) gives 1,2,4,5-tetraphenylpiperazine. The X–C bond of the halogenomethylaluminum dialkyls is activated by the metal in the α-position and also reacts with other Schiff bases (*e.g.* acetophenone anil), the nitrogen being quaternized *(1)*.



*(1)*

N-Heterocycles, *e.g.* acridine, initially give only secondary products of the quaternization step; only thereafter does a further acridine molecule add onto the al–C bond *(2)*.




*(2)*

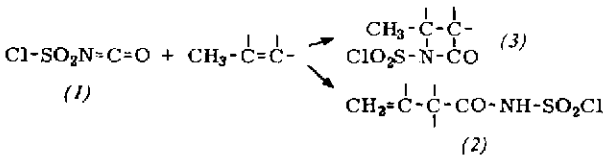
[10a] *H. Hoberg*, Liebigs Ann. Chem. *656*, 1, 15 (1962).

The reaction products show that it is the $al–CH_2–X$ group, and not a carbene formed by 1,1-elimination, that reacts with the C=N bond.

## Reactions of N-Carbonylsulfamyl Chloride with Dienes

*H. Hoffmann* and *H. D. Diehr*, Mainz (Germany)

According to *Graf* [11], N-carbonylsulfamyl chloride *(1)* reacts with olefins to form *N*-chlorosulfonylcarboxamides *(2)* or *N*-chlorosulfonyl-β-lactams *(3)*.



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

The following rules were discovered for the reaction of 1,3-dienes with *(1)*:

1. Dienes generally react with *(1)* much more readily than do comparable olefins.

2. *N*-Chlorosulfonyl-β-lactams *(3)* are predominantly formed at lower temperatures, and *N*-chlorosulfonylcarboxamides *(2)* at higher temperatures. *N*-Chlorosulfonyl-δ-lactams could not be detected.

3. The direction of addition is determined by the substituents, *e.g.* butadiene gives an *N*-chlorosulfonyl-β-lactam with a terminal amino group *(4)*, whereas 1-methylbutadiene gives an *N*-chlorosulfonyl-β-lactam with a terminal carbonyl group *(5)*.



*(4)* *(5)*

4. Compound *(1)* undergoes *cis*-addition with cyclic dienes. However, the initial products can be rearranged by subsequent reactions.

## Nucleophilic Substitutions on Silylamines

*J. Hundeck*, Munich (Germany)

Amino groups $NR_2'$ bonded to silicon may be substituted by acyl groups X by reaction with acids HX [12], *e.g.* according to Equation (1):

$$R_3Si–NR_2' + 2\,HX \rightarrow R_3SiX + NHR_2' \cdot HX \qquad (1)$$
$$(R = \text{Alkyl};\ R' = H, \text{Alkyl};\ X = \text{Acyl}).$$

Silylamines react analogously with alkyl halides R″X, particularly alkyl iodides, according to Equation (2):

$$R_3Si–NR_2' + 2\,R''X \rightarrow R_3SiX + NR_2'R'' \cdot R''X \qquad (2)$$

The silylammonium derivatives $[R_3Si(NR_2'R'')]X$ expected as the initial products of the reactions according to Equations (1) and (2) could not be isolated. They are, however, formed from tertiary amines $NR_3$ and iodosilanes, *e.g.* $(H_3C)_3SiI$ [13]:

$$(H_3C)_3SiI + NR_3 \rightarrow [(H_3C)_3Si–NR_3]I. \qquad (3)$$

Adducts of this type react as expected with protonic substances HX such as hydrogen sulfide (X = SH), or with alkyl halides RX, according to Equation (4):

$$[R_3Si–NR_3]I + HX \rightarrow R_3SiX + [HNR_3]I \qquad (4)$$

An adduct of *N,N*-diethyltrimethylsilylamine and $BF_3$ reacts in a similar manner:

$$(H_3C)_3Si–N(C_2H_5)_2 \cdot BF_3 + RX \rightarrow (H_3C)_3SiX + N(C_2H_5)_2R \cdot BF_3. \qquad (5)$$

[11] *R. Graf*, Liebigs Ann. Chem. *661*, 111 (1963).

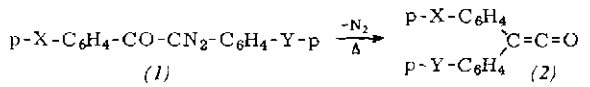
[12] *J. Hundeck*, Ph. D. Thesis, Universität München, 1961.

[13] *L. Kreuzbichler*, Diploma Thesis, Universität München, 1959, p. 25.

## New Diarylketenes and Their Autoxidation

*E. F. Jenny, H. Droescher,* and *A. Melzer,*
Freiburg/Brsg. (Germany)

Three new ketenes, di-*p*-anisyl- *(2a)*, di-*p*-nitrophenyl- *(2b)*, and *p*-anisyl-*p*-nitrophenylketene *(2c)* were prepared from diazoketones in solution.



*(1)* *(2)*

*(a)*: X = Y = $OCH_3$; *(b)* X = Y = $NO_2$; *(c)* X = $OCH_3$; Y = $NO_2$

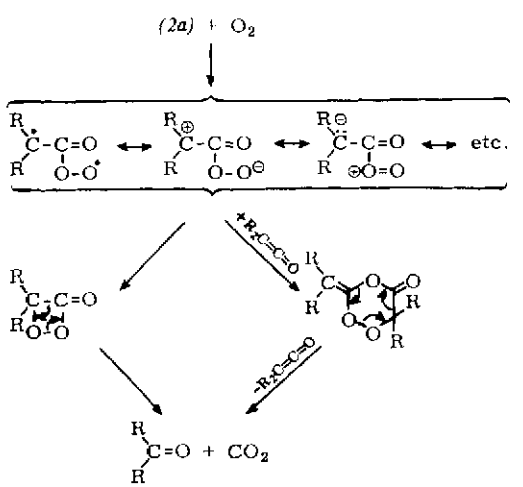
So far only *(2b)* has been isolated in crystalline form. Compound *(2a)* reacts much more readily with oxygen, and *(2b)* with nucleophilic reagents, than unsubstituted diphenylketene.

The kinetics of the thermal Wolff rearrangement of the diazoketones *(1a)*–*(1d)* [the latter with X=Y=H] in ethylene chloride were determined. The reaction is always of the first order and shows the following activation parameters.

| | $k_1$ (relative values) | $\Delta H^{\neq}$ [kcal/mole] | $\Delta S^{\neq}$ [cal/deg/mole] |
|---|---|---|---|
| *(1d)* | ca. 50 | 23.8 | −2.0 |
| *(1a)* | ca. 2000 | 20.3 | −6.7 |
| *(1b)* | ca. 2 | 28.0 | 4.6 |
| *(1c)* | ca. 1 | 28.5 | 4.5 |

These values form an isokinetic straight line. Since the thermal stabilities of *(1b)* and *(1c)* are approximately equal, we believe that even the "mixed" diazoketone, with substituents suitable for a synchronous rearrangement (X = $OCH_3$ favors migration; Y = $NO_2$ makes the formation of carbene difficult), is converted into the ketene via an intermediate ketocarbene. The correctness of this assumption should be confirmed by the results of further kinetic investigations.

Dianisylketene, which is produced *in situ* in benzene, reacts with oxygen to give 4,4'-dimethoxybenzophenone and $CO_2$ in a molar ratio of 1:1, the yield increasing rapidly at the expense of the copolymer as the dilution increases. Oxidation of *(2a)* with labelled oxygen gives labelled 4,4'-dimethoxybenzophenone and labelled carbon dioxide. This result indicates that the autoxidation of *(2a)* probably proceeds, at least at high dilutions, not via a copolymer, but via a four- and/or six-membered cyclic peroxide according to Scheme 1.



Scheme 1. Oxidation of di-*p*-anisylketene *(2a)* [R = *p*-$CH_3O$-$C_6H_4$-].

The mechanism of this reaction will be deduced from the distribution of $^{18}O$ in the oxidation products and from the effect of the various *p*-substituents on the rate of oxidation.

## Proton Resonance Investigations on the Conformational Mobility of Cyclic Di- and Trisulfides

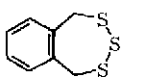
*S. Kabuss, H. Friebolin,* and *A. Lüttringhaus,*
Freiburg/Brsg. (Germany)

The rate and enthalpy of activation $\Delta G^{\neq}$ of the conformational rearrangements of cyclic disulfides (which exist in enantiomeric forms, owing to the non-planar conformation around the S–S group) and cyclic trisulfides of various ring sizes were determined from the temperature-dependence of their proton resonance frequencies. The maximum $\Delta G^{\neq}$ value for cyclic disulfides is 15 kcal/mole, and conformational inversion occurs more than ten times per second at room temperature. The free enthalpies of activation of the trisulfides are mostly significantly higher than those of the corresponding 1,2- and 1,3-dithia compounds (see Table 1).

Table 1. Frequencies k of conformational inversion and free enthalpies of activation $\Delta G^{\neq}$ of cyclic di- and trisulfides at their coalescence temperature $T_A$.

| | $T_A$ [°C] | k [$sec^{-1}$] | $\Delta G^{\neq}$ [kcal/mole] |
|---|---|---|---|
| 1.3-Dithiane | −80 | 100 | 9.4 |
| 1.2-Dithiane [14] | −46 | 46 | 11.6 |
| 1,2,3-Trithiane | −8 | 78 | 13.2 |
| 5,5-Dimethyl-1,3-dithiane | −65 | 73 | 10.3 |
| 5,5-Dimethyl-1,2,3-trithiane | +20 | 91 | 14.6 |
| 2*H*, 4*H*, 7*H*-1,3-Dithiepin | −100 | 67 | 8.5 |
| 4*H*, 7*H*-1,2,3-Trithiepin | −90 | 120 | 8.9 |
| 2*H*, 4*H*, 7*H*-1,3-Benzo-[*e*]dithiepin | −55 | 64 | 10.9 |
| 3*H*, 6*H*, 7*H*-1,2-Benzo-[*d*]dithiepin | −3 | 58 | 14.3 |
| 4*H*, 7*H*-1,2,3-Benzo[*e*]trithiepin | +110 | 93 | 19.3 |

The "stiffening" of the ring system by the third sulfur atom is particularly pronounced in the case of 4*H*,7*H*-1,2,3-benzo[*e*]trithiepine *(1)*, $\Delta G^{\neq}$ being 19.3 kcal/mole. Separation of the conformational isomers is therefore almost possible.

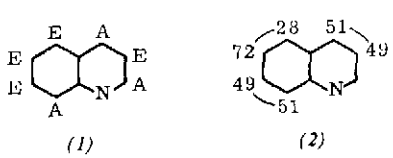


*(1)*

## Investigations on Heterocyclic Arynes

*Th. Kauffmann, J. Hansen, K. Udluft,* and *R. Wirthwein,*
Darmstadt (Germany)

In the reaction in ether at 35 °C of lithium piperidide/piperidine with quinolines which are monohalogenated on the isocyclic ring, halogen in the 5-, 6-, and 7-positions is substituted by an elimination mechanism (E; cf. [15]) involving 5,6- and 7,8-dehydroquinoline, while halogen in the 8-position is unexpectedly substituted entirely by an addition-elimination mechanism (A). Thus, for reactions of monohalogenoquinolines (Hal = Cl or Br) with lithium piperidide/piperidine, the "mechanism chart" *(1)* can be drawn up. The ratio of products obtained in the addition of piperidine onto 5,6-, 7,8-, and 3,4-dehydroquinoline [15] is shown by *(2)*



*(1)* *(2)*

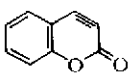
[14] *G. Claeson, G. M. Androes,* and *M. Calvin,* J. Amer. chem. Soc. *82*, 4428 (1960); ibid. *83*, 4357 (1961).

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

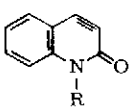
When piperidine is heated with 4-chloropyrimidine, 4-bromocoumarin, 4-bromo-*N*-methylcarbostyryl, and 4-bromocarbostyryl, it yields only the 4-piperidino compounds, but on heating at 180 °C with 5-bromopyrimidine, it gives a mixture of 4- and 5-piperidinopyrimidines; the analogous reactions (40–180 °C) with the 3-halogeno compounds (Hal = Br or Cl) of coumarin, *N*-methylcarbostyryl, and carbostyryl give mixtures of the 3- and 4-piperidino compounds. Formation of the mixture is most simply explained by assuming the intermediates *(3)*, *(4)*, *(5)*, and *(6)* or *(7)* [16]. Formation of the intermediate *(4)* in the reaction with 3-bromocoumarin is supported by the fact that, although this compound is stable to methanol and aniline under the experimental conditions, it gives 4-methoxy- or 4-anilinocoumarin as well as 3- and 4-piperidinocoumarin (ratio ca. 1:2) when subjected simultaneously to piperidine + methanol or piperidine + aniline.



*(3)*

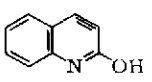


*(4)*



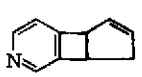
*(5)*, R = $CH_3$

*(6)*, R = H

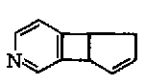


*(7)*

3,4-Dehydropyridine produced from pyridine-3-diazonium-4-carboxylate, was treated with cyclopentadiene. The adduct (53 % yield) forms cinchomeronic acid on oxidative degradation; in contrast to the dehydrobenzene-cyclopentadiene and 2,4-dehydropyridine-furan adducts, it does not add on phenylazide, and must be assigned the constitution *(8)* or *(9)*.



*(8)*

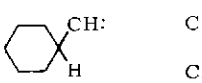


*(9)*

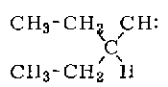
## Steric Effects in Carbene Reactions

*W. Kirmse* and *G. Wächterhäuser*, Marburg/Lahn (Germany)

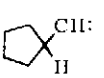
We have investigated the effect of steric factors on intramolecular insertion reactions of alkylcarbenes. The relative yields of olefins and cyclopropane derivatives in the series *(1)*–*(3)* point to a transition state for the insertion reaction in which the carbene carbon and the C–H bond lie approximately in a common plane.



*(1)*



*(2)*



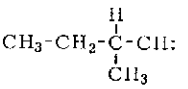
*(3)*

Olefin:Cyclopropane =

| 11.5 | 2.8 | 0.38 |
|---|---|---|

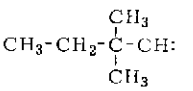
Thus the preferential formation of *trans*-1,2-dialkylcyclopropanes from alkylcarbenes, *e.g. (2)*, can be attributed to the "eclipsing effect" of the *cis*-transition state.

Similarly, the "natural" preference for secondary and tertiary hydrogens in the insertion reaction is reversed by the stepwise introduction of methyl groups [*(4)*–*(7)*].



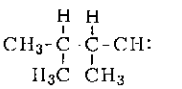
*(4)*

sec:prim (*trans*) 1.80
(*cis*) 0.75



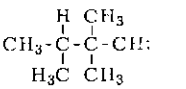
*(5)*

sec:prim 0.78



*(6)*

tert:prim 0.96



*(7)*

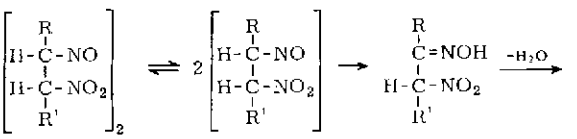
tert:prim 0.39

Equal steric "increments" [*(4) trans→(4) cis*; *(4) trans→(5)*; *(6) → (7)*] cause equal changes in the ratio of the products. With the aid of these results the "freedom" of the carbene intermediate can be more precisely defined than before.

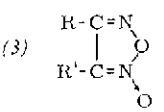
## Syntheses of α,ω-Diamines via Pseudonitrosites, Nitroximes, and Furoxans

*D. Klamann* and *W. Koser*, Hamburg (Germany)

Vicinal nitro and nitroso groups can be introduced into aliphatic or alicyclic hydrocarbons with particular ease by passing a freshly prepared mixture of nitrogen monoxide and air or oxygen into solutions of mono- or polyolefins. It was hitherto not generally possible to convert the resulting pseudonitrosites *(1)* into reactive compounds with both nitrogen functions intact. This requires monomerization of the dimeric nitroso groups, a process which can be achieved by heating in aprotic dipolar solvents; prolonged heating at lower or shorter heating at higher temperatures or treatment with superheated steam leads to rearrangement of *(1)* to the nitroximes *(2)*. The nitroximes do not undergo Beckmann rearrangements, but readily yield furoxans *(3)* on treatment with dehydrating agents; the latter can be reduced directly or in two stages to furazans. The furoxans can also be prepared directly from the pseudonitrosites *(1)*.



*(1)* *(2)*



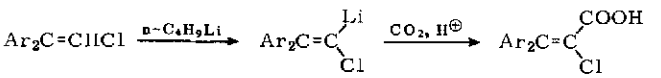
*(3)*

Catalytic hydrogenation of the furoxan molecule gives two primary amines $R-CH_2NH_2$ and $R'-CH_2NH_2$. Furoxans with alicyclic skeletons give α,ω-diamines, which can now be produced industrially by this method.

## Preparation and Reactions of Metallated Chloroethylenes

*G. Köbrich*, *H. Trapp*, *K. Flory*, *H. Fröhlich*, and *W. Drischel*, Heidelberg (Germany)

1,1-Diaryl-2-chloroethylenes *(1)* react at low temperatures with n-butyl-lithium to give the lithium compounds *(2)*, which were characterized as carboxylic acids *(3)*.

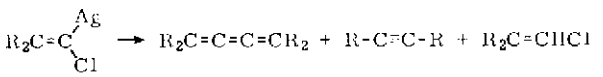


*(1)* *(2)* *(3)*

[16] *Th. Kauffmann* and *A. Risberg*, Tetrahedron Letters *1963* 1459.

The rate of metallation of *(1)* and the stability of the organolithium compounds *(2)* are affected by substituents on the aromatic nucleus, being decreased by electron-repelling groups. The compounds *(2)* rearrange on warming up to diarylacetylenes, with elimination of lithium chloride. Our experimental results show that this Fritsch-Buttenberg-Wiechell rearrangement proceeds from the (potential) carbanion and that the aromatic nucleus migrates with its bonding electron pair to the neighboring carbon atom.

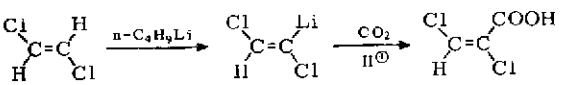
Compound *(2)*, Ar = $C_6H_5$, reacts with silver chloride to give *(4)*, which is more stable than *(2)*, but decomposes on warming up to form tetraphenylbutatriene, tolane, and diphenylchloroethylene.



*(4)*

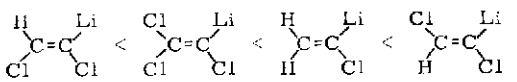
R = $C_6H_5$

1,2-Dichloroacrylic acid *(5)* is formed in 99 % yield by the reaction at −110 °C of *trans*-dichloroethylene with n-butyl-lithium and subsequent carboxylation; similarly, vinyl chloride gives 100 % α-chloroacrylic acid, and trichloroethylene gives 81 % trichloroacrylic acid. The stabilities of



*(5)*

the intermediate lithium compounds are represented by the series



The two less stable compounds probably decompose by *trans*-β-elimination, the others by α-elimination [17].

## Trifluorophosphinyl Complexes of Transition Metals

*Th. Kruck*, Munich (Germany) [18]

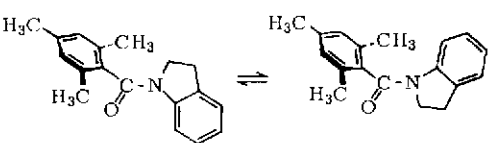
Hexakistrifluorophosphinylmetal(0) complexes $M(PF_3)_6$, which are closely analogous to the hexacarbonyls of the chromium group, have been prepared from dibenzenechromium(0) and dibenzenemolybdenum(0) with $PF_3$ at pressures of 300–500 atm. High pressure reaction of $PF_3$ with the tricarbonyls $M(CO)_3L_3$ (M = Cr, $L_3$ = 3 $NH_3$; M = Mo, $L_3$ = mesitylene) yields crystalline, extremely volatile tristrifluorophosphinylmetal(0) tricarbonyls $M(PF_3)_3(CO)_3$, with *cis*-arrangement of the three $PF_3$ ligands in an octahedral complex. Trifluorophosphine is a ligand with weak donor but pronounced acceptor properties (comparison of the C–O valence frequencies of molybdenum tricarbonyls) and is thus similar to carbon monoxide. It therefore seems very suitable for the stabilization of extremely low oxidation states of transition metals.

Thus the action at 500–800 atm of $PF_3$ (prepared from zinc fluoride and phosphorus trichloride, and purified only by recondensation) on dicobalt octacarbonyl gives the almost colorless, diamagnetic hydride $HCo(PF_3)_3CO$, b.p. 80.5 °C/715 mm, in ca. 90 % yield. The compound is formed very readily, and its thermal stability is considerably higher than that of cobalt carbonyl hydride; it is also stable toward oxidizing agents (atmospheric oxygen, $MnO_2$). It reacts with potassium amalgam with liberation of hydrogen to give the ether-soluble salt $K[Co(PF_3)_3CO]$, which is stable in dry air. Tristrifluorophosphinylcarbonylcobaltate(I) can be precipitated with bulky cations, and is the first known complex with anionically bound trifluorophosphine [19]. The potassium salt dissolves in water to give a neutral solution, volatile hydride being reformed on treatment with mineral acids. In the transition from $HCo(PF_3)_3CO$ to $[Co(PF_3)_3CO]^{\ominus}$, both the C–O and the P–F valence frequencies are displaced toward longer wavelengths.

## Rotational Isomers of Mesitylenecarboxamides

*A. Mannschreck*, Heidelberg (Germany)

Rotation about the C–N bond is restricted in amides, since the two planar conformations of the amide group are favored by resonance. If the substituents on the nitrogen atom are different, rotational isomers may occur. The proton magnetic resonance spectra of a series of *N*-substituted mesitylenecarboxamides prove the preferential occurrence of two conformations, *e.g. (1)* and *(2)*. The isomers could be unambiguously assigned on the basis of this steric arrangement of the groups; the ratio of *(1)*:*(2)* was found to be 66:34 in [$D_6$]acetone at 37 °C. The ratios of the isomers are governed predominantly by the steric requirements of the



*(1)* *(2)*

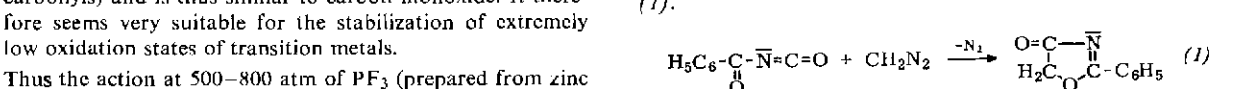
respective substituents on the nitrogen atom. The temperature-dependence of the spectra supports the explanation given above.

Since carboxamides in acids are protonated on the oxygen atom [20], two isomers exist in the equilibrium in strongly acidic solutions, too, *e.g.* the cations of *(1)* and *(2)* are present in trifluoroacetic acid in the ratio of 45:55. If a crystalline amide is dissolved in a strong acid, this equilibrium ratio is slowly established (*e.g.* $\tau_{1/2} \approx 5$ min in $CF_3COOH$ at 37 °C). Immediately after dissolution, the proton magnetic resonance spectrum shows that one of the isomers [*(1)* in the example chosen] greatly predominates. It can therefore be assumed that the crystal consists of one rotational isomer, which isomerizes partially after dissolution. The mechanism of this reaction has not yet been fully elucidated.

## Cycloadditions with Isocyanates as 1,4- and 1,2-Dipoles

*R. Neidlein*, Marburg/Lahn (Germany)

Equimolar quantities of benzoyl isocyanate [21] and diazomethane interact at room temperature in anhydrous ether with elimination of nitrogen to form 2-phenyloxazolin-4-one *(1)*.



*(1)*

The most suitable compounds which could theoretically enter into dipolar cycloadditions similar to those of methylene groups were isocyanides. Isocyanides can be regarded as stabilized carbenes. Equimolar quantities of benzoyl iso-

[17] Cf. *G. Köbrich* and *H. Trapp*, Z. Naturforsch. *18b*, 1125 (1963); *G. Köbrich*, *H. Trapp*, and *I. Hornke*, Tetrahedron Letters *1964*, 1131; *G. Köbrich* and *K. Flory*, ibid. *1964*, 1137.

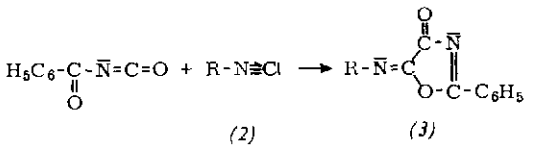
[18] In collaboration with *W. Lang*.

[19] To be published in detail in Chem. Ber.

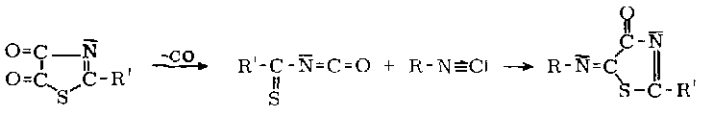
[20] *A. R. Katritzky* and *R. A. Y. Jones*, Chem. and Ind. *1961*, 722.

[21] *J. C. Sheehan* and *P. T. Izzo*, J. Amer. chem. Soc. *71*, 4059 (1949).

cyanate in absolute benzene react as 1,4-dipoles with isocyanides *(2)*, *e.g.* phenyl isocyanide, in anhydrous ether at room temperature by cycloaddition to form derivatives of 5-iminooxazolin-4-one *(3)*; the final products are only sparingly soluble and can be easily isolated. Reaction of equimolar quantities of thioacyl isocyanates *(4)* [22] as 1,4-dipolar compounds with isocyanides *(2)* similarly yields 5-iminothiazolin-4-one derivatives *(5)*. The thioacyl isocyanates are very reactive and are not isolated before being subjected to the latter reactions. They are supplied by 2-aryl- or 2-alkylthiazolin-4,5-diones [23], which expel CO on heating in boiling xylene; the nascent thioacyl isocyanate reacts with the isocyanide in the same solution (yields: 80–95 %).

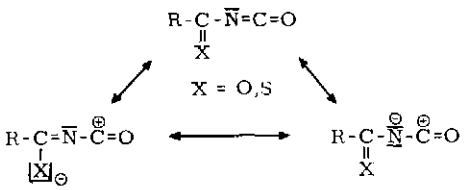


*(2)* *(3)*



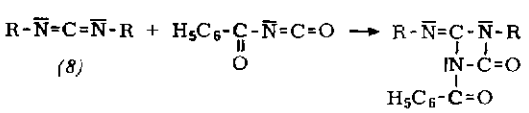
*(4)* *(2)* *(5)*

The acyl and thioacyl isocyanates react as 1,4-dipoles *(6)* in the cases mentioned, but they can also function as 1,2-dipoles *(7)*. The following resonance structures can be formulated for the isocyanates.



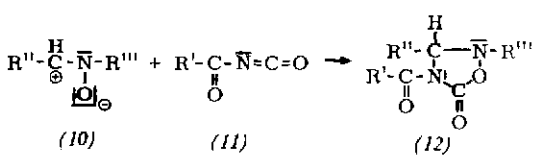
*(6)* *(7)*

For example, reaction of carbodiimides *(8)* at room temperature in an anhydrous 1:1 ether/benzene mixture with equimolar quantities of benzoyl isocyanate gives iminouretone derivatives *(9)* [24] in 60–70 % yields after removal of the solvent.



*(8)* *(9)*

1,3-Dipoles such as *N*-methylbenzaldoxime *(10)* – a nitrone – react with equimolar amounts of acyl isocyanate *(11)* at room temperature in an anhydrous 1:1 ether/benzene mixture to form five-membered rings, *viz.* 1,2,4-oxadiazolidin-5-ones (yields: 80–90 %).



*(10)* *(11)* *(12)*

[22] *J. Goerdeler* and *H. Schenk*, Angew. Chem. *75*, 675 (1963); Angew. Chem. internat. Edit. *2*, 552 (1963).

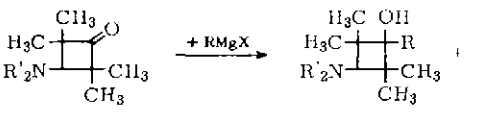
[23] *J. Goerdeler* and *H. Horstmann*, Chem. Ber. *93*, 671 (1960).

[24] Cf. *W. Neumann* and *P. Fischer*, Angew. Chem. *74*, 801 (1962); Angew. Chem. internat. Edit. *1*, 621 (1962).

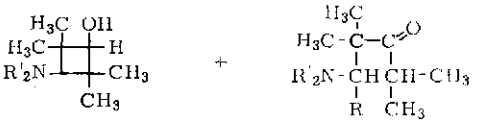
## Ring-Opening of β-Dialkylaminocyclobutanones

*G. Opitz* and *M. Kleemann*, Tübingen (Germany)

When heated, enolizable β-aminocyclobutanones rearranged with ring-opening to form β-aminovinyl ketones. Non-enolizable β-aminocyclobutanones *(1)* can form three products with Grignard reagents: 1. normal addition gives tertiary β-aminocyclobutanols *(2)*; 2. reduction gives secondary β-aminocyclobutanols *(3)*; and 3. ring-opening gives saturated β-amino ketones *(4)*. The β-amino ketones *(4)* can be converted into saturated ketones either by heating, with elimination of a vinylamine, or by warming with sodium hydroxide solution, with elimination of an aldehyde and a secondary amine.



*(1)* *(2)*



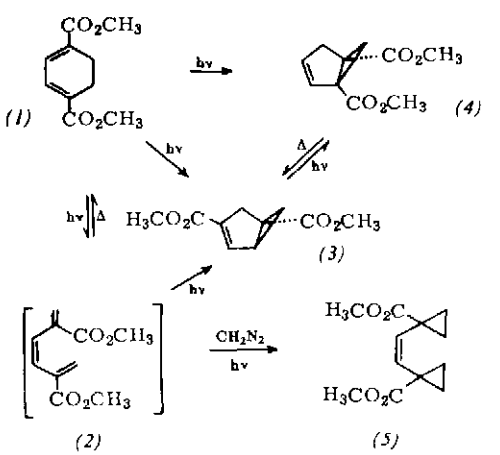
*(3)* *(4)*

The ring-opening is interpreted as a fragmentation reaction. The tendency for the ring to open is governed not by the basicity, but by the electromeric effect of the amino group (pyrrolidino > hexamethyleneimino > piperidino > morpholino). Whether the Grignard reaction proceeds normally or abnormally depends, in a manner which cannot yet be explained, on the solvent and on the organometallic residue.

## Photochemical Valence Isomerization of 1,3-Cyclohexadiene Derivatives

*H. Prinzbach* and *H. Hagemann*, Freiburg/Brsg. (Germany)

Unsensitized irradiation of dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate *(1)* ($\lambda_{max}$ = 307 mμ) in ether (uviol glass filter; Hg high-pressure lamp Q 81) yields the bicyclic diester *(4)* in 20–25 % yield in $1.5\times10^{-2}$ M solution or in at least 60 % yield in $3\times10^{-3}$ M solution. The sterically hindered open-chain 1,3,5-hexatriene-2,5-dicarboxylate *(2)* and the [3,1,0]-bicyclic ester *(3)* can be shown to be very probable intermediates in this photochemical isomerization. The *cis*-triene *(2)* ($\lambda_{max}$ = 240–245 mμ, $\varepsilon \approx 6500$) – which cannot be isolated, since the thermal reverse reaction to form *(1)* is very rapid ($\tau^1/_2 \approx 10$ min at 20 °C) – is trapped with diazomethane in 70 % yield as *(5)*. Compound *(2)* can be photochemically



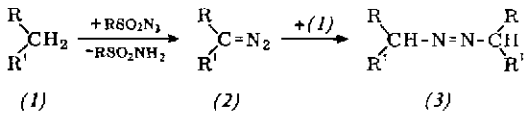
*(1)* *(4)* *(3)* *(2)* *(5)*

converted in the presence of iodine into the thermally more stable *trans*-1,3,5-hexatriene ($\lambda_{max}$ = 285 mμ, ε ≈ 13000). Irradiation of *(1)* through a pyrex filter leads to *(3)* ($\lambda_{max}$ = 237 mμ; ε = 6440) as the main product of the isomerization. The photochemical vinylcyclopropane isomerization of the thermodynamically more stable isomer *(3)* to *(4)* can be reversed thermally ($E_a$ = −26.3 kcal/mole).

## Synthesis of Aliphatic Azo and Diazo Compounds from Active Methylene Compounds and Sulfonyl Azides

*M. Regitz*, Saarbrücken (Germany)

Compounds with activated methylene groups *(1)* react with sulfonyl azides in the presence of bases to form diazo compounds *(2)* and sulfonamides [25].



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

(R and R′ are activating residues, *e.g.* >C = C<, >C=O, > $SO_2$, and aryl).

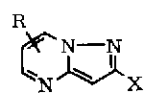
Depending on the proton mobility of the CH-acid component *(1)*, even aqueous ammonia, organic amines, or alkaline solutions are suitable as bases; more weakly acidic compounds are converted into their carbanions by alkali metal alkoxides or lithium alkyls. If the rate of coupling of the diazo compound *(2)* with the methylene component *(1)* which is still present is greater than the rate of formation of *(2)*, symmetrical azo compounds *(3)* are obtained. These can generally also be prepared from the CH-acids *(1)* with half an equivalent of sulfonyl azide and are occasionally (*e.g.* with dihydrothionaphthen-3-one 1,1-dioxide) susceptible to thermal azo decoupling. Methylene compounds *(1)* containing ester groups generally undergo nucleophilic substitution of the alkoxyl residue by the sulfonamide formed in the reaction. The sulfonamide also converts diazo compounds *(2)* with R = aryl and R′ = CO-aryl or CO-alkyl into carboxy sulfonamides with elimination of $N_2$, partly by a reaction similar to the Wolff rearrangement.

The usefulness of this reaction is shown by the preparation of the diazo derivatives of cyclohexadienes, β-diketones, β-keto sulfones, monoketones, and carboxylic esters, as well as the corresponding azo compounds.

## Synthesis of the 1,5,8a,9-Tetraazafluorene System [26]

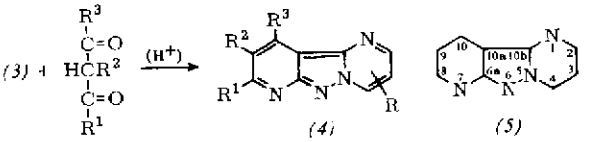
*W. Ried* and *K. P. Peuchert*, Frankfurt/Main (Germany)

2-Bromopyrazolo[1,5-*a*]pyrimidines *(2)* are prepared from 2-hydroxypyrazolo[1,5-*a*]pyrimidines *(1)* [27] and phosphorus oxybromide. The former react with ammonia to form 2-aminopyrazolo[1,5-*a*]pyrimidines.



*(1)*: X = OH
*(2)*: X = Br
*(3)*: X = $NH_2$

Proton-catalysed condensation of *(3)* with 1,3-dicarbonyl compounds gives a new, quasi-aromatic heterocyclic system, *viz.* 1,5,8a,9-tetraazafluorene *(4)*, numerous derivatives of which have been prepared.



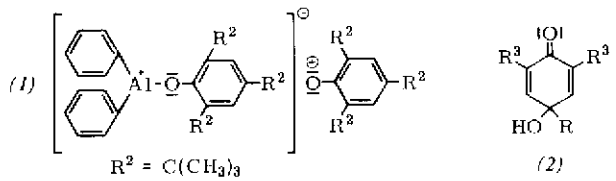
*(3)* *(4)* *(5)*

According to IUPAC rules, the new system should be referred to as pyrido[3′,2′:4,3]pyrazolo[1,5-*a*]pyrimidine and should be numbered as in *(5)*. The compounds exhibit fluorescence in solution, according to the nature and number of substituents present.

## Monovalent Reactions on Organometallic Compounds

*A. Rieker*, Tübingen (Germany)

The reaction of aroxyl radicals with organometallic compounds (RLi, RMgX, $R_2Mg$, $R_3Al$) causes liberation of carbon radicals R· via intermediate free-radical complexes; these carbon radicals dimerize or dehydrogenate the solvent or organometallic compound to form mainly hydrocarbons R–R and R–H in varying quantities (20–100 % overall). In the triphenylaluminum/2,4,6-tri-t-butylphenoxyl system, EPR measurements gave direct evidence of a free-radical complex, for which the constitution *(1)* has been proposed on the basis of isotope experiments. In this complex, the free electron on the aluminum has a finite spin density; a "mesomeric aluminum radical" is present.



*(1)* $R^2 = C(CH_3)_3$ *(2)*

Many sterically hindered quinones also behave as monovalent electron acceptors towards organomagnesium compounds. Combination of the components in equimolar ratios gives highly colored paramagnetic complexes, the structures of which are not yet known; they are not identical with the corresponding free semiquinones and decompose immediately in the presence of excess organomagnesium halide RMgX. The final products isolable are quinols *(2)* (25–80 %), hydroquinones, and, again, the hydrocarbons R–R and R–H (together up to 40 %).

## 1,5-Hydrogen Shifts in Cyclopentadiene and Indene

*W. Roth*, Köln (Germany)

We have examined the thermal hydrogen shift in cyclopentadiene using 5*H*-perdeuterocyclopentadiene. At temperatures around 50 °C, the NMR spectrum indicates reorientation of the hydrogen by successive 1,5-hydrogen shifts, the intramolecular nature of which was ascertained by mass-spectroscopic analysis of the starting material and rearranged product. The rate of rearrangement was followed between 45 and 65 °C, both in the gas phase and in solution. The reaction is of first order, is affected only to a negligible extent by the surface area of the reaction vessel and the polarity of the solvent, and can be described by the Arrhenius equation

$$k = 1.3 \times 10^{12} \cdot \exp(-24.3 \pm 0.5)\ \text{kcal/RT}\ [\text{sec}^{-1}].$$

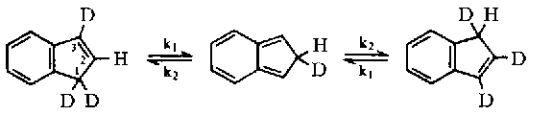
An analogous 1,5-hydrogen shift has been observed in indene leading to isoindene, which in turn undergoes another 1,5-

[25] *W. v. E. Doering* and *C. H. De Puy* [J. Amer. chem. Soc. *75*, 5955 (1953)] were the first to prepare diazocyclopentadiene in this manner.

[26] Part of the Ph. D. Thesis of *K.-P. Peuchert*, Universität Frankfurt/Main, 1964.

[27] *W. Ried* and *E.-U. Köcher*, Liebigs Ann. Chem. *647*, 116 (1961); *W. Ried* and *K.-P. Peuchert*, ibid. *660*, 104 (1962).

hydrogen shift at 220 °C with rapid reformation of indene. However, the occurrence of isoindene *(2)* can be detected during the isomerization of 1,1,3-trideuteroindene *(1)* by



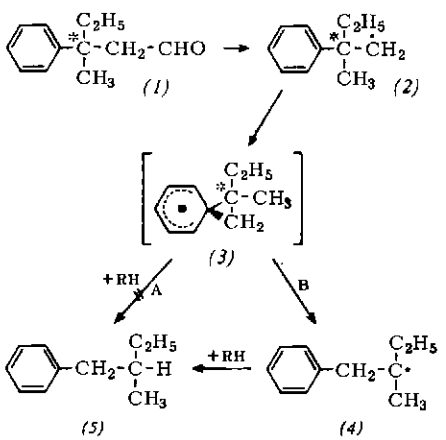
*(1)* *(2)*

introducing deuterium at C-2 of the indene. This reaction is also intramolecular and of the first order, and is not catalysed by the walls of the vessel.

## The Stereochemical Criterion for Phenyl Migration by a Free-Radical Mechanism

*C. Rüchardt* and *H. Trautwein*, Munich (Germany)

The stereochemistry of the decarbonylation of optically active 3-methyl-3-phenylvaleraldehyde *(1)* was studied in an attempt to find out whether, in aryl migrations proceeding via a free-radical mechanism, an intermediate *(3)* can react directly with the hydrogen donor [RH = *(1)*] (Route A), or whether the reaction proceeds through the isomeric radical *(4)*.



Detection of Route A would also be a direct proof that *(3)* is a true intermediate and not a transition state. The complete racemization of *(5)* shows that only Route B is significant, since optical activity should be retained by Route A, as with corresponding ionic intermediates.

The tendency of the phenyl group to migrate is greater in *(1)* than in the related neophylaldehyde, probably owing to steric effects. A photochemical Arndt-Eistert chain extension with migration of an optically active tertiary carbon atom, was carried out during the synthesis of *(1)*; complete retention of optical activity was found for this reaction.

## Olefination of $N_2O$ and other Attempts to Synthesize Diazomethane

*W. Rundel*, Tübingen (Germany)

By analogy to the reaction of *C*-nitroso compounds with Wittig reagents to form Schiff bases, that of $N_2O$ and methylenetriphenylphosphorane *(1)* should lead to the most straightforward synthesis of diazomethane.

$$(C_6H_5)_3P=CH_2 + N_2O \rightarrow (C_6H_5)_3P=O + H_2C=N_2$$

In practice, however, diazomethane or isodiazomethane is obtained only on hydrolysis of the precipitate formed from $N_2O$ and *(1)*. On the other hand, diazomethane is taken up by *(1)* in a 1:1 ratio, to form a precipitate *(2)*, which again yields (iso-)diazomethane on hydrolysis. The reaction should therefore be formulated as follows.

$$2\,(C_6H_5)_3P=CH_2 + N_2O \rightarrow (C_6H_5)_3P=O + [HCN_2^{\ominus} + (C_6H_5)_3\overset{\oplus}{P}CH_3] \quad (2)$$

$$(2) + H_2O \rightarrow [(C_6H_5)_3\overset{\oplus}{P}CH_3]\,OH^{\ominus} + H_2CN_2 \text{ (yield: 25 \%)}$$

The small yields are due to the indirect route through the diazomethyl anion and to side reactions, *e.g.* reduction of $N_2O$ to $N_2$, and addition of a further methylene group to the diazomethane molecule to form triphenylphosphine and hydrazine derivatives [28]. Higher diazoalkanes which do not form $RCN_2^{\ominus}$ anions cannot be obtained by this method. Chloramine and formaldoxime give 70–75 % yields of diazomethane [29], but no cyclic products.

$$\text{Diazirine} \leftarrow\!\!\!\!\!\!\diagdown\!\!\!\!\!\!\diagup \quad H_2C=NOH + NH_2Cl \xrightarrow{CH_3ONa} CH_2N_2$$

Diazomethane was also obtained – albeit in maximum yields of only 10 % – by introducing methylenetoluenesulfonylhydrazine *(3)* into hot potassium hydroxide solution in a current of nitrogen.

$$H_2C-N-NHSO_2C_7H_7 \xrightarrow{KOH} CH_2N_2 + RSO_2^{\ominus}$$
*(3)*

From formaldehyde and *p*-toluenesulfonylhydrazine hydrochloride compound *(3)* (or its dimer?) is obtainable as a colorless microcrystalline product but only in aqueous solution. It resinifies rapidly with decomposition on contact with organic solvents. Attempts to use *(3)* in carbene reactions were unsuccessful; only hydrogenation of C=C bonds, presumably by side reactions, was observed [30].

## Radiation-Induced Formation of Sulfuric Acid in the System $SO_2/O_2/H_2O$

*R. Schrader* and *S. Schönherr*, Freiberg/Sachsen (Germany)

Sulfuric acid can be obtained in appreciable quantities by the action of ionizing radiation on sulfur dioxide (gaseous, liquid or dissolved in water) and oxygen. For the reaction in aqueous solution, a mixture of sulfur dioxide and oxygen of constant composition is led in continuously. The solution is irradiated with 180 kV X-rays with a dose rate of $3\times10^{16}$ eV/ml/min. Sulfuric acid and traces of dithionic acid are formed. The rate of reaction of 0.2–0.9 M sulfurous acid remains approximately constant at $\approx$ 15 mmole/l/h in the irradiated solution between 20 and 80 °C. In the thermal reaction, the rate of reaction of the sulfurous acid increases with increasing concentration and temperature. For 0.2 M sulfurous acid at 20 °C, $G(H_2SO_4) \approx 560$ [31]. This figure decreases to $\approx$ 0.7 in the absence of oxygen. Thus the reaction cannot proceed only via the products of radiolysis of water.

Additions of 0.01 M $Cu^{2+}$, 0.01 M $Fe^{2+}$, and 0.01 M or 0.001 M $Fe^{3+}$ eliminate the irradiation effect. When the irradiation is interrupted, the rate of the irradiation reaction falls below that of the thermal reaction. Sulfur dioxide and oxygen are taken up during the reaction in roughly stoichiometric proportions.

The experimental results suggest a chain reaction, which can probably be represented by the overall reaction (a).

$$H + O_2 + 2\,SO_2 + 2\,H_2O \rightarrow 2\,H_2SO_4 + H \qquad (a)$$

[28] According to *G. Wittig* and *M. Schlosser* [Tetrahedron *18*, 1023 (1962)], this is the main reaction for the pair benzylidenetriphenylphosphorane/phenyldiazomethane (formation of dibenzylideneazine).

[29] *W. Rundel*, Angew. Chem. *74*, 469 (1962); Angew. Chem. internat. Edit. *1*, 403 (1962).

[30] Hydrogenation of olefins by *p*-toluenesulfonylhydrazine: Cf., for example, *R. S. Dewey*, J. Amer. chem. Soc. *83*, 3729 (1961).

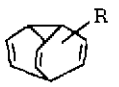
[31] $G(H_2SO_4)$ = number of sulfuric acid molecules formed per 100 eV of radiation energy absorbed.

## Molecules with Rapid Reversible Valence Isomerism. Synthesis and Properties of Bromobullvalene and Alkyl Bullvalyl Ethers

*G. Schröder, R. Merenyi,* and *J. F. M. Oth,*
Karlsruhe (Germany) and Brussels (Belgium)

Bromobullvalene [32] and potassium alkoxides interact in dimethyl sulfoxide at 20 °C to give excellent yields of the alkyl bullvalyl ethers.

It is remarkable that the rate of the valence isomerism of t-butyl bullvalyl ether *(1)* is greater than that of methyl bullvalyl ether *(2)*. Owing to steric hindrance, the π-orbitals of the double bond in *(1)* cannot lie parallel to the orbitals of the lone pair of electrons on the ether oxygen. Thus, the valence isomerism in *(1)* is only slightly, or not at all, hindered by conjugation. In *(2)*, conjugation of the vinyl ether system is not prevented by steric factors.



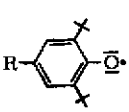
| R | M.p. [°C] | τ-Value of the bullvalene protons | Measuring temperature [°C] | Line width [cps] | Rel. rates at 0 °C |
|---|---|---|---|---|---|
| $OCH_3$ *(2)* | 23–26 | 5.97 | 91 | 30 | 12 |
| $OC_2H_5$ | 70–88 | 6.00 | 92 | 22 | 16 |
| $OCH(CH_3)_2$ | 28–32 | 6.02 | 93 | 15 | 20 |
| $OC(CH_3)_3$ *(1)* | 16–19 | 5.97 | 91 | 9 | 39 |
| Br | 41–43 | 5.78 | 90 | 6 | 53 |
| H (Bullvalene) | 96 | 5.78 | 92 | 1.68 | 100 |

## A Simple EPR Method for Measuring the g-Factors of Free Radicals, Applied to Substituted Aroxyls

*H. B. Stegmann* and *K. Scheffler*, Tübingen (Germany)

g-Factors of free radicals can be determined with great accuracy (± $5\times10^{-6}$ to ± $30\times10^{-6}$) depending on the line width of the signal studied with simple equipment adaptations. The method consists essentially in recording the EPR spectrum of a calibrated standard, diphenyl-*S*-(4-oxyl-3,5-di-t-butylphenyl) thiophosphorate, simultaneously with the EPR spectrum of the radical to be studied. The hyperfine structure for the standard radical is so designed that no overlapping of the two signals occurs in the central part of the spectrum. Since both radicals are situated at the same place in the $H_0$ field of a conventional EPR spectrograph during the measurement, the desired g-factor can be obtained simply by measuring the distance between the centers of the two signals.

The effects of substituents in aroxyls of type *(1)* were investigated. It was found that the g-factors were practically



*(1)*

constant (2.00451, 2.00461, and 2.00536) within each of the series

R = $CH_3$, $C_2H_5$, $CH(CH_3)_2$, $C(CH_3)_3$;

R = $OCH_3$, $OC_2H_5$, $OCH(CH_3)_2$, $OC(CH_3)_3$; and

R = $SCH_3$, $SC_2H_5$, $SCH(CH_3)_2$, $SC(CH_3)_3$; $S(CH_2)_3CH_3$, $SCH_2CH_2C_6H_5$.

For R = $SeC(CH_3)_3$, the g-factor was found to be 2.00846. Thus, whereas alkyl groups have no controlling effect on the g-factors, the latter can clearly be seen to depend on the atom linking the aroxyl group to the substituent. Thus, participation of spin-free atoms in the free-radical state can also be detected from g-factors.

[32] *G. Schröder, R. Merenyi,* and *J. F. M. Oth,* Tetrahedron Letters *1964*, 773.

## Preliminary Studies on Peptide Syntheses from Isocyanides [33,34]

*I. Ugi, K. Offermann,* and *H. Herlinger,*
Leverkusen (Germany)

L-(−)-α-Methylbenzylamine *(1)*, 2-methylpropanal *(2)*, benzoic acid *(4)*, and t-butyl isocyanide *(8)* combine almost quantitatively to form the L-valine derivative *(12t)* [33], m.p. 116–116.5 °C, $[\alpha]_{578} = +36°$, c = 5 in methanol, and the D-valine derivative *(12e)*, m.p. = 136–136.5 °C, $[\alpha]_{578} -200°$. The ratio *(12t)*:*(12e)* = Q depends on the reaction conditions and can be accurately determined [± 1 % *(12t)*] from the rotation of purified *(12t)* + *(12e)* (without separation of the diastereoisomers) and from the rotation of the valine obtained from *(12t)* and *(12e)* by acidic dealkylating hydrolysis [33].

If methanolic solutions of equivalent quantities of *(1)* + *(2)* + *(4)* or *(7)* + *(4)* of concentration $c_0$ are treated at 0 °C with *(8)*, the steric course of the reaction, within the limits of analytical error, follows Equation (a) with $Q_E = 3.72$, $Q_A = 0.15$, and f = 2.20 (cf. Equations (b) to (d) and Table).

| $c_0$ [mole/kg] | 0.010 | 0.050 | 0.105 | 0.256 | 0.522 | 1.075 | 1.59 | 2.41 |
|---|---|---|---|---|---|---|---|---|
| $Q_{found}$ | 3.52 | 3.28 | 2.97 | 2.36 | 1.78 | 1.23 | 0.96 | 0.72 |
| $Q_{calculated}$ from Eq. (a) | 3.65 | 3.34 | 3.05 | 2.43 | 1.81 | 1.21 | 1.00 | 0.71 |

This reaction course can be represented by the simplified model

$$A \leftarrow B \leftrightharpoons C \rightleftharpoons D \rightarrow E$$

in which *(5t)*, *(5e)*, *(6t')*, and *(6e')* are grouped together as reaction system B, *(4)* + *(1)* + *(2)* or *(4)* + *(3t)* + *(3e)* or *(4)* + *(7)* as C, and *(11)* as D. Product A, which is formed by insertion of *(8)* into the *threo-* and *erythro*-oriented ion pairs *(6t')* and *(6e')* [the reactive forms of *(5t)* and *(5e)*, which might be protomeric with H-bond adducts of *(4)* + *(7)*] that are unseparated by solvent molecules, corresponds to *(12t)* + *(12e)* in the ratio $Q_A$, while E stands for a mixture of *(12t)* + *(12e)* in the ratio $Q_E$, derived [via the intermediates *(10t)* and *(10e)*] from the solvated, unoriented ion pair *(11)*. Provided that the reactions B ⇋ C ⇌ D and *(6t')* ⇌ *(6e')* proceed more rapidly than B → A and D → E, and with the additional proviso that $c_B \ll c_0$, Equation (a) can be deduced with the aid of this model representation:

$$\frac{Q - Q_E}{Q - Q_A} = -f \cdot c_0 \quad \text{(a)},$$

$$\text{where } Q_A = \frac{k_{6t' \rightarrow 9t} \cdot K_{6e' \rightleftharpoons 6t'}}{k_{6e' \rightarrow 9e}} \quad \text{(b)},$$

$$Q_E = \frac{k_{11 \rightarrow 10t}}{k_{11 \rightarrow 10e}} \quad \text{(c) and}$$

$$f = \frac{(1+Q_E)\,(k_{6t' \rightarrow 9t} \cdot K_{6e' \rightleftharpoons 6t'} + k_{6e' \rightarrow 9e})\,K_{4+7 \rightleftharpoons 6t'+6e'}}{2\,(1+Q_A)\,(1+K_{6e' \rightleftharpoons 6t'})\,(k_{11 \rightarrow 9t} + k_{11 \rightarrow 9e})\,(1+\sqrt{K_{4+7 \rightleftharpoons 11}})\,\sqrt{K_{4+7 \rightleftharpoons 11}}} \quad \text{(d)},$$

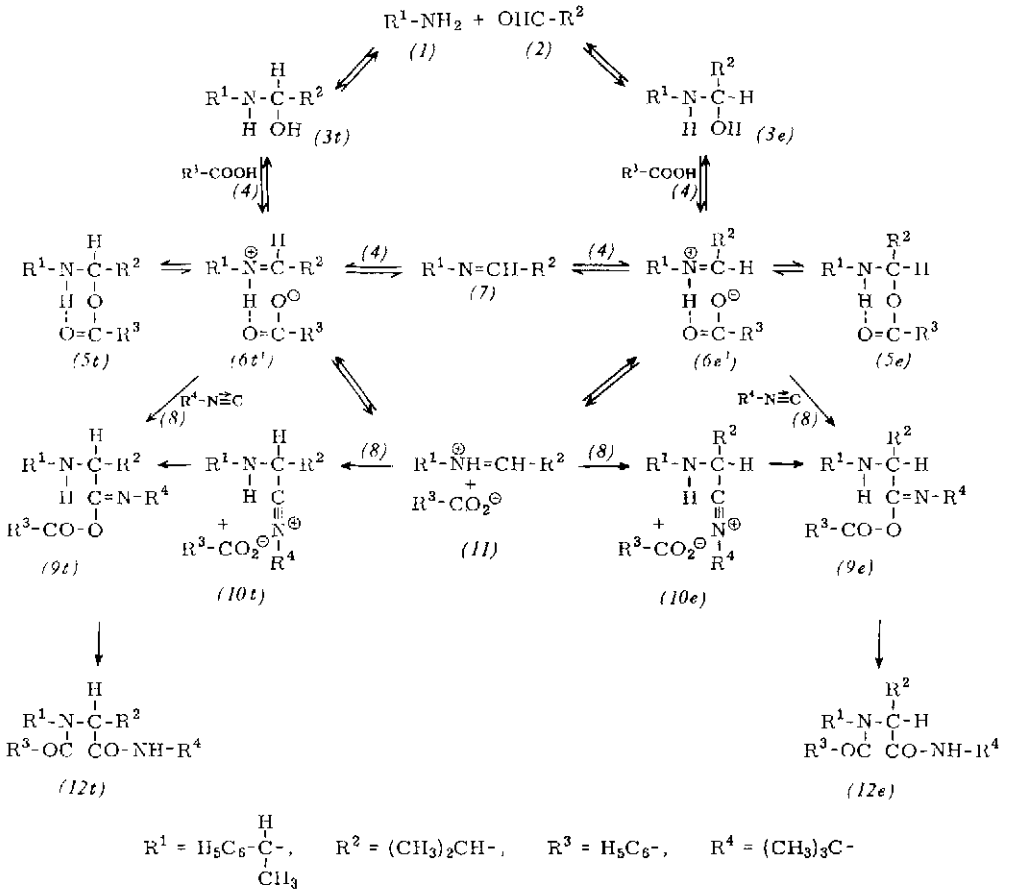
k being the reaction rate constant and K the equilibrium constant of the reaction specified by the subscripts.

The difference in the conformational strains of the two diastereoisomeric transition states is

$$F^{\rightleftharpoons}_{11 \rightarrow 10e} - F^{+}_{11 \rightarrow 10t} = 0.71 \text{ kcal/mole}$$

[33] Cf. *I. Ugi* and *K. Offermann*, Angew. Chem. *75*, 917 (1963); Angew. Chem. internat. Edit. *2*, 624 (1963); *K. Offermann*, Ph. D. Thesis, Universität München, 1964.

[34] *I. Ugi*, Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962); *K. Sjöberg*, Svensk kem. Tidskr. *75*, 493 (1963).



$R^1 = H_5C_6-\underset{CH_3}{\overset{H}{\underset{|}{\overset{|}{C}}}}-$, $R^2 = (CH_3)_2CH-$, $R^3 = H_5C_6-$, $R^4 = (CH_3)_3C-$

*t* = threo forms; *e* = erythro forms.

for the exclusively *kinetically controlled* branch of the reaction [cf. (c)], and for the equilibrium-dependent branch [cf. (b)], according to the Curtin-Hammett principle,

$$F^{+}_{6t' \rightarrow 9t} - F^{+}_{6e' \rightarrow 9e} = 1.02 \text{ kcal/mole}$$

## Promethium and Some of Its Compounds

*F. Weigel*, Munich (Germany)

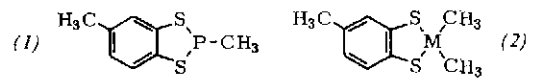
Promethium (element 61) was isolated from a crude concentrate from Oak Ridge National Laboratory. In addition to 50 curies of promethium 147, the concentrate also contained larger quantities of europium, samarium, neodymium, and americium. A promethium-americium fraction was first isolated using ion-exchange chromatography on Dowex 50 at 87 °C by elution with 0.5 M ammonium α-hydroxyisobutyrate at pH 3.5. The americium and promethium were then separated on a Dowex 1 anion-exchange column by elution with 8 M ammonium thiocyanate. The resulting pure promethium was freed from residual thiocyanate by repeated reprecipitation as the hydroxide. The last hydroxide precipitate was dissolved in $HNO_3$ to obtain a promethium(III) nitrate solution, which was used as the starting material for the production of the metal and the preparation of a few compounds. Several samples of about 300 μg of Pm metal each were obtained by reduction of $PmF_3$ with Li at about $10^{-6}$ mm in a tantalum double crucible system. Pm is a silvery-white metal, which is more stable in air than neodymium, but is similar in appearance to the latter. Its melting point was found by the "welded joint rupture" method to be 1090 ± 8 °C. The following promethium compounds were prepared: $Pm(OH)_3$ purplish pink, $PmCl_3 \cdot xH_2O$ lemon yellow, $Pm_2O_3$ purplish pink, $PmF_3$ purplish pink, $PmPO_4$ pink, $PmAsO_4$ pink, $Pm(IO_3)_3$ yellow pink, and $Pm_2(C_2O_4)_3 \cdot 10\ H_2O$ purplish pink.

Promethium(III) phosphate crystallizes in the monoclinic system with a = 6.71 Å; b = 6.905 Å; c = 6.36 Å; β = 103° 56′. The oxalate $Pu_2(C_2O_4)_3 \cdot 1\ OH_2O$ has a = 11.43 Å; b = 9.57 Å; c = 9.97 Å; β = 118° 55′. These values for the lattice constants are preliminary.

## Some Bicyclic Heterocycles

*M. Wieber* and *M. Schmidt*, Marburg/Lahn (Germany)

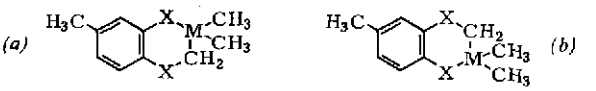
The organometalloid halides $CH_3PCl_2$, $(CH_3)_2SiCl_2$, $(CH_3)_2GeCl_2$ and $(CH_3)_2SnCl_2$ react in inert solvents with 3,4-dimercaptotoluene in the presence of stoichiometric quantities of triethylamine as hydrochloric acid acceptor to afford very good yields of the bicyclic heterocycles *(1)* and *(2)*.



M = Si, Ge, Sn

Organometalloid monohalides which are halogenated on the organic group, *e.g.* chloromethyldimethylchlorosilane or -germane, also react with 3,4-dimercapto toluene and its oxygen analogue with ring formation.

The $^1H$-NMR spectra showed that *(3a)* and *(3b)*, *(4a)* and *(4b)*, or *(5a)* and *(5b)* are formed.



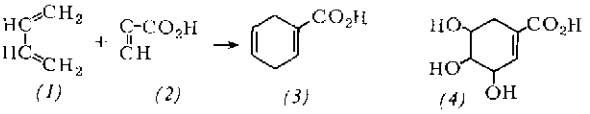
*(3)*: X = S, M = Si; *(4)*: X = S, M = Ge; *(5)*: X = O, M = Si

Form *(b)* is the predominant product [*(a)*:*(b)* :1.3].

The course of the hydrolysis of the 5- and 6-membered rings is fundamentally different. In the first case, 3,4-dimercaptotoluene is reformed, together with polymeric organometalloid oxide, whereas organosiloxanes or -germoxanes are formed in the second case. [VB 815/154 1E]

German version: Angew. Chem. 76, 573 (1964)
Translated by Express Translation Service, London

**A new synthesis of shikimic acid** *(4)* is described by *R. Grewe* and *J. Hinrichs*. Butadiene *(1)* and propiolic acid *(2)* react to form cyclohexadienecarboxylic acid *(3)*, m.p. 120 °C, in 85 % yield. The methyl ester, b.p. 98–99 °C/22 mm, is treated with hydrogen peroxide in formic acid to give the *trans*-dihydroxy ester, m.p. 97 °C, in 85 % yield; this is converted into methyl 4,5-diacetoxy-1-cyclohexene-1-carboxylate, m.p. – 61 °C, in 80 % yield by acetic anhydride in pyridine.



*(1)* *(2)* *(3)* *(4)*

This diacetate is brominated with *N*-bromosuccinimide in $CCl_4$, and the resulting 3-bromo compound is converted into methyl shikimate by treatment with silver acetate followed by hydrolysis with methanolic potassium hydroxide. The pure ester (m.p. 172 °C, yield 20 %) is separated on a cellulose column from isomeric compounds and from unbrominated methyl dihydroxycyclohexenecarboxylate (m.p. 97 °C, recovery 21 %). Free (–)-shikimic acid, m.p. 190–191 °C, is obtained by hydrolysis. The individual fractions are purified via the cyclohexylidene compound of the methyl esters; besides pure (–)-shikimic acid, (±)-shikimic acid, (±)-epishikimic acid, epiisoshikimic acid, and (±)-isoshikimic acid were also isolated. The cyclohexylidene compounds are obtained in almost quantitative yield in dimethylformamide/benzene in the presence of an acid ion-exchanger, the water formed being removed continuously by means of a separator. / Chem. Ber. *97*, 443 (1964) / –W. [Rd 938/275 IE]

**The relationship between the molar extinction coefficient ε of DNA and its guanine and cytosine content** was investigated by *S. L. Bunch* and *B. V. Siegel*. It was shown for 9 samples of DNA that $\varepsilon_{260\ m\mu}$ is a linear function of the content of guanine plus cytosine. Regression equations were calculated in order to estimate the individual contributions. Since the extrapolated values of ε for polyguanylic acid and polycytidylic acid corresponded to the values for guanylic acid and cytidylic acid, it was concluded that there is only weak hydrogen bonding between guanine and cytosine in the double helix. / Experientia *20*, 14 (1964) / –Re. [Rd 908/261 IE]

A **volumetric determination of silicon** is proposed by *H. Bartels* and *H. Erlenmeyer:* it is based on the formation of a 1:3 complex between silicon and catechol. The silicon compound, which should be present at a concentration of about $10^{-2}$ M, is mixed with a threefold excess of catechol or a catechol derivative and stirred or shaken with a known excess of NaOH, until complex formation is complete (15 min to a few hours, according to the nature of the silicon compound). For each mole of Si present, 2 moles of NaOH are neutralized by the $H^{\oplus}$ ions liberated during complex formation. The excess $OH^{\ominus}$ is back-titrated. / Helv. chim. Acta *47*, 13 (1964) / – Hz. [Rd 939/276 IE]

**The molecular weight of interferon** was determined by *C. Jungwirth* and *G. Bodo* by gel filtration. Interferon is a protein that is formed after the infection of cells by viruses. Fowl embryo tissue infected with influenza virus yielded interferon preparations which after purification were chromatographed on Sephadex G-100 columns. Comparisons with the behavior of test proteins gave a molecular weight of 32000 to 35000 for interferon. / Biochem. Z *339*, 382 (1964) / –Sch. [Rd 999/287 IE]

**Apamin, a polypeptide from bee venom** which causes excitation of the central nervous system, was isolated from lyophilized bee venom by *E. Habermann* and *K.-G. Reiz* using chromatography on Sephadex and carboxymethylcellulose. Apamin forms about 2–3 % of the dry weight of the venom and is a strongly basic polypeptide composed of 16 amino-acid residues; in rats, besides strongly increasing capillary permeability, it affects only the central nervous system, *e.g.* it increases spontaneous motor activity. This polypeptide appears to be the first naturally occurring peptide to show such effects. Apamin poisoning can perhaps be used as a model for the study of pathological excitation of the central nervous system. / Naturwissenschaften *54*, 61 (1964) / –Sch. [Rd 904/260 IE]

**The reduction of DPN during carbonic-acid assimilation** was observed by *L. Kiesow* in homogenates of *Nitrobacter winogradskii*. Assimilation of $CO_2$ by the chemoautotrophic *Nitrobacter* can only take place in the presence of nitrite, which provides the necessary energy for the assimilation by its oxidation from $NO_2^-$ to $NO_3^-$. The $CO_2$ fixation and $NO_2^-$ oxidation take place in equivalent amounts, as was shown by ionopherograms using $NaH^{14}CO_3$. The oxidation of $NO_2^-$ is linked to a reduction of DPN. By means of this reaction, the energy provided by oxidation of nitrite is chemically "bound" and converted so that it is available for $CO_2$ assimilation. The DPN reduction/$NO_2^-$ oxidation exhibits an optimum at pH 8.2–8.3. / Biochem. Z. *338*, 400 (1963) / –De. [Rd 905/259 IE]

**Peat has been used as a cation-exchanger in the purification of radioactive sewage** by *E. Schmid, P. Stipanits*, and *F. Hecht*. In comparison with cheap inorganic exchangers such as permutits, glauconites, and montmorillonites, which can be used only once, peat has roughly the same exchange capacity (about 37 % of the dry weight consists of humic acids) and offers important advantages: the volume containing the radioactivity after absorption can be greatly reduced by combustion (maximum ash content 8 %). Sorption tests carried out either in a standard column (diameter: 1 cm; length: 12 cm; flow: 1 ml/min) or in a batch process (shaking with peat suspensions) showed that the exchange capacities in the batch process are always lower. The peat was boiled with water, dried at 110 °C, ground, sifted, and washed free of cations with 5 N HCl. Free excess acid was then removed with distilled water. In the column, penetration capacities D of 0.05–0.10 and saturation capacities S of 0.3–0.6 mequiv/g of peat were found for $^{137}Cs$, $^{89}Sr$, $^{60}Co$, and $^{140}Ba$ at pH 3–5. A solution of 1 μC activity, free from carrier and extraneous electrolytes, could be quantitatively purified in the standard column. Owing to its varied acidic groups, the exchange capacity of peat depends on the pH: at pH 1, S ≈ 0.1, at pH 5, S ≈ 0.5, and above pH 6–7, S rises to about 2 mequiv/g, as a result of incipient precipitation of hydroxide. / Österr. Chem.-Ztg. *65*, 9 (1964) / – Jg. [Rd 935/272 IE]

**The degradation of DNA by cysteamine or L-cysteine** in the presence of metal complexing agents or catalase was studied by *K. Berneis* and *M. Kofler*. Cysteamine is a better radiation shield than L-cysteine and does not change the DNA structure. In contrast, in aqueous solution under aerobic conditions, L-cysteine causes a degradation of DNA which is greatly increased by ethylenediaminetetraacetic acid or catalase. It was concluded from model experiments that these agents promote autoxidation of cysteine. This is the converse of the situation in the degradation of DNA by $H_2O_2$, for the latter is strongly inhibited by ethylenediaminetetraacetic acid or catalase. / Experientia *20*, 16 (1964) / –Re. [Rd 909/262 IE]

**A new cell for the electrochemical determination of oxygen** has been developed by *E. Proksch* and *H. Bildstein*. It works on a principle resembling polarography: stationary diffusion of oxygen produces a diffusion boundary current at a noble metal cathode (an Ag gauze cylinder packed with Ag wool), which is proportional to the oxygen concentration. The cathode potential is not varied, but is present by an unpolarizable anode (Cd/Ni), in such a way as to remain within the range of the diffusion boundary current. The Ag cathode is placed in a horizontal glass tube, half-filled with 15 % KOH; the Cd/Ni anode is placed in a vertical limb (a Pt accessory electrode is used to regenerate the anode). The gas to be examined is saturated with water vapor and is passed over the KOH solution; the gas must be absorbed to the point of equilibrium or at a constant rate. The cell is connected in series with an electrolytic cell for calibration with known quantities of oxygen. The readings are strictly linear from 0.1 to 600 ppm of oxygen; using a calibration curve, up to 1000 ppm of oxygen can be determined. For contents of less than 100 ppm, the cell can be used for months without regeneration. The maximum sensitivity at 20 °C is 3–4 μA/ppm $O_2$, at a flow rate of 30–100 ml of gas/min. At 50 °C, the sensitivity is increased by a factor of about 4. In comparison with similar earlier cells, the sensitivity, the rate of response, and the linearity range (formerly a maximum of 150 ppm) have been considerably improved. The cell is easy and inexpensive to make, and can be used for automatic supervision of gas scrubbers and gas circulations, *e.g.* in nuclear reactors. Owing to its low cost, this method of determining oxygen is superior to gas chromatography and mass spectrometry. / Österr. Chem.-Ztg. *65*, 41 (1964) / –Jg.

[Rd 936/273 IE]

**The substrate of alcohol dehydrogenase is free acetaldehyde.** *B. Müller-Hill* and *K. Wallenfels* reached this conclusion by measuring the enzymatic reduction of aqueous acetaldehyde solutions at 0 °C. About 25 % of the aldehyde was immediately consumed, but it was impossible to follow the progress of this reaction by normal means. For the reduction of the remaining 75 % a monomolecular reaction was rate-determining. If a solution of acetaldehyde in anhydrous tetramethylurea was stirred into the reaction mixture, 80 % of the aldehyde reacted at once and the remainder with measurable velocity. Since, according to *Bell* and *Clunie* [1], 26.5 % of the acetaldehyde in aqueous solution exists in the free form at 0 °C, it can be concluded that only the free aldehyde and not the hydrate is the substrate of the enzyme. This result is important for the interpretation of the kinetics of the enzymatic reaction. / Biochem. Z. *339*, 349 (1964) / –Sch. [Rd 2/292 IE]

[1] *R. P. Bell* and *J. C. Clunie*, Trans. Faraday Soc. *48*, 439 (1952).

# BOOK REVIEWS

**Ullmanns Encyklopädie der technischen Chemie** (Ullmanns Encyclopaedia of Chemical Technology). Third completely revised edition, compiled by *W. Foerst*, edited by *Hertha Buchholz-Meisenheimer*. Verlag Urban & Schwarzenberg, München-Berlin. Vol. 11: Kunststoffe bis Lithium. 1960, XII, 798 pp., 308 illustrs.; Vol. 12: Lösungsmittel bis Nitrochlorobenzole und Toluole. 1960, XII, 800 pp., 226 illustrs.; Vol. 13: Nitro- und Nitrosofarbstoffe bis Picrinsäure. 1962, XV, 823 pp., 158 illustrs. Price per volume in linen binding DM 128.– (about $32.–). Subject Index for Vols. 3–13 (200 pp., paper back).

The present three volumes contain articles (in German) listed under key-word headings as follows: Vol. 11: Plastics to Lithium; Vol. 12: Solvents to Nitrobenzenes and -toluenes; Vol. 13: Nitro- and Nitroso Dyestuffs to Picric Acid.

It is noticeable that the experience gained in editing the original volumes of this handbook has been put to use in the later volumes. The aim to present truly encyclopaedic information, to give a general survey as well as to set forth methods and recipes in detail, and to provide straightforward directions for individual cases, is accomplished better than ever. This is successfully achieved by the enlistment of numerous specialists – over 200 authors have cooperated in the 3 volumes – and by intense editorial work to ensure a terse arrangement, to provide cross-references, and to eliminate duplication and overlapping. Let us look more closely at some individual chapters.

Vol. 11 contains 18 articles including: Plastics, 119 pp.; Paints and Surface Coatings, 138 pp.; Food stuffs, 128 pp.; Light Production and Measurement, 64 pp. The highlights of the article on plastics comprise the questions of their properties (27 pp.) and processing (27 pp.). A good introduction (14 pp.) provides the general context. In other sections, coloring, surface treatment, testing, and analysis are dealt with; a discourse on economic aspects and plastics literature concludes the article. Not all of the processes known for manufacturing plastics are discussed in this article – references to a large number of special topics are given here instead. Space is thus left for some more detailed information. The section on 'Properties' occupies only 5 pp. of text but 8 pp. of diagrams and 14 pp. of tables, thus giving an extremely concise survey of all the more important plastics, subdivided into groups according to their major properties. (Modified natural products, amorphous-crystalline and amorphous thermoplasts, cross-linked, non-cross-linked polymers, and so on.) In the chapter on surface treatment, a description is given, for example, of how velvet- and suede-like leather foils are produced by electrostatic flocculation of plastics and textile fibres. Recipes and 25 suitable pigments for coloring poly(vinyl chloride) are specified. The chapter on testing contains numerical data on 30 characteristic properties, a boon to the practician. Details on commercial information are rather scant. The chapter on the historical background gives historical data in great detail, but the development trends in individual classes of plastics (an account of the commercial and technical problems) would also have been worth mentioning here. – In addition to its comprehensive detailed information, this article fulfills its ultimate aim by references to numerous manufacturing processes, production technology, and equipment methodology as well as by correlation of this information with the theoretical-scientific aspects of the work. It thus fulfills as task which can no longer be accomplished by a monograph.

The section on food stuffs technology is fully up-to-date. Seventeen authors have contributed to the article on foodstuffs (126 pp.): 100 pp. are devoted to the preservation of food, 8 pp. to coloring, 4 pp. to analysis, and 10 pp. to packaging. These chapters are again predisposed to make it easy to find details. Thus, in the section on "Preservation by Chemical Means", the sub-headings "Official Regulations and Guide to Applications" or "Use of Chemical Preservatives for Confectionary and Bakery Products" are encountered. The methods of manufacturing cans are described, and a table gives informtaion on the tin and iron content in preserved foods in mg/kg as a function of the storage life for fruit, vegetables, fish, and meat – for a total of 25 goods. In conclusion, preservation by refrigeration is dealt with – from the beginning of the 19th century, when ice from Norway was sent to the tropics, to modern refrigeration technique and its technical and economical advantages. In the chapter on colors, 85 dyestuffs are given together with the statutory requirements for their admission in 51 countries. In the section on packaging technique, a table is given of 22 important packaging characteristic properties for each of 19 coated and non-coated films including their behavior towards moisture, gas

permeability, chemical resistance, and stability towards heat and ageing. The article is divided into 85 sub-chapters. It quotes numerous references to, for example, fruit juices, cereals, baking, milk, vitamins, microbiology, and freeze drying and thus simultaneously forms the guide to all the information on the hwole field of foodstuffs in *Ullmann*. Whoever finds himself in a developing country with the task of setting up a foodstuffs industry will be unable to find any better information in the literature with regard to completeness, conciseness, and arrangement.

Volume 12 contains 60 articles including among the larger ones: Milk and Milk Products, 50 pp.; Solvents and Solutions, 48 pp.; Magnesium, 31 pp.; and Microbiology, 27 pp. – The modern technology of dairying is fully treated; it is only the commercial information, consisting of a table from the FAO Production Year Book for 1958, that is too brief. – The article on microbiology both affords an account of the technology of microbiological processes (10 pp.) and provides an enhancement and scientific extension of foodstuffs chemistry. A number of drawings in the general introduction would have made the subject more comprehensible. The readability of articles of this type from borderline subjects could have been improved further if the author had added a small list of seldomly used expressions and their meanings. Not everyone knows what endspores and sexual spores are or is familiar with expressions such as heterotrophic, xerophilic, involution forms, and so on. Even better known expressions, *e.g.* adaptation, have sometimes changeable meanings in the literature. – The article on solvents and solutions (48 pp.) characterizes in its special section (32 pp.) 127 solvents arranged according to subject matter and supplemented by an alphabetical index. The excellent general section (16 pp.) starts with the theory of intermolecular forces, discusses the most important solvent properties, requirements for use in various fields such as extraction processes and chemical reactions, and finally deals with solvent transport, analysis, purification, and recovery. The space allotted to the present review does not leave roo for appraisal of other good smallom articles in Vol. 12. The articles on sodium carbonate and sodium hydroxide (19 pp.) and sodium chloride (20 pp.) are particularly good.

Volume 13 contains 26 articles of which the section on pharmatherapeutics (165 pp.) is especially noteworthy. After antibiotics, antihistamines, chemotherapeutics (antiseptics), homeopathic medicines, drugs, enzymes, hormones, and medicinal preparations had already heen dealt with in previous volumes, the wide field of medicaments has undergone comprehensive revision in this article. The main theme is the classical field of chemical medicaments which have chiefly symptomatic action; these are arranged according to the points of attack on the body. The presentation is comprehensive and takes into account modern development up to 1963. Thirty-three specialists from 9 companies in the chemical-pharmaceutical industry, including the Swiss firms Hoffmann-La Roche, Ciba, and Sandoz, have cooperated on this article. The individual sections contain general introductions on physiological and chemical aspects. A large number of substances are characterized under chemical properties, method of preparation, and commercial products. Since the article is of great interest in providing general information to chemists who are not experts on drugs, a short glossary with explanations of certain terms would also he worthwile here. Likewise, the brief hut pregnant article on parasitic infections falls into the medicinal field (8 pp.). In the discourse on the Pärchenegel (Schistosomiasis) one misses the name Bilharzia; the more familiar name of the disease Bilharziosis should also be mentioned.

Especially noteworthy in Volume 13 is the article on photography (92 pp.) under the direction of *H. Ulrich* and *E. Klein* from Agfa Leverkusen, in which further 13 specialists have cooperated. In its concise account covering the entire field of photography from elementary photographic processes via raw materials and production problems to application technique, the article is highly instructive. Here again fundamental to detailed relationships are set forth; *e.g.* timing arrangements and examples of recipes are given for the 13 processing stages in the development of cine color film. In this article, too, the commercial information is again limited to a scant table on the production and export and import in the German Federal Republic. For the technically interested reader, however, commercial statistics are important characteristic values from which he can measure the relative importance of various fields of work and production methods and record them in his mind. The paragraph on commercial aspects is generally too brief. This surely deserves a good treatment similar to that, for example, of the chapters on the toxicology of pigments so excellently prepared by *H. Oettel*. Along with Vol. 13, a new subject index for Volumes 3–13 has been published (Vols. 1 and 2 are not alphabetically arranged). It is to be replaced at a later date by a complete subject index of the alphabetically arranged part. In consideration of the vast amounts of subject matter arranged non-alphabetically within the large individual articles, increased importance must be attached to this strictly alphabetically arranged index. Once again, the editors have profited from the experience gained in compiling the earlier subject indices. The new subject index contains 24000 keywords which are fairly evenly distributed over the whole field, so that the location of required information no longer presents any difficulties.

In summary it can be said that in this encyclopaedia a new kind of differentiated hut editorially coordinated collaboration of specialists has been realized. The result is a very versatile work of reference which provides authoritative material and which despite its versatility and abundance of detail still remains handy for the user. It is hoped that the work will make rapid progress towards completion.

*H. Sachsse* [NB 213/95 IE]

## Erratum

In the Short Communication

Determination of the Sequence of a Code Triplet
by *F. Cramer, H. Küntzel,* and *J. H. Matthaei*
in Angew. Chem. internat. Edit *3*, 589 (1964)

the first and third lines in Column 1 of the Table should be exchanged. The Table should read:

| Amino acid | Aminoacyl-RNA bound [nμmoles] | | |
|---|---|---|---|
| | without polynucleotide | with poly-Up···UpU | with poly-Up···UpUpG |
| [$^3$H]Leu | 139 | 125 | 350 |
| [$^{35}$S]Cys | 482 | 465 | 480 |
| [$^{14}$C]Val | 780 | 788 | 716 |
| [$^3$H]Phe | 64 | 174 | 70 |

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# Structure and Acidity of Organic Compounds [1]

BY PRIV.-DOZ. DR. W. SIMON

LABORATORIUM FÜR ORGANISCHE CHEMIE
DER EIDGENÖSSISCHEN TECHNISCHEN HOCHSCHULE, ZÜRICH (SWITZERLAND)

*Elucidation of the structures of organic acids and bases with the aid of their acidity constants is greatly hindered by their low solubilities in water and by the small quantities of material normally available. Apparent acidity constants K* can be determined potentiometrically on small samples (about 0.5 mg) for many classes of compounds of medium acidity. The apparent acidity constants $K^*_{MCS}$ determined in the solvent system methyl cellosolve/water can be correlated, in a similar manner to thermodynamic quantities, with structural parameters (e.g. Hammett's σ and Taft's σ* values). $K^*_{MCS}$ values can yield information on the axial or equatorial position of carboxyl groups in cyclohexanecarboxylic acids.*

## I. Introduction

Some excellent reviews have been written on the relationships between structure and acidity of a wide range of compounds [2–5].

In this connection acids and bases are defined according to *Brønsted* [6] and *Lowry* [7] as proton donors and proton acceptors, respectively, so that acid-base equilibria in an amphiprotic [8] solvent LH of high dielectric constant may be formulated as follows:

$$AH + LH \rightleftarrows A^{\ominus} + LH_2^{\oplus} \qquad (1)$$

In Equation (1), AH is the acid to be investigated and $A^{\ominus}$ the base formed from AH by the removal of a proton. No assumptions will be made regarding the nature of AH and $A^{\ominus}$; it should merely be noted that $A^{\ominus}$ contains one hydrogen atom less, and carries one unit charge more, than AH. The pairs $AH/A^{\ominus}$ and $LH_2^{\oplus}/LH$ are referred to as conjugate acid-base pairs. For the equilibrium constant

$$K' = \frac{a_{A^{\ominus}} \cdot a_{LH_2^{\oplus}}}{a_{AH} \cdot a_{LH}} = \frac{c_{A^{\ominus}} \cdot f_{A^{\ominus}} \cdot c_{LH_2^{\oplus}} \cdot f_{LH_2^{\oplus}}}{c_{AH} \cdot f_{AH} \cdot c_{LH} \cdot f_{LH}} \qquad (2)$$

(a = activity; c = concentration; f = activity coefficient)

obtained by applying the law of mass action to Equilibrium (1), the following relationship is valid:

$$\Delta F = -2.303\ RT \log K' = 2.303\ RT\ pK' \qquad (3)$$

According to Equation (3), the pK′ value of the acid AH is directly proportional to the change in free energy ΔF of the acid-base reaction of Equation (1):

$$\Delta F = \Delta H - T\Delta S \qquad (4)$$

For a change in ΔF of 1.0 kcal/mole at 25 °C, Equation (3) gives a change in pK′ of 0.73 units. In principle, both ΔF (or pK′) and ΔH can be correlated with the structure of the compound studied. However, opinions are divided as to which of the two quantities is the more suitable one [3, 9–14].

[1] Lecture delivered at a meeting of the Chemical Society of Bern (Switzerland) on January 18th, 1963.

[2] *J. F. King* in *K. W. Bentley:* Elucidation of Structures by Physical and Chemical Methods. Part I, Interscience Publishers, New York-London 1963, pp. 317–403.

[3] *E. M. Arnett* in *S. G. Cohen, A. Streitwieser, Jr.*, and *R. W. Taft:* Progress in Physical Organic Chemistry. Interscience Publishers, New York-London 1963, Vol. I, pp. 223–403.

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Quantitative investigations on acid-base equilibria are generally carried out on systems in which relatively small quantities of AH are allowed to react with a large quantity of solvent LH. The activity $a_{LH}$ of LH at constant temperature and pressure may therefore be regarded as constant, and the dissociation constant is obtained from Equation (2):

$$K = K' \cdot a_{LH} = \frac{a_{A^\ominus} \cdot a_{LH_2^\oplus}}{a_{AH}} = \frac{c_{A^\ominus} \cdot f_{A^\ominus} \cdot a_{LH_2^\oplus}}{c_{AH} \cdot f_{AH}} \quad (5)$$

Instead of the pK value (pK = −log K) of an acid-base pair, the so-called basicity constant ($pK_B$) is sometimes used. In contrast to the pK value, this constant applies to an equilibrium of the type:

$$B + LH \rightleftarrows BH^\ominus + L^\ominus \quad (6)$$

To avoid confusion, this terminology will be avoided here as far as possible. Consequently, in the remainder of this article the basicity of the base B will be defined by the acidity of the conjugate acid $BH^\oplus$. Thus, for the acid $BH^\oplus$ there is an acid-base equilibrium similar to Equation (1):

$$BH^\oplus + LH \rightleftarrows B + LH_2^\oplus \quad (7)$$

## II. Determination of Acidity Constants

Routine determinations of dissociation constants are generally carried out by potentiometric or spectrophotometric methods [15]. In the potentiometric method the activity of the hydrogen ions is measured potentiometrically (*e.g.* with a glass electrode/calomel electrode combination [16]) for a given ratio $c_{A^\ominus}/c_{AH}$. Assuming that $f_{A^\ominus}/f_{AH} = 1$, the constant K can then be calculated from Equation (5). Errors due to neglect of the activity coefficients are about 0.05 pK units [17] for 1:1 electrolytes in aqueous systems with sample concentrations of 0.01 M. The ratio $c_{A^\ominus}/c_{AH}$ can be adjusted by mixing a given amount of the acid with varying amounts of its salt. At the half-neutralization point in the potentiometric titration [18–22] $c_{A^\ominus} \approx c_{AH}$ and $c_{A^\ominus}/c_{AH} \approx 1$, so that at this point the pH value of the solution ($pH = -\log a_{LH_2^\oplus}$) is equal to the pK of AH [cf. Equation (5)].

In spectrophotometric determinations of pK values [15,23–26], the sample is generally dissolved in a system of constant hydrogen ion activity (buffer solution), and the ratio $c_{A^\ominus}/c_{AH}$ is obtained by spectrophotometry. If the pH of the solution is known, K can be calculated from Equation (5), ignoring activity coefficients. Constants which have been obtained applying this approximation are often called apparent dissociation constants.

In the systematic determination of dissociation constants for qualitative analysis of organic natural products, two main restrictions must be considered:

a) It should be possible to carry out the measurements on small quantities of sample (0.3–1.5 mg).

b) Owing to the low solubility of most organic compounds in water, the determinations must be carried out in non-aqueous solvents.

Under these conditions, determinations of thermodynamic dissociation constants K must be abandoned in favor of those of apparent acidity or dissociation constants K*. Potentiometric microtitration [20,22,27] is the most suitable method for rapid routine determinations.

Solvents used so far include: alcohol and alcohol/water [28 to 32], ethylene glycol mixed with other organic solvents [33–35], acetonitrile [36–38], dimethylformamide [39–41], cyclohexanone [42], dioxane/water [43–45], benzene [46], nitrobenzene [36,48], acetone [47,49], pyridine [50,51], glacial acetic


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acid [52, 53], and methyl cellosolve [27, 54]. In these solvents the results of potentiometric determinations of acidity constants are reproducible only if all operations of the determination procedure are highly standardized [55, 56].

A standard method has been developed in our laboratory for the determination of apparent dissociation constants in the system methyl cellosolve/water (80:20% by weight), using samples of 0.1 mg and more [*]. The compound to be investigated is titrated according to a predetermined program using a glass-electrode/calomel-electrode combination which has been conditioned in water and calibrated with aqueous buffer solutions. The apparent pH of the solution [**] at half-neutralization of the functional group to be determined is assumed to be equal to $pK^*_{MCS}$, *i.e.* equal to the negative decadic logarithm of the apparent acidity constant $K^*_{MCS}$(MCS: methyl cellosolve, ethylene glycol monomethyl ether $CH_3OCH_2CH_2OH$).

Details of the standard method can be obtained from earlier publications [20, 55–60]. The standard deviations found for a single determination were 0.07 [58] and 0.04 $pK^*_{MCS}$ units [58] for semi-automatic [20] and fully automatic [56] titrations, respectively. With the semi-automatic titration equipment, 1 ml of a $3\times10^{-3}$ to $4\times10^{-3}$ M solution is normally titrated at a constant speed, and the neutralization curve is plotted simultaneously [20, 61]. The $pK^*_{MCS}$ values of well over a thousand organic acids and bases have been published so far [63–65].


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[*] Methyl cellosolve is a good solvent for many compounds. Admixture of 20% by weight of water increases the stability of the potential of the glass electrode, without greatly reducing its universal solvent power.

[**] Measured in accordance with the definition of pH values on the so-called practical pH scale [16, 57]. According to this scale, the pH values of aqueous solutions are determined on the basis of pH standards. By analogy, the apparent pH of the sample ($pH^*_{MCS}$) is defined with reference to a standard buffer solution as follows:

$$pH^*_{MCS} = pH_s - \frac{(E-E_s)}{0.05916}$$

where

$pH_s$ = 4.005 (pH of 0.05 M potassium hydrogen phthalate at 25 °C);

E = electromotive force [abs. volts] obtained at 25 °C with the electrode system in the solution being investigated;

$E_s$ = electromotive force [abs. volts] obtained at 25 °C with the electrode system in 0.05 M potassium hydrogen phthalate in water.

$E_s$ and E are given the sign of the conductor system of the glass electrode.

The denominator 0.05916 corresponds to the theoretical electrode function; it is adjusted to match the electrode function determined in aqueous systems.


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Figure 1 shows the glass-electrode/calomel-electrode measuring cell with an interchangeable electrode membrane (cup-type electrode) [20, 60, 62], which serves as titration vessel, and a piston burette with a digital readout; the titrant is displaced from the burette by means of a tantalum piston (normal rate of titration: 1.4 µl/min). A control unit starts and stops the titration and controls the flow of nitrogen for agitation of the solution. The signal of the pH meter [Type 7666, Leeds & Northrup Co., Philadelphia, Pa. (U.S.A.)] is registered by a strip chart recorder [Speedomax Type G, Leeds & Northrup Co.].

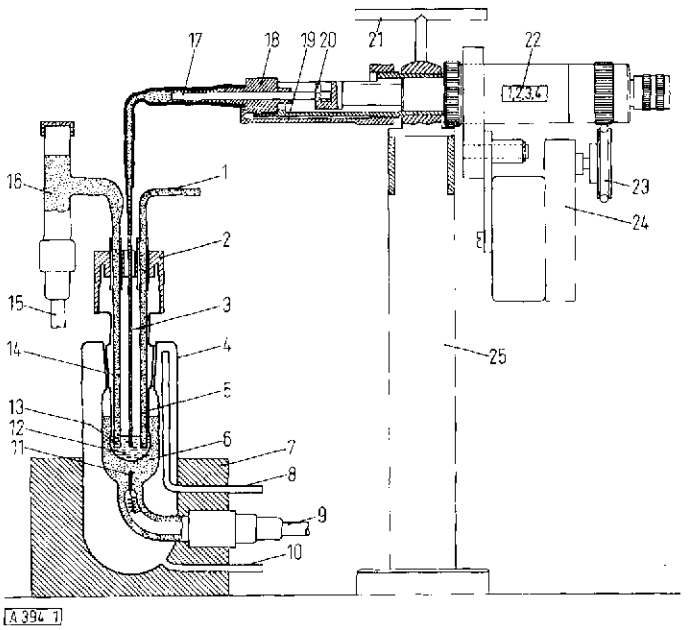



Fig. 1. Glass-electrode/calomel-electrode measuring cell with piston burette.

1. Nitrogen inlet for agitation of solution; 2. cover (chromium-plated brass); 3. burette tip; 4. glass envelope; 5. insert with electrode membrane; 6. glass-electrode buffer solution; 7. Araldit® block; 8,10. inlet and outlet for water (temperature regulation); 9. glass-electrode lead; 11. Ag/AgCl inner reference electrode; 12. sample; 13. porous sintered oxide plug; 14. tip of reference electrode (filled with saturated KCl); 15. reference-electrode lead; 16. reference electrode; 17. tantalum piston; 18. Teflon® stopper; 19. mount (aluminum); 20. adapter; 21. handle for raising burette; 22. digital readout; 23. drive; 24. motor; 25. burette support.

## III. Interpretation of Apparent Acidity Constants

At constant temperature and pressure the apparent acidity constants K* determined by the method outlined above are functions of the structure of the compound under investigation, as well as of the solvent, concentration, and determination procedure. These constants K* no longer have the well-defined thermodynamic significance of an equilibrium constant in the sense of Equations (2)–(5). Standardization (solvent, concentration, determination procedure, temperature, and pressure are kept constant) leads however to $pK^*_{MCS}$ values which depend only on the structures of the compounds under investigation. Since conclusions are to be drawn from these apparent acidity constants $K^*_{MCS}$ regarding the structure of organic compounds, the question arises as to how far it is justifiable to interpret these $pK^*_{MCS}$ values in a manner analogous

to thermodynamic pK values. It has been shown that such an analogous interpretation is justified [66, 67].

As an example, Figure 2 shows the $pK^*_{MCS}$ values for *m*- and *p*-substituted benzoic acids, phenols, and salicylic acids plotted as a function of the corresponding Hammett σ values [66] (which are independent of the

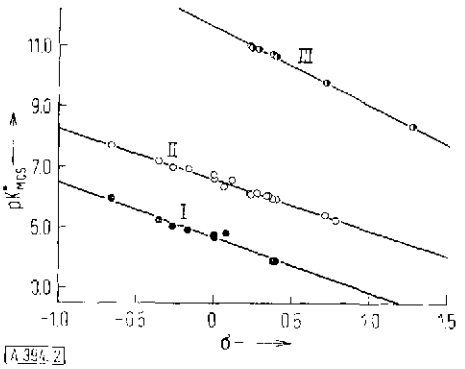



Fig. 2. $pK^*_{MCS}$ values for benzoic acids, phenols, and salicylic acids as a function of the corresponding Hammett σ values.
Curve I: Salicylic acids: 4-$NH_2$; 4-OH; 4-$OCH_3$; 4-$CH_3$; 5-OH; 3-OH; 4-$C_6H_5$—CONH; 5-Cl; 5-Br.
Curve II: Benzoic acids: *p*-$NH_2$; *p*-OH; *p*-$OCH_3$; *m*-$NH_2$; *m*-OH; H; *p*-F; *m*-$OCH_3$; *p*-Cl; *p*-Br; *p*-I; *m*-F; *m*-I; *m*-Cl; *m*-Br; *m*-$NO_2$; *p*-$NO_2$.
Curve III: Phenols: *p*-Cl; *p*-Br; *p*-I; *m*-Cl; *m*-Br; *m*-$NO_2$; *p*-$NO_2$.
(The order of the acids corresponds to the order of the plotted points, from left to right).

nature of the reaction, but depend on the type of substituent) in order to test the validity of Hammett's ρσ rule [9]

$$pK^*_{MCS} = pK^*_{MCS}(0) - \rho\sigma \qquad (8)$$

In Equation (8), the $pK^*_{MCS}(0)$ value corresponds to the $pK^*_{MCS}$ value of the unsubstituted compound. It can be seen from Figure 2 that the apparent acidity constants of the *m*- and *p*-substituted phenols, benzoic acids, and salicylic acids are affected in the same way by the substituents on the aromatic nucleus as the equilibrium and rate constants of other reactions of side-chain derivatives of benzene. The accuracy of the linear regression of the $pK^*_{MCS}$-values on σ is not significantly different from that of the corresponding K values [66].

## IV. Influence of Solvent on the Acidity Constant

The influence of the solvent used on the acidity constant is essentially due, on the one hand, to its dielectric constant DC [68], and on the other hand, to its protolytic character [69]. A basic solvent accepts a proton easier than an acidic one, so that acidity constants are higher (lower pK value) in basic solvents, *e.g.* pyridine, than in acidic solvents, *e.g.* glacial acetic acid [cf. Equation (1)]. With suitable solvents it is therefore possible to bring compounds of extremely high or low acidities into an easily measurable acid-base equilibrium with the solvent. For example, phenols can be studied in pyridine [70], and aromatic amines in glacial acetic acid [71].

In the interpretation of the effect of the dielectric constant, two fundamental types of acid-base equilibria must be distinguished:

$$AH + LH \underset{\text{(DC small)}}{\overset{\text{(DC large)}}{\rightleftharpoons}} LH_2^{\oplus} + A^{\ominus} \qquad (9)$$

$$AH^{\oplus} + LH \rightleftharpoons LH_2^{\oplus} + A \qquad (10)$$

According to the Born relationship[72], the energy required to form an ion is inversely proportional to the dielectric constant of the solvent and to the ionic radius. When a neutral acid AH dissociates, two ions are formed. This process requires more energy in organic media, as their dielectric constants are normally low compared with that of water (*e.g.* for methyl cellosolve:water (80:20 by weight) at 25 °C, DC = 32.0 [67]), so that in changing from water to organic solvents, the extent of dissociation should be expected to decrease (increase in the pK* values). For positively charged conjugate acids, the effect of the dielectric constant should be very small, since for each ion formed, another simultaneously disappears. However, some individuality should result from the different ionic radii, so that a simple correlation between the pK values determined in different media (cf. [32, 68, 73]) is not to be expected. As a result of the superposition of the effect of the dielectric constant and that of the protolytic character of the solvent, the pK* values of acids of the type shown in Equation (9) generally increase on changing from water to organic solvents, such as alcohols, glycols, and glycol ethers, while those of the type shown in Equation (10) decrease [30, 74] as a result of the increased basicity of the solvent [3].

In Figure 3, the $pK^*_{MCS}$ values of about 200 functional groups are compared with the pK values determined in water ($pK_{H_2O}$) [75]. Two regression lines can be recognized, one of which (II) can be assigned to equilibria of the type shown in Equation (9), the other (I) to that of Equation (10). As expected, the $pK^*_{MCS}$ values for the first type are higher, and those for the second type lower, than the corresponding $pK_{H_2O}$ values.

If a single regression line [76] is calculated for all the compounds considered in Figure 3, the standard deviation of the $pK^*_{MCS}$ values from this line is found to be 3.15 $pK^*_{MCS}$ units (95 % confidence limit). Calculation of the $pK^*_{MCS}$ values from $pK_{H_2O}$ — and vice versa — is thus in general completely useless. The $pK^*_{MCS}$ values can be predicted with much greater accuracy if we restrict ourselves to a single class of compounds (cf. Figure 3). Thus, for acids with an equilibrium of the type of Equation (9), the standard deviation of the $pK^*_{MCS}$ values from the regression line is 1.15 $pK^*_{MCS}$ units (95 % confidence limit). The standard deviation for acids of the equilibrium type of Equation (10) is of the same order

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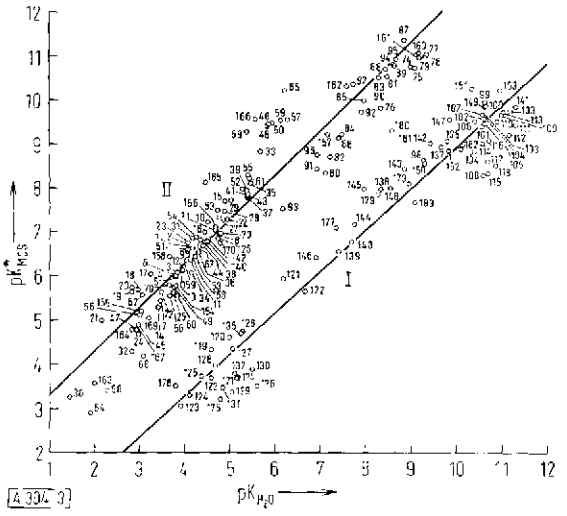



Fig. 3. Correlation of $pK^*_{MCS}$ values with $pK_{H_2O}$ values [75].
1: Benzoic acid

*Benzoic acids*:
2: *m*-Hydroxy; 3: *m*-Fluoro; 4: *m*-Chloro; 5: *m*-Bromo; 6: *m*-Iodo; 7: *m*-Nitro; 8: *m*-Amino; 9: *m*-Methoxy; 10: *p*-Hydroxy; 11: *p*-Fluoro; 12: *p*-Chloro; 13: *p*-Bromo; 14: *p*-Nitro; 15: *p*-Amino; 16: *p*-Methoxy; 17: *o*-Fluoro; 18: *o*-Chloro; 19: *o*-Bromo; 20: *o*-Iodo; 21: *o*-Nitro; 22: *o*-Amino; 23: *o*-Methoxy; 24: *o*-Hydroxy. 25: Formic acid; 26: Acetic acid; 27: Isovaleric acid; 28: Cyclohexanecarboxylic acid; 29: Pivalic acid; 30–31: Oxalic acid $pK_1-pK_2$; 32–33: Malonic acid $pK_1-pK_2$; 34–35: Succinic acid $pK_1-pK_2$; 36–37: Glutaric acid $pK_1-pK_2$; 38–39: Adipic acid $pK_1-pK_2$; 40–41: Pimelic acid $pK_1-pK_2$; 42–43: Suberic acid $pK_1-pK_2$; 44: Azelaic acid $pK_1$; 45–46: n-Propylmalonic acid $pK_1-pK_2$; 47–48: Isopropylmalonic acid $pK_1-pK_2$; 49–50: α,α-Dimethylsuccinic acid $pK_1-pK_2$; 51–52: α-Methylglutaric acid $pK_1-pK_2$; 53: β-Methylglutaric acid $pK_1$; 54–55: α,α-Dimethylglutaric acid $pK_1-pK_2$; 56–57: β,β-Dimethylglutaric acid $pK_1-pK_2$; 58–59: Citraconic acid $pK_1-pK_2$; 60–61: Itaconic acid $pK_1-pK_2$; 62–63: Mesaconic acid $pK_1-pK_2$; 64–65: Maleic acid $pK_1-pK_2$; 66–67: Fumaric acid $pK_1-pK_2$; 68–69: Phthalic acid $pK_1-pK_2$; 70–71: Isophthalic acid $pK_1-pK_2$; 72–73: Terephthalic acid $pK_1-pK_2$.

*Phenol*:
74: *m*-Chloro; 75: *m*-Bromo; 76: *m*-Nitro; 77: *p*-Chloro; 78: *p*-Bromo; 79: *p*-Iodo; 80: *p*-Nitro; 81: *o*-Chloro; 82: *o*-Nitro.

*Benzenesulfanilides of the type* $X-C_6H_4-SO_2-NH-C_6H_5$: 83: H; 84: *m*-Nitro; 85: *p*-Chloro; 86: *p*-Nitro; 87: *p*-Amino; 88: *p*-Methyl; 89: *p*-Methoxy.

*Benzenesulfanilides of the type* $C_6H_5-SO_2-NH-C_6H_4X$: 90: H; 91: *m*-Nitro; 92: *p*-Chloro; 93: *p*-Nitro; 94: *p*-Methyl; 95: *p*-Methoxy; 96: *p*-Acetoxy; 97: *p*-Carboxy.

98: Ammonia; 99: Methylamine; 100: Ethylamine; 101: Propylamine; 102: Butylamine; 103: Heptylamine; 104: Octylamine; 105: Cyclohexylamine; 106: Isobutylamine; 107: Isoamylamine; 108: Dimethylamine; 109: Diethylamine; 110: Dipropylamine; 111: Dibutylamine; 112: Diamylamine; 113: Diisopropylamine; 114: Diisobutylamine; 115: Trimethylamine; 116: Triethylamine; 117: Tripropylamine; 118: Tributylamine; 119: *o*-Phenylene diamine; 120: *m*-Phenylene diamine; 121: *p*-Phenylenediamine; 122: Aniline; 123: 1-Naphthylamine; 124: 2-Naphthylamine; 125: *o*-Toluidine; 126: *m*-Toluidine; 127: *p*-Toluidine; 128: *p*-Anisidine; 129: *N,N*-Dimethylaniline; 130: *N,N*-Dimethyl-*p*-toluidine; 131: *N*-Methylaniline; 132: *N*-Ethylaniline; 133: Piperidine; 134: *N*-Ethylpiperidine; 135: Piperazine; 136–137: 2,5-Dimethylpiperazine $pK_1-pK_2$; 138: Morpholine; 139: *N*-Methylmorpholine; 140: *N*-Ethylmorpholine; 141: Pyrrolidine; 142: β-Hydroxyethylamin; 143: Bis-β-hydroxyethylamine; 144: Tris-β-hydroxyethylamine; 145: Hydrazine; 146–147: Ethylene diamine $pK_1-pK_2$; 148–149: Trimethylene diamine $pK_1-pK_2$; 150–151: Tetramethylene diamine $pK_1-pK_2$; 152–153: Pentamethylene diamine $pK_1-pK_2$.

154: Glycolic acid; 155: Benzilic acid; 156: 3-Indolylacetic acid; 157: 2,6-Dichloro-*p*-cresol; 158: 1-Naphthoic acid; 159: 2-Naphthoic acid; 160: *m*-Nitrobenzenesulfonamide; 161: *p*-Nitrobenzenesulfonamide; 162: $C_6H_5-SO_2-NH-C_6H_3(OH)-COOH$ 163–166: Pyromellitic acid $pK_1-pK_4$; 167–168: D-Tartaric acid $pK_1-pK_2$; 169–170: *meso*-Tartaric acid $pK_1-pK_2$.

171: Pyridine; 172: 2-Aminopyridine; 173: 4-Aminopyridine; 174: Lepidine; 175: Quinoline; 176: Acridine; 177: Strychnine; 178: Neostrychnine; 179: α-Dihydrolysergic acid; 180: γ-Dihydrolysergic acid; 181: Allylamine; 182: Diphenylguanidine; 183: Tripheoylguanidine.

of magnitude. If we consider only classes in which the compounds are structurally closely related, *e.g.* *m*- and *p*-substituted benzoic acids (cf. Figure 4), *m*- and *p*-substituted phenols, benzenesulfanilides, anilines, *etc.*, the $pK^*_{MCS}$ values can be predicted with much greater accuracy on the basis of the $pK_{H_2O}$ values. The $pK^*_{MCS}$ values for *m*- and *p*-substituted phenols, for example, can be predicted from the $pK_{H_2O}$ values with an accuracy of 0.18–0.22 units (95% confidence limit).

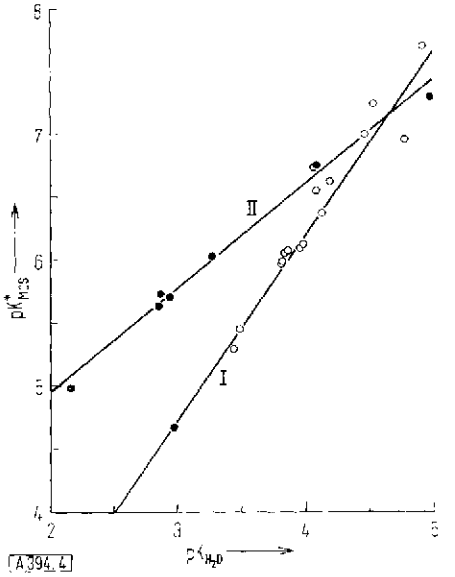
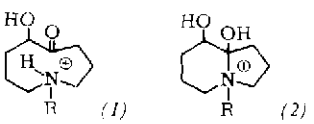



Fig. 4. Correlation of $pK^*_{MCS}$ values with $pK_{H_2O}$ values for benzoic acids [75].
Curve I: *m*- and *p*-substituted benzoic acids; *p*-$NO_2$; *m*-$NO_2$; *m*-Br; *m*-Cl; *m*-I; *m*-F; *p*-Br; *p*-Cl; *m*-OH; *m*-$OCH_3$; *p*-F; benzoic acid; *p*-$OCH_3$; *p*-OH; *m*-$NH_2$; *p*-$NH_2$.
Curve II: *o*-substituted benzoic acids; *o*-$NO_2$; *o*-Br; *o*-I; *o*-Cl; *o*-OH; *o*-F; *o*-$OCH_3$; *o*-$NH_2$.
Salicylic acid forms an exception owing to the pronounced hydrogen bonding between its *o*-hydroxyl group and its carboxylate group; it was therefore not considered in the calculation of the regression lines. The order of the acids corresponds to the order of the plotted points, from left to right.

The change in the acidity constant with the composition of the solvent can be used for the determination of the nature of the acid functions. Thus, for example, it has been shown [77] that in dimethylformamide/$H_2O$ (2:1) protonated 1-alkyl-1-azacyclononan-5-ol-6-one with




R = $CH_3$ or $C_2H_5$ exists as a bicyclic structure *(2)* and that it is the tertiary hydroxyl group which dissociates. The isopropyl and t-butyl compounds [R = $CH(CH_3)_2$ or $C(CH_3)_3$], on the other hand, are present in the monocyclic form *(1)*, and dissociation takes place at the nitrogen function [77].

## V. Acidity of Cyclohexanecarboxylic Acids

Valuable conclusions regarding the structure of cyclohexanecarboxylic acids can be drawn from their $pK^*_{MCS}$ values [78–80], since equatorial and axial carboxyl

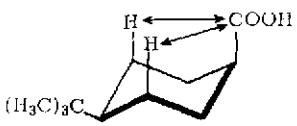
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Table 1. Differences in the free energies of cyclohexanecarboxylic acids and their corresponding anions, and ΔpK values at 25 °C.

| Solvent | ΔΔF = $\Delta F_{axial} - \Delta F_{equat.}$ [kcal/mole] | | ΔpK = $pK_{axial} - pK_{equat.}$ | | Ref. |
|---|---|---|---|---|---|
| | $C_6H_{11}COOH$ | $C_6H_{11}COO^-$ | from ΔΔF | [*] | |
| Water | 1.7 ± 0.2 | 2.4 ± 0.4 | 0.5 | — | [81] |
| Methyl cellosolve/water (80:20 by weight) | 1.6 ± 0.3 | 2.2 ± 0.3 | 0.4 | 0.48 | [82] |
| | | | | 0.50 | [87] |
| Ethanol/water (50:50 by volume) | 1.5 | 2.1 | 0.4 | 0.50 | [84] |
| Dimethylformamide/water (66:34 by volume) | | | | 0.44 | [81] |

[*] The values in this column are the differences in the pK values of *cis*- and *trans*-4-t-butylcyclohexane-1-carboxylic acids, and were determined potentiometrically. The values in the other columns were obtained from thermodynamic data in combination with the dissociation constants of unsubstituted or alkyl-substituted acids.

groups differ appreciably in acidity [81–84]. As can be seen from Table 1, the difference in the free energies of cyclohexanecarboxylic acids with axial and those with equatorial carboxyl groups is about 1.6 kcal/mole; the difference for the corresponding anions is about 2.2 kcal/mole [81,82,84]. The fact that the acidity of the axial isomer is 0.5 $pK^*_{MCS}$ units lower than that of the equatorial isomer can be attributed to hindrance of solvation of its anion by about 0.6 kcal/mole relative to the anion of the equatorial isomer [81,82,85] (cf. also [86]). This additional hindrance of solvation is essentially due to interactions with axial substituents in the γ-positions with respect to the axial carboxyl group (1,3-interactions) [cf. Formula *(3)*].




*(3)*

On the assumption that the effects of these axial substituents are additive, the $pK^*_{MCS}$ increment for one axial hydrogen atom in γ position to an axial carboxyl group is 0.25 units, relative to the acid without such an interaction. Within the range of validity of this assumption, it should be possible to estimate the $pK^*_{MCS}$ values by counting the 1,3-interactions [78–80]. The prediction of the $pK^*_{MCS}$ values of cyclohexanecarboxylic acids can be extended by taking into account the effects of substituents in the α-position relative to the carboxyl group.

Some indication of the effect of substituents R on the acidity of carboxylic acids of the type R–COOH is given

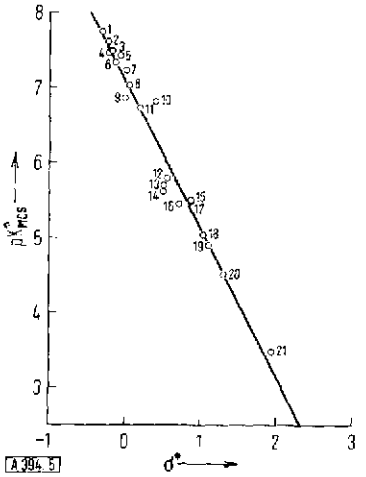



Fig. 5. $pK^*_{MCS}$ values of acids R–COOH as a function of the polar substituent constants σ*.
1: Pivalic acid; 2: Diethylacetic acid; 3: Cyclohexanecarboxylic acid; 4: α-Methylbutyric acid; 5: Cyclohexylacetic acid; 6: Isovaleric acid; 7: γ-Phenylbutyric acid; 8: β-Phenylpropionic acid; 9: Acetic acid; 10: Diphenylacetic acid; 11: Phenylacetic acid; 12: Glycolic acid; 13: Methoxyacetic acid; 14: Formic acid; 15: Iodoacetic acid; 16: Mandelic acid; 17: Phenoxyacetic acid; 18: Chloroacetic acid; 19: Fluoroacetic acid; 20: Cyanoacetic acid; 21: Dichloroacetic acid. From Helv. Chim. Acta *46*, 1736 (1963).

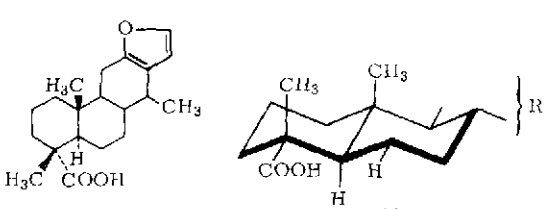
in Figure 5, in which $pK^*_{MCS}$ values are plotted as a function of Taft's polar substituent constants σ* [10] [cf. Equation (8)]. If a hydrogen atom on the carbon atom α to the carboxyl group is replaced by a methyl group, or if ring fusion takes place in the α-position, σ* changes by −0.10 to −0.12 units [10], corresponding to a mean increment in $pK^*_{MCS}$ of 0.22 units [cf. Figure 5].

Since the $pK^*_{MCS}$ value of cyclohexanecarboxylic acid is 7.44 [87], the $pK^*_{MCS}$ values of alicyclic monocarboxylic acids can be estimated, under certain assumptions, using the following rule [78–80]:

$$pK^*_{MCS} = 7.44 + 0.25\,a + 0.22\,b \qquad (11)$$

where a: number of 1,3-interactions; and
b=1 for an α-$CH_3$ or for ring-closure in the α-position;
b=0 for α-H.

Since the equilibrium contribution of the epimeric cyclohexanecarboxylic acid with an axial carboxyl group is only about 5 %, it may be neglected within the limits of accuracy of the $pK^*_{MCS}$ determinations (standard deviation s = 0.04 or 0.07 $pK^*_{MCS}$ units [88]). The rule given in Equation (11) for the evaluation of $pK^*_{MCS}$ values has so far been found to be valid for 60 compounds, some of which were very complex, *e.g.* vinhaticoic acid *(4)* [*]. No exceptions are yet




*(4)*

$pK^*_{MCS}$ calculated: 7.91
measured: 8.01

[79] *P. F. Sommer, C. Pascual, V. P. Arya*, and *W. Simon*, Helv. chim. Act. *46*, 1734 (1963).

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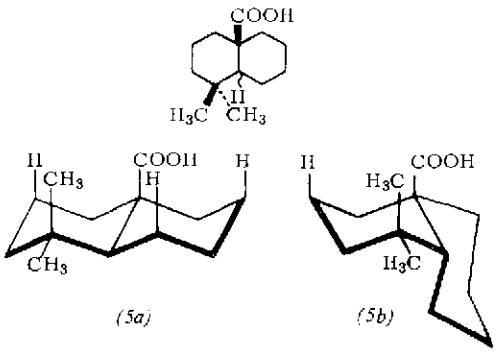
[86] *G. S. Hammond* and *D. H. Hogle*, J. Amer. chem. Soc. *77*, 338 (1955).

[87] *W. Simon*, unpublished work.

[*] The interaction of the equatorial hydrogen with the equatorial carboxyl group is geometrically equivalent to that between the corresponding axial substituents.

known. The standard deviation of the calculated values from the measured ones is 0.11 $pK^*_{MCS}$ units; the largest deviation observed was 0.24 $pK^*_{MCS}$ units.

For example, the rule expressed by Equation (11) was used for the determination of the structures of two isomeric decalincarboxylic acids *(5a)* and *(5b)* [m.p. 51 and 142–143 °C, respectively] prepared by *Brown* [89]. The problem was that of assigning the *cis* and *trans* ring



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

M. p. 51 °C — M. p. 142–143 °C

$pK^*_{MCS}$ calc. 8.66, found 8.86 — $pK^*_{MCS}$ calc. 8.16, found 8.30

fusion. Titration of 0.7 mg of each compound yielded the answer within an hour. On the basis of a comparison of the measured $pK^*_{MCS}$ values with the calculated ones, the compound which melts at 51 °C must be assigned the *trans*-ring fusion.[k] Definite assignment would hardly have been possible by other methods, and would certainly have required considerably more effort [89] (cf. also [90–97]).

## VI. The $pK^*_{MCS}$ Range

The maximum usable $pK^*_{MCS}$ range is determined by titration of a strong acid and titration of a strong base (hydrochloric acid and tetramethylammonium hydroxide) [*]. According to *Auerbach* and *Smolczyk* [98], two inflections are recognizable in the titration curves of dicarboxylic acids when the difference in pK of the two carboxyl groups is at least 1.2. Accordingly, an inflection should be discernible in the titration curve of an acid or base, when the $pK^*_{MCS}$ values are 1.2 units or more within the $pK^*_{MCS}$ range. The limiting values shown in Table 2 agree well with the observed values.

Table 2. $pK^*_{MCS}$ range for acid-base titrations in methyl cellosolve/$H_2O$ (80:20 by weight) [75].

| | |
|---|---|
| Maximum $pK^*_{MCS}$ range | 12.3–2.5 |
| Extreme $pK^*_{MCS}$ values at which inflections in the titration curve are still recognizable | 11.1–3.7 |

The $pK^*_{MCS}$ ranges for various classes of compounds are shown in Figure 6 [75]. The limiting $pK^*_{MCS}$ values for each class of compounds were in part determined experimentally; in some cases the range was calculated

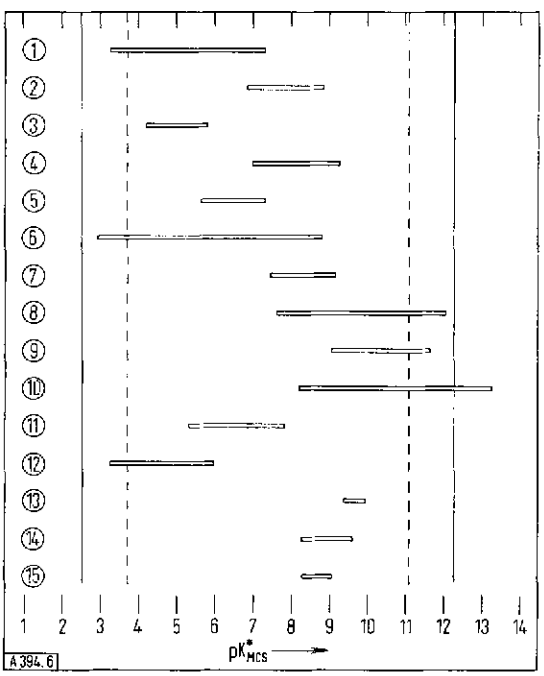



Fig. 6. $pK^*_{MCS}$ ranges for various classes of compounds [75]. Limiting values according to Table 2: (———) and (— — —).
1 and 2: Aliphatic dicarboxylic acids $HOOC-(CH_2)_n-COOH$, $pK_1$ and $pK_2$; 3 and 4: Phthalic acids $HOOC-C_6H_4-COOH$, $pK_1$ and $pK_2$; 5: Saturated aliphatic monocarboxylic acids $H-(CH_2)_n$ COOH; 6: Aliphatic monocarboxylic acids with a substituent in the α-position and a conjugation barrier between the substituent and carboxyl group; 7: Cyclohexanecarboxylic acids without an additional heteroatom; 8: Benzenesulfanilides $C_6H_5-SO_2-NH-C_6H_4X$ (X in the *m*- or *p*-position); 9: Benzenesulfanilides $X-C_6H_4-SO_2-NH-C_6H_6$ (X in the *m*- or *p*-position); 10: *m*- and *p*-substituted phenols; 11: *m*- and *p*-substituted benzoic acids; 12: 3-, 4-, or 5-monosubstituted salicylic acids; 13: Primary aliphatic amines n-alkyl-$NH_2$; 14: Secondary aliphatic amines $(n\text{-alkyl})_2NH$; 15: Tertiary aliphatic amines $(n\text{-alkyl})_3N$.

using the Hammett equation [9], *e.g.* for *m*- and *p*-substituted benzoic acids, phenols, disubstituted benzoic acids, and benzenesulfanilides, or the Ingold-Taft equation [10], *e.g.* for α-monosubstituted alkanoic acids.

## VII. Acidity Measurements in Acetic Acid

It can be seen from Figure 6 and Table 2 that differentiation between the acidities of very strong and very weak acids and bases is not possible in the solvent system methyl cellosolve/water (80:20 by weight). This

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[97] *H. Vorbrueggen* and *C. Djerassi*, J. Amer. chem. Soc. *84*, 2990 (1962).

[*] The $pK^*_{MCS}$ range is governed by the levelling effect of the solvent. The alkali error of the glass electrode should be negligible under the experimental conditions.

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requires the use of solvents with other levelling properties [8], *i.e.* other proton-donor and proton-acceptor properties. However, potentiometric pK* determinations according to the standard procedure described are possible only if electrode systems can be found which are suitable to measure the activity or concentration of the protonated solvent [$LH^{\oplus}_2$ in Equation (1)] in these solvents. It has been shown that certain glass electrodes satisfy this requirement for the solvents acetic acid, acetic acid/0.5 % water [99–102], and methyl isobutyl ketone [102]. Thus, in acetic acid with a water content of 0–0.5 % by weight, the glass electrode responds quantitatively over a wide acidity range to the concentration of protonated acetic acid (symholized by $[AcOH_2^{\oplus}]$), so that the quantity:

$$-\log [AcOH_2^{\oplus}] = pH_{AcOH} \qquad (12)$$

can be determined in the same manner as the pH of aqueous systems.

Acid-base equilibria in solvents of low dielectric constants are not easy to interprete, owing to the presence of ion-pairs and other associates. For example, in a solvent such as acetic acid (DC – 6.2 at 25 °C [107]), an acid AH forms an ion-pair:

$$AH + AcOH \rightleftharpoons AcOH_2^{\oplus}A^{\ominus} \qquad (13)$$

with the ionization constant

$$K_i^{AH} = \frac{[AcOH_2^{\oplus}A^{\ominus}]}{[AH]}$$

The ion-pair dissociates according to

$$AcOH_2^{\oplus}A^{\ominus} \rightleftharpoons AcOH_2^{\oplus} + A^{\ominus} \qquad (14)$$

with the dissociation constant [53,103–106]:

$$K_d^{AH} = \frac{[AcOH_2^{\oplus}]\,[A^{\ominus}]}{[AcOH_2^{\oplus}A^{\ominus}]}$$

In order to avoid misunderstanding in the characterization of acid-base equilibria in non-aqueous media, the expressions "ionization constant" and "dissociation constant" have been avoided in favor of the non-commital term "acidity constant" [cf. Equation (5)].

By analogy to the standard method for the determination of $pK^*_{MCS}$, it is possible to determine $pK^*_{AcOH}$ values which correspond essentially to the $pH_{AcOH}$ value of the half-neutralized sample [99,101]. If the pressure, temperature, sample and water concentrations, parameters of the apparatus, and determination procedure, are kept constant or are standardized, $pK^*_{AcOH}$ values are obtained which under certain conditions are essentially a function of the "overall dissociation constant" $K_{AH}$ of the acid AH (or base) under investigation [99,101]:

$$K_{AH} = \frac{[AcOH_2^{\oplus}]\,[A^{\ominus}]}{[AH] + [AcOH_2^{\oplus}A^{\ominus}]} = \frac{K_i^{AH} \cdot K_d^{AH}}{1 + K_i^{AH}} \qquad (15)$$

The strength of an acid AH in solvents of low dielectric constant is expected to be determined by the ionization constant $K_i^{AH}$ [105] assigned to the equilibrium of Equation (13). The constant $K_{AH}$ is in turn related to this ionization constant $K_i^{AH}$ and to the dissociation constant $K_d^{AH}$ of the equilibrium (14) by Equation (15). Since $K_d^{AH}$ is of the same order of magnitude for various acids (about $10^{-7}$) [104], $pK^*_{AcOH}$ values are mainly determined by the values of $K_i^{AH}$, and can therefore be correlated with the structure of organic compounds, analogously to other equilibrium constants, as shown, for example, in Figure 7. Similar considerations naturally also apply to bases B.

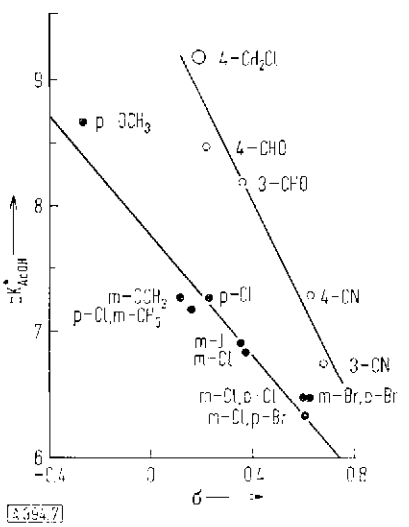
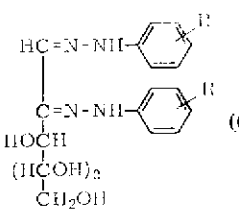



Fig. 7. $pK^*_{AcOH}$ values of pyridines (o) and glucose phenylosazones *(6)* (●) as a function of the Hammett substituent constant σ.

The lines were obtained by calculating linear regressions, assuming equal standard deviations for the individual experimental values [76]. From Helv. chim. Acta *45*, 962 (1962).




(6)

It is thus now possible, using new standard procedures, to carry out routine measurements of acid-base equilibria on small amounts of compounds having very high or low acidity [99,101].

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# Surface Oxides of Carbon

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*On oxidation of graphitic carbon, acidic surface oxides (or hydroxides in the presence of water) are formed at the boundaries of the carbon layers. It was found that the reaction of oxygen with microcrystalline carbon at 400–450 °C yields four groups of different acidities. One strongly acidic group and one weakly acidic carboxyl group have been detected, as well as a phenolic hydroxyl group; a carbonyl group is probably also present. With dissolved oxidizing agents, one equivalent of another strongly acidic carboxyl group is formed in addition at room temperature. The possible constitutions of the acidic surface oxides are discussed. Chemically detectable surface oxides are also formed on the surface of diamond. In the presence of oxygen at 800–900 °C under reduced pressure, diamond is transformed into black carbon. Surface oxides play a part in this transformation.*

## I. Introduction

The crystalline forms of elemental carbon are diamond and graphite. All the carbon aroms within the three-dimensional diamond lattice or the graphite layer structure are joined by covalent bonds. The free valences at the surface can be saturated by oxygen, for example, surface compounds being formed.

Surface oxides affect the properties of carbon surfaces, *e.g.* their wettability, the adsorptive power of active charcoal, or the dispersibility of ink blacks. The carbon blacks used as reinforcing fillers in rubber also invariably contain surface oxides [*]. Moreover, surface oxides of carbon play an important part as oxygen-transfering agents in atmospheric oxygen electrodes. The acidity and redox behavior of surface oxides can be used for the removal of salt from sea-water [1].

The surface oxides of microcrystalline black carbon have often been described. Active charcoal reacts with oxygen at temperatures as low as 300 °C, and part of the oxygen consumed remains bound to the surface, being liberated as CO and $CO_2$ only on subsequent heating [2, 3]. Surface oxides of carbon give a basic or acidic reaction, according to the conditions under which they are prepared [4].

If black elemental carbon is freed from all surface compounds by heating *in vacuo* followed by cooling in the absence of oxygen, its surface becomes covered with basic surface oxides on access of oxygen [5]. The constitution of these oxides is not yet known in detail.

Acidic surface oxides are formed on oxidation with oxygen at high temperatures or with dissolved oxidizing agents, *e.g.* NaOCl; these have been studied in much greater detail [6, 7]. The present article is a contribution to the knowledge of acidic surface oxides.

## II. Starting Material

Microcrystalline carbon is more suitable than graphite for investigations of the surface oxides of graphitic carbon, since its specific surface area is much larger. Hence it can bind correspondingly larger quantities of oxygen.

Black microcrystalline carbon, formerly referred to as "amorphous" carbon, is well known, *e.g.* in the form of active charcoal, carbon black, and carbon electrodes, and consists of extremely small crystallites built up, like graphite, of layers of six-membered carbon rings. These layers are stacked together in piles, but do not possess the mutual three-dimensional orientation observed in the graphite lattice. The distance between layers is larger than in graphite (3.44–3.65 Å and 3.354 Å, respectively). *Hofmann* et al. [8, 9] found that typical active charcoal contains layers with a diameter of ca. 30 Å; the average height of the stacks is 10–13 Å.

In our work we used mainly carbons prepared from sugar charcoal [10], since this can be obtained in very

[*] The surface oxides do not appear to be directly responsible for the reinforcing effect, since other finely divided substances, *e.g.* Aerosil® (silica which is morphologically very similar to the carbon blacks) have a similar action. However, many of the properties of carbon blacks are affected by surface oxides; for example, channel blacks in aqueous suspension give an acidic reaction, furnace blacks and thermal blacks give a basic reaction. How surface oxides affect the vulcanization and properties of the rubber has not yet been entirely explained.

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pure form. To make the pores as large as possible, thus ensuring easy accessibility to the surface, the sugar charcoals were "activated" by oxidation with $CO_2$ at 950 °C. In this way, individual crystallites are burned out of the structure. The specific surface area reaches a maximum when the loss by burning is about 50 %; it is only slightly affected by further oxidation [8, 11]. The products were partly coked, *i.e.* heated at 1100 °C in pure nitrogen. This treatment eliminates the greater part of the oxygen and hydrogen which they contain. The specific surface areas of activated and coked sugar charcoals were found by *Brunauer, Emmett*, and *Teller* [12] by nitrogen adsorption to be 900–1100 $m^2/g$. Technical active charcoal and a few typical carbon blacks were also investigated.

The products were coated with surface oxides either by exposing them to air during the cooling stage following activation or by oxidation in oxygen for 5–20 hours at 400–450 °C [13]. Cooling of the activated sugar charcoal in pure $CO_2$ gave only basic surface oxides.

In the "wet oxidation" method, the products were subjected to prolonged stirring with solutions of NaOCl, $KMnO_4$, or $(NH_4)_2S_2O_8$, followed by thorough washing. The $MnO_2$ which was formed in the oxidation with $KMnO_4$ was dissolved out by boiling with hydrochloric acid.

Crude sugar charcoal heated to a maximum of 450 °C was often also studied for comparison, although it is not pure carbon. However, its X-ray diffraction diagram still shows the characteristic reflexes of microcrystalline carbon.

## III. Chemical Reactions

### 1. Neutralization of the Acidic Groups

Direct potentiometric titration of the acidic surface oxides is difficult, since the end value of the potential is often attained only after long periods. We therefore determined the acidity by neutralization with bases of various basicities. The most suitable of these were $NaHCO_3$, $Na_2CO_3$, NaOH, and $NaOC_2H_5$. In 0.05 to 0.1 N solution, each of these bases gave characteristic maximum consumptions for neutralization. With higher concentrations of base, only sodium ethoxide gave a slight increase in consumption. Thus, in each case, only those acidic groups which were much more strongly dissociated than the conjugate acids of the bases were completely neutralized.

The pK values of the conjugate acids are: 6.37 and 10.25 for the first and second dissociations of carbonic acid, 15.74 for water, and 20.58 for ethanol.

Surprisingly, the quantities of bases neutralized generally bear simple, whole-number relationships to one another (cf. Table 1). In principle, all types of carbon

Table 1. Neutralization of acidic surface-oxides. The samples were oxidized with $O_2$ at 400–450 °C.

| Product [*] | Oxygen [%] [**] | Consumption [meq./100 g] | | | |
|---|---|---|---|---|---|
| | | $NaHCO_3$ | $Na_2CO_3$ | NaOH | $NaOC_2H_5$ |
| SC 3 coked ox. | 9.2 | 42 | 82 | 124 | 165 |
| SC 1, act. ox. | 7.3 | 21 | 43 | 71 | 89 |
| SC 1, act. coked ox. | 10.7 | 35 | 72 | 102 | 137 |
| SC 1, crude | 18.8 | 27 | 50 | 81 | - |
| Eponite, ox. | - | 15 | 34 | 62 | 106 |
| CK 3, ox. | 5.5 | 31 | 60 | 89 | — |
| CK 3, coked ox. | — | 14 | 27 | 39 | 70 |
| Philblack O, ox. | - | 57 | 109 | 164 | 233 |
| Spheron 6, ox. | — | 59 | 118 | 196 | 295 |

[*] SC: sugar charcoal. The number indicates a specific sample. For brevity, only one example is given for each type in this and in the following tables. Complete tables in: *E. Diehl*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1964, and in [26].

Eponite: active charcoal, Eponit BEN® of Degussa, Hanau (Germany).
CK 3: carbon black CK 3® of Degussa, Hanau (Germany).

Philblack 0: carbon black Philblack 0® of Phillips Petroleum Comp., U.S.A.

Spheron 6: Spheron 6® carbon black of Cabot Corp., U.S.A.

act. = activated by partial oxidation with $CO_2$ at 950 °C.

coked = coked by heating at 1100 °C in pure nitrogen.

ox. = coated with surface oxides by treatment with oxygen at 400 to 450 °C.

[**] By difference.

show the same behavior, but the simple numerical relationships are found only with completely oxidized products. Twice as many acidic groups are neutralized by $Na_2CO_3$ as by $NaHCO_3$. The differences between the quantities of NaOH and $Na_2CO_3$ used, and between the quantities of $NaOC_2H_5$ and NaOH used, are approximately equal to the quantity of $NaHCO_3$ used. If the amounts required for neutralization of various samples did not quite agree, the groups neutralized with $NaHCO_3$ and those neutralized with NaOH alone, as well as the groups neutralized with $Na_2CO_3$ and those neutralized with $NaOC_2H_5$, usually occurred none the less in equivalent quantities.

Activated or coked products which had not been oxidized neutralized practically no sodium hydroxide. Carbon blacks required more ethoxide than was expected. Carbon black contains appreciable quantities of disordered, tetrahedrally bonded carbon [14], which readily forms alcoholic or aldehydic groups which react with sodium ethoxide.

The agreement between these whole-number ratios of the quantities of base required for neutralization do not appear to be fortuitous, but rather indicates the presence of equivalent quantities of (at least) four different types of acidic groups of definite acidities. Thus, all four functions are probably constituents of a larger grouping. We shall refer to the groups as I to IV in order of increasing acidity, *e.g.* group II is neutralized only by $Na_2CO_3$ (or stronger bases), but not by $NaHCO_3$.

The simple numerical ratios observed in the neutralization experiments were also found in many other reactions. Thus, for example, the various carbon preparations were treated with a solution of KI and $KIO_3$. This solution reacts with $H^+$ ions with liberation of equivalent quantities of iodine; the pH of the solution remains at 7.5. The quantity of iodine

[11] *P. L. Walker, R. J. Foresti*, and *C. C. Wright*, Ind. Engng. Chem. *45*, 1703 (1955).

[12] *S. Brunauer, P. H. Emmett*, and *E. Teller*, J. Amer. chem. Soc. *60*, 309 (1938).

[13] *H. P. Boehm* and *E. Diehl*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 642 (1962).

[14] *U. Hofmann* and *E. Groll*, Ber. dtsch. chem. Ges. *65*, 1257 (1932); *L. E. Alexander* and *E. C. Sommer*, J. physic. Chem. *60*, 1646 (1956); *C. W. Snow, D. R. Wallace, L. L. Lyon*, and *G. R. Crocker*: Proceedings 3rd Conference on Carbon (Bufallo, N.Y., 1957). Pergamon Press, London 1958, p. 279.

liberated by the acidic surface oxides was always equivalent to the quantity of $NaHCO_3$ required for neutralization.

The ratios of the neutralization values after "wet" oxidation at low temperatures were somewhat different (Table 2). Here two groups which could be neutralized with $NaHCO_3$ were formed for every one group which could be neutralized with $Na_2CO_3$, NaOH, or $NaOC_2H_5$.

Table 2. Neutralization of the acidic surface oxides on wet-oxidized products.

| Product | Consumption [meq./100 g] | | | |
|---|---|---|---|---|
| | $NaHCO_3$ | $Na_2CO_3$ | NaOH | $NaOC_2H_5$ |
| SC 12, act. coked, ox. $KMnO_4$ | 61 | 89 | 125 | [illegible] |
| Eponite, coked, ox. $KMnO_4$ | 79 | 116 | 160 | 220 |
| Eponite, coked, ox. NaOCl | 107 | 163 | 214 | 262 |
| Eponite, coked, ox. $(NH_4)_2S_2O_8$ | 145 | 203 | 269 | 339 |
| CK 3, coked, ox. $(NH)_2S_2O_8$ | 21 | 30 | 36 | 57 |

Thus, the quantities of base required for neutralization are in ratios of 2:3:4:5. On subsequent heating, one of the two more strongly acidic groups is destroyed with liberation of the equivalent quantity of $CO_2$; this process starts at about 200 °C. The titrant ratios are then again found to be 1:2:3:4. The other groups are successively broken down at somewhat higher temperatures.

Again, the simple whole-number ratios were observed only after repeated, complete oxidation. The oxidation was complete as soon as small quantities of a brown colloid separated from the solid phase in alkaline media. Group IV and one of the two groups I are formed first in the oxidation, and group III and the second of the more strongly acidic groups I last (with simultaneous increase in the quantities of the other groups).

## 2. Methylation of the Acidic Groups

### a) *With Diazomethane*

The reaction with diazomethane has often been used for assaying acidic surface oxides [6, 15, 16]. Some of the resulting methoxyl groups can be readily hydrolysed with hot dilute hydrochloric acid.

The methylation was carried out using diazomethane, dissolved in some cases in dry ether and in others in ether saturated with water. As may be seen from comparison of Tables 1 and 3, the individual neutralization values are not accidentally governed by the strengths of the bases chosen. All the acidic groups which could be neutralized with NaOH, *i.e.* groups I–III, were methylated in dry ether. On the other hand, the methoxy values found after methylation in aqueous ether corresponded to the quantity of ethoxide required for neutralization. As expected, the methoxy values obtained with crude sugar charcoals in aqueous ether corresponded to the sum of the NaOH and $NaHCO_3$ consumptions.

The methoxyl groups which remained after hydrolysis with hot dilute hydrochloric acid corresponded, with only one exception, to group III, *i.e.* to the group which is neutralized by NaOH but not with $Na_2CO_3$. This behavior implies the presence of phenols. All the hydrolysable methoxy groups in the products which had been methylated in dry ether must have been esters of carboxylic acids or groups of similar acidity. The extra methoxy groups formed when moist ether is used in place of dry ether were not stable to hot dilute hydrochloric acid, and are not, therefore, methyl ethers of an alcohol.

Diazomethane generally forms readily hydrolysable methyl esters with carboxylic acids, but non-hydrolysable phenolic ethers with phenols. Diazomethane reacts with alcohols only in the presence of catalysts such as $BF_3$, $ZnCl_2$ [17], or $H_2O$ [18]: lactones of the fluorescein type are rearranged to their quinonoid form with methylation of the carboxyl groups [19].

After hydrolysis, the neutralization behavior towards $NaHCO_3$ and $Na_2CO_3$ remained unchanged, but the NaOH consumption fell to the $Na_2CO_3$ value (Table 3). This behavior was the same, regardless of whether the methylation had been carried out in dry or aqueous ether.

Table 3. Methylation of acidic surface oxides with diazomethane.

| Product | Methoxy groups [meq./100 g] [*] | | | Consumption of base [meq./100 g] after hydrolysis | | |
|---|---|---|---|---|---|---|
| | Total | non-hydrolysable | hydrolysable | $NaHCO_3$ | $Na_2CO_3$ | NaOH |
| SC 3, coked, ox. | 124 | 43 | 81 | 40 | 84 | 81 |
| SC 1, act. ox. | 72 (92) | 30 (30) | 42 (62) | 21 | 41 | 42 |
| Sc 1, act. coked ox. | (140) | (41) | (99) | 36 | [illegible] | 69 |
| SC 1, crude | 82 (109) | 32 (30) | 50 (79) | 27 | 49 | 54 |
| Eponite, ox. | (107) | (61) | (146) | — | — | — |
| CK 3, ox. | 89 | 33 | 56 | 32 | 57 | 55 |

[*] The values in brackets are for solutions in ether saturated with water, the others for solutions in pure ether.

Dimethyl sulfate gave the same results as dry diazomethane solutions when dilute sodium hydroxide was added slowly, so that the solution always remained slightly alkaline. If the methylation was carried out in the usual fashion in strongly alkaline medium, the methoxy content corresponded to the group III content.

### b) *With Methanol*

A few products were esterified with methanol plus hydrogen chloride. The quantities of methyl esters formed were equivalent to the group I or group II contents (Table 4).

[15] *M. L. Studebaker, K. W. D. Huffmann, A. C. Wolfe,* and *L. G. Nabors,* Ind. Engng. Chem. *48*, 162 (1956).

[16] *V. A. Garten, D. E. Weiss,* and *J. B. Willis,* Austr. J. Chem. *10*, 295 (1957).

[17] *E. Müller* and *W. Rundel,* Angew. Chem. *70*, 105 (1958).

[18] *H. Biltz,* Ber. dtsch. chem. Ges. *55*, 1069 (1922).

[19] *O. Fischer* and *E. Hepp,* Ber. dtsch. chem. Ges. *46*, 1951 (1913).

Table 4. Esterification of acidic surface oxides with methanol and hydrogen chloride.

| Product | Content [meq./100 g] | | |
|---|---|---|---|
| | Group I [b] | Group II [c] | Methoxyl |
| SC 3, coked, ox. | 42 | 40 | 44 |
| SC 1, act. ox. | 21 | 22 | 23 |
| SC 1, act. coked, ox. | 47 | 53 | 57 |
| CK 3, ox. | 31 | 29 | 35 |
| Eponite, coked, ox. NaOCl | 107 | 56 | 60 [d] |
| Eponite, coked, ox. $KMO_4$ [a] | 14 | 15 | 16 [d] |

[a] Incompletely oxidized.

[b] The group-I content was obtained by neutralization with $NaHCO_3$.

[c] The group-II content was determined from the difference between the $Na_2CO_3$ and $NaHCO_3$ consumptions.

[d] These products had been esterified by passing a mixture of methanol vapor and nitrogen over the material at 120 °C.

Which of the two groups had been esterified was determined by the neutralization behavior of an esterified product (SC 3, coked, ox.): the $NaHCO_3$ and $Na_2CO_3$ consumptions were equal (44 and 40 meq./100 g, respectively); thus, group II had been esterified. At the same time, the sodium ethoxide consumption fell to 82 meq./100 g. The esterification of group II apparently also led to inhibition of the reactivity of group IV towards ethoxide, so that only groups II and III remained neutralizable.

## 3. Detection of Phenolic Hydroxyl Groups

The quantitative agreement between the amount of non-hydrolysable methoxy groups and the difference between the NaOH and $Na_2CO_3$ titers indicates the presence of phenols. This assumption was confirmed by reaction with two typical phenol reagents, 2,4-dinitrofluorobenzene and *p*-nitrobenzoyl chloride.

Dinitrofluorobenzene does not react with carboxylic acids, and reacts only extremely slowly or not at all with alcohols.

Table 5. Detection of phenolic hydroxy groups in acidic surface oxides.

| Product | Content [meq./100 g] | | Conversion [meq./100g] with | |
|---|---|---|---|---|
| | Group III [a] | non-hydrolysable $OCH_3$ groups | 2,4-dinitrofluorobenzene [b] | *p*-nitrobenzoyl chloride |
| SC 3, coked, ox. | 42 | 43 | 42 | – |
| SC 1, act. ox. | 29 | 30 | 30 | – |
| SC 4, act. coked, ox. | 39 | – | 37 | 40 |
| SC 1, crude | 31 | 32 | 28 | – |
| CK 3, ox. | 32 | 33 | 13 | 29 |

[a] The group-III content was found from the difference between the NaOH and $Na_2CO_3$ titers.

[b] Reaction according to [21], followed by nitrogen determination.

Very weakly acidic phenolic hydroxy groups, such as that in salicylic acid (pK 13.4), also give no reaction, but can be methylated with dimethyl sulfate [20].

The close agreement of the phenolic hydroxy contents determined by four characteristic phenol reactions can be seen from Table 5.

## 4. Detection of Carboxyl Groups

The facts that the more strongly acidic groups can be neutralized by $NaHCO_3$ and that they form hydrolysable methoxy groups suggest that these are carboxyl groups. This assumption was confirmed by other reactions.

### a) *Reaction with Thionyl Chloride*

In the reaction with thionyl chloride, part of the chlorine is bound to the carbon in a readily hydrolysable form, whereas the remainder is stable even to hot sodium hydroxide solution [13]. The readily hydrolysable chloride must be present as the chloride of a carboxylic acid. Hydrolysis occurs only very slowly with pure water, and more rapidly with alkali, especially on warming. This behavior corresponds to that of aromatic acyl chlorides.

Table 6. Reaction of acidic surface oxides with thionyl chloride.

| Product | Content [meq./100 g] | | Change in consumption of base [meq./100 g] | | | |
|---|---|---|---|---|---|---|
| | Group II | Hydrolysable Chloride | $NaHCO_3$ | $Na_2CO_3$ | NaOH | $NaOC_2H_5$ |
| SC 1, coked, ox. | 15 | 16 | – | + 20 | + 18 | 0 |
| SC 3, act. ox. | 46 | 48 | + 47 | + 45 | + 41 | – 34 |
| SC 1, act. coked, ox. | 28 | 36 | – | – | + 33 | – |
| SC 3, act. ox. red. $LiAlH_4$ | 35 | 35 | + 35 | + 35 | + 35 | – 31 |
| SC 2, crude (degassed at 100 °C) | 61 | 61 | + 70 | + 61 | + 62 | – |
| SC 2, crude (degassed at 330 °C) | 9 | 11 | – | – | – | – |
| Eponite, coked, ox. $(NH_4)_2S_2O_8$ | 30 | 31 | + 30 | + 32 | + 30 | + 8 |

The chloride titrated was equivalent to the quantity expected for group II (Table 6).

This is clearly shown by the products "SO 3, act. ox.", "SC 3, act. ox., red. $LiAlH_4$", and a partially thermally decomposed sugar charcoal "SC 2"; most other preparations contained equal quantities of group I and II acids.

The products which had been treated with thionyl chloride were titrated with the four bases. Owing to neutralization of the hydrogen chloride formed, the titer corresponded to the sum of the original neutralization figure and the hydrolysable acyl chloride. However, the products described as "activated" required less ethoxide than originally (Table 6). The decrease corresponded to half of the $NaHCO_3$ consumption of the products.

The low $NaOC_2H_5$ consumption can be explained by an assumption which was later confirmed experimentally. The more strongly acidic carboxyl groups occur in pairs on directly adjacent sites and react with thionyl chloride to form a carboxylic anhydride. Acyl chlorides and anhydrides each consume only 1 mole of sodium ethoxide:

$$-CO-Cl + NaOC_2H_5 \rightarrow -CO-OC_2H_5 + NaCl,$$

$$-CO-O-CO- + NaOC_2H_5 \rightarrow -CO-OC_2H_5 + -COONa.$$

Thus, acyl chlorides consume the same quantity of ethoxide as the free carboxylic acids, whereas anhydrides consume only half as much. The anhydrides bind two moles of NaOH.

[20] *F. Sachs* and *V. Herold*, Ber. dtsch. chem. Ges. *40*, 2714 (1907).

[21] *H. Zahn* and *A. Würz*, Z. analyt. Chem. *134*, 183 (1951).

Nothing is yet known regarding the bonding of the hydrolysis-resistant chlorine which is present in a quantity corresponding to twice the $NaHCO_3$ titer.

b) *Reaction with Ammonia*

The pK values of two adjacent carboxyl groups generally differ by 2–3 units. Consequently, the ammonium salt of the more weakly acidic carboxyl groups has a strong tendency towards hydrolysis, and decomposes readily on heating. The behavior of the carbon preparations towards ammonia can give information as to the position of their more strongly acidic groups.

"Coked" and "crude" sugar charcoals which had been treated with 0.05 N ammonia and degassed at 20 °C contain a quantity of ammonia equivalent to the $NaHCO_3$ consumption. The same results were obtained when the products were allowed to react with gaseous or concentrated aqueous ammonia and degassed at 100 °C.

In the products which had formed anhydrides on treatment with thionyl chloride, half of the group-I ammonium salts were decomposed. Thus, the more strongly acidic carboxyl groups (I) in the activated sugar charcoals occur in pairs occupying adjacent sites, so that anhydrides or imides can be formed. When products which had been treated with concentrated aqueous or with gaseous ammonia were degassed at only 20 °C, more $NH_3$ was retained, but the quantity again corresponded to the $NaHCO_3$ or $Na_2CO_3$ consumption.

The ammonia contents of the products in these experiments were determined by expelling the $NH_3$ with hot 2 N NaOH. Since amides or imides both decompose under these conditions, the true ammonium salts were again determined with the weak base $Mg(OH)_2$. The consumption of 0.05 N HCl (taking into account the basic surface oxides already present) and the quantity of $NH_4^+$ ions formed were also measured. The quantity of ammonium ions almost always agreed with the $NH_3$ content determined by expulsion with NaOH. Thus the carboxyl groups I had not formed amides or imides even at 100 °C.

c) *Friedel-Crafts Reactions*

Several products, *e.g.* "Eponite coked, ox. $(NH_4)_2S_2O_8$", were converted into acyl chlorides by treatment with thionyl chloride (cf. Table 6), and were then treated with a solution of dimethylaniline and $AlCl_3$ in nitrobenzene. The nitrogen content of the reaction product corresponded to the chloride content, *i.e.* half of the bicarbonate consumption, and was therefore equivalent to group I or group II. The $NaHCO_3$ consumption decreased by half, and the neutralization values for the four bases were in the ratios of 1:2:3:4. Thus, in this wet-oxidized product, one of the two groups I (neutralizable with $NaHCO_3$) had formed a carbonyl chloride on reaction with thionyl chloride, as shown by the smooth progress of its subsequent Friedel-Crafts reaction. The other group I was thermally stable at 200 °C.

Group I also reacted in "coked" sugar charcoals which had been oxidized with oxygen; neutralization after the Friedel-Crafts reaction gave ratios of the acidic groups of 0:1:2:3. With an "activated" sugar charcoal which had been oxidized with oxygen, both the anhydride formed by reaction with $SOCl_2$ and the acyl chloride of group II reacted under the same conditions.

d) *Schmidt Degradation*

The carboxyl groups were detected directly by *Schroeter*'s variant [22] of the Schmidt degradation. After treatment with thionyl chloride, the product "Eponite coked, ox. $(NH_4)_2S_2O_8$" was treated with sodium azide in ethanol; the product contained a quantity of nitrogen corresponding to the replacement of one carboxyl group by a urethane group. The neutralization values decreased by half of the $NaHCO_3$ neutralization value.

5. Detection of Carbonyl Groups

The acidic groups detected so far account for only part of the oxygen content of the surface oxides. In the literature, the surface oxides are often formulated as carbonyl groups bonded to the periphery of the carbon layers. The consumption of ethoxide in the neutralization experiments may be due to carbonyl groups which react in the presence of a sufficient excess of alkali to form the salt of a hemiacetal. Secondary reactions, such as aldol condensations or Cannizzaro reactions, which take place readily under these conditions, cannot occur with carbonyl groups fixed at the peripheries of carbon layers. This assumption is plausible, since many aldehydes with adjacent negative substituents (hydroxy groups) contain appreciable quantities of acetal in aqueous solution [23]. In the presence of sodium ethoxide, the intermediate (hemiacetal) is fixed as the salt.

The consumptions of characteristic carbonyl reagents such as hydrazine, semicarbazide, or hydrogen cyanide were in the region of the quantity of $NaHCO_3$ or $Na_2CO_3$ required for neutralization. However, the consumptions of the various reagents were unequal.

After reaction with HCN, followed by hydrolysis, the $NaHCO_3$ consumption of a sample of activated and oxidized sugar charcoal increased to twice the initial value; thus an equivalent quantity of new carboxyl groups had been formed.

Almost all the carbonyl reagents used are also strong reducing agents, and furthermore, they can form salt-like compounds. Unambiguous interpretation of the results is therefore difficult.

6. Acetylation

Several products were treated with acetyl chloride. The acetyl contents of the purified products always corresponded to the quantity of NaOH required for neutralization. Pairs of adjacent carboxyl groups react with acetyl chloride to give cyclic anhydrides. Other carboxylic acids, phenols, and even alcohols bind acetyl groups. Thus, the subsequent reaction with sodium ethoxide is not a simple neutralization of an acidic hydroxyl group, since otherwise the acetyl content (of the "coked" products at least) should correspond to the $NaOC_2H_5$ consumption.

One product (SC 1, act. ox.) was boiled under reflux with acetic anhydride and a little sodium acetate. After the usual

[22] *G. Schroeter*, Ber. dtsch. chem. Ges. *42*, 3356 (1909).

[23] *N. C. Melchior*, J. Amer. chem. Soc. *71*, 3651 (1949).

purification, 182 meq. of NaOH/100 g of charcoal were required for neutralization. (The acetyl groups were not determined directly). If, as in the reaction with acetyl chloride, all the groups which could be neutralized with NaOH (70 meq./100 g) had been acetylated, the NaOH consumption should have doubled in alkaline hydrolysis. However, an additional 42 meq. of acetyl groups per 100 g of charcoal had apparently been bound (the formation of new acidic groups during acetylation is unlikely). These additional acetyl groups presumably did not react with hydroxyl groups, since acetyl chloride introduced 70 meq. of acetyl groups/100 g.

It is possible that a geminal diacetate $-CH(OAc)_2$ had been formed from an aldehyde [24]. We presume that the group IV (20 meq./100 g in the strating material) is an aldehyde or a ketone (see below).

### 7. Reductions

The acidic surface oxides behaved differently toward reducing agents (Table 7). On *Clemmensen* reduction with amalgamated zinc and hydrochloric acid, all four

Table 7. Change in the quantity of acidic groups after reduction of the acidic surface oxides.

| Product | Reduced with | Change in groups [b] | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| SC 3, coked, ox. [a] | – | (20) | (21) | (1) | (20) |
| | Zn/HCl (at 20 °C) | +18 | −19 | −1 | −19 |
| SC 3, act. ox. | – | (60) | (46) | (61) | (47) |
| | Zn/HCl (at 20 °C) | 0 | 0 | −16 | −13 |
| | Zn/HCl (at 100 °C) | −11 | −15 | −10 | −18 |
| | $LiALH_4$ | 0 | −11 | 0 | −14 |
| | $NaBH_4$ | 0 | −21 | −3 | −11 |

[a] This product was obtained by rapid quenching of oxidized sugar charcoal. Practically no groups III were formed during this treatment.

[b] The values in brackets give the content [meq./100 g] in the starting material; the figures without brackets are the changes after reduction.

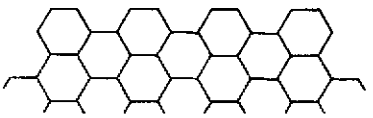
groups are usually, and group IV is always, attacked. The contents of groups II and III frequently decrease in the same proportion; the two groups are probably closely related.

In two products ("SC 3, coked, ox." reduced by the method of *Clemmensen*, and "SC 1, act. ox." reduced with $LiAlH_4$), the decrease in group II content was accompanied by an equivalent increase in group I. Thus, group II had become more strongly acidic as a result of the reduction. Group II is probably, like group I, a carboxyl group. However, in other cases, *e.g.* in "SC 3, act. ox.", group II was reduced with $LiAlH_4$ or $NaBH_4$ without formation of a more strongly acidic carboxyl group. This suggests that group II is normally present as a lactone. This result agrees with a structure similar to that of fluorescein [16], but other structures are possible also (see below).

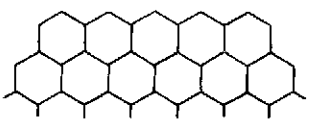
## IV. Possible Structures of Carbon Surface Oxides

The data available from the literature and from our own investigations are insufficient to afford complete and unambiguous information about the constitution of the acidic surface oxides. However, the most important results are reviewed briefly below. In comparing the work of different authors, it should be noted that the products used were rarely even similar.

Oxidation of single crystals of graphite with absolutely dry oxygen leads to an "arm chair" (11$\bar{2}$1) boundary *(1)* of the carbon layers, while a "zig-zag" (10$\bar{1}$1) boundary *(2)* is formed in the presence of water [25].



*(1)*

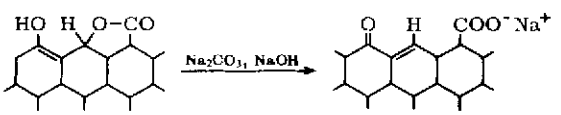


*(2)*

Our starting materials always contained hydrogen, and consequently, oxidation probably gave form *(2)*. It is not known which boundary is formed on oxidation with $CO_2$, *i.e.* on activation. We observed differences in the behavior of the surface oxides on coked and on activated sugar charcoals. It seems possible that the original boundary is largely retained on coating with surface oxides.

The acidic surface oxides are bound at the edges of the carbon layers. Carbon black graphitized at 2700 °C neutralizes no sodium hydroxide after oxidation at 450 °C with oxygen [26]. The surface of graphitized carbon black consists only of the basal planes of graphite [27] and contains only very few edge carbon atoms which can form acidic (*e.g.* phenolic) groups.

We detected four acidic groups of various strengths, which were generally present in equivalent quantities: a more strongly acidic carboxyl group (I), a more weakly acidic carboxyl group (II), a phenolic hydroxyl group (III), and a fourth group (IV) which is probably a carbonyl group. Groups II and IV appear to be closely related. One explanation for this would be that the more weakly acidic carboxyl group II is present as a hydroxy lactone which resembles phenolphthalein or fluorescein. A plausible arrangement of lactone and hydroxy groups is shown in formula *(3a)*. This would afford a satisfactory explanation of the lower acidity of the carboxyl group II, since phenolphthalein is known to form its colored salt, analogous to the form *(3b)*, with sodium carbonate, but not with sodium bicarbonate. This as-




*(3a)* *(3b)*

[24] *E. Knoevenagel*, Liebigs Ann. Chem. *402*, 127 (1914).

[25] *G. R. Hennig*, Proceedings 5th Conference on Carbon (Pennsilvania State University, 1961). Pergamon Press, London 1962, Vol. I, p. 143; Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 629 (1962).

[26] *H. P. Boehm, E. Diehl*, and *W. Heck*, Rev. gén. Caoutchouc *41*, 461 (1964).

[27] *H. P. Boehm*, Z. anorg. allg. Chem. *297*, 315 (1958).

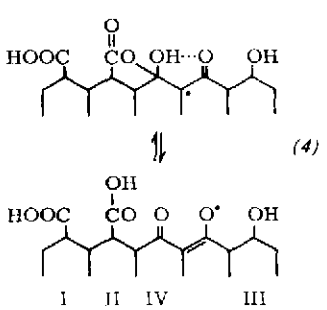
sumption is confirmed by an absorption band in the infrared spectrum of the strongly oxidized color black "Carbolac®", which was attributed to the carbonyl group of a γ-lactone [16].

The H–C bond in *(3a)* or *(3b)* could be the result of decarboxylation. Carbon oxidized at room temperature loses a carboxyl group on heating; on oxidation of the carbon at 400 °C, this carboxyl group is lost immediately after its formation.

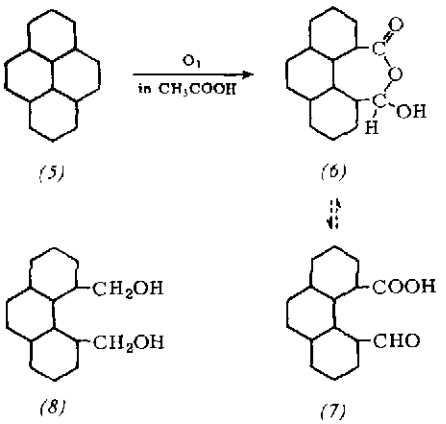
Sugar charcoal activated with $CO_2$ always contains pairs of carboxyl groups I which are so close together that they can form an anhydride (cf. the reaction with $SOCl_2$). A structural model of the surface oxides, which also takes these observations into account, is discussed in detail elsewhere [26].

Quinonoid groups have also been detected on the surfaces of carbon blacks [28]. During polarographic reduction, a wave occurred at a voltage corresponding to the reduction of quinones. The polarographic reduction wave disappeared after the carbon black had been treated with $LiAlH_4$. Hydroquinones have been detected in the same manner by polarographic oxidation. The carbon black could no longer be oxidized after methylation with diazomethane. The infrared spectrum of the color black "Carbolac" contains an absorption band at 1580 $cm^{-1}$ due to a hydrogen-bonded carbonyl group [28]. This absorption was displaced on methylation to ca. 1690 $cm^{-1}$, corresponding to a normal carbonyl group. Free radicals can be detected in oxidized carbon blacks [29,30]. The radicals are probably closely connected with the quinonoid groups [30].

Another explanation for the coupled occurrence of the carboxyl group II and the carbonyl group IV, which is also compatible with experimental findings, would be the presence of a lactone of a formylcarboxylic acid or of a ketocarboxylic acid.The model of a zig-zag edge containing all the groups detected, as well as such a lactol, is shown in *(4)*. (A further carboxyl group is formed on oxidation in acidic solutions.) The lactol is very similar to the fluorescein-like lactone.




The presence of such a lactol is supported by the following data: Oxidation of pyrene *(5)* with ozone in glacial acetic acid [31] or with $H_2O_2$ and $OsO_4$ [32] gives 4-formylphenanthrene-5-carboxylic acid *(7)* which normally exists as the lactol *(6)* [33,34]. Compound *(6)* or *(7)* reacts with diazomethane to form a hydrolysable methylcarboxylate [34]; on the other hand, alcohol plus mineral acid gives the pseudoester of the lactol form




[33,34]. Both compounds are reduced to the diol *(8)* by $LiAlH_4$ [35]. On reduction of *(7)* with amalgamated zinc and hydrochloric acid, both the aldehyde group and the carboxyl group are attacked, with formation of 1,8-dihydropyrene [33].

Ketocarboxylic acids whose functional groups are at the peri positions of a condensed ring system behave in a similar manner to formylcarboxylic acids [34].

The behavior of the acidic surface oxides on reduction can be explained on the assumption that a lactol is present. On reduction with amalgamated zinc, the carboxyl groups II and IV are attacked to an equal extent. The reaction with sodium ethoxide, when the latter is added in large excess, may be regarded as the formation of the salt of a hemiacetal of the aldehyde group. Secondary reactions, such as aldol condensation or the Cannizzaro reaction, cannot occur.

It is very difficult to decide whether it is preferable to formulate the surface oxides as a lactone *(3a)* or as a lactol *(4)*. The principles of organic chemistry derived from work on relatively small molecules cannot be applied directly to very large oxidized ring systems.

It is also conceivable that in each case only two acidic groups, *e.g.* I and III or II and IV are adjacent. The equal frequency of occurrence of all four groups could then be due to the fact that the two combinations are bonded to carbon edges with different structures occurring with equal probability.

The functional groups detected explain, at the most, 50 % of the analytically determined oxygen content. This has been confirmed by other authors [15,36]. When graphite was extremely finely ground and then oxidized, it evolved elemental oxygen as well as carbon dioxide on degassing *in vacuo* between 100 and 250 °C [36]. The bonding of this oxygen has not yet been explained. It is perhaps chemisorbed on sites of high π-electron density associated with defects in the layer planes.


[28] *J. V. Hallum* and *H. L. Drushel*, J. physic. Chem. *62*, 110, 1502 (1958).

[29] *J. B. Donnet* and *A. Henrich*, Bull. Soc. chim. France *1960*, 1609.

[30] *J. B. Donnet, G. Henrich*, and *G. Riess*, Rev. gén. Caoutchouc *38*, 1803 (1961).

[31] *H. Vollmann, H. Becker, M. Corell*, and *H. Streeck*, Liebigs Ann. Chem. *531*, 66 (1937).

[32] *F. G. Oberender* and *J. A. Dixon*, J. org. Chemistry *24*, 1226 (1959).

[33] *M. S. Newman* and *H. S. Whitehouse*, J. Amer. chem. Soc. *71*, 3664 (1949).

[34] *G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael*, and *A. I. Scott*, J. chem. Soc. (London) *1950*, 2326.

[35] *M. S. Newman* and *C. W. Muth*, J. Amer. chem. Soc. *73*, 4627 (1961).

[36] *Y.* and *A. Sarif, W. F. Kisselev, N. N. Leshnev, I. S. Novikova*, and *G. G. Fedorov*, Akad. Nauk S.S.S.R. *143*, 1358 (1962).

## V. Surface Oxides on Diamond

The diamond which is found in the "blue ground" of volcanic pipes of South Africa is hydrophobic, as is any freshly comminuted diamond. This permits its easy separation from the hydrophilic matrix rock, *e.g.* by flotation or, as formerly, with tarred or greased beds, to which the diamonds adhere, while the rock is washed away by water. On the other hand, diamonds which occur in sediments are hydrophilic. *K. A. Hofmann* observed that finely powdered diamond forms stable suspensions in dilute ammonia after treatment with calcium hypochlorite solution [37]. It was obvious to assume that this was due to the presence of surface oxides.

Investigation of the surface oxides on diamond seemed particularly attractive, since diamond can be regarded as the parent substance of aliphatic compounds, whereas aromatic compounds are derived from graphite. The surface oxides of diamond should therefore be expected to be different: *e.g.* phenolic hydroxyl groups cannot be formed.

Only relatively small specific surface-areas were available for the investigations on diamond, and correspondingly small quantities of surface oxides were therefore formed. Owing to the high price and limited availability of sufficiently finely-powdered diamond, the sample weights used could not be increased as desired. We managed to obtain diamond powder with a specific surface area of about 17 $m^2/g$, which is just high enough for investigations of surface oxides using modified analytical methods.

Diamond purified with aqua regia and hydrofluoric acid was oxidized with oxygen at 400 °C, or with solutions of sodium hypochlorite or ammonium persulfate at about 20 °C. The products were thoroughly washed, if necessary, and dried by degassing *in vacuo* at 100 °C.

The oxidation with oxygen was studied with the aid of a thermomicrobalance. Surface oxides start to form at about 260 °C. Perceptible liberation of oxides of carbon gradually begins at 350 °C and becomes very pronounced at 380 °C.

Potentiometric titrations of the acidic groups gave a curve which rose relatively slowly and showed no distinct inflexions. No simple ratios of the quantities of base consumed were observed on neutralization by shaking with bases of various basicities (Table 8). The results

Table 8. Neutralization of oxidized diamond powder.

| Product | Consumption [meq./100 g] | | | |
|---|---|---|---|---|
| | $NaHCO_3$ | $Na_2CO_3$ | NaOH | $NaOC_2H_5$ |
| Diamond, ox. $O_2$ | 3.3 | 4.9 | 5.2 | 6.9 |
| Diamond, ox. NaOCl | 0 | 1.2 | 1.4 | 2.8 |
| Diamond, ox. $(NH_4)_2S_2O_8$ | 1.2 | 2.7 | 3.4 | 4.8 |

of some other reactions are listed in Table 9. As can be seen from the agreement between the results of direct titration (to pH 7), neutralization with $NaHCO_3$, and reaction with thionyl chloride, the diamond contained about 2.5 meq. of more strongly acidic carboxyl groups per 100 g of sample. These were probably bound to the corners and edges of the diamond crystals.

[37] *K. A. Hofmann:* Anorganische Chemie. 1st Edit., Vieweg, Braunschweig 1918, p 287.

Table 9. Chemical reactions of the surface oxides of diamond.

| Pretreatment | Reaction | Conversion [meq./100 g] |
|---|---|---|
| ox. $O_2$ | titration to pH 7 | 2 [a] |
| ox. $O_2$ | $NaHCO_3$ | 2.5 |
| ox. $O_2$ | $SOCl_2$ | 2.5 |
| ox. NaOCl | diazomethane | 7.4 [a] |
| ox. NaOCl | acetyl chloride | 3.7 [a] |
| ox. $O_2$, degassed at 100 °C | potassium | 20 |
| ox. $O_2$, degassed at 500 °C | potassium | 11 |
| degassed *in vacuo* at 800 °C | $Cl_2$ (at 100 °C) | 20 |
| | $Cl_2$ (at 500 °C) | 17 |
| degassed at 800 °C, then Hr at 800 °C | potassium | 4.1 |

[a] These results were obtained with starting materials other than those used for the other values.

We assumed that the octahedral faces of the diamond crystals are saturated with tertiary hydroxyl groups. The active hydrogen content can be determined by salt formation with metallic potassium. This determination was carried out by distilling potassium *in vacuo* onto oxidized diamond; the excess potassium was then distilled off at 300 °C. On degassing between 25 and 400 °C, about 20 meq. of potassium per 100 g of diamond always remained fixed; this could be determined acidimetrically after hydrolysis (cf. Table 9). The number of active groups decreased above 400 °C; this agrees with the result of thermogravimetric analysis. At 800 °C, almost all the surface oxides were decomposed, and the consumptions of $NaHCO_3$ and NaOH required for neutralization fell respectively to zero and 0.5 meq./100 g.

We believed that free radicals were formed during the thermal decomposition of the surface coating. The quantity of these should be determinable by direct reaction of diamond degassed at 800 °C with elemental chlorine, without prior contact with air. The quantity of chlorine bound agreed very well with the result of the reaction with potassium, if this reaction and the subsequent degassing were carried out between 100 and 400 °C (conversion about 20 meq./100 g). The bound chlorine was resistant to hydrolysis, even with hot sodium hydroxide. The diamond powder was treated with hydrogen in a similar manner at 800 °C; it was then able to bind only very much less potassium (cf. Table 9). The products which had been degassed at high temperatures were hydrophobic, in contrast to the hydrophilic oxidized diamond. The heat of wetting [*] of an oxidized diamond preparation with water was 0.7 cal/g; the value for the same product after degassing at 800 °C was 0.5 cal/g, and 0.35 cal/g after treatment with hydrogen at 800 °C.

These reactions prove the existence of surface oxides on diamond. Some surface oxides are formed even on storage in air. This can cause appreciable interference in the technical separation of diamonds by flotation [38]. The coefficient of friction of diamond that has been heated *in vacuo* decreases significantly on admission of air [39].

[*] We wish to thank Dipl.-Chem. *W. Häbich* for conducting the measurements.

[38] *I. N. Plaksin, V. S. Alekseyev*, Chem. Abstr. *59*, 2194 (1963).

[39] *F. P. Bowden* and *A. E. Hanwell*, Nature (London) *201*, 1279 (1964).

The same phenomenon is known to occur with graphite [40] [**]. The surface oxides formed at room temperature in air are not acidic.

## VI. Transformation of Diamond into Black Carbon

During the thermal decomposition of surface oxides we made an interesting observation: at oxygen pressures of about $10^{-2}$ to $10^{-1}$ mm, diamond becomes dark in color. This blackening, which had been described earlier [41], is due to the transformation of diamond on the surface into the black, microcrystalline form of carbon, which is thermodynamically favored. The transformation is catalysed by traces of oxygen. The dark coating on the diamond was rapidly oxidized to oxides of carbon at 400 °C and an oxygen pressure of 1 atm.

In large diamond crystals, the (111) and (110) faces become covered with velvet-black carbon at an oxygen pressure of 0.4 mm between 650 and 850 °C; above 850 °C, the (100) surfaces become covered too [41]. Diamond remains unchanged *in vacuo* even at 1350 °C. In the presence of a little oxygen, the transformation proceeds more rapidly than the oxidation of the black carbon produced; the latter oxidizes more rapidly only at higher oxygen pressures.

Surface oxides must play a part in this catalysis by oxygen. In the stationary state of the black layer, the rate of transformation is governed by the diffusion of oxygen through the layer. Thus, oxygen is continuously being consumed; surface oxides are presumably formed, and these decompose to oxides of carbon and black carbon. We observed no transformation with pure CO at 900 °C, and only a slight darkening with pure $CO_2$. A Boudouard equilibrium such as

$$C_{diamond} + CO_2 \rightarrow 2\,CO \rightleftharpoons CO_2 + C_{black}$$

can therefore be ruled out.

We have proved that the darkening was actually due to the catalytic activity of the black microcrystalline carbon in the synthesis of hydrogen bromide.

The equilibrium

$$H_2 + Br_2 \rightleftharpoons 2\,HBr$$

lies almost completely to the right at 150 °C, but no HBr is formed in the homogeneous gas phase in the absence of catalyst. The reaction is catalysed by graphite and black microcrystalline carbon [42]. The catalytic efficiency is a measure of the specific surface area [43].

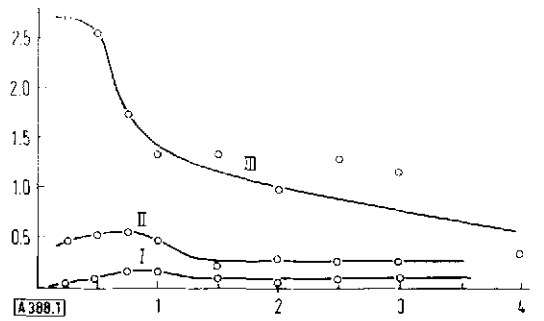



Fig. 1. Change of catalytic efficiency with time in the synthesis of HBr (T = 150.0 °C; $H_2$ pressure Q 1 atm; $Br_2$ pressure = 67 mm).

I: Diamond coated with surface oxides.

II: The same product as in I, after degassing *in vacuo* at 800 °C.

III: The same product as in II, after darkening at low $O_2$ pressure at 800 °C.

Ordinate: Catalytic efficiency [mmole of HBr per hour per g of carbon]; Abscissa: Time [h].

Figure 1 shows the catalytic efficiency of the same sample of diamond after various pretreatments. The diamond was used in three forms: after oxidation with NaOCl, after subsequent degassing *in vacuo* ($< 10^{-5}$ mm) at 800 °C, and finally after covering with the black coating by heating at 800 °C in oxygen at ca. $10^{-1}$ mm. With the third sample, the catalytic efficiency fell off gradually in a peculiar manner during the measurements, and became almost zero. The diamond powder was again light in color at the end of this experiment, *i.e.* the dark coating had volatilized off under the conditions of the HBr catalysis. It must be concluded from this that the coating of black carbon was extremely finely-divided and reactive. This is supported by an earlier observation [44] that diamond which had been heated in an evacuated Crookes' tube by a glow discharge and had become coated with carbon became lighter in color after storing for some years in air.

*We wish to thank the Deutsche Forschungsgemeinschaft and Union Carbide European Research Associates, Brussels, for their support in these investigations. Messrs. Diamanten-Winter, Hamburg, supplied us with finely powdered diamond at a special rate. We are deeply indebted to Prof. U. Hofmann for his help and valuable encouragement.*

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German version: Angew. Chem. 76, 742 (1964)
Translated by Express Translation Service, London

[40] *R. H. Savage*, J. appl. Physics *19*, 1 (1948); *F. P. Bowden* and *J. E. Young*, Proc. Roy. Soc.(London), Ser. A *208*, 444 (1951).

[**] One result of this is that diamond bearings and graphite-lubricated bearings cannot be used in spacecraft, since they wear out very rapidly. Monomolecular oxide layers initially present would be very rapidly removed from such bearings.

[41] *T. Evans* and *C. Phaal*, Proceedings 5th Conference on Carbon (Pennsilvania State University 1961). Pergamon Press, London 1962, Vol. I, p. 147.

[42] *U. Hofmann* and *W. Lemcke*, Z. anorg. allg. Chem. *208*, 194 (1932).

[43] *A. Clauss, H. P. Boehm*, and *U. Hofmann*, Z. anorg. allg. Chem. *290*, 35 (1957).

[44] *W. Crookes*, Chem. News *74*, 39 (1896).

# The Design of Phosphorylating Agents

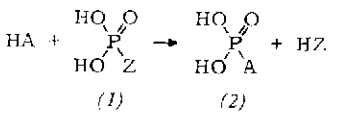
BY V. M. CLARK, D. W. HUTCHINSON, A. J. KIRBY, AND S.G. WARREN

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE (ENGLAND)

*Phosphorylating agents are compounds capable of transferring the group $(HO)_2P(O)-$ in free or esterified form. Numerous phosphorylating agents can be classified into P–XYZ systems, in which the element or group Z must be capable of accommodating the electrons of the P–X bond. Systematic classification of P–XYZ compounds and numerous examples of phosphorylation in chemistry and biochemistry are given.*

## I. Phosphorylation

Phosphorylation of alcohols to give phosphoric esters (phosphates) [*(2)*, A = RO], of amines to give phosphoramidates [*(2)*, A = R–NH], and of phosphates to give pyrophosphates [*(2)*, A = $(RO)_2P(O)$] requires the addition of a phosphoryl group $(HO)_2P(O)-$ to a nucleophilic center.



*(1)* *(2)*

This can be achieved, for example, when Z, the group bonded to the phosphorus atom in the phosphorylating agent *(1)*, is readily displaced as $Z^{\ominus}$; hence reagents of the acid-anhydride type might be expected to be good phosphorylating agents. However, phosphoric acid is tribasic, and the free hydroxyl groups in *(1)* can compete with external nucleophiles to give polymeric by-products. In practice, anhydride-type reagents are useful only if they bear two protecting groups, as in $(PhO)_2P(O)Cl$ [1].

Many naturally occurring phosphorus compounds are mono- or di-esters of ortho-, pyro-, or polyphosphoric acids (*e.g.* sugar phosphates, nucleotides): a few are *N*-substituted phosphoramidates (*e.g.* the phosphagens). During their synthesis, protecting groups may have to be removed and, although methods have been developed to accomplish this, the aim of much recent work has been to devise reagents which can transfer an unsubstituted phosphoryl group directly [1].

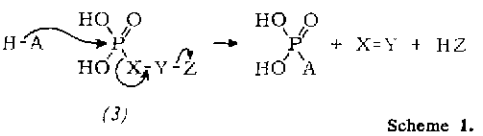
Two approaches have been used with some success. In one, the phosphorylating agent is generated *in situ* from an appropriate phosphate anion or phosphoric acid (*e.g.* in the carbodiimide and trichloroacetonitrile methods); in the other, a less reactive reagent, such as a phosphoramidate, is used. In both methods, the potential leaving group is probably first protonated, so that a neutral molecule is displaced. Fundamentally, whether the leaving group be $Z^{\ominus}$ or HZ, it must accommodate the electron pair that originally formed the P–Z bond. Consideration of how this can best be done is important not only for an understanding of the process of phosphorylation in general but also for the improvement of the design of reagents for particular purposes.

[1] *D. M. Brown* in *R. A. Raphael, E. C. Taylor,* and *H. Wynberg:* Advances in Organic Chemistry: Methods and Results. Interscience, New York 1963. Vol. 3, p. 75.

## II. The P-XYZ System

### A. Definition

Any molecule of general formula *(3)*, where X, Y, and Z are atoms of any element, but commonly H, C, N, O, S, or Hal, is a potential phosphorylating agent if the electrons of the P–X bond can be formally accommodated on Z. During phosphorylation, the bond-order between X and Y increases, and that between Y and Z decreases,



*(3)*

Scheme 1.

each by one unit (Scheme 1). Since Z acts as the primary electron-acceptor, it must be strongly electronegative or must become so via attack by an electrophile or an oxidizing agent.

### B. Advantages

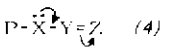
Examination of the properties of the generalized P-XYZ system suggests that it may have important advantages over simple P–Z type reagents. Two extra centers are involved in the transition state of the phosphorylative step, and it is therefore possible to alter the activation energy of the process by varying X and Y for a given Z, without necessarily varying the overall free-energy change for the reaction. Both in principle and in practice, stable unprotected phosphorylating agents with powerful leaving groups can be designed. For example, in contrast to phosphorochloridic acid $(HO)_2P(O)Cl$, which is highly reactive and is hydrolysed in water, 2-chloro decyl phosphonate $(HO)_2P(O)\text{-}CH_2\text{-}CHCl\text{-}C_8H_{17}$ can be kept in aqueous acidic solution [2]: in alkali,

[2] *J. A. Maynard* and *J. M. Swan*, Austral. J. Chem. *16*, 596 (1963).

rapid decomposition, with accompanying phosphorylation, ensues [*].

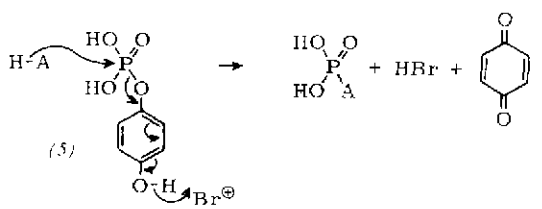
### C. The P-X Bond

The prerequisites for a P–XYZ system *(3)* to be a phosphorylating agent are that the P–X bond should be weak and that Z should be as strongly "electron-attracting" as possible. Bonds involving phosphorus and highly electronegative elements are particularly strong since the lone pair of electrons possessed by all such elements can be donated into the vacant 3d orbitals of the phosphorus atom, thereby augmenting the binding energy by virtue of a pπ–dπ contribution. In the system P–XYZ, pπ–dπ overlap is eliminated if X has no lone pair of electrons (*e.g.* when X = $sp^3$-hybridized carbon); alternatively, where such electrons are present, pπ–dπ bonding can be reduced by introducing pure pπ bonding with an $sp^2$-hybridized Y atom, as in system *(4)*.



*(4)*

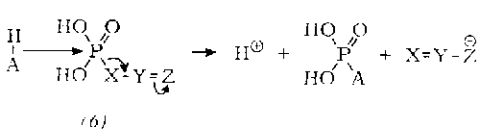
There is, of course, no reason why the Y–Z bond should not be part of an extended π-bonded system. Thus, in oxidative phosphorylation involving hydroquinone phosphates *(5)* [3], it is part of an aromatic ring:



*(5)*

### D. Entropy Effects

When a compound of the P–XYZ type *(6)* acts as a phosphorylating agent, a stable mesomeric anion may be displaced.

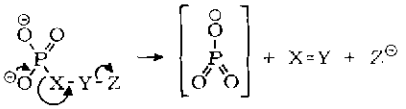


*(6)*

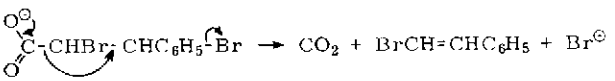
Alternatively, if Y and Z are singly bonded, fragmentation must occur, and the number of molecules present must increase during the phosphorylative step (cf. Scheme 1). The entropy change, and probably the entropy of activation, should be positive for this type of reaction.

### E. Metaphosphate Intermediates

Unprotected phosphorylating agents may react either by the bimolecular mechanism just considered, or by an initial unimolecular dissociation into monomeric metaphosphate, this being a (presumably) highly reactive and therefore non-selective phosphorylating agent [4].



This process corresponds to decarboxylation, *e.g.* of bromocinnamic acid *(7)*, in organic chemistry.



*(7)*

The advantages of the P–XYZ system hold equally well for this mechanism, and the entropy factor should be even more favorable. *Di Sabato* and *Jencks* [5] have shown that the (possibly unimolecular) hydrolysis of acetyl phosphate at pH 5 has a low positive $\Delta S^{+}$. For reactions according to Scheme 1, it should be higher still. Moreover, the reactivity of such phosphorylating agents should be strongly temperature-dependent, providing them with an additional valuable feature.

## III. Classification of P-XYZ Systems

### A. No pπ-dπ Contribution to the P-X Bond

a: P–C–C–Hal
b: P–C–C–C
c: P–C–C=O

### B. Attenuation of the pπ-dπ Contribution by Pure pπ Bonding

1. Attenuation in the ground state

a: P–N–C=O
b: P–N–N=N
c: P–N–N=O
d: P–O–C=O
e: P–O–N=O

2. Attenuation by electrophilic attack on Z

a: P–N–C=N
b: P–O–C=C
c: P–O–C=N
d: P–O–C=O
e: P–O–N=C

3. Attenuation by oxidative attack on Z

a: P–N–N–H
b: P–O–O–H

[*] The energy of activation for the P–C–C–Hal transphosphorylation process is sufficiently greater than that of P–Hal cleavage for phosphate polymerization to be negligible. On the other hand, the overall free-energy change in both reactions is approximately the same (bond energies: P–C = 62, C–C = 62; C–Cl = 77, P–Cl = 77 kcal/mole).

[3] *V. M. Clark, D. W. Hutchinson, G. W. Kirby,* and *A. R. Todd,* J. chem. Soc. (London) *1961*, 715.

[4] *J. D. Chanley* and *E. Feageson,* J. Amer. chem. Soc. *85*, 1181 (1963).

[5] *G. Di Sabato* and *W. P. Jencks,* J. Amer. chem. Soc. *83*, 4393 (1961).

4. Attenuation by loss of $Z^{\ominus}$

a: P C–C–Hal

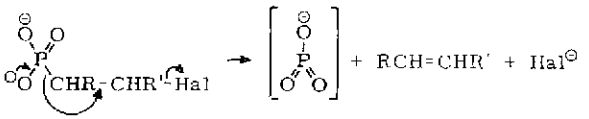
b: P–N–C Hal

c: P–S C Hal

## IV. Examples of P-XYZ Systems

### Aa: P—C– C—Hal (X = Y = C, Z = Hal); β-Halogenoalkylphosphonates

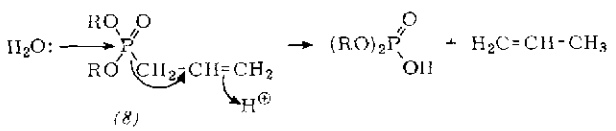
Saturated β-halogenoalkylphosphonates are stable in acidic solution, but in alkali undergo rapid decomposition to an olefin and phosphate with expulsion of a halide ion [2,6 9].



The alkali-catalysed decomposition may be either an intramolecular process (as indicated) or an intermolecular process involving external nucleophilic attack at the phosphorus atom. Compounds of this type have found use as phosphorylating agents in the presence of base [2].

### Ab: P—C—C=C (X = Y = Z = C): Allylphosphonates

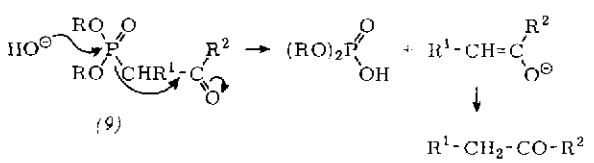
Electron withdrawal from Z can be effected by protonation: thus, allylphosphonates *(8)* undergo hydrolysis in aqueous acid to give an olefin and a phosphate [10].



*(8)*

### Ac: P—C—C=O (X = Y = C, Z = O) β-Ketoalkylphosphonates

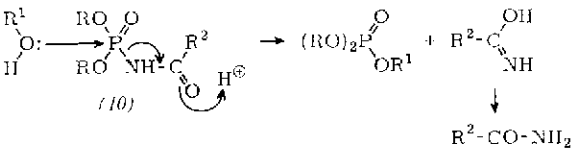
β-Ketoalkylphosphonates *(9)* undergo alkaline hydrolysis to phosphate and the carbonyl compound [11,12].



*(9)*

### B 1a: P–N–C=O (X = N, Y = C, Z = O): *N*-Acylphosphoramidates

*N*-Acylphosphoramidates *(10)*, in contrast to phosphoramidic esters, phosphorylate alcohols in neutral solution [13]. Their enhanced reactivity is due to the decrease in $p\pi-d\pi$ bonding between the nitrogen and phosphorus atoms in consequence of conjugation involving the carbonyl group and a p-orbital on the nitrogen atom.

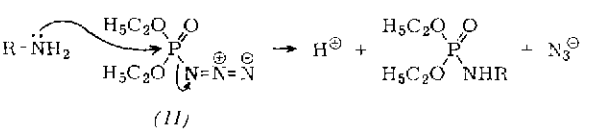


*(10)*

*N*-Acylphosphoramidates undergo hydrolysis in aqueous acid but here it is difficult to distinguish between a mechanism of the P–XYZ type and one following the accepted mode of hydrolysis of phosphoramidates, *i.e.* one involving protonation on the nitrogen [14]. The acidic hydrolysis of *N*-phosphorourethanes shows analogous features [15].

### B 1b: P—N—N=N (X = Y = Z = N): Phosphoroazidates

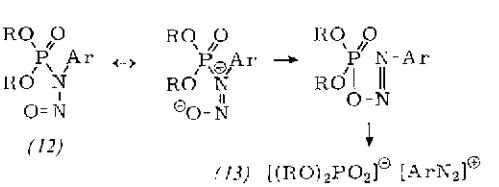
Azide ions have a catalytic effect similar to that of nitrite ions [35] on the alkaline hydrolysis of *N,N,N',N'*-tetraalkylphosphordiamidyl chlorides [16]. Phosphoroazidates *(11)* have in fact been isolated and have been used to phosphorylate amines [17].



*(11)*

### B 1c: P—N—N=O (X = Y = N, Z = O): *N*-Nitrosophosphoramidates

Nitrosation of *N*-arylphosphoramidates by nitrosyl hydrogen sulfate or nitrosyl chloride leads to the aryldiazonium salt *(13)* of the corresponding phosphoric acid [18]. The reaction probably proceeds by a rapid intramolecular rearrangement of the *N*-nitroso-*N*-arylphosphoramidate *(12)*.



*(12)* *(13)* $[(RO)_2PO_2]^{\ominus}\,[ArN_2]^{\oplus}$


[6] *J. B. Conant* and *A. A. Cook*, J. Amer. chem. Soc. *42*, 830 (1920).

[7] *J. B. Conant* and *S. M. Pollack*, J. Amer. chem. Soc. *43*, 1665 (1921).

[8] *J. B. Conant* and *B. B. Coyne*, J. Amer. chem. Soc. *44*, 2530 (1922).

[9] *E. Bergmann* and *A. Bondi*, Ber. dtsch. chem. Ges. *66*, 278 (1933).

[10] *D. W. Hutchinson*, unpublished results.

[11] *N. Kreutzkamp* and *H. Kayser*, Chem. Ber. *89*, 1614 (1956).

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[14] *M. Halmann*, *A. Lapidot*, and *D. Samuel*, J. chem. Soc. (London) *1960*, 4672.

[15] *M. Halmann* and *A. Lapidot*, J. chem. Soc. (London) *1960*, 419.

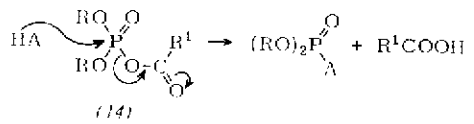
[16] *D. Samuel* and *F. H. Westheimer*, Chem. and Ind. *1959*, 51.

[17] *F. L. Scott*, *R. Riordan*, and *P. D. Morton*, J. org. Chemistry *27*, 4255 (1962).

[18] *P. J. Bunyan* and *J. I. G. Cadogan*, J. chem. Soc. (London) *1962*, 1304.

## B 1d: P—O—C—O (X = Z = O, Y = C) [*]: Acyl Phosphates

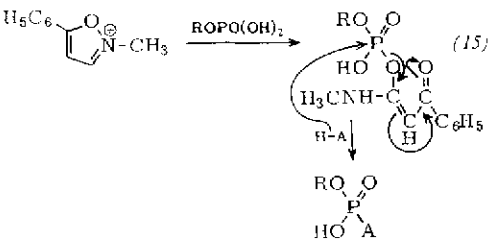
Acyl phosphates *(14)* can function as acylating or phosphorylating agents; in the latter reaction they are P XYZ systems.



*(14)*

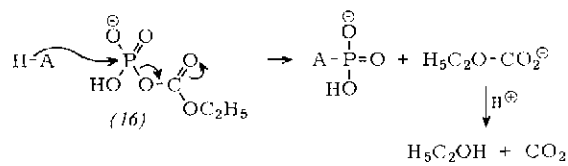
Nucleophilic attack usually occurs at the carbonyl carbon atom, with elimination of phosphate. However, evidence has been obtained which indicates that attack at the phosphorus can occur, especially during basic hydrolysis [20–22].

Nucleoside-$P^1$,$P^2$-diesters of pyrophosphoric acid have been synthesized by the action of acetyl chloride or acetic anhydride on mononucleotides [23]. The phosphorylating agent in this reaction must be an acetyl phosphate derivative. Moreover, treatment of phosphoric monoesters with isoxazolium salts [24] gives vinylogous acyl phosphates *(15)* which are also phosphorylating agents [25, 26].



*(15)*

In the alkaline hydrolysis of carbamyl phosphate [27–30], P–O bond fission occurs: again a P XYZ system is indicated. Moreover, hydrogenolytic debenzylation of dibenzyl ethoxycarbonyl phosphate *(16)* leads to extensive decomposition with evolution of carbon dioxide [31].



*(16)*

[*] Calculations of the electron density on the O in P–O–C–O [19] show that it is more electron deficient than the O in P–O–$CH_3$.


[19] *B. Grabe*, Biochim. biophysica Acta *30*, 560 (1958).

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[22] *G. Di Sabato* and *W. P. Jencks*, J. Amer. chem. Soc. *83*, 4400 (1961).

[23] *H. G. Khorana* and *J. P. Vizsolyi*, J. Amer. chem. Soc. *81*, 4660 (1959).

[24] *R. B. Woodward*, *R. A. Olofson*, and *H. Mayer*, J. Amer. chem. Soc. *83*, 1010 (1961).

[25] *F. Cramer*, *H. Neunhoffer*, *K. H. Scheit*, *G. Schneider*, and *J. Tennigkeit*, Angew. Chem. *74*, 387 (1962); Angew. Chem. internat. Edit. *1*, 331 (1962).

[26] *T. M. Jacob* and *H. G. Khorana*, Chem. and Ind. *1962*, 932.

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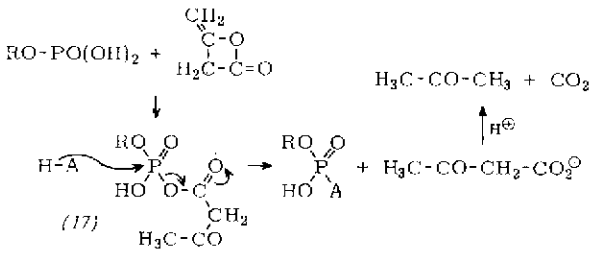
[28] *M. Halmann*, *A. Lapidot*, and *D. Samuel*, J. chem. Soc. (London) *1962*, 1944.

[29] *F. Cramer* and *M. Winter*, Chem. Ber. *92*, 2761 (1959).

[30] *R. B. Fox* and *W. J. Bailey*, J. org. Chemistry *26*, 2542 (1961).

[31] *A. Lapidot* and *M. Halmann*, J. org. Chemistry *28*, 1394 (1963).

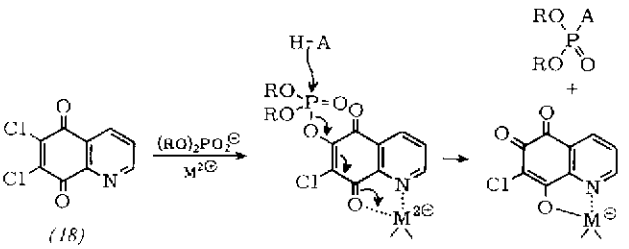

Diketene reacts with phosphoric monoesters to produce phosphorylating agents [32], nucleophilic attack occurring on



*(17)*

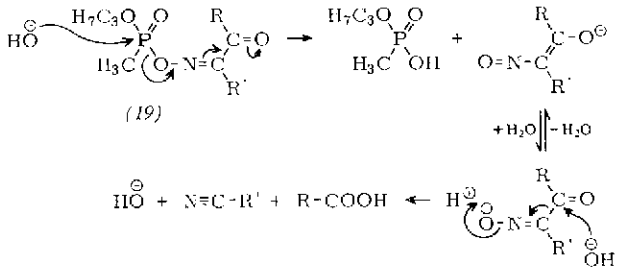
the intermediate *(17)* generated *in situ*, giving carbon dioxide, acetone, and the phosphorylated nucleophile.

6,7-Dichloroquinoline-5,8-quinone *(18)* can convert certain transition-metal salts of phosphoric diesters into phosphorylating agents [33]. The nitrogen and the quinone oxygen atoms chelate with the metal ion, thereby activating the quinonoid ring towards nucleophilic attack. The 6-chlorine atom can then be displaced by a phosphate mono-anion to give a vinylogous acyl phosphate.



*(18)*

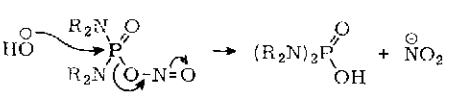
α-Hydroximino ketones react rapidly with Sarin (isopropyl methylphosphonofluoridate) in neutral or slightly alkaline solution [34], the initial reaction product *(19)* being an azavinylogue of an acyl phosphate which breaks down into isopropyl methylphosphonate, a carboxylic acid, and a nitrile.



*(19)*

## B 1e: P—O—N—O (X = Z = O, Y = N): Phosphoronitrites and Phosphoronitrates

The reaction of *N,N,N',N'*-tetraalkylphosphorodiamidyl chlorides with hydroxide ions is catalysed to a marked extent by nitrite ions [35], possibly via the mixed anhydride of the tetraalkylphosphorodiamidic acid and nitrous acid *(20)*.



*(20)*

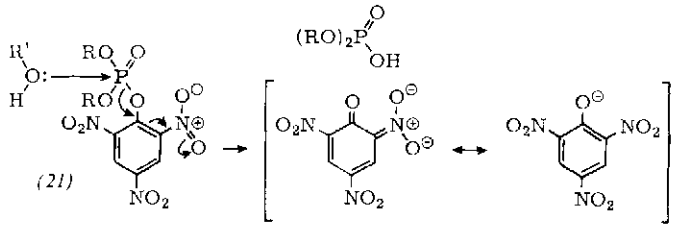

[32] *T. Mukaiyama*, *T. Hata*, and *O. Mitsonobu*, J. org. Chemistry *27*, 1815 (1962).

[33] *E. J. Corey* and *H. König*, J. Amer. chem. Soc. *84*, 4904, (1962).

[34] *A. L. Green* and *B. Saville*, J. chem. Soc. (London) *1956*, 3887.

[35] *E. W. Crunden* and *R. F. Hudson*, J. chem. Soc. (London) *1962*, 3591.

Mixed anhydrides of this type have not yet been isolated, but their vinylogues are known to be phosphorylating agents. Thus, picryl chloride has been used to form nucleoside 2',3'-cyclophosphates from a mixture of the nucleoside 2'- and 3'-phosphates [36,37], and phosphoric esters have been isolated from the reaction of an alcohol with phosphate ion in the presence of picryl chloride [37]. The reactive intermediate must be a picryl phosphate *(21)*, *i.e.* a vinylogue of the phosphoronitrates.

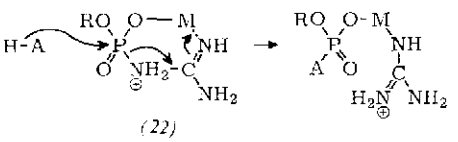


*(21)*

### B 2a: P—N—C=N (X = Z = N, Y = C): *N*-Phosphoroguanidates

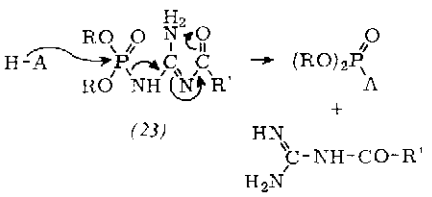
In contrast to phosphoramidates [38], phosphoroguanidates are difficult to hydrolyse, even with acid. They are not phosphorylating agents in the usual sense.

The guanidine moiety can exist in two different tautomeric forms, in one of which the carbon-nitrogen double bond is in conjugation via d-orbitals with the phosphorus atom. This gives rise to strong pπ–dπ interaction between the phosphorus and nitrogen atoms. If this interaction is weakened by withdrawal of electrons, *e.g.* by formation of a metal-ion complex, the phosphoroguanidate becomes a phosphorylating agent *(22)* [39].



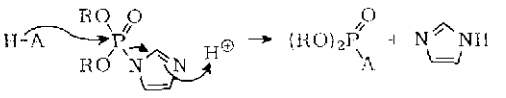
*(22)*

Acylation of the guanidine residue has a similar effect; *N*-acylphosphoroguanidates *(23)* function as phosphorylating agents under weakly basic conditions [40].



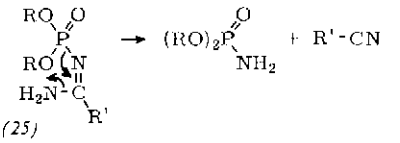
*(23)*

In contrast, *N*-phosphoroimidazoles *(24)* [41–45] are phosphorylating agents in the presence of acid.



*(24)*

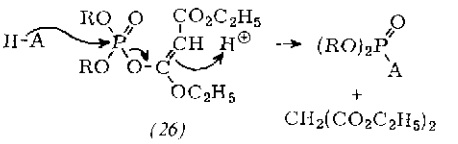
A further example of a P–N–C=N system is to be found in the *N*-phosphoroamidinates *(25)* [46] which rearrange probably through a four-centre transition state.



*(25)*

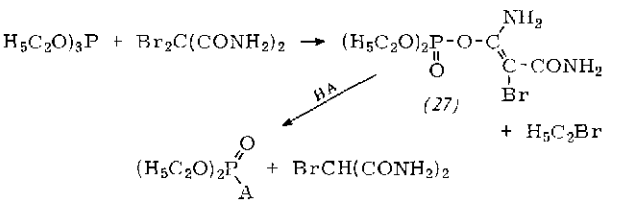
### B 2b: P—O—C=C (X = O, Y = Z = C): Enol Phosphates

Under conditions leading to electron withdrawal from the carbon-carbon double bond, *e.g.* by protonation or oxidation, enol phosphates are phosphorylating agents [47]. Thus, for example *(26)* can react with a carboxylic or phosphoric acid to produce an anhydride [48–50].



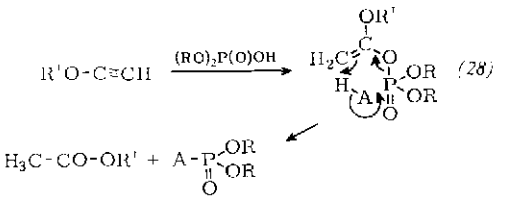
*(26)*

Moreover, catalytic amounts of mineral acid in ethanol cleave any dialkyl enol phosphate ester selectively to give the corresponding dialkyl ethyl phosphate and the appropriate carbonyl compound [47]. On the other hand, in aqueous acid or alkali, hydrolysis leads to a dialkyl phosphate [51]. Vinyl phosphates *(27)* are produced in the reactions of trialkyl phosphites with dibromomalonamide [52].



*(27)*

Such mixtures have been used to carry out phosphorylations. In addition, alkoxyacetylenes can activate phosphoric acids by forming 1-alkoxyvinyl phosphates [53,54].



*(28)*

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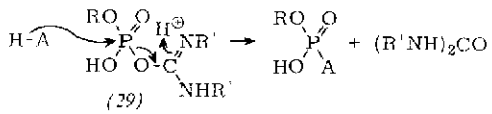
[52] *T. Mukaiyama, T. Hata*, and *T. Tasaka*, J. org. Chemistry *28*, 481 (1963).

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[54] *H. H. Wasserman* and *D. Cohen*, J. Amer. chem. Soc. *82*, 4435 (1960).

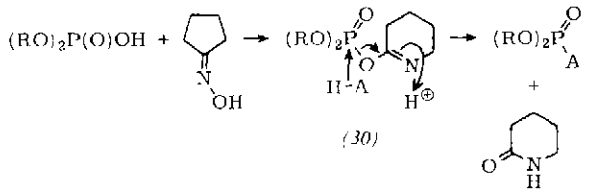
### B 2c: P—O—C=N (X = O, Y = C, Z = N): Imidoyl Phosphates

Imidoyl phosphates *(29)* [55] are formed *in situ* during the reaction of phosphate esters with carbodiimides [56,57], cyanamides [58], nitriles [59], keteneimines [60], and isocyanates [29,30]: no intermediate has ever been isolated, although the corresponding acid chlorides are well known [61,62]. In the presence of proton donors, imidoyl phosphates are powerful phosphorylating agents and have been used extensively in the synthesis of both phosphoric and pyrophosphoric diesters [63].



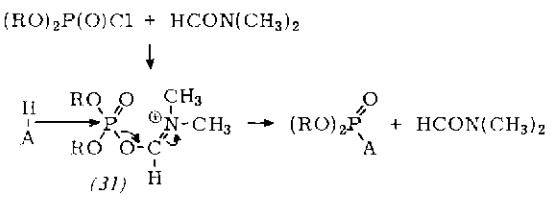
*(29)*

Beckmann rearrangement of an oxime in the presence of a phosphoric acid also leads to an imidoyl phosphate *(30)* [64].



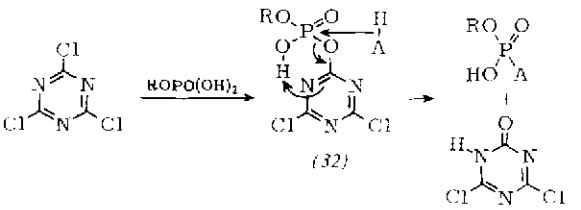
*(30)*

Catalysis of the reaction between an alcohol and a phosphorochloridic diester by *N,N*-dimethylformamide has been observed: again an imidoyl phosphate *(31)* is believed to be the key intermediate [65].



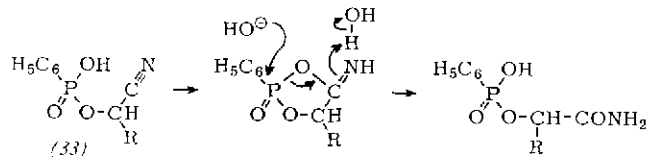
*(31)*

In the presence of cyanuryl chloride, phosphoric monoesters are good phosphorylating agents [66]; an imidoyl phosphate *(32)* is the probable intermediate.



*(32)*

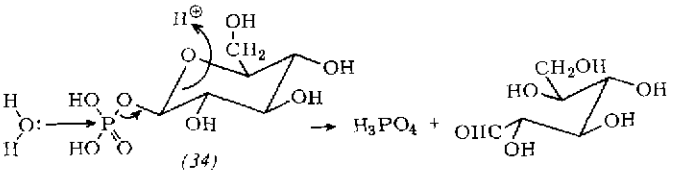
Phosphonic esters of α-hydroxy nitriles *(33)* are hydrolysed in alkali to the corresponding amides [67]. The cyclic imidoyl phosphate which is presumably formed as an intermediate can be attacked at phosphorus by hydroxide ions.



*(33)*

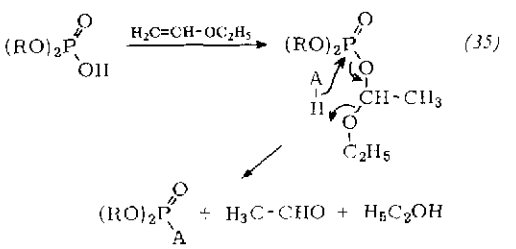
### B 2d: P—O—C—O (X = Z = O, Y = C): 1-Alkoxyalkyl Phosphates

The hydrolysis of glucose 1-phosphate *(34)* is catalysed by acids and proceeds with ring opening [68,69]; the alkaline hydrolysis of acetoxymethyl phosphate could well proceed by an analogous route [70].



*(34)*

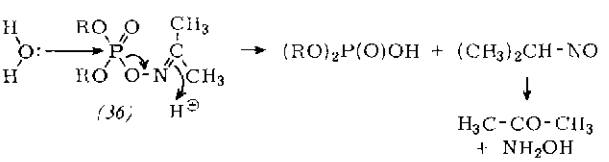
Phosphoric diesters react with ethyl vinyl ether to give 1-ethoxyethyl phosphates *(35)*. In the presence of appropriate nucleophiles, these are phosphorylating agents [32].



*(35)*

### B 2e: P—O—N=C (X = O, Y = N, Z = C): *O*-Phosphoryloximes

Acidic hydrolysis of *O*-phosphoryloximes *(36)* can lead to a ketone, but the nature of the phosphorylated intermediate has not yet been determined [71].



*(36)*


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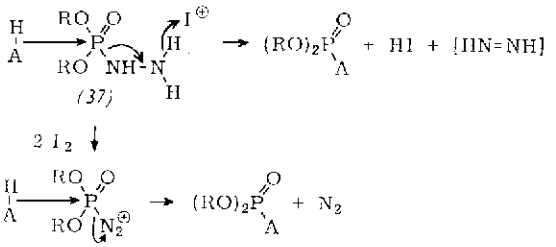
[70] *P. Pratesi,* Ber. dtsch. chem. Ges. *72*, 1459 (1939).

[71] *J. F. Allen,* J. Amer. chem. Soc. *79*, 3071 (1957).

The acceleration of hydrolysis of phosphorohalidates by hydroxamic acids [35] or by oximes [72] may be due to the formation of analogous structures.

### B 3a: P—N—N—H (X = Y = N, Z = H): Phosphorohydrazidates

Phosphorohydrazidates *(37)* can act as phosphorylating agents either in the presence of acid, where their behavior may parallel that of phosphoramidates [38,73], or under oxidizing conditions, where they can react as shown in Scheme 2 [73,74].

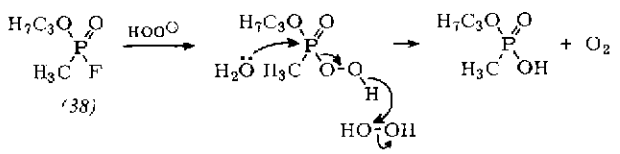


Scheme 2.

The actual course of this oxidative acylation reaction has yet to be determined.

### B 3b: P—O—O—H (X = Y = O, Z = H): Peroxyphosphates and Hydroquinone Phosphates

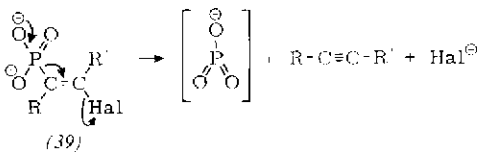
The reaction between Sarin (isopropyl methylphosphonofluoridate) *(38)* and hydrogen peroxide proceeds by attack of the perhydroxide ion on phosphorus. The peroxyphosphate formed can be oxidized to give oxygen and isopropyl methylphosphonate [75].



Hydroquinone phosphates are, in a formal sense, vinylogous peroxyphosphates (cf. Section IIC); both transfer phosphate under oxidizing conditions [3,76,77].

### B 4a: P—C=C—Hal (X = Y = C; Z = Halogen): β-Halogenovinylphosphonates

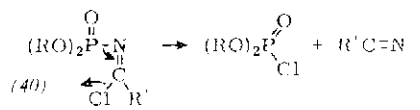
Vinylogues of phosphorochloridic acid *(39)* are much more stable than the parent acids, *e.g.*, β-halogenovinylphosphonates are stable in acidic solution. However, in alkaline solution, such phosphonates are hydrolysed to acetylenes with concurrent expulsion of halide ion [8,9].



As with saturated β-halogenoalkylphosphonates, the alkaline hydrolysis can proceed either intra- or intermolecularly. The fragmentation which occurs in both cases favors this type of reaction by the consequent gain in entropy.

### B 4b: P—N=C—Hal (X = N, Y = C, Z = Hal): *N*-Phosphoroimidoyl Halides

When heated *in vacuo*, *N*-phosphoroimidoyl chlorides *(40)* undergo rearrangement to give a phosphorochloridate and a nitrile [78].

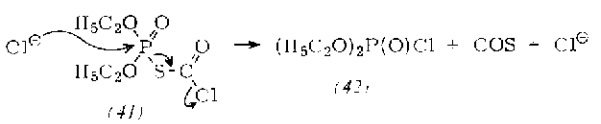


Scheme 3

Such rearrangements might be intramolecular, as shown in Scheme 3, or might be due to attack of external chloride on the phosphorus atom. Again, fragmentation occurs with concurrent gain in entropy.

### B 4c: P—S—C—Hal (X = S, Y = C, Z = Hal): *S*-Halocarhonyl Thiophosphates

Salts of *O,O'*-diethyl phosphorothioic acid react with phosgene to give diethyl phosphorochloridate *(42)* [79]. Diethyl *S*-chlorocarbonyl phosphorothioate *(41)* is presumably formed first and is subsequently attacked by chloride ion to give *(42)* and carbon oxysulfide.



## V. Biological Phosphorylations

Phosphorylating agents capable of converting ADP into ATP *in vivo* are of the types B1 (pπ–dπ interaction attenuated in the ground state by competitive pπ–pπ overlap), B2, or B3 (pπ–dπ interaction removed by electrophilic or oxidative attack on Z). Acetyl phosphate *(43)* [80,81], acetyl-AMP *(44)* [82,83], carbamyl phosphate *(45)* [84,85], and 1,3-diphosphoglyceric acid

[72] *B. E. Hackley, R. Plapinger, M. Stolberg*, and *T. Wagner-Jauregg*, J. Amer. chem. Soc. *77*, 3651 (1955).

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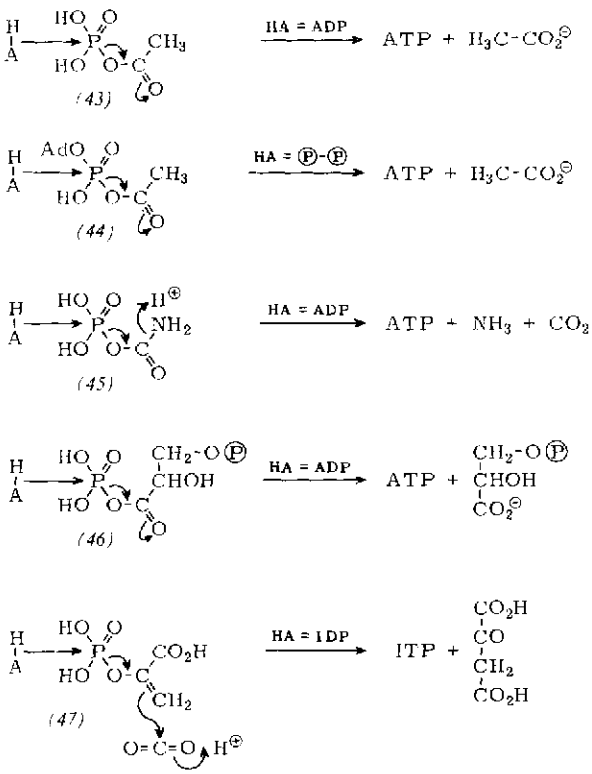
[82] *P. Berg*, J. biol. Chemistry *222*, 991, 1015 (1956).

[83] *F. Lipmann, M. E. Jones, S. Black*, and *R. M. Flynn*, J. Amer. chem. Soc. *74*, 2384 (1952).

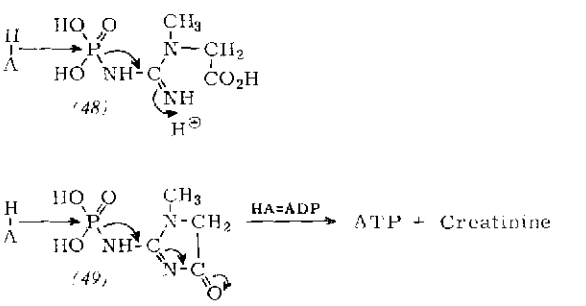
[84] *M. E. Jones, L. Spector*, and *F. Lipmann*, J. Amer. chem. Soc. *77*, 819 (1955).

[85] *M. E. Jones*, Science (Washington) *140*, 1373 (1963).

*(46)* [86] are of the B1 (X = Z = O, Y = C) type, while the phosphorylating reactions of phosphoenolpyruvate *(47)* [87–90] fall into the B2 (X = O, Y = Z = C) category.




Phosphagens, *e.g.* phosphorocreatine *(48)*, can be considered as B2 reagents (X = Z = N, Y = C), but recent chemical evidence [40] suggests that the active entity could be the cyclic *anhydro*-form [*e.g.* phosphocreatinine *(49)*] with a B1 type of XYZ activation (vinylogous X = N, Y = C, Z = O).





[86] *T. Bücher*, Biochim. biophysica Acta *1*, 292 (1947).

[87] *K. Kurahashi, R. J. Pennington*, and *M. F. Utter*, J. biol. Chemistry *226*, 1059 (1957).

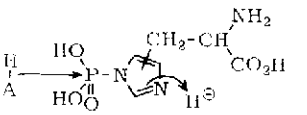
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Less well understood are the various reactions by which ATP is synthesized during oxidative [91,92] and photosynthetic [93,94] phosphorylation. In the cytochrome chain [95], ATP is generated from ADP at three sites, two of which probably involve, respectively, a flavoprotein [96] and a quinone [97]. The oxidation of hydroquinone phosphates with the production of ATP has already been mentioned; this reaction is regarded as a model for the *in vivo* process [98,99].

These chemical speculations are supported in some instances by experimental evidence, but they still require biochemical confirmation. However, they do provide a critical, as well as an analytical basis for further discussion. Thus, it is clear that phosphohistidine



*(50)*

*(50)* is a phosphorylating agent of the B2a type and cannot be implicated in oxidative reactions of the B3 type. Although *(50)* may play a role in oxidative phosphorylation [100], unlike the nicotinamide nucleotides [101,102], it cannot interconvert a redox and an acylating system.

In this way, the P–XYZ classification of phosphorylating agents has both a predictive and a critical aspect.


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# Metallo-Complexes

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*Ternary and quasiternary compounds consist of either one cationic and two anionic, or one anionic and two cationic components. The size of the ions and the bonding forces between them determine the structure of the compounds. A compound is regarded as a complex when its lattice contains structural groups in which the interaction between the constituent atoms is substantially greater than or different from that between these structural groups and the other components of the compound. Metallo-complexes are built up of one cationic and two anionic components; in contrast to the complexes with cationic central atoms which have been thoroughly investigated, they contain an anionic central atom surrounded by cationic ligands. A list is given of many compounds which can be formulated as metallo-complexes after discussion of methods for their preparation and their chemical properties; the reason that only few metals can function as ligands of an anionic central atom is deduced from the pertinent crystal structures.*

## A. Introduction

In modern chemistry, a salt is defined as a substance whose components are arranged in an ionic lattice [2]. If we consider a salt $K_mA_p$ in which the lattice sites are occupied by cations K and anions A, the type of lattice assumed is determined by the sizes of the ions involved, the bonding forces between them, and the principle of electrical neutrality. In ternary compounds

$K(1)_mK(2)_nA_p$ or $K_mA(1)_pA(2)_q$,

either the K or the A sites are occupied by two different elements. The magnitudes of the bonding forces K(1)-A and K(2)-A or K-A(1) and K-A(2) are normally different, and hence play a significant part in determining the crystal structure. Typical mixed crystals are formed when the bonding forces are approximately equal in magnitude, and typical complex salts result when the bonding forces are vastly different.

Although complex salts of the form $K(1)_m[K(2)_nA_p]$ have been investigated in great detail ever since the studies of *Werner*, little attention has been given to ternary compounds of the type $[K_mA(1)_p]A(2)_q$.

The names of such complexes can be formed in various ways according to the I.U.P.A.C. Rules for Nomenclature of Inorganic Chemistry [3]:

1. The addition of protons to mono-atomic anions yields cations of the type $[XH_4]^+$, which are named by adding -onium to the Latin name of the anionic element (Rule 3.14). If the protons are displaced by other cations (a possibility not considered in the I.U.P.A.C. Rules), the names remain unchanged (Rule 7.321) and terms such as trisilversulfonium nitrate for $[SAg_3]$ $[NO_3]$ are obtained.

2. If substitutive nomenclature is to be avoided in inorganic chemistry, the name of the complex $[SAg_3]^+$ can be formed by listing the partners. In this case neither the cationic ligand silver (Rule 7.321) nor the central atom sulfur (Rule 7.24) are given a distinguishing termination. The name of $[SAg_3]$ $[NO_3]$ would then be trisilversulfur nitrate.

3. Rule 7.321, which requires that the name of a cationic ligand be used without change, does not list any pertinent example. This is to be regretted, since otherwise it would have become clear that it seems advisable to denote the position of a positive ligand within a complex also by using the ending -o.

$[SAg_3]$ $[NO_3]$ may thus be referred to as trisilversulfonium nitrate, trisilversulfur nitrate, triargentosulfonium nitrate, or triargentosulfur nitrate. In this article, the last system of nomenclature will be used, in accordance with *Lieser* [4]. Complexes with an anionic central atom and cationic ligands may be conveniently designated general as metallo-complexes.

## B. A Systematic Classification of Multicomponent Compounds

### 1. Ternary Compounds

In order to arrive at an unambiguous definition of metallo-complexes, let us arrange the structures of the ternary compounds $K(1)_mK(2)_nA_p$ and $K_mA(1)_pA(2)_q$ into a series, with the difference in bond strengths of K(1)-A and K(2)-A or of K-A(1) and K-A(2) as parameter. Four groups are formed.

*Group 1 – Solid Solutions and Double Salts with Binary-Salt Type Structures*

If the sizes and polarizability of the elements K(1) and K(2) at the K-sites or A(1) and A(2) at the A-sites are very similar, then K(1) and K(2) or A(1) and A(2) are mutually interchangeable. They are randomly distributed, and the relative proportions of the elements need not even be stoichiometric, so that mixed crystals can occur as well as double salts (Table 1).

[1] Excerpts from the Habilitation Thesis of *G. Bergerhoff*, Universität Bonn, 1962 (D 5).

[2] See, for example, *G. Schwarzenbach:* Allgemeine und anorganische Chemie. S. Hirzel, Stuttgart 1948, p. 76.

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[4] *K. H. Lieser*, Z. anorg. allg. Chem. *295*, 106 (1958).

*Group 2 – Double Salts with Structures Derived from Binary-Salt Structures by Ordered Distribution of the Two Types of Cations or Anions*

A greater difference in bond strengths forces the elements to assume an ordered distribution, resulting in a new type of structure. However, the essential structural relationships of the binary salts are retained, and consequently the coordination numbers of K(1) and K(2) or A(1) and A(2) are practically equal (Table 1).

**Table 1.** Examples of the classification of ternary compounds [a].

| Group | a: $K(1)_mK(2)_nA_p$ | | Ref. | b: $K_mA(1)_pA(2)_q$ | | Ref. |
|---|---|---|---|---|---|---|
| | Compound | Structure [b] | | Compound | Structure [b] | |
| 1 | (K,Na)Cl | NaCl type, mixed crystals | | Ag(Br,I) | NaCl type, mixed crystals | |
| | $KLaF_4$ | Fluorite type, double salt | [5] | HoOF | Fluorite type, double salt | [6] |
| 2 | $CuFeS_2$ | Related to zinc blende | [7] | $Cu_4(OH)_6Br_2$ | Related to burcite | [8] |
| 3 | $RbMgF_3$ | Perovskite type CN of K(1):12 CN of K(2):6 | [9] | β-$Ag_3SI$ | Antiperovskite CN of A(1):6 CN of A(2):12 | [10] |
| | $MgAl_2O_4$ | Spinel type CN of K(1):4 CN of K(2):6 | [9] | PbFCl | Layer lattice CN of A(1):4 CN of A(2):5 | [11] |
| 4 | $K_2[SO_4]$ | Island complex | | $[(ClHg)_3O]Cl$ | Two-shell complex | [17] |
| | $K_2[Cr_2O_7]$ | Polynuclear complex | | | | |
| | $K_2[CuCl_3]$ | Chain complex | [18] | $[Hg(NH_2)]Br$ | Chain complex | [17] |
| | $K_2[NiF_4]$ | Layer complex | [19] | | | |
| | $Ba[ZnO_2]$ | Framework | [20] | $[Hg_2N]Br$ | Framework | [17] |

[a] Although $Cu_4(OH)_6Br_2$ and $Hg(NH_2)Br$ are quaternary compounds, they are included here since the proton practically disappears in the electron cloud of its bonding partner.
[b] CN = Coordination number.

*Group 3 – Lattice Compounds in which the Two Types of Cations or Anions have Different Properties*

If the difference in bond strengths is even greater, then K(1) and K(2) or A(1) and A(2) assume different coordination numbers, although the nature of the bonds between the cations and the anion or between the anions and the cation remains similar. The resulting structures can no longer be traced back to the binary-salt type (Table 1).

*Group 4 – Complex Compounds*

The series is terminated by compounds which were defined by *Werner* [12] in 1913 as follows: "If compounds of higher order are characterized by stability in aqueous solution, in that they do not dissociate into their components, they are called complex compounds". This definition is unsatisfactory nowadays, for we know that on principle complexes dissociate into their components in solution, although there are great differences among the complex formation constants and the rates of dissociation. Moreover, dissociation of complexes is regarded as a chemical reaction, the course of which depends on the nature of the reaction partners. A true complex compound may even be present when its components can be detected in solution. It seems useful to abandon this "dynamic" definition, and as with the concept of a "salt", to give a "static" definition based on the structure of the solid state:

*Complex compounds are compounds whose lattices contain structural groups in which the interaction between the constituent atoms is substantially greater than or different from that between these structural groups and the other components of the compound.*

Of course, the interaction between the atoms of a crystal lattice cannot be determined readily by experiment; however, assignments can be made in most cases from considerations based on bonding theory. For example, it may be plausible, from the electron configuration of the atoms or from comparison of the interatomic distances, to assume that the bonding for a given compound is homopolar. Sometimes it can be determined from the size and charge of the ions, and from their polarizability and polarizing action, whether the compound in question is a complex.

Structural groups consisting of discrete units made up of a central atom surrounded by ligands are usually known as "island complexes". If these ligands in turn act as central atoms and become surrounded by a second outer ligand sphere, which is also to be regarded as part of the structural group, the compounds are referred to as two-shell or supercomplexes [13, 14].

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However, the ligands of a complex can also link up several central atoms to form polynuclear complexes, and these logically include complexes which extend in one or more directions to infinity (polymeric complexes) [15]. It appears to be convenient to refer to the atom with the greater coordination number as the central atom; it is then possible to differentiate between complexes with cationic and anionic central atoms. Some examples are shown in Table 1.

### 2. Quasiternary Compounds

The above division into four groups provides a basis for a systematic classification of inorganic complex structures; which largely reflects the relationships between the various lattice types. Groups 1 and 2 have been characterized already by the fact that their structures can be traced back to those of binary compounds. If lattice sites are occupied by complexes (in the sense of discrete structural groups), ternary compounds, such as $K_2[SO_4]$, can be regarded as quasibinary compounds, and quaternary or higher-order compounds, such as $[K(H_2O)_6]\,[Al(H_2O)_6]\,[SO_4]_2$, as quasiternary.

The series can now be extended to include quasiternary compounds. Some examples are shown in Table 2.

Table 2. Examples of the application of the systematic classification to quasiternary compounds.

| Group | a: $K(1)_mK(2)_nA_p$ | | | b: $K_mA(1)_pA(2)_q$ | | |
|---|---|---|---|---|---|---|
| | Compound | Structure | Ref. | Compound | Structure | Ref. |
| 1 | (Ba,Sr) $[SO_4]$ | Barite type | [21] | $Mg_2(OH)_3Cl$ | Related to brucite | [22] |
| 2 | $CaMg[CO_3]_2$ | Related to calcite | [23] | $Cu_4(OH)_6[NO_3]_2$ | Related to brucite | [24] |
| 3 | $Mg_3Al_2Si_3O_{12}$ | Garnet type | [25] | $Pb_5[PO_4]_3Cl$ | Apatite type | [26] |
| 4 | $K_4[Ni(NO_2)_6]$ | | [27] | $[Hg_3O_2][SO_4]$ | | [17] |

## C. Metallo-Complexes

### 1. General Discussion and Examples

The examples of Group 4b in Tables 1 and 2 will be referred to as metallo-complexes. *Werner* [28], in the systematic application of his coordination theory, distinguished between "the great majority of coordination compounds, in which the centers of complex formation are elementary atoms which are more electropositive than the elementary atoms which accept the linkages of the added molecular components", and a "small group of compounds in which the opposite is the case". By way of example, *Werner* [28] quoted the compound $[IAg_3][NO_3]_2$, in which *Hellwig* [29] had observed migration of a complex ion $[IAg_3]^{2+}$ during electrolysis. This salt and similar silver salts are still the classical examples of this type of complex, although the number of compounds which can be formulated as metallo-complexes has steadily grown. Evidently the lack of a good example of a typical island complex was the reason for alternative formulations. Thus, *Hayek* [30] regarded whole "salt molecules" as ligands, *e.g.* in $[Hg(HgI_2)_2][ClO_4]_2$, because he required cationic central atoms as in conventional complexes. *Yatsimirskii* [31] listed numerous compounds which can be described as complexes with anionic central atoms, but did not prove his assumptions. It is only recently that modern physical methods have been applied to silver compounds and that mercury compounds in particular have been investigated by X-ray methods. As prerequisites for the formation of metallo-complexes, *Lieser* [32] named high polarizability of the negative central atom, and *Yatsimirskii* its low electron affinity. Obviously not all metals are capable of forming complexes of this type; according to *Yatsimirskii*, a high ionization potential is necessary. Frequently, the difficulties encountered in preparing compounds of this type indicate that their free enthalpy of formation is not very great, so that even small effects can reverse its sign. The extra-complex ion A(2) is also of importance, since it can change the lattice energy, and can even act as a complexing ligand for a cationic central atom.

Table 3 shows some compounds which can be formulated as metallo-complexes. Their structures are known only in a few cases. The Table, which is not meant to be complete, shows how many structures might be ordered using the concept of "metallo-complexes". However, only an elucidation of these structures will finally prove the value of this list.

[15] See [13], pp. 180, 200, 290, and [2], p. 101.

[16] See [12], p. 305.

[17] See references in Table 3.

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[27] *A. Ferrari*, *L. Cavalca*, and *M. Nardelli*, Gazz. chim. ital. *81*, 945 (1951).

[28] See [12], p. 300.

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Table 3. Compounds which can be formulated as metallo-complexes

| Central atom | Stoichiometry of the complex ion | Known counter-ion | Structure of the complex ion | Ref. |
|---|---|---|---|---|
| C | $[CHg_3O]^+$ | $Cl^-$, $OH^-$, $SO_4^{2-}$, $MnO_4^-$ and others | Framework | [33] |
| N | $[NHg_2]^+$ | $Br^-$, $I^-$, $OH^-$, $F^-$ | Framework | [34] |
| | | $SO_4^{2-}$, $HAsO_4^{2-}$, $HPO_4^{2-}$ | | [35] |
| | $[(NH)_2Hg_3]^{2+}$ | $(HgBr_3, Br)^-$ | Layer | [36] |
| | $[(NH_2)Hg]^+$ | $Br^-$ | Chain | [37] |
| | $[N(SO_3)Hg]^-$ | $K^+$ | Chain | [38] |
| P | $[PAg_6]^{3+}$ | $NO_3^-$ | Framework | [39] |
| | $[PHg_2]^+$ | $HgCl_3^-$ | | [40] |
| As | $[AsAg_6]^{3+}$ | $NO_3^-$ | | [39] |
| Sb | $[SbAg_6]^{3+}$ | $NO_3^-$ | | [39] |
| O [*] | $[O(HgCN)_2]$ | | Two-shell complex | [41] |
| | $[O(HgCl)_3]^-$ | $Cl^-$ | Two-shell complex | [42] |
| | $[O(HgCH_3)_3]^+$ | $Cl^-$, $ClO_4^-$, $PF_6^-$ | | [43] |
| | $[OH\,Hg]^+$ | $ClO_3^-$ Br | Chain | [44] |
| | $[O_2Hg_3]^{2+}$ | $SO_4^{2-}$, $SeO_4^{2-}$ | Layer | [45] |
| | | $ClO_4^-$ | | [46] |
| | | $Cl^-$ | | [47] |
| | $[OBe_4]^{6+}$ | $CH_3COO^-$ | Two-shell complex | [48] |
| | | $NO_3^-$ | | [49] |
| | | $C_6H_5COO^-$ | | [50] |
| | | $C_2H_5COO^-$, $CH_2ClCOO^-$ | | [51] |
| | | $CO_3^{2-}$ | | [52] |
| | $[OZn_4]^{6+}$ | $CH_3COO^-$ | Two-shell complex | [53] |
| | $[OZn_3]^{4+}$ | $SO_4^{2-}$ | | [54] |
| | $[O_2Cd_2]^{3+}$ | $SO_4^{2-}$ | | [55] |
| | $[OPb_2]^{2+}$ | $SO_4^{2-}$ | | [56] |
| | | $SeO_4^{2-}$, $CrO_4^{2-}$, $SO_4^{2-}$ | | [57] |
| | $[OFe_3]^{7+}$ | $CH_3COO^-$ | | [58] |
| S | $[SAg_3]^+$ | $NO_3^-$ | Framework | [59] |
| | $[SAg_4]^{2+}$ | $SO_3^{2-}$ | | [60] |
| | | $SO_4^{2-}$ | | [39] |
| | $[SHg_2]^{2+}$ | $ClO_4^-$ | | [61, 62] |
| | | $CH_3COO^-$ | | [63] |
| | | $I^-$ | | [64] |
| | | $Cl^-$ | | [65] |
| | $[S_2Hg_3]^{2+}$ | $Cl^-$, $NO_3^-$ | Framework | [40] |
| | | $ClO_4^-$ | | [62] |
| | | $I^-$ | | [64] |
| | $[SCd_3]^{4+}$ | $I^-$ | | [66] |
| | $[SCd_2]^{2+}$ | $X^-$ | | [31] |
| | $[SPb_2]^{2+}$ | $X^-$ | | [31] |
| | $[STl_3]^+$ | $Cl^-$ | | [67] |
| | $[STl_6]^{4+}$ | $SO_3^{2-}$ | | [68] |
| Se | $[SeHg_2]^{2+}$ | $X^-$ | | [31] |
| | $[Se_2Hg_3]^{2+}$ | $Cl^-$ | Framework | [40] |
| Te | $[TeAg_7]^{5+}$ | $NO_3^-$ | | [69, 70] |
| | $[TeAg_8]^{6+}$ | $NO_3^-$ | | [70] |
| | $[Te_2Hg_3]^{2+}$ | $Cl^-$, $Br^-$ | Framework | [40] |
| Cl | $[ClAg_7]^+$ | $NO_3^-$ | | [29] |
| | $[Cl_2Zn_2]^{2+}$ | $SO_4^{2-}$ | | [71] |
| Br | $[BrAg_2]^+$ | $F^-$ | | [72] |
| | | $NO_3^-$ | | [29] |
| I | $[IAg_3]^{2+}$ | $NO_3^-$ | Chain | [4] |
| | | $ClO_4^-$ | | [46] |
| | $[IAg_2]^+$ | $F^-$ | | [72, 73] |
| | $[I_2HgAg_2]^{2+}$ | $NO_3^-$ | | [74] |
| Pseudohalogen-Komplexes | $[(CN)Ag_3]^{2+}$ | $NO_3^-$ | Framework | [29, 75] |
| | $[(SCN)Ag_3]^{2+}$ | $NO_3^-$ | Framework | [29, 75] |
| | $[(SeCN)Ag_3]^{2+}$ | $NO_3^-$, $ClO_4^-$ | | [76] |

[*] This group includes a few "basic salts"; most of these form structure of Groups 1, 2, and 3.

## 2. Preparation of Metallo-Complexes

Metallo-complexes can be conveniently prepared by three methods:

$$p\,KA(1) + q\,KA(2) \rightarrow [A(1)_pK_{p+q}]A(2)_q \quad (a)$$

$$(p + m)\,KA(1) + q\,A(2)X \rightarrow [A(1)_pK_{p+m}]A(2)_q + A(1)_mX_q \quad (b)$$

$$(q + m)\,KA(2) + p\,A(1)X \rightarrow [A(1)_pK_{q+m}]A(2)_q + A(2)_mX_p \quad (c)$$

Metallo-complexes are formed according to Equation (a) either in melts [71], *e.g.* $[IAg_3]\,[NO_3]_2$, or on annealing by reaction in the solid state, *e.g.* $[S_2Hg_3]Cl_2$. This stage may be preceded by another reaction, such as a redox reaction in the preparation of $[SAg_4]\,[SO_4]$ from silver nitrate and sulfur. The salts KA(1) are often only sparingly soluble in water, but dissolve to an appreciable extent in a sufficient excess of KA(2) solution. Thus, the salts AgI, AgCNS, $Ag_2Te$, *etc.* are soluble in concentrated aqueous solutions of silver nitrate, complexes being precipitated on careful dilution. Mercury(II) iodide is soluble in hot aqueous mercury(II) perchlorate, and $I_4Hg_3]\,[ClO_4]_2$ crystallizes out on cooling [46].

Addition of A(2) according to Equation (b) leads to the formation of $\{[OBe_4]\,[CH_3COO]_6\}$ from beryllium hydroxide and acetic anhydride since excess hydroxide ions are taken up by the acetic anhydride to form acetic acid.

Very many metallo-complexes are formed according to Equation (c). Thus, at the beginning of the precipitation with hydrogen sulfide of many heavy metals, such as thallium, lead, or mercury, brightly colored "sulfobasic" salts appear, *e.g.* $[STl_3]Cl$. "Basic salts", which may also be metallo-complexes, are generally formed when the pH is increased, *i.e.* on addition of $OH^-$ or $O^{2-}$ ions. The formation of complexes with a central nitrogen atom is so far known only for mercury, with ammonia as the source of A(1); in this reaction the driving force is probably the insolubility of the "salts of Millon's base". Phosphine can give phosphorus complexes with silver or mercury compounds.

However, these methods of preparation usually yield the compounds at best only in microcrystalline form. Larger crystals can be obtained if A(1) is slowly formed by chemical reaction. Of the series methyl iodide, isopropyl iodide, and 2,4-dinitroiodobenzene, only the middle member forms large crystals of triargentoiodine nitrate with concentrated silver nitrate solution:

$$(CH_3)_2CHI + H_2O + 3\,AgNO_3 \rightarrow [IAg_3]\,[NO_3]_2 + HNO_3 + (CH_3)_2CHOH.$$

Carbon disulfide can be used as the source of sulfur for the preparation of large crystals of triargentosulfur nitrate:

$$CS_2 + 2\,H_2O + 6\,AgNO_3 \rightarrow 2\,[SAg_3]\,[NO_3] + 4\,HNO_3 + CO_2.$$

The crystal size can be further increased if the compounds are formed in silica gel, for in this colloidal capillary system, the crystal seed is held fast and can grow by influx of material from all sides by diffusion. For example, crystals of $[SAg_3]\,[NO_3]$ up to 1 mm long have been obtained as well-defined rhombohedra.

The capillary structure of silica gel containing silver nitrate can be very elegantly demonstrated by covering the gel with a layer of reducing agent; this procedure results in growth of silver whiskers up to 1 cm long in which, according to rotating crystal photographs, the filament direction is always [110].

## 3. Structure of Metallo-Complexes

The structures of only a few metallo-complexes are known at present. All of them represent well-known complex types.

Thus, trischloromercury(I)-oxygen chloride $[O(HgCl)_3]Cl$ is a two-shell complex or supercomplex (Fig. 1).

In the first sphere, the central oxygen atom occupies the apex of a trigonal pyramid [77], the base of which is formed by three mercury atoms at distances of 2.06 Å (sum of the covalent radii – 2.10 Å apart); these in turn are linked to chlorine at a distance of 2.29 Å (Hg–Cl distance in $HgCl_2$ = 2.34 Å), forming a second sphere of covalently bonded ligands around the central oxygen atom. In contrast, the chloride ions at a distance of 2.99 and 3.09 Å from the mercury atoms should be regarded as


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lying outside the complex. Another example is "basic beryllium acetate" $\{[OBe_4][CH_3COO]_6\}$. In this complex, the central oxygen atom is tetrahedrally surrounded by four beryllium atoms; the carboxyl groups link the beryllium atoms in pairs, in the manner of chelates, thus forming an inner complex salt. The beryllium atoms, like the oxygen atom, therefore have a coordination number of four, so that the compound might also be regarded as a tetranuclear complex of beryllium; however, oxygen certainly is the central atom.

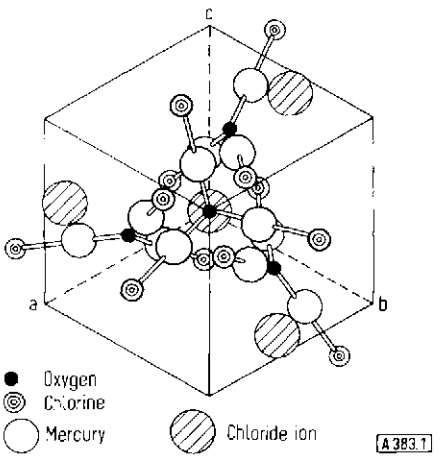



Fig. 1. Projection of the [O(HgCl)] [Cl] structure in the direction of one of its threefold axes (anions omitted) [77].

"Basic mercury chlorate" or hydridomercury(I)-oxygen chlorate [OHHg] $[ClO_3]$ forms a chain complex (Fig. 2), in which the oxygen and the mercury atoms alternate.

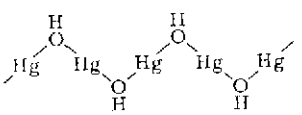


Fig. 2. Chain structure of the [HOHg] $(ClO_3]$ complex (anions) omitted.

However, the oxygen atom has a coordination number of three, owing to the additional bond to the hydrogen, while that of the mercury atom is only two, since the chlorate ions lie at the ionic bond distance. "Mercuryamido bromide" $[(NH_2)Hg]Br$ has a similar structure. The lattice is traversed by chains of alternating mercury and nitrogen atoms. The coordination number of the nitrogen atom is four, so that it must be regarded as the central atom.

The class of layer complexes is represented by the mercury(I)-oxygen compound $[O_2Hg_3][SO_4]$, and also by "mercuryimido bromide" $[(NH)_2Hg_3]$ $[HgBr_3]Br$. According to preliminary structural determinations, mercury atoms and oxygen or nitrogen atoms form networks, the meshes of which receive the oppositely charged ions (Fig. 3).

The oxygen or nitrogen atom has a coordination number of three and is the central atom of the complex. The sulfate groups in trimercury(I)-dioxygen sulfate are bonded ionically (Hg–O distance in the complex = 2.03 Å; Hg–$OSO_3$ distance = 2.47 Å).

Examples of framework complexes are dimercury(I)-nitrogen salts such as $[NHg_2]Br$, dimercury(I)-phosphorus chloromercurate(II) $[PHg_2]$ $[HgCl_3]$, and tri-

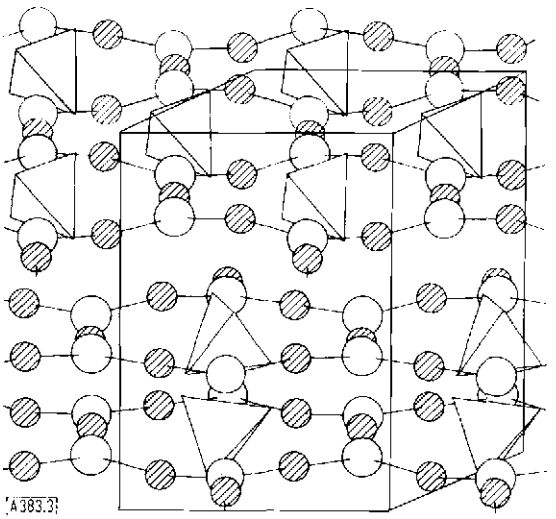



Fig. 3. Section of three layers of $(O_2Hg_3)$ $(SO_4)$. After [45]. The upper layer has been continued backwards. Hatched circles = mercury; open circles = oxygen; terahedra = sulfate.

argentosulfur nitrate $[SAg_3][NO_3]$. The mercury(I)-complexes have a tridymite structure in which the tetrahedrally coordinated silicon atom is replaced by nitrogen or phosphorus, and in which mercury takes the place of the 2-coordinate oxygen atom. The oppositely charged ions are situated in the spaces between the tetrahedra. Similarly, $[SAg_3][NO_3]$, which is cubic, contains approximately trigonal prismatic $SAg_6$ structural groups [78], linked through common corners to form a three-dimensional framework (Fig. 4). The cavities are sufficiently large to accommodate the nitrate groups which are ionically bonded.

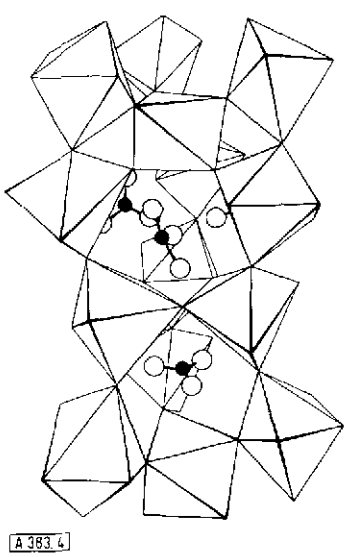



Fig. 4. Three-dimensional structure of the SAg $NO_3$ complex showing the $SAg_6$ polyhedra and the nitrate ions (● = N; o = O).

[78] The structure published earlier [59] has meanwhile been more accurately calculated by the method of least squares, using an IBM 704 computer. The program made it possible to presuppose the planar arrangement of the nitrate groups and the N–O distance of 1.218 Å [79], and used the difference $F_{obs}-F_{calc}$ for the weighting, with $w = 1/(F_{obs}-F_{calc})^2 + 0.5$ [80]. A reliability factor of $R = 14\%$ (only with $F \neq 0$) was obtained. The following parameters were finally obtained:

Ag: 12b; $x = 0{,}308 \pm 2$ $y = 0.9942 \pm 3$ $z = 0.3582 \pm 2$ $B = 2.82 \pm 5$

S: 4a; $x = 0.1367 \pm 8$ $B = 2.3 \pm 1$

N: 4a; $x = 0.414 \pm 1$

O: 12b; $x = 0.532$ $y = 0.318$ $z = 0.391$ } $B = 1.2 \pm 2$

## 4. Requirements for the Formation of Metallo-Complexes

Examination of all the metallo-complex structures described shows that island and polynuclear complexes are not encountered. Both types have a common factor, namely that their structural units must contain terminal metal atoms; a hypothetical island complex $[SAg_3]^-$ and a dinuclear complex $[Ag_2SAg_2SAg_2]^{2+}$ would contain metal atoms with a coordination number of 1. The tendency towards formation of structures of this type is obviously small.

It is known that the orbitals of cationic central atoms undergo hybridization when ligands are added, so that the resulting coordination polyhedron is more or less symmetrical. Anionic ligands, on the other hand, can be bonded by a singly occupied atomic-p-orbital, *i.e.* one-sidedly. In the sulfate ion, for example, if double-bond contributions are neglected, the electron structure may be pictured as follows: sulfur, with the ground state $s^2p^4$, gives up two electrons, and the remaining $s^1p^3$-electrons occupy four new tetrahedrally arranged equivalent orbitals. These hybridized orbitals overlap with the singly occupied atomic p-orbitals of four oxygen ions in the configuration $s^2p^5$, which are formed by the uptake of four electrons – two from the sulfur, and two through formation of the counter-ions.

The structure of metallo-complexes becomes understandable if it is assumed that the more electropositive atom of a complex, whether it be the central atom or a ligand, always appears to have a stronger tendency towards hybridization than the more electronegative atom. In general, the negative atom (central atom) is already hybridized. The tendency of the positive ligands to form hybrids will therefore be even greater. However, since hybridization allows the existence of at least two bonds in two directions, the ligand cannot be terminal in the structural group, *i.e.* it can never be monodentate. Instead, it will either attach itself to a second central atom, giving rise to polynuclear complexes, or will become saturated by other anionic ligands to form a two-shell complex. Conversely, the formation of two-shell complexes is not to be expected with cationic central atoms, since a cationic element cannot terminate a structural group. Thus, *Werner*'s [16] example $[Co(NH_3)_5NCSAg]\ [NO_3]_3$ probably has some other structure. The only exception to this rule is the hydrogen atom. Owing to its small size, it is largely embedded in the electron cloud of its bonding partner, so that hydroxo-complexes are not regarded as two-shell complexes, nor hydroxides as complexes.

It follows also from the structure of the metallo-complexes that not every element can participate in complexes of this type. As may be seen from Table 3, all elements which occur as anions are suitable, but of the cationic elements, only those which have low specific coordination numbers can take part. The reason is that the coordination number of the ligands must, by definition, be lower than that of the central atom, and that for steric reasons, ligands belong to more than two coordination polyhedra only in special cases.

These requirements are satisfied for example by elements of the B groups of the periodic table. In the case of ions with a $d^{10}$-electron configuration this behavior can be attributed to the development of a ds-hybrid, for which the excitation energy is relatively small, particularly for the $Cu^+$, $Ag^+$, $Au^+$, and $Hg^{2+}$ ions [81]. The crystal field theory shows that an octahedral environment is then so strongly distorted that two strong linear bonds remain.

A second group of elements with apparently lower coordination numbers forms ions which possess s-electrons in addition to ten d-electrons. A hybrid of s- and p-orbitals is now partially occupied by the electrons of the atom, and this leads to development of extremely unsymmetrical and low coordination states. Numerous examples of this are provided by the structures of compounds of $Tl^+$, $Sn^{2+}$, $Pb^{2+}$, $Bi^{3+}$, and $Sb^{3+}$.

## 5. Properties of Metallo-Complexes

*Lieser* determined the stability constants of argento-halogen complexes [82] in aqueous solution; these increase with the size of the central atom. However, it is not known to what extent the tendency of metal ligands towards coordination in solution is satisfied by the associated water molecules. The roles of the central atom and the ligand can be interchanged in competitive reactions, so that complexes with cationic central atoms are formed. Thus, for example, all argento-complexes decompose upon contact with molecules containing nitrogen, *e.g.* ammonia or acetonitrile, the corresponding silver complex being formed immediately.

The metallo-complexes are predominantly polynuclear complexes. The most notable of their reactions are those in which the complex ion remains stable and the compounds assume ion-exchanger characteristics. Thus, *Lieser* was able to exchange nitrate ions in $[IAg_3]\ [NO_3]_2$ for hydroxide or chloride ions. *Weiss* et al. displaced alkali ions from $K[NHg(SO_3)]$ with tetraalkylammonium ions. Similarly, $[S_2Hg_3]Cl_2$ reacts with dilute nitric acid to yield $[S_2Hg_3]\ [NO_3]_2$ [40], and almost any desired group can be built into the framework of the $[CHg_3O]^+$ ion.

These chemical properties show clearly how reasonable it is to single out structural groups from lattices, even when the former occur as "infinitely" extended components of a complex compound.

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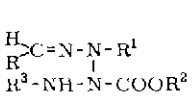
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## The Structure of the "Tetrazanes" Produced from Alkoxycarbonylazo Compounds and Aldehyde Phenylhydrazones

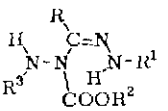
By Priv.-Doz. Dr. E. Fahr and Dipl.-Chem. H.-D. Rupp [1]

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The reaction of azodiformates ROOC-N=N-COOR or ethyl phenylazoformate with aldehyde phenylhydrazones gives 1:1 adducts for which 1-alkylidene-2-phenyltetrazane structures *(1)* [2] and hydrazidine structures *(2)* [3] have been proposed. We have shown by ultraviolet, infrared, and $^1$H-NMR spectroscopy and by synthesis of the previously unknown hydrazidines *(2)*, $R^3$ = $COOR^2$ or $C_6H_5$, that the adducts actually possess 1-azo-1-hydrazinoalkane structures *(3)*, $R^3$ = $COOR^2$ or $C_6H_5$.

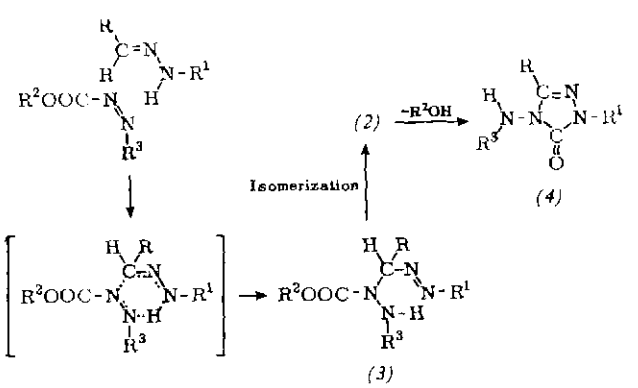


*(1)*



*(2)*

The adducts give a band at ca. 400 mμ which can be assigned to the n-π* transition of the azo group of *(3)* but to no part of the tetrazane or hydrazidine structures *(1)* or *(2)* (Table). The molecular extinction of this band for each adduct corresponds to those of other azo compounds and, with increasing dielectric constant of the solvent, the band is shifted to shorter wavelengths as expected for an n-π* transition. In agreement with structure *(3)*, the infrared spectra show only one N–H band. The $^1$H–NMR spectra of compounds *(3a)* and *(3g)* show signals at τ = 3.17 and 3.19 ppm, respectively, corresponding to the α-benzyl proton of *(3)*. Hydrogenation of *(3a)* with diimine, which can attack the N=N bond of *(3)* but not the C=N bond of *(2)* or the N–N bond of *(1)* [4], gives benzaldehyde phenylhydrazone and *N,N'*-bisethoxycarbonylhydrazine; this confirms structure *(3)*.




The 1-azo-1-hydrazinoalkanes *(3)*, $R^3$ = $COOR^2$ or $C_6H_5$, can be isomerized to the corresponding hydrazidines *(2)*, $R^3$ = $COOR^2$ or $C_6H_5$, by dissolution in a small amount of pyridine at room temperature. After a few minutes, the base is evaporated *in vacuo*, and the residual oil is induced to crystallize by scratching under ligroin. The hydrazidines *(2)* are unstable and, when heated in solution or treated with acid or alkali, they lose alcohol to give dihydrotriazole derivatives *(4)* [3]. The structures of the hydrazidines *(2)* were proved by their elementary analyses, molecular weights, and infrared spectra, which show the two N–H bands required by *(2)* (Table).

| | R | $R^1$ | $R^2$ | $R^3$ | *(3)* $\lambda_{max}$ [mμ] | *(3)* ε [a] | *(2)* Fp [°C] | *(2)* N–H Bands [μ] [d] |
|---|---|---|---|---|---|---|---|---|
| a | $C_6H_5$ | $C_6H_5$ | $C_2H_5$ | $CO_2C_2H_5$ | 403 | 187 | 149 | 2.95 3.07 |
| b | $C_6H_5$ | $C_6H_5$ | $C_2H_5$ | $C_6H_5$ | 406 | 194 | 116–118 | 2.97 3.02 |
| c | $CH_3$ | $C_6H_5$ | $C_2H_5$ | $CO_2C_2H_5$ | 404 | 159 | [e] | |
| d | o-HO–$C_6H_4$ | $C_6H_5$ | $C_2H_5$ | $CO_2C_2H_5$ | 400 | 184 | 165 | 2.94 3.07 |
| e | $CH_3$ | $C_6H_5$ | $C_2H_5$ | $C_6H_5$ | 406 | 154 | [e] | |
| f | $C_6H_5$ | m-$CH_3$–$C_6H_4$ | $C_2H_5$ | $CO_2C_2H_5$ | 405 | 192 | 135 | 2.95 3.07 |
| g | o-$NO_2$–$C_6H_4$ | $C_6H_5$ | $C_2H_5$ | $CO_2C_2H_5$ | [b] | | 141 | 2.95 3.07 |
| h | m-$NO_2$–$C_6H_4$ | $C_6H_5$ | $C_2H_5$ | $CO_2C_2H_5$ | [c] | | 176 [f] | 2.95 3.07 |
| i | $C_6H_5$ | $C_6H_5$ | $CH_2$–$C_6H_5$ | $CO_2CH_2$–$C_6H_5$ | 405 | 192 | 103 | 2.95 3.06 |

[a] In methanol. — [b] Shoulder. — [c] The substance isomerized so rapidly in solution that its ultraviolet spectrum could not be determined accurately. — [d] In $CCl_4$. — [e] The hydrazidine could not be prepared. On isomerizing the azo hydrazino compound we obtained the dihydrotriazole derivative. — [f] *M. Busch* et al. [2] prepared this product in an impure state by fusing a mixture of the components; they described it as a tetrazane.

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German version: Angew. Chem. 76, 684 (1964)

[1] *H.-D. Rupp*, Part of Ph. D.Thesis, Universität Würzburg, 1964.

[2] *M. Busch, H. Müller*, and *E. Schwarz*, Ber. dtsch. chem. Ges. *56*, 1600 (1923).

[3] *B.T. Gillis* and *F. A. Daniher*, J. org. Chemistry *27*, 4001 (1962).

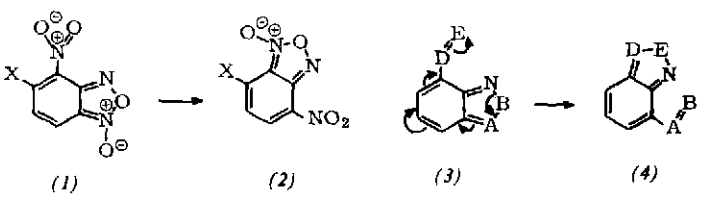
[4] Cf. review by *S. Hünig, H. R. Müller*, and *W. Thier*, Angew. Chem. *77* (1965) and Angew. Chem. internat. Edit. *4* (1965), in the press.

## A General Rearrangement of Heterocycles, and Novel Syntheses of the Benzotriazole, Benzofurazan, and Anthranil Systems [1]

By Dr. A. J. Boulton, P. B. Ghosh, and Prof. Dr. A. R. Katritzky [2]

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The ease of isomerization [*(1)* → *(2)*] of 4-nitrobenzofuroxans [3] led us to postulate the reaction *(3)* → *(4)* as a new general rearrangement of heterocyclic compounds; A and D

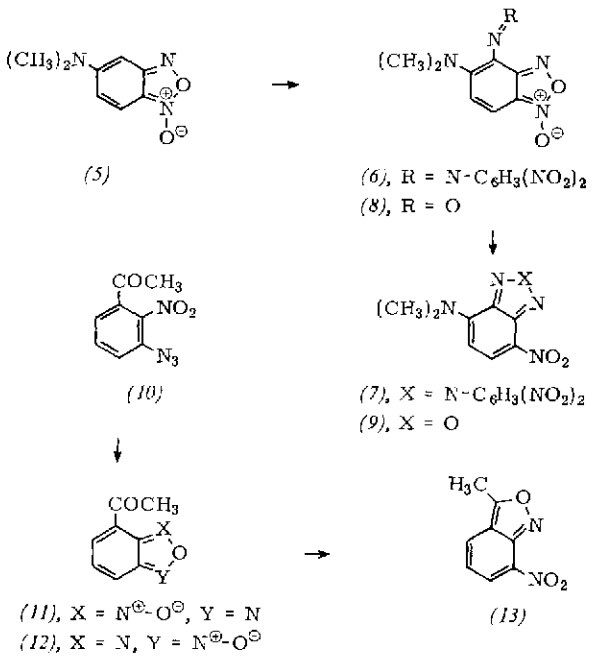


*(1)* *(2)* *(3)* *(4)*

may represent N, $N^{\oplus}$–$O^{\ominus}$, or CR, and B and E may represent O, NR, or CHR. The number of possible combinations is large. Here we wish to report three examples, which simultaneously constitute novel syntheses of the benzotriazole, benzofurazan, and anthranil systems.

5-Dimethylaminobenzofuroxan *(5)*, m.p. 123–124 °C, was prepared from 3,4-dinitro-*N,N*-dimethylaniline by replace-

ment of the 3-nitro group by an amino group, followed by diazotization of the latter, treatment of the diazonium salt with $NaN_3$, and thermal decomposition of the 3-azido-4-nitro-*N*,*N*-dimethylaniline, m.p. 82–83 °C (decomp.), produced. The dimethylamino compound *(5)* reacted with



*(5)*

*(6)*, R = N-C$_6$H$_3$(NO$_2$)$_2$
*(8)*, R = O

*(7)*, X = N-C$_6$H$_3$(NO$_2$)$_2$
*(9)*, X = O

*(10)*

*(11)*, X = $N^{\oplus}$-$O^{\ominus}$, Y = N
*(12)*, X = N, Y = $N^{\oplus}$-$O^{\ominus}$

*(13)*

either 2,4-dinitrobenzenediazonium sulfate or nitrous acid in $H_2SO_4/H_2O/C_2H_5OH$ (1:3:20 v/v) at 15–20 °C, but in each case the initial reaction products *(6)* and *(8)* rearranged spontaneously to yield the benzotriazole *(7)*, m.p. 287 °C (decomp.), or the benzofurazan *(9)*, m.p. 215–216 °C, respectively, as shown by infrared and NMR spectroscopy and by chemical evidence.

Heating of the azide *(10)*, m.p. 140–141 °C (decomp.), which was prepared from the corresponding amino derivative, did not give rise to the benzofuroxan [*(11)* ⇌ *(12)*] but instead to a 60 % yield of the anthranil *(13)*, m.p. 165–166 °C, as shown by the infrared spectrum.

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German version: Angew. Chem. *76*, 816 (1964)
Publication deferred until now at the authors' request

[1] Heterocyclic Rearrangements, Part 3. – The publications [2a] and J. chem. Soc. (London) *1961*, 2083 are considered as Parts 2 and 1, respectively.

[2] We wish to thank the Department of Scientific and Industrial Research for a Research Studentship (to P.B.G.) and Lederle Laboratories and the American Cyanamid Co. for financial support.

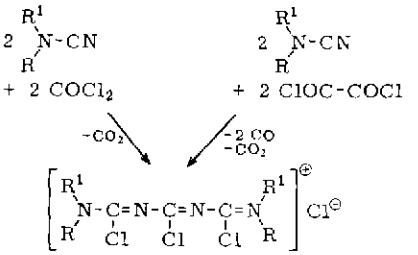
[3] *A. J. Boulton* and *A. R. Katritzky* [a] Proc. chem. Soc. (London) *1962*, 257; [b] Revue de Chimie (Roumania) *7*, 691 (1962).

## Interaction of Disubstituted Cyanamides with Phosgene and Oxalyl Chloride

By Dr. K. Bredereck and Dipl.-Chem. R. Richter

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It is known that acyl chlorides, *e.g.* benzoyl chloride, add on readily to molecular compounds of nitriles and electrophilic metal chlorides to form *N*-acylnitrilium salts [1]. We have found that phosgene reacts particularly readily without catalysis by metal chlorides with disubstituted cyanamides, *i.e.* with nitriles whose cyano group is joined to electron-donating groups. Surprisingly, however, the phosgene does not add onto the cyano group; instead, the reaction proceeds with elimination of carbon dioxide, yielding very reactive compounds which, judging from their properties, elementary analysis, and reactions, are assumed to have the structure *(1)*. The same products are formed when oxalyl chloride is used instead of phosgene.



*(1a)*, R = R$^1$ = CH$_3$
*(1b)*, R + R$^1$ = -(CH$_2$)$_5$-
*(1c)*, R + R$^1$ = -(CH$_2$)$_2$-O-(CH$_2$)$_2$-

The products *(1)* react with amines to yield triazine derivatives. Thus, (5-dimethylamino-1,3,5-trichloro-2,4-diazapenta-2,4-dien-1-ylidene)dimethylammonium chloride *(1a)*, m.p. 125 °C, is converted by ammonia in chloroform under mild conditions into 2,4-dimethylamino-6-chloro-1,3,5-triazine [2]. The action of aqueous ammonia on *(1a)* yields 2-amino-4,6-dimethylamino-1,3,5-triazine [3].

In order to prepare *(1)*, equimolar proportions of the components are kept in an indifferent solvent at room temperature for 20 h. In ether or benzene, the products *(1)* separate out as crystals or oils. In chloroform or methylene chloride, the products remain in solution and are obtained by concentration. The yields exceed 90 %.

Other acyl chlorides also yield definite reaction products; the study of their reactions is in progress.

Received, July 14th, 1964 [Z 784/608 IE]
German version: Angew. Chem. *76*, 714 (1964)

[1] *H. Meerwein, P. Laasch, R. Mersch*, and *J. Spille*, Chem. Ber. *89*, 209 (1956).

[2] *W. Pearlman* and *C. Banks*, J. Amer. chem. Soc. *70*, 3726 (1948).

[3] *W. Zerweck* and *K. Keller*, U.S.-Pat. 2228161 (1941).

## Solvent Effects on the Position of the First Overtone of the O–H Valence Vibration

By Dr. G. Habermehl

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We reported recently on the use of the first overtone of the O–H valence band to distinguish between primary, secondary, and tertiary alcohols [1]. The values measured in $CCl_4$ were 7090–7115 cm$^{-1}$ for primary alcohols, 7067 to 7078 cm$^{-1}$ for secondary alcohols, and 7042–7053 cm$^{-1}$ for tertiary alcohols.

It can be seen from the Table that these three groups are just as sharply separated in the non-polar solvent n-hexane. Also, in all the other solvents so far examined the frequency of the first overtone for primary alcohols is always greater than that for secondary, and this in turn is greater than that for tertiary alcohols, although the frequency regions sometimes overlap. Apart from n-hexane and $CCl_4$ triethylamine, acetone, and acetonitrile are suitable solvents for the differentiation of primary, secondary, and tertiary alcohols.

The dielectric constant of the solvent has no influence on the position of the first overtone of the O–H band. In polar solvents and those with π-electron systems, the band lies at lower frequencies than in n-hexane and $CCl_4$. This shift is due to the formation of hydrogen bonds. The amount of shift is a measure of the length of the hydrogen bond [2].

| Solvent | DK | Band position for primary, secondary, tertiary alcohols [a] |
|---|---|---|
| n-Hexane | 1.88 | 7109—7135<br>7089 7096<br>7046—7073 |
| Cyclooctatetraene | 1.94 | 7048—7070<br>7039—7048<br>7026—7043 |
| Carbon tetrachloride | 2.22 | 7090—7115<br>7067—7078<br>7042—7053 |
| Benzene | 2.28 | 7061—7067<br>7031—7047<br>7011—7039 |
| Furan | 2.95 | 7064—7083<br>7035—7055<br>7015—7041 |
| Triethylamine | 3.20 | 7092—7112<br>7085—7094<br>7045—7071 |
| Chloroform | 4.84 | 7066—7091<br>7043—7060<br>7026—7047 |
| Acetone | 21.45 | 7077—7099<br>7022—7080<br>6890—6930 |
| Nitrobenzene | 36.45 | 7032—7072<br>7023—7039<br>7016—7031 |
| Acetonitrile | 38.80 | 7076—7099<br>7021—7028<br>6957—6989 |

[a] *Primary alcohols*: methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, isoamyl alcohol, *N*-methylaminoethanol, 2-amino-2-methyl-propanol.

*Secondary alcohols*: 2-propanol, 2-butanol, cyclohexanol, 1-amino-propan-2-ol, sedamine, samandarine, cholesterol.

*Tertiary alcohols*: trimethylmethanol, triphenylmethanol, 1-phenylcyclohexanol, ethylmethylphenylmethanol, dimethylethylmethanol.

Received, July 15th, 1964 [Z 787/624 IE]
German version: Angew. Chem. 76, 715 (1964)

[1] *G. Habermehl*, Angew. Chem. *76*, 271 (1964); Angew. Chem. internat. Edit. *3*, 309 (1964).

[2] *H. E. Hallam* in *M. Davies:* Infrared Spectroscopy and Molecular Structure. Elsevier, Amsterdam 1963, p. 413.

## The Preparation of 3-Hexen-2-one from 1-Methoxybut-1-en-3-one

By Prof. Dr. W. K. R. Franke and Dr. W. Ring

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The interaction of acetoacetaldehyde dimethylacetal *(1)* and ethylmagnesium bromide and subsequent alkaline hydrolysis affords 1,1-dimethoxy-3-methylpentan-3-ol *(2)*, b.p. 93 °C/20 mm, $n_D^{20} = 1.4270$. On successive treatment of *(1)* with triethylaluminum in benzene and alkali one obtains, in addition to *(2)*, ethylene and 1,1-dimethoxybutan-3-ol *(3)* (b.p. 84 °C/20 mm, $n_D^{20} = 1.4196$). Compounds *(2)* and *(3)* are formed in the approximate ratio 1:3, irrespective of the reaction temperature. Yields decrease with increasing temperature, because of the formation of products of higher molecular weight: 0–10 °C: 13 % *(2)*, 43.6 % *(3)*; 15–20 °C: 8.9 % *(2)*, 34.4 % *(3)*, 35 °C: 10.3 % *(2)*, 29.3 % *(3)* [1].

Triisobutylaluminum reacts with *(1)* producing isobutene and *(3)* [56 % yield at 35–40 °C]. A product corresponding to *(2)* was not identified, its formation being probably prevented by steric factors.

The interaction of 1-methoxybut-1-en-3-one *(4)* with triethylaluminum at 0–5 °C produces 21.4 % *trans*-3-hexen-2-one (b.p. 55.5 °C/28 mm, $n_D^{20} = 1.4391$). Thus, methoxybutenone behaves only partially as a vinylogous carboxylic ester: the methoxy group is replaced by alkyl, but the carbonyl group remains largely intact. The reaction mixture contains only about 4 % of unsaturated alcohols free of methoxy groups. There are also formed compounds of higher molecular weight that have so far not been identified (distillation: residue: 52 %).

In all cases, only one of the three alkyl groups of the organoaluminum compound reacted with *(1)* or *(4)*, in agreement with previous observations by *K. Ziegler* [2].

Received, July 20th, 1964 [Z 807/635 IE]
German version: Angew. Chem. 76, 817 (1964)

[1] Because of the solubility in water of the dimethoxy alcohols, we were unable to isolate compounds *(2)* and *(3)* completely by ether-extraction of the strongly basified reaction mixture.

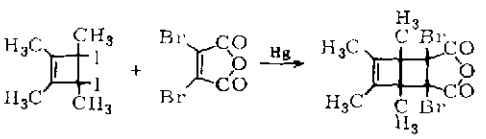
[2] *K. Ziegler, K. Schneider*, and *J. Schneider*, Liebigs Ann. Chem. *623*, 9 (1959).

## A Crystalline Derivative of "Dewar Benzene"

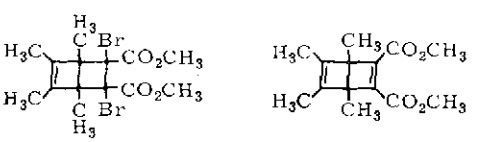
By Prof. Dr. R. Criegee and Dipl.-Chem. F. Zanker

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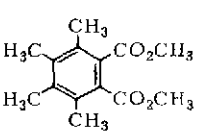
A solution in ether of 3,4-diiodotetramethylcyclobutene *(1)* [1] and dibromomaleic anhydride *(2)* was stirred with mercury for 48 h, under nitrogen and afforded 67 % of the tricyclic anhydride *(3)*, which was converted into the dimethyl ester *(4)*, m.p. 104 °C. Elimination of bromine from *(4)* was achieved with the copper-zinc couple in boiling ether. The halogen-free dimethyl "Dewar tetramethylphthalate" *(5)*, m.p. 32–33 °C, was obtained in 92 % yield; decagram quantities are easy to prepare. The NMR spectrum [*] of *(5)* in *o*-dichlorobenzene contains three sharp singlets of equal areas with τ-values of 9.06 (bridgehead methyl groups), 8.72 (methyl groups at the double bond), and 6.64 (ester methyl groups). On heating at 130 °C, *(5)* is rapidly and quantitatively converted into dimethyl tetramethylphthalate *(6)* [3], m.p. 127 °C (NMR spectrum in *o*-dichlorobenzene:



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



*(4)* *(5)*



*(6)*

3 singlets of equal areas at τ-values of 8.26, 8.08, and 6.06) According to NMR measurements, the half-life of *(5)* in the valence-bond isomerization *(5)* → *(6)* in *o*-dichlorobenzene at 90.1 °C is 4.7 h. Compound *(5)* is thus considerably more stable than the unsubstituted "Dewar benzene" of *van Ta-*

*melen* and *Pappas* [4], which is stated to have a half-life of 48 h at 20 °C. The monoester of *(5)* was also prepared in pure form (m.p. 111–112 °C).

Received, July 20th, 1964 [Z 788/623 IE]
German version: Angew. Chem. 76, 716 (1964)

[*] We wish to thank Dr. *H. A. Brune* for the determination and discussion of the NMR spectra.

[1] Obtained from the diol [2] and hydrogen iodide; cf. also *R. Riemschneider* and *U. Becker*, Mh. Chem. *90*, 524 (1959).

[2] *R. Criegee* and *G. Louis*, Chem. Ber. *90*, 417 (1957).

[3] *R. Criegee* and *P. Ludwig*, Chem. Ber. *94*, 2038 (1961).

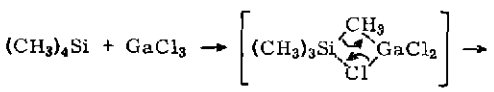
[4] *E. E. van Tamelen* and *S. P. Pappas*, J. Amer. chem. Soc. *85*, 3297 (1963).

## A Simple Route to Organogallium Compounds

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der Universität Marburg/Lahn (Germany)

Tetramethylsilane reacts, even at temperatures only slightly above room temperature, with anhydrous gallium trichloride to form trimethylchlorosilane and methylgallium dichloride:



$$(CH_3)_4Si + GaCl_3 \rightarrow \left[(CH_3)_3Si(CH_3)GaCl_2(Cl)\right] \rightarrow$$

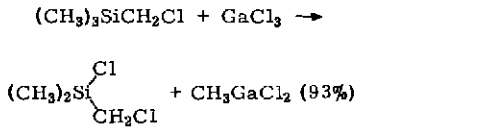
$$(CH_3)_3SiCl + CH_3GaCl_2$$

Simplicity and high yields (>90 %) make this reaction the best method for the preparation of organogallium dihalides. Similarly, triethylchlorosilane and ethylgallium dichloride are obtained from tetraethylsilane and $GaCl_3$.

*$CH_3GaCl_2$*
M.p. 75–76 °C [2, 3].
Sublimation temperature: 70 °C/1 mm.
Molecular weight: 314 (calc. for dimer: 311.34).
NMR: $\delta = -48.0$ c.p.s. [4].
IR [5]: 2881 cm$^{-1}$(m), 2870 cm$^{-1}$ (sh) [νCH];
1263 cm$^{-1}$(m), 1210 cm$^{-1}$ (w) [$\delta_s CH_3$];
837 cm$^{-1}$ (sh), 813 cm$^{-1}$ (sh), 751 cm$^{-1}$ (vst) [ρCH$_3$].

*$C_2H_5GaCl_2$*
M.p. 44 °C, b.p. 64 °C/1 mm.
Molecular weight: 346 (calc. for dimer: 339.39).
NMR: $A_3B_2$-multiplet with $\delta_{CH_3} = -79.0$ c.p.s., $\delta_{CH_2} = -82.3$ c.p.s., and $J_{HCCH}$ ca. 8.0 c.p.s. [4].
IR [5]: 2959 cm$^{-1}$(vst), 2915 cm$^{-1}$(sh), 2874 cm$^{-1}$(st) [νCH];
1462 cm$^{-1}$(st), 1418 cm$^{-1}$(m), 1383 cm$^{-1}$(m) [δCH$_3$, CH$_2$];
1205 cm$^{-1}$(m), 1012 cm$^{-1}$(vst), 966 cm$^{-1}$(m), 952 cm$^{-1}$(m) [νC–C, ρCH$_3$];
752 cm$^{-1}$(w), 669 cm$^{-1}$ (vst) [ρCH$_2$].

When electron-donating substituents are present on the carbon, the unsubstituted alkyl groups are preferentially transferred:



$$(CH_3)_3SiCH_2Cl + GaCl_3 \rightarrow$$

$$(CH_3)_2Si(Cl)(CH_2Cl) + CH_3GaCl_2 \ (93\%)$$

Similarly, gallium trichloride is completely converted to methylgallium dichloride (yield: 91 %) by tetramethylgermane under even milder conditions (<20 °C):

$$(CH_3)_4Ge + GaCl_3 \rightarrow (CH_3)_3GeCl + CH_3GaCl_2$$

Tetramethyltin undergoes a distinctly exothermic reaction with $GaCl_3$ at 0 °C; in this reaction, $(CH_3)_3SnCl$ and $CH_3GaCl_2$ are produced in the form of a coordination compound *(1)*:

$$(CH_3)_4Sn + GaCl_3 \rightarrow (CH_3)_3SnCl\text{-}CH_3GaCl_2 \quad (1)$$

This compound can also be synthesized from trimethylchlorostannane and methylgallium dichloride [1]. When *(1)* is distilled, the two components go over together, and the overall composition is displaced only slightly in favor of $CH_3GaCl_2$.

Indium trichloride does not react with tetramethylsilane even at 220 °C. Above 200 °C, tetramethylgermane yields a little $(CH_3)_3GeCl$. $CH_3InCl_2$ is no longer stable at these temperatures.

Received, July 28th, 1964 [Z 801/628 IE]
German version: Angew. Chem. 76, 752 (1964)
Translated by Express Translation Service, London

[1] Regarding complexes of $(CH_3)_3SnCl$ with aluminum halides, see *W. P. Neumann*, Angew. Chem. *75*, 225 (1963); Angew. Chem. internat. Edit. *2*, 165 (1963).

[2] Differing data (*G. E. Coates:* Organometallic Compounds. Methuen, London 1960) could not be confirmed.

[3] *C. A. Kraus* and *F. E. Toonder*, Proc. nat. Acad. Sci. U.S.A. *19*, 302 (1933).

[4] Varian A 60, 60 Mc/sec, $CCl_4$ solutions, 35 °C, tetramethylsilane as internal standard.

[5] Perkin-Elmer 221, melt of the pure substance. – sh = shoulder; vst = very strong; st = strong; m = medium.; w = weak.

## Cleavage of Siloxanes with Gallium Trichloride

By Priv.-Doz. Dr. H. Schmidbaur and
Dipl.-Chem. W. Findeiss

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Hexamethyldisiloxane is cleaved by boron and aluminum trihalides at the Si–O–Si bridge only. The products are trimethylhalogenosilane and trimethylsiloxyboron halide or trimethylsiloxyaluminum halide [1, 2]. On cleavage with gallium trichloride, alkylation of the gallium also occurs:

$$x\ (CH_3)_3SiOSi(CH_3)_3 + x\ GaCl_3 \rightarrow x\ (CH_3)_3SiCl + x\ CH_3GaCl_2 + [(CH_3)_2SiO]_x.$$

The yields of $CH_3GaCl_2$ are about 85 %.

Dimethylpolysiloxanes are also cleaved by $GaCl_3$ with simultaneous transalkylation

$$[(CH_3)_2SiO]_x + GaCl_3 \rightarrow CH_3GaCl_2 + [CH_3SiClO]_x,$$

in contrast to the reactions with $BCl_3$ and $AlCl_3$ [3, 4]. The yields of alkylgallium halide are again higher than 85 %, so that both reactions provide simple methods for the monoalkylation of gallium trihalides [5].

No di- or trialkylation of the gallium has so far been observed. $InCl_3$ does not react with siloxanes, even at temperatures far in excess of 200 °C.

Received, July 28th, 1964 [Z 802/632 IE]
German version: Angew. Chem. 76, 753 (1964)
Translated by Express Translation Service, London

[1] *E. Wiberg* and *V. Krüerke*, Z. Naturforsch. *8b*, 608 (1953); *J. Emeléus* and *M. Onyschuk*, J. chem. Soc. (London) *1958*, 604.

[2] *M. G. Voronkov*, *B. N. Dolgov*, and *A. N. Dimitrieva*, Dokl. Akad. Nauk SSSR *84*, 959 (1952); *N. F. Orlov*, ibid. *114*, 1033 (1957); *A. H. Cowley*, *F. S. Fairbrother*, and *N. Scott*, J. chem. Soc. (London) *1959*, 717; *H. Schmidbaur*, *H. Hussek*, and *F. Schindler*, Chem. Ber. *97*, 255 (1964); *M. Schmidt* and *H. Schmidbaur*, J. Amer. chem. Soc. *84*, 1069 (1962).

[3] *P. A. McCusker* and *Th. Ostdick*, J. Amer. chem. Soc. *80*, 1103 (1958); *81*, 5550 (1959).

[4] *K. A. Adrianov*, Russian chem. Rev. *1963* (5), 253; *H. Schmidbaur* and *W. Findeiss*, unpublished work.

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

## Double Silanolates of the Alkali Metals

By Priv.-Doz. Dr. H. Schmidbaur and Susanne Waldmann

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The alkali metal trimethylsilanolates $MOSi(CH_3)_3$, with M = Li, Na, K, Rb, or Cs, form a class of compounds with unusual properties and difficult structural relationships [1, 2]. We have now found that silanolates react with one another to form complex compounds having the composition $M^1\{M^2[OSi(CH_3)_3]_3\}$.

| | | M.p. [°C] | NMR [c.p.s.] [3] | | |
|---|---|---|---|---|---|
| | | | $\delta$ | $J(^1H-^{13}C)$ | $J(^1H-C-^{29}Si)$ |
| *(1)* | $Na\{Li[OSi(CH_3)_3]_2\}$ | 232–235 | − 2.75 | 116 | 6.45 |
| *(2)* | $K\{Li[OSi(CH_3)_3]_2\}$ | 258–260 | +3.20 | 115.5 | 6.35 |
| *(3)* | $K\{Na[OSi(CH_3)_3]_2\}$ | 235–237 | +3.00 | 114.5 | 6.40 |

Potassium trimethylsilanolate is only sparingly soluble in organic solvents [1, 2], but dissolves practically instantaneously in solutions of the lithium and sodium silanolates. Careful evaporation of the clear solutions leads to crystallization of the double silanolates *(2)* and *(3)*. Compound *(1)* crystallizes in the pure form from a solution of equimolar quantities of lithium and sodium trimethylsilanolates in carbon tetrachloride.

The structural identity of the two siloxy residues is shown by the fact that the NMR spectra of *(1)*, *(2)*, and *(3)* in $CCl_4$ show only one sharp signal accompanied by weak $^1H-^{13}C-$ and $^1H-C-^{29}Si$ satellites [2, 4].

All the important bands in the infrared spectra of the double silanolates differ markedly from those of the alkali metal silanolates. The spectroscopic results indicate that the siloxy oxygen atoms in the double silanolates are alternately coordinated to the different alkali metal atoms. Since the influence of the lighter alkali metal predominates, the compounds are formulated as $M^1\{M^2[OSi(CH_3)_3]_2\}$.

Received, July 28th, 1964 [Z 803/631 IE]
German version: Angew. Chem. *76*, 753 (1964)
Translated by Express Translation Service, London

[1] *W. S. Tatlock* and *E. G. Rochow*, J. org. Chemistry *17*, 1555 (1950).

[2] *H. Schmidbaur, J. A. Perez-Garcia*, and *H. S. Arnold*, Z. anorg. allg. Chem. *328*, 105 (1964). The m.p. of $NaOSi(CH_3)_3$ is 265–267 °C, contrary to earlier data.

[3] Varian A 60, 60 Mc/sec, $CCl_4$ solution, 35 °C, tetramethylsilane as internal standard.

[4] *H. Schmidbaur*, J. Amer. chem. Soc. *85*, 2336 (1963).

## Electrophilically Induced Cyclodimerization of Methylacetylene by Hydrogen Bromide [1]

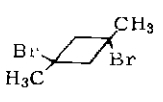
By Dr. K. Griesbaum

Central Basic Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey (U.S.A.)

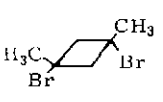
Contrary to a previous report [2] the reaction of hydrogen bromide with methylacetylene affords not only the classical diadduct 2,2-dibromopropane *(2)*, but at least four additional components in the indicated ratios [3].

$H_3C-CBr=CH_2$ *(1)*, 24%

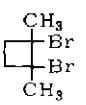
$H_3C-CBr_2-CH_3$ *(2)*, 34%



*(3)*, 32%



*(4)*, 9%



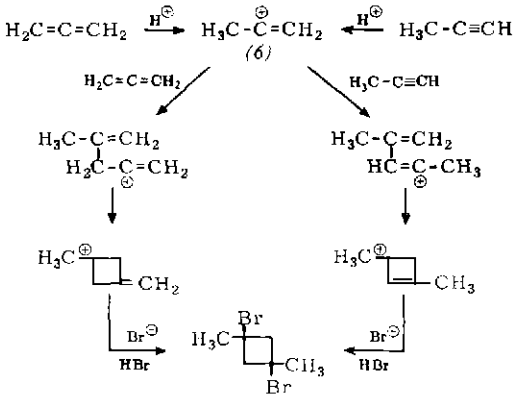
*(5)*, < 1%

Vacuum distillation of the crude adduct mixture afforded the conventional adducts *(1)* and *(2)*. The two cyclodimerization products *(3)* and *(4)* were isolated as a crystalline mixture from the distillation residue. Separation of this mixture by preparative gas chromatography yielded the pure compounds *(3)* and *(4)*.

Compound *(3)* was identified by comparison of its physical and spectral properties with those of an authentic sample [1].

The structure proof of *(4)*, m.p. 75–76 °C, is based on the following data: elemental analysis pointed to the empirical formula $(C_3H_5Br)_n$. The mass spectrum showed the characteristic 1:2:1 pattern (m/e = 240, 242, 244 respectively) of a dibromo compound [4] for the parent peak, thus establishing the formula $C_6H_{10}Br_2$. Neither the infrared nor the NMR spectrum of *(4)* contained any evidence for a double bond. The NMR spectrum exhibited a singlet signal at $\tau = 8.12$ with a relative intensity of 3 and a four-line pattern centered at $\tau = 6.81$ [5] with a relative intensity of 2.

Compound *(5)* could not be isolated pure. Combined gas-liquid chromatography and time-of-flight mass spectroscopy [6] showed, however, that the compound is a dibromide exhibiting the same molecular ion and fragment ions as *(3)* and *(4)*. It is assumed, therefore, that *(5)* may represent one of the isomeric 1,2-dibromo-1,2-dimethylcyclobutanes.




The results reported here demonstrate that the electrophilic addition of hydrogen bromide to methylacetylene cannot be exhaustively described by the classical theory of addition reactions. It seems that the particular nature of the vinylcarbonium ion intermediate *(6)* [7] may be the key in understanding the cyclodimerization reactions of both methylacetylene and allene [1].

Received, July 28th, 1964 [Z 808/603 IE]
German version: Angew. Chem. *76*, 782 (1964)

[1] Cyclobutane Compounds, Part II. – Part I: *K. Griesbaum*, J. Amer. chem. Soc. *86*, 2301 (1964).

[2] *M. S. Kharasch, J. G. McNab*, and *M. C. McNab*, J. Amer. chem. Soc. *57*, 2463 (1935).

[3] Percent by weight based on capillary gas chromatography. In some cases, substantial amounts of the isomeric 1-bromopropenes were also formed, apparently by concurring radical addition reactions. This complication could, however, be effectively suppressed by the addition of inhibitors to the reaction mixture.

[4] *J. H. Beynon:* Mass Spectrometry and Its Application to Organic Chemistry. Elsevier, Amsterdam 1960, p. 299.

[5] The midpoint of this quartet has the same position as the methylene singlet signal of the *trans*-compound *(3)*. This is an argument against the alternate possible structure of a 1,2-dibromo-1,2-dimethylcyclobutane for *(4)*. Since the methylene groups in such a 1,2-dibromo compound would be vicinal to only one bromine atom each, one would expect their signals at higher fields.

[6] *R. A. Brown* and *E. R. Quiram*, Appl. Spectroscopy *17*, 33 (1963).

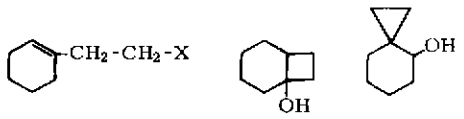
[7] *P. E. Peterson* and *J. E. Duddey* [J. Amer. chem. Soc. *85*, 2865 (1963)] pointed out recently that the nature and the chemistry of vinylcarbonium ions is rather ill-defined.

## The Preparation of Condensed Cyclobutane Derivatives and spiro-Cyclopropane Compounds by Homoallylic Rearrangement

By Doz. Dr. M. Hanack and Dipl.-Chem. H.-J. Schneider

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The easily accessible cyclohexenylethyl derivatives *(1)*, X = $NH_2$, OH, open up a simple route for the synthesis of the previously unknown spiro[2.5]octan-4-ol *(3)*, and of the bicyclo[4.2.0]octan-1-ol *(2)* [1] which could so far only be obtained with difficulty.



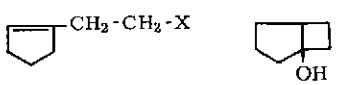
*(1)* *(2)* *(3)*

The primary homoallyl cation, formed from *(1)*, X = $NH_2$, by deamination, or from *(1)*, X = *p*-$O_3S$–$C_6H_4$–$CH_3$, by hydrolysis, rearranges to the more stable secondary cyclopropylmethyl and tertiary cyclobutyl cations [2].

When cyclohexenylethylamine *(1)* X = $NH_2$, [3] (prepared in 77 % yield by reduction of cyclohexenylacetonitrile with $LiAlH_4$) was treated with aqueous $HClO_4$ and $NaNO_2$ at pH 4 for 5hr. under nitrogen, a mixture of alcohols, containing 81 % of *(2)*, 12 % of *(1)*, X = OH, 3 % of *(3)*, and 4 % of an unidentified compound, was formed. Pure bicyclo[4.2.0]octan-1-ol *(2)* could be obtained in 30 % yield by fractional distillation. The melting points of the alcohol and its phenylurethane agree with those previously reported [1]. Its infrared and NMR spectra are in agreement with the structure given. Compound *(2)* is formed predominantly by rearrangement of the unstable spiro-alcohol *(3)*. If the deamination is carried out at 20 °C under potentiometric control at pH 6, *(3)* and *(2)* are formed in the ratio 70:30, together with other products. The spiro-alcohol *(3)* can be rearranged to *(2)* and *(1)*, X = OH, with toluenesulfonic acid at pH 5.

The pure spiro-alcohol *(3)* was prepared as follows: cyclohexenylethanol *(1)*, X = OH, [4] (obtained in 88 % yield by reduction of cyclohexenylacetic acid with $LiAlH_4$) was converted to the tosyl derivative which was then solvolysed at 85 °C for 10 days in acetone/water (20:80) with addition of $CaCO_3$. The reaction product contained 65 % of the alcohol *(3)*, 33 % of the alcohol *(2)* and 2 % of the alcohol *(1)*, X = OH. Pure *(3)* (b.p. 88–89 °C/20 mm, m.p. of the *p*-nitrobenzoate: 84.5–85.5 °C, 50 % yield) was obtained by distillation through a spinning-band column; its infrared and NMR spectra are in agreement with the structure given (singlet at $\tau$ = 7.92; multiplets at $\tau$ = 6.9, ca. 8.5, 7.6, and 9.9; ratio of peak areas 1:1:8:2:2).

Cyclopentenylethylamine *(4)*, X = $NH_2$, (prepared in 40 % yield by reduction of cyclopentenylacetonitrile with $LiAlH_4$ [5]) gave, on deamination in weak perchloric acid solution (pH 4, 4 hr., 50 °C), a mixture of alcohols which contained 65 % bicyclo[3.2.0]heptan-1-ol *(5)* and 6 % cyclopentenylethanol *(4)*, X = OH; three further components (29 %) were not identified.



*(4)* *(5)*

Compound *(5)* (m.p. 47–48 °C; m.p. of *p*-nitrobenzoate 117.5–118 °C) could be separated by preparative gas chromatography. Its infrared and NMR spectra are in agreement with the structure given (singlet at $\tau$ = 6.09; multiplets at $\tau$ = 7.7 and ca. 8.4; ratio of peak areas 1:1:10). As expected for a tertiary alcohol, *(5)* gives a chromate ester with $CrO_3$ in $CCl_4$.

Cyclopentenylethanol *(4)*, X = OH [6], (prepared in 84 % yield by reduction of ethyl cyclopentenylacetate with $LiAlH_4$) was converted to the β-naphthalenesulfonyl derivative *(4)*, X = $O_3S$–$C_{10}H_7$, which was hydrolysed in acetone/water as described above to give a mixture of alcohols containing 21 % of *(5)*, 68 % of *(4)*, X = OH, and 11 % of the same by-products as were produced on deamination.

Received, July 29th, 1964 [Z 804/626 IE]
German version: Angew. Chem. 76, 783 (1964)

[1] *A. C. Cope* and *R. W. Gleason*, J. Amer. chem. Soc. *84*, 1928 (1962), isolated the alcohol *(2)* in 1.3 % yield from the ozonolysis products of bicyclo[4.2.0]octane by preparative gas chromatography.

[2] Cf. *M. Hanack* and *H.-J. Schneider*, Tetrahedron *20*, 1863 (1964).

[3] Cf. *R. A. Benkeser, R. F. Lambert, P. W. Ryan*, and *D. G. Stoffey*, J. Amer. chem. Soc. *80*, 6573 (1958).

[4] *R. A. Benkeser, C. Arnold, R. F. Lambert*, and *O. H. Thomas*, J. Amer. chem. Soc. *77*, 6042 (1955).

[5] *M. Protiva, V. Mychoylyszyn*, and *J. O. Jilek*, Chem. Listy *49*, 1045 (1955).

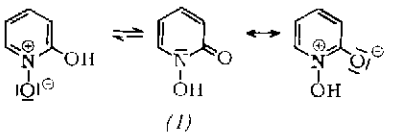
[6] *L. Toldy, T. Nógrády, L. Vargha, G. Ivánovics*, and *J. Koczka*, Acta chim. Acad. Sci. hung. *4*, 303 (1954).

## Water-Stable, Cationic Complexes of Silicic Acid with 1-Hydroxypyridine N-Oxide

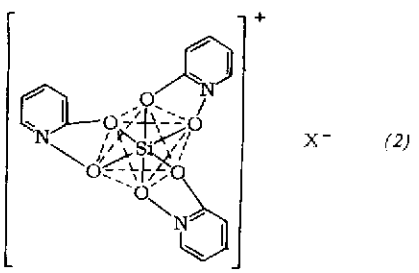
By Prof. Dr. Armin Weiss and Dr. D. R. Harvey

Institut für Anorganische Chemie
der Universität Heidelberg (Germany)

1-Hydroxypyridine *N*-oxide *(1)* [1] forms a cationic silicon complex *(2)* [2], which was characterized as its chloride, chloroferrate(III) and hexachlorostannate(IV).



*(1)*



*(2)*

| X | color | soluble in |
|---|---|---|
| Cl | white | $H_2O$, $C_2H_5OH$, $C_2H_2Cl_4$ |
| $[FeCl_4]$ | pale yellowish | $H_2O$, $C_2H_2Cl_4$ |
| $1/2\ [SnCl_6]$ | white | |

The chloroferrate(III) darkens above 220 °C without melting. In the case of the chlorostannate(IV) a change begins at 204–206 °C. The chloride appears macroscopically unchanged even at 300 °C, but X-ray studies show it to be amorphous.

Orthosilicic acid (<110 mg $SiO_2$/l) also can be smoothly converted into the cationic complex *(2)* at pH 6. Experiments with colloidal silicic acid showed that the complex forms faster than polysilicic acids are depolymerized.

When compared with the corresponding complexes formed by 1,3-diketones [2a], the addition compounds of silicon halides and pyridine *N*-oxide [3], or the silicon ester complex of 1-hydroxypyridine, the stability of the complex *(2)* in water appears striking. The chloride is recovered unchanged on evaporation of an aqueous solution. This stability prob-

ably depends on the fact that the positive charge in *(2)* can be distributed over several atoms. Comparison of the infrared spectra with those of anionic silicon-*o*-diphenol suggests an octahedral structure for the cation.

The complex *(2)* appears of interest in connection with the observation by *Schlipköter* [4], that polyvinylpyridine *N*-oxide in animal experiments inhibits significantly the formation of silicotic tissue after the application of the quartz. Model experiments have revealed no direct interaction between polyvinylpyridine *N*-oxide and silicon dioxide or the silicic acid dissolved from it. Therefore, a direct effect on the macrophages has recently been discussed [5].

However, if one assumes that pyridine *N*-oxide can be oxidized by the organism, then 1-hydroxypyridine *N*-oxide merits attention. Animal experiments with derivatives of 1-hydroxypyridine *N*-oxide and quartz are therefore desirable.

Received, August 3rd, 1964 [Z 797/625 IE]
German version: Angew. Chem. *76*, 818 (1964)

[1] *J. N. Gardner* and *A. R. Katritzky*, J. chem. Soc. (London) *1957*, 4375.

[2] For the sake of brevity only one of the mesomeric forms is given.

[2a] *W. Dilthey*, Ber. dtsch. chem. Ges. *36*, 923 (1906).

[3] *K. Issleib* and *H. Reinhold*, Z. anorg. allg. Chem. *314*, 113 (1962).

[4] *H. W. Schlipköter* and *A. Brockhaus*, Dtsch. med. Wschr. *85*, 920, 933 (1960); Klin. Wschr. *39*, 1182 (1961).

[5] *H. W. Schlipköter* and *A. Brockhaus* in: Fortschritte der Staublungenforschung. Verlag Niederrhein, Dinslaken 1963, p. 397; *H. Antweiler*, Beiträge zur Silikose-Forschung, Sonderband Grundfragen *5*, 153 (1963).

## Silicon Diiodide $[SiI_2]_x$

By Prof. Dr. M. Schmeisser and Dipl.-Chem. K. Friederich

Institut für Anorganische Chemie und Elektrochemie der Technischen Hochschule Aachen (Germany)

Following the preparation of $[SiBr_2]_x$ [1], $[SiCl_2]_x$ [2], and $[SiF_2]_x$ [3], the hitherto unknown $[SiI_2]_x$ [4,5] has now been synthesized by three routes:

1. When $SiI_4$ is passed over silicon in a high vacuum at 800 to 900 °C, a solid, brittle, amorphous, yellow-red substance of the composition $[SiI_2]_x$ is formed in about 1 % yield (based on $SiI_4$).

2. The pyrolysis of $SiI_4$ under the same conditions yields the same product, which is soluble in benzene and very sensitive to hydrolysis; it turns brown in dry air, with separation of iodine, and on heating with oxygen it burns to give $SiO_2$ and iodine vapor.

3. When $SiI_4$ vapor is subjected to a glow discharge in a high vacuum, a 60 to 70 % yield (based on $SiI_4$) of a solid, amorphous, yellow-red silicon subiodide of the composition $[SiI_{2.2}]_x$, which is insoluble in all common solvents, is obtained in quantities of 60 to 90 g per experiment.

$$x\ SiI_4 \rightarrow [SiI_{2.2}]_x + 0.9\ x\ I_2.$$

Pyrolysis of this substance at 220 to 230 °C in a high vacuum leads to the formation of a deep red $[SiI_2]_x$, together with $SiI_4$ and $Si_2I_6$.

The chemical properties of the compounds $[SiI_2]_x$ obtained in this manner are identical, with the exception of their solubilities in benzene.

Pyrolysis of $[SiI_2]_x$ at 350 °C in a high vacuum yields $SiI_4$, $Si_2I_6$, and an orange-red, brittle solid of the composition $[SiI]_x$. The compound $[SiI_2]_x$ reacts with chlorine or bromine at temperatures between −30 and +25 °C to form benzene-soluble, mixed silicon subhalides such as $[SiClI]_x$ and $[SiBrI]_x$. At higher temperatures, the Si–Si chains are cleaved by chlorine or bromine, with simultaneous complete displacement of the iodine. The products are compounds of the type $Si_nX_{2n+2}$ (n = 2–6 in the case of Cl, and 2–5 in the case of Br; X = Cl or Br). On reaction with iodine at 90 to 120 °C in a sealed tube, $[SiI_2]_x$ is completely converted to $SiI_4$ and $Si_2I_6$.

The compound $Si_2I_6$, which had formerly been difficult to prepare [5], is now available in any desired quantities by pyrolysis of $[SiI_{2.2}]_x$ or $[SiI_2]_x$ or by reaction of these compounds with iodine, and can be easily separated from $SiI_4$ by sublimation in a high vacuum.

Received, July 31st, 1964 [Z 799/637 IE]
German version: Angew. Chem. *76*, 782 (1964)
Translated by Express Translation Service, London

[1] *M. Schmeißer* and *M. Schwarzmann*, Z. Naturforsch. *11b*, 278 (1956).

[2] *M. Schmeißer* and *P. Voss*, Z. anorg. allg. Chem., in the press; *P. Voss*, Diploma Thesis, Technische Hochschule Aachen, 1961; Ph. D. Thesis, Technische Hochschule Aachen, 1962; *P. W. Schenk* and *H. Bloching*, Z. anorg. allg. Chem., in the press; *H. Bloching*, Ph. D. Thesis, Freie Universität Berlin, 1961.

[3] *M. Schmeißer* and *K.-P. Ehlers*, Angew. Chem. *76*, 781 (1964); Angew. Chem. internat. Edit. *3*, 700 (1964).

[4] *C. Friedel* and *A. Ladenburg*, Liebigs Ann. Chem. *203*, 244 (1880).

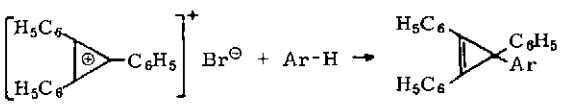
[5] *R. Schwarz* and *A. Pflugmacher*, Ber. dtsch. chem. Ges. *75*, 1062 (1942).

## The Synthesis of a Methylenecyclopropene Derivative

By Dr. B. Föhlisch and Dipl.-Chem. P. Bürgle

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Activated aromatic compounds may be *C*-alkylated by cyclopropenylium salts. Substituted tetraarylcyclopropenes *(2)* are produced when triphenylcyclopropenylium bromide *(1)* is heated in glacial acetic acid/pyridine (10:1) with dimethylaniline, anisole, di-*O*-methylresorcinol, 2-methoxynaphthalene, or anthrone.




*(1)* *(2)*

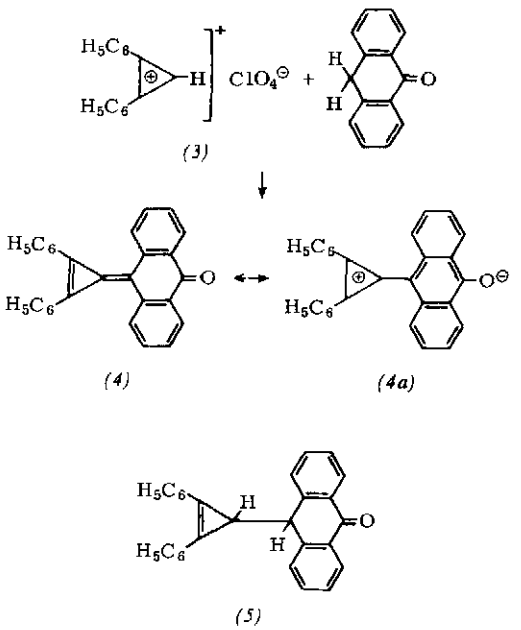
*(2a)*: Ar = *p*-dimethylaminophenyl, m.p. 189–190 °C
*(2b)*: Ar = *p*-methoxyphenyl, m.p. 124–126 °C
*(2c)*: Ar = 2,4-dimethoxyphenyl, m.p. 193 °C
*(2d)*: Ar = 2-methoxynaphthyl, m.p. 123–125 °C
*(2e)*: Ar = anthron-10-yl, m.p. 198–199.5 °C

The infrared spectra of *(2)* show the characteristic band at ca. 1800 $cm^{-1}$ assigned to the $\nu_{C=C}$-vibration of the cyclopropene ring.

Diphenylcyclopropenylium perchlorate *(3)* reacts with anthrone to give 10-(diphenylcyclopropenylidene)anthrone *(4)*, a thermally very stable derivative of methylenecyclopropene [1].

We believe that 10-(diphenylcyclopropenyl)anthrone *(5)*, formed initially from anthrone and *(3)*, is dehydrogenated with a further molecule of *(3)* to *(4)* *via* the cyclopropenylium ion. In agreement with this, the yield of *(4)* is considerably greater when 2 moles of *(3)* per mole of anthrone are used. Compound *(4)* is also obtained from bis(diphenylcyclopropenyl)ether and anthrone under the same conditions. It

gives yellow needles, m.p. 322–324 °C (from n-butanol), $\lambda_{max}$ (in chloroform): 242 mμ (log ε = 4.59), 275 (4.47), 315 (shoulder), 368 (shoulder); broad band with indistinct structure at 405 mμ (log ε = 4.10). It dissolves in conc. $H_2SO_4$ to give a carmine-red solution, $\lambda_{max}$ (in $H_2SO_4$): 251 mμ (log ε = 4.68), 287 (4.26), 379 (4.11), 432 (4.04),



(3) (4) (4a) (5)

540 (4.15). The zwitterionic structure *(4a)* contributes to the ground-state of *(4)* as the $\nu_{C=O}$-vibration occurs at 1639 $cm^{-1}$ (in chloroform), *i.e.* at a much lower wavelength than that of derivatives of 10-methyleneanthrone [2].

Received, August 5th, 1964 [Z 800/627 IE]
German version: Angew. Chem. 76, 784 (1964)

[1] Derivatives of methylenecyclopropene have been synthesized by: *A. S. Kende*, J. Amer. chem. Soc. *85*, 1882 (1963); *M. A. Battiste*, ibid. *86*, 944 (1964); *W. M. Jones* and *J. M. Denham*, ibid. *86*, 944 (1964).

[2] Compound *(2e)* absorbs at 1659 $cm^{-1}$, 10-cinnamylideneanthrone at 1653 $cm^{-1}$ (in chloroform).

## Silicon Difluoride $[SiF_2]_x$

By Prof. Dr. M. Schmeisser and Dr. K.-P. Ehlers

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Following the syntheses of $[SiBr_2]_x$ [1] and $[SiCl_2]_x$ [2], we turned our attention to $[SiF_2]_x$ which, by analogy to the disproportionation of the hexahalogenodisilanes to $SiX_2$ and $Si_nX_{2n+2}$ [3–5], should be obtainable as follows:

$$x\ Si_2F_6 \rightarrow [SiF_2]_x + x\ SiF_4$$

Preliminary experiments [6] have shown the feasibility of this reaction, but the analyses of the products were not unambiguous.

Gas chromatography showed that the $Si_2F_6$ prepared according to [7] by fluorination of $Si_2Cl_6$ with $ZnF_2$ was always contaminated with $SiCl_3F$ and $SiCl_4$, which could scarcely be separated from each other by distillation. Purification of $Si_2F_6$ was possible by preparative gas chromatography (identification by analysis and infrared spectroscopy). Fluorination of $Si_2Br_6$, instead of $Si_2Cl_6$, with $ZnF_2$ gave mixtures which could be separated by distillation.

Pyrolysis of pure $Si_2F_6$ at 700 °C in a high vacuum yielded $SiF_4$ together with $SiF_2$, which condenses out as a yellow solid in liquid air. Above −80 °C $SiF_2$ polymerizes to yield colorless $[SiF_2]_x$. Both products are extremely sensitive to moisture and oxygen.

The same products resulted from the reaction of $SiF_4$ with silicon at 1200 °C in a sealed silica tube, as has already been described in a patent application [8]. However, silicon difluoride obtained in this way contained oxygen (probably derived from the silica of the tube [Si:F:$H_A$:O = 1:1.75:1.75:032] whereas $[SiF_2]_x$ prepared from $Si_2F_6$ had Si:F:$H_A$ = 1:2.03:1.90 ($H_A$ = hydrogen evolved by alkali, in atoms of H/atom of Si).

Received, July 31st, 1964 [Z 798/636 IE]
German version: Angew. Chem. 76, 781 (1964)
Translated by Express Translation Service, London

[1] *M. Schmeißer* and *M. Schwarzmann*, Z. Naturforsch. *11b*, 278 (1956).

[2] *M. Schmeißer* and *P. Voss*, Z. anorg. allg. Chem., in the press; *P. Voss*, Diploma Thesis, Technische Hochschule Aachen, 1961; Ph.D. Thesis, Technische Hochschule Aachen, 1962; *P. W. Schenk* and *H. Bloching*, Z. anorg. allg. Chem., in the press; *H. Bloching*, Ph.D. Thesis, Freie Universität Berlin, 1961.

[3] *C. J. Wilkins*, J. chem. Soc. (London) *1953*, 3409.

[4] *G. Urry* and *A. Kaczmarcyk*, Angew. Chem. *72*, 387 (1960); J. Amer. chem. Soc. *82*, 751 (1960).

[5] *U. Wannagat* and *F. Vielberg*, unpublished work; *F. Vielberg*, Ph. D. Thesis, Technische Hochschule Aachen, 1956.

[6] *M. Schmeißer* and *J. Kreuder*, unpublished work; *J. Kreuder*, Ph.D. Thesis, Technische Hochschule Aachen, 1960.

[7] *W. C. Schumb* and *E. L. Gamble*, J. Amer. chem. Soc. *54*, 583 (1932).

[8] *D. C. Pease*, U.S.-Pat. 2840588 (E.I.Du Pont de Nemours and Co.) 1958; Chem. Abstr. *1958*, 19245c.

## Tris(trifluorophosphine)nitrosylcobalt and Bis(trifluorophosphine)dinitrosyliron [1]

By Dr. Th. Kruck and Dipl.-Chem. W. Lang

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A trifluorophosphine nitrosyl complex was first prepared by the reaction of nitrosylcobalt chloride with trifluorophosphine at 350 atm and 50 °C:

$$[Co(NO)_2Cl]_2 + 6\ PF_3 + 2\ Cu \rightarrow 2\ Co(NO)(PF_3)_3 + 2\ NO + 2\ CuCl$$

The compound, which is an analogue of nitrosylcarbonylcobalt, is a red-brown, light-sensitive, extremely volatile liquid, m.p. −92 °C, b.p. 81 °C/732 mm. It is fairly stable to moisture and oxidizing agents. Its intensely yellow vapors are almost odorless. Its decomposition point (163 °C) lies by more than 100 °C above that of $Co(NO)(CO)_3$. The infrared spectrum [2] of the diamagnetic compound contains ν(P–F) vibrations at 931, 900, 890, and 864 $cm^{-1}$ and an intense N–O valence vibration at 1844 $cm^{-1}$, which is by 22 $cm^{-1}$ below that of the isosteric nitrosylcarbonylcobalt.

With trifluorophosphine at 350 atm and 50 °C, dimeric nitrosyliron bromide yields volatile $Fe(NO)_2(PF_3)_2$, which – similar to the analogous nitrosylcarbonyliron – is a red-brown, diamagnetic liquid, decomposing at 118 °C. Its infrared spectrum contains two sharp ν(N–O) bands at 1838 and 1788 $cm^{-1}$ as well as three ν(P–F) bands at 907, 887, and 864 $cm^{-1}$.

We have indications that the manganese compound $Mn(NO)_3PF_3$ also exists, as would be expected from the nitrosyl displacement principle.

Received, August 6th, 1964 [Z 805/630 IE]
German version: Angew. Chem. 76, 787 (1964)

[1] Communication No. IV on Metal Trifluorophosphine Complexes. – Communication No. III: *Th. Kruck* and *A. Prasch*, Z. Naturforsch. *19b* (1964), in the press.

[2] Gas absorptions measured with the Perkin-Elmer Spectrophotometer, Model 21, NaCl-optics.

## Rhenium-Cobalt Enneacarbonyl

By Dr. Th. Kruck and Dipl.-Chem. M. Höfler

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der Technischen Hochschule München (Germany)

Binuclear mixed metal carbonyls $[L_n(CO)_{5-n}MM'(CO)_m]$, n=0, and their substitution products with *o*-phenanthroline ($L_2 = C_{12}H_8N_2$) [1] can be prepared by thermal decomposition of carbonyl salts such as $[M(CO)_{6-n}L_n]^+[M'(CO)_m]^-$ (M = Mn(I), Re(I); M' = Co(−I), Mn(−I); m = 4 or 5). The reaction is initiated by an intramolecular redox process. With the loss of one molecule of CO per molecule of carbonyl salt the two carbonyl radicals are linked by a metal-metal bond.

In addition to the compounds $MnCo(CO)_9$ [2] and $MnRe(CO)_{10}$ [3], which were already known and were also prepared by us [4] from the carbonyl salt $[Mn(CO)_6][Co(CO)_4]$ or by the reaction of $[Mn(CO)_6]Cl{\cdot}HCl$ with $Na[Re(CO)_5]$ and of $[Re(CO)_6]Cl{\cdot}HCl$ with $Na[Mn(CO)_5]$, respectively, rhenium-cobalt enneacarbonyl was now obtained:

$$[Re(CO)_6][Co(CO)_4] \xrightarrow{60\,^\circ C} (CO)_5ReCo(CO)_4 + CO$$

The diamagnetic compound sublimes at 40–50 °C/$10^{-3}$ mm yielding orange-brown, matted needles, m.p. 66 °C, decomposition point 148 °C. The infrared spectrum of the solution in $CCl_4$ contains three intense, sharp bands at 2064, 2035, and 1990 $cm^{-1}$, *i.e.* in the range for terminal CO groups; no bands characteristic for bridging CO groups were observed.

Dry heating of $[Re(CO)_4(C_{12}H_8N_2)][Co(CO)_4]$ produces the deep-red *o*-phenanthrolinetricarbonylrhenium-tetracarbonylcobalt. According to the reaction

$$[Re(CO)_4(C_{12}H_8N_2)][Co(CO)_4] \xrightarrow{90\,^\circ C} (C_{12}H_8N_2)(CO)_3ReCo(CO)_4 + CO$$

and to the infrared spectrum [$\nu_{C-O}$ = 2048(st), 2039(st-m), 2010(vst), 1931(vst), and 1892(vst) $cm^{-1}$] the bidentate ligand is associated with the rhenium, and a pure rhenium-cobalt bond exists. This structure is supported by a photoreaction in tetrahydrofuran which yields the yellow compound $[Re(CO)_3(C_{12}H_8N_2)]_2$.

Received, August 6th, 1964 [Z 806/629 IE]
German version: Angew. Chem. *76*, 786 (1964)

[1] See also *Th. Kruck* and *M. Höfler*, Chem. Ber. *97*, 2289 (1964).

[2] *K. K. Joshi* and *P. L. Pauson*, Z. Naturforsch. *17b*, 565 (1962).

[3] *A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova*, and *I. S. Kolomnokov*, Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk *1963*, 194.

[4] Soon to be reported in detail.

## A Stable Radical-Cation of a Hydrocarbon [1]

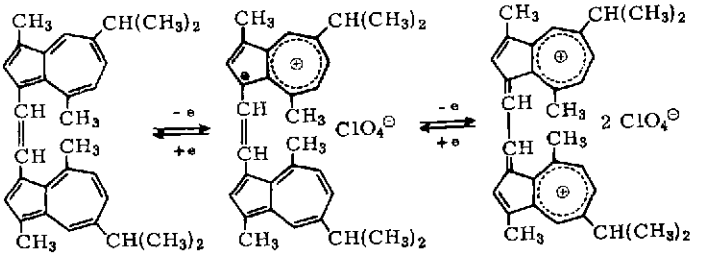
By Prof. Dr. S. Hünig, Dipl.-Chem. D. Scheutzow, and Dr. H. J. Friedrich

Chemisches Institut der Universität Würzburg (Germany)

Guaiazulene [1a], glyoxal, and perchloric acid in acetonitrile readily yield the diperchlorate *(1)* [2]; this is converted in hot methanol into a blue monoperchlorate from which perchloric acid in acetonitrile reforms the diperchlorate *(1)*. *Kirby* and *Reid* [2] considered an acid-base reaction and ascribed an allene structure *(4)* to the monoperchlorate.

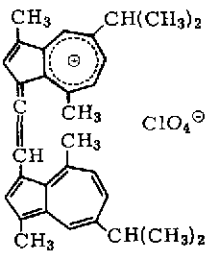
We have found, however, that methanol acts as a reducing agent. The blue monoperchlorate has structure *(2)* and appears to be the first stable radical-ion of a hydrocarbon.

A $2.5\times10^{-2}$ M solution of *(2)* in ethylene chloride/methylene chloride (1:9) shows, immediately on dissolution, a paramagnetic molecular susceptibility $\chi^{mol}_{para} = 1232\times10^{-6}$ and a paramagnetic moment $\mu$ = 1.70 B. M. [3]. This corresponds




*(3)* *(2)*, blue *(1)*, red

to a radical content of at least 95 %; in the concentrated solution this decreases rapidly and disappears within one day. In $10^{-5}$ M solution in methylene chloride, *(2)* is considerably more stable and shows characteristic absorption bands at 718 mμ (log ε = 4.85) and 995 mμ (log ε = 4.26).




*(4)*

Reduction of *(2)* by $NaBH_4$ gave a hydrocarbon – so far not completely pure – which might be formulated as *(3)*.

The action of one equivalent of *(3)* on *(1)* ($10^{-5}$ mole/l) in methylene chloride yields $1.6\times10^{-5}$ mole/l of *(2)*; coproportionation must therefore have occurred. The regeneration of *(1)* from *(2)* by perchloric acid in acetonitrile must therefore be regarded as a disproportionation, during which *(3)* is removed from the equilibrium by protonation.

Received, August 11th, 1964 [Z 810/634 IE]
German version: Angew. Chem. *76*, 818 (1964)

[1] Cf. *S. Hünig* et al., Liebigs Ann. Chem., in the press; Tetrahedron Letters *1964*, 181.

[1a] We thank Prof. *K. Hafner*, München (Germany), for a sample of azulene.

[2] *D. H. Reid* et al., J. chem. Soc. (London) *1963*, 1422; *1961*, 3580.

[3] Method: *H. J. Friedrich*, Z. Naturforsch. *19b*, 280 (1964); Angew. Chem. *76*, 496 (1964); Angew. Chem. internat. Edit. *3*, 440 (1964).

## The Preparation of Difluorodiazine and the Existence of Chlorofluorodiazine

By Dr. H. W. Roesky, Prof. Dr. O. Glemser, and cand. chem. D. Bormann

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The methods known for the preparation of difluorodiazine [1–5] are either not very productive or very dangerous.

We have found a simple, safe method for continuous preparation of large quantities of $N_2F_2$ (1–2 ml of *trans*-$N_2F_2$ per h). Technical sodium azide (98–99 % pure) is allowed to react at room temperature with elemental fluorine in a revolving-cylinder reactor made of nickel. The $N_3F$ formed as an intermediate is not isolated but is immediately decomposed by heating at 70–75 °C in a nickel spiral, so that the reaction proceeds without explosion via the biradical $\cdot\dot{N}F$ to $N_2F_2$:

$$2\,N_3F \rightarrow 2\,N_2 + 2\cdot\dot{N}F$$
$$2\cdot\dot{N}F \rightarrow N_2F_2$$

During the thermal decomposition of $N_3F$, excess fluorine must not be present, otherwise the $N_2F_2$ is fluorinated to $NF_3$. This is prevented by having a large excess of sodium azide in the reactor. Admixture of water vapor or preferably of hydrogen fluoride to the fluorine stream increases the yield of $N_2F_2$. The product is contaminated with $N_2O$ [6] and displays the characteristic infrared absorption band of *trans*-$N_2F_2$ at 995 $cm^{-1}$; after vacuum distillation the molecular weight was found to be 66.5 (calculated for $N_2F_2$: 66). When the nickel spiral is heated to about 85 °C, *cis*-$N_2F_2$ [7] occurs together with *trans*-$N_2F_2$ [8].

Sodium azide slightly dampened with water reacts with chlorine in the revo ·r g-cylinder reactor at room temperature to give chloroa de which is completely decomposed in the nickel spiral by heating at 110 °C. When fluorine is mixed with the chlorine stream ($Cl_2$: $F_2$ – 1:1) and the nickel spiral is heated to 120 °C, a gaseous product results which condenses in a trap cooled with liquid air to give a solid whose color is yellower than that of chloroazide. Purification was not possible since violent explosions occurred on condensation and distillation *in vacuo* of this material. The infrared spectrum of the gaseous product showed the bands of *cis*- and *trans*-$N_2F_2$ and $N_2O$, plus bands at 1540, 1060, and 670 $cm^{-1}$ which were attributed to $\nu_{N-F}$, $\nu_{N=N}$, and $\nu_{N-Cl}$ frequencies.

The existence of the new compound chlorofluorodiazine F–N=N–Cl is therefore probable.

Received, July 9th, 1964 [Z 778/618 IE]
German version: Angew. Chem. 76, 713 (1964)

[1] *J. F. Haller*, Ph.D. Thesis, Cornell University, Ithaca, N.Y. (USA), 1942.

[2] U.S.-Pat. 3109711 (June 15th, 1960); inventors: *E. A. Lawton* and *D. Pilipovich*.

[3] *C. B. Colburn, F. A. Johnson, A. Kennedy, K. McCallum, L. C. Metzger*, and *C. O. Parker*, J. Amer. chem. Soc. *81*, 6397 (1959).

[4] *M. Schmeisser* and *P. Sartori*, Angew. Chem. *71*, 523 (1959).

[5] *S. Morrow, P. D. Perry*, and *M. S. Cohen*, J. Amer. chem. Soc. *81*, 6338 (1959).

[6] If HF is mixed with the fluorine stream, the $N_2O$ content of the product is low.

[7] *R. L. Kuczkowski* and *E. B. Wilson*, J. chem. Physics *39*, 1030 (1963).

[8] *cis*-$N_2F_2$ also results on heating *trans*-$N_2F_2$. At 285 °C, for example, there is an equilibrium between 13 % *trans*- and 87 % *cis*-$N_2F_2$. At 300 °C $N_2F_2$ decomposes into $N_2$ and $F_2$ [3].

## The Synthesis of New Organoarsenic and Organophosphorus Amines

By Dr. O. J. Scherer and Prof. Dr. Max Schmidt

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der Universität Marburg/Lahn (Germany)

Dimethylchloroarsine *(1)* reacts with methylamine or *N,N'*-dimethylethylenediamine *(3)* in ether to form bis(dimethylarsino)methylamine *(2)* [b.p. 70–72 °C/14 mm, m.p. –34 °C],

$$2\,(CH_3)_2AsCl + 3\,CH_3NH_2 \quad (1)$$

$$\rightarrow (CH_3)_2As\text{-}\underset{\displaystyle CH_3}{N}\text{-}As(CH_3)_2 + 2\,CH_3NH_2\cdot HCl \quad (2)$$

$$2\,(1) + 2\,(3) \rightarrow (4) + (5)$$

(4): $(CH_3)_2As\text{-}\underset{\displaystyle CH_3}{N}\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle CH_3}{N}\text{-}As(CH_3)_2$

(5): $(H_3C\text{-}HN\text{-}CH_2\text{-})_2\cdot 2\,HCl$

and *N,N'*-bis(dimethylarsino)dimethylethylenediamine *(4)* [b.p. 94–96 °C/1 mm], respectively, with very good yields (80–90 %).

The As–N bond in *(2)* is very easily broken using methyllithium [1,2]:

$$(2) + LiCH_3 \rightarrow (CH_3)_2As\text{-}\underset{\displaystyle CH_3}{N}\text{-}Li + As(CH_3)_3 \quad (6)$$

The lithium (dimethylarsino)methylamide *(6)* formed is very reactive and is a useful starting material for further reactions; for example, with trimethylchlorosilane it produces dimethylarsino(trimethylsilyl)methylamine *(7)* [b.p. 66–68 °C/14 mm, m.p. –50 °C.].

$$(6) + (CH_3)_3SiCl \rightarrow (CH_3)_2As\text{-}\underset{\displaystyle CH_3}{N}\text{-}Si(CH_3)_3 + LiCl \quad (7)$$

Using *(3)* and phosphorus or arsenic trichlorides, one does not obtain the halogen analogues of *(4)*, but rather 2-chloro-1,3-dimethyl-1,3,2-diazophospholidine *(8)* [b.p. 98–100 °C/14 mm, m.p. 1–3 °C] and 2-chloro-1,3-dimethyl-1,3,2-diazoarsenolidine *(9)* [b.p. 103–105 °C/14 mm, m.p. 19–21 °C] The yields are about 50 %.

$$2\,(3) + MCl_3 \rightarrow (5) + Cl\text{-}M\langle \text{1,3-dimethyl-1,3,2-diazaheterolidine} \rangle \quad (8),\ M = P;\ (9),\ M = As$$

Received, August 11th, 1964 [Z 809/633 IE]
German version: Angew. Chem. 76, 787 (1964)

[1] *O. J. Scherer* and *M. Schmidt*, Angew. Chem. *76*, 144 (1964); Angew. Chem. internat. Edit. *3*, 137 (1964).

[2] *O. J. Scherer, J. F. Schmidt*, and *M. Schmidt*, Z. Naturforsch. *19b*, 447 (1964).

## Valence-Bond Isomerization of cis,trans-Cyclodeca-1,5-dienes

By Dr. P. Heimbach

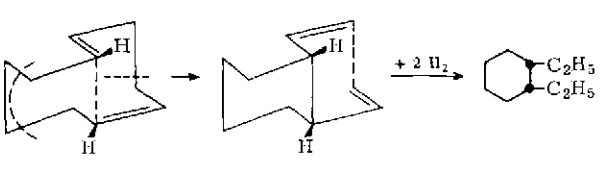
Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

*Cis,trans*-cyclodeca-1,5-diene *(1)* can be prepared in high yield from butadiene and ethylene, using new nickel-based π-complex catalysts [1]. The thermal rearrangement of *(1)* [1] (see Table 1) is stereospecific (>99.7 %), and yields *cis*-1,2-divinylcyclohexane *(2)*. The oxidative degradation of *(2)* leads exclusively to *cis*-hexahydrophthalic acid (m.p. 190 to 191 °C) in 55 % yield.

Table 1. Rearrangement of *cis,trans*-cyclodeca-1,5-diene *(1)*

| 60 °C [a] | | 80 °C [a] | | 120 °C [a] | | 150 °C [a] | |
|---|---|---|---|---|---|---|---|
| Time [h] | Yield [%] | Time [h] | Yield [%] | Time [h] | Yield [%] | Time [h] | Yield [%] |
| 170 | 3.3 | 3 | 7.3 | 1 | 12 | 0.25 | 38 |
| | | 20 | 15.8 | 6.9 | 56 | 1.25 | 88 |
| | | 170 | 63.3 | 47 | 99 | 5.25 | 99 |

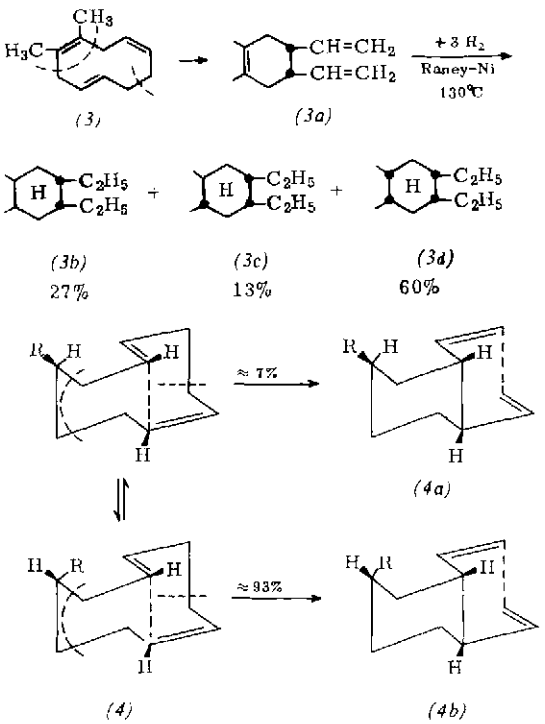
[a] Reaction temperature ± 2 °C.




(1) (2) (2a)

Acetylene, 2-butyne, and styrene also combine, like ethylene, with butadiene on catalysts such as those used for the synthesis of cycloocta-1,5-diene [1] to give mono- or disub-

stituted *cis,trans*-cyclodeca-1,5-dienes (or *cis,cis,trans*-cyclodeca-1,4,7-trienes) [3]. These ten-membered cyclic compounds, like *(1)*, show no tendency to thermal polymerization such as that exhibited by *cis,trans*-cycloocta-1,5-diene [2] or *cis,trans*-cyclonona-1,5-diene [4]; instead, like *(1)*, they are converted by heat, *via* a four-center arrangement [5] to mono- or di-substituted *cis*-1,2-divinylcyclohexanes (or *cis*-1,2-divinylcyclohexenes), *e.g.* *(3)* gives *(3a)*, while *(4)* gives *(4a)* and *(4b)*. Unsubstituted *(3)* is converted to unsubstituted *(3a)* which gives *(2a)* on hydrogenation.




The *cis*-form *(4b)* predominates, probably because it is thermodynamically more stable than the *trans*-form *(4a)*. *Trans*-1,2-divinylcyclohexanes (or *trans*-1,2-divinylcyclohexenes) are also formed to a small extent. These may arise from a six-center arrangement of *cis,trans*-cyclodeca-1,5-dienes, or from a four-center arrangement of the *trans,trans*-dienes [3], which are present in small quantities. Some of the physical properties of the compounds are shown in Table 2.

Table 2. Physical properties of the compounds *(1)*, *(2)*, *(2a)*, *(3a)*–*(3d)*, and *(4b)*.

| Compound | B.p. [°C/mm Hg] | $n_D^{20}$ |
|---|---|---|
| *(1)* | 38/2 | 1.4958 |
| *(2)* | 63/20 | 1.4704 |
| *(2a)* | 92.5/50 | 1.4479 |
| *(3a)* | 92/20 | 1.4869 |
| *(3b,c,d)* [a] | | 1.4520 |
| *(4b)* | 168/20 | 1.5368 |

[a] A definite assignment of the isomers is not yet possible but all evidence so far points to the assignment given.

Received, July 29th, 1964 [Z 815/650 IE]
German version: Angew. Chem. *76* 859 (1964)
Translated by Express Translation Service, London

[1] *G. Wilke* and *P. Heimbach*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

[2] *K. Ziegler* and *H. Wilms*, Liebigs Ann. Chem. *567*, 1 (1950).

[3] *G. Wilke* and *P. Heimbach*, unpublished work.

[4] *E. Vogel, W. Grimme*, and *E. Dinne*, Angew. Chem. *75*, 1103 (1963); Angew. Chem. internat. Edit. *2*, 739 (1963); Rearrangement of *cis,trans*-cyclonona-1,5-diene in *cis*-1,2-divinylcyclopentane.

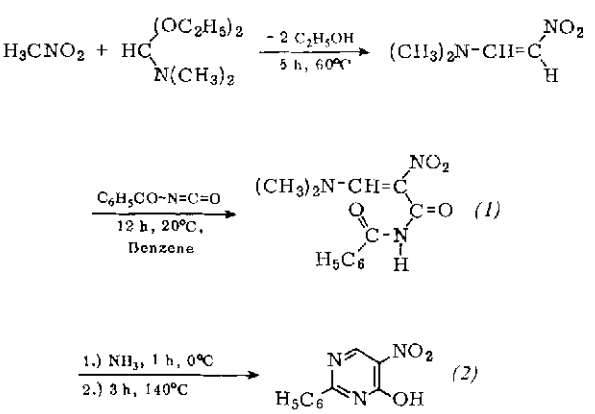
[5] *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962); Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963).

## Synthesis of 4-Hydroxy-5-nitropyrimidines

By Dr. G. Simchen

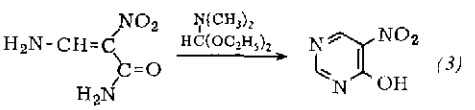
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5-Nitropyrimidines in which only the 4-position is substituted by a first-order substituent have until now not been obtainable by direct synthesis. We have succeeded in preparing 2-phenyl-4-hydroxy-5-nitropyrimidine *(2)*, starting from




nitromethane, by reacting the intermediate *N*-benzoyl-α-nitro-β-dimethylaminoacrylamide *(1)* with ammonia in dimethylformamide. The final yield of *(2)* (m.p. 278 °C) was 42 %, based on the nitromethane.

4-Hydroxy-5-nitropyrimidine *(3)* (m.p. 192 °C) was obtained in 20 % yield from α-nitro-β-aminoacrylamide by reaction with dimethylformamide diethyl acetal in ethanol at 50 °C.




The hydroxynitropyrimidines *(2)* and *(3)* can be used for the synthesis of condensed heterocyclic systems.

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## Preparation of Volatile Mixed Hydrides of Phosphorus, Arsenic, Nitrogen, and Germanium, and of Triphosphine and Triarsine

By Prof. Dr. P. Royen, Dipl.-Chem. C. Rocktäschel, and Dr. W. Mosch

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Acidic hydrolysis of phosphides, arsenides, nitrides, and germanides of magnesium and calcium yields phosphines, arsines, ammonia, and germane. Mixed hydrides are formed on hydrolysis of the corresponding solid solutions [1] (magnesium phosphide/magnesium arsenide, magnesium phosphide/magnesium nitride, or magnesium arsenide/magnesium nitride). Since the reaction has a radical mechanism, the formation of mixed hydrides of phosphorus, arsenic, nitrogen, and germanium also occurs in good yields even when compressed or tempered mixtures of the finely crystalline salts are hydrolysed.

The phosphides, arsenides, and germanides of calcium and magnesium were obtained from magnesium powder [99.85 % purity from Messrs. Schuchardt, München (Germany)] or

calcium turnings (99.5 % purity, from same source) and red phosphorus or resublimed arsenic or germanium (99.999 % purity, from Messrs. Schuchardt) in stoichiometric proportions by heating at 1100 °C for 24 h in evacuated quartz ampoules. Magnesium nitride and calcium nitride were produced by passing gaseous ammonia over magnesium or calcium turnings at 850 °C.

The starting materials were mixed in 1:1 molar ratios and compressed under a pressure of 10000 kg/cm² or sintered in evacuated quartz tubes at 1000 °C for 48 h.

The gases resulting from the hydrolysis were identified by mass spectroscopy [2]. In order to preclude decomposition of readily labile hydrides before their introduction into the spectrometer, the crystalline mixed phases were decomposed with 2 N HCl with cooling (0 °C) in an evacuated apparatus directly within the instrument. Apart from the known hydrides of phosphorus, arsenic, nitrogen, and germanium, the following products were obtained:

$P_3H_5$, $As_3H_5$, and $PH_2AsH_2$ from $Mg_3P_2/Mg_3As_2$;
$P_3H_5$, $PH_2NH_2$, $PH(NH_2)_2$, $P(NH_2)_3$, and $P_2H_3NH_2$ from $Mg_3P_2/Mg_3N_2$;
$As_3H_5$, $AsH_2NH_2$, $AsH(NH_2)_2$, and $As(NH_2)_3$ from $Mg_3As_2/Mg_3N_2$;
$P_3H_5$ and $GeH_3PH_2$ [3] from $CaGe/Ca_3P_2$,
$As_3H_5$ and $GeH_3AsH_2$ [3] from $CaGe/Ca_3As_2$;
$GeH_3NH_2$ and $GeH_2(NH_2)_2$ from $CaGe/Ca_3N_2$.

Received, July 29th, 1964 [Z 821/642 IE]
German version: Angew. Chem. 76, 860 (1964)

[1] *P. Royen* and *C. Rockstroh*, Angew. Chem. *76*, 302 (1964); Angew. Chem. internat. Edit. *3*, 314 (1964). The two mixed hydrides $Si_2GeH_8$ and $SiGe_2H_8$ described in this publication as "hitherto unknown" had actually been prepared previously by *C. S. G. Phillips, P. Powell, J. A. Semlyen*, and *P. L. Timms*, Z. analyt. Chem. *197*, 202 (1963) from an Mg/Si/Ge alloy and identified by gas chromatography. Cf. also *C. S. G. Phillips* and *P. L. Timms*, Analyt. Chem. *35*, 505 (1963); *P. L. Timms, C. C. Simpson*, and *C. S. G. Phillips*, J. chem. Soc. (London) *1964*, 279 1467.

[2] We wish to thank Dr. *W. Mosch* for carrying out the mass spectrographic investigations.

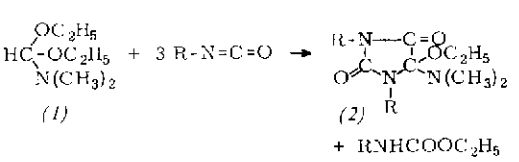
[3] *I. E. Drake* and *W. L. Jolly*, Chem. and Ind. *1962*, 1470. Here the compounds were prepared from Monogermane and phosphine or arsine by a silent electrical discharge.

## Reaction of Amide Acetals with Isocyanates. The Synthesis of Parabanic Acid O,N-Acetals

By Prof. Dr. H. Bredereck, Dr. G. Simchen and cand. chem. E. Göknel

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In the course of our investigations on the reaction of acetals of carboxamides with cumulative double-bond systems, we reacted dimethylformamide diethyl acetal *(1)* with isocyanates by heating a mixture of the components (molar ratio 1:1) at 100–130 °C for several hours. *O,N*-Acetals of 1,3-disubstituted parabanic acids [*(2a)*, m.p. 120 °C; *(2b)*, m.p. 93 °C] were obtained in 80 to 85 % yield, with elimination of ethanol (as urethane).



*(1)* + 3 R–N=C=O → *(2)* + $RNHCOOC_2H_5$

*(2a)*: R = $C_6H_5$; *(2b)*: R = $C_6H_{11}$

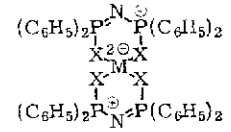
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## Imidodiphosphinatometal Chelates, Neutral Complexes with Carbon-Free Chelate Rings

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Only a few metal chelates are known in which the ring contains no carbon. In the course of our work on heterocycles containing P and N [1], we have prepared several compounds of a new type *(1)*. Here the donor functions X are bridged by $-(C_6H_5)_2P-N-P(C_6H_5)_2-$ groups.



| | X | M | Color | M.p. [°C] |
|---|---|---|---|---|
| *(1a)* | NH | Cu | blue | 178–180 (decomp.) |
| *(1b)* | O | Zn | colorless | 228–229.5 |
| *(1c)* | S | Ni | brown | 265–266 (decomp.) |
| *(1d)* | S | Cd | colorless | 309–311 (decomp.) |

A green precipitate separates from a methanolic solution of tetraphenylimidodiphosphinic diimide hydrochloride $N[(C_6H_5)_2PNH_2]_2Cl$ [2] and $CuCl_2 \cdot 2\,H_2O$ on treatment with sodium methoxide. Careful hydrolysis of this precipitate yields *(1a)*. Compound *(1b)* is formed from tetraphenylimidodiphosphinic acid $N[(C_6H_5)_2PO]_2H$ [3] and zinc dust in boiling benzonitrile. Compounds *(1c)* and *(1d)* are precipitated from a methanolic solution of $NiCl_2 \cdot 6\,H_2O$ or $CdCl_2 \cdot H_2O$ by potassium tetraphenyldithioimidodiphosphinate $KN[(C_6H_5)_2PS]_2$ [4].

The compounds are insoluble in water, and can be crystallized from polar organic solvents and benzene. According to osmometric and cryoscopic molecular-weight determinations, *(1a)* and *(1b)* are not associated. Further ligands, *e.g.* pyridine, can add onto *(1c)*.

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German version: Angew. Chem. 76, 860 (1964)
Translated by Express Translation Service, London

[1] Cf. *A. Schmidpeter, K. Düll*, and *R. Böhm*, Angew. Chem. *76*, 605 (1964).

[2] *I. I. Bezman* and *J. H. Smalley*, Chem. and Ind. *1960*, 839; *H. H. Sisler, H. S. Ahuja*, and *N. L. Smith*, Inorg. Chem. *1*, 84 (1962).

[3] *E. Fluck* and *F. L. Goldmann*, Chem. Ber. *96*, 3091 (1963).

[4] *A. Schmidpeter* and *H. Groeger*, unpublished work.

## Europium as an Alkaline Earth Metal

By Prof. Dr. W. Klemm, Dipl.-Chem. H. Kock, and W. Mühlpfordt

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According to their atomic volumes, europium and ytterbium do not fit into the series of the rare earth metals but resemble the alkaline-earth metals; their magnetic behavior also indicates that they contain the species $M^{2+}$, but not $M^{3+}$ [1]. The atomic volume of Eu lies between those of Ca and Sr, but closer to Ca; however, Eu does not crystallize in the face-centered cubic system like Ca and Sr, but in the body-centered cubic system like Ba.

*Behavior of europium towards calcium* [1a]: Extensive mixed crystal formation occurs in the system Ca/Eu. The lattices are face-centered from 0 to about 55 atom-% of Eu, and body-centered from about 60 to 100 atom-% of Eu. The miscibility gap for samples obtained by rapid cooling of the melt is only a few atoms percent. The variation of the lattice constants of the mixed crystals with a high Eu content roughly corresponds to that of Vegard's straight line for body-centered cubic Ca (stable only at high temperatures), the volume of which does not differ appreciably from that of face-centered cubic Ca. The face-centered mixed crystals with a high calcium content behave, as regards their lattice constants, as if the volume of Eu with a (hypothetical) face-centered crystal structure were a few percent more than the body-centered variety.

*Behavior towards magnesium* [1b]: Mg and Ca form an $Mg_2Ca$ phase, while in the system Mg/Sr, besides $Mg_2Sr$, the phase $Mg_{17}Sr_2$ and one or two phases in the range $Mg_5Sr$ $Mg_4Sr$ also occur [2]. The existence of MgSr is the subject of controversy [3]. We were able to detect the following phases by X-ray methods in the system Mg/Eu: $Mg_{17}Eu_2$ [4], one or two phases between $Mg_5Eu$ and $Mg_4Eu$, $Mg_2Eu$ [4], and MgEu (stable only below 500 °C). In this behavior, therefore, Eu resembles Sr, and not Ca. The lattice constants of $Mg_2Eu$ [$MgZn_2$-type (C 14), $D^4_{6h}$–$P6_3/mmc$; $a = 6.37_9$; $c = 10.30_8$ Å] lie between those of $Mg_2Ca$ [$a = 6.23$; $c = 10.12$ Å] and $Mg_2Sr$ [$a = 6.439$; $c = 10.494$ Å], and rather closer to the latter. The values for $Mg_{17}Eu_2$ [$Ni_{17}Th_2$-type, $D^4_{6h}$–$P6_3/mmc$; $a = 10.49$; $c = 10.33$ Å] and $Mg_{17}Sr_2$ [$a = 10.533$; $c = 10.341$ Å] are particularly similar. However, the lattice constant of MgEu [CsI-type (B 2), $O^1_h$–$Pm3m$; $a = 4.10_2$ Å] is not strictly compatible with the value given by *Nowotny* [3] for MgSr [$a = 3.908$ Å]. Whereas $Mg_{17}Eu_2$ is practically volume-additive, the formation of $Mg_2Eu$ and MgEu is accompanied by a pronounced contraction; the electronegativities of Sr and Eu must therefore be somewhat different [5]. Thus europium behaves towards magnesium as a typical alkaline earth metal, closely related to strontium. The extent to which the alloys mentioned contain the species $Eu^{2+}$ is being investigated [6].

The variation of the lattice constants in the case of the $MBe_{13}$ phases ($NaZn_{13}$-type, $O^6_h$–$Fm3c$; $EuBe_{13}$: $a = 10.300$ Å [7]; $CaBe_{13}$: $a = 10.312$ Å [8]; $SrBe_{13}$: $a = 10.470$ Å [9]) indicates that Eu occurs in the trivalent state. This will also be checked by magnetic measurements.

Received, August 24th, 1964 [Z 813/648 IE]
German version: Angew. Chem. 76, 862 (1964)
Translated by Express Translation Service, London

[1] *W. Klemm* and *H. Bommer*, Z. anorg. allg. Chem. *231*, 138 (1937).

[1a] Experiments by *H. Kock*, preliminary experiments by *R. de Medicis*.

[1b] Experiments by *W. Mühlpfordt*.

[2] *M. Hansen:* Constitution of Binary Alloys. 2nd Edition, McGraw-Hill, New York 1958. *J. V. Florio, N. C. Baenzinger*, and *R. E. Rundle*, Acta crystallogr. *9*, 367 (1956), assumed the phase $Mg_9Sr$–$Mg_{17}Sr_2$($Ni_{17}Th_2$-typ).

[3] *H. Nowotny*, Z. Metallkunde *34*, 247 (1942).

[4] Our conclusions regarding $Mg_{17}Eu_2$ = $Mg_2Eu$ were confirmed recently by synthesis of these substances by *P. I. Kripyakevich, E. I. Gladyshevskii, O. S. Zarechnyuk, V. I. Evdokimenko, I. I. Zalutskii*, and *D. P. Frankevich*, Soviet Physics Crystallogr. *8*, 477 (1964) (English translation).

[5] Cf. *G. Gnutzmann, F. W. Dorn*, and *W. Klemm*, Z. anorg. allg. Chem. *309*, 224 (1961).

[6] As found by *A. Landelli*, Z. anorg. allg. Chem. *330*, 230 (1964), Eu appears bivalent in $EuAl_2$, $EuGa_2$, $EuIn_2$, and $EuTl_2$, whereas $Yb^{3+}$, as well as $Yb^{2+}$, is present in $YbAl_2$.

[7] *E. I. Gladyshevskii, P. I. Kripyakevich*, and *D. P. Frankevich*, Soviet Physics Crystallogr. *8*, 628 (1964) (English translation).

[8] *T. W. Baker* and *J. Williams*, Acta crystallogr. *8*, 519 (1955).

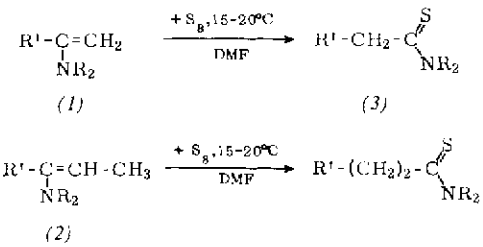
[9] $SrBe_{13}$ was synthetised recently by *D. Kunze* (Ph.D. Thesis, Universität Münster, 1964).

## Preparation of Thioamides from Alkenylamines and Sulfur at Room Temperature

By Prof. Dr. Roland Mayer and J. Wehl

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Elemental sulfur reacts with alkenylamines in some polar solvents (preferably dimethylformamide) at room temperature and atmospheric pressure to give thioamides. The yields from vinylamines of type *(1)* are about 75 %; those from propenylamines of type *(2)* lie between 20 and 60 %. Ketialkenylamines and amines derived from aldehydes react differently under these conditions.



*(1)* *(3)*



*(2)*

This useful variant of the Willgerodt-Kindler reaction can start directly from ketones, which are treated in the conventional manner with a secondary amine and sulfur, a catalyst, *e.g. p*-toluenesulfonic acid, then being added to accelerate the formation of the alkenylamine. Examples:

a) *N*-(α-styryl)morpholine (18.5 g), sulfur (3.5 g), and dimethylformamide (20 ml) are mixed together. The solution rapidly turns dark brown and loses its turbidity. After standing overnight at 15–20 °C, it is poured into 100 ml of a 1:1 methanol/water mixture and cooled to at least 0 °C. A crude product [1] separates out and is crystallized from 50 % methanol, giving *(3)*, $R' = C_6H_5$, $R_2 = -(CH_2)_2O-(CH_2)_2-$, m.p. 79–79.5 °C, in 75 % yield (16.3 g).

b) A mixture of acetophenone (12.0 g), *p*-toluenesulfonic acid (0.5 g), morpholine (18 g), and sulfur (3.2 g), is refluxed for 3 h at 130 °C and then poured into 50 ml of methanol and cooled to 0 °C. Work-up as above yielded 20.7 g (94 %) of the same product *(3)*. A control experiment without catalyst afforded a yield of only 49 %.

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German version: Angew. Chem. 76, 861 (1964)

[1] A separate report will be given on a yellow impurity $C_{16}H_{12}S_2$ formed in this reaction.

## Products of the Thermolysis of Sulfenic Acid Derivatives

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Sulfenic acid derivatives *(1)* are sensitive to heat and can therefore be distilled, if at all, only in a good vacuum [1]. We have found that these compounds decompose between 60 and 110 °C as indicated in the following equation. While



*(1)* *(2)*

| | | |
|---|---|---|
| *(a)* | $R = C_6H_5$; | $X = Cl$ |
| *(b)* | $R = p\text{-}CH_3\text{-}C_6H_4$; | $X = Cl$ |
| *(c)* | $R = p\text{-}CH_3O\text{-}C_6H_4$; | $X = Cl$ |
| *(d)* | R = Alkyl; | $X = Cl$ |
| *(e)* | $R = C_6H_5$; | $X = SCN$ |
| *(f)* | $R = C_6H_5$; | $X = SC_6H_5$ |

*(2)* can be isolated on a preparative scale, the sulfur generally occurs in subsequent products.

After 30 min at 100 °C, benzenesulfenyl chloride *(1a)* affords chlorobenzene *(2a)* in 60 % yield, together with diphenyl disulfide and $S_2Cl_2$. The *p*-methyl and *p*-methoxy groups on the benzene ring of *(1b)* and *(1c)*, respectively, accelerate the decomposition which is complete after only 10 min at 90 °C; nitro groups inhibit cleavage.

Aliphatic sulfenyl chlorides *(1d)*, especially those which branch at the α-carbon atom, also decompose at about 100 °C into alkyl chlorides, although here the yields are lower than in the aromatic series.

The requisite thermolysis temperature depends on the stability of the sulfenyl derivative in question. Thus, benzenesulfenyl thiocyanate *(1e)* forms phenyl isothiocyanate *(2e)* in 70 % yield at only 70 °C; since *(2e)* is stabilized by resonance, it only starts to decompose to benzonitrile at 190 °C.

Thermolytic cleavage of monosulfides into disulfides is already known [2] but proceeds at higher temperatures; it deserves a similar interpretation. For example, diphenyl disulfide *(1f)* gives an almost quantitative yield of diphenyl sulfide *(2f)* and sulfur within about an hour at 200 °C.

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German version: Angew. Chem. 76, 861 (1964)

[1] Cf. *H. Lecher* and *F. Holschneider*, Ber. dtsch. chem. Ges. *57*, 755 (1924); *H. Lecher, F. Holschneider, K. Köberle, W. Speer*, and *P. Stöcklin*, ibid. *58*, 409 (1925); *H. Rheinboldt* and *F. Mott*, ibid. *72*, 668 (1939); *E. Schneider*, Chem. Ber. *84*, 913 (1951).

[2] Cf. *C. Graebe*, Liebigs Ann. Chem. *174*, 189 (1874).

# CONFERENCE REPORTS

## Chemical Storage and Processing of Information in Biological Systems

The Gesellschaft für Physikalische Biologie and the Neuroscience Research Foundation organized a conference on May 5th and 6th in Berlepsch Castle near Göttingen (Germany). The subject of the conference was "Chemical Means of Storage and Readout of Information in Biological Systems". Some 90 participants, about one-third from abroad, discussed the four topics "Molecular Interactions", "Antigen-Antibody Reactions", "RNA Replication" and "Possible Relations to Psychic Memory". The very lively discussions were interrupted by an evening of chamber music, with works by Baroque composers, improvised by the participants themselves.

### Molecular Interactions

*M. Eigen*, Göttingen (Germany), opened the conference with an introduction to the problem of molecular interactions. Although our knowledge of the interactions occurring among simple inorganic ions is relatively good, the interactions of large organic ions and molecules are as yet largely unexplored. However, it is these very interactions that are important in biological systems.

Ionic interactions are normally non-specific, *i.e.* a free ion can be situated with almost equal probability at a point x or $x + \Delta x$. Although hydrogen bridges are spatially fixed, they are structurally non-specific, and hydrophobic interactions, as such, are also without appreciable specificity. In biological systems, however, interplay of these three types of interactions leads to considerable specificity, owing to the spatial fixation of the mutally interacting partners. Examples of this are seen in the tertiary structure of proteins, in antigen-antibody reactions, and in enzymatic processes.

Hydrophobic interactions, *e. g.* between uncharged side-chains of a protein or between the various heterocyclic bases of nucleic acids, are of importance to the molecular structure primarily in polar solvents, and hence particularly in aqueous solution. They cause the disappearance of the structure of the solvent between hydrophobic surfaces. The resulting gain in free energy, together with other effects, particularly $\pi-\pi$ interactions, leads to stabilization.

In many biologically important molecular structures, the interactions described are cooperative, *i.e.* one interaction facilitates the occurrence of another of the same type. Consequently, after a critical value has been reached, a relatively small change in the external conditions can lead to a radical change in structure. Thus, the pH or temperature range within which a nucleic-acid double helix changes into two coiled strands is much narrower than would be expected if the known interactions were simply additive in their effects. Systems with cooperative interactions can therefore respond to external influences by all-or-none reactions.

Owing to their short half-lives, all molecular interactions, whether ionic, hydrophilic, or hydrophobic in nature, are suitable only for transient assimilation of information. Permanent storage of information, *i.e.* for about the duration of a human life, probably requires reactions with an activation energy of at least 25 kcal/mole, *i.e.* reactions which lead to the formation of covalent bonds.

Incidentally, this lecture was based on a manuscript which had been sent in advance to the conference participants [*] and in which an attempt was made to redefine a number of concepts borrowed from psychology, but nevertheless applicable to molecular processes. These concepts range from simple "interaction" on the basis of a force law, through „distinction" and "recognition" to "memory", and include functions such as "storage", "transfer", and "readout" of information, and go on to "adaptation" and "learning". We are quite familiar with molecular processes of distinction and of storage, transfer, and recognition of information in enzymology and molecular genetics. Learning and memory functions, on the other hand, pass beyond a simple adaptation and are known only on the cellular level.

In the discussion, which was led by *L. Onsager*, New Haven, Conn. (U.S.A.), *J. Kendrew*, Cambridge (England), reported on the structure of myoglobin. Only 70 % of the molecule has a helical structure. Between the regions which are arranged in this manner, there are seven relatively short sections which are non-helical. The longest of these sections consists of eight amino acids. The amino-acid sequence (the myoglobin molecule contains a total of 153 amino-acid units) gives no answer, in the light of present-day knowledge, to the question why a helical region begins and why it ends. The four proline units in the molecule, which are sterically incompatible with an α-helix, evidently play a part, and so do the six serine and five threonine residues, whose side-chains interfere with the hydrogen-bonded structure of the α-helix. The end of a helical region is almost certainly also influenced by hydrogen bridges between the free carboxyl groups of aspartic acid units and amide NH groups in the main chain, since such interactions are possible only where a helical region ends.

[*] To be published.

Myoglobin has to a large extent the same tertiary structure as the α- and β-chains of hemoglobin. The homologies in the amino-acid sequences, *i.e.* in the primary structure of the three protein chains, are astonishingly slight in comparison with the similarities in tertiary structure: only 23 out of the 153 amino acids present, *i.e.* only about 15 %, are homologous. However, if we compare the amino acids whose side-chains are located in the interior of the spherical molecules, the number of homologies increases to about 33 %. It appears, therefore, that hydrophobic interactions are of major importance for the tertiary structure of myoglobin and hemoglobin, and hence also, indirectly, for the function of these proteins. This would agree with the fact that abnormal hemoglobins which are formed by mutations are almost always modified in the amino acids whose side-chains point outwards, as long as the mutations are not lethal.

*O. Sinanoglu*, New Haven, Conn. (U.S.A.), pointed out that deoxyribonucleic acid (DNA) can form a double helix in water, but is denaturated in other similar solvents (formamide or alcohols). In the search for a parallelism between this phenomenon and other physical properties of the solvent, a relationship was found to exist with the interfacial energy: the higher the interfacial energy, the smaller the denaturing influence of the solvent on the DNA structure.

*D. Crothers*, Göttingen (Germany), found that the relaxation period for the helix-coil transition in the DNA of T2 phages depends on the square of the molecular weight. This dependence disappears almost completely above a molecular weight of about $2\times10^7$. To explain this result, it was assumed that there are at least six single-strand bridges per T2–DNA molecule of molecular weight $>2\times10^7$, *i.e.* that the strands of the DNA double helix are broken at several points, and that the molecule is held together at these points only by the strand which is not broken. These measurements also permitted the calculation of a coefficient of friction for the unwinding of the double helix into two separate strands by rotary diffusion. This coefficient is about $10^3$ times greater than would be expected in water, probably owing to the greater microscopic viscosity of an ordered water structure in the immediate vicinity of the DNA molecule. The fact that the viscosity of the aqueous solution can be increased one hundredfold by addition of glycerol, without appreciably changing the coefficient of friction, lends support to this hypothesis.

*J. Lehninger*, Baltimore, Md. (U.S.A.), reported on higher forms of organization at the molecular level. Every enzyme has a catalytically active site at which transformation of the substrate into the product takes place. However, there are evidently also other centers which are independent of the catalytically active site and which interact with substances referred to as allosteric effectors. These alter the tertiary structure (and hence the activity) of the enzyme. This gives rise to a new possibility for the control and regulation of the activity of enzyme chains. The product of the enzyme last in a chain may be an allosteric effector which modifies a preceding enzyme of the chain in such a way that its activity is decreased. In contrast to enzyme inhibition by feedback, where the inhibitor must be similar to the substrate of the inhibited enzyme (since it interacts with the catalytically active site), the effector in allosteric inhibition does not need to resemble any substrate whatsoever of the enzyme chain (since its point of interaction is different from that of the substrates).

The enzymes of an enzyme chain probably always form complexes during the catalysis of successive steps, even when they are found to be soluble on isolation. The complex formation is probably due to the presence in the enzymes of bonding sites which may have the character of allosteric centers and which appear to be specific for one another. The enzyme complexes which have been most thoroughly studied to date, and which can be isolated as such, are the fatty-acid synthetase and the α-keto-acid dehydrogenase systems. In both systems, the substrate is bonded covalently to the enzyme complex while it passes through the reaction chain.

Membrane-bound enzyme systems exhibit another feature, namely directionality. For example, when an ATP-ase reaction ($ATP + H_2O \rightarrow ADP + PO_4^{3-}$) occurs in a membrane, it can give rise to a pH gradient across the membrane when the ions of water participating in the reaction come from different sides of the membrane. The same is true of the respiratory chain ($XH_2 + 1/2O_2 \rightarrow X + H_2O$), if the ions of the water formed are given up on different sides of the membrane.

Membranes themselves are forms of higher organization at the molecular level. They consist, among other things, of double layers of phospholipids separated by layers of protein. Membranes constitute about 60 % of the total cell material and reach large surface areas (for example, the total surface of the plasma membrane of a liver cell is about 8000 $\mu^2$ and the mitochondrial membranes of the same type of cell have a total surface area of 29000 ($\mu^2$). Bearing in mind that the phospholipids of a membrane, like proteins, have many side-chains of different types, it becomes clear that the membranes of a cell offer enormous possibilities for coding, *i.e.* for the storage of information. It would thus be feasible, for example, that proteins could be bonded to a membrane only according to the underlying phospholipid pattern.

## Antigen-Antibody Reactions

*G. Edelman*, New York (U.S.A.), gave an excellent introduction to the present-day knowledge of the structure of antibodies. Antigen-antibody reactions were discussed in this symposium because they are examples of "memory" at the cellular level.

If an antigen is injected into a mammal, antibodies can be detected in the serum from about the fifth day onwards and sediment out in the ultracentrifuge with a sedimentation constant of 19 S. Their production reaches a maximum after a further four days, and then decreases rapidly, provided the antigen dose does not exceed a threshold value. On injection of a quantity of antigen above this threshold value, the conditions are initially the same: 19S antibodies can be detected after about five days. Their production then declines, and 7S antibodies appear, whose quantity reaches a maximum which is not exceeded as long as no further antibody is injected.

The dimensions of a 7S antibody are about $240\times57\times19$ Å$^3$ (determined from small-angle X-ray scattering). 7S Antibodies consist of four proteins which are similar in pairs and which are referred to as the L and H components. The molecular weight of the L component is 20000–24000, that of the H component 55000–60000. Two H components are linked together by disulfide bridges, and one L component is bonded to each H component. H and L components can be separated and recombined, and it is possible in this way to obtain H/L hybrids from different antibodies of the same type of animal, and recently even of different types of animals. It has not yet been settled whether the information required for the formation of each specific antibody is already present in the cell and the antigen simply triggers off the corresponding reaction chain, or whether the cell "learns" the formation of the antibody from the antigen.

In the discussion, *O. Westphal*, Freiburg/Brsg. (Germany), reported on attempts to immunize cattle with pure *Pneumococcus* polysaccharides as antigens. There is an optimum dose, *viz.* 200–400γ of polysaccharide per injection. If more antigen is given, the quantity of antibody no longer increases, but decreases again on further increase of the antigen dose. The production of antibodies against various antigens is additive, but some cows form no antibodies at all against these antigens; this suggests that competent cells (competent for the recognition of antigens and production of antibodies) must be present. The larger the antigen, the better is the production of the antibody. It is increased by the use of cross-linked polysaccharide antigens.

It is an interesting fact that γ-globulin components which form precipitates with erythrocytes are found in the hemolymph of the horseshoe crab. This appears to indicate the presence of a primitive antigen-antibody system. So far antigen-antibody reactions have been detected only in higher animals.

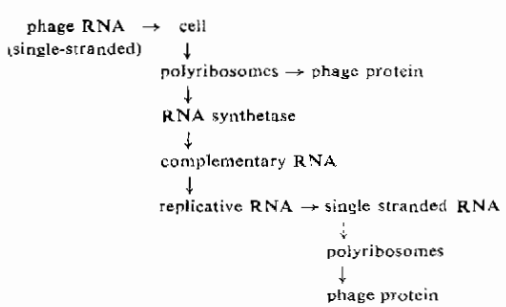
*A. Rubin*, Brookline, Mass. (U.S.A.), reported on the formation of antibodies after surgical transplantations. If 6-mercaptopurine is given to a patient on the same day as or on the day after a kidney graft, the transplanted organ is not rejected by the body. Thus, 6-mercaptopurine interferes with the formation of antibodies against the foreign kidney, probably at the stage of macrophage-RNA.

In experiments which have not yet been completed it is being checked whether the organs of an immunized animal which synthetize antibodies contain RNA types characteristic of the antibodies. To this end, rabbits were injected with human albumin and ferritin. At maximum antibody production the animals were slaughtered and the ribosomes in their spleens centrifuged in a density gradient.

## Ribonucleic Acid Replication

The introductory lecture was delivered by *R. Smellie*, Glasgow (Scotland). RNA-polymerase synthesizes ribonucleic acid from the four ribonucleoside triphosphates in the presence of DNA and $Mn^{2+}$. Native and single-stranded DNA (DNA from ΦX-174 phages or DNA preparations denatured by heating) may serve as matrices. The nucleotide sequence of the synthetic RNA is complementary to the base sequence of the DNA; this indicates pairing of complementary bases during the RNA synthesis. The complementary nature of the matrix and the product is shown by analysis of immediately adjoining bases (nearest-neighbor analysis), by the formation of DNA/RNA hybrids, and by the base ratios in the matrix and in the product. Both strands of native DNA are used *in vitro* as matrices for the formation of RNA, since single-stranded ΦX-174 DNA gives an RNA with a complementary base composition, whereas double-stranded ΦX-174 DNA gives a product with the identical base composition. On the other hand, only one of the two strands of native DNA is evidently copied *in vivo*. This is indicated by the following experiment: the two strands of a native phage DNA could be separated by centrifuging in a density gradient. Each of these strands gave RNA *in vitro*, whereas m-RNA synthetized by bacteria which had been infected with the phages forms a hybrid with only one of the two DNA strands.

The replication of virus RNA was the subject of the lecture by *S. Ochoa*, New York (U.S.A.). If *Escherichia coli* is infected with MS2 phages, which contain single-stranded RNA, the cells form an RNA synthetase, which can be isolated. The enzyme contains ribonucleic acid in a form which is partly stable towards ribonuclease. This is evidently double-stranded RNA. On annealing with other types of RNA, this RNA, which is referred to as the replicative form, gives a hybrid only with MS2-RNA. It must therefore be assumed that the cells infected with the MS2 phages first synthesize a complementary RNA strand which forms a double helix with the original bacteriophage RNA. This replicative form then serves as a matrix for the synthesis of new phage RNA. Destruction of the replicative RNA bound to the enzyme leads to irreversible inhibition of the enzyme. The formation of new bacteriophages in infected cells probably follows the scheme:




However, it is not yet known whether the RNA synthetase which has been isolated forms also the complementary RNA, or whether another enzyme is responsible for this reaction.

## Possible Relations to Psychic Memory

*H. Hydén*, Göteborg (Sweden), gave an introductory report on experiments with rats which had to learn a new mode of behavior and whose brains were then analysed for their RNA content in the appropriate sections (analysis of the cell nuclei of individual neurons; sensitivity of detection: μμg). "Right-handed" rats learned to take their food from a tube with the right fore-foot. The tube was then moved so that the food could only be reached with the left fore-foot. The part of the somatosensory cortex which determines whether the animal is right- or left-handed was then analysed. A distinct increase was observed in the RNA content in the cell layers of the right half of the brain. The corresponding cells of the left half of the brain were used as controls. The RNA isolated from the cells of the right (learning) half of the brain also exhibited a higher ratio of purine to pyrimidine bases.

In a second experiment, the animals had to crawl up a thin steel wire 1 m long and inclined at an angle of 45° in order to reach their food. With a daily learning period of 45 min, the rats took only 4–5 days to master the new mode of behavior. The large nerve cells and the neuroglia of the lateral vestibular nucleus were analysed, using neurons and neuroglia from other parts of the brain of the same animal and from other animals as controls. An increase in the RNA content of the nerve cells and in the adenine:uracil ratio of the nuclear RNA in the nerve cells and that of the neuroglia RNA was again found.

The interpretation of these results may be that repressed sections of the chromosomal DNA in the brain cells become active during learning and produce a corresponding RNA which in turn leads to the synthesis of specific proteins. The presence of these proteins or the rate of their production might then affect the transmission of nervous impulses. The neuroglia may also participate in this process, possibly by controlling the induction of the RNA synthesis in the neuron.

Finally, *F. O. Schmitt*, Cambridge, Mass. (U.S.A.), showed some possibilities for the storage of information in the central nervous system. The system consisting of neurons, nerve fibers, and synapses in the brain can be regarded as a three-dimensional network, resembling the tracks of a marshalling yard. The fate of an impulse then essentially depends on the part of the network through which it is transmitted. This may be decided by the neurons. One way in which they could carry out this decision is by sending specific proteins through their nerve fibers to the synapses; the proteins would then permit the transmission only of certain impulses. It is certain that protein is being constantly synthetized in the neurons and migrates through the nerve fibers to the synapses. However, it is not yet known whether this protein is used only for the metabolism of the nerve cells, or as a structural material for the production of specific routes of communication, or even as a molecular information store. [VB 824/151 IE]

German version: Angew. Chem. 76, 718 (1964)
Translated by Express Translation Service, London

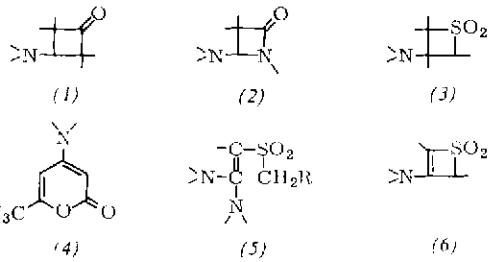
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## Cycloadditions of Alkenylamines and 1,1-Bisdialkylaminoethylenes

*G. Opitz*, Tübingen (Germany)

Cycloaddition of alkenylamines onto ketenes, isocyanates, or sulfenes affords β-dialkylaminocyclobutanones *(1)*, β-dialkylamino-β-lactams *(2)*, and β-dialkylaminotrimethylene sulfones *(3)*, respectively. Whereas the enolizable β-aminocyclobutanones rearrange on heating to alkyl β-aminovinyl ketones, compounds *(1)*, which are not capable of enolization, are thermally stable; so are β-aminotrimethylene sulfones *(3)*. At higher temperatures, β-amino-β-lactams *(2)*, which are also formed from amidines and ketenes, are in equilibrium with the corresponding alkyleneamines and isocyanates.

Interaction of non-enolizable β-aminocyclobutanones *(1)* with Grignard reagents may result in four different reactions: a) normal addition to form a tertiary β-aminocyclobutanol, b) reduction to form a secondary β-aminocyclobutanol, c) ring-opening to form a β-amino ketone, and d) reductive ring-opening to form a different β-amino ketone. The derivatives of pyrrolidine and hexamethyleneimine possess a more pronounced tendency towards ring-opening than those of piperidine and morpholine.



*(1)* *(2)* *(3)* *(4)* *(5)* *(6)*

On acetylation, followed by a diene synthesis with ketene and amine elimination, 1,1-bisdialkylaminoethylenes and ketene give rise to 4-dialkylamino-6-methylcoumalins *(4)* which react with phenylmagnesium bromide to yield 1,3,5-triphenylbenzene and which are degraded by sodium hydroxide to acetone, acetic acid, and dialkylamines. In the reaction of 1,1-bisdialkylaminoethylenes with aliphatic sulfonyl chlorides in the presence of triethylamine, acylation to give *(5)* competes with the cyclization to 3-dialkylaminothietene 1,1-dioxides *(6)*.

The synthesis of three-membered cyclic sulfones from diazoalkanes and aliphatic sulfonyl chlorides in the presence of triethylamine provides further support for the assumption of intermediate formation of sulfenes.

[GDCh-Ortsverband Wuppertal/Hagen (Germany), June 2nd, 1964] [VB 829/153 IE]

German version: Angew. Chem. 76, 724 (1964)

## The Reaction of White Phosphorus with Free Radicals from γ-Radiolysed Organic Liquids

*A. Henglein*, Berlin (Germany)

Irradiation of solutions of white phosphorus in $CCl_4$ with γ-rays produces trichloromethylphosphorus dichloride, phosphorus trichloride, red phosphorus, hexachloroethane, and a polymer $(CCl_2)_n$. At room temperature the main product is red phosphorus to which one trichloromethyl group (from radiolysis of the solvent) per 7 phosphorus atoms is chemically attached. Above 80 °C, the low molecular-weight phosphorus compounds are formed almost exclusively *via* a chain reaction. A mechanism is indicated whereby free radicals from the solvent add onto the $P_4$ molecules and the resultant $RP_4$ units either form red phosphorus or react with the solvent with abstraction of chlorine. Abstraction of a chlorine atom requires an activation energy of 8.2 kcal/mole and is therefore favored by high temperatures during the irradiation.

In cyclohexane, free cyclohexyl radicals (from radiolysis of the solvent) react with dissolved phosphorus to form red phosphorus containing one $C_6H_{11}$ group per 4 phosphorus atoms. About 30 % of the phosphorus added appears in the form of soluble organophosphorus compounds containing several phosphorus atoms per molecule. The radical attack in cyclohexane leads neither to the scission of all the P-P bonds of the $P_4$ molecules nor to a chain reaction. If $CCl_4$ is added, however, at higher temperatures, three simultaneous chain reactions appear, which lead to a) chloroform and cyclohexyl chloride, b) trichloromethylphosphorus dichloride, and c) cyclohexylphosphorus dichloride. The trichloromethyl radical is thus a common intermediate in the three chain reactions, which are linked with one another.

White phosphorus participates in the polymerization of styrene induced by γ-rays. The rate of polymerization is slightly increased, but the average molecular weight is greatly lowered. In addition, phosphorus is incorporated into the polymer (one atom/100 molecules of monomer). These results indicate that $P_4$ molecules intercept growing styrene chains, thereby initiating more than one new chain per interception, and that breakdown of the kinetic chain by mutual deactivation follows. It is concluded from the transfer constant found that white phosphorus is a relatively poor trap for free carbon radicals and does not react with them at each encounter.

Pulse radiolysis experiments with solutions of white phosphorus in cyclohexane and $CCl_4$ produced a short-lived intermediate which has an absorption maximum at 650 mμ and which disappears by reactions of first or second order, depending on the $P_4$ concentration, to give a stable entity which absorbs at 350 mμ. The short-lived species is probably either the $C_6H_{11}P_4$ or the $CCl_3P_4$ radical.

[GDCh-Ortsverband Darmstadt (Germany), June 23rd, 1964] [VB 834/160 IE]

German version: Angew. Chem. 76, 718 (1964)

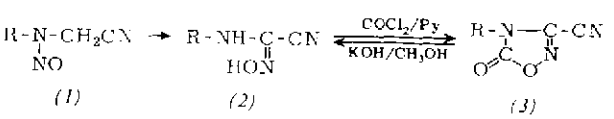
# SELECTED ABSTRACTS

**Isoenzymes of creatine kinase** were found by *A. Burger, R. Richterlich*, and *H. Aebi* in electrophoretic investigations of human, rabbit, and rat tissues. Three bands migrating at different speeds were detected. All three bands were found in smooth muscle, but in skeletal muscle only that migrating most slowly towards the cathode, and in the brain mainly the band moving very quickly towards the anode were observed. It is probable that – as in the case of lactic dehydrogenase – isoenzymes composed of different subunits [1] exist for this enzyme, which is responsible for ATP-production from creatine phosphate. There may be two different sub-units of creatine kinase which can combine to give three electrophoretically separable, enzymatically active dimers. In principle, the same observations were described by *Sjövall* and *Voigt* [2]. / Biochem. Z. *339*, 305 (1964) / –Sch. [Rd 998/289 IE]

[1] *T. Wieland* and *G. Pfleiderer*, Angew. Chem. *74*, 261 (1962); Angew. Chem. internat. Edit. *1*, 169 (1962).

[2] *K. Sjövall* and *A. Voigt*, Nature (London) *202*, 701 (1964).

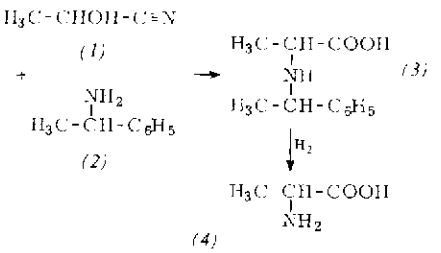
**A new type of base-catalysed rearrangement of nitroso groups** is reported by *H. U. Daeniker*. In methanol *N*-substituted *N*-nitrosoaminoacetonitriles *(1)* undergo an intramolecular rearrangement to form α-isonitrosoaminoacetonitriles *(2)*. If the cyano group of *(1)* is replaced by other active groups, no such rearrangement takes place, Schiff bases being formed instead. Reaction of *(2)* with phosgene in pyridine leads to 4-substituted 3-cyano-1,2,4-oxadiazolin-5-one derivatives *(3)*,



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

an unusual group of compounds accessible with difficulty. Examples for *(2)*: R = $C_6H_5$, m.p. 141–144 °C (decomp.); R = *p*-$ClC_6H_4$, m.p. 151–153 °C (decomp.); R = *p*-$CH_3O$-$C_6H_4$, m.p. 157–158 °C (decomp.); R = $CH_3$, m.p. 155 to 157 °C (decomp.); R = n-$C_4H_9$, m.p. 77–78 °C. / Helv. chim. Acta *47*, 33 (1964) / –Ma. [Rd 4/288 IE]

**A novel stereospecific synthesis of optically active α-amino acids** was described by *K. Harada* and *S. W. Fox*. Racemic lactonitrile *(1)*, for example, was allowed to stand at 25 °C for 48 h with D-( )-α-methylbenzylamine *(2)* in methanol. The crude product *(3)* was subjected to catalytic hydrogenolysis in alcohol and after working up and purification gave optically nearly pure L-(+)-alanine *(4)* in 17% yield. The



reaction mechanism is not known. Similar reactions may have been responsible for the formation of optically active compounds on the primitive earth under abiotic conditions. / Naturwissenschaften *51*, 106 (1964) / –Sch. [Rd 1000/286 IE]

**The problem of information transfer in chemistry** was studied by *H. Erlenmeyer* and *H. Bartels* taking thin-layer chromatography as an example. Silica gel precipitated in the presence of *N,N*-dimethyl- or *N,N*-diethylaniline and washed free from amines adsorbed dimethyl- or diethylaniline more strongly than untreated gel. Measurement of the adsorption isotherms showed that methyl orange and ethyl orange were also somewhat more strongly adsorbed by the gel after pretreatment with dimethyl- or diethylaniline. Evidently the dialkylamino group of the dialkylaniline molecule is able to influence the silica gel in such a way that more complicated molecules containing this grouping are more strongly adsorbed. / Helv. chim. Acta *47*, 46 (1964) / –Kr. [Rd 3/290 IE]

**The assimilation of carbon from carbonates,** formerly known only with algae, has now been observed in higher land plants by *J. Materna* and *R. Kohout*. Spruce and fir shoots and leaves of deciduous trees were immersed in solutions of $NaH^{14}CO_3$ and $Na_2{}^{14}CO_3$ for a few seconds to several hours. After extraction with methanol and water, an examination for the presence of labelled glycides and other organic compounds was carried out by paper chromatography. In all experiments (particularly those with spruce, fir, and oak), glucose, fructose, and sucrose labelled with $^{14}C$ were found after incubation periods of only a few seconds, together with other labelled compounds, including insoluble components of the shoots and leaves. / Naturwissenschaften *51*, 116 (1964) / De. [Rd 949/269 IE]

**The rate-determining step of the reaction catalysed by alcohol dehydrogenase from yeast** was established by *B. Müller-Hill* and *K. Wallenfels*. For many substrates, the conversion of the enzyme-substrate complex into the enzyme-product complex is rate-determining. Sometimes, however, the rate of diffusion of the substrate or coenzyme away from the enzyme is also decisive for the overall reaction velocity. Such diffusion-controlled processes are characterized by low activation energies. The very low activation energy which was found for the acetaldehyde-NADH-reaction above 20 °C leads to the conclusion that, at this temperature, removal of the NAD by diffusion becomes rate-determining. / Biochem. Z. *339*, 338 (1964) / –Sch. [Rd 1/291 IE]

# BOOK REVIEWS

**Magnetische Kernresonanz und chemische Struktur** (Nuclear Magnetic Resonance and Chemical Structure), by *H. Strehlow*. Fortschritte der physikalischen Chemie, Vol. 7. Dr. Dietrich Steinkopff Verlag, Darmstadt 1962. 1st edit. 179 pp., 94 illustr., 22 tables. Price DM 36.– (about $ 9.00).

The non-physical chemist who would like to apply nuclear magnetic resonance to chemical problems and to read the pertinent literature critically will be content at first with a minimum knowledge of physical theory but will want to become more thoroughly acquainted with the possibilities of structural determination. Experience shows that at this stage he faces two major difficulties: complex spin splittings and fast reactions such as chemical exchange or intramolecular motions. The study of such phenomena by perusal of original literature and detailed monographs is very laborious. The book by *H. Strehlow* thus fills a gap by dealing with the physical aspects of NMR primarily more qualitatively and without mathematical derivations; rigorous treatments are often added in a special chapter.

The book is not intended to be a working basis for structural elucidations, like *Bellamy*'s monograph for infrared spectroscopy. Nevertheless one would have liked the chapter on the determination of the structures of organic and inorganic compounds (22 pp.) to be somewhat more detailed. Quotation of the chemical shift in Hz [eps] relative to tetramethylsilane is disturbing here since, when dealing with that parameter earlier on in the book, the author has used δ-values based on benzene. In the chapter on spin-spin interaction there is unfortunately no mention of the frequently occurring ABX spectrum which may be analysed in an elementary manner; on the other hand tables for a number of more complex systems are listed. The brief discussion of fast reactions with many examples deserves special mention. Other chapters of importance to the chemist deal with the experimental technique as well as the use of nuclear magnetic resonance for solutions of electrolytes and solids.

The book is excellently written and can be highly recommended to every chemist who is interested in the principles of the method. It is to be regretted, however, that the high price of the paper-backed edition is rather a setback to wide circulation.

*A. Mannschreck* [NB 189/87 IE]

**Gmelins Handbuch der anorganischen Chemie** (Gmelin's Handbook of Inorganic Chemistry), 8th completely revised edition. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Initiated by *R. J. Meyer*, continued by *E. H. Erich Pietsch*. Verlag Chemie, GmbH., Weinheim/Bergstr.

**System No. 3: Oxygen.** Vol. 5 (Systems. Ordinary Water up to Chemical Behavior, excluding Electrochemical Behavior). 1963, IV, XVIII, 548 pp., 104 figs. cloth DM 410.– (about $ 105.–). Revised by *Krista von Baczko, Anna Bohne-Neuber, Erna Brennecke, P. Koch, H. K. Kugler*, and *Gertrud Pietsch-Wilcke*.

The previously published Vols. 1 (1943 Historical), 2 (1951 Occurrence, Technology), 3 (1958 Elemental Oxygen), and 4 (1960 Air, Active Oxygen, and Ozone) consisted of 1184 pp. with 208 figs. (total price DM 722.– or about $ 185.–) dealing with the element oxygen $O_2$ (including atomic oxygen O and ozone $O_3$), and so correspond to the usual Part A of the "Gmelin" arrangement. The present Volume 5 begins what would normally be Part B (Compounds of Oxygen). According to the Gmelin "last-place" principle, this Part B is confined to compounds with hydrogen, *i.e.* water and hydro-

gen peroxide. Vol. 5 is specially devoted to "ordinary" (natural) water, with the exception of its electrochemical behavior; this will be dealt with in Vol. 6, which is still in preparation. Further volumes will deal with the other 18 forms of "light" and "heavy" water (combinations of the hydrogen isotopes $^1H$, $^2H$, and $^3H$ with the oxygen isotopes $^{16}O$, $^{17}O$, $^{18}O$) and those of "light" and "heavy" hydrogen peroxide.

In particular, Vol. 5 deals with the systems $O_2$/inert gases, $O_2/H_2$, and $O_2/H_2O$ (7 pp.), up to the preparation of ordinary water in the pure form (16 pp.) and its properties (525 pp.), the last being divided, rather arbitrarily, into 10 chapters of varying importance: thermodynamics (6 pp.), the $H_2O$ system (34 pp.), special forms (1 p.), evaporation and condensation (33 pp.), physical properties (323 pp.), chemical behavior (37 pp.), behavior as a solvent (62 pp.), behavior towards radiation (15 pp.), behavior towards sound (6 pp.), and material transport by steam (8 pp.).

The brief data on the systems of oxygen with inert gases, with hydrogen, and with water are particularly interesting with regard to the stability and existence of possible compounds (*e.g.* oxygen hydrate).

Since technical processing and purification of water has already been described in Vol. 2, and since the synthesis of water from its elements has no preparative importance, the chapter on the preparation of pure water is confined to the production and purity testing of distilled water for laboratory use. Purity requirements vary according to whether conductivity water is desired for conductometric studies, perfectly neutral water for volumetric studies, metal-free water for biological studies, sterile water for medical studies, or dust-free water for optical work.

The thermodynamic discussions deal with the enthalpy, the free energy, the entropy of reaction, and the equilibrium constant of the decomposition and formation of water, according to the equation $H_2O \rightleftarrows H_2 + {}^1/_2O_2$, and with dissociations according to the equations $H_2O \rightleftarrows {}^1/_2H_2 + OH$, $H_2O \rightleftarrows H + OH$, and $H_2O \rightleftarrows H_2 + O$.

The chapter on the $H_2O$ system starts with a description of the phase diagram of water, due consideration being given to the range of stability and existence of the 6 stable and the 2 unstable modifications of ice known at present and to the variant and invariant equilibria between the different system phases. A detailed discussion is given of the existence of the individual phases outside their normal ranges, particularly the supercooling of liquid water and the transcendency of the stability limits of the various types of ice; superheating of liquid water and supercooling of steam are postponed to the later chapter on evaporation or condensation.

The section on special forms of water deals exclusively with the colloidal distribution of water and ice. Data on the preparation of single crystals are given in the later chapter on physical properties (crystallography); the production of vitreous ice is dealt with in the preceding chapter on the $H_2O$ system (modifications of ice), and the formation of films of water is discussed under physical properties (sorption).

The chapter on the evaporation and condensation of water is particularly interesting, especially since detailed investigations into the kinetics and retardation of these processes have been carried out. Condensation processes in the atmosphere (formation of mist, clouds, rain, hoar frost, snow, hail) and the artificial production of rain are also discussed.

The greater part ($\approx 60\,\%$) of this volume is taken up by the chapter on physical properties. This begins with brief details (9 pp.) of the $H_2O$ molecule (disposition of the electrons, configuration, moment of inertia, dipole moment, polarizability, force constants, molecular vibrations, dissociation energy, association) and then passes onto its crystallographic properties (26 pp.), including the crystal structure of the various modifications of ice, the preparation of single crystals, the growth of ice crystals on various matrices, the rate of crystallization, the regelation of ice, and the lattice energy. Prominent among the mechanical-thermal properties (218 pp.) are the anomalies of water due to structural factors (such as its density maximum at 4 °C, its decrease in compressibility with increasing temperature up to 50 °C, its decrease in internal friction with increasing pressure below 32 °C, its expansion on freezing, and its relatively too high boiling point). Of particular interest are the p–v–T relationships given in the steam tables, together with the equations of state which satisfy them, considerations on the melting and the boiling point of water as fixed points of the international temperature scale, and details on the adsorption of water on a wide range of surfaces. A brief (8 pp.) discussion is given of the acoustic properties (velocity of sound in water, absorption of sound by water, cavitation by the action of sound and ultrasonics). This is followed by the optical (38 pp.) and the magnetic and electrical properties (24 pp.). The dielectric constant is discussed in particular detail with regard to the use of water as reference basis in magnetic susceptibility measurements.

The chapter on the chemical behavior begins with general considerations on the macrostructure of water and the resulting inferences relative to its anomalous mechanical-thermal properties; it then deals with the electrolytic dissociation of water, which in turn leads on to the amphoteric nature of water. Remarks on the behavior of water toward elements and compounds are restricted to discussions of the chemical changes occurring in its coreactant; the solvent power of water without chemical change of the solutes is discussed in the following chapter.

The chapter dealing with water as a solvent is subdivided into sections on solubilities, hydration, physical properties of aqueous solutions, ionic mobility, diffusion rates and reactions in aqueous solution (neutralization, precipitation, complex formation, and redox reactions).

The volume closes with two chapters on the behavior of water on irradiation (decomposition of water by ionizing radiation, photochemical decomposition) and on acoustic irradiation (action of sound and ultrasonic waves), and a chapter on material transport by steam, in which the transport of readily volatilized substances (steam distillation) as well as that of substances which are difficult to volatilize (formation of pneumatolytic deposits, salting up of high-pressure steam turbines) are discussed in detail.

**System No. 9: Sulfur.** Part B, Vol. 3 (Conclusion of "Compounds"). 1963, IV, XLII, 745 pp., 245 figs. and 9 foldout tables, cloth, DM 612.– (about $155.–). Revised by *M. Atterer, Anna Bohne-Neuber, Inge Flachsbart, P. Koch, A. Kotowski, W. Lippert, E. Müller, W. Schröder,* and *L. Thaler.*

Vol. B 3 completes System No. 9 "Sulfur" (which now comprises a total of 2637 pp. and 586 figs. at a total price of DM 1777.– or about $450.–). It follows Vol. B1 (1953 Compounds of Sulfur with Hydrogen and Oxygen) and B2 (1960 Oxacids of Sulfur), and opens with a continuation of the report on aqueous solutions of $SO_2$ (400 pp.), which was started but not completed in Vol. B2. This is followed by a discussion of compounds of sulfur with nitrogen (167 pp.) and with halogens (178 pp.), dealing with all the sulfur compounds to be treated in the sulfur volume in accordance with the Gmelin "last-place" principle. All other compounds are discussed under higher system numbers.

The comprehensive report on the system $SO_2/H_2O$, which occupies more than half of Vol. B3, is divided into two chapters: the solubility of $SO_2$ in water and aqueous solutions (163 pp.), and the oxidation of aqueous solutions of $SO_2$ and sulfites (237 pp.).

The remarks on the solubility of $SO_2$ begin with data on the rates of its absorption in and desorption from water. This is followed by expert discussions on the p–t–x space diagram (pressure p, temperature t, concentration x), on the problems and methods associated with the determination of solubility (purity of starting material, preparation of solutions, equilibration, determination of total pressure, calculation of the partial pressure of $SO_2$, determination of the $SO_2$ concen-

tration), and finally on the numerous investigations concerning the solubility of $SO_2$ in water reported in the literature, mainly arising from technical problems (*e.g.* purification of waste gas). To illustrate the results in the form of comparative graphical summaries, the literature values (recalculated where necessary to bring them into alignment) are presented in tables and diagrams as two-dimensional sections of the p–t–x space diagram (dependence of one variable on a second when the third is kept constant), *i.e.* in the form of x–p isotherms (t constant), x–t isobars (p constant), and p–t isopleths (x constant). The results are also collected in a lucid graphical layout into eight large foldout tables, which are arranged from different points of view, which testify to the admirable consciousness of the abstractor, and which will undoubtedly be gratefully received by industry. The chapter closes with discussions on the validity of Henry's law applied to the solution of $SO_2$ in water, since this validity is upset at low temperatures and low $SO_2$ concentrations by the simultaneous formation of $H_2SO_3$. The experimental data are again illustrated by tables and graphs, including a foldout table. A similar treatment is then given for the solubility of $SO_2$ in aqueous solutions of acids (sulfuric acid, acetic acid, thiocyanic acid), salts (halides, thiocyanates, sulfates, nitrates, hydrosulfites), and technical absorbents, touching problems which are important for the removal of $SO_2$ from waste gases. The relationships between solubility and the constitution of the solutions is also discussed in this connection. The chapter on the oxidation of aqueous $SO_2$ and sulfite solutions begins with oxidation by oxygen (also in the presence of catalysts and inhibitors). This part is divided into sections on the homogeneous oxidation of aqueous $SO_2$ and sulfite solutions, the heterogeneous oxidation, and the theory of the oxidation reaction. All related questions are of vast importance, both scientifically and technically, and are therefore justifiably discussed in detail. Thus, the oxidation of sulfite, which is particularly sensitive toward many catalysts and inhibitors at pH 8–10, *i.e.* in the region of exclusive existence of $SO_3^{2-}$, has been widely studied as a model reaction for better understanding of the negative catalysis. The action of sulfite as an inductor in induced oxidation reactions has contributed greatly to the explanation of induced oxidations and, as one of the first reactions to be recognized as a chain process in solution, it has been of great importance to the theory of these reactions. The technical importance can be appreciated on consideration of the catalytic production of $H_2SO_4$ or $(NH_4)_2SO_4$ from the $SO_2$ of flue gases or the removal of corrosive oxygen from boiler feed-water by means of sulfite. All these results obtained with these various aims in mind are dealt with in this chapter from a uniform point of view. The same applies to the subsequent discussion of the oxidation of aqueous $SO_2$ and sulfite solutions by ozone (with and without additives).

The chemistry of the compounds of sulfur with nitrogen has been considerably extended in recent years, so that for the sake of developing a complete picture, it was necessary to include, even if imcompletely, many results from post-1949 literature, contrary to the usual fixed deadline for literature (the end of 1949). This chapter deals first with the nitrides of sulfur [such as $(S_2N)_2$, $(S_2N)_x$, SN, $(SN)_2$, $(SN)_4$, $(SN)_x$], placing emphasis on the preparation, constitution, and properties of tetrasulfur tetranitride $(SN)_4$, which has been studied particularly thoroughly in the past few years. This is followed by the amides and imides of sulfur such as $S_7NH$, $S_6(NH)_2$, and $S_4(NH)_4$. Of the S–N–O compounds, which belong to very different classes according to their constitution, particular mention should be made of dinitrosyl disulfate $(NO)_2S_2O_7$, and of the S–N–O–H compounds, of sulfamic acid $HSO_3NH_2$, sulfurylamide $SO_2(NH_2)_2$, nitrosyl hydrogen sulfate $(NO)HSO_4$, the "blue acid" $(N_2O_2)HSO_4$, and the system $N_2O_5/SO_3/H_2O$ [1].

The chapter on the compounds of sulfur with halogens is almost entirely (about 94 %) devoted to the fluorine (51 pp.) and chlorine (116 pp.) compounds, whilst the bromine, iodine, and astatine compounds are confined to 11 pp. Owing to the various valence states of sulfur and the small atomic radius and high electronegativity of fluorine, there is a relatively large number of binary S–F compounds ($S_2F_2$, $SF_2$, $SF_4$, $S_2F_{10}$, $SF_6$), which have all been studied in detail and are therefore discussed at length. Among the S–F–O compounds, thionyl fluoride $SOF_2$, sulfuryl fluoride $SO_2F_2$, and fluorosulfuric acid $HSO_3F$ are treated in particular detail. The S–N–F, S–N–F–O, and S–N–F–O–H compounds are rather too briefly discussed, since the 16 compounds listed in the volume [2], *viz.* SNF, NSF, $S_3N_3F_3$, $S_4N_4F_4$, $NSF_3$, $SN_2F_2$, $S_3N_2F_2$, $SF_5NF_2$, $HNSOF_2$, $(NSOF)_n$, $OS(F)NH_2$, $H_2NSO_2F$, $F_2NOSO_2F$, $FSO_2NO$, $NOSO_3F$, and $NO_2SO_3F$, all became known after 1949, and the references quoted on the subject are very incomplete, owing to observance of the literature deadline (the end of 1949). Of the chlorine compounds of sulfur, particular mention should be made of the details on the systems $S/S_2Cl_2$ and $S_2Cl_2/Cl_2$, the binary chlorides $S_2Cl_2$, $SCl_2$, and $SCl_4$, and the S–O–Cl and S–O–Cl–H compounds $SOCl_2$, $SO_2Cl_2$, $S_2O_5Cl_2$, and $HSO_3Cl$.

The fact that Vol. B 3 of sulfur completes another System No. moves the reviewer to cast a brief backward glance over the achievements of the Gmelin editorial staff to date. It is now exactly 40 years since the publication of the first volume (Zinc, 1924) of the present 8th edition of "Gmelin." Since then, 52 of the projected 71 System Numbers have been completed. However, 8 of these volumes are now more than 30 years old, another 22 more than 20 years old, and 6 more than 10 years old; only 5 volumes are of recent date, and supplements to the remaining 11 have recently been published. Six System Numbers (O, Si, Al, Cr, Fe, Cu) are drawing to a close, two others (Hg, Rare Earths) have been started [3] and two (C,P) are in preparation, but the 9 others (Sn, Pb, V, Nb, Tl, U, Mn, Ag, Transuranium Elements) have not yet been started. As this list shows, the Gmelin editorial staff still has extensive important work to do, and it can only be hoped that, even if the outstanding System Numbers cannot be completed by the 50th anniversary of the 8th edition of "Gmelin", it might be possible, by increasing the staff, at least to make a start on them. However, there will then be scarcely a single chemist who has witnessed both the beginning and final completion of the 8th edition, either as a contributor or as a beneficiary.

*E. Wiberg* [NB 214/91 IE]

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[1] Details on the system $N_2O_3/SO_3/H_2O$ are given under the compound $(NO)HSO_4$.

[2] Nitrosodifluoramine $F_2NNO$ is erroneously also included at this point in this sulfur volume; this compound contains no sulfur, and according to the Gmelin principle should be included in the System No. "Fluorine".

[3] However, the one volume on the Rare Earths published so far is now also 26 years old.

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# Fundamental Aspects of Diffusion Processes

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*A simple description of diffusion processes and a derivation of the general laws of diffusion are given. The distribution with time of particles according to a random-walk process is considered and compared with results derived from a differential equation. Diffusion coefficients for and examples of diffusion processes in various media (e.g. gases, solutions, solids, and high polymers) are given. "Uphill" diffusion, i.e. diffusion against the concentration gradient, is also discussed. In addition, diffusion in anisotropic systems, in systems consisting of more than one phase, and in multicomponent systems is treated.*

## I. Introduction

Diffusion is a process which, normally [*], leads to homogenization of a mixture. This process is easily understood in a qualitative way, if we treat it as a "random-walk" phenomenon in the molecular picture. A given molecule has, on the average, a definite kinetic energy equal to 3/2 kT (kT/2 per degree of freedom), where T is the absolute temperature, and k is Boltzmann's constant. The corresponding average velocity v is usually of the order of a few hundred meters per second for simple molecules, with such extremes as 1800 m/sec for the hydrogen molecule at room temperature and about 150 m/sec for the rather heavy molecule $UF_6$. A protein molecule of relative mole mass 1000000 would still have an average thermal velocity of 3 m/sec.

A molecule usually will not travel in one second the distance given by its speed multiplied by one second (except in extraterrestrial space), but only a much shorter distance, owing to the fact that its free path is limited by collisions. An oxygen molecule in air has a free path of roughly $10^{-5}$ cm, *i.e.* 1000 Å, which at a pressure of $10^{-5}$ atm (corresponding to a height of 100 km in the terrestrial atmosphere) would increase to 1 cm (cf. Figure 1, which applies for a pressure of 10 atm).

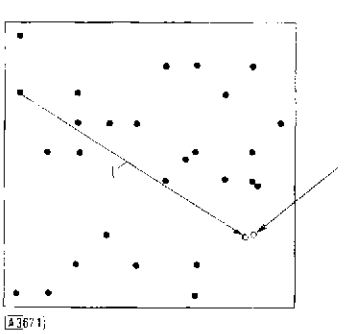


Fig. 1. Free path (ca. 90 Å) of oxygen molecules at 10 atm and room temperature (idealized molecule diameter ca. 3.0 Å; average intermolecular distance ca. 20 Å).

[*] The restriction refers to the following facts: we may have an originally homogeneous non-isothermal system of two components, and diffusion processes lead to a partial separation of the components. Instead of an equalization we may even have a very efficient separation of isotopes as applied in *Clusius'* separation tube, a multistage thermal diffusion column.

There are numerous examples of diffusion in solid phases where the presence of an unequally distributed third component may induce separation of the two main compenents without phase splitting. Similar phenomena may occur even in almost ideal gas mixtures [1–3]. Analogous phenomena are observed in liquids. In systems consisting of more than one phase, "uphill" diffusion, *i.e.* diffusion from lower to higher concentrations, may almost always be achieved if the solute is initially present in the solvent of lower dissolving power (*e.g.* iodine in water, with carbon tetrachloride as second solvent).

These cases, when properly formulated, do not lead to contradictions. The simple diffusion laws hold for binary mixtures at constant temperature and pressure and not too far from ideal behavior, *i.e.* especially in dilute solutions. A phase is defined by *Gibbs* as a homogeneous region of matter. Here we shall treat a region with continuously changing concentration as one phase, which in thermodynamics is objectionable.

[1] *E. J. Hellund*, Physic. Rev. *57*, 319, 328, 737 (1940); cf. *J. B. Duncan* and *H. L. Toor*, A.I.Ch.E. Journal *8*, 38 (1962).

[2] *W. Jost:* Diffusion in Solids, Liquids, Gases. 3rd Revised Edit., Academic Press, New York 1960; *W. Jost:* Diffusion, Methoden der Messung und Auswertung. Steinkopff, Darmstadt 1957; *W. Jost:* Diffusion und chemische Reaktion in festen Stoffen. Steinkopff, Dresden und Leipzig 1937.

[3] *S. Chapman* in *J. F. Masi* and *D. H. Tsai:* Progress in International Research on Thermodynamic and Transport Properties. Academic Press, New York-London 1962, pp. 257 et seq.

## II. Diffusion and State of Aggregation

It is a basic problem of diffusion theory to find the average distance which such a particle travels in unit time when delayed and forced to make detours by the many collisions suffered in one second (*e.g.* ca. $3\times10^9$ collisions per second at atmospheric pressure).

The phenomena are largely analogous, irrespective of the state of aggregation, but the free paths available differ widely. In a liquid, the free path is usually below the dimensions of the molecule, while for oxygen in the atmosphere, it is almost 1000 times the molecular dimensions and 30 times the average distance between the molecules at atmospheric pressure.

In liquids and solids (to which high polymers are closely related), there is a fundamental difference compared with gases. A gas molecule almost always moves freely, except during the very short time intervals during collisions. For particles in liquids and solids, the opposite is true: they never move freely, except during short intervals of favorable geometric and energetic constellations. In a solid, each particle is restricted to a definite lattice site about which it is oscillating. Its center of gravity usually does not undergo any average displacement. However, owing to a process to be discussed later, it may happen that a neighboring lattice site is empty. If in addition to this favorable geometric constellation the particle has enough energy to overcome any energetic barriers, then it can move over just one lattice distance into a new equilibrium position (cf. Fig. 2). Instead of the presence of an empty site next to a mobile

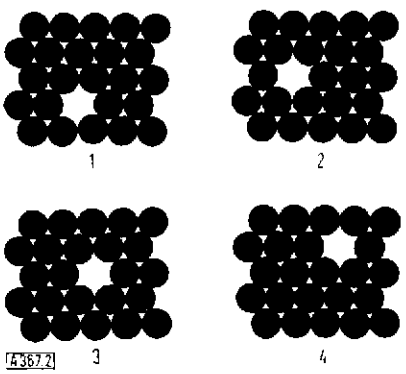



Fig. 2. Close-packed plane crystal lattice with a vacancy migrating by successive displacements of neighboring particles ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4$)

particle, the following process, which also creates vacancies, may be considered (this is, however, not the only possible process): A lattice particle may accumulate sufficient energy by fluctuations to leave its lattice site and move into an interstitial site (cf. Fig. 3) [*]. Thus a vacancy and a mobile interstitial site are created (*I. Frenkel*, 1926). At equilibrium, there is always a definite fraction of lattice defects present in solids; they are responsible for any diffusion (and, if the particles are charged, for the ionic conduction) occurring in the solids. Unoccupied lattice sites from

[*] According to usual concepts, the interstices may be "too small" to accommodate the particle. This means that sufficient energy must be supplied to make the transition possible.

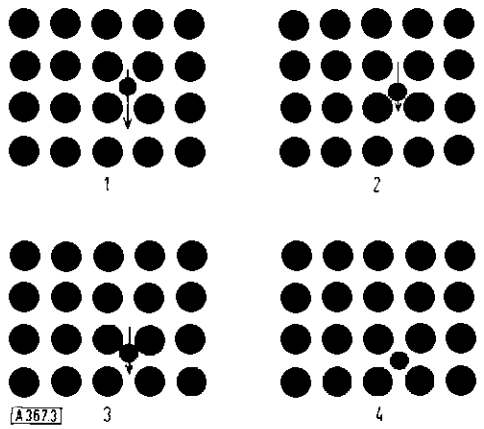



Fig. 3. Interstital particle migrating across a potential barrier ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4$); energy maximum between steps 2 and 3 (maximum in the direction of movement; saddle point when increase to the sides is taken into consideration).

suitable sources, *e.g.* surfaces or dislocations, can also diffuse into the interior of a crystal, or in other words, particles diffuse out of the lattice into unoccupied sites on surfaces or dislocations. The thermodynamic theory of lattice defects was developed by *W. Schottky* and *C. Wagner* in 1929; first quantitative calculations on the energies involved have been carried out by *Jost* since 1933, cf. [2]. The fraction of particles capable of surmounting an energy barrier of E cal/mole is given to a certain approximation by $\exp[-E/RT]$, *i.e.* by a Boltzmann factor. We may express this situation, somewhat arbitrarily, as follows: in a solid, a particle can move over a free path d (equal to its lattice distance) with an average speed $\bar{v}\cdot\exp[-E/RT]$, *i.e.* a very small average speed. During most of its oscillations (*e.g.* roughly $10^{13}$ per sec), the particle does not move away from its site at all, but in the fraction of oscillations given by the Boltzmann exponential, it moves with speed $\bar{v}$. In other words, the particle moves once over the distance d in an average time $\tau$ of roughly $d/(\bar{v}\cdot\exp[-E/RT])$.

The picture for a liquid is similar, though less precise. In liquids, the particle is not fixed to a definite lattice site, because a liquid has a much less rigid structure than a crystal. However, if we look at the surroundings of a given particle (Fig. 4.1), there is still something like a "short-distance" order resembling somewhat the

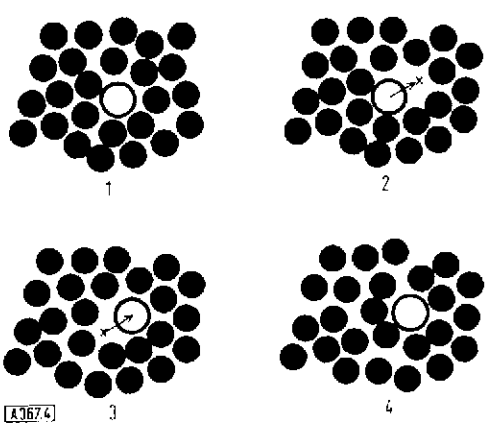



Fig. 4. Migration ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4$) of a particle dissolved in a liquid by displacement of neighboring particles.

arrangement in a crystal, but the nearest neighbors are slightly farther away from the central atom, and are less ordered. This has been described as the "cage" model of a liquid. The central atom moves in a "cage" of neighboring atoms, without changing its average position over a certain period of time (Fig. 4.2). Then, very similar to a true crystal, a constellation of the cage may arise (Fig. 4.3) which provides a new equilibrium position for the central atom. This position, unlike that in the crystal, may be less than a lattice distance away from the original position, and the energy barrier obstructing the movement will accordingly be considerably smaller than that in the crystal (*e.g.* in Fig. 6 but not in Fig. 5).

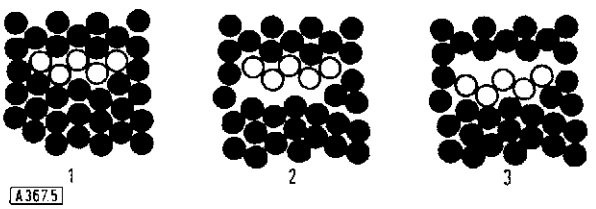



Fig. 5. Migration (1 → 2 → 3) of a rigid molecule in a liquid. This is an unfavorable and hence improbable mechanism.

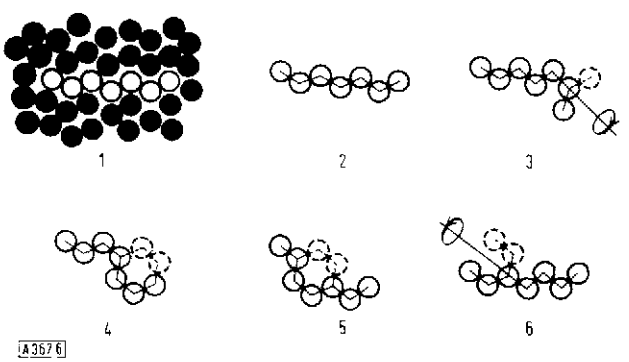



Fig. 6. Diffusion (migration) of a large, non-rigid molecule requiring less free space (compared to the rigid molecule in Figure 5).

The resulting expression for $\tau$ or $\bar{v}$ will be very similar in form, but will give a much higher average mobility than in a crystal [*].

## III. Models for the Diffusion of Single Mobile Particles

In the following, using a simplified picture, we shall trace the path of a single particle, irrespective of the underlying model. We shall introduce some simplifications compared to the process occurring in nature, but these will not affect essentially the results to be derived.

### 1. With a Discontinuous Source

In Figures 7 and 8, the motion of a single particle is represented beginning with the time t = 0. The abscissa gives the displacement of the particle, +1, +2l, *etc.* to

[*] There are exceptional cases where the mobility in a crystal is as high as in solution, *e.g.* that of protons in palladium or of the cations in α-CuI, α-CuBr, and α-AgI. The ionic conductance of α-AgI and of α-CuBr near the melting point is even higher than that of the melt.

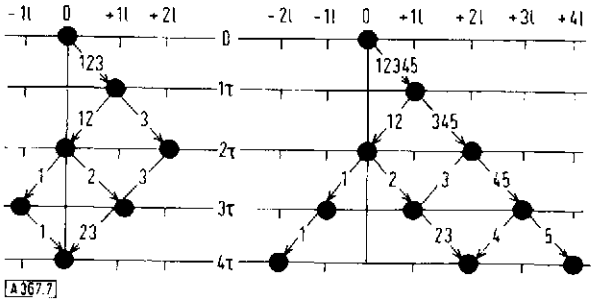



Fig. 7. Model of random walk: examples for the motion of 3 particles (1, 2, 3) moving discontinuously from t = 0 to t = 4 τ [left], and of 5 particles (1, 2, 3, 4, 5) [right].

the right of x = 0, its position at t = 0, and −1, −2l, *etc.* to the left of x = 0. The ordinate is time with the values τ, 2τ, *etc.* Since any displacement by x = ± l during time τ is of equal probability, the particle after time t − τ, may

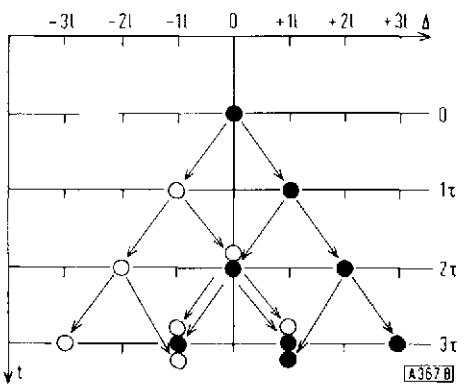



Fig. 8. Distribution of particles moving at random (cf. Figure 7).

be at ± 1, after t = 2τ at 0, ± 2l, *etc.* For t = τ, the positions ± l can be reached in one way each, and for t = 2τ there is one possibility for positions ± 2l, but two possibilities for x = 0, *etc.*

In the second column of Table 1, the number of possibilities n is listed for t = 0τ, 1τ, *etc.* in accordance with Figure 8; the next column gives the possible displacements Δ; Column 4 gives the sum of the squared displacements $\Sigma\Delta^2$; every displacement has been counted separately, *i.e.* for t = 3τ once the displacements ± 3l, three times the displacements ± l, thus altogether 2×4 = 8 displacements. Column 5 contains the sum of all the squared displacements divided by the number n of displacements.

Table 1. Mean square displacement $\overline{\Delta^2}$ for random walk as a function of the diffusion time.

| t | n | Δ | $\Sigma\Delta^2$ | $\frac{1}{n}\Sigma\Delta^2 = t \cdot l^2/\tau = \overline{\Delta^2}$ |
|---|---|---|---|---|
| 0 τ | 1 | 0 | 0 | 0 |
| 1 τ | 2×1 | ± 1 l | 2 l² | l² |
| 2 τ | 2×2 | 0 ; ± 2 l | 8 l² | 2 l² |
| 3 τ | 2×4 | ± l, ± 3 l | 24 l² | 3 l² |

Thus, from this simple model we obtain empirically the relation for the "mean square" displacement

$$\overline{\Delta^2} = \frac{1}{n}\Sigma\Delta^2 = t\,\frac{l^2}{\tau},$$

*i.e.* $\overline{\Delta^2}$ is proportional to the time.

If we set

$$\frac{l^2}{2\tau} = D,$$

and call this magnitude – of dimension [length]$^2$·[time]$^{-1}$ – a diffusion coefficient, then we arrive at the relationship

$$\overline{\Delta^2} = 2Dt,$$

an expression which was first derived from another starting point by *Einstein* in 1905.

In diffusion experiments, we do not observe the mean displacement of a single particle (as we actually can do with Brownian movement), but instead the concentration distribution at a time t, starting from a given initial distribution at t = 0. The mean behavior in the above example should approach the concentration distribution given by a differential equation when t and x are sufficiently large. This differential equation is for the "one-dimensional" case, *i.e.* diffusion in the ±x direction only, in a vessel of constant cross-section in a plane perpendicular to x, for the sake of simplicity assumed to have an area of 1 cm$^2$:

$$(1) \qquad \partial c/\partial t = D\,\partial^2 c/\partial x^2 .$$

Equation (1) is a linear partial differential equation, which for the initial conditions corresponding to the above example (amount s of substance at x = 0 at the time t = 0) and for an infinite system (*i.e.* no boundary conditions for x) is solved by

$$(2) \qquad c = \frac{s}{2\sqrt{\pi\, Dt}} \cdot \exp[-x^2/4Dt]$$

In Figures 9–11, the concentration distribution given by Equation (2) is compared with that derived from the former model for 256 particles (= s) at x = 0 for t = 0. In Figure 9, a diffusion curve is shown that has been calculated according to Equations (1) and (2), assuming that in an infinite cylinder of 1 cm$^2$ cross-sectional area the total amount of substance s (here set equal to 256)

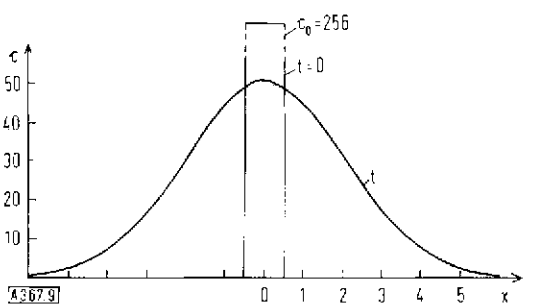



Fig. 9. Concentration distribution of 256 particles according to Equation (2) for:
a) D = 2 × 10$^5$ cm$^2$/sec; t = 10$^{-5}$ sec;
b) D = 0.7 cm$^2$/sec; t = 3 sec ($H_2$—$O_2$);
c) D = 0.6 × 10$^{-5}$ cm$^2$/sec; t = 3 × 10$^5$ sec;
d) D = 5 × 10$^{-8}$ cm$^2$/sec; t = 4 × 10$^7$ sec.

had been present at x = 0 at time t = 0. The curve denoted by t would result for thermal neutrons in graphite after $10^{-5}$ sec, for interdiffusing hydrogen and oxygen after 3 sec, for a low molar-mass compound dissolved in water, or for Cu ions diffusing in solid α-AgI above 147 °C (approximately 400 °C below its melting point) after about 3.5 days, and for protein molecules diffusing in water after a time of the order of one year.

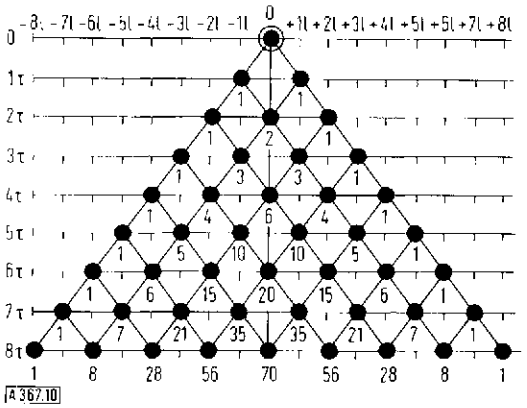



Fig. 10. Most probable distribution for 256 particles starting from x = 0 at time t = 0, up to t = 8 τ (last line).

In Figure 10 we show the distribution of particles under the original assumption of random walk, if at t = 0 we had 256 particles at x = 0 and they were moving by random-walk processes over distances ± l for t = τ. Thus for t = τ, with equal probabilities for ±l, we would have 128 particles both for x = l and x = −l. For t = 2τ, there would be 128 particles at x = 0 and 64 particles at both x = 2l an x = −2l, *etc.* Finally, at t = 8τ, we should have the distribution indicated in Figure 10: *viz.* 70 particles at x = 0, 56 particles eacn at x = ±2l, 28 particles each at x = ±4l, 8 particles each at x = ±6l, and 1 particle each at x = ±8l.

This distribution, of course, is a spezilization again, for we assume that the 256 particles move according to the maximum probability. Actually, other (especially asymmetric) distributions will occur in addition to the most probable distribution, but the average of many experiments will approach the distribution of Fig. 10. In Fig. 11 discontinuos distributions are shown for t = 0, τ, 2τ, etc. A comparison with the corresponding continuous distributions is possible only, if we compare corresponding areas under the curve, as is done in Fig. 11. It is seen that, except for t = 0 and x = 0, there is no exact agreement between the two sets of diagrams. The agreement, however, is as close as one might reasonably expect, and for t = 8τ is already rather good.

### 2. With Several Discontinuous Sources

From the preceding we have some idea of the depth of penetration Δ of diffusing particles whose mean square ($\overline{\Delta^2}$) equals 2Dt. Normally we do not have a discontinuous source at x = 0 but a certain concentration distribution over a finite distance in x. How this affects the result will again be easily seen. Figure 12 shows an "initial distribution" corresponding to four "instantaneous sources" of strengths 2s at x = ±h/4 and x = ±3h/4. We consider this a certain approximation

towards a homogeneous distribution of concentration $c_0$ between $x = -h$ and $x = +h$; naturally a better approximation is obtained by assuming twice the number of

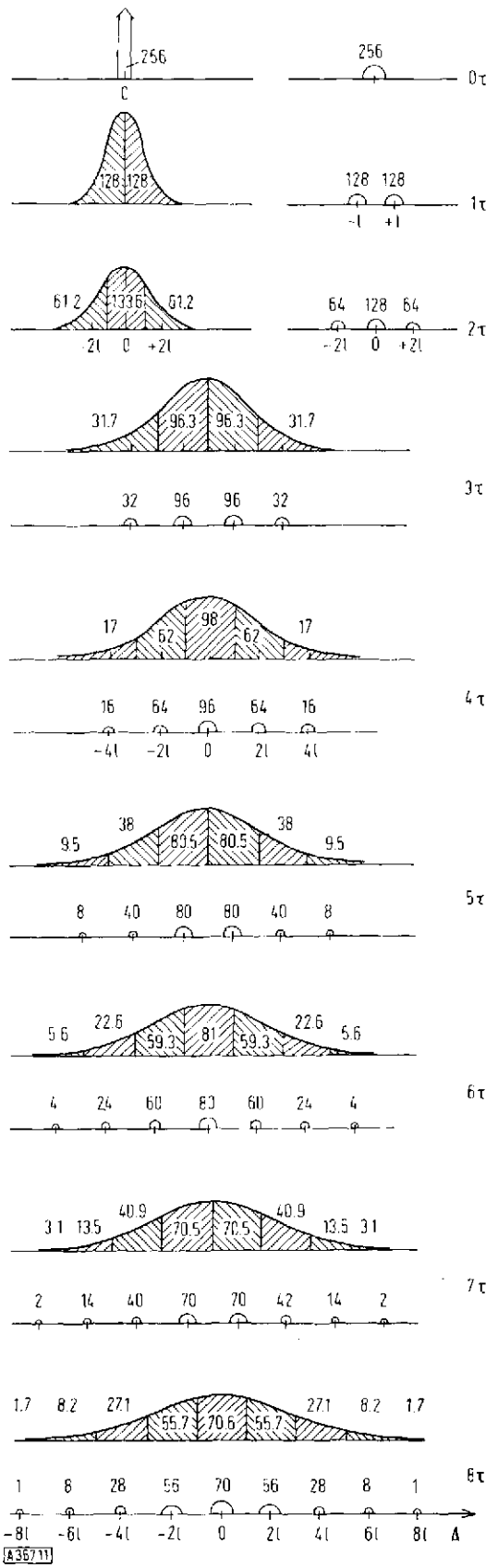



Fig. 11. Distribution of 256 particles, starting from $x = 0$ at time $t = 0$ and after times $\tau$, $2\tau$, ..... $8\tau$ according to the molecular model (cf. Fig. 10) [right or below], and according to Equation (2) [left or above].

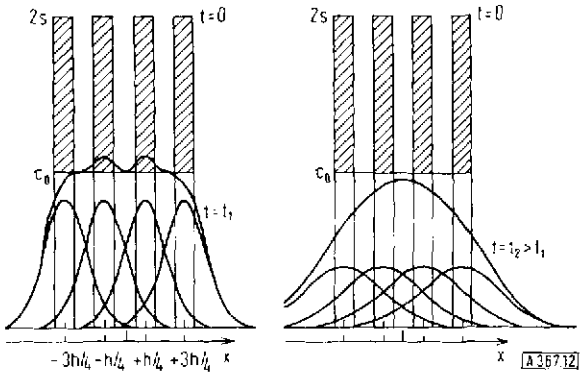



Fig. 12. Approximation of a continuous distribution by superposition of discontinuous distributions from four sources at $-3h/4$, $-h/4$, $+h/4$, $+3h/4$ at time $t = 0$ (above) and for two other times $t_2 > t_1 > 0$ (below).

sources of half the above strength and at half the above spacing, *etc.*

We claim that the concentration (particle) distribution resulting from superposition of these sources is obtained simply by superposition of the distributions arising from the individual sources. In the particle picture, this follows immediately, because the particles are considered to move independently of each other. In the picture of the continuous concentration distribution it is a consequence of the linearity of the underlying diffusion equation [Equation (1)]. In the upper part of Figure 12, the concentration (particle) distribution for $t = 0$ is indicated, and underneath the individual concentration distributions resulting from diffusion from the original sources for a time $t = t_1 > 0$ and for a later time $t_2 > t_1$ are shown together with the superposition obtained.

Analytically, the following expression would be obtained for the limiting continuous distribution with $c = c_0$ for $-h < x < +h$ and $c = 0$ for $|x| > h$ at $t = 0$:

$$(3)\quad c = c_0\left[\operatorname{erf}\frac{(h+x)}{2\sqrt{Dt}} + \operatorname{erf}\frac{(h-x)}{2\sqrt{Dt}}\right],$$

where erf is the Gauss error integral or error function [*]

$$(4)\quad \operatorname{erf}(\xi) = \frac{2}{\sqrt{\pi}}\int_0^{\xi} e^{-\eta^2}\,d\eta\,.$$

Examples for Equation (4) are contained in Figure 13.

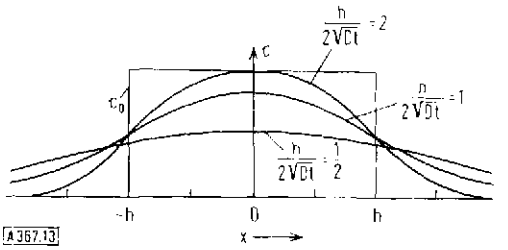



Fig. 13. Concentration distributions according to Equation (3); rectangular distribution at $t = 0$ (increasing argument $h/2\sqrt{Dt}$ corresponds to decreasing time).

[*] Values for this function are to be found in tables, so that it is very easy to apply, cf. [2].

## IV. Special Types of Diffusion

### 1. Diffusion Resulting in Directed Flow

So far we have considered only examples involving complete symmetry with respect to $x = 0$, *i.e.* no mean displacement of the center of gravity of the particles or of the diffusing substance. Normally, however, we have a preferential direction of diffusion.

The question is then how can this directed flow result if forward and backward movements of a particle are equally probable? It should be noted that the distributions obtained either by random walk or from the diffusion equation were symmetrical with respect to $x = 0$, *i.e.* all distributions found are even functions of x and there is no resulting mean displacement of a particle. If we cut our system in two at $x = 0$, leaving half the particles to the left and half to the right, then nothing would be changed. Consequently, the distributions for $x > 0$ are maintained, if half the original concentration is given at $t = 0$ and an impermeable boundary is introduced at $x = 0$. An illustration of the influence of the wall on the random-walk model is given in Figure 14. Here one possible path for a particle is shown (full circles) lying totally to the right of $x = 0$. Instead of the last two steps, we might just as well have a path to the left (open circles).

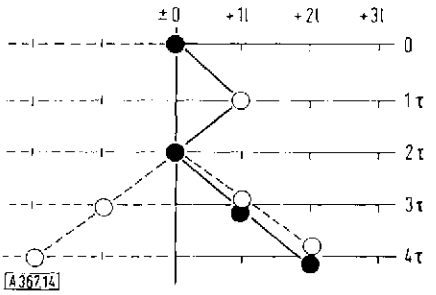



Fig. 14. Random motion of a particle near $x = 0$, with and without a separating wall. (At $x = \pm l$ and $t = \tau$ there should be a full circle).

Owing to the wall at $x = 0$, we must assume that this path is "reflected" at $x = 0$, giving the path to the right (open circles). However we had concluded that the introduction of the wall does not change anything. This is to be understood as follows: In the original model, without the wall, there was another path, the mirror image of the full circles. Up to $t = 2\tau$ this path is situated to the left of $x = 0$, and then corresponds to the open circles at $x > 0$. Cutting the distribution at $x = 0$ actually does not change anything, because the new reflected path is identical with another path which was initially present but whose first half has been cut away.

The same conclusion can be reached using the differential equation (1). This equation is a consequence of Equation (5), the equation for the diffusion flux in the $-x$ direction

$$(5) \quad J = -D\partial c/\partial x ,$$

This is to be understood in the following way: The diffusion flux J, *i.e.* the amount of substance crossing unit area perpendicular to the x direction in unit time in the $+x$ direction, is proportional to the negative of the concentration gradient $\partial c/\partial x$; the factor of proportionality is the diffusion coefficient D identical with the value defined earlier. The concentration is given as the amount of substance per unit volume. The unit chosen for the amount of substance is irrelevant but must of course be the same in J and in c. The fact that diffusion normally leads to an equalization is expressed by the fact that J is set proportional to $-\partial c/\partial x$; this implies a diffusion flux from high to low concentrations.

Having qualitatively understood the meaning of Equation (5), we can see how the "boundary condition" at $x = 0$ for an impermeable wall is to be formulated. An impermeable wall means vanishing diffusion flux, and for non-vanishing D this vanishes only for $\partial c/\partial x = 0$ at $x = 0$. This, however, is automatically obtained by cutting the previous distributions at $x = 0$ where, on account of symmetry, the tangent is horizontal.

In the random-walk picture, unidirectional flow can be understood as follows. If we start with a distribution such as that shown in Figure 13, *i.e.* $c = c_0 = \text{constant}$ for $-h < x < +h$, which we assume cut at $x = 0$, then for $t = 0$ and $x < h$, the particles present will move with equal probability in the $+x$ or $-x$ directions. Some therefore cross the plane at $x = h$, thus giving rise to a flux in the $+x$ direction. Since at time $t = 0$ there are no particles present at $x > h$, no flux in the opposite direction can arise. For $t > 0$, there are particles present at $x > h$, but their concentration is smaller than that for $x < h$. Thus, there will be a preferential flow in the $+x$ direction. With increasing time, the concentration differences, $\partial c/\partial x$ and the diffusion flux J will diminish. Of course it must not be forgotten that at the boundary $x = 0$ all particles moving to the left are reflected; consequently, near $x = 0$, only a flux to the right is possible. Thus random walk leads to a complete qualitative understanding of diffusion phenomena.

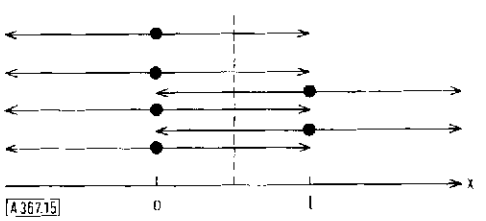



Fig. 15. Diffusion flux in the molecular model with more particles crossing the plane at $x = 1/2$ towards the right than towards the left.

Now we must consider the question of the "stationary flux". In order to obtain the "flux" of particles, we consider Figure 15. The particles at $x = 0$ have equal probability for moving by $\pm 1$ in time $\tau$. If their number ("concentration") is $n_0$, then we expect a flux $J_+$ in the $+x$ direction (number of moving particles times velocity):

$$(6) \quad J_+ = n_0 \, l/2\tau$$

$l/\tau$ being their average velocity in the $+x$ direction. Correspondingly, of $n_1$ particles at $x = 1$, there will move to the left (the minus sign indicating the direction):

$$(7) \quad J_- = -n_1 \, l/2\tau .$$

Both together give a resulting flux J in the +x direction, across a reference plane of unit area at x = 1/2:

$$(8) \quad J = J_+ + J_- = -(n_1 - n_0)1/2\tau = -\frac{(n_1 - n_0)}{1} \frac{l^2}{2\tau}.$$

If we denote the difference in the concentration of particles over the distance $\Delta x = 1$ by $\Delta c = n_1 - n_0$, we obtain

$$(9) \quad J = -(\Delta c/\Delta x) D,$$

using the definition of D from p. 716. In the limiting case we obtain

$$(10) \quad J = -\lim_{\Delta x \to 0} \frac{\Delta c}{\Delta x} D = -D\, \partial c/\partial x,$$

as equation for the diffusion flux (usually called Fick's First Law). We calculate the diffusion flux for a simple hypothetical example.

We assume a membrane 0.01 mm thick with the properties of water. We wish to find the amount of oxygen diffusing through this wall if at one side (I) a partial pressure of 0.2 atm is maintained, and 0.1 atm at the other (II). In the stationary state, we may replace $\partial c/\partial x$ by $\Delta c/\Delta x$, where $\Delta x$ is the thickness of the membrane and $\Delta c$ is the difference in concentration $c_2 - c_1$ for equilibrium conditions at the interfaces. If the solubility coefficient be $\alpha$, we have

$c_1 = \alpha p_I$, $c_2 = \alpha p_{II}$

and therefore

$J = -D\, \partial c/\partial x = -\alpha D\, (p_2 - p_1)/\Delta x.$

If $\alpha = 0.03$ cm³/atm/cm³ at S.T.P. and $D = 2 \times 10^{-5}$ cm²/sec,

we obtain

$J = -0.03 \times 2 \times 10^{-5}\, (0.1 - 0.2) \times 10^3 = 0.06 \times 10^{-3}$ cm/sec,

*i.e.* oxygen, referred to its partial pressure in air, would flow with a linear speed $v = 0.3\ 10^{-3}$ cm/sec through the membrane. Assuming a surface area comparable with that of the human lung (ca. $10^6$ cm²), this would correspond to an air volume of 300 cm³ passing per second; this is sufficient to account for all observed phenomena.

Of course, for the absorption coefficient any other definition could be taken instead of the one chosen above: cm³ of gas absorbed per cm³ of liquid, at atmospheric pressure. In problems of permeation one normally finds, as in the above example, a permeability coefficient equal to the product $\alpha \cdot D$.

## 2. Experimental Examples

In order to give some quantitative information about diffusion flux and concentration equalization, numerical values for diffusion coefficients under widely varied conditions are summarized in Tables 2a–2d. The diffusion coefficients for gases at room temperature and atmospheric pressure lie between 0.1 and 1 cm²/sec, those for solutions and liquids of moderate molar mass between $10^{-5}$ and $10^{-6}$ cm²/sec. Under favorable conditions, solids have diffusion coefficients of the same order of magnitude as liquid solutions (*e.g.* the cations in the $\alpha$-phases of AgI, CuI, CuBr, $Ag_2S$, $Cu_2S$, $Ag_2Se$, *etc.*). The diffusion coefficient of silver ions in solid silver bromide at room temperature is not below $10^{-16}$ cm²/sec, a rather small value. The quantities of interest for purposes of orientation are:

a) The time for an average mean displacement (roughly equal to the square root of the mean square displacement), which is comparable with the time necessary for marked equalization of concentration differences over the same distance.

b) The magnitude of the diffusion flux in a quasi-stationary or stationary state, *e.g.* the rate of transport through an artificial membrane or a cell wall.

Let us start with an extreme example, namely that of solid silver bromide. Its lattice distance is roughly $4 \times 10^{-8}$ cm. The time necessary for the corresponding square displacement is roughly

$$\tau < (4 \times 10^{-8})^2/2 \times 10^{-16} = 8 \text{ sec},$$

*i.e.* a silver ion in solid silver bromide changes its site every few seconds. For many this may be a rather unexpected result.

The time necessary for a penetration of one lattice distance in a solid is roughly the same as for the equalization of concentration differences in a gas over a distance of 1 cm. A penetration of 0.1 mm within gases is obtained in less than a millisecond.

The diffusion coefficient of sucrose in water at room temperature is roughly $5 \times 10^{-6}$ cm²/sec. In Table 3, some values for the diffusion of sucrose in water are given. Thus it takes about a day to penetrate a 1 cm layer, while an equalization of concentrations over 1 $\mu$ takes only a millisecond.

The diffusion coefficients of oxygen, nitrogen, and carbon dioxide in water do not differ widely, and are

Table 2a. Diffusion coefficients [$\times 10^5$ cm²/sec] in water at 18 °C.

| NaCl | KCl | Methanol | Glycerol | Phenol | Urea | Glucose | $H_2$ | $O_2$ | $N_2$ | $CO_2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1.35 | 1.7 | 1.1 | 0.8 | 0.8 | 1.1 | 0.6 | 3.6 | 2.0 | 1.6 | 1.5 |

Table 2b. Diffusion coefficients [cm²/sec] for interdiffusion of gases at S.T.P.

| $p$-$H_2$/$o$-$H_2$ | $H_2/O_2$ | $O_2/N_2$ | $O_2/CO_2$ |
|---|---|---|---|
| 1.29 | 0.70 | 0.18 | 0.14 |

Table 2c. Diffusion coefficients [$\times 10^5$ cm²/sec] of iodine in various solvents at 20 °C.

| n-Heptane | $CS_2$ | $CCl_4$ | $CH_3OH$ | $H_2O$ |
|---|---|---|---|---|
| 2.4 | 2.7 | 1.2 | 1.6 | 0.5 |

Table 2d. Diffusion coefficients [$\times 10^7$ cm²/sec] of some high polymers at 20 °C.

| Edestine/water | Tobacco mosaic virus/water | Soluble starch/water | Cellulose acetate/acetone |
|---|---|---|---|
| 3.2 | 0.5 | 11.5 | 5.4 |

Table 3. Diffusion times t for various depths of penetration (sucrose in water at room temperature).

| x [cm] | 1 | 0.1 | 0.01 | 0.001 | 0.0001 |
|---|---|---|---|---|---|
| t [sec] | $10^5$ | $10^3$ | 10 | $10^{-1}$ | $10^{-3}$ |

roughly four times those of sucrose. The rates of diffusion for small molecules in muscle and other tissues are comparable, though smaller than those in water. Thus, the above figures are adequate for estimates even in this case.

### 3. Three-Dimensional Case

Here it might only be mentioned that for the three-dimensional case Equation (10) should be replaced by Equation (11):

$$\text{(11)} \quad \mathfrak{J} = -D \operatorname{grad} c$$

which, specialized for Cartesian coordinates, gives for the three components of the flux vector

$$\text{(12)} \quad \begin{aligned} J_x &= -D\, \partial c/\partial x \\ J_y &= -D\, \partial c/\partial y \\ J_z &= -D\, \partial c/\partial z \end{aligned}$$

For non-isotropic systems, the diffusion coefficient would depend on direction, giving for the special case of the coordinate axes coinciding with the main axes of the diffusion tensor $\mathbf{D}$

$$\text{(13)} \quad \mathfrak{J} = -\mathbf{D} \operatorname{grad} c$$

$$\text{(14)} \quad \begin{aligned} J_x &= -D_x\, \partial c/\partial x \\ J_y &= -D_y\, \partial c/\partial y \\ J_z &= -D_z\, \partial c/\partial z \end{aligned}$$

with three main diffusion coefficients, two of which may be equal, *e.g.* in a crystal of hexagonal symmetry; in a crystal of cubic symmetry, all three coefficients are equal. Strongly direction-dependent diffusion coefficients are observed for the hexagonal crystals of zinc or bismuth. Only one diffusion coefficient occurs in each term of Equation (14) because of *Onsager*'s reciprocity relations, [2, 4, 5], but these cannot be discussed here.

### 4. Diffusion in Multicomponent Mixtures

Less simple is the case of unidimensional diffusion in a multicomponent mixture. For three components 1, 2, and 3, we write the "phenomenological relations":

$$\text{(15)} \quad \begin{aligned} J_1 &= -D_{11}\, \partial c_1/\partial x - D_{12}\, \partial c_2/\partial x \quad D_{13}\, \partial c_3/\partial x \\ J_2 &= -D_{21}\, \partial c_1/\partial x - D_{22}\, \partial c_2/\partial x - D_{23}\, \partial c_3/\partial x \\ J_3 &= -D_{31}\, \partial c_1/\partial x - D_{32}\, \partial c_2/\partial x - D_{33}\, \partial c_3/\partial x \end{aligned}$$

In Equations (15), in contrast to Equations (14), coupling coefficients $D_{ik}$ ($i \neq k$) appear as off-diagonal terms, although there are less than 9 independent coefficients. When we consider that the concentrations and consequently also the fluxes in a ternary system are not independent [*], and apply the Onsager reciprocity relations [**], we can show that of the nine coefficients in Equations (15), only three independent coefficients remain ($= 3\times 2/2$), or in general for an n-component system, there are $n(n-1)/2$ independent coefficients. Equations (15) do not yet contain the most general formulation possible.

We consider a special example, *viz.* the diffusion in a ternary gas mixture. *Hellund* [1] filled a diffusion tube fitted with a shutter in the middle, as follows. The lower half contained 570 mm Hg of both methane and carbon dioxide, while the upper half contained equal amounts of hydrogen and carbon dioxide. Both halves had a total pressure of 1140 mm Hg at 0 °C. The shutter was opened, and the partial pressure of $CO_2$ in the upper half rose by 68.2 mm. Thus, owing to the concentration gradients of $H_2$ and $CH_4$ and their interdiffusion, induced diffusion occurred with the $CO_2$ although originally it had no concentration gradient. This effect is sometimes called osmotic diffusion and is formally contained in Equations (15) as a result of the off-diagonal "coupling terms".

In the following, an attempt is made to understand this from a not purely formal point of view. When in the above example, the methane and hydrogen start to diffuse, each would move freely if it were not slowed down by the presence of the other component. Here the carbon dioxide causes resistance to the motion of the other two components, irrespective of the presence of a concentration gradient. Consequently, there is a frictional force between each pair of species, if only they are in relative motion.

According to the principle of action and reaction, the forces between two species i and k (referred to a volume element or to unit volume) will be of equal amount but of opposite sign, *i.e.*

$$\mathfrak{F}_{ik} = -\mathfrak{F}_{ki}.$$

These forces will naturally set the carbon dioxide in motion, even without a concentration gradient, except in the degenerate case where the frictional forces between $CO_2$ and $H_2$ are equal but of opposite sign to those between $CO_2$ and $CH_4$.

Thus we see that there may be considerable coupling forces in a ternary system, even for ideal gases. The preceding argument is essentially equivalent to the formal treatment by *Lamm* of diffusion in multicomponent systems [6]. We follow here a presentation given by *Ljunggren* [7].

If the total force acting on particle i ($i = 1, 2, 3$) is $\mathfrak{F}_i$, and if $N_i$ is the number of particles i per unit of volume, then

$$\text{(16)} \quad N_i \mathfrak{F}_i = -\sum_j{}' \Phi_{ij} (\bar{v}_i - \bar{v}_j), \quad i \neq j.$$

It is reasonable to set the frictional force between particles i and j proportional to the mean relative speed

[4] *I. Prigogine:* Etude de thermodynamique des Phenomenes irreversibles. Dunod, Paris-Liege 1947; Introduction to Thermodynamics of Irreversible Processes. Ch. Thomas, Springfield, Ill. 1955.

[5] *S. R. de Groot:* Thermodynamics of Irreversible Processes. North Holland Publishing Comp. Amsterdam 1951.

[*] Accordingly, in a binary system, there is only one coefficient of interdiffusion.

[**] Unfortunately, in the above formulation, these are not of the simple form $D_{ik} = D_{ki}$.

[6] *O. Lamm*, J. physic. Colloid Chem. *51*, 1063 (1947).

[7] *S. Ljunggren* in *J. W. Williams:* Ultracentrifugal Analysis in Theory and Experiment. Academic Press, New York 1963, pp. 29 et seq.

of the particles, $\Phi_{ij}$ being a factor of proportionality [*]. The choice of signs in Equation (16) is reasonable, because the friction will tend to decrease the relative speed. $\bar{v}_i$ and $\bar{v}_j$ are the mean speeds [**] of the interdiffusing particles (the frame of reference here, of course, is irrelevant). Naturally $\Phi_{ij}$ must be equal to $\Phi_{ji}$. If there are no external forces and the system is in thermal equilibrium [†], the system must be in mechanical equilibrium [††], *i.e.* $\sum_i N_i \mathfrak{F}_i = 0$. We now write Equations (16) explicitly for a three-component mixture:

$$
\begin{aligned}
N_1\mathfrak{F}_1 &= \quad * \quad - \Phi_{12}(\bar{v}_1-\bar{v}_2) - \Phi_{13}(\bar{v}_1-\bar{v}_3) \\
N_2\mathfrak{F}_2 &= \Phi_{21}(\bar{v}_2-\bar{v}_1) \quad * \quad - \Phi_{23}(\bar{v}_2-\bar{v}_3) \\
N_3\mathfrak{F}_3 &= -\Phi_{31}(\bar{v}_3-\bar{v}_1) - \Phi_{32}(\bar{v}_3-\bar{v}_2) \quad *
\end{aligned}
\qquad (16')
$$

with

$$\Phi_{12} = \Phi_{21}\ ;\ \Phi_{13} = \Phi_{31}\ ;\ \Phi_{23} = \Phi_{32}\ .$$

Obviously, the sum of the forces equals zero, *i.e.* $\sum_i N_i \mathfrak{F}_i = 0$. If we now assume that component 3 is the carbon dioxide in the above example and is originally at rest, *i.e.* $\bar{v}_3 \equiv 0$, Equations (16′) are reduced to

$$
\begin{aligned}
N_1\mathfrak{F}_1 &= \quad * \quad - \Phi_{12}(\bar{v}_1-\bar{v}_2) - \Phi_{13}\bar{v}_1 \\
N_2\mathfrak{F}_2 &= -\Phi_{12}(\bar{v}_2-\bar{v}_1) \quad * \quad - \Phi_{23}\bar{v}_2 \\
N_3\mathfrak{F}_3 &= +\Phi_{31}\bar{v}_1 + \Phi_{32}\bar{v}_2 \quad *
\end{aligned}
\qquad (16'')
$$

Thus

$$\mathfrak{F}_3 \neq 0\ ,$$

since for component 3 at rest

$$v_1 = -v_2$$

but except for singular conditions

$$\Phi_{31} \neq \Phi_{32}\ .$$

## 5. "Uphill" Diffusion

As mentioned above, there are other examples where the diffusion of one component is not simply proportional to a concentration gradient and in addition does not lead to concentration equalization. In order to understand this, we consider the lower part of Figure 16.

To the left we assume a shallow trough, to the right a deep one divided from the former by a porous wall. If we fill the left trough with water, this will slowly penetrate the wall and fill up the right trough to the level of the left one. If we compare the amount of water per unit area to the left and to the right, this amount has considerably increased, compared to that at the left, but in accordance with simple physical laws.

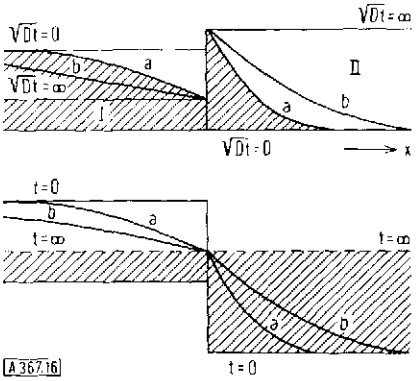



Fig. 16. Scheme for uphill diffusion. Above: concentration distribution for a partition coefficient ≠ 1 (cf. [2]). Below: model with two troughs of different depths.

Curve a: $t = t_1 > 0$

Curve b: $t = t_2 > t_1$.

For comparison: if a substance diffuses from one phase into another, *e.g.* iodine from water into carbon tetrachloride, then at equilibrium the "iodine level" in both phases is filled up not to equal concentrations, but to equal absolute activities (or equal chemical potentials) in both phases.

If a single phase is not homogeneous, it is not the drop in concentration that represents the driving force for diffusion, but the drop in chemical potential [*]. Diffusion in two-phase systems with distinct values of equilibrium concentrations (partition coefficient ≠ 1) and different diffusion coefficients were first treated by *Jost* in 1937 (cf. [2]). In a diffusing sample there may be concentration distributions for $t = 0$ and for $t = t_1 > 0$ as in Figures 17 and 18.

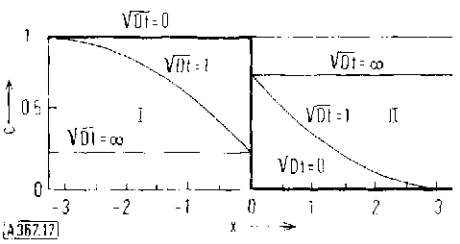



Fig. 17. Diffusion in an infinite system.
Original distribution of the concentration (bold line):

$c = 1$ for $x \leq 0$; $c = 0$ for $x > 0$.

There are two phases I ($x < 0$) and II ($x > 0$) for which $D_I = D_{II}$ and the partition coefficient $\varkappa = c_{II}/c_I = 3$.

[*] These considerations readily lead to a well known rational description of diffusion processes in non-ideal mixtures (cf. [2,4,5]). It is not reasonable simply to replace concentration by activity.

[*] $\Phi_{ij}$ plays the role of a friction coefficient between particles i and j. Of course $\Phi_{ii}$ ought to vanish; consequently the summation $\Sigma'$ is marked as being carried out over $i \neq j$.

[**] These speeds are usually extremely small compared to the mean root square velocity $\sqrt{\overline{v^2}}$, being of the order of 1 cm/sec if $\sqrt{\overline{v^2}} \geq 10^4$ cm/sec.

[†] This is always assumed, although diffusion actually causes small temperature differences owing to the so-called diffusion thermo-effect, the reverse effect of thermal diffusion.

[††] We might continue here by setting

$$\Phi_{ij} = R_{ij} N_i N_j$$

and showing that the new friction coefficients fit into the usual scheme of thermodynamics of irreversible proceses; cf. [7].

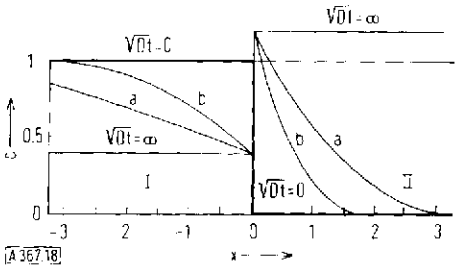



Fig. 18. Diffusion in an infinite system.
(cf. Fig. 17). $D_I = 4\ D_{II}$; $\varkappa = c_{II}/c_I = 3$.
Curve a: $\sqrt{D_I}$ t = 2; $\sqrt{D_{II}}$ t = 1.
Curve b: $\sqrt{D_I}$ t = 1; $\sqrt{D_{II}}$ t = 0.5.

*Darken* [8] obtained corresponding curves experimentally for the diffusion of carbon in alloyed steels, *e.g.* steels containing low and high amounts of Si or Mn. In a triangular diagram for the system Fe–Si–C (Fig. 19), the following course of the concentration with time may be observed: If the original samples A and B have different silicon contents but equal carbon contents, then, owing to the gradient in chemical potential of the carbon

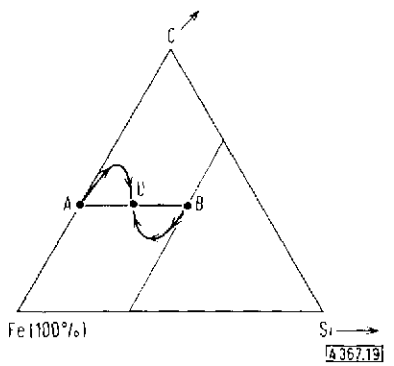



Fig. 19. Diffusion in the three-component system Fe—Si—C (steel); A and B indicate the original concentrations, U gives their final state. The curve marked with arrows indicates the change in concentration with time.

[8] *L. S. Darken*, Amer. Inst. Mining metallurg. Engr., techn. Publ., Metals Technology *15*, 2311 (1948).

caused by the different silicon contents, the carbon concentrations at A and B may shift in opposite directions, leading to differences in carbon content. Later, when the concentration of the slower diffusing silicon becomes equalized, the carbon concentration again becomes homogeneous. Locally a rise (fall) and then a fall (rise) in carbon concentration with time is observed, similar to that of the $CO_2$ concentration in the above example for gas diffusion. However, in the gas example, a gas-kinetic effect was responsible for the result, the gas mixture exhibiting almost ideal behavior, whereas in the iron-silicon-carbon system, deviations from ideal behavior are responsible for the observed phenomena.

Historically, the iron-carbon diffusion system is one of the oldest and most important ones. The Saga of Wieland der Schmied is supposed to provide information on the cementation of iron, *i.e.* carbonization of iron surfaces by diffusion, and surface hardening produced in this way. This technique must have been known in the early iron age. It is closely connected with the art of Damascening (Damascus steel, Damascus swords) by welding iron and steel. According to *Böhme* [9], the East Gothic king Theodorich described Damascened sword blades in a letter in the year 520 A. D. At about 1000 °C, diffusion coefficients of over $10^{-7}$ cm²/sec have been measured for carbon in iron. This would give a depth of penetration per day of $> 1$ mm, a depth which may appear unexpectedly high to those unfamiliar with diffusion phenomena in solids, and which is quite sufficient for hardening the surfaces of sword blades.

Incidently, the diffusion of carbon in iron (as well as that of nitrogen atoms and hydrogen atoms in many metals) does not involve a disorder in the basic metal. These particles are built-in on interstitial sites, and by surmounting a potential barrier can move from one interstitial site to a corresponding neighboring site.

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German version: Angew. Chem. *76*, 473 (1964)

[9] *Cl. Böhme*, Arch. Eisenhüttenw. *34*, 227 (1963).

# Stereospecific Homopolymerization of Cyclopentene [*]

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*The polymerization of cyclo-olefins, like that of olefins with an internal double bond, is sterically hindered. Within recent years it has become possible to prepare copolymers of these compounds with ethylene, with the aid of anionic coordination Ziegler catalysts. This copolymerization always results in cis-opening of the double bond. Despite the steric hindrance, cyclobutene and cyclopropene have also been homopolymerized, with opening of the double bond. – Rather surprisingly, the best catalysts for homopolymerization of cyclopentene are those which exhibit low activity in the polymerization of ethylene. Ring cleavage occurs with $MoCl_5/Al(C_2H_5)_3$ to give the cis-polypentenamer, whereas $WCl_6/Al(C_2H_5)_3$ gives the trans-polypentenamer. Both polypentenamers exhibit elastomeric properties. – Evidence from infrared spectra and oxidative degradation indicates that the monomer units in the trans-polypentenamer are linked head-to-tail. It is presumably the single bond adjacent to the double bond that is broken. Using X-ray methods at −50 °C, it was possible to determine the crystal structure of the crystalline trans-polypentenamer at about 400 % elongation.*

## I. Introduction

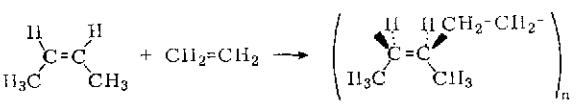
In theory, cyclo-olefins should be able to polymerize, either with opening of the double bond to form polycycloalkenes, or with ring cleavage to form unsaturated linear polymers.

Until a few years ago, all attempts to convert cyclo-olefins into high molecular-weight homopolymers were unsuccessful. To find the reason for failure, it is necessary to consider the two possible modes of reaction.

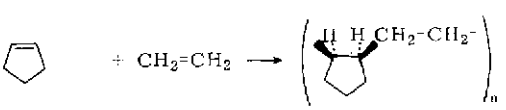
Cyclo-olefins are related to acyclic olefins which have an internal double bond. It is well known that such olefins (*e.g.* 2-butene) show very little or no tendency to polymerize. One of the reasons which have long been adduced to explain this behavior is steric hindrance due to the bulk of the substituents on both carbon atoms of the double bond. In recent years we have been able to show [1–5] that steric hindrance is indeed the main reason why these olefins do not tend to polymerize *via* opening of the double bond. We have succeeded, with the aid of suitable catalysts, in obtaining high molecular-weight products by copolymerization of both aliphatic and cyclic olefins with a comonomer such as ethylene, which has only slight steric hindrance on the carbon atoms of the double bond. Particularly suitable catalysts for this type of copolymerization are those which act by an anionic coordination mechanism, especially those prepared from vanadium salts and organoaluminum compounds.

However, even in these copolymers there is no direct linkage of monomer units derived from an olefin with an internal double bond; instead, each unit of this type alternates with one or more ethylene units. By using high molar ratios of olefins with an internal double bond to ethylene in the liquid reaction phase, we have succeeded in preparing so-called alternating copolymers, *i.e.* copolymers in which each monomer unit derived from an olefin with an internal double bond is followed by only one ethylene unit, and vice versa.

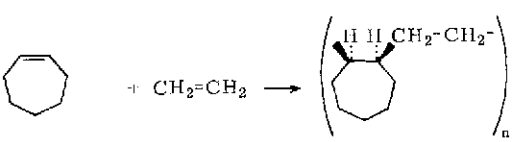
In the case of *cis*-2-butene [1,2], cyclopentene [3], and cycloheptene [4], we were able to prepare alternating copolymers in which the tertiary carbon atoms are stereoregular, with the result that these copolymers could be crystallized. The structures assigned to these alternating copolymers are shown in formulae *(1a)* · *(1c)*. In all



*(1a)*



*(1b)*



*(1c)*

[*] Lecture given by *G. Dall'Asta* at the Gordon Research Conference on Polymers, Santa Barbara, Calif. (U.S.A.) in January, 1964, and to the Macromolecular Colloquium in Freiburg/Breisgau (Germany), in March, 1964.

[1] *G. Natta, G. Dall'Asta, G. Mazzanti, I. Pasquon, A. Valvassori,* and *A. Zambelli,* J. Amer. chem. Soc. *83,* 3343 (1961).

[2] *G. Natta, G. Dall'Asta, G. Mazzanti,* and *F. Ciampelli,* Kolloid-Z. *182,* 50 (1962).

[3] *G. Natta, G. Dall'Asta, G. Mazzanti, I. Pasquon, A. Valvassori,* and *A. Zambelli,* Makromolekulare Chem. *54,* 95 (1962).

[4] *G. Natta, G. Dall'Asta,* and *G. Mazzanti,* Chim. e Ind. *44,* 1212 (1962).

[5] *G. Dall'Asta* and *G. Mazzanti,* Makromolekulare Chem. *61,* 178 (1963).

three crystalline alternating copolymers, the double bonds have opened exclusively in the *cis*-direction, resulting in an *erythro*-ditactic (and in this particular case *erythro*-diisotactic) structural regularity.

Until a few years ago, *cis*-opening of double bonds during polymerizations was regarded as unlikely. Classical organic chemistry has many examples of *trans*-additions to double bonds, and this mode of reaction is also regarded as preferable on thermodynamic grounds. Surprisingly, however, all polymerizations in which the direction of the addition to the double bond has been determined in recent years on the basis of a regular steric structure of the polymer have been found to be *cis*-additions. This was first demonstrated with poly(alkenyl alkyl ethers) [6] which are prepared by cationic coordination polymerization, and subsequently for the stereospecific cationic polymerization of both *cis*- and *trans*-β-chlorovinyl ethers [7]. Investigations of Japanese workers [8,9] on the infrared spectra of crystalline polymers of deuterated propylene prepared in our Institute [10] showed that the stereospecific polymerization of propylene to isotactic polymers also proceeds exclusively by *cis*-opening of the double bond; the same is true of the polymerization of ethylene with Ziegler catalysts [11].

The apparent reasons for the *cis*-opening of the cyclo-olefins and of *cis*-2-butene during their copolymerization with ethylene were recently discussed in detail [5].

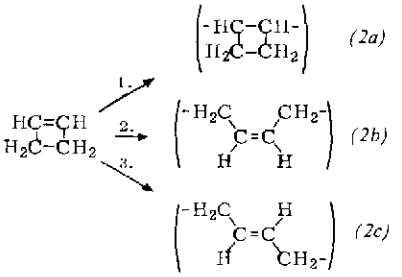
Our investigations have indicated that steric hindrance, which, as mentioned above, makes direct linkage of monomer units derived from cyclo-olefins extremely difficult and usually impossible, is of decisive importance only in cycloalkenes higher than cyclobutene. Cyclo-olefins with smaller rings behave differently. Following the success of American workers [12] in demonstrating that a polymer obtained by spontaneous polymerization of cyclopropene is built up of interlinked, saturated three-membered rings, we succeeded in obtaining crystalline homopolymers by stereospecific anionic coordination polymerization of cyclobutene (which does not undergo spontaneous polymerization) using vanadium catalysts [13,14]. These homopolymers have the structure of saturated polycyclobutylenes *(2a)*; their formation has evidently been accompanied by opening of the double bond [*].

The main reasons for the direct linkage of cyclo-olefin units during polymerization of cyclopropene and cyclobutene are probably the following:

1. In contrast to larger ring systems, both cyclopropene and cyclobutene have planar conformations. Transition to the saturated polymer *(2a)* enables cyclobutene to assume non planar conformations, resulting in a much larger gain in energy than in the polymerization of larger rings.

2. Steric hindrance around the doubly-bonded carbon atoms is much less in the small rings, so that effective mutual approach of the monomer molecules is appreciably easier.

Moreover, with cyclobutene we first encountered another mode of polymerization of cyclo-olefins [13], namely polymerization with ring cleavage, so that the monomer units in the polymer still contain the double bond. This mode of polymerization occurs preferentially in anionic coordination polymerization with catalysts based on titanium. Depending on the type of catalyst used, the products are predominantly either *cis*- *(2b)* or *trans*-polybutadienes *(2c)*.




It should be pointed out in this connection that, in recent years, polymerizations accompanied by either opening of the double bond or ring cleavage have also been described for norbornene [16,17]. Its endocyclic methylene group makes this monomer a special one from both the steric and energetic points of view, and results in very high reactivity. We shall return to this case in Section IV.

Steric hindrance probably plays a much smaller part in polymerization of cyclobutene with ring cleavage than in polymerization involving opening of the double bond. For this reason, the former mode of polymerization ought to be favored. However, the opposite is in fact true. Pure polycyclobutenes can be obtained from cyclobutene, but it is impossible, even under the most favorable conditions, to convert cyclobutene into pure polybutadienes with the catalysts mentioned; this reaction is always accompanied by the formation of appreciable amounts of polycyclobutenes.

It might be supposed from the observations described above that cyclo-olefins higher than cyclobutene would show no significant tendency to form polymers by ring cleavage. Nevertheless, we decided to investigate the question whether higher cyclo-olefins, particularly cyclopentene, can homopolymerize by ring cleavage.

[6] *G. Natta, M. Farina, M. Peraldo, P. Corradini, G. Bressan*, and *P. Ganis*, Rend. Accad. naz. Lincei (8) *28*, 442 (1960).

[7] *G. Natta, M. Peraldo, M. Farina*, and *G. Bressan*, Makromolekulare Chem. *55*, 139 (1962).

[8] *T. Miyazawa* and *Y. Ideguchi*, Polymer Letters *1*, 389 (1963).

[9] *H. Tadokoro, M. Ukita, M. Kobayashi*, and *S. Murahashi*, Polymer Letters *1*, 405 (1963).

[10] *M. Peraldo* and *M. Farina*, Chim. e Ind. (Milano) *42*, 1349 (1960).

[11] *M. Tasumi, T. Shimanouchi, H. Tanaka*, and *S. Ikeda*, J. Polymer Sci. A *2*, 1607 (1964).

[12] *K. B. Wiberg* and *W. J. Bartley*, J. Amer. chem. Soc. *82*, 6375 (1960).

[13] *G. Dall'Asta, G. Mazzanti, G. Natta*, and *L. Porri*, Makromolekulare Chem. *56*, 224 (1962).

[14] *G. Natta, G. Dall'Asta, G. Mazzanti*, and *G. Motroni*, Makromolekulare Chem. *69*, 163 (1963).

[*] According to the nomenclature adopted by the IUPAC Commission [15], polymers of this type should be referred to as poly-2-cyclobutylenamers.

[15] *M. L. Huggins*, J. Polymer Sci. *8*, 257 (1952).

[16] *W. L. Truett, D. R. Johnson, I. M. Robinson*, and *B. A. Montague*, J. Amer. chem. Soc. *82*, 2337 (1960).

[17] *G. Sartori, F. Ciampelli*, and *N. Cameli*, Chim. e Ind. *45*, 1478 (1963).

## II. Attempts to Homopolymerize Cyclopentene

### 1. Catalysts with Anionic Coordination Reaction Mechanisms

We first carried out series of experiments in the presence of catalysts known to be suitable for the homopolymerization of ethylene and α-olefins to high molecular-weight linear polymers. To improve the expected low tendency of cyclopentene to polymerize, the experiments were carried out in the absence of solvent, and the catalyst was prepared directly in the cyclopentene itself. The results are shown in Table 1.

Table 1. Attempts to homopolymerize cyclopentene in the presence of catalysts (containing Ti, Zr, V, or Cr) with anionic coordination polymerization mechanisms (experimental conditions: 6 h at −30 °C, followed by 14 h at +20 °C; molar ratio of cyclopentene: transition metal = 30:1; all samples undiluted).

| Catalyst system | Yield of polymer [%] | X-ray investigation | Chemical structure of polymer |
|---|---|---|---|
| $TiCl_4 + Al(C_2H_5)_3$ | 1 | crystalline | *trans*-polypentenamer |
| $TiBr_4 + (Al(C_2H_5)_3$ | 2 | crystalline | *trans*-polypentenamer |
| $ZrCl_4 + Al(C_2H_5)_3$ | 1 | crystalline | *trans*-polypentenamer |
| $VCl_4 + Al(C_2H_5)_3$ | 1 | crystalline | alternating ethylene-cyclopentene copolymers |
| $VOCl_3 + Al(C_2H_5)_2Cl$ | 3 | crystalline | |
| V(triacac) [*] + $Al(C_2H_5)_2Cl$ | 1.5 | crystalline | |

[*] (triacac) = triacetylacetonate. No polymers were obtained with the catalyst systems $CrBr_3/Al(C_2H_5)_3$, $Cr(triacac)/Al(C_2H_5)_2Cl$, and $CrO_2Cl_2/Al(C_2H_5)_3$.

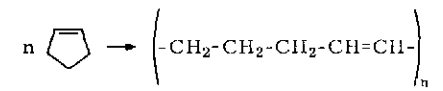
The following conclusions can be drawn from the experiments:

a) The behavior of cyclopentene depends largely on the transition element present in the catalyst.

b) Chromium-containing catalysts do not polymerize cyclopentene.

c) Vanadium-containing catalysts cannot homopolymerize cyclopentene. However, if ethylaluminum compounds are used in preparing the catalysts, the crystalline alternating cyclopentene/ethylene copolymers described above are formed. The tendency of the vanadium compounds to promote the formation of such products is evidently so strong that even the small quantities of ethylene eliminated from $Al(C_2H_5)_3$ during the reaction with the vanadium salts are sufficient for the formation of the copolymer.

d) Catalysts containing a Group IV metal, *e.g.* titanium or zirconium, can bring about homopolymerization of cyclopentene with ring cleavage to yield *(3)*.



As discussed in detail later, polymer *(3)* contains almost exclusively *trans*-double bonds. We shall term this polymer (which has not yet been described in the literature [*]) *trans*-polypentenamer, in accordance with the IUPAC nomenclature [15]. It is completely free from cyclopentene units resulting from opening of the double bond. The chemical and steric purity of the polymer *(3)* are the reasons for its crystallinity which can be observed to a small extent in the X-ray diagram of even the unstretched polymer.

e) However, polymerization of cyclopentene using the titanium or zirconium catalysts (Table 1) gives very low yields of *trans*-polypentenamer. This appeared to confirm our original supposition that the reactivity of cyclopentene would be very low compared with that of cyclobutene.

Despite the low conversion into polypentenamer with titanium or zirconium catalysts, it was observed with surprise that the reaction proceeded exclusively by ring cleavage. In view of the low ring strain in cyclopentene and the fact, mentioned above, that pure polybutadiene *(2b)*/*(2c)* is never obtained from cyclobutene under similar conditions, the polymer obtained from cyclopentene should also be expected to contain at best both possible forms of the monomer units. These observations led us to extend our investigations to other catalyst systems which, although they also act by an anionic coordination mechanism, are either inactive or nearly so in the homopolymerization of ethylene and α-olefins. The results are shown in Table 2.

The catalyst systems contained metals of Groups VI, VII, and VIII of the periodic table. These experiments have, surprisingly, shown the following:

a) Catalysts based on uranium, iron, manganese or cobalt are completely ineffective for polymerizing cyclopentene.

b) Catalysts based on molybdenum or tungsten promote homopolymerization of cyclopentene into polymers with the polypentenamer structure, in high yield. These

Table 2. Attempts to homopolymerize cyclopentene in the presence of catalysts with anionic coordination polymerization mechanisms. Experimental conditions: 4 h at −30 °C, followed by 14 h at 0 °C; molar ratio of cyclopentene: transition metal = 30:1; all samples undiluted. — No polymers were obtained with the catalyst systems $UF_4/Al(C_2H_5)_3$, $UO_2Cl_2/Al(C_2H_5)_2Cl$, $MnCl_2/Al(C_2H_5)_3$, $FeCl_3/Al(C_2H_5)_3$, $CoCl_2(Py)_2/Al(C_2H_5)_2Cl$, and $BaFeO_4/Al(C_2H_5)_2Cl$.

| Catalyst system | Yield of polymer [%] | Infrared analysis of polymer | | X-ray investigations | Chemical structure of polymer |
|---|---|---|---|---|---|
| | | Cyclopentylene units [%] | Pentenamer units [%] | | |
| $MoCl_5 + Al(C_2H_5)_3$ | 21 | 0 | 100 | amorph. | *cis*-polypentenamer |
| $WCl_6 + Al(C_2H_5)_3$ | 39 | 0 | 100 | cryst. | *trans*-polypentenamer |

[*] Polymers formed to a very low extent by ring cleavage of cyclopentene, are mentioned in the patent literature; however, the double bonds in the polymers obtained show no stereoregularity.

polymers contain no monomer units formed by opening of the double bond. It is of interest that, in the homopolymerization of cyclobutene, these catalyst systems neither exhibit high catalytic activity nor yield polymers with a pure polybutadiene structure.

c) The polypentenamer obtained with the catalyst system prepared from $WCl_6$ and $Al(C_2H_5)_3$ has the same steric structure as that obtained with the titanium or zirconium catalysts described above, *i.e.* it is essentially pure *trans*-polypentenamer. The polypentenamer obtained in the presence of the catalyst prepared from $MoCl_5$ and $Al(C_2H_5)_3$, on the other hand, has essentially a *cis*-polypentenamer structure. This polymer, too, has hitherto not been described in the literature. The next Section shows how the structures of the two polypentenamers were elucidated.

## 2. Chemical and Steric Structure of the Polypentenamers

The infrared spectra of the various polypentenamers enabled us to draw important conclusions regarding their chemical structures. It was first shown that the various polymers obtained in the presence of catalysts containing titanium, zirconium, or tungsten have practically identical infrared spectra (Fig. 1). These all show an intense absorption band at 10.35 $\mu$, characteristic of *trans*-double bonds; *cis* double bonds are present to an extent of only 2–3 %. Absorption bands due to other types of double bonds (*e.g.* vinyl, vinylidene, conjugated or other cumulative double bonds) are absent. Cyclic structures can be excluded owing to the absence of certain characteristic bands between 8 and 8.5 $\mu$, but mainly owing to the absence of the absorption band at 3.39 $\mu$, characteristic rather of cyclopentane structures. Quantitative determination of the double bonds gives almost exactly one double bond per pentenamer unit [*]. This interpretation of the infrared spectrum is sufficient to enable us to assign a *trans*-polypentenamer structure.

The infrared spectrum of the polymers obtained with the catalyst prepared from $MoCl_5$ and $Al(C_2H_5)_3$ is shown in Figure 2. The absorption bands at 7.12 and 13.8–13.9 $\mu$ can be ascribed to *cis*-double bonds. Only a small percentage of *trans* double bonds are present; other types of double bond are essentially absent. These spectra are also completely free from bands characteristic of cyclic structures. Quantitative determination again shows exactly one double bond per pentenamer unit [**]. Interpretation of the spectrum enables us to assign a *cis*-polypentenamer structure.

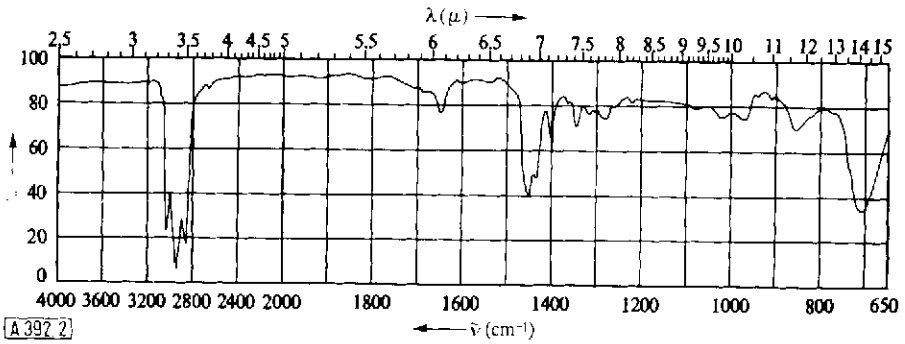



Fig. 2. Infrared spectrum of *cis*-polypentenamer (Perkin-Elmer 221 spectrophotometer; NaCl optics; film cast from benzene solution).

In order to define the chemical structure of the polymers precisely it is necessary to specify whether the monomer units are linked in a head to-tail or a head-to-head-tail-to-tail arrangement. The polymers expected in the two cases differ in the number of methylene groups between the pairs of double bonds. In head-to-tail polymers, each consecutive pair of double bonds must be separated by three methylene groups. In head-to-head-tail-to-tail polymers, on the other hand, two

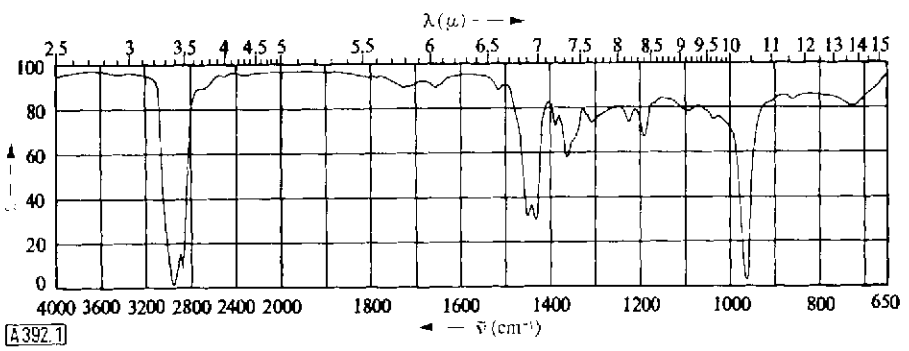



Fig. 1. Infrared spectrum of *trans*-polypentenamer (Perkin-Elmer 221 spectrophotometer; NaCl optics; film cast from benzene solution).

[*] The quantitative determination of the *trans*-double bonds was based on the following absorption coefficient: $K(10.35\ \mu) = 10 \times 10^4$ [mole·cm²/g] [18].

[**] Quantitative determination of the *cis*-double bonds was based on the following absorption coefficient: $K(7.12\ \mu) = 0.83 \times 10^4$ [mole·cm²/g] [18].

[18] *D. Morero, A. Santambrogio, L. Porri,* and *F. Ciampelli,* Chim. e Ind. *41*, 758 (1959).

structures are possible, according to the position in which the cyclopentene ring has been opened. If the single bond adjacent to the double bond is broken, the number of methylene groups between consecutive double bonds should be alternately six and none. If the ring opens at the single bond remote from the double bond, we should find alternately two and four methylene groups between two consecutive double bonds.

Since the infrared spectrum excludes the presence of conjugated double bonds, we rejected the possibility of an alternating series of six and no methylene groups, which would correspond to a polymer with pairs of conjugated double bonds. The remaining two cases, *viz.* head-to-tail and head-to-head-tail-to-tail linkages, are shown in formulae *(4)* and *(5)*, respectively.

$$-CH{=}CH-CH_2-CH_2-CH_2-CH{=}CH-CH_2-CH_2-CH_2-CH{=}CH-$$
*(4)*

$$-CH{=}CH-CH_2-CH_2-CH{=}CH-CH_2-CH_2-CH_2-CH_2-CH{=}CH-$$
*(5)*

In order to decide between these two possibilities, the *trans*-polypentenamer was ozonized in carbon tetrachloride and subjected to oxidative degradation with hydrogen peroxide. The sole degradation product from the first polypentenamer *(4)* should be glutaric acid, while the second polymer *(5)* should give equimolar amounts of succinic and adipic acids. The *trans*-polypentenamer yielded glutaric and succinic acids in a molar ratio of about 4:1, but no adipic acid [*].

In interpreting this result, it must be borne in mind that the oxidative degradation method used generally yields not only the expected acid, but also considerable quantities of the acid having one less carbon atom, as demonstrated by *Ziegler* et al. [19]. Degradation of the acid to the next lower homologue occurs during the treatment with hydrogen peroxide, probably by oxidation of an α-carbon atom followed by decarboxylation.

In view of this and of the fact that no adipic acid was found, it may be concluded that the polymer in question is head-to-tail *trans*-polypentenamer. Although our investigations on the *cis*-polypentenamer are not complete, we have good reason to believe that this polymer is also built up of units linked in a head-to-tail arrangement. The head-to-tail linkage was confirmed for the *trans*-polypentenamer by X-ray analysis. This polymer exhibits the behavior typical of many elastomers, particularly natural rubber: it is practically amorphous or only slightly crystalline in the unstretched state at room temperature, but on cooling or stretching it crystallizes to a considerable extent. A filament stretched to 400 % elongation and cooled to about −50 °C gives the spectrum of a highly oriented fiber with a large number of reflections (Fig. 3). According to this spectrum, the *trans*-polypentenamer has an orthorhombic unit cell with the following constants: a = 7.28 Å; b = 4.97 Å; c (fiber axis) = 11.9 Å.

[*] The acids were determined by thin-layer chromatography.

[19] *K. Ziegler, W. Hechelhammer, H. D. Wagner,* and *H. Wilms,* Liebigs Ann. Chem. *567*, 99 (1950).

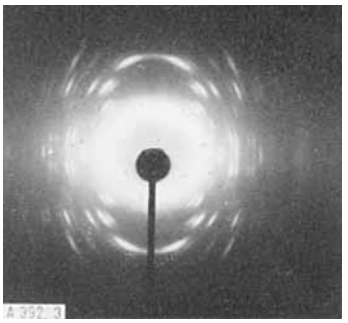


Fig. 3. X-ray fiber spectrum of the head-to-tail *trans*-polypentenamer (elongated by about 400 %; temperature ≈ −50 °C).

The model suggested by us for the macromolecule in the crystal lattice is shown in Figure 4. This model is characterized by a series of internal rotation angles of 120 ° and 240 ° about the single bonds adjacent to the double bond, and of 180 ° about all the other bonds.

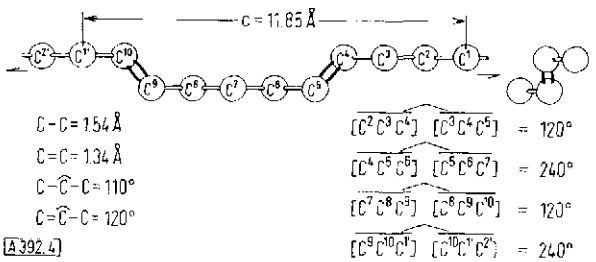



Fig. 4. Model of the crystalline *trans*-polypentenamer in side and front elevations (internal rotation angles which are not given separately are 180 °).

The recurring unit contains two monomer units; the symmetry element relating them is a twofold screw axis. The identity period of 11.85 Å calculated for this model agrees very closely with the experimental value.

Further interpretation of the fiber spectrum is possible on the basis of the unit cell described above; the most likely space group is either $C_{2v}^9$ or the centrosymmetric $D_{2h}^{16}$. The structural factors for these models agree closely with the experimental values.

## III. Properties of Polypentenamers with a Head-to-Tail Structure

The polypentenamers with regular *cis*- or *trans*-double bond structures described above are soluble in aromatic, alicyclic, and chlorinated hydrocarbons, but insoluble in alcohols, aliphatic ketones, and aliphatic ethers. The intrinsic viscosity [*] may lie between about 0.3 and 10, and was found to be between 2 and 8 for most polymers investigated.

The melting point of the *trans*-polypentenamer, +23 °C, was determined by dilatometry; that of the *cis*-polypentenamer, though probably much less than 0 °C, is still undetermined. In this connection, it should be recalled that the melting point of pure *trans*-polybutadiene is +145 °C, and that of pure *cis*-polybutadiene is +2 °C. Hence, as regards their melting points, it can be seen that an analogy exists between the polypentenamers

[*] The intrinsic viscosity is ten times the Staudinger viscosity z l/g).

and polybutadienes. Chemically, the former differ from the latter in possessing an additional methylene group per monomer unit. This additional methylene group produces considerable changes in the symmetry of the macromolecule and evidently causes *inter alia*, an appreciable depression of the melting point of the two polypentenamers. The very different melting points involve considerable differences in certain physical characteristics, especially the elastomeric properties.

It is well known that *cis*-polybutadiene possesses good elastomeric properties, whereas the *trans*-isomer is a thermoplastic material, mainly owing to its very high melting point, and exhibits no elastomeric properties at room temperature, even after vulcanization. The appreciable depression of the first-order transition temperature observed on passing from the polybutadienes to the polypentenamers brings both the *trans*- and the *cis*-polypentenamer into the elastomer field. In fact, *trans*-polypentenamer possesses excellent elastomeric properties.

Preliminary analysis indicates that these properties are due both to the large number of sequences of methylene groups, which confer high flexibility on the chains, and to the fact that the melting point is close to room temperature, like that of natural rubber.

The *trans*-polypentenamer can be readily vulcanized with all the systems commonly used for unsaturated elastomers. For example, we have vulcanized *trans*-polypentenamer using recipes based on either sulfur and accelerators or sulfur donors and accelerators.

The mechanical properties of these rubbers are excellent both with and without reinforcing fillers, *e.g.* carbon black. The stress-strain curve (Fig. 5) shows that the pure gum vulcanizate (curve I) gives the strong upward curvature characteristic of rubbers (*e.g.* natural rubber) which crystallize on stretching. Vulcanizates prepared in the presence of reinforcing fillers (curve II) show excellent mechanical and dynamic properties.

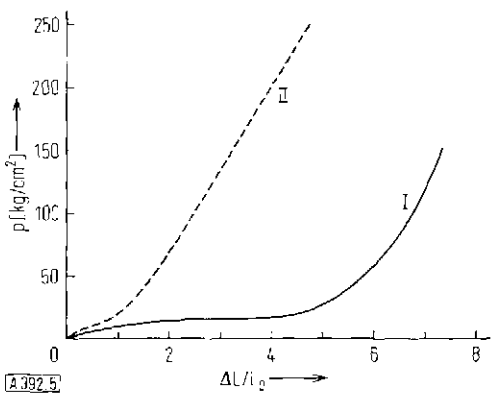



Fig. 5. Stress-strain diagram for unreinforced vulcanizates (curve I) and for rubber vulcanizates reinforced with HAF black (curve II).
Ordinate: Stress [kg/cm²].
Abscissa: Relative change in length.

The resilience [*] is shown in Figure 6 as a function of temperature. The temperature at which the rebound reaches a minimum is evidently very low. In this respect, the behavior of *trans*-polypentenamer resembles that of *cis*-1,4-polybutadiene, and differs from that of natural rubber.

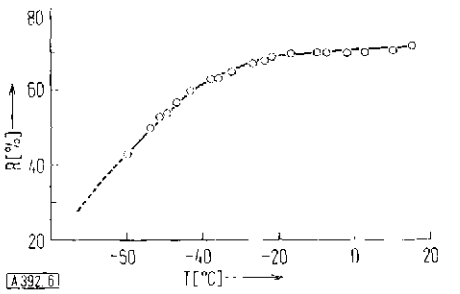



Fig. 6. Temperature-dependence of the rebound (R) of pure rubber vulcanizates.
(Micropendulum from Pirelli, S.p.A., Milan (Italy); height of fall = 0.125 mm).

## IV. Observations Concerning the Mechanism of Homopolymerization of Cyclopentene with Catalyst Systems Based on Molybdenum or Tungsten

The peculiar behavior of cyclopentene in the presence of catalysts prepared from molybdenum or tungsten salts and organoaluminum compounds induced us to investigate the mechanism of these catalysts in greater detail.

The polymerization mechanism is probably of the anionic coordination type. Evidence for this is provided by the observation that the individual components from which the catalyst is prepared and which normally exhibit a cationic or classical anionic mechanism, cause practically no polymerization of cyclopentene when used alone. The same is true of other Friedel-Crafts catalysts and a catalyst which acts by a free-radical mechanism (Table 3).

Table 3. Attempts to polymerize cyclopentene in the presence of various catalyst systems with different polymerization mechanisms.

| Catalyst | Solvent | Polymerization mechanism | Yield of polymer [*] |
|---|---|---|---|
| $TiCl_4$ | none | cationic | 0 |
| $CrO_2Cl_2$ | toluene | cationic | 0 |
| $CrO_2Cl_2$ | n-heptane | cationic | 0 |
| $WCl_6$ | none | cationic | slight; oil |
| $Al(C_2H_5)_2Cl$ | none | anionic | 0 |
| $Al(C_2H_5)_3$ | none | anionic | 0 |
| $CuCl_2 + Al(C_2H_5)_3$ | none | free-radical | 0 |

[*] After a reaction time of 24 h.

Another important point is to check whether any analogy exists between the mechanism of these polymerizations and that of the polymerization of aliphatic olefins (such as ethylene) in the presence of the same catalysts. For this reason, the experiments listed in Table 4 were carried out. It was found that the molybdenum and tungsten catalysts homopolymerize cyclopentene rapidly, but homopolymerize ethylene much more slowly. On the other hand, attempts to copolymerize cyclopentene with ethylene yielded no copolymers, but only homopolymers of cyclopentene, as if no ethylene had been present.

[*] The resilience is defined by the relative rebound height (cosine value) of a pendulum after impact on the sample (measure of the conversion of kinetic energy into heat on impact.)

Table 4. Attempts to homopolymerize cyclopentene or ethylene and to copolymerize cyclopentene with ethylene.

| Catalyst system | Monomers [a] | | Conversion [moles of monomer/ moles of catalyst] | Structure of polymer |
|---|---|---|---|---|
| | Cyclo-pentene | Ethylene | | |
| $MoCl_5 + Al(C_6H_{13})_3$ | – | + | 1 | polyethylene |
| $WCl_6 + Al(C_2H_5)_2Cl$ | – | + | 10 | polyethylene |
| $MoCl_5 + Al(C_6H_{13})_3$ | + | – | 20 | *cis*-polypent-enamer |
| $MoCl_5 + Al(C_6H_{13})_3$ | + | + | 20 | *cis*-polypent-enamer [b] |
| $WCl_6 + Al(C_2H_5)_2Cl$ | + | + | 30 | *trans*-polypent-enamer [b] |

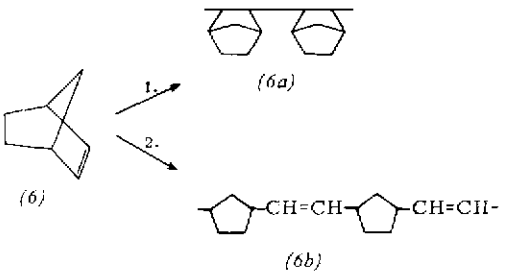
[a] A minus sign indicates the absence, plus sign the presence of the monomer in question.

[b] The absence of ethylene units in the polypentenamer obtained from copolymerization of cyclopentene with ethylene was demonstrated using ethylene labelled with $^{14}C$.

The most likely explanation for this is that the coordination of cyclopentene to the catalytically active centers is greatly favored, *i.e.* the cyclopentene immediately occupies all active centers, so that the ethylene is unable to participate in the reaction.

As regards the position at which the cyclo-olefin ring opens during the polymerization, two possibilities arise in theory: cleavage of a single bond adjacent to the double bond, or cleavage of a single bond remote from the double bond. It is not easy to solve this problem by direct methods since, in a head-to-tail polymer, the structure of the macromolecule must be the same, irrespective of the position at which the ring opens. However, various considerations have led us to adopt the view that the cyclopentene ring opens at a single bond next to the double bond. The following two points support this view.

1. In the polymerization of norbornene *(6)*, in the presence of catalysts acting by an anionic coordination mechanism [16], the unsaturated five-membered ring is cleaved exclusively at the single bond adjacent to the double bond. The position of cleavage in this molecule is known with certainty from the structure of the polymer *(6b)*. However, this ring cleavage of norbornene is due to special circumstances, since the polymer which would be formed by cleavage of the unsaturated five-membered ring at a bond not adjacent to the double-bond would still contain a ring unsaturation (in the six-membered ring).




2. The double bond of cyclopentene is a *cis*-double bond. Ring cleavage at a single bond remote from the double bond would therefore be expected to yield exclusively, or at least predominantly, *cis*-polypentenamer, since this type of double bond is already present. Cleavage of a single bond next to the double bond, on the other hand, should have very little or no effect on the steric structure of the double bond in the polypentenamer, since the formation of *trans*-polypentenamer would require only isomerization of an electron pair. In this type of reaction the catalyst would probably determine the steric structure of the double bond in the growing chain. This consideration agrees with the experimental findings.

It is not easy at present to formulate a detailed reaction mechanism which explains all the observations reported above, including some others which will be reported later; however, it is hoped that this will be possible when more detailed information is available.

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# Photochemical Substitutions on Metal Carbonyls and Their Derivatives

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*The photochemical reaction of n- and π-electron donors with metal carbonyls or their derivatives, which was discovered some years ago, provides a means of preparing a wide range of new metal-carbonyl derivatives which are obtainable only in poor yields or not at all by thermal reactions. – Preparative methods are described. The mechanism of this photochemically induced substitution was elucidated for selected examples, and an attempt has been made to gain an insight into the polarity of the metal-ligand bond. – This paper is intended as a survey of work published recently in this field.*

## I. Introduction

Two fundamental types of reaction have been observed for the action of electron donors D on metal carbonyls $M(CO)_x$ or their derivatives $Y_aM(CO)_x$ (M = metal; Y = ligand):

a) Substitution reactions, in which one molecule of carbon monoxide is eliminated from the metal carbonyl $Y_aM(CO)_x$ and replaced by the donor D:

$$Y_aM(CO)_x + D \rightarrow Y_aM(CO)_{x-1}D + CO.$$

b) Base reactions, in which the metal carbonyl disproportionates to form substituted ionogenic metal carbonylates [1], *e.g.*

$$3\ Mn_2(CO)_{10} + 12\ D \rightarrow 2\ [MnD_6][Mn(CO)_5]_2 + 10\ CO.$$

Whether a given metal carbonyl and a particular electron donor should be expected to give a substitution or a base reaction has already been discussed in detail in the literature [1]. Thus, the carbonyls of group VI metals undergo substitution with n-electron donors, while the carbonyls of group VII and VIII metals undergo a base reaction with donors incapable of back-donation (cf. p. 735); however, even the latter metal carbonyls are preferentially substituted as the tendency of the donor to participate in back-donation increases. The present work is concerned only with substitutions in which the photochemical reaction of π-electron donors [2a] and n-electron donors [2b] has been used as a new principle.

## II. The Difference between Thermal and Photochemical Substitutions

Thermal substitutions may proceed by an $S_N1$ mechanism, in which the intermediate electron acceptor $Y_aM(CO)_{x-1}$ is formed by thermal dissociation:

$$Y_aM(CO)_x \rightleftharpoons Y_aM(CO)_{x-1} + CO$$

This then adds onto the donor to fill up its electron deficiency. This $S_N1$ mechanism has been shown to occur in the formation of $Ni(CO)_2[P(C_6H_5)_3]_2$ from $Ni(CO)_4$ and $P(C_6H_5)_3$ [3]. It is also supported by the very rapid $^{14}CO$ exchange in $Ni(CO)_4$ [4]. On the other hand, the carbonyls of group VI metals, arene metal tricarbonyls, cyclopentadienylmanganese tricarbonyl, and $Mn_2(CO)_{10}$ undergo practically no exchange with $^{14}CO$ at room temperature [5], so that an $S_N1$ mechanism is ruled out for these carbonyls in thermal substitutions. They probably react by an $S_N2$ mechanism *via* a transition complex:

$$Y_aM(CO)_x + D \rightarrow [Y_aM(CO)_x \cdots D] \rightarrow Y_aM(CO)_{x-1}D + CO.$$

In contrast, the primary photochemical act in the preparation of metal-carbonyl derivatives by irradiation of dissolved metal carbonyls involves initial formation of an electron acceptor $\{Y_aM(CO)_{x-1}\}$ by removal of one molecule of CO from the excited molecule $\{Y_aM(CO)_x\}^*$. The existence of an electron acceptor $\{M(CO)_5\}$ has been proved both chemically [6] and spectroscopically [7]. The half-life of this unstable acceptor is of the order of a few minutes. The monosubstituted compound $Y_aM(CO)_{x-1}D$ is then formed simply by addition of an n- or π-electron donor into the electron deficiency of the photochemically generated acceptor. This reaction is basically a photochemically induced $S_N1$ process:

$$Y_aM(CO)_x + h\nu \rightarrow \{Y_aM(CO)_x\}^* \rightarrow \{Y_aM(CO)_{x-1}\} + CO$$
$$\xrightarrow{D} Y_aM(CO)_{x-1}D.$$

## III. Range of Application of Photochemical and Thermal Substitution Reactions

Experience has shown that thermal substitution of the carbonyls of group VI, VII, and VIII metals can generally be carried out between 50 and 150 °C, if a

[1] *W. Hieber, W. Beck,* and *G. Zeitler,* Angew. Chem. *73*, 364 (1961).

[2a] German Pat. 1146053 (Aug. 2nd, 1960), inventors: *E. O. Fischer* and *H. P. Kögler.*

[2b] *W. Strohmeier* and *K. Gerlach,* Z. Naturforsch. *15b*, 413 (1960).

[3] *W. S. Meriwether* and *M. L. Fiene,* J. Amer. chem. Soc. *81*, 4200 (1959).

[4] *F. Basolo* and *A. Wojcicki,* J. Amer. chem. Soc. *83*, 520 (1961).

[5] *A. Wojcicki* and *F. Basolo,* J. inorg. nuclear Chem. *17*, 77 (1961).

[6] *W. Strohmeier* and *K. Gerlach,* Chem. Ber. *94*, 398 (1961).

[7] *I. W. Stolz, G. R. Dobson,* and *R. K. Sheline,* J. Amer. chem. Soc. *84*, 3589 (1962); *85*, 1013 (1963).

strong donor is used as co-reactant. However, there are certain metal carbonyl derivatives, *e.g.* cyclopentadienylmanganese tricarbonyl $C_5H_5Mn(CO)_3$, which do not undergo thermal reaction, *e.g.* with triphenylphosphine, even at 200 °C [8]. From the thermodynamic point of view, the reaction could be forced to occur by increasing the temperature. However, the maximum temperature which can be used for thermal substitutions is limited by the range of stability of the starting materials and final products, which experience has shown to become narrower for metal carbonyl derivatives, the weaker the donor properties of D.

However, in the photochemical reaction of metal carbonyl derivatives, the intermediate unstable acceptor $\{Y_aM(CO)_{x-1}\}$ is produced photochemically in the primary process, which can take place at or below room temperature. This makes it possible to isolate even relatively unstable substitution products, since the addition of a weak donor D to the acceptor always takes place at low temperatures. Thus, as is shown by the following Tables, a wide range of new compounds, which were not available by other methods, have become accessible by the photochemical route. Another advantage of photochemical procedures is that they permit specific preparation of mono- or disubstitution products, a feature which can be achieved only with difficulty, if at all, by thermal substitution reactions. Thus, $W(CO)_6$ undergoes direct thermal reaction with $CH_3CN$ to give the trisubstituted compound $W(CO)_3(CH_3CN)_3$ [9], but $W(CO)_5CH_3CN$ and $W(CO)_4(CH_3CN)_2$ have been prepared photochemically [10]. Moreover, the photochemical process is suitable for reactions with both n- and π-electron donors.

## IV. Procedures

### 1. Preparation of Metal Carbonyl Derivatives

The general method for the photochemical preparation of metal carbonyl derivatives involves ultraviolet irradiation of a solution of the metal carbonyl in the presence of the donor D, the CO liberated being removed from the solution by a stream of nitrogen. The course of the reaction can be followed by quantitative determination of the CO removed. An optical arrangement for quantitative measurements with monochromatic light has been described earlier [6]. For preparative work on a larger scale, the simpler arrangement shown in Figure 1 can be used.

The solution to be irradiated is placed in a vessel A, which is equipped with ground glass joints. A double-walled Pyrex-glass vessel B, containing a high-pressure mercury burner C (Type Q 81, Hanau) and cooled by running water, is inserted into A. If necessary, the burner can be cooled with compressed air *via* inlet P. The CO liberated is removed at $H_2$ by a current of nitrogen led in through the three-way tap $H_1$.

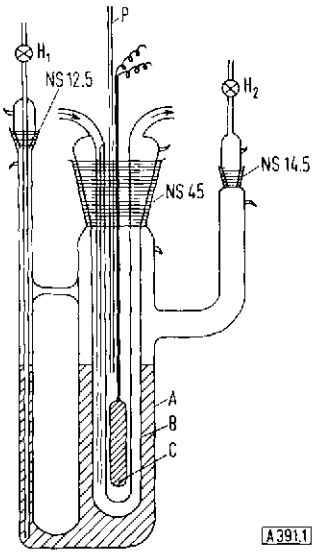



Fig. 1. Irradiation apparatus for preparative work. (Capacity about 50 ml.)

When the reaction is complete, the solution can be displaced from the irradiation vessel at tap $H_1$ by nitrogen or argon introduced through $H_2$, *i.e.* with exclusion of air. After removal of the solvent and the starting materials, the crude product is purified by recrystallization or sublimation *in vacuo*. The following is an example of a typical preparation. Precise procedures for each compound are to be found in the appropriate original publications (see Tables 2, 3, and 4).

Piperidinochromium pentacarbonyl: 270 mg (1.23 mmole) of $Cr(CO)_6$ and 1 ml of piperidine were dissolved in 25 ml of tetrahydrofuran and irradiated until 1.02 mmole of CO had been liberated; the solvent was then removed from the yellow solution at a bath temperature of 30 °C in a flash evaporator at 20 mm Hg. The yellow-brown oily residue was taken up in petroleum ether and freed from residual piperidine by shaking with 1 N HCl. The petroleum ether solution was dried and the solvent pumped off, the residue being immediately sublimed *in vacuo* at 60 °C bath temperature. The yield was 170 mg (60 %).

The operations must be carried out under nitrogen or argon, since most metal carbonyl derivatives are more or less sensitive to air in solution depending on the donor D. It has been shown experimentally that relatively slight decomposition is sufficient to make the isolation of a pure product difficult or impossible (poor crystallizability and great sensitivity of the contaminated crude product towards air).

### 2. Influence of the Solvent

The choice of a suitable solvent is of vital importance to the yield and isolation of pure samples of many photochemically prepared metal carbonyl derivatives. We have observed that the most suitable solvent varies from one metal carbonyl to another and with the nature of the donor. The best results were achieved with the solvents given in Table 1.

The following points have also been found to be important, under certain circumstances, to the yield and purity of the product.

a) The reaction product should be only sparingly soluble in the solvent, so that it is precipitated during irradiation. Analytically pure products were often obtained directly in this way, *e.g.* $C_5H_5Mn(CO)[(CH_3)_2SO]_2$ in diethyl ether [23]. A good rule of thumb is that monosub-

[8] *W. Strohmeier* and *C. Barbeau*, Z. Naturforsch. *17b*, 848 (1962).
[9] *D. P. Tate, J. M. Augl*, and *W. R. Knipple*, Inorg. Chem. *1*, 434 (1962).
[10] *W. Strohmeier* and *G. Schönauer*, Chem. Ber. *94*, 1346 (1961).

Table 1. Solvents for the photochemical preparation of metal carbonyl derivatives. (THF = tetrahydrofuran.)

| Metal carbonyl | Donor | | | | | |
|---|---|---|---|---|---|---|
| | nitrogen compound | $R_2S{=}O$ | phosphorus compound | nitrile | π-electron donors | $R_2S$ |
| $Cr(CO)_6$ | $CH_3OH$, THF | benzene | | benzene | | |
| $Mo(CO)_6$ | THF | | | benzene | | |
| $W(CO)_6$ | THF | benzene | | benzene | | |
| $ArM(CO)_3$ | benzene | benzene, $CH_3OH$ | benzene | benzene, $CH_3OH$ | THF | $CH_3OH$ |
| $C_5H_5Mn(CO)_3$ | THF, $CH_3OH/H_2O$ | benzene | benzene | $CH_3OH/H_2O$ | heptane | heptane |

stitution products are more readily soluble than disubstitution products, and these in turn are more readily soluble than trisubstitution products (for examples, see [11]).

b) If the photochemical reaction leads directly to the disubstitution product, it is advisable to carry out the elimination of CO – paradoxically – under a current of CO using a solvent in which the disubstituted compound is readily soluble. This derivative is then reconverted to the monosubstituted compound according to Equation 9.

c) With donors such as *p*-phenylene diamine which are photochemically unstable, the best method is donor exchange. The relatively weak donor tetrahydrofuran is used as solvent, and the tetrahydrofuran derivative, *e.g.* $Cr(CO)_5THF$, is first prepared photochemically. The photolabile donor D is then added to the solution, the solvent is removed, and $Cr(CO)_5D$ is obtained according to:

$$Cr(CO)_6 + THF \xrightarrow{h\nu} Cr(CO)_5THF \xrightarrow{D} Cr(CO)_5D + THF.$$

This method often yields very pure products.

## V. Reaction Mechanism and Quantum Yield

The reaction mechanism [6,12] and the quantum yield [12,13] have been elucidated in particular for photochemical reactions involving metal hexacarbonyls. As far as such investigations have been carried out on other metal carbonyls they agree with the results obtained on the hexacarbonyls. The quantum yield $\Phi$ of the photochemical primary reaction was found in all cases, independent of the central atom M and the donor D, to be 1.0 for time $t = 0$ at wavelengths $\lambda = 3660$ and 4360 Å. The quantum yield steadily decreases with increasing times of irradiation, since the reaction products themselves absorb light and undergo further chemical reactions. Several dark reactions also occur simultaneously at various rates. These secondary reactions depend on the central atom, on the nature of the metal carbonyl, and on the donor D. Intensive investigations indicated the following reaction scheme for metal hexacarbonyls:

Primary photochemical reaction:

$$M(CO)_6 + h\nu \rightarrow \{M(CO)_6\}^* \rightarrow \{M(CO)_5\} + CO \quad (1)$$

Secondary reactions:

$$\{M(CO)_5\} + D \rightarrow M(CO)_5D \quad (2)$$

$$\{M(CO)_5\} + (CO)_{solv} \rightarrow M(CO)_6 \quad (3)$$

$$M(CO)_5D + (CO)_{solv} \rightarrow M(CO)_6 + D \quad (4)$$

Reaction 3 (CO also acts as a donor) can be suppressed by removing the photochemically liberated CO and by using an excess of D.

Reaction 4 is unimportant at room temperature in the presence of excess donor, but it can be detected at higher temperatures and in the absence of the donor; it predominates at high CO pressures. In all systems in which the monosubstituted compound $M(CO)_5D$ is formed photochemically, the rate of Reaction 2 is greater than that of Reactions 3 and 4. The combined effect of Reactions 1–4 can best be seen, empirically and qualitatively, from the CO liberation curves [13a], since the quantity of CO liberated and removed at a given time is directly proportional to the photochemically formed products. At the same time, it is immediately seen how many equivalents of CO can be liberated photochemically.

The mechanism of the formation of photochemical substitution products of metal-carbonyl derivatives was elucidated for complexes $M(CO)_5D$. In the primary photochemical reaction, CO or the ligand D are split off from the excited molecule $\{M(CO)_5D\}^*$ according to either Equation 5 or 6. Since the photochemical reaction 6 does not contribute to the formation of the disubstitution product $M(CO)_4D_2$, the quantum yield $\Phi$ for the preparation of disubstitution products of metal carbonyl derivatives cannot be unity, even at time $t = 0$. It was found to be 0.05–0.3, depending on the system examined [13].

Primary photochemical reaction:

$$M(CO)_5D + h\nu \rightarrow \{M(CO)_5D\}^* \begin{cases} \nearrow \{M(CO)_4D\} + CO & (5) \\ \searrow \{M(CO)_5\} + D & (6) \end{cases}$$

Secondary reactions:

$$\{M(CO)_4D\} + D \rightarrow M(CO)_4D_2 \quad (7)$$

$$\{M(CO)_4D\} + (CO)_{solv} \rightarrow M(CO)_5D \quad (8)$$

$$M(CO)_4D_2 + (CO)_{solv} \rightarrow M(CO)_5D + D \quad (9)$$

$M(CO)_4D_2$ is formed in Reaction 7 and is consumed in Reaction 9. The contributions of Reactions 8 and 9 depend on the central atom and the solvent; that of Reaction 9 increases rapidly with temperature. Thus, if $M(CO)_4D_2$ is insoluble in the solvent, Reaction 9 is

[11] *W. Strohmeier, K. Gerlach,* and *D. v. Hobe,* Chem. Ber. *94,* 164 (1961).

[12] *W. Strohmeier* and *D. v. Hobe,* Chem. Ber. *94,* 2031 (1961).

[13] *W. Strohmeier* and *D. v. Hobe,* Chem. Ber. *94,* 761 (1961); Z. physik. Chem. N.F. *34,* 393 (1962).

[13a] *W. Strohmeier, D. v. Hobe, G. Schönauer,* and *H. Laporte,* Z. Naturforsch. *17b,* 502 (1962).

practically eliminated, and the reaction of $M(CO)_6$ leads directly to $M(CO)_4D_2$, *e.g.* $Mo(CO)_4D_2$ from $Mo(CO)_6$, even when, for example, only 1.6 moles of CO per mole of $M(CO)_6$ have been split off photochemically. If the final product $M(CO)_4D_2$ is soluble in the solvent, then at 80 % elimination of CO (*i.e.* 1.6 moles of CO per mole of hexacarbonyl), $Mo(CO)_6$ gives a mixture of $Mo(CO)_5D$ and $Mo(CO)_4D_2$, whereas $Cr(CO)_6$ gives only $Cr(CO)_5D$ [12]. Reactions 8 and 9 are more important in the case of $Cr(CO)_6$, in contrast to that of $Mo(CO)_6$, so that $Cr(CO)_4D_2$ can only be formed after all the $Cr(CO)_6$ has first been converted to $Cr(CO)_5D$.

The number of carbon monoxide ligands in a metal carbonyl or its derivatives which can be replaced photochemically by the donor D depends on both the type of metal carbonyl and donor concerned, and must be determined for each individual system, preferably by plotting the CO elimination curves [13a]. The differences in ability of the CO groups to undergo replacement is due to differences in the strengths of the M–CO and M–D bonds. These differences are chiefly responsible for the participation of Reactions 5 and 6 in the primary photochemical act.

## VI. Photochemical Preparation of Derivatives with n- and $\pi$-Electron Donors

The photochemical substitution products of metal carbonyls or their derivatives described so far in the literature are listed in Tables 2 and 3.

Table 2. Derivatives of metal carbonyls prepared photochemically with n-electron donors.

| Metal carbonyl | Donor |
|---|---|
| $Cr(CO)_6$ | aniline, pyridine [2]; n-propylamine, pyrrolidine, hexamethylene tetramine [53]; triethylamine, piperidine [*] [11]; α-picoline, 2,6-lutidine, 4-chloropyridine, quinoline, isoquinoline [16]; acetonitrile, benzonitrile [21]; dimethyl sulfoxide [28]. |
| $Mo(CO)_6$ | *p*-phenylene diamine [*], 4-aminopyridine [*] [29]; piperidine [*] [11]; pyridine [*] [14]; acetonitrile [*] [10]. |
| $W(CO)_6$ | aniline, pyridine [*] [15]; triethylamine, piperidine [*] [11]; acetonitrile [*] [10]; dimethyl sulfoxide [28] |
| $[(H_3CO_2C)_2C_6H_4]Cr(CO)_3$ | aniline, quinoline, acetonitrile, benzonitrile [20]; piperidine, pyridine, triphenylphosphine, dimethyl sulfoxide [17]; cyclohexyl isonitrile [54b] |
| $C_6H_6Cr(CO)_3$ | piperidine [**], quinoline, cyclohexyl isonitrile [54b]; pyridine, triphenylphosphine, dimethyl sulfoxide [17]; acetonitrile [**], benzonitrile [**] [20] |
| $[1,3,5\text{-}(CH_3)_3C_6H_3]Cr(CO)_3$ | piperidine [**], quinoline, benzonitrile [**], cyclohexyl isonitrile [54b]; pyridine, triphenylphosphine, dimethyl sulfoxide [17]. |
| $[(CH_3)_6C_6]Cr(CO)_3$ | piperidine [**], pyridine [**], quinoline, benzonitrile [**], triphenylphosphine, cyclohexyl isonitrile [**] [54b] |
| $Mn_2(CO)_{10}$ | triethylphosphine, triphenylphosphine, triphenyl phosphite [24] |
| $C_5H_5Mn(CO)_3$ | tetrahydrofuran [**] [55]; aniline, piperidine, triphenylstibine [51]; trimethylamine, dimethylamine, n-propylamine, n-hexylamine, pyrrolidine, 2,5-dimethylpyrrolidine, triethylamine[**], quinoline, ammonia[26]; piperazine, hexamethylene tetramine, triethylene diamine [22]; pyridine [18]; acetonitrile, benzonitrile [25]; triphenylphosphine [*] [8]; 1,2-bisdiphenylphosphinylethane [*], triphenylarsine [24]; sulfur dioxide, tetramethylene sulfoxide, diphenyl sulfoxide, ethylene glycol sulfite, hydrogen sulfide[**]diethyl sulfide, tetramethylene sulfide, diphenyl sulfide[27]; dimethyl sulfoxide [*] [23]; cyclohexyl isonitrile [54a]. |
| $[CH_3C_5H_4]Mn(CO)_3$ | piperidine [19]; pyridine [18]; triphenylphosphine, 1,2-bisdiphenylphosphinylethane [*], triphenylarsine [24]; sulfur dioxide, dimethyl sulfoxide, diphenyl sulfoxide [28]. |
| $[CH_3COC_5H_4]Mn(CO)_3$ | triphenylphosphine [28] |
| $Fe(CO)_5$ | triphenylphosphine [*], triphenylarsine [*], *o*-phenylene bisdimethylarsine [*] [24]. |

[*] Both mono- and disubstitution products were found.

[**] Experiments in which the photochemical formation of a compound was detected by infrared measurements, by elimination of CO, or indirectly by donor exchange but in which the compound could not be isolated in pure form.


[14] *W. Strohmeier* and *K. Gerlach*, Chem. Ber. *93*, 2087 (1960).

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[16] *W. Strohmeier*, *G. Matthias*, and *D. v. Hobe*, Z. Naturforsch. *15b*, 813 (1960).

[17] *W. Strohmeier* and *H. Hellmann*, Chem. Ber. *96*, 2859 (1963).

[18] *W. Strohmeier* and *K. Gerlach*, Z. Naturforsch. *15b*, 675 (1960).

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[20] *W. Strohmeier* and *H. Hellmann*, Z. Naturforsch. *18b*, 769 (1963).

[21] *W. Strohmeier* and *K. Gerlach*, Z. Naturforsch. *15b*, 622 (1960).

[22] *W. Strohmeier* and *J. F. Guttenberger*, Chem. Ber. *96*, 2112 (1963).

[23] *W. Strohmeier* and *J. F. Guttenberger*, Z. Naturforsch. *18b*, 667 (1963).

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[26] *W. Strohmeier* and *J. F. Guttenberger*, Chem. Ber. *97*, 1256 (1964).

[27] *W. Strohmeier* and *J. F. Guttenberger*, Chem. Ber. *97*, 1871 (1964).

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[29] *W. Strohmeier* and *G. Schönauer*, Chem. Ber. *95*, 1767 (1962).

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[31] *E. O. Fischer*, *H. P. Kögler*, and *P. Kuzel*, Chem. Ber. *93*, 3006 (1960).

[32] *E. O. Fischer* and *M. Herberhold*, Z. Naturforsch. *16b*, 841 (1961).

Table 3. Derivatives of metal carbonyls prepared photochemically with π-electron donors.

| Metal carbonyl | Donor |
|---|---|
| $C_5H_5V(CO)_4$ | butadiene, 2,3-dimethylbutadiene, 1,3-cyclohexadiene [31] |
| $[(CH_3)_3C_6H_3]Cr(CO)_3$ | ethylene [36] |
| $Mo(CO)_6$ | butadiene [31] |
| $W(CO)_6$ | acrylonitrile [38] |
| $C_5H_5Mn(CO)_3$ | ethylene [37]; cyclopentene, cycloheptene, cyclooctene, cyclononene, norbornadiene, dicyclopentadiene, benzene [54a]; butadiene [31]; 1,3-cyclohexadiene [32]; hexafluorobut-2-yne [46]; diphenylacetylene [49]. |
| $(CH_3C_5H_4)Mn(CO)_3$ | diphenylacetylene [50] |
| $[Mn(CO)_5]^-$ | dimethylacetylene [47]. |
| $Fe(CO)_5$ | acrylonitrile [39]; vinyl acetate, methyl methacrylate [40]; dimethyl fumarate, dimethyl maleate, maleic anhydride [41]; isoprene, cyclooctadiene [30]; tetraphenylbutadiene, diphenylacetylene [42]; 1,3-cyclohexadiene [34]; cyclooctatetraene [44], [45]; dimethylacetylene, 2-pentyne, 3-hexyne [48]. |
| $Co_2(CO)_8$ | butadiene [33]. |
| $C_5H_5Co(CO)_2$ | cyclooctadiene [43]; dimethylacetylene, diphenylacetylene [47]. |
| $Os_3(CO)_{12}$ | 2,3-dimethylbutadiene [35] |
| $C_5H_5Rh(CO)_2$ | cyclooctatetraene [52] |
| $[C_5H_5Cr(CO)_3]_2$ | butadiene [31]. |


[33] *E. O. Fischer, P. Kuzel,* and *H. P. Fritz,* Z. Naturforsch. *16b,* 138 (1961).

[34] *R. D. Fischer,* Ph.D. Thesis, Universität München, 1961.

[35] *K. Bittler,* Ph.D. Thesis, Technische Hochschule München, 1962.

[36] *E. O. Fischer* and *P. Kuzel,* Z. Naturforsch. *16b,* 475 (1961).

[37] *H. P. Kögler* and *E. O. Fischer,* Z. Naturforsch. *15b,* 676 (1960).

[38] *A. G. Massey,* J. inorg. nuclear Chem. *24,* 1172 (1962).

[39] *S. F. A. Kettle* and *L. E. Orgel,* Chem. and Ind. *1960,* 49.

[40] *E. Koerner von Gustorf, M. J. Jun,* and *G. O. Schenk,* Z. Naturforsch. *18b,* 503 (1963).

[41] *G. O. Schenk, E. Koerner von Gustorf,* and *M. J. Jun,* Tetrahedron Letters *23,* 1059 (1962).

[42] *G. N. Schrauzer,* J. Amer. chem. Soc. *81,* 5307 (1959).

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[49] *W. Strohmeier* and *D. v. Hobe,* Z. Naturforsch. *16b,* 402 (1961).

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[51] *W. Strohmeier, J. F. Guttenberger,* and *H. Hellmann,* Z. Naturforsch. *19b,* 353 (1964).

[52] *K. S. Brenner, E. O. Fischer, H. P. Fritz,* and *C. G. Kreiter,* Chem. Ber. *96,* 2632 (1963).

[53] *W. Hösl,* Diploma Thesis, Universität Würzburg, 1964.


Since the method is generally applicable and is limited only by the stability and hence the possibility of isolation of the reaction product, no attempt was probably made in many cases to obtain all other possible derivatives by analogous methods. Thus, for example, it was shown that substituted pyridines react photochemically with $Cr(CO)_6$, but the analogous reactions with $Mo(CO)_6$ and $W(CO)_6$ were not carried out.

In the particular case of $Mn_2(CO)_{10}$, photochemical reactions with strong donors such as $PR_3$ give diamagnetic substances $[Mn(CO)_4PR_3]_2$ [24], whereas thermal reactions yield paramagnetic compounds $Mn(CO)_4PR_3$ [54].

π-Electron donors such as olefins, oligo-olefins, and acetylenes react in the primary act in the same way as n-electron donors, *i.e.* the double or triple bond adds on at the coordination vacancy of the highly reactive fragment $\{Y_aM(CO)_{x-1}\}$. However, in addition to the photochemical substitution reaction, acetylene derivatives are often observed to undergo cyclization by addition of carbon monoxide. The structure and formula of the reaction products can be derived from the original publications (see Table 3).

## VII. Polynuclear Compounds with Bifunctional Donors

Bifunctional donors of general formula B–R B, where B is an atom from group V or VI of the periodic table or a residue containing double or triple bonds, can act as bridge ligands and form polynuclear substitution products according to the equation:

$$2\,Y_aM(CO)_X + B{-}R{-}B \rightarrow Y_aM(CO)_{X-1}B{-}R{-}B(CO)_{X-1}MY_a + 2\,CO$$

Such compounds can also be prepared advantageously by a photochemical method, as shown in Table 4. The structure of the reaction products obtained with bi- or multi-functional π-electron donors for any particular case can be found in the original literature; cyclizations were also observed, particularly with $Fe(CO)_5$.

Table 4. Polynuclear derivatives of metal carbonyls prepared photochemically with bifunctional donors B–R–B.

| Metal carbonyl | Donor |
|---|---|
| $Cr(CO)_6$ | triethylene diamine [53] |
| $C_5H_5Mn(CO)_3$ | piperazine, triethylene diamine [22]; 1,2-bisdiphenylphosphinylethane, *o*-phenylene bisdimethylarsine [24]; 1,3-cyclohexadiene [32]; 1,5-cyclooctadiene, norbornadiene [54a] |
| $[CH_3C_5H_4]Mn(CO)_3$ | 1,2-bisdiphenylphosphinylethane, *o*-phenylene bisdimethylarsine [24]. |
| $Fe(CO)_5$ | 1,2-bisdiphenylphosphinylethane [24]; cyclooctatetraene [45]; diphenylacetylene [42] |
| $C_5H_5Rh(CO)_2$ | cyclooctatetraene [52] |


[54] *W. Hieber* and *W. Freyer,* Chem. Ber. *92,* 1765 (1959).

[54a] *M. Herberhold,* Ph.D. Thesis, Universität München, 1963.

[54b] *W. Strohmeier* and *H. Hellmann,* Chem. Ber. *97,* 1877 (1964).

## VIII. Photochemical Reactions with Donors Containing Oxygen

In contrast to the photochemical reaction of group V donors with metal carbonyl derivatives, there actions with donors containing oxygen do not proceed uniformly. Ethers such as tetrahydrofuran (THF) yield monosubstitution products $M(CO)_{x-1}THF$, which are stable for a time only in solution, whereas condensation occurs with ketones such as acetone and methyl ethyl ketone or with aldehydes [55]. It is particularly interesting in this connection that, in the presence of ketones or acetaldehyde, all the carbon monoxide ligands can be removed photochemically from $C_5H_5Mn(CO)_3$ or $Mn_2(CO)_{10}$, although it has not yet been possible to isolate a definite substitution product [55]. This behavior is similar to that of epoxides, *e.g.* propylene oxide [55]. However, ethers, ketones, epoxides, and acetaldehyde react much more slowly with $Mo(CO)_6$, and the reaction stops after about one mole of CO has been split off. The experimental evidence obtained to date indicates that $Mn_2(CO)_{10}$ and $C_5H_5Mn(CO)_3$ occupy a special position as regards photochemical reactions with donors containing oxygen, such as epoxides, ketones, and aldehydes. However, it has been proved that the primary photochemical act – again in analogy to Equation 1 – proceeds according to Equation 10 with a quantum yield of $\Phi = 1.0$ [55].

$$C_5H_5Mn(CO)_3 + h\nu \rightarrow \{C_5H_5Mn(CO)_3\}^* \rightarrow \{C_5H_5Mn(CO)_2\} + CO \quad (10)$$

In contrast to monofunctional ketones, bifunctional ketones such as hexafluoroacetylacetone or acetylacetone react photochemically with metal carbonyls with liberation of hydrogen and CO to form chelates, the metal atom being simultaneously oxidized [56]. The question whether thioethers and thioketones behave differently has not yet been investigated.

## IX. Stability of the Metal Carbonyl Derivatives

The donor-acceptor bond between the donor D and the central metal atom M which functions as electron acceptor in $Y_aM(CO)_{x-1}D$ is a $\sigma$-bond and is formed with nitrogen or oxygen compounds. Donors whose functional atom belongs to the second or a higher period of the periodic table have energetically favorable d-orbitals, so that charge is returned from the central atom to the original donor ("back-donation" or $d_\pi$-$d_\pi$ bonding). A similar situation prevails in the bonding between the metal and $\pi$-electron donors ($d_\pi$-$p_\pi$ bonding). The central atom is thus an electron acceptor with respect to the $\sigma$-bond, and a donor with respect to the superimposed $\pi$-bond. The reverse is true for the ligand D. The stability of the $\sigma$-bond in the metal-carbonyl derivatives depends on the donor strength of the ligand D and the acceptor strength of the unstable photochemical primary product $\{Y_aM(CO)_{x-1}\}$. Investigations to date on organic donors containing nitrogen have shown that the donor strength depends on the bond angle, and consequently on the hybridization of the nitrogen. The most stable derivatives were obtained from ligands with a C–N–C bond angle of 109°, *i.e.* with $sp^3$-hybridization [26]. The situation appears to be similar for donors containing oxygen, which are much weaker [57]. So far it has only been possible to isolate one derivative here, *viz.* that with tetrahydrofuran (C–O–C bond angle 111°, *i.e.* $sp^3$-hybridization of oxygen); none at all has been obtained with ketones ($sp^2$-hybridization of oxygen).

Preliminary investigations on the relative acceptor strengths of the central atoms M in complexes $Y_aM(CO)_2D$ gave the following results:

$$H_3CO_2C-C_6H_4-CO_2CH_3)Cr(CO)_2D \approx$$
$$Cr(CO)_3D > C_5H_5Mn(CO)_2D > C_6H_6Cr(CO)_2D > [(CH_3)_3C_6H_3]Cr(CO)_2D.$$

For a given metal carbonyl, the stability of the derivative $Y_aM(CO)_{x-1}D$ generally increases according to the donor, in the order:

$$\text{O-compound} < \text{nitrile} < \text{N-base} < \text{P-compound} < CO.$$

However, this series has not been investigated quantitatively. The carbonyl absorption frequency is generally regarded as a measure of the bond stability: a decrease in the wave number $\tilde{\nu}_{C=O}$ of the carbonyl bond of the substituted compounds $Y_aM(CO)_{x-1}D$ with respect to that of $Y_aM(CO)_x$ indicates an increase in the double-bond character of the M–C bond in M–C–O and weaker M–D bonding. However, the changes in $\tilde{\nu}_{C=O}$ reflect only large differences, such as the transition from donors containing nitrogen to those containing phosphorus.

## X. Polarity of the Metal-Ligand Bond

The donor-acceptor bond M–D in $Y_aM(CO)_{x-1}D$ naturally possesses some polarity; accurate information about this aspect can be obtained from dipole moment measurements and by calculation of the partial dipole moment $\mu$(D–M) [58]. Experimental investigations on many photochemically produced metal carbonyl derivatives led to the interesting result that the magnitude of the partial moment $\mu$(D–M) depends practically exclusively upon the central atom and the nature of the donor [59]. The values obtained are listed in Table 5.

In Table 5, $\mu$(Ar-M) is the partial dipole moment of the ring-metal bond in arene-metal tricarbonyl and cyclopentadienylmanganese tricarbonyl derivatives, $\mu$(OC-M) is the partial dipole moment of the metal-CO bond, and $\mu$(D-M) is the partial dipole moment of the metal-ligand bond. Positive values of the partial moment are directed towards the central atom, as is indicated by the order in the notation, *e.g.* $\mu$(Ar-M) [58].

[55] *W. Strohmeier, C. Barbeau*, and *D. v. Hobe*, Chem. Ber. *96*, 3254 (1963).

[56] *J. C. Goan, C. H. Huether*, and *H. E. Podall*, Inorg. Chem. *2*, 1078 (1963).

[57] *C. Barbeau*, Ph.D. Thesis, Universität Würzburg, 1963.

[58] *W. Liptay, W. Strohmeier*, and *H. Hellmann*, Ber. Bunsenges. physik. Chem. *64*, 91 (1964).

[59] *W. Strohmeier* and *H. Hellmann*, Ber. Bunsenges. physik. Chem. *64* (1964), in the press.

The values shown in Table 5 have been confirmed as regards their order and relative magnitudes; however, their absolute values are dependent upon the magnitude of the M–CO moment $\mu(OC-M) = 0.8$ Debyes. Since $\mu(OC-M)$ is invariably small, variations in $\mu(OC-M)$ cause only insignificant changes in the values given. The estimated margin of error in the partial moment $\Delta\mu$ was $\pm$ 0.3 Debyes.

Table 5. Partial dipole moments in metal carbonyl derivatives.

| Acceptor | μ(Ar–M) [*] [Debyes] | μ(OC–M) [*] [Debyes] | μ(OC–M) [**] [Debyes] | μ(D–M) for the donors | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | N-bases | RCN | $OSR_2$ | $P(C_6H_5)_3$ | RNC |
| $[H_3CO_2C)_2C_6H_4]Cr(CO)_2$ | 4.9 | 0.8 | 0.8 | 3.9 | 2.1 | | 3.1 | 2.0 |
| $C_6H_6Cr(CO)_2$ | 5.5 | 0.6 | 0.2 | 4.0 | 2.2 | | 2.8 | 1.7 |
| $[1,3,5-(CH_3)_3C_6H_3]Cr(CO)_2$ | 6.0 | 0.5 | 0.0 | 4.0 | 2.1 | | 2.6 | |
| $[(CH_3)_6C_6]Cr(CO)_2$ | 6.5 | 0.3 | 0.0 | 4.0 | | | 2.8 | |
| $C_5H_5Mn(CO)_2$ | 4.5 | 0.8 | 0.8 | 5.3 | 3.0 | | 4.4 | 3.0 |
| $Cr(CO)_5$ | | 0.8 | 0.8 | 5.3 | 4.0 | ca. 4 | 4.5 | 2.9 |
| $Mo(CO)_5$ | | 0.8 | 0.8 | 5.3 | | | | |
| $W(CO)_5$ | | 0.8 | 0.8 | 5.9 | | ca. 5 | 4.8 | |

[*] Measured in $XArCr(CO)_3$ or $M(CO)_6$.

[**] Measured in $XArCr(CO)_2D$ or $M(CO)_5D$.

The largest partial moments $\mu(D-M)$ were found for the nitrogen bases, as donors without back-donation. With ligands capable of back-donation, *e.g.* donors containing sulfur and phosphorus ($d_\pi$-$d_\pi$ bonding) and isonitriles ($d_\pi$-$p_\pi$ bonding), the partial dipole moments are smaller. However, no conclusion can be drawn from the relative decreases in $\mu(D-M)$ regarding increases in back-donation, since, for example, the partial dipole moments of the $\sigma$-bonds in derivatives containing nitriles as ligands are already smaller than those in nitrogenous derivatives. A detailed discussion of the variation of the partial dipole moments with the donor and substitution on the aromatic ring can be found in the original publications [59].

## XI. Photochemically Induced Exchange Reactions with $^{14}C$-Labelled Ligands

Most metal carbonyls and their derivatives do not undergo exchange of their CO ligands with $^{14}CO$ at room temperature and at higher temperatures [60,61], so that it was necessary to prepare the $^{14}CO$-labelled metal carbonyls by total synthesis.

On ultraviolet irradiation of metal carbonyls, CO is split off in the primary photochemical process, and is added on again in a dark reaction in the absence of a donor; this observation led to a simple photochemical method for the preparation of $^{14}CO$-labelled metal carbonyls and their derivatives: the inactive metal carbonyl is irradiated in an atmosphere of $^{14}CO$ [61,62], thus avoiding the complicated total synthesis with $^{14}CO$.

[60] *D. F. Keeley* and *R. E. Johnson*, J. inorg. nuclear Chem. *11*, 33 (1959).

[61] *W. Strohmeier* and *R. Müller*, Z. physik. Chem. N.F. *28*, 112 (1961).

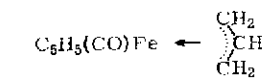
[62] *W. Strohmeier* and *D. v. Hobe*, Z. Naturforsch. *18b*, 770 (1963).

Further investigations on these photochemically induced exchange reactions led to the interesting result that, on ultraviolet irradiation of arene-metal tricarbonyls in the presence of the corresponding [$^{14}C$]arenes, the latter were also exchanged [63]. It was therefore concluded that, in the photo-excited molecule $ArM(CO)_3$, not only is the M–CO bond broken, but also, to a certain extent, the Ar–M bond:

$$ArM(CO)_3 + Ar^* \xrightarrow{h\nu} Ar^*M(CO)_3 + Ar$$

## XII. Photochemical Rearrangements and Disproportionations

While the photochemical reactions of metal carbonyls and their derivatives described so far are generally applicable, mention will now be made of a few interesting photochemical reactions of metal carbonyl derivatives, for which there is no evidence as yet that they occur in other systems. Thus, for example, on ultraviolet irradiation and elimination of CO, the $\sigma$-allyl compound $C_5H_5Fe(CO)_2-CH_2CH=CH_2$ rearranges to form the $\pi$-allyl compound *(1)* [64]. An analogous



*(1)*

photochemical rearrangement was also achieved with $C_5H_5Mo(CO)_2-CH_2CH=CH_2$ [65]. A few photochemical rearrangements are also known for iron carbonyl acetylene derivatives. Thus, ultraviolet irradiation of $Fe_2(CO)_6[H_5C_6-C\equiv C-C_6H_5]_2$ yields tetraphenylcyclobutadienyliron tricarbonyl, and, in the presence of sulfur, tetraphenylthiophene. $Fe_2(CO)_7[H_6C_5-C\equiv C-C_6H_5]_2$ also undergoes photochemical rearrangement to give new compounds [66].

Disproportionations of metal carbonyls by the action of ultraviolet light have been described for the system $Fe(CO)_5 + (CH_3)_2SO$ [or $OAs(C_6H_5)_3$ or $OP(C_6H_5)_3$] [67]. These lead to carbonyltetraferrates and octacarbonyldiferrates.

[63] *W. Strohmeier* u. *D. v. Hobe*, Z. Naturforsch. *18b*, 981 (1963).

[64] *M. L. H. Green* and *P. L. I. Nagy*, J. chem. Soc. (London) *1963*, 189.

[65] *M. L. H. Green*, J. chem. Soc. (London) *1963*, 889.

[66] *W. Hübel* and *E. H. Braye*, J. inorg. nuclear Chem. *10*, 250 (1959).

[67] *W. Hieber* and *A. Lipp*, Chem. Ber. *92*, 2085 (1959).

## XIII. Toxicity of Metal Carbonyl Derivatives

It is known that the vapors and dusts of metal carbonyls are highly toxic, but so far little systematic and quantitative work has been carried out. For some metal carbonyl derivatives – mostly prepared photochemically – the mouse test, in which the substances were injected intravenously, also showed occasionally high toxicities, with $LD_{50}$ values below 1 mg/kg [68]. A few examples are shown in Table 6.

Table 6. Toxicity of metal carbonyl derivatives in the mouse test.

| Substance | $LD_{50}$ [mg/kg] | Confidence limit [mg/kg] |
|---|---|---|
| Cycloheptatrienyl-$Cr(CO)_3$ | 0.708 | 0.501–1.00 |
| Cycloheptatrienyl-$Mo(CO)_3$ | >20 | – |
| Piperidino-$Cr(CO)_5$ | 0.708 | 0.562–0.891 |
| Piperidino-$W(CO)_5$ | 0.631 | 0.501–0.796 |
| $C_5H_5Mn(CO)_3$ | 3.16 | 0.316–31.6 |
| Piperidino-$Mn(CO)_2C_5H_5$ | 6.31 | 5.01–7.94 |
| $(C_6H_5)_3PMn(CO)_2C_5H_5$ | >20 | – |

The investigations so far have shown no connection between the toxicity and the ligands. All future preparative work on the production of metal carbonyl derivatives should therefore be carried out with care.

## XIV. Prospects

The photochemical reaction of metal carbonyls and metal carbonyl derivatives with n- and π-electron donors makes it possible to prepare a large number of hitherto unknown compounds. The principal advantage of the photochemical method is that it permits the synthesis of unstable derivatives. Moreover, since it is known that metal carbonyls are important catalysts which almost certainly involve their unstable derivatives as intermediates in the reaction mechanism, this phenomenon can now be investigated in greater detail if the photochemically prepared derivative is used directly as reaction partner instead of the metal carbonyl itself.

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# Phosphonium Salt Formation of the Second Kind

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*Organic compounds containing a positively polarized halogen atom react with tertiary phosphines either with reductive elimination of the halogen or with formation of phosphonium salts and quasi-phosphonium salts, depending on the solvent. In this reaction, the phosphine first attacks the halogen.*

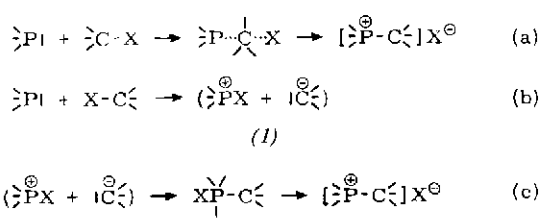
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## I. Introduction

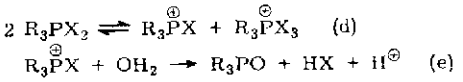
Owing to their strongly nucleophilic character, tertiary phosphines generally react with alkyl halides by an $S_N2$ mechanism. No comprehensive kinetic studies of the dependence of the rate of reaction on the constitution of the halogeno compound have yet been carried out for the formation of phosphonium salts by this process. However, the substituent effect may be assumed to be the same as that found for other $S_N2$ reactions: fundamentally, the reaction can be accelerated by both electron donors and electron acceptors. Since it involves both the formation and cleavage of bonds, the decisive factor is which of the two processes is further advanced in the transition state.

However, strong electron acceptors can cause a fundamental change in the reactivity of the halogeno compound by polarizing the carbon-halogen bond, thus giving the halogen atom a partial positive charge and simultaneously stabilizing the carbanion remaining after removal of a halogen cation. This favors nucleophilic attack on the halogen. The center of the $S_N2$ reaction is thus shifted from the carbon atom [Equation (a)] to the halogen [Equation (b)].

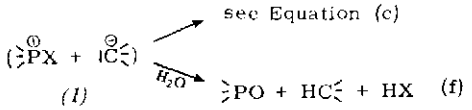
This means that, in the reaction of organic halides with tertiary phosphines, an ion pair with a halogenophosphonium cation and a carbanion is formed first [Equation (b)], instead of an alkylphosphonium cation and a halogen anion [Equation (a)]. As was first demonstrated by *Haszledine* [1], a phosphonium salt can be formed from the ion pair according to Equation (c) [2]. The initial product is an associate with a pentacovalent phosphorus atom, from which the halogen dissociates as an anion.



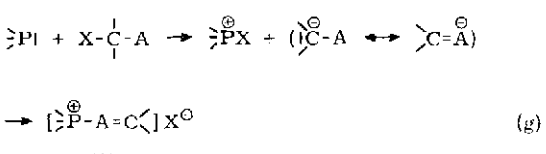
Such a *phosphonium salt formation of the second kind* can lead *via* reactive intermediates [Equations (b) and (c)] to the same product as direct $S_N2$ substitution of the halogen by primary attack of the phosphine on the carbon. The two reactions can be distinguished by the reactivity of the halogenophosphonium cation. It is known from studies of phosphine dihalides [Equation (d)] [3] that halogenophosphonium cations react extremely readily with solvolytic agents according to Equation (e).



Reactions involving initial attack on the halogen are therefore characterized by the fact that in solvolytic solvents phosphonium salt formation is partially or completely suppressed in favor of reductive dehalogenation of the organic halide [Equation (f)], the extent of suppression depending on the ratio of the rates of association and solvolysis.



Phosphonium salt formation of the second kind is therefore always to be expected when the carbanions formed by the primary dehalogenation are stabilized by resonance. However, as a result of the mesomerism of the anion, the linkage to the phosphorus in the association step can take place through heteroatoms A according to Equation (g).



[1] *R. N. Haszledine* and *B. O. West*, J. chem. Soc. (London) *1956*, 3631.

[2] Cf. *L. Horner* and *H. Oediger*, Chem. Ber. *91*, 437 (1958).

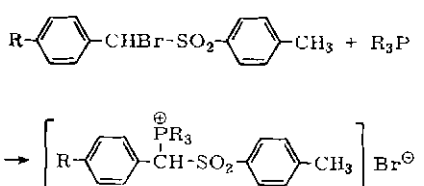
[3] See, for example, *L. Horner*, *H. Oediger*, and *H. Hoffmann*, Liebigs Ann. Chem. *626*, 26 (1959).

Thus, quasi-phosphonium salts *(2)* [4] can also be formed by a mechanism of the second kind. A few examples [5] of these reactions will be discussed below.

## II. C-Phosphonium Salts

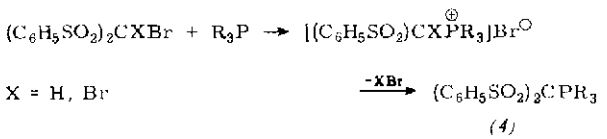
### 1. From α-Bromo Sulfones

Sulfone groups acidify adjacent C–H bonds owing to their strongly electron-attracting properties. For the same reason, the halogen in α-halogeno sulfones can be readily transferred as a cation, but undergoes anionic substitution only with difficulty [6]. The reactions of α-halogeno sulfones are therefore good examples of phosphonium salt formations of the second kind [7]. The reaction rates characteristically increase with increasing positive polarization of the halogen: in toluene, the sulfone *(3a)* forms a phosphonium salt only after prolonged boiling, but the nitro compound *(3b)* reacts practically instantaneously.



*(3a)*: R = H
*(3b)*: R = $NO_2$

Bisphenylsulfonylbromomethane and bisphenylsulfonyldibromomethane also react very rapidly, but the phosphonium salts initially formed are unstable. They lose hydrogen bromide or bromine spontaneously to give a very stable ylide *(4)*.



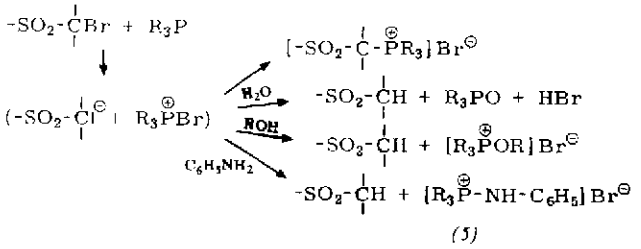
Although the phosphonium salts and the ylides *(4)* are stable to hydrolysis, only dehalogenated sulfone, phosphine oxide, and hydrogen bromide are found after reaction of the components in the presence of water. In the presence of other reagents which can react with the bromophosphonium cation, the reaction proceeds in a similar manner. In alcohol an alkoxyphosphonium bromide which decomposes spontaneously to phosphine oxide and alkyl halide is formed together with dehalogenated sulfone. Reaction in aniline yields a phenylaminophosphonium salt *(5)* which can be isolated.

[4] The term "quasi-phosphonium salt" is applied to onium compounds of phosphorus in which organic residues are linked to the phosphorus through heteroatoms, *e.g.* $[R_3\overset{\oplus}{P}-OR']X^{\ominus}$ and $[R_2\overset{\oplus}{P}-NHR']X^{\ominus}$.

[5] Only reactions with *C*-halogeno compounds are mentioned.

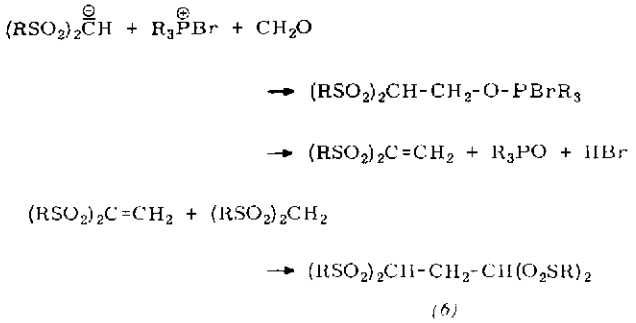
[6] *T. Thomson* and *T. S. Stevens*, J. chem. Soc. (London) *1932*, 69; *W. M. Ziegler* and *R. Connor*, J. Amer. chem. Soc. *62*, 2596 (1940).

[7] *H. Hoffmann* and *H. Förster*, Tetrahedron Letters *1963*, 1547.



(5)

Formation of the tetrasulfone *(6)* in the reaction of bisphenylsulfonylbromomethane with triphenylphosphine in the presence of formaldehyde can be attributed to a trapping



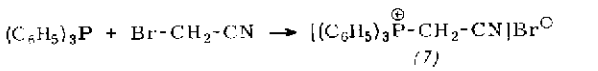
(6)

reaction of a sulfone carbanion. The same compound *(6)* is formed from bisphenylsulfonylmethane and formaldehyde on addition of base [8].

However, the possibility of carrying out the same condensations with the bisphenylsulfonylbromomethane/phosphine system as with the bisphenylsulfonylmethane/base system is very slight. As a rule, the carbanions react more rapidly with the bromophosphonium cation than with the added carbonyl compound.

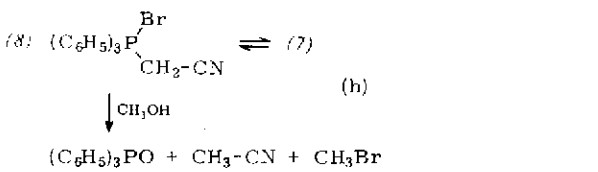
## 2. From α-Bromo Nitriles

According to *Schiemenz* and *Engelhard* [9], bromoacetonitrile and triphenylphosphine react in benzene to form cyanomethyltriphenylphosphonium bromide *(7)*.



(7)

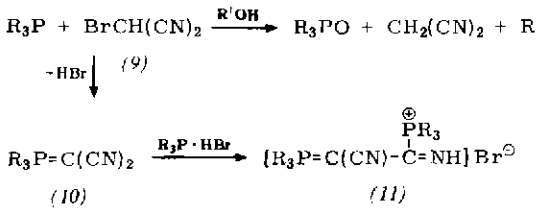
Although *(7)* does not react with alcohols, the yield in benzene containing methanol is much lower as dehalogenation predominates. *Schiemenz* showed that this reaction does not proceed by a free-radical mechanism, and assumed that a compound *(8)* containing pentacovalent phosphorus is formed directly, and is then either dissociated or solvolysed [Equation (h)].



(h)

Because of the equilibrium *(7)* ⇌ *(8)* this assumption is, however, incompatible with the stability of the phosphonium salt towards alcoholysis. Thus, here too the solvolysis must begin with the preceding carbanion-bromophosphonium ion pair [10].

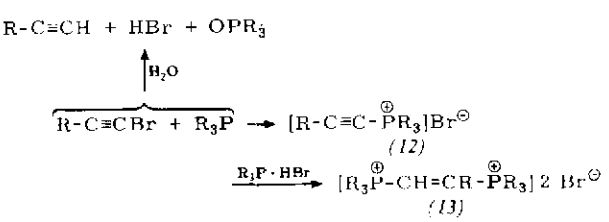
It is noticeable that, in contrast to the behavior of bromo sulfones, phosphonium salt formation with bromoacetonitrile is not entirely suppressed in the presence of alcohol. Thus, here the rate of solvolysis must be comparable with the rate of association. However, the stability of the carbanion can be increased by introduction of a second cyano group, with a resultant decrease in the rate of association. Thus, bromomalonodinitrile reacts with phosphines in alcohol with complete dehalogenation [11]. In acetonitrile, the reaction of bromomalonodinitrile *(9)* is complicated by secondary reactions: addition of a phosphonium bromide onto the ylide *(10)* formed first results in a compound with the supposed constitution *(11)*.



## 3. From Phenylbromoacetylene

Theoretical considerations and *Arens'* studies [12] of the behavior of phenylbromoacetylene toward thiols indicate that the formation of phenylethynyltriphenylphosphonium bromide *(12)* described by *Viehe* and *Franchimont* [13] also involves initial attack on the halogen.

Like almost all other known phosphonium salts, *(12)* is not hydrolysed by water (either neutral or acidic). If phenylbromoacetylene is treated with triphenylphosphine in aqueous acetonitrile, only half of the acetylenic compound is converted into a phosphonium salt; the other half is dehalogenated to phenylacetylene. The dehalogenation gives rise to hydrogen bromide, which causes excess phosphine to add onto the ethynylphosphonium salt to form a bisphosphonium salt *(13)* [14].



Phosphonium salt formation is again only partly supressed in aqueous media. This may be explained by equality of the rates of solvolysis and C-phosphonium salt formation.

[8] *A. Kötz*, Ber. dtsch. chem. Ges. *33*, 1120 (1900).

[9] *G. P. Schiemenz* and *H. Engelhard*, Chem. Ber. *94*, 578 (1961).

[10] *A. J. Speziale* and *L. R. Smith*, J. Amer. chem. Soc. *84*, 1868 (1962).

[11] *H. Hoffmann* and *H. Beller*, unpublished work.

[12] *J. F. Arens*, Recueil Trav. chim. Pays-Bas *82*, 182 (1963).

[13] *H. G. Viehe* and *E. Franchimont*, Chem. Ber. *95*, 319 (1962).

[14] *H. Hoffmann* and *H. Förster*, Tetrahedron Letters *1964*, 983.

An alternative interpretation would envisage simultaneous phosphonium salt formation of both the first and second kinds. Since the reaction rates in dry and aqueous acetonitrile are practically equal, dehalogenation by the mechanism described for α-halogenophosphine oxides and α-bromocamphor (cf. Sections II.5 and III.2) can be ruled out.

### 4. From Polyhalogenomethanes

As mentioned above, *C*-phosphonium salt formation with initial attack of the phosphine on the halogen was first discussed by *Haszledine* [1] for the reaction of trifluoroiodomethane with trimethylphosphine. In addition to small quantities of trifluoromethane, this reaction yields mainly trifluoromethyldimethylphosphine, since the trifluoromethyltrimethylphosphonium iodide initially formed is demethylated by excess trimethylphosphine [see Equation (i)].

$$(CH_3)_3P + ICF_3 \rightarrow [(CH_3)_3\overset{\oplus}{P}\text{-}CF_3]I^{\ominus}$$

$$\xrightarrow{(CH_3)_3P} (CH_3)_2P\text{-}CF_3 + [(CH_3)_4\overset{\oplus}{P}]I^{\ominus} \quad \text{(i)}$$

The assumption of initial attack on the halogen agrees with various other reactions of trifluoroiodomethane: *e.g.* its reaction with hydroxide ions yields trifluoromethane and hypoiodite [15]. Tertiary amines also attack the iodine. However, since the electron octet on nitrogen cannot be expanded, no quaternary ammonium salt is formed; the trifluoromethyl anion reacts with the solvent to form trifluoromethane [1].

Despite the weaker positive polarization of their halogen atoms, carbon tetrabromide [16] and carbon tetrachloride [17, 18] are also initially attacked by triphenylphosphine at the halogen. In inert solvents, trihalogenomethylphosphonium salts are formed first, and these react with additional phosphine to form ylides *(15)*. In alcohol, the ion pair *(14)* initially formed is solvolysed with formation of trihalogenomethane, phosphine oxide, and alkyl halide [18].

$$R_3PO + HCX_3 + R'X$$

$$\uparrow R'OH$$

$$R_3P + CX_4 \rightarrow (R_3\overset{\oplus}{P}X + \overset{\ominus}{C}X_3) \rightarrow [R_3\overset{\oplus}{P}\text{-}CX_3]X^{\ominus}$$

*(14)*

$$\downarrow R_3P$$

$$R_3P{=}CX_2 + R_3PX_2$$

*(15)*

*Rabinowitz* [17] was able to rule out a free-radical mechanism for the reaction of tertiary phosphines with carbon tetrachloride. A carbene mechanism is also unlikely, since no cyclopropane derivative is formed in the presence of tetramethylethylene, although the latter is a better carbene scavenger than triphenylphosphine [17].

In contrast to the carbon tetrahalides, bromoform appears to react with triphenylphosphine by a free-radical chain reaction [19].

$$R_3P + {}^{\bullet}CHBr_2 \rightarrow R_3\overset{\bullet}{P}\text{-}CHBr_2 \xrightarrow{+Br_3CH}$$

$$[R_3\overset{\oplus}{P}\text{-}CHBr_2]Br^{\ominus} + {}^{\bullet}CHBr_2 \quad \text{(k)}$$

This reaction [Equation (k)] proceeds spontaneously at elevated temperatures and is initiated at room temperature by light or chain starters. On the other hand, in the presence of strong bases, ylides *(16)* are formed from bromoform, chloroform, or methylene chloride with tertiary phosphines *via* a carbene mechanism [20].

$$R_3P + IC\begin{matrix}X\\Y\end{matrix} \rightarrow R_3P{=}C\begin{matrix}X\\Y\end{matrix}$$

*(16)*

### 5. From α-Halogenoalkylphosphonium Salts and α-Halogenoalkylphosphine Oxides

The increase in the acidity of the hydrogen atom attached to the carbon atom adjacent to the phosphorus in phosphonium salts and phosphine oxides corresponds to a slight increase in the positive polarization of the halogen in α-halogenoalkylphosphonium salts and phosphine oxides. Consequently, the reaction of phenyllithium with the bromo- or iodomethyltriphenylphosphonium cation *(17)* results in removal of halogen cations as well as of protons. Methylenetriphenylphosphorane and the halogenomethylenetriphenylphosphorane are formed together (see Equation (l) [20, 21]):

$$[R_3\overset{\oplus}{P}\text{-}CH_2X]X^{\ominus} + RLi \begin{matrix}\nearrow R_3P{=}CH_2 + RX + LiX\\ \searrow R_3P{=}CHX + RH + LiX\end{matrix} \quad \text{(l)}$$

*(17)*

R = $C_6H_5$; X = Br, I

On the other hand, only protons are split off from the corresponding chloromethylphosphonium salt [22] since nucleophilic attack on chlorine is more difficult than on bromine, while chlorine increases more strongly the acidity of the C–H bond.

Chloromethylphosphonium cations *(17a)* react with tertiary phosphines only in acidic solution, where they undergo dehalogenation [23].

$$[R_3\overset{\oplus}{P}\text{-}CH_2Cl] + PR_3 + H^{\oplus} \rightarrow \left[R_3\overset{\oplus}{P}\text{-}\overset{H}{C}H_2 \cdots \overset{Cl}{P}R_3\right]$$

*(17a)*

$$\downarrow$$

$$[R_3\overset{\oplus}{P}\text{-}CH_3] + Cl\overset{\oplus}{P}R_3$$

[15] *R. N. Haszeldine*, J. chem. Soc. (London) *1952*, 4259.

[16] *F. Ramirez, N. P. Desai*, and *N. McKelvie*, J. Amer. chem. Soc. *84*, 1745 (1962).

[17] *R. Rabinowitz*, J. Amer. chem. Soc. *84*, 1312 (1962).

[18] *A. J. Burn* and *J. I. G. Cadogan*, J. chem. Soc. (London) *1963*, 5788.

[19] *F. Ramirez* and *N. McKelvie*, J. Amer. chem. Soc. *79*, 5829 (1957).

[20] *A. J. Speziale, G. J. Marco*, and *K. W. Ratts*, J. Amer. chem. Soc. *82*, 1260 (1960); see also [22].

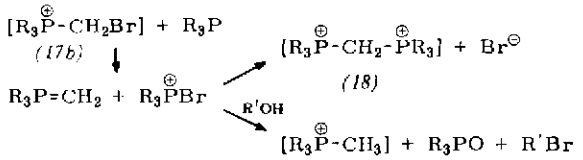
[21] *D. Seyferth, J. K. Herren*, and *S. O. Grimm*, J. org. Chemistry *26*, 4783 (1961); cf. *G. Köbrich*, Angew. Chem. *74*, 33 (1962); Angew. Chem. internat. Edit. *1*, 51 (1962).

[22] *G. Wittig* and *M. Schlosser*, Chem. Ber. *94*, 1373 (1961).

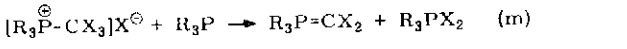
[23] *H. Hoffmann*, Habilitation Thesis, Universität Mainz, 1962.

This reaction evidently represents the limiting case: the positive polarization of the halogen is so slight that it can only be split off if a proton is available to neutralize the charge on the carbanion (push-pull reaction).

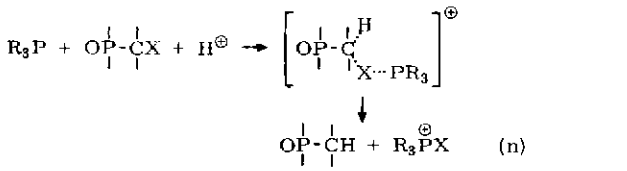
The bromomethyltriphenylphosphonium cation *(17b)* is sufficiently reactive to be dehalogenated by triphenylphosphine in alcohol [24] or to form a bisphosphonium salt in inert solvents [25].



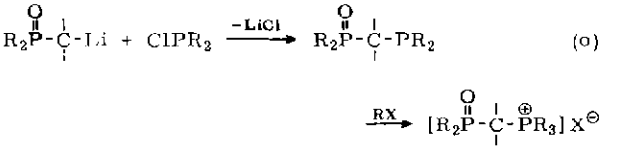
According to this formulation, the bisphosphonium salt *(18)* should be formed from the ylide and a bromophosphonium cation. However, such a reaction is evidently possible only with very reactive ylides. Thus, it can be concluded from findings of *Ramirez* [16] and *Rabinowitz* [17] that no bisphosphonium salts are formed from trichloromethyl- and tribromomethyltriphenylphosphonium salts, since Reaction (m) stops at the ylide.



Since the electron attraction of the phosphine oxide group is weaker than that of the phosphonium group, in the examples investigated so far, both α-chloroalkyl- and α-bromoalkylphosphine oxides are dehalogenated by phosphines only in acidic solution [see Equation (n)] [23].



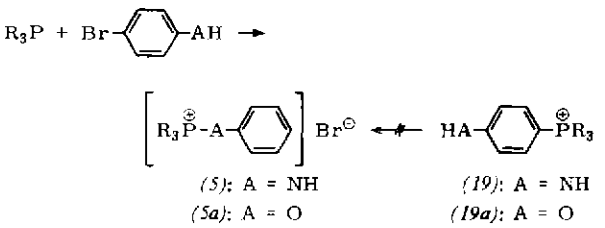
Phosphoniophosphine oxides were not obtained in these reactions. However, they can be prepared by the route indicated in Equation (o) [23].



## III. Formation of Quasi-Phosphonium Salts

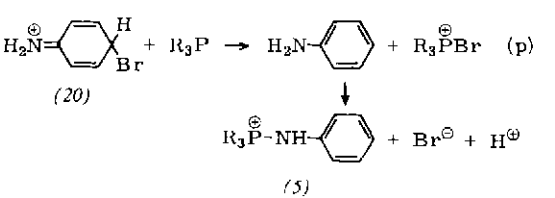
### 1. From Bromoarylamines and Bromophenols

It is solely *C*-phosphonium salts that are formed in the examples of phosphonium salt formation of the second kind referred to so far. The overall reaction corresponded to direct substitution of the halogen by the phosphine. However, as mentioned above, if the system formed by removal of the bromo cation is capable of resonance, quasi-phosphonium salts *(2)* can also be obtained. Examples of this are given by the reaction of *o*- and *p*-bromo- or iodoarylamines and -phenols [26, 27]. On reaction with tertiary phosphines in inert solvents or in the melt, these compounds form arylamino- or aryloxyphosphonium salts, *e.g. (5)* and *(5a)*.



Here the constitution of the products shows that no direct nucleophilic substitution of the halogen has occured. The unlikely hypothesis of initial formation and subsequent rearrangement of aminoaryl- or hydroxyarylphosphonium salts was easily disproved: compounds *(19)* and *(19a)*, which can be prepared by another route, do not undergo rearrangement.

From bromoarylamines and phosphines the corresponding dehalogenated amines are formed together with phosphine oxide and hydrogen bromide or alkyl halides in the presence of water or alcohol, even when conditions are applied under which the arylaminophosphonium salts are stable to solvolysis. A significant point in the explanation of the reaction mechanism is that the reaction of the halogenated arylamines is catalysed by the minute amounts of acid which are formed when these compounds are heated. This observation suggests that it is not the amine itself which reacts, but the cation *(20)* formed by addition of a proton at the *o*- or *p*-position. A halogen cation is removed from this by the phosphine at a rate which depends on its nucleophilicity. The resulting bromophosphonium cation then reacts either with the solvent or in a known manner with the amine (or phenol) according to Equation (p).



The formation of quasi-phosphonium salts from tertiary amines, *e.g. p*-bromodimethylaniline, is not possible, but the primary dehalogenation can occur [27a]. Thus, if *p*-bromodimethylaniline is treated with tertiary phosphines in the presence of aniline, the phenylaminophosphonium salt *(5)* is formed together with dimethylaniline.

[24] *D. W. Grisley jr.*, Tetrahedron Letters *1963*, 435.

[25] *F. Ramirez, N. B. Desai, B. Hansen*, and *N. McKelvie*, J. Amer. chem. Soc. *83*, 3539 (1961).

[26] *H. Hoffmann, L. Horner, H. G. Wippel*, and *D. Michael*, Chem. Ber. *95*, 523 (1962).

[27] *H. Hoffmann* and *D. Michael*, Liebigs Ann. Chem. *626*, 26 (1959).

[27a] Iodoresorcinol dimethyl ether is also dehalogenated (*H. Hoffmann* and *E. Oppenheimer*, unpublished work):

$$R_3P + H^{\oplus} + C_6H_3I(OCH_3)_2 \rightarrow R_3\overset{\oplus}{P}I + C_6H_4(OCH_3)_2$$

## 2. From α-Halogeno Ketones and α-Halogeno Aldehydes

The reactions of α-halogenocarbonyl compounds with tertiary phosphines are particularly interesting. On the one hand, the conditions for phosphonium salt formation of the second kind are satisfied, since the halogen is positively polarized by the strongly electron-attracting carbonyl group, and the anion formed by removal of a halogen cation is capable of resonance. On the other hand, the α-halogen is in a type of allylic position and should therefore be readily susceptible to anionic substitution. The behavior of α-halogenocarbonyl compounds toward tertiary phosphines also appears to correspond to this "ambivalent" situation of the halogen: either β-keto- (aldehydo-) phosphonium salts *(21)* or enolphosphonium salts *(22)* are formed, depending on the structure of the halogenocarbonyl derivative (see Table 1) [28–30]; *mixtures* may also be formed in limiting cases.

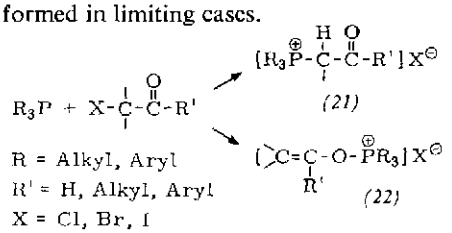
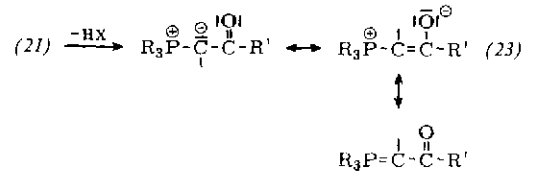



Table 1. Reactions of α-halogeno aldehydes and ketones with tertiary phosphines.

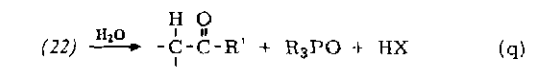
| α-Halogeno aldehyde or ketone | Phosphine | Reaction product [*] | Ref. |
|---|---|---|---|
| $ClCH_2$–CHO | $(C_6H_5)_3P$ | A (in water E) | [43] |
| $Cl_3C$–CHO | $(C_6H_5)_3P$ | E | [28,30] |
| $Cl_3C$–CHO | $C_6H_5P(C_2H_5)_2$ | E | [30] |
| $CH_3$–CO–$CH_2Br$ | | K | [31] |
| $C_6H_5$–CO–$CH_2Cl$ | $(C_6H_5)_3P$ | K | [36] |
| $C_6H_5$–CO–$CH_2Br$ | $(C_6H_5)_3P$ | K (in alcohol E) | [36] |
| $C_6H_5$–CO–CHCl–$C_6H_5$ | $(C_6H_5)_3P$ | K (26 %), E (64 %) (in ethanol) | [11], cf. [28,30] |
| $C_6H_5$–CO–CHCl–$C_6H_5$ | $C_6H_5P(C_2H_5)_2$ | K (82 %), E (17 %) (in ethanol) | [11] |
| | | K (77 %), E (21 %) (in benzene) | [11] |
| | | K (94 %) (in acetonitrile) | [11] |
| $C_6H_5$–CO–CHCl–$C_6H_5$ | $(C_2H_5)_3P$ | K (77 %), E (20 %) (in benzene) | [11] |
| | | K (50 %), E (38 %) (in ethanol) | [11] |
| $C_6H_5$–CO–CHBr–$C_6H_5$ | $(C_6H_5)_3P$, $C_6H_5P(C_2H_5)_2$, $(C_2H_5)_3P$ | K (85–95 %) (in ethanol, benzene) | [11] |
| $C_6H_5$–CO–CHBr–$C_6H_5$ | $(C_6H_{11})_3P$ | K (49 %), E (46 %) (in methanol) | [11] |
| $C_6H_5$–CO–$CCl_2$–$C_6H_5$ | $(C_6H_5)_3P$ | E | [30] |
| $C_6H_5$–CO–CClBr–$C_6H_5$ | $(C_6H_5)_3P$ | E (bromide) | [30] |
| $C_6H_5$–$CBr_2$–CO–CHBr–$C_6H_5$ | $C_6H_5P(C_2H_5)_2$ | E | [11] |
| $(C_6H_5)_2CCl$–CO–$C_6H_5$ | $(C_6H_5)_3P$ | E | [44] |
| $(C_6H_5CO)_2CHBr$ | $(C_6H_5)_3P$ | E | [30] |
| $(C_6H_5CO)_2CBr_2$ | $(C_6H_5)_3P$ | E | [30] |
| $C_6H_5$–CO–CH=CH–$CCl_3$ | $(C_6H_5)_3P$ | E (80 %) | [11] |
| $C_6H_5$–CO–CH=CH–$CCl_3$ | $C_6H_5P(C_2H_5)_2$ | E (45 %), K (50 %) (in ether or alcohol) | [11] |
| 2-Bromocyclohexanone | $(C_6H_5)_3P$ | E | [29] |
| 2-Bromodimedone | $(C_6H_5)_3P$ | E | [29] |
| 2-Bromo-2-methylcyclohexanone | $(C_6H_5)_3P$ | E | [29] |
| 2-α-Bromocholestanone | $(C_6H_5)_3P$ | E | [29] |
| 2-Bromo-2-phenylindane-1,3-dione | $(C_6H_5)_3P$ | E | [11] |

[*] K = ketophosphonium salt. A = aldehydophosphonium salt. E = enolphosphonium salt.

The two isomeric classes of phosphonium salts can be easily differentiated by their behavior on solvolysis. As *C*-phosphonium salts, the ketophosphonium salts *(21)*, which have been known for some time, are stable in neutral and acidic media. They react with bases, even in aqueous solution, to form ylides *(23)*, which are stabilized by the keto group.

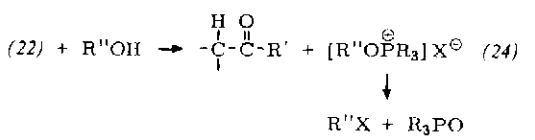



On the other hand, like the constitutionally related aryloxyphosphonium salts, enolphosphonium salts *(22)* are extremely sensitive to solvolysis. They decompose with water to give the (singly) dehalogenated carbonyl compounds, phosphine oxide, and hydrogen halide, according to Equation (q).

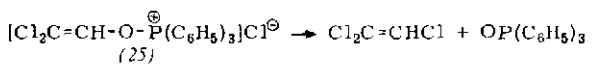



(q)

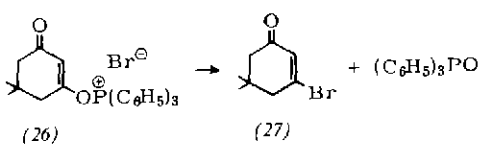
When *(22)* is treated with alcohol, the alkenyloxy residue is exchanged for an alkoxy residue. An alkoxyphosphonium salt *(24)* is formed and immediately decomposes with formation of an alkyl halide.



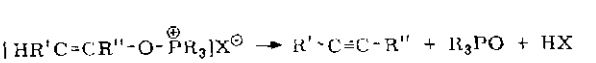

The enolphosphonium salts *(22)* are sometimes very stable in the absence of solvolysing agents, *e.g.* the phosphonium salt *(25)* obtained from chloral and triphenylphosphine decomposes only on heating at 300 to 350 °C into trichloroethylene and triphenylphosphine oxide [30].




A similar cleavage of *(26)* to give *(27)* was described by *Borowitz* and *Grossmann* [29] and apparently proceeds even at low temperatures.




Enolphosphonium salts with hydrogen in the β-position can be decomposed thermally or by bases to acetylene derivatives [31,30].




[28] *S. Trippett*, J. chem. Soc. (London) *1962*, 2337.

[29] *I. J. Borowitz* and *L. I. Grossmann*, Tetrahedron Letters *1962*, 471.

[30] *H. Hoffmann* and *H. J. Diehr*, Tetrahedron Letters *1962*, 583.

[31] *S. T. D. Gough* and *S. Trippett*, J. chem. Soc. (London) *1962*, 2533.

As enol derivatives, the enolphosphonium salts add on bromine [30] to give adducts which also readily undergo solvolysis to yield a ketone with the same degree of halogenation as the original compound. This reaction allows partial exchange of chlorine for bromine, *e.g.* according to Equation (r):

$$R_3P + R'\text{-}CCl_2\text{-}CO\text{-}R' \rightarrow [R'\text{-}CCl{=}CR'\text{-}O\text{-}\overset{\oplus}{P}R_3]Cl^{\ominus} \quad (r)$$

$$\xrightarrow{Br_2} [R'\text{-}CClBr\text{-}CR'Br\text{-}O\text{-}\overset{\oplus}{P}R_3]Cl^{\ominus} \xrightarrow{H_2O}$$

$$R'\text{-}CClBr\text{-}CO\text{-}R' + R_3PO + HCl + HBr$$

$R' = C_6H_5$

It should be mentioned that, in the enolphosphonium salts, not only the alkenyloxy group but also the phosphine residue can be readily exchanged. Thus if an enolphosphonium salt prepared from triphenylphosphine is treated with a more nucleophilic phosphine, *e.g.* $C_6H_5P(C_2H_5)_2$, triphenylphosphine is liberated and the enolphosphonium salt of the more nucleophilic phosphine is formed [11]. With excessive phosphine, some enolphosphonium salts form vinylphosphonium salts [11], for example (R = $C_6H_5$):

$$R\text{-}CO\text{-}CH{=}CR\text{-}O\overset{\oplus}{P}R_3 + R_3P \rightarrow R\text{-}CO\text{-}CH{=}CR\text{-}\overset{\oplus}{P}R_3 + R_3PO$$

There are two similar reactions with tertiary phosphites corresponding to the reaction of the α-halogenocarbonyl compounds with phosphines to form keto- and enolphosphonium salts: the formation of β-ketophosphonates (a special case of the Michaelis-Arbuzow reaction) and the formation of enolphosphates according to *Perkow* [32]. The analogy between these two pairs of competing reactions is complete if it is assumed that the products are formed by elimination of alkyl halide from intermediate quasi-phosphonium salts.

$$\begin{array}{l} [\rangle C{=}CR'\text{-}O\text{-}PO(OR)_2] \\ \uparrow -RX \\ [\rangle C{=}CR'\text{-}O\text{-}\overset{\oplus}{P}(OR)_3]X^{\ominus} \quad (28a) \\ \rangle CX\text{-}CO\text{-}R' + (RO)_3P \\ [(RO)_3\overset{\oplus}{P}\text{-}\underset{|}{C}\text{-}CO\text{-}R']X^{\ominus} \quad (28b) \\ -RX \downarrow \\ (RO)_2OP\text{-}\underset{|}{C}\text{-}CO\text{-}R' \end{array}$$

It is therefore generally assumed that the formation of enolphosphonium salts and the first step of the Perkow reaction proceed by the same mechanism. However, despite numerous investigations, this mechanism is itself still in dispute. In principle, the initial attack on the phosphine or phosphite may be at one of the four following positions:

a) on the α-carbon,
b) on the carbonyl carbon,
c) on the carbonyl oxygen, or
d) on the halogen.

All of these possibilities have been discussed for the Perkow reaction.

Initial attack on the α-carbon would mean that the enolphosphonium salts must be formed by rearrangement of initially formed ketophosphonium salts [see Equation (s)].

$$R_3P + X\text{-}\underset{|}{C}\text{-}CO\text{-} \rightarrow R_3P\text{-}\overset{CO}{\underset{|}{C}}\text{-}X \quad (s)$$

$$\rightarrow [R_3\overset{\oplus}{P}\text{-}\underset{|}{C}\text{-}CO]X^{\ominus} \rightarrow [\rangle C{=}\underset{|}{C}\text{-}O\text{-}\overset{\oplus}{P}R_3]X^{\ominus}$$

R = Alkyl, Aryl, O-Alkyl

A mechanism of this type was suggested by *Cramer* [33] for the Perkow reaction (R – O-Alkyl), but could not be directly proved owing to the instability of the keto-quasi-phosphonium salt. This mechanism can be definitely ruled out for the formation of enolphosphonium salts. For example, α-benzoylbenzyl halides give ketophosphonium salts *(29)* as well as enolphosphonium salts *(30)* [30, 11]; the β-ketophosphonium salts *(29)* are stable and cannot be rearranged.

$$\begin{array}{l} [C_6H_5\text{-}CO\text{-}CH(C_6H_5)\text{-}\overset{\oplus}{P}R_3]Cl^{\ominus} \\ \quad (29) \\ C_6H_5\text{-}CO\text{-}CHCl\text{-}C_6H_5 \\ + \\ R_3P \\ [R_3\overset{\oplus}{P}\text{-}O\text{-}(C_6H_5)C{=}CH\text{-}C_6H_5]Cl^{\ominus} \\ \quad (30) \end{array}$$

Stronger arguments can be presented for primary attack on the carbonyl carbon. Thus, halogen-free aldehydes (and ketones) react with tertiary phosphines in the presence of electrophilic reagents to form phosphonium salts such as *(31)* and *(32)* by linkage through the carbonyl carbon [34,35].

$$\begin{array}{l} R_3P + R'CHO \\ \downarrow \\ R_3\overset{\oplus}{P}\text{-}\underset{|}{\overset{\ominus}{O}}\text{-}CHR' \quad (31) \\ \xrightarrow{HX} [R_3\overset{\oplus}{P}\text{-}\underset{|}{OH}\text{-}CHR']X^{\ominus} \quad (31) \\ \xrightarrow{R''COCl} [R_3\overset{\oplus}{P}\text{-}CHR'\text{-}O\text{-}CO\text{-}R'']X^{\ominus} \quad (32) \end{array}$$

Halogeno ketones or aldehydes and phosphines or phosphites could therefore feasibly form adducts such as *(33)*, which then undergo a synchronous rearrangement to yield the enolphosphonium salt *(22)*.

$$Cl\text{-}\underset{|}{C}\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' \xrightarrow{+PR'_3} Cl\text{-}\underset{|}{C}\text{-}\underset{|}{\overset{\ominus}{O}}\text{-}\overset{\oplus}{P}R_3 \quad (33)$$

$$\rightarrow (22)$$

$$\rightarrow [\rangle C\text{—}\overset{O}{\diagup\diagdown}CR'\text{-}\overset{\oplus}{P}R_3]Cl^{\ominus} \quad (34)$$

[32] *F. W. Lichtenthaler*, Chem. Reviews *61*, 607 (1961).

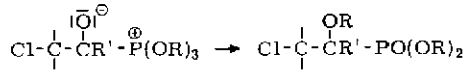
[33] *F. Cramer*, Angew. Chem. *72*, 236 (1960).

[34] See, for example, *H. Hoffmann*, Angew. Chem. *72*, 77 (1960).

[35] Mention should also be made of the formation of diphenylhydroxytrichloroethylphosphine from diphenylphosphine and chloral (*H. Diehr*, Diploma Thesis, Universität Mainz, 1962):

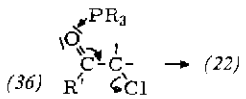
$$Cl_3C\text{—}CHO + HP(C_6H_5)_2 \rightarrow Cl_3C\text{—}CH(OH)\text{—}P(C_6H_5)_2$$

An objection to a mechanism of this type is that compounds with structure *(33)* should be converted at least in part into epoxides (cf. [32], or with phosphites, to α-alkoxy-β-chloroalkylphosphonates *(35)*.



*(35)*

Other authors therefore reject the assumption of initial adduct formation and postulate direct attack on the carbonyl oxygen which, according to *(36)*, should lead to electron displacement with simultaneous elimination of the halogen anion.



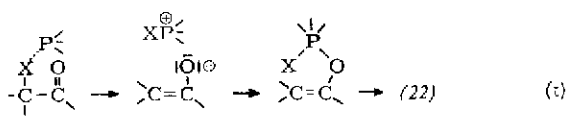
*(36)* → *(22)*

Models for such a process would be the well known $S_N2'$ reactions of allyl compounds. However, in order to apply the concepts developed for these reactions to α-halogenocarbonyl compounds, the nucleophilic reagent must be assumed to attack at a position of high electron density. The analogy therefore appears somewhat far-fetched. It can be argued further that $S_N2'$ reactions could occur not only with halides, but also – extremely readily – with the corresponding *p*-toluenesulfonates. "Perkow esters" or enolphosphonium salts should therefore also be formed from the tosylates of α-hydroxy ketones. However, the reaction of the *p*-toluenesulfonate of benzoin with triphenylphosphine yields the β-ketophosphonium salt *(37)* [11], while the main product from α-benzoylbenzyl chloride is the enolphosphonium salt.



*(37)*

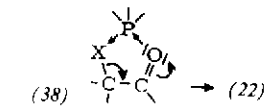
The mechanism of the formation of the enolphosphonium salt is easy to explain if it is considered that, even in the α-halogenocarbonyl compounds, the halogen is under the influence of a strongly electron-attracting group. This undoubtedly facilitates attack by the phosphine on the halogen [29,30,38]. Removal of the halogen is then exactly analogous to the removal of a proton with bases [see Equation (t)].



*(22)* (t)

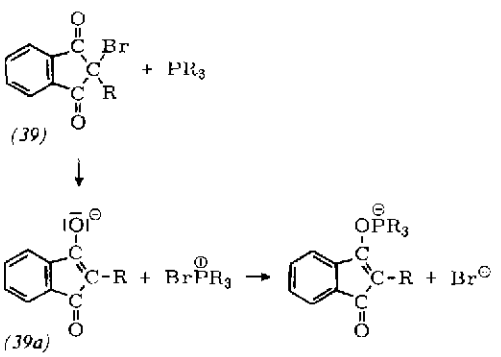
The main advantage of a mechanism according to Equation (t) is that it permits an explanation of the fact that the ratio of the enolphosphonium salt to the ketophosphonium salt obtained depends on the constitution of the substrate: the quantity of enolphosphonium salt increases with increasing positive polarization of the halogen and increasing stability of the alkenyloxide ion. Thus, phenacyl chloride and triphenylphosphine give only the ketophosphonium salt, whereas α-benzoylbenzyl chloride gives a mixture of the keto- and enolphosphonium salts, and α-benzoylbenzylidene dichloride gives only the enolphosphonium salt (for further examples, see Table 1).

If the phosphine is assumed to attack initially on the halogen, the additional question arises whether the removal of the halogen and formation of the O–P bond occur in steps [as in Equation (t)], or synchronously.



*(38)* → *(22)*

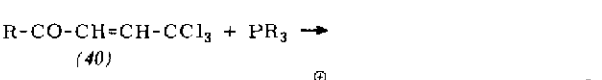
A synchronous mechanism *via* the transition state *(38)* would require close proximity of the carbonyl group to the halogen. It was found, however, that enolphosphonium salts could also be formed from cyclic ketones in which the carbon-halogen bond and the carbonyl group can no longer lie in the same plane. Examples of such ketones are 2-α-bromocholestanone [29] and bromophenylindanedione [11]. With bromophenylindanedione *(39)*, the stepwise mechanism is also supported by the brief appearance of a deep red color characteric of the alkenyloxide ion *(39a)*.



*(39)* *(39a)*

R = $C_6H_5$

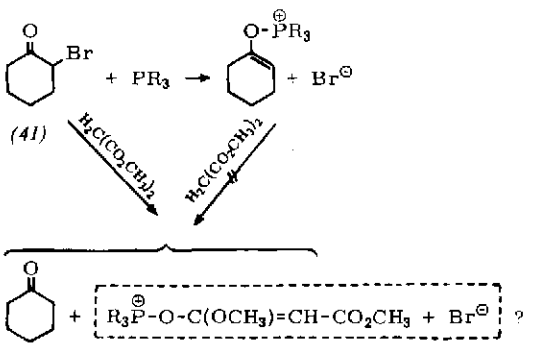
A synchronous mechanism is also very unlikely for vinylogous halogeno ketones such as *(40)*, which forms an enolphosphonium salt with triphenylphosphine [11].



*(40)*

R = $C_6H_5$

A strong argument in favor of intermediate formation of an ion pair is the observation made by *Borowitz* and *Virkhaus* [36] that enolphosphonium salts are formed from 2-bromocyclohexanone *(41)* and triphenylphosphine when the reaction is carried out in the presence of



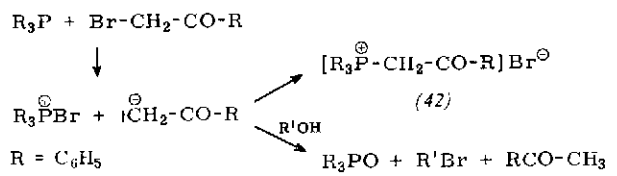
*(41)*

[36] *I. J. Borowitz* and *R. Virkhaus*, J. Amer. chem. Soc. *85*, 2184 (1963).

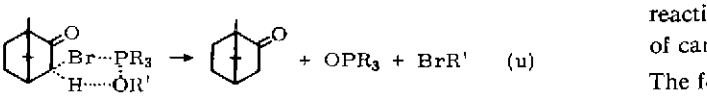
dimethyl malonate. The latter is sufficiently acidic to protonate the carbanion, but cannot decompose the enolphosphonium salt once it has been formed.

On the other hand, it can be argued that, like α-halogenoalkylphosphine oxides, α-halogeno ketones can be dehalogenated in the presence of acidic compounds by a "push-pull" mechanism. Independently of this, however, it is certainly justifiable to assume at least that a synchronous mechanism must not occur in every case. However, if an ion pair is formed from an alkenyloxide ion (or carbanion) and a halogenophosphonium cation [cf. *(1)* in Equation (b)], it is possible that the association will give rise not only to enolphosphonium salts, but also to ketophosphonium salts by a reaction of the second kind. This mechanism of formation might apply to ketophosphonium salts which are formed only in the absence of solvolytic agents.

For example, triphenylphosphine and phenacyl bromide give phenacyltriphenylphosphonium bromide *(42)* only in inert solvents; dehalogenation occurs in the presence of water or alcohol [36]:



However, the possibility of active participation in the reaction of the alcohol when the halogen is only weakly positively polarized must not be neglected. Thus, α-bromocamphor is smoothly dehalogenated by phenyldiethylphosphine in alcohol according to Equation (u), although no reaction occurs in acetonitrile under comparable conditions [11].

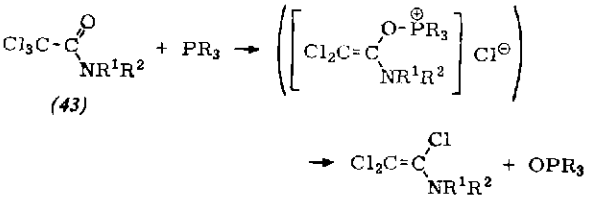


(u)

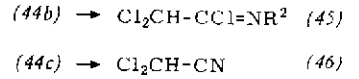
Formation of a ketophosphonium salt by an $S_N2$ mechanism of the first kind can always be expected when debalogenation by the alcohol is not appreciably favored. This is the situation, for example, in the reaction of α-benzoylbenzyl chloride with phenyldiethylphosphine: in ethanol, in benzene, and in a mixture of the two solvents, the ratio of the ketophosphonium salt to the enolphosphonium salt (or dehalogenation products) is fairly constant at 4:1.

### 3. Amides and Esters of α-Halogenocarboxylic Acids

The halogens in α-halogenated derivatives of carboxylic acids are subject to the same influences as those in α-halogeno ketones, but to a somewhat lesser extent. α-Chlorocarboxamides were investigated in detail in the comprehensive work of *Speziale* [37,38], who found that an initial step similar to that involved in the formation of enolphosphonium salts was followed by replacement of the phosphinoxy group by chlorine. Thus, *N,N*-disubstituted trichloroacetamides *(43a)* react with triphenylphosphine to yield tertiary trichlorovinylamines *(44a)*. *N*-Monosubstituted and unsubstituted acetamides give *N*-alkyl- or *N*-aryltrichlorovinylideneimines *(45)* and dichloroacetonitrile *(46)*, respectively, *via* similar reaction steps:

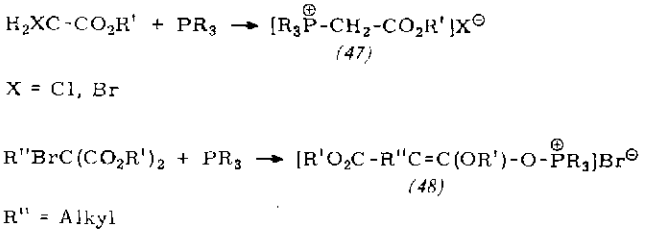


*(44a)*: $R^1 = R^2$ = Alkyl, Aryl
*(44b)*: $R^1$ = H; $R^2$ = Alkyl, Aryl
*(44c)*: $R^1 = R^2$ = H

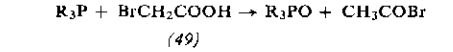


The reactivity of α-halogenocarboxamides also depends strongly upon their structure. Aryl groups on the nitrogen or on the α-carbon increase the reactivity, since they promote formation of a carbanion, either by direct interaction of the aryl residue with carbanion electrons in the *C*-aryl derivative, or by reduction of the electron-donor character of the amino group in the *N*-aryl compound. Consequently, arylated dichloroacetamides still give good yields of dichlorovinylamines, whereas other dichloroacetamides react only sluggishly or with formation of *C*-phosphonium salts. It is interesting that even *N,N*-diethyldichlorofluoroacetamide is only weakly reactive. This can be explained by the lower stabilization of carbanions by fluorine [39].

The formation of enolphosphonium salts also increases rapidly with increasing positive polarization of the halogen in α-halogenocarboxylic esters; chloroacetates and bromoacetates yield *C*-phosphonium salts *(47)* [40], but bromomalonates give quasi-phosphonium salts *(48)* derived from the enolic form [9,30].



Only few experiments as yet have given information on the behavior of free α-halogenocarboxylic acids: chloroacetic acid reacts with triphenylphosphine to form a phosphonium salt [40], but bromoacetic acid *(49)* gives acetyl bromide and phosphine oxide [41].



[37] *A. J. Speziale* and *R. C. Freeman*, J. Amer. chem. Soc. *82*, 903 (1960).

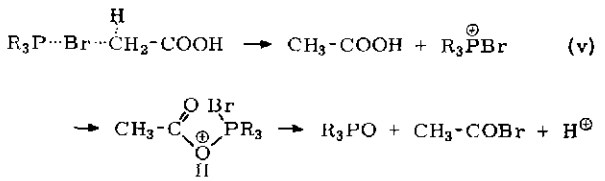
[38] *A. J. Speziale* and *L. R. Smith*, J. Amer. chem. Soc. *84*, 1868 (1962).

[39] *J. Hine, M. W. Burske, M. Hine*, and *P. B. Langford*, J. Amer. chem. Soc. *79*, 1406 (1957).

[40] *A. Michaelis*, Liebigs Ann. Chem. *293*, 193 (1896).

[41] *D. B. Denney* and *L. C. Smith*, J. org. Chemistry *27*, 3404 (1962); Chem. and Ind. *1961*, 290; *G. Aksnes*, Acta chem. scand. *15*, 438 (1961).

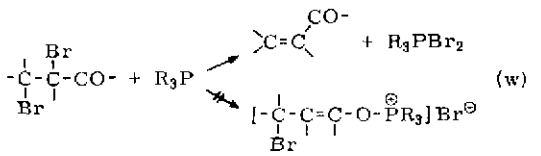
Proton-induced dehalogenation presumably takes place with *(49)* (as with α-halogenoalkylphosphine oxides), *e.g.* according to Equation (v).



(v)

4. From α,β-Dihalogenocarbonyl Compounds

The behavior of α,β-dihalogenocarbonyl compounds shows that removal of the α-halogen by phosphine does not necessarily lead to phosphonium-salt formation. Here, too, the phosphine first removes the α-halogen as a cation. However, just like the abstraction of the α-proton by bases, this process is accompanied by synchronous elimination of the β-halogen. Thus the reaction of triphenylphosphine with α,β-dibromophenethyl phenyl ketone does not yield an enolphosphonium salt, but phenyl styryl ketone and triphenylphosphine dibromide. Similarly, *meso*-dibromosuccinic acid is dehalogenated to fumaric acid by triphenylphosphine [see Equation (w)] [30].



(w)

If the mechanism given is correct, the elimination of the halogen should be a stereospecific *trans*-elimination [42], but since only *trans*-substituted ethylenes have been obtained so far from *erythro*-compounds, and there are no examples known of the formation of *cis*-compounds from *threo*-dibromides, this point has not yet been finally proved.

*We are indebted to the Deutsche Forschungsgemeinschaft and to the Fonds der Chemischen Industrie for support of the experimental work described here.*

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Translated by Express Translation Service, London

[42] *A. J. Speziale* and *C. C. Tung*, J. org. Chemistry *28*, 1353, 1521 (1963).

[43] *S. Trippett* and *D. M. Walker*, J. chem. Soc. (London) *1961*, 1266.

[44] *A. J. Speziale* and *R. D. Partos*, J. Amer. chem. Soc. *85*, 3312 (1963).

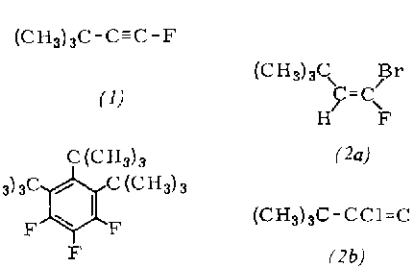
# COMMUNICATIONS

## Formation of 1,2,3-Tri-t-butyltrifluorobenzene by Spontaneous Trimerization of t-Butylfluoroacetylene [1]

By Dr. H. G. Viehe, Dipl.-Ing. R. Merényi, Dr. J. F. M. Oth, and P. Valange [2]

Union Carbide European Research Associates, Brussels (Belgium)

t-Butylfluoroacetylene *(1)* has been prepared as the first example of an alkylated fluoroacetylene by dehydrohalogenation of the fluorohalogenoethylenes *(2a)* and *(2b)* with solid potassium hydroxide at about 120 °C and 35 mm pressure. When undiluted, *(1)* can be kept only at low temperatures; at room temperature it can be handled unchanged only as a gas or in dilute solution in ether for a short time. Even below 0 °C, liquid *(1)* spontaneously and exothermally forms various oligomers, mainly trimers. The major component of the crystalline portion of the mixture of oligomers was examined first; on the basis of physical measurements, particularly its characteristic nuclear magnetic resonance spectrum, it appears to have the structure *(3)*. The fluorine atom seems to be essential for the oligomerization, since t-butylchloroacetylene which is analogous to *(1)*, is thermally stable.



*(3)*, m.p. 112–114 °C
IR: C=C at 6.28 μ.
UV: $\lambda_{max}$ = 209; 228; 266; 319 mμ
$\varepsilon \cdot 10^{-3}$ = 14.7; 19.1; 4.1; 0.79

NMR-fluorine signals (internal standard $CCl_3F$): doublet at +127.7 ppm with a relative intensity of 2; triplet at +154.8 ppm with a relative intensity of 1 ($J_{FF(ortho)}$ = 19.5 cps).

NMR-t-butyl proton signals (internal standard tetramethylsilane): multiplet at −1.45 ppm with a relative intensity of 2; singlet at −1.39 ppm with a relative intensity of 1. The multiplet can be explained by long-range coupling [3] between protons of the flanking t-butyl groups and the neighboring fluorine atoms.

Assuming a coupling constant $J_{FF(meta)} = (J_{XX})$ of 4 cps, the proton multiplet would be part A of an $A_2X_2$ system with a coupling constant $J_{HF} = (J_{AX})$ of 1.3 cps. Because of the high multiplicity to be expected, this coupling appears in the doublet of the fluorine spectrum only as a line broadening; $F\text{-}F_{meta}$ coupling is not observed at all.

The spectral data exclude the 1,2,4- and 1,3,5-trifluoro isomers.

The formation of *(3)* represents the first trimerization of an acetylene derivative to yield a 1,2,3-trisubstituted benzene; this is especially surprising here because of the strain introduced by three neighboring t-butyl groups [4].

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[1] Heterosubstituted Acetylenes, Part X. – Part IX: Angew. Chem. *76*, 572 (1964); Angew. Chem. internat. Edit. *3*, 582 (1964).

[2] Responsible for the experimental work.

[3] *B. Rickborn*, *D. A. May*, and *A. A. Thelen*, J. org. Chemistry *29*, 91 (1964), where further references are given.

[4] Cf. *C. Hoogzand* and *W. Hübel*, Tetrahedron Letters *1961*, 637.

## Generation of Light by Fluorine Reactions in Flash Lamps

By Dr. L. M. Nijland, N.V. Philips' Gloeilampenfabrieken, Lichtgroep, Eindhoven (Holland)

and Dr. J. Schröder, Philips Zentrallaboratorium, Aachen (Germany)

Flash lamps should radiate the largest possible quantity of light during some milliseconds, the color temperature of the flash should correspond, as closely as possible, to daylight (*i.e.* the color temperature of a black body at 6000 to 6500 °K), and the lamps should be small, handy and safe. For this purpose, zirconium, in the form of fine wool, is burnt with oxygen in conventional combustion flash lamps.

A combustion flash lamp is essentially a thermal radiator. The heat of reaction heats the substance to be burnt, or already burnt, and causes it to emit radiation. Emission of visible radiation rapidly increases with rising temperature. The combustion reaction should therefore yield as much heat as possible per quantity of substances reacted. For many reactions (for examples see Table 1) this amount of heat at 25 °C and 1 atm is equal to the negative value for the enthalpy of formation, $\Delta H$, of the compound formed.

Table 1. Enthalpy of formation $\Delta H$ [kcal/mole] at 1 atm and 25 °C.

| Reaction | $\Delta H$ |
|---|---|
| $H_2 + 0.5\ O_2 \rightarrow H_2O$ | −58 |
| $H_2 + F_2 \rightarrow 2\ HF$ | −128 |
| $Be + 0.5\ O_2 \rightarrow BeO$ | −146 |
| $Be + F_2 \rightarrow BeF_2$ | −227 |
| $Zr + O_2 \rightarrow ZrO_2$ | −258 |
| $Zr + 2\ F_2 \rightarrow ZrF_4$ | −457 |
| $Si + O_2 \rightarrow SiO_2$ | −205 |
| $Si + 2\ F_2 \rightarrow SiF_4$ | −370 |

The temperature attainable in combustion is limited, among other factors, by the dissociation of the combustion products. If high temperatures are to be reached, the compounds formed by the combustion must be as stable as possible. Their stability is determined, among other factors, by the free enthalpy of formation, $\Delta G$ (see Table 2).

Table 2. Free enthalpy of formation $\Delta G$ [kcal/g-atom Zr], extrapolated to 4000 °K.

| Reaction | $\Delta G$ |
|---|---|
| $Zr + O_2 \rightarrow ZrO_2$ | −90 |
| $Zr + 4\ F \rightarrow ZrF_4$ | −160 |

Table 2 shows that reactions with fluorine can proceed at higher temperatures than those with oxygen.

Since elementary fluorine is difficult to handle, gaseous compounds with a high fluorine content are used as a source of fluorine. Some of these are thermally rather unstable and chemically rather inert under normal conditions, ($OF_2$: $\Delta H = +7.6$ kcal/mol; $NF_3$: $\Delta H = -27$ kcal/mol). Moreover, compounds of this type yield a larger number of free highly reactive atoms than does molecular fluorine per molecule in the course of dissociation. The bulb volume may therefore be reduced for the same amount of substance reacted. Examples are the enthalpies of formation, at 25 °C and 1 atm, of the reaction of zirconium with equal volumes of $O_2$, $F_2$, $NF_3$ and $OF_2$, as shown in Table 3.

Table 3. Enthalpy of formation $\Delta H$ [kcal] at 1 atm and 25 °C.

| Reaction | $\Delta H$ |
|---|---|
| $2\ O_2 + 2\ Zr \rightarrow 2\ ZrO_2$ | −516 |
| $2\ F_2 + 1\ Zr \rightarrow ZrF_4$ | −457 |
| $2\ NF_3 + 1.5\ Zr \rightarrow 1.5\ ZrF_4 + N_2$ | −630 |
| $2\ OF_2 + 2\ Zr \rightarrow ZrF_4 + ZrO_2$ | −729 |

The most important results of our experiments with fluorine reactions in flash lamps may be summarized as follows:

1. Fluorine as well as some fluorine compounds, *e.g.* $NF_3$ and $OF_2$, supply light in the course of the reaction with finely divided metals, *e.g.* Zr.

2. The color temperatures of the light emitted in the course of the fluorine reactions are up to 20 % higher than in the case of analogous oxygen reactions.

3. The quantities of light, calculated on the same amount of substance reacted, are up to 50 % larger than in the case of combustion with oxygen.

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German version: Angew. Chem. 76, 890 (1964)

## A New Group of Co-carcinogens from Croton Oil [1]

By Prof. Dr. E. Hecker, H. Kubinyi, and Dr. H. Bresch

Max-Planck-Institut für Biochemie, München, and Biochemisches Institut am Deutschen Krebsforschungszentrum, Heidelberg (Germany)

In combination with biological tests for toxic, inflammatory and co-carcinogenic effects [1a], a substance group B [1b], which appears to be homogeneous in thin-layer chromatograms, can be separated chromatographically [2] from croton oil in addition to a substance group A [3]. By multiple counter current distribution B is separated into at least three components (B1, B2, and $B_X$), of which B1 and B2 were obtained pure.

B1 and B2 are colorless, optically active resins of the same Rf value, insoluble in water and soluble in nearly all organic solvents. B1: $C_{37}H_{58}O_8$, $[\alpha]_{578}^{26} = 54°$ (1.76 % in $CHCl_3$), $\lambda_{max} = 232$ and 335 mμ, $\varepsilon_{max} = 7000$ and 80 (in ethanol); IR-spectrum (in KBr): hydroxyl (2.95 μ), carbonyl (5.84 μ), C=C-double bonds (6.09; 6.14 μ); NMR-spectrum: $\delta = 0.9$; 1.3; 1.8; 2.3; 3.2; 3.9; 5.3; 5.6; 7.5 ppm (in $CCl_4$, internal standard: tetramethylsilane). B2: $C_{35}H_{54}O_8$, $[\alpha]_{578}^{26} = 50°$ (3.08 % in $CHCl_3$). The remaining spectral data agree within the limits of error with those of B1.

The two natural products are not aromatic; in addition to three free and two esterified hydroxy groups, each contains an α,β-unsaturated carbonyl group, which is not detectable with the usual reagents. One hydroxy group is esterified with (+)-*(S)*-2-methylbutyric acid, the other with lauric acid in the case of B1 and with capric acid in the case of B2. The third free hydroxy group of B1 and B2 may be esterified with pyridine/acetic anhydride and, on the basis of the NMR-spectra as well as of oxidation by $MnO_2$, can be regarded as primary and situated as in allyl alcohol. The resinous aldehyde obtained by oxidation yields a crystalline 2,4-dinitrophenylhydrazone (B1: $C_{43}H_{60}O_{11}N_4$, m.p. 108.5–109.5 °C; B2: $C_{41}H_{56}O_{11}N_4$, m.p. 119.5–120.5 °C). The two non-esterifiable hydroxy groups in B1 and B2 are tertiary. The natural products B1 and B2 are esters of the diterpenoid parent alcohol $C_{20}H_{28}O_6$ [3].

As is apparent from Table 1, the two substances show high and comparable biological activity with that of co-carcinogen A1 [3] in the inflammation test on the mouse ear (EE) and in the co-carcinogen test on the skin of the back of the mouse.

Table 1. Biological activity of the pure co-carcinogens B1 and B2. Tests according to [1a].

| Substance | E. E. (μg/ear) | Co-carcinogen test [a] | |
|---|---|---|---|
| | | μg/application [b] | papilloma/mouse [c] |
| B 1 | 0.009 | 10 | 5 |
| B 2 | 0.009 | 10 | 7 |
| A 1 | 0.009 | 10 | 9 |

[a] Carcinogen: 1 μMol 9,10-dimethylbenzanthracene.

[b] Application: twice weekly for 12 weeks. [c] After 12 weeks.

After our first communications [1a, 2] appeared, a biologically active product from croton oil has been described without detailed characterization [4] which on hydrogenation yields a fatty acid ester of a polyphenol containing capric acid, lauric acid, and 2-methylbutyric acid. The hydrogenated product possibly is a mixture of the substances B 1 and B 2 described above.

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German version: Angew. Chem. 76, 889 (1964)

[1] Supported by the Deutsche Forschungsgemeinschaft.

[1a] *E. Hecker*, Z. Krebsforsch. *65*, 325 (1963).

[1b] Earlier (cf. [2]) denoted by b.

[2] *E. Hecker*, Angew. Chem. *74*, 722 (1962); Angew. Chem. internat. Edit. *1*, 602 (1962); cf. also Chemiker-Ztg. *86*, 272 (1962).

[3] *E. Hecker, H. Bresch*, and *Ch. v. Szczepanski*, Angew. Chem. *76*, 225 (1964); Angew. Chem. internat. Edit. *3*, 227 (1964).

[4] *B. L. van Duuren, E. Arroyo*, and *L. Orris*, J. med. pharmac. Chem. *6*, 616 (1963); Nature (London) *200*, 1115 (1963).

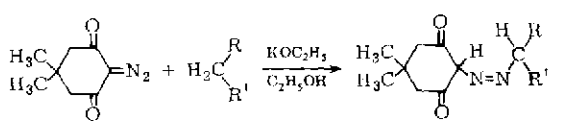
## Azo Coupling of α-Diazo-β-diketones with Non-phenolic Methylene Compounds

By Dr. M. Regitz and cand. chem. D. Stadler

Institut für organische Chemie
der Universität des Saarlandes, Saarbrücken (Germany)

Recently, *Severin* [1] reported on the azo-coupling of 2-diazodimedone *(1)* with highly reactive phenols, *e.g.* phloroglucinol; however, the dyestuffs he obtained were mostly amorphous and were difficult to purify [2].

We have found that readily crystallizable, purely aliphatic azo-compounds *(3)* are obtained with non-phenolic compounds containing an active methylene group when *(1)* or other α-diazo-β-diketones, *e.g.* 2-diazoindane-1,3-dione or 2-diazo-*peri*-naphthindane-1,3-dione, are treated with the methylene component *(2)* and potassium ethoxide in ethanol.

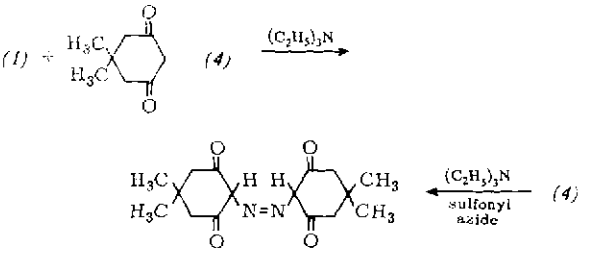


*(1)* *(2)* *(3)*

| *(2)* | *(3)* M.p. [°C] | Color | λmax [mμ] | ε [a] |
|---|---|---|---|---|
| Indane-1,3-dione | 196 | brown-violet | 446<br>246 | 26 500<br>25 300 |
| Diethyl malonate | 114–116 | yellow | 376<br>293 | 16 800<br>7 800 |
| Ethyl benzoylacetate | 96 | orange-brown | 392<br>287 | 15 200<br>10 700 |
| Ethyl cyanoacetate | 131 | yellow | 384<br>290 | 18 450<br>6 850 |
| Benzyl β-naphthyl ketone | 141 | yellow-orange | 384<br>295 | 12 300<br>16 300 |
| 1-Phenyl-3-methyl-pyrazol-5-one | 185 | red | 245<br>416 | 20 400<br>21 200 |

[a] In methylene chloride.

Symmetrical aliphatic azo compounds such as the orange-red derivative α,α'-azodimedone *(5)* are obtained by coupling *(1)* with dimedone *(4)*. However, since *(1)* can be obtained from *(4)* by diazo-group transfer using sulfonyl azides in a basic medium [3], and since it couples with *(4)* under the same conditions, *(5)* can also be obtained directly from dimedone by treating it with half of an equivalent of a sulfonyl azide in ethanol in the presence of triethylamine as base [4].



*(5)*

Dihydroresorcinol, 5,5-spiropentamethylenecyclohexane-1,3-dione, and 6,6-spiropentamethylenepyran-2,4-dione react analogously.

Received, July 29th, 1964 [Z 818/639 IE]
German version: Angew. Chem. 76, 920 (1964)

[1] *Th. Severin*, Angew. Chem. *70*, 745 (1958).

[2] *B. Eistert, D. Greiber*, and *J. Caspari*, Liebigs Ann. Chem. *659*, 72 (1962).

[3] *M. Regitz*, Liebigs Ann. Chem. *676*, 101 (1964); cf. *M. Regitz* and *G. Heck*, Chem. Ber. *97*, 1482 (1964).

[4] For the preparation of analogous aromatic compounds see *J. M. Tedder* and *B. Webster*, J. chem. Soc. (London) *1960*, 4417; *W. Pelz*, U.S.-Patent 2950273 (August 23rd, 1960); Chem. Abstr. *55*, 2116i (1961).

## Synthesis of 3(5)-Aminopyrazole and 1-Alkyl-5-aminopyrazoles [1]

By Dr. H. Dorn, Prof. Dr. G. Hilgetag, and Dipl.-Chem. A. Zubek

Institut für organische Chemie der Deutschen Akademie der Wissenschaften zu Berlin (Germany)

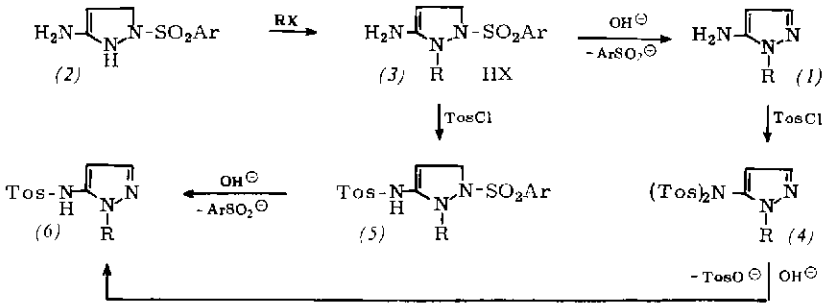
Up to the present, 1-alkyl-5-aminopyrazoles *(1)*, R = alkyl, could be obtained only by saponification and decarboxylation of 1-alkyl-5-amino-4-ethoxycarbonylpyrazoles, which are obtained by condensation of ethyl α-cyano-α-ethoxymethyleneacetate and alkylhydrazines [2].

A new synthetic route leading to *(1)*, R = alkyl, was discovered after we obtained salts of 1-alkyl-2-arenesulfonyl-5-amino-$\Delta^4$-pyrazolines *(3)* in very good yields from 3-amino-$\Delta^3$-pyrazoline and alkylating agents, *e.g.* particularly well with alkyl *p*-toluenesulfonates in dimethylformamide; the 3-amino-$\Delta^3$-pyrazoline is in turn readily accessible from hydrazine and acrylonitrile in water.

| Ar | R | X | M.p. [°C] |
|---|---|---|---|
| *p*-$H_3C$–$C_6H_4$– | $CH_3$– | TosO– | 206.5–207.5 |
| *p*-Cl–$C_6H_4$– | $CH_3$– | TosO– | 200–201 |
| $C_6H_5$– | $CH_3$– | TosO– | 188.5–190 |
| *p*-$H_3C$–$C_6H_4$– | $C_2H_5$– | TosO– | 175–176 |

Mild alkaline hydrolysis of each salt *(3)*, *e.g.* even with basic ion exchangers, affords 1 mole of an arenesulfinate and a 1-alkyl-5-aminopyrazole *(1)*. Correspondingly, elimination of 1 mole of sulfinate from non-alkylated monoarenesulfonyl derivatives *(2)*, which can be obtained in excellent yields from 3-amino-$\Delta^3$-pyrazoline and arenesulfonyl chlorides in methylene chloride plus triethylamine or even better in aqueous sodium hydrogen carbonate [*(2)*, Ar = $C_6H_5$, m.p. 167–168 °C; Ar = *p*-Cl–$C_6H_4$, m.p. 161–163 °C; Ar = *p*-$H_3C$–$C_6H_4$, m.p. 185–186 °C], gives almost quantitative yields of (3)5-aminopyrazole *(1)*, R = H, b.p. 155–157 °C/12 mm, m.p. 36–38 °C, a compound which was hitherto difficult to prepare [3, 4].

1-Methyl-5-aminopyrazole can be tosylated to give *(4)*, R = $CH_3$, m.p. 188–190 °C, the structure of which has been substantiated by the characteristic position of its sulfonyl absorption [5] in the infrared and by the synthesis [4] of analogous derivatives of *(1)* with two different arenesulfonyl residues. The salts *(3)* react with *p*-toluenesulfonyl chloride to give very good yields of 1-alkyl-2-arenesulfonyl-5-(*p*-toluenesulfonamido)-$\Delta^4$-pyrazolines *(5)*, Ar = *p*-$H_3C$–$C_6H_4$,



R = $CH_3$, m.p. 189–190 °C, which like *(3)* can also lose 1 mole of sulfinate. The structures of *(2)* and *(3)* are certified by the fact that alkaline cleavage of *(4)*, R = $CH_3$, and *(5)*, R = $CH_3$, leads to the same compound, *viz.* 1-methyl-5-(*p*-toluenesulfamido)pyrazole *(6)*, R = $CH_3$, m.p. 151.5 to 152.5 °C.

Received, August 31st, 1964 [Z 835/659 IE]
German version: Angew. Chem. 76, 921 (1964)

[1] Redox Cleavage of Sulfonamides, Part I.

[2] *P. Schmidt, K. Eichenberger, M. Wilhelm*, and *J. Druey*, Helv. chim. Acta *42*, 349, 763 (1959).

[3] *L. Knorr*, Ber. dtsch. chem. Ges. *37*, 3522 (1904); *H. Reimlinger, A. van Overstraeten*, and *H. G. Viehe*, Chem. Ber. *94*, 1036 (1961).

[4] *P. Schmidt* and *J. Druey*, Helv. chim. Acta *39*, 986 (1956).

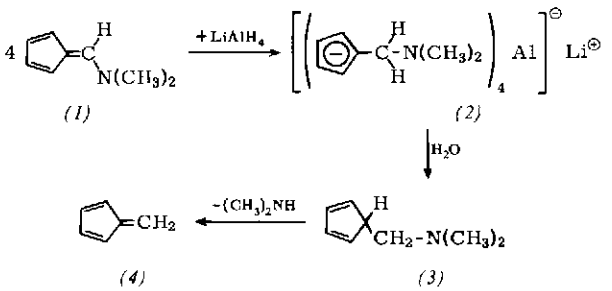
[5] *H. Dorn, G. Hilgetag*, and *A. Rieche*, Angew. Chem. *73*, 567 (1961).

## A Simple Synthesis of Fulvene and Its 6-Alkyl Derivatives

By Dipl.-Chem. E. Sturm and Prof. Dr. K. Hafner

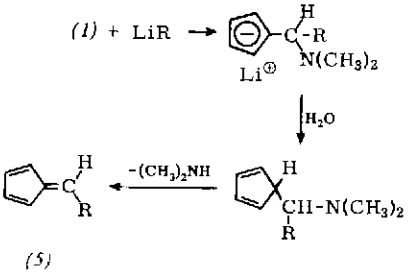
Institut für Organische Chemie
der Universität München (Germany)

The base-catalysed condensation of cyclopentadiene with formaldehyde or a homologue affords fulvene *(4)* or its 6-alkyl derivative *(5)* respectively, but only in yields of less than 5 % [1]. We have found that *(4)* is obtained in ca. 60 % yield from the "reductive deamination" of the readily accessible 6-dimethylaminofulvene *(1)* [2] with lithium aluminium hydride in ether.



The cyclopentadiene-metal compound first formed, which can be isolated, is converted on hydrolysis at 0 °C into the Mannich base *(3)*, which rapidly loses dimethylamine above 100 °C in high vacuum or during chromatography on alumina (neutral, activity grade II) with ether or n-pentane. On reaction with methyl iodide at 0 °C, *(3)* yields a quaternary salt which immediately splits out trimethylammonium iodide to give *(4)* which is isolated by distillation (b.p. ~5 °C/15 mm) as a pale yellow oil and is very sensitive to heat and oxygen. Its ultraviolet spectrum agrees with that given in the literature [1]. The NMR spectrum of *(4)* in $CCl_4$ shows a multiplet between 3.6 and 4.1 τ.

Compound *(1)* reacts similarly with organolithium compounds to form fulvenes of type *(5)* in yields of 80–90 %.



For example, 6-methylfulvene *(5)*, R = $CH_3$, is obtained in 81 % yield from *(1)* and methyl-lithium as a yellow oil, b.p. 19–21 °C/12 mm; ultraviolet spectrum in ethanol: $\lambda_{max}$ = 255 mμ (log ε = 4.24), 357 (2.50); NMR spectrum in $CCl_4$: multiplet between 3.7 and 4.1 τ *(5)*, doublet at 8.0 τ *(3)*. Numerous 6-arylfulvenes can be readily prepared in the same manner.

Received, September 3rd, 1964 [Z 817/651 IE]
German version: Angew. Chem. 76, 862 (1964)

[1] *J. Thiec* and *J. Wiemann*, Bull. Soc. chim. France *1956*, 177; *1957*, 366; *1960*, 1066. The preparation of *(4)* and *(5)* by the method of *W. Freiesleben*, Angew. Chem. *75*, 576 (1963), Angew. Chem. internat. Edit. *2*, 396 (1963), has not yet been described; *D. Meuche, M. Neuenschwander, H. Schaltegger*, and *H. U. Schlunegger*, Helv. chim. Acta *47*, 1211 (1964).

[2] *H. Meerwein* et al., Liebigs Ann. Chem. *641*, 1 (1961); *K. Hafner* et al., ibid. *661*, 52 (1963).

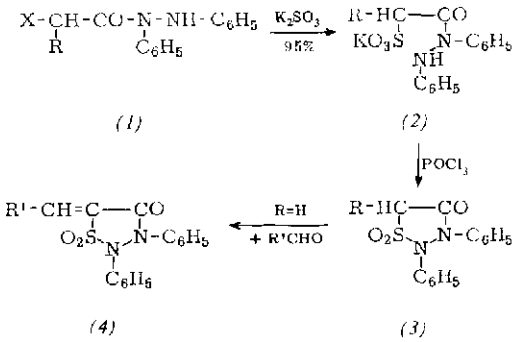
## Synthesis of 2,3-Diphenyl-1,1,4-trioxo-1,2,3-thiadiazolidines

By Prof. Dr. A. Mustafa, Dr. M. Kira, and H. Hanna

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When *N'*-chloroacetylhydrazobenzene *(1)*, R = H, X = Cl [1], and potassium sulfite are boiled in ethanol/water (2:1) for 3 h under reflux, the potassium salt of sulfoacetylhydrazobenzene *(2)*, R = H, is formed with 95 % yield (colorless crystals, m.p. 245 °C, from aqueous ethanol). This salt was readily cyclized by phosphorus oxychloride to *(3)*, R = H, m.p. 150 °C, in about 50 % yield [2].

Similarly, α-bromobutyryl hydrazobenzene *(1)*, R = $C_2H_5$, X = Br [3], yielded 5-ethyl-2,3-diphenyl-1,1,4-trioxo-1,2,3 thiadiazolidine *(3)*, R = $C_2H_5$, m.p. 109 °C.



5-Aralkyl derivatives of *(3)* have been obtained in almost quantitative yields by catalytic hydrogenation (10 % Pd-charcoal; dioxane; room temperature; 10 h) of the yellow 5-arylidene derivatives *(4)* which are readily available by the condensation of aldehydes with the active methylene group of *(3)*, R = H. The following compounds were prepared:

*(4)*, $R' = C_6H_5-$, m.p. 176 °C
*(4)*, $R' = p\text{-}CH_3OC_6H_4-$, m.p. ca. 290 °C (decomp.)
*(4)*, $R' =$ 2-furyl, m.p. 183 °C
*(4)*, $R' = o\text{-}HOC_6H_4-$, m.p. 230 °C
*(4)*, $R' = C_6H_5-CH=CH-$, m.p. 197 °C
*(3)*, $R = C_6H_5-CH_2-$, m.p. 181 °C
*(3)*, $R = p\text{-}CH_3OC_6H_4-CH_2-$, m.p. ca. 290 °C (decomp.)
*(3)*, R = 2-furylmethyl, m.p. — 116 °C

Compounds *(3)*, R = H or alkyl, have anti-inflammatory activity. They are stable towards hydrazine and amines, whereas alkali hydroxide cleaves the ring and liberates hydrazobenzene. Also, the attempted alkylation of *(3)* with alkyl halide and NaOH resulted in the formation of hydrazobenzene.

Received, September 9th, 1964 [Z 822/652 IE]
German version: Angew. Chem. 76, 920 (1964)

[1] *St. Goldschmidt*, Liebigs Ann. Chem. *437*, 213 (1924).

[2] While this work was in progress, a patent has appeared, describing the synthesis of *(3)*, R=H, from sulfoacetic acid dichloride and hydrazobenzene without reporting the yield: *R. Doson* and *V. Papesch*, U.S.-Patent 3037027; Chem. Abstr. *57*, 12502 (1962).

[3] *A. Michaelis* and *F. Schmidt*, Liebigs Ann. Chem. *252*, 308 (1889).

## Gas-Chromatographic Separation and Analysis of Isomeric Halogenated Hydrocarbons

By Dr. Elisabeth Bendel, cand. phys. W. Meltzow, and Dr. Li-Hoan Kung

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After chlorination or bromination of high-molecular, straight-chain hydrocarbons with, for example, *N*-chloro- or *N*-bromosuccinimide, t-butyl hypochlorite or hypobromite [1] the isomeric chlorides of n-heptane, n-octane, n-decane and the isomeric bromides of n-heptane and n-octane were quantitatively separated by gas chromatography on a Ucon LB 550 X Golay column (200 m; internal diameter 0.5 mm). A capillary chromatograph with a flame-ionization detector was used. The carrier gas was helium (4.5 ml/min), and the temperatures used are shown in Table 1.

Table 1. Temperatures of flash heater, column, and detector.

| Isomers | Column | Detector | Flash heater |
|---|---|---|---|
| Chloro-n-heptanes | 70 °C | 70 °C | 170 °C |
| Bromo-n-heptanes | 90 °C | 90 °C | 170–175 °C |
| Chloro-n-octanes | 90 °C | 90 °C | 175–179 °C |
| Bromo-n-octanes | 90 °C | 90 °C | 230 °C |
| Chloro-n-decanes | 120 °C | 120 °C | 232 °C |

The retention times of the isomeric halogenated hydrocarbons and the resolution obtained for each individual pair of isomers are set out in Table 2.

The quantitative evaluation of the chromatograms was confirmed by the analysis of test mixtures. The maximum relative error found was about 5 %, so that the use of correction factors is unnecessary.

The gas-chromatographic analysis of the unstable bromo-n-decanes still presents difficulties.

Table 2. Retention times ($t_r$) and effective resolution ($\vartheta$) [*] for the isomeric halogenated hydrocarbons.

| Isomer X R | Chloro-n-heptanes | | Bromo-n-heptanes | | Chloro-n-octanes | | Bromo-n-octanes | | Chloro-n-decanes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $t_r$ [min] | $\vartheta$ [%] | $t_r$ [min] | $\vartheta$ [%] | $t_r$ [min] | $\vartheta$ [%] | $t_r$ [min] | $\vartheta$ [%] | $t_r$ [min] | $\vartheta$ [%] |
| 1-X–R | 164 | 100 | 135 | 100 | 168 | 100 | 170 | 100 | 151 | 100 |
| 2-X R | 114 | 96.1 | 94 | 98.7 | 113 | 98.9 | 119 | 100 | 114 | 94.4 |
| 3-X–R | 110 | 100 | 91.5 | 100 | 110 | 100 | 115 | 100 | 110 | 100 |
| 4-X–R | 103 | -- | 85 | — | 102 | - | 105 | - | 103 | 94.4 |
| 5-X–R | — | | — | | — | | — | | 101 | |

[*] Defined according to [2].

Received, September 7th, 1964 [Z 827/657 IE]
German version: Angew. Chem. 76, 890 (1964)

[1] *Li-Hoan Kung*, Ph. D. Thesis, Technische Hochschule Aachen 1964.

[2] *H. Kaiser*: Chromatographie in der Gasphase. Bibliographisches Institut, Mannheim 1960, Vol. II, p. 32.

## An External Magnetocatalytic Effect

By Doz. Dr. W. Haberditzl and Dipl.-Chem. Klaus Müller

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The existence of external magnetocatalytic effects, *i.e.* alterations of catalytic activity within external magnetic fields, has been the subject of much controversy. We have now detected such an effect with the enzyme glutamic dehydrogenase (GlDH).

GlDH catalyses the reaction:

$$\alpha\text{-Oxoglutarate} + NH_3 + DPNH \rightleftharpoons \text{Glutamate} + DPN + H_2O$$

The changes in the concentration of DPNH with time were followed by spectrophotometry [1], and the catalytic activity was calculated in units per ml [2]. The reaction mixture comprised 3 ml of 0.05 M triethanolamine buffer (pH 8.0), 0.045 ml of 0.01 M DPNH, 0.03 ml of 0.26 M EDTA, 0.1 ml of 3 M ammonium acetate, and 0.03 ml of $10^{-7}$ M GlDH. After addition of 0.06 ml of 0.4 M sodium α-oxoglutarate, the extinction of the solution at 366 mμ was measured at one-

minute intervals. After 5 min, the sample cell (light path 1 cm) was placed between the poles of an electromagnet in an inhomogeneous field (distance from poles 13.5 mm, magnetic field strength 15000 Gauss) for 40–50 min. The extinction was thereafter again measured at one-minute intervals for 5 min. A duplicate determination was carried out on a cuvette not placed within the magnetic field. There was generally a difference in temperature of 0.1 to 0.3 °C between the solutions within and ouside the magnetic field. The temperature dependence of the enzymatic activity was 1.5 units/°C at 25 °C and 1.8 units/°C at 27 °C.

In four replicate experiments, the activity of the GIDH inside the magnetic field was 12–15 % (in one series of experiments 7 %) less than that outside the magnetic field.

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German version: Angew. Chem. 76, 891 (1964)

[1] *E. Schmidt* in *H. U. Bergmeyer:* Methods of Enzymatic Analysis. Verlag Chemie, Weinheim/Bergstraße, and Academic Press, New York, 1963, p. 752.

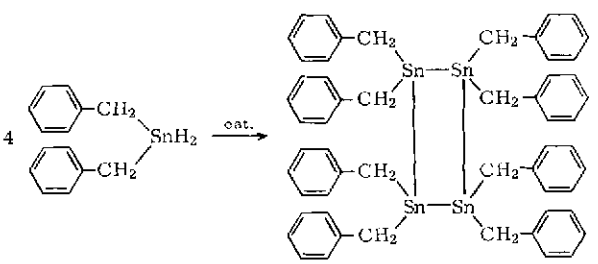
[2] *T. Bücher*, Z. Naturforsch. *8b*, 555 (1953). One unit is the amount of enzyme dissolved in 1 ml which alters the extinction at 366 mμ (light path: 1 cm) by 0.100 within 100 sec at 25 °C.

## Synthesis of Octabenzylcyclotetrastannane

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Catalytic condensation of dialkyltin dihydrides and diaryltin dihydrides gives rise to crystalline aliphatic [1] and aromatic [2] cyclostannanes containing five-, six-, or nine-membered rings. We have now succeeded in preparing an analogous compound with a four-membered ring, *viz.* octabenzylcyclotetrastannane. It is formed from dibenzyltin dihydride in almost quantitative yield at 50 °C in dimethylformamide, which also acts as catalyst, and a trace of dibenzyltin dichloride as co-catalyst; the product is very sensitive to air but crystallizes from toluene/ligroin as beautiful pale yellow prisms (m.p. 226–228 °C with partial decomposition). It is highly soluble in hot benzene but sparingly soluble in cold benzene. On degradation with iodine in benzene, it affords a quantitative yield of pure dibenzyltin diiodide. This reaction, together with its molecular weight (determined by osmometry), analyses, and spectra substantiate its structure.




When the condensation was carried out in pyridine, a crystalline mixture containing higher cyclic homologues was obtained; these probably included the five- and six-membered ring compounds. The ring size in the products formed depends not only on the catalyst used, but also on the nature of the organic substituent on the tin (cf. [1, 2]). Recently, the analogous octa-t-butyl compound was prepared by a different route as the first example of a cyclotetrastannane [3].

Our starting material, dibenzyltin dihydride, was hitherto unknown and was prepared from pure dibenzyltin dichloride using lithium aluminohydride in ether at 0 °C ($\nu_{SnH}$ at 1843 cm$^{-1}$, broad absorption); it was used without previous distillation. It ignites spontaneously on filter paper in contact with air.

Received, September 14th, 1964 [Z 823/643 IE]
German version: Angew. Chem. 76, 892 (1964)

[1] *W. P. Neumann*, Angew. Chem. *74*, 122 (1962); Angew. Chem. internat. Edit. *1*, 165 (1962); *W. P. Neumann* and *J. Pedain*, Liebigs Ann. Chem. *672*, 34 (1964).

[2] *W. P. Neumann* and *K. König*, Angew. Chem. *74*, 215 (1962); Angew. Chem. internat. Edit. *1*, 212 (1962); Liebigs Ann. Chem. (1964), in the press.

[3] *W. V. Farrar* and *H. A. Skinner*, J. organomet. Chem. *1*, 434 (1964).

## Preparation of Malonic Acid by Carboxylation of Acetic Acid

By Dr. B. Raecke

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The decarboxylation of malonic acid may be regarded as an equilibrium reaction. Salts of malonic acid can be produced from acetates and carbon dioxide if the hydrogen ions liberated during the reaction are removed [1].

The carboxylation proceeds especially smoothly with potassium acetate, which in the presence of potassium carbonate reacts with $CO_2$ under pressure and above 200 °C to give potassium malonate:

$$CH_3COOK + CO_2 + K_2CO_3 \longrightarrow KOOC{-}CH_2{-}COOK + KHCO_3$$

Suitable catalysts include finely powdered metals and metal oxides, especially iron and $Fe_2O_3$.

When anhydrous potassium acetate (30 g) is heated with anhydrous potassium carbonate (120 g) and iron powder (1 g) in an autoclave at 300 °C for 3 h at ca. 500 atm $CO_2$, pure malonic acid (ca. 24 g; 75.2 %) can be isolated from the reaction mixture.

Other carboxylic acids with hydrogen atoms in the α-position can also be carboxylated in this way, although the yields are considerably lower.

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German version: Angew. Chem. 76, 892 (1964)

[1] German Patent Application H 49,852 IVb/120, Henkel & Cie. GmbH.

## A Simple Synthesis of Organic Di- and Polystannanes

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Organotin hydrides [1] can be condensed with organotin oxides, giving rise with surprising ease and occasionally even in an exothermic reaction either to symmetrical and unsymmetrical hexaalkyldistannanes [Equation (a)], or to the octaalkyltristannanes [Equation (b)] hitherto obtainable only with difficulty, or to polystannanes [Equation (c)]. Aryltin compounds react faster than the corresponding alkyltin compounds. When R = iso-$C_4H_9$, reaction (c) leads to a polydiisobutyltin polymer which still contains some Sn-O-Sn groups [2].

$$2\,R_3SnH + (R'_3Sn)_2O \longrightarrow 2\,R_3SnR'_3 + H_2O \qquad (a)$$

$$2\,R_3SnH + R_2SnO \longrightarrow R_3Sn{-}R_2Sn{-}SnR_3 + H_2O \qquad (b)$$

$$R_2SnH_2 + R_2SnO \longrightarrow 1/n\,(-R_2Sn{-}R_2Sn{-})n + H_2O \qquad (c)$$

| $R_3SnH$ R = | $(R'_3Sn)_2O$ R' = | Temp. [°C] | Product | B.p. [°C/mm] (M.p. [°C]) | Yield of pure product [%] |
|---|---|---|---|---|---|
| n-$C_4H_9$ | n-$C_4H_9$ | 110 | $(C_4H_9)_3Sn-Sn(C_4H_9)_3$ | 144/0.09 | 90 |
| $C_6H_5$ | $C_6H_5$ | 20 | $(C_6H_5)_3Sn-Sn(C_6H_5)_3$ | (232) | 89 |
| $C_6H_5$ | $C_2H_5$ | 25 | $(C_6H_5)_3Sn-Sn(C_2H_5)_3$ | $186/10^{-4}$ | 80 |
| $C_2H_5$ | $C_6H_5$ | 25 | $(C_6H_5)_3Sn-Sn(C_2H_5)_3$ | (16) | 73 |
| $C_2H_5$ | $C_2H_5$ | 130 | $(C_2H_5)_3Sn-Sn(C_2H_5)_3$ | 145/11 | 86 |
| iso-$C_4H_9$ | $C_2H_5$ | 110 | $(iso\text{-}C_4H_9)_3Sn-Sn(C_2H_5)_3$ | 75/0.11 | 42 [3] |
| $C_2H_5$ | $(C_2H_5)_2SnO$ | 110 | $(C_2H_5)_3Sn-(C_2H_5)_2Sn-Sn(C_2H_5)_3$ | $133/10^{-5}$ | 47 [3] |

Often a slow H–O exchange [Equation (d)] can be detected alongside the condensation reactions, *e. g.* by removal of the small amount of volatile triethyltin hydride formed:

$$2\ (iso\text{-}C_4H_9)_3SnH + [(C_2H_5)_3Sn]_2O \overset{60\,^\circ C}{\rightleftharpoons} [(iso\text{-}C_4H_9)_3Sn]_2O + 2\ (C_2H_5)_3SnH \qquad (d)$$

Oxygen is exchanged for hydrogen in hydrides much more slowly than deuterium [4] or halogen [5]; a complex can be assumed as transition state.

The exchange proceeds quickly at temperatures as low as 25 °C with dialkyltin dihydrides [Equation (e)]; the dialkyltin oxide precipitates almost quantitatively and can be filtered or centrifuged off.

$$R_2SnH_2 + (R'_3Sn)_2O \rightarrow 2\ R'_3SnH + R_2SnO \qquad (e)$$

where *e.g.* R = $C_2H_5$, iso-$C_4H_9$, and R' = $C_2H_5$, n-$C_4H_9$, $C_6H_5$.

When R = R' = $C_6H_5$, ligand exchange and the condensation reaction compete with each other; the final result is a mixture $(C_6H_5)_3Sn-[(C_6H_5)_2Sn]_n-Sn(C_6H_5)_3$.

The synthesis of Sn–Sn bonds according to Equation (f) has obviously much more scope than was hitherto envisaged.

$$R_3SnH + R'_3SnX \longrightarrow R_3Sn-SnR'_3 + HX \qquad (f)$$

In this reaction, X can be not only $-CF-CF_2$ [6], $-OR$ [7] (particularly $-OCH_3$ [Equation (g)] [2, 8]), $-NR-CHO$, and $-NR-NHR$ [9], but also, for example, halogen [Equation (h)], $-OSnR_3$, $-N(C_2H_5)_2$ [Equation (i)], or another electronegative residue. Organotin dihydrides also react readily in this manner. A few new examples may serve to illustrate this. All the substances were obtained in good yields and were characterized by their analyses, melting or boiling points, molecular weights, and infrared spectra.

$$(C_4H_9)_2SnH_2 + (C_4H_9)_2Sn(OCH_3)_2 \xrightarrow[-2\ CH_3OH]{20\,^\circ C} 2/n\ [(C_4H_9)_2Sn]_n \qquad (g)$$

crystalline, yellow, sensitive to air [3, 8]

$$(C_6H_5)_3SnH + (C_2H_5)_3SnCl + N(C_2H_5)_3 \xrightarrow{\text{exothermic}} (C_6H_5)_3Sn-Sn(C_2H_5)_3 + HN(C_2H_5)_3Cl \qquad (h)$$

$$(C_4H_9)_2SnH_2 + 2\ (C_2H_5)_3SnN(C_2H_5)_2 \xrightarrow{\text{exothermic}} 2\ HN(C_2H_5)_2 + (C_2H_5)_3Sn-(C_4H_9)_2Sn-Sn(C_2H_5)_3 \qquad (i)$$

B.p. 140 °C/$10^{-3}$ mm, $n_D^{20} = 1.5641$ [3, 8]

Received, September 11th, 1964 [Z 819/640 IE]
German version: Angew. Chem. *76*, 891 (1964)

[1] *W. P. Neumann* and *R. Sommer*, Liebigs Ann. Chem. *675*, 10 (1964), where further references are given.

[2] A similar experiment was conducted by *A. K. Sawyer*, but was not published; cited by *H. G. Kuivila*, Adv. organomet. Chem. *1*, 47 (1964).

[3] Compounds which to our knowledge have not yet been described.

[4] *W. P. Neumann* and *R. Sommer*, Angew. Chem. *75*, 788 (1963); Angew. Chem. internat. Edit. *2*, 547 (1963).

[5] *W. P. Neumann* and *J. Pedain*, Tetrahedron Letters *1964*, 2461.

[6] *D. Seyferth*, *G. Raab*, and *K. A. Brändle*, J. org. Chemistry *26*, 2934 (1961).

[7] *J. Valade*, *M. Pereyre*, *J. C. Pommier*, and *R. Calas*, Lecture at the IUPAC Congress in London, 1963, Abstracts A, p. 170; *F. Kleiner*, Diploma Thesis, Universität Gießen 1963.

[8] Work carried out by *R. Sommer*, Gießen.

[9] *J. G. Noltes*, Rec. trav. chim. Pays-Bas *83*, 515 (1964), where further references are given.

## α-Addition of Dichlorocarbene to Cyclohexyl Isonitrile

By Dr. A. Halleux

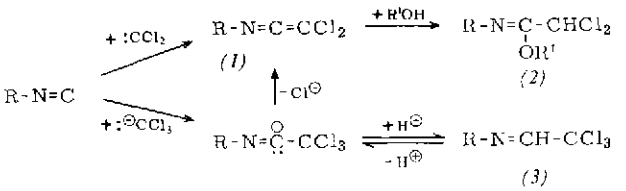
Union Carbide European Research Associates, Brussels (Belgium)

Because of their electronic structure, isonitriles should undergo nucleophilic reactions with dichlorocarbene to give, by α-addition, *N*-substituted dichloroketeneimines *(1)*.

A suspension of anhydrous potassium alcoholate R'OK, R' = $CH_3$, $C_2H_5$, $(CH_3)_3C$, in hexane was added to a solution of cyclohexyl isonitrile in hexane, and chloroform or ethyl trichloroacetate was then added dropwise to the vigorously stirred suspension. *N*-Cyclohexyldichloroacetimidate *(2)*, R = $C_6H_{11}$, was obtained from the reaction mixture in up to 75 % yield but no dichloroketeneimine *(1)* or trichloroethylidenecyclohexylamine *(3)* was isolated.

The imidates *(2)* [R = $CH_3$; b.p. 65 °C/$10^{-1}$ mm; $n_D^{25} = 1{,}4889$; R = $C_2H_5$: b.p. *ca.* 50 °C/$10^{-2}$ mm; R = $(CH_3)_3C$: b.p. 60–65 °C/$10^{-2}$ mm, decomposes to *N*-cyclohexyldichloroacetamide, m.p. 140 °C [1], on prolonged standing] were obtained pure by vacuum distillation or preparative gas-liquid chromatography and were characterized by elemental analysis, IR spectrum and acid hydrolysis.

Two reaction mechanisms are possible: either nucleophilic reaction of the isonitrile with dichlorocarbene or electrophilic reaction [2] with the trichloromethyl carbanion.




Compound *(1)* is also formed from trichloroethylideneimine *(3)*, prepared from the amine and chloral.

Competitive experiments in the presence of cyclohexene showed that the ratio of the products depends characteristically on the concentration of the added cyclohexene [3]. The relative reactivities of cyclohexene and cyclohexyl isonitrile were 1:6. The ratio of the products was determined by gas-liquid chromatography.

The results show that the reaction occurs exclusively *via* the carbene. Thus, the possibility that the reaction of cyclohexyl isonitrile with chloramine T, described by *Aumüller* [4], occurs *via* a nitrene cannot be excluded.

Received, September 18th, 1964 [Z 829/661 IE]
German version: Angew. Chem. *76*, 889 (1964)

[1] *B. J. Heywood*, Chem. Abstr. *50*, 1083[d] (1956).

[2] *A. Treibs* and *A. Dietl*, Chem. Ber. *94*, 298 (1961).

[3] *H. Reimlinger*, Chem. Ber. *97*, 339 (1964).

[4] *W. Aumüller*, Angew. Chem. *75*, 857 (1963); Angew. Chem. internat. Edit. *2*, 616 (1963).

## A New Method for the Preparation of Phosphorus-Nitrogen Compounds [1]

By Dr. R. Schmutzler

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During the reaction of hexamethyldisiloxane and trimethylsilyl ethers with Lewis-acid phosphorus fluorides such as $RPF_4$ and $(C_6H_5)_2PF_3$ [2] cleavage of the Si—O bond and liberation of the trimethylsilyl groups as trimethylfluorosilane were observed.

Application of this principle to dialkylaminotrimethylsilanes allows the preparation of novel types of phosphorus-fluorine-nitrogen compounds [3]:

$$PF_5 + (CH_3)_3SiN(C_2H_5)_2 \xrightarrow[-78 \text{ to } +60^\circ C]{} (C_2H_5)_2NPF_4 + (CH_3)_3SiF \quad (1)$$

$$(C_2H_5)_2NPF_4 + (CH_3)_3SiN(C_2H_5)_2 \xrightarrow[150-170^\circ C]{} [(C_2H_5)_2N]_2PF_3 + (CH_3)_3SiF \quad (2)$$

$$H_5C_6PF_4 + (CH_3)_3SiN(CH_3)_2 \longrightarrow H_5C_6PF_3N(CH_3)_2 + (CH_3)_3SiF \quad (3)$$

$$H_5C_6PF_4 + \text{(N-Si(CH}_3\text{)}_3\text{ ring)} \longrightarrow H_5C_6PF_3N\text{(ring)} + (CH_3)_3SiF \quad (4)$$

The above method, which can be referred to as a controlled dialkylaminolysis of the phosphorus fluoride with $(CH_3)_3Si$ functioning as a "protecting group", is generally applicable. By reaction of $PF_5$ and fluorophosphoranes with *N*-substituted hexamethyldisilazanes, $[(CH_3)_3Si]_2NR$, four-membered P—N ring systems are formed [4]. Presumably there is a nucleophilic attack on the pentacoordinate phosphorus atom by the silazane-nitrogen atom. Nucleophilic reaction of the fluorine atom with silicon then cleaves the Si—N bond.

$$(CH_3)_3Si\text{-}NR_2 \xrightarrow{R'_nPF_{5-n}} (CH_3)_3Si\text{-}NR_2 \rightarrow (CH_3)_3SiF + R'_nPF_{4-n}NR_2$$

$$F\text{-}P(F_{4-n})(R'_n)$$

$n = 0, 1$; $R' =$ Alkyl or Aryl

The stereochemistry of the resulting tri- and tetrafluorophosphoranes was investigated by $^{19}F$- and $^{31}P$-NMR spectroscopy (see Table 1). The data for trifluorophosphoranes, as for dialkyl(diaryl)trifluorophosphoranes [5], were interpreted in terms of a trigonal bipyramidal model in which two fluorine atoms are in axial positions and one in an equatorial site. The $^{19}F$-NMR spectrum of $(C_2H_5)_2NPF_4$, in analogy with tetrafluorophosphoranes having hydrocarbon groups as substituents, consists of a simple doublet (P—F coupling) at room temperature, but is temperature-dependent, and at lower temperature the expected non-equivalence of the fluorine atoms is evident [6].

Table 1. Physical properties of compounds *(1)*—*(4)*.

| Compound | B.p. [°C/mm] | NMR Data $J_{P-F}$ [c] | $\delta$[p.p.m.] [a] $^{19}F$ | $^{31}P$ |
|---|---|---|---|---|
| (1) | 99—100 | 863 | 66.5 | 70.2 |
| (2) | 79/14 | (a) 755 | 59.5 | 63.7 |
| | | (e) 883 | 67.5 | |
| (3) | 48/0.25 | (a) 822 | 40.3 | 52.8 |
| | | (e) 954 | 68.1 | |
| (4) | 73—74/0.35 | (a) 860 | 39.2 | 60.0 [b] |
| | | (e) 978 | 69.0 | |

[a] $CCl_3F$ was used as internal standard for $^{19}F$, and $H_3PO_4$ (85 %) as external standard for $^{31}P$—NMR measurements.

[b] Measured by *G. S. Reddy*, Gibbstown, N.J. (U.S.A.).

[c] a = axial, e = equatorial.

Received, September 18th, 1964 [Z 826/660 IE]
German version: Angew. Chem. 76, 893 (1964)

[1] Phosphorus-Fluorine Chemistry, Part XIV — Part XIII: *R. Schmutzler* and *G. S. Reddy*, Inorg. Chem., in the press.

[2] *R. Schmutzler*, Inorg. Chem. *3*, 410 (1964); J. chem. Soc. (London) *1964*, in the press.

[3] *D. H. Brown, G. W. Fraser*, and *D. W. A. Sharp*, Chem. and Ind. *1964*, 367, obtained $(CH_3)_2NPF_4$ by pyrolysis of the $(CH_3)_2HN \rightarrow PF_5$ adduct. Brother *G. C. Demitras* and *A. G. MacDiarmid* prepared $(CH_3)_2NPF_4$ by a method analogous to ours (personal communication).

[4] *R. Schmutzler*, unpublished work.

[5] *E. L. Muetterties, W. Mahler*, and *R. Schmutzler*, Inorg. Chem. *2*, 613 (1963).

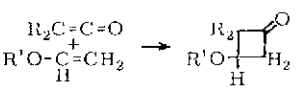
[6] *E. L. Muetterties, K. J. Packer, W. Mahler*, and *R. Schmutzler*, Inorg. Chem. *3*, 1298 (1964).

## Stereospecific Addition of Ketenes onto Enol Ethers

By Prof. Dr. R. Huisgen, Dipl.-Chem. L. Feiler, and Dr. G. Binsch

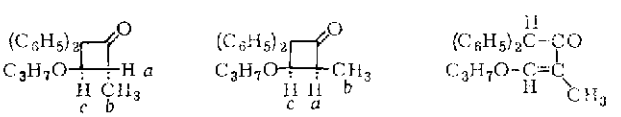
Institut für Organische Chemie der Universität München (Germany)

Ketenes react with enol ethers to form 3-alkoxycyclobutanones *(1)* [1—3] by addition in the electronically favored direction; the products are compatible with the occurrence of the resonance-stabilized intermediate *(2)*.



*(1)* *(2)*

Treatment of *trans*-propenyl propyl ether [4] with diphenylketene in absolute ether at 20 °C for seven days and removal of some ketene dimer gives an 86 % yield of *(3)*, m.p. 35 to 37 °C, $\nu_{C=O} = 1780$ cm$^{-1}$. The reaction of diphenylketene with *cis*-propenyl propyl ether [4] is complete after one hour and gives *(4)* in 85 % yield as an analytically pure oil, $\nu_{C=O} = 1778$ cm$^{-1}$. The NMR spectra of the crude products from both reactions do not indicate any mutual contamination of the adducts *(3)* and *(4)*, although 2.5 % of *(4)* in *(3)* and 3.8 % of *(3)* in *(4)* were readily detectable in synthetic mixtures. Competitive experiments revealed that the *cis*-enol ether reacts with diphenylketene 170 times faster than its *trans*-isomer.



*(3)* *(4)* *(5)*

The NMR spectra indicate that each of the two geometrically isomeric enol ethers has retained its original configuration in the adduct. A methyl group displaces the NMR signal of a *cis*-hydrogen on the adjacent carbon atom to higher field, and that of a *trans*-hydrogen to lower field; the doublet for the tertiary proton *c* appears at 5.62 $\tau$ for *(3)* and at 5.28 $\tau$ for *(4)*. The methyl doublet *b* lies at 8.74 and 8.77 $\tau$, respectively. $J_{ac}$ is 7.0 cps for the *trans*-adduct and 8.1 cps for the *cis*-

compound; however, *Karplus'* rule [5] does not strictly apply to four-membered rings.

In boiling xylene, both *(3)* and *(4)* are converted almost quantitatively into the same acyclic acylpropenyl propyl ether *(5)*. The structure of *(5)* was determined from elemental analysis, NMR and infrared spectra, and from acid hydrolysis to form 1,1-diphenylbutan-2-one.

Dimethylketene also adds onto both *trans*- and *cis*-propenyl propyl ether stereospecifically to yield diastereoisomeric cyclobutanones. Again the *cis*-form reacts faster. In the NMR spectra, the doublet for the tertiary proton on C-3 appears at 6.52 τ ($J_{ac}$ = 6.4 cps) in the *trans*-adduct and at 6.12 τ ($J_{ac}$ = 8.3 cps) in the *cis*-adduct.

The stereoselective *cis*-addition renders the formation of an intermediate such as *(2)* improbable. We assume that a one-stage multicentered cycloaddition takes place.

Received, September 24th, 1964 [Z 832/654 IE]
German version: Angew. Chem. 76, 892 (1964)

[1] *H. Staudinger* and *E. Suter*, Ber. dtsch. chem. Ges. *53*, 1092 (1920); *H. Staudinger* and *P. J. Meyer*, Helv. chim. Acta 7, 19 (1924).

[2] *C. D. Hurd* and *R. D. Kimbrough*, J. Amer. chem. Soc. *82*, 1373 (1960).

[3] *R. H. Hasek*, *P. G. Gott*, and *J. C. Martin*, J. org. Chemistry *29*, 1239 (1964).

[4] *W. Rottig* and *O. Liethen*, Ruhrchemie AG., German Patent 1019090 (1957); Chem. Abstr. *54*, 10403 (1960).

[5] *M. Karplus*, J. chem. Physics *30*, 11 (1959); *H. Conroy:* Advances in Organic Chemistry. Interscience, New York 1960, Vol. 2, p. 308.

## Pentakis(trifluorophosphine)iron(0) [1]

By Priv.-Doz. Dr. T. Kruck and Dipl.-Chem. A. Prasch

Anorganisch-Chemisches Laboratorium der Technischen Hochschule München (Germany)

Anhydrous ferrous iodide reacts with highly purified trifluorophosphine at 140 °C and 500 atm in the presence of copper powder (to trap the iodide) to give over 40 % yield of pale yellow crystals of pentakis(trifluorophosphine)iron(0).

$$FeI_2 + 2\,Cu + 5\,PF_3 \rightarrow Fe(PF_3)_5 + 2\,CuI$$

This reaction represents the first direct synthesis of a homogeneous trifluorophosphine-metal(0) complex. The compounds $Cr(PF_3)_6$, $Mo(PF_3)_6$, and $Ni(PF_3)_4$ isolated previously were all prepared by elimination reactions from preformed hexa- or tetra-coordinate metal(0) complexes [2]. The iron complex is volatile and is readily soluble in the usual organic solvents; it remains undecomposed for a short time even in moist air, and in this and in other respects is very similar to its analogue pentacarbonyliron [3]. The infrared spectrum of the diamagnetic complex contains ν(P–F) vibrations at 949 (w), 922 (vs), 907 (s) 894 (sh), and 858 (s) $cm^{-1}$ plus two other sharp bands at 2044 (w) and 2017 (w) $cm^{-1}$ [4]. These weak absorptions in the 5-μ-region are due to combination vibrations and are characteristic of trifluorophosphine-metal(0) complexes.

Received, September 21st, 1964 [Z 833/655 IE]
German version: Angew. Chem. 76, 892 (1964)

[1] Trifluorophosphine-metal Complexes, Part V. – Part IV: *T. Kruck* and *W. Lang*, Angew. Chem. *76*, 787 (1964); Angew. Chem. internat. Edit. *3*, 700 (1964).

[2] *T. Kruck* and *A. Prasch*, Z. Naturforsch. *19b*, 669 (1964), where further references are given.

[3] For example, $Fe(PF_3)_5$ can be reduced smoothly with potassium amalgam in ether or tetrahydrofuran to give colorless potassium trifluorophosphineferrate.

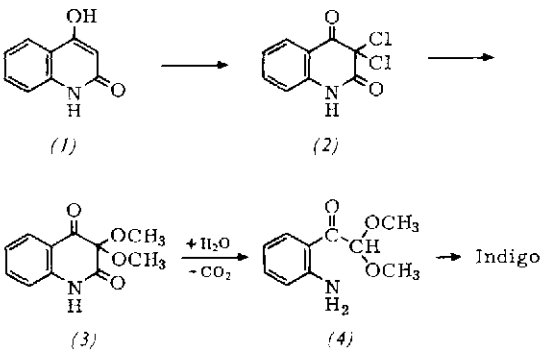
[4] Measured on $Fe(PF_3)_5$ gas with a Perkin-Elmer 21 spectrophotometer with NaCl optics. – w = weak, s = strong, vs = very strong, sh = shoulder.

## A New Synthesis of Indigo

By Prof. Dr. E. Ziegler and Dr. Th. Kappe

Institut für Organische and Pharmazeutische Chemie der Universität Graz (Austria)

We have succeeded in obtaining indigo [1] in excellent yield and purity from 4-hydroxycarbostyril *(1)* which in turn is produced in 90–93 % yield by fusing malonodianilide with $NaCl/AlCl_3$ at 240–250 °C [1].




The dichloro compound *(2)*, obtained in practically quantitative yield by chlorination of *(1)* [2], exchanges its two atoms of chlorine readily for two methoxy groups on treatment with 2 moles of sodium methoxide in methanol at 50 °C, to give the ketal *(3)*, m.p. 165–165 °C, in 93 % yield. Hydrolysis of *(3)*, by refluxing it for 1 h in 2 N NaOH, causes ring opening and decarboxylation to give the dimethylacetal *(4)*, m.p. 100–102.5 °C, in 92 % yield. Treatment of *(4)* with dilute acid converts it rapidly and quantitatively *via* unisolable *o*-aminophenylglyoxal into indigo.

Starting from the dichloro compound *(2)*, indigo can be prepared in 90 % yield in a single run and in the same reaction vessel by treating *(2)* in series with methanolic sodium methoxide for 10 min at 50 °C, with boiling 2 N NaOH for 60 min, and finally with dilute mineral acid.

The principal advantage of this new procedure is that instead of merely *(1)*, various substituted 4-hydroxycarbostyrils, or the cyclic malonyl derivatives of α- and β-naphthylamine, 6-aminocoumarin, 9-aminophenanthrene, 1,2,3,4-tetrahydroquinoline, *etc.* can be used as starting materials. Benzidine or 1,2,3,4-tetrahydroquinoxaline thus give rise to indigoids of higher molecular weight in which the above series of reactions has taken place twice in the same molecule.

Received, October 5th, 1964 [Z 839/665 IE]
German version, Angew. Chem. 76, 921 (1964)

[1] *T. Kappe*, Ph.D. thesis, Universität Graz, 1961. We wish to thank the J. R. Geigy AG. for supporting our investigations.

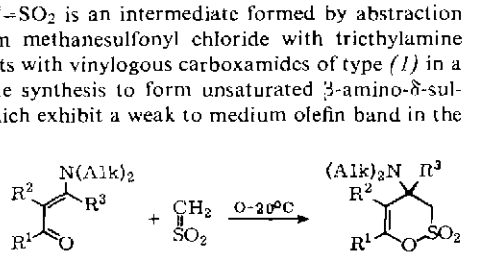
[2] *E. Ziegler*, *R. Salvador*, and *Th. Kappe*, Mh. Chem. *93*, 1376 (1962).

## Sulfene as a Dienophile

By Priv.-Doz. Dr. G. Opitz and Dipl.-Chem. E. Tempel

Chemisches Institut der Universität Tübingen (Germany)

Sulfene $H_2C{=}SO_2$ is an intermediate formed by abstraction of HCl from methanesulfonyl chloride with triethylamine [1,2]; it reacts with vinylogous carboxamides of type *(1)* in a kind of diene synthesis to form unsaturated 3-amino-δ-sultones *(2)* which exhibit a weak to medium olefin band in the

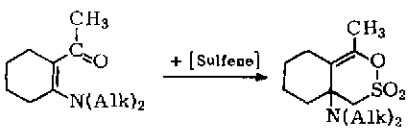


| | $R^1$ | $R^2$ | $R^3$ | $N(Alk)_2$ |
|---|---|---|---|---|
| *a* | $CH_3$ | $CH_3$ | H | Piperidino |
| *b* | $CH(CH_3)_2$ | H | H | Pyrrolidino |
| *c* | $CH_3$ | H | $CH_3$ | Dimethylamino |

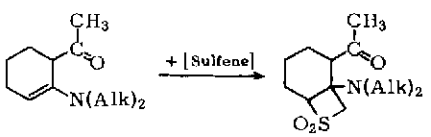
infrared at 1674–1682 $cm^{-1}$ and sulfonate bands at 1360 and 1150 $cm^{-1}$. This cyclization corresponds to the formation of α-pyrones from vinylogous carboxamides and ketene [3].

1-Piperidino-2-methylbut-1-en-3-one *(1a)* reacts with methanesulfonyl chloride in the presence of triethylamine in ether at room temperature to give the β-amino-δ-sultone *(2a)*, in 80 % yield, as colorless crystals, m.p. 108–109 °C (from methanol). Analogously, 1-pyrrolidino-4-methylpent-1-en-3-one *(1b)* gives the β-aminosultone *(2b)*, m.p. 94–95 °C in 75 % yield. The trisubstituted ethylene bond in *(1a)* gives rise to an intensified C=C valence vibration in its infrared spectrum at 1681 $cm^{-1}$ and to a weak =C–H band at 3070 $cm^{-1}$. 2-Dimethylaminopent-2-en-4-one *(1c)*, which is obtained from acetylacetone and dimethylamine, gives only 7 % of the β-aminosultone *(2c)*, m.p. 91–92 °C.

With the aid of this new Diels-Alder reaction and the formation of β-aminotrimethylenesulfones [1] from simple alkenylamines and methanesulfonyl chloride plus triethylamine it can be shown that acylation of 1-dialkylaminocyclohexene with acetyl chloride and triethylamine leads to mixtures of vinylogous carboxamides *(3)* and their unconjugated isomers *(5)*.




*(3)* *(4)*




*(5)* *(6)*

The reaction of mesyl chloride plus triethylamine with *(3)* + *(5)*, $N(Alk)_2$ = pyrrolidino, produces 32 % *(4)*, m.p. 80 to 82 °C, and 8 % *(6)*, m.p. 133–134 °C; with *(3)* + *(5)*, $N(Alk)_2$ = piperidino, it produces 9 % *(4)*, m.p. 108–109 °C, and 57 % *(6)*, m.p. 118–119 °C, and with *(3)* + *(5)*, $N(Alk)_2$ = morpholino, it affords 5 % *(4)*, m.p. 153–155 °C, and 66 % *(6)*, m.p. 123–124 °C. It is easy to identify the β-aminotrimethylenesulfone derivatives *(6)* by their strong carbonyl band in the infrared.

Received, October 6th, 1964 [Z 836/662 IE]
German version: Angew. Chem. 76, 922 (1964)

[1] *G. Opitz* and *H. Adolph*, Angew. Chem. *74*, 77 (1962); Angew. Chem. internat. Edit. *1*, 113 (1962).

[2] *G. Opitz* and *K. Fischer*, Z. Naturforschg. *18b*, 775 (1963).

[3] *A. Berchtold*, *G. R. Harvey*, and *G. E. Wilson*, J. org. Chemistry *26*, 4776 (1961).

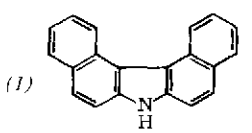
## Rearrangement of Dibenzo[*c*,*g*]carbazole to Dibenzo[*a*,*g*]carbazole

By Dr. M. Zander and W. H. Franke

Rütgerswerke und Teerverwertung AG.,
Castrop-Rauxel (Germany)

During attempts to convert dibenzo[*c*,*g*]carbazole *(1)* into the unknown compound 1,12-iminoperylene by heating it with $AlCl_3$ in boiling benzene for 2.5 h or in an $AlCl_3$/NaCl melt at 140 °C for 7 min, we obtained, surprisingly, dibenzo[*a*,*g*]carbazole *(2)* in yields of 14 % ($AlCl_3$/benzene) and 25 % ($AlCl_3$/NaCl melt) instead.

Compound *(2)* was identified by comparing its melting point and ultraviolet, infrared, and phosphorescence spectra to those of an authentic sample [1]; the melting point of a mixture of the two materials showed no depression. Compound *(1)* used for the experiments was prepared from 2,2'-dihydroxy-1,1'-binaphthyl and $NH_3$ [2] and was pure, as




careful examination of its melting point and ultraviolet, infrared, and phosphorescence spectra indicated. The dibenzo[*a*,*g*]carbazole *(2)* must, therefore, have been formed by intramolecular rearrangement of *(1)*.

Although rearrangements of polynuclear aromatic hydrocarbons [3] such as benz[*a*]anthracene, dibenz[*a*,*h*]anthracene, picene, *etc.* are known, this is probably the first example of the rearrangement of a carbazole benzologue.

Received, October 6th, 1964 [Z 837/663 IE]
German version: Angew. Chem. 76, 922 (1964)

[1] Prepared according to *N. P. Buu-Hoi*, *Ng. Hoán*, and *N. H. Khôi*, J. org. Chemistry *14*, 492 (1949); *D. G. I. Felton*, J. chem. Soc. (London) *1952*, 1668.

[2] *A. Rieche* and *H. Seifert*, German Patent 624563 (1936); Chem. Zbl. *1936*, II, 868.

[3] *M. Zander*, Naturwissenschaften *49*, 300 (1962); *N. P. Buu-Hoi* and *D. Lavit-Lamy*, Bull. Soc. Chim. France *1962*, 1398.

## Valence-Bond Isomers of (Substituted) Benzene

### Simultaneous Formation of Substituted Tetracyclohexane, Tricyclohexene, and Bicyclohexadiene by Spontaneous Trimerization of t-Butylfluoroacetylene [1]

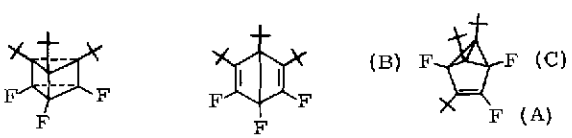
By Dr. H. G. Viehe, Dipl.-Ing. R. Merényi, Dr. J. F. M. Oth, J. R. Senders [2], and P. Valange [2]

Union Carbide European Research Associates,
Brussels (Belgium)

t-Butylfluoroacetylene is an extremely reactive compound which undergoes exothermal oligomerization [3]. Of the trimeric products formed in this reaction, only 1,2,3-tri-t-butyltrifluorobenzene [3] is aromatic; all the others are derivatives of valence-bond isomers of benzene [4].

The component of this mixture which was easiest to purify by gas chromatography is the "prismane" derivative *(1)*, which melts at 187 °C and is stable up to 250 °C. Its infrared spectrum contains no C=C absorptions, and its ultraviolet spectrum in n-hexane down to 200 mμ shows only end absorption. Its NMR spectrum contains a singlet at −1.18 ppm for the t-butyl protons and another at +176 ppm for the fluorine atoms [5]. In contrast to *(2)* and *(3)*, compound *(1)* does not react with $Br_2$ in $CCl_4$ or with $O_3$ in petroleum ether at room temperature. An X-ray analysis of its structure is being made.

The derivative *(2)* of "Dewar benzene" is more sensitive and could be separated only by cautious crystallization, but even then only in admixture with some *(1)*. Brief heating at 100 °C suffices to convert *(2)* quantitatively into 1,2,3-tri-t-




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

⊣ = t-Butyl

butyltrifluorobenzene. However, the structure of *(2)* appears to be well established by the following findings: a sample containing about 30% *(1)* showed only end absorption in n-hexane down to 200 mμ but exhibited a C=C absorption in the infrared at 5.96 μ. The NMR spectrum of *(2)* [5] has two signals each for the protons and fluorine atoms, both with relative intensities of 2:1; the proton signals are at −1.2 and −1.12 ppm, the fluorine signals at +103 and +181 ppm. All the F F coupling constants are less than 2 cps.

The third component is a derivative *(3)* of tricyclo[2,1,1,$0^{5,6}$]-hex-2-ene, which we call benzvalene; this is a liquid, b.p. ca. 140 °C/11 mm (air bath), which is readily separated by column chromatography. It has a strong C=C absorption at 5.98 μ. Its ultraviolet spectrum has $\lambda_{max}$ = 232 mμ (ε = 2500) and 300 mμ (ε = 300); this makes a bicyclohexadiene structure highly improbable. The ultraviolet spectrum is readily explicable by the assumption of optimum conjugation between the cyclopropane ring and the double bond with the plane of each mutually at right angles [6]. The NMR spectrum of *(3)* [5] has two signals for t-butyl protons with intensity ratios of 1:2 (a doublet at −1.22 and a multiplet at −1.16 ppm) and three fluorine signals of equal intensity: a broad band at +102 (A), a doublet at +182 (B), and a quadruplet at +184 ppm (C). The respective coupling constants are $J_{AB} < 2$ cps, $J_{AC} = 4$ cps, and $J_{BC} = 10$ cps. Compound *(3)* gives rise to a liquid dibromide which has no maxima in its ultraviolet spectrum and no C=C absorption in the infrared. Debromination of this derivative with magnesium in tetrahydrofuran yields *(3)* again. When heated to 220 °C, *(3)* is transformed into 1,2,4-tri-t-butyltrifluorobenzene, m.p. 53–54 °C, which has a C–C band at 6.22 μ and ultraviolet maxima at 201, 238, and 297 mμ (ε = 25000, 6600, and 1500).

The NMR spectrum [5] of 1,2,4-tri-t-butyltrifluorobenzene contains an asymmetric multiplet centered around −1.45 ppm for the t-butyl protons and three signals of equal intensity for the fluorine, *viz.* a multiplet at +102 ppm, and two double multiplets for the *ortho*-fluoro substituents at +133 and +135 ppm. The latter signals give a value for $J_{FF\ ortho}$ of 16 cps.

Received, October 19th, 1964 [Z 848/670 IE]
German version: Angew. Chem. 76, 923 (1964)

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[1] Communication No. XI on Heterosubstituted Acetylenes. Communication No. X: *H. G. Viehe, R. Merényi, J. F. M. Oth,* and *P. Valange*, Angew. Chem. *76*, 888 (1964); Angew. Chem. internat. Edit. *3*, 746 (1964).

[2] Responsible for the experimental work.

[3] See Part X of this series [1].

[4] "Dewar benzene" structures have already been synthesized: *E. E. van Tamelen* and *S. P. Pappas*, J. Amer. chem. Soc. *84*, 3781 (1962); *85*, 3297 (1963); *R. Criegee* and *F. Zanker*, Angew. Chem. *76*, 716 (1964); Angew. Chem. internat. Edit. *3*, 695 (1964). – Tricyclohexyl derivatives: *A. Small*, J. Amer. chem. Soc. *86*, 2091 (1964); *S. Masamune* and *N. T. Castellucci*, Proc. chem. Soc. (London) *1964*, 298.

[5] The chemical shifts are referred to tetramethylsilane and trichlorofluoromethane as internal standards.

[6] *N. H. Cromwell* and *G. V. Hudson*, J. Amer. chem. Soc. *75*, 872 (1953); *E. M. Kosower* and *M. Ito*, Proc. chem. Soc. (London) *1962*, 25; *I. M. Klotz*, J. Amer. chem. Soc. *66*, 88 (1944). – The resemblance to bullvalene is striking: *G. Schröder*, Angew. Chem. *75*, 722 (1963); Angew. Chem. internat. Edit. *2*, 481 (1963); Chem. Ber., in the press.

# CONFERENCE REPORTS

## Second International Dyestuff Symposium [*]

April 21st to 24th, 1964 at Schloß Elmau (Germany)

From the lectures:

### The Solvent-Dependence of the Wave Number of Electronic Absorption Bands and its Physico-chemical Basis

*W. Liptay*, Würzburg (Germany)

The solvent-dependence of the wave numbers of absorption and emission bands is essentially determined by polarization and dispersion interactions between the dissolved molecule and the surrounding solvent molecules, provided that specific interactions, *e.g.* the formation of electron donor/electron-acceptor complexes or hydrogen bridge associates, can be excluded. The solvent properties of the medium are approximated by functions of the dielectric constant and of the refractive index.

For neutral, dipole-free, dissolved molecules, dispersion interactions are important. Starting from a generally valid relationship and using the Thomas-Reiche-Kuhn summation principle, an equation was obtained according to which the displacement of the absorption and emission bands for an electron transition between the ground state and any excited state must always be toward smaller wave numbers in a solution than in the gaseous state (bathochromic shift). If the wave functions of the dissolved molecule are approximated by Slater determinants, the following approximate equation is obtained for the displacement of the wave number of the absorption and emission bands by dispersion interactions:

$$\Delta\tilde{\nu} = -\frac{n^2-1}{2n^2+1}\,D'$$

$$D' = \frac{1}{a^3 hc}\,\frac{E_a}{(\bar{E}_n - E_a)\bar{E}_n}\left[\frac{3\hbar^2 e^2}{2m} + (2\bar{E}_n - E_a)\,\mu_{ag}^2\right]$$

where n is the refractive index of the solvent; $E_a$ and $\mu_{ag}$ are respectively the energy and transition moment of the excitation in question; a is an empirical constant of the order of magnitude of the molecular radius; $\bar{E}_n$ is a constant of the order of magnitude of the ionization energy of the dissolved molecule; $h = 2\pi\hbar$ is Planck's constant; e and m are the charge and mass of an electron; and c is the velocity of light. The bathochromic shift due to dispersion interactions is thus approximately a linear function of $(n^2-1)/(2n^2+1)$, and is determined by two terms. The first term depends only on the magnitudes of the energies, whilst the second also depends on the probability of transition of the band in question. To an approximation, therefore, the bathochromic shift increases with increasing intensity of the absorption and remains finite even for the weakest bands; this agrees well with experimental findings.

The band displacement of dissolved neutral molecules with a dipole moment is determined by both dispersion and polarization interactions. Classical and quantum mechanical treatments lead to identical results as regards the terms and show that the polarization component of the solvent-dependence of the absorption (emission) depends essentially on the dipole moment in the ground state (excited state) and on the change in dipole moment occurring during the excitation (emission). The calculation of the problem was carried out, taking the polarizability of the dissolved molecule completely into account for the first time. An increase in the dipole moment on excitation causes a bathochromic shift of the absorption, and a decrease causes a hypsochromic shift; the

magnitude of the latter depends on the dielectric constant and the refractive index of the solvent, and is superimposed on the bathochromic shift due to dispersion interactions. Various approximate equations which are suitable for application were discussed and applied to a few examples.

The solvatochromism of the merocyanine-type dyes has frequently been interpreted as being due to a change in their resonance. It was shown that the change in resonance and the polarization of the dissolved molecule are identical, and should therefore also be better described by this term. However, the strong solvatochromism of various merocyanines is not due to their polarizability, but to their large dipole moment in the ground state and the large change in the dipole moment during excitation. The anomalies in the dependence of the absorption bands on the dielectric constant, found by *Brooker*, are probably always due to associates, particularly hydrogen-bonded associates.

## Methods for Determining the Charge Distribution in Electronically Excited States

*H. Labhart*, Basel (Switzerland)

The main experimental methods for determining the charge distribution in electronically excited molecular states are summarized in Table 1. It can be seen that, with the exception of substituent effects, which permit the estimation of charge variations on the atoms of conjugated systems, all the methods solely yield the dipole moments in the excited states. However, these experimental dipole moments can be used to check theoretically determined atomic charges. By taking into account the configurational interaction between the nine lowest singly excited configurations, SCF Pariser-Parr-Pople calculations yielded charge distributions such as those given in Table 2 for *p*-nitrosodimethylaniline. Table 2 also shows a comparison of the theoretical and experimental dipole moments.

Table 2. Charge distributions and dipole moments of *p*-nitrosodimethylaniline.

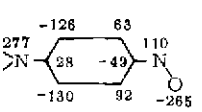
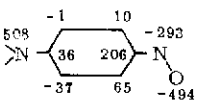
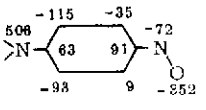
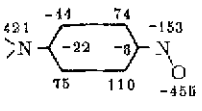
| State | Charge distribution in $10^{-3}$ protonic charges | π-Dipole moment, calculated [Debye] | Total dipole moment, experimental [Debye] |
|---|---|---|---|
| Ground state |   | 5.96 | 6.45 |
| First excited π-π* state λ = 390 mμ |   | 17.7 | 13.5 |
| Second excited π-π* state λ = 300 mμ |   | 12.9 | — |
| Third excited π-π* state λ = 270 mμ |   | 14.8 | 13.4 |

Table 1. Experimental methods for determining the charge distribution in electronically excited states.

| Effect | Interpretation | Result | Notes |
|---|---|---|---|
| Influence of substituents on the spectrum | Perturbation of the π-electron system by inductive effects | Change in the atomic charges on optical excitement | Advantages: local charge variations<br>Disadvantages: perturbation often too great or mesomeric |
| Solvent effects on the absorption and fluorescence spectra | Stark effect in the reaction field of the solvent | Dipole moment in the lowest excited singlet state | Advantages: observation simple<br>Disadvantages: size of the reaction field uncertain; suitable only for fluorescent molecules |
| Band displacement in an external electric field | Stark effect of the partially oriented molecules in the applied field | Dipole moments in several excited singlet states | Advantages: also suitable for non-fluorescent molecules<br>Disadvantages: effect often small |
| Polarization of luminescence in an external electric field | Degree of orientation of excited molecules in the field | Dipole moments in the lowest excited singlet or triplet state | Advantages: dipole moments of triplet states can be determined<br>Disadvantages: luminescence essential |

It should be pointed out that, without calculation, it is impossible to predict such charge distributions in excited states, even qualitatively, by writing down resonance structures.

[*] All lectures together with discussion remarks will soon be published.

## The Dependence of the Color of Fluorescence on the Medium

*E. Lippert*, Stuttgart (Germany)

One of the characteristics of a good optical brightener is that its absorption spectrum begins with a very intense O–O transition near the long-wave end of the ultraviolet spectral region. It is to be expected that it will completely absorb the ultraviolet components of the incident daylight or artificial light, and that its fluorescent light is distributed over the violet and blue regions of the spectrum. The fluorescent color of fluorescent dyes must agree with their absorption color. In both cases, the quantum yield of the fluorescence should be close to unity. Competing mechanisms for the conversion of electronic excitation energy, which depend on the surrounding medium, should thus be excluded [1]. Consequently, for example, it cannot be concluded from the observation that a substance is only weakly fluorescent in solution that it is necessarily a poor optical brightener. The

[1] For a survey of these mechanisms see *E. Lippert* et al., Angew. Chem. *73*, 695 (1961).

color of the fluorescence also depends on the substrate, not only owing to the intermolecular interactions which also affect the absorption color, but also owing to the solvent-dependent relaxation effects which always occur during the life of the fluorescent excited state and which are based on the Franck-Condon principle and on the fact that the various electronic states of a system are associated with different charge distributions and equilibrium nuclear configurations. The consequent photophysical relaxation cycles for solutions of Dilthey-Wizinger dyes (structure: chromophore-aromatic system-auxochrome; *e.g.* *p*-amino-*p'*-nitrobiphenyl) were described.

### Influence of the Dielectric Properties of Solvents and Substrates on the Light Absorption and Photochemical Behavior of Cationic Dyes

*F. Feichtmayr* and *J. Schlag*, Ludwigshafen/Rhein (Germany)

A dye salt in solution and on solid substrates may either be dissociated into individual ions or exist in ion pairs. Furthermore, similarly charged ions of the dye may be present as the monomer or dimer, or in higher associates. For dyes deposited on solid substrates, little is known concerning the position of the equilibria between these states, since most methods of investigation can only be used in solution. For symmetrical triphenylmethane dyes, such as Crystal Violet and Victoria Blue, the forms of the dye salts taking part in the equilibria can be distinguished by their absorption spectra in the visible region. The equilibria for these dyes can therefore be spectroscopically investigated both in solution and on solid substrates.

It was found that, for such dyes in solution and on solid substrates, the dielectric properties of the surroundings of the dye stuff molecule determines the dissociation of the salts and the association of the dye cations. The dye salts are undissociated in non-polar media, and dissociated in polar media. Association of similarly charged dye ions occurs only in strongly polar media.

The photochemical stability of the dye salts depends on their state of dissociation and association. Dissociated salts are more stable towards light than undissociated salts. Furthermore, the "light-fastness" depends on the nature of the anion of the salt. In solution and on substrates in which the rate of diffusion of the reaction products is high, the rate of fading of the dye salt increases with the ease with which the anion can give up its electron, *i.e.* with decrease in the electron affinity of the anion. It is therefore concluded that the first step in the reaction involved in photochemical fading is an electron transition from the anion to the photoexcited dye cation. In substrates in which the anion and the dye cation cannot diffuse away from each other sufficiently rapidly after the electron transition, the "light-fastness" of the dye salt is no longer determined by the electron affinity of the anion. Here it increases with the activation energy for the secondary reaction of the free radical formed from the anion (detected by ESR spectroscopy) with the substrate (hydrogen abstraction).

### Relationship between the Constitution of Cationic Triphenylmethane Dyes and their Light-Fastness on Polyacrylonitrile

*R. F. Johnson*, *O. A. Stamm*, and *H. Zollinger*, Zürich (Switzerland)

In investigations on 20 triphenylmethane dyes of the type of Malachite Green (R = $CH_3$, X = H), Doebner's Violet (R = H, X = H), and 4-dimethylaminotriphenylcarbonium chloride, the acidity constants of the carbonium ion $\rightleftharpoons$ carbinol equilibrium, the light-fastness of the dyes on Orlon 42, Dacron 64, and mordanted and cyanoethylated cottons, and (for most of the dyes) the adsorption isotherms on Orlon 42 were measured. The standard affinities ($-\Delta_\mu^0$) were calculated from the Langmuir isotherms.

The $pK_a$ values and the light-fastness (blue scale) on Orlon 42 and on Dacron 64 of *m*- and *p*-substituted malachite-green derivatives follow the Hammett relationship for benzene derivatives, whilst their light-fastness on pretreated cotton does not. For standard affinities, an additional influence is presumably superimposed upon a simple Hammett relationship. Photolytic oxidation (according to *C. H. Giles*) is not the only interpretation for the observed Hammett relationship. It was concluded

1. that the much higher light-fastness of cationic dyes on polyacrylonitrile fibers than on pretreated cellulose fibers is not due to covalent fiber-dye bonding;

2. that free-radical formation from the excited state is compatible with the observed substituent effects;

3. that the difference in light-fastness is probably due to the nature of the fiber's counterion ($SO_3^\ominus$ and $-COO^\ominus$) and on the rate of recombination and/or of the secondary reactions of the free radicals initially formed;

4. that the Hammett relationship is of limited importance for final clarification of a bleaching mechanism.

### Changes in the Light-Fastness and Color of Organic Dyes on Various Substrates

*M. Pestemer*, Leverkusen (Germany) [*]

The light-fastness of dyes (*e.g.* triphenylmethane, anthraquinone, cyanine, phthalocyanin, and azo dyes) depends mainly on their bonding to the substrate and on their particle size. The color hues can vary very considerably with the substrate, particularly with polar dyes. Samples were shown of dyeings on wool, silk, cotton, acetate rayon, polyacrylonitrile, polyamide, polyester, and polypropylene fibers. Treatment to improve crease-resistance and wash-fastness also has a decisive influence on the competition between deactivation and chemical reaction of dye molecules which have been activated by light absorption. As a result of fiber treatment, dyes generally become more finely divided, with resulting deterioration of their light-fastness. The photochemical reaction also depends on the substrate and generally leads initially to reduction of dyestuffs on wool, silk, and gelatin, whilst on all other substrates it results in oxidation of the dyes. It was shown with examples how important the role of water may be in this reaction. For certain green combinations of blue phthalocyanin dyes and yellow 3-methyl-1-phenylpyrazolone azo dyes, the wet-fastness falls off rapidly compared with the light-fastness under normal conditions. The increased light-fastness of many cationic dyes (*e.g.* triphenyl methane, phenoxazine, and indole derivatives) on polyacrylonitrile is probably attributable to the chemical inertia of this fiber. Many polar azo dyes exhibit phototropism on fibers, *i.e.* "displacement" toward other color tones, which is reversed in the dark. Some phthalocyanin derivatives also exhibit phototropism as a result of treatment of the textiles with melamine-HCHO or urea-HCHO condensates to improve their crease-resistance.

### Study of Intermediates in Flash Photolysis

*G. Porter* and *A. D. Osborne*, Sheffield (England)

Flash photolysis was the first method which permitted concentration of intermediates by optical excitation to such an extent that they could be observed optically [1] (generally $10^{-5}$–$10^{-2}$ sec after the flash photolysis). Whereas the rate constant k can be calculated directly for photolysis which

[*] Based on contributions from Badische Anilin- und Soda-Fabrik, Ludwigshafen, Farbenfabriken Bayer, Leverkusen, and Farbwerke Hoechst, Frankfurt/Main-Höchst (Germany).

[1] *G. Porter*, Proc. Roy. Soc. (London), Ser. A *200*, 284 (1950).

proceed by first-order kinetics, only $k/\varepsilon$ is initially obtained for a second-order reaction. The extinction coefficient $\varepsilon$ of the intermediate can be determined from the decay time of the collision-controlled reaction in viscous media [2, 3]. A process which can occur with low activation energy at each collision with a luminescence extinguisher (Q) is: $T_1 + S_Q \rightarrow S_0 + T_Q$ ($T_1$ and $T_Q$: triplet states of the substrate and the extinguisher; $S_Q$ and $S_0$: singlet states of the extinguisher and the substrate). Thus, for example, benzophenone is deactivated by naphthalene as an extinguisher, its reduction to benzopinacol being prevented by the solvent.

The rate constant for a collision-controlled, second-order luminescence extinction is given by

$$k_Q = 8\,RT/200\,\eta \text{ [l/mole·sec]} \qquad (\eta = \text{viscosity})$$

Since the potential curve of any excited substituted aromatic compound (this is generally similar to its curve in the ground state) is intersected by the potential curve (repulsion term) of a free radical state, the aromatic compound can undergo cleavage at an exocyclic bond, *e.g.*

$$C_6H_5-CH_3 + h\nu \rightarrow C_6H_5-CH_2\cdot + H\cdot$$

This reaction is scarcely affected by the temperature and the solvent. On the other hand, the reaction, for example, of S* or T*-excited aldehydes and ketones with solvent molecules is strongly dependent on the solvent and temperature. Thus, the following reaction proceeds through an $n$-$\pi^*$ triplet state, and is completely suppressed below $-40\,^{\circ}C$:

$$(C_6H_5)_2C{=}O \xrightarrow{h\nu} [(C_6H_5)_2C{=}O] \xrightarrow{RH} (C_6H_5)_2\dot{C}-OH + R\cdot$$

Whereas the solvent radicals recombine rapidly, large radicals of the substance (*e.g.* 2,4,6-tri-t-butylphenoxyl and rhodamine-B radicals) may be stable for minutes or even hours in the absence of oxygen. Carbonyl compounds (benzaldehydes, benzophenones, anthraquinones) with hydroxyl or amino substituents in the *ortho*-position are completely resistant to photolysis owing to hydrogen bonding (such compounds are therefore used, as dye stabilizers, for example). On the other hand, some benzophenones and anthraquinones without these *ortho*-substituents sensitize fiber damage. As *Porter* and *Suppan* [4] found, the electron-donating substituent in the stable carbonyl compounds causes a long-wave charge-transfer triplet state. Owing to a $\delta$-charge, the carbonyl oxygen is no longer chemically reactive in the excited state.

## Classification of the Excited Electronic States of Organic Molecules with the Aid of the Degree of Polarization of the Fluorescence and Phosphoresence

*F. Dörr*, München (Germany)

The degree of polarization of the luminescence produced by selective excitation in the various absorption bands with polarized light yields information on the position and form of masked absorption bands, the relative orientation of transition moments, the symmetry of structural vibrations, and the effective mechanism of the triplet-singlet emission. These data are particularly useful for checking theoretical models, which generally give the number and the direction of the polarization of transitions with greater reliability than their energy and intensity.

Special examples: The appearance of a cross-polarized band during the photoisomerization of unbranched polymethine dyes led to the conclusion that a *trans* → *cis*-rearrangement had occurred. The first and second absorption bands of Malachite Green are polarized perpendicularly to each other. On the other hand, the first band of Crystal Violet is degenerate; the degree of polarization drops within the band from about 0.5 to zero. The high value of 0.5 does not agree with a threefold axis of symmetry and rules out a propeller form for the molecule. Two rings probably lie in one plane, while the third is twisted out of plane.

In phosphorescence, heavy substituents have a pronounced effect on the degree of polarization even when they affect the spectra only slightly.

[2] See, for example, *R. M. Noyes* in *G. Porter*: Progress in Reaction Kinetics. Pergamon Press, Oxford-London-New York-Paris 1961, p. 133.

[3] *A. Beckett, A. D. Osborne*, and *G. Porter*, Trans. Faraday Soc. (1964), in the press.

[4] *G. Porter* and *P. Suppan*, unpublished work.

## Current Ideas on Spectral Sensitization

*E. Klein* and *R. Matejec*, Leverkusen (Germany)

In photographic and electrophotographic processes, the primary process (formation of free charge carriers) is the same. Both processes can consequently be spectrally sensitized.

The classes of dyes which can be used for sensitization (particularly fluoresceins and cyanins) and the requirements placed on them (light absorption, adsorption, no desensitization, good sensitization) were discussed, together with the observed attendant effects (super-, anti-, and desensitization; formation of dye aggregates, crowding, singlet and triplet transitions).

The quantum yield of spectral sensitization generally decreases with decreasing temperature, and cannot be increased above a maximum value of $\varphi \approx 0.25$, even by supersensitization [*]. The main effect of supersensitization is to prevent reduction of this quantum yield at lower temperatures; this effect falls off only at very low temperatures ($T < -183\,^{\circ}C$). The relationship between absorption spectra, sensitization spectra, and photoconductivity spectra were discussed with examples (AgBr + sensitizer; AgBr + another dye; AgBr + sensitizer + supersensitizer; CdS + sensitizer; ZnO + sensitizer).

It was found from both photolytic investigations on AgBr and photoconduction measurements on ZnO that a sensitizer molecule is capable of effecting sensitization several times (in the limiting case, infinitely often). This discovery is extremely important for the mechanism of spectral sensitization. There are two main questions in the discussion of the mechanism of sensitization:

1. how can the dye in the photoconductor (or in the silver halide) initiate photophysical processes on absorption of an appreciably smaller quantum of energy than the specific absorption of the silver halide or the photoconductor?

2. are electrons or energy transferred from the sensitizer to the photoconductor?

The probable answer to the first question is that spectral sensitization is a surface process; however, the semiconductor surface certainly has a electronic structure different from that of the interior of the semiconductor (bending upwards of the electron bands; surface terms, *etc.*), so that, taking account of the probability of transition, the energy relationships found for spectral sensitization are different from those to be expected from the electronic structure of the interior of the semiconductor (*i.e.* from the distance between the valence band and the conductivity band).

With regard to the second question, barrier-layer effects indicate electron transfer. Estimation of the probability with which the electrons could "tunnel" through the potential barrier which is presumably present between the photoconductor and the dye shows that electron transfer may also be physically possible. On the other hand, energy transfer is indicated particularly by experiments in which the energy from a receiver dye absorbing the incident light is passed

[*] The term "supersensitization" refers to a "catalytic" increase in sensitization by very small amounts of foreign compounds.

through a layer of barium stearate about 200 Å thick or across several solvent molecules without radiation to a receiver substance which emits fluorescent light. Similar energy transfer phenomena are known to occur in systems such as anthracene/tetracene, and in the 'plastic scintillators' used in nuclear technology.

### Fiber Damage due to Anthraquinonoid Dyes

*F. Dörr*, München (Germany)

Yellow anthraquinone dyes dehydrogenate their substrate on exposure to light. The known dyes can be divided into two groups according to the electronic structure of their lowest excited state. In the first group, which included most yellow dyes, the lowest excited state is a triplet n-$\pi^*$ state in which a non-bonding, localized n-electron from the oxygen of the keto group passes into a delocalized $\pi^*$-orbital of the carbon skeleton. The free-radical electron remaining on the oxygen reacts with the surroundings. Almost all the dyes which cause active damage belong to this group. In the second group, the lowest triplet level of the delocalized $\pi$-electrons T($\pi$-$\pi^*$) is depressed below the T(n-$\pi^*$) level by the action of substituents. This group includes the inactive dyes.

This hypothesis is supported by the detection of n-$\pi^*$ absorption bands in dyes which cause damage, by the flash-spectroscopic detection of ketyl radicals in active benzophenone derivatives, and of semiquinone radicals in active anthraquinone derivatives. These radicals react further by second-order kinetics. They are absent from all the inactive compounds investigated. Flavanthrone, which belongs to the second group, is progressively reduced on cellophane to the semiquinone radical ion, when irradiated with light of 365 mμ wavelength in its second, weak absorption band. It is assumed that a T(n-$\pi^*$) state, which lies above the T($\pi$-$\pi^*$) level, can also react in the case of hindered deactivation.

[VB 837/161 IE]

German version: Angew. Chem. 76, 819 (1964)
Translated by Express Translation Service, London

## Modern Methods of Organic Analysis

A symposium under the above title organized by the Analytical Chemistry Sections of the Royal Dutch Chemical Society and the German Chemical Society was held in Eindhoven (Holland) from May 20th to 23rd, 1964.

From the lectures:

### Determination of Acetoacetic Acid in 0.1 ml of Blood

*F. Bahner*, Heidelberg (Germany)

Acetone is liberated from the acetoacetic acid in the blood sample and isolated by microdiffusion. Disadvantages of the Conway microdiffusion apparatus are that the diffusion cell is not gas-tight at 30–40 °C, and a temperature gradient cannot be maintained between the inner and outer chambers. In a new apparatus described, a temperature difference can be maintained between the two reacting solutions. Acetone reacts in alkaline solution with salicylaldehyde to form red 1,3-disalicylideneacetone. The reaction is influenced by 1. the reactant concentrations; 2. oxygen; 3. daylight; and 4. slow thermal dissociation of the disalicylideneacetone in alkaline solution; this last factor makes the final color dependent on temperature. Under appropriate conditions, $10^{-8}$ mole of acetone can be separated and determined.

### Improvement and Automation of the Determination of Creatinine

*K. Beyermann*, Mainz (Germany)

Creatinine can be separated rapidly and selectively by precipitation as its tetraphenyl borate complex in the presence of butylamine as carrier. The optimum conditions for precipitation (pH 3 ± 1, $10^4$-fold excess of tetraphenyl borate and $10^3$-fold excess of butylamine, room temperature) were determined by studies with [$^{14}$C]creatinine [1]. For $10^{-2}$–$10^3$ μg of creatinine per ml, the efficiency of isolation is 97–100 %. About 300 substances representing either normal constituents of biological materials or pharmaceutical preparations did not interfere. The few compounds which are coprecipitated do not interfere in practice with the subsequent determination. The precipitate is dissolved in dimethylformamide, and the red color produced by reaction between creatinine and picric acid is determined spectrophotometrically. Protein must first be separated off by precipitation with trichloroacetic acid; this results in a creatinine loss of less than 1 %. Other separation procedures (ion exchange, adsorption on Fuller's earth) gave lower recoveries. A fully automatic, programmed apparatus makes it possible to complete 10 creatinine determinations per hour.

[1] *K. Beyermann*, Z. analyt. Chem., in the press.

### Thin-Layer Chromatography on Silica Gel Impregnated with Silver Nitrate

*F. C. den Boer*, Vlaardingen (Holland)

Substances with C–C double bonds form complexes with silver ions. Hence olefinic substances can be separated on thin layers of silica gel previously impregnated with silver nitrate. The thin layers can be prepared quickly, and 0.1 to 100 mg of mixtures can be separated quickly, readily identified, and isolated quantitatively.

Typical analyses include the separation of the methyl esters of the fatty acids in soya oil having the same chain length but different numbers of double bonds, analysis of a mixture of the triglycerides of linoleic, oleic, and stearic acid, and the analysis of a mixture of acetylated methylsterols.

### Separation of Steryl Acetates by Thin-Layer Chromatography

*J. W. Copius-Peereboom*, Leiden (Holland)

Mixtures of animal and vegetable fats were analysed by identifying the sterol types present by means of a thin-layer chromatography reversed-phase technique on kieselguhr G impregnated with undecane (b.p. 190–220 °C). On development of the plates with acetic acid/acetonitrile (25:75), various steryl acetates, *e.g.* the acetates of β-sitosterol, stigmasterol, cholesterol, desmosterol, and $\Delta^{9(11)}$-dehydroergosterol, are separated into small semi-circular bands.

The rates of migration of sterols are characterized by their carbon numbers (Nc values), *i.e.* the number of carbon atoms minus the number of double bonds.

Unfortunately, in this system, certain sterol pairs have equal $R_F$ values, *e.g.* cholesterol and brassicasterol; ergosterol and 7-dehydrocholesterol. Such "critical pairs" of sterols were separated by adding 0.5 % bromine to the mobile phase according to the procedure of *Kaufmann*.

Critical pairs of sterols can also be separated on silica gel-G layers impregnated with silver nitrate. The acetates of various sterols are separated with chloroform/light petroleum/acetic acid (25:75:0.5) as solvent, *e.g.* the pairs: dihydrocholesterol/cholesterol, $\Delta^7$-cholesterol/cholesterol, $\Delta^7$-cholesterol/5-dihydroergosterol, lanosterol/agnosterol. Sterols with a greater number of ethylenic linkages display lower $R_F$ values in this system.

### Colorimetric Sub-micro Determination of Bromine in Organic Compounds

*T. R. F. W. Fennell* and *J. R. Webb*, Farnborough, Hants (England)

Sulfophthalein dyes in strongly acidic solution exhibit high intensity absorption in the 500–550 mμ spectral region. It was found that on treating bromide with bromate in the acidic dye solutions, a decrease of the absorption intensity occurred which was proportional to the amount of bromide present. Detailed investigations with several dyes showed that *o*-cresolsulfophthalein (cresol red) was most suitable for the determination of bromide.

By varying the initial concentration of dye, 2–10, 5–20, and 10–40 μg amounts of bromide were determined with standard deviations of 0.08, 0.12, and 0.16 μg respectively. Within these ranges, straight-line calibration curves were obtained. Apart from chloride and iodide, ions in the amounts that occur in sub-micro analyses do not interfere provided that oxidizing and reducing agents are absent.

### Analysis of Drugs in Biological Fluids by the Tropäolin Method

*A. Häussler* and *P. Hajdu*, Frankfurt/Main-Hoechst (Germany)

The formation of chloroform-soluble complexes with Tropäolin-00 (4-Phenylaminoazobenzene-4′-sulfonic acid) by many basic pharmaceuticals can be used for both qualitative and quantitative analysis [2]. Using an Autoanalyzer [3], a continuous record of reaction kinetics can be obtained by this method, *e.g.* of the ester hydrolysis of local anesthetics at low concentrations (10–50 μg/ml) in serum. The calculated reaction constants show that the rate of hydrolysis is strongly species-dependent. This finding is in agreement with the literature [4]. Complex formation can also be used to extract basic drugs selectively from body fluids. By fluorimetry of the extract, less than $10^{-6}$ g of drug material can be detected.

### Automatic Combination of Thin-Layer Chromatography and a Temperature-Programmed Gas-Chromatograph

*R. Kaiser*, Ludwigshafen/Rhein (Germany)

With increasing molecular weight, the uncertainty in the qualitative identification of compounds by gas chromatography increases sharply. Here automatic combination of a gas chromatograph and a thin-layer chromatograph can help. A thin-layer plate is attached to the adapted, strongly heated outlet of a temperature-programmed gas-chromatograph and is moved from one end to the other, the movement being controlled either by time or by recorder output. The material from each small gas-chromatographic peak, and the impurities between peaks, are deposited as individual spots or as a line by local cooling. Large peaks (relatively large quantities of material) are deposited in several spots on the start line. The thin-layer plate is then developed with a suitable mobile phase. In this way, the substances contained in the gas-chromatographic peaks are rechromatographed, but on the basis of different principles, so that better separations can be achieved. The developed thin-layer plates are treated with specific chemical reagents; the finished thin-layer chromatograms provide, in association with the gas chromatogram, an abundance of frequently surprising additional information.

### The Reaction of Nucleotides and Nucleic Acids with Diazonium Salts

*H. Kössel*, Munich (Germany)

As *Zillig* and *Verwoed* [5] showed by the example of the reaction of hydroxylamine with s-RNA, chemical methods are useful for the base-specific degradation or base-specific modification of nucleic acids for sequence analysis. The reaction of diazonium salts with nucleotides and nucleic acids was examined from this aspect.

The diazonium salts used were diazotized *p*-sulfanilic acid, diazotized 2,4-dichloroaniline, diazotized *p*-nitroaniline, and diazotized 4-nitroaniline-3-sulfonic acid, all in 3- to 10-fold excess at 2 °C. The reactions with the nucleotides guanylic acid (Gp), adenylic acid (Ap), and cytidylic acid (Cp) were readily followed by extinction measurements in the 370–440 mμ region and by high-voltage paper electrophoresis.

Gp, Ap, and Cp all reacted with diazotized *p*-sulfanilic acid, Gp quickly and quantitatively, but Cp only to the extent of about 20 %. Uridylic and thymidylic acids did not react. The pH optima were 10.2 (Gp) and 10.7 (Ap, Cp). The dyestuffs produced were not, or were only in small part, true azo compounds, but rather diazoamino derivatives with the structure $R^1-N=N-NH-R^2$; this was deduced from the following observations:

1. The dyes decompose in weakly acidic medium to reform the starting materials.

2. They show spectroscopic $pK_a$ values of 11.9 (Gp) and 9.0 (Ap, Cp).

3. Their formation is inhibited by formaldehyde, which reacts with amino groups.

The dye formed with Ap is the one most readily reconverted into the starting materials. Decomposition of the product from Gp gives some xanthidylic acid, the deamination product of guanylic acid.

Diazotized *p*-sulfanilic acid reacts correspondingly with RNA and DNA; cytidylic acid does not react. In contrast, *Beer* and *Mouchrianakis* [6] observed base-specific coupling of diazotized aminonaphthalenetrisulfonic acid with DNA.

Only the purine nucleotides react with the diazonium salts of 2,4-dichloroaniline, *p*-nitroaniline, and 4-nitroaniline, but again Gp reacts faster than Ap. The pH optimum for both nucleotides is 8.5 for all three diazonium salts.

### NMR-Spectroscopy for the Analysis of Organic Compounds with Known Functional Groups

*N. van Meurs*, Amsterdam (Holland)

High-resolution NMR spectra can be used a) to distinguish between primary, secondary, and tertiary monobasic acids and for quantitative analysis of binary mixtures of these

[2] *A. Häussler* and *P. Hajdú*, Arzneimittel-Forsch. *12*, 411 (1962).

[3] *A. Häussler* and *P. Hajdú*: Wandel in der chemischen Technik. Hanser, München 1963, p. 112.

[4] *R. Muschaweck*, Lokalanästhesie und Lokalanästhetika. Thieme, Stuttgart 1959, p. 103.

[5] *W. Zillig*, *D. W. Verwoed*, and *H. Kohlhage*, Hoppe-Seylers Z. Physiol. Chem. *332*, 184 (1963).

[6] *M. Beer* and *E. N. Mouchrianakis*, Proc. nat. Acad. Sci. U.S.A. *48*, 409 (1962).

acids, and b) to differentiate between primary, secondary, and tertiary monohydric alcohols and for the quantitative analysis of binary and ternary mixtures of these alcohols.

The three types of monobasic acids can be distinguished by the multiplet structure and intensity ratio of the α-$CH_2$ and α-CH proton resonance signals, provided that these do not overlap with the β-proton multiplets. The intensities of the signals are determined relative to that of the carboxylic proton resonance signal. For quantitative analysis of binary mixtures, the intensity ratio can be used.

For the analysis of alcohols, the preparation of the sample constitutes an important part of the procedure, for it must ensure that any exchange of the hydroxyl protons comes to a standstill [7]. The three types of alcohol then show differences in the multiplicity of the hydroxyl signal and in its chemical shift. This depends on the solvent and the temperature.

A second procedure, based on comparison of peak heights gives results of similar absolute accuracy (±5 %) in suitable cases.

### Relations between Structure and Rate Constants for the Dissociation and Recombination of Carboxylic Acids

*H. W. Nürnberg*, Jülich (Germany)

The rate constants for the dissociation and recombination of 12 aliphatic and aromatic carboxylic acids in 1 M LiCl have been determined for the first time by a new electrochemical method termed "High Level Faradaic Rectification" [8].

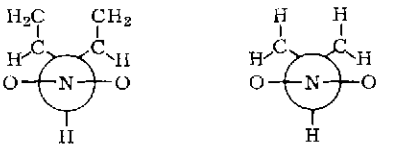
With the kinetic data now available for a greater number of acids, the formulation of a correlation between the rate constants and the structure of the acid molecules and their anions is possible; previously such considerations had to be based solely on equilibrium constants. Normally, recombination depends only upon diffusion, and a common value ($k_r \approx 3.5 \times 10^{10}$ liter·mole$^{-1}$·sec$^{-1}$) is obtained for the rate constant for recombination in 1 M LiCl, since the diffusion coefficient of the hydrogen ion exerts the dominating influence. Consequently there is a linear relationship between the dissociation constant $k_d$ and the equilibrium constant. Hence, for acids with normal behavior, $k_d$ can be predicted from a knowledge of the equilibrium constant. The influence of structure with its inductive and mesomeric effects plays a part in determining the value of $k_d$. Deviations from normal behavior arise if recombination is retarded by steric effects, *e.g.* particularly by the formation of intramolecular hydrogen bridges in the anion (lactic acid, salicylic acid). With these acids, only kinetic measurements give complete information on the dissociation and recombination behavior. In addition, the stability constant of the intramolecular hydrogen bridges follows from a knowledge of $k_r$. Finally, evidence of the salt effect on the rate of dissociation and recombination can be obtained.

### Conformational Analysis of Nitrosteroids by Circular Dichroism

*G. Snatzke*, Bonn (Germany)

Nitrosteroids show a Cotton effect at 280 mμ, and sometimes their absorption band at 320 mμ also is circular dichroitic. Both bands involve $n \rightarrow \pi^*$ transitions, but only the first transition exhibits the symmetrical properties of carbonyl excitation. The rules found for ketones can thus be applied to the 280 mμ band with slight modifications [9].

For nitro compounds in which free rotation of the $NO_2$ group is hindered, the relationship between the circular dichroism and the axial or equatorial conformation of the $NO_2$ group has been deduced; a modified octant rule is applicable for nitro groups. The two planes of symmetry of the $NO_2$ group and a third plane perpendicular to them lying between the nitrogen atom and the two oxygen atoms divide the space around the molecule as in ketones; the contributions of the carbon atoms are, however, calculated with opposite signs. Measurements of the circular dichroism of *gem*-nitrohalogenosteroids at −188 °C support the rule given. From the results it follows that in unhindered nitrocyclohexanes the following conformations are energetically most favored:



Axial $NO_2$ group  equatorial $NO_2$ group

### Preparative Thin-Layer Chromatographic Separation of Phosphatides and Thin-Layer Chromatographic Identification of Their Hydrolysis Products

*O. W. Thiele* and *W. Wober*, Göttingen (Germany)

Phosphatides can be separated by thin-layer chromatography on silica gel-G with isobutyl ketone/formic acid/water (40:15:2). Staining agents which have proved generally applicable are: borate-buffered bromothymol blue solution for lipids; ninhydrin for primary amines; and Dragendorff's reagent, followed by ninhydrin on the same plate, for quaternary amines.

Since column-chromatographic separation of phosphatides seldom yields pure fractions, exclusive use of thin-layer chromatography on the preparative scale is of great value. The mixture is placed on the start line in a strip 18 cm long (0.1 mg/cm). After development of the chromatogram and staining of a narrow guide strip, the absorption material containing the desired fraction is scraped off the plate and extracted.

After hydrolysis of the phosphatides, fatty acids, amines, and phosphate esters (which alone are resistant to hydrolysis) are obtained. The fatty acids are separated by gas chromatography of their methyl esters. The amines are separated by thin-layer chromatography on silica gel-G with 96 % v/v ethanol/water (63:37), or n-butanol/glacial acetic acid/water (3:1:1), or n-propanol/34 % ammonia (67:33). For the identification of phosphate esters, a thin-layer chromatographic procedure on cellulose sheets is employed, using either an ammoniacal (*e.g.* 0.5 N ammonia/methanol, 2:3) or an acidic system (*e.g.* glacial acetic acid/n-propanol/water 1:2:1) as mobile phase. Compared with paper-chromatographic procedures, thin-layer chromatography on cellulose has the advantages of improved zone sharpness, clean applicability of phosphate reagents (Hanes-Isherwood spray reagent), and good resistance of the cellulose layers to aggressive spray reagents. [VB 819/147 IE]

German version: Angew. Chem. *76*, 691 (1964)

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### Verdazyls and Related Nitrogen-Containing Free Radicals

*R. Kuhn*, Heidelberg (Germany)

Verdazyls *(1)* [1] may be prepared from sugar phenylhydrazones; the solubility of such 1,5-diphenylverdazyls in polar solvents is improved by hydrophilic substituents in the 3-position (*T. Schwarz-Fischer*). The following compounds have been prepared: 3-[D-*gluco*-, 3-[D-*galacto*-, and 3-[D-

[7] Proton exchange is suppressed by careful neutralization of solvents and solutes.

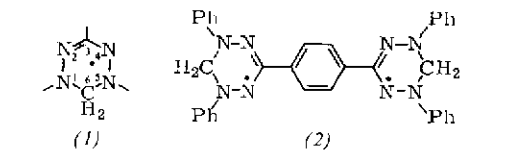
[8] *H. W. Nürnberg* and *G. C. Barker*, Naturwissenschaften *51*, 191 (1964).

[9] *C. Djerassi*: Optical Rotatory Dispersion. McGraw-Hill, New York 1960.

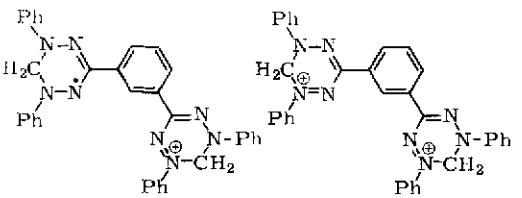
[1] *R. Kuhn* and *H. Trischmann*, Mh. Chem. *95*, 457 (1964); Angew. Chem. *75*, 294 (1963); Angew. Chem. internat. Edit. *2*, 155 (1963).

*manno*-pentahydroxypentyl]-1,5-diphenylverdazyls, and 3-[D-*arabo*-, 3-[D-*rhamno*- and 3-[D-*xylo*-tetrahydroxybutyl]-1,5-diphenylverdazyls. Free radicals of this type affect the decomposition of $H_2O_2$ by catalase.

Combination of two 3-verdazylyl residues by a 1,3- or 1,4-phenylene bridge (*F. A. Neugebauer* and *H. Trischmann*) gives fully conjugated, planar, green biradicals with properties which correspond to those of the simple verdazyls. Examples of these compounds are 1,3-bis-[1,5-diphenyl-3-verdazylyl]benzene, m.p. 184–185 °C (decomp.), magnetic moment $\mu/\mu_B$ = 2.46 (found), $\lambda_{max}$ = 719 mμ (ε = 8200), and 1,4-bis-[1,5-diphenyl-3-verdazylyl]benzene *(2)*, m.p. 190–192 °C (decomp.), $\lambda_{max}$ = 732 mμ (ε = 7400). The ESR spectra of these biradicals (*K. H. Hausser* and *P. Fischer*) do not show the 9 lines characteristic of verdazyls; they indicate interaction between the two unpaired electrons (also observed with the *m*-compound). Reversible polarographic oxidation yields the diamagnetic, violet, divalent-cation *(4)* via the violet monoradical cation *(3)*, which gives a typical verdazyl ESR spectrum with 9 lines.



*(1)* *(2)*



*(3)* *(4)*

Ph = Phenyl

Some nitrogen-containing free radicals, arranged in order of decreasing dehydrogenating power, are: tetraphenylpyrryl > *N,N*-diphenyl-*N'*-picrylhydrazyl > 1,1,5,5-tetraphenyl-1,2,4,5-tetraazapentenyl, 1,1,5,5-hisbiphenylene-3-azapentadienyl > 1,3,5-triphenylverdazyl, 1,1,5,5-bisbiphenylene-2,3-diazapentadienyl. Each of the nitrogen radicals can abstract a hydrogen atom from the NH-compounds derived from radicals lower in this series, being thereby converted itself into the parent NH-compound.

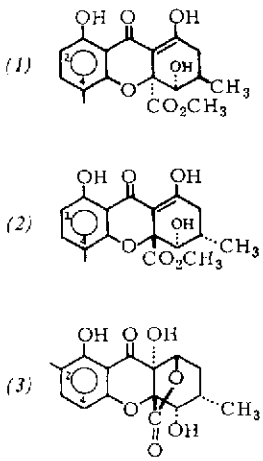
[GDCh-Ortsverband Mainz [(Germany),
June 4th, 1964] [VB 831/157 IE]

German version: Angew. Chem. *76*, 691 (1964)

## Ergot Pigments

*B. Franck*, Kiel (Germany) [1].

The ergot pigments secalonic acid A, secalonic acid B, and ergoflavin are symmetrical dimerization products of the monomers *(1)*, *(2)*, and *(3)*, respectively, with a 2,2'- or 4,4'-bond [2, 3]. Three further similar, pale yellow pigments, which we denote as secalonic acid C, ergochrysin A, and ergochrysin B, have been isolated as pure crystalline individuals. Their analyses, infrared, ultraviolet, and NMR spectra, and specific rotations show them to be unsymmetrical dimerization products of *(1)*, *(2)*, and *(3)*.



*(1)*



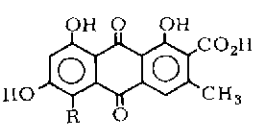
*(2)*



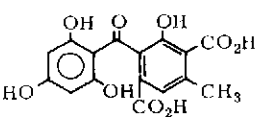
*(3)*

Secalonic acid A: 1-1
Secalonic acid B: 2-2
Ergoflavin: 3-3
Secalonic acid C: 1-2
Ergochrysin A: 1-3
Ergochrysin B: 2-3

The anthraquinonecarboxylic acids endocrocin *(4)* and clavorubin, isolated in collaboration with *T. Reschke* [4], form a second group of ergot pigments. The structure of 3-methyl-1,5,6,8-tetrahydroxyanthraquinone-2-carboxylic acid *(5)* has now been determined for clavorubin, and confirmed by synthesis.



*(4)*, R = H
*(5)*, R = OH



*(6)*

Endocrocin is considered to be the biogenetic precursor both of the 80 natural anthraquinone pigments known so far and of the 6 pale yellow ergot pigments [5]. In contrast to the anthraquinone derivatives, however, the ergot pigments are derived from endocrocin *via* an oxidative ring cleavage *(4)* → *(6)* → *(1)*, *(2)*, or *(3)*, analogous to the Baeyer-Villiger oxidation. The six dimeric ergot pigments are subsequently formed from *(1)*, *(2)*, and *(3)* by phenol oxidation.

[GDCh-Ortsverband Freiburg-Südbaden (Germany)
June 5th, 1964] [VB 836/159 IE]

German version: Angew. Chem. *76*, 864 (1964)

[1] In collaboration with *G. Baumann*, *U. Ohnsorge*, and *I. Zimmer*.

[2] *B. Franck*, *E. M. Gottschalk*, *U. Ohnsorge*, and *G. Baumann*, Angew. Chem. *76*, 438 (1964); Angew. Chem. internat. Edit. *3*, 441 (1964).

[3] *J. W. Apsimon*, *I. A. Corran*, *N. G. Creasey*, *K. Y. Sim*, and *W. B. Whalley*, Proc. chem. Soc. (London) *1963*, 209.

[4] *B. Franck* and *T. Reschke*, Chem. Ber. *93*, 347 (1960).

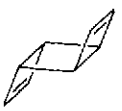
[5] *T. A. Geissman* in *P. Bernfeld*: Biogenesis of Natural Compounds. Pergamon Press, New York 1963, p. 589; *S. Gatenbeck*, Svensk. kem. Tidskr. *72*, 188 (1960).

# SELECTED ABSTRACTS

**Iron(III) siloxane compounds** are reported by *H. Schmidbaur*. Reaction of anhydrous $FeCl_3$ with three equivalents of sodium trimethylsiloxide in ether gives tristrimethylsiloxyiron(III), m.p. 179–181 °C, sublimation at 135–160 °C/1 mm, yield 40 %, in the form of yellow-green, waxy crystals which are readily soluble in inert organic solvents. Cryoscopic measurements show that the compound is dimeric in solution. Reaction either of this compound with 1 equivalent of alkali trimethylsiloxide or of $FeCl_3$ with 4 equivalents of alkali trimethylsiloxide gives good yields of alkali tetrakistrimethylsiloxyferrates(III). These are yellowish, finely crystalline, and, with the exception of the Li compound, hardly soluble in organic solvents. They decompose slowly above 200 °C, becoming brown in color. / Chem. Ber. *97*, 836 (1964) / – Ko. [Rd 948/268 IE]

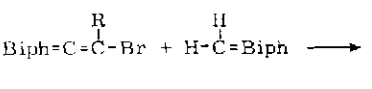
**Nuclear magnetic resonance spectra of new organolead compounds,** *viz.* trimethylcyclopentadienylplumbane *(1)*, dimethyldicyclopentadienylplumbane, and triethylcyclopentadienylplumbane, have been recorded by *H. P. Fritz* and *K. E. Schwarzhans*. The compounds were prepared from methyl- and ethylchloroplumbanes with cyclopentadienylsodium, under nitrogen in absolute benzene. The resultant yellow to green solutions are unstable, even under nitrogen. Only *(1)* could be obtained as a yellow crystalline solid, namely from absolute diethyl ether below 0 °C; it decomposed above +10 °C with deposition of a lead mirror. The NMR spectra of the methyl compounds show only one sharp signal, accompanied by two satellites, for the cyclopentadienyl and methyl protons. / J. organometallic Chemistry *1*, 297 (1964) / –Hz. [Rd 940/277 IE]

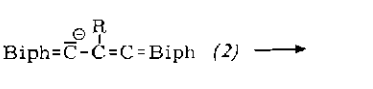
**Two stereoisomeric dimers of cyclobutadiene** have been synthesized by *C. D. Nenitzescu* et al. from *cis*-3,4-dichlorocyclobutene. Its reaction with sodium amalgam in ether at room temperature gives 46–51 % yields of *syn*-tricyclo[4,2,0,$0^{2,5}$]-octa-3,7-diene *(1)*, which is identical with a product previously obtained from 1,2,3,4-tetrabromocyclobutane (m.p. of the silver nitrate complex: 138–140 °C). If lithium amalgam

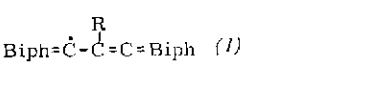
*(1)*   *(2)*

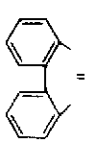
is used instead of sodium amalgam, a 55 % yield of the *anti*-compound *(2)* is obtained (m.p. of the silver nitrate complex: 148–152 °C). Both *(1)* and *(2)* can be largely purified by fractional distillation. Compound *(2)* can be obtained in pure form by conversion into its tetrabromide and re-elimination of the bromine. Ozonization of *(1)* gives *all-cis*-cyclobutane-1,2,3,4-tetracarboxylic acid, while *(2)* gives the *cis-trans-trans*-acid. With 2,5-diphenylbenzo[*c*]furan, *(1)* gives an adduct of m.p. 288–290 °C, and *(2)* gives an adduct of m.p. 252 °C. Both tricyclooctadienes are readily converted above 100 °C into cyclooctatetraene. The infrared spectra of *(1)* and *(2)* differ appreciably and point to deviations from the ideal molecular shape. / Chem. Ber. *97*, 382 (1964) / –W. [Rd 937/274 IE]

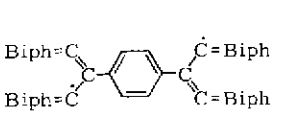
**Stable 2-aryl-1,3-bisdiphenyleneallyl radicals** *(2)* have been prepared by *R. Kuhn* and *F. A. Neugebauer*. Fluorene reacts as a nucleophile with diphenylenevinyl bromides in dimethylformamide in the presence of $KOCH_3$. HBr is eliminated with direct formation of the anions of acidic propene derivatives *(2)*, which are converted into the radicals with $K_3[Fe(CN)_6]$. The diradical *(3)* was obtained similarly.









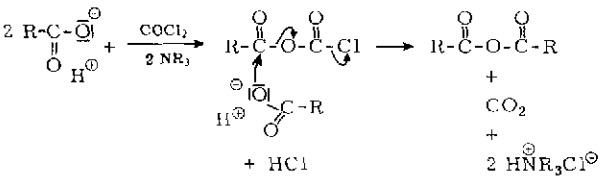


*(3)*

The radicals are stable toward hydroquinone, ascorbic acid, and $Na_2SO_3$. This stability is due to the strong electron-attraction of the fluorene, which is amplified by aryl substitution. Magnetic measurements have shown the radicals to be monomeric, even in the solid state, up to 77 °C. / Mh. Chem. *95*, 3 (1964) / –Rc. [Rd 941/278 IE]

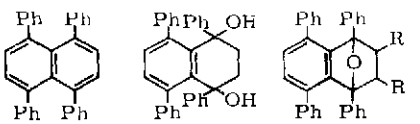
**Reactions of *N*-bromobistrifluoromethylamine** have been investigated by *H. J. Emeleus* and *B. W. Tattershall*. When irradiated with ultraviolet light, $(CF_3)_2NBr$ *(1)* dissociates into $(CF_3)_2N\cdot$ and Br· radicals; the former can combine to form perfluorotetramethylhydrazine, $(CF_3)_2N{-}N(CF_3)_2$. Ultraviolet irradiation of a mixture of $(CF_3)_2NBr$ and $NO_2$ gave *inter alia* *O*-nitroso-*N*,*N*-bistrifluoromethylhydroxylamine $(CF_3)_2N{-}O{-}NO$. Compound *(1)* reacts with NO even at room temperature to form bistrifluoromethylnitrosamine $(CF_3)_2N{-}NO$. Reaction of *(1)* with CO at room temperature gives bistrifluoromethylcarbamyl bromide $(CF_3)_2N{-}CO$ Br. *(1)* adds onto olefins (ethylene and tetrafluoroethylene) and acetylene to form $(CF_3)_2N{-}CR_2{-}CR_2{-}Br$ (R = H, F) and $(CF_3)_2N{-}CH{=}CHBr$, respectively. The action of AgCN on *(1)* did not yield the expected *N*-cyano derivative but $CF_3{-}N{=}CF_2$; *(1)* plus $Ag_2CO_3$ gave perfluoroazomethane $CF_3{-}N{=}N{-}CF_3$. / Z. anorg. allg.Chem. *327*, 147 (1964) / Ko. [Rd 944/264 IE]

**A simple new synthesis of anhydrides** has been discovered by *H. Rinderknecht* and *Viktoria Ma*. Reaction of carboxylic acids with 0.5 mole of phosgene at room temperature in the presence of trialkylamines gives anhydrides, generally in yields of over 80 %. If the reaction is carried out in benzene, the solution of the anhydride can be used directly, after filtering off the insoluble trialkylamine hydrochloride. The reaction, which is suitable for the preparation of labile anhydrides such as nicotinic and isonicotinic anhydrides, is assumed to proceed as follows:

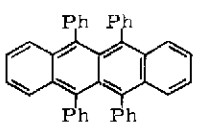


Helv. chim. Acta *47*, 162 (1964) / –Re. [Rd 942/279 IE]

**Bis-peri-tetraphenylnaphthalene** *(1)* has been synthesized for the first time by *C. Dufraisse* and *Y. Lepage* by four routes: alkali fusion of 1,4,6,7,10,11-hexaphenyl-5,12-naphthacenequinone; alkali fusion of 5,8,9,10-tetraphenyl-1,4-anthraquinone; from 5,8-diphenylnaphthoquinone → the 2,3-dihydro compound $\xrightarrow{C_6H_5Li}$ the tetraphenyl diol *(2)* $\xrightarrow{\text{dehydration}}$ *(1)*; and from tetraphenylisobenzofuran $\xrightarrow{\text{acrylic acid}}$ adduct *(3)* $\xrightarrow{\text{acetic acid/}H_2SO_4}$ *(1)* in 40 % yield. Compound *(1)*, m.p.



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



*(4)*

279–280 °C, is colorless and, in contrast to rubrene *(4)*, is not photo-oxidizable. C. R. hebd. Seances Acad. Sci. *258*, 1507 (1964) / –Ma. [Rd 950/270 IE]

**A simple synthesis of disecondary diarsines and alkali phenylarsides** has been described by *A. Tzschach* and *G. Pacholke*. Phenylarsine reacts with Li, Na, or K on heating in dioxane to give monoalkali phenylarsides *(1)* in 90 % yield. These

compounds are obtained as dioxane solvates and are extremely sensitive to air and hydrolysis. Their reaction

$$2M-AsH-C_6H_5 + X-(CH_2)_n-X \rightarrow \underset{(1)}{} \qquad n = 3,4$$

$$H_5C_6-AsH-(CH_2)_n-AsH-C_6H_5 \quad (2)$$

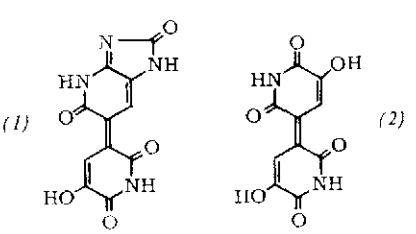
with α,ω-halogenoalkanes gives 60–70 % yields of the secondary arsines *(2)* as distillable oils which are converted by $CH_3I$ into crystalline arsonium salts

$[H_5C_6CH_3)_2As^{\oplus}-(CH_2)n-As^{\oplus}(CH_3)_2C_6H_5]\ 2\ I^{\ominus}$.

On reaction of *(1)*, M = K, with 1,2-dibromoethane, a bromine atom is first exchanged for a potassium atom. Since the resulting intermediates are very unstable, only ethylene, arsenobenzene, and phenylarsine could be detected. / Chem. Ber. *97*, 419 (1964) / –Re. [Rd 943/263 IE]

**The cause of the pyrophoric behavior of finely divided iron** has been investigated by *W. Feitknecht* and *A. Durtschi*. Their starting materials were samples of $Fe_3O_4$, $Fe_{3-x}O_4$, and ferric hydroxide; these were reduced in a current of hydrogen at 300–500 °C. α-$Fe_2O_3$ (formed from $Fe(OH)_3$ at 280 °C) and $Fe_{3-x}O_4$ are first reduced to $Fe_3O_4$, which is then directly reduced to Fe; FeO may also occur as an intermediate. Since the formation of iron nuclei is relatively slow, more coarsely crystalline oxides give roughly one Fe crystal from one $Fe_3O_4$ crystal at 300 °C, whereas with more finely crystalline material, even at 300 °C, each iron nucleus grows at the expense of several oxide crystals, so that particle growth results. Pyrophoric behavior is exhibited by all iron preparations with a specific surface area of more than about 3 $m^2/g$. Pyrophoric iron is inactivated by the action of a stream of gas consisting of nitrogen and a little oxygen; during inactivation, the temperature of the sample rises by about 10 °C and then remains constant for a time. The time of inactivation is proportional to the specific surface area. From the quantity of oxygen adsorbed, it is calculated that the thickness of the oxide layer is about 13 Å (about 6 layers of oxygen ions). The heat liberated during the formation of this primary oxide layer is estimated at 7.5 $cal/m^2$ of layer, *i.e.* sufficient to raise the temperature of 1 g of iron by about 70 °C. For a specific surface area of 3 $m^2/g$, this gives a temperature rise of about 210 °C. This agrees well with the experimental ignition temperature of iron with a specific surface area of 3 $m^2/g$ (240 °C). This ignition temperature is lower for more finely divided iron, and higher for coarser preparations. / Helv. chim. Acta *47*, 174 (1964) / –Ko. [Rd 946/266 IE]

**The structure and synthesis of the blue dye from** *Corynebacterium insidiosum* was reported by *R. Kuhn, W. Blau, H. Bauer, H.-J. Knackmuss, D. A. Kuhn*, and *M. P. Starr*. The extracellularly produced dye particles were isolated by fractional sedimentation and reduced with $Na_2S_2O_4$ to the leuco compound, oxidation of which with oxygen gave the dye of structure *(1)*. Hydrolysis of *(1)* with HCl gave rise to $CO_2$, $NH_3$, and fragment *(2)*. Compound *(2)* was also obtained by synthesis from 2-hydroxy-5-aminopyridine and citrazinic acid (2,6-dihydroxyisonicotinic acid). The dye *(1)* itself was also synthesized starting from either 2-hydroxy-5-aminopyridine



*(1)* *(2)*

(reactions with $H_2SO_4$, urea, and $KBrO_3$) or citrazinic acid (reactions with $N_2O_3$, Sn/HCl, KNCO, and $O_2$). Both synthetic routes seem biosynthetically feasible. / Naturwissenschaften *51*, 194 (1964) / –Ma. [Rd 7/284 IE]

**Large quantities of xenon tetrafluoride** were prepared by *E. Schumacher* and *M. Schaefer* using a circulatory apparatus. A circulating pump blows a $Xe/F_2$ mixtures (molar ratio 1:3) at atmospheric pressure through a Monel-metal tube furnace filled with pieces of nickel plate heated at 560 °C. $XeF_4$ crystals separate out in a cold trap at 0 °C. Unreacted gas is recirculated to the tube furnace, if necessary, after addition of fresh feed gas. The apparatus delivers 11 g of $XeF_4$ per hour: the yield is over 97 % based on the xenon fed in. / Helv. chim. Acta *47*, 150 (1964) / –Ko. [Rd 945/265 IE]

**The synthesis of phosphorus nitride dichlorides** from $PCl_5$ and $NH_4Cl$ has been further investigated by *Margot Becke-Goehring* and *W. Lehr*. The $PCl_4^{\oplus}$ cation formed by dissociation of $PCl_5$ reacts with $NH_3$ (from $NH_4Cl$) to give $Cl_3P=N-H$, which rapidly undergoes further reaction with another $PCl_4^{\oplus}$ ion to yield the cation $[Cl_3P-N=PCl_3]^{\oplus}$ *(1)*, which can be isolated as its sparingly soluble hexachlorophosphate. In a similar manner, *(1)* gives rise to the higher homologue $[Cl_3P=N-PCl_2=N-PCl_3]^{\oplus}$ *(2)*. Reaction of *(2)* with $Cl_3P=NH$ leads successively to longer-chain cations $[Cl_3P=N-(PCl_2-N)n-PCl_3]^{\oplus}$ *(3)*, whose salts are considerably more soluble than those of *(1)* or *(2)*. On reaction with $NH_3$, *(2)* and *(3)* form chains with terminal NH groups *(4)*:

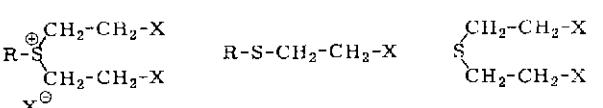
$$[Cl_3P=N-(PCl_2=N)_n-PCl_3]^{\oplus} + NH_3 \rightarrow$$

*(2)*: n = 1 *(3)*: n = 2, 3, ...

$$Cl_3P=N-(PCl_2=N)_n-PCl_2=NH + HCl + H^{\oplus} \quad (4)$$

Compounds *(4)* are stable when n is large, and are found in phosphorus nitride dichloride oils. When n = 1 or 2, *(4)* can eliminate HCl and undergo ring closure to form stable trimeric or tetrameric phosphorus nitride dichlorides. To prepare longer-chain phosphorus nitride dichloride oils selectively, the reaction is carried out in the molten state in a sealed tube. For preferential preparation of the trimer, the reaction is carried out in tetrachloroethane at the maximum possible dilution; the primary product is the cation *(2)*, and dilution favors ring closure of its secondary product *(4)*, n = 1. For preparation of the tetramer, the chloride of *(1)* is made first and then treated with $NH_4Cl$, the formation of trimer being thus completely suppressed. / Z. anorg. allg. Chem. *327*, 128 (1964) / Ko. [Rd 947/267 IE]

**Sulfonium salts exhibit high reactivity toward mercaptide ions** (at physiological pH values) as *A. Lüttringhaus* and *H. Machatzke* found in kinetic investigations employing polarographic methods. The alkylating properties of these sulfonium compounds can explain their cytostatic activity. The substances most effective against both Yoshida sarcoma in rats and Ehrlich carcinoma in mice have been found to be those of structure *(1)* which, on transalkylation of one ligand onto the SH compound, yields products *(2)*, and not the highly toxic sulfur mustard gas *(3)*.



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

X= Halogen

Since the cytostatic effect of the salts increases with their ability to block the SH group, it can be concluded that at least one of the principles of action of sulfonium salt cytostatics consists in blocking biologically important SH groups. The residue R affects the transport characteristics, the affinity for cell components, and the distribution behavior of the cytostatic compound. / Liebigs Ann. Chem. *671*, 165 (1964) / Sch. [Rd 951/271 IE]

**The dipole moments of isomeric 1,2,3,4,5,6-hexachlorocyclohexanes** were investigated by *C. Quivoron* and *J. Neel*. Seven of the 13 theoretically possible conformations with a chair carbon-skeleton are known, being those confirmations in which the partial structure of "2 axial chlorine atoms on the next-but-one carbon atoms" occurs only once or not at all. The dipole moments of these compounds cannot be calculated by simple vector addition of the partial moments, since mutual induction can cause the effective moment of the C Cl bond to vary by a factor of 2. By making allowances for the polarizability of the C–Cl bond and for a finite dipole moment of the C H bonds, the dipole moments of the 5 more readily available isomers (α to ε) can be calculated. The results agree well with the experimental values and help to assign conformations to the isomers. The dipole moments of the ϰ- and ϑ-isomers were predicted on the same basis. / J. Chim. physique *61*, 554 (1964) / –Hz. [Rd 8/285 IE]

**An instrument for estimating oxygen by gas-phase polarography** has been designed by *G. Halpert*, *A. C. Madsen*, and *R. T. Foley*. In it an oxygen concentration gradient is built up by diffusion through a semipermeable teflon membrane which is held under tension touching a microelectrode made of gold or platinum. The microelectrode is immersed together with a silver/silver chloride reference electrode in potassium chloride solution buffered at pH 6. Oxygen analyses can be carried out with an accuracy of 1 % between –20 and +80 °C at pressures down to 10 mm over a concentration range of 0.001 to 100 % $O_2$. / Rev. sci. Instruments *35*, 950 (1964) / –Hz. [Rd 108/295 IE]

# BOOK REVIEWS

**Gmelins Handbuch der anorganischen Chemie** (Gmelin's Handbook of Inorganic Chemistry), 8th completely revised edition. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in the Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Initiated by *R. J. Meyer*, continued by *E. H. Erich Pietsch*. Verlag Chemie GmbH., Weinheim/Bergstrasse.

**System No. 52: Chromium:** Part A, Vol. 1 (Historical, Occurrence, Technology, Element [up to physical Properties]). 1962. IV, XX, 418 pp. 38 figs., cloth, DM 316.– (about $ 80. ). Revised by *M. Atterer*, *Anna Bohne-Neuber*, *G. Czack*, *R. Glauner*, *A. Hirsch*, *Erna Hoffmann*, *G. Huschke*, *Eleonore Kirchberg*, *Isa Kubach*, *H. Lehl*, *Gertrud Pietsch-Wilcke*, *N. Polutoff*, *F. Rex*, *K. Rumpf*, and *F. Seuferling*.

**System No. 52: Chromium:** Part A, Vol. 2 (Electrochemical Behavior, Chemical Behavior, Alloys), 1963. IV, XVIII, 312 pp., 111 figs., cloth, DM 241.– (about $ 61.–). Revised by *H. Balters*, *Marie-Luise Klaar*, *G. Krause*, *Margarete Lehl-Thalinger*, *K. Swars*, and *Hildegard Wendt*.

**System No. 52: Chromium:** Part B (Compounds [Excluding Complexes with Neutral Ligands]), 1962. IV, LXXIX, 942 pp., 74 figs., cloth, DM 715.– (about $ 180.–). Revised by *M. Atterer*, *H. Balters*, *H. Feicht*, *R. Glauner*, *A. Hirsch*, *H. K. Kugler*, *A. Kunze*, *Gertrud Pietsch-Wilcke*, *P. Stiess*, *K. Swars*, *Ursula Trobisch-Raussendorf*, *E. Ühlein*, and *Ursula Venzke-Sante*.

The volume "Chromium" of the foregoing 7th edition of "Gmelin" was published in 1912, and is thus more than half a century (!) out of date. So much the greater, therefore, is the pleasure with which chemists now receive the chromium volume of the 8th edition, of which Parts A (Elemental Chromium) and B (Compounds of Chromium) are now available (total price DM 1272. or about $ 320. ). An impressive indication of the advances made since time of the earlier edition is the fact that the principal chromium volume at that time contained 390 pp., and was compiled by a single writer, whereas even excluding Part C, which is now in preparation and which deals comprehensively with the chemistry of chromium complexes, the new System No. "Chromium" already comprises 1672 pp. and 223 figs., and its preparation has involved the cooperation of almost three dozen writers.

**Part A.** Part A (DM 557.– or about $ 140. –), which is published in two volumes with a total of 730 pp. and 149 figs., begins with sections (284 pp.) on the history (5 pp.), occurrence (186 pp.), technology (83 pp.), and toxicology (10 pp.) of chromium and its compounds. This is followed by a description of elemental chromium (446 pp.), divided as usual into chapters on its formation and preparation (9 pp.), physical properties (125 pp.), electrochemical behavior (204 pp.), chemical behavior (87 pp.), and alloys (21 pp.).

Chromium was discovered in Siberian crocoite ($PbCrO_4$) by the French chemist *Louis Nicolas Vauquelin* in 1797, and its name (from χρῶμα = color) was chosen on account of the magnificent colors of some of its compounds. Since the element is still relatively "young", its history requires only a few pages. This section is arranged according to the chromium-bearing minerals of the greatest importance to the history of the discovery of the metal, namely crocoite $PbCrO_4$, emerald $Be_3Al_2Si_6O_{18}$ (chromium oxide as coloring agent, discovery of beryllium by *Vauquelin*), ruby $Al_2O_3$ (chromium oxide as the coloring component), and chromite $FeCr_2O_4$.

The section on the occurrence of chromium begins with a discourse on its extraterrestrial occurrence, which has been the subject of many investigations, since the metal is easily detectable by its blue and green spectral lines. The sections dealing with the terrestrial occurrence are arranged under geochemistry, topography, and minerals. In the geochemical section, special attention should be called to the comprehensive tabular summaries of the chromium content of minerals, its diadochic relationships to other elements, and the formation and transformation of chromium deposits. The topographical survey begins with an economic statistics chart showing that the global production of chromium ore has now grown to almost 5 million tons per year, *i.e.* it has increased by a factor of about thirty since the beginning of the First World War. The topographical survey then goes on to consider workable deposits, particularly those in the six principal producing countries (the Soviet Union, The Union of South Africa, the Philippines, Southern Rhodesia, Turkey, and Albania), and ends with a comprehensive list of chromium minerals. This chapter is of particular importance since the economy of modern states, in peace or at war, is no longer conceivable without a suitable supply of chromium ore.

The importance of chromium in present-day economy becomes even more evident in the chapter on the technology of chromium and its inorganic compounds. This chapter deals in detail with the processing of the ores, the degradation of the principal technical chromium ore, *viz.* chrome iron ore $FeCr_2O_4$, the production of metallic chromium and its principal inorganic compounds [chromium(III) and chromium(VI) oxides, chromium(III) hydroxide, nitrate, chloride, sulfate, potassium chrome alum, and the alkali metal chromates and dichromates], and the preparation of the most important inorganic chrome pigments (chrome yellow, chrome red, chrome green, and many mixed pigments containing chromium). It presents an impressive picture of the technological processing and importance of chromium ores, about 50 % of which are used in metallurgy (chromium alloys), about 35 % in ceramics (refractory bricks), and about 15 % in the chemical industry (chromium compounds).

The section on toxicology deals with physiological damage caused by chromium compounds (symptoms, toxic doses, prophylaxis, therapy), on the basis of comprehensive technical literature.

Since the industrial production of chromium is dealt with earlier in the technology section, the section on the prepara-

tion of metallic chromium is confined to laboratory methods of obtaining chromium by reduction of chromium compounds, the production of special forms (*e.g.* powder, sponge, crystals, suspensions, sols), and the concentration and separation of chromium isotopes.

Under physical properties, treatment of the atom and the atomic nucleus is followed by a discussion of the crystallographic properties of the metal, which exists in several modifications. In connection with the production of a form of chromium which is ductile at normal temperature, interesting data are given on its structure and deformation, and on the effect of extraneous components in the lattice; these are discussed in detail in a special section. After a treatment of thermal and thermochemical data, the optical behavior of chromium is discussed at length, *e.g.* the reflectance of chromium mirrors, its optical line spectrum (arc spectrum, first to forteenth spark spectrum), and its X-ray spectrum.

In the section on its magnetic and electrical properties, particular attention is aroused *inter alia* by the discussions on the hitherto unexplained anomaly in its electrical resistance between 35 and 40 °C; this anomaly is also found in its elastic properties.

The chapter on the electrochemistry of Cr includes a report on the standard potentials of the various oxidation stages of chromium, the potentials of the metal with respect to 65 different solutions and melts, 54 electrochemical cells described in the literature, the behavior of chromium at the dropping mercury electrode, overvoltages on chromium, the behavior of chromium as an anode and cathode, and the electrolytic deposition of chromium. Special mention should be made of the discussions on the last two problems. As an element with a pronounced tendency towards both an "active" and a "passive" state, chromium has been the subject of numerous investigations on reductive activation and oxidative passivation and the causes of this phenomenon. It is on account of this phenomenon that active chromium can be regarded as a base Metal with a standard potential of −0.71 volt ($Cr/Cr^{III}$), lying between zinc and iron in the electrochemical series, whereas passive chromium is a noble metal with a standard potential of +1.33 volt ($Cr^{III}/Cr^{IV}$), lying between mercury and gold. As is shown by the discussions on the theory of passivity, the most obvious explanation of this phenomenon is still the formation and destruction of a film of chromium oxide on the surface of the metal. The detailed report on the electrolytic deposition of chromium (about three-quarters of the chapter on electrochemistry) is justified by the fact that chromium plating of metals, which was introduced some 40 years ago, is now one of the most important fields in electroplating and once revolutionized the plating industry as a result of the introduction of an entirely new type of bath (deposition from chromic acid solutions). The section is introduced by a comprehensive list of references arranged in chronological order, and then gives a detailed account of the nature and composition of chromium-plating baths, the influence of reaction conditions on the yield and quality of the chromium deposit, the action of bath additives, of bright, matt, black, and hard chromium-plating, of the anodes and cathodes used, the pre-treatment and after-treatment of the objects to be plated, special plating processes, and the properties and testing of the chromium deposit, the theoretical explanation of the phenomena always being included.

The special properties of chromium become evident in the chapter on its chemical behavior, as in that on its electrochemistry: *e.g.* its passivation by oxidizing agents and activation by reducing agents or agents which dissolve the surface layer, and the resulting difference in chemical behavior in the passive and active states; this difference is so great, in fact, that it was once assumed – erroneously – that chromium was allotropic. The section on the general reactions of chromium ions ($Cr^{2+}$, $Cr^{3+}$, $CrO_4^{2-}$, $Cr_2O_7^{2-}$) is particularly valuable. This section also deals with the redox transitions between these ions and with the analytically important reactions of chromium, so that – particularly in view of the volume on this subject in *Fresenius–Jander's* Handbuch der analytischen Chemie – the short section on the detection and determination of chromium can be confined to a comprehensive bibliography and a survey of the most sensitive reactions of chromium.

The last chapter of Part A, which deals with alloys of chromium, gives an account of its alloys with metals of system numbers lower than that of chromium, *i.e.* the metals Sb, Bi, Be, Ca, Zn, Cd, Hg, Ti, Zr, Hf, Th, Ge, Sn, Pb, V, Nb, and Ta, with special emphasis on the more thoroughly investigated systems with Sb, Be, Zn, Hg, Zr, and Ta. The alloys with Mg, Al, and rare earth metals are grouped with these metals, a departure from the Gmelin "last-place" principle. Alloys of chromium with metals of system numbers lower than that of antimony are dealt with under compounds of chromium in Part B of the "Chromium" volume, which is reviewed on below.

**Part B.** This part embraces all the "normal" compounds of chromium and all of its complexes with acidic ligands, including the related hydrates and aquo-complexes (*e.g.* the compounds $CrCl_3$, $[Cr(H_2O)_6]Cl_3$, $[CrCl_2(H_2O)_4]Cl{\cdot}2H_2O$, $K_3[CrCl_6]$); complexes with neutral ligands other than $H_2O$ (*e.g.* the ammoniates and ammine complexes) will form the subject of Part C, which has not yet been published. Part B includes information on compounds with non-metals (454 pp.) as well as on compounds with metals of system numbers lower than that of chromium (488 pp.). Thus the discussions cover the compounds of chromium with the non-metals: H (7 pp.), O (149 pp.), N (18 pp.), F, Cl, Br, I (120 pp.), S, Se, Te, Po (49 pp.), B (8 pp.), C, Si (85 pp.), P, As, Sb, Bi (18 pp.), and the chromates, acidochromates, and double salts of chromium with the metals Li, Na, K, Rb, and Cs – including the ammonium salts – (319 pp.), Be, Mg, Ca, Sr, and Ba (77 pp.), Zn, Cd, and Hg (40 pp.), Al, Ga, In, and Tl (13 pp.), Ti, Zr, Hf, and Th (5 pp.), Ge, Sn, and Pb (30 pp.), and V, Nb, and Ta (4 pp.). Compounds of chromium with more than one of the above elements are dealt with, as usual, under the element of highest system number. The compounds of chromium with the rare earths are excluded; in contrast to the "last-place" principle, these are discussed under the rare-earth metals.

The material dealt with is so extensive that the index alone fills no fewer than 79 pages. Consequently, only a few examples have been selected in the following paragraphs.

The account of the chromium/hydrogen system is particularly important with regard to the electrodeposition of chromium, since the mechanical properties of chromium plating are considerably influenced by the hydrogen content of the plating bath.

The chapter on oxygen compounds of chromium deals with the oxides CrO, $Cr_2O_3$, $CrO_2$, $CrO_3$, $CrO_4$, and $CrO_5$, the related aquo-oxides and aqueous solutions, and many intermediate oxides such as "$Cr_3O_4$" ($CrO_{1.3}$), "$Cr_5O_9$" ($CrO_{1.8}$), "$Cr_8O_{15}$" ($CrO_{1.9}$), "$Cr_4O_9$" ($CrO_{2.3}$), "$Cr_5O_{12}$" ($CrO_{2.4}$), "$Cr_2O_5$" ($CrO_{2.5}$), "$Cr_5O_{13}$" ($CrO_{2.6}$), "$Cr_3O_8$" ($CrO_{2.7}$), all of which require more detailed investigation. The majority of the text (over 80 %) is naturally concerned with the preparation and properties of the oxides $Cr_2O_3$ and $CrO_3$ and their systems with water, *i.e.* $Cr_2O_3{\cdot}nH_2O$ [*e.g.* $Cr(OH)_3$ and $CrO(OH)$] and $CrO_3{\cdot}nH_2O$ [*e.g.* $H_2CrO_4$, $H_2Cr_2O_7$, and polychromic acids $H_2Cr_nO_{3n+1}$].

Compounds of chromium with nitrogen include its nitrides, azides, amides, and nitrates; the nitrates are used as tanning agents.

Chromium halides and their aquo-complexes and hydrates are discussed in great detail since the literature on these compounds is very extensive. Besides compounds of trivalent chromium, those of monovalent (*e.g.* CrF, CrCl, CrBr, CrI), divalent (*e.g.* $CrF_2$, $CrCl_2$, $CrBr_2$), tetravalent (*e.g.* $CrF_4$, $CrCl_4$), pentavalent (*e.g.* $CrF_5$), and hexavalent chromium (*e.g.* $CrO_2F_2$, $CrO_2Cl_2$, $CrO_2Br_2$) are also discussed. Most of the chapter (over 75 % of the text) is occupied by the chlorine compounds. Particular mention should be made

of the sections on $CrCl_3$ hydrates and aqueous solutions of $CrCl_3$, which give occasion to deal comprehensively with the isomerism of the $CrCl_3$ hexahydrates ($[Cr(H_2O)_6]Cl_3$, $[CrCl(H_2O)_5]Cl_2 \cdot H_2O$, $[CrCl_2(H_2O)_4]Cl \cdot 2H_2O$) and the other hydrates of $CrCl_3$ (decahydrate $[CrCl_2(H_2O)_4]Cl \cdot 6H_2O$, tetrahydrate $[CrCl_2(H_2O)_4]Cl$, and trihydrate $[CrCl_3(H_2O)_3]$).

The section on the sulfur compounds of Cr deals with the sulfides and sulfates, such as CrS, $Cr_2S_3$, $CrSO_4$, $Cr_2(SO_4)_3$, and $H_2[CrO_3(SO_4)]$ ("chromosulfuric acid"). Particular attention is paid to chromium(III) sulfate $Cr_2(SO_4)_3$ (hydrates, acid sulfates, basic sulfates; problems of constitution), owing to its importance in chrome tanning.

The compounds of chromium with boron include chromium borides ($Cr_4B$, $Cr_2B$, $Cr_5B_3$, $Cr_3B_2$, CrB, $Cr_3B_4$, $CrB_2$, and $Cr_2B_5$) and chromium borates. Of particular interest here are the data on sintered hard metals based on CrB, since these alloys have recently become technically important.

The section on carbon compounds of Cr includes accounts of the chromium carbides $Cr_{23}C_6$ ("$Cr_4C$"), $Cr_7C_3$ ("$Cr_{15}C_2$"), and $Cr_3C_2$, chromium hexacarbonyl $Cr(CO)_6$, chromium carbonates, cyanides, and thiocyanates, and on chromium salts of carboxylic acids (formates, acetates, propionates, oxalates, malonates, tartrates, and citrates). Special mention should be made of the review on the preparation, properties, and derivatives of chromium hexacarbonyl, and on the chromium(III) acetates, which are important tanning agents.

Among the phosphorus compounds of Cr, the phosphides $Cr_3P$, $Cr_2P$, CrP, $Cr_2P_2$, and $CrP_2$, the chromium(III) phosphates $CrPO_4 \cdot nH_2O$, and adducts of chromium and phosphorus halides, such as $CrCl_3 \cdot PCl_5 = PCl_4[CrCl_4]$ are discussed.

More than half of Part B is now devoted in the following sections to the chromates, acidochromates, and chromium double salts of metals. This indicates the importance of these compounds in pure science and in industry, and shows the wide range of combinations that can be formed by chromium, for it occurs in various valence states, and forms chromates(III) and chromates(VI) with all metals, in some cases even chromates(V). The discussion here covers not only true chromates (and polychromates), but also acidochromates such as halogeno-, sulfato-, or oxalatochromates, and metal double salts of chromium, such as chrome alums. The major part (about 65 %) of the chapter is concerned with the Cr compounds of the alkali metals, particularly the compounds $Na_2CrO_4$, $K_2CrO_4$, $(NH_4)_2CrO_4$, $Na_2Cr_2O_7$, $K_2Cr_2O_7$, $(NH_4)_2Cr_2O_7$, and $KCr(SO_4)_2 \cdot 12H_2O$. Of these, sodium dichromate $Na_2Cr_2O_7$, which is produced industrially by alkali fusion of chrome iron ore, is important as the basis of all other compounds of chromium(VI), and chrome alum $KCr(SO_4)_2 \cdot 12H_2O$ is an important tanning agent. Mention should also be made of lead, zinc, and barium chromates, which are important chrome pigments. The latter have had keen competition in recent years from coal-tar dyes, which are non-toxic and extremely intensely colored, but chromates are involved indirectly as oxidizing agents in the manufacture of these coal-tar dyes.

To summarize, these three chromium volumes represent an impressive accomplishment by the Gmelin staff. The reference lists are complete up to the end of 1949, a closing date for literature perusal which was fixed in 1950, with the result that the "Gmelin" is no less than 15 years behind the present-day literature situation. An attempt has been made to alleviate this apparent deficiency by reference to more recent literature in particularly important cases; but this is only a makeshift remedy, which cannot replace exhaustive collation of the literature up to the time of publication of the volume. It must therefore be urgently requested that the decision taken in 1961 to introduce a "progressive closing date for literature screening" (complete reportage up to the year of publication of the volume in question) should be realized as soon as possible.

*E. Wiberg* [NB 215/92 IE]

Translated by Express Translation Service, London

**Handbuch der Papierchromatographie** (Handbook of Paper Chromatography). Edited by *I. M. Hais* and *K. Macek*. Gustav Fischer Verlag, Jena 1963. Vol. I: Basis and Techniques. Translated from Czechoslovakian into German by *J. Liebster*. 2nd Edit., xv + 1069 pp., 235 illustrs., 178 tables, cloth, together DM 72.40 (about $ 18.50). Vol. III: Bibliography 1957–1960 and Applications. 1st Edit., xix + 700 pp., cloth, DM 40.90 (about $ 10.25).

Although since the appearance of the first edition the importance of paper chromatography has declined in favor of thin-layer chromatography, this consistent and painstaking revision of the standard handbook proves to be an important production. The additional procedures developed during the past five years in numerous laboratories, and not least in the author's own, have been harmoniously worked into the original highly successful work. The 225 pages of the general part in the first edition have been expanded to 263 – even though paper electrophoresis has been entirely neglected – and the specialized part has increased from about 500 pages to 640. The type used is unchanged, and the extreme care taken in production is noticeable throughout. Anyone using paper (or thin-layer) chromatography can save himself much time and vexation by having Hais-Macek in his laboratory. Anyone wanting a convenient introduction to further study of the literature used in the handbook will find this in Volume III, with its ca. 8300 pertinent literature references, a 100-page author index, and a 150-page subject index for 1957–1960. Furthermore, the price for this excellently produced volume is by no means excessive.

*Th. Wieland* [NB 186/84 IE]

**Die Nobelpreisträger der Chemie. Ein Kapitel Chemie-Geschichte** (Nobel Prize Winners in Chemistry. A Chapter in Chemical History), by *W. v. Bonin*. Heinz Moos Verlag, München 1963. 1st edit., 89pp., 69 portraits, half-linen, DM 14.80 (about $ 3.75).

As the highest scientific award, the Nobel Prize marks the great milestones of scientific discovery. *Wulf von Bonin* has skilfully and vividly reviewed these milestones in chemistry in the 45-page comprehensive text of the present book. It is pleasing to note that any national appraisement of the Nobel Prize was carefully avoided.

The text is followed by photographs of all the Nobel laureates in chemistry to date beginning with *Jacobus Henricus van't Hoff* and ending with *Guilio Natta* and *Karl Ziegler*.

This series of photographs gives rise to thoughtful reflection, although more care should have been devoted to the retouching (was it really necessary?). Altogether a volume to be recommended to many chemists.

*H. Grünewald* [NB 184/80 IE]

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# Recoil Reactions of Tritium with Organic Compounds

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*After "cooling", the hot tritium atoms formed above thermal energies by nuclear reactions abstract or replace hydrogen atoms, and replace substituents X (e.g. alkyl, $NH_2$, $NO_2$, OH, COOH, F, Cl, Br, or I) in organic compounds. Isotope effects have been observed for protonated vs. deuterated compounds in several hot reactions. Models and mechanisms are discussed for the abstraction and replacement, for specific reactions on certain carbon atoms, and for the isotope effects. These are based on steric, bond-energy, and kinetic considerations.*

## I. Introduction

In most chemical reactions, the necessary activation energy is obtained from an equilibrium distribution among all reactants; on the other hand, nuclear recoil processes produce highly energetic atoms within an otherwise unchanged system. In almost all nuclear transformations, recoil atoms, which are frequently radioactive, are generated with kinetic energies far above the energies of chemical bonds [1]. These atoms are not originally in thermal equilibrium with the surrounding medium, but must first be "cooled" into the range of chemical reaction energies before reaching a stable form *via* chemical reactions.

In 1934, *Szilard* and *Chalmers* first reported the chemical consequences of a nuclear reaction [1a]. They were able to show that neutron irradiation of liquid ethyl iodide led to water-extractable radioactive elemental iodine, *i.e.* a fraction of the $^{128}I$ formed by the nuclear reaction $^{127}I(n,\gamma)$ [1b] must have ruptured the original carbon-iodine bonds.

*Szilard* and *Chalmers* concluded that the recoil energy released in the nuclear reaction with iodine is sufficient to break its chemical bond to the carbon atom. Calculation of the energy released by this nuclear transformation shows that the recoiling atom can indeed escape its chemical binding and may be shot for many Ångstroms into the surrounding medium [2]. Many publications on the chemical consequences of nuclear reactions have appeared since these experiments with ethyl iodide. For such experiments, nuclear transformations on $^{3}He$, $^{6}Li$, $^{12}C$, $^{14}N$, $^{37}Cl$, $^{81}Br$, $^{127}I$, and many other isotopes have been utilized, and the reactions have been carried out with a large number of organic and inorganic compounds [3].

For the investigation of recoil reactions, those elements (isotopes) are especially useful which will give radioactive daughter isotopes in sufficient concentration and with convenient half-lives *via* nuclear transformations.

## II. Significance of Tritium Recoil Chemistry

The recoil chemistry of tritium is of special interest for several reasons. Tritium is the only radioactive isotope with the chemical properties of hydrogen. (Here we ignore isotope effects which are of minor importance in this connection.) Moreover, hydrogen is a component of most compounds and much is known about its thermal reactions. Table 1 shows that tritium can be

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[1] In nuclear isomeric transitions, it is not the resulting recoil energy which is decisive but the high electronic excitation [3].

[1a] *L. S. Szilard* and *T. Chalmers*, Nature (London) *134*, 462 (1934).

[1b] $^{128}I$ is a $\beta$- and $\gamma$-emitter with a half-life of 25 min.

[2] *A. C. Wahl* and *N. A. Bonner*: Radioactivity Applied to Chemistry. Wiley, New York 1951.

[3] Chemical Effects of Nuclear Transformations. International Atomic Energy Authority, Vienna 1961, Vols. 1 and 2.

easily produced in good yields by neutron irradiation of $^6Li$ and $^3He$ for investigations in the solid, liquid, and gaseous phases. Modern methods of measurement permit the determination of the weak $\beta$-rays ($E_{max} \approx 0.018$ MeV) of tritium in practically every chemical form. Combination of gas-chromatographic separation with a flow proportional counter, for instance, allows precise quick measurements for both gas-phase and condensed-phase experiments [4–6]. It should be noted that "carrier-free" and therefore unweighably small amounts of radioactively labelled compounds can also be identified [7] since they have the same retention or elution times in separation columns as the analogous hydrogen compounds [*]. Investigations in solid compounds often require more complicated analyses [10].

Gas-phase recoil experiments with tritium are usually carried out in 10–30 ml ampoules made of quartz or Pyrex 1720 glass, containing a mixture of the substance to be investigated with $^3He$ at a partial pressure of 10–30 mm. A simple calculation shows that irradiation of 0.5 ml of $^3He$ (at STP) for 1 h in a neutron flux of $10^{11}$ n/cm²/sec (thermal neutrons) yields about $2.5 \times 10^{13}$ tritium atoms; this corresponds to ca. $2.5 \times 10^6$ decays per minute. It should be pointed out that double labelling is extremely improbable since about $10^7$ times fewer tritium atoms are produced than the number of parent molecules present during irradiation.

If lithium is to be used as the source of tritium, then about 10 % by weight of a lithium salt is mixed with the target substance. The natural abundance of $^6Li$ (about 7.5 %) permits the use of any lithium compound which is chemically inert in the investigated system, and which does not produce unwanted radioactivity from nuclear reactions with another element.

Table 1. The most important data on the nuclear reactions which are used as tritium sources for recoil experiments.

| Target isotope | $^6Li$ | $^3He$ |
|---|---|---|
| Natural abundance of the isotope [%] | ca. 7.5 | $1.3 \times 10^{-4}$ [*] |
| Nuclear reaction | $^6Li(n,\alpha)T$ | $^3He(n,p)T$ |
| Thermal neutron cross-section [barns] | 945 | 5400 |
| Tritium recoil energy [MeV] | 2.73 | 0.192 |
| Recoil energy of the emitted particle ($\alpha$ or p) [MeV] | 2.06 | 0.57 |

[*] Isotopically "pure" $^3He$ can be purchased (§ 150 per liter at STP); however, it must be purified from tritiated impurities for tritium-recoil experiments [53].

[4a] *R. L. Wolfgang* and *F. S. Rowland*, Analytic. Chem. *30*, 903 (1958).

[4b] *J. K. Lee* et al., Analytic. Chem. *34*, 741 (1962).

[5] *W. Herr, F. Schmidt-Bleek*, and *G. Stöcklin*, Z. analyt. Chem. *170*, 310 (1959).

[6] *G. Stöcklin* et al., Z. analyt. Chem. *194*, 406 (1963).

[7] *F. Cacace*, Nucleonics *19*, 5, 45 (1961).

[*] *K. Yang* [8] recently reported that gas-chromatographic separation of deuterated and tritiated methanes of masses 16, 17, 18, 19, 20, and 24 is possible with activated charcoal columns. Such separations have also been observed in our group: *e.g.* cyclobutane (mass 56) can be separated from tritiated cyclobutane (mass 58) on a 15-meter safrole-on-chromosorb column [9]. These effects, however, are extremely small for most labelled compounds under normal conditions.

[8] *K. Yang* and *P. Gant*, Continental Oil Company, personal communication.

[9] *J. W. Root, E. K. C. Lee*, and *F. S. Rowland*, Science (Washington) *143*, 676 (1964), and unpublished results.

[10] *F. S. Rowland* et al., [3] Vol. 2, p. 67.

## III. Reactions of Hot and Thermal Tritium

Each recoil tritium atom is created with so much energy that it cannot undergo chemical reactions or compound formation immediately after its formation (see Table 1). Only after it has lost sufficient energy – first by ionic interactions [11], then by elastic and inelastic collisions with the medium – can the atom acquire a stable chemical form by chemical reaction.

In 1958, *Wolfgang* and co-workers [12,13] argued very convincingly that the recoil tritium atom is already electrically neutral at kinetic energies below 1000 eV. It may be assumed further that the reacting tritium atom is in the electronic ground state. None of the experimental results to date disagree with these hypotheses.

Why, then, have reactions other than those already well known for thermal hydrogen and deuterium atoms been postulated for recoil tritium atoms? Why is the term "hot" reaction used? Recoil experiments with tritium in methane [10,14] and cyclopropane [15] have shown that tritium atoms produced by nuclear transformations can replace hydrogen atoms in these compounds, or abstract hydrogen from them with formation of HT. These reactions are not observed for thermal deuterium atoms at these temperatures, and are typical of the "hot" reaction discussed below. Definitions for such hot reactions have been advanced by various authors [13,16]; to us the following appears to be clearest: *Hot reactions are brought about by energetic atoms which have never been in thermal equilibrium with their surroundings.*

The energy necessary for chemical reaction is exclusively (or almost exclusively) furnished by these atoms.

The following criteria are used to distinguish between hot reactions of a recoil atom and its thermal reactions:

1. Since the energy of reaction is furnished exclusively by the hot atom, hot reactions should to a first approximation be independent of temperature.

2. The yield of the products of hot reactions should not be influenced by the addition of small amounts of radical scavengers. Radical scavengers such as $O_2$, $I_2$, or NO eliminate thermalized recoil atoms and their reaction products (*e.g.* radicals produced by addition of tritium onto an olefin or by abstraction of hydrogen by thermal atoms).

3. The yield of hot reaction products should be influenced by moderators (inert gases); these should alter the energy distribution of the recoil atoms without taking part in the reactions.

If we define the probability of reaction (per collision) of a recoil atom with a reaction partner in the system

[11] *S. K. Allison*, Rev. mod. Physics *30*, 1137 (1958).

[12] *M. Amr El-Sayed, P. Estrup*, and *R. L. Wolfgang*, J. physic. Chem. *62*, 1356 (1958).

[13] *M. Amr El-Sayed* and *R. L. Wolfgang*, J. Amer. chem. Soc. *79*, 3286 (1957).

[14] *A. A. Gordus* et al., J. Amer. chem. Soc. *79*, 8432 (1957).

[15] *J. K. Lee, B. C. Musgrave*, and *F. S. Rowland*, Canad. J. Chem. *38*, 1756 (1960).

[16] *P. J. Estrup* and *R. L. Wolfgang*, J. Amer. chem. Soc. *82*, 2665 (1960).

as $P_i(E)$, then the value of $P_i(E)$ for a very energetic tritium atom will be zero. Collisions in an energy range well above 20 eV are much too energetic for the formation of a stable tritium bond (see Figure 1). The hot tritium atom becomes more and more moderated in energy by collision until it enters a range below $E_2$ in which it can form chemical bonds, *i.e.* $P_i(E) > 0$ within the limits $E_2 > E > E_1$. ($E_1$ is the minimum energy necessary for reaction; $E_1 > E_{thermal}$.)

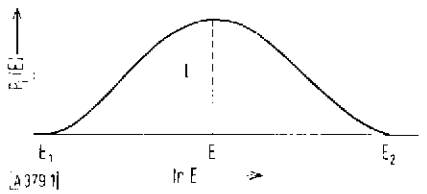



Fig. 1. Dependence of reaction probability of a hot reaction on the kinetic energy of the tritium atom.

We will return to this diagram later and indicate the dependence of the yield of hot reactions upon $P_i(E)$ and other parameters.

## IV. Prototype "Hot" Tritium Reactions in Organic Systems

### A. Substitution of Tritium for Hydrogen

In 1955, *Wolfgang*, *Rowland*, and *Turton* reported the first results of a tritium recoil experiment [17]. They observed the incorporation of tritium into glucose after thermal-neutron irradiation of a mixture of glucose and $Li_2CO_3$. Stepwise degradation of the irradiated compound showed that the distribution of tritium in the molecule was non-statistical.

*Rowland* and co-workers showed in 1959 [18] that the substitution of hydrogen by tritium at an asymmetrical carbon atom, *viz.* in crystalline L-(+)-alanine, occurred with almost complete retention of the configuration. Later, *Wolfgang* et al. [19] found over 90 % retention of configuration in gas-phase experiments with secondary butyl alcohol, and showed further that about 70 % of *cis*- and *trans*-dichloroethylene remained in the original conformation after the tritium hydrogen exchange [20]. These results imply a very rapid, direct exchange mechanism.

### B. Abstraction of Hydrogen by Tritium

In 1956/57, *Wolfgang*, *Rowland*, and co-workers, and *Willard* and co-workers [13,14,17,21,47] were able to show that abstraction of hydrogen plays as important a role in tritium-recoil systems as substitution reactions. Recoil experiments in liquid methane or ethane and in gaseous methane showed that the most important reaction products are HT and RT (RT = tritiated mother molecule). These authors showed further that the addition of radical scavengers to methane scarcely changed the yield of $CH_3T$ but lowered the yields of HT. Moreover, the postulated temperature independence as well as the influence of moderators ($^4He$) on the distribution of reaction products was experimentally demonstrated [12]. It has since been shown that the reactions

$$T + RH \rightarrow RT + H \quad \text{(a) (Substitution)}$$

and

$$T + RH \rightarrow R + HT \quad \text{(b) (Abstraction)}$$

are the most important ones for the formation of the products in almost all the systems that have been investigated: 5–60 % of the total tritium activity appears in labelled parent molecules, and in most cases more than 25 % is found as HT.

### C. Abstraction and Replacement of Larger Groups and Atoms

Recoil experiments with tritium and substituted benzoic acids showed that the extent of replacement of substituents X (X = $NH_2$, $NO_2$, OH, COOH, F, Cl, Br, and I) by tritium increases strongly as the binding energy of the group to the aromatic ring becomes smaller [23]. By analogy to Reactions (a) and (b), we can assume that the Reactions (c) and (d) are also involved in the formation of reaction products:

$$T + RX \rightarrow RT + X \quad \text{(c)}$$

$$T + RX \rightarrow R + TX \quad \text{(d)}$$

Since then, numerous investigations with alkyl halides have been carried out [24–29]. The replacement of alkyl groups in hydrocarbons by tritium [12,51,52,54] will be discussed in detail later.

### D. Tritium Addition to Double Bonds

*Urch* and *Wolfgang* were able to show in a series of experiments that hot tritium adds onto double bonds, and can result in geometric isomerization. Moreover, the formation of smaller olefins demonstrated the decomposition of excited radicals formed by the tritium addition [30,31].


[17] *R. L. Wolfgang*, *F. S. Rowland*, and *C. N. Turton*, Science (Washington) *121*, 715 (1955).

[18] *J. G. Kay*, *R. P. Malsan*, and *F. S. Rowland*, J. Amer. chem. Soc. *81*, 5050 (1959).

[19] *M. Henchman* and *R. L. Wolfgang*, J. Amer. chem. Soc. *83*, 2991 (1961).

[20] *D. Urch* and *R. L. Wolfgang*, J. Amer. chem. Soc. *83*, 2997 (1961).

[21] *J. K. Lee*, *B. C. Musgrave*, and *F. S. Rowland*, J. physic. Chem. *64*, 1950 (1960).

[22] *J. W. Root*, unpublished results.

[23] *R. M. White* and *F. S. Rowland*, J. Amer. chem. Soc. *82*, 4713 (1960).

[24] *V. V. Pozdeev*, *A. N. Nesmeyanov*, and *B. G. Dzantiev*, Radiokhimiva (USSR) *5*, 395 (1963).

[25] *R. Odum* and *R. L. Wolfgang*, J. Amer. chem. Soc. *83*, 4668 (1961).

[26] *R. Odum* and *R. L. Wolfgang*, J. Amer. chem. Soc. *85*, 1050 (1963).

[27] *E. K. C. Lee* and *F. S. Rowland*, J. Amer. chem. Soc. *85*, 2907 (1963).

[28] *Y. N. Tang*, *E. K. C. Lee*, and *F. S. Rowland*, J. Amer. chem. Soc. *86*, 1280 (1964).

[29] *H. C. Jurgeleit* and *R. L. Wolfgang*, J. Amer. chem. Soc. *85*, 1057 (1963).

[30] *D. Urch* and *R. L. Wolfgang*, J. Amer. chem. Soc. *81*, 2025 (1955).

[31] *D. Urch* and *R. L. Wolfgang* [3], Vol. 2, p. 99.

### E. Formation and Decomposition of Excited Intermediates

In 1957, *Hoff* studied the recoil chemistry of tritium in liquid ethanol [32]. In order to explain the formation of the [$^3$H]acetaldehyde found as a reaction product, *Rowland* and *Hoff* suggested the formation and subsequent decomposition of an excited intermediate:

(e) $T + CH_3{-}CH_2{-}OH \rightarrow (CH_3{-}CHT{-}OH)^* + H$

(f) $(CH_3\ CHT\ OH)^* \rightarrow CH_3\ CTO + 2\,H$

Later, *J. K. Lee*, *Musgrave*, and *Rowland* [15,34] assumed similar excited intermediates in recoil experiments with cyclopropane, for they found that the yield of tritiated cyclopropane increased as the pressure in the irradiated ampoule was raised (collision stabilization). Subsequently, *E. K. C. Lee* [35] showed in a detailed investigation with cyclobutane that tritiated ethylene is formed as the result of the reaction sequence:

(g) $T + C_4H_8 \rightarrow (C_4H_7T)^* + H$

(h) $(C_4H_7T)^* \rightarrow CH_2{=}CH_2 + CH_2{=}CHT$

(i) $(C_4H_7T)^* + M \rightarrow C_4H_7T + M$

Applying known data on the unimolecular decomposition of cyclobutane [36,37], he was able to calculate from the observed pressure dependence of the yield of $C_2H_3T$ that the tritium atom in Reaction (g) transfers an average of 5 eV excitation energy to the cyclobutane product.

### F. Primary and Secondary Isotope Effects

If recoil tritium is allowed to react with $CH_3CD_3$ or $CH_2D_2$ [21,22,38], then about 30 % more HT than DT is formed with either compound. Furthermore, the experimental results obtained with the pairs of compounds $CD_4/CH_4$, $n\text{-}C_4D_{10}/n\text{-}C_4H_{10}$, $CD_3Cl/CH_3Cl$, and $CD_3F/CH_3F$ can be summarized as follows [27,29,38]:

1. For abstraction reactions [cf. Reaction (b)], the abstraction ratio of concentrations $[HT]/[DT] \approx 1.3$.

2. For the substitution of hydrogen isotopes [cf. Reaction (a)], the substitution ratio $[RH_{n-1}T]/[RD_{n-1}T] \approx 1.3$.

3. For the substitution of the group X in $CH_3X$ and $CD_3X$ [cf. Reaction (c)]. The substitution ratio $[CH_3T]/[CD_3T] \approx 1.4$.

This shows that:

a) An energetic tritium atom abstracts and replaces protium more easily than deuterium. The abstraction and substitution ratios are not very dependent upon the type of compound and are of about the same magnitude (primary isotope effect).

b) An energetic tritium atom replaces fluorine and chlorine more easily in a protonated than in a deuterated compound. The substitution ratio is about 1.4 (secondary isotope effect).

Explanation of these isotope effects is of great importance for an understanding of the reactions of hot tritium atoms. Satisfactory quantitative explanations for all the experimental data have not yet been found, but we shall discuss some aspects below.

## V. Reaction Models

1. The most frequent reactions of hot tritium atoms in organic systems are the substitution and the abstraction of hydrogen [Reactions (a) and (b)]. *Henchman, Urch,* and *Wolfgang* [20,31,33] proposed a steric model which depends upon the geometric properties of the compound for these reactions. They assumed that the formation of HT (abstraction of hydrogen) occurs preferentially if the tritium attacks the carbon-hydrogen bond almost co-axially. On the other hand, if the approach of the tritium to the carbon-hydrogen bond occurs at an oblique angle, the probability of reaction to form RT (substitution for hydrogen) is greater.

At these angles, the geometric arrangement of the reacting molecule could have an influence on the exchange of tritium for hydrogen, whereas the abstraction of hydrogen should be independent of molecular structure. By using an obstruction parameter $\Omega$, *Wolfgang* and co-workers developed Equation (1) for the relative frequency of abstraction and substitution.

$$\frac{[HT]}{[RT]} = \frac{n}{n_0 - n_1(1-\Omega) - n_2(1-\Omega)^2 + n_3(1-\Omega)^3} \qquad (1)$$

where $n$ = the number of hydrogen atoms in the compound

$n_0$ = the number of hydrogen atoms in methane

$n_1$, $n_2$, and $n_3$ = the number of primary, secondary and tertiary hydrogen atoms in compounds with more than 1 carbon atom.

Good agreement of experimental results with Equation (1) was found for a whole series of hydrocarbons with $\Omega = 0.45$.

In 1962 and 1963, experiments from our laboratory were published which questioned the exclusive steric dependence assumed by *Wolfgang* and co-workers. *Root* investigated the recoil chemistry of tritium in mixtures of n-butane and methane [39] and found that the ratio of the specific activities (per molecule) of n-butane to methane had the value of 2.3. Equation (1) predicted a value of 1.13, assuming equal abstraction probabilities for all the hydrogen atoms in both molecules.

As *E. K. C. Lee* later showed [35], the experimental values for the specific activities of cyclobutane/methane

[32] *W. J. Hoff* and *F. S. Rowland*, J. Amer. chem. Soc. *79*, 4867 (1957).

[33] *M. Henchman, D. Urch*, and *R. L. Wolfgang*, Canad. J. Chem. *38*, 1722 (1960).

[34] *J. K. Lee, B. C. Musgrave*, and *F. S. Rowland*, J. Amer. chem. Soc. *81*, 3803 (1959).

[35] *E. K. C. Lee* and *F. S. Rowland*, J. Amer. chem. Soc. *85*, 897 (1963).

[36] *F. Kern* and *W. D. Walters*, Proc. nat. Acad. Sci. USA *38*, 937 (1952).

[37] *C. T. Genaux, F. Kern*, and *W. D. Walters*, J. Amer. chem. Soc. *75*, 6196 (1953).

[38] *J. W. Root* and *F. S. Rowland*, J. Amer. chem. Soc. *85*, 1021 (1963).

[39] *J. W. Root* and *F. S. Rowland*, J. Amer. chem. Soc. *84*, 3027 (1962).

and cyclobutane/n-butane mixtures also did not agree with the values calculated from Equation (1). The compounds $CH_3-CD_2-CH_3$ and $CD_3-CH_2-CD_3$ were also exposed to energetic tritium atoms by *Breckenridge* and *Root* [40]; abstraction of hydrogen from the center carbon atoms was found to occur 1.4 times oftener than from the terminal carbon atoms, per C–H bond.

These and other experimental results [22] lead *Rowland* and co-workers to suggest that the characteristic differences in the ratio [HT]/[RT] for the various alkanes may depend not only on steric differences in the substitution reaction but also on differing probabilities of abstraction from compound to compound. This assumption led to the further conclusion that the binding energy of the carbon-hydrogen bond exerted an influence on the probability of formation of HT [*].

If one compares the relative yield of HT (yield per C–H bond) from different compounds with the bond dissociation energy of the C–H bond, Figure 2 is obtained.

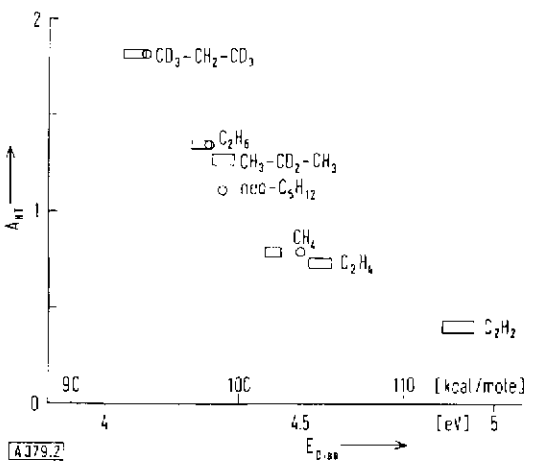



Fig. 2. Dependence of the relative yield $A_{TH}$ on the C–H bond dissociation energy $E_{Diss}$ of various hydrocarbons. The relative yield $A_{HT}$ is defined as the yield per C–H bond.
O: $E_{Diss}$ according to [48].
□: $E_{Diss}$ according to [49].

The fact that the measured points form a smooth curve indicates the dependence of the formation of HT upon the C–H bond dissociation energy.

Only stepwise degradation of the hot reaction products and location of the specific activity in the various positions in each molecule can decisively determine the extent to which differences in the substitution reactions contribute to the measured [HT]/[RT] ratios [**].

2. In the reactions of recoil tritium with many hydrocarbons, the tritium atom, after rupture of a carbon-carbon bond, attaches preferentially to the smaller fragment. Thus, for example, the ratio $[CH_3T]/[C_2H_5T]$ after irradiation of propane is 2.7 [20,41] and the ratio $[CH_3T]/[iso\text{-}C_4H_9T]$ from neopentane is 8.0 [20]. Similar selectivity of tritium incorporation has been observed for other compounds: substitution of tritium for fluorine occurs more easily in $CH_3F$ than in $CH_2F_2$ (the yield of $CH_3T$ from the former is larger than the yield of $CH_2TF$ from the latter) [25].

To account for these results, *Odum* and *Wolfgang* [26] proposed a reaction model that involves the inertia of the fragments produced in the reaction. This can be briefly explained for the molecules $CH_3Cl$ and $CH_2Cl_2$ (see Figure 3, a and d): after fission of a C–Cl bond by collision with the hot tritium atom (Figure 3, b and e), the $CH_3$ formed from $CH_3Cl$ can rotate quickly into a position favorable for bond formation with the tritium (Figure 3, c), whereas the $CH_2Cl$ formed from $CH_2Cl_2$ rotates more slowly because of its higher moment of inertia and allows sufficient time for the tritium atom to escape before $CH_2TCl$ can be formed.

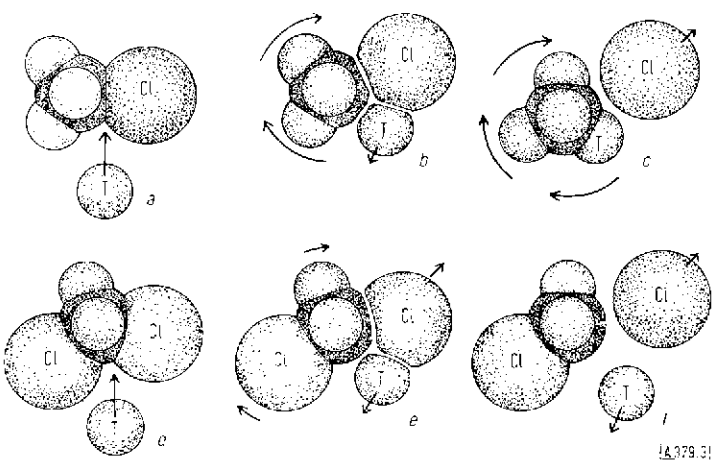



Fig. 3. Rotational inertia hypothesis of *Wolfgang* [36]. Substitution of Cl by T in $CH_3Cl$ and $CH_2Cl$.
b: Rotating $CH_3$ group
c: Formation of C–T bond
f: Failure to form a C–T bond
e: Rotating $CH_2Cl$ group.

As discussed above, the formation of excited intermediate compounds has now been shown in a series of investigations [15,34,35].

Since the instability of such intermediates is sure to affect the yield of some reaction products, dependence of the reaction products on pressure is expected, and a discussion of reaction mechanism is meaningful only after careful evaluation of the "original" yields of the hot reactions. Experimentally, the original yields can be obtained from investigations at high pressures (or in the liquid phase), where the excited species can undergo rapid collisional stabilization. In certain cases, *e.g.* with the $CH_3Cl$ system [28], the sum of the yields of collision-stabilized hot reaction products and their decomposition products is independent of the pressure. Such an indirect determination of the original yield can only be used when only few secondary products are formed, and when the radical decomposition products can be converted by a selective free-radical scavenger into a stable, radiochemically measurable form.

As a further test of the model proposed by *Wolfgang* and co-workers, *Schmidt-Bleek* examined a series of compounds of the type $n\text{-}C_3H_7X$ (X–$NH_2$, OH, F, Cl, or Br) [41]. The ratios $[C_2H_5T]/[CH_2TX]$ should be approximately 1.0 for n-propylamine, n-propyl alcohol, and n-propyl fluoride, if only the masses of the frag-

[40] *W. Breckenridge, J. W. Root*, and *F. S. Rowland*, J. chem. Physics *39*, 2374 (1963).

[*] Only the ratio [HT]/[RT] may be compared here because the absolute yield of HT or RT in different compounds can be influenced by variations in the energy spectrum of the tritium (see also Paragraphs 2 and 3).

[**] *Wolfgang* and co-workers recently investigated the distribution of recoil tritium in isobutane. They found that the ratio of tritium in the tertiary position to tritium in the primary position (per C–H bond) is 0.79 [J. chem. Physics *40*, 3730 (1964)].

[41] *F. Schmidt-Bleek*, unpublished results.

ments have an important influence on product formation. The observed value for $[C_2H_5T]/[CH_2TX]$ is about 10 for liquid n-propyl alcohol and 20 for liquid n-propylamine, while in gaseous n-propyl fluoride a pressure-independent (from 50 to 600 mm) ratio of 1.7 has been obtained.

These results have not yet been explained by a completely satisfactory reaction model. The rotational inertias of the reaction partners are certainly not the only important parameters for the formation of the reaction products. It is possible, for example, that the electron density of the various fragments is an important factor.

3. In Figure 1, the dependence of the probability of reaction of a hot tritium atom on its kinetic energy was illustrated. One of the main goals of recoil chemistry is to describe the kinetics of these hot reactions quantitatively.

In 1950, *Miller* and *Dodson* [42] expressed the reaction probability of a recoil atom in mathematical form for the first time. In 1960, *Estrup* and *Wolfgang* [43] applied the equations proposed by *Dodson* and co-workers to recoil tritium.

In the following, the mathematical treatment of *Wolfgang* and co-workers is briefly reviewed. For details we refer the reader to the original publications [43, 44].

If the total number of hot atoms present in the region $E_2-E_1$ (see Figure 1) is $N_s$, and their relative collision probabilities with molecules i is $f_i$, then the total number of atoms of reaction products $N_g$ is given by

$$N_g = N_s \sum_i \int_{E_1}^{E_2} f_i \, P_i(E) \, n(E) \, dE \qquad (2)$$

Equation (2) where n(E)dE is the number of collisions in the energy range E + dE to $E_1$, and $P_i(E)$ is the reaction probability of the hot atom per collision.

In order to calculate n(E), *Wolfgang* and co-workers made the following assumptions based upon theoretical calculations for the slowing down of fast neutrons [44a]:

(a) The energy loss per collision can be described by the relationships for collisions of elastic spheres.

(b) The original kinetic energy of the recoil atom is so high (see Table 1) that the tritium atom has already made many collisions before it reaches $E_2$. In this way, a statistically well-defined energy distribution can be formed between $E_2$ and $E_1$.

(c) $E_1$ is large compared to thermal energies.

As long as the probability of reaction of the hot tritium is zero [$P_i(E) = 0$], n(E) is given by Equation (3),

$$n(E) = -\frac{1}{\alpha E} \qquad (3)$$

where $\alpha$ is the average logarithmic energy loss per collision [*]:

$$\alpha = \ln(E_0/E) \qquad (4)$$

Since $P_i(E)$ is not zero between $E_2$ and $E_1$, the actual number of collisions in the energy range E + dE to E (see Equation 2) is less than $-1/\alpha E$.

$$n(E) = -\frac{1}{\alpha E}\left[1 - \sum_i \int_{E_2}^{E} f_i \, P_i(E) \, n(E) \, dE\right] \qquad (5)$$

Transformation of this expression and its insertion into Equation (2) finally gives for the relative yield $N_g/N_s$ of all hot products:

$$N_g/N_s = 1 - e^{-f \cdot I/\alpha} \qquad (6)$$

where

$$I = \int_{E_2}^{E_1} P_i(E) \, d\ln E \qquad (7)$$

*i.e.* the area under the curve in Figure 1.

Equation (6) is valid only if tritium encounters only the pure substance to be investigated as reaction partner, *i.e.* in a gaseous two-component system. On addition of a third collision partner, *e.g.* an inert "moderator", the relationships become more complicated. *Wolfgang* et al. gave the following approximate equation for the addition of inert gases:

$$N_g/N_s = 1 - \exp[-f_a I_a/\alpha_{ab}] \qquad (8)$$

in which the indices a and b stand for the starting material and the moderator, respectively. *Rowland* and *Coulter* [45] showed by Monte Carlo computer calculations that Equation (8) leads to satisfactory values only for the addition of helium.

It should be pointed out that the authors made several simplifying approximations during the derivation of these equations. For example, inelastic collisions, anisotropic scattering, and the dependence of the reaction cross-section on the energy of the colliding particles may have influences on the yield of hot reactions. However, good agreement was occasionally obtained between experimental results and the theoretical values [43]. The data available so far permit only approximate measurement of the magnitude of the area under the curve in Figure 1. The shape of this curve cannot yet be determined.

*Estrup* [45a] recently pointed out that quantitatively accurate measurements of I depend very strongly on the use of more realistic interaction potentials than those of the hard spherical models used so far. The effect is especially important in the calculations of $\alpha$ and f.

4. The kinetic model of hot tritium reactions described in paragraph 3 leads to several possible isotope effects. If the average energy loss of the tritium atom in a non-reacting collision in the energy range $E_2-E_1$ (see Figure 4) is different for isotopically substituted molecules, then the number of hot collisions of the tritium will be different in a given energy range. If we assume, for example, that a collision with RD leads to a greater energy loss for tritium than its collision with RH, then the tritium atom will undergo fewer collisions with RD and fewer reactions with RD than with RH within a comparable energy range. The yield from Reaction (k)

$$(k)\quad T + RD \rightarrow RT + D$$

would then be lower than that from Reaction (i).

$$(i)\quad T + RH \rightarrow RT + H$$

[42] *J. M. Miller* and *R. W. Dodson*, J. chem. Physics *18*, 865 (1950).

[43] *P. J. Estrup* and *R. L. Wolfgang*, J. Amer. chem. Soc. *82*, 2661 (1960).

[44] *R. L. Wolfgang*, J. chem. Physics *39*, 2983 (1963).

[44a] See for instance *S. Glasstone:* Principles of Nuclear Engineering. Van Nostrand, New York 1958.

[*] n(E) has a negative sign because the integration is carried out from the larger to the smaller value of E.

[45] *F. S. Rowland* and *P. Coulter*, Radiochimica Acta *2*, 163 (1964).

[45a] *P. Estrup*, J. chem. Physics *41*, 164 (1964).

This effect has been called a moderator isotope effect [29] (see Figure 4a).

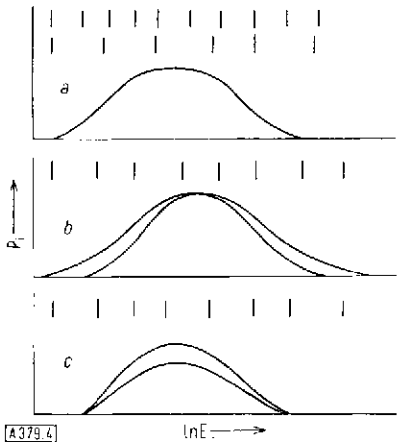



Fig. 4. Influence of various isotope effects on reaction probability and reaction energy of hot tritium atoms. (The short vertical lines signify energies at which collisions occur.)

a: Moderator effect (different energy losses for collisions with different molecules)

b: Probability-integral effect (different energy ranges for collisinns with different molecules).

c: Probability-integral effect (different probabilities of reaction for collisions with different molecules).

On the other hand, it is also possible that the energy ranges for Reactions (k) and (l) are different (see Figure 4b), or that differences occur in the probability of reaction of the tritium with isotopically different substances (see Figure 4c). These two effects are both included in the term "probability integral" isotope effects [27].

All three effects may exert influences on the reaction of the tritium and produce observable differences in the yields from isotopic molecules.

Experimentally, the moderator isotope effect can be distinguished from the probability integral isotope effect if the abstraction and substitution of protium and deuterium is measured simultaneously in a single molecule. In this way, the same energy spectrum of hot tritium is available for all reactions, and moderator isotope effects are excluded. The investigations of the compounds $CH_2D_2$ and $CH_3CD_3$ are good examples. For these two partially deuterated molecules, about 30 % more hydrogen than deuterium is abstracted; this led to the hypothesis that the effects illustrated in Figures 4b and 4c are also of decisive influence in other systems [39].

## VI. The Influence of Radiation Chemistry

Neutron irradiation of $^6Li$ and $^3He$ produces not only tritons but also high energy $\alpha$-partieles and protons. Moreover, each system is subjected to fast neutrons and $\gamma$-rays during irradiation in a nuclear reactor. Hence the danger exists that these accompanying irradiations may cause alterations which are difficult to separate from tritium recoil events. Also, each recoiling atom must itself dissipate its energy in the system, leaving a path of radiolysis products behind it.

For simplification, we might say that tritium can react with hydrocarbons in two distinctly different energy regions. In the "hot" zone extending from $E_2$ to $E_1$, the reactions we have described in detail occur. However, if the tritium escapes from this hot reaction zone without having formed a stable chemical bond, its further reactions are no longer separable from the well-known reactions of thermal hydrogen and deuterium atoms. Such reactions are chiefly addition to olefins and the abstraction of hydrogen.

The excited radicals formed by additions onto olefins ($H + CH_2{=}CH_2$, for example, leads to ethyl radicals with about 40 kcal/mole excitation energy) [46]) can undergo further abstraction reactions with molecules, or combination and disproportionation reactions with other radicals. The probabilities of these thermal reactions depend upon the equilibrium concentrations of the reactive components encountered by the tritium after passing through the hot reaction zone. It is obvious that the concentrations of many species will be different under different irradiation conditions. The influence of these radiation effects can be investigated by determining the dependence of the yields of hot products upon the total radiation dose and dose rate. The findings of various authors leave no doubt that the influence of radiation chemistry must be considered in all recoil experiments [3]. In our investigations, however, it is clear that the tritium reactions in the hot reaction zone are independent of the radiation damage at least so long as the concentration of the stable products formed by irradiation is so small that decomposition of the products is also kept within low limits. Furthermore, the addition of radical scavengers can control conditions such that the thermalized tritium atoms and radiation-damaged components are forced to react to give products which can easily be distinguished from products of recoil reactions. It has been demonstrated in many systems that this experimental technique leads to distributions of hot products which are independent of the radiation dose within wide limits [3].

## VII. Conclusion

Investigations of the chemical consequences of nuclear reactions aim at solution of the following problems:

1. How can the energy loss of the recoil atom be mathematically described in the hot reaction zone?

2. How large is the probability of reaction of the colliding particle in terms of its kinetic energy?

3. At what energies do recoil reactions occur?

4. What are the reaction mechanisms involved?

5. What products are formed when the excited labelled molecules decompose?

Scarcely any other recoil system appears to be as satisfactory for studying these problems as the recoil of tritium in organic molecules.

The decomposition of excited intermediates has been demonstrated in many experiments, and the products formed definitely determined. Quantitative estimation and comparison of the hot products formed in a large number of

[46] *E. W. R. Steacie:* Atomic and Free Radical Reactions. Reinhold, New York 1954.

[47] *R. L. Wolfgang, J. Eigner,* and *F. S. Rowland,* J. physic. Chem. *60,* 1137 (1956).

[48] *G. C. Fettis* and *A. F. Trotman-Dickensen,* J. chem. Soc. (London) *1961,* 3037.

[49] *R. R. Bernecker* and *F. A. Long,* J. physic. Chem. *65,* 1565 (1961).

systems have led to clarification of the reaction mechanisms entailed. Experiments in cyclobutane have shown that during hot exchange reactions tritium transfers an energy of about 5 eV from its kinetic energy to excitation of the product molecule. Finally, first approaches have been made to theoretical expressions for the reaction probability of energetic tritium atoms, as well as for their energy losses in collisions.

The investigations into recoil systems have required the development of radiogas-chromatographic measurement methods of high sensitivity. The techniques developed here are useful in many other areas of work: for example, as little as $10^9$ molecules of any tritiated compound can be determined with certainty in a gas stream.

For some time now, the problem has been considered of how tritium atoms (and other isotopes) can be produced with much smaller kinetic energies than those formed in nuclear transformations. Precise kinetic investigations of hot reactions would require tritium atoms with well defined energies between 20 and 1 eV. Attempts, for example, to accelerate $^{14}C$ ions onto a target with the help of specially constructed mass spectrometers have so far met with difficulties [3].

Experiments with shock waves are also not yet possible. In our laboratory, experiments are now proceeding on the use of photolytic decompositions (*e.g.* with Tl), following the successful experiments for producing deuterium and protium atoms [50]. The atoms formed by photolysis possess about 3 eV of energy and may lead to an increase in our knowledge of hot reactions. For the present, however, nuclear recoil systems offer the most promise for answering the questions given above.

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[53] *J. K. Lee* and *F. S. Rowland*, J. inorg. nuclear Chem. *10*, 336 (1959).

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# Proton-Addition Complexes of Aromatic Hydrocarbons

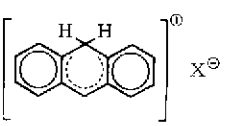
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*The structures of proton-addition complexes of aromatic hydrocarbons were hitherto known only with respect to their stoichiometric compositions but can now be clarified by ultraviolet, infrared, and NMR spectroscopic methods. For example, it has been possible to prove by NMR soectroscopy that the expected addition of protons into 9,10-dimethyl-[a]benzanthracene actually does take place. Two isomeric proton adducts of toluene have been found by means of infrared spectra. On addition of protons, the ultraviolet spectra of aromatics change considerably; excellent agreement is sometimes observed between the band maxima calculated by quantum mechanics and those found by experiment.*

## I. Introduction

It has long been known that aromatic hydrocarbons form solid or liquid compounds with Lewis acids such as $AlCl_3$ in the presence of hydrogen halides [1]. It is also known that aromatic hydrocarbons yield carbonium ions in strong acids [2]. Proton-addition complexes are involved in both processes; *Gold* and *Tye* [3] have put forward certain proposals for the structures of these adducts, *e.g.*, the structure *(1)* for the anthracene complex.

*(1)* 

The pronounced interference with the aromatic system associated with the addition of protons gives rise to numerous striking properties of these complexes, *e.g.* their intense colors.

These complexes are of importance because similar entities must be assumed as intermediates in numerous electrophilic substitutions at aromatic rings [4], as was postulated relatively early on theoretical grounds [5]. *Brown* et al. [6] later

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[1] *G. G. Gustavson*, Ber. dtsch. chem. Ges. *11*, 1841, 2151 (1878); J. prakt. Chem. *42*, 250 (1890); *68*, 209 (1903); *72*, 57 (1905).

[2a] *J. F. Norrish* and *D. Rubinstein*, J. Amer. chem. Soc. *61*, 1163 (1939).

[2b] *J. F. Norrish* and *J. N. Ingraham*, J. Amer. chem. Soc. *62*, 1298 (1940).

[3] *V. Gold* and *F. L. Tye*, J. chem. Soc. (London) *1952*, 2173, 2181 2184.

[4] *E. S. Gould:* Mechanism and Structure in Organic Chemistry. Henry Holt, New York 1959.

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[6] *H. C. Brown* and *J. D. Brady*, J. Amer. chem. Soc. *74*, 3570 (1952).

reconsidered these assumptions, and initiated attempts to detect complexes appearing as intermediates in electrophilic substitution reactions.

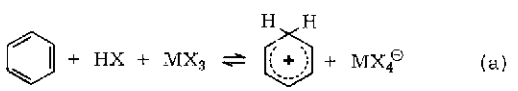
In addition to proton-addition complexes, it is necessary to consider complexes arising by interactions between aromatic hydrocarbons and Lewis acids. Such complexes are primarily π-complexes according to *Dewar* [7], which, in *Mulliken*'s classification [8], must be designated as π-v-complexes. The complexes arise by a typical electron-donor/electron-acceptor mechanism, in which the donor has a π-electron system and the acceptor an electron deficiency (v = vacancy). Furthermore, sometimes complexes with a covalent bond between the aromatic hydrocarbon and the Lewis acid, without participation of protons, must be taken into account; like the proton-addition complexes, these should also be designated as σ-complexes.

Summing up, when the interaction of weak acids with aromatic hydrocarbons is disregarded, three types of complexes must be considered: 1. proton-addition complexes: aromatic hydrocarbon/HX/$MX_3$, 2. π-v-complexes: aromatic hydrocarbon/$MX_3$, and 3. σ-complexes: aromatic hydrocarbon/$MX_3$.

Only proton-addition complexes of the type aromatic hydrocarbon/HX/$MX_3$ will be discussed here.

## II. Composition of the Proton-Addition Complexes

The following equation holds formally for the formation of a proton-addition complex with participation of a Lewis acid.



$MX_3$ = $BF_3$, $AlCl_3$, $AlBr_3$, $GaCl_3$, $GaBr_3$

Equation (a) is idealized, since in reality Lewis acids are present partly as dimers, as follows from their solubilities in organic solvents [9–11] and from the Raman spectra of molten $AlCl_3$, $AlBr_3$, $AlI_3$, and $GaCl_3$ [12,13].

Consequently, the anion in Equation (a) may also be formulated as $M_2X_7^{\ominus}$. Because of this dimerization of Lewis acids, we find not only complexes of the composition benzene/HX/$MX_3$ = 1:1:1, but also 1:1:2 [14]. Different stoichiometric ratios may be found for various hydrocarbons, *e.g.* 3:1:2 and 1:1:2 for isolated crystalline mesitylene/HBr/$AlBr_3$, and 2:1:2 and 1:1:2 for 1,2,5-triethylbenzene/HBr/$AlBr_3$ [15]. Xylene complexes have the empirical composition $(Ar)_x \cdot Al_2Br_6 \cdot HBr$ with $x > 2$ [16]. On the other hand, *Lien, Shoemaker*, and *McCaulay* [17] found 1:1:1 complexes for the systems aromatic hydrocarbons/HF/$BF_3$. *Olah* et al. [18] confirmed these results by isolating complexes of various methylbenzenes with HF/$BF_3$ at low temperatures (see Table 1).

Table 1. Physical characteristics of some $ArH^+ \cdots BF_4^-$ complexes [18].

| Aromatic hydrocarbon (Ar) | log K [19] [a] | M. p. [°C] | Conductivity, [mho/cm] [c] | Color [d] | Empirical formula | $BF_4^-$ [%] calc. | $BF_4^-$ [%] found |
|---|---|---|---|---|---|---|---|
| Toluene | 6.3 | −65 | $0.8 \times 10^{-2}$ | yellow-green | $C_7H_9BF_4$ | 48.3 | 47.5 |
| *m*-Xylene | −3.2 | −55 | $2.0 \times 10^{-2}$ | yellow | $C_8H_{11}BF_4$ | 44.6 | 43.2 |
| Mesitylene | −0.4 | −15 | $1.6 \times 10^{-2}$ | yellow | $C_9H_{13}BF_4$ | 41.8 | 40.9 |
| 1,2,3,4-Tetramethylbenzene | −2.0 [b] | −10 | $0.6 \cdot 10^{-2}$ | orange | $C_{10}H_{15}BF_4$ | 39.1 | 38.6 |

[a] The basicity constant [19] is defined as $[K] = \frac{[ArH^+]}{[Ar] \cdot [H^+]}$

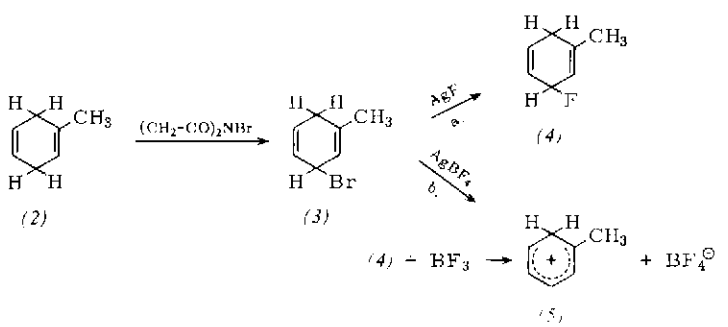
[b] Calculated approximately in accordance with [45].

[c] At the melting point.

[d] Of the solid complex.

The analytical results given in the last column of Table 1 agree very well with expectations for 1:1:1 complexes. The melting points (partial dissociation begins at the melting point) show that the stability obviously increases with the basicity of the methylbenzenes.

The synthesis of a proton-addition complex described by *Olah* et al. [20] is of interest in this connection: 1-methyl-1,4-cyclohexadiene *(2)* was converted with the aid of *N*-bromosuccinimide into 1-methyl-3-bromo-1,4-



*(2)* *(3)* *(4)* *(5)*

[7] *M. J. S. Dewar*, J. chem. Soc. (London) *1946*, 406, 777.

[8] *R. S. Mulliken*, J. physic. Chem. *56*, 801 (1952).

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[10] *F. Fairbrother, N. Scott*, and *H. Prophet*, J. chem. Soc. (London) *1956*, 1164.

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[20] *G. A. Olah* and *S. J. Kuhn*, J. Amer. chem. Soc. *80*, 6541 (1958).

cyclohexadiene *(3)* which reacted with AgF to give the fluorine derivative *(4)*. $BF_3$ causes elimination of the fluorine anion from *(4)*, the products being a tetrafluoroborate anion and the proton-addition complex of toluene *(5)*.

Since replacement of bromine with fluorine by Route a presented difficulties, *(3)* was converted directly into *(4)* with $AgBF_4$ (Route b). Thus, a 1:1:1 composition has been established for this proton-addition complex aromatic hydrocarbon/HF/$BF_3$.

In order to clarify the complicated mode of interaction of aromatic hydrocarbons with Lewis acids such as $AlCl_3$ and $AlBr_3$ in the presence of halogen halides, *Lieser* and *Pfluger* investigated the formation of phases in the ternary systems toluene/HCl/$AlCl_3$ [21] and mesitylene/HCl/$AlCl_3$ [22] by vapor pressure measurements. Their results led to the conclusion that there are several phases with relatively large regions of homogeneity. Of these, the phase toluene:HCl:$AlCl_3$ = 6:1:2 is obviously favored in the toluene system. With mesitylene, the composition of the phase showing the orange color typical of proton-addition complexes was shown by conductivity measurements to be mesitylene: HCl:$AlCl_3$ = 4:1:2.

Here, as in other investigations, it turned out that generally more molecules of the aromatic hydrocarbon are fixed than are necessary for the formation of a proton addition complex. *Lieser* and *Pfluger* [21,22] therefore assumed that the molecules in excess are bound in a solvation sheath. The fact that the aromatic molecules present in excess in the complex are relatively free and therefore cannot be substantially involved in the interaction had already been discussed by *Luther* and *Pockels* [23] on the basis of ultraviolet spectra of the systems benzene/HCl(HBr)/$AlCl_3$($AlBr_3$) and toluene/HCl(HBr)/$AlCl_3$($AlBr_3$).

As *Perkampus* and *Baumgarten* [24] have shown for benzene, the changes in the infrared spectrum of benzene associated with the formation of proton-addition complexes are practically independent of the type of the Lewis acid. To illustrate this, the infrared spectra of some benzene/HX/$MX_3$ systems are shown schematically in Figure 1. These differ markedly from the spectrum of pure benzene but are identical with one another [*], proving that the anion exerts only a slight influence. Thus, it must be the addition of protons onto the aromatic hydrocarbon which is responsible for the marked effects during complex formation.

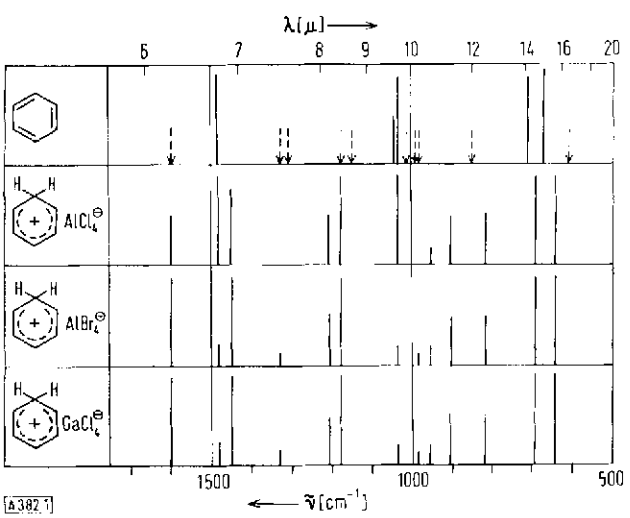



Fig. 1. Infrared spectra of solid proton-addition complexes of benzene with various Lewis acids at 77 °K; infrared-inactive vibrations of benzene are shown in dotted lines. (Schematic)

## III. Structure of the Proton-Addition Complexes

### 1. Proton Magnetic Resonance Spectra

The decisive factor in the addition of protons onto aromatic hydrocarbons is the transition of a trigonally $sp^2$-hybridized carbon atom into a tetragonally $sp^3$-hybridized one. Owing to this fact, any proton-addition complex can be detected directly from the nuclear magnetic resonance signals of its protons. *McLean, van der Waals*, and *Mackor* [25] investigated several mononuclear and polynuclear aromatic hydrocarbons and obtained direct proof of the structures formulated by *Gold* and *Tye* [3]. Figure 2 shows the proton magnetic resonance spectra of 9,10-dimethylbenz[*a*]anthracene and its proton-addition complex. The proton adds on in the 9-position. Figure 2a shows two bands for the methyl protons, indicating that the two $CH_3$ groups are no longer equivalent. As soon as the proton-addition complex is formed, the configuration $>CH-CH_3$ arises in the 9-position and one of the signals is strongly displaced as shown in Figure 2b.

The signals for the two methyl groups are easy to assign, since the neighboring single proton causes the signal for one of them to appear as a doublet and, conversely, the three protons of the methyl group cause the signal of the single proton to appear as a quadruplet. The quadruplet disappears in the corresponding deuteron-addition complex (cf. Fig. 2c), since the resonance frequency of the deuteron is located in a different region [26]. Finally, Figure 2d, which shows the PMR spectrum of 9,10-dihydro-9,10-dimethylanthracene, gives a reliable example of a $>CH-CH_3$ configuration. In this molecule the two methyl groups are equivalent, so that only a doublet appears for the $CH_3$ protons and a quadruplet for the CH proton. Similar results have been obtained for pentamethylbenzene, hexamethylbenzene, hexaethylbenzene, pyrene, and benzo[*c*]pyrene [25].

[21] *K. H. Lieser* and *Cl. E. Pfluger*, Chem. Ber. *93*, 176 (1960).
[22] *K. H. Lieser*, and *Cl. E. Pfluger*, Chem. Ber. *93*, 181 (1960).
[23] *H. Luther* and *G. Pockels*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 159 (1955).
[24] *H.-H. Perkampus* and *E. Baumgarten*, Ber. Bunsenges. physik. Chem. *67*, 576 (1963).

[*] The differences in Figure 1 are due to the fact that the extent of conversion increases markedly from $AlCl_3$ to $GaCl_3$. Free benzene is still present in the $AlCl_3$ complex, so that its bands are still relatively intense.

[25] *C. MacLean, J. H. van der Waals*, and *E. L. Mackor*, Molecular Physics *1*, 247 (1958).
[26] Cf. *H. Strehlow*: Magnetische Kernresonanz und chemische Struktur. Steinkopff, Darmstadt 1962.

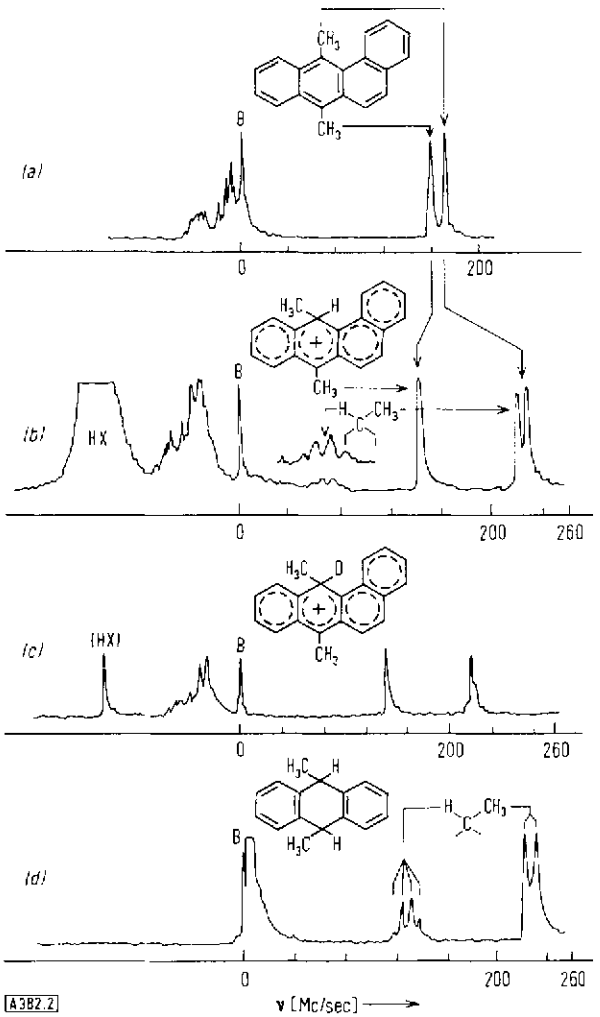



Fig. 2. Proton magnetic resonance spectrum at 50 Mc/sec and 298 °K [25] of:

(a) 9,10-dimethylbenz[*a*]anthracene in $CCl_4$;

(b) the proton-addition complex of a) in $CF_3COOH$ + 22 mole-% $H_2O \cdot BF_3$;

(c) the deuteron-addition complex of a) in $CF_3COOD$ · 24 mole-% $D_2O \cdot BF_3$;

(d) 9,10-dihydro-9,10-dimethylanthracene in $CCl_4$.

B = Benzene as standard.

## 2. Infrared Spectra

Although infrared spectra are generally little affected by the medium, only few aromatic-proton complexes have been investigated by infrared spectroscopy, since the preparation of moisture-free samples and the development of a usable cell present great difficulties. We managed to overcome these difficulties by measuring the spectra of the solid complexes in high vacuum [27]. For this purpose, an evacuable cell for accomodating solids was employed; this cell could still be used at 60 °K, the temperature of solid nitrogen [28].

Figure 1 shows a schematic reproduction of the infrared spectra recorded for the ternary systems benzene/HCl/$AlCl_3$, benzene/HBr/$AlBr_3$, and benzene/HCl/$GaCl_3$ in the solid state at 77 °K [24] [*]. Compared with the infrared spectrum of crystalline benzene, numerous new bands appear, which can only be ascribed to C–C and C–H vibrations, since the Lewis acids used do not absorb in this region. Comparison of the spectrum with that of the complex perdeuterobenzene/DCl/$GaCl_3$ allows differentiation between the C–C and C–H vibrations. As can be seen from Figures 3a and 3b, the

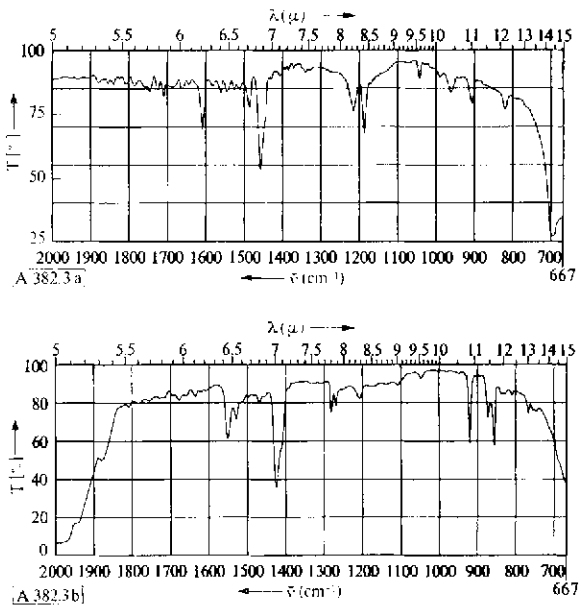
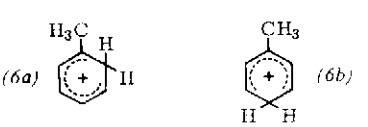



Fig. 3. Infrared spectrum of the solid proton-addition complex benzene/HCl/$GaCl_3$ (a) and the solid deuteron-addition complex perdeuterobenzene/DCl/$GaCl_3$ (b), at 77 °K.

position of some bands – those in the region from 1400 to 1600 $cm^{-1}$ – remain practically unchanged, while the bands of longer wavelength are bathochromically displaced [24].

Analysis of the infrared spectra shows that the new bands can be assigned to infrared-inactive (*i.e.* symmetry-forbidden) benzene vibrations. This means that the addition of the proton is associated with a lowering of the symmetry. Thus, the $D_{6h}$ symmetry of benzene is probably lowered to $C_{2v}$ symmetry in the complex.

With methylbenzenes [29], particularly marked changes occur on complex formation in the region between 670 and 900 $cm^{-1}$. According to *Bellamy* [30], the number and position of the bands in this region depend on the number of adjacent hydrogen atoms. The carbon atom to which the proton is added must be regarded as "substituted". Thus, two isomeric proton-addition complexes are conceivable for toluene, since its *ortho*- and *para*-positions have the same basicities.




[*] The proton-addition complex of benzene is only stable up to about 220 °K; this is probably why this complex had not previously been detected.

[27] *H.-H. Perkampus* and *E. Baumgarten*, Ber. Bunsenges. physik. Chem. *67*, 16 (1963).

[28] *H.-H. Perkampus* and *E. Baumgarten*, Spectrochim. Acta *17*, 1295 (1961).

[29] *H.-H. Perkampus* and *E. Baumgarten*, Ber. Bunsenges. physik. Chem. *68*, 70 (1964).

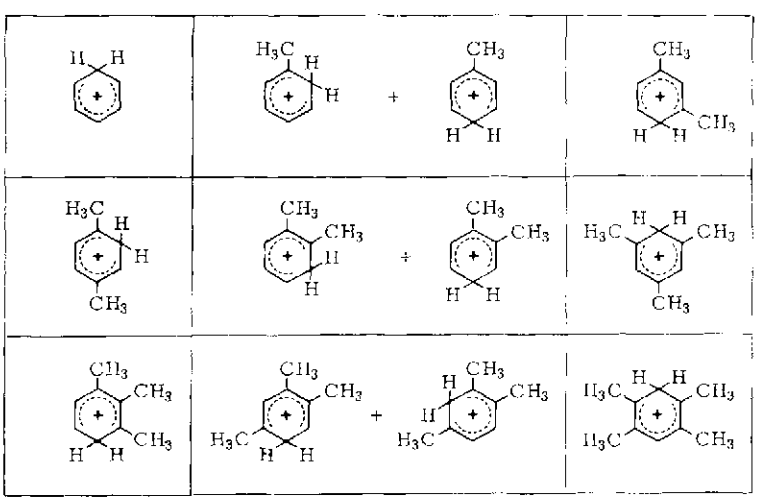
[30] *L. J. Bellamy:* Ultrarotspektrum und chemische Konstitution. Steinkopff, Darmstadt 1955.

Table 2. Expected and observed γ-C–H vibrations of some proton-addition complexes of aromatic hydrocarbons.

| No. of neighboring "free" H atoms | 5 | 4 | 3 | 2 | 1 |
|---|---|---|---|---|---|
| | Regions of the C–H bands expected [cm$^{-1}$] | | | | |
| Complex | 730–770 (vs) 690–715 (s) | 735–770 (vs) | 750–810 (vs) 660–725 (m) | 800–860 (vs) 700–750 (m) | 860–900 (m) |
| Benzene·H$^+$ | 690 (vs) | | | | |
| Toluene·H$^+$ | | 742 (vs) | | 848 (vs) 709 (vs) | |
| *o*-Xylene·H$^+$ | | | 797 (m) 710 (s) | | |
| *m*-Xylene·H$^+$ | | | | 829 (s) 732 (s) | 875 (s) |
| *p*-Xylene·H$^+$ | | | | 857 (vs) 720 (s) | 873 (m) |
| Mesitylene·H$^+$ | | | | | 867 (m) |
| Hemimellito·H$^+$ | | | | 784 (vs) 729 (s) | |
| Pseudocumene·H$^+$ | | | | 824 (s) 734 (s) | 876 (m) 888 (m) |
| Durene·H$^+$ | | | | | 889 (m) |
| Hexamethylbenze·H$^+$ | – | – | | | – |

Symbols: m = medium strong; vs = very strong; s = strong

In the case of *(6a)*, characteristic bands for four, and in the case of *(6b)*, those for two neighboring hydrogen atoms should appear; toluene itself exhibits the bands for five neighboring H atoms. The proton-addition complex of toluene does in fact give bands indicating the existence of the two isomeric complexes *(6a)* and *(6b)* side by side.



A 382.4

Fig. 4. Structures of the proton-addition complexes of various methylbenzenes (from top left to bottom right: benzene, toluene, *m*-, *p*-, *o*-xylenes, mesitylene, hemellitol, pseudocumene, and durene).

As can be seen from Table 2, new bands appear in the regions of the γ-C–H vibrations for all the proton-addition complexes of methylbenzenes investigated so far. It is thus possible to establish the position of addition of the proton for each individual methylbenzene in a simple manner. The structures determind in this way, and also the isomeric complexes, can be seen from Figure 4. The positions of addition agree with the positions of the methylbenzenes that are most active for D/H exchange [31]. The changes appearing in the infrared spectrum of *p*-xylene (Fig. 5), on proton addition can be seen particularly clearly, since only one

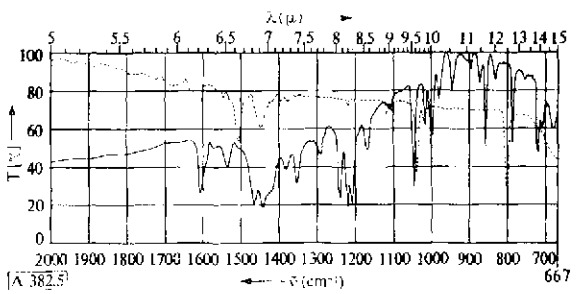



Fig. 5. Infrared spectrum of *p*-xylene (– – –) and its proton-addition complex (———) in the solid state at 77 °K. In the formation of the complex, tempering of the film of material with consequent displacement of the intensity background cannot be avoided.

proton-addition complex is produced. Comparison of the bands in the infrared spectrum of the proton-addition complex of *p*-xylene with the bands calculated for *p*-xylene [32,33] shows that the new bands correspond to the infrared-inactive vibrations of *p*-xylene [29]. Similar remarks apply to the proton-addition complexes of other methylbenzenes.

### 3. Ultraviolet Absorption Spectra

*Eley* and *King* [34] and *Reid* [35] were the first to investigate the ultraviolet spectra of some ternary (aromatic hydrocarbon/HX/$MX_3$) and binary (aromatic hydrocarbon/$MX_3$) systems. Since, however, their results ex-


[31] *E. L. Mackor, P. J. Smit,* and *J. H. van der Waals,* Trans. Faraday Soc. *53*, 1309 (1957).

[32] *M. A. Kovner,* Dokl. Akad. Nauk SSSR *97*, 229 (1954).

[33] *E. D. Schmid, J. Brandmüller,* and *J. Nonnenmacher,* Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 960 (1960).

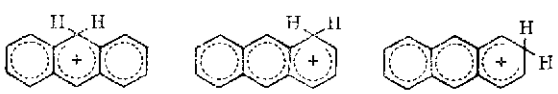
[34] *D. D. Eley* and *P. J. King,* J. chem. Soc. (London) *1952*, 2577, 4972.

[35] *C. Reid,* J. Amer. chem. Soc. *76*, 3264 (1954).

hibited some contradictions and obscurities, *Luther* and *Pockels* [23] reinvestigated the spectra of the binary and ternary systems of benzene, toluene, and α- and β-methylnaphthalenes with $AlBr_3$, $AlCl_3$, HBr, and HCl. The results for the ternary systems were on the whole confirmed, but those for the binary systems were very different.

Over the last few years, *Hoijtink*, *Mackor*, *Dallinga* et al. studied the ultraviolet spectra of pure proton-addition complexes of aromatic hydrocarbons in hydrofluoric acid [36] and in trifluoroacetic acid/$H_2O$/$BF_3$ mixtures [37]. They also used ultraviolet spectroscopy to study the interaction in the binary systems aromatic hydrocarbon/Lewis acid in 1,2-dichloroethane as solvent [38]. Other investigations of the ultraviolet spectra of such binary systems [39–41] were carried out on thin films in high vacuum in the absence of solvent [42].

If a covalent C–H bond is formed during the addition of protons, the π-electron structure is profoundly changed. Thus, in the 9-anthracenium ion *(7a)* one π-electron pair of the aromatic hydrocarbon is claimed by the methylene group in the complex. *Mackor*, *Kruizinga*, and *Verrijn Stuart* [43,44] carried out quantum-mechanical calculations by the HMO and SCF methods [*] for this model, and found that structures *(7b)* and *(7c)* must also be taken into account.



*(7a)* *(7b)* *(7c)*

Comparison of the ultraviolet spectra calculated for the structures *(7a)–(7c)* with the measured spectrum of the anthracene adduct unambiguously indicates the *meso*-configuration *(7a)*, as was to be expected [36,43]. A long-wave band at about 25000 $cm^{-1}$ can be calculated for the benzene complex; *Luther* and *Pockels* [23] observed an intense band at 30000 $cm^{-1}$, *i.e.* greatly displaced towards the red as compared with the corresponding band in the benzene spectrum, and a shoulder at about 25000 $cm^{-1}$. A similar spectrum had previously been given by *Eley* and *King* [34]. When methyl substituents are present, the intense band is found at lower frequencies, but the appearance of the spectrum is unaltered (cf. Table 3).

Table 3. Position and intensity of the strongest band in the proton-addition complexes of benzene [23] and some of its methyl derivatives [38].

| Proton-addition complex | $\tilde{\nu}_{max}$ [$cm^{-1}$] | $\varepsilon_{max}$ |
|---|---|---|
| Benzene·$H^+$ | 30100 | |
| Mesitylene·$H^+$ | 28200 | 11000 |
| 1,2,3,5-Tetramethylbenzene·$H^+$ | 27400 | 7500 |
| Pentamethylbenzene·$H^+$ | 26550 | 9800 |

The ultraviolet spectrum of the binary system benzene/$AlCl_3$ measured in the solid state at low temperatures by *Perkampus* and *Kranz* [40,41] is also in agreement with that given by *Luther* and *Pockels* [23]. Since infrared measurements [24] have shown that, with intensively dried benzene, interaction can only be observed when hydrogen halide is present in addition to the Lewis acid, a proton-addition complex is also probably present in this case. Normally, the protons must arise from traces of water that may be present in the benzene or adsorbed on the cell walls.

As we have recently shown, interactions without participation of a proton can also be detected by infrared spectroscopy in binary systems aromatic hydrocarbon/Lewis acid. These interactions depend markedly on the donor strength of the aromatic hydrocarbon and on the acceptor strength of the Lewis acid [45]. However, benzene undergoes no interaction with $AlCl_3$. For this reason, the ultraviolet spectrum measured in the solid state must be ascribed to a ternary system, *i.e.* to a proton-addition complex.

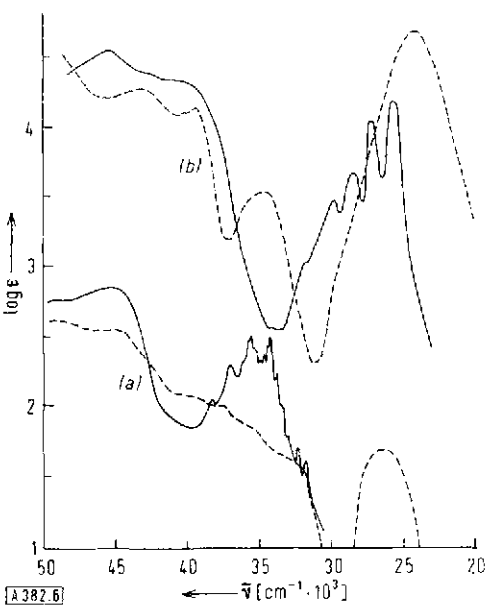



Fig. 6. Ultraviolet spectra of solid naphthalene (a), anthracene (b), and their solid $AlCl_3$ complexes. The extinction coefficients apply only to (b); for (a) only the extinctions were determined.
Pure hydrocarbon: (——); complex: ( – – ).

Figure 6 gives the absorption spectra for solid anthracene/$AlCl_3$ and naphthalene/$AlCl_3$ complexes [39]. As regards the positions of the bands, the two spectra agree surprisingly with those given by *Mackor* et al.

[36] *G. Dallinga*, *E. L. Mackor*, and *A. A. Verrijn Stuart*, Molecular Physics *1*, 123 (1958).

[37] *W. Ij. Aalbersberg*, *G. J. Hoijtink*, *E. L. Mackor*, and *W. P. Weijland*, J. chem. Soc. (London) *1959*, 3049.

[38] *W. Ij. Aalbersberg*, *G. J. Hoijtink*, *E. L. Mackor* and *W. P. Weijland*, J. chem. Soc. (London) *1959*, 3054.

[39] *H.-H. Perkampus* and *Th. Kranz*, Z. physik. Chem. N.F. *34*, 213 (1962).

[40] *Th. Kranz*, Ph. D. Thesis, Technische Hochschule Hannover, 1963.

[41] *H.-H. Perkampus* and *Th. Kranz*, Z. physik. N.F., in the press.

[42] *H.-H. Perkampus*, Z. physik. Chem. N.F. *13*, 278 (1957); *19*, 206 (1959).

[43] *A. A. Verrijn Stuart* and *E. L. Mackor*, J. chem. Physics *27*, 826 (1957).

[44] *A. A. Verrijn Stuart* and *J. H. Kruizinga*, unpublished work; cf. [36].

[*] HMO Hückel molecular orbital.
SCF = self-consistent field.

[45] *H.-H. Perkampus* and *E. Baumgarten*, unpublished work.

[36,43] for the proton-addition complexes. In the case of the naphthalene/$AlCl_3$ complex, moisture may have been present. However, for the anthracene/$BF_3$ complex in 1,2-dichloroethane as solvent, *Hoijtink*, *Mackor*, et al. [38] found a spectrum similar to that given in Figure 6 and to that of the proton-addition complex.

These authors exclude the participation of protons and assume a σ-complex with a structure similar to that of the proton-addition complex. According to *Mackor*, *Hofstra*, and *van der Waals* [46], the basicity [*] increases from naphthalene to anthracene by about eight powers of ten, so that a σ-complex between anthracene and a Lewis acid is quite conceivable. In tetracene and the still higher homologues of naphthalene, the basicity increases further, in proportion to the decrease in ionization energy [47]. It is therefore understandable that, under the same conditions as for anthracene, a σ-complex is also assumed for tetracene/$BF_3$ [38]. According to our own infrared measurements, σ-complexes can be detected in the products obtained from methylnaphthalenes, but not in that from naphthalene itself [48]; this is in harmony with the increased basicity of the methylnaphthalenes due to their methyl groups [19].

Table 4. Experimentally determined and theoretically predicted ultraviolet absorption maxima of some proton addition complexes [36,37,43].

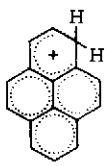
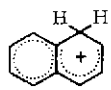
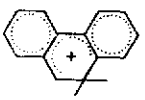
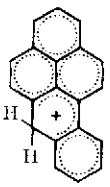
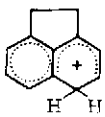
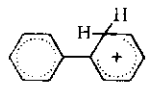
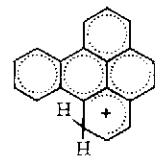
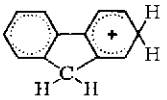
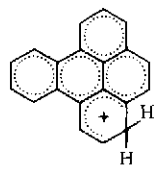
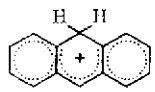
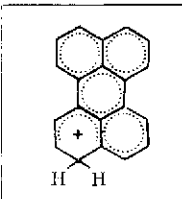
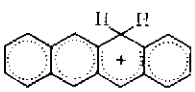
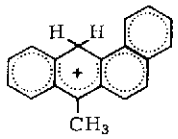
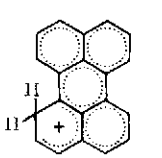
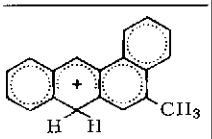
| Carbonium ion | $\tilde{\nu}$max [cm$^{-1}$] obs. | $\tilde{\nu}$max [cm$^{-1}$] calc. | Carbonium ion | $\tilde{\nu}$max [cm$^{-1}$] obs. | $\tilde{\nu}$max [cm$^{-1}$] calc. |
|---|---|---|---|---|---|
|  | 30100 | 25000 |  | 21000<br>26400 | (15600)<br>23600<br>28900 |
|  | 25600 | 24700 | | | |
|  | 19600 | 18800<br>17800 |  | 19200<br>26100 | 22600<br>25900 |
|  | 23800<br>28300 | 24700 | | | |
|  | 22500 | 21300 |  | 18200<br>20600<br>25000 | 20200<br>27100 |
|  | 26900 | 25400 |  | | 21450<br>25100<br>29500 |
|  | 24500 | 25100 |  | 16600<br>21600<br>25000 | 17900<br>21000<br>27500 |
|  | 19000<br>22350 | 18250<br>24300 | | | |
|  | 22500 | 24100 |  | | |
|  | 19250 | 20200 | | | |

Table 4 gives the positions of the most intense bands of some proton-addition complexes as determined experimentally and calculated by *Mackor* et al. [36,37,43]. Occasionally, *e.g.* with benzo[*a*]pyrene and perylene, two carbonium ions are to be expected with approximately equal probability, so that the observed spectrum probably results from superposition of the spectra of these two [36]. The agreement of the experimental and theoretical values in Table 4 must be regarded as very good. This again shows that the model upon which the calculations were based, *viz.* the cation arising from an aromatic hydrocarbon by removal of an electron, has a relatively high probability. The light absorption of proton-addition complexes is therefore determined by the π-electron state of the positive aromatic ions.

The counterion, *i.e.* the anion, has only a small influence, comparable in its order of magnitude with solvent effects. Thus, according to *Luther* and *Pockels* [23], the ternary complexes benzene/HCl/$Al_2Cl_6$ and benzene/HBr/$Al_2Br_6$ and the complexes toluene/HCl/$Al_2Cl_6$ and toluene/HBr/$Al_2Br_6$ differ in the position of the maxima by only $\Delta\tilde{\nu} = 600$ cm$^{-1}$. *Kranz* [49] found a similar small effect for the systems anthracene/$AlCl_3$ and anthracene/$AlBr_3$ in the solid state, $\Delta\tilde{\nu}$ being only 300 cm$^{-1}$.

If we assume that the formulation of the binary complexes anthracene/$BF_3$ and tetracene/$BF_3$ in 1,2-dichloroethane as σ-complexes is correct [38], then it should be impossible to distinguish, by means of ultraviolet spectra alone, between a proton-addition complex and a σ-complex with a Lewis acid. Light absorption is therefore determined only by the π-electron system of the aromatic cation.

The mode of stabilization of the aromatic carbonium ions can, however, be deduced by comparing the ultraviolet absorption spectra of the free aromatic hydrocarbons with those of the proton-addition complexes. At least two effects must be taken into account [41]: the carbonium ion can be stabilized either by charge resonance or by aromatization of the ring systems, which are independent in the complex. In view of the almost equal polarities of the two states [50], the first effect implies convergence of the ground and excited states, *i.e.* the complex has a smaller energy of excitation than the free aromatic hydrocarbon. In contrast, the second effect should increase the difference between ground and excited states, since aromatization of the independent ring systems affects the ground and excited states differently, so that the complex has a greater excitation energy than the free hydrocarbon.

[46] *E. L. Mackor, A. Hofstra*, and *J. H. van der Waals*, Trans. Faraday Soc. *54*, 66 (1958).

[*] For the definition of the basicity of aromatic hydrocarbons, see Table 1.

[47] *G. Briegleb:* Elektronen-Donator-Acceptor-Komplexe. Springer, Berlin-Göttingen-Heidelberg 1961.

[48] *H.-H. Perkampus* and *E. Baumgarten*, unpublished work.

[49] *Th. Kranz*, Diploma-Thesis, Technische Hochschule Hannover, 1960.

[50] *Th. Förster*, Z. Elektrochem., Ber. Bunsenges. physikal. Chem. *45*, 548 (1939).

Since with increasing linear annulation, as in the acenes, the second effect acquires significance [51], the opposing trends of the two effects become clearly expressed in the acenium ion series as the number of rings increases.

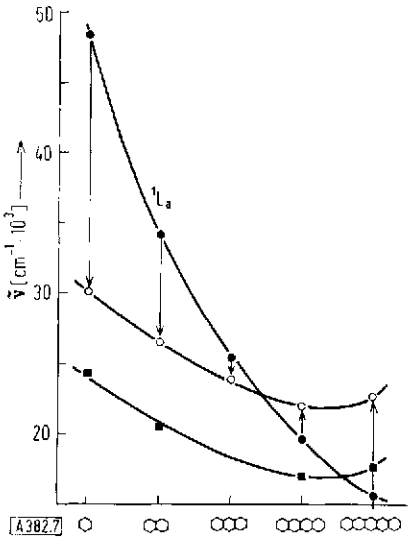



Fig. 7. Position of the bands (o) and pre-bands (■) of the proton-addition complexes and the $^1L_a$ bands (●) of acenes as a function of the number of rings. The spectra were measured at ca. 100 °K in the solid state.

In Figure 7, the maxima of the $^1L_a$ bands as well as the bands and pre-bands of the complexes are plotted for acenes as functions of the number of ring. The bathochromic shift of the absorption bands of the complexes relative to the $^1L_a$ bands of the free acenes decreases from benzene to anthracene; from tetracene onwards the main bands of the complexes have a hypsochromic shift relative to the $^1L_a$ bands. It is interesting to note that there must be some relationship between the main and pre-bands of the complexes, since the distances between the two bands remain practically constant.

The difference between the proton-addition complexes of anthracene and pentacene is the following: with anthracene, a resonance-stabilized carbonium ion is still present, whereas with pentacene, after addition of the proton, both naphthalene partial systems contribute substantially to the stabilization of the complex. In the first case, the positive charge is distributed over the whole molecule, whereas in the second it must be regarded as being localized in the center "dearomatized" ring. While the tendency to form separate aromatic ring systems follows from the reactivity of the acenes [51], and also from theory [52], charge resonance can be considered to occur in the complexes of various benz- and dibenzanthracenes (judging from their ultraviolet spectra) [39], and has been detected spectroscopically in the system 2-aminoanthracene/$AlCl_3$ [53]. In the solid state, 2-aminoanthracene and $AlCl_3$ form a complex the ultraviolet spectrum of which coincides with that of the anthracene/$AlCl_3$ complex. However, the ultraviolet spectrum of the 1-aminoanthracene/$AlCl_3$ complex is the same as that of free anthracene, *i.e.* here the $AlCl_3$ molecule adds onto the amino group. Thus, because of its auxochromic character, an amino group in the 2-position promotes charge resonance of the anthracenium ion.

It must be noted, however, that owing to great experimental difficulties, it is still impossible to provide a comprehensive description of the spectroscopic and energetic situation – *e.g.* in the form of a term scheme – for proton-addition complexes and for σ-complexes not involving a proton.

In summary, it has at least been possible to detect proton-addition complexes by means of ultraviolet spectroscopy. Since σ-complexes not involving protons give the same ultraviolet spectra, ultraviolet spectroscopic detection of these complexes is not definite. Other methods, *e.g.* infrared spectroscopy, are therefore required for this purpose [45,48].

## IV. Summary

From kinetic investigations it must be assumed that species of the type of the proton-addition complexes occur as intermediates in electrophilic substitution reactions of the benzene nucleus [54]. However, it is only when the structures of these intermediate cationic complexes become known that it will be possible to say something definite about the reaction mechanism. The present paper was primarily concerned with spectroscopic methods, since they yield information on the structure of proton addition complexes either directly or in combination with theoretical considerations. As has been shown, the results of PMR and ultraviolet spectroscopy complement one another without contradictions, so that, for example, the structures of the proton-addition complexes of the methylbenzenes given in Figure 4 can be taken as established.

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[51] *E. Clar:* Aromatische Kohlenwasserstoffe. 2nd Edit., Springer, Berlin-Göttingen-Heidelberg 1952; *H. Hartmann:* Theorie der chemischen Bindung auf quantenmechanischer Grundlage. Springer, Berlin-Göttingen-Heidelberg 1954.

[52] *H. Hartmann*, Z. Naturforsch. *3a*, 29 (1947); *E. Hückel* and *B. Krause*, ibid. *6a*, 112 (1951).

[53] *H.-H. Perkampus* and *Th. Kranz*, Z. physik. Chem. N.F. *36*, 238 (1963).

[54] *H. C. Brown* and *L. M. Stock*, J. Amer. chem. Soc. *84*, 3298 (1962); *S. U. Choi* and *H. C. Brown*, ibid. *85*, 2596 (1963).

# Gradient and Low-Temperature Thin-Layer Chromatography

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*The preparation and the use of gradient layers for thin-layer chromatography are described. On a gradient layer there are three flow surfaces, all differing in their separation behavior. It is therefore possible to determine, for example, the basicity and/or activity which gives the optimum separation for a mixture of substances. Gradient thin-layer chromatography was also carried out at low temperatures, after the effect of temperature on the separation of various mixtures had been studied.*

Thin-layer chromatography [1–6] on silica gel was first used for the separation of lipophilic substances. The method was next extended to hydrophilic substances, and new fine-grained inorganic and organic adsorbents were used. It was then found that the separation of amino acids was better, more sensitive, and more rapid, when it was carried out on fine-grained layers than on the fibrous paper [7].

Today a large number of adsorbents is available for thin-layer chromatography [8]. This is important, since a successful separation depends on the correct choice of both stationary and mobile phases. Whereas the stationary phase is more or less given in paper chromatography, the same is true for the mobile phase in gas chromatography. It is only in column and thin-layer chromatography that both phases can be widely varied.

We have attempted to find other methods of improving the efficiency of separation, and these attempts will be reported here, with the main emphasis on equipment.

## Influence of Temperature on the Separation

Temperature differences between 4 and 20 °C appear to have no appreciable influence on the developing time and the $R_f$ values [9] in thin-layer chromatography. However, according to *Malins* and *Mangold* [10], "low-temperature chromatography" (4–6 °C) on siliconized layers of silica gel G often gives a better separation of certain fatty acids. It still remained to be shown whether a change in temperature could lead to a general improvement of the separation in thin-layer chromatography.

We were interested in "low-temperature" thin-layer chromatography for the following reasons:

1. the possibility of using low-boiling solvents and liquefied gases as developing solvents;
2. thin-layer chromatography of volatile compounds which, under normal conditions, either completely or partly evaporate out of the layer;
3. "freezing-in" of excited molecular states during chromatography.

In order to carry out chromatography at constant temperature over a wider range (+50 to −50 °C), the conventional Desaga trough chamber was enclosed in a thermostatically controlled jacketing vessel (Fig. 1).

However, not only the chamber but also the plate supporting the layer should be at the desired temperature. It must therefore be suspended in the chamber in




Fig. 1. Thermostatically controlled "Kryobox" chamber for low-temperature thin-layer chromatography (Photograph: Desaga).

[*] Lecture, Achema Conference, 1964, in Frankfurt/M. Also Communication No. 14 on Thin-Layer Chromatography. – Communication No. 13: *E. Stahl*, Lab. Practice *13*, 496 (1964).

[1] *E. Stahl*, Chemiker-Ztg. *82*, 323 [1958].

[2] *J. M. Bobbitt*: Thin-Layer Chromatography. Reinhold Publishing Co., New York 1963.

[3] *Y. Hashimoto*: Thin-Layer Chromatography. Hirokawa-Shotten Ltd., Tokyo 1962.

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[6] *E. V. Truter*: Thin-Film Chromatography. Cleaver-Hume Press, London 1963.

[7] *M. Brenner, A. Niederwieser*, and *G. Pataki*: in [5].

[8] *P. J. Schorn*, Z. analyt. Chem. *205*, 298 (1964).

[9] *E. Stahl*, Pharmazie *11*, 633 (1956).

[10] *D. C. Malins* and *H. K. Mangold*, J. Amer. Oil Chem. Soc. *37*, 576 (1960).

such a way that it does not dip into the solvent until it has reached the chosen temperature. At lower temperatures, this often requires 30 to 45 minutes. A striking feature of this equilibration is that it reduces the developing time by half without any noticeable change in the $R_f$ values. For example, the developing time for a 10 cm separation distance is 21 min if the plate is dipped into the solvent immediately, and only 9 min after temperature equilibration for 30 minutes. This may be due to the fact that the solvent vapor coats the particles of the adsorbing agent. Such a coated layer would then present only a small "frictional drag" to the solvent ascending in the capillaries.

It was found that ®Frigens can be used as developing solvents at lower temperatures. With Frigen 21 (monofluorodichloromethane, b.p. 8.9 °C) at −10 °C mixtures of geranyl acetate, asarone, carotol, and hydroxycaryophyllene could be nicely separated, which is otherwise difficult [11]. With other solvents the separation was less effective in this temperature range, and there was no separation at room temperature. According to *Hückel* et al. [12,13], low-temperature thin-layer chromatography is also suitable for the separation of terpenes. These authors separated terpene mixtures on alumina columns at −40 to −78 °C, using dimethyl ether (b.p. −23.6 °C) and propene (b.p. −47.0 °C) [*].

We therefore investigated the separation of mixtures of this type on layers of silica gel H using a 1:1 pentane-hexane mixture. It was found that the $R_f$ values decreased with falling temperatures (Fig. 2, left).

The readily volatile α-pinene apparently no longer evaporates off at lower temperatures and can be detected after separation. When more highly polar solvents such as methylene chloride and/or chloroform are used, the temperature effect is generally less pronounced (Fig. 2, right). Carotol constitutes an exception in that a clear separation from geranyl acetate is obtained only at low temperatures.

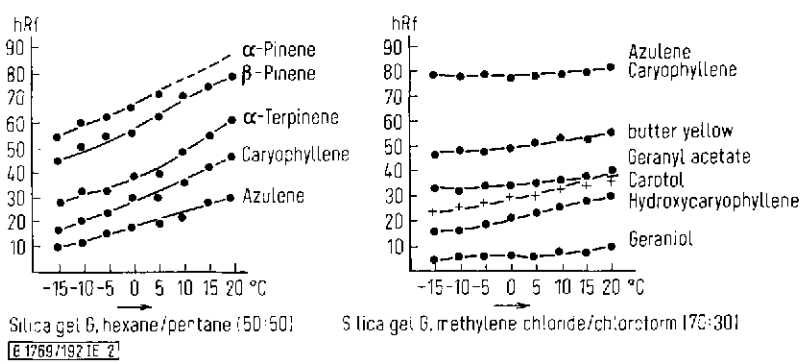



Fig. 2. Influence of temperature on the $R_f$ values of various substances. Note the separation of the geranyl acetate/carotol mixture.

[11] *E. Stahl*, Arch. Pharmaz. *297*, 500 (1964).

[12] *W. Hückel* and *W. Hornung*, Chem. Ber. *90*, 2023 (1957).

[13] *W. Hückel* and *G. Meinhardt*, Chem. Ber. *90*, 2025 (1957).

[*] After completion of this manuscript, a paper was kindly sent to us by *C. Mathis* (Ph. D. Thesis, Strasbourg 1963), describing the separation of terpene hydrocarbons on silica gel/silver nitrate layers and on layers of silica gel G at −15 °C.

Low-temperature thin-layer chromatography is of great value for the separation of mixtures of sensitive natural products, *e.g.* carotenes and carotenoids; decomposition can be largely suppressed in such cases [14].

## Devices for the Production of a Gradient Layer

As a model, we first solved the problem of mixing a uniformly colored silica gel H suspension with one of another color, or an uncolored suspension, and then depositing the mixture in such a way that the layer shows a continuous gradation of color intensity.

### a) Division of Dissimilar Coating Materials (Fixing the Gradient)

A simple solution to the problem seemed to be the use of a rectangular trough divided diagonally into two compartments (Fig. 3 top). The colored suspension of the adsorbent could then be placed in one compartment, and the same volume of the uncolored suspension in the other. Corresponding to its function, we describe this simple device as a "divider box".

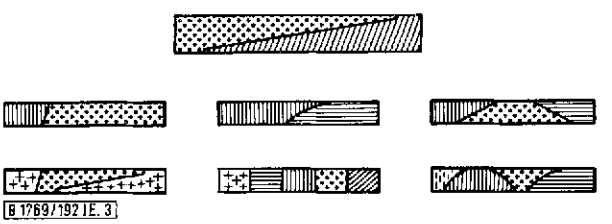



Fig. 3. Various forms of the divider box (viewed from above). The diagonal divider (top center) was preferred for the preparation of gradient layers.

It was found advantageous to make the partition removable, and to give it a certain shape at the ends. Any desired gradients can be achieved by different, non-diagonal arrangements of the partition, or by the use of several partitions (Fig. 3, lower part).

The next problem was to mix the suspensions present in the divider box in such a way, that the mixing effect occurred roughly transversely to the longitudinal axis of the divider and that the gradient was maintained. The simplest method would have been to remove the partition and carry out the mixing process in the divider box itself. However, the corners of the trough interfered with the mixing process, and a separate

[14] *E. Stahl*, Laboratory Practice *13*, 496 (1964).

cylindrical mixing vessel was therefore used. This raised the necessity of opening the base of the divider box in such a way that the two suspensions fall into the mixing vessel without mixing.

b) Mixing of the Coating Materials

Once again, there are a number of possibilities. The necessity of avoiding longitudinal mixing led us to divide the mixing vessel into numerous small compartments (Fig. 4). The disc-shaped partitions between

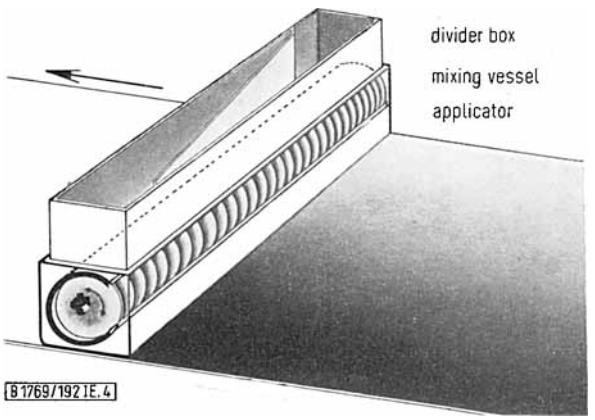



Fig. 4. Simplified semi-diagrammatic representation of the GM applicator during deposition of a gradient layer.

the compartments were fitted to a rotating shaft, which was turned by a hand-operated crank. The mixing effect could be intensified by making the mixer shaft execute a slight lifting motion with each rotation.

Other modes of mixing, *e.g.* by vibration, or (in the absence of partitions) by a kitchen twirl, an ointment mill, or rotating brushes, did not give the desired results.

c) Special Devices for Thin-Layer Chromatography

It was now necessary to adapt the divider box and the mixing vessel to the applicator which we had previously developed, in such a way, that the three processes (division, mixing, and application) could be carried out in one piece of equipment. For economic reasons, we looked for a solution which would make it possible to convert the standard applicator into the GM applicator (G = gradient, M = mixer) (Fig. 5) in a simple manner.

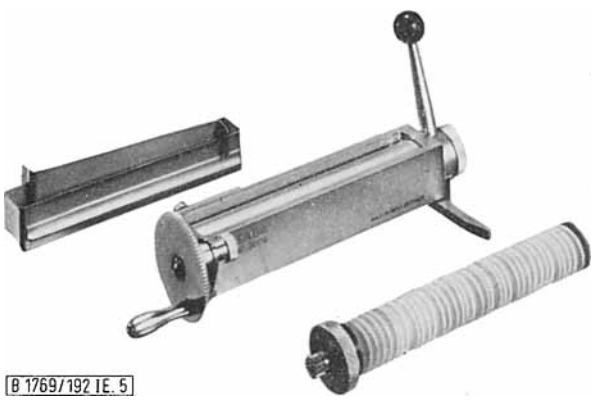



Fig. 5. Individual parts of the GM applicator.
Left: the attachable diagonal divider box; center: the actual applicator with cogwheel drive fitted; right: mixing shaft with thirty partition discs. (Photograph: Desaga).

With this in mind, the mixing shaft was located in the sleeve of a normal applicator for thin-layer chromatography, provided with a slit. The divider box can then be attached to this combined "mixer-applicator" (Fig. 6). The bottom of the divider box in this case is formed

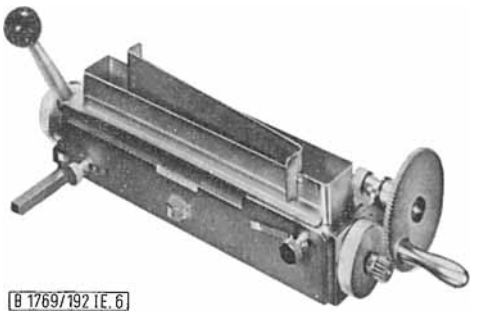



Fig. 6. Front view of the assembled GM applicator with layer-thickness adjustment. (Photograph: Desaga).

by the rotating sleeve of the applicator. The diagonal partition must be suitably mounted in the divider box. To fit the divider box, it was only necessary to enlarge the feed slot of the applicator block and the sleeve. The problem of admitting air during the coating process was solved by setting the sleeve slot correspondingly (Fig. 8 C).

In preparing the gradient layers (see operating instructions) it is necessary to observe the following points:

d) Adsorbents for the Gradient Layer and Testing the Layer

The particle size distributions of the adsorbents must correspond to the normal requirements for thin layer chromatography, and should not differ appreciably between the adsorbents mixed. Consistency of the coating material is of fundamental importance in the formation of the gradient layer. The method fails if the materials are too viscous or even pasty, while difficulties are encountered in sealing the equipment in the case of excessively thin or watery suspensions. The most suitable proportions for the mixture are easily determined in preliminary experiments.

In the case of colored layers it can be seen if the transition is continuous. For observing details we used the "Chromoscan" [*] automatically recording double-beam reflection densitometer. Fig. 7 shows that a practically stepless gradient was in fact achieved. However, colored adsorbents are not normally used in thin-layer chromatography. Since it may nevertheless be necessary to check the gradient, the following method was developed: An inorganic fluorescent tracer is added to one of the two adsorbents, and the continuity of the gradient is checked under an ultraviolet lamp after the layer has dried. An example is given in the following Section. If there is a pH gradient, the success of the preparation can be determined by spraying a strip with universal indicator.

[*] We should like to thank the manufacturers, Messrs. Joyce, Loebl and Company, Ltd., Gateshead-on-Tyne (England), and the distributors, Messrs. Kurt Hillerkus, Krefeld (Germany), for loan of the apparatus.

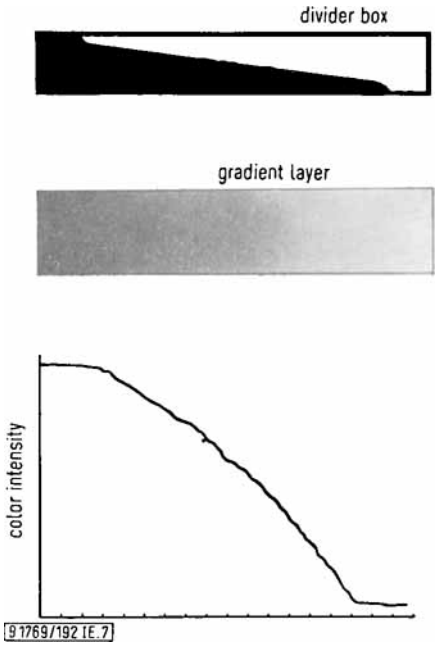



Fig. 7. Photometric test of a color-gradient layer (center), prepared with the GM applicator (diagonal divider box above). The densitometer curve (below) indicates a continuous change in the color intensity.

## Procedure

Numerous experiments have led to the following procedure for the use of the GM applicator [**].

### I. *Preparation of the coating material for five plates 20×20 cm²*

1a) Kieselguhr G ("Merck") for thin-layer chromatography (20 g) is shaken in a 100 ml wide-neck Erlenmeyer flask with 45 ml of distilled water, to form a uniform suspension.

1b) Silica gel $HF_{254}$ (18 g) is mixed with 45 ml of water in a second flask.

2. Portions of silica gel G (20 g each) are shaken with 45 ml of (a) 0.1 N potassium hydroxide solution and (b) 0.1 N orthophosphoric acid.

### II. *Preparation of the equipment*

The template of the basic Desaga apparatus must be perfectly horizontal since any tilting leads to undesirable longitudinal mixing in the gradient layer. The glass plates are then laid down in the usual manner and the GM applicator is placed on the 5 cm starting plate.

Assembling the GM applicator: (a) The mixing shaft is introduced into the rotating sleeve of the applicator and the threaded cover is screwed on. (b) The cogwheel crank drive is attached to the applicator by two screws. The drive wheel can be easily withdrawn and set at the required distance by means of a clamping bolt. The mixing shaft must turn freely in both directions. (c) The lever of the sleeve is turned so that the feed orifice is closed (see Fig. 8A). (d) The divider box housing with the diagonal partition is fitted and tested for leaks at the seating.

Filling the divider box: (a) The suspensions (see 1a and 1b) are placed one in each of the two compartments of the divider box. Care must be taken that the compartments are filled to the same level all over, and that the levels in the two compartments are equal. (b) The housing of the divider box is held firmly in position and the diagonal partition is carefully removed. (c) Still holding the housing firmly and pressing the applicator down on the starting plate, the sleeve is now brought into the filling position by means of the long tipping lever (Fig. 8B).

[**] Manufacturer: C. Desaga, Heidelberg (Germany).

### III. *Mixing process*

The crankshaft is rotated 30 to 40 times (ca. 30 seconds per turn) in both directions. The divider housing can now be removed. The applicator is firmly pressed down with the left hand, and the sleeve is turned to the original position (Fig. 8A). The outlet slot must, however, first be closed by bringing the adjustable front plate to the "O" position. The mixing is then repeated as described above by turning the crank.

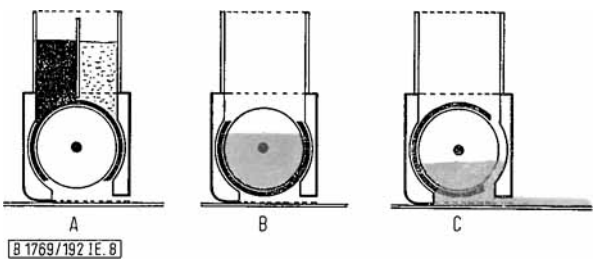



Fig. 8. Positions of the rotating sleeve of the GM applicator (cross-section) during the preparation of a gradient layer.

A. Two different adsorbents are placed in the two compartments of the divider box.

B. The partition has been removed and the sleeve is rotated by 180. The suspensions are mixed inside the sleeve.

C. During application the position of the sleeve is such that the compartments are accessible to air.

Since there must be no reduction in pressure in the compartment during the application process, the sleeve is placed in position "C" (Fig. 8C) by means of the tipping lever, which should then point upwards. This application position is easy to find owing to a built-in detent ball. Special care must be taken during tipping to ensure that the applicator is not raised, even partially, from the glass plate. The two setscrews are then loosened and the front plate is adjusted to the "open" position. The thickness of the layer should be adjusted on the scale to 0.35 mm.

### IV. *Coating the plates*

The application and drying of the gradient layers and chromatography on these layers are carried out in the usual manner (standard method [5]).

### V. *Control and presentation of results*

Before using the gradient layer, the quality of the gradient should be checked. In example 1.1a, a uniform decrease in the intensity of the green fluorescence must be observed, when the layer is examined in ultraviolet light (254 mμ). In the case of layers with a pH gradient, most of the chromatography surface is masked, and a narrow strip of the layer (above the later solvent front), which runs perpendicular to the direction of application, is sprayed with an indicator (pH 0 to 5 or pH 4 to 10) possibly diluted with acetone.

In the presentation of the results on gradient layers, all details, including the form of the divider box, the nature of the adsorbent suspension, and the method by which the quality of the layer was checked, must be given in order to ensure reproducibility. In diagrams the gradient should be indicated (see, for example, Figs. 10–12).

## Types and Applications of Gradient Layers

Using the procedure described above, it is possible to achieve a continuous transition between two sorption properties. It is easy to see, for example, the advantages of a gradient layer in which the sorption properties pass from active to inactive. In Fig. 9 the active part of the layer is represented by dark shading and the inactive part is light. It can be seen that, in contrast to the conventional uniform layers, a gradient layer offers three flow directions with different layer properties (Fig. 9A, B, C).

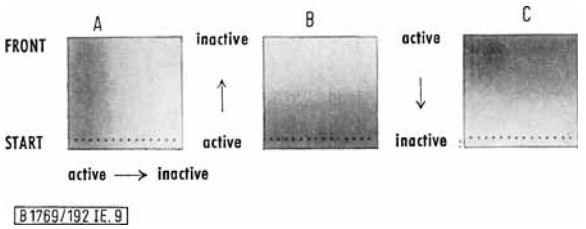



Fig. 9. The three possible applications of a gradient layer (ascending development). Shading and arrows indicate the gradient.

In case "A", which in our opinion will attract particular attention, we have numerous "open separating columns", all with slightly different properties, lying alongside one another. In the example chosen, the most active "columns" lie on the left, while the inactive ones are on the right. The different separation effects on a layer of this type can be demonstrated if a mixture of dyes is applied onto numerous starting points alongside one another (Fig. 10A). This also provides a rapid method of determining the ratio of adsorbents at which the best separation is achieved. We have used combinations of the following adsorbents:

| | |
|---|---|
| Silica gel | Kieselguhr |
| Alumina, basic | Glass powder |
| Alumina, neutral | Cellulose |
| Alumina, acidic | Cellulose derivatives |
| Magnesium silicate | Perlon |

With arrangement "A", it is also possible to determine rapidly whether and at what concentration a certain "impregnation" gives an improved separation. The "impregnant" is added to the water used in the preparation of the coating material. The following additives may be included: Acids and acid salts, bases and basic salts, buffer mixtures, silver nitrate and other heavy metal salts, polyethylene glycol, glycerol, and sugar. Solids can also be used in very finely powdered form.

The actual gradient of the layer is employed in chromatography using arrangements "B" and "C" (see Fig. 9). In this case the sorption property of the layer changes from the start to the front.

In classical column chromatography, use has already been made of columns arranged in series, packed with adsorbents of different strengths [15]. *Hesse* et al. [16] showed that active alumina columns can be made into a kind of gradient column (inactive-active) by sucking through a certain quantity of water vapor.

[15] *L. Gattermann*: Die Praxis des organischen Chemikers. 37th Edition, Walter de Gruyter, Berlin 1956.

Figure 10B shows the result of separating the dye mixture, already used for the chromatogram in Fig. 10A, now using arrangement "B" (flow direction from active to inactive). This is compared to "C", *i.e.* flow direction from inactive to active (Fig. 10C). Mixtures of substances with acidic or basic properties can be separated on pH-gradient layers.

## "Three-Dimensional" Thin-Layer Chromatography

The two-dimensional technique of chromatography consists in separating a mixture on a chromatogram and rechromatographing the zones in a direction perpendicular to the original one using another developing solvent. When the two-dimensional method is used on a gradient layer, the gradient always has an additional influence in one of the two flow directions, and so has the effect of another "dimension"; in such cases we can speak of a "three-dimensional" chromatogram.

However, since this expression does not coincide with the usual picture of a third dimension, and since two-dimensional chromatography is not carried out in every case, it is better to speak of chromatography on a gradient layer. It will therefore be necessary in future to differentiate between chromatography with "gradient elution", as described by *Wieland* and *Determann* [17] and "thin-layer chromatography on a gradient layer". In some cases it is even possible to combine the two methods. With regard to the "gradient elution" technique, which is undoubtedly gaining importance in thin-layer chromatography, the reader is referred to the "gradient" mixed batteries developed by *Peterson* and *Sober* [18].

## Further Uses and Outlook

Using the principle described above, it is also possible to set up chromatography columns in such a way, that the packing exhibits a gradient. Details of this arrangement and its possible uses will be reported later.

The difficulties in the preparation of gradient layers, as regards both apparatus and method, consumed more time than had been anticipated. It has therefore not yet been possible to study systematically a greater number of applications. The following examples have resulted from experiments which are still in progress.

Using gradient layers with a transition from basic to acidic alumina ("Woelm", thin-layer chromatography grade), it has been found that an optimum separation of alkaloid and amine mixtures could be achieved only at very definite mixing ratios of the two adsorbents. For the silver nitrate silica gel H layers which are frequently used we were able to determine the optimum $AgNO_3$ content by gradient-layer chromatography. A new method for the chromatographic characterization of basic, amphoteric, and acidic substances has been found in the use of acidic → basic silica gel G gradient layers.

[16] *G. Hesse*, Z. analyt. Chem. *181*, 274 (1961).

[17] *Th. Wieland* and *H. Determann*, Experientia *18*, 431 (1962).

[18] *E. A. Peterson* and *H. A. Sober*, Analytic. Chem. *31*, 857 (1959).

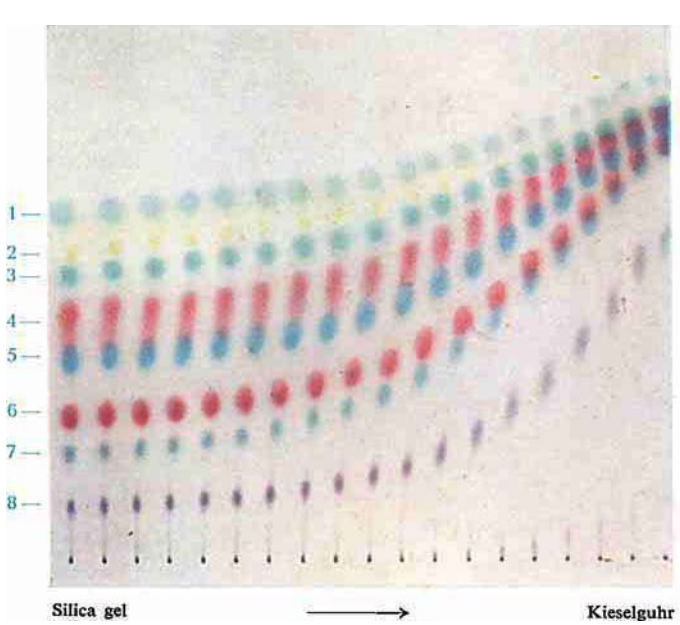



Fig. 10 A

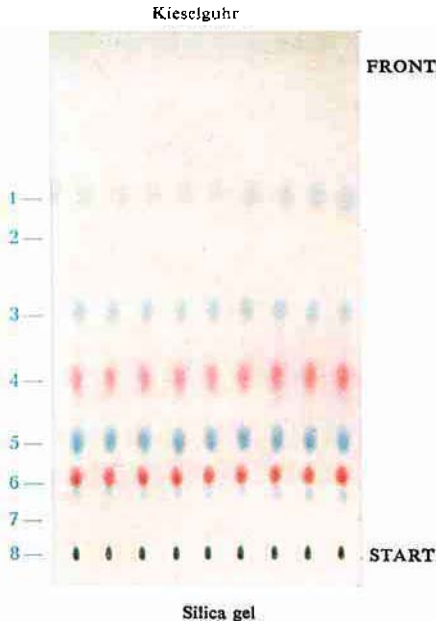



Fig. 10 B

Fig. 10. Separation of a mixture of eight fat-soluble dyes on a silica gel $GF_{254}$ → kieselguhr G gradient layer (diagonal divider box). Solvent: benzene. Saturated chamber, flow distance: 18 cm.

Chromatogram A:
Separation deteriorates with decreasing "activity" of the layer.

Chromatogram B:
Good separation in the upper part of the chromatogram.

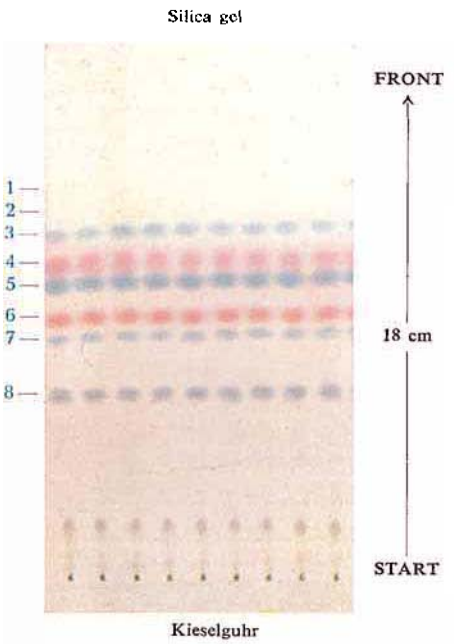



Fig. 10 C

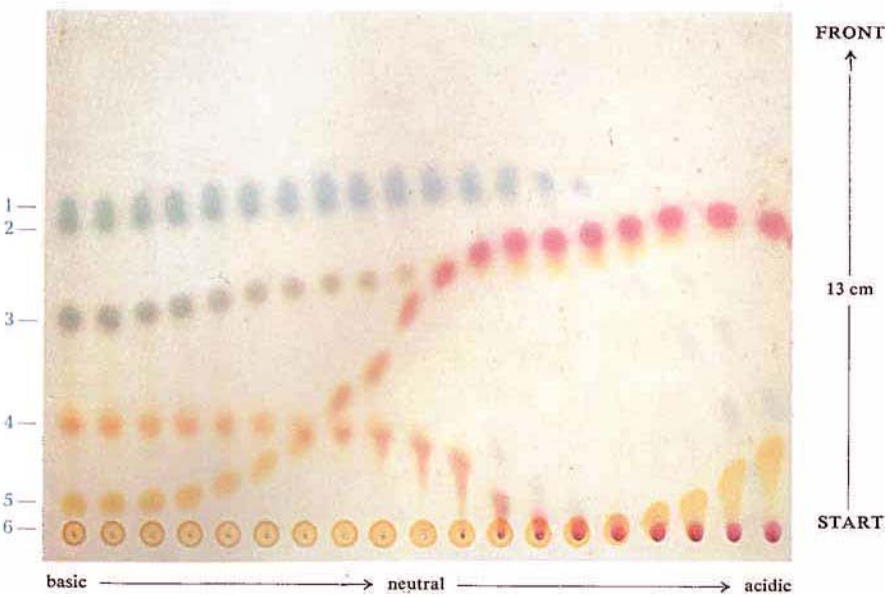



Fig. 11

Chromatogram C: Clean separation with the possibility of placing more strongly polar dyes in the lower part of the chromatogram.

The dyes are noted by figures:

1. Guaiazulene
2. Azobenzene
3. Sudan green
4. Ceres red
5. Ceres blue
6. Sudan red G
7. Indophenol
8. Ceres black.

Fig. 11. Separation of indicator dyes on a pH gradient layer (diagonal divider box) on silica gel G+ 0.1 N $H_3PO_4$ → silica gel G + 0.1 N KOH. Solvent: chloroform/acetone (50:50). Saturated chamber.

Note the form of the spots and the typical curves given by the individual indicator dyes on transition from basic to acidic.

1. Guaiazulene
2. Indophenol
3. α-Naphtholphthalein
4. Neutral red
5. Methyl red
6. Thymol blue.

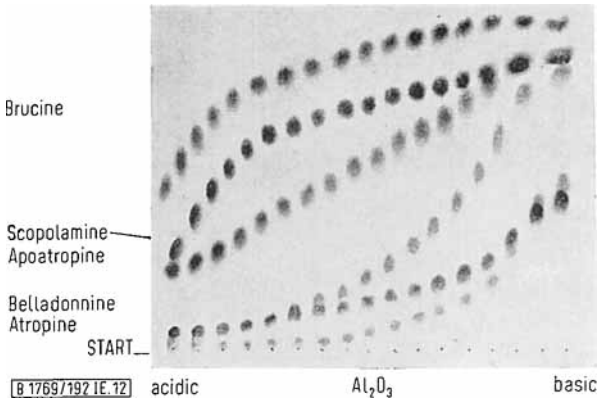



Fig. 12. Separation of a mixture of alkaloids on a gradient layer (diagonal divider box). Adsorbents: left: alumina, acidic, for thin-layer chromatography (Woelm) + 10 % gypsum; right: alumina, basic, for thin-layer chromatography (Woelm) + 10 % gypsum. Solvent: chloroform/methanol (95:5), chamber saturation. Flow distance: 15 cm. Below the spots for atropine a minor alkaloid (?) is seen.

As shown in Figs. 11 and 12, substance-specific curves, reminiscent of neutralization curves, are obtained.

The use of a gradient in the flow direction (Figs. 9, 10B, and C) offers considerable advantages, particularly in the separation of substances of different polarities. Whereas on a uniform layer of silica gel a carotene mixture from *Calendula* flowers could only be separated into seven zones, sixteen substances were recognized after chromatography on a gradient layer of kieselguhr-silica gel.

*I am grateful to J. Fuchs for his conscientious and able assistance with the experiments, to M. Kleinert of Messrs. Desaga for the careful production of equipment required, and to the Fonds der Chemischen Industrie for their support.*

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# Old and New Processes of Multiplicative Distribution (Liquid-Liquid Extraction) [1]

## A Comparison of the Methods of Material Flow and the Mode of Action

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*A new process is described for the separation of mixtures of materials by multiplicative distribution, which is characterized by repeated addition of the mixture throughout the whole process and by material exchange during the countercurrent flow of finite amounts of one, and infinitesimally small amounts of the other phase. The intrinsic features of the mode of action of the old distribution processes and the new one are developed, and their relationship to one another is discussed. In this connection, an attempt is made to clarify the confused situation in the terminology of this field by introducing clearer definitions. Reflux and "displacement distribution", another new distribution process, are treated briefly in two final sections.*

### 1. Introduction

*Multiplicative distribution* consists of the separation of dissolved materials by distribution between two co-existing liquid phases which flow in countercurrent to one another, and which are thereby repeatedly brought into contact with one another for the exchange of materials. In the ideal case equilibrium is set up. For a complete description of such a process, we must know:

1. the substances to be separated and the solvents;

2. the manner in which the mixture to be separated and the solvents are introduced into the process, passed from one material-exchange to the next, and finally removed; the total of these operations will be called the *method or scheme of material flow*;

3. the amounts or volumes of substance for each of these individual steps; and

4. the apparatus used and other technical details.

In the present paper, we shall concentrate on item 2.

In any distribution process, definite quantities and concentrations of the dissolved materials are set up in all parts of the apparatus. This pattern of quantities or concentrations coming into being at a given moment of time will be called the quantity-based or concentration characteristic, or, for the sake of brevity, the *characteristic*.

### 2. Classification of the Methods of Material Flow

We classify the various methods of material flow somewhat differently from the proposals of *Hecker* and *Allemann* [2] and *Jübermann* [3]. We use as the *main*

[1] For a more detailed treatment, see *W. Fischer*, Chemie-Ing.-Techn. *36*, 85 (1964).

[2] *E. Hecker* and *K. Allemann*, Angew. Chem. *66*, 557 (1954).

[3] *O. Jübermann* in *Houben-Weyl*: Methoden der organischen Chemie. Thieme-Verlag, Stuttgart 1958, Vol. I/1, pp. 227–339.

*classification characteristics* the method of adding the mixture to be separated and the method by which the two liquid phases are brought to the material-exchange.

### a) Method of Adding the Mixture

The mixture to be separated (subsequently called the "mixture" for short) is *added* either only *once* at the beginning of the process (discontinuous distributions) or *continuously* throughout the whole process (continuous distributions).

With a *single* addition, the mixture is separated in the course of the multistage multiplicative distribution *into numerous fractions*, all of which differ from one another in their composition. Under the *continuous* addition regime, on the other hand, the distribution system attains a stationary condition after a certain time. Here the mixture can be split only *into two fractions* differing in composition.

In some types of processes with repeated addition of the mixture, *e.g.* in which the mixture is added batchwise after equal intervals but one or both solvents is fed continuously, only quasi-stationary conditions are attained. The state of the system is subjected to periodic variations, but it repeats exactly at corresponding times of different periods. The periods are also known as *cycles*.

### b) Method of Bringing the Phases to Material Exchange

*Either finite or infinitesimal amounts of the two phases arrive at the individual steps of the material exchange process* or the process of establishing equilibrium. In this, no account is taken of back-mixing, *i.e.* of transient retrograde motion of parts of one or both phases, or of the formation of finite working volumes ("hold up", see below) in the individual distributing elements.

In this classification, there are obviously three possibilities:

1. *Both phases* are fed in *finite amounts* and brought into equilibrium, and are subsequently separated again. This applies, for example, to work with separating funnels or decanting vessels.

2. *Infinitesimal amounts of both phases* are caused to undergo material exchange and are then separated. This procedure is approached, for example, in a column when both phases are fed in countercurrent to one another with good intermixing. The same situation exists, however, when one of the two phases – subdivided almost infinitesimally – is fixed and only the other phase moves, as is the case in partition chromatography. This shows that our classification principle is *not identical* with that for the *transport* of the phases.

3. At any given moment an *infinitesimal amount of one phase* is brought into equilibrium with a *finite amount of the second phase*, is separated, and is then brought into contact with the next finite portion of the second phase. This case can be realized, *e.g.* with mixer-settlers, if one phase undergoes no movement but is present in the individual mixer-settlers in finite amounts and remains there, while the other phase is continuously passed in sequence through all the mixer-settlers, without appreciable amounts of this phase being retained in the individual units.

### c) The Various Schemes of Material Flow

By combining the two classification characteristics, therefore, *six different schemes of material flow* are obtained (Table 1). For the processes arranged in columns 1 and 2 the names proposed by *Hecker* and *Allemann* [2] are used.

Table 1. Classification of the methods of material flow in multiplicative distribution processes.

| Addition of the mixture | Arriving for material exchange or establishment of equilibrium | | |
|---|---|---|---|
| | 1<br>finite amounts of both phases | 2<br>infinitely small amounts of both phases | 3<br>finite amounts of one phase and infinitely small amounts of the other phase |
| A: single portion (discontinuous processes) | A 1<br>Craig process | A 2<br>Partition chromatography (pure [4]) and Cornish process | A 3<br>Johnson process |
| B: repeated (continuous processes) | B 1<br>O'Keeffe process | B 2<br>van Dijck process | B 3<br>new process |

Since the criterion of column 3 was not taken into account in the older classifications [2,3], processes A2 and A3 have not previously been distinguished. This is desirable however, since these processes exhibit very different characteristics and very different separating effects as a result of their different methods of material flow [1]. It is therefore also desirable to give the two processes different names. Pure [4] "distribution chromatography" and the "Cornish process" apply to class A2, while for A3 we propose the name of the "Johnson process", since, out of a number of authors who developed this process independently of one another (besides *Johnson* they are *Kies* and *Davis* [5], *Weygand* [6], *Fischer* and *Jübermann* [7]), *Johnson* was the first [8] to give it an exhaustive description and mathematical treatment [9].

Process B3 in Table 1 differs from the Johnson process only in that the addition of the mixture is repeated. We have developed and described this previously unknown process [10]. (Exhaustive treatment in the next Section and by *F. Horn* [11].)

[4] By this is understood pure partition chromatography without complications due to adsorption *etc.*

[5] *M. W. Kies* and *P. L. Davis*, J. biol. Chemistry *189*, 637 (1951).

[6] *F. Weygand*, *A. Wacker*, and *H. Dellweg*, Z. Naturforsch. *6b*, 130 (1951).

[7] *W. Fischer* and *O. Jübermann*, Chemie-Ing.-Techn. *23*, 299 (1951).

[8] *J. D. A. Johnson*, J. chem. Soc. (London) *1950*, 1743.

[9] A short description of the principle of this process and the derivation of the fundamental equation will be found in the general review of distribution processes by *S. Stene*, Ark. Kemi, Mineralog., Geol., Ser. *A 18*, no. 18, pp. 39 et seq. (1944).

[10] *W. Fischer*, German Patent 1050731 (March 6th, 1956).

[11] *F. Horn*, Chemie-Ing.-Techn. *36*, 99 (1964).

Other known distribution processes can be regarded as variants of the six fundamental types of Table 1, in which either the conditions are specially chosen (*e.g.* various methods of withdrawing the substances in the Craig process, addition of mixture at one end instead of to a middle stage of the cascade in continuous processes) or the apparatus brings about certain deviations from the selected and to some extent idealized classification criteria (*e.g.* back-mixing, only approximately infinitesimal subdividing of a phase).

## 3. The New Process

### a) Procedure

The new process is periodically quasi-stationary. The operations during one period are shown schematically in Figure 1. The process is preferably carried out in mixer-settler devices; in the example of Figure 1, five distribution elements are used.

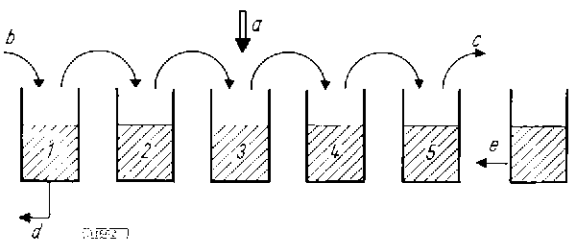



Fig. 1. Scheme of the new process.

1 to 5 mixer-settlers; a = introduction of an amount of mixture Z; b = introduction of the light phase $v_l$, in very small amounts $\Delta v_l$; c = removal of $\Sigma\Delta v_l = v_l$ with the amount of dissolved substance $m_{5,l}$; d = removal of an element at the end of the cycle with an amount of dissolved substance $m_{1,h}$ in a volume $v_h$; e = addition of an element at the end of a cycle with volume $v_h$.

At the beginning of the cycle, each mixer-settler contains a finite volume $v_h$ of the heavy phase, which remains in it as long as it takes part in the exchange; the whole cascade is free from the light phase. One of the distributing elements – the third in the example of Figure 1 – is supplied with an amount Z of the mixture to be separated. This can be added once at the beginning of the cycle, or gradually during the cycle. The light phase is added to element no. 1 in small (in the ideal case, infinitesimal) portions. Each of these portions is brought into equilibrium with the volume $v_h$, and is then immediately separated and transferred to the mixing chamber of the next unit, treated in a corresponding manner, and finally removed from element no. 5. When in this manner a certain volume $v_l$ of the light phase has been added and withdrawn continuously, the addition and removal of the finite volume $v_h$ of the heavy phase as a whole is carried out all at once. This is preferably performed by removing the mixer-settler no. 1 from the process, together with the heavy phase $v_h$ which it contains and the material dissolved in it, while a new mixer-settler containing a volume $v_h$ of pure heavy solvent is added at the other end of the distribution cascade. This completes the cycle.

The next cycle takes place in an analogous manner. In this, the previous mixer-settlers nos. 2 to 5 take over the roles of the previous nos. 1 to 4, and the newly added one the function of no. 5. Five stages are therefore in operation at any given time.

It is desirable to arrange the mixer-settlers in a circle or in two parallel lines close to one another. When more units are available than the number which must be operated simultaneously to obtain the required separating effect, and when all the units are provided with suitably arranged inlet and outlet conduits, the transition from one cycle to the next can be performed simply by operating suitable valves [10].

The process can be carried out in a similar way if the phases are treated in the reverse manner, with the light phase in finite portions and the heavy phase in infinitesimal portions.

It is impossible to achieve in practice the situation in which as presupposed above – only an infinitesimal amount of the continuously flowing phase is present in each mixer-settler. In actual fact, a finite "working volume" ("hold up") of this phase is necessary in the mixing and settling chambers. However, this affects the separating effect only slightly when the amount of material dissolved in this volume is small in comparison with the total amount of dissolved material present in the mixer-settler; cf. *Horn* [11]. A similar situation prevails in the Johnson process [12]. The following theoretical considerations are idealized throughout by the assumption of a vanishingly small working volume.

After a sufficiently large number of individual cycles under constant conditions, a quasi-stationary state is finally obtained. The concentration of the distributed materials for each stage can be calculated for this case [11], assuming constant distribution coefficients and the establishment of equilibrium at all stages; we also assume here that the mixture to be separated is introduced in the solvent-free state. *These three assumptions always apply, in what follows*, for the other processes as well, unless the contrary is expressly stated.

### b) Comparison with the O'Keeffe and van Dijck Processes

The result calculated in this way for the fractions removed from the two ends of a seven-stage distribution by the new process, with the addition of the mixture to be separated at the central (fourth) stage, are compared in Figure 2 with the situations in the O'Keeffe and van Dijck processes (which agree in their separating effects, cf. p. 798). The amounts of these end fractions are plotted logarithmically against the logarithm of the extraction factor

$$G = K \cdot \frac{v_l}{v_h} = \frac{c_l}{c_h} \cdot \frac{v_l}{v_h}$$

K being the partition coefficient, c the concentrations.

While the curves for B 1 and B 2 intersect at G = 1 and form mirror images of one another, this is not the case with the curves for the new process, which express the asymmetry of the flow of the two phases in this process. Moreover, the curves of the new process are steeper in their important sections. This means a better separating effect (cf. the following paragraph). This difference is particularly great at high values of G.

Figure 2 is also useful as a nomogram in the selection of the *operating conditions* for a given separating problem. If two substances a and b are to be separated, and the solvents have

[12] *W. Fischer* et al., Angew. Chem. 66, 319 (1954).

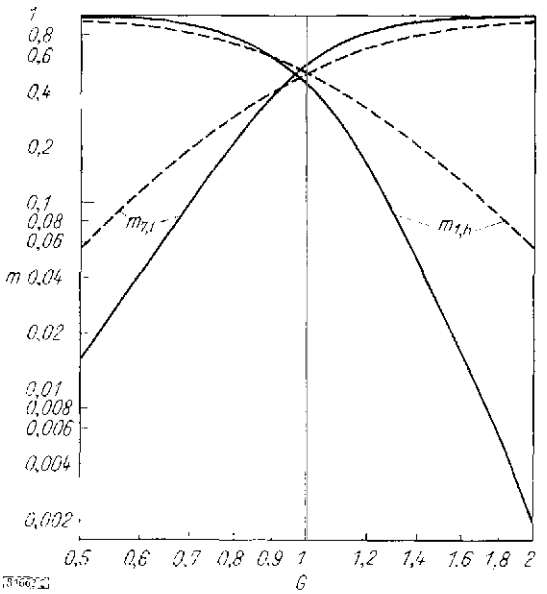



Fig. 2. *Amounts of the fractions* $m_{1,h}$ *and* $m_{7,l}$ *in fractions of the amount Z = 1 of material fed in as a function of the extraction factor G.*

Seven-stage distribution, addition of the material to be distributed to stage no. 4.

— — — O'Keeffe and van Dijck processes (B 1 and B 2)

——— new process (B 3), light phase infinitesimally subdivided.

been chosen, the partition coefficients $K_a$ and $K_b$ and the $G_a : G_b$ ratio are fixed. The absolute value of G can still be varied by the selection of $v_l : v_h$. If a rectangular aperture with a horizontal width of (log $G_a$–log $G_b$) is cut out of paper, its horizontal movement on Figure 2 corresponds to a change in $v_l : v_h$. It is then possible to read off from the ordinate the proportions of the two materials in the end fractions corresponding to any value of $v_l : v_h$ and thereby to determine the yield and purity of the separated products.

but with variations of the absolute magnitude of G; associated values for $G_a : G_b = 2$ are always adjacent to one another, while the absolute values of G decrease in the five double columns from left to right. In addition, Table 2 gives the so-called *migration ratio* or *rejection ratio* [14].

$$R = m_{7,l} : m_{1,h}.$$

In the bottom line of Table 2 is given the *overall separating effect* of the seven-stage cassade $T_{a,b} = R_a : R_b$.

*A comparison of the figures* of Table 2 shows the following facts (discussed exhaustively in [1]):

1. In processes B 1 and B 2, when the mixture is added at the central stage, a material with G = 1 (column 5a) is distributed equally in the two phases leaving the ends of the system: $m_{7,l} = m_{1,h} = 0.500$. The migration ratio R = 1.000. On the other hand, the new process operates unsymmetrically: a material with G = 1 migrates preferentially with the light phase: $m_{7,l} > m_{1,h}$ and $R > 1$.

2. If in processes B 1 and B 2 the values of G are chosen in such a way that $G_a = 1 : G_b$ (reciprocity rule), *i.e.* for our example $G_a = \sqrt{2} = 1.414$ and $G_b = 1 : \sqrt{2} = 0.707$, then $m_{7,l,a} = m_{1,h,b}$ and $m_{7,l,b} = m_{1,h,a}$. It can be seen from Table 2 (column 3, bottom) that material a is obtained in 80 % purity with 80 % yield with the light phase from stage 7, while material b is similarly obtained in 80 % purity with an 80 % yield with the heavy phase from stage 1. In order to arrive at the corresponding situation in the new process, we must make $G_a = 1.334$ and $G_b = 0.667$, *i.e.* the reciprocity rule does not apply to this case. However, as Table 2 (column 3, top) shows, both purity and yield are substantially higher, amounting to 92.3 % for a and b (cf. also R and T).

Table 2. Calculated figures for seven-stage distribution of two materials a and b under stationary conditions. Addition of the mixture in the amounts $Z_a = Z_b = 1$ to stage no. 4. The following relations hold for any two adjacent columns: $\beta = K_a : K_b = G_a : G_b = 2$.

I. Distribution according to the new process B 3; light phase infinitesimally subdivided.

| | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Material | a | b | a | b | a | b | a | b | a | b |
| G | 1.8 | 0.9 | 1.5 | 0.75 | 1.334 | 0.667 | 1.2 | 0.6 | 1.0 | 0.5 |
| $m_{7,l}$ | 0.995 | 0.362 | 0.971 | 0.150 | 0.923 | 0.077 | 0.830 | 0.042 | 0.541 | 0.015 |
| $m_{1,h}$ | 0.0052 | 0.638 | 0.029 | 0.850 | 0.077 | 0.923 | 0.170 | 0.958 | 0.459 | 0.985 |
| R | 191 | 0.567 | 33.5 | 0.177 | 12.0 | 0.083 | 4.88 | 0.0438 | 1.179 | 0.0152 |
| $T_{a,b}$ | 337 | | 190 | | 144 | | 111 | | 77 | |

II. Distribution according to the O'Keeffe process (B 1) or the van Dijck process (B 2).

| | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Material | a | b | a | b | a | b | a | b | a | b |
| G | 1.8 | 0.9 | 1.5 | 0.75 | 1.414 | 0.707 | 1.2 | 0.6 | 1.0 | 0.5 |
| $m_{7,l}$ | 0.913 | 0.396 | 0.835 | 0.240 | 0.800 | 0.200 | 0.675 | 0.115 | 0.500 | 0.0588 |
| $m_{1,h}$ | 0.087 | 0.604 | 0.165 | 0.760 | 0.200 | 0.800 | 0.325 | 0.885 | 0.500 | 0.941 |
| R | 10.50 | 0.656 | 5.06 | 0.316 | 4.00 | 0.25 | 2.074 | 0.1296 | 1.000 | 0.0625 |
| $T_{a,b}$ | 16 | | 16 | | 16 | | 16 | | 16 | |

The advantage of the new process is shown still more clearly by Table 2. In this Table are given some selected figures from Figure 2 for $m_{7,l}$ and $m_{1,h}$ for two substances with the constant separating factor

$\beta = K_a : K_b = G_a : G_b = 2$,

[13] This follows, for example, from calculations given by *Jübermann* [3] pp. 250–253, and by *Treybal* [14], formula 7.70 for $\varepsilon' = \varepsilon$ and $n' = n + 1$.

[14] *R. E. Treybal*: Liquid Extraction. 2nd Edit., McGraw Hill, New York 1963.

3. For separations by methods B 1 or B 2, the following relation holds [13] when the mixture is fed to the central stage ($\sigma$ = number of stages):

$$T_{a,b} = (G_a/G_b)^{(\sigma+1)/2}$$

and the overall separating effect is therefore independent of the absolute magnitudes of G (Table 2, II). On the other hand, in the new process the overall separating effect $T_{a,b}$ is much greater and depends not only on the ratio $G_a:G_b$ but also to a large extent on the absolute magnitudes of G (Table 2, I). This shows that *the new process is fundamentally different from those used hitherto.*

4. When the conditions are selected in accordance with the double column 3 of Table 2, the new process gives a separating effect $T_{a,b} = 144$, *i.e.* a figure which is somewhat greater than $(G_a/G_b)^7$. If it is desired to obtain the same separating effect by B 1 or B 2, thirteen or fourteen stages would have to be used, *i.e.* almost twice as many as in the new process.

*These differences*, shown here on the basis of a few examples, *are of general nature*, as *Horn* has pointed out [11]. This applies particularly to the finding that the new process requires only *half as many stages* as the older processes to obtain a given overall separating effect.

A further advantage of the new process is that it requires smaller volumes of solvents than the older processes to separate a given amount of a mixture with the same separating effect; cf. [1].

These theoretical results have been confirmed by a series of experiments [1, 10]. In these, the same separation was carried out both by the O'Keeffe process and by the new process in each case. An example is described here:

A 1:1 mixture of *succinic and oxalic acids* was distributed between *water* and *n-butanol* in seven stages with the addition of the mixture to stage 4. The temperature was 20 – 1 °C and $\beta = K_S:K_O = 1.03:0.57 = 1.81$. After stationary conditions had been achieved, figures for the overall separating effect T in the O'Keeffe distribution process varied between 8.6 and 9.4. They correspond to $\beta^{3.6}$ to $\beta^{3.8}$, while theoretically $\beta^4$ is expected. In the new process, the overall separating effect was between $30.6 = \beta^{5.8}$ and $34.8 = \beta^{6.0}$, while according to calculation $\beta^{6.9}$ would have been expected for idealized conditions. Thus, for both processes, the separating effect obtained was only slightly below the theoretical figures. However, above all, the experiments confirmed the expected improvement in the separation by the use of the new process.

## 4. Comparison of the Different Schemes of Material Flow, and Their Modes of Action

### a) Flow-Sheets

*Process A 1.* In the Craig process, which can be represented by a triangular scheme (Figure 3, top), the mixture to be separated is added in one portion at the apex D. At a given moment of time, the state of the apparatus is described by a horizontal row of the flow-sheet, *e.g.* by the row E–F, in which three distribution elements are in operation.

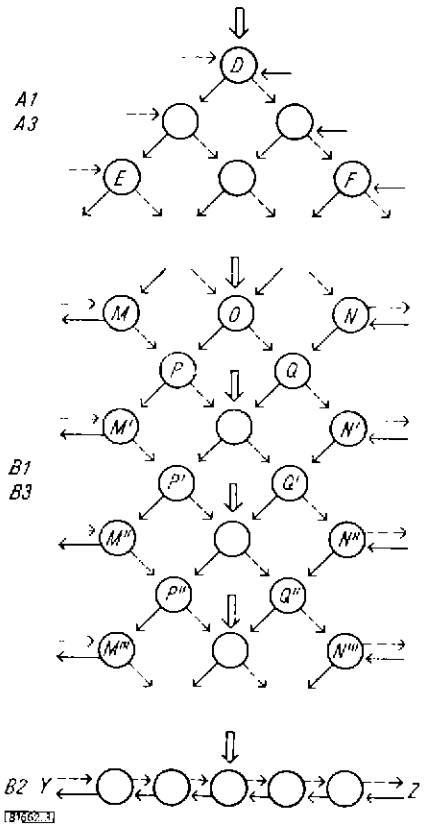



Fig. 3. Interrelationships of the various schemes of material flow. Each circle denotes one distribution operation. (For explanation, see text).
Broken arrows: light phase.
Full arrows: heavy phase.
Double line arrows: introduction of the mixture.

*Process A 3.* The Johnson process is represented in the triangular flow-sheet at the top of Figure 3 by a line D–F or D E, according to whether the heavy or the light phase is used in a state of finite subdivision. Here, as an example, we shall deal only with the first case. All the distribution elements from D to F are provided from the start with equal finite amounts of the heavy phase which remain in them during the whole process. The mixture is added to element D only once at the beginning of the process. The light phase then flows in infinitesimally small amounts successively through the individual distribution elements of the row D–F, until the desired degree of separation of the components has been achieved.

*Process B 1.* The O'Keeffe process is described by the central part of Figure 3. It is derived from the Craig process if fresh amounts of mixture are added regularly and the light and heavy phases are taken off from the ends, so that the number of stages in operation (see p. 796) remains constant. The horizontal rows M–N and P–Q together form one cycle, which is always repeated in the same manner.

*O'Keeffe* [15] worked with a doubled scheme, in such a way that two similar processes were carried out together with a displacement lasting half a cycle. This is only the mechanical

[15] *A. E. O'Keeffe, M. A. Dolliver*, and *E. T. Stiller*, J. Amer. chem. Soc. *71*, 2452 (1949).

addition of two individual processes completely separate from one another as regards materials, and consideration of the simple flow-sheet of the center of Figure 3 is therefore sufficient.

*Process B 2.* In the van Dijck process, the light and heavy phases flow continuously and simultaneously in opposite directions through all distribution elements of the series, while the mixture is likewise fed in continuously at a suitable point. The process can therefore be shown, for example, by the flow-sheet Y–Z at the bottom of Figure 3.

*Process B 3.* The *new process* is shown in Figure 3 by the oblique rows M–N″, M′–N‴, *etc.*, or by N–M″, N′–M‴, *etc.* according to whether the heavy or the light phase is used in the form of finite amounts, in a similar manner to the Johnson process (A 3). In the case where the heavy phase is divided into finite portions, the row M–N″ forms a cycle. When, after the addition of mixture, the necessary amount of light phase has been passed through the process in infinitesimal amounts, M is removed, P–N″ take the position of M′–Q″, and N‴ is added, as described above. This completes the cycle.

b) Definitions

Before the separating effects of the individual methods of material flow can be compared, some questions of nomenclature must be discussed, since considerable confusion exists in this respect. Here we wish to propose some definitions, particularly in view of the current efforts to arrive at an internationally uniform terminology in the field of distribution processes.

n = *Number of distribution steps.* A distribution step means an establishment of equilibrium with all the distribution elements simultaneously in operation. The term can only be used with respect to processes with two finitely subdivided phases, *i.e.* processes A 1 and B 1.

N = *Number of distribution cycles*; cf. p. 792. This term is meaningful only with continuous processes with at least one finitely subdivided phase, *i.e.* processes B 1 and B 3.

z = *Number of distribution elements* (also called elements, for short) of an apparatus. This number can obviously be given only for apparatus which consist of individual distribution elements, *i.e.* not for packed columns and the like.

$\sigma_{pr}$ = *Number of practical stages.* Again, we can speak of practical stages only in the case of an apparatus consisting of individual distribution elements. We define $\sigma_{pr}$ as the number of distribution elements traversed by the mobile phase from its introduction to its removal. If both phases are transported, the number of distribution elements traversed by each phase is the same. – In processes A 2, A 3, B 2, and B 3, so far as apparatus consisting of individual distribution elements are used, $\sigma_{pr} = z$. It must be particularly noted that this equality does not apply to the O'Keeffe and the Craig processes. In the latter case (*i.e.* in the Craig process), the number of practical stages in the above sense is generally not clear-cut, while there is no doubt about the number z of elements. Consequently the concept of stages should not be used in this case. In the O'Keeffe process, for the example given in the center of Figure 3, $\sigma_{pr} = 5$, while throughout only three (row M–N) or two (row P–Q) elements, alternately, are simultaneously filled and in operation.

$\sigma_{th}$ = *Number of theoretical stages* = number of practical stages which, with complete establishment of equilibrium *in each individual distribution operation, give the same* overall separation effect. as a process without individual distribution elements and/or without establishment of equilibrium.

We shall speak of the *separating power* of a process when we mean the separation achieved only in a general sense. As *measurable* magnitudes we propose the following:

1. The *separation factor*

$$\beta = K_a : K_b = G_a : G_b = \frac{c_{l,a} : c_{h,a}}{c_{l,b} : c_{h,b}} = \frac{c_{l,a} : c_{l,b}}{c_{h,a} : c_{h,b}}$$

As a material constant, it is *independent* of the type of multiplicative scheme of material flow used.

All measurable magnitudes for the change in the ratio of the amounts of two components of a mixture within a multiplicative distribution cascade that *depend* on the method of material flow, shall be called *separating effects.* We distinguish:

2. The *overall separating effect T* of a distribution cascade. It has already been defined on p. 794 as the quotient of the migration ratios R of two substances. If, in accordance with p. 794, the corresponding ratio of amounts is put for R and the last distribution element of the cascade is denoted by ω, we obtain the following expression for T, which can also be formulated with the concentrations:

$$T_{a,b} = R_a : R_b = \frac{m_{\omega,l,a} : m_{1,h,a}}{m_{\omega,l,b} : m_{1,h,b}} = \frac{m_{\omega,l,a} : m_{\omega,l,b}}{m_{1,h,a} : m_{1,h,b}} = \frac{c_{\omega,l,a} : c_{\omega,l,b}}{c_{1,h,a} : c_{1,h,b}}$$

Consequently, we may also regard $T_{a,b}$ as the ratio of the amounts or concentrations of the two materials a and b in the light phase of the last distribution element (= *purity ratio* of this fraction) divided by the corresponding purity ratio in the heavy phase of the first element.

3. We denote by the term *partial separating effect U* the quotient formed in the same way from the concentration ratio in any two distinct distribution elements i and j, now, however, within the *same phase* of the two elements:

$$U_{a,b} = \frac{c_{i,h,a} : c_{i,h,b}}{c_{j,h,a} : c_{j,h,b}}.$$

The quotient relating to the light phase is identical with that for the heavy phase under equilibrium conditions with a constant separation factor.

4. An important special case of the above, the *separating effect S from stage to stage*, is based on the definition of a stage given above, i and i-1 being neighboring stages:

$$S_{a,b} = \frac{c_{i,h,a} : c_{i,h,b}}{c_{i-1,h,a} : c_{i-1,h,b}}.$$

The separating effects defined in this way must be supplemented for a complete characterization of the separating power of a process or a plant by data on the *yield* (*i.e.* the fraction of the amount of a component added that is removed from the plant in enriched form), and on the *separating output*, by which is understood the amount of mixture passed through and subjected to a given separating effect, referred to the time or to the volumes of the two solvents. These two differently based forms of the separating output are connected with one another and with the rate of throughput of the solvents. The reciprocal of the separating output referred to volumes is also called the *solvent demand.*

c) Comparison of the Processes

*Process A 1.* Figure 4a gives the quantity-based characteristics of three distributed materials with different extraction factors G at a certain moment of the process for a *Craig distribution* (fundamental process) with a large number of distribution elements. It is noteworthy that the curves for the two materials with the reciprocal G values 0.1 and 10 are symmetrical to one another, and are precisely the same with respect to steepness and height [16].

It follows from the well-known calculations [17] of this method of working that between neighboring distribution elements in *simultaneous* operation (in Figure 3, top, these are the neighboring elements of a *horizontal* row, *e.g.* the row E–F), the separating effect, $U_{a,b} = \beta_{a,b}$. If $G_a = 1{:}G_b$, it follows similarly for the distribution operations *succeeding one another in time* of the *oblique* row D–F of Figure 3 that $U_{a,b} = \sqrt{\beta_{a,b}}$.

*Process A 2.* A description of this scheme is not necessary in order to understand the considerations predominating here. A comparative discussion of its mode of action is to be found in the German text [1].

*Process A 3.* The characteristics of the Johnson process differ in a quite definite manner from those of the Craig process, as shown by Figure 4b on the basis of the separation of a ternary mixture at a given moment of time. With increasing magnitude of the extraction factor G, the curves become flatter and broader, and reciprocal G figures do not yield curves of the same steepness and height, as in the Craig process. For the separating effect from stage to stage, *e.g.* in row D–F of Figure 3, we have $S_{a,b} = \beta_{a,b}$ [12].

*Comparison of A 1 and A 3.* We again consider a Johnson process in which the heavy phase is present in a state of finite subdivision in stages D–F of Figure 3 and the light phase flows uniformly without the formation of a finite working volume. With this, we compare a fundamental process of the Craig method, in which decantation vessels may be used. In this case again each portion of the heavy phase is associated with a definite distribution element and the light solvent forms the mobile phase, which however is transferred in batches.

[16] See, for example, *O. Jübermann* [3], p. 261.

[17] See, for example, *E. Hecker*: Verteilungsverfahren im Laboratorium. Verlag Chemie, Weinheim 1955.

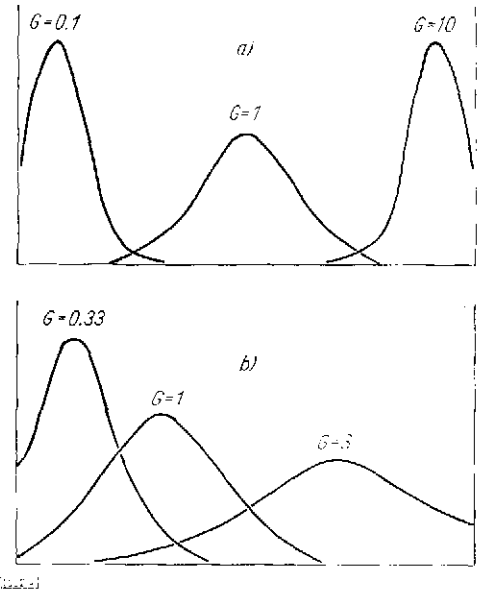



Fig. 4. Example showing the characteristics
a) of the Craig process (A 1); b) of the Johnson process (A 3).
Abscissa: Number of the distribution elements.
Ordinate: Content of the distribution elements, m.

We can now alter to some extent the temporal sequence of the individual operations in the Craig process without changing the principle, by first passing only one portion of the light phase through all three distribution elements from D to F. All three elements are then again free of the light phase, and the state is comparable with that of the Johnson process after the same amount of light phase has been passed through. As is well known [18], the extraction effect, and therefore the separation effect, are increased when a given volume of the extracting solvent is used in the form of separate small portions. It therefore becomes understandable that in process A 1 the separating effect between two neighboring elements of row D–F is only $\sqrt{\beta}$ while in process A 3 it is $\beta$. In the normal Craig process, two further portions of light phase have been brought into operation in the meantime, so that the three elements are then in the state E–F. The separating effect between neighboring elements has then increased to $\beta$ in the Craig process as well, which, as compared with row D–F, arises from the fact that the heavy phase which has been placed in D has now been treated with three times the volume corresponding to the Johnson process, the middle element with twice the volume, and only the element F with the same volume. The Craig process therefore achieves the advantage of the Johnson process by pursuing the separating operation partially, *i.e.* in the flow-sheet of Figure 3 towards the left-hand end in increasing degree. Mathematical treatment of the cases shows that the disadvantage for the separating effect between neighboring elements resulting from establishment of equilibrium with finite portions of the light phase is just compensated by the partial pursuit of the process. This result is not obvious.

Thus, using an equal number of distribution elements, processes A 1 and A 3 give the same separating effect but possess different characteristics. Furthermore,

[18] See, for example, *O. Jübermann* [3], pp. 234–235.

process A 3 has a smaller solvent demand for the same output [19].

*Processes B 1 and B 2.* The van Dijck process B 2 can be carried out in columns or in *mixer-settlers*. We shall first consider the second case In operation, mixers and settlers contain certain working volumes ("hold up") of the two phases, their amounts and concentrations in each distribution element being constant in time under stationary conditions. The magnitudes of the working volumes are obviously irrelevant to theoretical considerations with idealized conditions, and are to be chosen only according to practical points of view (*e.g.* the velocity of mass transfer and the rate of settling). For these reasons, in the idealized calculation of the concentration characteristics it is possible to leave the working volumes out of consideration. The van Dijck process is then considered as if infinitesimal amounts of the two phases were brought directly to mass exchange with one another – in the ideal case, brought into equilibrium – and then separated, and passed to the subsequent stages. On the one hand this justifies the classification of the van Dijck process, when carried out in mixer-settlers, in our category B 2. On the other hand, these considerations show that the idealized van Dijck process can be regarded as an O'Keeffe process with the feed and transport of infinitesimal amounts of all the participating materials, from which it follows that the characteristics, the separating effects, the yields, and generally the entire separating power of the two processes are identical, provided all other experimental conditions are equal.

If, on the other hand, the van Dijck process is carried out in a *column* (without back-mixing), the scheme of material flow corresponds completely to the conditions of our category B 2. However, in general, the time of contact of two infinitesimal portions of the two phases is so short that their concentrations will remain further from equilibrium than in mixer-settlers.

The calculation is most simply carried out by the use of a fictitious "height equivalent to a theoretical stage", by analogy with rectification. Thus the calculation of the van Dijck process in a column and its conception within the framework of our considerations leads back to the method of working with mixer-settlers sketched above, and the same conclusions follow.

When $G_a$ is chosen as equal to $1/G_b$ in the van Dijck process [20], the relation $S_{a,b} = \sqrt{\beta_{a,b}}$ holds [21,22] for the separating effect from (theoretical) stage to stage in row Y–Z of Figure 3. The same applies in the O'Keeffe process for neighboring stages, *i.e.* in Figure 3 for the row M–P–O–Q–N.

*Process B 3.* The *new process* has already been compared with processes B 1 and B 2 above. Figure 5 shows in addition a comparison of the quantity-based characteristics for a seven-stage distribution with the addition of the mixture to the middle stage for two materials with $G_a = 2$ and $G_b = 1/G_a = 0.5$, *i.e.* $\beta = 4$. The symmetrical character of the O'Keeffe procedure is reflected in the fact that the curve for the content of material a in the light phase in the individual stages forms a mirror image of that for material b in the heavy phase. The unsymmetrical flow of the phases in the new process leads to curves which deviate markedly from a mirror-image relationship; the material with $G_b = 0.5$ is somewhat held up in the first stages, while in particular the material with $G_a = 2$ is greatly displaced towards higher-numbered stages as compared with the O'Keeffe process.

While in the O'Keeffe distribution in the case under consideration the separating effect between neighboring stages $S_{a,b} = \sqrt{\beta} = 2$ and is constant, with the new process it is on average somewhat more than 4, *i.e.* somewhat larger than $\beta$, and varies from one pair of stages to another in a characteristic manner [1].

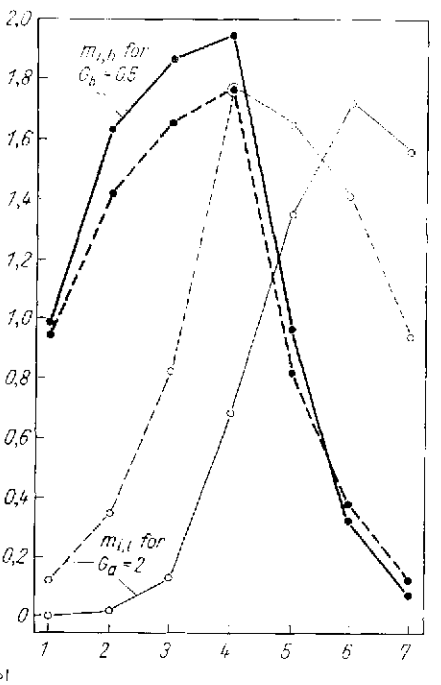



Fig. 5. Examples of the quantity-based characteristics at the end of a cycle in seven-stage distribution.

- - - - - O'Keeffe process (B 1).

—— New process (B 3), light phase infinitesimally subdivided.

Addition of the material to be distributed in an amount of Z = 1 per cycle to stage 4.

Abscissa: stage no. i.

Ordinate: amount of distributed material in the heavy phase $m_{i,h}$ and in the light phase $m_{i,l}$ of stage i.

*Summarizing*, it can be stated that the *new process*, at the same yield and with a smaller consumption of solvent, requires only about half as many stages to obtain a given overall separating effect as the O'Keeffe and van Dijck processes. Its characteristics distinguish it markedly from the other two processes. The separating effect from stage to stage varies with the position of the stages within the cascade, and the overall separating effect rises with the absolute values of K at a constant

[19] *O. Jübermann* [3], pp. 276 et seq.

[20] In the German text [1], on p. 95 and in Table 5, this prerequisite was erroneously omitted.

[21] According to *O. Jübermann* [3], pp. 243–244, and 250, or according to *R. E. Treybal* [14] using equation 7.84.

[22] With addition of the mixture to the middle stage, the following expression holds for the average separating effect from stage to stage: $S = T^{1/(\sigma+1)} \sqrt{\beta}$, even if $G_a \neq 1/G_b$.

value of $\beta_{a,b} = K_a : K_b$. These phenomena also differentiate the new process from the Johnson process with which it otherwise has much in common, particularly in the method of the flow of phases.

## 5. Reflux

If in processes B 1 or B 2 complete reflux of the dissolved material at both ends of the cascade is used, the relation $S_{a,b} = \beta_{a,b}$ holds [23,24] for the separating effect from stage to stage under stationary conditions; it is therefore greater by a power of two than in the absence of reflux.

A corresponding situation exists [1] when the new process B 3 is carried out with complete reflux. The separating effect from stage to stage is thereby again squared and, on average, becomes equal to $\beta^2$. This superior separating effect, which was previously shown in the Johnson process and in the new process without reflux, is obviously characteristic for the third method of phase flow (Table 1).

## 6. Displacement Distribution [25]

When certain extreme deviations from the Nernst distribution law exist (cf. Figure 6), peculiar phenomena may arise in multiplicative distribution.

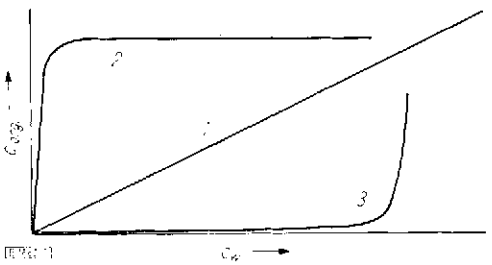



Figure 6. Distribution isotherms.
Curve 1: Nernst distribution law.
Curves 2 and 3: Extreme cases which can lead to displacement distribution.
c = Concentration, w = aqueous phase, org = organic solvent phase.

In the first place, these cases often offer a convenient possibility of working with reflux at both ends of the distribution cascade. An example of this is given by extractions of complexes by the scheme:

$$MCl_w + HX_{org} = MX_{org} + HCl_w,$$

when the chloride ion is present only in the aqueous solution and the complex-forming agent X only in the organic solution. The marked dependence of these equilibria on the hydrogen ion concentration of the aqueous phase permits reflux to be carried out: if the pH is kept high at that end of the cascade at which the organic solvent and the complex-forming agent are added, the metal M can be transferred here completely from the aqueous to the organic phase; if aqueous acid is fed at the other end of the cascade, the reverse process can be brought about there.

A further feature appears under these conditions. The extraction from the aqueous phase follows the peculiar Curve 2 in Figure 6 and leads to a saturation of the organic solvent with the metal M, the height of which is determined by the predetermined concentration of X but is independent of the metal concentration in the aqueous phase.

If, with a multistage distribution cascade, it is arranged that the aqueous phase of all stages with the exception of the first and the last contains the same concentration of MCl, the organic phase flows past the aqueous phase without a change occurring in the concentration of the metal in the two phases. If a mixture of several metals is present, the same applies for their total (equivalent) concentration; but in the middle stages there is an interphase exchange of the individual metals with one another, corresponding to the different stabilities of their X-complexes. Thus, there is a rectangular concentration characteristic for the sum of the metals within which the various metals separate from one another in the course of the process as individual bands. The picture is thus substantially analogous to displacement chromatography, and the reason is the same: extreme positions of the equilibria at the front of the mixture and at the front of the eluent, combined with saturation phenomena. Because of this analogy, we propose for multiplicative distribution processes with rectangular concentration characteristics the name *displacement distribution*.

When the extreme shape of the equilibrium isotherms is given, this type of distribution can be carried out with all three different methods of phase flow (p. 792). It differs from a distribution in a system for which the Nernst distribution law holds by the fact that in this latter case – even with complete reflux – there are no rectangular concentration characteristics, the concentration varying from stage to stage. In case the Nernst distribution law applies, discontinuous multiplicative distribution corresponds to elution chromatography.

The occurrence of displacement distribution is not restricted to the complex equilibria mentioned [1]. We have also observed cases in which distribution isotherms of the shape of Curve 3 in Figure 6 lead to displacement distribution [1].

We have applied displacement distribution particularly to the scheme of the new process B 3, and have obtained very good separating effects under these conditions – particularly with partial reflux. A theoretical treatment of the problem on a digital computer with simplified assumptions made by *M. Krüger* on the basis of preliminary work by *U. Neitzel* showed that the separating effects from stage to stage vary in a complex manner with the position of the stages within the cascade, the magnitude of the reflux, and the ratio of the amounts of the components to be separated, but are sometimes even greater than for the new process B 3 when the distribution law applies. This and the associated experiments will be reported in detail elsewhere.

[23] If in [3] ${}_1A_S = A$ and ${}_nA_R = a$ are put in Figure 10b, p. 242, the above result follows from the equations on pp. 243–244. Similarly from [14], equation 7.62.

[24] This relation also holds when $G_a = 1/G_b$.

[25] Cf. *U. Neitzel*, Ph. D. Thesis, Technische Hochschule Hannover, 1961.

*The present paper has been produced on the basis of the experiments and results of many collaborators. The following may be mentioned in particular: K.-J. Bramekamp, J. Busemann, P. Eger, G. Fricke, H. Galster, K. H. Grothe, M. Krüger* and *D. Schutte. – We thank the Fonds der Chemischen Industrie, the Bundesministerium für Wissenschaftliche Forschung, and the Deutsche Forschungsgemeinschaft for financial support of our work.*

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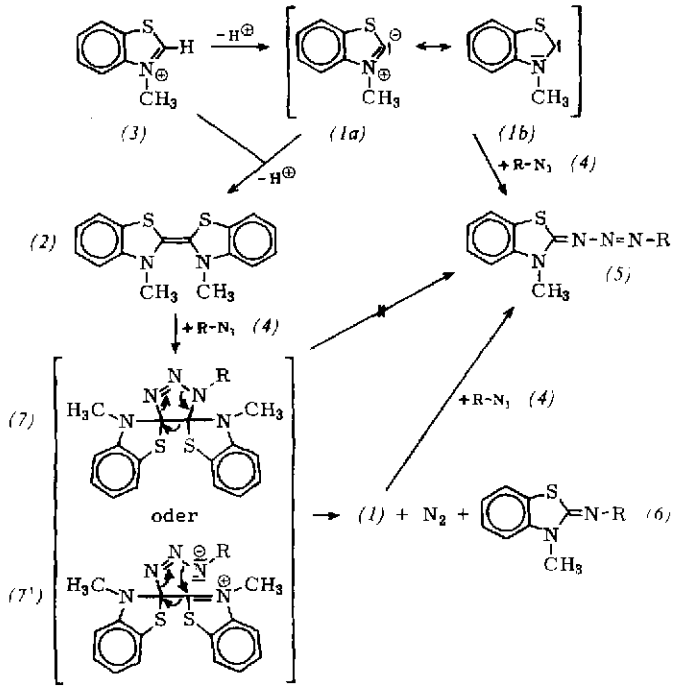
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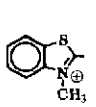
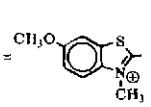
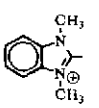
## Detection of a Heterocyclic Nucleophilic Carbene [*]

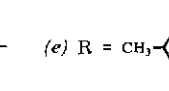
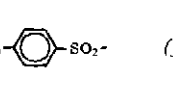
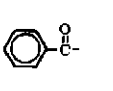
By Dr. H. Quast and Prof. Dr. S. Hünig

Chemisches Institut der Universität Würzburg (Germany)

After it has not been proven so far that tetra-aminoethylenes dissociate into nucleophilic carbenes [1–3], numerous reactions which have been ascribed to nucleophilic carbenes [4] probably must be given a new interpretation. Since a yellow crystalline substance recently described [5,6] is not *(1)* but its "dimer" *(2)* [7], there are no reactions known – apart from the rapid exchange of the protons on the α-carbon atom of quaternary heterocycles [8] and the formation of dimers of type *(2)* [3–6,9] – which definitely proceed *via* a carbene and not *via* its dimer.



*(4-7)* *(a)* R =  *(b)* R =  *(c)* R = 

*(d)* R =  *(e)* R =  *(f)* R = 

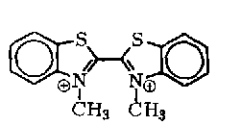
We have now succeeded in producing a short-lived nucleophilic carbene *(1)* by deprotonation of 3-methylbenzthiazolium salts *(3)*, *e.g.* in acetonitrile with triethylamine or diisopropylethylamine [10], and in differentiating it by means of its reactions from its dimer *(2)* which is also formed under comparable conditions [5,6]. Compound *(2)* is obtained in 70–75 % yield from *(3)* with sodium hydride in dioxan under nitrogen and reacts with 2 moles of the azidinium salt *(4a,b)* [11] or with 1 mole of *p*-toluenesulfonylazide *(4e)* in acetonitrile at 5 °C to give 1 mole of nitrogen and mixtures of compounds *(5)* and *(6)*, *e.g.* 21 % *(5a)* + 41 % *(6a)*, 14 % *(5b)* + 50 % *(6b)*, or 45 % *(5e)* + 79 % *(6e)*. The less reactive compound *(4d)* gives only 1.3 moles of *(6d)* and 1.5 moles of nitrogen.

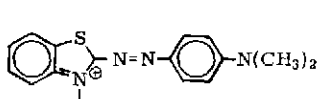
In contrast, uniform products are isolated when *(1)* is prepared from *(3)* in the presence of the azides *(4)*: compounds *(4a)*, *(4b)*, and *(4c)* undergo a very rapid reaction to form almost exclusively triazacyanines [11], *viz.* 75–80 % *(5a)*, 69 % *(5b)*, and 32 % *(5c)*, whereas *(4d)*, *(4e)*, and *(4f)* yield 70–80 % nitrogen and only the corresponding compounds containing only one N-atom in the chain [12], *viz.* 53 % *(6d)*, 62 % *(6e)*, and 44 % *(6f)*.

The products of the reactions with the carbene *in situ* show that the course of the reaction is decisively influenced by the electrophilicity of the azide. It is only with the strongly electrophilic azidinium salts *(4a)–(4c)* that the products expected from a reaction which traps the carbene *(1)* are actually obtained. The less reactive azides *(4d)*, *(4e)*, and *(4f)* are apparently unable to capture *(1)* in the presence of *(3)*. Since the dimer *(2)* is readily formed under the reaction conditions used [5,6], it must be assumed that the reaction with *(4e)* and *(4d)* proceeds *via (2)*.

The reaction of *(2)* with azides is understandable if it is assumed that an adduct *(7')*, or more probably *(7)*, is formed, and then decomposes by loss of nitrogen to form *(6)*. Just as in the decomposition of the adducts of electrophiles with tetra-aminoethylene [3], a carbene must be formed here too. The fate of this carbene is again determined by the most reactive electrophile present. The yield of nitrogen, the relative proportions of the products formed, and the observation that no iminodiazosulfone *(5e)* is formed from *(2)* and *(4e)* when *(2)* is produced directly in the solution from *(3)* prove that *(7)* cannot be transformed directly into *(5)* here.

In the reaction of *(2)* with 2 moles of a benzenediazonium fluoroborate (*p*-$NO_2$, *p*-$CH_3$, *p*-$N(CH_3)_2$), only 1 mole of nitrogen and the compound with two electrons less, *i.e. (8)* [13], could be isolated (43 %, 26 %, 22 % yields). Although

*(8)* 



*(9)*

*(9)* [14] is expected by reaction with *(1)* [6], only traces are formed. The red-brown color of the solutions is partially

due to the presence of unstable radical ions with an oxidation stage intermediate between that of *(2)* and *(8)* [13].

Received, October 8th, 1964 [Z 838/664 IE]
German version: Angew. Chem. 76, 989 (1964)

[*] Cf. *H. Balli*, Angew. Chem. *76*, 995 (1964); Angew. Chem. internat. Edit. *3*, 809 (1964).

[1] To maintain continuity with previous literature in this field, we have preserved the term "nucleophilic carbene", although the betaine resonance structure *(1a)* is probably more important.

[2] *N. Wiberg* and *J. W. Buchler*, Chem. Ber. *96*, 3000 (1963).

[3] *D. M. Lemal, R. A. Lovald*, and *K. I. Kawano*, J. Amer. chem. Soc. *86*, 2518 (1964).

[4] *H. W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1962).

[5] *J. J. Vorsanger*, Bull. Soc. chim. France *1964*, 119.

[6] *H. W. Wanzlick* and *H. J. Kleiner*, Angew. Chem. *75*, 1204 (1963); Angew. Chem. internat. Edit. *3*, 65 (1964).

[7] Compound *(2)* is very sensitive to air and forms various oxidation products [5]; one of these, 3,3'-dimethyldibenzthiazoline-2,2'-spirane, is readily isolable and was considered to be a dimer of *(2)* [6]. Identification of the compound was achieved from knowledge of its properties which were kindly reported to us by Prof. *Wanzlick*.

[8] *R. A. Olofson, W. R. Thomson*, and *J. S. Michelman*, J. Amer. chem. Soc. *86*, 1865 (1964); *H. A. Staab, M.-Th. Wu, A. Mannschreck*, and *G. Schwalbach*, Tetrahedron Letters *1964*, 843.

[9] *R. Piskala*, Tetrahedron Letters *1964*, 2587.

[10] *S. Hünig* and *M. Kiessel*, Chem. Ber. *91*, 380 (1958).

[11] *H. Balli* and *F. Kersting*, Liebigs Ann. Chem. *647*, 1 (1961); *663*, 96, 103 (1963).

[12] Cf. the reaction of tetramethoxyethylene with *p*-toluenesulfonylazide: *R. W. Hoffmann* and *H. Häuser*, Tetrahedron Letters *1964*, 1365.

[13] *S. Hünig* and *H. D. Scheutzow*, to be published in Tetrahedron Letters; cf. *S. Hünig*, Liebigs Ann. Chem. *676*, 32 (1964).

[14] *S. Hünig* and *K. H. Fritsch*, Liebigs Ann. Chem. *609*, 143 (1957).

## Synthesis of Tris(pentafluorophenyl)arsine, -stibine, and -phosphine and of Pentafluorophenyltrimethylsilane

By Dipl.-Chem. M. Fild, Prof. Dr. O. Glemser, and cand. chem. G. Christoph

Anorganisch-Chemisches Institut
der Universität Göttingen (Germany)

To prepare the title compounds, pentafluorophenylmagnesium bromide [1] is made by the reaction of pentafluorobromobenzene with magnesium in ether, and the corresponding amounts of $AsCl_3$, $SbCl_3$, $PSCl_3$, or $(CH_3)_3SiCl$ are added dropwise at −10 to −20 °C with vigorous stirring. The solution is then allowed to warm up to room temperature over 4 h and stirring is continued for a further 2 h. The mixture is then cooled to 0 °C, ice-water is added, and 3 N HCl is stirred in until the solution is acidic. The ether phase is separated off, dried, and the solvent distilled off; the residue is then recrystallized from methanol or petroleum ether. Each product was characterized by elemental analysis, molecular-weight estimation, and infrared spectra.

*Trispentafluorophenylarsine*, $As(C_6F_5)_3$: colorless platelets, m.p. 106 °C, 39 % yield. Infrared spectrum [2]: 6.08 (s); 6.58 (vs); 6.73 (vs); 7.20 (s); 7.75 (s); 7.75 (s); 9.22 (vs); 10.25 μ (vs).

*Trispentafluorophenylstibine*, $Sb(C_6F_5)_3$: colorless needles, m.p. 74 °C, 32 % yield. Infrared spectrum [2]: 6.08 (s); 6.58 (vs), 6.76 (vs), 7.23 (s), 7.78 (s), 9.20 (vs), and 10.31 μ (vs).

With $PSCl_3$ the reaction does not give $(C_6F_5)_3PS$, but instead leads to the known compound $(C_6F_5)_3P$ [3] in 25 % yield. Although the phosphine and arsine derivatives are stable towards water, caustic soda, and methanol, $Sb(C_6F_5)_3$ is slowly hydrolysed with loss of its pentafluorophenyl groups; on the other hand, the compounds are thermally remarkably stable.

With trimethylchlorosilane, the reaction affords pentafluorophenyltrimethylsilane, $(CH_3)_3SiC_6F_5$, as a colorless liquid, b.p. 60 °C/14 mm, in 42 % yield. Its infrared spectrum [2] has bands at 6.10 (s), 6.61 (vs), 6.82 (vs), 7.96 (vs), 9.21 (vs), 10.31 (vs), 11.80 (vs), and 12.31 μ (vs). Analogous experiments with dichlorodimethylsilane and methyltrichlorosilane yielded only polymeric products.

Received, October 12th, 1964 [Z 840/666 IE]
German version: Angew. Chem. 76, 953 (1964)

[1] *E. Nield, R. Stephens*, and *J. C. Tatlow*, J. chem. Soc. (London) *1959*, 166.

[2] Taken on a Leitz 072 instrument; s = strong, vs = very strong absorption.

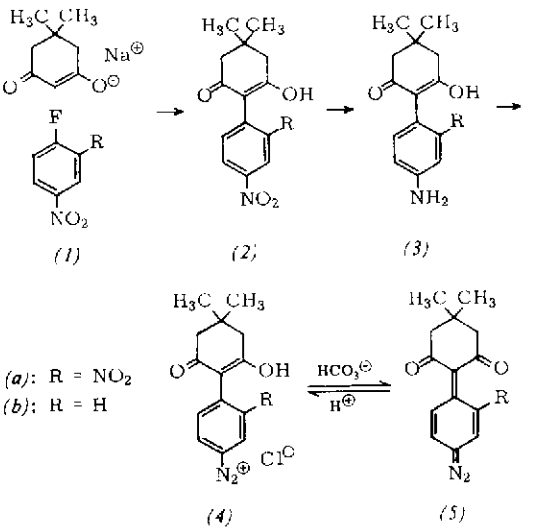
[3] *L. A. Wall, R. E. Donadio*, and *W. J. Pummer*, J. Amer. chem. Soc. *82*, 4846 (1960).

## Quinonoid Diazo Compounds

By Doz. Dr. Th. Severin and Apotheker J. Dahlström

Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg/Lahn (Germany)

Recently *Hartzler* [1] described the preparation of 3-diazo-6-dicyanomethylene-1,4-cyclohexadiene from *p*-aminophenylmalodinitrile. This has induced us to report some of our own syntheses of quinonoid diazo compounds. We obtained compounds *(5a)* and *(5b)* by the route indicated in the formulae.




2-(*p*-Nitrophenyl)dimedone *(2b)*, m.p. 231 °C, is obtained in 55 % yield by refluxing *p*-nitrofluorobenzene *(1b)* with the sodium salt of dimedone (5,5-dimethylcyclohexane-1,3-dione) for 4 h in dimethylformamide. 2-(2-Nitro-4-aminophenyl)dimedone *(3a)*, m.p. 202 °C, is formed in 51 % yield by reducing one nitro group of 2-(2,4-dinitrophenyl)dimedone *(2a)* [2] by passing $H_2S$ through a boiling solution of *(2a)* in ethanol/conc. ammonia (50:1) for 24 h. In order to procure compound *(3b)*, m.p. 218 °C, compound *(2b)* is dissolved in 2 N NaOH at 90 °C and treated with sodium dithionite until colorless; the yield is 75 %. When the hydrochlorides of *(3a)* and *(3b)* are treated with amyl nitrite in acetic acid and ether is then added, the yellow diazonium salt *(4a)* [diazo band at 2270 $cm^{-1}$] and the pale yellow salt *(4b)* [diazo band at 2260 $cm^{-1}$] are precipitated in 72 % and 67 % yields, respectively. The salt *(4a)* reacts with hypophosphorous acid to give 2-(*o*-nitrophenyl)dimedone [3]. This proves that it is the *para*-nitro group in *(2a)* that has been reduced.

Addition of $NaHCO_3$ to an aqueous solution of *(4a)* precipitates the red quinonoid diazo compound *(5a)* [diazo band at 2220 $cm^{-1}$] in 63 % yield. In contrast to the diazodicyanomethylene compound prepared by *Hartzler*, *(5a)* can be recrystallized from methanol by addition of ether and gives good results for its elemental analysis even after 24 h. On heating, it decomposes slowly without melting. The diazo compound *(5b)* is much less stable than *(5a)*. It is not precipitated by $NaHCO_3$ but can be extracted from its aqueous solution with methylene chloride or ethyl acetate. It decomposes within a few minutes and has, therefore, not yet been isolated in the solid form. If hydrogen chloride is passed into a fresh extract of *(5b)* in methylene chloride, *(4b)* is reformed. Compound *(5b)* also couples with β-naphthol to give an azo dye.

Received, October 12th, 1964 [Z 842/667 IE]
German version: Angew. Chem. 76, 954 (1964)

[1] *H. D. Hartzler*, J. Amer. chem. Soc. *86*, 2174 (1964).

[2] *H. G. Garg*, J. Indian chem. Soc. *38*, 343 (1961).

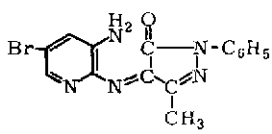
[3] *F. M. Beringer, P. S. Forgione*, and *M. D. Yudis*, Tetrahedron *8*, 49 (1960).

## Azaflavazole Derivatives — New Heterocycles

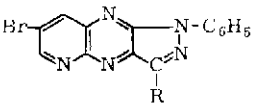
By Prof. Dr. G. Henseke and Dipl.-Chem. D. Lehmann

Institut für Organische Chemie der
Bergakademie Freiberg/Sachsen (Germany)

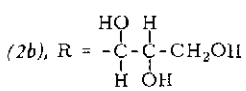
We have obtained azaflavazoles by three different routes. 2,3-Diamino-5-bromopyridine condenses with 1-phenyl-3-methyl-4,5-dioxopyrazoline in water slightly acidified with acetic acid to give the anil *(1)*, m.p. 218–220 °C (decomp.), as red brown crystals from aqueous acetic acid. When heated briefly in 1 N NaOH, the latter affords an 80 % yield of 6-bromo-3-methyl-1-phenyl-4-azaflavazole *(2a)* [1] as yellow prisms, m.p. 223–224 °C from ethanol.



*(1)*

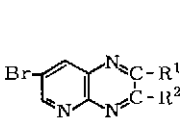


*(2a)*, R = $CH_3$; *(2c)*, R = $CO_2H$



*(2b)*, R = $-C(H)(OH)-C(H)(OH)-CH_2OH$

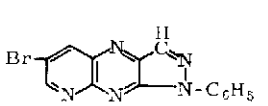
The reaction of 2,3-diamino-5-bromopyridine with dehydro-L-ascorbic acid and phenylhydrazine [2] at 25 °C leads to 20 % of the azaquinoxaline *(3a)* as red prisms, m.p. 281 to 283 °C (decomp.) from methanol; when *(3a)* is heated with 0.01 N NaOH, it is transformed quantitatively into 6-bromo-3-[L-*threo*-1,2,3-trihydroxypropyl]-1-phenyl-4-azaflavazole *(2b)*, yellow needles, m.p. 214–216 °C (decomp.) from ethanol.



*(3a)*, $R^1$ = OH; $R^2$ = $-C(H)(OH)-C(H)(OH)-CH_2OH$

*(3b)*, $R^1$ = $-CH=N-NH-C_6H_5$; $R^2$ = H

Dehydrogenative cyclization with phenylhydrazine of 7-bromo-5-azaquinoxaline-2-carboxaldehyde phenylhydrazone *(3b)* in water weakly acidified with mineral acid gives a 50 % yield of 5-bromo-1-phenyl-7-azaflavazole *(4)* as yellow prisms, m.p. 247–248 °C from ethanol.



*(4)*

Oxidation with alkaline peroxide at 30 °C of the aldehyde prepared from *(2b)* led to 6-bromo-1-phenyl-4-azaflavazole-3-carboxylic acid *(2c)*, yellow prisms, m.p. 268–270 °C from dioxan.

Received, October 12th, 1964 [Z 843/668 IE]
German version: Angew. Chem. 76, 954 (1964)

[1] Regarding the nomenclature, cf. *H. Ohle* and *G. A. Melkonian*, Chem. Ber. *74*, 280 (1941).

[2] Cf. *G. Henseke* and *K. Dittrich*, Chem. Ber. *92*, 1550 (1959).

## Reversibility of the Dissociation of Glutamate Dehydrogenase from Beef Liver into Its Polypeptide Chains [1]

By Dr. H. Sund

Chemisches Laboratorium
der Universität Freiburg/Breisgau (Germany)

In its native, associated state, glutamate dehydrogenase from beef liver is a prolate particle with a particle weight of $2\times10^6$. If it is considered as an ellipsoid of revolution, then its major and minor axes are about 930 and 70 Å long, respectively [2]. This particle is in a reversible, spontaneously attained equilibrium with subunits having particle weights of $1\times10^6$, $0.5\times10^6$, and $0.25\times10^6$, all of which exhibit enzymatic activity. Further cleavage into the polypeptide chains occurs in the presence of urea or long-chain alkyl sulfates or at pH values above 10 or below 4; this change is accompanied by loss of the native chain conformation and the enzymatic activity, and so far has been found to be always irreversible [2–7].

We have now succeeded in showing that this dissociation, too, is in fact reversible. Incubation of glutamate dehydrogenase in the presence of mercaptoethanol at pH 2.0–2.2 leads to complete inactivation of the enzyme. Subsequent dialysis against mercaptoethanol at pH 7.6 effects extensive reactivation: specific activity [8] before denaturation with acid: 6200 $min^{-1}$, after denaturation: 10 $min^{-1}$, after renaturation by dialysis at pH 7.6: 4500 $min^{-1}$. These results show that glutamate dehydrogenase from beef liver contains in its amino-acid sequence the information required for the chain conformation of the native, catalytically active enzyme protein.

Received, October 12th, 1964 [Z 841/669 IE]
German version: Angew. Chem. 76, 954 (1964)

[1] Reported at the Meeting of West-German Chemistry Lecturers in Freiburg/Breisgau, April 29th, 1964.

[2] *H. Sund*, Acta chem. Scand. *17*, S 102 (1963) and unpublished results.

[3] *B. Jirgensons*, J. Amer. chem. Soc. *83*, 3161 (1961).

[4] *H. F. Fisher, L. L. McGregor*, and *D. G. Cross*, Biochim. biophysica Acta *65*, 175 (1962).

[5] *J. Wolff*, J. biol. Chemistry *237*, 230 (1962).

[6] *C. Frieden*, J.biol.Chemistry *237*, 2396 (1962); *238*, 146 (1963).

[7] *H. Sund* in: Mechanismen enzymatischer Reaktionen (14th Mosbacher Colloquium of the Gesellschaft für Physiologische Chemie). Springer-Verlag, Berlin-Göttingen-Heidelberg 1964, p. 318.

[8] *H. Sund* and *Å. Åkeson*, Biochem. Z. *340*, 421 (1964).

## Explosion during the Oxidation of Tetralin with Hydrogen Peroxide in Acetone (Comments)

By Prof. Dr. W. Treibs, Heidelberg (Germany)

*H. Seidl* recently reported [1] on an explosion which occurred during the preparation of tetralone from tetralin in acetone using hydrogen peroxide.

Since publication of the original procedure [2], this method has been used in numerous experiments for oxidizing open-

chain and cyclic olefins and ketones, as well as terpenes and sesquiterpenes without any accidents. Since the description of the original procedure was rather terse, detailed instructions are given here for the production of α-tetralone.

One gram of vanadium pentoxide is placed in a beaker and a total of 30 ml of 10 % hydrogen peroxide is added in portions. Strong effervescence occurs and heat is liberated. The product is a green-brown voluminous mass, which is dissolved in 100 ml of a 20:80 v/v mixture of 10 % $H_2O_2$ and acetone. The solution is filtered and added to a solution of 500 g of tetralin in 5 l of acetone. The reaction mixture is stirred or shaken and 30–40 % $H_2O_2$ is added in portions of 50 ml, keeping the temperature at 30–40 °C; before each new addition, the color of the mixture should be allowed to change from yellow-red to green or brown-green. If the mixture separates into two phases, enough acetone is added to make the solution homogenous again. The oxidation is complete when the color change occurs only slowly. A little fresh tetralin is then added, and the whole is boiled for 1 h under reflux. The solvent is then distilled off, and the residue is separated in a separating funnel. The lower, aqueous phase is extracted with ether, and the extract is added to the upper, organic phase, which is then shaken with 100 ml of 2 N sodium hydroxide and washed thrice with 100 ml portions of distilled water. The ether is removed, and the residue is fractionated *in vacuo* on an oil bath.

The acetone used as solvent in the reaction is distilled beforehand from $KMnO_4$. Pure methanol can also be used as solvent, but after dilution with $H_2O_2$ it has less dissolving power than acetone. *Mineral acids must not be present, not even in traces.*

Received, October 15th, 1964 [Z 856/682 IE]
German version: Angew. Chem. 76, 990 (1964)

[1] *H. Seidl*, Angew. Chem. *76*, 719 (1964); Angew. Chem. internat. Edit. *3*, 640 (1964).

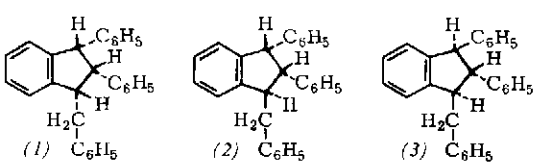
[2] *W. Treibs*, Ber. dtsch. chem. Ges. *72*, 7, 1194 (1939); Angew. Chem. *52*, 698 (1939); Brennstoffchemie *20*, 358 (1939); *W. Treibs, G. Franke, G. Leichsenring*, and *H. Roeder*, Chem. Ber. *86*, 616 (1953).

## Formation of 1-Benzyl-2,3-diphenylindanes from Stilbene in the Presence of Tin Tetrachloride under the Influence of γ-Radiation

By Dr. M. Salzwedel, V. Werner, and Priv.-Doz. Dr. D. Schulte-Frohlinde

Strahlenchemisches Laboratorium, Kernforschungszentrum Karlsruhe (Germany)

Irradiation of *cis*- or *trans*-stilbene in the presence of tin tetrachloride with γ-rays from $^{60}Co$ [1] led to trimers plus three isolable dimers *(1)–(3)*:




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

| | Mol. wt. | M.p. [°C] | $\lambda_{max}$ [mμ] |
|---|---|---|---|
| *(1)* | 360 | 99–100 | 274 |
| *(2)* | 360 | 114–115 | 275 |
| *(3)* | 360 | 147–148 | 281 |

The G value for the consumption of the stilbene in an equimolar mixture with tin tetrachloride was 105; the G value for the formation of the mixture of isomers was calculated to be 31.5 on complete reaction. The ultraviolet, infrared, mass and proton magnetic resonance spectra of the dimers as well as the products of their oxidative degradation [benzoic acid, *o*-benzoylbenzoic acid, anthraquinone, 2,3-diphenyl-$\Delta^2$-inden-1-one, and (*o*-benzoylphenyl)benzoylbenzylmethane] indicate that they are the stereoisomers *(1)–(3)* of 1-benzyl-2,3-diphenylindane.

Received, October 13th, 1964 [Z 850/676 IE]
German version: Angew. Chem. 76, 989 (1964)

[1] Dosage rate of the $^{60}Co$ source (10000 Curie): $7.7 \times 10^5$ r/h.

## Damped Oscillation of the Enzyme Synthesis in Yeast

By Dr. W. Bernhardt, cand. med. K. Panten, and Prof. Dr. H. Holzer [1]

Biochemisches Institut der Universität Freiburg/Breisgau (Germany)

When a disturbance enters a feedback system, the transition from the regulator's initial output to the new level consists of either a sudden jump, an asymptotic change, or a damped oscillation, depending on the nature of the feedback system.

While studying the regulation of DPN-dependent glutamate dehydrogenase (DPN-GluDH) [2] in yeast, we found that damped oscillations of the rate of enzyme synthesis can occur. Synthesis of the enzyme is repressed by ammonium ions [3,4]. When repressed cells are transferred to a medium containing glutamic acid as source of nitrogen, DPN-GluDH is synthesized as a result of "derepression". After some time, a new stationary content of DPN-GluDH, which is five to ten times higher, is attained. As is shown in Figure 1, the transition

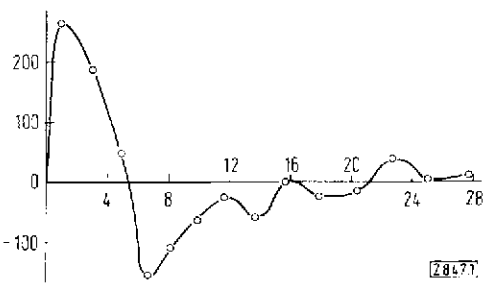



Fig. 1. Rate of change in the specific activity of DPN-dependent glutamate dehydrogenase in logarithmically growing cells of *Saccharomyces cerevisiae* R 59. The cells were grown on a medium with $NH_4^{\oplus}$ as sole source of nitrogen (for details see [4]), depleted of nitrogen and glucose for 3 h, and then administered L-glutamic acid and glucose at time zero.

Ordinate: Change in the specific activity per hour [activity units × (mg protein)$^{-1}$ × h$^{-1}$]. For definition of activity units see [4].

Abscissa: Time [h].

from the low to the high rate of synthesis of the enzyme proceeds by oscillations. These oscillations probably occur because the enzyme synthesis is part of a feedback system in which the ammonium ion acts as "co-repressor". The transition does not occur in a sudden jump or asymptotically because the feedback system has a time lag. This time lag is due to mainly two factors: 1. $NH_4^{\oplus}$ is released only slowly from the glutamic acid corresponding to the slow accumulation of DPN-GluDH; 2. free ammonium ions accumulate in the medium only after the $NH_4^{\oplus}$-dependent nitrogen reserves have been replenished. This interpretation is supported by our finding that oscillations occur only when nitrogen-deficient yeast cells are used for the experiments.

While the frequencies of oscillations observed for DPNH [5,6] and fermentation metabolites [7] are of the order of 1 min$^{-1}$, that for the enzyme synthesis is about 0.1–0.2 h$^{-1}$. Oscilla-

tions of this type may be involved in the mechanism of "biological clocks" [8], the periodicities of which lie in the range of hours or days.

Received, October 19th, 1964 [Z 847/674 IE]
German version: Angew. Chem. 76, 990 (1964)

[1] We wish to express our thanks to the Deutsche Forschungsgemeinschaft and to the Bundesministerium für wissenschaftliche Forschung for supporting this work.

[2] Glutamate dehydrogenase catalyses the reaction

L-Glutamate + $H_2O$ + DPN $\rightarrow$ α-Oxoglutarate + $NH_4^+$ + DPNH

[3] *H. Holzer* and *G. Hierholzer*, Biochim. biophysica Acta *77*, 329 (1963).

[4] *G. Hierholzer* and *H. Holzer*, Biochem. Z. *339*, 175 (1963).

[5] *B. Chance*, *R. W. Estabrook*, and *A. Ghosh*, Proc. nat. Acad. Sci. USA *51*, 1244 (1964).

[6] *B. Chance* in *W. D. McElroy* and *B. Glass*: Mechanism of Enzyme Action. Johns Hopkins Press, Baltimore 1954, p. 399.

[7] *H. Holzer* and *R. Freytag-Hilf*, Hoppe-Seylers Z. physiol. Chem. *316*, 7 (1959).

[8] Cold Spring Harbor Symp. quantitat. Biol. *25* (1960).

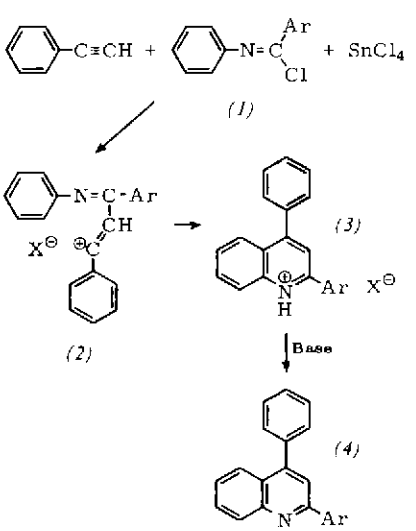
## A New Synthesis of Quinoline Derivatives

By Dr. Richard R. Schmidt

Institut für Organische Chemie der Technischen Hochschule Stuttgart (Germany)

The high reactivity of phenylacetylene when treated with aromatic acid chlorides and Lewis acids [1,2] led us to expect that the use of aromatic *N*-phenylimide chlorides *(1)* would result in the formation of 2,4,6-triaryl-*N*-phenylpyridinium compounds. However, the course of the reaction corresponded to the quinazoline synthesis discovered by *Meerwein* et al. [3] and thus afforded quinolinium salts *(3)*. Electrophilic substitution on the benzene ring apparently proceeds faster than the further addition of a molecule of phenylacetylene onto the expected intermediate *(2)*.

The reaction is carried out in anhydrous chloroform and is strongly exothermic. The phenylacetylene is therefore added to the reaction mixture at a rate which just keeps the chloroform refluxing gently. After cooling, the quinolinium salt *(3)* produced is filtered off, washed with chloroform, and treated with 1:1 aqueous ammonia. The quinoline derivative *(4)* formed is




| Compound | M.p. [°C] | Yield [%] based on *(1)* |
|---|---|---|
| *(4a)*, Ar = Phenyl | 112 (112 [4]) | 56 |
| *(4b)*, Ar = *p*-Tolyl | 106 | 68 |
| *(4c)*, Ar = *p*-Chlorophenyl | 104 | 69 |
| *(4d)*, Ar = *p*-Nitrophenyl | 160 | 70 |

extracted with toluene. Comparison of the product *(4a)* with an authentic sample of 2,4-diphenylquinoline [4] confirmed the course of reaction.

Received, October 23rd, 1964 [Z 853/679 IE]
German version: Angew. Chem. 76, 991 (1964)

[1] *R. R. Schmidt*, Angew. Chem. *76*, 437 (1964); Angew. Chem. internat. Edit. *3*, 387 (1964).

[2] *R. R. Schmidt*, Chem. Ber., in the press.

[3] *H. Meerwein*, *P. Laasch*, *R. Mersch*, and *J. Nentwig*, Chem. Ber. *89*, 224 (1956).

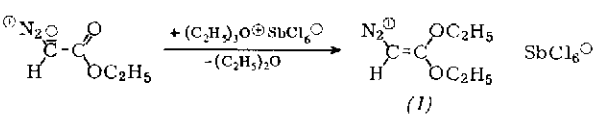
[4] *C. Beyer*, Ber. dtsch. chem. Ges. *20*, 1772 (1887).

## Stable Aliphatic Diazonium Ions [1]

By Dr. K. Bott

Institut für Organische Chemie der Universität München (Germany)

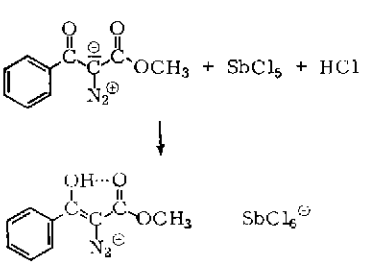
a) When triethyloxonium hexachloroantimonate is allowed to react with excess diazoacetic ester in ethylene dichloride the carbonyl oxygen of the ester is alkylated. The product, 2,2-diethoxyethylenediazonium hexachloroantimonate *(1)*, is stable at room temperature and is isolated by precipitation with carbon tetrachloride to give an about 50 % yield of the pure material as colorless crystals, m.p. 115 °C (decomp.).




*(1)*

The structure of *(1)* follows from its elemental analysis and its infrared spectrum. There is no absorption in the carbonyl region, and the N ⁻ N valence vibration of the diazo group is displaced to higher frequencies relative to that of diazoacetic ester, as is to be expected for a diazonium salt. This band is resolved and has two sharp peaks at 2180 and 2160 $cm^{-1}$, respectively.

b) When hydrogen chloride is bubbled through an equimolar solution of methyl benzoyldiazoacetate and antimony pentachloride in methylene chloride, the diazonium salt *(2)*, which




*(2)*

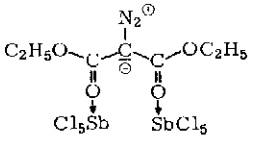
is derived from the enol form of methyl benzoylacetate, crystallizes out as colorless needles, m.p. 114 °C (decomp.) in a sealed tube; the yield is 78 %.

The chlorine and antimony analyses of *(2)* conform with the proposed formula. Its small HCl vapor pressure and the stability of its diazonium group are suggestive of a hydrogen-bridged chelate. The absorption maximum of the N≡N valence vibration lies at 2180 $cm^{-1}$.

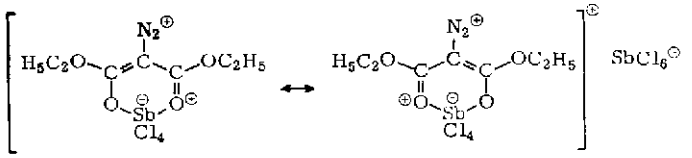
Reaction of *(2)* with a stoichiometric amount of triethylamine in methylene chloride reconverts it quantiatively into methyl benzoyldiazoacetate plus triethylammonium hexachloroantimonate.

c) When a solution of equimolar amounts of antimony pentachloride and diazomalonic ester in methylene chloride is saturated with HCl gas and carbon tetrachloride is added, a substance crystallizes out which surprisingly consists of two

moles of antimony pentachloride and one mole of diazomalonic ester. When the components are used in stoichiometric proportions, the same product is obtained in better yield (73 %) as colorless needles, m.p. 107–108 °C (decomp.) in a sealed tube.



(3)



(4)

Of the two possible structures (3) and (4) for this compound, the second is supported by the results of conductivity measurements in liquid $SO_2$ because the diazonium chelate (4) has salt-like character [2]. There is a sharp diazonium band in the infrared at 2220 $cm^{-1}$.

Received, October 23rd, 1964 [Z 844/671 IE]
German version: Angew. Chem. 76, 992 (1964)

[1] The preparation of a stable non-aromatic diazonium ion was described by *H. Reimlinger*, Angew. Chem. *75*, 788 (1963); Angew. Chem. internat. Edit. *2*, 482 (1963).

[2] A chelated diazonium salt containing chromium as central atom has been described by *J. P. Collman* and *M. Yamada*, J. org. Chemistry *28*, 3017 (1963).

## Triphenylphosphineazine $Ph_3P{=}N{-}N{=}PPh_3$ [1]

By Prof. Dr. R. Appel and Dr. R. Schöllhorn

Anorganisch-Chemisches Institut der Universität Bonn (Germany)

The action of dibromotriphenylphosphorane on hydrazine [2] yields hydrazinotriphenylphosphonium bromide (1). It was observed by *Zimmer* [3] and independently by us [4] that deprotonation of (1) with sodium amide in liquid ammonia yields *N*-aminotriphenylphosphineimine (2), m.p. 116 to 120 °C (decomp.), which can also be designated as triphenylphosphine hydrazone.

$$[Ph_3P{-}NHNH_2]\,Br \xrightarrow{+\ NaNH_2} Ph_3P{=}N{-}NH_2 + NaBr + NH_3$$

(1) (2)

When (2) reacts with ketones, it does not yield phosphazines, but instead, oxygen exchange occurs and triphenylphosphine oxide and the hydrazones of the ketones are formed.

We found that the second amino group of the hydrazine also reacts with dihalogenotriphenylphosphoranes when these are heated with hydrazine dihydrochloride to 180–200 °C.

$$2\ Ph_3PCl_2 + N_2H_4{\cdot}2\ HCl \rightarrow [Ph_3PNHNHPPh_3]Cl_2 + 4\ HCl$$

(3), 80 %

Compound (3) decomposes quantitatively above its melting point (265 °C) to form triphenylphosphine, nitrogen, and hydrogen chloride. Deprotonation of (3) with strong bases such as alkali metal amides or potassium t-butoxide affords triphenylphosphineazine (4). Oxidation of (2) with elemental bromine also yields (4).

$$Ph_3P{=}N{-}N{=}PPh_3 \qquad (4)$$

Triphenylphosphineazine forms garnet red crystals, m.p. 184 °C, which dissolve readily in benzene, tetrahydrofuran, alcohols, and cyclohexane. Its solution in cyclohexane has an absorption maximum at 400 mμ. The substance is diamagnetic and is stable under nitrogen, but reacts rapidly with atmospheric oxygen to give triphenylphosphine oxide and nitrogen. When heated above its melting point, it decomposes quantitatively into triphenylphosphine and nitrogen. It reacts with hydrogen chloride to reform (3), and with methyl iodide to give only the monomethyl derivative, m.p. 140 °C (decomp.).

Received, October 23rd, 1964 [Z 845/673 IE]
German version: Angew. Chem. 76, 991 (1964)

[1] The Chemistry of Non-metallic Imino Compounds, Part 17. – Part 16: *R. Appel, G. Köhnlein*, and *R. Schöllhorn*, Chem. Ber., in the press. We gratefully acknowledge material help from the Deutsche Forschungsgemeinschaft.

[2] *L. Horner* and *H. Oediger*, Liebigs Ann. Chem. *627*, 161 (1959).

[3] *H. Zimmer* and *G. Singh*, J. org. Chemistry *29*, 1579 (1964).

[4] Remarks during the discussion following a lecture by *H. Zimmer* in Bonn (Germany), July 6th, 1964.

## Aminolysis of Selenium Dioxide [1]

By Doz. Dr. R. Paetzold and Dipl.-Chem. E. Rönsch

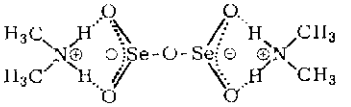
Institut für Anorganische Chemie der Universität Jena (Germany) and

Institut für Anorganische und Anorganisch-Technische Chemie der Technischen Universität Dresden (Germany)

Ammonolysis of selenium dioxide results in numerous products (including selenium nitride and elemental selenium) owing to redox and condensation reactions [2,3]; this makes it difficult to identify the primary solvolysis reactions. When dimethylamine is used instead of ammonia, the reaction should come to a standstill directly after the solvolysis.

We treated selenium dioxide at −20 °C with pure dimethylamine and with its solution in ether. Complete reaction occurs at a molar ratio $SeO_2:(CH_3)_2NH$ of 3:4. In both experiments the selenium dioxide dissolves with formation of two liquid phases.

The heavier phase is a thick resin which melts at about −35 °C. It is readily soluble in water, slightly soluble in alcohol, but insoluble in all organic solvents. Its Se content is 27.8 % and its $(CH_3)_2N$ content is 48.1 %. No N–H valence bands from isolated $(CH_3)_2NH_2^{\oplus}$ ions can be detected in the infrared spectrum, but there are strong broad bands from N–H···O= bridges with maxima at 2450, 2780, and 2970 $cm^{-1}$. The bands for the $SeO_2$ valence vibrations lie about 30 $cm^{-1}$ lower than those in the spectra of alkali diselenites [4]. This information indicates the structure shown in Formula (1).



(1)

In order to confirm these results, we also prepared dimethylammonium diselenite by reaction of an aqueous solution of $H_2SeO_3$ with dimethylamine in a molar ratio of 1:1. It has the same properties (melting point, Se and $(CH_3)_2N$ contents, infrared spectrum) as compound (1).

A colorless crystalline compound, m.p. 42 °C, can be separated from the lighter phase at −20 °C. Another component, a liquid boiling at 32.5 °C/14 mm, can be isolated at room temperature. The selenium and $(CH_3)_2N$ analyses as well as the infrared spectrum of the crystalline product indicate a formula $[(CH_3)_2N]_2SeO$; the data for the liquid suggest the

formula $[(CH_3)_2N]_2Se$. The solid is thermolabile, being converted with loss of oxygen into the liquid $[(CH_3)_2N]_2Se$. We have also prepared the solid $[(CH_3)_2N]_2SeO$ from $ScOCl_2$ and dimethylamine [5].

$[(CH_3)_2N]_2SeO$ and $[(CH_3)_2NH_2]_2Se_2O_5$ *(1)* are always formed together in a 1:1 molar ratio. Thus, the following equation can be written for the aminolysis of selenium dioxide:

$$3\ SeO_2 + 4\ (CH_3)_2NH \rightarrow [(CH_3)_2N]_2SeO + [(CH_3)_2NH_2]_2Se_2O_5$$

It therefore appears that not every Se-O-Se bridge in the selenium dioxide undergoes aminolysis. Terminal anionic groups apparently increase the stability of adjacent Se-O-Se bridges towards solvolysis. This interpretation is supported by the fact that the diselenites $(NH_4)_2Se_2O_5$ and $K_2Se_2O_5$ are resistant to liquid dimethylamine at room temperature and even to liquid ammonia.

Received, October 23rd, 1964 [Z 849/675 IE]
German version: Angew. Chem. 76, 992 (1964)

[1] Investigations of Selenium-Oxygen Compounds, Part 29. – Part 28: Z. anorg. allg. Chem., in the press.
[2] *J. Jander* and *V. Daetsch*, Angew. Chem. *70*, 704 (1958).
[3] *J. Jander* and *V. Daetsch*, Chem. Ber. *93*, 561 (1960).
[4] *A. Simon* and *R. Paetzold*, Z. anorg. allg. Chem. *303*, 39 (1960).
[5] *R. Paetzold* and *E. Rönsch*, Z. anorg. allg. Chem., in the press.

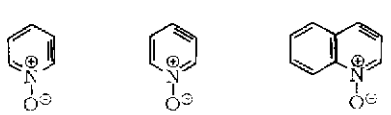
## Indications of the Transient Occurrence of 3,4-Dehydropyridine N-Oxide and 3,4-Dehydroquinoline N-Oxide

By Doz. Dr. Th. Kauffmann and cand. chem. R. Wirthwein

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

The reaction of 2-chloropyridine *N*-oxide with $KNH_2$ in liq. ammonia leads mainly to undefined products plus 5 % 2-aminopyridine *N*-oxide and 1 % 3-aminopyridine *N*-oxide; the latter two products are suggestive of the intermediate occurrence of 3,4-dehydropyridine *N*-oxide *(1)*. In contrast, 3-chloropyridine *N*-oxide yields only the 3-amino compound [1]. We heated 3-chloropyridine *N*-oxide for 8 days with piperidine in anhydrous benzene at 100 °C and obtained ca. 80 % of the starting material, non-identified products, and 3-piperidinopyridine *N*-oxide (82 % [2]; picrate has m.p. 189 °C), plus 4 % [2] 4-piperidinopyridine *N*-oxide (m.p. of picrate 153–154 °C), but could not detect the 2-piperidino isomer. Analogously, when 3-bromoquinoline *N*-oxide was heated with piperidine at 115 °C for three days, 22 % [2] 4-piperidinoquinoline *N*-oxide [3] (m.p. of picrate 132–133 °C) was isolated in addition to a small amount of starting material, non-identified products, and 3-piperidinoquinoline *N*-oxide (20 % [2]; m.p. of picrate 165–166 °C), but again no 2-piperidino isomer was found.

The formation of the 4-piperidino compounds indicates an elimination/addition mechanism for the substitution proceeding via the heterocyclic *N*-oxides *(2)* and *(3)* [4].



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

In contrast to the 3-halogeno compounds, 2- and 4-chloropyridine *N*-oxides and 4-chloroquinoline *N*-oxide appear to react completely according to the normal addition/elimination mechanism [5] when heated in piperidine to about 100 °C, for only the "non-rearranged" substitution products, *viz.* 2-piperidinopyridine *N*-oxide (m.p. 124.5–125.5 °C), 4-piperidinopyridine *N*-oxide, and 4-piperidinoquinoline *N*-oxide are formed in almost quantitative yield.

Received, October 26th, 1964 [Z 852/678 IE]
German version: Angew. Chem. 76, 993 (1964)

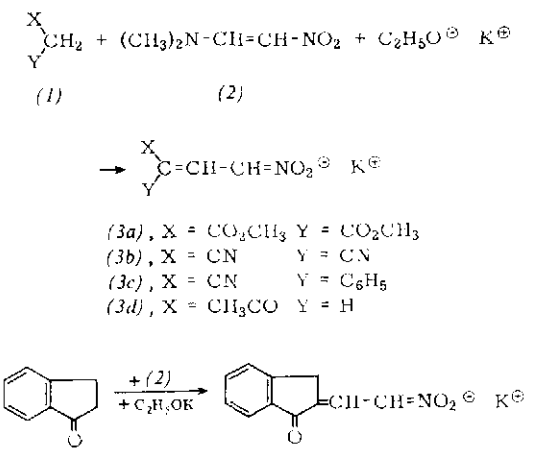
[1] *R. J. Martens* and *H. J. den Hertog*, Recueil Trav. chim. Pays-Bas *83*, 621 (1964).
[2] Yield based on the amount of aryl halide converted.
[3] *T. Okamoto*, *H. Hayatsu*, and *Y. Baba*, Chem. pharmac. Bull. (Tokyo) *8*, 892 (1960).
[4] For the formation of heterocyclic arynes during the reaction of piperidine with aryl halides, see *Th. Kauffmann*, *J. Hansen*, *K. Udluft*, and *R. Wirthwein*, Angew. Chem. *76*, 590 (1964); Angew. Chem. internat. Edit. *3*, 650 (1964).
[5] For abnormal addition/elimination mechanisms, see *F. G. Bordwell*, *B. B. Lampert*, and *W. H. McKellin*, J. Amer. chem. Soc. *71*, 1702 (1949).

## A Simple Nitrovinylation Reaction

By Doz. Dr. Th. Severin and Apotheker B. Brück

Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg/Lahn (Germany)

β-Dimethylaminonitroethylene *(2)* can be readily prepared from nitromethane and dimethylformamide diethylacetal [1]. We have found that *(2)* reacts with C–H-acidic compounds *(1)* in the presence of alkoxides by elimination of dimethylamine to give salts of substituted nitropropenes *(3)*.



*(1)* *(2)*

*(3a)*, X = $CO_2CH_3$ Y = $CO_2CH_3$
*(3b)*, X = CN Y = CN
*(3c)*, X = CN Y = $C_6H_5$
*(3d)*, X = $CH_3CO$ Y = H



Stoichiometric amounts of the reactants are heated together in ethanol for 3–5 min at about 70 °C. Compound *(3d)* is made preferably by adding a hot solution of potassium ethoxide in ethanol to a refluxing solution of *(2)* in acetone. The yields are always over 75 %. The products are purified by recrystallization from methanol, ethanol, or acetonitrile. Analogous reaction of *(2)* with phenylmagnesium bromide affords ω-nitrostyrene in 50 % yield. The action of acids on the salts *(3a)–(3d)* produces unstable oils, which are difficult to purify. 1,1-Disubstituted 3-nitropropenes have already been prepared by the reaction of nitromethane with ethoxymethylene derivatives of some β-dicarbonyl compounds [2].

Received, October 27th, 1964 [Z 846/672 IE]
German version: Angew. Chem. 76, 993 (1964)

[1] *H. Meerwein*, *W. Florian*, *N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).
[2] *A. Dornow* and *S. Lüpfert*, Liebigs Ann. Chem. *606*, 56 (1957).

## Synthesis of 5-Oxo-octahydroquinolines and Their Reduction with Lithium Aluminum Hydride

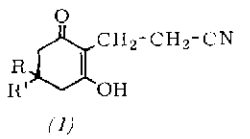
By Dr. H. Reinshagen [1]

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

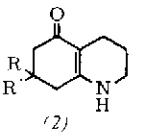
When dissolved in aqueous ammonia, 2-(β-cyanoethyl)-4,5-dihydroresorcinol *(1a)* and its derivatives *(1b)* and *(1c)* [2,3] rapidly absorb 2 moles of hydrogen over Raney nickel, being thereby converted into the corresponding primary amines, which are not isolated but undergo spontaneous dehydration to form 5-oxo-$\Delta^{9(10)}$-octahydroquinoline *(2a)* and its 7-methyl *(2b)* and 7,7-dimethyl derivatives *(2c)* in yields of 95–98 %. On the basis of their infrared spectra in KBr and of their NMR spectra, these new vinylogous amides are in the form of enol betaines *(4)* in the solid state, but occur as mixtures of the forms *(2)* and *(3)* in chloroform.

Ketones *(2a)* and *(2b)* react with methyl iodide to give the hydroiodides of the *O*-methylated bases [4].

Reduction of *(2a)* with excess lithium aluminum hydride produces $\Delta^{1(9)}$-octahydroquinoline *(5)*; analogous reduction of *(2b)* and *(2c)* yields the $\Delta^{5(10)}$-octahydroquinoline derivatives *(6)*. Hydrogenation of the hydrobromides of the bases *(5)* and *(6)* with $Pd/BaSO_4$ in water or ethanol affords mixtures of *cis*- and *trans*-decahydroquinoline, of the 7-methyl derivatives, and of the 7,7-dimethyl derivatives, respectively.

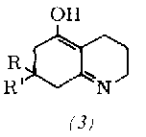


*(1)*

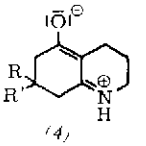


*(2)*

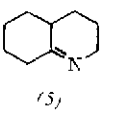
*(a)*, R = R' = H
*(b)*, R = H; R' = $CH_3$
*(c)*, R = R' = $CH_3$



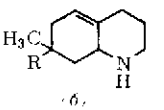
*(3)*



*(4)*



*(5)*



*(6)*

Received, October 30th, 1964 [Z 854/680 IE]
German version: Angew. Chem. 76, 994 (1964)

[1] I wish to express my gratitude to the Deutsche Forschungsgemeinschaft for material assistance.

[2] *J. N. Nazarov* and *S. I. Zav'yalov*, Zhur. obshchei Khim. *24*, 469 (1964).

[3] *H. Reinshagen*, Liebigs Ann. Chem., in the press.

[4] NMR signal at $\tau = 5.91$ ppm as a singlet, and no coloration with ferric chloride ($FeCl_3$ gives a red-violet coloration with the vinylogous amides). Compound *(2c)* does not react with methyl iodide.

# CONFERENCE REPORTS

## Colloquium in Honor of H. Bredereck

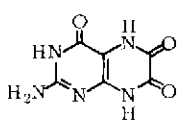
A colloquium was held on May 29th, 1964 in Stuttgart (Germany) on the occasion of the 60th birthday of Professor *Hellmut Bredereck*.

From the lectures:

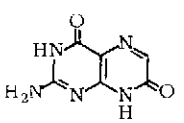
### Recent Work on Natural Pteridines

*W. Pfleiderer*, Stuttgart (Germany)

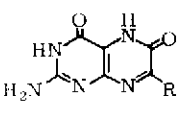
The best-known wing pigments of the *Pieridae* butterflies are the colorless compounds leucopterin *(1)* and isoxanthopterin *(2)*, the yellow compounds xanthopterin *(3)* and chrysopterin *(4)*, and the orange compound erythropterin *(5)*.



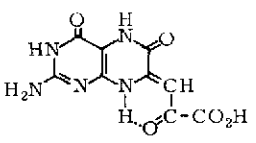
*(1)*



*(2)*

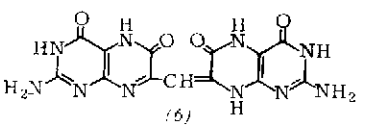


*(3)*, R = H
*(4)*, R = $CH_3$

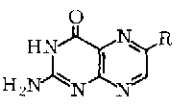


*(5)*

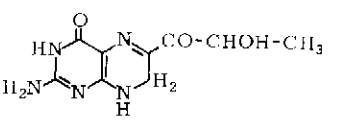
Since pure erythropterin is orange, the observation that the pierid *Appias nero* native to Java and Ceylon has intensely red wings initiated thorough investigations of the constituents of the wing pigments of tropical and indigenous butterflies. It was found that the deep pigmentation of *A. nero* was due to the presence of the dark-red compound pterorhodin *(6)*.



*(6)*



*(7)*, R = H
*(8)*, R = $CO_2H$



*(9)*

Two further compounds, *viz.* pterin *(7)* and pterin-6-carboxylic acid *(8)*, were isolated from the wings of *A. nero*; in addition, a very labile, yellow-fluorescent substance was separated from the other pteridines, concentrated, and identified as sepiapterin *(9)*. A number of other blue-fluorescent compounds were also detected but, owing to their low concentration, could not be isolated; their fluorescence and $R_f$ values indicate that they are 6-polyhydroxyalkylpterins. These compounds and *(9)* are probably intermediates in the conversion of purine-type pteridine precursors into the wing pigments, thus supporting the biogenetic scheme proposed by *Weygand* et al.

Sepiapterin and other pterins were also detected in the South American pierid *Catopsilia argante* and in the orange-tip butterfly *Euchloe cardamines*.

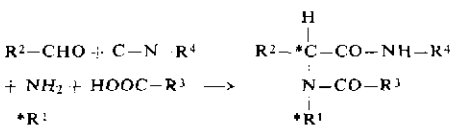
Chromatographic separation of the pigments from the brimstone butterfly (*Gonepteryx rhamni*) showed that the chrysopterin *(4)* isolated from this source in 1936 was not a natural butterfly pigment but was a hydrolysis product from the erythropterin which is located in its discoidal spot.

## Asymmetric Induction during the Synthesis of Amino Acids by the Passerini-Ugi Reaction

*H. Herlinger, D. Rücker,* and *H. Kleimann,*
Stuttgart (Germany)

In the presence of asymmetrically inducing components, such as optically active carbonyl compounds or primary amines, the Ugi variant of the Passerini reaction [1, 2] gives optically active amino-acid derivatives. On asymmetric 1,3-induction with D-(+)-α-methylbenzylamine in the system isobutyraldehyde/benzoic acid/t-butyl isocyanide at −70 °C with concentrations of 1 mole/kg of each of the components in methanol (reaction conditions A), a conformationally determined difference of 0.7–1.0 kcal/mole between the free energies of activation of the diastereoisomeric transition states results in formation of predominantly the L-(+)-valine derivative *(1)*. At 0 °C with concentrations of 0.1 mole/kg (reaction conditions B), however, the D-(−)-valine derivative *(2)* is formed in preponderance. Application of this synthetic method to n-butyraldehyde and L-(−)- or D-(+)-α-methylbenzylamine under reaction conditions A gives the D-(−)- and L-(+)-norvaline derivatives *(3)* and *(5)*, respectively. Under reaction conditions B, the L-(+)- and D-(−)-norvaline derivatives *(4)* and *(6)* are formed predominantly.

On combined asymmetric 1,2- and 1,3-induction, the D-(−)-*allo*-isoleucine derivatives *(7)* and *(10)*, and the L-(+)-isoleucine derivatives *(8)* and *(9)* were prepared from L-(+)-methylethylacetaldehyde and L-(−)- or D-(+)-α-methylbenzylamine, respectively. The reactions give yields of 90–95% and are 70–75% stereospecific. The pure amino-acid derivatives can be readily isolated from the diastereoisomeric mixtures by crystallization from high-boiling petroleum ether. The L-(+)- and D-(−)-amino acids can be obtained by hydrolysis with ca. 15% hydrochloric acid.



| | $R^2$ | Configuration $R^1$ | Configuration $R^2{-}\overset{H}{C}{-}CO{-}N{-}$ | $[\alpha]_{578}$ | M.p. [°C] |
|---|---|---|---|---|---|
| *(1)* | $(CH_3)_2CH-$ | D-(+) | L-(−) | +200° | 137 |
| *(2)* | | D-(−) | D-(+) | −35° | 117 |
| *(3)* | n-$C_3H_7$− | L-(−) | D-(+) | −177.5° | 99 |
| *(4)* | | L-(−) | L-(+) | −11.4° | 110 |
| *(5)* | | D-(+) | L-(+) | +177° | 100 |
| *(6)* | | D-(+) | D-(−) | +11.5° | 109.5 |
| *(7)* | L-$C_2H_5$−CH($CH_3$)− | L-(−) | D-(−) | −199.5° | 134 |
| *(8)* | | L-(−) | L-(+) | +28.6° | 133 |
| *(9)* | | D-(+) | L-(+) | +193° | 146 |
| *(10)* | | D-(−) | D-(−) | −34.9° | 127 |

$R^1$ = α-methylbenzyl, $R^4$ = t-butyl, $R^3$ = $C_6H_5$.

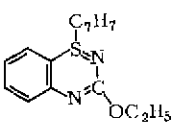
[1] *I. Ugi* and *K. Offermann*, Angew. Chem. *75*, 917 (1963); Angew. Chem. internat. Edit. *2*, 624 (1963). *I. Ugi*, Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962).

[2] *I. Ugi, K. Offermann,* and *H. Herlinger*, Angew. Chem. *76*, 613 (1964).

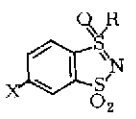
## Heterocyclic Compounds with Endocyclic Sulfur-Nitrogen Double Bonds

*A. Wagner,* Stuttgart (Germany)

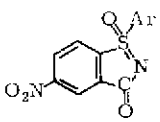
*N*-(*o*-Tolylthiophenyl)-*O*-ethylisourea hydrochloride can be cyclized by dehydrogenation with bromine and sodium methoxide in absolute methanol to give 1-tolyl-3-ethoxy-1*H*-1,2,4-benzothiadiazine *(1)*. In contrast to 1-substituted 1*H*-1,2,4-benzothiadiazin-3-ones, *(1)* is not hydrolysed by aqueous acids or alkalis. 1-Substituted 1*H*-1,3,2-benzodithiazole 3,3-dioxides can be oxidized with potassium permanganate to the corresponding 1-substituted 1*H*-1,3,2-benzodithiazole 1,3,3-trioxides *(2)*, X = $NO_2$, H, or Hal. The S=N double bonds in *(2)* are stable to hydrolysis. The 1-phenyl derivatives of *(2)* can be converted with nitrating mixture at 100 °C into the 1-(*m*-nitrophenyl) derivatives in good yield. The sulfoximino group is thus *meta*-directing. When in *(2)* X = $NO_2$ or Cl, it can be replaced by nucleophilic reagents ($RO^-$, $RS^-$, $N_3^-$, $NH_2R$, or $NH_2NH_2$). Similarly, 5-nitro-1-aryl-1*H*-benzisothiazol-3-one 1-oxides *(3)* can be nitrated in the aryl residue with nitrating mixture in the position *meta* to the sulfoximino group. Compounds *(3)* usually react with alkoxides with ring opening and formation of 2-alkoxy-5-nitrobenzamides; only small amounts of 5-alkoxy-1-aryl-1*H*-benzisothiazol-3-one 1-oxides [*(3)* with $NO_2$ replaced by RO] are formed by this reaction.



*(1)*



*(2)*



*(3)*

## Investigations on Cyclopropenes

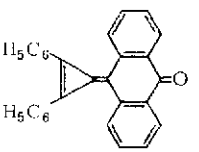
*B. Föhlisch,* Stuttgart (Germany)

As part of a series of experiments directed towards synthesis of compounds containing the methylenecyclopropene structure, preliminary experiments on the preparation of bicyclo-[3,1,0]hexa-1,3,5-triene *(1)* were carried out. Hofmann degradation of the quaternary ammonium salt derived from 6-aminobicyclo[3,1,0]hex-2-ene and methyl iodide resulted in destruction of the bicyclic ring system to give benzene [1]. Similarly, thermal decomposition of trimethyl(bicyclo[3,1,0]-hex-6-yl)ammonium hydroxide gave 1,3-cyclohexadiene.

Substituted tetraarylcyclopropenes were obtained by alkylation of activated aromatic compounds with triphenylcyclopropenylium bromide. An example of the reaction of disubstituted cyclopropenylium salts with aromatic compounds is the reaction of anthrone with diphenylcyclopropenylium salts; this gives rise to 10-(diphenylcyclopropenylidene)anthrone *(2)* – a stable compound with a methylenecyclopropene structure.



*(1)*



*(2)*

[VB 832/158 IE]

German version: Angew. Chem. *76*, 757 (1964)

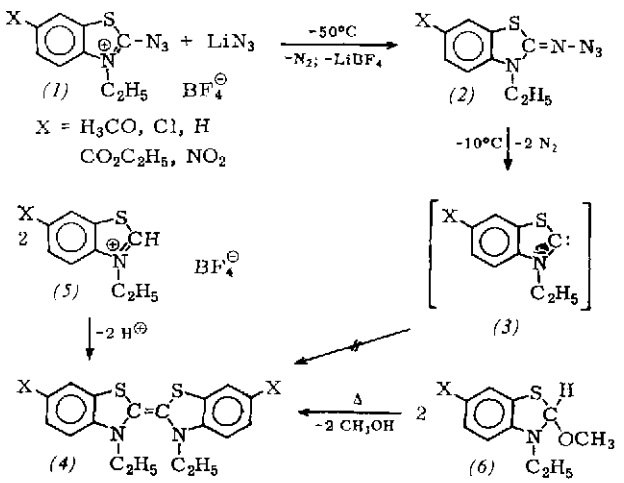
[1] *B. Föhlisch*, Chem. Ber. *97*, 88 (1964).

## Heterocyclic Diazo-azo Compounds as a Source of Nucleophilic Carbenes [*]

*H. Balli*, Marburg/Lahn (Germany)

Heterocyclic-diazo-azo compounds (tetrazo compounds) *(2)*, a new class of mesomeric compounds of the benzthiazole series, can be prepared from the azidinium salts *(1)* [1] and lithium azide at ca. −50 °C.

The "azohomologous" diazo compounds *(2)*, which are explosive in the dry state at room temperature, are protonated by $HBF_4$ at −50 °C with elimination of nitrogen (2 $N_2$) to give the benzthiazolium salts *(5)*. At ca. −10 °C in tetrahydrofuran or dimethylformamide, compounds *(2)* undergo controlled decomposition to give the nucleophilic heterocyclic carbenes *(3)*; these can be trapped by tetracyanoethylene, azidinium salts *(1)*, and diazonium salts to give respectively, cyclopropane derivatives, triazatrimethinecyanines [2,3] and quaternary heterocyclic azo dyes [3,4].




The kinetics of the process *(1)* → *(2)* → *(3)* → triazatrimethinecyanine (X = H) confirm the existence of the short-lived intermediate *(3)* (cf. in contrast [4]). As shown in the case of X = $NO_2$, a true dimerisation of the nucleophilic carbenes, *(3)* → *(4)*, could not be observed (cf. in contrast [4]). Compound *(4)* may be readily prepared *via (5)* or *(6)*. The configuration of *(4)* is unknown.

[GDCh-Ortsverband Krefeld (Germany), September 17th, 1964] [VB 860/164 IE]
German version: Angew. Chem. *76*, 995 (1964)

[*] See also *H. Quast* and *S. Hünig*, Angew. Chem. *76*, 989 (1964); Angew. Chem. *3*, 800 (1964).

[1] *H. Balli* and *F. Kersting*, Liebigs Ann. Chem. *647*, 1 (1961).
[2] *H. Balli* and *F. Kersting*, Liebigs Ann. Chem. *663*, 96, 103 (1963).
[3] *H. Balli*, Angew. Chem. *70*, 442 (1958).
[4] *H. W. Wanzlick* and *H. J. Kleiner*, Angew. Chem. *75*, 1204 (1963); Angew. Chem. internat. Edit. *3*, 65 (1964).

## Electrochemical Reactions at Semiconductor Surfaces

*H. Gerischer*, München (Germany)

The role that the bonding state of the electrons in a solid plays in the mechanism of surface reactions may be most clearly followed when the electrons are direct reactants. This can be demonstrated by electrochemical reactions such as anodic dissolution, cathodic evolution of hydrogen, or other redox reactions at the surfaces of semiconductors. During anodic dissolution of Ge, Si, and GaAs, holes are consumed in the rate-determining step, *i.e.* the release of surface atoms is initiated by donation of the bonding electrons to vacant electronic states in the valence band. In germanium, some of the four electrons per surface atom, which are given free from bonding states during oxidation, are transferred to the conduction band. In semiconductors with a larger band gap, *e.g.* Si or GaAs, the latter step is no longer possible and the release of atoms from the lattice results solely by uptake of holes.

In redox reactions one can discriminate between electron transfers involving either electrons of the conduction band or electrons of the valence band. For example, electrons from the conduction band are consumed during cathodic hydrogen discharge at all the three semiconductors mentioned. On the other hand, reduction of $Fe^{3+}$ ions at these semiconductors takes place by uptake of electrons from the valence band.

Comparison of the work functions for the emission of electrons from the conduction band, the valence band, and the components of the redox system suggests that electron exchange in the conduction band should be favored in redox systems with reducing properties, *i.e.* with a negative redox potential and a correspondingly lower electron affinity. Electron exchange in the valence band is preferred for redox systems with high redox potential, *i.e.* with a greater electron affinity. This theoretically expected result is confirmed by experimental findings.

[GDCh-Ortsverband Freiburg-Südbaden (Germany), July 10th, 1964] [VB 843/162 IE]
German version: Angew. Chem. *76*, 759 (1964)

# SELECTED ABSTRACTS

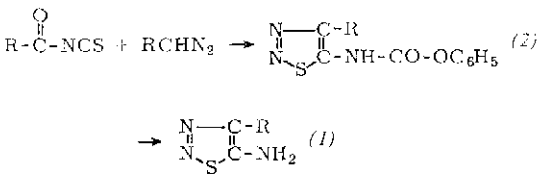
**Isocyanates of sulfuric acid react with dimethyl sulfoxide,** according to *R. Appel* and *H. Rittersbacher*, to form sulfuryldimethylsulfimines with elimination of $CO_2$. Amine oxides form adducts with sulfuryl di-isocyanate, which can be split up into their components again by chemical means. A colorless oil, which decomposes explosively above 0 °C, can be isolated from the reaction of the isocyanates of sulfuric acid with dimethyl sulfoxide under mild conditions below 0 °C. Sulfurylbisdimethylsulfimine *(1)*, m.p. 177 °C, is formed in 54 % yield, with evolution of $CO_2$ and heat, when sulfuryl di-isocyanate is treated with dimethyl sulfoxide at 20 °C.

$$O_2S(NCO)_2 + 2\ OS(CH_3)_2 \rightarrow (CH_3)_2S{=}N{-}SO_2{-}N{=}S(CH_3)_2$$
*(1)*

Dimethylsulfiminosulfuric acid, m.p. 171 °C, is formed in 75 % yield by hydrolysis of the product obtained from chlorosulfonyl isocyanate and dimethyl sulfoxide. The adduct of pyridine *N*-oxide and sulfuryl di-isocyanate melts at 138 to 139 °C, the trimethylamine *N*-oxide adduct melts at 68 °C. Water decomposes the adducts, occasionally with the appearance of flames, to give sulfamide, $CO_2$, and the *N*-oxide. / Chem. Ber. *97*, 852 (1964) / −W. [Rd 996/280 IE]

**The adsorption of cyanine dyes onto silver halides** has been investigated by *J. F. Padday*. The surface occupied by dyestuff molecules adsorbed on different silver halides is not always the same; this causes problems in the use of such dyes for estimating surface areas. The absorption spectrum of the adsorbed dyestuff also depends on the silver halide carrier and furthermore on the degree of coverage of the surface. Different absorption bands were found which can be ascribed to monomeric (M bands), dimeric (D or H bands), and polymeric (J bands) species of the dyestuff. The occurrence of H or J bands depends practically exclusively on the conditions of adsorption, and not upon the degree of coverage of the surface. It is therefore concluded that the association theory must be reexamined. / Trans. Faraday Soc. *60*, 1325 (1964) / −Hz. [Rd 113/300 IE]

**5-Amino-1,2,3-thiadiazoles** were prepared by *J. Goerdeler* and *G. Gnad*, by treating acyl isothiocyanates with diazoalkanes and carefully deacylating the *N*-phenoxycarbonylamines *(2)* thus obtained with weak bases in aqueous acetone. Other acyl groups cannot be removed without changing the structure of the ring. The parent compound *(1)* [R = H], m.p. 152 °C, is made by careful hydrolysis of 5-phenoxycarbonylaminothiadiazole. Other diazoalkanes give *(1)* with substituents in the 4-position, *e.g.* 4-methyl-1,2,3-thiadiazole, (m.p. 120 °C) and 4-ethoxycarbonyl-1,2,3-thiadiazole, m.p. 126 °C,

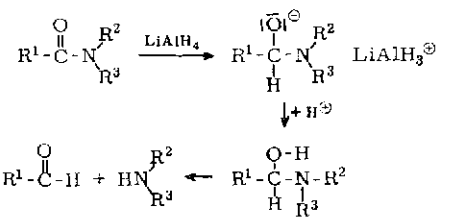


which were obtained from diazoethane and diazoethyl acetate, respectively. The amino group can be sulfonated, acylated, nitrosated, and diazotized. Some 5-substituted 1,2,3-thiadiazoles were obtained via the diazotized compounds. / Tetrahedron Letters *1964*, 795 / –W. [Rd 997/281 IE]

**Streptomycin alters the mechanism by which the messenger code is red,** according to *J. Davies, W. Gilbert*, and *L. Gorini*. During polypeptide synthesis *in vitro* with the system of *Matthaei* and *Nirenberg*, streptomycin exerts an inhibitory effect on protein synthesis by upsetting the mechanism by which the base sequence in the messenger RNA at the ribosomes is translated into the amino-acid sequence of the protein. The incorporation of phenylalanine into acid-insoluble material by the synthetic messenger polyuridylic acid is inhibited 50–75 % by streptomycin, whereas the incorporation of isoleucine (code UUA, UAA, CAU) is increased up to twentyfold. This effect depends upon the magnesium-ion concentration. The site of reaction of the streptomycin is the 30-S subunit of the 70-S ribosome. A cell-free system containing 30-S subunits from streptomycin-resistant bacteria does not exhibit this effect. Ribosomes which are resistant to streptomycin are not necessarily resistant to kanamycin and to neomycin although these substances act like streptomycin. The translating mechanism requires a specific conformation of the center on the ribosomes which attaches the transfer RNA to the messenger RNA. Streptomycin can probably modify this center in such a way that the "wrong" transfer RNA is accepted thus leading to incorporation of the "wrong" amino acid, *i.e.* U is read off as A, for example. Mutations can apparently alter the ribosome in such a way that it becomes insensitive to streptomycin or even requires streptomycin. / Proc. nat. Acad. Sci. U.S.A. *51*, 883 (1964) / –Sch.

[Rd 142/329 IE]

**Lithium aluminum hydride cleaves proline linkages in peptides,** as *M. A. Ruttenberg, T. E. King*, and *L. C. Craig* discovered when they treated peptides containing proline with $LiAlH_4$ in tetrahydrofuran. Tertiary amides are reduced much faster than primary or secondary amides under these conditions which do not lead to racemization. Complete solubility of the peptide in the anhydrous solvent does not appear to be necessary. The yields of cleavage products lie between 30 and 100 %. The products are a peptide with *N*-terminal proline and a peptide with a *C*-terminal aldehyde group, probably formed by the following reactions:



/ Biochemistry *3*, 758 (1964) / –Sch. [Rd 135/322 IE]

# BOOK REVIEWS

**Gmelins Handbuch der anorganischen Chemie** (Gmelin's Handbook of Inorganic Chemistry), 8th completely revised edition. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in the Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Initiated by *R. J. Meyer*, continued by *E. H. Erich Pietsch*. Verlag Chemie, GmbH, Weinheim/Bergstr.

**System No. 34: Mercury.** Part A, Vol. 2 (Electrochemistry. Chemical Behavior. Alloys). 1962, IV, XL, 709 pp., 285 figs., cloth, DM 534.– (about $135.–). Revised by *Erna Brennecke, Gertrud Glauner-Breitinger, Vera Haase, A. Kunze, K. Rehfeld, Ph. Stiess, K. Swars*, and *Ursula Trobisch-Raussendorf*.

Vol. A1 (466 pp., 53 figs.), which was published in 1960, dealt with the history, occurrence, preparation, and physical properties of mercury; the present Volume A2 (709 pp., 285 figs.) is concerned with its electrochemistry (316 pp.), chemical behavior (102 pp.), and alloys (291 pp.).

The chapter on the electrochemistry of mercury is naturally particularly comprehensive and comprises about 45 % of the present Volume. It opens with a discussion of the normal potentials of the redox systems $Hg/Hg_2^{2+}$, $Hg/Hg^{2+}$, and $Hg_2^{2+}/Hg^{2+}$ in aqueous and non-aqueous solutions; this is followed by sections on the position of mercury in the electrochemical series, its electrolytic solution pressure, its ion mobility, and its potentials with respect to 65 electrodes and over 214 galvanic cells described in the literature. Detailed consideration is given to mercury electrodes (such as $Hg/Hg_2O$, Hg/HgO, $Hg/Hg_2X_2$ [1], $Hg/HgX_2$ [1], $Hg/Hg_2(I_2O_3)$, Hg/HgS, $Hg/HgSO_4$, and $Hg/Hg_2CO_3$), and in particular to the $Hg/Hg_2Cl_2$ electrode (calomel electrode), the most important reference electrode. The section on the electrocapillary curves of mercury deals with both experimental results in aqueous and non-aqueous media and their theoretical interpretation.

In the section on the capacity and structure of the Hg/solution phase-boundary layer, consideration is also given, in view of the fundamental importance of this problem, to papers which appear essential to the presentation of the theory although they deal with other electrode metals. This section is supplemented and illustrated by many figures, descriptions of the methods of determining the phase-boundary capacity, and many individual data on measured specific capacities of Hg electrodes. The discussion of the mercury dropping electrode (polarography) does not attempt to give a complete account of all the available data, in view of the explosive increase in the pertinent literature over the past few years. Instead, reference is made to the review literature, and special attention is given to the behavior of mercury salts at the mercury dropping electrode, with quotation of the appropriate half-wave potentials. The details given of investigations of the hydrogen (deuterium) overvoltage on mercury are justified by the technical importance of this phenomenon. In this connection, and in connection with the theory of overvoltage, the behavior of mercury as an anode and a a cathode is considered. A discussion of the electro-

[1] X = F, Cl, Br, or I.

lytic deposition of mercury, which is of theoretical interest although it has no industrial importance, deals with deposition from solutions and melts. Finally, the mercury coulometer (voltameter), which is used to measure quantities of electricity, is discussed.

The chapter on the chemical behavior of mercury is subdivided into sections on elemental mercury and mercury ions ($Hg_2^{2+}$, $Hg^{2+}$). In both cases, the behavior towards both elements and inorganic and organic compounds is discussed. Particular mention should be made of the discussion of the behavior of metallic mercury toward acids, the general considerations on the existence of the characteristic diatomic Hg(I) ion $Hg_2^{2+}$, and its formation from and disproportionation into Hg + $Hg^{2+}$, and of the data on the degree of dissociation and complex formation of Hg(II) compounds. Among the ionic reactions of mercury, those which are suitable for analytical purposes are discussed in detail, so that a special chapter on the detection and determination of mercury has proved unnecessary, particularly in view of the "Fresenius-Jander" volumes on this subject.

The chapter on alloys of mercury is very extensive (more than 40 % of the volume) in view of the wide practical importance of amalgams. In accordance with the Gmelin "last-place" principle, all the alloys of mercury with metals of System Numbers lower than that of mercury are discussed, *i.e.* alloys with the metals Sb and Bi from the 5th main group, with Li, Na, K, Rb, and Cs from the first main group (including ammonium amalgam), with the metals Be, Ca, Sr, and Ba from the 2nd main group, and with Zn and Cd from the 2nd sub-group. Contrary to the Gmelin principle, the Tl alloys are also included here, and the Mg alloys, which should be dealt with here, are discussed earlier in the System No. "Magnesium." Alloys with metals of System Nos. higher than that of Hg are dealt with in the relevant System Numbers. Thus, data on alloys with Al, Ga, In, Ge, Ti, Zr, Th, Cr, Mo, W, U, Re, Fe, Co, Ni, platinum metals, and Au appear in volumes which have already been published, whilst the data on alloys of mercury with Ra, Ac, the rare earths, Sn, Pb, Hf, V, Nb, Ta, Pa, Mn, Tc, Cu, Ag, and the transuranium elements are still forthcoming. The chapter on amalgams includes phase diagrams and information on the formation and production, physical properties, and electrochemical behavior of the alloys and on intermetallic compounds and multicomponent alloys.

**System No. 58: Cobalt.** Part B, Supplement, Vol. 1 [Cobalt(I) and Cobalt(II) Compounds]. 1963, IV, XVIII, 314 pp., 48 figs., cloth, DM 241. (about $61.–). Revised by *K.-Ch. Buschbeck, H. Feicht, R. Gagarin, G. Krause, Irmingard Kreuzbichler, H. Lehl, W. Schaffernicht,* and *Edith Schleitzer-Steinkopf.*

This supplement, which is published in two volumes, is a continuation of the main volume "Cobalt, Part B" (376 pp., 2 figs.), which appeared in 1930. It embraces all the literature up to the end of 1949, with extensive supplements for the period 1950–1960, taking account of the developments right up to the present. This Volume 1 (314 pp., 48 figs.) deals with the complexes of mono- and divalent cobalt with neutral and inner complex-forming ligands; complexes of trivalent cobalt will be the subject of the second volume, which is still forthcoming. Recent literature on compounds of cobalt with acidic ligands (including aquo-complexes and hydrates) has already been evaluated in the supplement volume "Cobalt, Part A" (886 pp., 188 figs.) published in 1961 to bring the main volume "Cobalt, Part A" (502 pp., 32 figs.), published in 1931/32, up to date.

The supplement Volume B 1 which is reviewed here begins with short introductions and observations (5 pp.) on recent reviews (monographs, congress reports), on the arrangement of the material, and on general questions such as complex-formation constants, thermodynamic data, chelation effects, stability series, light absorption, and magnetic properties.

This is followed by a discourse on Co(I) complexes, which have only recently become known, so this only occupies 5 pp. The majority of the complexes are isocyanides of the type $[Co(RNC)_5]X$ containing the $[Co(RNC)_5]^{\oplus}$ cation, which is isoelectronic with $Fe(CO)_5$.

The major part of the volume (304 pp.) is devoted to Co(II) complexes. These are subdivided according to the complexing ligands, inorganic ligands ($H_2O$ [2], $NH_3$, $N_2H_4$) being dealt with first in 13 pp.; the remaining 291 pp. are devoted to organic ligands (compounds containing nitrogen, oxygen, sulfur, selenium, phosphorus, and arsenic). The discussions cover not only substances which have been isolated, but also those which have only been characterized by their stability constants. The data include all the factual material published to date, *i.e.* the structure, preparation, and physical and chemical properties, as well as the theoretical ideas proposed to explain the properties.

The organic ligands are subdivided into monoamines, diamines, polyamines, heterocycles with the heteroatoms O, N, and S (which are in turn subdivided according to the number of heteroatoms), alcohols, ethers, aldehydes, ketones, quinones, amino alcohols, amino acids, amine-*N*-polyacetic acids, cyanides, isocyanides, Schiff bases, azo compounds, formazans, oximes, urea, compounds containing sulfur and selenium, phosphines, and arsines. The widely studied complexes with ethylenediamine, phthalocyanine, pyridine, bipyridyl, quinoline, phenanthroline, histidine, acetylacetone, ethylenediaminetetraacetic acid, isocyanides, bis-*N*,*N'*(salicylidene)-ethylenediamine, dimethylglyoxime, dimethyl sulfoxide, phosphines, and arsines are discussed in particular detail. In the case of tetracoordinated cobalt complexes, consideration is given to the questions of their tetrahedral or planar structure and of their ability to take up oxygen reversibly. Their light absorption and optical activity are also considered.

Since it is difficult to find a given compound in the confusing superabundance of complexes discussed, the second volume of the supplement, which is due to appear in the near future, will contain indices of the ligands, arranged both alphabetically and according to their empirical formulae, an innovation which will be highly welcome.

**System No. 60: Copper.** Part D (Electrical Properties of Copper Oxides). 1963, IV, X, 168 pp., 136 figs., cloth, DM 134.– (about $ 34.–). Revised by *W. A. v. Meyeren* and *H.-G. Wuttke.*

Here 152 pp. and 126 figs. are devoted to Cu(I) oxide, and 16 pp. and 10 figs. to Cu(II) oxide. Apart from the electrical behavior proper, the thermoelectrical and photoelectrical properties are discussed. The discussion of CuO has for no apparent reason been inserted in the middle of the material on $Cu_2O$, under a heading which, owing to the size of the type, gives the false impression that all the subsequent material is a sub-chapter of the chapter "Copper(II) Oxide". It would have been better here to add the short CuO section at the end of the complete discussion of $Cu_2O$, as a final chapter to Part D.

The data on copper(I) oxide are divided – apart from discussions of its general electrical data (such as dielectric constants and contact potential), thermoelectric behavior (thermoelectric force, Peltier heat), and photoelectric behavior (photoemissive and photoconductive effects) – into two subchapters: "Electrical Conductivity of Copper(I) Oxide with Homogeneous Defect Distribution" (59 pp.) and "Electrical Conductivity of Copper(I) Oxide with Non-homogeneous Defect Distribution" (76 pp.).

The first subchapter (homogeneous defect distribution) deals with investigations which were of fundamental importance to the development of the theory and technology of semiconductors during the past decades, since $Cu_2O$ – or $Cu_xO$ ($x \ll 2$) – can be obtained relatively easily, in comparison with Se, the second standard substance for the investigation of semiconductors, from a metal which is readily obtainable in a

[2] The ligand $H_2O$ is only referred to, since the aquo-complexes of divalent cobalt are included in the supplementary volume "Cobalt, Part A" as Co(II) salts containing water of hydration.

state of high purity. The fact that, during the Second World War, the roles of Se and $Cu_xO$ as standard semiconductors were to a large degree taken over by Ge and Si in no way detracts from the importance of these investigations. The electrical conductivity at room temperature and at higher and lower temperatures is first discussed; the point of inflexion and other anomalies of the conductivity-temperature curve are indicated, and the mathematical representation of the temperature-dependence and the use of the temperature-dependence (resistance thermometer, high-resistance bolometer, pyroelectric conductor) are given. Considerable space is then devoted to the influence of the conditions of preparation of $Cu_xO$ on its electrical properties: the course of oxidation of Cu to $Cu_xO$ and CuO, dependence of the electrical conductivity on various factors (such as heat treatment, aging in air, packing density, grain size, layer thickness, mechanical surface-treatment, the action of pressure, surrounding gaseous and liquid media, stoichiometric composition, admixtures, electrodes, field strength), breakdown problems, surface conductivity, contact resistance (coherer effect, microphone effect), and magnetic resistance variation. This part is completed by observations on the mechanism of electrical conductivity according to the energy band model.

The second subchapter (non-homogeneous defect distribution) is concerned with the important field of the $Cu_2O$ rectifier, *i.e.* the rectification of alternating current at a $Cu_2O$–Cu contact, a phenomenon which was observed over 90 years ago but which was only applied technically and correctly interpreted theoretically at a much later date. This part deals first with the behavior of rectifier plates toward d.c. and a.c., the circuits and efficiency in the rectification of a.c., the loading capacity, reversible and irreversible changes under load, and the influence of moisture, impurities, and the conditions of production. This is followed, owing to the practical importance of the $Cu_2O$ rectifier, by detailed data on the production technology (pretreatment of Cu and oxidation to $Cu_2O$, annealing and cooling of the $Cu_2O$ layer, removal of the CuO surface layer, application of the counter-electrode to the CuO-free $Cu_2O$ surface, protection against moisture, production of rectifier assemblies), which is in turn followed by a section on fields of application (electroplating, battery chargers, a.c. ammeters and voltameters, telephone and signal equipment, radio engineering). Finally, the advantages and disadvantages of the $Cu_2O$ rectifier compared with Se rectifiers, which have gained ground in the past two decades, and the mechanism and theory of dry contact rectification are discussed.

The short chapter on copper(II) oxide deals, as that on copper(I) oxide, with the electrical and thermoelectric properties, and then gives an interpretation of its electrical volume conduction and surface conduction on the basis of the energy band model.

With the present Volume D, which completely covers the literature up to the end of 1959 and which, owing to the participation of only two (temporary) workers at the Gmelin Institute, has a peculiarly complete monograph-like character, the System No. "Copper" now reaches the impressive total of 2609 pp. and 657 figs. (total price DM 1645.– or about $415. -). This does not include the extensive volumes on complexes (Part B3) and alloys (Part C) of copper, and in the case of the previously published volumes of Part A (History. Occurrence. The Element) and B (Compounds of Copper), the work which has been published in the 15 years which have passed since the deadline for literature evaluation (1949) still awaits evaluation.

This shows that the extensiveness of reports on the individual elements is growing with time in a most alarming manner. It is consequently becoming increasingly difficult and time-consuming to find rapidly and completely the information on certain facts which, owing to the Gmelin classification of the substances and the Gmelin "last-place" principle, are inevitably dispersed throughout various sections of a System Number or even over various System Numbers. It is therefore appropriate to suggest that a detailed alphabetical subject and compound index (available as a separate part) should be added to each System Number on its completion; this should give references not only to the text of the System Number in question, but also cross-references to the relevant places in other System Numbers. In the reviewer's opinion, this would even further enhance the practical value of Gmelin's Handbook.

*E. Wiberg* [NB 232/94 IE]

Translated by Express Translation Service, London

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## Errata

A. In the paper "Immunochemistry", Angew. Chem. internat. Edit. *3*, 591 (1964), the following corrections must be made:

p. 591, right column, paragraph 4, line 6/7 read: 3-*O*-methylgalactose, insted of: 3-*O*-methylfucose.

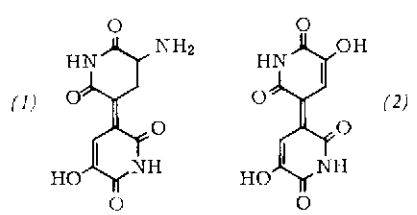
p. 591, right column, paragraph 5, line 2 read: moderate blood-group A specificity, instead of high blood-group A specificity. Here it should be mentioned, that only virus grown on chick embryos was investigated. Since chickens contain blood group A-like Forssman antigens, it is likely that the virus has incorporated this material from the host as part of its surface structure.

B. In the paper "Metallo Complexes", Angew. Chem. internat. Edit. *3*, 686 (1964), the following corrections must be made:

p. 690, right column, Section 3, first line of third paragraph: omit the words "In the first sphere".

p. 690/691: In Section 3 the notation " ... mercury(I)-..." which appears seven times in names of complexes must be changed to read "...mercuro(II)-...".

C. On p. 765, left column, last abstract, the formulae should read:




according to *R. Kuhn, H. Bauer, H.-J. Knackmuss, D. A. Kuhn*, and *M. P. Starr*, Naturwissenschaften *51*, 409 (1964).

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SC = Short communication LA = Literature abstract
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