ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 1
January 1977
Pages 1–64

New Varieties of Sandwich Complexes[**]

By Helmut Werner[*]

Metal sandwich complexes of the classical type $M(C_nH_n)_2$ and related structural analogs are characterized by a sandwich-like coordination of *one* central atom by its ligands. This structural principle has been extended in recent years now that *di-* and *tri-nuclear* sandwich-type complexes have become accessible. The best-known representatives are the triple-decker sandwich complexes. A survey of this topical field is presented in this report, which also underlines the utility of kinetic and mechanistic studies for the development of new synthetic pathways in organometallic chemistry.

1. Introduction

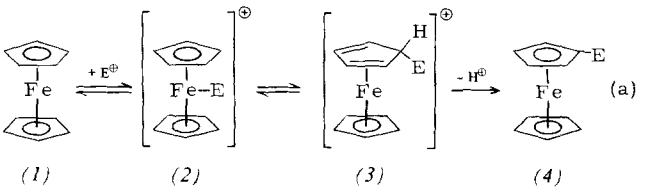
The chemistry of sandwich complexes celebrates its 25th anniversary in these months. In its second December issue of 1951, the journal "Nature" contained a paper by *Kealy* and *Pauson* entitled "A New Type of Organo-Iron Compound", which reported the preparation of a compound of composition $FeC_{10}H_{10}$[1a]. Shortly afterwards, in the March issue of the Journal of the Chemical Society, *Miller*, *Tebboth*, and *Tremaine* described an independent but just as unexpected synthesis of "dicyclopentadienyliron"[1b]. The unusual (one could say provocative) properties of this substance prompted a unique development of epoch-making scale in organometallic chemistry. The first moves are common knowledge: just a few months after publication of the paper in "Nature" *Wilkinson*[2] and *Fischer*[3] proposed the correct structure of the new compound, *Woodward*[4] proved its "aromatic character" (thereby introducing the name "ferrocene"), and still in 1952 the first dicyclopentadienyl complexes of other transition metals were obtained[5].

Today, 25 years after the birth of ferrocene, the chemistry of $M(C_5H_5)_2$ complexes has become a well-established field of broad proportions. The first representative of these compounds, ferrocene, which displays exceptional thermodynamic stability and obeys the 18-electron rule, has been joined by the electron-deficient "metallocenes" with M = V, Cr, and Mn, on the one hand, and the electron-rich compounds with Co or Ni as central atom on the other. Although the prototype compound $Fe(C_5H_5)_2$ has retained pride of place among the metallocenes, especially in the general chemical literature, recent studies on the reactions of the formerly somewhat neglected compounds $Co(C_5H_5)_2$ and $Ni(C_5H_5)_2$ have provided entry to completely new types of organometallic complexes with sandwich structures. Some of the pathways leading through this new territory will now be considered.

2. Triple-Decker Sandwich Complexes

2.1. Synthetic Studies

Ferrocene *(1)* is extremely susceptible to electrophilic substitution. The following mechanism is generally accepted for this reaction[6]:



[*] Prof. Dr. H. Werner
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[**] Based on a main lecture delivered at the General Meeting of the Gesellschaft Deutscher Chemiker at Cologne, September 1975.

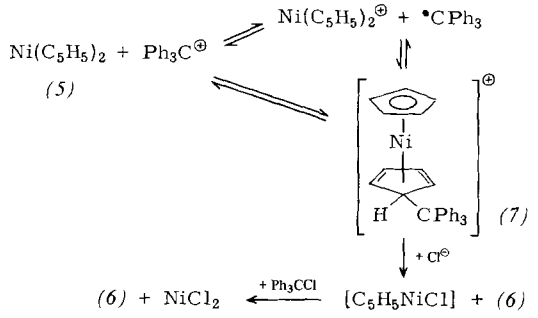
Initial attack by an electrophile accordingly takes place *at the metal*, and is followed by formation of a C—E bond and by expulsion of a proton to give the substituted complex *(4)*. The low stability of the intermediate *(3)* is explained in terms of the tendency of the iron atom, which has a 16-electron configuration, to complete its electron shell to give a species with 18 electrons.

If this interpretation is valid, a cation analogous to *(3)* containing Ni instead of Fe should be stable, since it would have 18 electrons in its valence shell. Owing to the failure of attempts to synthesize alkyl- or acyl-substituted nickelocenes starting from $Ni(C_5H_5)_2$[7], we first employed triphenylmethyl reagents in our studies instigated in 1970.

Nickelocene *(5)* reacts fast and quantitatively with Ph_3CCl[*] in nitromethane according to equation (b) to form *(6)*, an isomeric mixture of 1- and 2-triphenylmethylcyclopentadiene[8].

$$Ni(C_5H_5)_2 + 2\ Ph_3CCl \longrightarrow NiCl_2 + 2\ \text{(6)} \qquad \text{(b)}$$
(5)

We proposed the following mechanism for this reaction:



Scheme 1

The cation *(7)* was assumed to be kinetically very labile and should react further—even with weak Lewis bases—with cleavage of the nickel-diolefin bond.

In order to suppress such a reaction (and at the same time to trap the complex cation with a bulky anion) we treated nickelocene with $[Ph_3C]PF_6$. The result was more than surprising. Instead of the desired complex $[C_5H_5Ni(C_5H_5CPh_3)]PF_6$ we obtained a blackish brown compound *(8)* of remarkable stability. The yield was quantitative if the molar ratios given in eq. (2) were employed[9].

$$2\ Ni(C_5H_5)_2 + [Ph_3C]PF_6 \longrightarrow [Ni_2C_{15}H_{15}]PF_6 + \text{(6)} \qquad \text{(c)}$$
(5) *(8)*

An analogous product *(9)* is obtained from *(5)* and $[Ph_3C]BF_4$. The same compound [see eq. (d)] is also accessible starting from $[Ph_2CH]BF_4$, $[C_7H_7]BF_4$, $[OMe_3]BF_4$, and HBF_4.

$$2\ Ni(C_5H_5)_2 + [R]BF_4 \longrightarrow [Ni_2C_{15}H_{15}]BF_4 + C_5H_5R \qquad \text{(d)}$$
(5) *(9)*

[*] Abbreviations: Me = CH_3, Et = C_2H_5, Pr = C_3H_7, Bu = C_4H_9, Cp = C_5H_5, Ph = C_6H_5, Tol = $C_6H_5CH_3$.

The HBF_4/propionic anhydride system has also proved very suitable for the synthesis of the methyl- and *tert*-butylcyclopentadienyl complexes *(10)* and *(11)*[10].

$$2\ Ni(C_5H_4R)_2 + HBF_4 \longrightarrow [Ni_2C_{15}H_{12}R_3]BF_4 + C_5H_5R \qquad \text{(e)}$$
(10), R = Me
(11), R = *t*-Bu

The ^1H- and ^{13}C-NMR spectra of *(8)* and *(9)* recorded in $[D_3]$nitromethane each contain two sharp singlets in the intensity ratio 2:1, which do not change on warming or cooling. This suggests that the cation $[Ni_2C_{15}H_{15}]^{\oplus}$ contains three symmetrically π-*(pentahapto)*-bonded cyclopentadienyl ligands of which two should be equivalent. The goal of constructing a complex having a triple-decker sandwich structure—already pursued by one of the fathers of sandwich compounds[11]—thus appeared to be fulfilled.

Final confirmation took more than a year. The exceptional reactivity of *(8)* and *(9)* towards Lewis bases ruled out most of the solvents suitable for such salt-like complexes, and only after many futile attempts were single crystals of *(9)* finally obtained from propionic anhydride. The result of crystal structure analysis confirmed the structure we had proposed for the $[Ni_2C_{15}H_{15}]^{\oplus}$ ion[12]. As shown by Figure 1 the two nickel atoms are located between three mutually parallel five-membered rings adopting neither a staggered nor an eclipsed conformation. The Ni-ring center distances to the outer rings Cp_A and Cp_C are 1.728 Å (average value) and are significantly shorter than those to the central ring Cp_B, which are 1.788 Å (average value).

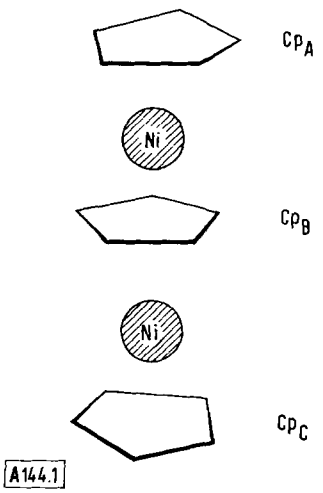


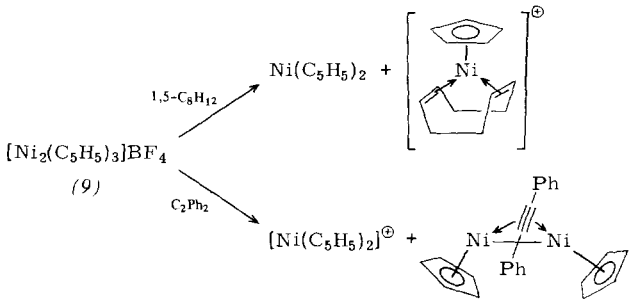
Fig. 1. Structure of the tris(η-cyclopentadienyl)dinickel cation, $[Ni_2(C_5H_5)_3]^{\oplus}$.

The reactions of compounds *(8)*—*(11)* are in full accord with this result. Reaction of one of the complex salts with a Lewis base L such as PR_3, $P(OR)_3$, AsR_3, or pyridine proceeds according to eq. (f) to give $Ni(C_5H_4R)_2$ and the salt of the corresponding cationic monocyclopentadienylnickel complex[13].

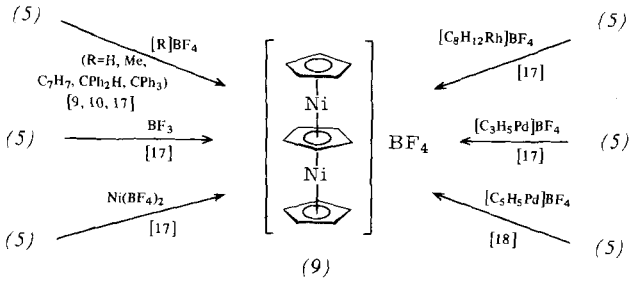
$$[Ni_2(C_5H_4R)_3]BF_4 + 2\ L \longrightarrow Ni(C_5H_4R)_2 + [C_5H_4RNiL_2]BF_4 \qquad \text{(f)}$$

The mechanism of this substitution reaction can be interpreted as follows: attack of the Lewis base L on one of

the nickel atoms removes a "storey" of the triple-decker sandwich and the resulting fragment $C_5H_4RNiL^{\oplus}$ is stabilized by addition of a further molecule L. Chelating ligands L—L (*e.g.* diphos = ethylenebis(diphenylphosphane) or bpy = 2,2'-bipyridine) give the compounds $[C_5H_4RNi(L—L)]BF_4$[13]. Using this approach, the first synthesis of cationic diolefin-nickel complexes $[C_5H_4RNi(diene)]^{\oplus}$ (diene = norbornadiene, 1,5-cyclooctadiene) has also been accomplished and their reactions with nucleophiles studied[14, 15]. Surprisingly, reaction of *(9)* with tolan does not give $Ni(C_5H_5)_2$ and $[C_5H_5Ni(C_2Ph_2)_2]BF_4$ or $[C_5H_5NiC_4Ph_4]BF_4$ but instead the tetrafluoroborate of the nickelocenium ion, otherwise difficult to prepare in pure form, and the previously described neutral complex *(12)*[16].



The synthetic procedure for *(9)* given in eq. (d) has meanwhile been supplemented by others (see Scheme 2). They also provide support for the idea that one of the two cyclopentadienyl rings of *(5)* can easily be liberated on interaction with a Lewis acid, and the resulting cation $C_5H_5Ni^{\oplus}$ readily reacts with $Ni(C_5H_5)_2$ to give the triple-decker sandwich.



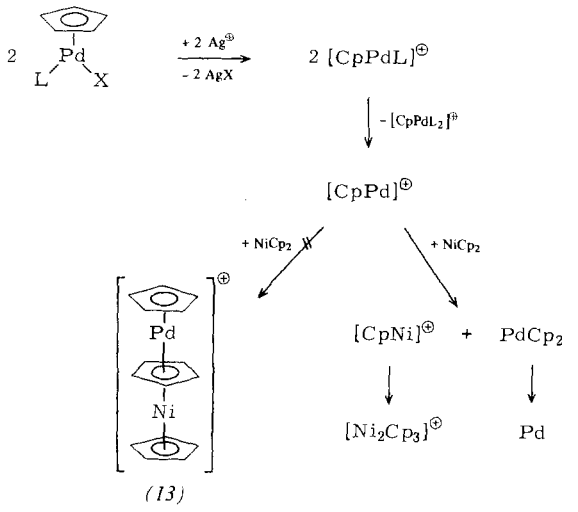
Scheme 2

Special mention should be made of the reaction of nickelocene with the 12-electron species $[C_8H_{12}Rh]^{\oplus}$ and $[C_3H_5Pd]^{\oplus}$ and the 14-electron species $[C_5H_5Pd]^{\oplus}$. *Schrock* and *Osborn*[19] have prepared the first two cations *in situ* from the corresponding chlorides $[C_8H_{12}RhCl]_2$ and $[C_3H_5PdCl]_2$, respectively, by treatment with $AgPF_6$ in tetrahydrofuran and established their coordinatively highly unsaturated character by numerous reactions with Lewis bases. Although $Ni(C_5H_5)_2$ clearly acts as a Lewis base towards *e.g.* $H^{\oplus}$, $R^{\oplus}$, or BF_3, it does not build a new storey to form the desired cations $[C_8H_{12}RhC_5H_5NiC_5H_5]^{\oplus}$ and $[C_3H_5PdC_5H_5NiC_5H_5]^{\oplus}$, respectively, on reaction with $[C_8H_{12}Rh]^{\oplus}$ and $[C_3H_5Pd]^{\oplus}$. Instead, reaction proceeds *via* ring ligand transfer[20] to form the corresponding cyclopentadienylrhodium and -palladium complexes and $[Ni_2(C_5H_5)_3]^{\oplus}$[17].

$$C_8H_{12}Rh]^{\oplus} + 2\ Ni(C_5H_5)_2 \longrightarrow C_8H_{12}RhC_5H_5 + [Ni_2(C_5H_5)_3]^{\oplus} \quad (g)$$

$$C_3H_5Pd]^{\oplus} + 2\ Ni(C_5H_5)_2 \longrightarrow C_3H_5PdC_5H_5 + [Ni_2(C_5H_5)_3]^{\oplus} \quad (h)$$

The synthesis of *(9)* from *(5)* and $[C_5H_5Pd]BF_4$ was discovered by accident. We had intended to produce a "mixed" triple-decker sandwich *(13)* by preparing $[C_5H_5Pd]^{\oplus}$ *in situ*, starting from $C_5H_5Pd(L)X$ (L = PR_3, $P(OR)_3$; X = Cl, Br, I), and subjecting it to reaction with *(5)*. NMR studies by *Turner*[18] show that the desired intermediate $[C_5H_5Pd]^{\oplus}$ is indeed formed, together with highly stable $[C_5H_5PdL_2]^{\oplus}$, but fails to undergo addition with *(5)*, rather reacting *via* ligand transfer and formation of $[Ni_2(C_5H_5)_3]^{\oplus}$[18].



Scheme 3

2.2. Reaction Mechanism

In view of the various synthetic approaches to the complex cation $[Ni_2(C_5H_5)_3]^{\oplus}$ the question occurs whether the reactions summarized in Scheme 2 (which all give practically *quantitative yields* of the triple-decker sandwich) proceed *via* a *common* intermediate or not. The most reasonable candidate would be the (electron-*deficient*) 14-electron species $[C_5H_5Ni]^{\oplus}$ which could react with the (electron-*rich*) $Ni(C_5H_5)_2$ according to eq. (i).

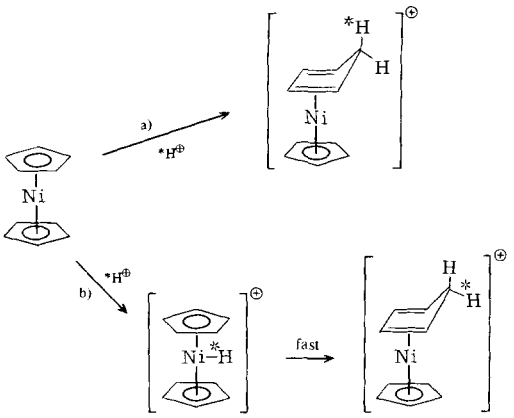
$$[C_5H_5Ni]^{\oplus} + Ni(C_5H_5)_2 \longrightarrow [C_5H_5NiC_5H_5NiC_5H_5]^{\oplus} \quad (i)$$

An *ion-molecule reaction* of this kind had already been detected by *Schumacher* and *Taubenest*[21] as the key step in the formation of the $[Ni_2C_{15}H_{15}]^{\oplus}$ ion in the mass spectrometer. We recently succeeded in isolating salts of the "single-decker" $[C_5H_5Ni]^{\oplus}$ by an unpredicted method. The impetus came from our continued interest in the mechanism of formation of the structurally so "simple" and long-sought complex $[Ni_2(C_5H_5)_3]^{\oplus}$.

In the proposal depicted in Scheme 1, we postulated a species $[C_5H_5Ni(C_5H_5CPh_3)]^{\oplus}$ as intermediate in the reaction of $Ni(C_5H_5)_2$ with $Ph_3C^{\oplus}$[8]. Use of $H^{\oplus}$ in place of $Ph_3C^{\oplus}$ should give $[C_5H_5NiC_5H_6]^{\oplus}$ (an analog of the complexes $[C_5H_5Ni(diene)]^{\oplus}$). All attempts to detect this cation on the action of HBF_4, HPF_6, HBF_3OH, or H_2SO_4 on *(5)* failed, even at −78 °C. Success came only when we used weaker acids. In anhydrous HF as solvent, nickelocene undergoes complete conversion into $[C_5H_5NiC_5H_6]^{\oplus}$, which is stable for several minutes under these conditions and can be unequivocally characterized by NMR spectroscopy[22]. Attempts to

precipitate the complex cation from HF solution as a stable salt $[C_5H_5NiC_5H_6]X$ ($X=BF_4$, SbF_6) by addition of a Lewis acid such as BF_3 or SbF_5 surprisingly led to the isolation of $[C_5H_5Ni]X$[22]. Conductivity measurements confirm the presence of a 1:1 electrolyte. $[C_5H_5Ni]BF_4$ reacts instantaneously and quantitatively with $Ni(C_5H_5)_2$ in nitromethane to form *(9)*, and $[C_5H_5Ni\{P(OPh)_3\}_2]BF_4$ is produced with triphenyl phosphite.

The site of proton attack on the sandwich compound *(5)* could also be elucidated. Two alternatives are possible in principle: (i) direct addition of $H^{\oplus}$ to one of the cyclopentadienyl ligands and (ii) attack of $H^{\oplus}$ on the metal followed by rearrangement with formation of a new C—H bond. In case (i) the proton added should assume an *exo* position in the CH_2 group of the cyclopentadiene, and in case (ii) an *endo* position. The former stereochemistry is found. In the frequency range of the alicyclic protons the ^{1}H-NMR spectrum of the cation $[C_5H_5NiC_5H_5D]^{\oplus}$ formed from *(5)* and CF_3COOD at -18 °C does not contain the signal of an AB system (as for $[C_5H_5NiC_5H_6]^{\oplus}$) but, instead, just a singlet broadened somewhat by H—D coupling, whose chemical shift agrees very well with that of the *endo*-methylene proton in the nondeuterated cation[23].



We therefore assume the following reaction sequence[24] to account for the formation of the triple-decker sandwich from *(5)* and HX (preferably HBF_4 in propionic anhydride[10]):

$$Ni(C_5H_5)_2 + H^{\oplus} \rightleftharpoons [C_5H_5NiC_5H_6]^{\oplus} \xrightarrow[-C_5H_6]{} [C_5H_5Ni]^{\oplus} \xrightarrow{+Ni(C_5H_5)_2} [Ni_2(C_5H_5)_3]^{\oplus}$$

(5)

It should be noted that nickelocene and ferrocene react *differently* with acids such as HBF_4. While attack of the proton is clearly directed at one of the *cyclic ligands* in the case of the nickel complex, reaction of the iron complex affords $[HFe(C_5H_5)_2]^{\oplus}$, *i.e.* attack occurs preferentially at the metal[17]. The latter statement accords with the course of electrophilic substitution formulated in eq. (a).

2.3. The 30-Electron/34-Electron Rule

We have also invested considerable effort in attempts to prepare triple-decker sandwich complexes of other transition metals. In their well known experiments, *Schumacher* and *Taubenest* demonstrated[21] not only the formation of $[Ni_2(C_5H_5)_3]^{\oplus}$, but also that of $[Fe_2(C_5H_5)_3]^{\oplus}$ and $[FeNi(C_5H_5)_3]^{\oplus}$ in the mass spectrometer. *King*[25] and also *Müller* and *Fenderl*[26] were later able to supplement and confirm these results. In the consensus of opinion, the reactions leading to the ions $[MM'(C_5H_5)_3]^{\oplus}$ should be formulated thus:

$$M(C_5H_5)_2 \xrightarrow{+e} [M(C_5H_5)_2]^{\oplus} \xrightarrow[-{}^{\bullet}C_5H_5]{} [C_5H_5M]^{\oplus}$$

$$\xrightarrow{+M'(C_5H_5)_2} [MM'(C_5H_5)_3]^{\oplus} \quad (M = M' = Ni, Fe, Cr; M = Ni, M' = Fe)$$

The corresponding reactions could not yet be reproduced in a Schlenk tube, except for that between $[C_5H_5Ni]^{\oplus}$ and $Ni(C_5H_5)_2$. When heated with $Cr(C_5H_5)_2$, the compound $[Cr(C_5H_5)_2]BF_4$ which is readily accessible from $Cr(C_5H_5)_2$ and HBF_4 in propionic anhydride[17], fails to give the desired dinuclear complex, and nor can a triple-decker sandwich be detected on thermolysis of a mixture of $[Fe(C_5H_5)_2]BF_4$ and $Fe(C_5H_5)_2$. The reaction of $[C_5H_5Ni]BF_4$[22] with $Fe(C_5H_5)_2$ does not afford $[FeNi(C_5H_5)_3]BF_4$ (although $[C_5H_5Ni]^{\oplus}$ reacts with $Fe(C_5H_5)_2$ in the mass spectrometer to give $[FeNi(C_5H_5)_3]^{\oplus}$[21]), but proceeds *via* oxidation of ferrocene to $[Fe(C_5H_5)_2]BF_4$.

An explanation for the failure of these attempted syntheses is provided by a very recent paper by *Hoffmann et al.*[27]. On the basis of EHT-MO calculations the authors conclude that triple-decker sandwich complexes of general composition $[C_5H_5MC_5H_5MC_5H_5]$ and $[(CO)_3MC_5H_5M(CO)_3]$ *having 30 and 34 valence electrons* should be stable. Part of the calculated MO scheme is reproduced in Figure 2.

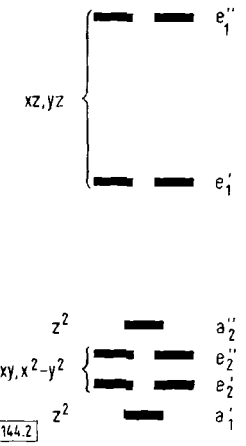
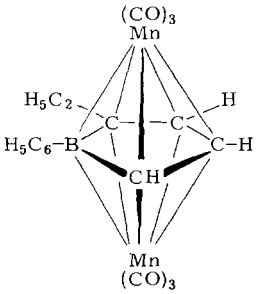


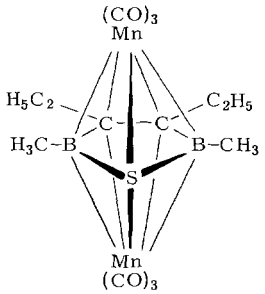
Fig. 2. Characteristic MO scheme for complexes of type $M_2Cp_3^{\oplus}$ and $(CO)_3MCpM(CO)_3^{\oplus}$ (section).

There result six low-lying orbitals (a'_1, e'_2, e''_2, and a''_2) and two pairs of degenerate orbitals (e'_1 and e''_1) of significantly higher energy. In the 34-electron species $[Ni_2(C_5H_5)_3]^{\oplus}$ the e'_1 orbital (which is weakly antibonding relative to the Ni—Cp_A and Ni—Cp_C bonds, and nonbonding relative to the Ni—Cp_B bonds, cf. Figure 1) is occupied by four electrons, while it is empty in the complexes $[C_5H_5Co(C_2B_3H_4R)CoC_5H_5]$ having a carbaborane bridge, which were discovered by *Grimes et al.*[28]. To the 30-electron species also belongs $[Fe_2(C_5H_5)_3]^{\oplus}$ or $[FeMn(C_5H_5)_3]$, whose synthesis is handicapped by the exceptional stability (*i.e.* the pronounced formation tendency) of ferrocene.

The calculations by *Hoffmann et al.*[27] on the preferred stability of triple-decker sandwich-like complexes having 30 and 34 valence electrons have also received support from the recently reported preparation of two $Mn_2(CO)_6$ compounds with boron-containing heterocycles as bridging ligands, *(14)*[29] and *(15)*[30].



(14)



(15)

Structurally analogous compounds containing three groups X in place of a bridging ring have been known for some time. *Hieber et al.*[31] prepared the complex anions $[(CO)_3M(OH)_3M(CO)_3]^{3\ominus}$ (M = Cr, Mo) as long ago as 1955; *White* and *Farona*[32] synthesized the corresponding halogeno and pseudohalogeno compounds $[(CO)_3MX_3M(CO)_3]^{3\ominus}$ (M = Cr, Mo, W; X = halogen, SCN, N_3, OEt) in 1972; and *Head* and *Nixon*[33] published an entry to the dinuclear complexes $[Ph_3P(L)ClRuCl_3RhCl(L)_2]$ (L = PPh_3, PBu_3, *etc.*) having two different metal centers in 1976. The interesting tris(μ-hydrido) complexes $[(CO)_3ReH_3Re(CO)_3]^{\ominus}$[34a] and [(triphos)-$FeH_3Fe$(triphos)]$^{\oplus}$ (triphos = $MeC(CH_2PPh_2)_3$)[34b] likewise belong to this series.

It is probably not too daring to predict that a whole range of similarly built 30-electron (and perhaps 34-electron) compounds will very soon exist and that the 30-electron/34-electron rule will then be as important for *dinuclear* complexes as the 18-electron rule for mononuclear complexes, especially with π-acceptor ligands.

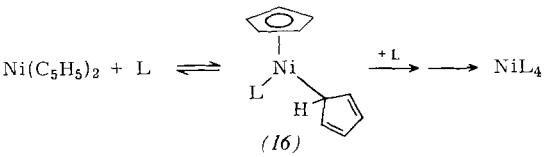
3. Reactions with Lewis Bases: Unexpected Pathways to Di- and Trinuclear Complexes

3.1. The Ambivalence of Nickelocene

As shown by the synthesis of the triple-decker sandwich complexes $[Ni_2(C_5H_5)_3]X$, nickelocene reacts with electrophiles or *Lewis acids* $R^{\oplus}$, by attack of the electrophile on *one of the cyclic ligands*. The charge distribution $(C_5H_5^{\delta-})$-$(Ni^{\delta+})(C_5H_5^{\delta-})$ deduced from PE spectra[35] appears to rationalize this behavior. In keeping with this charge distribution, *Lewis bases* L should react with nickelocene *via* attack of L on the metal. This also appears to be the case. Both the reactions of *(5)* with CO[36] and those of the sandwich complex with tertiary phosphanes or isocyanides[37] give very good yields of the nickel(0) compounds NiL_4 according to eq. (j).

$$\underset{(5)}{Ni(C_5H_5)_2} + 4\ L \longrightarrow NiL_4 + C_{10}H_{10} \qquad (j)$$

Ustynyuk et al.[38] have explained the mechanism of this ligand displacement reaction by assuming primary attack of L on the nickel to cause π-σ rearrangement of *one* cyclopentadienyl ligand, giving intermediate *(16)* which reacts with further L (possibly *via* subsequent cleavage of the Ni-σ-C_5H_5 bond) to give NiL_4.



(16)

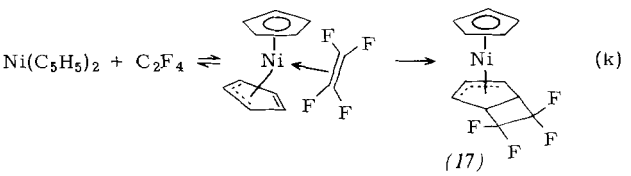
Preliminary results of our independent kinetic studies on the reaction of nickelocene with tertiary phosphites $P(OR)_3$ seemed to confirm this proposal[39]. There resulted a third-order rate law which was interpreted by assuming steady-state conditions for *(16)*.

However, refinement of the experimental data raised doubts about the extremely simple mechanistic picture sketched out above. Photometric studies in the temperature range 0 to 40 °C (in which the reaction according to eq. (j) is very slow) showed the 1 : 1 adduct to be formed very fast; the equilibrium constant *K* is (R = C_2H_5) 0.9 ± 0.2 mol/l at 30 °C in dioxane[40]. The rate-determining process is not formation of the 1 : 1 adduct but the transformation of *(A)* into *(B)* and of *(B)* into *(C)*.

$$Ni(C_5H_5)_2 + P(OR)_3 \overset{K}{\rightleftharpoons} \underset{(A)}{[(C_5H_5)_2NiP(OR)_3]}$$

$$(A) + P(OR)_3 \overset{k_2}{\underset{k_{-2}}{\rightleftharpoons}} (B) \xrightarrow[+\,P(OR)_3]{k_3} (C) \xrightarrow[+\,P(OR)_3]{fast} Ni[P(OR)_3]_4$$

A plausible proposal for the structure of the 1 : 1 adduct *(A)* is that of a *pentahapto*-cyclopentadienyl-*trihapto*-cyclopentadienylnickel phosphite complex. A corresponding change in coordination from η^5-C_5H_5 to η^3-C_5H_5 may also occur in the reaction of nickelocene with tetrafluoroethylene[41]; the complex *(17)* could arise by intramolecular, metal-catalyzed [2 + 2] cycloaddition of initially formed $(\eta^5$-$C_5H_5)Ni(\eta^3$-$C_5H_5)C_2F_4$.



(k)

(17)

The structure proposed for the adduct *(A)* obtained from $Ni(C_5H_5)_2$ and $P(OR)_3$ has not yet been unequivocally confirmed by spectroscopic measurements. With regard to the reaction mechanism, the precise structure of *(B)* also remains an open question. The most likely possibilities would be a $(\eta^5$-$C_5H_5)Ni(\eta^1$-$C_5H_5)[P(OR)_3]_2$ (formed by η^3-η^1 rearrangement of the π-allyl-type bonded five-membered ring) or a $(\eta^5$-$C_5H_5)Ni[P(OR)_3]_2$. Compounds of the type $(\eta^5$-$C_5H_5)Ni(PR_3)_2$ have already been isolated by *Uhlig et al.*[42].

We saw two possible ways of escape from the dilemma into which our kinetic and mechanistic studies had led us:

1) Using a *diamagnetic complex of similar structure* instead of *paramagnetic* nickelocene as starting material for the reaction with $P(OR)_3$ (or another Lewis base). This would provide a chance of gleaning some information about any intermediate(s) of the ligand displacement process by NMR studies (presumably at low temperature).

2) Reactions of a sandwich complex $M(C_nH_n)_2$ with a Lewis base L do not necessarily lead—as in eq. (j)—to cleavage of *both* ring-metal bonds; only *one* ring-metal bond may actually be broken (to form a compound $C_nH_nML_m$). Examples are known for $n=5$ or 6 and L=CO or PR_3[20,43]. Such a process would probably lead to a simpler rate law, and this could provide more precise information about the reaction mechanism.

3.2. Reaction of π-Allyl-π-Cyclopentadienylmetal Complexes

3.2.1. Mechanistic Studies

π-Allyl-π-cyclopentadienylnickel has a similar structure to nickelocene. The plane through the five C atoms of the cyclopentadienyl moiety and the plane through the three C atoms of the allyl ligand are parallel and enclose the metal in a sandwich fashion. Unlike nickelocene, $C_3H_5NiC_5H_5$ *(18)* is an 18-electron complex and hence *diamagnetic*.

Complete ligand displacement occurs in the reactions of *(18)* with excess phosphite, as in the reaction of *(5)* with $P(OR)_3$; $Ni[P(OR)_3]_4$ is formed[40]. The palladium complexes *(19)*—*(22)* react analogously.

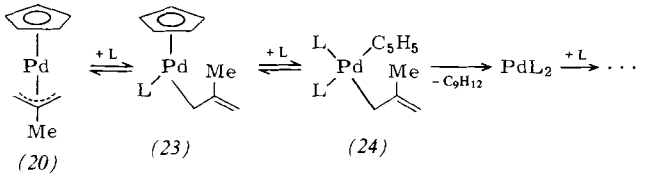
$$(all)MC_5H_5 + 4\ P(OR)_3 \longrightarrow M[P(OR)_3]_4 + C_5H_5(all) \qquad (1)$$

M = Ni; all = C_3H_5: *(18)*

M = Pd; all = C_3H_5: *(19)*
$2\text{-}MeC_3H_4$: *(20)*
$2\text{-}t\text{-}BuC_3H_4$: *(21)*
$1,1,2\text{-}Me_3C_3H_2$: *(22)*

Under pseudo-first order conditions we found a rate law of second order for the reaction of *(19)* with $P(OPh)_3$, but one of third order for that of *(18)* with $P(OEt)_3$[44]. These results justify the assumption of a multi-step mechanism, with either $(\pi\text{-}C_5H_5)M(\sigma\text{-all})P(OR)_3$ or $(\pi\text{-all})M(C_5H_5)P(OR)_3$ (C_5H_5 = *trihapto-* or *monohapto*-cyclopentadienyl ligand) as primary intermediate.

The former possibility was confirmed by NMR spectroscopy[45]. Compound *(20)* reacts at −50°C with L to give the σ-allyl complex *(23)*, whose kinetic stability is crucially dependent upon L. While further reaction to give PdL_4 is very fast for $L=P(OMe)_3$ above 0°C (probably *via (24)* as intermediate species), compound *(23)* can be isolated when $L=P(i\text{-}Pr)_3$[46]. The kinetics of its reaction with $P(i\text{-}Pr)_3$ to form $Pd[P(i\text{-}Pr)_3]_n$ is presently under investigation.



The organic product C_9H_{12} generated in this reaction is an allylcyclopentadiene[*]. NMR studies on the *(22)*/L system showed[45] that coupling of an allyl group with the cyclopentadienyl ring occurs at C_α. The initially formed 5-allylcyclopentadienes are highly labile and rearrange, like 5-alkylcyclopentadienes, *via* [1,5] H shift to give the 1-substituted isomers.

3.2.2. Unexpected Synthetic Results

Our efforts to isolate the primary intermediate *(23)* formed on reaction of *(20)* with L (initially with $L=P(OMe)_3$, $P(OPh)_3$, and PPh_3) led to a surprising result[47]. While the σ-allyl compound displays considerable kinetic stability at −50°C, *e.g.* in toluene, it reacts at higher temperature to give a new complex which can be recognized by a characteristic triplet for the cyclopentadienyl protons in the ^{1}H-NMR spectrum. Crystals of this product have the composition $(C_5H_5)(C_4H_7)Pd_2(PPh_3)_2$ *(26)* (for $L=PPh_3$).

The result of a crystal structure analysis performed on *(26)* is shown in Figure 3. The compound possesses an almost linear P—Pd—Pd—P arrangement with a Pd—Pd bond length of 2.679 Å, comparable with the interatomic distance in metallic palladium (2.74 Å). The mutually parallel cyclopentadienyl and 2-methylallyl ligands are coordinated to *both* palladium atoms and enclose the metal-metal bond in sandwich fashion. The Pd—C_{Cp} distances suggest that the five-membered ring may be bound as a *trihapto*-ligand *in the crystal* and two of the five carbon atoms participate only weakly in bonding to the metal atoms. Neither ^{1}H- nor ^{13}C-NMR spectra evidence nonequivalence of the CH groups of the cyclopentadienyl ring *in solution*; a single sharp resonance is still observed at −60°C for the ring carbon and hydrogen atoms. It would appear reasonable to attribute this observation to very fast rotation of the ring about an axis passing through its center and oriented perpendicular to the Pd—Pd bond, making the dinuclear complex a fluxional molecule in solution.

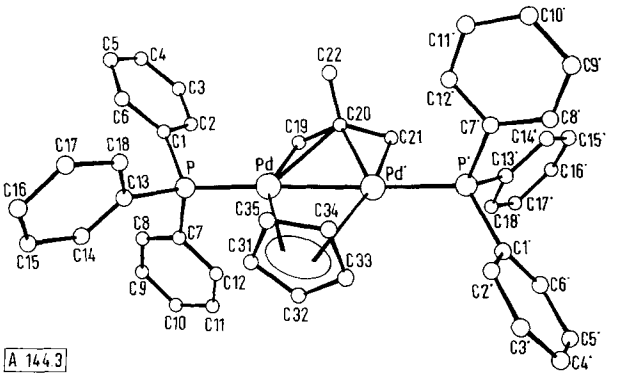
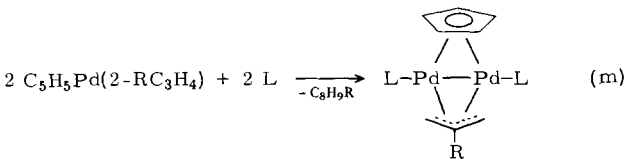


Fig. 3. Crystal structure of the dinuclear complex *(26)*.

The complexes *(25)* and *(27)*—*(35)* analogous to *(26)* could also be synthesized according to eq. (m)[48]. Compounds *(20)* and *(21)* react with $P(i\text{-}Pr)_3$ to give the highly stable 1:1 adducts $(\pi\text{-}C_5H_5)Pd(2\text{-}RC_3H_4)L$ as initial products [see *(23)*]; at higher temperatures (only at 90°C for R = *t*-Bu) and in the absence of excess L they react further to give the dinuclear complexes *(28)* and *(34)*, respectively. The crystal structure of *(31)* is completely analogous to that of *(26)*[48]. Reactions of $C_5H_5Pd(2\text{-}ClC_3H_4)$ with L in the molar ratio 1:1 *exclusively* give σ-2-chloroallyl derivatives of type *(23)*, some of which eliminate allene at room temperature to form $C_5H_5Pd(L)Cl$[49]. Preparation of $(C_5H_5)(2\text{-}ClC_3H_4)Pd_2L_2$ has not yet been accomplished.

On the basis of detailed NMR studies we proposed[50] the mechanism summarized in Scheme 4 to account for the

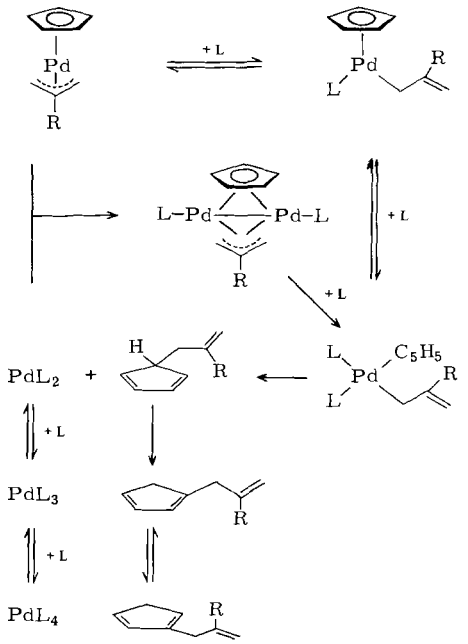
[*] On reaction of *(22)* with an excess of L, the expected allylcyclopentadienes are accompanied by cyclopentadiene and 2,3-dimethylbutadiene, which probably arise from the intermediate analogous to *(24)*. The yields of these hydrocarbons are largely determined by the nature of L, the molar ratio *(22)*: L, and the temperature [45].



(m)

L/R	H	CH_3	t-C_4H_9
PPh_3	*(25)*	*(26)*	*(32)*
PPh_2Me		*(27)*	*(33)*
$P(i\text{-}Pr)_3$		*(28)*	*(34)*
$P(OMe)_3$		*(29)*	
$P(OPh)_3$		*(30)*	
$P(O\text{-}o\text{-}Tol)_3$		*(31)*	*(35)*

formation of the dinuclear complexes *(25)* to *(35)*. These are the first representatives of a class of compounds in which a C_5H_5 ligand is bound in sandwich fashion to a M_2 fragment.



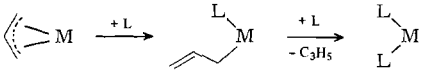
Scheme 4

This proposal was based on the key assumption that under the reaction conditions chosen (room temperature, molar ratio of $C_5H_5Pd(2\text{-}RC_3H_4)$:L = 1:1) the second reaction step is considerably faster than the first one, and that PdL_2 is formed from the postulated intermediate $C_5H_5Pd(\sigma\text{-}C_3H_4R)L_2$ of type *(24)* on loss of the organic cyclopentadiene derivative. This 14-electron complex should react with the starting material to give $C_5H_5(2\text{-}RC_3H_4)Pd_2L_2$.

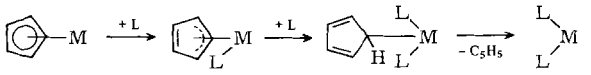
This hypothesis has recently been confirmed[46]. Both $Pd[P(i\text{-}Pr)_3]_2$[51] and $Pd[P(t\text{-}Bu)_3]_2$, which is accessible from *(20)*, yield the respective dinuclear complex *quantitatively* on reaction with *(20)* or *(21)*. Hence a new entry to this class of compounds has also become available, which is probably of potential utility for the synthesis of further complexes containing the L—M—M—L unit.

3.3. The "Supersandwich"

While studies on the reaction of complexes *(18)* to *(22)* with Lewis bases could provide no definite answer to the initial question of the mechanism of ligand displacement according to eq. (j), they nevertheless did show that cleavage of at least one (π-all)—M bond proceeds stepwise:



Evidence for a corresponding reaction course



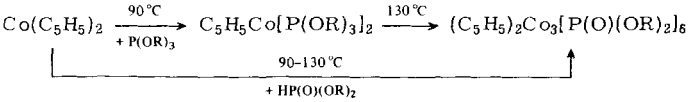
as described for the $Ni(C_5H_5)_2$/L system in Section 3.1, was only indirect in nature, and not necessarily conclusive. The question to be answered was whether a formally simpler reaction, such as

$$M(C_5H_5)_2 + n\,L \longrightarrow C_5H_5ML_n + \cdot C_5H_5 \qquad (n)$$

would give rise to a simpler and more readily interpretable rate law. We attempted to provide an answer by studying the ligand displacement reactions of cobaltocene with Lewis bases.

$Co(C_5H_5)_2$ *(36)* reacts according to eq. (n) with L = CO[52] or PF_3[53] to give $C_5H_5CoL_2$. An analogous reaction occurs with tertiary phosphites (which are better suited as reactants for kinetic studies than the volatile compounds CO and PF_3). Reaction with a 5 to 10-fold excess of phosphite at 90—120 °C gives very good yields of the complexes $C_5H_5Co[P(OR)_3]_2$ [R = Me: *(37)*, Et: *(38)*, Ph: *(39)*, *o*-Tol: *(40)*], which exhibit much greater stability than the carbonyl compound $C_5H_5Co(CO)_2$[54]. The rate of formation of the tri*alkyl* phosphite complexes *(37)* and *(38)* is considerably higher than that of the tri*aryl* phosphite complexes *(39)* and *(40)*. Hence, further studies concentrated on the reactions of cobaltocene with $P(OMe)_3$ and $P(OEt)_3$.

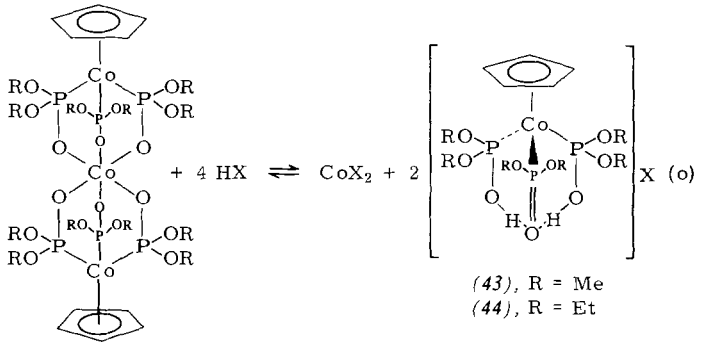
Although precise kinetic data have not yet been obtained (the NMR method of determining concentration changes cannot be applied because *(36)* is paramagnetic, and photometric measurements are difficult because *(36)*, *(37)*, and *(38)* are all intensely colored), an observation made during these experiments led to an interesting result. On prolonged reaction time or at elevated temperatures the $Co(C_5H_5)_2/P(OR)_3$ system (R = Me or Et) affords not only the compounds $C_5H_5Co[P(OR)_3]_2$ but small quantities of orange-yellow crystals were deposited on the wall of the reaction vessel. The crystals exhibit a number of properties unusual for organometallic complexes. They are completely stable towards air and do not decompose below about 350 °C. Elemental analyses and mass spectra confirm the composition $(C_5H_5)_2Co_3[P(O)(OR)_2]_6$ [R = Me: *(41)*, Et: *(42)*]. The novel trinuclear compounds are accessible in 50% yield by thermolysis of *(37)* and *(38)*, and almost quantitatively by reaction of *(36)* with $HP(O)(OR)_2$:



As shown by the crystal structure analysis[55] of *(41)* (known as the "supersandwich" in laboratory jargon), the two cyclopentadienyl ligands enclose the $Co_3[P(O)(OR)_2]_6$ fragment

in *sandwich* fashion. The three cobalt atoms are linearly arranged and bridged by the phosphonate groups. Two of the cobalt atoms are equivalent, while the third one is located at a center of symmetry. It is surrounded by six oxygen atoms occupying the corners of an octahedron in an almost ideal manner. This CoO_6 nucleus containing high-spin Co^{II} accounts for the paramagnetism of the trinuclear complexes. Assignment of the oxidation number +2 to the central cobalt atom and +3 to the other two is in accord with the results of ESCA studies[55].

Apart from their structure, the reactivity of complexes *(41)* and *(42)* towards Brønstedt acids also warrants particular attention. Conductivity measurements showed[56] that reaction with CF_3COOH in $(CF_3CO)_2O$ involves multiple protonation at the phosphonate oxygen atoms without complete destruction of the trinuclear structure. The complexes react according to eq. (o) with strong mineral acids such as H_2SO_4, H_3PO_4, or HNO_3.



+ 4 HX ⇌ CoX_2 + 2

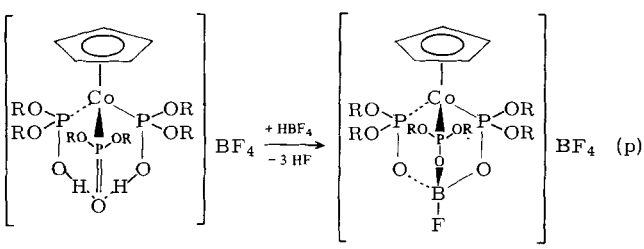
X (o)

(41), R = Me
(42), R = Et

(43), R = Me
(44), R = Et

Equilibration can be followed by NMR; the equilibrium lies entirely on the right-hand side in concentrated mineral acids. On use of a suitable solvent, either CoX_2 or the complex salts *(43)* and *(44)*, respectively, can be precipitated from the solutions[56]; the secondary phosphites $P(OH)(OMe)_2$ and $P(OH)(OEt)_2$, which are unstable in the free state, serve as ligands in these salts.

When performed with HBF_4 (in propionic anhydride) the reaction does not stop at *(43)* or *(44)*. Instead, complexes having the composition $[C_5H_5Co\{P(OR)_2O\}_3BF]BF_4$ [*(45)* and *(46)*, respectively] are obtained whose formation can be summarized as shown in eq. (p).



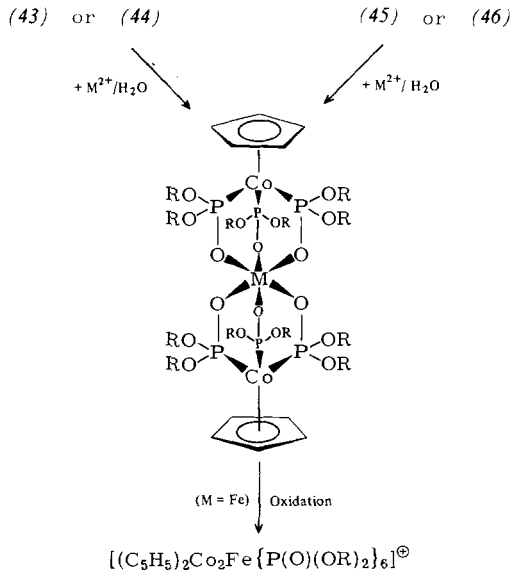
BF_4 $\xrightarrow[-3\ HF]{+\ HBF_4}$

BF_4 (p)

(45), R = Me
(46), R = Et

Crystal structure analysis of *(46)* shows that in addition to the cyclopentadienyl ring, a tris(diethoxyphosphito)boranate anion is coordinated to the cobalt as a tridentate chelate ligand[57]. Salts of such phosphitoboranate ions are, as yet, unknown in the free state and might be preparable by ligand displacement starting from *(45)* or *(46)*. The Co—C and Co—P bond lengths in *(46)* expectedly differ little from those in the trinuclear "supersandwich" complex.

The reverse reaction of eq. (o) has recently also been accomplished and the trinuclear complexes *(41)* and *(42)* prepared from the corresponding monocyclopentadienyl compounds *(43)* and *(44)* (X = BF_4) and CoX_2 (X = Cl, NO_3, $\frac{1}{2}$ SO_4)[58]. The phosphitoboranate complexes *(45)* and *(46)* can also be used for this purpose instead of *(43)* and *(44)*. The salts of various other transition metals react in the same way as CoX_2, thus providing a pathway to trinuclear complexes of general composition $(C_5H_5)_2Co_2M[P(O)(OR)_2]_6$ (M = Mn, Fe, Ni, Cu, Zn, Cd) having *two different metals as coordination centers in the same molecule* (see Scheme 5). The X-ray powder diagrams of compounds with R = Et reveal that they are all isotypic and therefore probably possess a structure very similar to *(41)*. Particular interest is warranted by the copper complex since the Jahn-Teller effect would be expected to lead to pronounced distortion of the CuO_6 octahedron. ESR studies at 4 K show that this is indeed the case at low temperature[59].



Scheme 5

4. Outlook

Sandwich complexes nowadays appear as veterans when viewed against the background of our hectic age, and yet their chemistry is just as topical as ever. The structural principle first demonstrated for ferrocene, formerly unknown but basically so simple, has time and time again fired the imagination of coordination and organometallic chemists and prompted countless synthetic experiments. As a result not only further "true sandwiches", such as dibenzenechromium and uranocene, but a whole variety of other sandwich-type or sandwich-like complexes have become accessible. Addition of another storey to a normal double-decker to give a triple-decker sandwich, long a mere pipe dream, has recently also been achieved in the preparation of the cation $[Ni_2(C_5H_5)_3]^{\oplus}$[9].

The chemist interested in molecular architecture will be tempted to construct a quadruple-decker or even higher "skyscrapers", and studies to this end are already in progress.

An attempt is made in Figure 4 to depict the trinuclear complexes *(41)* and *(42)*, and those of composition $(C_5H_5)_2Co_2M[P(O)(OR)_2]_6$ as variants of a quadruple-decker. Extension of these compounds of "supersandwich" type is also conceivable. Thus it has very recently been found, for example, that under the conditions of mass spectrometric degradation the compound $C_5H_5Ni[\{P(OMe)_2O\}_2H]$, characterized by a strong OHO hydrogen bond, yields the trinuclear complex $(C_5H_5)_2Ni_3[P(O)(OMe)_2]_4$ (possibly having a stability similar to that of *(41)*)[60]. The structure probably corresponds to that of the analogous cobalt compound.

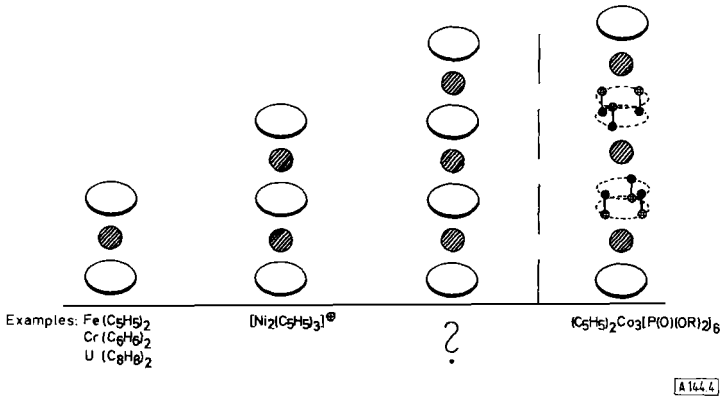


Fig. 4. Structural models of sandwich complexes.

Apart from the bidentate phosphonate ion, other typical bridging ligands—in the simplest case the CO group—should also be able to stabilize sandwich-like polynuclear structures. The calculations by *Hoffmann et al.* could signpost the way ahead. It would hardly come as a surprise if a further variant (ring)M(CO)$_3$M(ring) were to join the "true" triple-decker (ring)M(ring)M(ring) and the related type of compound (CO)$_3$M(ring)M(CO)$_3$; having 30 or 34 electrons in their valence shells they are predicted by *Hoffmann* to be stable.

Thanks should go first of all to those co-workers who participated in the work of the author's group: Ms. E. Deckelmann, Dr. T. L. Court, Dr. V. Harder, Dr. W. Kläui, Dipl.-Chem. A. Kühn, Dr. H. Neukomm, Dr. G. Parker, Dr. A. Salzer, Dr. M. Scotti, Dr. D. J. Tune, and Dr. G. K. Turner. I am also indebted to Prof. Dr. H. R. Oswald, Zürich, Doz. Dr. G. Huttner, München, and Dr. C. Krüger, Mülheim, as well as their colleagues, for performing the indispensable X-ray structure analyses. In conclusion, it should also be mentioned that the successful outcome of our studies would have been doubtful without the generous and unbureaucratic support of the Schweizerischer Nationalfonds.

Received: September 4, 1976 [A 144 IE]
German version: Angew. Chem. *89*, 1 (1977)

[1] a) *T. J. Kealy* and *P. L. Pauson*, Nature (London) *168*, 1039 (1951); b) *S. A. Miller, J. A. Tebboth*, and *J. F. Tremaine*, J. Chem. Soc. *1952*, 632.
[2] *G. Wilkinson, M. Rosenblum, M. C. Whiting*, and *R. B. Woodward*, J. Am. Chem. Soc. *74*, 2125 (1952).
[3] *E. O. Fischer* and *W. Pfab*, Z. Naturforsch. *7b*, 377 (1952).
[4] *M. Rosenblum, M. C. Whiting*, and *R. B. Woodward*, J. Am. Chem. Soc. *74*, 3458 (1952).
[5] *E. O. Fischer* and *H. P. Fritz*, Adv. Inorg. Chem. Radiochem. *1*, 56 (1959); *G. Wilkinson* and *F. A. Cotton*, Prog. Inorg. Chem. *1*, 1 (1959).
[6] *M. Rosenblum:* Chemistry of the Iron Group Metallocenes, Part 1. Wiley, New York 1965, p. 78.
[7] *E. O. Fischer*, personal communication.
[8] *H. Werner, G. Mattmann, A. Salzer*, and *T. Winkler*, J. Organomet. Chem. *25*, 461 (1970).
[9] *H. Werner* and *A. Salzer*, Synth. Inorg. Met.-Org. Chem. *2*, 239 (1972).
[10] *A. Salzer* and *H. Werner*, Angew. Chem. *84*, 949 (1972); Angew. Chem. Int. Ed. Engl. *11*, 930 (1972).
[11] *G. Wilkinson*, J. Am. Chem. Soc. *76*, 209 (1954).
[12] *E. Dubler, M. Textor, H. R. Oswald*, and *A. Salzer*, Angew. Chem. *86*, 125 (1974); Angew. Chem. Int. Ed. Engl. *13*, 135 (1974).
[13] *A. Salzer* and *H. Werner*, Synth. Inorg. Met.-Org. Chem. *2*, 249 (1972).
[14] *A. Salzer, T. L. Court*, and *H. Werner*, J. Organomet. Chem. *54*, 325 (1973).
[15] *G. Parker, A. Salzer*, and *H. Werner*, J. Organomet. Chem. *67*, 131 (1974).
[16] *A. Salzer* and *B. Ulrich*, unpublished.
[17] *A. Salzer*, Dissertation, Universität Zürich 1974.
[18] *G. K. Turner*, unpublished.
[19] *R. R. Schrock* and *J. A. Osborn*, J. Am. Chem. Soc. *93*, 3089 (1971).
[20] *H. Werner*, Fortschr. Chem. Forsch. *28*, 141 (1972).
[21] *E. Schumacher* and *R. Taubenest*, Helv. Chim. Acta *47*, 1525 (1964).
[22] *T. L. Court* and *H. Werner*, J. Organomet. Chem. *65*, 245 (1974).
[23] *G. K. Turner, W. Kläui, M. Scotti*, and *H. Werner*, J. Organomet. Chem. *102*, C 9 (1975).
[24] *H. Werner*, Nachr. Chem. Tech. *22*, 3 (1974).
[25] *R. B. King*, Chem. Commun. *1969*, 436.
[26] *J. Müller* and *K. Fenderl*, Chem. Ber. *104*, 2199 (1971).
[27] *J. W. Lauher, M. Elian, R. H. Summerville*, and *R. Hoffmann*, J. Am. Chem. Soc. *98*, 3219 (1976).
[28] *R. N. Grimes et al.*, J. Am. Chem. Soc. *95*, 3046 (1973); Inorg. Chem. *13*, 1138 (1974); J. Organomet. Chem. *113*, 29 (1976).
[29] *G. E. Herberich, J. Hengesbach, U. Kölle, G. Huttner*, and *A. Frank*, Angew. Chem. *88*, 450 (1976); Angew. Chem. Int. Ed. Engl. *15*, 433 (1976).
[30] *W. Siebert* and *K. Kinberger*, Angew. Chem. *88*, 451 (1976); Angew. Chem. Int. Ed. Engl. *15*, 434 (1976).
[31] *W. Hieber, W. Abeck*, and *H. K. Platzer*, Z. Anorg. Allg. Chem. *280*, 241, 243 (1955).
[32] *J. F. White* and *M. F. Farona*, J. Organomet. Chem. *37*, 119 (1972).
[33] *R. A. Head* and *J. F. Nixon*, J. Chem. Soc. Chem. Commun. *1976*, 62.
[34] a) *A. P. Ginsberg* and *M. J. Hawkes*, J. Am. Chem. Soc. *90*, 5930 (1968); b) *P. Dapporto, G. Fallani, S. Midollini*, and *L. Sacconi*, J. Am. Chem. Soc. *95*, 2021 (1973).
[35] *M. Barber, J. A. Connor, L. M. R. Derrick, M. B. Hall*, and *I. H. Hillier*, J. Chem. Soc. Faraday Trans. II *1973*, 559.
[36] *E. O. Fischer* and *O. Beckert*, unpublished experiments; *O. Beckert*, Dissertation, Technische Hochschule München 1957.
[37] *J. R. Olechowski, C. G. McAlister*, and *R. F. Clark*, Inorg. Chem. *4*, 246 (1965); *H. Behrens* and *K. Meyer*, Z. Naturforsch. *21b*, 489 (1966).
[38] *Yu. A. Ustynyuk, T. I. Voevodskaya, N. A. Zharikova*, and *N. A. Ustynyuk*, Dokl. Akad. Nauk SSSR *181*, 372 (1968).
[39] *H. Werner, V. Harder*, and *E. Deckelmann*, Helv. Chim. Acta *52*, 1081 (1969).
[40] *V. Harder*, Dissertation, Universität Zürich 1973.
[41] *D. W. McBride, P. L. Pruett, E. Pitcher*, and *F. G. A. Stone*, J. Am. Chem. Soc. *84*, 497 (1962).
[42] *E. Uhlig* and *H. Walther*, Z. Anorg. Allg. Chem. *409*, 89 (1974).
[43] *M. L. H. Green, L. C. Mitchard*, and *W. E. Silverthorn*, J. Chem. Soc. *A 1971*, 2929.
[44] *V. Harder* and *H. Werner*, Helv. Chim. Acta *56*, 549 (1973).
[45] *G. Parker* and *H. Werner*, Helv. Chim. Acta *56*, 2819 (1973).
[46] *A. Kühn*, unpublished.
[47] *H. Werner, D. Tune, G. Parker, C. Krüger*, and *D. J. Brauer*, Angew. Chem. *87*, 205 (1975); Angew. Chem. Int. Ed. Engl. *14*, 185 (1975).
[48] *H. Werner, A. Kühn, D. J. Tune, C. Krüger, D. J. Brauer, J. C. Sekutowski*, and *Yi-Hung Tsay*, Chem. Ber., in press.
[49] *D. J. Tune* and *H. Werner*, Helv. Chim. Acta *58*, 2240 (1975).
[50] *G. Parker* and *D. J. Tune*, unpublished experiments (see final report by *H. Werner* to the Schweizerischer Nationalfonds on Jan. 12, 1976).
[51] *W. Kuran* and *A. Musco*, Inorg. Chim. Acta *12*, 187 (1975).
[52] *E. O. Fischer* and *R. Jira*, Z. Naturforsch. *10b*, 355 (1955).
[53] *T. Kruck, W. Hieber*, and *W. Lang*, Angew. Chem. *78*, 208 (1966); Angew. Chem. Int. Ed. Engl. *5*, 247 (1966).
[54] *V. Harder, J. Müller*, and *H. Werner*, Helv. Chim. Acta *54*, 1 (1971).
[55] *V. Harder, E. Dubler*, and *H. Werner*, J. Organomet. Chem. *71*, 427 (1974).
[56] *W. Kläui*, unpublished.
[57] *W. Kläui, H. Neukomm, H. Werner*, and *G. Huttner*, Chem. Ber., in press.
[58] *W. Kläui* and *H. Werner*, Angew. Chem. *88*, 187 (1976); Angew. Chem. Int. Ed. Engl. *15*, 172 (1976).
[59] *J. H. Ammetter*, unpublished.
[60] *Ngo Khac Tri*, Part of projected Diplomarbeit, Universität Würzburg 1976/77.

Intramolecular [4+2] and [3+2] Cycloadditions in Organic Synthesis

New synthetic methods (18)

By Wolfgang Oppolzer[*]

Dedicated to Professor Vladimir Prelog on the occasion of his 70th Birthday

Numerous examples of intramolecular cycloaddition of 1,3-dienes, nitrones, and azomethine imines attest the preparative value of this variant for regioselective and stereoselective synthesis of annelated and bridged ring systems. The common features, differences, and limitations of these types of reaction are systematically reviewed.

1. Introduction

Thermally induced additions of 1,3-dienes and of 1,3-dipoles to multiple bonds clearly lead to six- or five-membered rings with the simultaneous formation of two σ-bonds, *via* a highly ordered aromatic transition state[1-3]. The stereochemical consequences of a reaction course of this type are paralleled by reactivity and orientation phenomena ascribed to frontier orbital interactions[4]. The great preparative importance of these features of the mechanistically related reactions is shown, *inter alia*, by a multitude of fascinating applications of the bimolecular Diels-Alder reaction to the synthesis of complex molecules[2].

From investigations carried out in recent years it follows that the synthetic potential of such cycloadditions is decisively increased by the principle of intramolecularity. Intramolecular additions of this type result not only in the simultaneous formation of *two* rings, but also in certain consequences which are superimposed on those of the classical bimolecular variants.

The aim of the present review is to collect the common characteristics of intramolecular additions of 1,3-dienes, nitrones, and azomethine imines and to indicate the possibilities and limitations of these processes. Entropy factors and problems of kinetically controlled regio- and stereoselectivity deserve special attention which justifies their detailed discussion. An attempt is made, with the aid of selected examples, to demonstrate the scope and utility of these reactions in the synthesis and biogenesis of structurally complex natural products.

2. Intramolecular Diels-Alder Reactions

Bimolecular [4+2] cycloadditions (type I), whose general applicability was recognized by *Diels* and *Alder* nearly 50



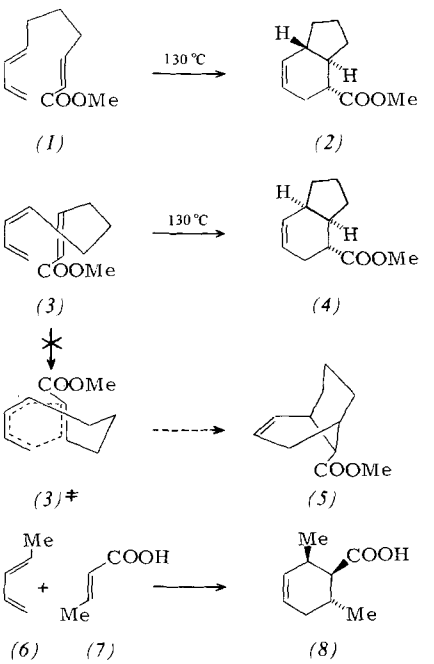
Scheme 1. [4+2]-cycloaddition of dienes.

years ago[5], are today one of the most important types of reaction used in organic synthesis[2]. Although *Alder* had already indicated the possibility of intramolecular [4+2] additions (type II) as early as 1953[6], and other authors later found occasional examples[7], it was not until the last decade that the general utility of this reaction became apparent[8].

2.1. Acyclic Dienes

2.1.1. Construction of 5,6- and 6,6-Ring Systems

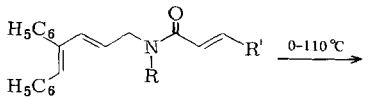
The first systematic investigation of this type of reaction, described by *H. O. House* in 1965[9], suffices to bring certain characteristic features to light. When heated to 130°C, the *trans*-diene unit in the triene *(1)* adds smoothly to the double bond of the acrylic ester linked to the diene by a bridge of three carbon atoms leading to the *trans*-annelated hydrindane derivative *(2)*. Surprisingly, under the same conditions the *cis*-substituted diene *(3)* reacts in a similar manner, but with exclusive formation of the *cis*-annelated product *(4)*. In view of the fact that *cis*-substituted open-chain 1,3-dienes usually undergo bimolecular Diels-Alder reactions only with difficulty, we are forced to the conclusion that the reaction *(3)*→*(4)* profits from entropy factors due to the spatial proximity of the reaction partners. (Examples given below show that nonactivated dienophiles smoothly undergo intramolecular cycloaddition for the same reason.)



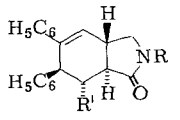
[*] Prof. Dr. W. Oppolzer
Département de Chimie Organique, Université de Genève
CH-1211, Geneva 4 (Switzerland)

A further notable feature of intramolecular [4+2] additions is the influence of orienting factors promoting the formation of annelated products. For example, the reaction of the *cis*-diene *(3)* gave no trace of the bridged positional isomer *(5)*; in this connection it should be remembered that the addition in the intramolecular reactions *(1)*→*(2)* and *(3)*→*(4)* takes place in the opposite direction to that strongly favored in the bimolecular reaction *(6)*+*(7)*→*(8)*[10].

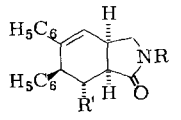
Consideration of models (see Section 2.6.2) shows that the formation of a bridged adduct from *(1)* is blocked by strain, whereas the formation of the transition state *(3)*$^+$ from *(3)* does not require any deformation of the bond angles; thus, the absence of *(5)* after thermolysis of *(3)* is due to other causes, presumably the (entropically favored) easier closure of a five-membered ring than that of a six-membered ring. The pronounced stereoselectivity of the conversion *(3)*→*(4)*, on the other hand, appears to be due to a strongly strained transition state, which would have to be overcome in the alternative reaction *(3)*→*(2)* (see Section 2.6.3). The *endo*-position of the ester group appears to be decisive for favoring the reaction *(1)*→*(2)* over the reaction *(1)*→*(4)*.



(9)



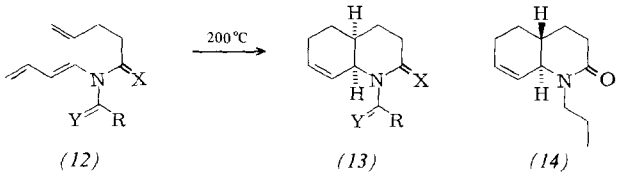
(10)



(11)

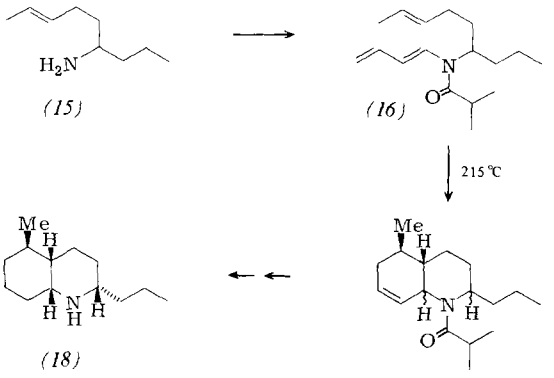
The results of kinetic and stereochemical studies[11] of the thermal reaction *(9)*→*(10)*+*(11)* are in accord with the above conclusions. For example, an activation entropy of $\Delta S^+ = -14.4$ cal K^{-1} mol^{-1} is found for the intramolecular addition of the acrylamides *(9)*, R = *tert*-butyl, R′ = H, whereas bimolecular Diels-Alder reactions have considerably more negative ΔS^+ values (between −30 and −40 cal K^{-1} mol^{-1}). Furthermore, the reaction *(9)*→*(10)*+*(11)* becomes increasingly slower as the size of the nitrogen substituent R decreases (probably for conformational reasons). The stereochemistry of these kinetically controlled additions reflects again the preferential *endo*-orientation of terminal π-substituents R′, *i.e.* the *trans*-fused adducts *(10)* are formed selectively from the amides *(9)*, R′ = COOEt or C_6H_5. This opens a simple route to polysubstituted perhydroisoindoles with stereochemical control of up to five chiral centers.

A close connection between systematic study and direct application of intramolecular Diels-Alder reactions to the synthesis of natural products is shown in the following example. Attempts to synthesize the physiologically active (but almost inaccessible) alkaloid pumiliotoxin C *(18)* in a stereoselective manner led to a study of the intramolecular additions of dienamides *(12)*, X or Y = O[12]. It transpired that the amide *(12)*, X = H_2, Y = O, R = CH_3, is converted at 200°C into the very nearly pure *cis*-fused octahydroquinoline *(13)*, whereas the amide *(12)*, X = O, Y = H_2, R = C_2H_5, affords, with lower but reversed selectivity, the *trans*-lactam *(14)* and its *cis*-isomer *(13)* in the ratio of 3:2. The different courses of the reaction can be due to a preferred coplanar arrangement of the amide and diene units in the corresponding transition states. Incidentally, this investigation provided the impetus for the development of a productive general synthesis of the then unknown *N*-butadienylamides[13].



(12) *(13)* *(14)*

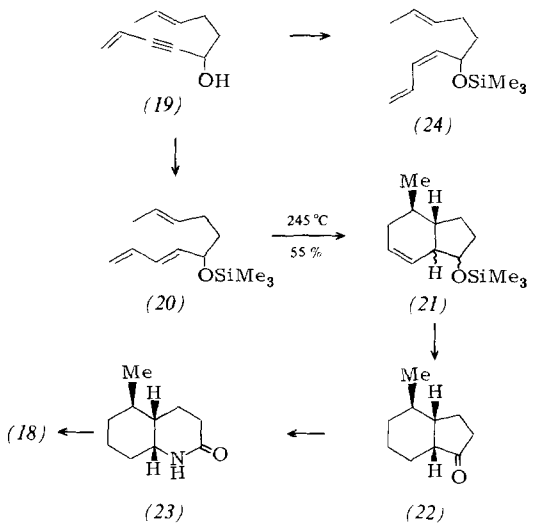
Using this process the readily available amine *(15)* could be converted in two stages into the dienamide *(16)*. When



(15) *(16)* *(18)* *(17)*

heated in toluene for 24 h at 215°C in a sealed, silylated glass tube, *(16)* undergoes efficient intramolecular cycloaddition[14a,14b]; the adducts *(17)* (isolated in 60 to 90% yield), when hydrogenated and hydrolyzed, finally afforded the racemic alkaloid *(18)* in 60% yield together with three stereoisomers (in yields of 17, 15, and 2%). The remarkable feature of this synthesis is the simultaneous control over all four chiral centers in the key step *(16)*→*(17)*, dictated by the *trans*-configuration of the dienophile and, presumably, by the double-bond character of the amide group.

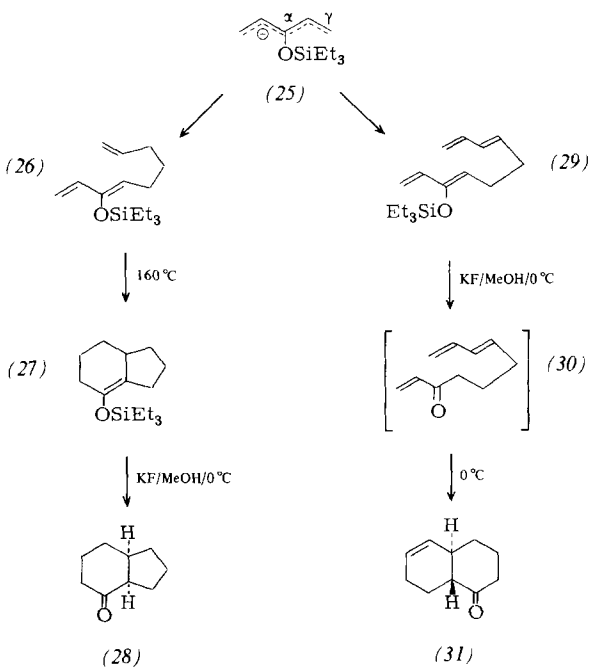
Another route to pumiliotoxin C[14c] is also based on an intramolecular [4+2] addition [*(20)*→*(21)*], which favors an *endo*-orientation of the three-carbon bridge; hydrogenation and oxidation of the adduct *(21)* lead thus to an easily separable 2:1 mixture of the *cis*-hydrindanone *(22)* and its *trans*-annelated isomer. After Beckmann rearrangement of the main product the carbonyl group of the perhydroquinolone *(23)*



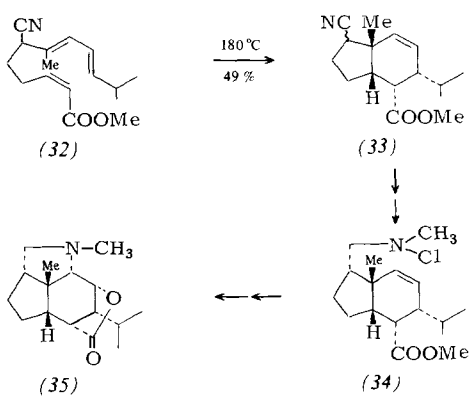
(19) *(24)* *(20)* *(21)* *(18)* *(23)* *(22)*

serves for simple and stereoselective introduction of the propyl group. For the preparation of *cis*-2,3,3a,6,7,7a-hexahydro-7a-methyl-1-indenone by thermolysis of *trans*-2-methyl-1,6,8-nonatrien-3-one, see Ref.[15].

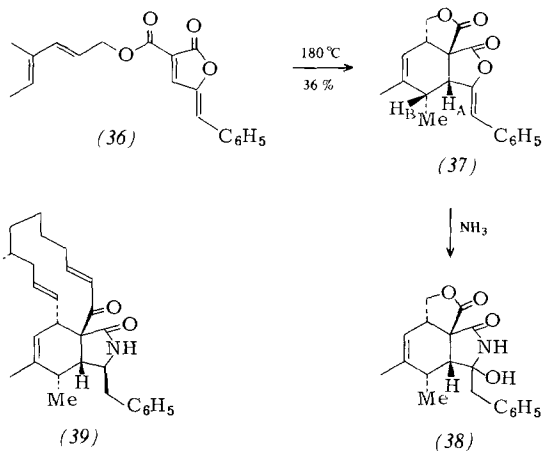
In the synthesis of carbocyclic systems by intramolecular Diels-Alder reactions there occasionally arose the problem of how to prepare the necessary polyene substrates by a rational route. In this connection the (triethylsilyloxy)pentadienyl anion *(25)* recently became available as a convenient building block for the construction and attachment of functionalized diene and dienophile units because of its reactivity toward electrophiles[16]. Thus, γ-alkylation of *(25)* led stereoselectively to (*Z*)-silyloxydienes, for example *(26)* or *(29)*. The triene *(26)* underwent an intramolecular cycloaddition at 160 °C and after ether cleavage afforded the hydrindanone *(28)* in an overall yield of 55 %. When, however, the tetraene *(29)* was treated at 0 °C with potassium fluoride, the *trans*-octalone *(31)* was produced directly (in 62 % yield) in an astonishingly smooth (kinetically controlled) *exo*-addition of the unisolable vinyl ketone *(30)*.



A recent attempt to synthesize the alkaloid dendrobine yielded its 8-*epi*-isomer *(35)*[17]. The *endo*-oriented addition *(32)* → *(33)* occurred with stereochemical control of all chiral centers except the center next to the nitrile group. It is assumed that *(32)* is formed by thermal isomerization from its (*Z*)-isomer (central double bond) prior to its conversion into *(33)*. In subsequent steps the newly formed double bond of the adduct *(33)* served as a bifunctional site to close the pyrrolidine and the lactone rings of *(35)*.

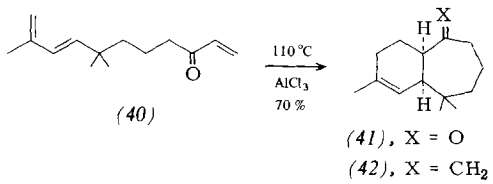


An elegant solution of stereochemical problems is also encountered in the thermal conversion of *(36)* into *(37)*, which was conceived as the key step for construction of the microbial metabolic product proxiphomine *(39)*[18]. The sole adduct obtained, *(37)*, apparently (concluded from the NMR coupling $J_{AB} = 7$ Hz) contains the correct relative configuration of the natural product *(39)* with respect to all four chiral centers. Treatment of *(37)* with ammonia led to the isoindole system *(38)*.

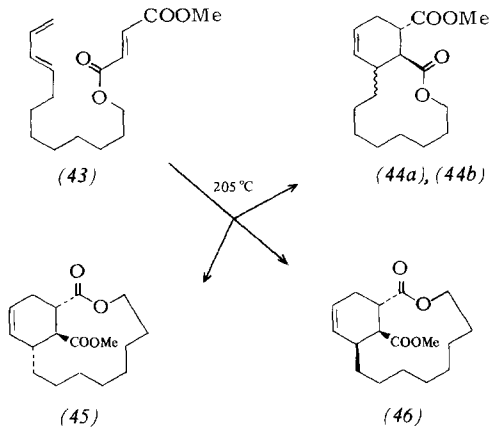


2.1.2. Construction of 6,7- and 6,12-Ring Systems

It can be assumed that bicyclic systems containing seven- or more-membered rings may be constructed by intramolecular addition if the distance between the diene and dienophile units is increased.



The validity of this assumption is demonstrated by the Lewis acid-catalyzed conversion of the triene *(40)* into the annelated cycloheptanone *(41)* (70 %), which was transformed by methylenation into the sesquiterpene α-himachalene *(42)*[19].



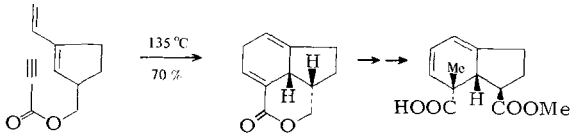
The fact that 12- and 13-membered rings can also be closed by intramolecular cycloaddition to *activated* dienophiles is exemplified by the thermolysis of *(43)*[20]. When low steady state concentrations are used (to suppress the undesired bimolecular addition), a 7:3:4:1 mixture of the stereo- and position-isomeric products *(44a)*, *(44b)*, *(45)*, and *(46)* is obtained in 80 % yield. This (kinetically and/or partially thermodynamically controlled) product ratio reflects the loss of the control over regio- and stereochemistry that characterizes the previously discussed construction of 5,6- and 6,6-ring systems.

2.2. Endocyclic Dienes

Intramolecular cycloadditions of 1,3-dienes which are partly or wholly incorporated in a ring may provide complicated ring systems which are accessible by other routes only with difficulty.

2.2.1. 1-Vinylcycloalkenes

This is illustrated, *inter alia*, by a model study on the synthesis of gibberellic acid in which the cycloaddition *(47)*→*(48)* is the key step[21]. Stereoselective methylation

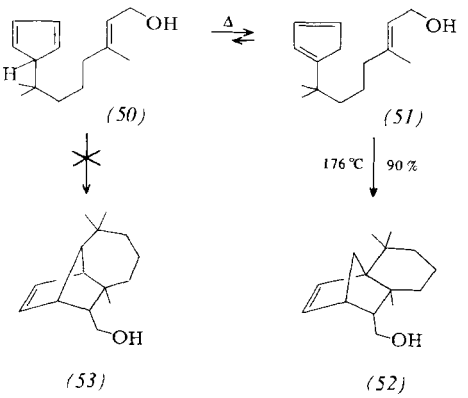


(47) *(48)* *(49)*

of the cyclohexadiene component in the adduct *(48)*, followed by modification of the lactone ring, leads to the indane derivative *(49)*. This compound has the correct spatial arrangement of functional groups for the construction of rings A and B of gibberellic acid.

2.2.2. Cyclopentadienes

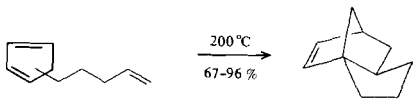
Earlier work, whose objective was also the synthesis of a natural product, examined the thermal behavior of the mixture of cyclopentadienes *(50)* and *(51)*[22]. When



(50) *(51)* *(53)* *(52)*

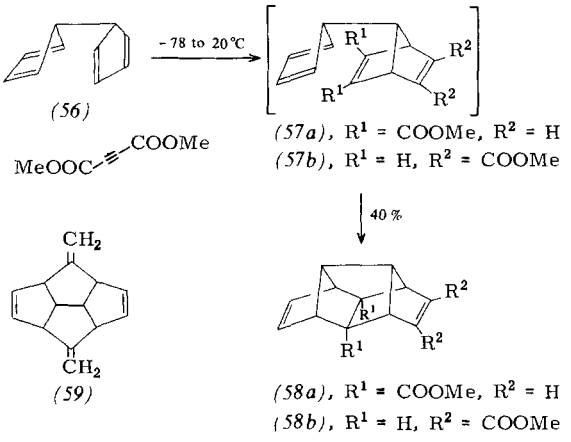
this mixture was heated at 176 °C for 48 h the norbornene *(52)* was the sole product, with no trace of the desired adduct *(53)* which could have served as a direct precursor of the sesquiterpene longifolene. Hence it can be concluded that *(50)* and *(51)* equilibrate (by a 1,5-hydrogen shift) and that the irreversible addition *(51)*→*(52)* proceeds faster than the expected reaction *(50)*→*(53)*, although here thermodynamic control cannot be completely ruled out.

Similar considerations apply for the reaction *(54)*→*(55)*[23].



(54) *(55)*

An interesting sequence of thermal inter- and intramolecular cycloadditions that leads in one synthetic operation to the formation of four C—C bonds (see also [7b]) is provided by the reaction of *(56)* with dimethyl acetylenedicarboxylate[24]. At low temperature (to avoid hydrogen shifts) a 3:2 mixture of *(58a)* and *(58b)* is immediately obtained *via* the intermediate bimolecular adducts *(57a)* and *(57b)*. The product *(58a)* was converted in several steps into *(59)*.



(56)

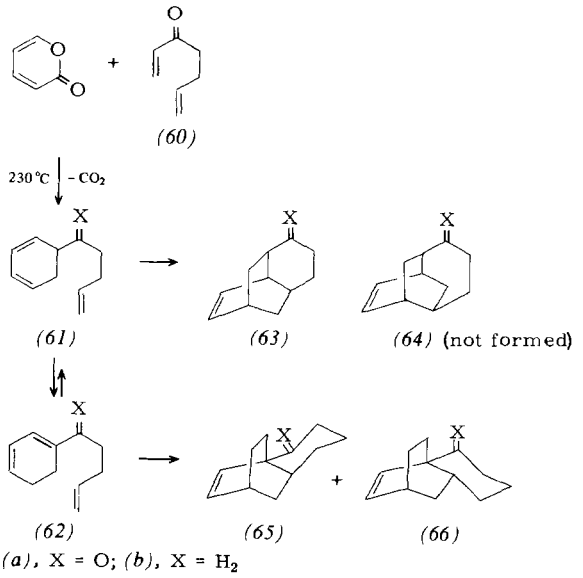
(57a), R^1 = COOMe, R^2 = H
(57b), R^1 = H, R^2 = COOMe

(59)

(58a), R^1 = COOMe, R^2 = H
(58b), R^1 = H, R^2 = COOMe

2.2.3. Cyclohexadienes

Another sequence of thermal (cycloaddition-cycloreversion and hydrogen-shift) reactions, involving participation of the intermediate compounds *(61a)* and *(62a)*, occurs when α-pyrone is heated with the dienone *(60)* at 230 °C[25]; the isomeric products *(63a)*, *(65a)*, and *(66a)*, are obtained directly in yields of 37, 43, and 11 %, respectively. Thermolysis of the pentenylcyclohexadiene *(61b)* is appreciably more selective, as it yields the adduct *(63b)* in 73% yield with small amounts of *(65b)* and *(66b)*; clearly the hydrogen shift *(61b)*→*(62b)* is slower than the addition *(61b)*→*(63b)*. Particularly noteworthy here is the fact that



(60)

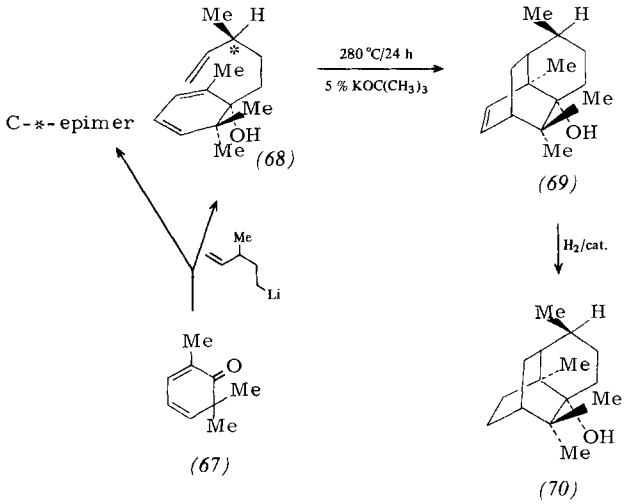
(61) *(63)* *(64)* (not formed)

(62) *(65)* *(66)*

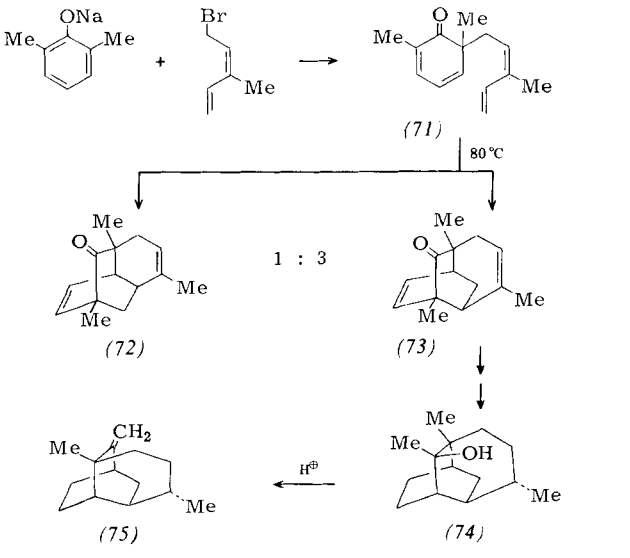
(a), X = O; *(b)*, X = H_2

the thermal reactions of *(61a)* and *(61b)* yield no trace of the position-isomeric adduct *(64)*, although (owing to the *cis*-configuration of the diene with respect to the dienophilic chain) no strain opposes that reaction.

The same regioselectivity that we encountered earlier in the reaction *(3)*→*(4)* also characterizes the intramolecular cycloaddition *(68)*→*(69)*[*], which provides the complex skeleton of the sesquiterpene patchoulol *(70)* in a single step[26]; the racemic natural product *(70)* is obtained by simple hydrogenation of the adduct *(69)*. In comparison with several multistage syntheses of patchoulol[27], the reaction sequence *(67)*→*(68)*→*(69)*→*(70)* demonstrates the effectiveness of intramolecular cycloadditions.



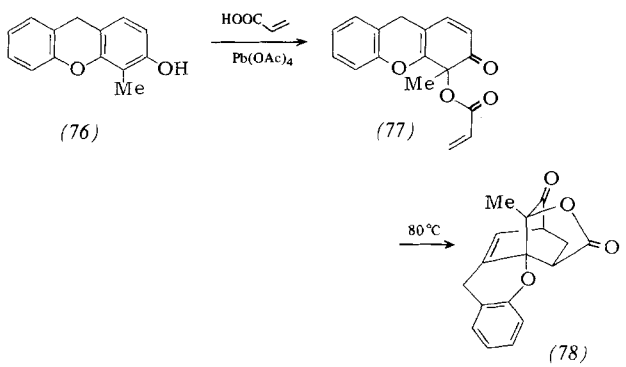
No less impressive is a route to the structurally related sesquiterpene seychellene *(75)*, in which a smooth intramolecular addition of the easily accessible cyclohexadienone *(71)* is used[28a]. Already at 80 °C a kinetically controlled reaction gives, as with the analogous alkenylcyclohexadienones[28b], the regioisomeric adducts *(72)* and *(73)* in a ratio of 1:3. The main product *(73)* was converted into the alcohol *(74)*, which on acid catalysis rearranged to the desired terpene *(75)*. Remarkably, the formation of *(73)* as the main product



[*] Addition of a strong base appears to be decisive for this addition to proceed successfully.

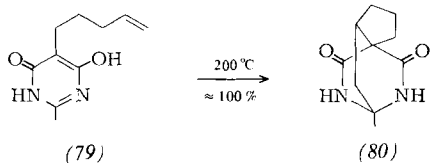
requires bond formation between the terminal dienophile center and the nearer end of the endocyclic diene system in *(71)*. This orientation, opposite to that in the examples mentioned above, is probably due to an overlap of the dienophile with the double bond conjugated thereto. In the formation of *(72)* such an overlap is impossible on the grounds of strain[28c].

A further application of intramolecular additions of cyclohexadienones exploits the easy preparation of *(77)* by Wessely oxidation of the phenol *(76)* in the presence of acrylic acid. On heating *(77)* in boiling benzene the lactone *(78)*[29] is formed, the ring system of which is a component of the natural products morellin and gambogic acid.



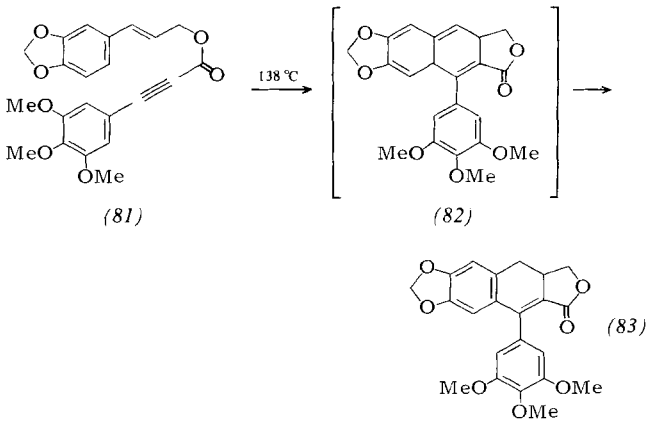
2.2.4. Endocyclic Heterodienes

The efficient intramolecular Diels-Alder addition of an isolated double bond to a 4,6-dihydroxypyrimidine has been demonstrated recently by the thermolysis *(79)*→*(80)*[30].



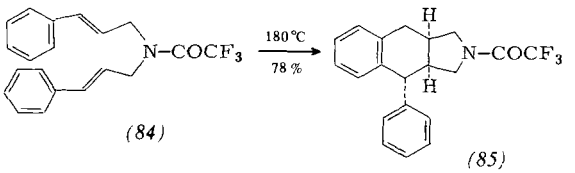
2.3. Styrenes as Diene Components

An extremely simple synthetic route to Podophyllum lignans[31], described by *L. H. Klemm*, may be taken as the first application of an intramolecular [4+2] cycloaddition to the synthesis of natural products. Thus, the natural lactone *(83)* is obtained by merely heating the arylpropargyl ester

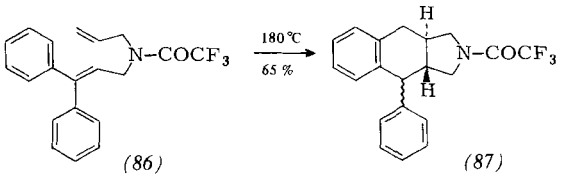


(81) in boiling acetic anhydride. In this reaction the styrene unit of *(81)* clearly reacts as the diene and the triple bond as the dienophile with the formation of an intermediate adduct *(82)* which aromatizes to *(83)* by a 1,3-hydrogen shift.

Furthermore, at higher temperatures (180 to 235 °C) olefinic double bonds that are relatively unreactive add intramolecularly to styrenes[32a]. For example, the *cis*-fused isoindoline derivative *(85)* is obtained exclusively by thermolysis of the *N,N'*-bis(cinnamyl)amide *(84)*, while the *trans*-system *(87)* is obtained selectively from the isomeric amide *(86)*. Steric

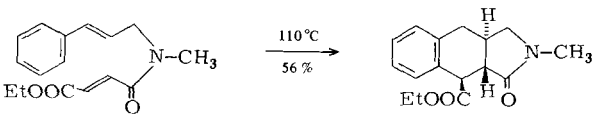


(84) *(85)*



(86) *(87)*

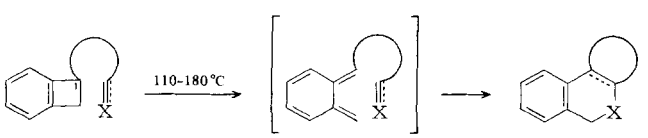
interactions of the phenyl substituents are probably responsible for this mutually exclusive steric control which disfavors on the one hand the *exo*-orientation of the chain in *(84)* and on the other the *endo*-addition of *(86)*. It is worth noting the exclusive formation of 1:1 adducts in the above cases, whereas bimolecular Diels-Alder reactions of styrenes often yield the (undesirable) 2:1 addition products[2a]. This difference underlines once more the preparatively advantageous influence of entropy factors on the reaction rate of intramolecular cycloadditions, as also shown by the smooth thermal transformation *(88)*→*(89)*[32b].



(88) *(89)*

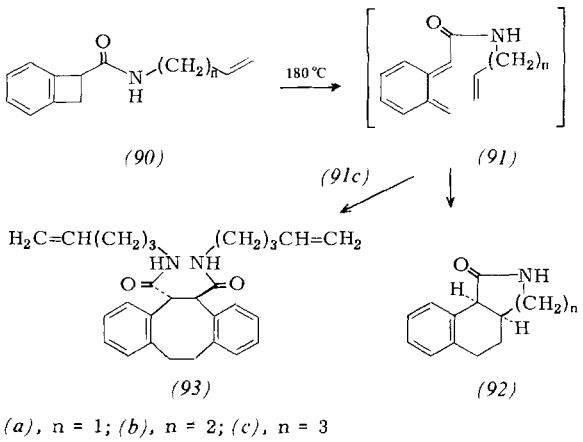
2.4. *o*-Quinodimethanes

Another reaction sequence that is interesting from the preparative point of view and whose course involves participation of an aromatic system was developed in the laboratories of Sandoz Ltd.[33]. Accordingly, tricyclic systems of the type *(iii)* are obtained in excellent yield by heating the readily accessible benzocyclobutenes *(i)* that carry on C-1 a chain of five or six atoms with a terminal multiple bond. Here, according to stereochemical and kinetic findings[33b] we have a primary reversible opening of the four-membered ring to a nonaromatic intermediate (*E*)-quinodimethane *(ii)*, which undergoes irreversible cycloaddition to



i *ii* *iii*

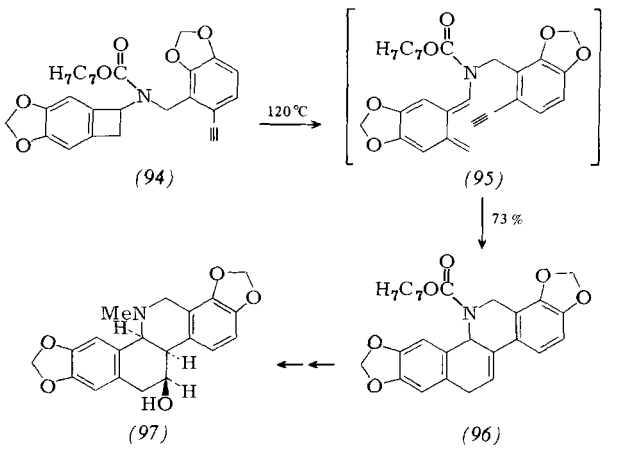
the multiple bond in the chain (with concomitant formation of the arene system). This addition occurs smoothly even with unreactive dienophiles, *e.g.* with isolated C—C and C—N double or triple bonds[33c], presumably because of the entropic assistance resulting from the proximity of the reaction partner. (For intramolecular cycloadditions of nitriles to 1,3-dienes see [34].)



(90) *(91)* *(93)* *(92)*

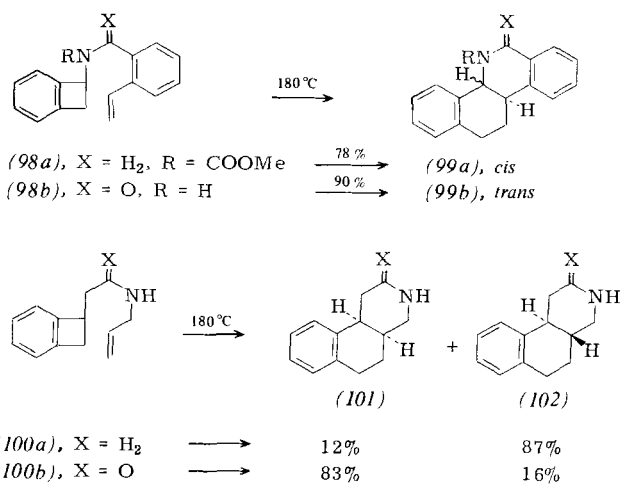
(a), n = 1; *(b)*, n = 2; *(c)*, n = 3

The limits of this influence are revealed when one compares the efficient reactions *(90a)*→*(92a)* and *(90b)*→*(92b)* (both give an 80% yield) with the thermal behavior of the higher homolog *(90c)*[33a]; even at high-dilution the adduct *(92c)* is formed in drastically reduced yield (20%), together with the dimerization product *(93)* (6% yield).



(94) *(95)* *(97)* *(96)*

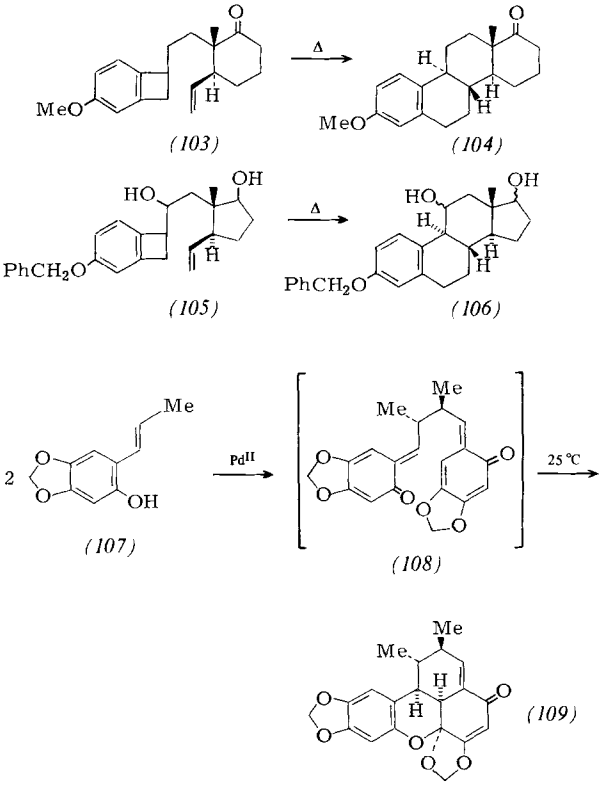
Of the numerous possible variations offered by the inclusion of heteroatoms and rings in the benzocyclobutene *(i)*, the



thermal reaction of *(94)* may be selected as an example; already at 120°C it provides *(69)* in 73% yield and forms the key step in the synthesis of the alkaloid chelidonine *(97)*[35].

The steric course of the related thermal transformations of *(98a)*, *(98b)*, *(100a)*, and *(100b)* may be cited as examples to illustrate how intramolecular cycloadditions can be directed toward *endo*- or *exo*-products merely by changing the conformation of the bridge[33d, 35].

High stereoselectivity was similarly observed in the key steps *(103)*→*(104)* and *(105)*→*(106)* of two independent steroid syntheses[36].

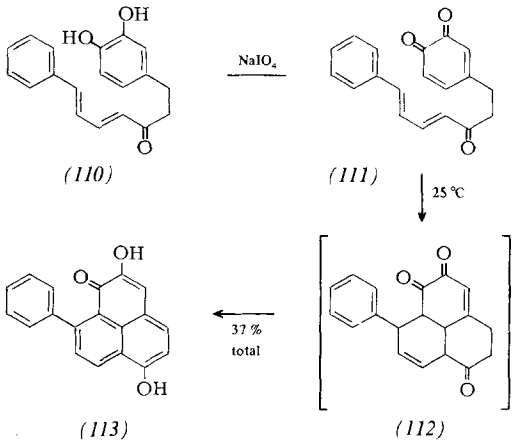


A similar concept is encountered in the elegant biomimetic synthesis of the lignan carpanone *(109)*[37a]. This route, which is characterized by remarkable control over five chiral centers, leads *via* phenol coupling of *(107)* to an intermediate bis-(quinodimethide) *(108)*; spontaneous intramolecular Diels-Alder reaction of this gives the lignan *(109)* in 46% yield.

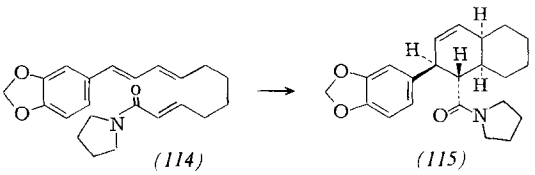
2.5. Biogenesis of Natural Products

The striking utility of intramolecular [4+2]-cycloadditions for the synthesis of complicated natural products leads inevitably to the question whether this reaction principle is also used in nature. In answer to this, it may be recalled that the synthesis of carpanone was patterned along the lines of biogenetic ideas[37b]. The intermediacy of *(108)* in the biogenesis of *(109)* appears convincing in view of the mild conditions of the laboratory synthesis, the absence of optical activity in the natural alkaloid *(109)*, and the occurrence of the methyl ether of the precursor *(107)* in the same plant.

Considering an earlier hypothesis[38a] it was very recently suggested that the biogenetic pathway to the plant pigment

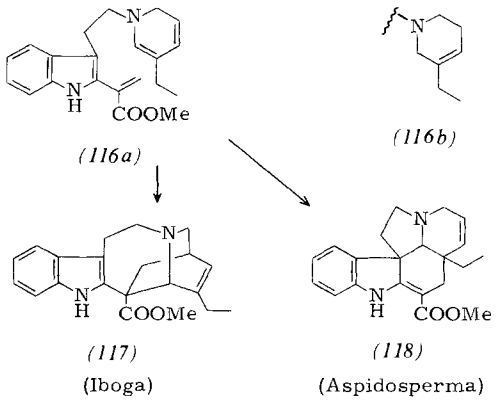


lanchnanthocarpone *(113)* also involves an intramolecular Diels-Alder reaction: *(111)*→*(112)*. In fact, the natural product *(113)* could be obtained in one synthetic operation by oxidation of the catechol *(110)* with $NaIO_4$; the ensuing cycloaddition *(111)*→*(112)* proceeds readily at 25°C[38b].



Similar facts apply to the racemic natural product cyclopiperstachine *(115)*[39]; this was isolated under mild conditions from *Piper trichostachyon* and to all appearances arises in nature by intramolecular cycloaddition of piperstachine *(114)*, which occurs in the same plant. This process was carried out in the laboratory, but required temperatures above 110°C to give stereochemically pure *(115)* in 33% yield.

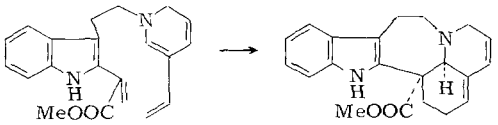
It is considerably more difficult to prove the key role postulated for the dihydropyridineacrylic ester *(116a)* (dehydrosecodine, not yet either isolated or synthesized) in the biosynthesis of iboga and aspidoderma alkaloids[40].



Nevertheless, it seems reasonable to regard intramolecular Diels-Alder reactions of *(116a)* responsible for the natural occurrence of catharanthine *(117)* and tabersonine *(118)*. In favor of this assumption, for example, is the *in vivo* incorporation of secodine *(116b)* into the aspidosperma skeleton[41], whereas some *in vitro* experiments on indirect detection of the bio-intermediate *(116a)* are subject to debate[42]. However, this hypothesis provided the stimulus for a biomimetic total synthesis of the aspidosperma alkaloid minovine based

on a bimolecular [4+2]-addition (of a tetrahydropyridine to a 2-(2-indolyl)acrylic ester)[43].

Nature seems to follow similar principles in the synthesis of the alkaloid andraginine *(120)*[44]; both its racemic char-



(119) *(120)*

acter and its partial synthesis by thermolysis of precondylocarpine acetate find a reasonable interpretation in the intramolecular cycloaddition of the postulated secodine derivative *(119)*.

2.6. Discussion

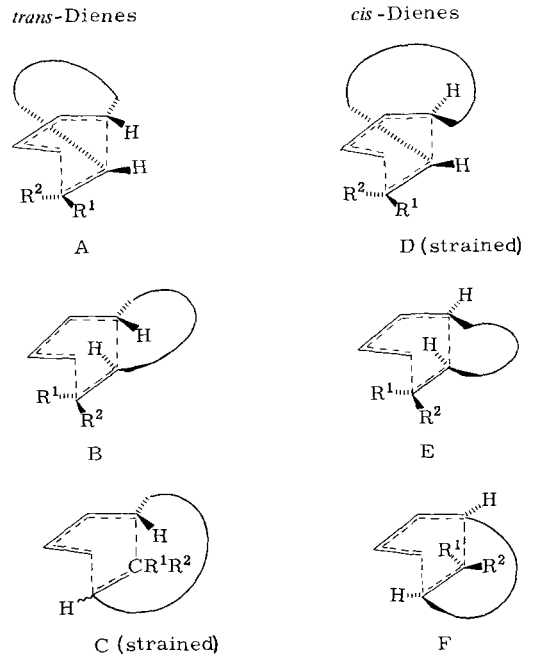
It is anticipated that the above features relating to intramolecularity are in general limited to [4+2]-additions in which the diene and dienophile partners are linked by a bridge of three or four atoms. The longer and more flexible this bridge, the more the conditions resemble those for bimolecular addition, as is shown by the reactions of *(43)* and *(90c)*. It must also be stated that the regio- and stereoselectivity of intramolecular Diels-Alder reactions as discussed below rely on a kinetically-controlled reaction course. To avoid loss of this selectivity by the formation of thermodynamically controlled products it is recommended that such reactions be carried out at the lowest possible temperatures even if longer reaction times are necessary. These limitations apply equally to the [3+2]-additions discussed in Section 3.

2.6.1. Entropic Assistance

Intramolecular Diels-Alder reactions (type II in Scheme 1) take place under considerably milder conditions than are required for the analogous bimolecular reactions (type I in Scheme 1) [see, *inter alia*, the reactions of *(9)*, R=CH_3, R′=COOEt, *(30)*, *(57)*, *(108)*, and *(111)*]. The influence of entropy is illustrated by the $\Delta S^{\neq}$ values for the reactions of *(9)*, which are less negative than -20 cal K^{-1} mol^{-1}; their free activation energies ($\Delta G^{\neq}$) are thus lower by 5 to 7 kcal/mol than those for intermolecular [4+2]-additions. For the same reason, not only unactivated dienophiles, *e.g.* isolated olefins, oxime ethers, and nitriles but also unreactive (*e.g. cis*-substituted) 1,3-dienes undergo smooth intramolecular additions. [Catalysis of Diels-Alder reactions by Lewis acids has been used only to a limited extent in the intramolecular variants, *e.g.* in the reaction *(40)*→*(41)*.]

2.6.2. Direction of Addition

As follows from model considerations, intramolecular [4+2]-additions to *trans*-dienes are necessarily oriented in the direction A or B, since the orientation C is too strained (Scheme 2). Furthermore, from *cis*-dienes, *e.g. (3)*, *(24)*, *(61)*, *(68)*, and *(79)*, annelated rather than bridged adducts are generally obtained; the observed preference for direction E could here be ascribed to the fact that bond formation between the nearer ends of the diene and the dienophile is entropically more favorable than the orientation F. However, this influence can be overridden by other factors, as shown by the reaction *(71)*→*(73)*.



Scheme 2. Transition states of intramolecular [4+2]-additions. The bridge length is three or four atoms.

2.6.3. Stereochemistry

[4+2]-Additions I and II are synchronous multicenter processes with characteristic stereospecificity. Intramolecular additions II, however, exhibit supplementary features which differentiate between the *endo*- and *exo*-mode of addition (Scheme 2). On models it can be seen that in intramolecular addition of *cis*-dienes the dienophile chain is forced into the *exo*-position E, the transition state D being too strained. The *cis*-adducts thus arising with high stereoselectivity, *e.g. (4)*, *(21)* [from *(24)*], and *(63)*, can nevertheless be accompanied, or even outweighed, by products of competing sigmatropic or *cis*/*trans*-isomerization processes, *e.g.* in the formation of *(33)*.

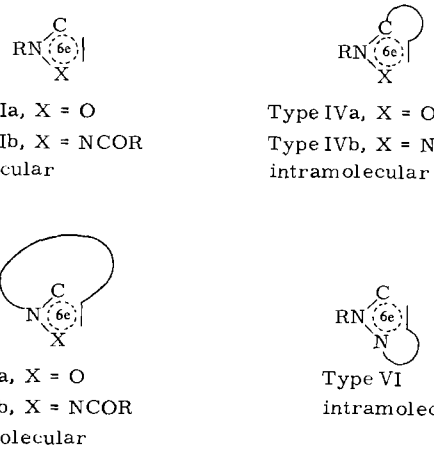
In the thermally more stable *trans*-dienes the orientations A and B are both strain-free; as a result, the energy difference between these two transition states depends on the bonding and nonbonding interactions of the substituents and on other conformational influences that are less clearly predictable. For example, *trans*-dienophiles with *terminal* carbonyl or phenyl groups lead selectively to *trans*-fused adducts, *e.g. (2)* and *(10)*, which, as in the bimolecular Diels-Alder reaction, reflects the favored *endo*-position of sp^2 substituents. However, this is *not* so for dienophiles as soon as the sp^2 substituent forms an integral part of the bridge, as follows from the reactions *(9)*, R′=H, → *(10)*+*(11)*, *(30)*→*(31)*, *(36)*→*(37)*, and *(98b)*→*(99b)*. The repulsive forces due to the phenyl substituents appear to influence the spatial characteristics of the reactions of *(84)* and *(86)*. Other examples, such as the thermolyses of *(12)*, *(98b)*, and *(100b)*, show the stereochemical influence of amide groups built into the bridge. Quite generally, it should be possible, by conformational modification of the bridge, to direct intramolecular cycloadditions more or less completely in the direction of *trans*- or *cis*-anellated products.

Finally, it is of preparative importance to note the steric induction of chiral centers by centers already present in the bridge; here the conformational requirements of a highly ordered transition state come into play. For example, in the

thermolyses of *(16)*, *(47)*, *(68)*, *(103)*, *(105)*, and *(108)* up to five chiral centers can be controlled simultaneously.

3. Intramolecular Cycloadditions of Nitrones and Azomethine Imines

It is due mainly to *Huisgen* and his school that the concept of [3+2]-cycloaddition and its general application to the synthesis of five-membered heterocycles has been visualized[3]. These reactions are closely related to the Diels-Alder reaction. Examples are, *inter alia*, the bimolecular additions of nitrones and azomethine imines to multiple bonds (Type IIIa and IIIb, respectively, in Scheme 3).



Scheme 3. [4+2]-Additions of nitrones (Types IIIa, IVa, Va) and azomethine imines (Types IIIb, IVb, Vb, VI).

Although intramolecular variants have recently been the subject of a review[45], it seems justifiable to consider their special features systematically in this article. However, the discussion will be limited to a small selection of reactions in which C—C double bonds are concerned (Types IV to VI in Scheme 3).

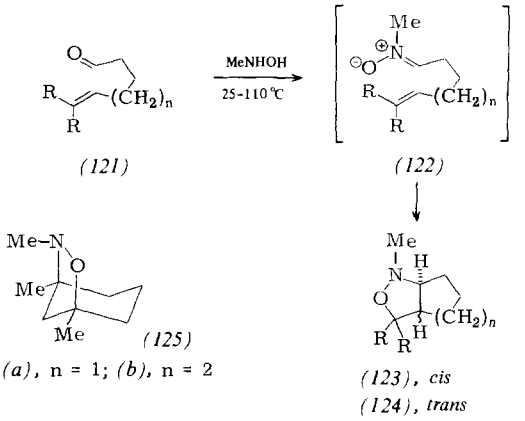
3.1. Nitrones

Nitrones occupy a special place among the 1,3-dipoles[46], not least because of their easy accessibility and the facility with which their adducts can be modified. Thus, *Beckmann* described cycloaddition of the nitrone *N*-benzylidenebenzylamine *N*-oxide to phenyl isocyanate as early as 1890[47], but the addition of nitrones to C—C double bonds was first reported—simultaneously by several groups of workers—only about 70 years later[48]. It seems remarkable that bimolecular and intramolecular nitrone-olefin additions were discovered at the same time.

3.1.1. *C*-Alkenylnitrones (Additions of Type IVa)

Le Bel et al. showed[48c,49] that intramolecular additions of intermediate *C*-alkenylnitrones (Type IVa) can be easily effected if olefinic aldehydes *(121)* are condensed with *N*-alkylhydroxylamines; annelated isoxazolidines *(123)* and/or *(124)* are obtained in this way.

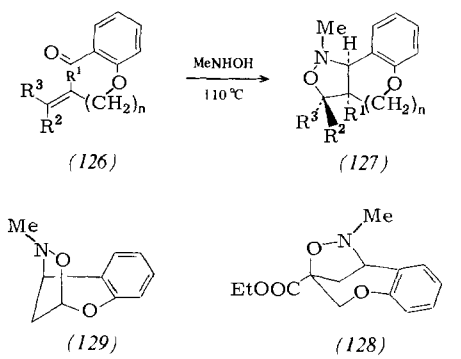
It is interesting that many of these additions to unactivated C—C double bonds take place smoothly at 25°C, whereas the bimolecular variant IIIa requires a higher temperature



and/or activation of the olefinic component[4]; this difference, which is useful for syntheses, again reflects the entropic influence in intramolecular reactions. It is also worth noting the regioselectivity of the addition of *(122)*, which leads mainly, if not exclusively, to annelated adducts (see Section 3.3.2). An exception is provided by the formation of bridged isoxazolidines such as *(125)* from *C*-alkenylketonitrones, probably owing to nonbonding interaction of the substituents.

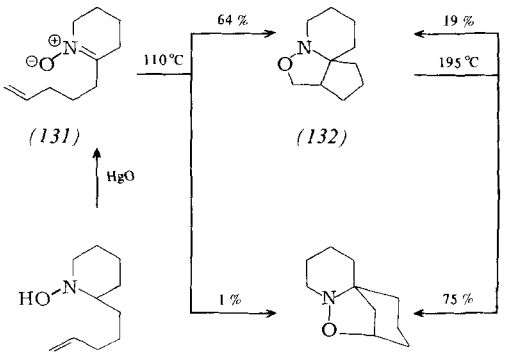
Concerning the stereochemical aspects (see Section 3.3.3) it appears that the *C*-(3-alkenyl)nitrones *(122a)* react highly selectively to give *cis*-condensed isoxazolidines *(123a)*. The kinetically controlled reaction of the homologous *C*-(5-alkenyl)nitrones *(122b)*[50] occurs less selectively; the *trans*-adducts *(124b)* are the main products, along with varying amounts of the *cis*-isomers *(123b)*. However, at higher temperatures (180—300°C) equilibration of the *trans*- and *cis*-adducts *(124b)* and *(123b)* occurs, presumably by 1,3-dipolar cycloreversion, to afford finally the thermodynamically more stable isomer *(123b)*.

Isoxazolidines that are *cis*-fused to a six-membered ring are, on the other hand, formed regio- and stereoselectively from ε,ζ-unsaturated aldehydes under kinetic control, provided that carbons α and β[51a,51b] (or γ and δ[51c]) are part of an aromatic ring. This is illustrated by the efficient reactions *(126a)*→*(127a)*, ($R^1=R^2=R^3=H$, 80% yield), which



nevertheless become less efficient with increasing distance between the reaction partners [*(126b)*→*(127b)*, $R^1=R^2=R^3=H$, 26% yield]. It was also not unexpected to find that ethoxycarbonyl or ether substituents (on the nearer end of the alkene unit) can direct the intramolecular addition partially towards bridged products, *e.g.* *(128)*, or *(129)*; this was also observed during model studies on the synthesis of tetracycline[51d]. The fact that the formation of annelated isoxa-

zolidines is generally dominant in additions of type IVa to nonpolarized C—C double bonds is shown particularly clearly in a model study for the synthesis of the alkaloid histrionicotoxin[52]. Namely, at 110 °C the endocyclic ketonitrone *(131)*,

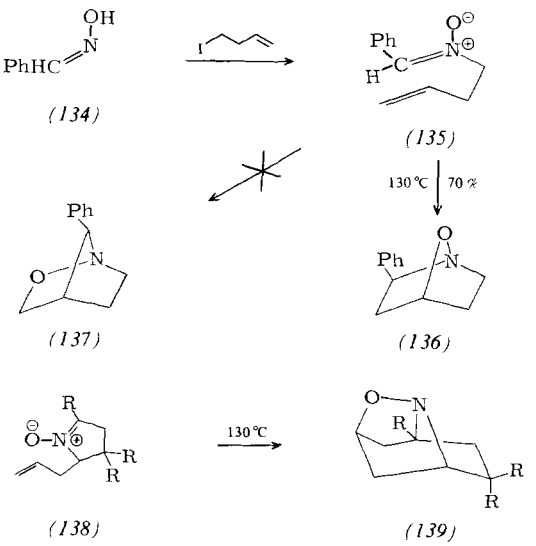


(131) *(132)* *(130)* *(133)*

prepared by oxidation of the hydroxylamine *(130)*, gave mainly the annelated adduct *(132)*, and only a trace of the desired bridge isomer *(133)* which after cleavage of the N—O bond affords the histrionicotoxin skeleton. It should be noted that the conversion *(132)*→*(133)* could be accomplished at higher temperatures, apparently *via* 1,3-dipolar cycloreversion. It follows that the bridged adduct *(133)* is thermodynamically more stable than the annelated isomer *(132)*, whose formation is kinetically controlled.

3.1.2. *N*-Alkenylnitrones (Additions of Type Va)

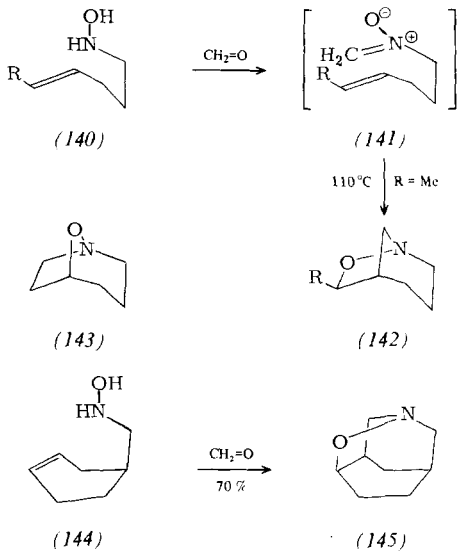
Intramolecular additions of Type Va, which necessarily lead to bridged isoxazolidines, attracted little attention until very recently. The first example was the thermolysis of the *N*-(3-butenyl)nitrone *(135)*, which was obtained by alkylation of benzaldehyde oxime *(134)*[53]; *(136)* was formed as the sole adduct, with no trace of the position isomer *(137)*. This result corresponds to a regiospecific formation of the C—C bond to the less substituted (terminal) alkene-carbon, as in most bimolecular additions of nitrones (Type IIIa) to monosubstituted olefins. The high stereochemical control of the intramolecular process indicates an *endo*-addition of the (*Z*)-nitrone *(135)*, the alternative *exo*-transition state being excluded by angular strain (see Section 3.3.3).



(134) *(135)* *(137)* *(136)* *(138)* *(139)*

The same direction of addition is followed by the reaction *(138)*, R = H, CH_3→*(139)*, which leads to the tropane skeleton[54] (after cleavage of the N—O bond).

In contrast, in the recently investigated intramolecular addition of *N*-(4-alkenyl)nitrones *(141)*[55], it is mainly the nearer alkene carbon that becomes linked to the nitrone-carbon. The nitrones *(141)* are formed *in situ* by condensation of formaldehyde with olefinic hydroxylamines *(140)*, which are readily accessible by reduction of oximes with sodium cyanoborohydride. On heating the non-isolated nitrones *(141a)*

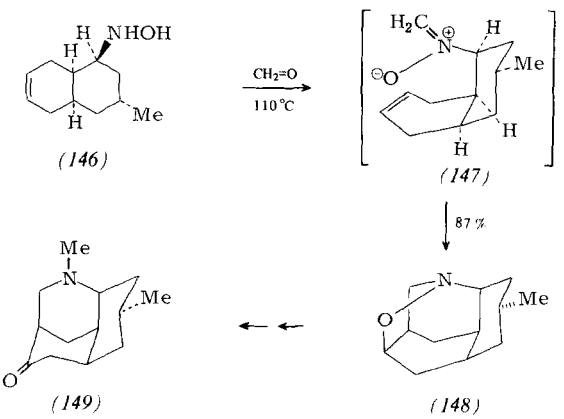


(140) *(141)* *(143)* *(142)* *(144)* *(145)*

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

at 110 °C, a 2:1 mixture of the two positional isomers *(142a)* and *(143)* was obtained in 75 % yield in a kinetically controlled reaction. Much higher directional selectivity was observed in the corresponding reaction of *(140b)* which gave exclusively the adduct *(142b)* in 90 % yield. Similarly the hydroxylamine *(144)*, which also contains a 1,2-disubstituted double bond, afforded *(145)* as the sole adduct.

The ready accessibility of *N*-(4-alkenyl)nitrones (from *N*-alkenylhydroxylamines) and the unequivocal direction of their intramolecular additions to nonconjugated "symmetric" C—C bonds recently allowed a simple[56a] and enantioselective[56b] synthesis of the lycopodium alkaloid luciduline *(149)*.



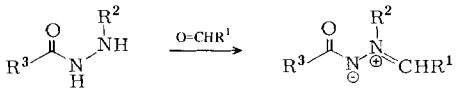
(146) *(147)* *(149)* *(148)*

Heating of the easily available hydroxylamine *(146)* with an excess of paraformaldehyde and molecular sieves in toluene furnished directly an 87 % yield of the isoxazolidine *(148)*, which on methylation, reduction and oxidation gave the alka-

loid *(149)* in high yield. Comparison with another, multistage, preparation of racemic *(149)*[56c] demonstrated for the first time in the synthesis of natural products a superiority of intramolecular nitrone additions over other types of reaction.

3.2. Azomethine Imines

The history of these dipoles is more recent than that of nitrones; the cycloadditions [type IIIb] of a few endocyclic azomethine imines to multiple bonds were described by *Huisgen et al.* in 1960[3a, 57]. Surprisingly, it was only a few years ago that convenient methods for the preparation of open-chain (unstable) azomethine imines, analogous to those for the preparation of nitrones, were found in the laboratories of Sandoz Ltd.

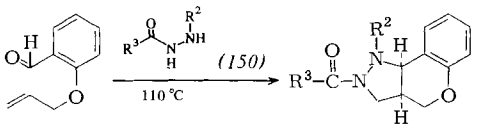


(150) *(151)*

Azomethine imines *(151)* were then obtained *in situ* from *N*-acyl-*N'*,*N'*-dimethylhydrazines *via* mercury compounds[58] or preferably by condensation of aldehydes with *N*-acyl-*N'*-alkylhydrazines *(150)*[59]; subsequent trapping by bimolecular addition (Type IIIb) to dipolarophiles such as styrene, furnished pyrazolidines in high yields. The simple reaction *(150)*→*(151)* now allows olefinic substituents R^1, R^2, and R^3 to be introduced specifically into the three positions of the dipole; thus the intramolecular cycloadditions IVb, Vb, and VI may be easily realized.

3.2.1. *C*-Alkenylazomethine Imines (Additions of Type IVb)

C-Alkenylazomethine imines are conveniently accessible *in situ* by condensing olefinic aldehydes with *N*-acyl-*N'*-alkylhydrazines *(150)* and undergo a spontaneous, regioselective addition of Type IVb[60].

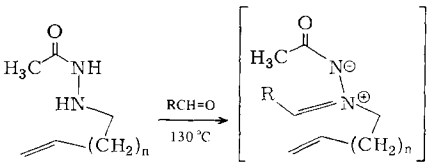


(152) *(153)*

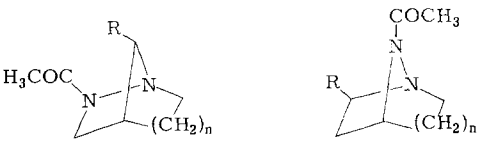
As shown by the example *(152)*→*(153)*, *cis*-annelated pyrazolidines are formed directly and preferentially (although the stereoselectivity is here less marked than for the analogous additions of nitrones). Remarkably, the reaction of *N*,*N'*-bis(*p*-methoxybenzyl)hydrazine does not produce isolable pyrazolidine derivatives on reaction under similar conditions with *(152)* or with paraformaldehyde in styrene[59, 60]; this is not in agreement with the postulate[3a, 61] that intermediate azomethine imines are formed when the last-mentioned hydrazine reacts with aldehydes in the presence of carbon disulfide (or acrylonitrile).

3.2.2. *N*-Alkenylazomethine Imines (Additions of Type Vb)

As expected, the condensation of *N*-acyl-*N'*-alkenylhydrazines with aldehydes leads to azomethine imines (with an alkenyl group on the central nitrogen of the dipole), which can undergo intramolecular additions of type Vb[62].



(154) *(155)*



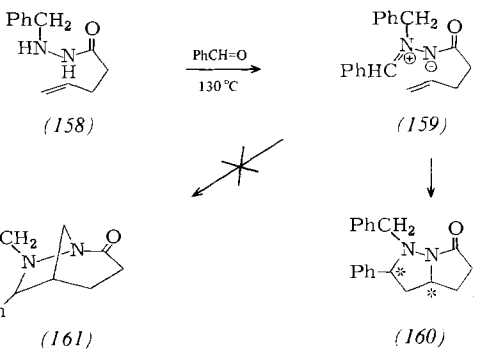
(157) *(156)*

(a), n = 1; *(b)*, n = 2

For example, the adduct *(156a)*, R = H, was formed regioselectively on treatment of *(154a)* with formaldehyde. Similarly to the analogous additions of nitrones of Type Va, the direction of the addition is reversed with the higher homologs *(154b)*, R = H; one obtains only the regioisomer *(157b)*, R = H. The same direction of addition is preferred on heating the hydrazide *(154b)* with benzaldehyde; the positional isomers *(156b)*, R = Ph, and *(157b)*, R = Ph are formed in the ratio of 1:7, in a total yield of 54%, together with smaller amounts of two stereoisomeric products. The stereochemistry observed in these reactions is consistent with predominant addition of the (*Z*)-dipole *(155b)*, R = Ph.

3.2.3. *N*-Alkenoylazomethine Imines (Additions of Type VI)

Finally, the third reaction type, VI, requires that the dipolarophile chain is attached to the terminal nitrogen of the dipole.



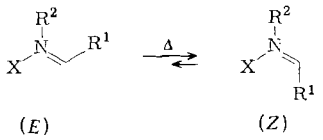
(158) *(159)* *(161)* *(160)*

A reaction of this type can be smoothly effected by heating *N*-alkenoyl-*N'*-alkylhydrazines together with aldehydes[62], as shown by the regio- and stereoselective conversion *(158)*→*(159)*→*(160)*. The sole product is the sterically homogeneously annelated adduct *(160)* (whose configuration has not yet been clarified) with no trace of the bridged isomer *(161)*.

3.3. Discussion

The mechanistic relationship between 1,3-dipolar addition and the Diels-Alder reaction makes it possible to discuss the features of their intramolecular variants on a common basis. However, nitrones and azomethine imines can add also intramolecularly to C—C double bonds that are linked by a short chain to the central atom of the dipole. In contrast,

the analogous Diels-Alder reaction would be blocked by the formation of a developing bridgehead double bond. A further difference concerns the rotation barriers of C—N and C—C double bonds (Scheme 4). It seems reasonable to assume that



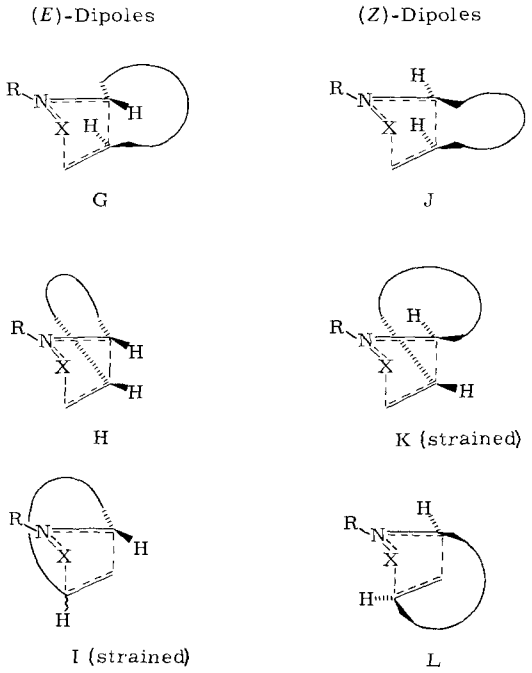
Scheme 4. Rotation of acyclic nitrones and azomethine imines.

(*Z*)/(*E*)-isomerizations of acyclic nitrones and azomethine imines are comparable in rate with the cycloaddition process[46a, 63], which has been taken into account in the discussion of the orientation rules (Section 3.3.2). Furthermore, it must be remembered that, with the exception of strain, the proposed orienting forces may be overridden by other factors. As in the Diels-Alder reaction, cycloreversion can occur at higher temperatures with the formation of thermodynamically controlled products; this is occasionally of preparative use, as in the reaction *(132)*→*(133)*.

3.3.1. Entropic Assistance

In view of the strongly negative activation entropies of bimolecular additions of Type III[3b], there can be no doubt (despite the lack of data) that intramolecular reactions of Types IV, V, and VI are entropically favored. This is indicated by the smooth intramolecular addition of sensitive, unisolable dipoles to unreactive double bonds, which becomes less effective with increasing distance between the dipole and the isolated alkene unit [see the reaction *(126b)*→*(127b)*].

3.3.2. Direction of Addition



Scheme 5. Transition states of the additions IV (see Scheme 3).

Examination of models shows that in intramolecular additions of *C*-alkenyl-nitrones and -azomethine imines (Scheme 5) both (*Z*)- and (*E*)-dipoles are capable of forming annelated products. Bridged products, *e.g. (128)* and *(129)*, cannot arise by way of the strongly strained orientation I but only from (*Z*)-dipoles *via* the strain-free transition state L. However, in additions of Type IV to nonpolarized double bonds, the orientation L is disfavored compared with J and K, as is manifested by the predominant formation of annelated products. This kinetically controlled regioselectivity, which is illustrated by the reaction sequence *(131)*→*(132)*→*(133)*, may be due to the fact that bond formation between the nearer ends of the dipole and dipolarophile is entropically favored.

This may also apply for the regioselectivity of the addition *(159)*→*(160)*; in this case the dipolarophile is attached to the terminal nitrogen of the dipole.



Scheme 6. Transition states of additions V (see Scheme 3).

It is more difficult to predict the direction of the additions of type V. In these compounds the alkenyl chain is attached to the central nitrogen of the dipole (Scheme 6). Thus, the length of the chain as well as alkyl substituents on the alkene component may influence the preference between the orientations M and N. For example, transition state M predominates in intramolecular additions of *N*-(4-alkenyl)-nitrones and -azomethine imines.

3.3.3. Stereochemistry

For the kinetically controlled formation of *cis*- and/or *trans*-annelated adducts from *C*-alkenyl-nitrones and -azomethine imines the transition states G, H, J, and K may be considered (Scheme 5); however, a model of the (*Z*)-*endo*-transition state K proves to be strained. This strain clearly becomes more pronounced when the two reactants are separated from each other either by only three atoms or by a chain of four atoms two of which belong to one double bond. If (for reasons given below) we assume predominant addition of (*Z*)-dipoles, then this explains the selective formation of *cis*-annelated adducts in the reactions of *(121a)*, *(126)*, and *(152)* (also in the reaction of citral with *N*-methylhydroxylamine) by way of the strain-free (*Z*)-*exo*-transition state J. On the other hand, the observed formation of *trans*-fused addition products from the nitrones *(122b)* is consistent with the (*E*)-*exo*-transition state G, provided we assume that cycloaddition is now slower than the (*Z*/*E*)-isomerization. However, this does not preclude the participation of a (*Z*)-*endo*-transition state K, where angle deformation is diminished by the longer bridge.

In the intramolecular addition of *N*-alkenyl-nitrones and -azomethine imines we meet unequivocal steric relationships (Scheme 6). These reactions (Type V) can occur only through the *endo*-transition states M and/or N, since the alternative *exo*-orientations O require an inadmissible deformation of the bond angles. As a result, the stereochemistry of the additions of type V depend only on the configuration of the dipolarophile and the dipole; that the latter reacts preferably in the (*Z*)-form is probable in view of the observed conversions *(135)*→*(136)* and *(155b)*, R = Ph, → *(156b)*, R = Ph.

The stereochemistry of the additions of Type VI has not yet been investigated, although, as previously mentioned, the reaction *(159)→(161)* is known to take place stereoselectively.

4. Final Considerations

Intramolecular concerted cycloaddition reactions of 1,3-dienes, nitrones and azomethine imines have provided the organic chemist with the opportunity of synthesizing in one operation complex polycyclic molecules both in a regio- and stereoselective manner. The large number of the classical bimolecular variants indicates that the preparative wealth conferred by intramolecularity on these types of reaction is by no means exhausted. As a further possibility we may mention as an example the formation of more than two bonds by a controlled combination of successive pericyclic reactions. In the future it is to be hoped that new efficient routes to appropriately functionalized precursors, together with a better understanding of the theoretical implications will significantly increase the scope of these reactions.

Some of our own work mentioned in this article was carried out at Sandoz AG, Basle, and some at the University of Geneva. The latter investigations were kindly supported by the Fonds National Suisse de la Recherche Scientifique, Sandoz AG, Basle, and Givaudan SA, Vernier. I am indebted to Frau Kathrin Keller and to Roland Achini, Bartholomeus Bakker, Charles Fehr, Wolfgang Fröstl, Emil Pfenninger, Martin Petrzilka, Samuel Siles, Roger L. Snowden and Jochen Warneke for their valuable collaboration, and to my colleagues Prof. Charles W. Jefford and Dr. Roger L. Snowden for helpful suggestions during the writing of this manuscript.

Received: 30th August, 1976 [A 143 IE]
German version: Angew. Chem. *89*, 10 (1977)
Translated by Express Translation Service, London

[1] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781 (1969).
[2] Review: a) *J. Sauer*, Angew. Chem. *78*, 233 (1966); Angew. Chem. Int. Ed. Engl. *5*, 211 (1966); b) Angew. Chem. *79*, 76 (1967); Angew. Chem. Int. Ed. Engl. *6*, 16 (1967); c) *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967; d) *S. Seltzer*, Adv. Alicyclic Chem. *2*, 1 (1968); e) *H. Wollweber*: Diels-Alder-Reaktion. Thieme, Stuttgart 1972.
[3] a) *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. Int. Ed. Engl. *2*, 565 (1963); b) Angew. Chem. *75*, 742 (1963); Angew. Chem. Int. Ed. Engl. *2*, 633 (1963); c) J. Org. Chem. *41*, 403 (1976).
[4] Review: *K. N. Houk*, Acc. Chem. Res. *8*, 361 (1975).
[5] *O. Diels* and *K. Alder*, Justus Liebigs Ann. Chem. *460*, 98 (1928).
[6] *K. Alder* and *M. Schumacher*, Fortschr. Chem. Org. Naturst. *10*, 66 (1953).
[7] a) *E. T. McBee*, *J. O. Stoffer*, and *H. P. Braendlin*, J. Am. Chem. Soc. *84*, 4540 (1962); b) *D. J. Cram* and *G. R. Knox*, *ibid. 83*, 2204 (1961); *D. J. Cram*, *C. S. Montgomery*, and *G. R. Knox*, *ibid. 88*, 515 (1966).
[8] Review: *R. G. Carlson*, Annu. Rep. Med. Chem. *9*, 270 (1974).
[9] *H. O. House* and *T. Cronin*, J. Org. Chem. *30*, 1061 (1965).
[10] *K. Alder* and *W. Vogt*, Justus Liebigs Ann. Chem. *564*, 120 (1949).
[11] *H. W. Gschwend* and *H. P. Meier*, Angew. Chem. *84*, 291 (1972); Angew. Chem. Int. Ed. Engl. *11*, 294 (1972); H. W. Gschwend, A. O. Lee, and *H. P. Meier*, J. Org. Chem. *38*, 2169 (1973); *H. W. Gschwend*, Helv. Chim. Acta *56*, 1763 (1973).
[12] *W. Oppolzer* and *W. Fröstl*, Helv. Chim. Acta *58*, 590 (1975).
[13] a) *W. Oppolzer* and *W. Fröstl*, Helv. Chim. Acta *58*, 587 (1975); b) unpublished work.
[14] a) *W. Oppolzer* and *W. Fröstl*, Helv. Chim. Acta *58*, 593 (1975); b) unpublished work; c) *W. Oppolzer*, *C. Fehr*, and *J. Warneke*, lecture (*W. O.*) at the 4th. Int. Symp. "Synthesis in Organic Chemistry", Cambridge, July 1975; Helv. Chim. Acta, in press.
[15] *J. J. S. Bajorek* and *J. K. Sutherland*, J. Chem. Soc. Perkin 1, *1975*, 1559.
[16] *W. Oppolzer* and *R. L. Snowden*, Tetrahedron Lett. *1976*, 4187.
[17] *R. F. Borch*, *A. J. Evans*, and *J. J. Wade*, J. Am. Chem. Soc. *97*, 6282 (1975).
[18] *J. Auerbach* and *S. M. Weinreb*, J. Org. Chem. *40*, 3311 (1975).
[19] *E. Wenkert* and *K. Naemura*, Synth. Commun. *3*, 45 (1973).
[20] *E. J. Corey* and *M. Petrzilka*, Tetrahedron Lett. *1975*, 2537.
[21] *E. J. Corey* and *R. L. Danheiser*, Tetrahedron Lett. *1973*, 4477.
[22] *G. Brieger*, J. Am. Chem. Soc. *85*, 3783 (1963).
[23] *E. J. Corey* and *R. S. Glass*, J. Am. Chem. Soc. *89*, 2600 (1967).
[24] *L. A. Paquette* and *M. J. Wyvratt*, J. Am. Chem. Soc. *96*, 4671 (1974); *D. McNeil*, *B. R. Vogt*, *J. J. Sudol*, *S. Theodoropulos*, and *E. Hedaya*, *ibid. 96*, 4673 (1974).
[25] *A. Krantz* and *C. Y. Lin*, J. Am. Chem. Soc. *95*, 5662 (1973).
[26] *F. Näf* and *G. Ohloff*, Helv. Chim. Acta *57*, 1868 (1974).
[27] *G. Büchi*, *R. E. Erickson*, and *N. Wakabayashi*, J. Am. Chem. Soc. *83*, 927 (1961); *G. Büchi*, *W. D. MacLeod*, *Jr.*, and *J. Padilla O*, *ibid. 86*, 4438 (1964); *S. Danishefsky* and *D. Dumas*, Chem. Commun. *1968*, 1287; *R. N. Mirrington* and *K. J. Schmalzl*, J. Org. Chem. *37*, 2871 (1972).
[28] a) *G. Frater*, Helv. Chim. Acta *57*, 172 (1974); b) *H. Greuter*, *G. Frater*, and *H. Schmid*, *ibid. 55*, 526 (1972); c) *G. Frater*, private communication.
[29] *D. J. Bichan* and *P. Yates*, J. Am. Chem. Soc. *94*, 4773 (1972); Can. J. Chem. *53*, 2054 (1975).
[30] *P. G. Sammes* and *R. A. Watt*, J. Chem. Soc. Chem. Commun. *1975*, 502.
[31] *L. H. Klemm* and *W. Gopinath*, Tetrahedron Lett. *1963*, 1243; *L. H. Klemm*, *D. R. Olson*, and *D. V. White*, J. Org. Chem. *36*, 3740 (1971); *L. H. Klemm*, *T. M. McGuire*, and *K. W. Gopinath*, *ibid. 41*, 2571 (1976).
[32] a) *W. Oppolzer*, *R. Achini*, *E. Pfenninger*, and *H. P. Weber*, Helv. Chim. Acta *59*, 1186 (1976); Belg. Pat. 805504 (1974); b) *M. T. Cox*, J. Chem. Soc. Chem. Commun. *1975*, 903.
[33] a) *W. Oppolzer*, J. Am. Chem. Soc. *93*, 3833 (1971); b) *93*, 3834 (1971); c) Angew. Chem. *84*, 1108 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1031 (1972); d) Tetrahedron Lett. *1974*, 1001; cf. also Angew. Chem. *84*, 712 (1972); Angew. Chem. Int. Ed. Engl. *11*, 728 (1972).
[34] *Y. Butsugan*, *S. Yoshida*, *M. Muto*, and *T. Bito*, Tetrahedron Lett. *1971*, 1129; *K. H. Pfoertner* and *W. E. Oberhänsli*, Helv. Chim. Acta *58*, 840 (1975).
[35] *W. Oppolzer* and *K. Keller*, J. Am. Chem. Soc. *93*, 3836 (1971).
[36] a) *T. Kametani*, *H. Nemoto*, *H. Ishikawa*, *K. Shiroyama*, and *K. Fukumoto*, J. Am. Chem. Soc. *98*, 3378 (1976); b) *W. Oppolzer* and *M. Petrzilka*, unpublished work.
[37] a) *O. L. Chapman*, *M. R. Engel*, *J. P. Springer*, and *J. C. Clardy*, J. Am. Chem. Soc. *93*, 6696 (1971); b) *G. C. Brophy*, *J. Mohandas*, *M. Slaytor*, *S. Sternhell*, *T. R. Watson*, and *L. A. Wilson*, Tetrahedron Lett. *1969*, 5159.
[38] a) *R. Thomas*, Biochem. J. *78*, 807 (1961); b) *A. C. Bazan*, *J. M. Edwards*, and *U. Weiss*, Tetrahedron Lett., in press.
[39] *B. S. Joshi*, *N. Viswanathan*, *D. H. Gawad*, *V. Balakrishnan*, and *W. v. Philipsborn*, Helv. Chim. Acta *58*, 2295 (1975).
[40] *A. I. Scott*, Acc. Chem. Res. *3*, 151 (1970); *A. R. Battersby*, *ibid. 5*, 148 (1972).
[41] *J. P. Kutney*, *J. F. Beck*, *N. J. Eggers*, *H. W. Hanssen*, *R. S. Sood*, and *N. D. Westcott*, J. Am. Chem. Soc. *93*, 7322 (1971); *S. Escher*, Dissertation Nr. 4887, ETH Zürich 1972; *J. P. Kutney*, Heterocycles *4*, 169, 429 (1976).
[42] *A. I. Scott*, J. Am. Chem. Soc. *94*, 8262 (1972); *A. I. Scott* and *C. C. Wei*, *ibid. 94*, 8263, 8264, 8266 (1972); *R. T. Brown*, *G. F. Smith*, *J. Poisson*, and *N. Kunesch*, *ibid. 95*, 5778 (1973).
[43] *F. E. Ziegler* and *E. B. Spitzner*, J. Am. Chem. Soc. *95*, 7146 (1973).
[44] *C. Kan-Fan*, *G. Massiot*, *A. Ahond*, *B. C. Das*, *H.-P. Husson*, *P. Potier*, *A. I. Scott*, and *C. C. Wei*, J. Chem. Soc. Chem. Commun. *1974*, 164.
[45] *A. Padwa*, Angew. Chem. *88*, 131 (1976); Angew. Chem. Int. Ed. Engl. *15*, 123 (1976).
[46] Reviews: a) *J. Hamer* and *A. Macaluso*, Chem. Rev. *64*, 473 (1964); b) *G. R. Delpierre* and *M. Lamchen*, Quart. Rev. Chem. Soc. *19*, 329 (1965); c) *D. S. C. Black*, *R. F. Crozier*, and *V. C. Davis*, Synthesis *1975*, 205.
[47] *E. Beckmann*, Ber. Dtsch. Chem. Ges. *23*, 1680, 3331 (1890); *27*, 1957 (1894).
[48] a) *C. W. Brown*, *K. Marsden*, *M. A. T. Rogers*, *C. M. B. Tylor*, and *R. Wright*, Proc. Chem. Soc. (London) *1960*, 254; b) *R. Grashey*, *R. Huisgen*, and *H. Leitermann*, Tetrahedron Lett. *12*, 9 (1960); c) *N. A. LeBel* and *J. J. Whang*, J. Am. Chem. Soc. *81*, 6334 (1959).
[49] *N. A. LeBel*, *M. E. Post*, and *J. J. Whang*, J. Am. Chem. Soc. *86*, 3759 (1964); *N. A. LeBel*, Trans. N. Y. Acad. Sci. *27*, 858 (1965).
[50] *N. A. LeBel* and *E. G. Banucci*, J. Org. Chem. *36*, 2440 (1971).
[51] a) *W. Oppolzer* and *K. Keller*, Tetrahedron Lett. *1970*, 1117; b) *W. Oppolzer* and *H. P. Weber*, *ibid. 1970*, 1121; c) *W. Oppolzer* and *K. Keller*, *ibid. 1970*, 4313; d) *J. E. Baldwin*, *D. H. R. Barton*, *N. J. A. Gutteridge*, and *R. J. Martin*, J. Chem. Soc. *C 1971*, 2184.
[52] *E. Gössinger*, *R. Imhof*, and *H. Wehrli*, Helv. Chim. Acta *58*, 96 (1975).

[53] W. C. Lumma, Jr., J. Am. Chem. Soc. 91, 2820 (1969).
[54] a) J. B. Bapat, D. S. C. Black, R. F. C. Brown, and C. Ichlov, Aust. J. Chem. 25, 2445 (1972); b) J. J. Tufariello and E. J. Trybulski, J. Chem. Soc. Chem. Commun. 1973, 720.
[55] W. Oppolzer, M. Petrzilka, B. Bakker, and S. Siles, unpublished work.
[56] a) W. Oppolzer and M. Petrzilka, J. Am. Chem. Soc. 98, 6722 (1976); b) unpublished work; c) W. L. Scott and D. A. Evans, J. Am. Chem. Soc. 94, 4779 (1972).
[57] R. Huisgen, R. Fleischmann, and A. Eckell, Tetrahedron Lett. 1960, No. 12, p. 1; R. Huisgen and A. Eckell, ibid. 1960, No. 12, p. 5.
[58] W. Oppolzer and H. P. Weber, Tetrahedron Lett. 1972, 1711.
[59] W. Oppolzer, Tetrahedron Lett. 1970, 2199.
[60] W. Oppolzer, Tetrahedron Lett. 1970, 3091.
[61] R. Grashey, R. Huisgen, K. K. Sun, and R. M. Moriarty, J. Org. Chem. 30, 74 (1965).
[62] W. Oppolzer, Tetrahedron Lett. 1972, 1707.
[63] J. Bjørgo, D. R. Boyd, and D. C. Neill, J. Chem. Soc. Chem. Commun. 1974, 478.

Structural Rules for Globular Proteins

By Georg E. Schulz[*]

Is it possible to reach a detailed understanding of the complex three-dimensional structures of native polypeptide chains? In view of the wealth of common physicochemical and phylogenetic features discovered among proteins this question has become reasonable. The current state of discussion is presented in this report.

1. Introduction

The structure of a globular protein was first elucidated 16 years ago[1]. Meanwhile about 40 proteins have been analyzed at atomic resolution, and the polypeptide chain fold is known in about ten more cases. Thus the pioneering era has undoubtedly come to an end. Protein structure models have become everyday tools of the biochemist; with their aid he can design and interpret his experiments much more soundly than ever before.

The wealth of structural data available not only favors biochemical aspects, but also challenges us to understand the architecture of the observed structures and thus to trace biology back to its physical roots on a much more fundamental scale than was previously possible. Given an intimate knowledge of their architecture, a substantial increase in the number of analyzable proteins can be predicted because those proteins also become accessible which do not crystallize. Furthermore, the study of historical relationships, and especially very early stages of evolution, can be put on a firmer basis. Therefore, efforts invested in this field may be expected to yield considerable rewards.

2. Energy Balance

Globular proteins consist of linear polypeptide chains (Fig. 1), which are synthesized from 20 different amino acids[4]. During or after synthesis these chains fold spontaneously to an exact three-dimensional structure. The spontaneity of folding is regarded as a generally valid principle, because it could be demonstrated in renaturing experiments with several proteins[5–7]. Thus all information pertaining to three-dimensional structure is already implicit in the chemical structure of the chain, *i. e.* in the amino acid sequence. Folding is merely a transition to an energetically more favorable state of the chain.

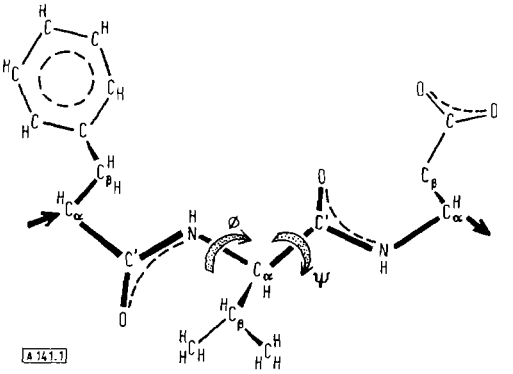


Fig. 1. Part of a peptide chain. Because of resonance the peptide bonds are planar [2]. Therefore the dihedral angles ϕ and ψ at the C_α atoms determine the chain fold. Steric hindrance permits adoption of only 15% of all possible ϕ, ψ orientations [3]. The relatively low mobility of the side chains should be noted.

The principal types of interactions involved in folding are: van der Waals forces between nonpolar groups, dipole forces between polar groups, in particular hydrogen bonds, and "hydrophobic forces" (a synonym for water entropy) which describe the tendency of the apolar side chains to form a separate hydrophobic phase—*i. e.* a kind of oil droplet[8]. In the free energy balance

$$\Delta G = \Delta H_{bond} - T \cdot \Delta S_{water} - T \cdot \Delta S_{chain} \quad (1)$$

the binding enthalpies and the water entropy together oppose the chain entropy term. Only when their contribution is sufficient can the chain entropy be overcome and the chain "immobilized", *i. e.* constrained to a definite structure. For chains containing about 100 residues a rough estimate yields values of several hundred kcal/mol for the opposing contributions. However, the resulting ΔG is of the order 10 kcal/mol[9]. Thus we are dealing with a delicately balanced system, which renders detailed understanding more difficult.

Hydrophobic nuclei are found in all structurally known proteins, confirming the importance of the water entropy term in eq. (1). The packing density of these nuclei is as high as in

[*] Dr. G. E. Schulz
Max-Planck-Institut für medizinische Forschung
Jahnstrasse 29, D-6900 Heidelberg (Germany)

the most densely packed crystals stabilized by van der Waals forces[10, 11], *i.e.* the number of van der Waals contacts and thus the corresponding bond enthalpy term are maximized. This is also reflected in the comparatively low compressibility of proteins[12, 13] ($\kappa_{oil}/\kappa_{protein} \approx 20$). However, the interior of proteins is not entirely apolar but contains about half of all the polar groups—in particular the C=O and N—H groups of the peptide bonds[14]. Being shielded from water 90% of these dipoles form hydrogen bonds with a relatively high energy contribution[15]. Thus although proteins are stabilized by the oil drop effect they bear little resemblance to a disordered and loosely packed oil droplet, rather they are similar to a densely packed crystal.

Equation (1) rationalizes the natural selection of α-amino acids and not β-amino acids, although the latter are produced in comparable quantities by experiments designed to simulate prebiotic synthesis[16]. A peptide chain made up of β-amino acids would exhibit almost free rotation about the $C_\alpha—C_\beta$ bond and thus have a much higher chain entropy content. Hence much greater bond enthalpies and/or water entropies would be necessary for stabilizing the three-dimensional structure. In contrast, a chain composed of α-amino acids is far less flexible (Fig. 1) can be immobilized much more easily. For analogous reasons the side chains used are also comparatively rigid (Fig. 1).

3. Folding Pathway

Folding of a chain of 100 α-amino acid residues requires the adjustment of about 300 parameters (Fig. 1). Even if each parameter is restricted to only two values, some 2^{300} conformations become possible. Random adoption of each conformation until the chain stumbles upon an energetically stable one would require a time exceeding the age of the earth, even if only 10^{-13} s were assumed for each trial. Hence the parameter values must be run through in a directed manner, *i.e.* there must be a folding pathway.

For pancreatic trypsin inhibitor the existence of such a pathway has been proved experimentally. This was done by tracing the sequence of S—S bridge formation on going from a random coil to the native state[17]. Of the $\binom{6}{2} = 15$ possibilities, initially one of the native bridges is formed with maximum yield (Fig. 2). The cysteines of the accompanying non-native bridges are proximate in the native three-dimensional structure (Fig. 2). Accordingly, the chain regions around residues 5, 30, and 53 approach each other in the first stage of folding. Various false linkages occur also in the ensuing stages (Fig. 2). The conformational mixture is therefore broad; folding is not absolutely "single tracked".

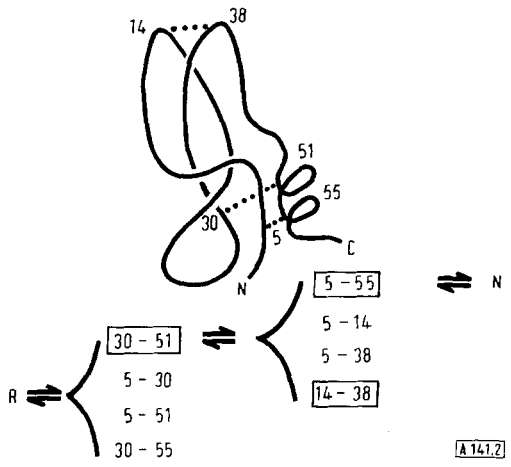


Fig. 2. Sequence of S—S bridge formation on renaturing of pancreatic trypsin inhibitor, according to *Creighton* [17]. The cysteine side chains are linked by disulfide exchange reagents. It is generally assumed that bridge formation is not necessary for chain folding; it only indicates the vicinity of the cysteines. The native bridges are shown in boxes. Premature formation of the native bridge 14–38 obstructs further folding. *Creighton*'s experiment shows unequivocally that a specific folding pathway is followed.—The chain fold is sketched according to *Huber et al.* [18]. R = random coil, N = native.

Renaturation experiments were performed with lysozyme at 84 °C[19]. Although this temperature exceeds by far the denaturation temperature of lysozyme (*ca.* 50 °C) a transient renaturation is observed. Hence, even at such high temperature folding is faster than thermal unfolding. However, fast folding is feasible only if a defined folding pathway exists and little time is lost with trial-and-error fitting. Since such a pathway greatly reduces the conformational space to be considered, there is hope that it can by elucidated and reproduced with theoretical models.

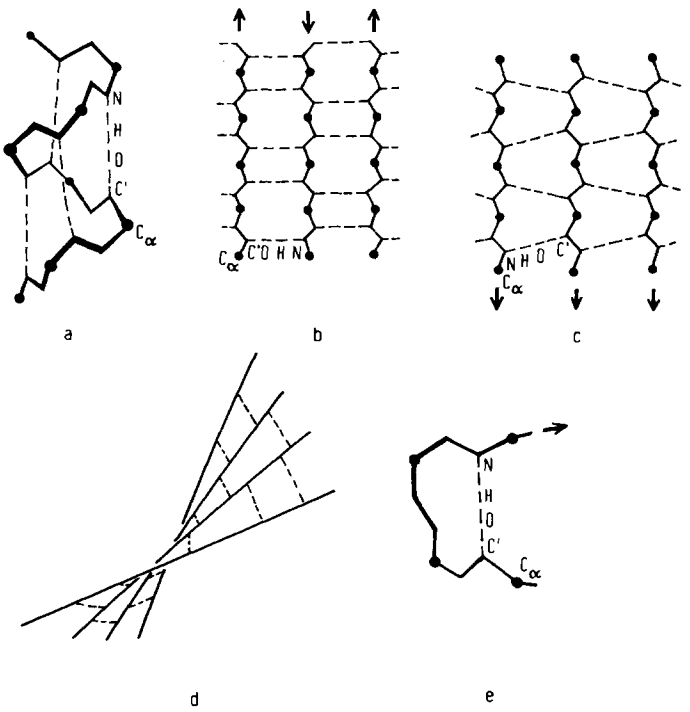
As the native three-dimensional structure is reached *via* a definite pathway it need not correspond to the absolute energy minimum in the entire conformational space. Extremely uneven energy surfaces with numerous local minima are to be expected for complicated structures[7]. Thus a defined pathway probably leads to a local minimum. However, it is fundamentally impossible to distinguish between a local and the global minimum because scrutinization of the entire conformational space would be required. Neither the chain itself nor any kind of computer simulation can do that. Moreover, all kinetically inaccessible minima are irrelevant even if they include the absolute minimum. Any discussion of this question[6, 7, 19] therefore resembles the arguments of the scholastics.

4. Hierarchy

Several degrees of organization are perceptible in the proteins of known structure (Table 1). The amino acid sequence represents the basis. As mentioned above, it implicitly contains the entire structural information. The next higher stage is seen in the secondary structures depicted in Figure 3. These are regular chain arrangements permitting optimal hydrogen bonding. Secondary structures are very common, extending over 75% of the chain in some proteins. This is probably related to the energetic necessity of compensating internal polar groups by forming hydrogen bonds.

Table 1. Levels of organization in proteins. The order is vertical and partially hierarchic, *i.e.* the structural elements of a particular level, *e.g.* α-helices (a secondary structure) are essentially determined only by the elements contained therein from the next lower level (*e.g.* amino acid residues).

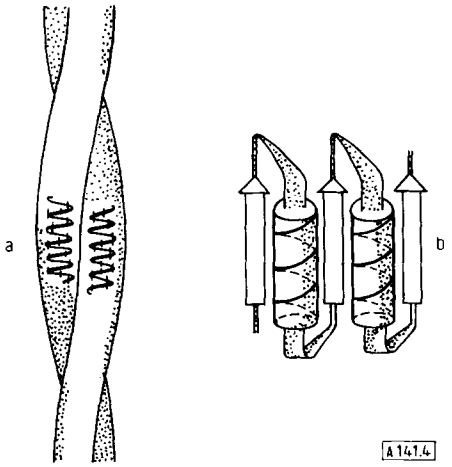
Aggregates
↑
Globular proteins
↑
Domains
↑
Secondary structure aggregates
↑
Secondary structure
↑
Sequence of amino acid residues



A 141.3

Fig. 3. Secondary structures in polypeptide chains. a) α-helix, b) antiparallel β-pleated sheet, c) parallel β-pleated sheet, d) twist found in all pleated sheets, e) β-bend. In all secondary structures hydrogen bonds are formed between the C=O and N—H groups of the peptide bonds.

In some cases, secondary structures form regular aggregates, so-called "supersecondary structures". One undisputed example is the double α-helix[20] in which the side chains of two α-helices are meshed together and the helices are wound around each other with a repeat distance of about 180 Å (Fig. 4).

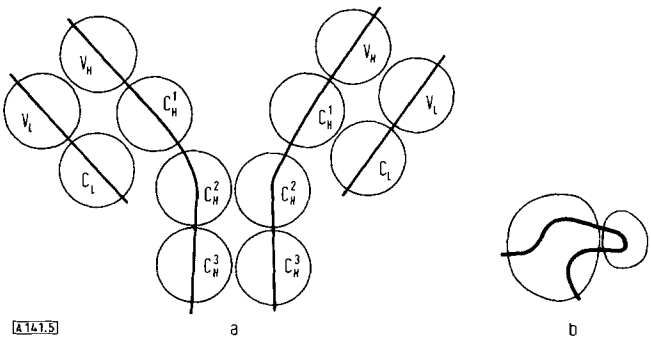


A 141.4

Fig. 4. Secondary structure aggregates or "supersecondary structures". a) Double α-helix according to *Crick* [20], observed in paramyosin [21]; myosin [22], α-keratin [23], and tropomyosin [24]. Similar structures seem to occur in hemerythrin [25] and bacteriorhodopsin [26]. b) Pleated sheet/helix combination, consisting of three strands of pleated sheet and two α-helices, found in lactate dehydrogenase [27], malate dehydrogenase [28], alcohol dehydrogenase [29], and glyceraldehyde 3-phosphate dehydrogenase [30], adenylate kinase [31], flavodoxin [32, 33], subtilisin [34], phosphoglycerate kinase [35], and phosphorylase [36].

Another supersecondary structure is the pleated sheet/helix combination found in some dehydrogenases[27] and other proteins (Fig. 4). Apart from these clearly defined supersecondary structures there are several structural preferences to be regarded as less well-defined manifestations of the same principle. They are described below.

The next higher degree of complexity is encountered in the domain. Most of the proteins with more than about 150 amino acid residues can be structurally subdivided into two or more spatially separated regions or domains. This is seen most clearly in the immunoglobulins whose light and heavy chains, respectively, form two and four separate domains (Fig. 5). The domains appear to contain those regions of the chain which fold independently to their three-dimensional structure.



A 141.5

Fig. 5. Domain structure of globular proteins. a) The light (L) and heavy (H) polypeptide chains of immunoglobulins fold into two and four domains [37], *i.e.* spatially separated structural regions. b) Adenylate kinase forms one large and one small domain which are not linked in the usual manner by one, but by two strands. Consequently, the large domain shows a smaller neighborhood correlation than the small one.

Globular proteins with one or more domains (Table 1) are not always the ultimate stage of self-assembly. In many cases protein surfaces are constructed in such a way that globules combine into larger aggregates, *e.g.* enzyme complexes, ribosomes, virus coats, muscle fibers. If only one or two kinds of components join together the aggregates are usually symmetrical (*e.g.* subunits of glutathione reductase[38] or lactate dehydrogenase[39], regulatory and catalytic subunits of aspartate transcarbamylase[40], pentone and hexone subunits of the adenovirus coat[41], myosin forming a myosin filament[22]). Symmetry arises because surface contacts are optimized and everywhere the same.

Understanding of chain folding would be greatly facilitated if this vertical order were strictly hierarchic, *i.e.* if the structural elements of a given level (*e.g.* α-helix) were influenced only by the elements of the immediately preceding level contained therein (*e.g.* amino acid residues) and not by other parts of the protein or other structural levels. The folding could then be analyzed for each step separately, and the difficult overall problem resolved into several much easier problems. Fairly strict hierarchy is found between globular proteins and aggregates (Table 1) because in most cases the globular monomer is rather stable and hardly altered during association. If the monomer structure is known the structure of the aggregate can be derived from surface characteristics of the monomer. However, this does not apply for some ribosomal proteins with almost completely extended chains[42], the monomer being too flexible to assume a defined structure on its own. Its structure is determined only on association with other ribosomal components.—Hierarchy is also found between amino acid sequence and α-helices (Table 1) because the formation of α-helices is probably largely independent of the three-dimensional structure eventually adopted. The same applies to the association of domains to globular

proteins. Accordingly, while the vertical order of Table 1 is not strictly hierarchic it is nevertheless sufficiently hierarchic to provide an acceptable working hypothesis.

5. Separation of the Secondary Structure

Once the secondary structures postulated by *Pauling* and *Corey*[43,44] had been detected in several globular proteins, a test for hierarchy between secondary structure and amino acid sequence (Table 1) suggested itself. Assuming strict hierarchy, an α-helix, for example, should be determined exclusively by its constituent amino acids and by no other part of the chain; and the correlation function between helix formation and amino acid sequence should be deducible from experimental data. Knowing the correlation function, the amino acid sequences of structurally uncharacterized proteins could then be examined and helical regions predicted.

This approach has been pursued for some time by several research teams, who predicted α-helices, β-pleated sheet strands, and β-bends (Table 2). The purely statistical and readily applicable methods stem from early optimistic days. Meanwhile they have been overtaken by more elaborate systems. Furthermore, attempts have been made to improve the correlation by including other physical data. On the whole, readily applicable methods are far more popular than those which in effect can be used only by the authors themselves. However, their information content suffers as a result of their simplifying formulation.

Table 2. Classification of prediction methods for secondary structures.

	Purely statistical evaluation of structural data	Incorporation of further data: energy balance, structures of synthetic polymers, steric considerations
Applicable without computer program and data bank	References [44–47]	References [48–50]
Applicable only with computer program and data bank	References [51–54]	References [55]

For a long time predictions attracted little interest because they either determined known secondary structures *a posteriori* or, when dealing with proteins of unknown structure, were rather out on a limb. This situation changed with the test case of adenylate kinase where the object of study was a freshly determined but still generally unknown structure[56,57]. The results depicted in Figure 6 clearly demonstrate the success of an approach based on strict hierarchy (Table 3). However, a second test with T4 phage lysozyme[58] having less pronounced secondary structure revealed only slight correlations (Table 3). This modified the overall impression but did not efface it.

Table 3. Correlation coefficients between predicted and experimentally observed secondary structure [56, 58]. Because of the high helix content (54%) of adenylate kinase a relatively good helix prediction leaves only small regions for other secondary structures. This is one reason for their correlation coefficients being so high.

	α-Helix	β-Pleated sheet	β-Bend
Adenylate kinase	+0.44	+0.51	+0.49
T4 phage lysozyme	+0.28	+0.05	+0.13

In both tests α-helices were found much more exactly than β-pleated sheets and β-bends (Table 3). Since the data bases for all three types of secondary structures are of comparable size, this shows that the assumption of hierarchy (Table 1) is best fulfilled for α-helices. Thus, helix formation is least influenced by distant parts of the chain. Therefore helices are most likely to fold on themselves; they are candidates for nucleation sites, *i.e.* regions of initial chain folding. The better they can be predicted, the more likely candidates they are.

Conspicuously, in both tests the α-helices were detected better in the N-terminal than in the C-terminal region of

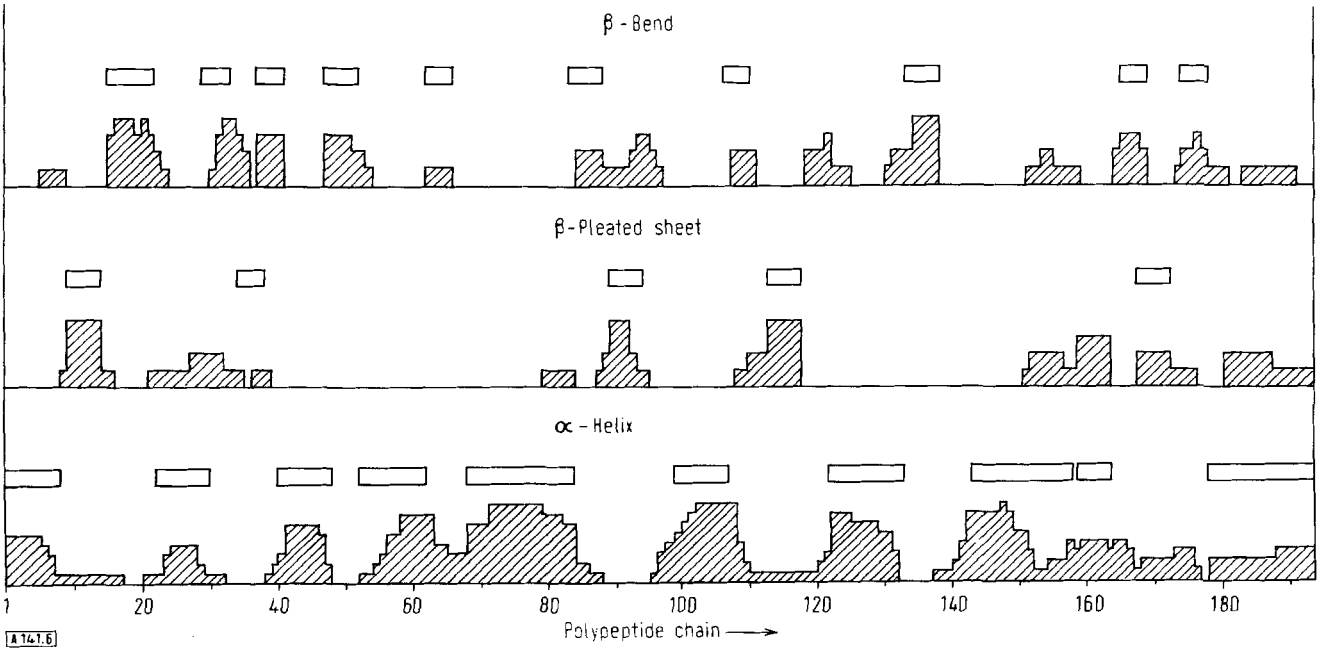


Fig. 6. Additive summary of all secondary structure predictions (hatched) for adenylate kinase [56]. Each method was given the same weight. The experimentally observed secondary structure (boxes) is included for comparison.

the chain, indicating that folding begins in the N-terminal region. Since on ribosomes the chain is synthesized from the N- to the C-terminal end folding may already start during chain production. Therefore, renaturation experiments using complete polypeptide chains may not simulate conditions *in vivo* and it is hardly surprising that some do not renature under these circumstances. In adenylate kinase three helices (residues 41—84) in the N-terminal half of the chain forming a small domain were fairly accurately recognized (Fig. 6). This indicates that folding may start by forming this domain.

The strands of β-pleated sheets may be widely separated along the polypeptide chain. They come together only when the connecting chain segment assumes particular conformations. With such a dependence upon other parts of the chain strict hierarchy cannot be expected. Accordingly, the accuracy of corresponding predictions is low (Table 3).

β-Bends are usually located on protein surfaces[59]. Energetically they are not much favored for they contain just a single hydrogen bond, which in many cases has to compete with the surrounding water; therefore they are best regarded as passive kink sites. Probably the kink position is defined not only by the local amino acid sequence but also by the folding of adjacent chain regions, giving rise to a rather ill-defined hierarchic order. β-Bends were predicted with considerable accuracy in adenylate kinase (Fig. 6) but with poor accuracy in T4 phage lysozyme (Table 3).

The varying success with these two proteins reflects the differences between their structures. While adenylate kinase contains a central pleated sheet surrounded by helices, and is therefore highly ordered, T4 phage lysozyme has less and hardly ordered secondary structure. Moreover, one has to expect that the folding mechanics differ greatly. Therefore it seems reasonable to classify proteins according to their secondary structure (Table 4), because the folding problem will probably have to be tackled differently in the individual classes.

Table 4. Structural classes of globular proteins.

Structural class	Examples
Proteins with few and hardly ordered secondary structures	Ribonuclease [60], lysozyme [61], ferredoxin [62]
Proteins with predominantly antiparallel pleated sheet	Immunoglobulins [63—66], superoxide dismutase [67], concanavalin A [68], prealbumin [69], chymotrypsin [70], bacteriochlorophyll protein [71]
Proteins with a central, generally parallel pleated sheet and surrounding helices	Malate dehydrogenase [28], lactate dehydrogenase [39], adenylate kinase [31], phosphoglycerate kinase [35], triose phosphate isomerase [72], carboxypeptidase [74], several glycolytic enzymes [73]
Proteins with predominant α-helix	Myoglobin [1], hemoglobin [75], hemerythrin [25], bacteriorhodopsin [26]

6. Structural Preferences

Secondary structures are very common in globular proteins. Among the helices, the α-helix having straight hydrogen bonds between the nth and $n+4$th residues predominates. To a slight extent one observes 3_{10}-helices with n and $n+3$, but never π-helices with n and $n+5$. The scarcity of the 3_{10}-helix can be explained by the energetic disadvantage of the bend in its hydrogen bonds. The π-helix does not exploit all the possible van der Waals contacts because it forms a large cavity around its axis. Therefore it is energetically disfavored in spite of its straight hydrogen bonds.

Among pleated sheets no preference for the parallel, antiparallel, or mixed type can yet be discerned (Fig. 3). It is, however, striking that no pleated sheet is flat; they all have a right-handed twist (Fig. 3). This is plausible because sheet twisting compensates for a twist of the individual chains around their axis (about 20° per residue) along a distance of about five residues; and the chain twist itself corresponds to an energetically favorable chain conformation, *i.e.* particularly low steric hindrance at the C_α atoms (Fig. 1). Energetically, the twisted sheet is about 0.5 kcal/mol per residue more favorable than the flat sheet[76]. This demonstrates again how important small energy contributions are in protein folding.

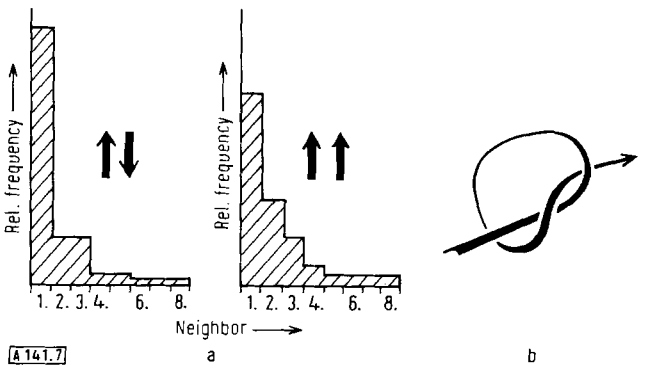


Fig. 7. Structural preferences in globular proteins. a) Observed neighborhood correlation in antiparallel and parallel β-pleated sheets, *i.e.* relative probability of a given strand of a pleated sheet to be connected in the chain direction to the 1st, 2nd, ... neighboring strand. b) Knots in a polypeptide chain; not yet observed.

The only undisputed secondary structure aggregate (Table 1) is the double α-helix. In addition, there are several less well-defined folding preferences of the chain. The individual strands in β-pleated sheets for instance display a very clear neighborhood correlation[67] which is even more pronounced for the antiparallel strands than for the parallel ones (Fig. 7). Regions occur close together in the three-dimensional structure which are not very distant from each other along the

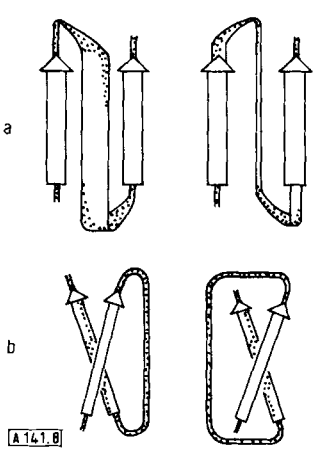


Fig. 8. Chirality of the β-strand-α-helix-β-strand group in parallel pleated sheets. The α-helix is shown as a smooth ribbon. The pleated sheet strands are not necessarily adjacent. The right-handed group has a much better neighborhood correlation than the left-handed one. a) frontal view, b) side view.

chain. In a crude approximation, the polypeptide chain behaves like a piece of string held vertically and allowed to fall onto a flat surface. The resulting coil is not random, it shows neighborhood correlation, it does not entangle, and it can easily be lifted up again. This picture is confirmed by the absence of "knots" in all the structures elucidated so far, the term knot not being used in a mathematical sense (mathematical knots exist only in closed threads), but in the everyday sense (Fig. 7).

Between strands of parallel pleated sheets the chain must go from the upper to the lower end of the sheet (Fig. 8). It thereby passes either over the front or over the back side of the sheet, forming a right- or a left-handed screw with the two pleated sheet strands (Fig. 8). In the known structures the right-handed screw predominates in a ratio of about 50:1[77]. Owing to the right-handed twist of pleated sheets, the right-hand screw permits a better neighborhood correlation than the left-handed screw (Fig. 8). Conversely, the observed predominance shows how important the neighborhood correlation is.

Other structural preferences are seen in the formation of domains, typical examples being immunoglobulin molecules (Fig. 5). Domains are usually joined together by a single strand of the peptide chain, and are therefore separated not only spatially but also along the chain[37]. This single chain linkage ensures a better neighborhood correlation within each domain than multiple chain linkages (Fig. 5). Since the neighborhood correlation within the domains is much greater than between domains, the domains are expected to fold separately. This is supported by the structure of chymotrypsin[70]. In the interior of the protein there are 13 water molecules between the two pleated sheet barrels, which can be regarded as domains (Fig. 9). The barrels are presumed to fold separately and capture the water molecules on association. The active center of chymotrypsin is located between the two domains. A similar location of the active center is observed in many other enzymes.

The limiting size of a domain is about 150 amino acid residues. As derived from the energy balance [eq. (1)] the formation of larger domains should be favored because in larger globules the surface/volume ratio is smaller, and the energy of the hydrophobic bonds (ΔS_{water}) and that of the internal hydrogen bonds can be increased. In spite of this fact long chains always fold to several smaller domains with high neighborhood correlation. Therefore, folding of several smaller domains seems to be much easier than folding of a single large and thus more complex domain.

As in the case of adenylate kinase there are often two linkages between smaller domains. With two linkages one domain has a higher neighborhood correlation than the other (Fig. 5). One has to expect that the domain with the higher correlation folds first and then serves as a support for construction of the remaining molecule. For adenylate kinase this assumption is corroborated by the great accuracy of secondary structure predictions in the domain with the higher neighborhood correlation (Fig. 6).

As described above, symmetric structures arise on aggregation of monomeric proteins when only few kinds of building units are utilized. This symmetry is also apparent in the aggregation of domains, particularly if they are structurally similar like those of the light and heavy chains of immunoglobulins[63-66], the domains of rhodanese[78], ferredoxin[62], dehydrogenases[79], and triose 3-phosphate isomerase[72] (Fig. 9). Not only domains, but also secondary structures appear

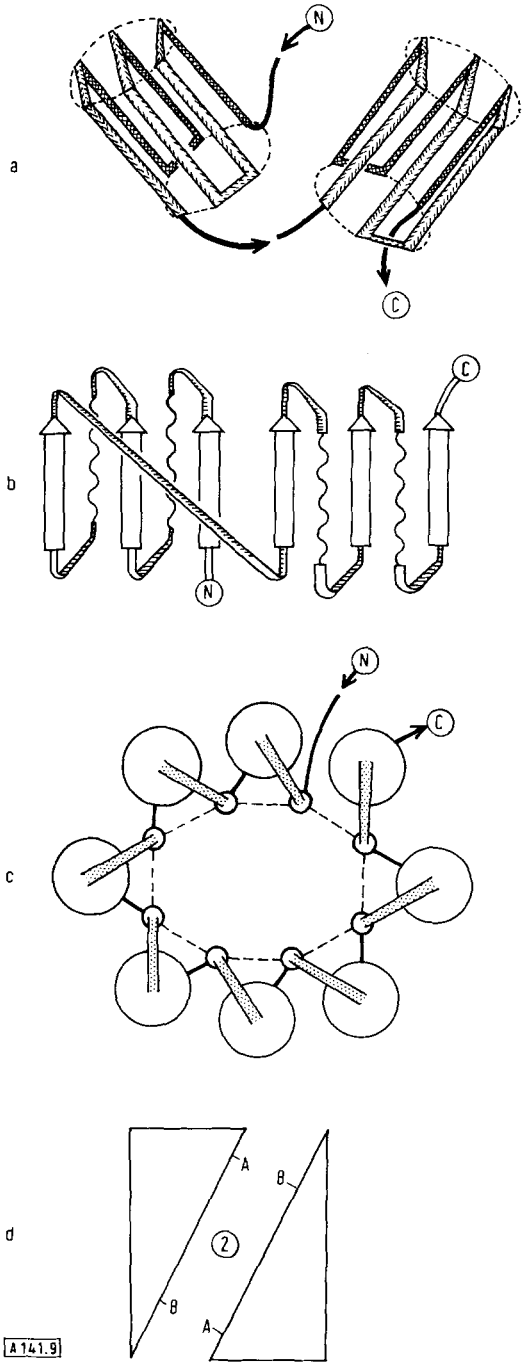


Fig. 9. Symmetry in chain folds (schematic representation). a) Chymotrypsin [70]. The pleated-sheet barrels correspond to one domain each; they are antiparallel and possess twofold internal symmetry. b) The double nucleotide-binding domain of lactate dehydrogenase and other proteins [39, 79, 93]. It contains a vertical twofold axis. c) The extremely symmetrical structure of triose phosphate isomerase [72], consisting of a parallel pleated-sheet barrel and eight surrounding α-helices. d) Optimization of contacts and symmetry: when the A-B contact is particularly favorable it is repeated, giving rise to twofold symmetry. In monomers, only twofold symmetry axes have so far been observed while the point groups 2, 3, 17 (protein of tobacco mosaic virus), 222, 32, 432 (apoferritin), 532 (spherical viruses) are found in aggregates.

to aggregate symmetrically, *e.g.* in parvalbumin[80, 81] and within the pleated sheet barrels of chymotrypsin (Fig. 9). The reason for symmetry lies in the optimization of contacts (Fig. 9). Obviously, this optimization is also important in very early stages of chain folding.

7. Structural Rules from Phylogenesis

The historical background of proteins is a great help in understanding their structures. In the course of biological evolution all these structures have continuously evolved either in parallel or by diverging from each other. Thus, nature has provided us with a wealth of completed experiments. We only need to interpret the results, *i.e.* extract information of general validity from common structural features.

The basic step in the evolution of proteins is the modification of a side chain. Others are insertions and deletions of amino acid residues which affect also the main chain and which can extend over long chain segments. Usually exchanges in the interior of proteins are conservative (apolar for apolar side chains, *etc.*), and the energy balance is hardly perturbed. Furthermore, any gaps that may arise (*e.g.* by omission of a methyl group on isoleucine→valine) are compensated by another exchange, *i.e.* the high packing density is retained. Apparently the packing density is of great importance for the energy balance.

The influence of amino acid exchanges on the folding process has been studied for the globin family[82]. It was found that all α-helices carry at their N-terminal end either a proline or a short polar side chain which can hydrogen-bond to the main chain (Asn, Asp, His, Ser, Thr). These hydrogen bonds and/or the proline, which fixes the dihedral angle ϕ (Fig. 1) to the α-helix value, are probably required for helix initiation because they limit the number of conformations at this site at an early stage of folding, *i.e.* form a miniature folding nucleus.

In the course of time the modifications accumulate; and when about 80% of the amino acids have been exchanged common features can be recognized only in special cases from the sequence. However, it was found, first on comparison of myoglobin[11] with hemoglobin chains[83] and later in cytochrome c[84] and the serine proteases[85] that the amino acids vary much faster than the chain fold. The course of the chain and the sites of prosthetic groups (*e.g.* hemes) are exceptionally well conserved. The observed chain fold conservation cannot be a consequence of keeping the delicate energy balance [eq. (1)] intact; because in meeting the energy requirements the amino acids utilized appear to be much more important than the chain fold. Therefore, chain fold conservation indicates that the folding mechanics and with it the folding pathway, impose stringent conditions on the protein.

Apart from continuous small evolutionary changes there are drastic discontinuous ones caused by gene fusion and gene duplication. A recent example of fusion is observed in the immunoglobulins where the genes of the variable chain regions are probably linked with those of the constant regions[86]. Gene separation and fusion must also have occurred in dehydrogenases because lactate dehydrogenase has the NAD-binding domain as N-terminal half, whereas an extremely similar domain is utilized in the C-terminal half of alcohol dehydrogenase[29]. Most gene duplications lead to separate chains and thus to proteins which develop separately[87]: globins, serine proteases, midbrain hormones, lysozyme, and α-lactalbumin, *etc.* However, some duplications double the chain length, *e.g.* in ferredoxin[62], rhodanese[78], chymotrypsin[88], parvalbumin[80, 81], troponin C[89], within the NAD-binding domains of dehydrogenases[79], in tropomyosin[90], *etc.* As described above, most such chains display internal symmetry. The folding mechanism is probably modified only insofar as now two nuclei fold similarly but separately and subsequently aggregate. The wealth of examples discovered show[87] these discontinuous modifications to play a considerable role in the production of new protein structures.

8. Phylogenesis on the Basis of Structures

The previous section demonstrated that the historical development of proteins permits deduction of structural rules. Conversely, structural analysis provides information about phylogenetic relationships. It becomes particularly important when proteins have diverged so much that there are no longer similarities between the amino acid sequences, but only between chain folds. Since chain folds are particularly well conserved, such resemblances indicate interrelationships in very early stages of evolution. Of special interest in this context is the evolution of metabolic pathways which are otherwise hardly accessible to study.

Structural similarity is not necessarily of phylogenetic origin, but may be an expression of a structural rule. For instance, nobody would think that α-keratin[23] is related to tropomyosin[24] merely because they both form a double α-helix structure (Fig. 4). This structural aggregate just happens to be energetically favored; therefore it is adopted independently by several proteins and the structural coincidence is not significant. A different situation is encountered in T4 phage lysozyme[91], hen egg white lysozyme[61], and α-lactalbumin[92], whose structures are complicated but nevertheless similar. Their chain folds are not unique in any particular way; for there are many other kinds of complicated protein structures. Consequently, the structural coincidence of these proteins is a significant event which can only be explained by assuming a phylogenetic relation. These examples show that the degree of significance is of decisive importance in structural resemblance and that this significance can only be established with a knowledge of structural rules.

This significance becomes extremely high when the amino acid sequences display common features. For example, 45 amino acids are common to hen egg white lysozyme and α-lactalbumin[92]. The probability of a random coincidence is $1:20^{45}$, giving rise to a significance of $20^{45}:1$. Admittedly, this value has to be reduced because 84 other amino acids are different, the sequences have been shifted relative to each other to achieve optimal fit, and the amino acids are not distributed randomly. Nevertheless the significance still remains so high that a phylogenetic relationship can be unequivocally concluded.

Significances based solely on three-dimensional structural features have been calculated for a group of proteins having central pleated sheets[93] which no longer display any similarity in the amino acid sequences (Fig. 9). The pleated sheet was defined as reference structure and the chain fold referred thereto. Viewed in such a way, an n-stranded pleated sheet can assume $M = 2^{n-2} \cdot n!$ different chain topologies. If two proteins have identical topologies the significance of this coincidence[93] is $M:1$ (Table 5). These values are reduced, however, by the observed predominance of the right-handed screw in connections between pleated sheet strands (Figs. 8 and 9)[77]. A further reduction arises from the neighborhood correlation in pleated sheets (Fig. 7) because in the case considered most of the

strands are proximate. If the symmetry in the pleated sheet is caused by gene duplication another reduction is necessary. On the other hand the significance is raised if not only the chain topology but also the location of active center and substrates is taken into account (Table 5). Moreover, it should be remembered that this comparison is restricted to a single structural class (Table 4). Extension of the comparison to all proteins enhances the significance. Some of these contributions are difficult to estimate. In conclusion, only within the dehydrogenases are the resulting significances large enough to indicate a phylogenetic relationship (Table 5); the other structural similarities can be of purely physical origin. In a similar way the β-pleated sheets of superoxide dismutase and immunoglobulin domains were subjected to a topological comparison[67]. Including neighborhood correlations a significance of about 3000:1 was found, which clearly indicates a phylogenetic relationship.

The calculations given above require the definition of a chain topology which is only possible if the chain fold is referred to a rigid substructure such as a pleated sheet. Comparisons are then restricted to the protein class containing this substructure (Table 4). In contrast, direct geometrical comparison of chain folds is a much more general approach. In this case, similarity is expressed in terms of the average distance of corresponding C_α atoms $\langle \Delta C_\alpha \rangle$, or by closely related indices. However, this comparison has the drawback that structure rules can be considered only with difficulty and no value can be derived for the significance, which eventually decides whether or not a resemblance is of phylogenetic origin.

In principle, a relationship between $\langle \Delta C_\alpha \rangle$ value, structure rules, and significance can be established by simulating chain folds with the aid of a random number generator on a computer and comparing them with one another[99]. In this procedure all known structural rules, such as neighborhood correlations, *etc.*, should be considered. The chain length should correspond approximately to that of a domain (Fig. 5). The initial task in the comparison is to find the relative orientation which corresponds to the minimal $\langle \Delta C_\alpha \rangle$ value. This would lead to a frequency distribution of minimal $\langle \Delta C_\alpha \rangle$ values resembling that sketched out in Figure 10. If we want to derive the significance of the similarity of two protein structures having, for example, $\langle \Delta C_\alpha \rangle = 3$ Å, then we are actually enquiring as to how many structures N there are with $\langle \Delta C_\alpha \rangle$ exceeding 3 Å, because this quantity N corresponds to the significance. To determine N it is by no means necessary to simulate all possible structures. One only has to randomly generate G structures and compare them with each other. This yields Z coincidences with $\langle \Delta C_\alpha \rangle \leq 3$ Å (Fig. 10). As in the counting

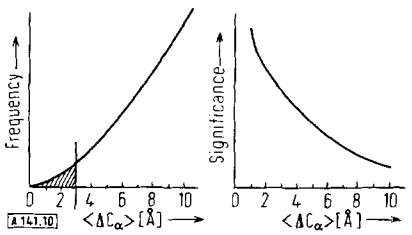


Fig. 10. Schematic frequency distribution of average C_α distances $\langle \Delta C_\alpha \rangle$ between all pairs taken from a set of G simulated chain folds. The significance N of a structural similarity between any two proteins having a given $\langle \Delta C_\alpha \rangle$ is derived from $N = G^2/Z$, where Z is the integral of the frequency distribution taken from zero to the $\langle \Delta C_\alpha \rangle$ value considered.

of radiation quanta[94] the simulated structures obey Poisson statistics, *i.e.* the coincidence ratio Z/G equals the average population G/N. Thus the total number N of different structures with $\langle \Delta C_\alpha \rangle \geq 3$ Å, *i.e.* the desired significance, can be determined from $N = G^2/Z$. Using the frequency distribution of $\langle \Delta C_\alpha \rangle$, the significance of a structural similarity between two proteins can be deduced for any mean C_α distance $\langle \Delta C_\alpha \rangle$, because the number of coincidences Z is known for any $\langle \Delta C_\alpha \rangle$ (Fig. 10).

9. Outlook: Determination of Protein Structures without Crystals

Usually, protein structures can only be solved if the proteins have been crystallized and subsequently analyzed by X-ray diffraction. However, one of the ultimate goals, determination of a three-dimensional structure from the amino acid sequence alone, has already been reached in a number of special cases. For example, the known three-dimensional structure of a given protein can be used in determining the structure of all its phylogenetic relatives once their sequences are known. For that purpose the sequence is fitted into the known chain fold. Remaining discrepancies are ameliorated by subsequent energy minimization[95]. Since the chain fold is extremely well conserved during evolution the method can be applied even to such distant relatives as thrombin and trypsin[88]. In the case of the muscle proteins parvalbumin and troponin C, not only the same chain fold but also internal molecular symmetry are postulated. Similarities between the sequences indicate that troponin C contains four of the substructures found in parvalbumin (one Ca^{2+} binding site and two neighboring α-helices)[89]. In parvalbumin, these substructures have aggregated symmetrically, forming a twofold axis. It therefore appears reasonable to assume that in troponin C the two other substructures are added with twofold symmetry, leading

Table 5. Significance of structural similarities on topological comparison of proteins with parallel pleated sheets.

	Significance including the location of the active center [93]	Significance after accounting for the preferred chirality of the β-α-β groups [77]
Adenylate kinase/subtilisin	2400:1	340:1
Adenylate kinase/flavodoxin	240:1	30:1
Adenylate kinase/any dehydrogenase	160:1	20:1
Subtilisin/flavodoxin	4800:1	350:1
Subtilisin/any dehydrogenase	2400:1	180:1
Flavodoxin/any dehydrogenase	4800:1	350:1
Any dehydrogenase/other dehydrogenase	115200:1	4420:1

to overall 222 (D_2) symmetry. Hence a structural model of troponin C can be built on the basis of the sequence[96]. Once again these examples demonstrate the utility of the phylogenetic relationships for solving protein structures.

Although the direct determination of a three-dimensional structure from an amino acid sequence is still a distant aim, the first steps in this direction have already been taken: an attempt was made to derive the known three-dimensional structures of myoglobin and pancreatic trypsin inhibitor *a posteriori* with the aid of simple rules. Strict hierarchy was assumed for the α-helices in both cases. In other words, it was assumed that they can be determined by secondary structure prediction methods and that they do fold first. The folding simulation then assumes ready-made α-helices. Since myoglobin contains practically only helices, in this case folding is merely helix association; the accessible conformational space is appreciably reduced. A simple scheme was postulated for calculating the packing energy of helices; and the folding pathway was determined as the direct route to the energy minimum[97]. At this minimum the native structure was obtained, confirming the validity of the method. However, this method is limited to purely helical proteins. Pancreatic trypsin inhibitor, on the other hand, contains only one short α-helix. In this case, the geometry of peptide bonds and side chains as well as the determination of the bond energies were simplified. Folding to reach the energy minimum was then simulated by an iterative energy minimization procedure. The most favorable simulation run yielded a structure with an average C_γ distance to the native structure of 6.3 Å[98].

These simulations and all the structural analyses of proteins described above nurture our hope that in the distant future three-dimensional structures can be derived merely from the amino acid sequence. In any case, they show how well the initial shock caused by the complexity of protein structures has been overcome. Moreover, some degree of order has already been established in the wealth of existing data. It may be expected that this order will become all the greater the more data become available, *i.e.* the more X-ray structure analyses succeed.

Received: June 29, 1976 [A 141 IE]
German version: Angew. Chem. 89, 24 (1977)

[1] *J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips,* and *V. C. Shore,* Nature *185,* 422 (1960).
[2] *R. E. Marsh* and *J. Donohue,* Adv. Protein Chem. *22,* 235 (1967).
[3] *G. N. Ramachandran* and *V. Sasisekharan,* Adv. Protein Chem. *23,* 283 (1968).
[4] *A. L. Lehninger:* Biochemie. Verlag Chemie, Weinheim 1975.
[5] *C. B. Anfinsen,* Science *181,* 223 (1973).
[6] *D. B. Wetlaufer* and *S. Ristow,* Annu. Rev. Biochem. *42,* 135 (1973).
[7] *C. B. Anfinsen* and *H. A. Scheraga,* Adv. Protein Chem. *29,* 205 (1975).
[8] *W. Kauzmann,* Adv. Protein Chem. *14,* 1 (1959).
[9] *B. Furie, A. N. Schechter, D. H. Sachs,* and *C. B. Anfinsen,* J. Mol. Biol. *92,* 497 (1975).
[10] *F. M. Richards,* J. Mol. Biol. *82,* 1 (1974).
[11] *A. I. Kitaigorodsky:* Molecular Crystals and Molecules. Academic Press, New York 1973.
[12] *J. F. Brandts, R. J. Oliveira,* and *C. Westort,* Biochemistry *9,* 1038 (1970).
[13] *d'Ans-Lax:* Taschenbuch für Chemiker und Physiker. Vol. 1. Springer-Verlag, Berlin 1967.
[14] *B. Lee* and *F. M. Richards,* J. Mol. Biol. *55,* 379 (1971).
[15] *C. Chothia,* Nature *248,* 338 (1974).
[16] *S. L. Miller,* J. Am. Chem. Soc. *77,* 2351 (1955).
[17] *T. E. Creighton,* J. Mol. Biol. *95,* 167 (1975).
[18] *R. Huber, D. Kukla, A. Rühlmann, O. Epp,* and *H. Formanek,* Naturwissenschaften 57, 389 (1970).
[19] *D. Wetlaufer, E. Kwok, W. L. Anderson,* and *E. R. Johnson,* Biochem. Biophys. Res. Commun. *56,* 380 (1974).
[20] *F. H. C. Crick,* Acta Crystallogr. *6,* 689 (1953).
[21] *C. Cohen* and *K. C. Holmes,* J. Mol. Biol. *6,* 423 (1963).
[22] *H. E. Huxley,* Science *164,* 1356 (1969).
[23] *R. D. B. Fraser* and *T. P. MacRae,* Nature *233,* 138 (1971).
[24] *C. Cohen,* Sci. Am. *234,* 36 (Nov. 1975).
[25] *W. A. Hendrickson* and *K. B. Ward,* Biochem. Biophys. Res. Commun. *66,* 1349 (1975).
[26] *R. Henderson* and *P. N. T. Unwin,* Nature *257,* 28 (1975).
[27] *S. T. Rao* and *M. G. Rossmann,* J. Mol. Biol. *76,* 241 (1973).
[28] *E. Hill, D. Tsernouglou, L. Webb,* and *L. J. Banaszak,* J. Mol. Biol. *72,* 577 (1972).
[29] *I. Ohlsson, B. Nordström,* and *C. I. Brändén,* J. Mol. Biol. *89,* 339 (1974).
[30] *M. Buehner, G. C. Ford, D. Moras, K. W. Olsen,* and *M. G. Rossmann,* Proc. Natl. Acad. Sci. USA *70,* 3052 (1973).
[31] *G. E. Schulz, M. Elzinga, F. Marx,* and *R. H. Schirmer,* Nature *250,* 120 (1974).
[32] *K. D. Watenpaugh, L. C. Sieker, L. H. Jensen, J. Legall,* and *M. Dubourdieu,* Proc. Natl. Acad. Sci. USA *69,* 3185 (1972).
[33] *R. D. Andersen, P. A. Apgar, R. M. Burnett, G. D. Darling, M. E. Lequesne, S. G. Mayhew,* and *M. L. Ludwig,* Proc. Natl. Acad. Sci. USA *69,* 3189 (1972).
[34] *C. Schubert-Wright, R. A. Alden,* and *J. Kraut,* Nature *221,* 235 (1969).
[35] *C. C. F. Blake* and *P. R. Evans,* J. Mol. Biol. *84,* 585 (1974).
[36] *R. J. Fletterick,* personal communication (1976).
[37] *P. A. Peterson, B. A. Cunningham, I. Berggård,* and *G. M. Edelman,* Proc. Natl. Acad. Sci. USA *69,* 1697 (1972).
[38] *G. E. Schulz, H. Zappe, D. J. Worthington,* and *M. A. Rosemeyer,* FEBS Lett. *54,* 86 (1975).
[39] *M. J. Adams, G. C. Ford, R. Koekoek, P. J. Lentz, A. McPherson, M. G. Rossmann, I. E. Smiley, R. W. Schevitz,* and *A. J. Wonacott,* Nature *227,* 1098 (1970).
[40] *S. G. Warren, B. F. P. Edwards, D. R. Evans, D. C. Wiley,* and *W. N. Lipscomb,* Proc. Natl. Acad. Sci. USA *70,* 1117 (1973).
[41] *M. Grütter* and *R. M. Franklin,* J. Mol. Biol. *89,* 163 (1974).
[42] *G. W. Tischendorf, H. Zeichardt,* and *G. Stöffler,* Proc. Natl. Acad. Sci. USA *72,* 4820 (1975).
[43] *L. Pauling* and *R. B. Corey,* Proc. Natl. Acad. Sci. USA *37,* 729 (1951).
[44] *A. V. Guzzo,* Biophys. J. *5,* 809 (1965).
[45] *J. W. Prothero,* Biophys. J. *6,* 367 (1966).
[46] *R. Leberman,* J. Mol. Biol. *5,* 23 (1971).
[47] *P. N. Lewis, F. A. Momany,* and *H. A. Scheraga,* Proc. Natl. Acad. Sci. USA *68,* 2293 (1971).
[48] *M. Schiffer* and *A. B. Edmundson,* Biophys. J. *8,* 29 (1968).
[49] *P. Y. Chou* and *G. D. Fasman,* Biochemistry *13,* 222 (1974).
[50] *V. I. Lim,* J. Mol. Biol. *88,* 873 (1974).
[51] *B. Robson* and *R. H. Pain,* Biochem. J. *141,* 883 (1974).
[52] *K. Nagano,* J. Mol. Biol. *84,* 337 (1974).
[53] *E. A. Kabat* and *T. T. Wu,* Proc. Natl. Acad. Sci. USA *70,* 1473 (1973).
[54] *A. V. Finkelstein* and *O. B. Ptitsyn,* J. Mol. Biol. *62,* 613 (1971).
[55] *P. N. Lewis, N. Gō, M. Gō, D. Kotelchuck,* and *H. A. Scheraga,* Proc. Natl. Acad. Sci. USA *65,* 810 (1970).
[56] *G. E. Schulz, C. D. Barry, J. Friedman, P. Y. Chou, G. D. Fasman, A. V. Finkelstein, V. I. Lim, O. B. Ptitsyn, E. A. Kabat, T. T. Wu, M. Levitt, B. Robson,* and *K. Nagano,* Nature *250,* 140 (1974).
[57] *E. A. Kabat* and *T. T. Wu,* Proc. Natl. Acad. Sci. USA *71,* 4217 (1974).
[58] *B. W. Matthews,* Biochim. Biophys. Acta *405,* 442 (1975).
[59] *I. D. Kuntz,* J. Am. Chem. Soc. *94,* 4009 (1972).
[60] *H. W. Wyckoff, D. Tsernouglou, A. W. Hanson, J. R. Knox, B. Lee,* and *F. M. Richards,* J. Biol. Chem. *245,* 305 (1970).
[61] *C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips,* and *V. R. Sarma,* Nature *206,* 757 (1965).
[62] *E. T. Adman, L. C. Sieker,* and *L. H. Jensen,* J. Biol. Chem. *248,* 3987 (1973).
[63] *P. M. Colman, J. Deisenhofer, R. Huber,* and *W. Palm,* J. Mol. Biol. *100,* 257 (1976).
[64] *R. J. Poljak, L. M. Amzel, B. L. Chen, R. P. Phizackerley,* and *F. Saul,* Proc. Natl. Acad. Sci. USA *71,* 3440 (1974).
[65] *D. M. Segal, E. A. Padlan, G. H. Cohen, S. Rudikoff, M. Potter,* and *D. R. Davies,* Proc. Natl. Acad. Sci. USA *71,* 4298 (1974).
[66] *A. B. Edmundson, K. R. Ely, E. E. Abola, M. Schiffer,* and *N. Panagiotopoulos,* Biochemistry *14,* 3953 (1975).
[67] *J. S. Richardson, D. C. Richardson, K. A. Thomas, E. W. Silverton,* and *D. R. Davies,* J. Mol. Biol. *102,* 221 (1976).
[68] *K. D. Hardman* and *C. F. Ainsworth,* Biochemistry *11,* 4910 (1972).
[69] *C. C. F. Blake, M. J. Geisow, I. D. A. Swan, C. Rerat,* and *B. Rerat,* J. Mol. Biol. *88,* 1 (1974).
[70] *J. J. Birktoft* and *D. M. Blow,* J. Mol. Biol. *68,* 187 (1972).
[71] *R. E. Fenna* and *B. W. Matthews,* Nature *258,* 573 (1975).
[72] *D. W. Banner, A. C. Bloomer, G. A. Petsko, D. C. Phillips, C. I. Pogson, I. A. Wilson, P. H. Corran, A. J. Furth, J. D. Milman, R. E. Offord, J. D. Priddle,* and *S. G. Waley,* Nature *255,* 609 (1975).
[73] *C. C. F. Blake,* Essays Biochem. *11,* 37 (1975).
[74] *F. A. Quiocho* and *W. N. Lipscomb,* Adv. Protein Chem. *25,* 1 (1971).

[75] *M. F. Perutz, H. Muirhead, J. M. Cox,* and *L. C. G. Goaman,* Nature *219,* 131 (1968).
[76] *C. Chothia,* J. Mol. Biol. *75,* 295 (1973).
[77] *M. J. E. Sternberg* and *J. M. Thornton,* J. Mol. Biol., *105,* 367 (1976).
[78] *J. Bergsma, W. G. J. Hol, J. N. Jansonius, K. H. Kalk, J. H. Ploegman,* and *J. D. G. Smit,* J. Mol. Biol. *98,* 637 (1975).
[79] *M. G. Rossmann, D. Moras,* and *K. W. Olsen,* Nature *250,* 194 (1974).
[80] *A. D. McLachlan,* Nature New Biol. *240,* 83 (1972).
[81] *R. H. Kretsinger,* Nature New Biol. *240,* 85 (1972).
[82] *O. B. Ptitsyn,* J. Mol. Biol. *88,* 287 (1974).
[87] *M. F. Perutz,* J. Mol. Biol. *13,* 646 (1965).
[84] *T. Takano, O. B. Kallai, R. Swanson,* and *R. E. Dickerson,* J. Biol. Chem. *248,* 5234 (1973).
[85] *R. M. Stroud,* Sci. Am. *233,* 74 (July 1974).
[86] *G. M. Edelman,* Science *180,* 830 (1973).
[87] *M. O. Dayhoff:* Atlas of Protein Structure. Natl. Biomed. Res. Foundation, Washington 1972.
[88] *B. S. Hartley,* Philos. Trans. R. Soc. London, Ser. B: *257,* 77 (1970).
[89] *J. H. Collins, J. D. Potter, M. J. Horn, G. Wilshire,* and *N. Jackman,* FEBS Lett. *36,* 268 (1973).
[90] *A. D. McLachlan, M. Stewart,* and *L. B. Smillie,* J. Mol. Biol. *98,* 281 (1975).
[91] *B. W. Matthews* and *S. J. Remington,* Proc. Natl. Acad. Sci. USA *71,* 4178 (1974).
[92] *W. J. Browne, A. C. T. North, D. C. Phillips, K. Brew, T. C. Vanaman,* and *R. L. Hill,* J. Mol. Biol. *42,* 65 (1969).
[93] *G. E. Schulz* and *R. H. Schirmer,* Nature *250,* 142 (1974).
[94] *G. Friedlander* and *J. W. Kennedy:* Introduction to Radiochemistry. Wiley, New York 1959.
[95] *M. Levitt,* J. Mol. Biol. *82,* 393 (1974).
[96] *R. H. Kretsinger* and *C. D. Barry,* Biochim. Biophys. Acta *405,* 40 (1975).
[97] *O. B. Ptitsyn* and *A. A. Rashin,* Biophys. Chem. *3,* 1 (1975).
[98] *M. Levitt* and *A. Warshel,* Nature *253,* 694 (1975).
[99] *G. E. Schulz,* J. Mol. Evol., in press.

Experimental Electron Densities and Chemical Bonding

By Philip Coppens[*]

Some recent results of charge density analysis by X-ray and neutron diffraction are discussed. Problems that have been studied in a number of laboratories include the nature of single, double, and triple bonds, lone-pair hybridization, bonding in some metals, alloys, and organometallic compounds, and the derivation of physical properties from X-ray diffraction densities. At the present stage of development of methods studies of series of related compounds are feasible and expected to find widespread application.

Clearly a molecule is much more complicated than an atom. So the question arises: what happens to an atom when it becomes part of a molecule? [*C. A. Coulson,* Mem. Soc. R. Sci. Liege Collect 8° *6* (2), 143 (1971)].

1. Introduction

Part of the answer to this deceptively simple question can be provided by X-ray and neutron crystallography. Since X-ray scattering is primarily a result of the interaction between X-rays and electrons, it contains information on the electron distribution in the scattering material. As early as 1918, *Debye* and *Scherrer* discussed the determination of electron orbits[1], but for reasons more easily understood now their determination proved to be an elusive goal. Much pioneering work in the fifties and early sixties[2] was necessary before technical breakthroughs such as automatic diffractometry and high speed computing led to improvements in accuracy which made details of the electron distribution accessible to the experimentalist.

One of the problems to be faced has been that both the electron distribution and the positions and thermal vibrations of the atoms had to be deduced from the measurements. A significant step forward was therefore made possible with the advent of high-flux neutron beams at nuclear reactors which allowed an independent determination of the atomic parameters because neutrons interact with atomic nuclei (through nuclear forces) rather than with electrons. More recent developments in methodology described below have also been centered on obtaining the combined information from accurate low-temperature X-ray measurements alone so that the double effort and expense of measuring both X-ray and neutron data sets is not always necessary.

Today, charge density analysis with accurate diffraction methods is becoming increasingly sophisticated and applicable to crystals of sufficient complexity to be of chemical interest. Here, we will outline some typical chemical and physical information that can be obtained at the present stage of development, rather than attempt to describe all recent work in the field. A more comprehensive review (up to early 1974) and a comparison of experimental and theoretical results have been published elsewhere[3, 4].

1.1. Difference Densities and Experimental Considerations

The effect of bonding on the electron density is of a rather small magnitude when compared with the total number of electrons in a solid. This means that to a fairly good approximation the electron density ρ is equal to the sum of the densities the constituent atoms would have if all interactions with their neighbors were neglected. Since we are interested precisely in the small bonding effects it is most opportune to calculate the difference between the observed density and the density of the free atoms in their electronic ground state centered at the atomic positions in the crystal. This function may be called the deformation density $\rho_{\text{deformation}}$ because it represents the deformation that occurs when the atoms interact to form chemical bonds. Thus:

[*] Prof. Dr. P. Coppens
Chemistry Department
State University of New York at Buffalo
Buffalo, New York 14214 (USA)

$$\rho_{\text{deformation}} = \rho_{\text{observed}} - \sum_{\text{all atoms}} \rho_{\text{free atom}} \quad (1)$$

In other cases we may want to study the distribution of all the valence electrons involved in chemical bonding, in which case the inner shells (cores) of all atoms are to be subtracted to give the valence distribution ρ_{valence}:

$$\rho_{\text{valence}} = \rho_{\text{observed}} - \sum_{\text{all atoms}} \rho_{\text{inner shells}} \quad (2)$$

This second function will show bonding less clearly because it represents many more electrons, but is sometimes useful for comparison with theoretical results which are not always cast in the form of expression (1).

For both expressions (1) and (2) the observed density is evaluated by a Fourier summation of the observed X-ray amplitudes, while the calculated atomic part is obtained in a similar way from X-ray amplitudes *calculated* for the free atom functions. This latter calculation requires, of course, a knowledge of where the atoms are and how much their density is smoothed by thermal vibrations in the crystal. It is at this point that the neutron diffraction information becomes important.

It is common crystallographic practice to obtain the parameters describing the atoms by varying these parameters to obtain the least-squares fit between the calculated and the observed structure factors. But in the calculation of the structure factors the not entirely justified assumption is routinely made that the atoms have a spherical distribution as if they were not bonded. This corresponds to $\rho_{\text{deformation}}$ in expression (1) being zero everywhere! So when the least squares refinement is performed the incorrect assumption of spherical atoms will shift the atoms somewhat to make $\rho_{\text{deformation}}$ as close to zero as possible. In other words, X-ray diffraction bond lengths (and vibrational parameters) will be biased when atoms are in an asymmetric chemical environment, like terminal oxygen and nitrogen and especially hydrogen atoms. No such bias exists when the information is obtained with neutrons, which are scattered by the atomic nuclei rather than by the electrons in the crystal. As a result CH, NH, and OH bond lengths from X-ray analyses are typically less by 0.1—0.2 Å than spectroscopic or neutron diffraction values, while non-hydrogen atom shifts of up to 0.01 Å are not uncommon[5].

Because the neutron diffraction parameters are used in the calculated part that is subtracted out from the density observed with X-rays the label "X − N" (X minus N) is frequently used.

It is of great practical interest that good approximations to X − N densities can often be obtained when very many X-ray intensities have been collected. For this it is generally necessary to cool the specimen crystal which reduces the thermal vibrations of the atoms. This reduction may be considered as giving a higher degree of order in the crystal because the atoms are, on the average, closer to their equilibrium positions. The extra ordering especially increases the intensity of the X-ray reflection at high Bragg angles (see Fig. 1a) which are often too weak to be measured at room temperature. According to the theory of X-ray scattering the intensity of these high-angle reflections is almost exclusively determined by the distribution of the inner electron shells of the atoms and relatively unaffected by the valence density, which is the subject of chemical interest (Fig. 1b).

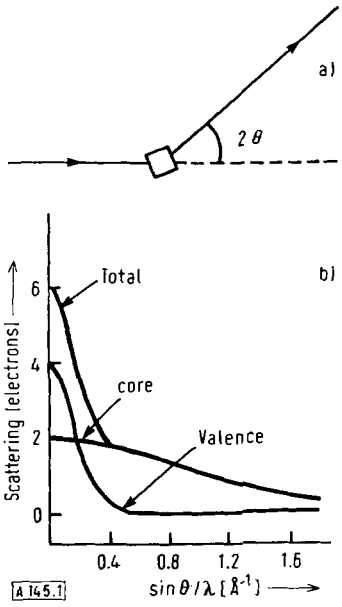


Fig. 1. a) Definition of the Bragg angle θ as half the angle between the incident and diffracted beams. b) Dependence of the scattering of the atomic core and valence shell of an isolated carbon atom on $\sin\theta/\lambda$. λ is the wavelength of the radiation used. The unit on the ordinate corresponds to the scattering of a classical point electron. In the direction of the incident beam (where $\theta = 0$) the scattering reaches the value for the total number of electrons.

This physical fact suggests a second way of separating the bonding effects on the valence density from the determination of atomic parameters by obtaining the latter from a least squares refinement of the high-angle data and the deformation density from a Fourier summation of the low-angle reflection. Electron densities obtained in this way will be referred to here as X − X densities because both the observed and the calculated densities in expressions (1) and (2) are now based on the X-ray data. Such X − X densities reproduce X − N results quite closely in bonds between non-hydrogen atoms, but are much less reliable in the vicinity of H atoms, which scatter little in the high angle region and can therefore not be well determined in a high-order refinement.

Some typical deformation densities are shown in Figures 2—8. Before discussing the chemical implication of these maps it is worthwhile to consider the magnitude of the experimental error in the density. As expressed by (1) and (2), the deformation and valence densities are both differences between an observed density and a calculated distribution. If the standard deviations in these are respectively $\sigma(\rho_{\text{obs}})$ and $\sigma(\rho_{\text{calc}})$ we get

$$\sigma^2(\rho_{\text{deformation}}) = \sigma^2(\rho_{\text{obs}}) + \sigma^2(\rho_{\text{calc}}) \quad (3)$$

with a similar expression for ρ_{valence}. It has been shown that the error function $\sigma(\rho_{\text{deformation}})$ in (3) is fairly constant in the crystallographic unit cell *except* near crystallographic symmetry elements and in the vicinity (< 0.3 Å) of the atomic nuclei[6]. The errors in the latter region are especially pronounced and prevent conclusions about the density near the atoms. They arise essentially because the deformation density here is the difference between two relatively large densities. On the other hand, the bond and lone-pair regions are relatively reliable with standard deviations of 0.05—0.07 e Å^{-3} or better reached in several accurate studies. As bond and lone pair peak heights are typically 0.3—0.7 e Å^{-3} the signal to noise ratio in the experimental maps is significant.

2. Density Maps

We shall proceed by describing a number of representative studies in which chemical information is derived from experimental charge densities.

2.1. The Electron Distribution in the Chemical Bond

A covalent chemical bond may be considered as resulting from the pairing of electrons of opposite spin, whose orbitals overlap in the bonding region. Theory indicates that the electron pairing leads to extra density in the bond compared to the density corresponding to the superposition of spherical atoms. This means that density should appear in the bonds in the deformation maps, a prediction which is readily confirmed on examination of the experimental results. For example, in CC, CN, and CO bonds peaks are found which typically have a height of 0.3 to 0.6 e Å^{-3}. There are also clear differences between single, triple, and double bonds which are most apparent when sections through the bond midpoints perpendicular to the bond axes are calculated. In these sections single and triple bonds appear as round, cylindrically symmetric density peaks, but double bonds are elongated in the direction of the p_π orbital axis[7,8], again as predicted by theory. The elongation of the double bond peaks is well demonstrated in the cumulene skeleton of tetraphenylbutatriene, where adjacent multiple bonds are mutually perpendicular, corresponding to a predominance of, respectively, p_x and p_y atomic orbitals in the π MOs of adjacent bonds (Fig. 2)[9].

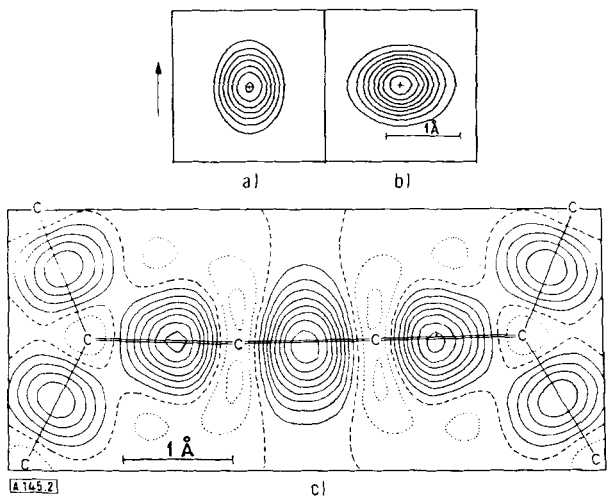


Fig. 2. Deformation density of tetraphenylbutatriene. Sections perpendicular to the outer (a) and inner (b) bonds of the butatriene chain through their midpoints. The arrow is perpendicular to the butatriene plane. c) Deformation density in the butatriene plane. Contours at 0.10 e Å^{-3}. Irregularities have been eliminated by fitting of smooth functions to the experimental data. From *Berkovitch-Yellin, Leiserowitz,* and *Nader* [9].

Unusual features occur in the maps of strained three-membered ring systems such as cyclopropane, ethyleneimine, and ethylene oxide[10], where the deformation density peaks are not exactly on the lines connecting the atoms, but located somewhat outside the nuclear triangles (Fig. 3). This observation provides experimental confirmation that the bonds in these small rings are bent. Such bending results from the geometrical constraint imposed by the three-membered ring: the 60° angle in the ring cannot be reproduced exactly by the atomic orbitals of the electron forming the bond, which are therefore pointing not exactly at the adjacent atoms. Such bonds are somewhat weaker than ordinary "straight" bonds and explain the strain energy which reduces the stability of small ring compounds.

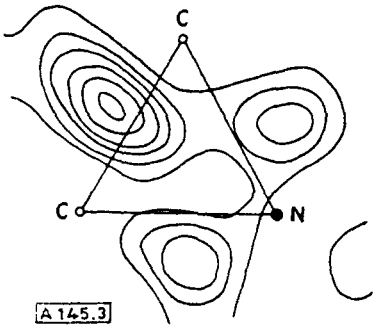


Fig. 3. Deformation density in the plane of the three-membered ring of 2,3:5,6-bisepimino-*p*-benzoquinone at 143 K. Contours at 0.05 e Å^{-3}. Negative contours omitted. Open circles represent carbon atoms. From *Ito* and *Sakurai* [10b].

In all the bonds discussed here, which are between first-row atoms, the deformation density peaks at or near the bond midpoint. But other density maps containing S—S and Ni—Ni bonds indicate that for heavier atoms changes nearer to the nucleus often dominate the deformation density, so that the peak may no longer be located at the midpoint of the bond.

2.2. Hybridization of Lone Pair Electrons

The concept of hybridization has been tremendously successful in explaining trends in molecular properties like bond strengths and distances, bond angles, force constants, and NMR coupling constants. More recently, atomic hybridization has also been related to the results of SCF molecular orbital theory through the use of truncated or localized molecular orbitals[11]. The measurement of the electron density provides a unique opportunity for directly obtaining information on atomic hybridization.

The wave function for the lone pair orbital may be written as a linear combination of 2s and 2p atomic orbitals $\phi(2s)$ and $\phi(2p)$:

$$\psi(\text{lone pair}) = a\phi(2s) + b\phi(2p) \qquad (4)$$

where a and b are constants, often referred to as the mixing coefficients. The corresponding electron density distribution is proportional to ψ^2 and therefore contains a cross-term equal to $2ab\phi(2s)\phi(2p)$ in addition to the terms depending on $\phi^2(2s)$ and $\phi^2(2p)$. As the function $\phi(2s)$ is positive in all directions from the nucleus the product $\phi(2s)\phi(2p)$ will be positive where $\phi(2p)$ is positive. Thus, the location of a lone pair peak near an atom gives evidence on the nature of the 2p orbital involved. For example, a lone pair peak is observed at the "back" of the nitrogen atom in the C≡N groups in tetracyanoethylene[8] (Fig. 4) and NaC≡N·2H$_2$O (Fig. 5)[12] and at the back of the oxygen atoms in benzene tricarbonylchromium[13] and hexacarbonylchromium[14] (Fig. 6). This indicates that the p orbital in (5) has its positive lobe in a direction opposite to the N—C (and O—C) vectors, while the fact that only one lone pair peak is observed leads, according to the arguments of valence bond theory, to the conclusion that an sp hybrid is involved in the bonding [*i.e.* $a=1$ and $b=1$ in expression (5)].

In these examples the lone pair belongs to an atom which participates in a triple bond. But when the terminal atom is doubly bonded such as the oxygen atom in the C=O group there are two lone pairs as found in a number of

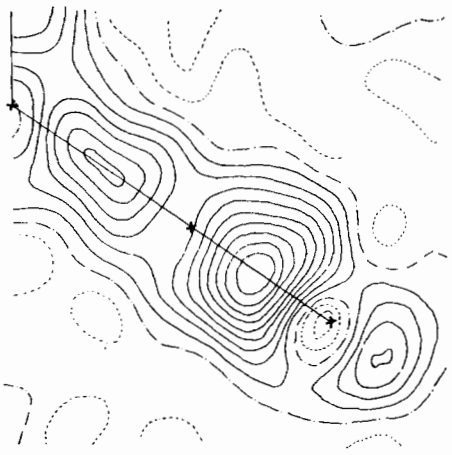


Fig. 4. X – N density in the molecular plane of tetracyanoethylene. Contours at 0.10 e Å^{-3}; negative contours (– – –); zero contour (–·–·–). Only one quarter of the molecule is shown as the remainder is related by symmetry to the part given. The cross to the right indicates the nitrogen atom, while the carbon atoms are to the left. From *Becker et al.* [8].

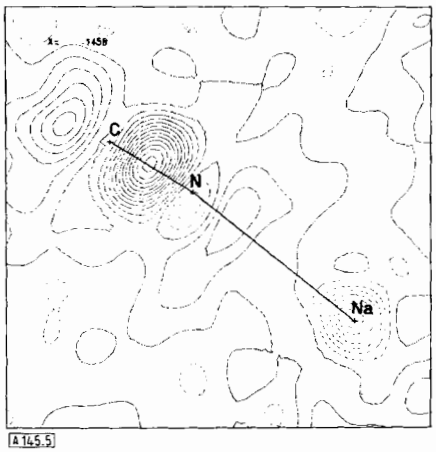
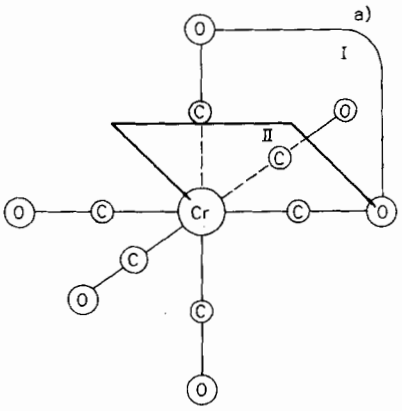


Fig. 5. Deformation density in $NaCN \cdot 2H_2O$ at 150 K. Contours at 0.05 e Å^{-3}. Negative contours broken. Lone pair electron density is especially pronounced at the carbon atom. From *Bats* [12].

compounds, including glycylglycine[15], glycine[16], cyanuric acid[17], and oxalic acid[18] (Fig. 7). All these have conjugated systems of double bonds and the lone pair peaks are found in the plane of the conjugated system at about 120° from the C=O bond axis. This arrangement corresponds to sp^2 hybridized lone pairs in the language of valence bond theory. Yet another type of hybridization is evidenced at the oxygen atom of the nitroxo group in *p*-nitropyridine *N*-oxide[19] (Fig. 8) where the density is again in the molecular plane, but at right angles to the bond axis. The interpretation is that the two oxygen lone pairs are unhybridized and described by s and p atomic orbitals respectively. The lone pair peaks seen in Figure 8 correspond to the latter orbital, because the s electrons have a spherical distribution as in the free atom and will not appear in the deformation density map, which is the difference between the observed and the free atom densities. The difference between the hybridization of



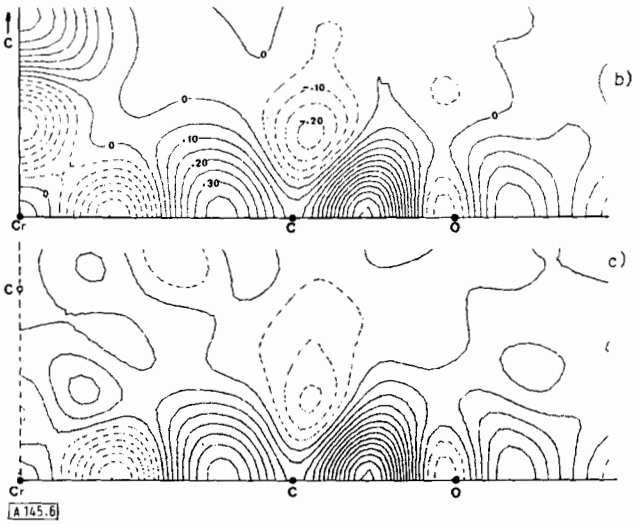


Fig. 6. Deformation density in $Cr(CO)_6$ at 78 K. a) Geometry of the molecule; b) section of plane I; c) section of plane II. Contours as indicated. From *Rees* and *Mitschler* [14].

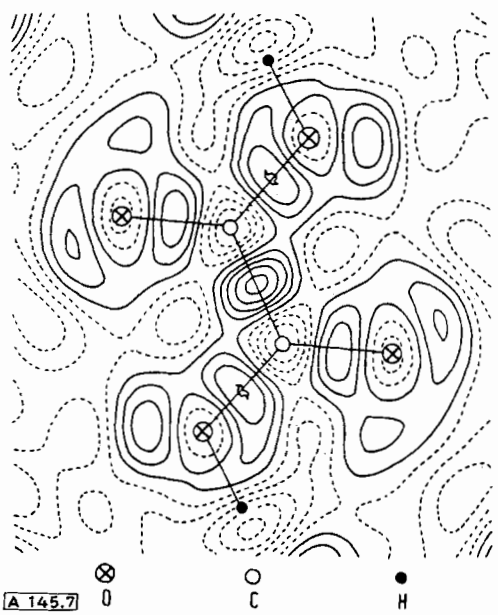


Fig. 7. Deformation density through the molecular plane of the oxalic acid molecule at room temperature. Contours at 0.05 e Å^{-3}. Zero and negative contours dashed. From *Coppens et al.* [18].

the oxygen atom in N—O and C—O may be related, as proposed by *Bent*[20], to the influence of the greater electro-

negativity of the nitrogen atom (compared with the carbon) on the electronic structure of the oxygen atom.

It is interesting to note that the excess density on the nitroxo oxygen in *p*-nitropyridine *N*-oxide is on the side of the bond and not towards the periphery of the molecule, yet a very



Fig. 8. Deformation density in the plane of *p*-nitropyridine *N*-oxide at 30 K. The NO_2 group is at the lower right, the NO part of the molecule at the upper left of the figure. Contours at 0.10 eÅ^{-3}. Negative contours broken. From *Wang et al.* and *Coppens* and *Lehmann* [19].

strong hydrogen bond exists between pyridine *N*-oxide and trichloroacetic acid[21]. The unanswered question arises whether the electron distribution in the nitroxo group in this complex is as observed in *p*-nitropyridine *N*-oxide or perhaps perturbed by the strong hydrogen bonding (O···O = 2.4 Å).

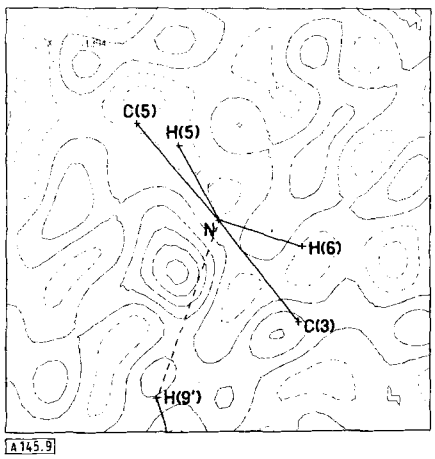


Fig. 9. Deformation density in sodium sulfanilate dihydrate at 78 K. The section shown is through the nitrogen atom of the NH_2 group perpendicular to the C—N bond. The carbon atoms indicate the projection of the benzene ring plane. The dotted line represents a hydrogen bond. Contours as in Fig. 5. From *Bats* [22].

A final example of lone pair density is given in Figure 9. Low temperature X-ray diffraction shows the NH_2 group in sodium sulfanilate dihydrate to be slightly pyramidal[22]. The deviation from planarity is much less than in ammonia, the average angle at the nitrogen being 116°, so one may ask whether the non-planarity sufficiently influences lone pair hybridization to give excess density at the apex of the pyramid only rather than at both sides of the nitrogen atom. The section shown in Figure 9 is through the amine nitrogen atom perpendicular to the exocyclic C—N bond. The orientation of the molecule is indicated by the projection of two ring carbon atoms and two amine hydrogen atoms onto the section of the figure. The lone pair is at only one side of the nitrogen atom. A possible cause for this asymmetry is suggested by the hydrogen bond geometry shown in the figure by the broken line to a hydrogen atom belonging to the water molecule incorporated in the crystal lattice.

2.3. The Nature of the Hydrogen Bond

Theoretical charge density analyses of hydrogen bonded systems have emphasized the difference between the density in the hydrogen bonded dimer and the superposition of isolated molecules.

The comparison between theoretical density maps is hampered by lack of uniformity of the contour intervals in different studies. Often the height of a peak cannot be assessed because of lack of detail in the logarithmic contour scale which is commonly selected by theoreticians. But calculations on the water dimer by *Diercksen*[23] and by *Yamabe* and *Morokuma*[24] on $(HF)_2$ and $H_2O \cdot HF$ by *Kollman* and *Allen*[25], and on the formamide dimer by *Dreyfus* and *Pullman*[26] agree on a depletion of charge on the H-bond hydrogen atom and an increase in the covalent bond to this hydrogen. This change in density upon H-bonding is largest for the strongest hydrogen bonds and exceeds 0.02 ea_0^{-3} (0.14 eÅ^{-3}) in the $HF \cdot H_2O$ complex and the HF dimer. Such a change should be experimentally detectable where non-hydrogen bonded reference systems are available. But reference states like the superposition of spherical atoms must be used in experimental work because the non-hydrogen bonded monomers do generally not exist in the crystalline state. The difference between the two is negligible near the midpoint of the H···X bond, so in this region the effect of hydrogen bonding can be studied experimentally. Studies on glycylglycine[15], 2-amino-5-chloropyridine[27], and on cyanuric acid[17] and glycine[16] do not show any charge accumulation in the H···X hydrogen bond, in agreement with the theoretical work and supporting an electrostatic rather than a covalent interpretation of the XH···X interaction. The study of 2-amino-5-chloropyridine is of especial interest because only one of the two N—H bonds is involved in hydrogen bonding. There is a marked difference between the two N—H lengths which are 1.009(3) Å for the N—H bond participating in H-bonding and 0.980(3) for the second bond. The deformation density shows a much larger peak in the former bond, in agreement with theoretical calculations which predict that a pronounced change on H-bonding is exactly the enhancement of the density in the donor N—H bond[25, 26].

Above all in crystals containing molecules which are very strong acids much shorter hydrogen bonds occur which represent stronger interactions. For very short bonds the hydrogen may be exactly in the middle of the two adjacent atoms, so that the distinction between a hydrogen donor and a hydrogen acceptor group becomes meaningless. This may occur for example, when the O···O distance is less than 2.45 Å. A very early theoretical calculation on the FHF^- ion[28], which is a well known example of a species containing a

very short hydrogen bond, shows a general charge depletion on both sides of the proton suggesting an electrostatic nature of both H···F bonds. But recent experimental studies on 2,3-pyridinedicarboxylic acid (at room temperature) in which the two carboxylate groups are bridged by a strong hydrogen bond (with O···O = 2.398 Å)[27], and on sodium bisacetate (at 80 K)[29], in which two acetate ions are similarly linked, are more indicative of two at least partially covalent OH bonds (schematically represented by O—H—O) because density peaks are found in both O—H regions. A low temperature study of 2,3-pyridinedicarboxylic acid, as well as theoretical and experimental studies on other strong hydrogen bonded systems, are presently being undertaken[30, 31].

2.4. Compounds Containing 3d Transition Metals

Organometallic compounds are of great chemical interest from both fundamental and practical points of view. Much of what we know about the bonding in these compounds is based on the analysis of their varied geometry or deduced from spectroscopic measurements. Direct determination of the charge density distribution adds a completely new tool to existing techniques, but some caution is required because charge density studies become increasingly difficult as the number of electrons in the atomic cores increases. The atomic cores are very little affected by chemical bonding and their X-ray scattering is a strong signal on which the chemically interesting valence scattering is superimposed. For atoms with many electrons the deformation density according to expression (1) is the rather small difference between two functions (ρ_{observed} and $\rho_{\text{free atom}}$) with large values in the vicinity of the heavy atoms. As $\sigma(\rho)$ is in first approximation proportional to ρ, this means that the experimental errors according to (3) are larger for transition metal compounds than for the organic molecules we have discussed up to this point.

For this reason, early studies concentrated on crystals containing first and second row atoms only. More recently several research groups have made a serious start at studying compounds of 3d transition metals which are relatively light and therefore the most promising transition-metal compounds. A number of studies by *Saito et al.*[32, 33] and by *Rees* and *Mitschler*[14] on octahedral complexes of chromium, cobalt, and nickel indicate excess charge in the t_{2g} metal orbitals in $NiSiO_4$, $Co(NH_3)_6Co(CN)_6$, $Co(NH_3)_6Cr(CN)_6$, and $Cr(CO)_6$. The asymmetries in the deformation maps are reproduced in recent *ab-initio* calculations of MnO_4^-, CoO_6^{10-}, and $Ni(CH_3)_2$ by *Johansen*[34], though they appear at shorter distances from the metal atoms in these calculations. Since no single transition metal compound has been studied both experimentally and theoretically at this time it is not known whether the discrepancy is due to inadequacies in the calculation of differences between compounds.

The study of hexacarbonylchromium $Cr(CO)_6$ is an excellent example of what can be achieved in careful low temperature work. The molecule itself has octahedral symmetry but three out of the six CO groups are not related by crystallographic symmetry elements and therefore measured independently in the diffraction experiment. The planes shown in Figure 6 are averages over such chemically but not crystallographically independent parts of the molecule. The averaging is useful in eliminating the background noise in the experimental maps and correspondingly reducing the experimental errors. The section shown in Figure 6b contains the Cr atom and two CO groups, while the one of Figure 6c is inclined by 45° to the first plane (see Fig. 6a). The density in the CO ligand is very similar in the two planes but a significant difference occurs near the chromium atom where Figure 6b shows a peak along the diagonal of the drawing, interpreted as extra density in the t_{2g} orbitals of the chromium atom, which have their maxima in this direction[15]. A detailed analysis of these differences and a comparison with theoretical values for the chromium atom enabled *Rees* and *Mitschler* to conclude that the occupation of the two types of d orbitals which in the isolated atom is 40% and 60% for e_g and t_{2g} respectively, becomes 25% and 75% in the complex. Comparison of the density in the CO ligand with a theoretical result for the isolated CO molecule further suggested that antibonding π^* orbitals of the ligand are partially occupied by a donation of electrons from the metal orbitals into these ligand orbitals. This is in agreement with the "classical" Dewar-Chatt model of the metal-ligand bonding inferred earlier from less direct spectroscopic and structural evidence[35].

A binuclear metal-metal complex was the subject of a recent study of $(\eta^5\text{-}C_5H_5Ni)_2CH{\equiv}CH$[36]. The acetylene CC density was found to be displaced away from the Ni—Ni region as if the carbon bonding hybrids are bent away from the bond axis (Fig. 10) much like the distortion of the bonds in strained three-membered ring compounds discussed above. The analogy suggests a NiNiCC tetrahedron which is strained at the carbon atoms. The drastic effect on the density is not surprising because the geometry of the acetylene ligand is very different from that of the free acetylene molecule: The C—C bond length is lengthened from 1.21 Å to 1.341(6) Å while the CCH bond angle is changed from 180° to 148°. The lengthening of this CC bond again indicates that the bond is weakened by population of electrons in antibonding orbitals. Such antibonding orbitals have zero value in the plane perpendicular to the bond through its midpoint. This plane cuts the section shown in Figure 10 through the vertical line passing through the bond midpoint. The density along this line is indeed lower than elsewhere in the C≡C bond, in accordance with the explanation of the lengthening of the bond.

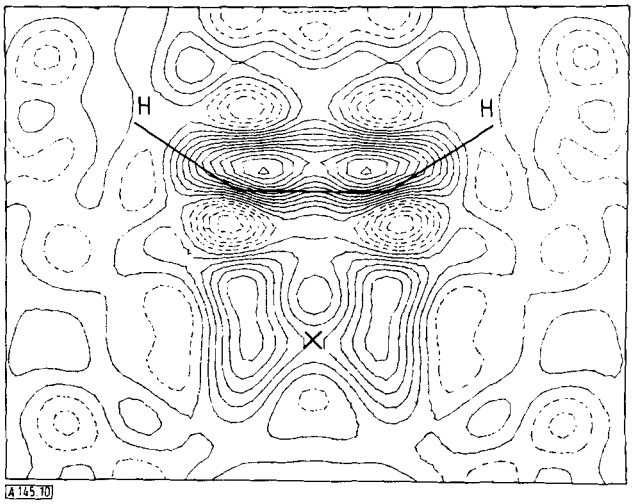


Fig. 10. Deformation density in μ-acetylenebis(η^5-cyclopentadienylnickel). The section shown contains the carbon and hydrogen atoms of the C_2H_2 ligand and is perpendicular to the Ni—Ni bond through its midpoint (indicated by X). Contours as in Fig. 5. From *Wang* and *Coppens* [36].

The changes in the structure of small molecules on coordination to a metal atom have been compared to the electronic excitation which occurs for example on absorption of a light quantum[37]. Such a drastic change will affect the chemical behavior of molecules and is therefore of importance in the study of catalysis of reactions by transition metal atoms.

2.5. Charge Density Studies of Covalent and Metallic Solids

Silicon is one of the very few solids of which perfect crystals are available. This allows unusually accurate measurement of the X-ray structure amplitudes[38]. The corresponding deformation density in the bonds has an estimated standard deviation of better than 0.01 $e\text{Å}^{-3}$ and agrees in peak height, but not in shape with an earlier pseudopotential calculation[39], the experimental density peak being elongated along, rather than perpendicular to the bond. But soon after the experimental results became available introduction of an additional parameter in the theoretical calculation effectively reduced the discrepancy (Fig. 11) and also lead to better agreement with photoemission and reflectance spectra[40]. This shows that semiempirical methods may be successfully parametrized using experimental densities.

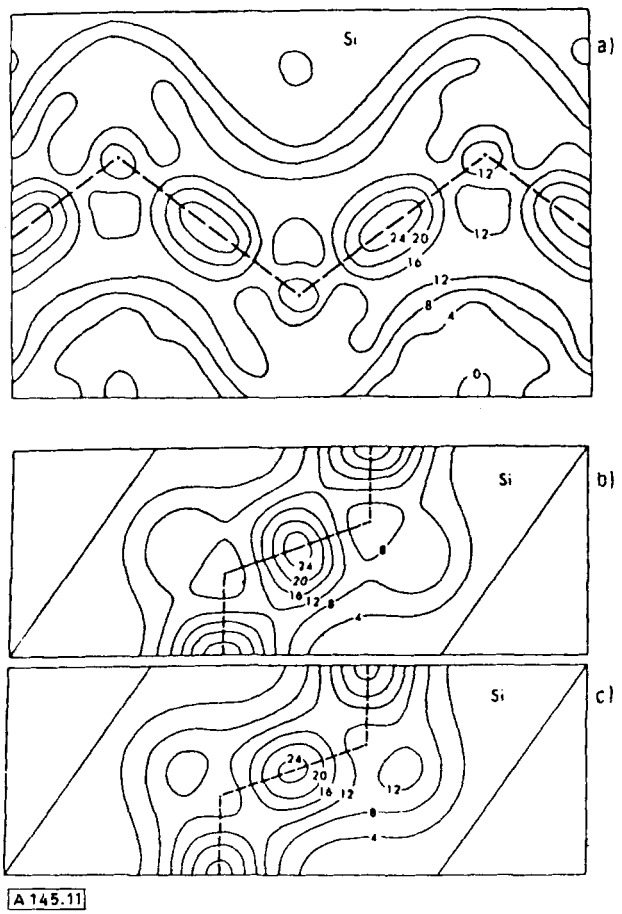


Fig. 11. Valence electron density in silicon. The broken lines indicate the bonds between the Si atoms which are at the corners of the zig-zag curve. Two other equivalent bonds to each atom are above and below the plane shown. a) Experimental density from *Yang* and *Coppens* [39]. b) Charge density from a local pseudopotential calculation [39]. c) Charge density according to a more recent energy-dependent non-local pseudopotential calculation by *Chelikowsky* and *Cohen* [40]. Contour units indicated are in 0.025 $e\text{Å}^{-3}$. The newer calculation is in better agreement with the experimental result.

No theoretical density has been calculated for the silicon containing alloy V_3Si which is a "high-temperature" ($T = 16.85$ K) superconductor. It contains linear chains of vanadium atoms which are more closely spaced, at 2.36 Å, than in vanadium metal where the nearest neighbor distances are 2.62 Å. The experimental X−X density at room temperature indicates accumulation of density between the vanadium atoms typical for covalent bonding (Fig. 12)[41]. There is no peak between nearest neighbor Si and V atoms and a general charge depletion of the region around the Si atom. A simple theoretical explanation of the superconducting properties of V_3Si and related compounds by *Labbe* and *Friedel*[42] is indeed based on a one dimensional (*i.e.* in the chain direction) band of electrons formed by the vanadium d-orbitals. The strong V-V interaction supports a one-dimensional analysis as a first approximation, but more detailed examination of the density maps shows a much lower than cylindrical symmetry of the density in the linear chains, which can only be explained by the effect of the crystal environment. A parallel study on the isomorphous compound Cr_3Si, which has no superconducting properties, shows a lower peak height and therefore less covalency between the Cr atoms[43]. Further variable temperature studies of these systems are presently being undertaken.

A certain degree of covalency has even been observed in Be metal where deformation density is observed within tetrahedra formed by four Be atoms, suggesting an electron deficient multicenter bond[44], comparable with the density observed within the triangle of two-electron three-center bonds in decaborane[45]. The analogy is perhaps not surprising as the number of nearest neighbors in metallic Be (12) far exceeds the number of available valence electrons per atom (2). Similar studies on Al metal are inconclusive due to lack of good single-crystal data on this solid[44b]. But it seems clear that careful charge density measurements will contribute to our understanding of metals and especially alloys which often crystallize in complicated structures with incompletely understood bonding arrangements.

3. Further Analysis of the Charge Density: Net Charges and Dipole Moments

The three-dimensional electron density distribution is the most detailed function obtainable from the X-ray data and it lends itself to rapid qualitative interpretation as discussed above. But we may want to proceed beyond qualitative results to the derivation of functions such as net charges, molecular dipole and quadrupole moments, or the electrostatic potential which are in principle known once the electron density has been obtained (within the limitations imposed by the experimental errors and the fact that the observed X-ray intensities correspond to the electron density averaged over the thermal vibrations of the crystal).

The simplest example of such a derived function is the total number of electrons n on an ion or molecule. If the electron density ρ is known as a function of the positional coordinates x, y, z the electron population in a volume of the crystal is obtained by a three dimensional integration:

$$n_{\text{electrons}} = \iiint_{\text{volume}} \rho(x,y,z)\,dx\,dy\,dz$$

Methods of evaluating such integrals are well-developed[46, 47], but the choice of the volume to be associated with an atom, ion, or molecule is more controversial. A meaningful definition of such a volume is really only possible when the constituents of the crystal are well separated. This occurs for example, when the electron density has a zero or very small value between the ions in an ionic crystal. In this case the boundary between the ions may be taken where the electron density is small and the exact choice of the position of the boundary will then have little effect on the results of the integration. Of course, such a surface of low density will in general not have the regular shape of, for instance, a sphere or an ellipsoid but rather be dependent on the detailed geometry of the crystal. One solution proposed by the author is to define a polyhedral boundary surface composed of planes perpendicular to the lines connecting atoms (see Fig. 13). By performing the integration for various positions of these boundary planes a curve of integrated electron population against plane-position is obtained which will have zero slope when the plane is located in a region of small electron population.

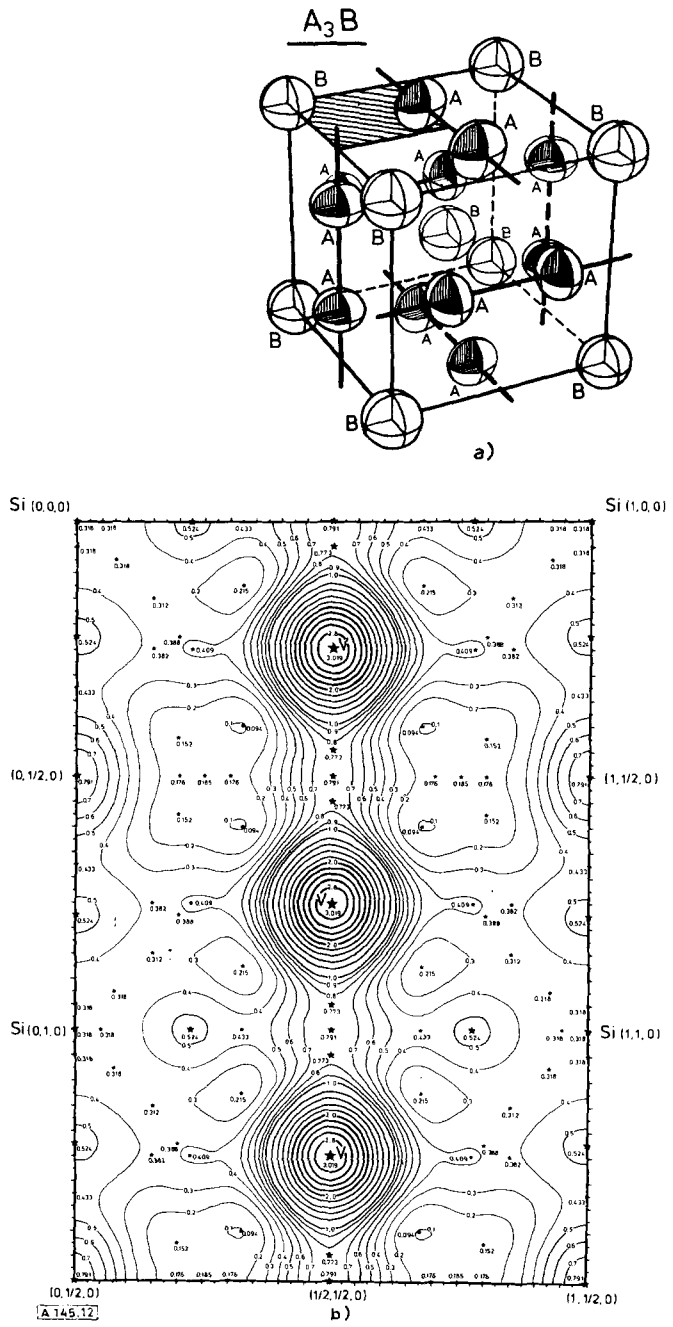


Fig. 12. a) Structure of V_3Si (A = V, B = Si). The hatched area indicates the plane shown in part b. b) Valence electron density in a plane containing a vanadium chain and silicon atoms (at the edges as indicated). The accumulation of density between the nearest neighbor vanadium atoms is characteristic for covalent bonding. Contours at 0.1 eÅ^{-3}. Lowest contour at 0.1 eÅ^{-3}. From *Staudenmann et al.* [41, 43].

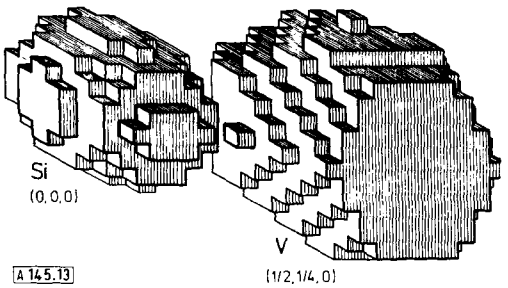


Fig. 13. Atomic volumes of integration in V_3Si type structures. The volumes touch even though they are shown separate here for illustration purposes. The steps are a necessity of the numerical integration method employed. They approximate boundary planes perpendicular to the inter-atomic lines. See text for further details. From refs. [41, 43].

A crystal which contains distinct entities to which this method has been applied is $NaCN \cdot 2H_2O$[22], in which the Na ions are found to have only very small positive charges (<0.15 electron units, the net charge being defined as the total electron population minus the nuclear charge). The result seems to be general as similar conclusions have been reached in studies of NaSCN[53] and the mineral kernite[48] ($Na_2B_4O_6(OH)_2 \cdot 3H_2O$). The sodium ions (or should we say atoms?) in $NaCN \cdot 2H_2O$ are each surrounded by four water molecules (which are in turn each shared by two Na ions) and as in kernite part of the positive charge is found on this hydration mantle in which each H_2O molecule is found to have a net charge of +0.23 units. Similar positive charges have been found on water molecules which are not coordinated to metal atoms as in oxalic acid dihydrate[49].

The volume of integration can be defined very well in molecular crystals in which molecules are held together by weak van der Waals interactions. A numerical integration of the charge density in the organic conductor TTF-TCNQ (tetrathiofulvalene-tetracyanoquinodimethane) indicates a charge transfer of a fraction of an electron (0.55 ± 0.15) from the TTF to the TCNQ molecule[47], in good agreement with less direct evidence from the sulfur chemical shift in the photoelectron spectrum of TTF[50]. This solid has a very high one-dimensional conductivity above 53 K at which temperature a phase transition to an insulating state occurs. Its properties and the mechanism of the phase transition are intricately linked to the number of electrons per molecule. *Comes et al.* concluded from the lattice periodicity in the insulating phase that 0.59 electrons are transferred[51], again in good agreement with the X-ray values. There are many related organic conductors in which the charge transfer is unknown and which would be fruitful subjects for further studies.

Very few examples are available in which a dipole moment has been evaluated from the charge distribution. For both the water molecules in $NaCN \cdot 2H_2O$ dipole moments of about 1.8D were obtained, in surprising agreement with the solution dipole moment of 1.84D. In a similar analysis

of the zwitterion NH_3SO_3 (sulfamic acid) the X-ray dipole moment of 6.5 D is much smaller than the solution value of 12.5 D[52]. This could mean that the dipole moment is markedly lowered upon crystallization, but such a conclusion is premature until error estimates are obtained and other compounds are studied[53]. Calculation of dipole moments represents one of the frontiers of charge density analysis and much further work is indicated.

4. Concluding Remarks

Charge density analysis is a new method for analyzing solids which has fairly general applicability. It requires an accurate X-ray data set, preferably recorded at low temperature, containing many multiple measurements to provide a check on data quality. This means that the great majority of existing data sets are inadequate for this purpose. But methods for interpretation of the data and for analysis of errors have now been developed and systematic analyses of bonding in related compounds is now possible. The technique is inherently slow with X-ray sources presently available, but the information obtained is unusually detailed and not otherwise accessible experimentally.

The author would like to thank several of his colleagues: Dr. J. W. Bats, Dr. B. Rees, Dr. J. L. Staudenmann, and Dr. Z. Berkovitch-Yellin for communicating results prior to publication. Financial support by the National Science Foundation for the part of the work done at SUNY/Buffalo is gratefully acknowledged.

Received: July 12, 1976 [A 145 IE]
German version: Angew. Chem. *89*, 33 (1977)

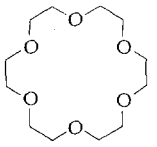
[1] *P. Debye* and *P. Scherrer*, Phys. Z. *19*, 474 (1918).
[2] *R. Brill*, Solid State Phys. *20*, 1 (1967); *S. Göttlicher* and *W. Wölfel*, Z. Elektrochem. *63*, 891 (1959).
[3] *P. Coppens*, MTP Int. Rev. Sci., Phys. Chem. Ser. II, *11*, 21 (1975).
[4] *P. Coppens* and *E. D. Stevens*, Adv. Quantum Chem. *10* (1977), in press.
[5] *P. Coppens*, Acta Crystallogr. *B 30*, 255 (1974).
[6] *D. W. J. Cruickshank*, Acta Crystallogr. *2*, 65 (1949); *B. Rees*, *ibid. A 32*, 483 (1976); *E. D. Stevens* and *P. Coppens*, *ibid. A 32*, 915 (1976).
[7] *R. B. Helmholdt*, *A. J. F. Ruysink*, *H. Reynaers*, and *G. Kemper*, Acta Crystallogr. *B 28*, 318 (1972).
[8] *P. Becker*, *P. Coppens*, and *F. K. Ross*, J. Am. Chem. Soc. *95*, 7604 (1973).
[9] *Z. Berkovitch-Yellin* and *L. Leiserowitz*, J. Am. Chem. Soc. *97*, 5627 (1975).
[10] a) *A. Hartmann* and *F. L. Hirshfeld*, Acta Crystallogr. *20*, 80 (1966); b) *T. Ito* and *T. Sakurai*, *ibid. B 29*, 1594 (1973); c) *D. A. Matthews* and *G. D. Stucky*, J. Am. Chem. Soc. *93*, 5954 (1971).
[11] *W. N. Lipscomb*, Acc. Chem. Res. *6*, 257 (1973), and references given therein.
[12] *W. Bats*, to be published.
[13] *B. Rees* and *P. Coppens*, Acta Crystallogr. *B 29*, 2516 (1973).
[14] *B. Rees* and *A. Mitschler*, J. Am. Chem. Soc., in press.
[15] *J. F. Griffin* and *P. Coppens*, J. Am. Chem. Soc. *97*, 3496 (1975).
[16] *J. Almlöf*, *Å. Kvick*, and *J. O. Thomas*, J. Chem. Phys. *55*, 1821 (1971).
[17] *P. Coppens* and *A. Vos*, Acta Crystallogr. *B 27*, 146 (1971).
[18] *P. Coppens*, *T. M. Sabine*, *R. G. Delaplane*, and *J. A. Ibers*, Acta Crystallogr. *B 25*, 2451 (1969).
[19] *Y. Wang*, *R. H. Blessing*, *F. K. Ross*, *P. Coppens*, and *M. S. Lehmann*, Acta Crystallogr. *B 32*, 572 (1976); *P. Coppens* and *M. S. Lehmann*, *ibid. B 32*, 1777 (1976).
[20] *H. A. Bent*, Chem. Rev. *61*, 275 (1961).
[21] *L. Golic*, *D. Hadzi*, and *F. Lazarini*, Chem. Commun. *1971*, 860.
[22] *W. Bats*, to be published.
[23] *G. H. F. Diercksen*, Theor. Chim. Acta *21*, 335 (1971).
[24] *S. Yamabe* and *K. Morokuma*, J. Am. Chem. Soc. *97*, 4458 (1975).
[25] *P. A. Kollman* and *L. C. Allen*, J. Chem. Phys. *52*, 5085 (1970).
[26] *M. Dreyfus* and *A. Pullman*, Theor. Chim. Acta *19*, 20 (1970).
[27] *Å. Kvick*, Acta Univ. Ups. *322*, 46 (1974); *Å. Kvick*, *R. Thomas*, and *T. F. Koetzle*, Acta Crystallogr. *B 32*, 224 (1976).
[28] *S. Bratoz*, C. R. Acad. Sci. *249*, 1881 (1959).
[29] *E. D. Stevens*, *M. S. Lehmann*, and *P. Coppens*, to be published.
[30] *Å. Kvick* and *T. F. Koetzle*, personal communication.
[31] *H. Hope*, personal communication.
[32] *F. Marumo*, *M. Isobe*, *Y. Saito*, *T. Yagi*, and *S. Akimoto*, Acta Crystallogr. *B 30*, 1904 (1974).
[33] *M. Iwata* and *Y. Saito*, Acta Crystallogr. *B 29*, 822 (1973).
[34] *H. Johansen*, Acta Crystallogr. *A 32*, 353 (1976).
[35] *M. J. S. Dewar*, Bull. Soc. Chim. Fr. *18*, C 71 (1951); *J. Chatt* and *L. A. Duncanson*, J. Chem. Soc. *1953*, 2939.
[36] *Y. Wang* and *P. Coppens*, Inorg. Chem. *15*, 1122 (1976).
[37] *C. K. Ingold* and *G. W. King*, J. Chem. Soc. *1953*, 2702, 2704, 2706.
[38] *S. Tanemura* and *N. Kato*, Acta Crystallogr. *A 28*, 69 (1972); *P. J. E. Aldred* and *M. Hart*, Proc. R. Soc. London *A 332*, 223 (1973).
[39] *Y. W. Yang* and *P. Coppens*, Solid State Commun. *15*, 1555 (1974).
[40] *J. R. Chelikowsky* and *M. L. Cohen*, Phys. Rev. *B 10*, 5095 (1974).
[41] *J. L. Staudenmann*, *P. Coppens*, and *J. Muller*, Solid State Commun. *19*, 29 (1976).
[42] *J. Labbe* and *J. Friedel*, J. Phys. (Paris) *27*, 153, 303 (1966).
[43] *J. L. Staudenmann*, Dissertation, Université de Genève 1976.
[44] a) *R. F. Stewart*, personal communication; b) *Y. W. Yang*, Thesis, SUNY/Buffalo 1976.
[45] *R. Brill*, *H. Dietrich*, and *H. Dierks*, Acta Crystallogr. *B 27*, 2003 (1971).
[46] *K. Kurki-Suonio*, Ital. Crystallogr. Assoc. Meeting, Bari 1971.
[47] *P. Coppens*, Phys. Rev. Lett. *35*, 98 (1975).
[48] *W. F. Cooper*, *F. K. Larsen*, *P. Coppens*, and *R. F. Giese*, Am. Mineral. *58*, 21 (1973).
[49] *P. Coppens*, *D. Pautler*, and *J. F. Griffin*, J. Am. Chem. Soc. *93*, 1051 (1971).
[50] *W. D. Grobman*, *R. A. Pollak*, *D. E. Eastman*, *E. T. Maas, Jr.*, and *B. A. Scott*, Phys. Rev. Lett. *32*, 534 (1974); *A. J. Epstein*, *N. O. Lipari*, *P. Nielson*, and *D. J. Sandman*, *ibid. 34*, 667 (1975).
[51] *R. Comes*, *S. M. Shapiro*, *G. Shirane*, *A. F. Garito*, and *A. J. Heeger*, Phys. Rev. Lett. *35*, 1518 (1975).
[52] *W. Bats*, *T. F. Koetzle*, and *P. Coppens*, Acta Crystallogr. *A 31*, S 221 (1975); *ibid.*, in press.
[53] *W. Bats* and *P. Coppens*, to be published.

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

Crown Ether Catalyzed Reduction of Aromatic Nitro Compounds to Give Amines[1]

By *Howard Alper*, *Daniel Des Roches*, and *Hervé des Abbayes*[*]

Aromatic nitro compounds are reduced to amines by refluxing with an equimolar amount of $Fe_3(CO)_{12}$ in benzene/methanol for 10 to 17 h[2]. We have found that this reaction is catalyzed by the crown ether [18]crown-6 *(1)* in the presence of 1 N KOH. Only half the amount of $Fe_3(CO)_{12}$ is needed, and the reaction proceeds within 1.5 to 2.5 h on stirring of the reactants in benzene at room temperature. Work-up is simpler and the yields are just as good (see Table 1).



(1)

$$ArNO_2 + Fe_3(CO)_{12} \xrightarrow[1\,N\,KOH,\ C_6H_6]{(1)} ArNH_2$$

Table 1. Reaction times and yields.

Amine formed	Reaction time [h]	Yield [%]
Aniline	2.5	60
p-Toluidine	1.5	65
p-Anisidine	2.0	78 [a]
p-Chloroaniline	2.5	79 [b]
2-Fluorenylamine	2.0	84 [c]

[a] 3% in the absence of *(1)*.
[b] 2% in the absence of *(1)*.
[c] 33% in the absence of H_2O.

The nitro compound was almost completely recovered when the reaction was repeated in the absence of the crown ether *(1)* (see Table 1), and the use of solid KOH, *i.e.* the absence of water, gave the amines in significantly lower yields.

[*] Prof. Dr. H. Alper [+], Dr. D. Des Roches, and Dr. H. des Abbayes [**]
Department of Chemistry, University of Ottawa
Ottawa, Ontario, Canada K1N 6N5
[+] To whom correspondence should be addressed.
[**] France-Canada exchange scientist.

We assume the reaction to proceed as follows: The crown ether *(1)* bonds the K^+ ion of KOH to give the unsolvated and highly reactive OH^- ion. This species attacks $Fe_3(CO)_{12}$ in the organic phase, affording $[Fe_3(CO)_{11}]^{2-}$[3] which yields the ions OH^- and $[HFe_3(CO)_{11}]^-$ with water. The latter ionic product reduces the nitro compound.

Procedure:

To a mixture of nitroarene (1.0 mmol), $Fe_3(CO)_{12}$ (0.5 mmol), and [18]crown-6 (0.1 mmol) in benzene (10 ml), is added 1 N KOH (10 ml). The solution was vigorously stirred at room temperature for 1.5—2.5 hours (N_2 atmosphere). The layers were separated and the aqueous layer was washed with ether; the washings are added to the separated organic layer, dried ($MgSO_4$), and evaporated *in vacuo*. The residue is chromatographed on a silica gel column using benzene or benzene/ether as the eluant.

Received: August 30, 1976;
revised: September 30, 1976 [Z 574 IE]
German version: Angew. Chem. *89*, 43 (1977)

CAS Registry numbers:
(1), 17455-13-9; aniline, 62-53-3; *p*-toluidine, 106-49-0; *p*-anisidine, 104-94-9; *p*-chloroaniline, 106-47-8; 2-fluorenylamine, 153-78-6; nitrobenzene, 98-95-3; 1-methyl-4-nitrobenzene, 99-99-0; 1-methoxy-4-nitrobenzene, 100-17-4; 1-chloro-4-nitrobenzene, 100-00-5; 2-nitro-9*H*-fluorene, 607-57-8; $Fe_3(CO)_{12}$, 17685-52-8

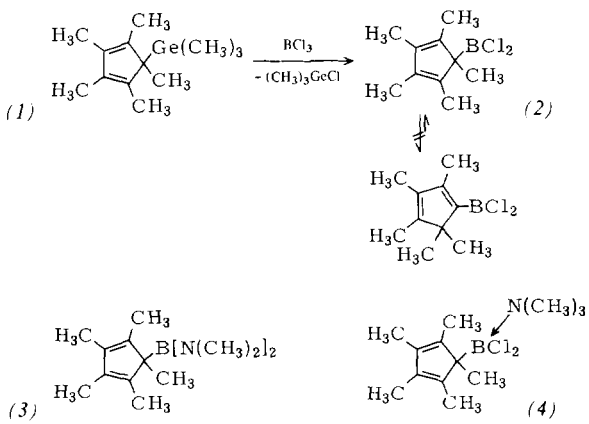
[1] This work was supported by the National Research Council of Canada.
[2] *J. M. Landesberg*, *L. Katz*, and *C. Olsen*, J. Org. Chem. *37*, 930 (1972).
[3] *W. Hieber* and *G. Brendel*, Z. Anorg. Allg. Chem. *289*, 338 (1957).

Synthesis and Dynamic Behavior of Pentamethylcyclopentadienylboranes[**]

By *Peter Jutzi* and *Arnulf Seufert*[*]

The pentamethylcyclopentadienylboranes described here are the first representatives of this type of compounds in which boron is bound to the cyclopentadiene ring in the allyl position. The preferred vinyl isomers in all previously known cyclopentadienylboranes[1] cannot be formed here owing to the high activation energy of the 1,2-methyl shift.

Synthesis of the surprisingly thermally stable dichloro(pentamethylcyclopentadienyl)borane *(2)* has been achieved by



(1) *(2)* *(3)* *(4)*

[*] Doz. Dr. P. Jutzi and Dipl.-Chem. A. Seufert
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)
[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

reaction of trimethyl(pentamethylcyclopentadienyl)germane *(1)*[2] with boron trichloride. Reaction of *(2)* with dimethylamine affords the bis(dimethylamino)(pentamethylcyclopentadienyl)borane *(3)*, and with trimethylamine the adduct *(4)*[3].

These three compounds differ in their dynamic behavior, since the rate of migration of the boryl group depends on the Lewis acidity of the boron atom.

Compound *(2)* has a fluxional structure owing to very rapid degenerate sigmatropic rearrangements of the BCl_2 group. At 40°C a sharp ^{1}H-NMR signal is observed at $\delta = 1.81$ ppm (in CH_2Cl_2) for the three types of chemically non-equivalent methyl groups; cooling to −80°C leads to a slight broadening of the signal.

Compound *(3)* has a static structure at 40°C. The ^{1}H-NMR spectrum (in CH_2Cl_2) shows separate signals for vinylic and allylic methyl groups: δCH_3 vinyl.: 1.83 ppm S(12); δCH_3 allyl.: 1.15 ppm S(3); $\delta N{-}CH_3$: 2.55 ppm, broad (12). However, on increasing the temperature rearrangements also take place in the case of *(3)* and lead to coalescence of the signals of all methyl groups attached to the cyclopentadiene ring. In addition, the non-equivalence of the *N*-methyl groups effects a temperature-dependent hindrance to rotation.

Compound *(4)* is a static molecule at all temperatures. The ^{1}H-NMR spectrum still shows sharp separated signals for the various methyl groups attached to the cyclopentadiene ring, even at 100°C: δCH_3 vinyl.: 2.07 ppm S(6), 1.85 ppm, S(6); δCH_3 allyl.: 1.22 ppm S(3); $\delta N{-}CH_3$: 2.75 ppm S(9).

Experimental:

Compound *(2)*: A solution of *(1)* (6.6 g, 26 mmol) in CH_2Cl_2 (20 ml) is added dropwise and slowly at −30°C to a solution of BCl_3 (3.2 g, 27 mmol) in CH_2Cl_2 (20 ml). After one hour's stirring at room temperature *(2)* is isolated by fractional distillation *in vacuo* as a colorless liquid, b.p. 55°C/0.5 torr; yield 3.2 g (57 %); $M^{\oplus}$: *m/e* = 216 (0.5 %).

Compound *(3)*: A solution of *(2)* (3.2 g, 15 mmol) in pentane (20 ml) is added at −30°C to a solution of $HN(CH_3)_2$ (2.7 g, 59 mmol) in pentane (25 ml). After filtration, *(3)* is obtained by fractional distillation *in vacuo* as a colorless viscous liquid, b.p. 74°C/0.05 torr; yield 1.8 g (52 %); $M^{\oplus}$: *m/e* = 234 (1.5 %).

Compound *(4)*: $N(CH_3)_3$ (0.2 g, 3 mmol) is added at −20°C to a solution of *(2)* (0.4 g, 2 mmol) in pentane (35 ml). The precipitate is filtered off and recrystallized from methylcyclohexane; m.p. 135°C (dec.), yield 0.4 g (73%); $M^{\oplus}$: *m/e* = 275 (0.1 %).

Received: October 14, 1976 [Z 579 IE]
German version: Angew. Chem. *89*, 44 (1977)

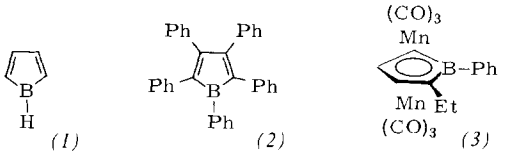
CAS Registry numbers:
(1), 26168-10-5; *(2)*, 60828-63-9; *(3)*, 60828-64-0; *(4)*, 60828-65-1; BCl_3, 10294-34-5; $HN(CH_3)_2$, 124-40-3; ^{11}B, 14798-13-1

[1] *P. Jutzi* and *A. Seufert*, Angew. Chem. *88*, 333 (1976); Angew. Chem. Int. Ed. Engl. *15*, 295 (1976); and literature cited therein.
[2] *A. Davison* and *P. E. Rakita*, Inorg. Chem. *9*, 289 (1970).
[3] The constitutions of *(2)*, *(3)*, and *(4)* are confirmed by analytical data.

Two Routes to Complex Derivatives of Borole[1]

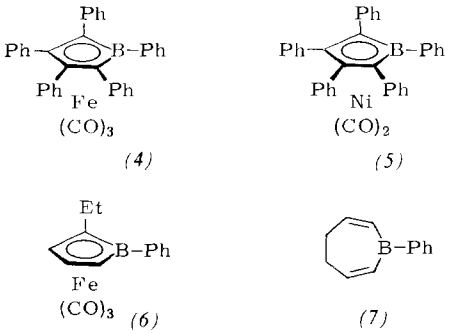
By *Gerhard E. Herberich*, *Joachim Hengesbach*, *Ulrich Kölle*, and *Wolfgang Oschmann*[*]

Unsubstituted borole *(1)* is unknown. The only non-complex derivative reported so far is pentaphenylborole *(2)*[2], and the only complex derivative the triple-decker complex *(3)*[3], a *closo*-metallocarborane. We report here on two extensions to borole chemistry which lead to complexes of the *nido* type.



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

Pentaphenylborole *(2)* reacts with $Fe_2(CO)_9$ to give tricarbonyl(η-pentaphenylborole)iron *(4)*[4], and with excess $Ni(CO)_4$ to give dicarbonyl(η-pentaphenylborole)nickel *(5)*[4].



(4) *(5)* *(6)* *(7)*

1-Phenyl-4,5-dihydroborepin *(7)*[5] tends to undergo ring contraction[3] in complexation reactions carried out under drastic conditions. Reaction with $Fe(CO)_5$ in boiling mesitylene leads to tricarbonyl[η⁵-(2-ethyl-1-phenylborole]iron *(6)*[4], and a mixture of stereoisomeric bis(2-methyl-1-phenylborinato)iron complexes which was not investigated any further.

The borole ligands in *(4)* to *(6)* are bound to the metal as pentahapto four-electron ligands. The boron-metal bond suppresses the cleavage of the phenyl group at boron in the mass spectra and in the case of *(6)* is directly detectable by the ^{11}B-shift of $\delta = +19.6$ ppm[6]. Further, in contrast to the extremely water-sensitive pentaphenylborole *(2)*, compounds *(4)* to *(6)* are stable towards water.

Table 1. Data for borole complexes *(4)* to *(6)*.

(4): MS (70 eV): *m/e* (from 10 % $I_{rel.}$) 584 (7; M^+), 556 (20; −CO), 500 (100; −3 CO), 322 (48; $C_2BPh_3Fe^+$), 264 (22; 322 $-H_2$, −Fe), 250 (14; $C_4BPh_5Fe^{2+}$), 178 (16; $C_2Ph_2^+$). IR (*n*-hexane): 2056 w, 2001 w, 1992 cm^{-1} w; (KBr): 2048, 1997, 1990 cm^{-1}; for comparison: $(C_4Ph_4)Fe(CO)_3$ in KBr [7]: 2033, 1965, 1931 cm^{-1}; $(C_5Ph_4O)Fe(CO)_3$ in KBr [7]: 2062, 2012, 1988 cm^{-1}.

(5): MS (70 eV): *m/e* (from 3 % $I_{rel.}$) 558 (3; M^+), 530 (24; −CO), 502 (100; −2 CO), 444 (12; $C_4BPh_5^+$), 324 (52; $C_2BPh_3Ni^+$), 251 (14; $C_4BPh_5Ni^{2+}$), 178 (11; $C_2Ph_2^+$). IR (*n*-hexane): 2073 w, 2031 cm^{-1} w.

(6): MS (70 eV): *m/e* (from 15 % $I_{rel.}$) 308 (32; M^+), 280 (30; −CO), 252 (36; −2 CO), 224 (100; −3 CO), 222 (17; 224 $-H_2$), 146 (30; 224 $-C_6H_6$), 56 (58; Fe^+). IR (*n*-hexane): 2067 w, 2007 w, 2000 cm^{-1} w. ^{1}H-NMR (τ values, in C_6D_6 at room temperature, 100 and 270 MHz): 2.24 m (2 H_o), 2.66 m (2 H_m, H_p), 5.34 pseudotriplet (3-H), 5.49 dd (4-H), 6.63 dd (5-H), 7.86 and 8.26 2 × 6 lines from qq (CH_2), 9.12 t (CH_3); $^3J_{34} = 2.5$, $^3J_{45} = 4.5$, $^4J_{35} = 1.7$, $^2J_{CH_2} = 14.2$, $^3J_{CH_2-CH_3} = 7.0$ Hz.

Experimental:

(4): A mixture of *(2)*[8] (670 mg, 1.51 mmol) and $Fe_2(CO)_9$ (750 mg, 2.06 mmol) in toluene (50 ml) is stirred at 45 to 50°C until the blue color of *(2)* has disappeared. Evaporation of volatiles, chromatography on Al_2O_3 (7 % H_2O) with pentane/CH_2Cl_2 (85:15) and recrystallization from pentane/CH_2Cl_2 furnishes *(4)* in 40 % yield (350 mg), m.p. 218 to 220°C, decomposition above 260°C; pale yellow crystals,

[*] Prof. Dr. G. E. Herberich, Dipl.-Chem. J. Hengesbach, Dr. U. Kölle, and Dipl.-Chem. W. Oschmann
Institut für Anorganische Chemie der Technischen Hochschule
Prof.-Pirlet-Strasse 1, D-5100 Aachen (Germany)

light- and air-sensitive in solution, readily soluble in toluene and CH_2Cl_2.

(5): A solution of *(2)*[8] (980 mg, 2.21 mmol) in toluene (80 ml) is added dropwise at 20°C to a solution of $Ni(CO)_4$ (1.2 ml, 9.3 mmol) in toluene (10 ml). Workup as for *(4)* and recrystallization from CH_2Cl_2 affords 654 mg *(5)* (53 % yield), m.p. 214 to 216°C (dec.); wine-red crystals, somewhat sensitive to light, light- and air-sensitive in solution, readily soluble in toluene and CH_2Cl_2.

(6): A mixture of 1-phenyl-4,5-dihydroborepin *(7)*[5] (2.0 g, 11.9 mmol) and $Fe(CO)_5$ (6.5 ml, 48 mmol) in mesitylene (50 ml) is heated under reflux until *ca.* 5.4 liters of CO (20°C) has been liberated. Removal of solvent (10^{-2} torr) and chromatography on acidic Al_2O_3 (4 % H_2O) with pentane affords *ca.* 300 ml of a golden-yellow eluate containing *(6)* in 18 % yield (650 mg), amber-colored oil, solid at −30°C; air- and light sensitive. Further elution with pentane/diethyl ether (90:10) furnishes 650 mg of a mixture of stereoisomeric bis(2-methyl-1-phenylborinato)iron complexes as a brown-red, semisolid oil.

Received: October 15, 1976 [Z 581 IE]
German version: Angew. Chem. *89*, 43 (1977)

CAS Registry numbers:
(2), 20195-59-9; *(4)*, 60840-47-3; *(5)*, 60840-46-2; *(6)*, 60840-45-1; $Fe_2(CO)_9$, 20982-74-5; $Ni(CO)_4$, 13463-90-1; $Fe(CO)_5$, 13463-40-6; *(7)*, 59269-92-0

[1] Part 1 of Derivatives of Borole.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[2] *J. J. Eisch, N. K. Hota,* and *S. Kozima,* J. Am. Chem. Soc. *91*, 4575 (1969).

[3] *G. E. Herberich, J. Hengesbach, U. Kölle, G. Huttner,* and *A. Frank,* Angew. Chem. *88*, 450 (1976); Angew. Chem. Int. Ed. Engl. *15*, 433 (1976).

[4] Correct C, H, B, and metal analyses obtained.

[5] *D. Sheehan,* Ph. D. Thesis, Yale University 1964; Diss. Abstr. *25*, 4417 (1965); cf. also *A. J. Leusink, W. Drenth, J. G. Noltes,* and *G. J. M. van der Kerk,* Tetrahedron Lett. *1967*, 1263.

[6] In C_6D_6, referred to $Et_2O \cdot BF_3$ (positive signs at low field).

[7] *W. Hübel* and *E. H. Braye,* J. Inorg. Nucl. Chem. *10*, 250 (1959).

[8] Synthesized from 1,1-dimethyl-2,3,4,5-tetraphenylstannole and $C_6H_5BCl_2$ in toluene, cf. [2]. Good samples of *(2)* are deep blue, m.p. 243 to 245°C (dec): *W. Oschmann,* Diplomarbeit, Technische Hochschule, Aachen 1976.

The First Oxoferrate(III) Having a Ring Structure: $Na_{14}[Fe_6O_{16}]$[1]

By *Gerold Brachtel* and *Rudolf Hoppe*[*]

During our search for the hitherto unknown Na_3FeO_3, which in the meantime we have isolated in the form of yellow translucent crystals, a further phase was obtained as lustrous, yellow, single crystals which rapidly decompose in air. For the preparation, an intimate mixture of Na_2O_2 and FeO (Na : Fe = 2.2 : 1) was heated in a small Ni bomb (600°C, 5 d). The product was handled in an argon atmosphere and single crystals picked out under the microscope. According to Weissenberg and precession photographs $Na_7Fe_3O_8$ is seen to crystallize triclinically (diffractometer data): $a = 11.47_2$, $b = 8.33_7$, $c = 5.96_6$ Å, $\alpha = 109.3$, $\beta = 87.7$, $\gamma = 111.2°$, $Z = 2$. For the structure determination 2116 symmetry-independent reflections were measured[2] (Mo-K_α, graphite monochromator). The structure was solved by direct methods and interpretation of the Patterson synthesis[3]. Refinement of all particles with anisotropic temperature parameters gave an R-value of 4.8 % (space group $P\bar{1}$) for 1932 reflections with $F > 2.5\sigma(F)$.

The structural analysis reveals the following (see Fig. 1): *Primary structure:* iron is surrounded almost tetrahedrally by O (mean bond lengths: Fe—O (terminal) = 1.84 Å, Fe—O (bridge) = 1.91 Å. The coordination sphere of the sodium

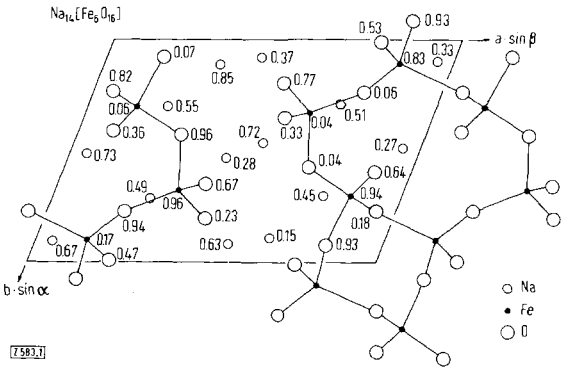


Fig. 1. Crystal structure of $Na_{14}[Fe_6O_{16}]$. Values of z in fractions of c.

particles is irregular. Calculation of the Effective Coordination Number (ECoN)[4] of Na towards O gives a value of 4 for the Na particles.

Secondary structure: Within the region of the unit cell the structure is predominated by six-membered rings of Fe: the Fe particles are bound to one another by O bridges.

Tertiary structure: Along [010] two thirds of the FeO_4 tetrahedra are coupled in the form of a "Dreier-Doppelkette", which has been proposed in the case of the silicate $Na_2Ca_3[Si_6O_{16}]$[5].

The compound described here illustrates once again the analogy between oxometalates with d^5 configuration and silicates[6]. This is also apparent in the compounds with island structure, Na_5FeO_4[7] and $Na_8Fe_2O_7$[8], previously prepared by us. However, the type of structure where two tetrahedra are coupled by a common edge, as has been observed in $K_6[Fe_2O_6]$[9] and $K_6[Mn_2O_6]$[10], has not yet been observed in the silicates.

The Madelung Part of the Lattice Energy, MAPLE[11] (8643.0 kcal/mol) is in excellent agreement with the sum of the MAPLE values of the binary oxides (8612.5 kcal/mol, $\Delta = 0.4$ %).

Received: October 4, 1976 [Z 583 IE]
German version: Angew. Chem. *89*, 45 (1977)

CAS Registry numbers:
$Na_{14}[Fe_6O_{16}]$, 60920-55-0

[1] Part of the Dissertation by *G. Brachtel,* Universität Giessen.

[2] The measurements were carried out with a Philips PW 1100 four-circle diffractometer in our Institute by Dr. *M. Jansen.*

[3] SHEL-X-Programmsystem, *G. Sheldrick,* unpublished.

[4] *D. Fink* and *R. Hoppe,* Z. Anorg. Allg. Chem. *422*, 1 (1976).

[5] *I. Maki,* Yogyo Kyokai Shi 76, 203 (1968).

[6] *M. Jansen,* Z. Anorg. Allg. Chem. *417*, 35 (1975); *M. Jansen* and *R. Hoppe, ibid. 409*, 152 (1974).

[7] *G. Brachtel* and *R. Hoppe,* Naturwissenschaften *62*, 138 (1975).

[8] *G. Brachtel* and *R. Hoppe,* Z. Anorg. Allg. Chem., in press.

[9] *H. Rieck* and *R. Hoppe,* Angew. Chem. *85*, 589 (1973); Angew. Chem. Int. Ed. Engl. *12*, 673 (1973); Z. Anorg. Allg. Chem. *408*, 151 (1974).

[10] *G. Brachtel* and *R. Hoppe,* Naturwissenschaften *63*, 339 (1976).

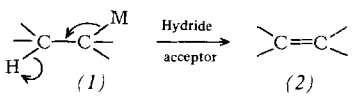
[11] *R. Hoppe,* Angew. Chem. *78*, 52 (1966); Angew. Chem. Int. Ed. Engl. *5*, 95 (1966); Angew. Chem. *82*, 7 (1970); Angew. Chem. Int. Ed. Engl. *9*, 25 (1970); Adv. Fluorine Chem. *6*, 387 (1970); *R. Hoppe:* Crystal Structure and Chemical Bonding in Inorganic Chemistry. Amsterdam 1975, p. 127.

[*] Prof. Dr. R. Hoppe and Dipl.-Chem. G. Brachtel
Institut für Anorganische und Analytische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Giessen (Germany)

Stereoselective Hydride Elimination from Organo-Lithium and -Magnesium Compounds[**][1]

By *Manfred T. Reetz* and *Wilfried Stephan*[*]

In contrast to olefin formation by base-induced hydrogen halide elimination, little is known concerning hydride abstraction from carbanions. We report here on hydride acceptors which effect elimination of β-hydrogen atoms from organolithium and -magnesium compounds under mild conditions. Using triphenylmethyltetrafluoroborate[2], tricyclohexylborane, and tri(*sec*-butyl)borane[3] as hydride acceptors we were able to convert structurally different lithium and magnesium compounds *(1)* into olefins *(2)* with simultaneous formation of triphenylmethane and trialkylborohydrides, respectively (see Table 1).



(1) *(2)*

M = Li, Mg

Table 1. Olefins from organo-lithium and -magnesium compounds.

Metal compound	Hydride acceptor	Olefin [a]	Yield [%]
2-Hexylmagnesium chloride	Triphenylmethyltetrafluoroborate	1-Hexene (79) *trans*-2-Hexene (10) *cis*-2-Hexene (11)	74
Cyclohexylmagnesium chloride		Cyclohexene	75
1-Decylmagnesium chloride		1-Decene	28
1,1-Diphenyl-1-hexyllithium		1,1-Diphenyl-1-hexene	65
tert-Butyllithium	Tri(*sec*-butyl)borane	Isobutene	>95
1,1-Diphenyl-1-hexyllithium		1,1-Diphenyl-1-hexene	80
9,10-Dihydro-9-anthracenyllithium		Anthracene	86
2-Hexyllithium		1-Hexene (68) *trans*-2-Hexene (23) *cis*-2-Hexene (9)	60
1-Decyllithium		1-Decene	< 4
2-Hexyllithium	Tricyclohexylborane	1-Hexene (68) *trans*-2-Hexene (22) *ci*-2-Hexene (10)	62
1-Decyllithium		1-Decene	< 4

[a] Isomeric ratio given in brackets.

The good yields of olefin obtained with triphenylmethyltetrafluoroborate are surprising, since reaction of carbanions with carbenium ions should lead to C—C bond formation[4]. While this hydride acceptor promotes smooth eliminations within an hour already at −20 to −78 °C, the isoelectronic, but neutral trialkylboranes require longer reaction times (>16 hours) at 30 to 55 °C. It can been seen from Table 1 that the yields of olefin depend on the structure of the organometallic compound and increase clearly within the series primary < secondary < tertiary. This is due to the influence of steric factors on the competition between hydride elimination and carbanion addition[4]. Formation of the thermodynamically less stable Hofmann product is consistently favored. This selectivity may arise, not so very much from a possibly increased "hydride character" of the β-hydrogen atom on the alkyl residue, but rather from steric influences: the attack of the hydride acceptor on the lesser substituted alkyl residue is easier due to steric reasons[5]. The *cis/trans* ratios are more difficult to explain.

Experimental

To a solution of triphenylmethyltetrafluoroborate (3.3 g, 0.01 mol) in dry methylene chloride (40 ml) at −78 °C is added 0.01 mol of 2-hexylmagnesium chloride. The mixture is stirred at −78 °C for 1 h, allowed to warm to room temperature and hydrolyzed. The ethereal phase is analyzed gas-chromatographically (squalane, 90 m capillary column, 60 °C, 40 ml He/min): 74 % yield of hexene; isomer ratio see Table 1.

Received: October 19, 1976 [Z 584a]
German version: Angew. Chem. *89*, 46 (1977)

CAS Registry numbers:
2-hexylmagnesium chloride, 13406-08-1; cyclohexylmagnesium chloride, 931-51-1; 1-decylmagnesium chloride, 20157-33-9; 1,1-diphenyl-1-hexyllithium, 3462-81-5; *tert*-butyllithium, 594-19-4; 9,10-dihydroanthracenyllithium, 17228-13-6; 2-hexyllithium, 13406-09-2; 1-decyllithium, 4416-59-5; triphenylmethyl tetrafluoroborate, 341-02-6; tri-(*sec*-butylborane), 1113-78-6; tricyclohexylborane, 1088-01-3; 1-hexene, 592-41-6; *trans*-2-hexene, 4050-45-7; *cis*-2-hexene, 7688-21-3; cyclohexene, 110-83-8; 1-decene, 872-05-9; 1,1-diphenyl-1-hexene, 1530-19-4; isobutene, 115-11-7; anthracene, 120-12-7

[1] Part 2 of Hydride Eliminations.—Part 1: *M. T. Reetz* and *C. Weis*, Synthesis, in press.

[2] Triphenylmethyltetrafluoroborate is frequently employed as a hydride acceptor in carbenium ion chemistry: *L. F. Fieser* and *M. Fieser:* Reagents for Organic Synthesis, Wiley, New York 1967, Vol. 1, p. 1256; Reactions with alkylmercury compounds: *J. M. Jerkunica* and *T. G. Traylor*, J. Am. Chem. Soc. *93*, 6274 (1971).

[3] Triphenylborane was first employed by *Wittig* to effect hydride transfer in tertiary phenyl-substituted alkyllithium compounds: *G. Wittig* and *W. Stilz*, Justus Liebigs Ann. Chem. *598*, 85 (1956); cf. *E. I. Negishi*, J. Organomet. Chem. *108*, 281 (1976).

[4] In some cases addition products are detected as well as olefins.

[5] *H. C. Brown* and *I. Motitani*, J. Am. Chem. Soc. *75*, 4112 (1953); *D. C. Griffith*, *D. L. Meges*, and *H. C. Brown*, Chem. Commun. *1968*, 90.

[*] Doz. Dr. M. T. Reetz and W. Stephan
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

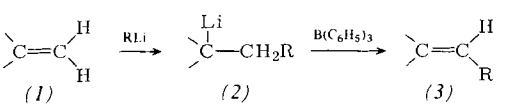
[**] This work was supported by the Fonds der Chemischen Industrie.

Nucleophilic Substitution of Vinylic Hydrogen Atoms by Carbanions[**][1]

By *Manfred T. Reetz* and *Dieter Schinzer*[*]

Hydride abstractions from carbanions are of preparative utility, since organometallic compounds are not only accessible *via* halogen-metal exchange or ether cleavage, but also by addition to activated olefins, by deprotonation, and by rearrangement. We report here on addition-elimination reactions which effect the substitution of vinylic hydrogen atoms by a variety of carbon residues in a one-pot reaction.

When activated olefins of type *(1)* were allowed to react with organolithium compounds, the lithium derivatives *(2)*[2] were obtained from which a hydrogen atom β to lithium could be eliminated as hydride ion by reaction with triphenylborane[3]. The end products were the olefins *(3)*.



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

Table 1 shows that these C—C bond formations with conservation of the olefin function proceeds smoothly even when

[*] Doz. Dr. M. T. Reetz and Dipl.-Ing. D. Schinzer
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

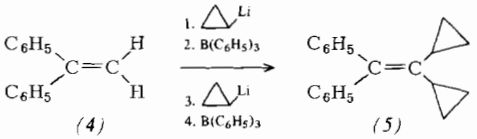
[**] This work was supported by the Fonds der Chemischen Industrie.

Table 1. Trisubstituted olefins by addition-elimination reactions [a].

Starting olefin	Alkyllithium	Product	Yield [%]
1,1-Diphenylethylene	*n*-Butyllithium	1,1-Diphenyl-1-hexene	89
	tert-Butyllithium	1,1-Diphenyl-3,3-dimethyl-1-butene	65
	Phenyllithium	Triphenylethylene	84
	Cyclopropyllithium	1-Cyclopropyl-2,2-diphenylethylene	70
1-Phenyl-1-(trimethylsilyl)ethylene	*n*-Butyllithium	1-Phenyl-1-(trimethylsilyl)-1-hexene [b]	75
	tert-Butyllithium	1-Phenyl-1-(trimethylsilyl)-3,3-dimethyl-1-butene [b]	80
	Cyclopropyllithium	1-Cyclopropyl-2-phenyl-2-(trimethylsilyl)ethylene [b]	85
1-Phenyl-1-(diphenylphosphino)-ethylene	*n*-Butyllithium	1-Phenyl-1-(diphenylphosphino)-1-hexene [b]	90

[a] Addition in tetrahydrofuran at 0°C; hydride abstraction with triphenylborane [3] at room temperature.
[b] Stereochemistry and composition of the *Z*/*E* mixture at present uncertain.

such sterically demanding groups as *tert*-butyl residues are incorporated. The applicability of the reaction to vinylsilanes is noteworthy, since these are readily modifiable and synthetically interesting[4]. Finally, it should be mentioned that double substitutions in one-pot reactions are also possible, as demonstrated by the preparation of *(5)* from *(4)* (61 % yield).



(4) *(5)*

Preparation of 1,1-diphenyl-1-hexene

13 ml of a 1.65 M solution of *n*-butyllithium in *n*-hexane is added dropwise at 0°C to a solution of 1,1-diphenylethylene (3.65 g, 0.02 mol) in anhydrous tetrahydrofuran (50 ml). The mixture is stirred for 85 min at room temperature and the resulting deep-red solution treated with 5 g (0.021 mol) triphenylborane[3] in 30 ml tetrahydrofuran; a gradual decolorization takes place. After 15 h the mixture is diluted with 50 ml petroleum ether (b.p. 40 to 60°C), the two phases that are formed are separated, and the lower phase is extracted twice with petroleum ether. The combined petroleum ether phases are washed with a 10 % sodium hydroxide solution and water and dried over sodium sulfate. Removal of solvent from the dried solution yields 4.2 g (89 %) of pure 1,1-diphenyl-1-hexene; ^{1}H-NMR spectrum identical with that of an authentic sample[5].

Received: October 19, 1976 [Z 584b IE]
German version: Angew. Chem. *89*, 46 (1977)

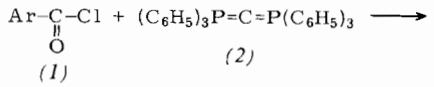
CAS Registry numbers:
1,1-diphenylethylene, 530-48-3; 1-phenyl-1-(trimethylsilyl)ethylene, 1923-01-9; 1-phenyl-1-(diphenylphosphino)ethylene, 17620-97-2; *n*-butyllithium, 109-72-8; *tert*-butyllithium, 549-19-4; phenyllithium, 591-51-5; cyclopropyllithium, 3002-94-6; 1,1-diphenyl-1-hexene, 1530-19-4; 1,1-diphenyl-3,3-dimethyl-1-butene, 23586-64-3; triphenylethylene, 58-72-0; 1-cyclopropyl-2,2-diphenylethylene, 14799-59-8; *Z*-1-phenyl-1-trimethylsilyl-1-hexene, 60896-02-8; *E*-1-phenyl-1-trimethylsilyl-1-hexene, 60896-03-9; *Z*-1-phenyl-1-(trimethylsilyl)-3,3-dimethyl-1-butene, 60896-04-0; *E*-1-phenyl-1-(trimethylsilyl)-3,3-dimethyl-1-butene, 60896-05-1; *Z*-1-cyclopropyl-2-phenyl-2-(trimethylsilyl-ethylene, 60896-06-2; *E*-1-cyclopropyl-2-phenyl-2-(trimethylsilyl)ethylene, 60896-07-3; *Z*-1-phenyl-1-(diphenylphosphino)-1-hexene, 60896-08-4; *E*-1-phenyl-1-(diphenylphosphino)-1-hexene, 60896-09-5

[1] Part 3 of Hydride Eliminations.—Part 2: *M. T. Reetz* and *W. Stephan*, Angew. Chem. *89*, 46 (1977); Angew. Chem. Int. Ed. Engl. *16*, 44 (1977).
[2] The addition of alkyllithium compounds to conjugated olefins was first described by *K. Ziegler*, *F. Crossmann*, *H. Kleiner*, and *O. Schäfer*, Justus Liebigs Ann. Chem. *473*, 1 (1929); for a review of addition reactions of lithium compounds see *U. Schöllkopf* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1970, Vol. 13/1, p. 1.
[3] Tri-(*sec*-butyl)boranes can also be employed [1].
[4] Review: *R. F. Cunico*, J. Organomet. Chem. *109*, 1 (1976).
[5] *G. Köbrich* and *J. Stöber*, Chem. Ber. *103*, 2744 (1970).

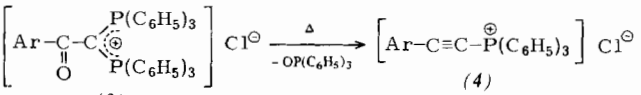
Simple Synthesis of (Arylethynyl)triphenylphosphonium Salts

By *Hans Jürgen Bestmann* and *Wolfgang Kloeters*[*]

Ethynylphosphonium salts are interesting synthetic building blocks[1]. We have now found a simple entry to the (arylethynyl)triphenylphosphonium salts *(4)*.

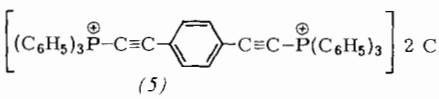


(1) *(2)*



(3) *(4)*

(a), Ar = C_6H_5; *(b)*, Ar = *p*-CH_3O-C_6H_4; *(c)*, Ar = α-$C_{10}H_7$



(5)

Reaction of aromatic acid chlorides *(1)* with hexaphenylcarbodiphosphorane *(2)*[2] leads initially to the compounds *(3)*, which on heating lose triphenylphosphane oxide and are converted into the phosphonium salts *(4)*. *(4a)*: m.p. 180°C, IR: 2175 cm^{-1} (C≡C), ^{31}P-NMR: δ = −6.52 ppm[3], yield 65 %.—*(4b)*: m.p. 183°C, IR: 2165 cm^{-1} (C≡C), ^{31}P-NMR: δ = −5.86 ppm[3], yield 68 %.—*(4c)*: m.p. 161°C, IR: 2170 cm^{-1} (C≡C), ^{31}P-NMR: δ = −6.45 ppm[3], yield 56 %.

When phthaloyl dichloride is used as starting compound the reaction furnishes the bisphosphonium salt *(5)*, m.p. 138°C; IR: 2175 cm^{-1} (C≡C), ^{31}P-NMR: δ = −6.52 ppm[3], yield 71 %[4].

In the ^{31}P-NMR spectra of the phosphonium salts *(3)*, both phosphorus atoms give a signal between δ = −18.5 and −20.0 ppm[3]. In the case of the ethynylphosphonium salts *(4)*, on the other hand, only one signal is observed at δ = −5.5 to −6.8 ppm, which can be ascribed to a strong interaction between the π-electron system of the triple bond and the phosphorus atom[5].

General procedure:

A solution of the freshly distilled acid chloride *(1)* (20 mmol) in anhydrous benzene (20 ml) is added dropwise under nitrogen to a solution of hexaphenylcarbodiphosphorane *(2)* (20 mmol)

[*] Prof. Dr. H. J. Bestmann and Dipl.-Chem. W. Kloeters
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-8520 Erlangen (Germany)

in anhydrous benzene (100 ml). The white precipitate is filtered off, washed with benzene, and dried in a vacuum (1 torr) at 40 °C. A suspension of the recovered salt *(3)* in anhydrous toluene (100 ml) is boiled under reflux for 12 to 18 hours under nitrogen. The undissolved ethynylphosphonium salt *(4)* is filtered off, washed with benzene, and dried in a vacuum.

Received: October 20, 1976 [Z 585 IE]
German version: Angew. Chem. *89*, 55 (1977)

CAS Registry numbers:
(1a), 98-88-4; *(1b)*, 100-07-2; *(1c)*, 879-18-5; *(2)*, 7533-52-0; *(3a)*, 60896-10-8; *(3b)*, 60934-64-7; *(3c)*, 60896-11-9; *(4a)*, 60896-12-0; *(4b)*, 60896-13-1; *(4c)*, 60896-14-2; *(5)*, 60896-15-3

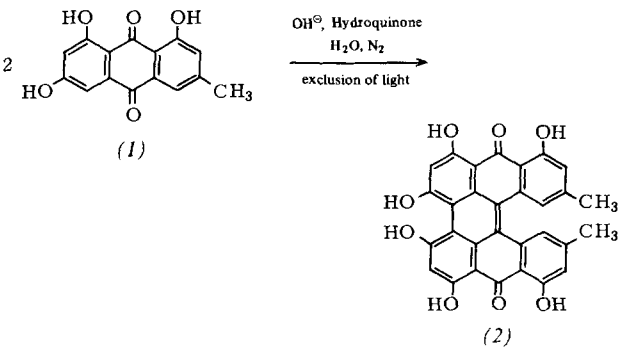
[1] *H. Hoffmann* and *H. Förster*, Tetrahedron Lett. *1964*, 983; *E. E. Schweizer, Ch. S. Kim, C. S. Labaw*, and *W. P. Murray*, J. Chem. Soc. Chem. Commun. *1973*, 7; *E. E. Schweizer* and *S. V. DeVoe*, J. Org. Chem. *40*, 144 (1975).
[2] *F. Ramirez, N. B. Desai, B. Hansen*, and *N. McKelvie*, J. Am. Chem. Soc. *83*, 3539 (1961).
[3] Referred to H_3PO_4 as external standard.
[4] All phosphonium salts *(4)* and *(5)* gave correct elemental analyses.
[5] *T. A. Albright, W. J. Freeman*, and *E. E. Schweizer*, J. Am. Chem. Soc. *97*, 2946 (1975).

Synthesis of Protohypericin from Emodin[**]

By *Dietrich Spitzner*[*]

Apart from hypericin and pseudohypericin, *Hypericum perforatum* L. contains two further photodynamically active pigments, *viz.* protohypericin *(2)* and protopseudohypericin, which readily transform into the first-named compounds on exposure to light and oxygen[1]. *Brockmann et al.*[2] obtained *(2)* by oxidation of penicilliopsin or emodin anthrone.

We have now found that *(2)* is also formed on alkaline dimerization of emodin *(1)* by the method of *Steglich et al.*[3], provided that light is excluded during the reaction and work-up. The violet pigment isolated in 25% yield (color in acetone and alkaline solution violet) is identical with an authentic sample of *(2)*[4, 5] [paper chromatography; spectra (FD-MS: $M^+ = 506$ mass units; UV (MeOH): $\lambda_{max} = 540$ nm; ^{1}H-NMR ([D_5]pyridine): $\delta = 2.06$ (CH_3), 6.91 (2(7)-H), 7.13 (11(14)-H), 7.47 (4(5)-H)]. Irradiation in acetone quantitatively affords hypericin identical with authentic material in all its properties.



(1) *(2)*

Decoupling experiments on *(2)* [irradiation at the CH_3 frequency gives a doublet ($J = 1.5$ Hz) for H-2(7) and H-4(5); irradiation at the H-4(5) frequency gives a doublet ($J = 0.5$ Hz) for CH_3 and a suggestion of a quartet ($J = 0.5$ Hz) for H-2(7)] establish the aromatic protons *ortho* to the CH_3 group. Admixture of authentic *(2)* does not change the spectrum. Hence the orientation of the two emodin halves in *(2)* is confirmed.

Procedure:

Compound *(1)* is heated with 1.8 mol. equiv. of 0.6 N KOH and 1 mol. equiv. of hydroquinone under N_2 with exclusion of light for 20 d at 100 °C in a bomb tube. The violet mixture is acidified with 0.1 N HCl, the precipitate filtered off, washed, dried, and exhaustively extracted with ethyl acetate. The resulting crude pigment is chromatographed on cellulose with DMF/water/butyl acetate (1 : 1 : 2) in the absence of light. After an orange primary zone (anthraquinone components), compound *(3)* is eluted.

Received: September 3, 1976 [Z 586a IE]
German version: Angew. Chem. *89*, 55 (1977)

CAS Registry numbers:
(1), 518-82-1; *(2)*, 548-03-8

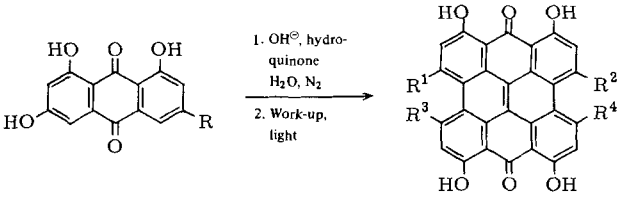
[1] *H. Brockmann*, Fortschr. Chem. Org. Naturst. *14*, 141 (1957); *H. Brockmann* and *D. Spitzner*, Tetrahedron Lett. *1975*, 37.
[2] *H. Brockmann* and *H. Eggers*, Chem. Ber. *91*, 81, 547 (1958).
[3] *W. Steglich* and *R. Arnold*, Angew. Chem. *85*, 88 (1973); Angew. Chem. Int. Ed. Engl. *12*, 79 (1973); *G. Rodewald, R. Arnold, J. Griesler*, and *W. Steglich*, Angew. Chem. *89*, 56 (1977); Angew. Chem. Int. Ed. Engl. *16*, 46 (1977).—I am grateful to Professor *W. Steglich* for communicating his findings and for a sample of synthetic hypericin.
[4] I am indebted to Priv.-Doz. *G. Höfle* for recording the 270-MHz spectra.
[5] I wish to thank Professor *H. Brockmann*, Göttingen, for *(2)*.

Synthesis of Hypericin and Related *meso*-Naphthodianthrones by Alkaline Dimerization of Hydroxyanthraquinones[**]

By *Gisbert Rodewald, Rüdiger Arnold, Johannes Griesler*, and *Wolfgang Steglich*[*]

In 1957 *Brockmann et al.* obtained hypericin *(4)*, the photodynamic component of *Hypericum perforatum*, in a multistep synthesis starting from 1-bromoemodin trimethyl ether[1]. One year later the preparation of *(4)* was accomplished in two steps from emodin-9-anthrone[2].

In 1973 we reported the alkaline condensation of emodin *(1)* to give a *meso*-naphthodianthrone which we assigned the formula of an isohypericin *(5)*[3]. On repeating the experiment it was found that hypericin *(4)* is actually formed[4].



(1), R = CH_3
(2), R = H
(3), R = CO_2H

(4), $R^1 = R^3 = OH$, $R^2 = R^4 = CH_3$
(5), $R^1 = R^4 = OH$, $R^2 = R^3 = CH_3$
(6), $R^1 = R^3 = OH$, $R^2 = R^4 = H$
(7), $R^1 = R^3 = OH$, $R^2 = R^4 = CO_2H$

[*] Dr. D. Spitzner
Institut für Chemie der Universität Hohenheim
Emil-Wolff-Strasse 14, D-7000 Stuttgart 70 (Germany)

[**] Note added in proof (November 23, 1976): In the meantime *D. W. Cameron et al.*, Aust. J. Chem. *29*, 1509 (1976), reported similar results.

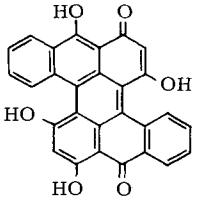
[*] Dipl.-Chem. G. Rodewald, Dr. R. Arnold, Dipl.-Chem. J. Griesler, and Prof. Dr. W. Steglich
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

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

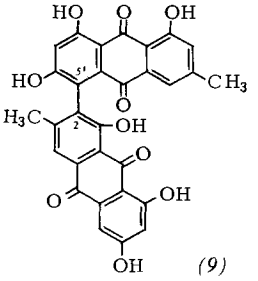
Compound *(1)* is heated with 1.5 mol. equiv. of hydroquinone and 2.5 mol. equiv. of potassium *tert*-butoxide in water (corresponding to 0.5 N KOH) under N_2 for three weeks in a sealed tube at 110 °C. Acidification of the reaction mixture, filtration, and washing of the filter cake neutral with water, followed by dissolution of the solid in ethyl acetate and chromatography of the filtered and concentrated solution on silica gel (ethyl acetate with acetone gradient) furnishes *(4)* in 29 % yield. The compound and its hexaacetate, m.p. 265 °C (dec.), agree in all their properties with authentic hypericin and its hexaacetate[5].

To *Spitzner*[6] as well as *Cameron*[4] goes the credit for the important observation that the reaction yields protohypericin if light is carefully excluded during the reaction and the product is worked up in the dark. Initially formed protohypericin is apparently transformed into *(4)* under the reaction conditions we employed.

The condensation reaction can also be applied to 1,3,8-trihydroxyanthraquinone *(2)* and emodic acid *(3)*. Bisdemethylhypericin *(6)*[7] and hypericindicarboxylic acid *(7)*[4] are obtained in 28 and 25 % yield, respectively, on workup in daylight. Under same conditions, 1,3-dihydroxyanthraquinone surprisingly affords a dark red product, the molecular weight of which (FD-MS: $M^+ = 460$ mass units) shows it to contain two H atoms less than the expected *meso*-naphthodianthrone. Since all attempts at cyclization to a *meso*-naphthodianthrone by irradiation were unsuccessful, the compound probably has the structure *(8)*, which is compatible with spectroscopic data (Table 1). In the absence of a 3-OH group, as in the case of 1,8-dihydroxyanthraquinone, no condensation occurs on heating with alkali.



(8)



(9)

Table 1. Spectroscopic properties of compounds *(6)* to *(9)*.

UV	^{1}H-NMR [5], δ [ppm] *vs.* TMS
(6) $\lambda_{max} = 574$ nm ($\varepsilon = 30100$), 531 (16800), 497 (7600), 463 (11600), 440 (sh, 10100), 380 (8300), 334 (22600), 323 (21200), 281 (28100), 273 (28100), 245 (34900), 220 (55000) [in MeOH]	$\delta = 6.60$ (s); 7.36, 8.84 (each d, $J = 9$ Hz); 14.50, 14.78 (each s) [in D_6-DMSO/$CDCl_3$ = 7:3]
(7) $\lambda_{max} = 591$ nm ($\varepsilon = 20000$), 547 (10700), 508 (4400), 475 (6800), 380 (5900), 327 (15700), 280 (19400), 255 (sh, 23900), 230 (34100), 213 (41800) [in MeOH]	$\delta = 6.65$, 7.82, 14.22, 14.65 (each s) [in D_6-DMSO/$CDCl_3$ = 7:3]
(8) $\lambda_{max} = 535$ nm (sh, $\varepsilon = 5700$), 473 (12900), 342 (5380), 273 (24100), 247 (38400), 205 (27000) [in MeOH with one drop of HCl]	$\delta = 6.41$ (s); 7.25, 7.51 (each ddd, $J = 7.5$, 7.5, 1.5 Hz); 7.88, 8.44 (each dd, $J = 7.5$, 1.5 Hz) [in D_6-acetone]
(9) $\lambda_{max} = 446$ nm ($\varepsilon = 12200$), 276 (21000), 253.5 (sh, 18700), 220.5 (30000) [in EtOH]	$\delta = 2.18$ (d, $J = 0.8$ Hz) [3-CH_3]; 2.38 (t, $J = 0.8$ Hz) [3'-CH_3]; 6.39 (s) [7'-H]; 6.68 (d, $J = 2.5$ Hz [7-H]; 7.10 (broad) [2'-H]; 7.32 (d, $J = 2.5$ Hz) [5-H]; 7.35 (broad) [4'-H]; 7.74 (s, broadened) [4-H]; 10.2 [6- and 6'-OH]; 12.00, 12.20, 12.31, 12.78 [in D_6-acetone]

If the dimerization of *(1)* is performed without a protective gas and addition of hydroquinone, the yield of *(4)* obtained after three weeks is only 10 %. Workup after only 24 h reaction showed the reaction mixture to contain not only traces of *(4)* and 70 % of unreacted *(1)* but also 18 % of 2,5'-bisemodinyl *(9)* [no m.p., decomposition above 215 °C; MS: $m/e = 538$ (90 %, M^+), 523 (100), 521 (17), 510 (6), 270 (6), 269.5 (4), 269 (11); IR (KBr): 1670, 1610 (C=O) cm^{-1}]. The linkage of the two emodin halves follows from the ^{1}H-NMR spectra of the dehydro-dimer and its hexaacetate, m.p. 155 °C (dec.), and from the result of reductive cleavage of *(9)* with sodium dithionite in $D_2O/OD^{\ominus}$. In the ^{1}H-NMR spectrum of the resulting compound *(1)* the signal of 2-H is only half as intense as that of 4-H. Under the conditions of cleavage 7-H is exchanged completely, and 5-H to a large extent.

The formation of *(9)* on heating of *(1)* in alkali is remarkable, in that *Franck et al.*[8] always obtained 5,7'-bisemodinyl and only a little 5,5'-bisemodinyl (skyrin) on oxidative dimerization of *(1)*.

Received: October 20, 1976 [Z 586b IE]
German version: Angew. Chem. 89, 56 (1977)

CAS Registry numbers:
(1), 518-82-1; *(2)*, 52431-74-0; *(3)*, 478-45-5; *(4)*, 548-04-9; *(5)*, 41689-58-1; *(6)*, 60935-17-3; *(7)*, 60483-14-9; *(8)*, 60935-18-4; *(9)*, 60935-19-5

[1] *H. Brockmann, F. Kluge,* and *H. Muxfeldt,* Chem. Ber. *90*, 2302 (1957).
[2] *H. Brockmann* and *H. Eggers,* Chem. Ber. *91*, 547 (1958).
[3] *W. Steglich* and *R. Arnold,* Angew. Chem. *85*, 88 (1973); Angew. Chem. Int. Ed. Engl. *12*, 79 (1973).
[4] *G. Rodewald,* Diplomarbeit, Technische Universität Berlin 1974. Australian researchers recently obtained the same result: *H. J. Banks, D. W. Cameron,* and *W. D. Raverty,* Aust. J. Chem. *29*, 1509 (1976).
[5] We are grateful to Dr. *G. Höfle,* Berlin, for recording the FT-NMR spectrum *(4)*: δ = 2.70 (CH_3), 6.53 (6-H), 7.26 (broad, 3-H) [in [D_6]-acetone].
[6] *D. Spitzner,* Angew. Chem. *89*, 55 (1977); Angew. Chem. Int. Ed. Engl. *16*, 46 (1977). We thank Dr. *Spitzner* for communicating his results, for recording FD mass spectra, and for a sample of authentic *(4)* and hypericin hexaacetate.
[7] *D. W. Cameron* and *W. D. Raverty,* Aust. J. Chem. *29*, 1523 (1976).
[8] *B. Franck, R. Cahin, H.-G. Eckert, R. Langenberg,* and *V. Radtke,* Angew. Chem. *87*, 846 (1975); Angew. Chem. Int. Ed. Engl. *14*, 819 (1975).

Heat of Hydrogenation of Compounds Containing Isolated and Conjugated C=N Double Bonds

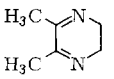
Günter Häfelinger and *Ludger Steinmann*[*]

The heats of hydrogenation of compounds containing C=N double bonds have not previously been determined directly. We have now measured[1] the heats of hydrogenation of the imines *(1a)* to *(1c)*, the diimines *(2)* and *(3)*, and the pyrazine *(4)* in a heat of hydrogenation calorimeter based on the instrument of *Bretschneider* and *Rogers*[2].

R^1–CH=N–R^2 *(1)*

(a): $R^1 = n\text{-}C_3H_7$, $R^2 = n\text{-}C_4H_9$
(b): $R^1 = CH_3$, $R^2 = CH(CH_3)_2$
(c): $R^1 = CH_3$, $R^2 = C(CH_3)_3$

$(CH_3)_3C$–N=CH–CH=N–$C(CH_3)_3$ *(2)*



(3)



(4)

[*] Prof. Dr. G. Häfelinger and Dr. L. Steinmann
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

The results listed in Table 1 have been corrected for the heats of solution and dilution determined in a blank experiment.

Table 1. Heats of hydrogenation of compounds *(1)* to *(4)* in methanol with 5 % of Pd/active charcoal as catalyst.

	Heat of hydrogenation [kcal/mol]	[kJ/mol]	Number of independent determinations
(1a)	20.5±0.7	86.2±2.6	2
(1b)	21.9±1.0	91.6±4.1	3
(1c)	23.0±1.4	96.4±5.9	3
(2)	45.0±0.5	188.1±1.6	3
(3)	40.5	169.4	1
(4)	48.1±0.7	207.2±2.8	3

Compounds *(1a)* to *(1c)* give an average heat of hydrogenation of 21.8±1.3 kcal/mol (91.2±5.4 kJ/mol) for an isolated C=N bond. As the degree of branching of the substituent bonded to nitrogen increases (primary < secondary < tertiary) so do the heats of hydrogenation, indicating increasing steric hindrance. The average value is in good agreement with the average heats of hydrogenation of 20.9±1.6 kcal/mol (87.6±6.7 kJ/mol) determined indirectly by *Jackman* and *Packham*[3] from the reaction enthalpy of the reduction of five *N*-alkylaldimines with $LiAlH_4$, but lies below the value of 24.3±2.7 kcal/mol (101.7±11.3 kJ/mol) determined with less accuracy by combustion calorimetry for *N*-isobutylidenepropylamine[4].

The heat of hydrogenation of an isolated N=C double bond is therefore lower than that of an isolated C=C double bond [the values measured for *ca.* 50 monoolefins[1] lay between 25.2 and 32.8 kcal/mol (105.2 and 137.3 kJ/mol)] but is higher than the heat of hydrogenation of an isolated C=O double bond [14.3±2.4 kcal/mol (59.6±10 kJ/mol) for five compounds[5]].

As expected, the 1,4-diimines *(2)* and *(3)* show a slight empirical delocalization energy (eDE) of 1.0±1.4 and 0.5 kcal/mol relative to *(1c)* and *(1a)*, respectively.

Relative to the average heat of hydrogenation of two isolated C=N double bonds and to the heat of hydrogenation of dissolved cyclohexene (26.8 kcal/mol)[6] the eDE of the cyclically conjugated pyrazine *(4)* amounts to 22.3±3.3 kcal/mol (93.3±13.8 kJ/mol) and thus corresponds to only 62 % of the eDE value for benzene (36 kcal/mol). The eDE of *(4)* was calculated from bond energy increments as 16 kcal/mol[7], 18 kcal/mol[8], and 38 to 57.4 kcal/mol[9], and determined as 14 kcal/mol[7] and 24.3 kcal/mol[10] by combustion calorimetry.

Received: October 20, 1976 [Z 587 IE]
German version: Angew. Chem. *89*, 48 (1977)

CAS Registry numbers:
(1a), 4853-56-9; *(1b)*, 27719-14-8; *(1c)*, 7020-80-6; *(2)*, 24764-88-3; *(3)*, 15986-92-2; *(4)*, 290-37-9

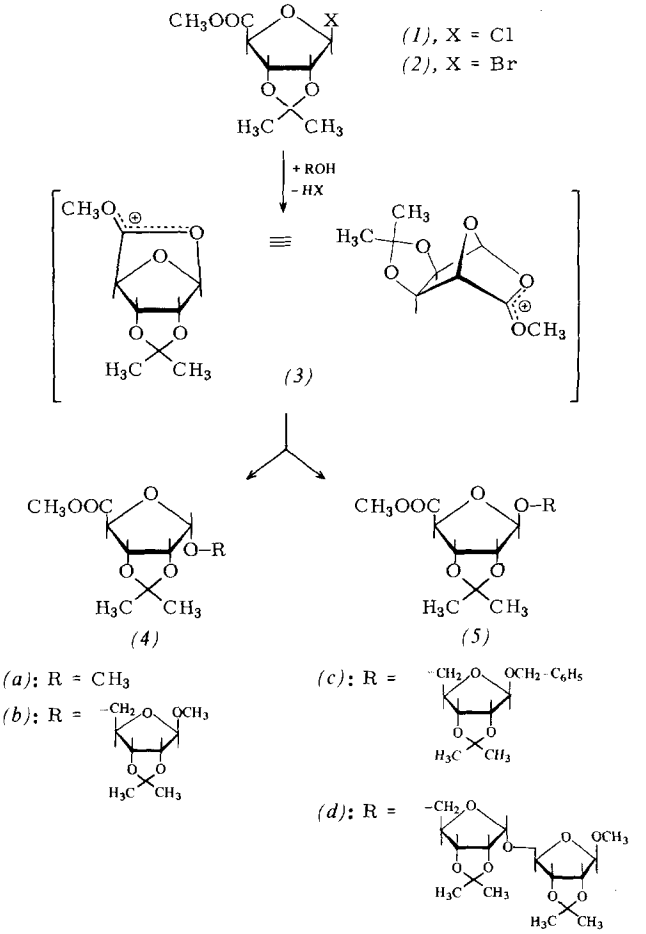
[1] *L. Steinmann*, Dissertation, Universität Tübingen 1975.
[2] *E. Bretschneider* and *D. W. Rogers*, Mikrochim. Acta *1970*, 482.
[3] *L. M. Jackman* and *D. J. Packham*, Proc. Chem. Soc., London *1957*, 349.
[4] *A. F. Bedford*, *P. B. Edmondson*, and *C. T. Mortimer*, J. Chem. Soc. *1962*, 2927.
[5] *M. A. Dolliver*, *T. L. Gresham*, *G. B. Kistiakowsky*, *E. A. Smith*, and *W. E. Vaughan*, J. Am. Chem. Soc. *60*, 440 (1938); *J. B. Conn*, *G. B. Kistiakowsky*, and *E. A. Smith*, *ibid. 61*, 1868 (1939).
[6] *D. W. Rogers* and *F. J. McLafferty*, J. Chem. Educ. *48*, 548 (1971); Tetrahedron *27*, 3765 (1971).
[7] *J. Tjebbes*, Acta Chem. Scand. *16*, 916 (1962).
[8] *J. D. Cox*, Tetrahedron *19*, 1175 (1963).
[9] *P. George*, Chem. Rev. *75*, 85 (1975).
[10] *A. F. Bedford*, *A. E. Beezer*, and *C. T. Mortimer*, J. Chem. Soc. *1962*, 2927.

α-Glycosidic Linkage of D-Ribofuranose[**]

By *Richard R. Schmidt* and *Peter Hermentin*[*]

The stereoselective formation of glycosides and oligosaccharides from halogenoses is attributable primarily to neighboring group participation of vicinal acyloxy groups in halogen substitution[1]. The formation of β-anomers is therefore favored for the best-known sugars owing to the configuration at C-2[1a, 2]. Methods for the selective synthesis of α-anomers are practically unknown in the case of furanoses.

The steric control of halogen substitution due to vicinal acyloxy groups should also be achievable with nucleophilic groups in other positions. We considered the α-directing effect of the carboxylate group in furanosid- and pyranosiduronic acids to hold considerable promise. Our first task was to design syntheses for methyl 1-deoxy-1-chloro- and 1-deoxy-1-bromo-2,3-*O*-isopropylidene-β-D-ribofuranosiduronate *(1)*



and *(2)*[3]. Reaction of these compounds with methanol under Koenigs-Knorr conditions affords the α- and β-methyl furanosides *(4a)* and *(5a)* in the ratio 8:1 to 9:1[4]; the overall yield is practically quantitative. The disaccharides *(4b)*, *(4c)*, *(5b)*, and *(5c)* were obtained in yields that were almost as good and with a likewise excellent stereochemical result. So were the trisaccharides *(4d)* and *(5d)* on reduction of

[*] Prof. Dr. R. R. Schmidt [+] and Dipl.-Chem. P. Hermentin
Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität
Pfaffenwaldring 55, 7000 Stuttgart 80 (Germany)

[+] Correspondence should be addressed to: Fachbereich Chemie der Universität, Postfach 7733, D-7750 Konstanz (Germany)

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

(4b) with $LiAlH_4$ to the alcohol, which was used for oligosaccharide synthesis (see Table 1).

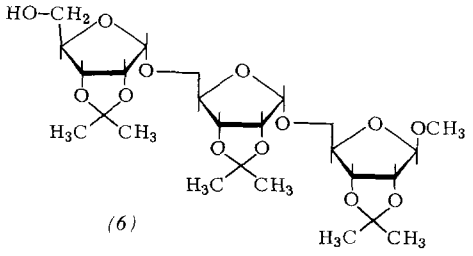
Table 1. Glycosides and oligosaccharides synthesized [a].

Cpd.	Yield [b] [%]	M.p. [°C]	$[\alpha]_{546}^{20}$ [°]
(4a)	83	viscous oil	+81.5 (2.696 [c])
(4b)	87	57	−21.4 (2.183 [c])
(4c)	83	93	−36.2 (2.150 [c])
(4d)	77	viscous oil	+ 9.2 (1.489 [c])
(6)	94	106	+20.8 (0.255 [c])
(7)	79	viscous oil	+64.8 (1.164 [d])

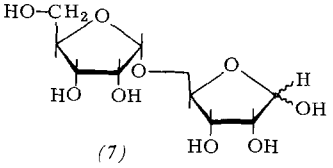
[a] All compounds gave correct elemental analyses.
[b] Isolated yield.
[c] Concentration in $CHCl_3$.
[d] Concentration in CH_3OH.

Since the anomeric ratios depend neither upon the halogenose used, nor upon the reaction temperature[5], nor upon the molar excess of the alcohol component[5], we assume the intermediacy of a dioxanorbornene *(3)* which is attacked mainly from the side facing away from the carboxylate group, *i.e.* from the α-side[6].

The carboxylate function serving as assisting and protecting group in this oligosaccharide synthesis can be reduced by $LiAlH_4$ to the hydroxymethyl group. In this way the protected trisaccharide *(6)* was obtained quantitatively from *(4d)*. However, the isopropylidene group can only be removed without



(6)



(7)

decomposition of the remaining compound if an α-glycosidic bond is present or the compound is unsubstituted at C-1. The unprotected α-linked disaccharide *(7)* is therefore accessible in good yield from *(4c)* by reduction of the carboxylate group, hydrogenolytic removal of the benzyl group, and acid-catalyzed removal of the isopropylidene group.

Received: October 21, 1976 [Z 588 IE]
German version: Angew. Chem. 89, 58 (1977)

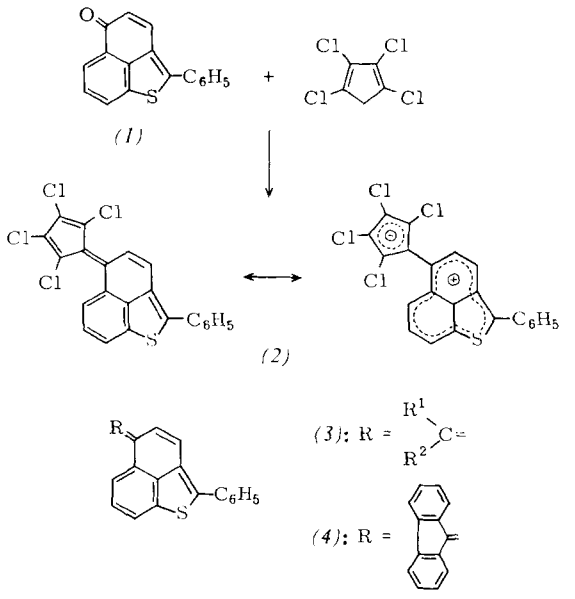
CAS Registry numbers:
(1), 60949-62-4; *(2)*, 60949-63-5; *(4a)*, 60949-64-6; *(4b)*, 60949-65-7; *(4c)*, 60949-66-8; *(4d)*, 60949-67-9; *(5a)*, 50767-74-3; *(5b)*, 60949-68-0; *(5c)*, 60949-69-1; *(5d)*, 60949-70-4; *(6)*, 60949-71-5; *(7)*, 60949-72-6

[1] a) *G. Wulff* and *G. Röhle*, Angew. Chem. *86*, 163 (1974); Angew. Chem. Int. Ed. Engl. *13*, 157 (1974); b) *C. Schuerch*, Acc. Chem. Res. *6*, 184 (1973), and references cited therein.
[2] *H. Paulsen*, Adv. Carbohydr. Chem. *26*, 127 (1971); *H. Paulsen, H. Behre*, and *C. P. Herold*, Fortschr. Chem. Forsch. *14*, 472 (1970).
[3] *R. R. Schmidt, D. Heermann*, and *K. H. Jung*, Justus Liebigs Ann. Chem. *1974*, 1856; *K. H. Jung*, Dissertation, Universität Stuttgart, in preparation.
[4] The isomer ratio was determined by NMR spectroscopy.
[5] Temperature range 0 to 60°C; 0 to 100 molar excess of the alcohol component.
[6] Other mechanistic interpretations cannot be ruled out, particularly since the mechanism of the Koenigs-Knorr reaction is not known in detail [1a].

Fulvenes and Fulvalenes of a Heterocyclic System with 12π Electrons—Pseudophenafulvenes and Pentapseudophenafulvalenes[**][1]

By *Richard Neidlein* and *Arnold D. Kraemer*[*]

We recently reported the first synthesis of deeply colored cations[2] which we could prepare from 2-phenyl-5*H*-naphtho[1,8-*bc*]thiophen-5-one *(1)*[3]. We have now found an entry to deeply colored fulvenes *(3)* and fulvalenes [*(2)*, *(4)*] of this system.



(1)

(2)

(3): R = $R^1R^2C=$

(4): R =

Heating of *(1)* with 1,2,3,4-tetrachlorocyclopentadiene in acetic anhydride affords the deep blue crystalline fulvalene *(2)*. The compounds listed in Table 1 react analogously with *(1)* to form the fulvenes *(3a)* to *(3f)*.

Treatment of *(1)* in anhydrous benzene under nitrogen and at room temperature with an equivalent amount of diphenylketene gives compound *(3g)* with evolution of CO_2. Finally, *(1)* reacts with fluoreneketene to form the fulvalene *(4)* (spectroscopic properties given in Table 2).

Procedures

Syntheses of *(2)*: Compound *(1)* (2 mmol) and tetrachlorocyclopentadiene (2 mmol) are heated under reflux for 6 h in acetic anhydride (10 ml). The solvent is distilled off and the residue chromatographed with benzene on silica gel 60 (Merck). Recrystallization from benzene gives deep blue crystals; yield 21 %, m.p. 166 to 168°C.

Synthesis of *(3a)* to *(3f)*: Compound *(1)* (2 mmol) and one of the compounds listed in Table 1 (2 mmol) are heated under reflux for 10 min in acetic anhydride (7.7 ml) and glacial acetic acid (3.8 ml). Workup as described for *(2)*.

Synthesis of *(4)*: Compound *(1)* (2 mmol) is dissolved in anhydrous benzene (10 ml) under nitrogen. Fluoreneketene (2 mmol) is added and the mixture heated under reflux for 1 h. The residue obtained on removal of the solvent is chromatographed with benzene on silica gel 60 (Merck). Recrystallization from *n*-hexane gives blue-black needles with a metallic luster; yield 38 %, m.p. 169°C.

[*] Prof. Dr. R. Neidlein and Dr. A. D. Kraemer
Pharmazeutisch-Chemisches Institut der Universität
Im Neuenheimer Feld 364, D-6900 Heidelberg (Germany)

[**] Heterocyclic 12π and 14π Systems, Part 2. This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft.—Part 1: ref. [2].

Table 1. Compounds of type *(3)* synthesized.

Reaction of *(1)* with	Product	R^1	R^2	M.p. [°C]	Yield [%]	Color
1,3-Dimethylbarbituric acid	*(3a)*	—CO—N(CH_3)—CO—N(CH_3)—CO—		285	86	black-green
2-Thiobarbituric acid	*(3b)*	—CO—NH—CS—NH—CO—		>350	67	black
N-Benzoylglycine	*(3c)*	—N=C(C_6H_5)—O—CO—		296	75	black-blue
1,3-Indandione	*(3d)*	—CO—(1,2-phenylene)—CO—		233	69	metallic black-blue
$CH_2(CN)_2$	*(3e)*	—CN	—CN	279	16	red-violet
$NC—CH_2CO_2C_2H_5$	*(3f)*	—CN	—$CO_2C_2H_5$	159	20	red-violet
$(C_6H_5)_2C=C=O$	*(3g)*	—C_6H_5	—C_6H_5	138	84	yellow

Table 2. Spectroscopic properties of compounds *(2)*, *(3g)*, and *(4)*.

(2): ^{1}H-NMR ($CDCl_3$): $\delta = 7.51$—8.05 ppm (H_3, H_4, H_7, phenyl protons), 8.20 (d, H_6, $J = 7.6$ Hz), 8.04 (d, H_8, $J = 7.6$ Hz); UV (*n*-heptane): $\lambda_{max} = 334$ nm ($\varepsilon = 8347$), 568 (20353); (CH_3CN): 326 (8052), 568 (19663); (CH_3OH): 330 (6949), 580 (18795).

(3g): UV (CH_3OH): $\lambda_{max} = 413$ nm ($\varepsilon = 22131$), 307 (13319), 277 (12909); ^{1}H-NMR ($CDCl_3$): $\delta = 7.51$—8.05 (H_3, H_4, H_7, phenyl protons), 8.20 (d, H_6, $J = 7.6$ Hz), 8.04 (d, H_8, $J = 7.6$ Hz).

(4): UV (*n*-heptane): $\lambda_{max} = 344$ nm ($\varepsilon = 13076$), 532 (30192); (CH_3CN): 340 (15702), 532 (33471); (CH_3OH): 334 (12986); 532 (29762).

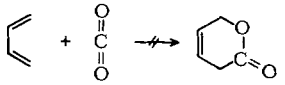
Received: October 18, 1976 [Z 589 IE]
German version: Angew. Chem. *89*, 48 (1977)

[1] Lectures by *R. Neidlein* at Tel-Aviv, Jerusalem, Haifa, Rehovot, Heidelberg, and Hamburg.
[2] *R. Neidlein* and *H. Seel*, Angew. Chem. *88*, 810 (1976); Angew. Chem. Int. Ed. Engl. *15*, 775 (1976).
[3] *D. G. Hawthorne* and *Q. N. Porter*, Aust. J. Chem. *19*, 1909 (1966).

δ-Lactones by Carbonylation of Vinyloxiranes[1]

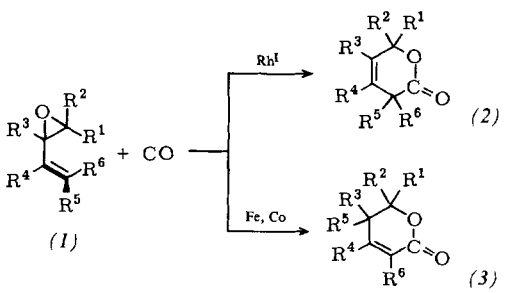
By *Rudolf Aumann* and *Horst Ring*[*]

No method is yet available for the direct linkage of carbon dioxide with 1,3-dienes after the manner of a Diels-Alder reaction to give δ-lactones[2].



However, transformation of 1,3-dienes into δ-lactones can be conveniently accomplished in two steps if the diene is first epoxidized and the epoxide *(1)* subsequently carbonylated in the presence of transition metals.

Fractional distillation gives the lactones in 10 to 75 % yield. Use of Rh^I catalysts affords β,γ-unsaturated lactones *(2)*, while Fe and Co catalysts lead predominantly to α,β-unsaturated lactones *(3)*. Competing reactions are: isomerizations to open-chain β,γ- and α,β-unsaturated ketones[3]; deoxygenation; and polymerization. R^3 = alkyl favors lactone formation; $R^5 = CO_2CH_3$ leads to almost quantitative deoxygenation with formation of CO_2; R^1 and R^6 = alkyl promotes formation of acyclic ketones.



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

5-Methyl-3,6-dihydropyran-2-one (2), $R^3 = CH_3$, $R^1 = R^2 = R^4$ to $R^6 = H$

Isoprene epoxide[4] (7.0 g, 83 mmol) and [1,5-cyclooctadiene-RhCl]$_2$[5] (0.2 g, 0.4 mmol) in anhydrous carbon tetrachloride (40 ml) are shaken under 150 atm of carbon monoxide for 50 h at 70 °C in a stainless steel autoclave. Fractional distillation of the yellow reaction mixture affords 5-methyl-3,6-dihydropyran-2-one (6.5 g, 75 %), b.p. 53—54 °C/0.1 torr, $n_D^{20} = 1.4762$. Reaction and workup must be performed with exclusion of air! ^{1}H-NMR (CCl_4): $\delta = 1.72$ ppm (br s, 3H), 2.88 (m, 2H), 4.64 (m, 2H), 5.26 (m, 1H). MS (70 eV): $m/e = 112$ (M^+, 72 %). IR (film): 1744, 1400, 1210, 1070, 796 cm^{-1}.

Received: October 25, 1976 [Z 590 IE]
German version: Angew. Chem. *89*, 47 (1977)

CAS Registry numbers:
(1), 1838-94-4; *(2)*, 60920-98-1

[1] Organic Syntheses with Transition Metal Complexes, Part 5.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 4: *R. Aumann*, Chem. Ber., in press.
[2] *R. A. Ruden* and *R. Bonjouklian*, J. Am. Chem. Soc. *97*, 6892 (1975), and references cited therein.
[3] *G. Adams*, *C. Bibby*, and *R. Grigg*, J. Chem. Soc. Chem. Commun. *1972*, 491.
[4] *E. J. Reist*, *I. G. Junga*, and *B. R. Baker*, J. Org. Chem. *25*, 1673 (1960). The compound is conveniently obtained by epoxidation of isoprene with peroxyacetic acid in dichloromethane.—*M. Korach*, *D. R. Nielsen*, and *W. H. Rideout*, J. Am. Chem. Soc. *82*, 4328 (1960).
[5] *J. Chatt* and *L. M. Venanzi*, J. Chem. Soc. *1957*, 4735.

Elimination of CO from Cyclic Carbonyl Compounds by Flow Pyrolysis[1]

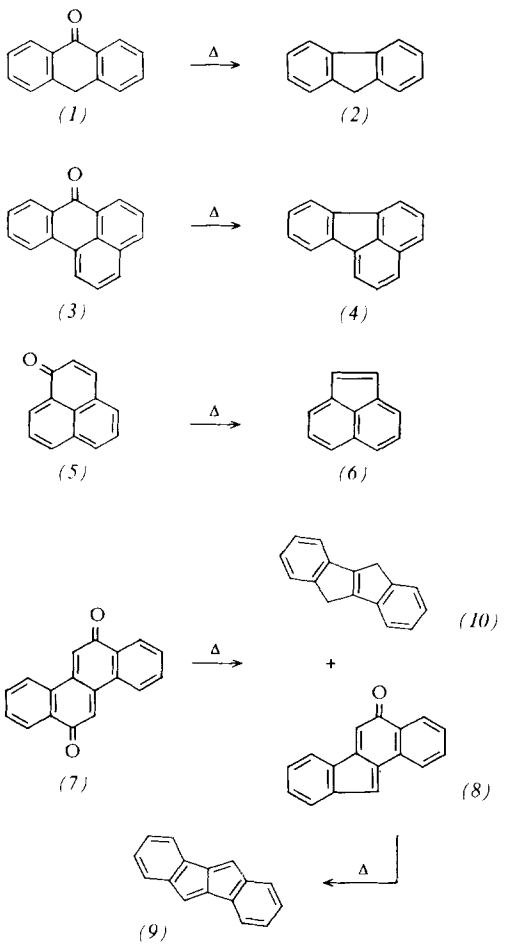
By *Gerhard Schaden*[*]

Some carbonyl compounds eliminate CO on heating, on electron impact, or in a glow discharge. In view of the facile mass-spectrometric elimination of CO from anthrone *(1)*, 7*H*-benz[*de*]anthracen-7-one *(3)*, 1*H*-phenalen-1-one *(5)*, and chrysene-6,12-dione *(7)*, thermal elimination of CO to give fluorene *(2)*, fluoranthene *(4)*, acenaphthylene *(6)*, and indeno[2,1-*a*]indene (dibenzopentalene) *(9)*, respectively, appeared to be promising.

Curie point pyrolysis at 900 °C and subsequent gas chromatography/mass spectrometry[2] demonstrated formation of the expected products. In order to produce larger amounts of material, *(1)*, *(3)*, *(5)*, and *(7)* were pyrolyzed in a high-vacuum flow apparatus. Compounds *(1)*, *(3)*, and *(5)* afforded *(2)*, *(4)*, and *(6)* in yields of 29 %, 42 %, and 41 %, respectively. The major product obtained on pyrolysis of *(7)*

[*] Priv.-Doz. Dr. R. Aumann and Dipl.-Chem. H. Ring
Organisch-Chemisches Institut der Universität
Orléansring 23, D-4400 Münster (Germany)

[*] Dr. G. Schaden
Fachbereich Pharmazie und Lebensmittelchemie der Universität
Marbacher Weg 6, D-3550 Marburg (Germany)



was found, by comparison of its UV, IR, and mass spectrum and of its gas chromatogram with those of authentic material[4], to be indeno[2,1-*a*]indene *(9)*. Small amounts of 5,10-dihydroindeno[2,1-*a*]indene *(10)* could also be detected. In addition, a slight amount of the primary pyrolysis product 5*H*-benzo[*a*]fluoren-5-one *(8)* was isolated. The compound likewise afforded *(9)* on Curie point pyrolysis.

Thus a simple entry is now available to indeno[2,1-*a*]indene (dibenzopentalene) *(9)*, which was formerly accessible only with difficulty. The method also suggests a new synthetic pathway to other molecules derived from pentalene or to the parent compound[5].

Procedure

Chrysene-6,12-dione *(7)*[6] (100 mg) was passed at 5×10^{-3} torr through a quartz tube (12 mm diameter, 70 mm length) filled with quartz wool and heated to 960 °C. The product was condensed in a trap cooled with liquid nitrogen[3]. Chromatography of the pyrolysis mixture (33 mg) on Al_2O_3 (activity grade 3, basic) with light petroleum/benzene afforded 12 mg (15 %) of pure *(9)*.

Received: October 27, 1976 [Z 593 IE]
German version: Angew. Chem. *89*, 50 (1977)

CAS Registry numbers:
(1), 90-44-8; *(2)*, 86-73-7; *(3)*, 82-05-3; *(4)*, 206-44-0; *(5)*, 548-39-0; *(6)*, 208-96-8; *(7)*, 19301-82-7; *(8)*, 60921-06-4; *(9)*, 248-58-8; *(10)*, 6543-29-9

[1] Flow Pyrolysis and Spectroscopy of Unstable Compounds, Part 4.—Presented in part during lectures at a conference held by the Arbeitsgemeinschaft Massenspektrometrie at Willingen, April 23, at the 7th International Mass Spectrometry Conference at Florence, August 31, 1976, and at the 3rd International Symposium on Analytical Pyrolysis at Amsterdam, September 9, 1976. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 3: ref. [3a].

[2] a) *G. Schaden*, Chem. Ber. *106*, 2084 (1973); b) *W. Simon* and *H. Giacobbo*, Chem.-Ing.-Tech. *37*, 709 (1965); c) *G. Schaden*, Adv. Mass Spectrom. *6*, 93 (1974).
[3] *J. F. King*, *P. deMayo*, *C. L. McIntosh*, *K. Piers*, and *D. J. H. Smith*, Can. J. Chem. *48*, 3704 (1970).
[4] *C. C. Chuen* and *S. W. Fenton*, J. Org. Chem. *23*, 1538 (1958).
[5] *K. Hafner*, *R. Dönges*, *E. Goedecke*, and *R. Kaiser*, Angew. Chem. *85*, 362 (1973); Angew. Chem. Int. Ed. Engl. *12*, 337 (1973).
[6] *M. Zander* and *W. H. Franke*, Chem. Ber. *101*, 2404 (1968), and references cited therein.

Diradical-Type Behavior of Tri-*tert*-butylcyclobutadiene[1][**]

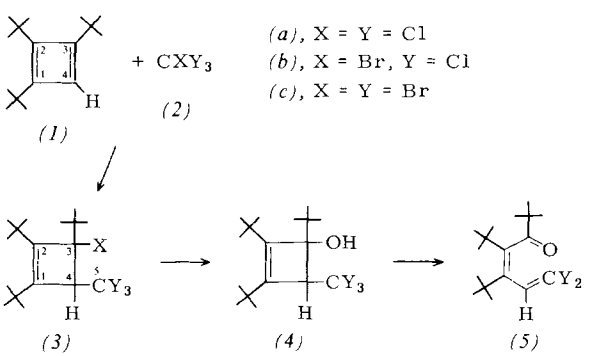
By *Günther Maier* and *Wolfgang Sauer*[*]

The geometry of cyclobutadienes and the multiplicity of the parent hydrocarbon and its alkyl derivatives in the ground state have not yet been elucidated. The two aspects are interrelated, for most calculations require that square cyclobutadiene should have a triplet ground state, while a cyclobutadiene with a lower symmetry is predicted to have a singlet ground state.

The IR spectrum of unsubstituted cyclobutadiene suggests an "effectively square" structure[2]. Assuming a dynamic Jahn-Teller effect it becomes understandable why this molecule exhibits singlet character instead of the triplet character predicted on theoretical grounds[2].

In this communication we show for the first time that the converse behavior is also possible: tri-*tert*-butylcyclobutadiene *(1)*[3], for which a rectangular structure is to be assumed[4], can undergo reactions typical of a triplet molecule.

In spite of pronounced steric hindrance, tri-*tert*-butylcyclobutadiene *(1)* is capable of not only synchronous cycloadditions but also ionic additions in which it proves to be an exceptionally good nucleophile and a strong base[5]. We have classed the autoxidation of *(1)* to give an isolable dioxetane derivative[6] as a radical addition, but only with reservation because this unusually fast reaction does not appear to be affected by the necessary change of multiplicity. Meanwhile we have found that the autoxidation has parallels in the addition of tetrahalomethanes, which already proceeds at room temperature in the dark and without addition of radical initiators.



If cyclobutadiene *(1)*[3] prepared by matrix irradiation of 2,3,4-tri-*tert*-butylcyclopentadienone is allowed to react after thawing with an excess of carbon tetrachloride the product is found to contain no dimer of *(1)* but exclusively the adduct

[*] Prof. Dr. G. Maier and Dipl.-Chem. W. Sauer
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

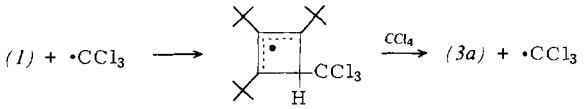
[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

(3a) [^{1}H-NMR (CCl_4): $\tau = 6.09$ (1H), 8.60 (18H), 8.83 (9H); ^{13}C-NMR ($CDCl_3$): $\delta = 156.9$ ppm (C1 or C2), 149.5 (C1 or C2), 101.7 (C5), 82.2 (C3), 68.0 (C4, off resonance: d), 41.7, 34.5, 33.8, 31.4, 30.4, 28.4 (*tert*-butyl groups)].

The regiospecificity of the addition can be seen from the structure of the secondary products *(4a)* and *(5a)*. The alcohol *(4a)* is formed from *(3a)* on standing in air. Heating or chromatography of *(3a)* or *(4a)* leads to the stable end product *(5a)* [m.p. 96 °C; ^{1}H-NMR: $\tau = 3.68$ (1H), 8.69 (18H), 8.84 (9H); ^{13}C-NMR: $\delta = 213.5$ ppm, 149.8, 136.2, 133.2 (off resonance: d), 125.5, 44.5, 37.7, 34.4, 32.9, 32.3, 29.5; IR (CCl_4): 1680 cm^{-1}; correct elemental analysis].

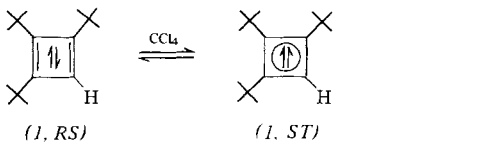
The adducts formed by the action of bromotrichloromethane and tetrabromomethane[8] *(3b)* and *(3c)* are even more sensitive than *(3a)*[7]. On hydrolysis and subsequent ring cleavage, *(3b)* affords *(4a)* and *(5a)*. The CBr_4 adduct *(3c)* is transformed particularly readily *via* the alcohol *(4c)* into the acyclic ketone *(5c)* [m.p. 103 °C; ^{1}H-NMR: $\tau = 3.19$ (1H), 8.70 (9H), 8.73 (9H), 8.86 (9H); ^{13}C-NMR: $\delta = 213.3$ ppm, 149.3, 141.6 (off resonance: d), 138.5, 96.9, 44.7, 37.4, 34.4, 32.8, 32.5, 29.7; IR: 1680 cm^{-1}; correct elemental analysis].

Thus tri-*tert*-butylcyclobutadiene *(1)* undergoes reactions expected of a diradical. A possible mechanism, formulated for the reaction with CCl_4, is seen in the radical chain proceeding *via* the intermediate *(6)*.

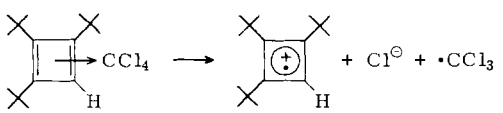


(6)

Since the rectangular singlet and the square triplet state of *(1)* are of similar energy and CCl_4 can accelerate the interconversion of these species by a heavy atom effect[9], it is possible that the reactions observed might involve the triplet molecule *(1,ST)* in equilibrium with the rectangular singlet cyclobutadiene *(1,RS)*. However, the explanation may lie in the extremely good donor properties[5] of *(1)*. In analogy with similar reactions of amines[10] and electron-rich olefins[11], an electron transition in *(7)* with formation of the



(1, RS) *(1, ST)*



(7) *(8)*

radical *(8)* and the trichloromethyl radical is to be regarded as initiation reaction. Even if this explanation is valid, cyclobutadiene still occupies a special place since the electronic transition does not require additional excitation[12] by light or metal ions, in contrast to the case of amine/CCl_4 complexes[10].

Received: October 26, 1976 [Z 592 IE]
German version: Angew. Chem. *89*, 49 (1977)

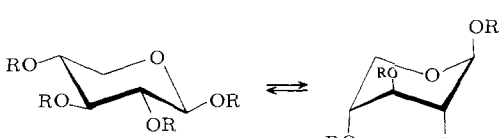
CAS Registry numbers:
(1), 51067-53-9; *(2a)*, 56-23-5; *(2b)*, 75-62-7; *(2c)*, 558-13-4; *(3a)*, 60921-41-7; *(3b)*, 60921-42-8; *(3c)*, 60921-43-9; *(4a)*, 60921-44-0; *(4c)*, 60921-45-1 *(5a)*, 60921-46-2; *(5c)*, 60921-47-3

[1] Small Rings, Part 20.—Part 19: ref. [2].
[2] *G. Maier* and *H. P. Reisenauer*, Tetrahedron Lett. *1976*, 3591.
[3] *G. Maier* and *A. Alzérreca*, Angew. Chem. *85*, 1056 (1973); Angew. Chem. Int. Ed. Engl. *12*, 1015 (1973).
[4] *G. Lauer, C. Müller, K.-W. Schulte, A. Schweig, G. Maier*, and *A. Alzérreca*, Angew. Chem. *87*, 194 (1975); Angew. Chem. Int. Ed. Engl. *14*, 172 (1975).
[5] *G. Maier* and *W. Sauer*, Angew. Chem. *87*, 675 (1975); Angew. Chem. Int. Ed. Engl. *14*, 648 (1975).—The ^{13}C-NMR spectrum has meanwhile been recorded: It displays three signals at $\delta = 151.4$ ppm (C1 + C3), 144.7 (C2), and 126.2 (C4) for the olefinic C atoms in 2,2-dimethylbutane / *n*-pentane / 2-methylbutane / *n*-butyltris(trideuteriomethyl)silane. Neither the ^{13}C-NMR signal for the positions C1 and C3, nor the ^{1}H-NMR signal for the *tert*-butyl groups located there show any broadening on lowering the temperature to −140 °C. We have determined the ^{13}C-^{1}H coupling constant as 176.8 Hz.
[6] *G. Maier*, Angew. Chem. *86*, 491 (1974); Angew. Chem. Int. Ed. Engl. *13*, 425 (1974).
[7] The identity of the compounds of type *(3)* and *(4)*, which could not be isolated in analytically pure state, is established by their spectral data (^{1}H-NMR, ^{13}C-NMR, IR, MS).
[8] Preliminary experiments suggest that an analogous radical addition of the two fragments Br• and •$CHBr_2$ occurs on reaction of *(1)* with bromoform. In contrast, chloroform does not react; the dimer of *(1)* is obtained on addition thereof.
[9] *P. G. Gassman* and *R. L. Cryberg*, J. Am. Chem. Soc. *91*, 5176 (1969), have discussed such an effect in connection with the transition of singlet to triplet nitrenes.—We are indebted to Professor *R. Keese*, Bern, for this information.
[10] *K. G. Hancock* and *D. A. Dickinson*, J. Org. Chem. *39*, 331 (1974); *J. R. L. Smith* and *Z. A. Malik*, J. Chem. Soc. (B) *1970*, 920.—We are grateful to Dr. *J. W. Scheeren*, Nijmegen, for drawing our attention to these papers.
[11] Very pronounced in tetraaminoethylenes: *N. Wiberg*, Angew. Chem. *80*, 809 (1968); Angew. Chem. Int. Ed. Engl. *7*, 766 (1968); *R. W. Hoffmann*, Angew. Chem. *80*, 823 (1968); Angew. Chem. Int. Ed. Engl. *7*, 754 (1968).
[12] Only phosphanes also add CCl_4 in the absence of radical initiators: *R. Rabinowitz* and *R. Marcus*, J. Am. Chem. Soc. *84*, 1312 (1962).

Tetraaxial Conformation of 1,2,3,4-Tetra-*O*-benzoyl-β-D-xylopyranose[**]

By *Peter Luger*, *Gabriele Kothe*, and *Hans Paulsen*[*]

During our studies[1] on the conformation of β-D-xylopyranosyl halides in solution and in the crystalline state we had observed a 1,3-diaxial arrangement of two *O*-benzoyl groups to be particularly favorable from an energetic standpoint. The 1,3-diaxial interaction between two *O*-acyl groups is probably much smaller[2] than hitherto assumed[3]. Estimates[4] based on model compounds belonging to the 1,5-anhydropentitol series indicate the interaction between two *O*-benzoyl groups to be 0.2 to 0.6 kcal/mol smaller than that between two *O*-acetyl groups; the reason for this difference has yet to be explained.



(1) *(a)*: R = Ac *(2)*
(b): R = Bz

[*] Priv.-Doz. Dr. P. Luger and Dipl.-Chem. G. Kothe
Institut für Kristallographie, Fachbereich 21 (Chemie) der Freien Universität
Takustrasse 6, D-1000 Berlin 33 (Germany)
Prof. Dr. H. Paulsen
Institut für Organische Chemie und Biochemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)

[**] Conformational Analysis, Part 18.—Part 17: *P. Luger* and *H. Paulsen*, Carbohydr. Res., in press.

We have now examined the crystal structure of 1,2,3,4-tetra-*O*-benzoyl-β-D-xylopyranose, in which the $^4C_1$ form *(1b)* having four equatorial *O*-benzoyl groups coexists with the $^1C_4$ form having four axial *O*-benzoyl groups. In acetone the conformational equilibrium contains 28% of the $^1C_4$ form *(2a)* in the case of the tetraacetate but 50% of the $^1C_4$ form *(2b)* in the case of the tetrabenzoate[5].

The tetrabenzoate *(1b)*⇌*(2b)* crystallizes in the monoclinic space group $P2_1$ with four molecules in the unit cell. Two independent molecules are found in the asymmetric unit, so that 84 heavy atom positions have to be determined. The phase problem can be solved with the MULTAN program. Refinement is possible as far as an *R* value of 0.044. The two independent molecules are both seen to exist in the unusual tetraaxial conformation *(2b)*. The structure of one of the two molecules is shown in Figure 1.

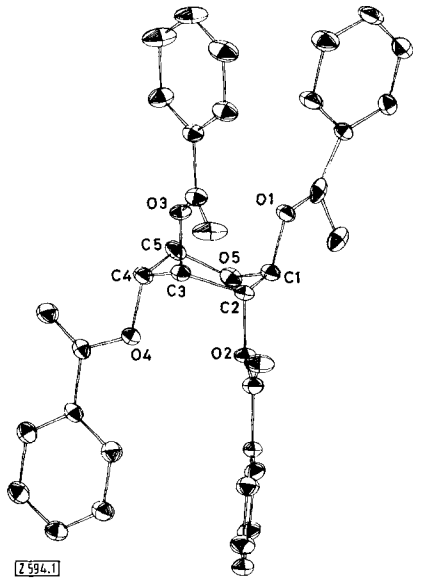


Fig. 1. Tetraaxial structure of 1,2,3,4-tetra-*O*-benzoyl-β-D-xylopyranose. Only one of the two independent molecules is shown.

Bond lengths and angles are very similar in the two molecules. Differences are observed in the orientation of the benzoyl groups relative to the ring. Thus the benzoyl groups at C2, C3, and C4 are twisted in a positive sense out of the normal position in one molecule but in a negative sense in the other. In the normal position the acylcarbonyl groups and the hydrogen atoms of the ring are orientated *syn*-parallel[1].

The distances between O1 and O3 and between O2 and O4 are 2.888 and 2.853 Å, respectively, corresponding to about twice the van der Waals radius of oxygen. The benzene rings of the benzoyl groups are not parallel but mutually inclined at various angles. Hence these groups will hardly be expected to exert attractive forces influencing the conformation.

Received: October 27, 1976 [Z 594 IE]
German version: Angew. Chem. *89*, 51 (1977)

CAS Registry number:
1,2,3,4-Tetra-*O*-benzoyl-β-D-xylopyranose, 22435-09-2

[1] *P. Luger, P. L. Durette,* and *H. Paulsen,* Chem. Ber. *107*, 2615 (1974); *G. Kothe, P. Luger,* and *H. Paulsen,* Carbohydr. Res. *37*, 283 (1974); *P. Luger, G. Kothe,* and *H. Paulsen,* Chem. Ber. *109*, 1850 (1976).
[2] *H. Paulsen* and *M. Friedmann,* Chem. Ber. *105*, 718 (1972).
[3] *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *G. A. Morrison:* Conformational Analysis. Interscience, New York 1965, p. 52.
[4] *H. Paulsen* and *F. Heiker,* unpublished.
[5] *P. L. Durette* and *D. Horton,* J. Org. Chem. *36*, 2658 (1971).

Lithiomethyl(diphenyl)arsane Oxide, a New Reagent[**]

By *Thomas Kauffmann, Heinz Fischer,* and *Annegret Woltermann*[*]

Arsanes containing at least one alkyl group are cleaved by halogens (Cl_2, Br_2, I_2) at moderate temperatures according to equation (a) (halodemetalation); under these conditions, phenyl groups usually remain attached to the arsenic[1].

$$R_2As\text{–}Alk \xrightarrow{Hal_2} \begin{matrix} Hal & Hal \\ \diagdown & \diagup \\ & R_2As\text{–}Alk \end{matrix} \xrightarrow{\Delta T} \begin{matrix} Hal\text{–}Alk \\ + \\ R_2As\text{–}Hal \end{matrix} \qquad (a)$$

Since the $(C_6H_5)_2As$ is thus equivalent to Hal, the reaction of electrophilic organic compounds with lithiomethyl(diphenyl)arsane *(1)* followed by a dehalometalation should provide a method for the nucleophilic introduction of halogenated C atoms into organic compounds. Lithiomethyl(diphenyl)arsane oxide *(2)* could also be utilized in place of *(1)* because arsane oxides can easily be reduced to arsanes[1, 2].

$(C_6H_5)_2As\text{–}CH_2\text{–}Li$ *(1)*

$(C_6H_5)_2As(O)\text{–}CH_2\text{–}Li$ *(2)*

While attempts to synthesize *(1)* failed, the lithium compound *(2)*, which to our knowledge has likewise not been reported previously, is formed almost quantitatively on treatment of methyl(diphenyl)arsane oxide[3] with lithium diisopropylamide in THF at −40 °C for 30 min. Compound *(2)* reacts with organic halides or carbonyl compounds with CC linkage to give the products listed in Table 1.

$$(2) \xrightarrow{Hal\text{–}R} (C_6H_5)_2As(O)\text{–}CH_2\text{–}R \quad (3)$$

$$(2) \xrightarrow[2.\ H_2O]{1.\ R\text{–}CO\text{–}R'} (C_6H_5)_2As(O)\text{–}CH_2\text{–}C(OH)RR' \quad (4)$$

Table 1. Reaction of *(2)* with electrophilic compounds (molar ratio 1:1) in THF.

Reactant		Product	Yield [%]	M.p. [°C]
n-Butyl bromide [a]	*(3a)*,	R = $-(CH_2)_3CH_3$	72	84
Allyl bromide [a]	*(3b)*,	R = $-CH_2-CH=CH_2$	70	140–141
Benzyl bromide [b]	*(3c)*,	R = $-CH_2-C_6H_5$	61	139
n-Butyraldehyde [a]	*(4a)*,	R = H, R′ = $-(CH_2)_2CH_3$	60	141–142
Benzaldehyde [a]	*(4b)*,	R = H, R′ = $-C_6H_5$	82	159–160
Cyclohexanone [b]	*(4c)*,	R + R′ = $-(CH_2)_5-$	53	204–206
Benzophenone [a]	*(4d)*,	R = R′ = $-C_6H_5$	81	200–202

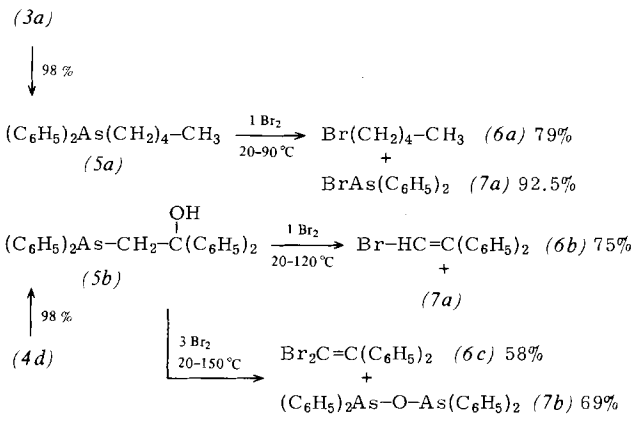
[a] Reaction temperature −40 to +65 °C; reaction time 1.25 h.
[b] Reaction temperature −40 to +20 °C; reaction time 1 h.

For the examples of compounds *(3a)* and *(4d)* we could demonstrate that $LiAlH_4$ reduction to the arsane [*(5a)*, oil, $n_D^{20} = 1.588$; *(5b)*, m.p. 94 to 96 °C] and subsequent bromolysis gives preparatively useful yields of organic bromides. Whereas

[*] Prof. Dr. Th. Kauffmann, Dr. H. Fischer, and A. Woltermann
Organisch-Chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

[**] New Reagents, Part 3.—This work was supported by the Fonds der Chemischen Industrie.—Part 2: *Th. Kauffmann, D. Berger, B. Scheerer,* and *A. Woltermann,* Chem. Ber., in press.

(3a) furnishes the expected pentyl bromide *(6a)*, compound *(4d)* affords either 1-bromo-2,2-diphenylethylene *(6b)* (m.p. 40 to 41 °C; lit. value[4] m.p. 41 to 42 °C) or 1,1-dibromo-2,2-diphenylethylene *(6c)* (m.p. 83 to 84 °C; lit. value[5] m.p. 83 °C), depending on the amount of bromine used.



Thus compound *(2)* can be utilized for stepwise chain elongation of alkyl halides by one C atom at a time. The available experimental data are not yet sufficient to provide a basis for general statements about the synthetic operations possible on carbonyl compounds with the aid of *(2)*.

The structures of the newly prepared compounds follow from the results of elemental analysis and from their spectroscopic data (MS, IR, ^{1}H-NMR).

Procedure for the chain elongation of n-butyl bromide

(All reactions performed in a nitrogen atmosphere and in anhydrous N_2-saturated solvents.)

a) *n*-Pentyl(diphenyl)arsane oxide: A freshly prepared solution of lithium diisopropylamide (17.6 mmol) in THF (40 ml) is added dropwise at −40 °C to a stirred solution of methyl(diphenyl)arsane oxide (4.16 g, 16.0 mmol)[3] in THF (250 ml). Methyl(diphenyl)arsane oxide precipitated at −40 °C dissolves during the reaction. After 30 minutes' stirring, *n*-butyl bromide (2.19 g, 16.0 mmol) in THF (10 ml) is added dropwise to the resulting clear yellow solution and the mixture warmed to 65 °C for 1 h. Water and chloroform are added to the almost colorless solution, the phases are separated, the aqueous phase extracted with chloroform, and the dried chloroform phases are evaporated down. The crystalline residue is worked up by column chromatography [silica gel, chloroform/ethanol (85:15)]: 3.6 g (72 %) of *(3a)* and 0.90 g (21 %) of methyl(diphenyl)arsane oxide are obtained.

b) *n*-Pentyl(diphenyl)arsane: After reduction of *(3a)* with $LiAlH_4$ (190 mg, 5.0 mmol) in THF (55 ml) at room temperature, work-up [by analogy with a), but without chromatography] affords 2.94 g (98 %) of the oily arsane which is homogeneous on chromatography.

c) *n*-Pentyl bromide: A solution of Br_2 (1.12 g, 7 mmol) in CCl_4 (5 ml) is added dropwise at room temperature to a solution of the arsane (2.10 g, 7 mmol) in CCl_4 (15 ml). A yellow solution is formed above a brownish red oil. The solvent is drawn off *in vacuo*, and the residue heated to 90 °C for 2 h. The resulting *n*-pentyl bromide (79 % according to gas chromatography) can be separated from chloro(diphenyl)arsane (92.5 %) by distillation.

Received: October 16, 1976;
revised: October 28, 1976 [Z 595 IE]
German version: Angew. Chem. *89*, 52 (1977)

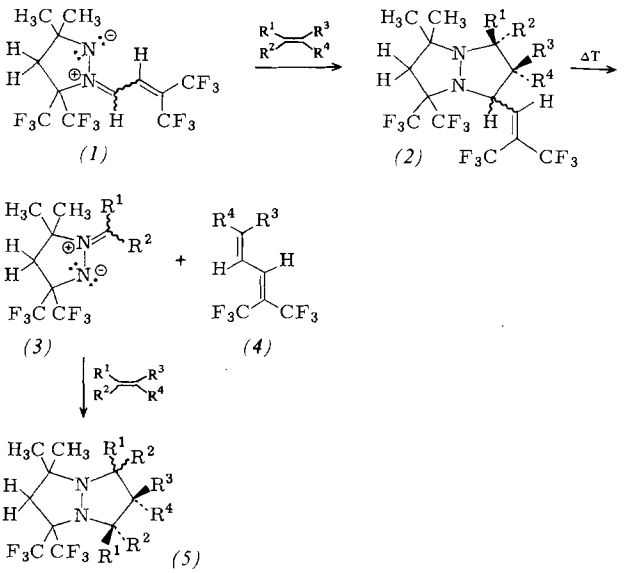
CAS Registry numbers:
(1), 61024-98-4; *(2)*, 61024-99-5; *(3a)*, 61024-00-1; *(3b)*, 61025-01-2; *(3c)*, 61025-02-3; *(4a)*, 61025-03-4; *(4b)*, 61025-04-5; *(4c)*, 61025-05-6; *(4d)*, 61025-06-7; *(5a)*, 38563-47-2; *(5b)*, 61025-07-8; *(6a)*, 110-53-2; *(6b)*, 13249-58-6; *(6c)*, 2592-73-6; *(7a)*, 3095-87-2; *(7b)*, 2215-16-9; $Br(CH_2)_3CH_3$, 109-65-9; $BrCH_2CH{=}CH_2$, 106-95-6; $BrCH_2Ph$, 100-39-0; $CH_3(CH_2)_2COH$, 123-72-8; C_6H_5COH, 100-52-7; $(CH_2)_5CO$, 108-94-1; PhCOPh, 119-61-9

[1] *G. O. Doak* and *L. D. Freedman*: Organometallic Compounds of Arsenic, Antimony and Bismuth, Wiley, New York 1970.
[2] Halodemetalations are also known for stibanes, bismuthanes, germanes, stannanes, and plumbanes. We are investigating whether these reactions are also suitable for the introduction of halogen atoms and halogenated hydrocarbon units into organic compounds.
[3] Prepared according to *G. J. Burrows* and *E. E. Turner*, J. Chem. Soc. *117*, 1381 (1920); *119*, 428 (1921); *A. Merijanian* and *R. A. Zingaro*, Inorg. Chem. 5, 187 (1966).
[4] *P. Lipp*, Ber. Dtsch. Chem. Ges. *56*, 569 (1923).
[5] *K. Ziegler*, Justus Liebigs Ann. Chem. *434*, 61 (1923).

Dipole Metathesis[**]

By *Klaus Burger*, *Helmut Schickaneder*, and *Claus Zettl*[*]

1,5 Dipoles of type *(1)*[1] are accessible by electrocyclic ring opening from 1,5-diazabicyclo[3.3.0]oct-2-enes[2]. The azomethinimine system present in *(1)* reacts with double bond systems by [3+2] cycloaddition. The cycloadducts fulfil the requirements necessary for a [3+2] cycloreversion. The initiation temperature depends upon the nature of the substituents at C-3 and C-4.



Reaction of *(1)* with ethylenetetracarbonitrile proceeds *via (2)* to give the stable 1,3 dipole *(3a)* and 4,4-bis(trifluoromethyl)buta-1,3-diene-1,1-dicarbonitrile *(4a)*. Reaction of *(1)* with fumaronitrile affords, apart from two stereoisomeric [3+2] cycloadducts [*(2b')*, *(2b'')*] and the cycloreversion products [*(3b)*, *(4b)*], a [3+2] cycloadduct *(5a)* derived from *(3b)* and fumaronitrile, which becomes the major product on use of an excess of fumaronitrile and at higher temperature. The reactions of *(1)* with dimethyl fumarate and maleate proceed in a similar manner; however, in these cases only one cycloadduct of structure *(2)* could, as yet, be isolated along with *(5)* in each case.

[*] Priv.-Doz. Dr. K. Burger, Dr. H. Schickaneder, and Dipl.-Chem. C. Zettl
Institut für Organische Chemie der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Project Bu 277/4) and the Fonds der Chemischen Industrie.

Table 1. Compounds *(2)* to *(5)* prepared. All compounds gave correct elemental analyses.

	R^1	R^2	R^3	R^4	Yield [%]	M.p. [°C]	IR [cm^{-1}]
(2b')	CN	H	H	CN	35	121	2250 [a], 1675 [b]
(2b'')	H	CN	CN	H	9	127—129	2250 [a], 1680 [b]
(2c)	CO_2CH_3	H	H	CO_2CH_3	41	76	1750—1730, 1675 [b]
(2d)	CO_2CH_3	H	CO_2CH_3	H	30	oil	1760—1710, 1680 [c]
(3a)	CN	CN	—	—	81	133—135	2215, 2195, 1468 [b]
(4a)	—	—	CN	CN			2240, 2220, 1655, 1610 [c]
(4b)	—	—	H	CN			2220, 1650, 1595 [c]
(5b)	CN	H	H	CN	30	131	2255 [a, b]
(5c)	CO_2CH_3	H	H	CO_2CH_3	17	92	1760—1730 [b]
(5d)	CO_2CH_3	H	CO_2CH_3	H	20	105	1758, 1742 [b]

[a] Very weak. [b] In KBr. [c] As film.

The reaction sequence *(1)* → *(2)* → *(3)*, comprising a [3+2] cycloaddition and subsequent [3+2] cycloreversion, is a dipole metathesis. It provides a general entry to variously substituted azomethinimines *(3)* and a new 1,3-butadiene synthesis. The reaction *(1)* → *(2)* → *(3)* → *(5)* is a new variant of the dipolar cyclosynthesis.

General procedure

Compound *(1)* (4.10 g, 10 mmol) and a little more than an equimolar amount of a dipolarophile are heated in tetrahydrofuran (50 ml) under reflux for 2 to 5 d. After the solvent has been distilled off, any solids are removed and the remaining oil is fractionated by column chromatography with chloroform on silica gel.

Received: September 13, 1976 [Z 591a IE]
German version: Angew. Chem. *89*, 60 (1977)

CAS Registry numbers:
(1), 60935-02-6; *(2)*, 60949-91-9; *(2b)*, 60935-03-7; *(2c)*, 60935-04-8; *(3a)*, 60935-05-9; *(3b)*, 60935-06-0; *(4a)*, 60935-07-1; *(4b)*, 60935-08-2; *(5b)*, 60935-09-3; *(5c)*, 60935-10-6; ethylenetetracarbonylnitrile, 670-54-2; fumaronitrile, 764-42-1; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6

[1] 1,5 Dipoles are defined as 1,3 dipoles with internal octet stabilization which are in conjugation with an unsaturated substituent (*H. Reimlinger*, Chem. Ber. *103*, 1900 (1970)).

[2] *K. Burger, H. Schickaneder*, and *C. Zettl*, Synthesis *1976*, 803.

A General Procedure for Generating Conjugated 1,*x* Dipoles[**][1]

By *Klaus Burger, Helmut Schickaneder*, and *Claus Zettl*[*]

1,5 Dipoles of structure *(1)*[2] add substances with triple bonds to form 1,5-diazabicyclo[3.3.0]oct-2-enes *(2)*; with methyl propiolate the orientational isomers *(2a)* and *(2b)* are formed.

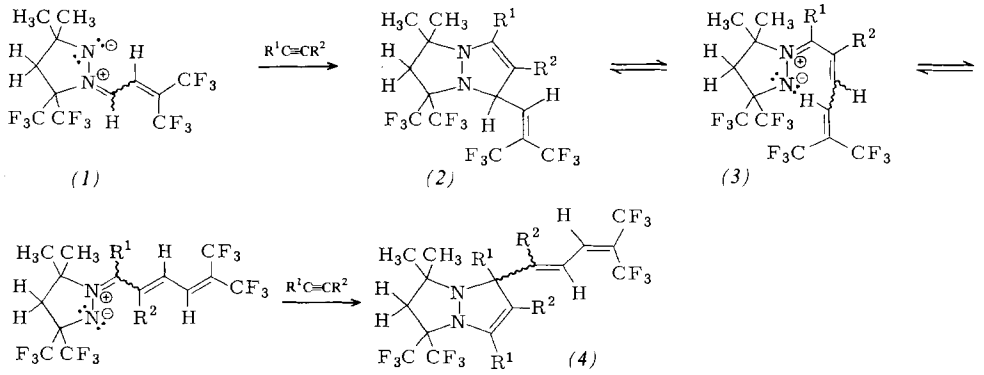
The cycloadducts *(2)* are able to undergo electrocyclic ring opening. The position of the equilibrium *(2)* ⇌ *(3)* depends upon the nature of the substituents R^1 and R^2[3]. While *(2a)* coexists with the 1,7 dipolar species *(3a)* in a 78:22 equilibrium at room temperature in $CDCl_3$, only the 1,7 dipolar species *(3b)* can be detected by ^{19}F-NMR spectroscopy in the case of the orientational isomer *(2b)*. The adduct of *(1)* with dimethyl acetylenedicarboxylate exists entirely as *(2c)* under the same conditions.

Table 1. Compounds *(2)* to *(4)* prepared. All compounds gave correct elemental analyses.

	R^1	R^2	Yield [%]	M.p. [°C]	IR [cm^{-1}]
(2a)	H	CO_2CH_3	49	107	1670 (br), 1572 [a]
(2c)	CO_2CH_3	CO_2CH_3	73	107	1752, 1690 (br), 1580 [a]
(3b)	CO_2CH_3	H	15	oil	1715, 1617 [b]
(4a)	H	CO_2CH_3	70	oil	1720—1670, 1650, 1587 [b]

[a] In KBr. [b] As film.

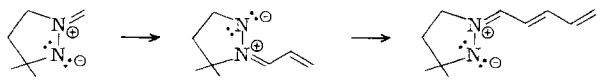
The 1,7 dipole *(3a)* likewise reacts with substances containing triple bonds as an azomethinimine; the major product *(4a)* can again undergo electrocyclic ring opening as a 1,5-diazabicyclo[3.3.0]oct-2-ene.



Repetition of the reaction sequence of [3+2] cycloaddition of an acetylene and electrocyclic ring opening permits construction of 1,*x* dipoles from 1,3 dipoles. During each extension step the dipole end shifts from one to the other nitrogen atom. The reaction is also a new type of oligomerization of acetylenes.

[*] Priv.-Doz. Dr. K. Burger, Dr. H. Schickaneder, and Dipl.-Chem. C. Zettl
Institut für Organische Chemie der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Project Bu 277/4) and the Fonds der Chemischen Industrie.



General procedure

Compound *(1)* or *(2a)*⇌*(3a)* (5 mmol) are heated under reflux for 3 d with an equimolar amount of a dipolarophile in anhydrous tetrahydrofuran (60 ml). After distilling off the solvent, the crude product is purified by column chromatography with hexane/chloroform (2:1) on silica gel. Further purification of *(3b)* was accomplished by preparative layer chromatography on ready-made plates (silica gel 60 F_{254}, Merck).

Received: September 13, 1976 [Z 591b IE]
German version: Angew. Chem. *89*, 61 (1977)

CAS Registry numbers:
(1), 60935-02-6; *(2a)*, 60935-11-7; *(2b)*, 60935-12-8; *(2c)*, 60935-13-9; *(3a)*, 60935-14-0; *(3b)*, 60935-15-1; *(4a)*, 60935-16-2; methyl propiolate, 922-67-8; dimethyl acetylenedicarboxylate, 762-42-5

[1] The designation 1,*x* dipole refers to the resonance structure of a compound in which the two charges are separated by the maximum distance, see 1,3 dipoles.
[2] *K. Burger, H. Schickaneder,* and *C. Zettl,* Synthesis *1976*, 803.
[3] *G. Maier:* Valenzisomerisierungen. Verlag Chemie, Weinheim 1972, and references cited therein.

Preparation of Halogen-Bridged Cationic Dinuclear Complexes of Manganese and Rhenium[**]

By *Rüdiger Mews*[*]

While halogen-bridged anionic complexes of type *(1)*[1] and also neutral representatives of this type[2] are already known, the cations *(2)* isoelectronic with *(1)* have not previously been reported. To our knowledge a bridging function of individual halogens in cationic complexes has so far only been demonstrated for complexes of iron[3].

$[(CO)_5MXM(CO)_5]^-$ *(1)*, M = Cr, Mo, W

$[(CO)_5MXM(CO)_5]^+$ *(2)*, M = Mn, Re

We have now found that four possible pathways are available for the synthesis of complex cations of type *(1)*:

Reaction of the SO_2 complexes *(3)*[4] with carbonylmetal halides [eq. (a)] or with metal halides [eq. (b)].

$$[M(CO)_5SO_2]^+AsF_6^- + M'(CO)_5X \quad (a)$$
(3)

$$\xrightarrow[-SO_2]{} [(CO)_5MXM'(CO)_5]^+AsF_6^-$$
(4)

(a): M = M' = Mn, X = Cl
(b): M = M' = Re, X = Cl
(c): M = Mn, M' = Re, X = Br

$$2\,[M(CO)_5SO_2]^+AsF_6^- + X^- \quad (b)$$
(3)

$$\xrightarrow[-SO_2]{} [(CO)_5MXM(CO)_5]^+AsF_6^- + AsF_6^-$$
(4)

(d): M = Mn, X = I; *(e)*: M = Re, X = I

Reaction of carbonylmetal halides *(5)* with $AgAsF_6$ in SO_2 [eq. (c)]. Isolation of the intermediate SO_2 complexes is unnecessary in the synthesis of symmetrical cations.

$$2\,M(CO)_5X + AgAsF_6 \xrightarrow[-AgX]{SO_2} [(CO)_5MXM(CO)_5]^+AsF_6^- \quad (c)$$
(5) *(4)*

(f): M = Mn, X = Br; *(g)*: M = Re, X = Br

Exchange of bridging halogens in *(4)* with the aid of silver salts in SO_2 [eq. (d)].

$$(4f) + AgNCS \xrightarrow[-AgBr]{SO_2} [(CO)_5MnNCSMn(CO)_5]^+AsF_6^- \quad (d)$$
(4h)

Whereas reactions according to eq. (a) are complete within a few minutes, and those according to (c) and (d) within a few hours, it is difficult to obtain clean products according to eq. (b).

The strongly yellow manganese salts and their colorless rhenium counterparts are readily soluble in SO_2, but dissolve only sparingly with decomposition in organic solvents.

The complexes *(4)* are thermally stable up to more than 100°C. They were characterized by elemental analysis and their IR spectra. Although the spectra are complex in the CO stretching region, the absence of bands below 1900 cm^{-1} rules out bridging by carbonyl groups. The manganese compounds show a strong band at 700 cm^{-1} ($\nu_3AsF_6^-$). The splitting of this band observed with the rhenium compounds, and especially the chlorine derivative (715 m, 699 vs), indicates distortion of the AsF_6^- ion in the solid.

Procedure:

To a precisely stoichiometric mixture of the reactants (2 to 3 mmol each) at −196°C is condensed SO_2 (*ca.* 10 ml), and the reaction mixture is allowed to warm slowly. Reaction (a) is complete within a short time of reaching room temperature. A clear solution is obtained from which the pure products precipitate on evaporation of SO_2. In the case of reactions (b) to (d) the precipitated silver halide or alkali metal hexafluoroarsenate is filtered off before evaporation of the SO_2.

Received: October 29, 1976 [Z 597 IE]
German version: Angew. Chem. *89*, 53 (1977)

CAS Registry numbers:
(3), M = Mn, 55853-06-0; *(3)*, M = Re, 55853-08-2; *(4a)*, 61025-92-1; *(4b)*, 61025-93-2; *(4c)*, 61025-95-4; *(4d)*, 61025-97-6; *(4e)*, 61025-99-8; *(4f)*, 61026-01-5; *(4g)*, 61026-03-7; *(4h)*, 61026-05-9; *(5)*, M = Mn, 14516-54-2; *(5)*, M = Re, 14220-21-4; $Mn(CO)_5Cl$, 14100-30-2; $Re(CO)_5Cl$, 14099-01-5

[1] *H. Behrens* and *D. Hermann*, Z. Naturforsch. *21b*, 1234 (1966); *E. Lindner* and *H. Behrens*, Spectrochim. Acta *23A*, 3025 (1967); *J. K. Ruff*, Inorg. Chem. *7*, 1821 (1968).
[2] *H. Behrens* and *R. Schwab*, Z. Naturforsch. *19b*, 768 (1964).
[3] *E. O. Fischer* and *E. Moser*, J. Organomet. Chem. *3*, 16 (1965); Z. Anorg. Allg. Chem. *342*, 156 (1966).
[4] *R. Mews*, Angew. Chem. *87*, 669 (1975); Angew. Chem. Int. Ed. Engl. *14*, 640 (1975).

[*] Dr. R. Mews
Anorganisch-chemisches Institut der Universität
Tammanstrasse 4, D-3400 Göttingen (Germany)

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

cis-Bis(dinitrogen)tetrakis(trimethylphosphane)chromium

By *Hans Heinz Karsch*[*]

Almost all transition metals are known to form complexes with molecular nitrogen, but in the case of some metals—nota-

[*] Dr. H. H. Karsch
Anorganisch-chemisches Institut der Technischen Universität
Arcisstr. 21, D-8000 München 2 (Germany)

bly chromium—the examples are few and far between. The higher homologs, molybdenum and tungsten, on the other hand, readily bind nitrogen and can even coordinate two N_2-ligands[1, 2]. To our knowledge, such complexes with metals of the first transition series have not as yet been reported[3].

During investigations on the behavior of trimethylphosphane in the presence of low-valency metals[4] it was found that the complex *cis*-$[(CH_3)_3P)]_4Cr(N_2)_2$ *(1)* can be isolated on reduction of $CrCl_3$ with Mg in the presence of $P(CH_3)_3$ in tetrahydrofuran under nitrogen. Initially, reaction of $CrCl_3$ with $P(CH_3)_3$ in THF leads to an adduct *(2)*, which is crystallizable from ether as brown-violet needles (m.p. 144—147 °C).

$$CrCl_3 \xrightarrow{P(CH_3)_3/THF} [(CH_3)_3P]_3CrCl_3$$
(2)

On reduction of *(2)* with Mg in the presence of excess phosphane a deep blue solution is formed, from which crystalline *(3)*[5] (m.p. 51 °C) can be isolated.

$$(2) \xrightarrow{P(CH_3)_3/THF/Mg} [(CH_3)_3P]_3CrCl_2$$
(3)

(3) readily liberates $P(CH_3)_3$ in a vacuum at 25 °C and the crystals become brighter.

In the presence of $P(CH_3)_3$ under nitrogen, however, *(3)* can be reduced further to a deep brown solution:

$$(3) \xrightarrow[10\,^\circ C]{P(CH_3)_3/THF/Mg/N_2} \begin{matrix} (CH_3)_3P \\ (CH_3)_3P \\ (CH_3)_3P \\ (CH_3)_3P \end{matrix} \!\!\begin{matrix} \diagup \\ \diagdown \end{matrix}\!\! Cr \!\!\begin{matrix} \diagdown \\ \diagup \end{matrix}\!\! \begin{matrix} N\equiv N \\ N\equiv N \end{matrix}$$
(1)

After removal of volatile components, dark brown *(1)* can be extracted from the residue with pentane/$P(CH_3)_3$ and then isolated after removal of solvent at −30 °C. Complex *(1)* slowly decomposes at room temperature with liberation of N_2 and $P(CH_3)_3$. Its *cis*-octahedral structure is confirmed by spectroscopic findings.

The IR spectrum (Nujol) shows, in addition to the typical bands for coordinated $P(CH_3)_3$, two very strong bands of equal intensity at 1990 and 1918 cm^{-1} along with two weaker bands, also of equal intensity, at 562 and 513 cm^{-1}. The percentage decrease in frequency (P = 16.2) of $\nu_{N\equiv N}$ through fixation of the N_2 is twice as large as that in the known simple N_2-complexes of chromium, and thus about equally as large as in *cis*-$L_4M(N_2)_2$ with M = Mo[2] or W[1]. Since the isoelectronic carbonyl complexes *cis*-$L_4M(CO)_2$ (M = Cr,Mo,W)[6] prove to have corresponding P-values of the same order of magnitude, it is clear that there is an extensive analogy in the bonding of these complexes.

The *cis* array derived from the IR spectrum leaves the remaining positions of an octahedral configuration to the four phosphane ligands which is recognized in the $\{^1H\}$-^{31}P-NMR spectrum of *(1)* (24 MHz, toluene, −20 °C, H_3PO_4 ext.) as an A_2B_2 pattern ($^2J(AB)/(\nu_A - \nu_B) = 0.15$, similarly as, *e.g.* in *cis*-$[(CH_3)_3P]_4Fe(CH_3)_2$[7]) with $\delta P_A = +13.8$, $\delta P_B = +9.4$ ppm; $^2J P_A P_B \approx 16$ Hz. For $[(CH_3)_3]_4Cr(CO)_2$ two "signals" (1 : 1) were found at +16.5 and +5.4 ppm[6].

The bis(dinitrogen) complex *(1)* reacts with carbon monoxide to give $[(CH_3)_3P]_4(CO)_2$[6] *(4)* and $[(CH_3)_3P]_3Cr(CO)_3$[6] *(5)*.

$$L_4Cr(N_2)_2 + 2\,CO \xrightarrow[-2\,N_2]{} L_4Cr(CO)_2 \xrightarrow[-P(CH_3)_3]{CO} L_3Cr(CO)_3$$
(1) *(4)* *(5)*

L = $P(CH_3)_3$

Reduction of *(3)* with Mg at higher temperatures (above 15 °C) leads to a further brown, decomposable paramagnetic complex, which likewise contains nitrogen ($\nu_{N\equiv N}$ 1992 cm^{-1}) but, in addition, also a hydridochromium unit (νCrH: 1850 vs (br) cm^{-1}). The IR spectrum also shows bands for coordinated THF (1030 and 840 cm^{-1}) and $P(CH_3)_3$. Whether the CrH— function is formed by C—H cleavage of a $P(CH_3)_3$ ligand[4], as in the reduction of $FeCl_2/P(CH_3)_3$ with Mg, is still uncertain.

Received: November 10, 1976 [Z 601 IE]
German version: Angew. Chem. 89, 57 (1977)

CAS Registry numbers:
(1), 61202-60-6; *(2)*, 61202-61-7; *(3)*, 61202-62-8; ^{31}P, 7723-14-0

[1] *B. Bell, J. Chatt*, and *G. J. Leigh*, Chem. Commun. *1970*, 842.
[2] *J. Chatt* and *A. G. Wedd*, J. Organomet. Chem. *27*, C 15 (1971); *T. A. George* and *C. D. Siebold*, *ibid. 30*, C 13 (1971).
[3] The complexes determined spectroscopically only in a matrix at lower temperature are not included here.
[4] *H. H. Karsch, H.-F. Klein*, and *H. Schmidbaur*, Chem. Ber., in press.
[5] *D. A. Berman*, Diss. Abstr. *18*, 1240 (1958).
[6] *R. Mathieu, M. Lenzi*, and *R. Poilblanc*, Inorg. Chem. *9*, 2030 (1970).
[7] *H. H. Karsch*, Chem. Ber., in press.

Electrochemical Reduction of 2,2,2-Trichloroethanols[**]

By *Andreas Merz*[*]

The reductive dehalogenation of vicinal dihalides has been studied very thoroughly[1]. In contrast, little is known about the concomitant reductive elimination of a halogen and an adjacent substituent bonded *via* an oxygen atom[2].

We have found that 2,2,2-trichloroethanols *(1)*, readily accessible for example by OH^- phase-transfer catalyzed addition of chloroform to aldehydes and ketones[3], can be reduced at a mercury cathode at −1.3 to −1.5 V in acidic electrolytes to give 1,1-dichloroolefins *(2)*; in some cases good yields are obtained (Table 1). 2,2-Dichloroethanols *(3)* arise as by-products. Suitable electrolytes are aqueous-organic solvent mixtures containing a mineral acid and an acidic supporting electrolyte, *e.g.* triethylammonium chloride. The low current yields due to competing evolution of hydrogen can be improved by admixture of tetraethylammonium *p*-toluenesulfonate.

The reaction also commands mechanistic interest on account of its analogy to the electrochemical dehalogenation of vicinal dihalides, which is regarded as a synchronous reaction because of its pronounced stereoselectivity[1b, 4].

$$\begin{matrix} R^1 \\ R^2 \diagup C\text{–}CCl_3 \\ \quad\; OH \end{matrix} \xrightarrow{2\,e^\ominus,\,-Cl^\ominus} \begin{matrix} R^1 \\ R^2 \diagup C{=}CCl_2 \end{matrix} + \begin{matrix} R^1 \\ R^2 \diagup C\text{–}CHCl_2 \\ \quad\; OH \end{matrix}$$
(1) *(2)* *(3)*

Since a C—O single bond is not attacked electrochemically at the working potentials employed[5], electron transfer must occur at the trichloromethyl group; in this case a dichloro-

[*] Dr. A. Merz
Institut für Chemie im Fachbereich Chemie und Pharmazie der Universität
Universitätsstrasse 31, D-8400 Regensburg (Germany)

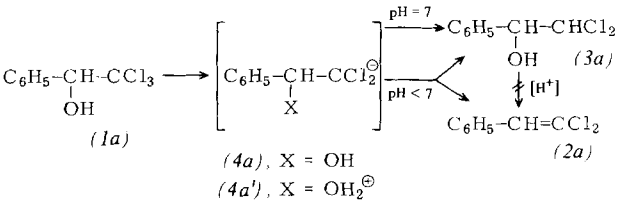
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Table 1. 1,1-Dichloro olefins *(2)* from 2,2,2-trichloroethanols *(1)*. By-products: 2,2-dichloroethanols *(3)*. For conditions, see *Procedure*.

	R^1	R^2	E [V] [a]	Conversion [%] [b]	*(2)* MY [%] [c]	*(2)* CY [%] [c]	*(3)* MY [%] [c]	*(3)* CY [%] [c]	*(2)* Pure yield [%]	*(2)* B.p. [d] [°C/torr]
(a)	C_6H_5	H	−1.3	98	97	70	3	2.2	85	92/12
(b)	p-$CH_3OC_6H_4$	H	−1.4	98	97	39	3	1.2	83	100/12
(c)	CH_3	CH_3	−1.5	78	89	26	10	3	33	107/760
(d)	CH_3	C_2H_5	−1.5	76	92	25	8	2.5	24	125/760
(e)	$-(CH_2)_4-$		−1.5	71	86	29	14	4.4	27	65/12
(f)	$-(CH_2)_5-$		−1.5	75	93	38	7	2.7	32	80/12

[a] Electrode potential measured *versus* saturated colomel electrode (SCE).
[b] Determined by gas chromatography.
[c] Material (MY) and current yields (CY) based on reacted *(1)*.
[d] The compounds *(2)* prepared have been previously reported in the literature.

methyl anion [*e.g. (4a)*] is to be expected as reactive intermediate[6]. Protonation of *(4a)* by the solvent leads to *(3a)*, and nucleofugal elimination of the OH group—comparable with the second step of an E1cb elimination—to *(2a)*.



(1a) *(4a)*, X = OH *(4a')*, X = $OH_2^{\oplus}$ *(3a)* *(2a)*

Reduction of *(1a)* in a *neutral* medium (95% aqueous DMF, 0.1 M $Et_4N^+Br^-$, $E_{1/2}$ −1.76 V) leads exclusively to *(3a)*. Since H^+-catalyzed dehydration of *(3a)* to *(2a)* could be ruled out experimentally under the electrolysis conditions, the reduction must take a different course in an *acidic* medium: it appears that the protonated alcohol is then reduced, as also follows from the shift of the reduction potential by *ca.* 0.4 V towards positive values. The protonated OH group in *(4a')* is such a good leaving group that elimination to give *(2a)* greatly predominates. However, the existence of the zwitterion *(4a')* is unlikely in solution. Consequently, either a reaction from the adsorbed state on the electrode surface or a synchronous electron transfer and elimination not involving *(4a')* has to be assumed.

Procedure:

Electrolyte (1.5 M HCl, 0.1 M $Et_4N^+OTos^-$, 0.5 M $Et_3NH^+Cl^-$ in 95% ethanol) is transferred into the cathode and anode compartments of a divided electrolysis cell (*e.g.* according to ref. [1b]) fitted with a cooling jacket and having a magnetically stirred mercury cathode and a graphite anode. The cathode potential is adjusted[7] (cf. Table 1) and the resulting initial current is measured. After addition of *(1)* (*ca.* 0.35 M) electrolysis is continued until the electrolysis current falls below the previously measured initial current. After pouring the electrolyte from the cathode compartment into water the product is extracted with pentane and distilled.

Received: October 21, 1976 [Z 598 IE]
German version: Angew. Chem. 89, 54 (1977)

CAS Registry numbers:
(1a), 2000-43-3; *(1b)*, 14337-31-6; *(1c)*, 57-15-8; *(1d)*, 15811-72-0; *(1e)*, 10292-51-0; *(1f)*, 3508-84-7; *(2a)*, 698-88-4; *(2b)*, 41448-64-0; *(2c)*, 6065-93-6; *(2d)*, 10562-75-1; *(2e)*, 39547-03-0; *(2f)*, 1122-55-0; *(3a)*, 2612-36-4; *(3b)*, 58622-56-3; *(3c)*, 4773-53-9; *(3d)*, 61104-45-8; *(3e)*, 41055-91-8; *(3f)*, 52183-64-9

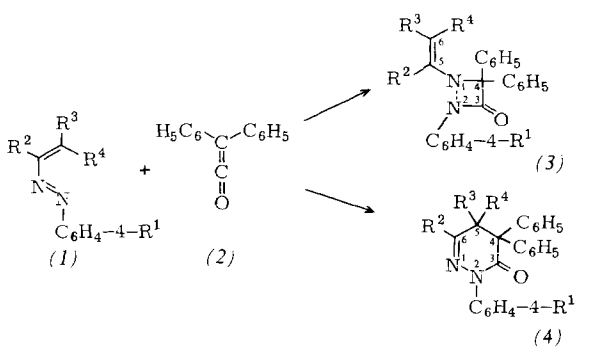
[1] a) Chemical methods: *W. H. Saunders jr.* and *A. F. Cockerill*: Mechanisms of Elimination Reactions. Wiley, Interscience, New York 1973, pp. 332ff.; b) electrochemical methods: *J. Casanova* and *H. R. Rogers*, J. Org. Chem. *39*, 2408 (1974).
[2] Electrochemical examples: *H. Lund*, Acta Chem. Scand. *17*, 2139 (1963); *J. C. Webb, C. K. Mann*, and *H. M. Walborsky*, J. Am. Chem. Soc. *92*, 2042 (1970).
[3] *A. Merz* and *R. Tomahogh*, Chem. Ber., in press.
[4] *T. Krupicka, J. Zavada*, and *J. Sicher*, Collect. Czech. Chem. Commun. *28*, 1644 (1963).
[5] *V. G. Mairanowsky*, Angew. Chem. *88*, 283 (1976); Angew. Chem. Int. Ed. Engl. *15*, 281 (1976).
[6] *M. R. Rifi* in *M. M. Baizer*: Organic Electrochemistry. Marcel Dekker, New York 1973, pp. 279ff.
[7] We used a Bank Wenking 70 HV 1 laboratory potentiostat.

[2+2]- and [4+2]-Cycloadditions of Arylazoalkenes to Diphenylketene[1]

By *Sven Sommer*[*]

It is known that (*E*)-azobenzenes react only very slowly with diphenylketene *(2)* to give 1,2-diazetidinones, even under drastic conditions (100 °C, in substance)[2]. Arylazocarbonyl compounds, on the other hand, react exothermally with *(2)* in solution to give [2+2]-[3], and in one case also [4+2]-cycloadducts[3c]. We have now investigated how an olefin bond conjugated to an arylazo group affects the reaction of arylazoalkenes *(1)*[4] with *(2)*.

In our studies, we found that compounds *(1a)*—*(1g)*, unlike the (*E*)-azobenzenes, react with *(2)* (1:1 in benzene) to give 1:1 cycloadducts within 2 h to a week, even at room temperature. The reactions of *(1a)*, *(1b)*, and *(1e)* with *(2)* lead exclusively to the [2+2]-cycloadducts *(3a)*, *(3b)*, and *(3e)* within the ^{1}H-NMR detection limit, while only the [4+2]-cycloadducts *(4f)* and *(4g)* are formed in the reaction of *(1f)* and *(1g)* with *(2)*. *(1c)* and *(1d)* each react with *(2)* to give two cycloadducts, namely *(3c)* and *(4c)* (67:33)[5] and *(3d)* and *(4d)* (83:17), respectively[5].



(1) *(2)* *(3)* *(4)*

[*] Dr. S. Sommer
Organisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

Table 1. Synthesized compounds *(3)* and *(4)*.

Cpd.	R^1	R^2	R^3	R^4	*(3)* M.p. [°C]	*(3)* Yield [%] [a]	*(4)* M.p. [°C]	*(4)* Yield [%] [a]
(a)	H	H	C_6H_5CO	H	148 [b]	86	205—206 [f]	80 [g]
(b)	H	H	CH_3CO_2	H	80—81 [c]	85	168—169 [d]	83 [g]
(c)	H	CH_3	CH_3CO_2	H	149—150 [d]	46	138—139 [d]	13 90 [g]
(d)	Cl	CH_3	CN	H	175—176 [e]	75	147 [d]	10 97 [g]
(e)	Cl	CH_3	H	CN	165—166 [e]	89		
(f)	H	$-(CH_2)_4-$		H			196—197 [e]	72
(g)	H	H	morpholino	H			164—165 [d]	84

[a] Referred to isolated pure compound.
[b] Ethanol.
[c] Cyclohexane; crystallized from 1/4 cyclohexane.
[d] Methanol.
[e] Ethyl acetate.
[f] Chloroform/methanol.
[g] Yield in the rearrangement of *(3)* into *(4)*.

Table 2. IR- and ^{1}H-NMR data of *(3)* and *(4)*.

Cpd.	*(3)* IR [cm^{-1}] (KNr) [a]	*(3)* ^{1}H-NMR [c, d]	*(4)* IR [cm^{-1}] (KBr) [g]	*(4)* ^{1}H-NMR [c, d]
(a)	1787, 1650, 1615	—, 7.03, 6.11, — [e]	1672, 1672, 1625	—, 5.43, [h], — [j]
(b)	1789, 1705, 1628	—, 7.14, 5.11, 3.55 [f]	1688, 1738, 1635 (CCl_4)	—, 4.33, 7.46, 3.50 [k]
(c)	1786, 1710, 1622	1.89, —, 5.35, 3.53	1680, 1733, 1645	2.17, 4.28, —, 3.52
(d)	1791, [b], 1617	1.71, —, 4.63, —	1695, [i], 1648 (CCl_4)	2.27, 4.58, —, —
(e)	1771, [b], 1620	1.60, —, 4.65, —		
(f)			1671, —, 1628 ($CHCl_3$)	—, 3.18, —, —
(g)			1660, —, 1625	—, 3.97, 7.55, — [l]

[a] $\nu_{C=O}$(ring), $\nu_{C=O}$, $\nu_{C=C}$. [b] $\nu_{C\equiv N} = 2215\ cm^{-1}$. [c] δ-value [ppm], in $CDCl_3$ rel. to TMS int. [d] δ_{CH_3}, $\delta_{5\text{-H}}$, $\delta_{6\text{-H}}$, δ_{OCH_3}. [e] $J_{5,6} = 13.4$ Hz. [f] $J_{5,6} = 13.8$ Hz. [g] $\nu_{C=O}$(ring), $\nu_{C=O}$, $\nu_{C\equiv N}$ (very weak). [h] Hidden by aromatic signals. [i] $\nu_{C\equiv N} = 2255\ cm^{-1}$. [j] $J_{5,6} = 4.6$ Hz. [k] $J_{5,6} = 4.1$ Hz. [l] $J_{5,6} = 4.0$ Hz.

If acetonitrile, which is more polar than benzene, is used as medium in the reaction of *(1c)* with *(2)* the adduct ratio is shifted in favor of the four-membered ring *(3c)* [*(3c)*:*(4c)* = 81:19][5]. Interconversion of the compounds *(3)* and *(4)* does not take place under the reaction conditions. However, on treatment with small amounts of trifluoroacetic acid in dichloromethane the four-membered rings *(3a)*—*(3d)* rearrange in high yields into the six-membered rings *(4a)*—*(4d)*.

It should be pointed out that the configuration at the C=C double bond of compound *(1)* in the adducts unaltered in [2+2]-cycloadditions of the (*E,Z*)-isomeric azoalkenes *(1d)* and *(1e)*[4] to *(2)*. On treatment with catalytic amounts of trifluoroacetic acid, compound *(3e)* rapidly isomerizes to *(3d)*, which subsequently rearranges slowly into the six-membered ring *(4d)*.

The structures of the cycloadducts follow from correct CHN-analyses and from IR-, ^{1}H-NMR-, and ^{13}C-NMR-data (Table 2). The regiochemistry of the four-membered ring adduct, which cannot be clarified by these techniques, follows from the hydrolysis of *(3b)* to the well-known 2,4,4-triphenyl-1,2-diazetidin-3-one[3a].

The above findings show that arylazoalkenes behave similarly to α,β-unsaturated carbonyl compounds[6] towards *(2)*. Both heterodiene systems are capable of forming [2+2]- and [4+2]-cycloadducts with *(2)*, six-membered ring formation predominating over four-membered ring formation with increasing donor capacity of the substituents on the C=C bond of the heterodiene. The cycloadditions described here render possible a simple entry to the previously unknown *N*-vinyl-1,2-diazetidinone system and to novel 4,5-dihydro-2*H*-pyridazin-3-one derivatives.

Received: November 4, 1976 [Z 600 IE]
German version: Angew. Chem. *89*, 59 (1977)

CAS Registry numbers:
(1a), 61178-13-0; *(1b)*, 61178-14-1; *(1c)*, 61178-15-2; *(1d)*, 61178-16-3; *(1e)*, 61178-17-4; *(1f)*, 41350-71-4; *(1g)*, 61178-18-5; *(2)*, 525-06-4; *(3a)*, 61178-19-6; *(3b)*, 61178-20-9; *(3c)*, 61178-21-0; *(3c)*, 61178-22-1; *(3e)*, 61178-23-2; *(4a)*, 61178-24-3; *(4b)*, 61178-25-4; *(4c)*, 61178-26-5; *(4d)*, 61178-21-6; *(4f)*, 61178-28-7; *(4g)*, 61178-29-8

[1] Reactions with Azo Compounds, Part 3.—Part 2: *S. Sommer*, Tetrahedron Lett., in press.
[2] *H. Staudinger:* Die Ketene. F. Enke Verlag, Stuttgart 1912, p. 91.
[3] a) *C. W. Bird*, J. Chem. Soc. *1963*, 674; b) *R. C. Kerber, T. J. Ryan*, and *S. D. Hsu*, J. Org. Chem. *39*, 1215 (1974); c) *S. Sommer*, Angew. Chem. *88*, 449 (1976); Angew. Chem. Int. Ed. Engl. *15*, 432 (1976).
[4] With the exception of *(1d)* and *(1e)* all the azoolefins mentioned here have already been described in the literature. *(1d)* (m.p. 92—93°C, from methanol) and *(1e)* (m.p. 127—128°C, from methanol) were synthesized according to a general experimental procedure for the preparation of 3-arylazocrotononitriles[7]. Separation of the isomeric mixture [*(1d)*:*(1e)* = 82:18], which was obtained in 75% yield, was achieved by column chromatography on silica gel (hexane/ethyl acetate 3:1). The procedure cited here [7], contains no information about the stereochemistry of the azoalkenes thus prepared, nor about the occurrence of stereoisomers.
[5] The product ratio was determined from the integrals of the methyl signals in the ^{1}H-NMR spectrum of the crude solution.
[6] Review: *R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. Int. Ed. Engl. *8*, 312 (1969).
[7] *A. Quilico* and *R. Justoni*, Rend. Ist. Lomb. Sci. Lett., Rend. *2*, 69, 587 (1936).

Reviews

Abstracts of selected progress reports and review articles

Picosecond chemistry is the subject of a review by *G. E. Busch* and *P. M. Rentzepis*. A picosecond (ps) is 10^{-12} s. In most measurements the sample was irradiated with a laser pulse of a few ps duration, and investigated before, during, and after this excitation. Novel areas of application include, *inter alia*, the behavior of solvated electrons in solvents and of free electrons in water, the rapid relaxation of the triphenylmethane dyes crystal violet and malachite green, as well as the photobiochemistry of reaction centers in bacteriochlorophyll. The photosystems in chloroplasts and the primary processes of vision were also investigated by this technique. [Picosecond Chemistry. Science *194*, 276—283 (1976); 39 references]

[Rd 902 IE—F]

Reviews of papers published during 1974 form the contents of a volume of the Journal of Organometallic Chemistry. *J. Boersma* deals with zinc and cadmium, *M. I. Bruce* reports on the structure of organotransition metal complexes, *P. M. Treichel's* themes are manganese, technetium, and rhenium, *D. J. Darensbourg* and *M. Y. Darensbourg* cover chromium, molybdenum, and tungsten, and *M. E. Howden* and *R. D. W. Kemmitt* report on cobalt, rhodium, and iridium. [Annual Surveys covering the year 1974. J. Organomet. Chem. *115*, 1—16, 17—176, 177—220, 221—325, 327—415 (1976); 47, 406, 153, 364, 377 references]

[Rd 903 IE—F]

Inorganic pyro-compounds of type $M_a[(X_2O_7)_b]$ are reviewed by *G. M. Clark* and *R. Morley*. Compounds with this stoichiometry exhibit an extraordinary variety of structures. Thus, $Ca_2Ta_2O_7$ is a complex with the continuous pyrochlorite structure, $Y_2Pb_2O_7$ has a continuous oxide structure of the defect fluorite type, $Na_2Mo_2O_7$ contains an infinite unidimensional $Mo_2O_7^{2-}$ chain. Especially interesting are the island structures, in which $X_2O_7^{2-}$ is a discrete pyroanion and for which those with X = As, Be, Cr, Ge, P, S, Si and V have been demonstrated. These pyro-compounds crystallize with structures like $Sc_2Si_2O_7$ or $K_2Cr_2O_7$. The review contains numerous informative diagrams of molecular and crystal structures as well as summarized data on pyro-compounds in which the island structure of the anion has been confirmed. [Inorganic Pyro-compounds $M_a[(X_2O_7)_b]$. Chem. Soc. Rev. *5*, 269—295 (1976); 144 references]

[Rd 904 IE—F]

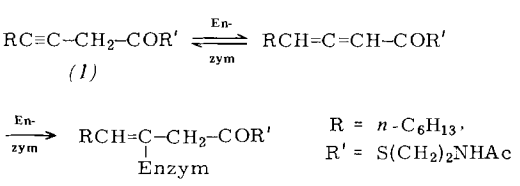
Nuclear reactions with heavy ions are the subject of a review by *J. R. Huizenga*. Interest in these reactions evolved from the predicted increased stability of elements with atomic numbers between 110 and 126, which it was hoped could be generated with the aid of heavy ions. The article deals with the interactions that can take place between two large complex nuclei, with emphasis on the recently discovered strongly damped collision process. [Nuclear Reactions Revisited with Very Heavy Ions. Acc. Chem. Res. *9*, 325—333 (1976); 56 references]

[Rd 907 IE—L]

An effective method for designing synthetic approaches to natural products is afforded by studying degradation processes in the mass spectrometer. The method has been used successfully by *T. Kametani* and *K. Fukumoto* in the case of protoberberine, phthalideisoquinoline, spirobenzylisoquinoline and quinazolinocarboline alkaloids, as well as olivacine and yohimbine. The most important types of mass spectrometric fragmentations are CC bond cleavages, concerted cleavages of the retro Diels-Alder type, and cleavages involving heteroatoms; the reverse reactions carried out "chemically" were used in the alkaloid syntheses. [Total Synthesis of Natural Products by Retro Mass Spectral Synthesis. Acc. Chem. Res. *9*, 319—325 (1976); 39 references]

[Rd 906 IE—L]

Suicide inactivators for enzymes are a special type of inhibitors according to *R. H. Abeles* and *A. L. Maycock*. Unlike a classical inhibitor, which resembles the natural substrate of an enzyme, a suicide inactivator must be transformed by the enzyme into the active form. This binds covalently and irreversibly to the active site of the enzyme, which thus becomes



inactive.—An example is the suicide inactivation of β-hydroxydecanoyl thioester dehydrase by the ester *(1)*. Suicide inactivators are suitable for probing the structure and function of enzymes and ought to be useful in the development of drugs. [Acc. Chem. Res. *9*, 313—319 (1976); 28 references]

[Rd 905 IE—L]

"Uncommon" amino acids in plants forms the subject of a review by *A. Bell*. Such amino acids include all those which are not fragments of proteins and which do not occur in the "usual" metabolic pathways. More than 200 of them are already known; some make up a considerable portion of the plant material. Little is known about their biosynthesis, their metabolism and their biological importance. Only a part of them are directly related to the "usual" amino acids, many are formed in completely novel metabolic pathways. In contrast to the ubiquitous "usual" amino acids, the "unusual" types are suitable for phylogenetic studies. Several of them exhibit special biological, in part toxic action, which would indicate their usefulness in medicine. The "unusual" amino acids might serve as protective agents in the plant's growth, either as a deterrent against consumption by animals or against competing germinant seeds of other plants. ["Uncommon" Amino Acids in Plants. FEBS Lett. *64*, 29—35 (1976); 31 references]

[Rd 908 IE—R]

Immobilized enzymes form the theme of an article by *K. Mosbach*. The past few years have seen great progress in the coupling of biologically important substances, and of enzymes, to insoluble carriers. With such immobilized enzymes kinetic parameters can by investigated under conditions in

which the free enzymes undergo undesirable side reactions (association, self consumption). Furthermore, biologically relevant model systems can be constructed, for enzymes are not freely mobile in their natural environment but are bound to membranes or surrounded by a gel-like phase. In addition, immobilized enzymes are gaining increasing importance for preparative and analytical purposes. Immobilized coenzymes have general utility as affinity adsorbents. [Immobilized Enzymes. FEBS Lett. *62* (Suppl.), E80—E95 (1976); 84 references]

[Rd 909 IE—R]

DNA ligases of eukaryotes are reviewed by *S. Söderhäll* and *T. Lindahl*. These enzymes act together with the DNA polymerases in replication and the repair of strand breaks. Mammalian enzymes differ from the better known enzymes of microorganisms. Thus, only ATP has been detected as energy donor, whereas bacterial enzymes also use NAD^+. In contrast to microorganisms, mammalian cells contain two different DNA ligases. The dominating enzyme I is relatively large (175—200000 Dalton) and occurs mainly in dividing cells. It can couple growing DNA fragments *in vitro*. Enzyme II, with a molecular weight of 85000 Dalton, occurs only in small amounts (5—20%). It is less specific than enzyme I. A ligase similar to enzyme II has also been detected in mitochondria. [DNA Ligases of Eukaryotes. FEBS Lett. *67*, 1—8 (1976); 73 references]

[Rd 911 IE—R]

A review of methods for the analysis of kinetic data in biochemistry is given by *M. Markus, B. Hess, J. H. Ottaway*, and *A. Cornish-Bowden*. The review is based on discussions held at a conference devoted to this theme. The advantages and disadvantages of the total trace of the curve as well as the various methods for the linearization of kinetic functions are discussed. [The Analysis of Kinetic Data in Biochemistry. A Critical Evaluation of Methods. FEBS Lett. *63*, 225—230 (1976); 59 references]

[Rd 910 IE—R]

BOOK REVIEWS

Werkstoff Glas (Glass as a Material). By *K. Kühne*. Akademie-Verlag, Berlin 1976. 1st edit., 329 pp., various figs., paperback, *ca.* 12.50 DM.

The history of glass goes back many thousands of years. Scientific penetration into glass technology began at the end of the nineteenth century (*e.g.* by *Schott* at Jena), but one can validly speak of a science of glass only from about 1950. Today glass with almost any desired properties can be made.

After a short section of the history of glass the book discusses "the vitreous state", in which, *inter alia*, views on the structure of glass and its segregation are discussed. The following chapter describes the glass-forming systems and applications of glass, while Chapter 4 concerns the properties of glasses and the possibilities of their modification. The next (very extensive) chapter deals with the production and working of glass. Finally there is a short section on "Special Glasses", followed by literature references and several indexes.

The author has succeeded in giving a very good and easily readable review of the field. The presentation is perhaps a little too classical, and in some places one could have hoped for the latest results obtained by modern methods of investigation. Nevertheless, the book can be very warmly recommended to all interested in glass, *e.g.* to students at universities or technical colleges and to scientists in industry.

G. H. Frischat [NB 356 IE]

Reaktionen der organischen Chemie (Reactions of Organic Chemistry). By *H. Krauch* and *W. Kunz*. 5th, revised and extended edit. By *W. Kunz* and *E. Nonnenmacher*. Dr. Alfred Hüthig Verlag, Heidelberg 1976. xxxi, 875 pp., linen, DM 134.—.

The original "Named Reactions" title of "Krauch-Kunz" was generalized to "Reactions of Organic Chemistry" already in the 3rd edition (1966), when some important reactions not known by their discoverers' names were added, with brief descriptions and literature references. In the present 5th edition this tendency to broaden the scope has led to a changeover from the mode of arrangement by authors' names to arrangement by the description of content. For example, the degradation processes of carboxylic acids due to *Barbier-Wieland*, *Gallagher-Hollander*, *Krafft*, and *Mieschер* are no longer scattered all over the text but are treated one after the other (pp. 216ff.). Simultaneously with this rearrangement, the authors have tried to make the reaction terminology more standardized, with dubious success, judging by the lack of consistency in the descriptions selected. Thus, the degradation of carboxylic acids according to *Simonini* and to *Hunsdiecker-Borodin* is treated under "Decarboxylation of Silver Salts" (p. 700), and ring syntheses from α,ω-difunctional alkanes are discussed in one place as cyclization (*Gustavson-Hass*, p. 302) and in another as ring closure (*Ladenburg*, p. 687), and finally also as propane ring closure (*Freund*, p. 650), starting from the educt. Fortunately, the volume contains not only an extensive author and subject index but also an index of named reactions, so that "Krauch-Kunz" can still be used, as before, for reference to a reaction under its "trivial name(s)".

Along with the new principle of arrangement in the 5th edition, some of the descriptions of the reactions have been revised and the references have been extended, apparently to the end of 1974. Only 15 new reactions have been added among the present total of *ca.* 580. Even if we allow that the choices made by the authors must necessarily be subjective, we may surely ask whether the last ten years have not brought forth a larger number of "named" reactions which at the same time supersede older processes. In this respect the current revision has not always succeeded in eradicating the patina of age. This also appears in the often old-fashioned nomenclature, although actual errors, such as the description of the bicyclobutonium ion by mesomerism of two cations (p. 686), are refreshingly rare. In all, value of "Krauch-Kunz" as a revision text has decreased, but for rapid information about a reaction, and for gaining an entry into the primary and secondary literature, this volume remains irreplaceable.

Ernst Schaumann [Nb 357 IE]

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (dec.), and *W. M. Weigert*. Vol. 10: Dentalchemie bis Erdölverarbeitung. Verlag Chemie, Weinheim 1976. 4th edit., xvi, 714 pp., 345 figs., 228 tables, half-linen, subscription price DM 345.—; final price DM 385.—. Cumulative index to vols. 7 to 9; 133 pp., DM 38.—.

The present volume[*] of the new Ullmann is the fourth of the alphabetically arranged main Parts dealing with the products and processes of the chemical industry and of related important fields. A considerable proportion of this volume is devoted to Natural Gas [Erdgas], Petroleum [Erdöl], and Petroleum Processing [Erdölverarbeitung] (excluding formation, exploration, occurrence, and recovery, which are dealt with in volume 11; total 132 pp.), and to Iron and Iron Compounds [Eisen, Eisenverbindungen] (together 124 pp.); steels, steelmaking, iron alloys, and cast iron, however, are not dealt with here but separately under their own headings. Another extensive entry is Enzymes [Enzyme] (86 pp.), where one chapter deals with the immobilized enzymes, which are particularly important today; further chapters are devoted to, *inter alia*, the industrial use of enzymes, enzyme analysis, and enzyme therapy. Pharmacy in its wider sense is also represented, *viz.* by Dental Chemistry [Dentalchemie] (27 pp.), Dermatological agents [Dermatotherapeutica] (9 pp.), Disinfectants [Desinfektionsmittel] (18 pp.), Diagnostic agents [Diagnostica] (38 pp.) and Diuretics [Diuretica] (6 pp.). Among the entries on organic chemical precursors and intermediates included in this volume we may mention Dialkyl Sulfates [Dialkylsulfate] (12 pp.), Dicarboxylic Acids [Dicarbonsäuren] (9 pp.), Dioxane [Dioxan] (4 pp.), and Epoxides [Epoxidverbindungen] (18 pp.), and from the sector of dyes and precursors, we have Disperse Dyes [Dispersionsfarbstoffe] (11 pp.), Printing Inks [Druckfarben] (13 pp.), as well as Diazo Compounds and Diazo Reactions [Diazoverbindungen und Diazoreaktionen] (24 pp.). Under Fertilizers [Düngemittel] (56 pp.) are summarized mainly the various aspects of industrial application; the technology of the production of individual fertilizers is, however, described under the appropriate chemical keywords. Other applied fields dealt with in this volume include Thin Layers [Dünne Schichten] (12 pp.), Enamels [Email] (14 pp.), and Emulsions [Emulsionen] (25 pp.).

As in the previous volumes, the authors of the individual articles are experts mainly from industrial circles. What should be emphasized is the unfailing expertise of the editors in achieving a balanced and clearly arranged presentation of topics in spite of the by no means small number of authors. Especially useful are the numerous charts containing, *e.g.* material constants and economic data, as well as a list of uses, as in the chart of fertilizer types (with data on composition and application) and the two tables of radiopharmaceuticals (though here the half-lives and energies of the individual isotopes would also have been useful). The work is up to date too: in the entry on Noble Gases [Edelgase] (42 pp.) there is a 1975 reference according to which krypton difluoride and particularly $[KrF]^+[AuF]_6^-$ are extremely good fluorinating agents.

Alongside Volume 10 a cumulative index for the first alphabetical Volumes 7 to 9 has been published in German and English. It is planned to publish cumulative indexes immediately after the appearance of successive sets of three volumes, *i.e.* the next cumulative index (for Volumes 7 to 12) will be available with Volume 13. These cumulative indexes are most useful for cross-referencing, for they are subdivided in great detail; for example, the present index lists about 9000 entries.

Ulfert Onken [NB 361 IE]

[*] Cf. Angew. Chem. Int. Ed. Engl. *15*, 448 (1976).

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Liquid Scintillation. Science and Technology. Edited by *A. A. Noujaim, C. Ediss*, and *L. I. Weibe*. Academic Press, New York 1976. xiv, 352 pp., bound, $ 17.50.—ISBN 0-12-522350-1

Basic Gas Chromatography. By *H. M. McNair*. American Chemical Society Audio Course. 6 Audiotape Cassettes (4 hours duration) with handbook (VII, 100 pp., stitched) $ 95.00. Prices for additional copies of the handbook: $ 7.00 each for 1—9 copies; $ 6.00 each for 10—49 copies; $ 5.50 each for more than 50 copies.

Advances in Carbohydrate Chemistry and Biochemistry, Vol. 33. Edited by *R. St. Tipson* and *D. Horton*. Academic Press, New York 1976. x, 464 pp., bound, $ 44.00.—ISBN 0-12-007233-5

Intensivkurs Mathematik. Programmierte Prüfung für das Selbststudium. By *W. Schmidt*. Vol. 54 of the series "taschentext". Verlag Chemie/Physik Verlag, Weinheim 1976. iv, 187 pp. + folding tables, stitched, DM 16.80.—ISBN 3-527-21062-8 (Verlag Chemie); 3-87664-562-X (Physik Verlag)

Reviews in Macromolecular Chemistry, Vol. 14B. Edited by *G. B. Butler, K. F. O'Driscoll*, and *M. Shen*. Marcel Dekker, New York 1976. xvi, 315 pp., bound, $ 32.50.—ISSN 0557-6458

Catalysis Reviews. Science and Engineering. Vol. 13. Edited by *H. Heinemann* and *J. J. Carberry*. Marcel Dekker, New York 1976. xvi, 337 pp., bound, $ 32.50.—ISSN 0008-7645

Experimental Methods in Catalytic Research, Vol. II. Edited by *R. B. Anderson* and *P. T. Dawson*. Vol. 15-II of the series "Physical Chemistry". Edited by *E. M. Loebl*. Academic Press, New York 1976. xiv, 283 pp., bound, $ 26.50.—ISBN 0-12-058660-6

Advances in Infrared and Raman Spectroscopy, Vols. 1 and 2. Edited by *R. J. H. Clark* and *R. E. Hester*. Heyden, London 1976. Vol. 1: xiii, 306 pp., bound, DM 101.—; Vol. 2: xv, 343 pp., bound, DM 112.—.—ISBN 0-85501-181-5 (Vol. 1); ISBN 0-85501-182-3 (Vol. 2)

Adverse Effects of Environmental Chemicals and Psychotropic Drugs. Neurophysiological and Behavioural Tests. Vol. 2. Edited by *M. Horváth*. Elsevier Scientific Publishing Co., Amsterdam 1976. xv, 334 pp., bound, Dfl. 103.00.—ISBN 0-444-41498-3

Chemistry of Organic Fluorine Compounds. A Laboratory Manual with Comprehensive Literature Coverage. By *M. Hudlicky*. Ellis Horwood Ltd., Chichester; Halsted Press, a division of John Wiley & Sons, London 1976. 2nd, revised edition, xiv, 903 pp., bound, £ 35.50.—ISBN 85312-008-0 (Ellis Horwood); 0-470-41835-4 (Halsted Press)

Gift-Tiere und ihre Waffen. Eine Einführung für Biologen, Chemiker und Mediziner. Ein Leitfaden für Touristen. By *G. Habermehl*. Springer-Verlag, Berlin 1976. 126 pp., stitched DM 22.80.—ISBN 3-540-07807813-4

Peptide Synthesis. By *M. Bodanszky, Y. S. Klausner*, and *M. A. Ondetti*. From the series "Interscience Monographs on Organic Chemistry". Edited by *G. A. Olah*. John Wiley & Sons, New York 1976. 2nd Edit., xiv, 208 pp., bound, $ 24.80.—ISBN 0-471-08451-4

Experimental Methods in Catalytic Research, Vol. III. Characterization of Surface and Adsorbed Species. Edited by *R. B. Anderson* and *P. T. Dawson*. Vol. 15-III of the series "Physical Chemistry". Edited by *E. M. Loebl*. Academic Press, New York 1976. xiv, 327 pp., bound, $ 29.50.—ISBN 0-12-058662-2

Advances in Heterocyclic Chemistry, Vol. 20. Edited by *A. R. Katritzky* and *A. J. Boulton*. Academic Press, New York 1976. x, 324 pp., bound, $ 33.50.—ISBN 0-12-020620-X

Handbook of Chemical Lasers. Edited by *R. W. F. Gross* and *J. F. Bott*. John Wiley & Sons, New York 1976. x, 744 pp., bound, 31.00.—ISBN 0-471-32804-9

Fundamentals of Electrochemical Analysis. By *Z. Galus*. From the series "Ellis Horwood Series in Analytical Chemistry". Edited by *R. A. Chalmers*. Ellis Horwood Ltd., Chichester 1976. ix, 520 pp., bound, £ 23.50.—ISBN 85312-036-6

Cryochemistry. Edited by *M. Moskovits* and *G. A. Ozin*. John Wiley & Sons, New York 1976. xi, 532 pp., bound, $ 39.00.—ISBN 0-471-61870-5

Applications of Biochemical Systems in Organic Chemistry, Part I and II. Edited by *J. B. Jones, Ch. J. Sih*, and *D. Perlman*. Vol. X of the series "Techniques of Chemistry". Edited by *A. Weissberger*. John Wiley & Sons, London 1976. Part I: xii, 506 pp., bound, £ 24.25—ISBN 0-471-93267; Part II: x, 1065 pp., bound, £ 26.65—ISBN 0-471-93270-1

Advances in Radiation Chemistry, Vol. 5. Edited by *M. Burton* and *J. L. Magee*. John Wiley & Sons, London 1976. xi, 337 pp., bound, £ 29.50.—ISBN 0-471-01669-1

Geschichte der mechanischen Prinzipien und ihrer wichtigsten Anwendungen. By *I. Szabó*. Birkhäuser Verlag, Basel 1977. ix, 491 pp., bound, *ca.* DM 58.—.

The New World of Quantum Chemistry. Edited by *B. Pullman* and *R. Parr*. D. Reidel Publishing Company, Dordrecht 1976. viii, 356 pp., bound, Dfl. 75.—.—Proceedings of the Second International Congress of Quantum Chemistry, New Orleans 1976—ISBN 90-277-0762-6

Ion Cyclotron Resonance Spectrometry. By *Th. A. Lehman* and *M. M. Bursey*. John Wiley & Sons, London 1976. xi, 230 pp., bound, £ 17.00.—ISBN 0-471-12530-X

Laborbücher Chemie: Einführung in die Analysemethoden. By *H. Kiechle*. Edited by *L. Fischer-Blunk*. Diesterweg Salle, Frankfurt/Verlag Sauerländer, Aarau 1976. viii, 88 pp., spiral binding DM 18.—.—ISBN (Diesterweg) 3-425-05080-II; (Sauerländer) 3-7941-1520-1

Methods of Seawater Analysis. By *K. Grasshoff*. Verlag Chemie, Weinheim 1976. xiv, 317 pp., geb. DM 98.—.—ISBN 3-527-25631-8

Organometallic Chemistry, Vol. 5. Senior Reporters: *E. W. Abel* and *F. G. A. Stone*. The Chemical Society, London 1976. xviii, 520 pp., bound, £ 29.00—A volume of the series "Specialist Periodical Reports"—ISBN 0-85186-541-0

Spectroscopic Properties of Inorganic and Organometallic Compounds, Vol. 6. Senior Reporter: *N. N. Greenwood*. The Chemical Society, London 1976. xii, 544 pp., bound, £ 28.00—A volume of the series "Specialist Periodical Reports"—ISBN 0-85186-083-4

Trivialnamenkartei, 5th supplementary issue. Verlag Chemie, Weinheim 1976. 1024 supplementary cards, DM 208.—.

Organic Chemistry Series Two. Edited by *D. H. Hey*. Vol. 8: Steroids. Edited by *W. F. Johns*. From the series "International Review of Science". Butterworths, London 1976. 278 pp., bound, £ 13.45.

Topics in Applied Physics. Founded by *H. K. V. Lotsch*. Vol. 2: Laser Spectroscopy of Atoms and Molecules. Edited by *H. Walther*. Springer-Verlag, Berlin 1976. xvi, 383 pp., bound, DM 97.00.

Modern Fluorescence Spectroscopy, Vols. 1 and 2. Edited by *E. L. Wehry*. Heyden, London 1976. Vol. 1: xvi, 238 pp.; Vol. 2: xx, 459 pp., total price DM 224.—. ISBN 0-85501-218-8 (Vol. 1); 0-85501-219-6 (Vol. 2)

Subnuclear Components. Preparation and Fractionation. By *G. D. Birnie*. Butterworths, London 1976. 334 pp., bound, £ 15.00.

Einführung in die Chemie und Technologie der Kunststoffe. By *F. Runge* (deceased) and *E. Taeger*. Akademie-Verlag, Berlin 1976. xiv, 682 pp., bound, *ca.* DM 88.00.

Lexikon Biochemie. Edited by *H.-D. Jakubke* and *H. Jeschkeit*. Revised by *G. Adam*. Verlag Chemie, Weinheim 1976. 605 pp., bound, DM 32.—.—ISBN 3-527-25662-8

Silicate Science. By *W. Eitel*. Vol. VII: Glass Science. Academic Press, New York 1976. xvi, 611 pp., bound, $ 52.50.

Advances in Liquid Crystals, Vol. 2. Edited by *G. H. Brown*. Academic Press, New York 1976. xi, 308 pp., bound, $ 30.00.—ISBN 0-12-025002-0.

Gas-Solid Reactions. By *J. Szekely, J. W. Evans*, and *H. Y. Sohn*. Academic Press, New York 1976. xiii, 400 pp., bound, $ 39.50.—ISBN 0-12-680850-3.

Lecture Notes in Chemistry. Edited by *G. Berthier, M. J. S. Dewar, H. Fischer, K. Fukui, H. Hartmann, H. H. Jaffé, J. Jortner, W. Kutzelnigg, K. Ruedenberg, E. Scrocco*, and *W. Zeil*. Vol. 1: Introduction to Elementary Molecular Orbital Theory and to Semiempirical Methods. By *G. H. Wagnière*. Springer-Verlag, Berlin 1976. v, 109 pp., paperback, DM 14.80.—ISBN 3-540-07865-7.

Thermodynamics of Polymerization. By *H. Sawada*. Marcel Dekker, New York 1976. xiii, 403 pp., bound, SFrs. 130.—.—ISBN 0-8247-6470-6.

Amors vergifteter Pfeil. Kulturgeschichte einer verschwiegenen Krankheit. By *E. Bäumler*. Hoffmann und Campe, Hamburg 1976. 480 pp., bound, DM 34.—.—ISBN 3-455-08962-3.

Chemisorption: An Experimental Approach. By *G. Wedler*. Butterworths, London 1976. 250 pp., bound, £ 12.00.—ISBN 0-408-10611-5

Chemie und Physik der Polymeren. Eine Einführung. By *J. M. G. Cowie*. Verlag Chemie, Weinheim 1976. xi, 321 pp., bound, DM 69.—.—ISBN 3-527-25666-0

Warning on copyright

Before photocopying, xerocopying or reproducing an article from this journal please check whether you may be violating the legal provisions of copyright and thus rendering yourself liable to prosecution.
Copyright law allows the photocopying of individual articles only, and then only as single copies for private or personal use. The production of copies for any other purpose is not permitted without payment of copyright fees.

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English

Volume 16 · Number 2
February 1977
Pages 65–124

Chiral Derivatives of Achiral Molecules: Standard Classes and the Problem of a Right-Left Classification

By Ernst Ruch[*]

Chemistry judging by its applications, physics according to its methods, and heavily reliant upon the tools of mathematics—that is what makes theoretical chemistry. And yet that is where its strength lies—in the variety of these sciences. It is quite natural that, in answer to specific problems, results and methods can sometimes be developed whose scope extends far beyond the original application. Rather it is a mark of quality if consequences can be found in chemistry and physics and the pathway leads *via* new mathematical procedures and concepts. Regrettably, any publication aiming to present such aspects will usually encounter little resonance since the linguistic confusion in science, its disciplines, and subdisciplines, lies like a veil over our understanding. The author nevertheless wishes to attempt to present, in a series of articles, results of research into chemical themes in a manner designed to appeal to the interest of chemists, without neglecting interdisciplinary aspects. All that is required to understand the argumentation is a lively interest.

The first two articles are concerned with the chirality of molecules, and in particular with questions relating to the chirality phenomenon of molecules in the framework of molecular classes. In view of the algebraic nature of the mathematical methods adopted, it is not surprising that precise statements result. It appears of primary interest to establish the degree to which such statements can be considered valid for molecular models or molecules themselves.

1. Chirality

The intuitive concept that we call symmetry refers to geometrical properties of an object. It can be mathematically defined in terms of a "symmetry group", *i.e.* by the entire set of rotation and reflection operations ("symmetry operations") leading to no visible change of the object and its spatial position.

An object that differs from its mirror image[**] is called chiral, otherwise it is achiral. In other words, it is termed achiral if only its position in space changes on reflection or rotation-reflection, but chiral if a different object is produced. Thus for achiral objects there are symmetry operations involving a reflection. Hence, chirality indicates the absence of certain symmetry elements—the symmetry of an object contains neither mirror planes, nor improper symmetry axes, nor a center of symmetry.

Our approach shows that it is reasonable to classify the symmetries themselves and accordingly to distinguish between chiral and achiral symmetries. Thus a symmetry shall be called chiral if the symmetry group contains no reflection operation, and shall otherwise be called achiral. An achiral symmetry will contain chiral subsymmetries; "no symmetry" is a special case of chiral symmetry.

The definition of chirality as a property of objects therefore simplifies to the trivial statement: *An object is called chiral*

[*] Prof. Dr. E. Ruch
Institut für Quantenchemie der Freien Universität
Holbeinstrasse 48, D-1000 Berlin 45 (Germany)

[**] The "mirror image" of an object is once again an object generated from the original one by any reflection operation, *e.g.* by reflection in an arbitrarily chosen plane.

or achiral depending upon whether its full symmetry is chiral or achiral.

Molecules are objects which can be successfully studied experimentally and theoretically in terms of chirality. It proves advantageous to discuss various examples having common features, *i.e.* various kinds of molecules from suitably selected classes. It is hardly surprising that a phenomenon observable for various kinds of objects will, when referred to a suitably chosen set, provide conclusions and insights which will not be forthcoming from analysis of a single case.

Sections 2 to 4 of this article are concerned generally with the type of such sets. The principal factors determining the choice of set type are ready susceptibility to mathematical analysis and maximum applicability to chemical problems. These requirements are satisfied by sets of objects which we call "standard classes". There exists a—predominantly algebraic—theory of the chirality of standard classes[1, 2], of the related problems of classification[3], and of quantum mechanical models concerned with specific chirality phenomena on the pattern of the algebraic theory[4, 5]. The results of these studies increase in value when viewed against the background of an extensive area of application, and once it has been established to what extent the objects investigated serve as good models for molecules and that real molecules themselves can be objects of such sets. Preliminary applications will be considered in Sections 5 and 6[6].

2. Symmetry and Chirality of Objects of a Special Class

In order to pave the way for an understanding of the term "standard class" to be defined later, let us first consider a set of objects consisting of a uniform skeleton having the symmetry of a regular tetrahedron and spheres of varying sizes located at the tetrahedral corners (Fig. 1).

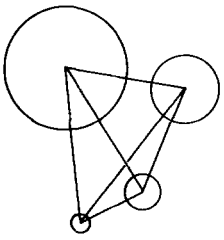


Fig. 1. An example taken from the set of objects having a regular tetrahedral skeleton.

The symmetry of the objects is that of the skeleton if all four spheres have the same diameter. Otherwise the symmetry of the objects will differ from that of the skeleton and depend upon the number of spheres having the same or different diameters; it does not depend upon the size of differences in the diameter of the spheres. In total there are five possible object symmetries which are depicted in Figure 2. The corresponding partition diagram, in which the boxes in a row each represent spheres of the same size, is shown alongside each picture.

The objects shown in Figure 2 are achiral if two or more spheres have the same diameter. Hence the only chiral object is seen at the bottom of the Figure. No two spheres are identical.

Symmetry operations on the tetrahedron subject the objects to rotations or rotation-reflections by which the skeleton is brought into coincidence with itself. When performed on a spatially rigid skeleton, such operations are manifested in an interchange of the spheres. These interchanges or permutations can therefore be used to describe the given rotations and rotation-reflections of the objects.

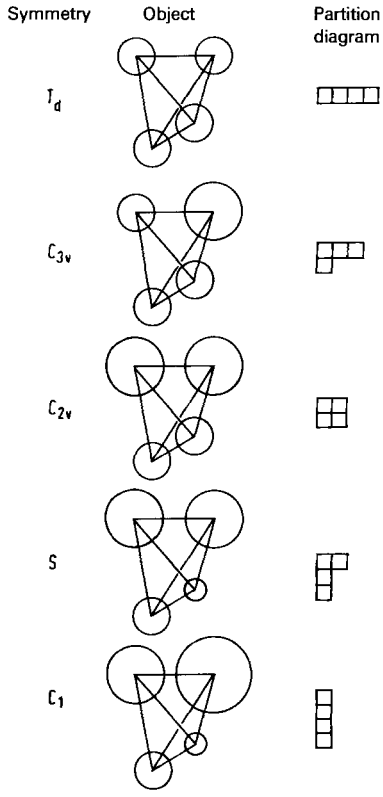


Fig. 2. The partitioning of sphere diameters is characteristic of the five possible object symmetries. It is depicted by partition diagrams in which boxes in the same row represent spheres of equal size and boxes in different rows correspond to spheres of differing size.

To what extent can the concept of the object be extended in the present case without falsifying conclusions about the symmetry of the objects?

The limitation to spheres of various sizes is certainly unnecessary; ligands such as circular cylinders, cones, trigonal prisms, *etc.*, can also be included. The symmetry of an object is then determined solely by the identity or non-identity of ligands at the various sites provided that the site symmetry is not impaired by the ligands, *i.e.* the mirror planes of each tetrahedral corner coincide with the mirror planes of the ligand located there. This condition defines the type of ligands permitted and the manner of their attachment. The partition diagrams of Figure 2 are still characteristic for the symmetry of the objects, the boxes in a given row not necessarily corresponding to spheres of equal size but to ligands of the same kind. However, the relation between object symmetry and ligand partition no longer applies if ligands are present which possess only one or two mirror planes or if ligands having C_{3v} symmetry are twisted out of the required orientation.

Ligands of the same and of different kinds located at the corners of a tetrahedron as a sufficient criterion for the symmetry of the objects in a class, in which the objects having

spheres of equal and different size are symmetry-determining, is what characterizes our class type. It is therefore reasonable to cast aside all prerequisites which are not necessary for this criterion. It may readily be seen that the required T_d skeletal symmetry for objects with ligands of one single type imposes a constraint upon the ligand type admitted that corresponds to the condition of site symmetry. If the attachment of the ligands is the same in all objects as in the objects having ligands of a single type the proper symmetry is guaranteed, also in any object of the class. However, to achieve this symmetry property the ligand attachment need not necessarily be the same in all objects. For the more general concept of a class the sufficient requirement is that the symmetry of an object remains unchanged on replacing ligands of different kinds by spheres of different sizes.

This formulation has many advantages. Referring neither to the ligands nor to the skeleton directly, it retains its validity even when a distinction between skeleton and ligand is not unequivocally possible or is to be avoided. It is applicable to classes of objects having an arbitrary achiral skeleton and then affords the necessary and sufficient condition for permitted ligands. It permits greater expression of specific peculiarities in the individual members of a class of objects. The first- and last-mentioned aspects, in particular, correspond precisely to the demands placed on good models for molecules.

Objects of the kind discussed having a rigid invariant skeleton are apparently suitable as grossly simplified models for methane and its derivatives, for particular adamantane derivatives, for inorganic tetrahedral complexes having a common central metal atom, or for other classes of molecules having a corresponding skeleton. The term skeleton can refer, as for methane, to an atom with four directed bonds, or, as for adamantanes, to a construction containing several atoms with four available valences in a regular tetrahedral arrangement (*e.g.* in positions 1, 3, 5, and 7 of tricyclo[3.3.1.1^{3,7}]decane). The permitted ligands include monoatomic ones, diatomic ones which can bind in the direction of their axis, tetraatomic groups such as CH_3, CCl_3, NH_3, *etc.*

Even if rigid constellations are accepted as models for real molecules, the above model concept must be viewed with reservations. For example, the skeleton will certainly not have the same shape in all methane derivatives, and ligands of the same kind are exposed to different neighboring group effects in different compounds; they deform in various ways. The occurrence of individual peculiarities is especially obvious in methane derivatives because the valence angles of the central carbon atom are components of the skeleton and very dependent upon interactions between the ligands.

The model concept can be improved to accommodate such corrections without necessitating any change in the symmetry of the "naive model". This can be demonstrated for the cases shown in Figure 2. A search through the field of chemistry for facts concerning the shape of compounds having tetrahedral molecular shape reveals the following empirical rule which is broken in only few cases[*]: *The symmetry of the molecules is determined by the ligand partition according to Figure 2 provided that this is not precluded by steric hindrance or the symmetry of the isolated ligands.*

This conclusion is not surprising since the geometry of molecules can be explained by naive models in which the symmetry is determined by the partitioning of the ligands and deforming intramolecular forces are at work. Such force fields generally have the symmetry of the native models and in the absence of special reasons will not lead to any symmetry-reducing deformations.

As a term applied to real objects, molecule refers to arrangements of atoms which are not rigid and frequently occur in several different conformations. Ascertainment of molecular symmetry is therefore usually a statement about an average value of geometrical possibilities. The result of such a symmetry ascertainment will of course depend upon the nature of the experiment, and the concept of symmetry has a well-defined meaning only in relation to experiment. In as much as molecular symmetry can be interpreted as an average value, real molecules can be objects of a class with the symmetry criteria according to Figure 2.

3. Standard Classes

Experience gained in the preceding example leads us to the general concept of a "standard class". It appears appropriate for the definition of this concept to use the usual concepts of chemistry independently of their application to molecules and to supplement them in an appropriate manner.

A "class of derivatives" should be taken to mean a set of objects which differ in the nature and distribution of ligands over given sites of a skeleton. The skeleton is the determining feature of a class of derivatives; however, it can exhibit geometric deviations in different derivatives of the same class. Ligands of the same kind can also have deviating shapes in a modified environment. Two derivatives having the same ligand assortment but differing distribution of the ligands over the sites are called "permutational isomers". Derivatives which are mirror images of each other are called "enantiomers". We call derivatives having ligands of a single kind "basis derivatives"[*].

To these derivatives we can assign models consisting of a rigid, simply constructed skeleton which is invariant within a given class and spheres of various sizes in place of ligands of different kinds. We term such models "standard models" and assume the skeleton to be achiral. The symmetry of the standard model is established once it is known where spheres of equal size are located on the skeleton. The symmetry operations of the skeleton subject the standard models to rotations and rotation-reflections which are interpretable as permutations of the spheres with reference to a spatially rigid skeleton. For a skeleton having n labeled sites the following sets of permutations can be distinguished:

S_N = group of all $n!$ permutations of the n ligands,
$\mathfrak{G}$ = group of those permutations which effect only rotations or reflections of the objects[**],
$\mathfrak{N}$ = group of those permutations which effect only rotations of the objects.

[*] A possible exception is the methane derivative CH_2Li_2 recently reported by *Schleyer* [13].

[*] According to this definition a molecule of the chemical parent compound methane is itself a derivative, being a basis derivative of the tetrahedral class!

[**] In the tetrahedral class of the preceding Section, S_N is identical to $\mathfrak{G}$.

Comparison of derivatives and standard models—on the one hand objects completely adapted to those occurring in nature such as molecules and on the other hand geometrical constructions without individual peculiarities in skeleton and ligands in the specific members—facilitates representation of a theoretical situation taken from an apparently complex chemical world: The principal reason is because the symmetry of standard models can also apply to the assigned derivatives without individual geometric features of the skeleton and ligands being eliminated.

Derivatives having the symmetry of the assigned standard models are called "standard derivatives" and a class of standard derivatives a "standard class". Thus, as for standard models, the symmetry of the derivatives of a standard class is determined by the distribution of like ligands. The symmetry of the "bare skeleton" and that of "isolated ligands" are to be found in the basis derivatives of a standard class. The fact that basis derivatives have the symmetry of the bare skeleton characterizes the ligands as permissible.

In standard derivatives a ligand permutation should designate a rearrangement, including the inherent deformations. Permutations effecting rotations or transition to the enantiomer in standard models have the same action on the standard derivatives, provided that the pertinent deformations are also considered.

The best rigid models of molecules which are conventionally described as derivatives of an achiral compound and whose ligands all belong to basis derivatives having the same achiral symmetry are generally the objects of a standard class. This is understandable because the intramolecular force field in a hypothetical molecule with the symmetry of a standard model normally also possesses the symmetry of the molecule, and therefore changes of geometry but not of symmetry may be expected. Since statements of symmetry may be referred to time-averaged values, chemical derivatives may themselves be members of a standard class. In a certain sense, standard classes represent the "pure case" or "standard case" upon which the discussion of other derivatives, which are not standard derivatives, is preferably based.

It can be demonstrated for cyclopropanone derivatives that the selection criterion for ligands in standard classes is generally not sufficiently formulated by the requirement of site symmetry of the ligands (cf. Section 2) but only by the symmetry requirement for basis derivatives (Fig. 3).



Fig. 3. Skeleton of cyclopropanone with specified sites (a) and a basis derivative (b), which shows that the effect of the environment can induce chirality in achiral ligands without destroying the overall symmetry of the ligand.

Cyclopropanone has C_{2v} symmetry. The requirement of site symmetry for ligands in cyclopropanone does not lead to any specification of the kind of ligand as the ligand sites do not lie in mirror planes or on axes of rotation. Accordingly, chiral ligands are also permitted. Derivatives having four chiral ligands of the same kind are chiral however; they do not possess the C_{2v} symmetry of the assigned standard models with four identical spheres and therefore do not belong to a standard class.

The C_{2v} symmetry required for basis derivatives of a standard class presupposes, for example, that the ligand at site 1 is the mirror image of the ligand at site 2 (Fig. 3). Since the two ligands in basis derivatives must be of the same kind by definition, they can only be deformed as object and mirror image and are achiral when not exposed to the effect of their environment ("isolated ligands"). Requirement of basis derivatives having C_{2v} symmetry therefore means that only achiral ligands are permitted. It may readily be demonstrated that the symmetry of the assigned standard models (C_{2v}, S, C_2, and C_1) is always possible in cyclopropanone derivatives with achiral ligands.

There are no standard classes having an achiral skeleton and chiral ligands, as follows from the achiral symmetry of the basis derivatives. Thus if the discussion is to include chiral ligands, then an extension of the concept of "standard classes" becomes essential. An adequate generalization consists in the somewhat less rigorous requirement that derivatives possess (at least) the full chiral subsymmetry of the standard models. Hence, a minimum symmetry of C_2 would be required for basis derivatives in the case of cyclopropanone. Almost all of what we shall discover later[6] about the chirality phenomenon in standard classes can be extended to the corresponding situation with chiral ligands. However, owing to the mathematical and conceptual complexity we shall not discuss this extension, but content ourselves with a reference to pertinent literature[7, 8].

4. Chirality Functions

The special theoretical importance of standard classes is based *inter alia* upon the simple relation between the symmetry of a standard derivative and the partition of its ligand system. It is thus fitting and proper to speak of "active ligand partitions" and thereby characterize the type of ligand systems which on suitable distribution over the skeletal sites give chiral derivatives. A simple criterion is also available for achiral classes: *i.e.* no chiral derivatives exist in a standard class if the two permutational groups $\mathfrak{N}$ and $\mathfrak{G}$ coincide ($\mathfrak{N}=\mathfrak{G}$). The standard derivatives of the benzene type are an apt example.

Owing to the equivalence of certain ligand permutations with rotations, properties independent of spatial position are invariant towards ligand permutations from the group $\mathfrak{N}$ in standard derivatives. A scalar property such as the energy changes neither on rotation nor on reflections and can be described as a function $f(l_1, l_2 \ldots l_n)$ of the ligands l_i located at the skeletal sites which remains unchanged if l_i is subjected to a permutation from group $\mathfrak{G}$. Pseudoscalar properties, on the other hand, such as optical activity or circular dichroism, are independent of rotations and change their sign on reflection. They can accordingly be described by a function $\varphi(l_1, l_2 \ldots l_n)$ which is invariant towards permutations from $\mathfrak{N}$ and its sign changes on permutations from $\mathfrak{G}$ which do not belong to $\mathfrak{N}$. We call such functions "chirality functions".

Chirality functions prove to be particularly successful tools for studying the phenomenon of chirality in standard classes. In order to correctly assess the relevance of such analyses it should be borne in mind that the above transformation

properties apply not only to standard models but also to standard derivatives. Hence it follows that the insights gained with the aid of chirality functions are frequently valid for the real world of molecules without any limitation by approximative hypotheses. The question of right-left classification of standard derivatives introduced in the next section serves as a first illustration of the utility of chirality functions.

5. Homochirality

Sets of objects can in principle be subdivided into three subsets, two containing exclusively chiral objects, but no enantiomers, and the subset of achiral objects. The membership of achiral objects is evident, but not that of chiral ones. Separating enantiomers generally does not mean collecting chiral objects which are geometrically or physically related in a certain sense. Thus, for example, any subdivision which arises from exchanging mirror images would be just as arbitrary as the one from which it arose. This uncertainty in the assignment can be eliminated in specific cases by recourse to a principle of classification which somehow naturally expresses a kind of chiral relatedness. However, there are sets for which natural classification criteria of this sort just do not exist: this situation corresponds to the general rule. Some examples will help to illustrate this state of affairs.

The task of dividing a set of shoes into two classes such that mirror images are separated leads—apparently without any further instructions—to a classification according to "right" and "left". Although right and left shoes may be very different in shape, size, color, material, *etc.*, there is clearly a principle which allows classification of "related" members according to chirality, necessarily separating mirror images. It is only specific reference to what our task does not require which shows classification according to the concept "right" and "left" to prescribe more that the mere separation of mirror images. The same applies to screws. Here, the classification can be carried out according to the direction in which a screw moves when twisted in a clockwise sense. This criterion constitutes a rule which is sufficient for unequivocal classification of any set of screws without need for any arbitrary decision.

A completely different situation is encountered when mirror image potatoes are to be separated and distributed among three boxes, two of them for chiral and one for achiral potatoes. This task cannot be performed without arbitrariness. Any potato being chiral but neither identical with nor a mirror image of one already allocated to a given box necessitates deciding an alternative for which no obligatory principle is available. Concepts like right or left are meaningless; nothing like chiral similarity can be introduced without very artificial definitions.

It is surprising and of significance for applications in stereochemistry that the analysis of the corresponding problem for standard classes with an achiral skeleton results in the statement that some classes are comparable with shoes, others with potatoes. One consequence, among others, is that a nomenclature for derivatives designed to distinguish enantiomers may be based on a natural classification for certain sets, but is necessarily an artifact for others.

A distinction between chiral objects which leads to assignment into two classes and thus to separation of mirror images is natural if objects belong to the same subset because they can be designated as "chirally equivalent" by reference to a geometrical or physical similarity. Similarity and chirality of standard derivative can be traced back to a concept of similarity of ligands. Standard derivatives are similar if similar ligands are located at corresponding sites of the skeleton, and are chiral if ligands of different kinds are located at various skeletal sites. It may therefore be expected that chiral equivalence in the above sense—if at all possible—is completely determined provided that a suitable concept is available for similarity of ligands. Such a classification would be rigorous, and natural provided that the concept of ligand similarity is natural. Of course, the existence of such a classification will not be affected by the nature of the ligands present, but is solely the consequence of specific skeletal characteristics. Therefore, we call skeletons whose derivatives are governed by the desired classification principle *type a* skeletons; and the others are termed skeletons of *type b*. Standard classes of type a and of type b, abbreviated as a- and b-classes, are distinguished accordingly.

In order to grasp the existence of standard classes of both types, it is necessary to delve into the mathematics of the problem. Our first task is to develop the similarity concept for ligands in more precise terms. We distinguish between the kinds of ligands by values of a continuously variable parameter and call two kinds similar if they are represented by points sufficiently close together on the parameter scale. Thus defined, the similarity concept may be natural, such as the similarity of spheres as an expression of only slightly different diameters; it may also relate to a particularly interesting property of the ligands, *e.g.* their dipole moment or their polarizability, or it may formally express an arbitrarily chosen proximity on a scale. In this way, a similarity definition is fundamentally always possible for any finite or infinite set of ligands. Under no circumstances is a similarity concept for ligands which is based on more than one parameter suitable for accomplishing the desired classification.

On describing kinds of ligands by *one* parameter, standard derivatives having n skeletal sites are represented by n parameter values, *i.e.* by points in an n-dimensional parameter space; it should be noted that points arising from each other by certain permutations of their coordinates denote the same derivatives (in a rotated position). We distinguish between "chiral" and "achiral points" according to whether they denote chiral or achiral derivatives. Since similar ligands have adjacent values on a parameter scale, similar derivatives are characterized by the proximity of representative points in the parameter space. A curve devoid of achiral points expresses a relationship based on "chiral similarity". We therefore describe chiral points as chirally connected if there is a connecting path which does not pass through achiral points. It may be appreciated that chirally connected points could designate chirally equivalent derivatives in the sense of our intended classification if it were established that this equivalence cannot exist between enantiomers. Whether that is the case is determined by the individual features of the skeleton, and leads to a distinction between a and b skeletons. In b-type standard classes there are chirally connected points representing enantiomers; this is not the case in a-type standard classes.

Only in a-classes is a separation of all chiral derivatives into two subsets with resolution of enantiomers explained

by the chiral connection of points in the parameter space. We call two chiral derivatives *homochiral* if they belong to the same subset, and otherwise *heterochiral*. Homochirality, membership of the same subset, is established with a one-parameter ligand similarity concept.

The difference between a-type and b-type skeletons is manifested in the existence of a kind of chirality functions limited to a-type classes. Chirality functions $\varphi(\lambda_1,\lambda_2\ldots\lambda_n)$, depending upon the values of a ligand-specific parameter λ at the various skeletal sites, vanish at all achiral points of the parameter space and possibly also at other places. The "achiral zeros" are the same for all functions φ, while the "chiral zeros" are not; rather they are accidental, *i.e.* different functions φ do not have the same chiral zeros. It is clear that a continuous chirality function must have at least one zero on any path between two "enantiomeric points" in the parameter space. Since in b-type skeletons enantiomeric points exist which by definition are chirally connected, it follows that there can be no relevant continuous chirality functions $\varphi(\lambda_1,\lambda_2\ldots\lambda_n)$ without chiral zeros. On the other hand, it can be proved that there are continuous chirality functions without chiral zeros for a-type classes, and we call them "homochirality functions". Their sign thus characterizes homochiral derivatives in a-type classes, and this classification is unequivocal once a convention has been agreed for the similarity of ligands. The following theorems have been rigorously proved[3], and appear reasonable in view of the above argumentation.

Theorem 1: Homochirality functions exist for standard classes with skeletons of type a, and only for such classes. Only then is classification according to the homochirality concept possible. Homochiral derivatives are characterized by the same sign, heterochiral derivatives by opposite signs of a homochirality function, and achiral derivatives by the value zero.

According to Theorem 1 homochirality functions are characteristic for skeletons of type a and can therefore be used for analysis of their geometric features. The result of such a study is summarized in Theorem 2.

Theorem 2: A skeleton having two skeletal sites[*] is always of type a. Skeletons having more than two sites are of type a if, and only if, they possess mirror planes and $n-2$ sites lie in each of these mirror planes (n=total number of sites).

Chirality functions can be chosen in a variety of ways for any skeleton. Among such functions which vary continuously with a ligand-specific parameter λ_i at each skeletal site i, polynomials of the lowest degree in λ_i are distinguished by mathematical simplicity (the degree of the polynomial has a lower limit set by the required transformation properties). It can be demonstrated that for a-classes chirality polynomials of lowest degree in λ_i are homochirality functions. Theorem 3 shows that their construction is particularly facile.

Theorem 3: The homochirality polynomial of lowest degree can be written in the form:

$c(\lambda_1-\lambda_2)$ for skeletons with two skeletal sites (c=const.);

$c\prod_{i<k}(\lambda_i-\lambda_k)$ for skeletons with more than two sites (c=const.), the pair of subscripts of a factor referring to the two sites lying outside the mirror plane (the degree of the polynomial is thus equal to the number of mirror planes).

In Figure 4 a list is given of a-type skeletons together with the corresponding homochirality polynomials, which permits verification of Theorems 2 and 3 for specific examples. It may be proved that chirality polynomials for b-type skeletons cannot have the form of a product like the homochirality

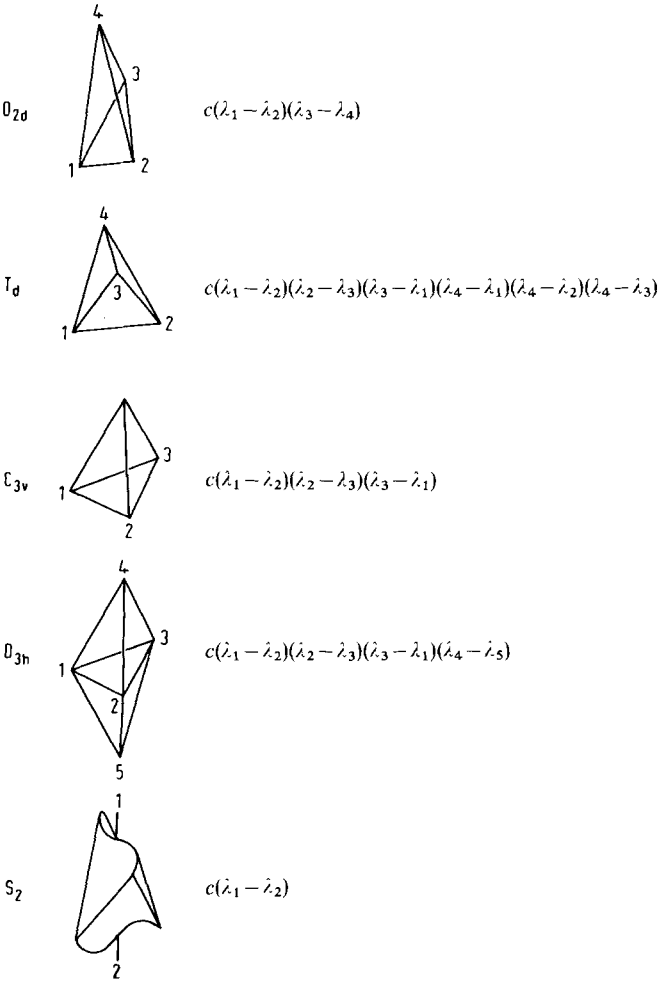
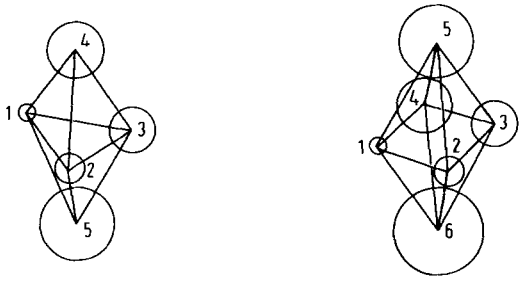


Fig. 4. Skeletons of type a and corresponding homochirality polynomials.



$c(\lambda_1-\lambda_2)(\lambda_2-\lambda_3)(\lambda_3-\lambda_1)(\lambda_4-\lambda_5)$

$c(\lambda_1-\lambda_3)(\lambda_2-\lambda_1)(\lambda_5-\lambda_6)(\lambda_6-\lambda_2+\lambda_3-\lambda_4)$

Fig. 5. Standard models having a trigonal and a tetragonal bipyramid as skeleton of type a and type b, respectively, together with the corresponding chirality polynomials.

[*] A site lying in the center of symmetry of a skeleton is not counted.

polynomials. Thus the mere form of the lowest degree chirality polynomial for the tetragonal bipyramid (Fig. 5) reveals the skeleton to be of type b. This result is also confirmed by Theorem 2, because mirror planes are present which contain only two, *i.e.* less than $6-2=4$ skeletal sites. The polynomial accordingly possesses chiral zeros: it vanishes, for example, when $\lambda_1=1$, $\lambda_2=2$, $\lambda_3=4$, $\lambda_4=3$, $\lambda_5=5$, $\lambda_6=6$.

Comparison of a tetragonal bipyramid with a trigonal bipyramid illustrates the idea of homochirality for a specific case. Working on the basis of standard models, the ligands are considered as spheres and the ligand-specific parameter is their diameter. Figure 5 depicts standard models for each skeleton in which all the spheres are different (their diameters were chosen as proportional to the site number). Both derivatives are chiral. We appeal to the imagination of the reader in following the subsequent argumentation.

In the case of the trigonal bipyramid, it is easily confirmed that transformation of a chiral derivative into its mirror image by a continuous change in sphere diameters necessarily leads *via* an achiral situation, *i.e.* two spheres on opposite sides of the skeleton mirror plane will inevitably become momentarily equal. Along any such transformation path the homochirality function has an achiral zero; it is readily seen from the form of the function to possess no other zeros. Non-zero values of the same sign denote homochiral derivatives.

The situation is completely different for the tetragonal bipyramid. Let us perform the transition from the derivative shown in Figure 5 to its enantiomer in two consecutive steps. The spheres at sites 1 and 2 are first continuously changed until the sphere at site 1 has a diameter of two units and that at site 2 a diameter of one unit. A corresponding operation involving the spheres at sites 3 and 4 finally leads to a sphere of four units in diameter at site 3 and one of three units in diameter at site 4. The result of this transformation is the mirror image of the original derivative. If the originally larger sphere is monotonically diminished and the originally smaller sphere monotonically enlarged in each step, then the overall transformation path cannot contain an achiral point. Hence the derivative shown in the figure and its enantiomer are chirally connected.

In its points the latter transformation path represents an arrangement of chiral derivatives corresponding typologically to similarity. Since the separation of enantiomers is an essential requirement of our intended classification, the connection between the endpoints must be broken at some place between them. No position along the transformation path is better suited as a separation point than any other. Therefore an arbitrary decision must be made, *i.e.* a decision which cannot be justified from arguments relating to chirality. As a corollary, continuous chirality functions must have at least one chiral zero somewhere along the transformation path—the position is not fixed and will generally be different for different chirality functions.

6. Chemical Aspects Summarized

A set of experimental data for derivatives of a standard class pertaining to a pseudoscalar phenomenon, such as experimental rotations for the optical activity at a particular wavelength, constitute a chirality function, *i.e.* they transform as a result of ligand permutation in the manner described. Theories relating to such experiments—whether classical, quantum mechanical, or semiempirical—also lead to chirality functions. Of course, chirality functions may also be purely mathematical constructions.

Every pseudoscalar property and every chirality function provides an opportunity of distinguishing between enantiomers on the basis of the sign. However, this does not apply to chiral derivatives for which the value zero happens to be measured or the chirality function vanishes (chiral zero).

As demonstrated in Section 5, any distinction between enantiomers which follows compellingly from a classification in compliance with a physically justifiable aspect of "similarity" is restricted to standard classes of type a. There are no homochirality functions for type b classes, *i.e.* no chirality functions which depend monotonically upon continuously variable properties of the ligands and do not possess chiral zeros. Any binary criterion distinguishing between enantiomers is necessarily arbitrary in the case of classes of type b, and is no more than a binary nomenclature symbol. The need for such a nomenclature for purposes of chemical systematization is not disputed—it is merely asserted that no physically relevant nomenclature can be found.

A completely different situation exists in standard classes with a skeleton of type a. Standard derivatives from an a-class are resolved into two heterochiral sets of homochiral members and into achiral derivatives according to the sign and zero, respectively, of a homochirality function. The concept of homochirality is based on a one-parameter specification of kinds of ligands. Classification "by homochiral derivatives" is unequivocal if the ligand specification is established.

The ligand-specific parameters may describe a physical or a geometrical property of the ligand or merely a formal sequence of kinds of ligands; the homochirality classification depends solely upon the physical or geometrical property, *i.e.* upon the sequence of parameter values. This assertion is confirmed as follows:

Two parameters λ and λ' can be taken as representing the same property if they admit the interpretation that the same situation can be measured on different scales. This is the case if one parameter is a monotonic function of the other one, *i.e.* if:

$$\lambda=\lambda(\lambda'); \quad \text{where} \quad \frac{d\lambda}{d\lambda'}>0 \tag{1a}$$

With reference to kinds of ligands l_A, l_B ... we can write:

$$\frac{\lambda(l_A)-\lambda(l_B)}{\lambda'(l_A)-\lambda'(l_B)}>0; \quad \text{for all } l_A \neq l_B \tag{1b}$$

The relation (1b) clearly shows that λ and λ' define the same sequence of ligands. Since homochirality polynomials are shown by Theorem 3 (Section 5) to be products of differences of the form $(\lambda_i-\lambda_k)$, the sign will therefore not change on replacing the ligand parameter λ by another one λ', which according to (1b) describes the same property or the same sequence of ligands.

In standard models of class a, a homochirality concept based on the size of the spheres affords a natural distinction between "right" and "left". It is immaterial for the sequence

of parameter values, and hence for the classification, whether the sphere diameter, or surface area, or volume is selected as parameter in the corresponding homochirality function.

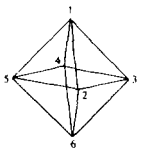
Only in standard classes of type a are geometrically or physically relevant aspects of classification encountered, which provide an alternative for chiral derivatives. If such a classification exists which does not display the accidental features of a special case, then a fitting homochirality concept may be expected to lie at the root, *i.e.* there is a sequence of ligands for which the homochirality polynomial yields a corresponding sign distribution. "Accidental features" would be observed *e.g.* in the sign distribution of the optical rotation which is valid only for a narrow wavelength range. Accepting the hypothesis that a homochirality relation exists, an attempt can be made to determine the corresponding parameter sequence from the experimental data.

In the case of allene derivatives—the allene skeleton is of type a—we have used experimental optical rotation data[9, 10] to determine the values of a ligand parameter. The experimental data were assumed to be correctly represented by the homochirality polynomial (cf. the first polynomial in Fig. 4). Since the number of different allene derivatives is increasing faster than the number of available ligands, such a procedure is suitable for the prediction of optical rotatory values. The result of this investigation far exceeded our expectations; for the derivatives studied the agreement between theory and experiment lies within the limit of experimental error[9, 10]. This same is true of a recently concluded study on spirane derivatives[11]. This result reveals far more than a mere physical relevance of the homochirality concept; it testifies to the quality of our *Ansatz* with the homochirality polynomial for quantitative purposes. Against this background, confirmation of the correct prediction of the experimentally determined sign seems little more than a self-evident by-product.

Irrespective of the question of relevance of a classification, there is a need for a corresponding nomenclature. Any binary nomenclature for differentiating enantiomers within a standard class corresponds to the signs of a chirality function without chiral zeros. Homochirality polynomials are suitable for use in a classes, while discontinuous chirality functions are employed in b classes.

Adopting the ligand sequence due to *Cahn*, *Ingold*, and *Prelog*[12], the *R,S* nomenclature is obtained in a-classes in that the signs of the homochirality polynomial are represented by the symbols *R* and *S*.

In the case of b classes, of the many chirality functions without chiral zeros one must be chosen arbitrarily for purposes of nomenclature. For instance, a nomenclature is obtained for the octahedral skeleton with the signs of the following (discontinuous) chirality polynomial



$$(\lambda_1-\lambda_2)(\lambda_2-\lambda_4)(\lambda_3-\lambda_5)$$
$$(\mu_{12}-\mu_{64})(\mu_{14}-\mu_{62})$$
$$(\mu_{23}-\mu_{45})(\mu_{25}-\mu_{43})$$
$$(\mu_{31}-\mu_{56})(\mu_{51}-\mu_{36})$$

with

$$\mu_{ij}=\mu_{ji};\quad \mu_{ij}=\mu_{kl}\Leftrightarrow\lambda_i=\lambda_k,\lambda_j=\lambda_l \quad \text{or} \quad \lambda_i=\lambda_l,\lambda_j=\lambda_k$$

$$\mu_{ij}>\mu_{kl}\Leftrightarrow \left\{\begin{array}{l}\max(\lambda_i\lambda_j)>\max(\lambda_k,\lambda_l)\\ \min(\lambda_i\lambda_j)<\min(\lambda_k,\lambda_l),\ \text{if}\ \max(\lambda_i\lambda_j)=\max(\lambda_k,\lambda_l)\end{array}\right\}$$

Based on the *R,S* sequence of ligands the sign distribution of this polynomial does not represent the *R,S* nomenclature proposed by *Prelog* for the octahedron. It is very similar, however. *Prelog*'s nomenclature is described by the signs of the given polynomial if a different definition is given for the relation $\mu_{ij}>\mu_{kl}$ on the basis of a complicated case-to-case distinction. Viewed from the standpoint of mathematical simplicity this approach appears artificial and is therefore not pursued any further. This result confirms our assertion that there is no natural preference for any of the possible nomenclatures in the case of b-type skeletons.

Received: July 19, 1976 [A 149 IE]
German version: Angew. Chem. *89*, 67 (1977)

[1] *E. Ruch* and *A. Schönhöfer*, Theor. Chim. Acta *19*, 225 (1970).
[2] *E. Ruch*, Acc. Chem. Res. *5*, 49 (1972).
[3] *E. Ruch*, Theor. Chim. Acta *11*, 183 (1968).
[4] *D. Haase* and *E. Ruch*, Theor. Chim. Acta 29, 189 (1973).
[5] *D. Haase* and *E. Ruch*, Theor. Chim. Acta *29*, 247 (1973).
[6] Cf. also *E. Ruch*, Angew. Chem., in press; Angew. Chem. Int. Ed. Engl., in press.
[7] *A. Mead*, *E. Ruch*, and *A. Schönhofer*, Theor. Chim. Acta *29*, 269 (1973).
[8] *C. A. Mead*, Top. Curr. Chem. *49*, 1 (1974).
[9] *E. Ruch*, *W. Runge*, and *G. Kresze*, Angew. Chem. *85*, 10 (1973); Angew. Chem. Int. Ed. Engl. *12*, 20 (1973).
[10] *G. Kresze*, *W. Runge*, and *E. Ruch*, Justus Liebigs Ann. Chem. *756*, 112 (1972).
[11] *H. Neudeck* and *K. Schlögl*, Chem. Ber., in press.
[12] *R. S. Cahn*, *C. K. Ingold*, and *V. Prelog*, Angew. Chem. *78*, 413 (1966); Angew. Chem. Int. Ed. Engl. *5*, 385 (1966).
[13] *P. von R. Schleyer*, Nachr. Chem. Techn. *24*, 571 (1976); *J. B. Collins*, *J. D. Dill*, *E. D. Jemmis*, *Y. Apeliog*, *P. von R. Schleyer*, *R. Seeger*, and *J. A. Pople*, J. Am. Chem. Soc. *98*, 5419 (1976).

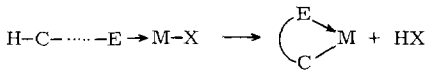
Cyclometalation Reactions

By Michael I. Bruce[*]

Reactions of transition metal complexes in which an organic ligand undergoes intramolecular metalation with formation of a metal-carbon σ bond are termed cyclometalation reactions. This article provides a general summary of our knowledge of these reactions, and discusses them in terms of their scope, mechanisms, and utility in organic synthesis, particularly of heterocyclic molecules.

1. Introduction

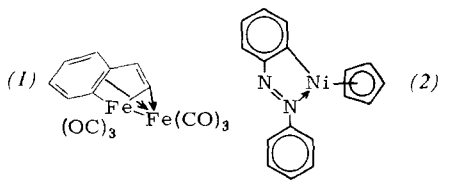
The term "cyclometalation" was introduced by *Trofimenko*[1] to describe those reactions of transition metal complexes in which a ligand undergoes an intramolecular (or more rarely, intermolecular) metalation with formation of a chelate ring containing a metal-carbon σ bond:

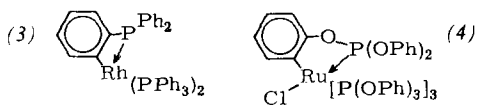


Scheme 1. Cyclometalation. E = donor atom, M = transition metal, X = leaving group.

Metalations of phenyl-substituted ligands have been most frequently described, and termed *ortho*-metalation, but the wider scope of these reactions now recognized is covered by the term used in the title.

One of the earliest examples of an *ortho*-metalated complex is the "benzometallole" *(1)* obtained from reactions between carbonyliron compounds and diphenylacetylene[2]. Other related reactions appeared sporadically in the literature of the 1960's, including cyclometalations of azobenzene-nickel complexes to give *(2)*[3], of palladium and platinum[4] complexes, and of other complexes containing phenyl-phosphane *(3)*[5,6] and -phosphite *(4)*[7-9] ligands.

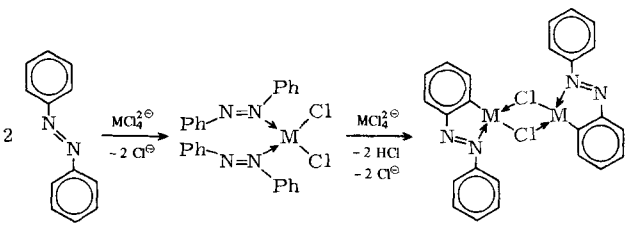




Attention was focused on this area in 1970 by *Parshall*[10], who has more recently considered the general problem of the activation of C—H bonds by transition metals[11]. The purpose of the present article is to summarize our present knowledge of cyclometalation reactions, to survey current ideas concerning the mechanism of formation of the metal-carbon σ bond, and to discuss the utility of these reactions in organic synthesis. Some earlier articles have described aspects of these reactions[12-14].

2. Formation and Detection of the Metal-Carbon σ Bond

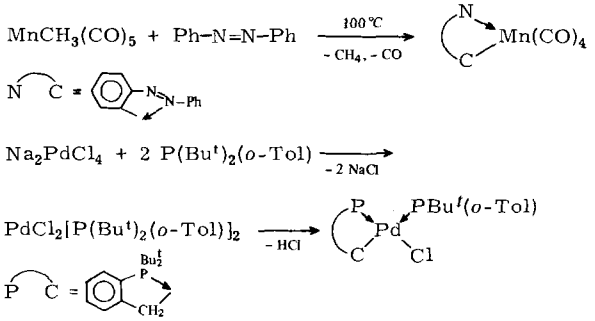
In general, formation of the metal-carbon σ bond occurs more or less readily by direct interaction of the ligand and metal substrate, and elimination of the hydrogen by combination with a suitable leaving group. In most cases, an intermediate ligand-metal complex without a metal-carbon σ bond is formed, which may or may not be isolable:



M = Pd, Pt

Scheme 2.

Many reactions occur on pyrolysis (50–200 °C) of the reaction mixture, an inert solvent often being used as the reaction medium and heat transfer agent (Scheme 3).



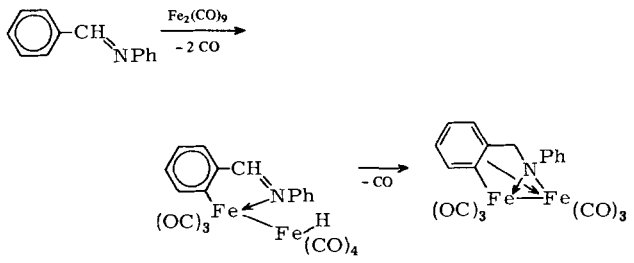
Scheme 3. A common method of indicating a metalated ligand is the symbol $\overset{\frown}{E\ C}$, where E is the donor atom, and C the metalated carbon atom (see also Scheme 1). Bu' = *tert*-butyl, *o*-Tol = *o*-tolyl.

The cyclometalation reaction is facilitated by choice of a good leaving group in the metal complex, which combines with the hydrogen atom displaced from the metalated carbon atom. Thus, the well studied cyclometalation reactions of alkyl(carbonyl)metal compounds with azobenzene[15] (see Scheme 3, top) involve loss of alkane.

[*] Prof. Dr. M. I. Bruce
Department of Physical and Inorganic Chemistry
University of Adelaide
P.O. Box 498, Adelaide, South Australia 5001 (Australia)

Addition of lithium acetate to a solution of $PdCl_2(PPh_3)_2$ affords the cyclometalated complex directly together with acetic acid and LiCl[16], and reactions involving the loss of a variety of small molecules are now known.

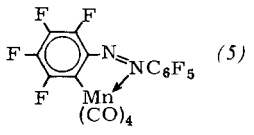
In some cases, notably with carbonyliron and -ruthenium compounds, dinuclear complexes are produced in which the formation of the cyclometalated complex is accompanied by hydrogen transfer (perhaps *via* a metal hydride) and interaction with a second metal atom (Scheme 4).



Scheme 4.

In this and related reactions, the dinuclear complex is stabilized by interaction of one metal atom with the aromatic π-electron system[17].

There are few reports of the loss of atoms or groups other than hydrogen from the metalated carbon atom. Consideration of the mechanisms of the metalation reactions of azobenzenes (see below) led us to examine the reactions of polyfluorinated derivatives with electron-rich metal complexes. Nucleophilic attack on $C_6F_5N{=}NC_6F_5$ by $Mn_2(CO)_{10}$ or $RuCH_3(PPh_3)_2(C_5H_5)$[83] afforded complexes [*e.g. (5)*] by elimination of a fluorine atom possibly as the metal fluoride, or as CH_3F.



(5)

The formation of cyclometalated, and particularly *ortho*-metalated, complexes, is generally revealed by conventional analytical and spectroscopic methods. The presence of an *ortho*-metalated ligand is shown in the infrared spectrum by extra bands (compared with the nonmetalated complex) characteristic of an *ortho*-disubstituted benzene nucleus, in the 700—800 and 1100 cm^{-1} regions[5, 8, 9]. Similarly, the appearance of multiplets upfield (for N-donor ligands) or downfield (for P-donor ligands) from the main aromatic proton signals, variously assigned to the proton *ortho* to the metal or donor atom group, has been indicative of the presence of a metalated ligand[9]. More recently, ^{13}C-NMR spectroscopy has been used to determine the presence of a metal-carbon σ bond in this type of complex[18]. If available, the mass spectrum provides strong evidence for the presence of the chelate group, as this appears to have some stability in the spectrometer. Care must be taken to ensure that the formation of such an ion is not a mass spectrometric reaction, as observed with certain molybdenum and ruthenium[19] complexes. In some cases, the observation of particularly intense (stable) ions of this type may indicate the ready macrochemical formation of cyclometalated complexes.

The final arbiter of the presence of the chelating metalated ligand is X-ray structure analysis, and numerous examples of such complexes have now been characterized in this way.

3. Scope of the Cyclometalation Reaction

Cyclometalated complexes will be considered from three points of view, namely those of the central metal atom, the type of carbon atom σ-bonded to the metal (or the system metalated), and the nature of the donor atom used to form the chelate ring.

3.1. Nature of the Metal

The majority of transition elements contained in Groups VI-VIII, with the exception of technetium, have been reported to form metal-carbon σ bonds. Complexes containing the $Ru(PPh_3)(C_5H_5)$ group are particularly prone to form cyclometalated derivatives[20]. The particular stereochemistry of the Group IB elements results in complexes containing formally metalated ligands being di- or poly-nuclear; complexes of this kind containing copper and silver have been obtained albeit indirectly (see Section 6.2). The elements of Groups IV and V are represented by $\eta^1{:}\eta^5$-cyclopentadienyl derivatives (Section 3.2), and a similar example is also known for thorium. Titanocene derivatives, such as $\overline{Ti[C_6H_4C(O)O]}(C_5H_5)_2$, have been obtained from reactions between $TiPh_2(C_5H_5)_2$ and CO_2, which may proceed *via* the phenylene intermediate $Ti(C_6H_4)(C_5H_5)_2$[20a].

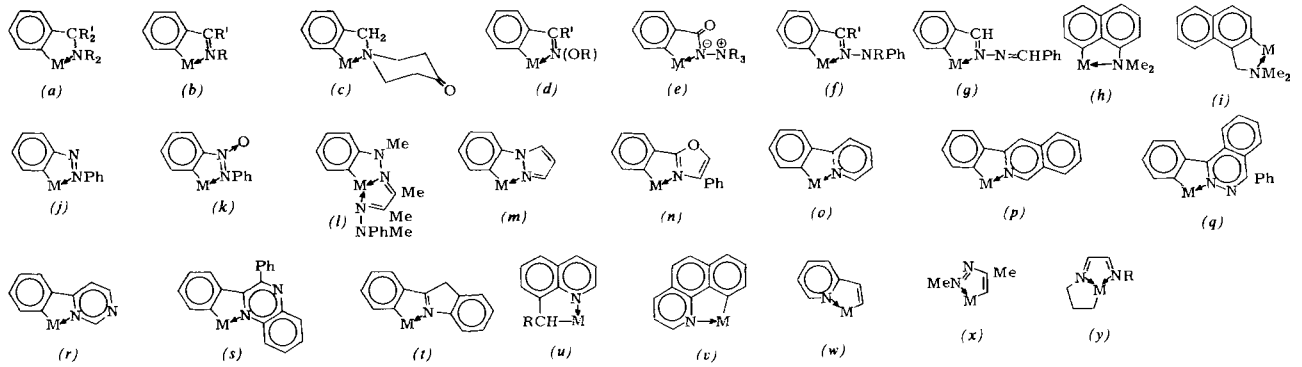
3.2. Nature of the Metalated System

As mentioned in Section 1, most cyclometalated systems bear a phenyl group. Examples of *ortho*-metalated ligands containing nitrogen, phosphorus, or arsenic donor atoms are shown in Table 1, and the variety of nitrogen-containing ligands is noteworthy. A general stereochemical requirement for formation of a five-membered ring can apparently be met by many phenyl-substituted nitrogen-heterocycles, and numerous examples containing manganese or palladium have been reported[21, 22].

Examples of the metalation of polycyclic aromatic systems are being reported with increasing frequency, and it appears that the fused-ring metallocyclic systems so formed have considerable stability. Ligands which have been metalated in this way include naphthyl-amines[1], -phosphanes, and -arsanes[23], and benzo[*h*]quinoline, which forms tetracyclic derivatives with many metals[24] including the tricarbonylchromium complex *(6)*. The tendency for metalation in these systems is very high, and is further illustrated by the formation of *(7)* on heating the corresponding methyl(naphthylmethyl)platinum complex[25]. A general discussion of metallocyclic complexes and intermediates falls outside the scope of this article, however.

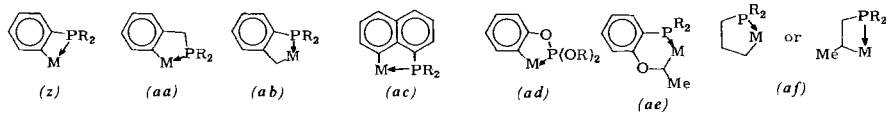
Table 1. Representative cyclometalated ligands containing nitrogen, phosphorus, or arsenic as donor atoms.

N-donor ligands:



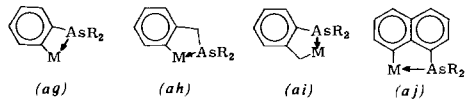
(a) *N,N*-disubstituted benzylamines [1, 30, 31, 33, 36], *(b)* Schiff bases [32], *(c)* *N*-benzyl-4-piperidone [33], *(d)* oximes (R = H) [34], oxime ethers, *(e)* *N*-ammoniobenzimidate [37], *(f)* phenylhydrazones [33, 35], *(g)* benzylideneazine, *(h)* *N,N*-dimethyl-1-naphthylamine [30], *(i)* 1-(*N,N*-dimethylaminomethyl)naphthalene [33], *(j)* azobenzene [13], *(k)* azoxybenzene [36, 38], *(l)* biacetylbis(*N*-methyl-*N*-phenyl)hydrazone [39], *(m)* 1-phenylpyrazole [1, 21], *(n)* 2,4-diphenyloxazole [21], *(o)* 2-phenylpyridine [21, 40], *(p)* 2-phenylisoquinoline [40], *(q)* 1,4-diphenylphthalazine [21], *(r)* 4-phenylpyrimidine [21], *(s)* 2,3-diphenylquinoxaline [21], *(t)* 2-phenyl-3*H*-indole [42], *(u)* 8-alkylquinoline [41, 43], *(v)* benzo[*h*]quinoline [24, 33, 41], *(w)* 2-vinylpyridine [44], *(x)* 2-(methylazo)propene [45], *(y)* *N*-alkyldiazadiene [45a]

P-donor ligands:

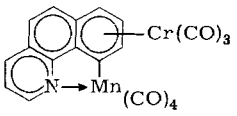


(z) phenylphosphanes [5, 6], *(aa)* benzylphosphanes [48], *(ab)* *o*-tolylphosphanes [49], *(ac)* 1-naphthylphosphanes [46], *(ad)* aryl phosphites [9], *(ae)* 2-alkoxyphenylphosphanes [47], *(af)* propylphosphanes [49]

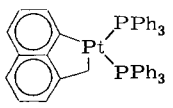
As-donor ligands:



(ag) phenylarsanes [5], *(ah)* benzylarsanes [48], *(ai)* *o*-tolylarsanes [50], *(aj)* 1-naphthylarsanes [46]

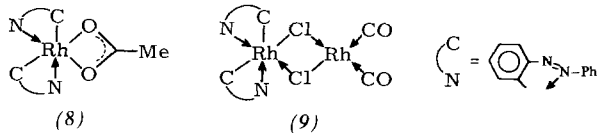


(6)

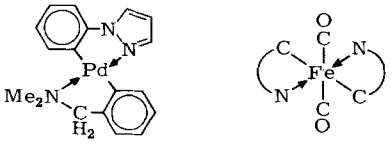


(7)

Complexes containing more than one metal-carbon σ bond [*(8)* and *(9)*] have been obtained directly from reactions between rhodium complexes and azobenzene[26, 27]. Treatment of halo complexes containing one cyclometalated ligand also



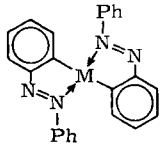
(8) *(9)*



(10)

(11)

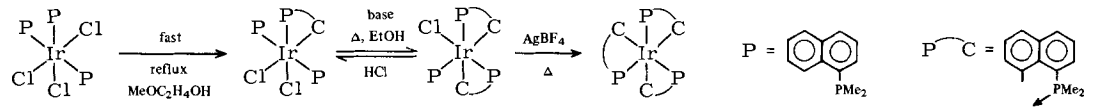
gives complexes of this type, such as *(10)*, obtained from $[Pd(2\text{-(pyrazolyl)phenyl})Cl]_2$ and *o*-$LiC_6H_4CH_2NMe_2$[1], while *(11)* is formed from $Fe(CO)_5$ and azobenzene in low yield[28]. Reactions between mercurated azobenzene and metal(0) complexes such as Pd_2(dibenzylideneacetone)$_3$ or $Pt(PPh_3)_4$, have given the spiro complexes *(12)* and *(13)*[29].



(12), M = Pd
(13), M = Pt

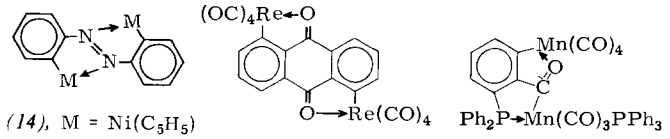
Using PMe_2(Nap) (Nap = 1-naphthyl), a series of mono-, di-, and tri-metalated derivatives of iridium has been prepared, by stepwise conversion of *mer*-$IrCl_3[PMe_2(Nap)]_3$[30] (Scheme 5).

Ligands with more than one donor site can form polynuclear complexes, and known examples include nickel and manganese derivatives of azobenzene *(14)* and *(15)*[51, 52], and complexes derived from anthraquinone [*(16)* and its "1,8"-isomer][53]. The formation of a cyclometalated complex may be accom-



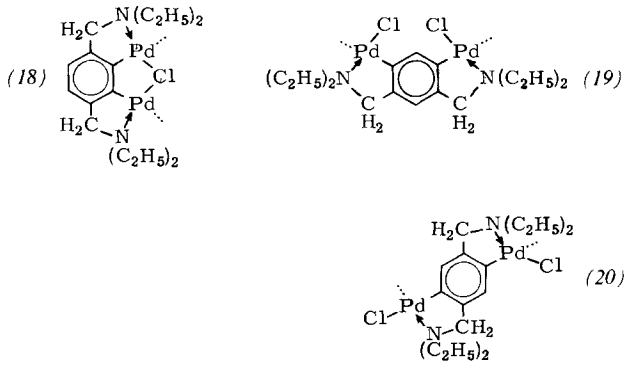
Scheme 5.

panied by insertion of a small molecule, *e.g.* CO, with generation of a second donor site. Examples of this are provided by products [*e.g. (17)*] isolated from high temperature reactions between $MnCH_3(CO)_5$ and PPh_3[54]. Other complexes



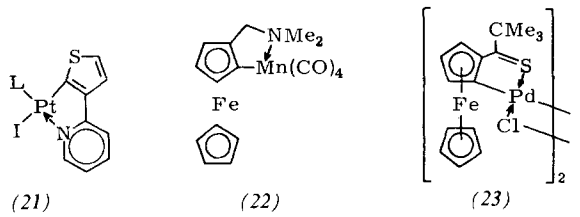
(14), M = $Ni(C_5H_5)$
(15), M = $Mn(CO)_4$ *(16)* *(17)*

containing dimetalated aryl groups *(18)*—*(20)* have been obtained from tetraethylxylenediamines; the presence of the first palladium atom on the benzene ring activates the ring towards further substitution[11].



(18) *(19)* *(20)*

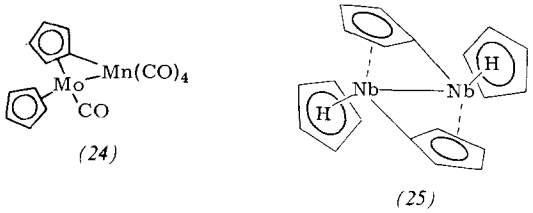
Metalation of other systems commonly thought to exhibit aromatic character has been achieved. Thus the reaction between 2-(2-thienyl)pyridine and K_2PtCl_4 affords *(21)*[55], while metalation of nitrogen and sulfur derivatives of ferrocene has given complexes such as *(22)*[56,57] and *(23)*[58].



(21) *(22)* *(23)*

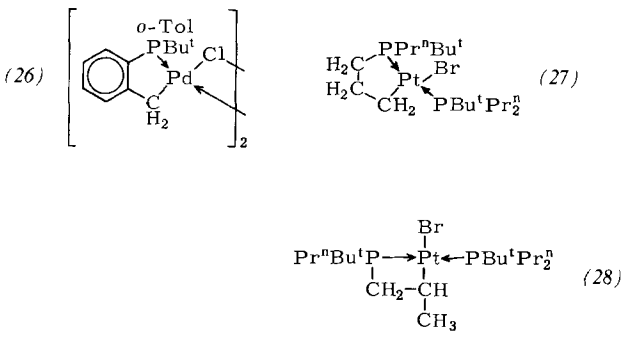
L = 2-(2-Thienyl)pyridine

The *inter*molecular metalation of η^5-cyclopentadienyl complexes to give new binuclear derivatives containing $\eta^1:\eta^5$-C_5H_4 ligands is related to the more conventional cyclometalation reactions. It was first described in the reaction between $MoH_2(C_5H_5)_2$ and $MnCH_3(CO)_5$, which afforded *(24)*[59]. Several related complexes of electron deficient transition metals such as thorium[60] or niobium [*(25)*][61] have since been described, and the transformation of $M(\eta^5\text{-}C_5H_5)$ moieties into $M(\eta^5:\eta^1\text{-}C_5H_4)_2M$ systems is an important reaction in low-valent transition metal chemistry.



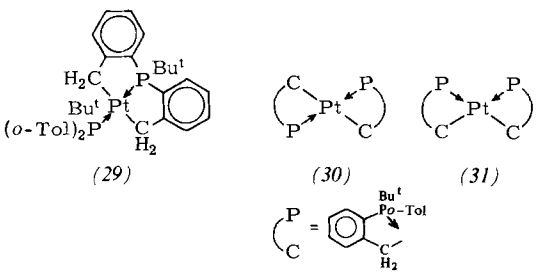
(24) *(25)*

Metalation of aliphatic carbon atoms has been reported by several groups. Typical of these reactions are those of complexes containing tertiary phosphanes containing sterically bulky groups, such as CMe_3. The elegant work of *Shaw et al.* has demonstrated that the steric effects of coordinating



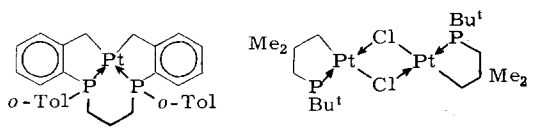
(26) *(27)* *(28)*

several of these ligands to one metal atom considerably enhance the tendency to form cyclometalated derivatives. Complexes containing metalated *o*-tolyl *(26)* or *n*-propyl *(27)* and *(28)*[49] groups were obtained. In one case the three isomeric complexes *(29)*—*(31)* were characterized[62], while pyrolysis of $PtMe_2[(o\text{-Tol})_2P(CH_2)_3P(o\text{-Tol})_2]$ afforded



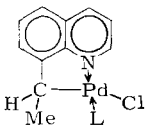
(29) *(30)* *(31)*

(32)[63]. Metalation of the aliphatic chain in $PBu^t_2(CH_2CMe_3)$ with $PtCl_2(NCPh)_2$ affords *(33)*, although $PBu^t_2Pr^n$ gives only P-donor complexes such as $[PtCl_2(PBu^t_2Pr^n)]_2$, a difference ascribed to favorable conformational and entropy factors arising from the presence of *gem*-di-*tert*-butyl and *gem*-dimethyl groups[64].



(32) *(33)*

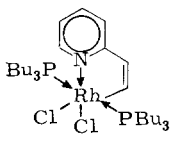
The metalation of alkyl groups has been observed with alkylquinolines. With 8-ethylquinoline, the metalated carbon is a chiral center, and ready resolution of the diastereoisomers



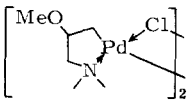
(34), L = (+)–PhCH(Me)–NH_2

was achieved by crystallization of the (+)-1-phenethylamine derivative *(34)*[65]. Similar rhodium derivatives of 8-methylquinoline have been described[43].

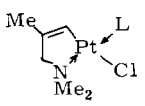
Chelating ligands have also been formed by metalation of alkenyl carbon atoms; for example, 2-vinylpyridine gives *(35)*[44]. Alkylamines are cyclopalladated by Li_2PdCl_4 in methanol to give *(36)* but cycloplatination affords products of type *(37)*[66]. The complexes *(35)* may be formed



(35)



(36)

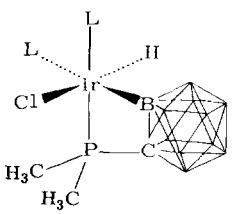


L = Amine, tert. Phosphane

(37)

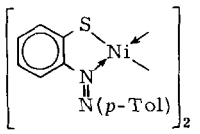
by nucleophilic attack of alkoxide on an intermediate η-olefin-ammine complex, rather than by direct metalation. A number of related reactions leading to chelating ligands containing metal-carbon σ bonds and Group V donor atoms have been described by *Nyholm*[67] and *Bennett*[68].

Organolithium derivatives of a variety of dimethylaminomethyl substituted systems have been prepared, including benzene[69], thiophene[70], and ferrocene[71]. The preferred formation of an α-lithio derivative has been explained in terms of chelation of lithium by the donor atom. The precise relationship between this type of reaction and the cyclometalation by transition metal compounds has not been explored in detail. However, in 1-(dimethylaminomethyl)naphthalene palladation occurs in the 2-position, while lithiation occurs at the 8-position[72]. *Parshall*[10] has pointed out that the formal analogy between palladation and lithiation may not be valid mechanistically because lithiation of arenes is not an electrophilic reaction, but this may not be true for all cyclometalation reactions (see Section 7.3).

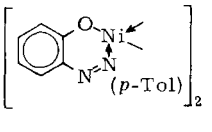


(38)

One example of a ligand metalated at an atom other than carbon in a reaction similar to those described above is *(38)*, resulting from the reaction between 1-Me_2P-1,2-$C_2B_{10}H_{11}$ and $[IrCl(C_8H_{14})_2]_2$[73]. This reaction is wholly comparable with the internal metalation of $IrCl(PPh_3)_3$, and further exemplifies the formal analogy between some carboranes and aromatic systems.



(39)



(40)

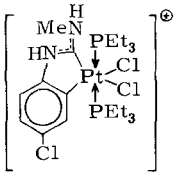
Reactions in which elements other than carbon are metalated are common in the chemistry of metal azo dyes[74], and generally fall outside the scope of this article. Recent examples include structural studies establishing ring sizes in the nickel complexes *(39)* and *(40)*[75]. Moreover, the various factors influencing *C*- and *O*-metalation of methoxy- and hydroxy-phenylphosphanes in reactions with platinum or iridium complexes have also been considered[47,76].

3.3. Effect of the Donor Atom

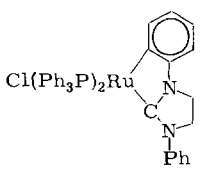
Systematic studies of the effect of the donor atom on the tendency for metalation are largely lacking, although the wide differences in types of complex formed with differing donor atoms is evident from the discussion already given. Qualitative observations on reactions between $PhCH_2EMe_2$ (E = N, P, As), or $PhCH_2XMe$ (X = O, S), and $MnR(CO)_5$ (R = Me or CH_2Ph) or $PdCl_2$ suggest that the ease of manganation decreases in the order N > P > As, and S > O, but only with $PhCH_2NMe_2$ were any palladated complexes obtained[48].

3.3.1. Carbon

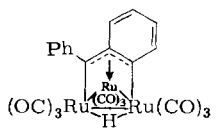
Complexes containing cyclometalated ligands with carbon as the donor atom have been obtained in the course of other studies, and include derivatives of alkynes, such as *(1)*. Chlorination of *trans*-$[PtCl\{C(NHMe)(NHPh)\}(PEt_3)_2]ClO_4$ has



(41)



(42)



(43)

given the metalated carbene complex *(41)*[77], while reaction between $RuCl_2(PPh_3)_3$ and the imidazolidine derivative $[CH_2N(Ph)]_2C{=}C[N(Ph)CH_2]_2$ afforded *(42)*[78]. A low yield of *(43)* was obtained from LiPh and $Ru_3(CO)_{12}$[79]; this complex contains an *ortho*-metalated CPh_2 ligand, the structural features of which are similar to the cluster-bonded allyl complexes obtained from reactions between alkenes[80] or 1,5,9-cyclododecatriene[81] and $Ru_3(CO)_{12}$.

3.3.2. Nitrogen

The majority of studies of the metalation of N-donor ligands have been made with azobenzene and related compounds, although the palladation reactions first described by *Cope* have now been extended to many other nitrogenous ligands. Indeed there seem to be few restrictions on the latter reaction if a five-membered ring, containing both nitrogen and the *ortho*-carbon, can be formed. Structural studies[82] on the compounds Mn(C—N)$(CO)_2$ (C—N = metalated benzylideneaniline or *N*,*N*-dimethylbenzylamine) have compared the

conformations of the five-membered chelate rings and the distortions resulting from the presence of CH=N and CH_2N units, respectively.

3.3.3. Phosphorus

The extensive use of triphenylphosphane as a P-donor ligand has resulted in the isolation of many *ortho*-metalated derivatives as by-products from reactions designed to proceed in other ways[82]. Where bulky alkyl groups are present, the metalation reaction predominates, especially where more than one *tert*-butyl group is present, for example. The ligands $PBu^t(o\text{-Tol})_2$ and $PBu^t_2(o\text{-Tol})$ are metalated in the tolyl methyl group, showing the preference for formation of a five-membered ring[49].

Similar reactions have been described for aryl phosphites, and *Robinson* has systematically examined the metalation of $P(OPh)_3$ or $P(OTol)_3$ ligands by metals of the second and third periods[84]. More recently, examples with the first period transition elements Mn[85], Fe[86], and Co[87] have been reported.

3.3.4. Arsenic and Antimony

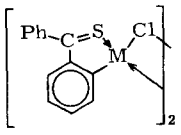
Relatively few examples of metalated As and Sb donor ligands have been described. The iridium complexes $IrCl(EPh_3)_3$ (E = As, Sb) readily afford $IrHCl(E{-}C)(EPh_3)_2$ on heating[88], while elimination of toluene in the reaction between $Mn(CH_2Ph)(CO)_5$ and $AsMe_2(CH_2Ph)$ has given $Mn(C_6H_4CH_2AsMe_2)(CO)_4$[48].

3.3.5. Oxygen

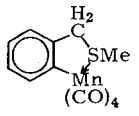
Some *ortho*-metalated derivatives of aromatic ketones have been obtained from reactions with $MMe(CO)_5$ (M = Mn or Re)[53], and *(17)* is formed in the reaction between $MnMe(CO)_5$ and PPh_3. The complex $Cr(C_6H_4OMe)_3$[88a] and a similar derivative of 2-phenyldioxolane[88b] are also known.

3.3.6. Sulfur

Thioketones or *O*-alkyl thioesters form dinuclear complexes when treated with carbonyl-iron or -ruthenium compounds (see Section 4), and mononuclear complexes such as *(44)* have been obtained with palladium and platinum[89]. Generally, however, S-donor ligands tend to form simple σ-donor complexes, and metalation occurs only with the more reactive metal substrates. Thus, $PhCH_2SMe$ forms only $MCl_2(PhCH_2SMe)_2$ (M = Pd, Pt) on attempted metalation[90, 91], although $MnR(CO)_5$ (R = Me or $PhCH_2$) reacts to give $Mn(C_6H_4CH_2SMe)(CO)_4$ *(45)*[92], characterized by an X-ray structure analysis of the PPh_3 derivative[93]. In the reaction between $Re_2(CO)_{10}$ and thiobenzophenones, the isolable intermediate $Re_2(CO)_9[SC(C_6H_4X)_2]$ can be converted into the *ortho*-metalated $Re[XC_6H_3C(S)C_6H_4X](CO)_5$, possibly by elimination of $ReH(CO)_5$[94].



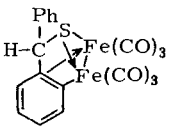
(44), M = Pd, Pt



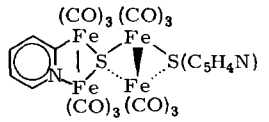
(45)

4. Metalation Involving Two or More Metal Atoms

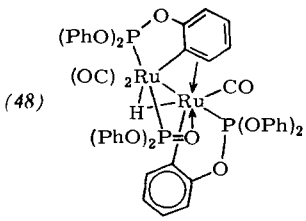
Many complexes of iron and ruthenium containing cyclometalated ligands are dinuclear, with the second metal atom interacting with an aromatic ring. Examples are *(1)*, and derivatives of sulfur ligands, such as *(46)*[95]. The reaction between pyridinethiol and $Fe_3(CO)_{12}$ has given *(47)*, containing a metalated pyridine ring[96], while a pyrolysis product of $Ru_3(CO)_9[P(OPh)_3]_3$ has structure *(48)*[97]. A solitary manganese example *(49)*, obtained from $MnPh(CO)_5$ and azobenzene, is also known[52].



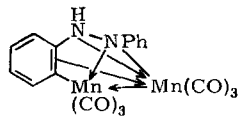
(46)



(47)

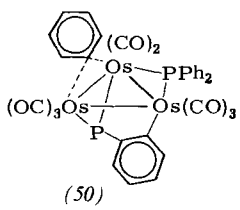


(48)

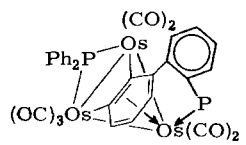


(49)

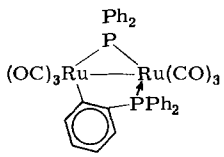
The propensity of metal clusters, particularly those containing ruthenium or osmium, to metalate aromatic compounds



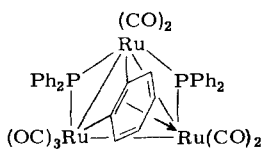
(50)



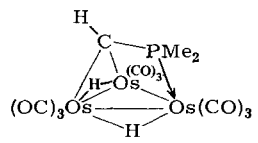
(51)



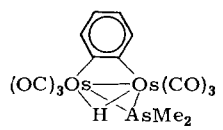
(52)



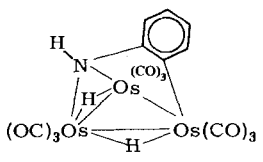
(53)



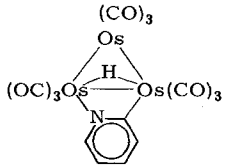
(54)



(55)



(56)

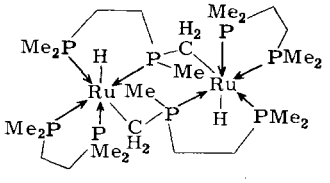


(57)

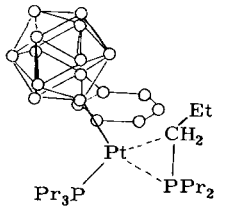
has been spectacularly demonstrated by their reactions with tertiary phosphanes. The reaction between $Os_3(CO)_{12}$ and PPh_3 gives a variety of products, including *(50)* and *(51)*[98], while pyrolysis of carbonylruthenium-tertiary phosphane clusters has given complexes such as *(52)* and *(53)*[99]. The stabilized dehydrobenzene group found in *(51)* can also be considered as a doubly-metalated phenyl group. A wide variety of polynuclear complexes containing singly- and doubly-metalated aromatic groups has been obtained and characterized *via* X-ray diffraction methods. These reactions are not limited to tertiary aryl phosphanes, complexes *(54)*—*(57)* being obtained from reactions using PMe_3, $AsMe_2Ph$, aniline, or pyridine, for example[100].

5. Chelate Ring Size

It has been noted above (Section 3.3.2) that metalation of nitrogen-donor ligands does not occur if the chelate ring produced has fewer than five atoms, while the metalation of tertiary phosphanes, arsanes, or stibanes may produce complexes containing four-membered rings. Metalation of aryl phosphites gives five-membered rings, as do reactions with the bulky phosphanes containing Bu^t or *o*-tolyl groups. The five-membered ring is sterically favored, and is formed where there is a choice, with $\overline{PtCl[CH_2C_6H_4PPh(o\text{-}Tol)][PPh(o\text{-}Tol)_2]}$[49] or $\overline{RuCl(CO)[MeC_6H_3OP(o\text{-}Tol)_2][P(o\text{-}Tol)_3]}$[8].

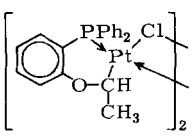


(58)

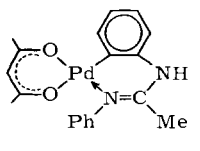


(59)

Reduction of $FeCl_2(PMe_3)_2$ with sodium amalgam affords monomeric $H\overline{Fe(CH_2PMe_2)}(PMe_3)_3$, containing a three-membered ring[101]. In contrast, internal metalation of $Ru(dmpe)_2$ [dmpe = $Me_2P(CH_2)_2PMe_2$] affords the dinuclear derivative *(58)*[102]. The presence of an $\overline{IrPC}$ ring has been established crystallographically in *(59)*, for which the phosphorus-ylide ($P{=}CH_2$) formulation is favored[102a].



(60)



(61)

Six-membered rings have been obtained from 2-alkoxyphenylphosphanes in the case of *(60)*[47], and by palladation of *N*-aryl-amidines or -amides *(61)*, for which the usual five-membered ring cannot be formed[103].

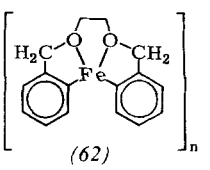
6. Other Reactions Leading to the Formation of Cyclometalated Products

6.1. Ligand Exchange

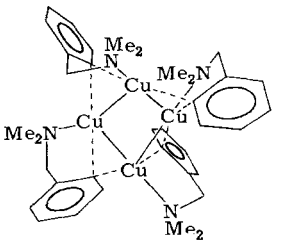
Treatment of $[\overline{PdCl(C_6H_4N{=}NPh)}]_2$ with carbonylmetalates, such as $[Re(CO)_5]^-$ or $[Co(CO)_4]^-$, affords the corresponding carbonyl(phenylazophenyl)metal complexes[104]. In contrast, reaction with $[Fe(CO)_4]^{2-}$ gave only bis(phenylazophenyl)palladium[28]. More recently, the preparation of $HgCl(C_6H_4N{=}NPh)$ by direct mercuration of azobenzene[105] has allowed the synthesis of several transition metal complexes[106].

6.2. Reaction with Organo-lithium or -magnesium Reagents

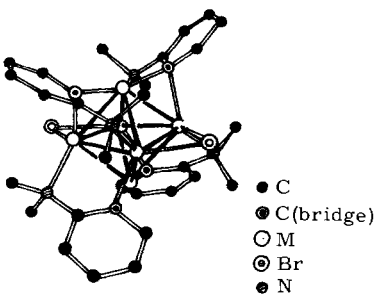
Reactions between the appropriate organolithium or Grignard reagent and metal halide have been used to prepare several complexes containing *ortho*-metalated ligands. This type of reaction is especially useful for ligands containing weak donor atoms, and for obtaining complexes in unusual oxidation states. Thus, $Co(\overline{C_6H_4CH_2NMe_2})_3$[107] and *(62)*[108] can be obtained from the appropriate mono- and



(62)



(63)



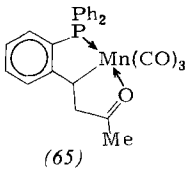
(64), M = Cu, Ag

dilithio derivatives. *Chini et al.* have described the syntheses of complexes containing $C_6H_4CH_2NMe_2$ ligands from *o*-$LiC_6H_4CH_2NMe_2$ and appropriate nickel, palladium, or platinum precursors[109], and of similar complexes derived from $KCH_2C_6H_4PPh_2$[110].

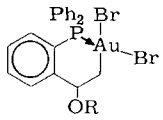
Reactions between copper(I) or silver(I) halides and *o*-$LiC_6H_4CH_2NMe_2$ or di- and tri-methoxyphenyllithium reagents have given polynuclear complexes [*e.g. (63)*] containing metalated ligands bridging the Group IB metals. These compounds are thermally stable, and contain tetranuclear clusters. Hexanuclear complexes such as *(64)* are formed on further reaction with the Group IB metal halide[111].

6.3. Insertions and Reactions with CC Double Bonds

The formation of metal-carbon σ-bonds by attack of nucleophiles on coordinated double bonds has been briefly alluded to already. An alternative route is the insertion of an unsaturated center into a metal-hydrogen or metal-carbon bond to give new examples of chelating metalated ligands. The reactions of alkenylphosphanes with $HMn(CO)_5$ or $MeMn(CO)_5$



(65)

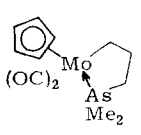


(66)

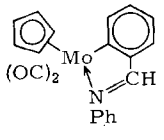
provide examples of these reactions, affording complexes such as *(65)*[112]. Similarly, electrophilic attack on complexes containing alkenyl-phosphanes or -arsanes has given derivatives such as *(66)* containing stable chelate rings having metal-carbon σ-bonds. Extensive studies of these reactions by *Bennett et al.*[68] have given a variety of related complexes, while the occurrence of this type of heteroatom chelating group has been documented elsewhere[53,113]. A detailed discussion of these interesting and novel complexes falls outside the scope of the present review.

6.4. Miscellaneous Reactions

Other complexes containing cyclometalated ligands have been obtained from a wide variety of unrelated reactions, and the precise way in which they are formed is not obvious in all cases. Thus dehalogenation of $MoI(CO)_2[Me_2As(CH_2)_3Cl](C_5H_5)$ with sodium amalgam forms *(67)*[114], while reaction between *o*-$BrC_6H_4CH{=}NPh$ and $[Mo(CO)_3(C_5H_5)]^-$ afforded *(68)*, also obtained directly from $MoCl(CO)_3(C_5H_5)$ and the Schiff base, and separable into optical isomers[115]. The reaction between $LiC_2B_{10}H_{10}$ and $PdCl_2(bpy)$ gives $Pd(C_6H_4C_2B_{10}H_{10})(bpy)$, which oxidatively



(67)

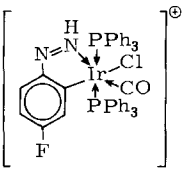


(68)

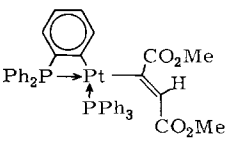
adds bromine to give stable palladium(IV) complex containing two Pd—C σ-bonds[116], while a similar reaction with $IrCl(PPh_3)_3$ has given $Ir(C_6H_4PPh_2)(PPh_3)_2$[117].

One of the products from the reaction between *Vaska*'s complex and *p*-$FC_6H_4N_2^+$ BF_4^- contains the *ortho*-metalated cation *(69)*, which can be readily hydrogenated to give the hydrazine complex[118]. Spontaneous cyclometalation of other aryldiazoiridium complexes occurs in chloroform[119]. Oxidative addition of azobenzenes or *o*-bromoazobenzene to *Vaska*'s complex gives iridium(III) complexes, *e.g.* $Ir(C_6H_4N{=}NPh)HCl(PPh_3)_2$[120].

Photolysis of the species $Pt(C_2O_4)(PPh_3)_2$ furnishes $[Pt(C_6H_4PPh_2)(PPh_3)]_2$ in moderate yields[121]. Attempted



(69)



(70)

carbonylation of the oxidative adduct of $Pt(PMePh_2)_4$ with $CF_2{=}CFBr$ afforded the platinum(IV) derivative $HBrPt(C_6H_4PMePh)(CF{=}CF_2)(PMePh_2)$[121a]. Pyrolysis of the η^2-alkyne complex $Pt[C_2(CO_2Me)_2](PPh_3)_2$ gives *(70)* *via* a two-step sequence in which oxidative addition of the aryl C—H bond to platinum is followed by insertion of the alkyne into the resulting Pt—H bond[122].

7. Mechanisms of Cyclometalation Reactions

7.1. Effect of Leaving Groups

The metalation of aromatic substrates proceeds with the elimination of the *ortho*-hydrogen together with the group leaving the metal. Some representative small molecules eliminated are indicated in Table 2.

Using a variety of precursors, the relative ease of metalation of azobenzene by $MnR(CO)_5$ has been qualitatively established as R = $PhCH_2$ > Et > Me > $CH_2C_6Me_5$[48], the pronounced ease of metalation with the benzyl complex probably being related to the thermodynamic stability of toluene. On use of PdX_2L_2 (L = hindered tertiary phosphane) the order is

Table 2. Influence of leaving group on cyclometalation.

$2\,PdCl_2$	+	$2\,PhN{=}NPh$	→	$[PdCl(C_6H_4N{=}NPh)]_2$	+	$2\,HCl$			[4]
$MnCH_3(CO)_5$	+	$PhN{=}NC_6F_5$	→	$Mn(C_6H_4N{=}NC_6F_5)(CO)_4$	+	CH_4	+	CO	[16]
$Mn(CH_2Ph)(CO)_5$	+	$C_6H_5CH_2SMe$	→	$Mn(C_6H_4CH_2SMe)(CO)_4$	+	$PhCH_3$	+	CO	[92]
$2\,Pd(OAc)_2$	+	$2\,PhCH{=}NPh$	→	$[Pd(C_6H_4CH{=}NPh)(OAc)]_2$	+	$2\,HOAc$			[32]
$Pt(NO_3)[CH_2C_6H_4PBu^t(o\text{-}Tol)][PBu^t(o\text{-}Tol)_2]$			→	$Pt[CH_2C_6H_4PBu^t(o\text{-}Tol)]_2$	+	HNO_3			[123]
$Pt(C_3H_5)(C_5H_5)$	+	$PhN{=}NPh$	→	$Pt(C_6H_4N{=}NPh)(C_5H_5)$	+	C_3H_6			[19]
$Ni(C_5H_5)_2$	+	$PhCH{=}NPh$	→	$Ni(C_6H_4CH{=}NPh)(C_5H_5)$	+	C_5H_6			[42]
$Mn_2(CO)_{10}$	+	$PhN{=}NPh$	→	$Mn(C_6H_4N{=}NPh)(CO)_4$	+	$MnH(CO)_5$	+	CO	[15]
$IrHCl(C_{10}H_6PMe_2)[PMe_2(Nap)]_2$			→	$IrCl(C_{10}H_6PMe_2)_2[PMe_2(Nap)]$	+	H_2			[124]

Cl < Br < I. In contrast, with tertiary phosphites, the reverse order was established, suggesting that different mechanisms are operative in these cases.

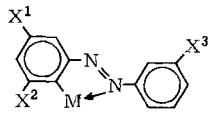
In several instances, the metalation of ligands by loss of hydrogen has been reported: *e.g.*, complex $IrHCl(P{-}C)(P)_2$ [P = PMe_2(naphthyl); P—C = $C_{10}H_6PMe_2$] is reported to melt with gas evolution, resolidifying to give $IrCl(P{-}C)_2P$[124]. In contrast, metalation of azobenzene with $Mn_2(CO)_{10}$ does not give greater than 50% yields of $Mn(C_6H_4N{=}NPh)(CO)_4$, with the balance probably forming $MnH(CO)_5$, which does not react further. The complex $RuH(PPh_3)_2(C_5H_5)$ is stable for days in refluxing dibutyl ether. In some cases, therefore, it would appear that formation of H_2 in the metalation reaction is a relatively difficult process.

7.2. Steric Factors

In a series of complexes of tertiary phosphanes, the presence of bulky groups promotes the metalation reaction, and a five-membered chelate ring is favored. If this is a thermodynamic effect, *Shaw*[125] has proposed that metalation results in a decrease of steric interaction, and thus formation of stronger M—P bonds. He further suggests that the change in entropy on metalation of a bulky phosphane (which has already lost much of its entropy, for example by constraints on rotation) would be considerably less than for a freely rotating tertiary phosphane ligand of low bulk. This argument can be extended to account for palladation of $PhCH_2NMe_2$, but not of the analogous P and As ligands, although, as pointed out above, a suitable choice of leaving group can markedly affect the course of these reactions.

7.3. Electronic Effects

A variety of qualitative evidence is available in the literature which gives some insight into mechanism. Thus, palladation of *para*-substituted azobenzenes gives results consistent with an electrophilic attack of the ring, palladation of the substituted ring occurring more easily along the series: Cl < H < Me < OMe[126]. Similarly *para*-tolylphosphanes show an increased tendency (over the phenyl derivatives) to be metalated by platinum(II). For $IrClL_3$ [L = $P(C_6H_4X\text{-}p)_3$], the rate of metalation increases in the order X = F < H < OMe < Me[88].



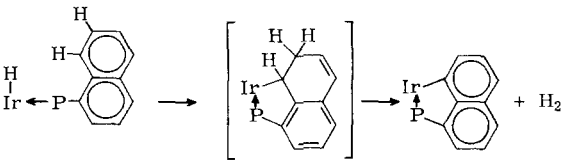
(71), M = $Mn(CO)_4$
(72), M = $Pd(C_5H_5)$

	X^1	X^2	X^3
a	H	F	H
b	H	H	F
c	F	H	H

We used *meta*-substituted azobenzenes. The substituent will therefore be *ortho* or *para* to the metalated carbon in the resulting complex. In this way we have shown that reactions of substituted azobenzenes with $MnCH_3(CO)_5$ or $PdCl_2$ proceed in a manner which is consistent with a nucleophilic reaction of the electron-rich manganese complex, or an electrophilic reaction of the palladium complex[127]. Thus, with *m*-fluoroazobenzene, $MnCH_3(CO)_5$ affords 80% *(71a)* and 20% *(71b)*, while palladium(II) chloride reacts to produce < 1% *(72a)*, 80% *(72b)*, and 20% *(72c)*.

Two possible mechanisms have been considered for the metalation of tertiary phosphane or phosphite ligands: *viz.* electrophilic substitution and oxidative addition, which may be followed by reductive elimination of a small molecule. In some reactions, *e.g.* the metalation of iridium(I) complexes $IrCl(EPh_3)_3$ (E = P, As, or Sb), or the reaction between $IrCl(CO)(PPh_3)_2$ and azobenzene, the product is the iridium(III) complex. Similarly, the rate of metalation of some platinum complexes with bulky phosphanes, which increases in the order Cl < Br < I, agrees with oxidative addition to form a platinum(IV) complex, which then eliminates hydrogen halide. On the other hand, with tertiary aryl phosphite complexes of palladium(II) or platinum(II), the ease of metalation shows the opposite trend, *i.e.* I < Br < Cl.

The rate of iridiation of PMe_2(Nap) is enhanced by replacement of Cl by H in the iridium complex. Although this argues against an electrophilic reaction, the iridium is coordinatively saturated in these complexes, so that metalation probably does not proceed by oxidative addition. A hydrogen addition-elimination mechanism has been suggested[124] (Scheme 6).

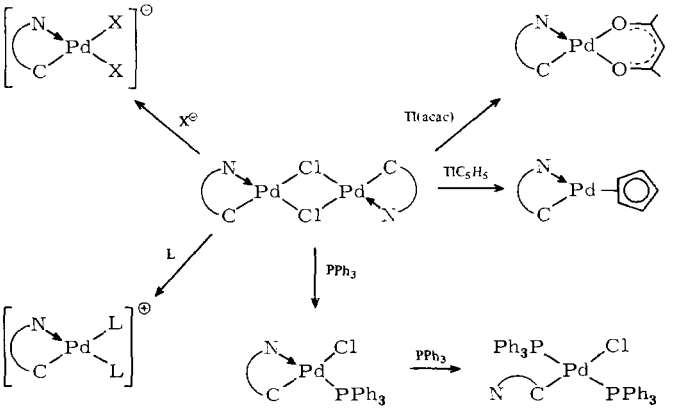


Scheme 6.

These results suggest that cyclometalation reactions may proceed *via* different mechanisms, according to metal and substrate, or more probably, the balance of steric and electronic factors in each case determines the nature of the final product. Certainly, this is one aspect of the cyclometalation reaction which requires further detailed and careful study.

8. Reactions of Cyclometalated Complexes

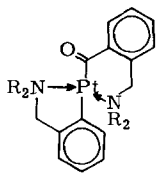
The metal-carbon σ bond in cyclometalated complexes is remarkably robust, and a variety of conventional reactions can be successfully carried out, for example on the halide complexes which leave it intact. Scheme 7 illustrates a selection



Scheme 7.

of reactions reported for some palladium derivatives, and involve the formation of anionic and cationic, as well as neutral, derivatives[128-131]. The replacement of halide by β-dionate or η^5-C_5H_5 ligands has often been used to facilitate the characterization of rather intractable halide complexes.

The donor atom of many cyclopalladated nitrogen-containing ligands can be readily displaced by other donor ligands, such as tertiary phosphanes, with formation of substituted phenylpalladium complexes[129]. Similar reactions have been found with platinum compounds, and phosphane exchange proceeds by intramolecular nucleophilic reactions in these complexes[132]. The chelate ring in $[Ru(C_6H_4N{=}NPh)Cl(CO)_2]_2$ can be opened by treatment with TlC_5H_5 or K[HB(pyrazolyl)$_3$], and subsequently reformed by thermal or photochemical reactions[133].



(73)

Platinum derivatives of *N,N*-dialkylbenzylamines react with CO with displacement of the coordinated nitrogen and migration of the aryl group to form the acyl complex *(73)*[109].

9. Cyclometalated Complexes in Synthesis

9.1. Hydrogen/Deuterium Exchange

In several cases, the cyclometalation reaction can be reversed by hydrogenolysis of the metal-carbon σ-bond. The activation of molecular hydrogen by transition metal complexes is a well-known reaction, and many examples of H_2/D_2 exchange catalyzed by such complexes are known. Of particular interest in the present context is the specific *ortho*-hydrogen/deuterium exchange observed on treatment of complexes such as $RhCl[P(OPh)_3]_3$ or $RuHCl(PPh_3)_3$ with D_2[134], a reaction which may be extended to the catalytic *ortho*-deuteration of phenol using $RuHCl[P(OPh)_3]_4$. In this case a catalytic cycle involving consecutive metalation-demetalation reactions can be constructed (Scheme 8).

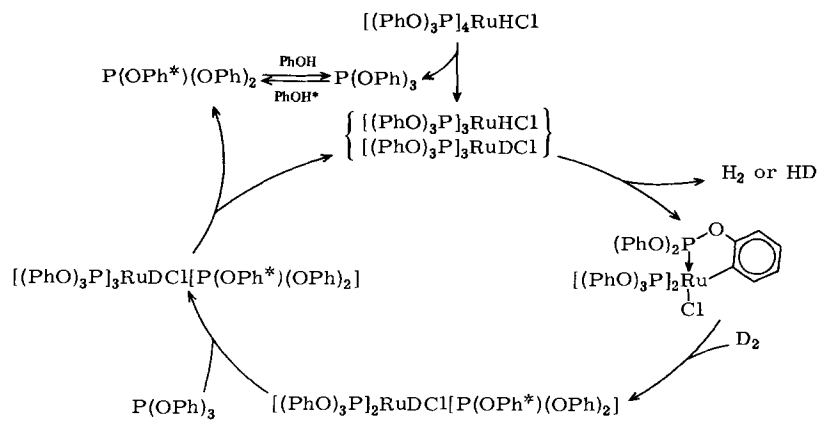
In addition to *ortho*-hydrogen exchange, olefin deuteration studies using $RuHCl(PPh_3)_3$ or $CoH[P(OPh)_3]_4$ (giving deuterated ethylenes and ethanes)[10], hydrogenation of olefins by $NiBr_2(PPh_3)_2$ in the *absence* of hydrogen[135], and the formation of *trans*-(*o*-DC_6H_4)CH=CDPh [catalyzed by $RhCl_3(py)_3/NaBH_4/HCONMe_2$][136] all implicate intermediate *ortho*-metalated complexes.

9.2. Synthesis of Heterocycles

Simple ring-closure of metalated complexes with elimination of the metal group from the chelate ring, with or without replacement by small molecules, offers a simple synthesis of many unusual heterocyclic molecules. Indeed the formation of heterocycles by "hydroformylation" of azobenzenes and Schiff bases in the presence of cobalt carbonyl catalysts[137] has been rationalized by CO insertion into the Co—C bond of an intermediate metalated species[104]. *Rosenthal*[138] has provided an excellent summary of early accounts of reactions of this type, and Table 3 lists some heterocyclic systems that have been obtained from cyclometalated intermediates.

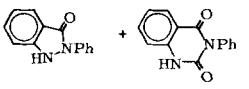
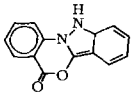
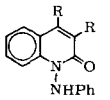
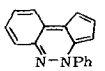
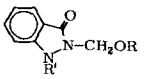
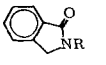
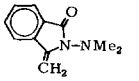
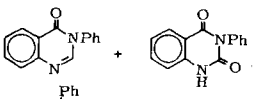
Mechanistic patterns in the carbonylation of cyclopalladated ligands have been determined, and enable products from these reactions to be predicted[22]. Similarly, carbonylation of metalated sulfur ligands has proved to be a convenient route to benzo[*c*]thiophenes[95], and similar treatment of Schiff bases in the presence of rhodium complexes afforded isoindolones[140].

These carbonylation reactions generally correspond to the replacement of the metal atom in the chelate ring by a molecule of CO. The arylcyclopenta[*c*]cinnolines formed from reactions between $Ni(C_6H_4N{=}NPh)(C_5H_5)$ and derivatives with *o*-chloro- or *o*-bromo-azobenzene contain the azobenzene fragment from the original complex, and correspond to a formal replacement of the metal atom by a double bond of the C_5 ring[141]. A C_3 unit replaces cobalt in the reaction between $Co(C_6H_4N{=}NPh)(CO)_3$ derivatives and $C_2(CF_3)_2$, when an

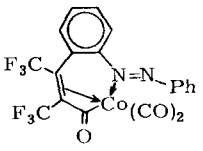


Scheme 8. OPh* = OC_6H_4D-*o*.

Table 3. Some heterocyclic syntheses involving cyclometalated complexes.

Ligand	Metal	Small molecule	Heterocycle		Ref.
Azobenzene	Co	CO		Indazolone + quinazolinedione	[137]
	Pd	CO		Indazolone	[144]
	Rh	CO		2(3-Hydroxy-2-indazolyl)benzo-lactone	[140]
	Co	CO, C_2R_2		*N*-Anilinoquinolone	[142]
	Ni	C_5H_6		4-Aryl-4*H*-cyclopenta-[*c*]cinnoline	[141]
Benzylideneaniline	Pd	CO		Isoindolone, R = Ph	[22]
Benzaldimines	Pd	CO		R = CH(OAc)Ar	[22]
Benzaldazine	Pd	CO		R = N=CHPh	[22]
Dialkylbenzylamine	Pd	CO		R = Alkyl	[22]
Formaldehyde phenyl-hydrazone	Pd	CO		Indazolone, R = Et or Ac	[138]
Acetophenone dimethyl-hydrazone	Pd	CO		2-(Dimethylamino)-3-methyleneiso-indolone	[138]
Schiff bases Aromatic nitriles Aromatic ketoximes	Co	CO		Isoindolone	[139]
Phenylhydrazines	Co	CO		Isoindolones + *N*-(*N'*-Phenylcarbamoyl)-isoindolones	[138]
Aniline	Co, Mo or Cr	CO, CCl_4		Quinazolinone + Quinazolinedione	[144]
Thiobenzophenone	Fe	CO		Oxobenzo[*c*]thiophene	[95]

anilinoquinolone can be isolated. Formation of this heterocycle proceeds *via* the unusual complex *(74)*[142]. These heterocyclic syntheses often proceed in high yield, to give products which are otherwise only available *via* many-step syntheses.



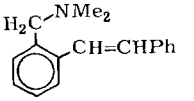
(74)

10. Other Reactions of the Metal-Carbon Bond

The metal-carbon σ-bond in cyclometalated complexes may be cleaved by a variety of reagents to give other organic products. Thus reductive cleavage of metalated azobenzene with $LiAlD_4$ affords *o*-deuterioazobenzene[4], while halogenation of azobenzene in the presence of $PdCl_2$ affords a mixture of *o*-haloazobenzenes, prolonged reaction affording good yields of 2,2',6,6'-tetrahaloazobenzenes. All these products are formed *via* the intermediate cyclopalladated complexes[143].

In contrast, chlorination of $\overline{PdCl(C_6H_4PPh_2)}(PPh_3)$ affords only $PdCl_2(PPh_3)(o\text{-}ClC_6H_4PPh_2)$[116]. Carbonylation of $\overline{[RhCl(C_6H_4N{=}NPh)_2]_2}$ causes linkage of the two azobenzene moieties to form 2,2'-bis(phenylazo)biphenyl[26].

Other reactions in which cyclometalated complexes are known or suspected to be intermediates include reaction of anilines, CCl_4, and CO in the presence of a cobalt complex to give quinazolinones and -diones[144], of *o*-lithiated *N,N*-dimethylbenzylamine with carbonyliron or -nickel compounds, followed by addition of organic halides (RX) to give ketones $Me_2NCH_2C_6H_4COR$[145], and carbonylation of the product from $Me_2NCH_2CH{=}CH_2$ and $PdCl_2$ to give esters 4-(*N,N*-dimethylamino)-3-methoxybutyric acid. Cyclopalladated complexes react with α-olefins, to give *e.g. (75)*[146], or substituted acrylic esters[72].



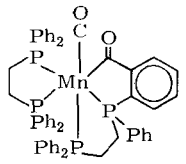
(75)

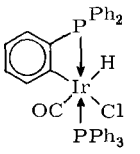
11. Other Cyclometalated and Related Complexes

The ready ring enlargement that can occur in reactions between internally metalated complexes containing a four-membered ring and small molecules such as CO or alkynes have been mentioned in Section 9. In cases where a chelating

bis-tertiary phosphane is metalated, the resulting bicyclic system of fused four- and five-membered rings would be expected to have greater reactivity. Reactions between $Mn_2(CO)_{10}$ and $Ph_2P(CH_2)_2PPh_2$(dppe) afford small amounts of *(76)* formed by insertion of CO into an initial cyclometalated intermediate[147].

(76)



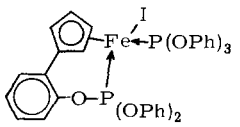


(77)

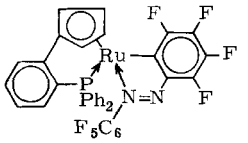
In the older literature, there are several reports of metal complexes of apparently unusual stoichiometry, which have been shown subsequently to be *ortho*-metalated complexes. Examples include $M[P(OPh)_3]_4$ (M = Rh or Ir)[148] and $\{Fe[P(OPh)_3]_2(C_5H_5)\}_2$, now known to be $\overline{M[(C_6H_4O)P(OPh)_2][P(OPh)_3]_3}$[7] and $\overline{Fe[(C_6H_4O)P(OPh)_2][P(OPh)_3](C_5H_5)}$[86], respectively.

An isomer *(77)* of *Vaska*'s complex, $IrCl(CO)(PPh_3)_2$, has been obtained by briefly heating $IrCl(N_2)(PPh_3)_2$ in Me_2SO, followed by reaction with CO. Surprisingly, *(77)* reverts to *Vaska*'s complex on standing or brief warming in benzene[149].

The interaction of *ortho*-C—H atoms with transition metals has been found in several complexes, by X-ray diffraction studies in $RuCl_2(PPh_3)_2$[150] and $[Ir(dppe)_2(S_2)]Cl$[151] for example, and by ^{1}H-NMR measurements on several other dppe complexes[152].

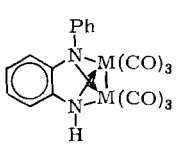


(78)



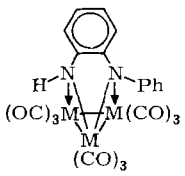
(79)

In two instances, complexes containing ligands formed by interaction of aryl groups with η^5-C_5H_5 groups have been characterized. One of the "isomers" of $FeI[P(OPh)_3]_2(C_5H_5)$ is *(78)*[153], and the reaction between $RuMe(PPh_3)_2(C_5H_5)$ and $C_6F_5N{=}NC_6F_5$ affords *(79)*[83]. The new ligands, containing substituted phenylcyclopentadienyl groups formed by formal elimination of hydrogen, may proceed by activation of the *ortho*-C—H bond by the metal.

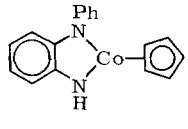


(80)

M = Fe, Ru



(81)



(82)

The activation of the *ortho*-C—H bond in azo compounds does not always result in the formation of a cyclometalated complex. Thus, reactions between azobenzenes and carbonyliron[28] or -ruthenium[154], or $M(CO)_2(C_5H_5)$[140, 155] (M = Co or Rh) afford complexes *(80)*—*(82)* containing rearranged ligands derived from *o*-semidine. Formally, the reaction consists of cleavage of the N=N bond, migration of the *ortho*-hydrogen to a nitrogen, and attachment of the nitrene to the *ortho*-carbon, the metal remaining σ-bonded to the nitrogens. The precise mechanism of this reaction remains obscure.

Cleavage of the N=N bond in azobenzenes, or the CH=N bond in Schiff bases, by rhodium complexes, gives the corresponding amines, isolated as the metal derivatives[156, 157].

12. Outlook

The foregoing account shows that cyclometalation reactions form a large and growing area of transition metal complex chemistry, and that the original *ortho*-metalation reaction is but one aspect of this field. It is also evident that chelation of ligands to induce specific *ortho*-H activation is but a specific example of the more general problem of the homogeneous catalytic activation of C—H bonds by transition metal complexes. We may expect that studies of cyclometalated intermediates will provide further clues to the ways in which C—H bonds may be induced to react with a variety of reagents under mild conditions.

Other exciting developments are occurring with studies directed toward the involvement of transition metals in organic synthesis. We must be ready to consider transition metals complexes as stoichiometric reagents in the synthesis of unusual organics, particularly heterocycles, in one- or two-step reactions. In these cases, the costs of the transition metal reagents, many of which are available commercially, are more than offset by savings in time and materials used in more conventional but tedious multi-step syntheses.

To these ends, much more detailed knowledge about the course of cyclometalation reactions is required, and the study of the reactions of the cyclometalated products is still in its infancy. It is likely that with enough foresight, three or four-component reactions proceeding to give products without the necessity for isolation of the cyclometalated intermediate will be developed. Further investigation of the reactions of cluster compounds with organic materials will serve to delineate the hydrogen-abstraction reactions which are becoming characteristic of these materials, and draw parallels with reactions of metal surfaces, which in turn may then be used to catalyze some of the reactions described above.

It is a pleasure to acknowledge the help and encouragement of Professor Gordon Stone, F. R. S., without whom this work would not have been started. Thanks are also extended to Drs. Zafar Iqbal and Brian Goodall, for their essential contributions, to my other coworkers mentioned in the references, and to Dr. Michael Green for stimulating discussions.

Received: July 30, 1976 [A 146 IE]
German version: Angew. Chem. 89, 75 (1977)

[1] *S. Trofimenko*, Inorg. Chem. *12*, 1215 (1973).
[2] *W. Hübel* and *E. H. Braye*, J. Inorg. Nucl. Chem. *10*, 250 (1959).
[3] *J. P. Kleiman* and *M. Dubeck*, J. Am. Chem. Soc. *85*, 1544 (1963).
[4] *A. C. Cope* and *R. W. Siekman*, J. Am. Chem. Soc. *87*, 3272 (1965).
[5] *M. A. Bennett* and *D. L. Milner*, Chem. Commun. *1967*, 581.
[6] *W. Keim*, J. Organomet. Chem. *14*, 179 (1968).
[7] *W. H. Knoth* and *R. A. Schunn*, J. Am. Chem. Soc. *91*, 2400 (1969).
[8] *J. J. Levison* and *S. D. Robinson*, J. Chem. Soc. *A 1970*, 639.

[9] *E. W. Ainscough, S. D. Robinson,* and *J. J. Levison,* J. Chem. Soc. *A 1971,* 3413.
[10] *G. W. Parshall,* Acc. Chem. Res. *3,* 139 (1970).
[11] *G. W. Parshall,* Acc. Chem. Res. *8,* 113 (1975).
[12] *A. J. Carty,* Organomet. Chem. Rev. Sect A 7, 191 (1971).
[13] *M. I. Bruce* and *B. L. Goodall* in *S. Patai:* The Chemistry of the Hydrazo, Azo and Azoxy Groups. Wiley, London 1975, p. 259.
[14] *J. Dehand* and *M. Pfeffer,* Coord. Chem. Rev. *18,* 327 (1976).
[15] *M. I. Bruce, M. Z. Iqbal,* and *F. G. A. Stone,* J. Chem. Soc. *A 1970,* 3204.
[16] *D. M. Fenton,* J. Org. Chem. *38,* 3192 (1973).
[17] *M. M. Bagga, W. T. Flannigan, G. R. Knox, P. L. Pauson, F. J. Preston,* and *R. I. Reed,* J. Chem. Soc. *A 1968,* 36.
[18] *A. R. Garber, P. E. Garrou, G. E. Hartwell, M. J. Smas, J. R. Wilkinson,* and *L. J. Todd,* J. Organomet. Chem. *86,* 219 (1975).
[19] *M. I. Bruce,* unpublished results.
[20] *M. I. Bruce, R. C. F. Gardner,* and *F. G. A. Stone,* J. Organomet. Chem. *40,* C 39 (1972).
[20a] *I. S. Kolomnikov, T. S. Lobeeva, V. V. Gorbachevskaya, G. G. Aleksandrov, Y. T. Struchkov,* and *M. E. Vol'pin,* Chem. Commun. *1971,* 972.
[21] *M. I. Bruce, B. L. Goodall,* and *I. Matsuda,* Aust. J. Chem. *28,* 1259 (1975).
[22] *J. M. Thompson* and *R. F. Heck,* J. Org. Chem. *40,* 3667 (1975).
[23] *L. Sindellari, L. Volponi,* and *B. Zarli,* Inorg. Nucl. Chem. Lett. *11,* 319 (1975).
[24] *M. I. Bruce, B. L. Goodall,* and *F. G. A. Stone,* J. Organomet. Chem. *60,* 343 (1973); *M. Nonoyama,* Bull. Chem. Soc. Jpn. *47,* 767 (1974), and references cited therein.
[25] *J. A. Duff, B. L. Shaw,* and *B. L. Turtle,* J. Organomet. Chem. *66,* C 18 (1974).
[26] *A. R. M. Craik, G. R. Knox, P. L. Pauson, R. J. Hoare,* and *O. S. Mills,* Chem. Commun. *1971,* 168.
[27] *M. I. Bruce, M. Z. Iqbal,* and *F. G. A. Stone,* J. Organomet. Chem. *40,* 393 (1972).
[28] *M. M. Bagga, W. T. Flannigan, G. R. Knox,* and *P. L. Pauson,* J. Chem. Soc. *C 1969,* 1534.
[29] *V. I. Sokolov, L. L. Troitskaya,* and *O. A. Reutov,* J. Organomet. Chem. *93,* C 11 (1975).
[30] *A. C. Cope* and *E. C. Friedrich,* J. Am. Chem. Soc. *90,* 909 (1968).
[31] *M. I. Bruce, B. L. Goodall, M. Z. Iqbal, F. G. A. Stone, R. J. Doedens,* and *R. G. Little,* Chem. Commun. *1971,* 1595.
[32] *R. L. Bennett, M. I. Bruce, B. L. Goodall, M. Z. Iqbal,* and *F. G. A. Stone,* J. Chem. Soc. Dalton Trans. *1972,* 1787; *H. Onoue* and *I. Moritani,* J. Organomet. Chem. *43,* 431 (1972).
[33] *B. N. Cockburn, D. V. Howe, T. Keating, B. F. G. Johnson,* and *J. Lewis,* J. Chem. Soc. Dalton Trans. *1973,* 404.
[34] *H. Onoue, K. Minami,* and *N. Nakagawa,* Bull. Chem. Soc. Jpn. *43,* 3480 (1970).
[35] *P. Braunstein, J. Dehand,* and *M. Pfeffer,* Inorg. Nucl. Chem. Lett. *10,* 521 (1974).
[36] *R. L. Bennett, M. I. Bruce,* and *I. Matsuda,* Aust. J. Chem. *28,* 1265 (1975).
[37] *S. A. Dias, A. W. Downs,* and *W. R. McWhinnie,* J. Chem. Soc. Dalton Trans. *1975,* 162.
[38] *A. L. Balch* and *D. Petridis,* Inorg. Chem. 8, 2247 (1969).
[39] *L. Maresca, G. Natile, L. Cattalini,* and *F. Gasparrini,* J. Chem. Soc. Dalton Trans. *1975,* 1601.
[40] *A. Kasahara,* Bull. Chem. Soc. Jpn. *41,* 1272 (1968).
[41] *G. E. Hartwell, R. V. Lawrence,* and *M. J. Smas,* Chem. Commun. *1970,* 913.
[42] *Y. A. Ustynyuk, V. A. Chertov,* and *I. V. Barinov,* J. Organomet. Chem. *19,* C 53 (1971).
[43] *M. Nonoyama,* J. Organomet. Chem. *74,* 115 (1974).
[44] *R. J. Foot* and *B. T. Heaton,* J. Chem. Soc. Chem. Commun. *1973,* 838.
[45] *J. F. van Baar, K. Vrieze,* and *D. F. Stufkens,* J. Organomet. Chem. *85,* 249 (1975).
[45a] *H. tom Dieck* and *M. Svoboda,* Chem. Ber. *109,* 1657 (1976).
[46] *J. M. Duff, B. E. Mann, B. L. Shaw,* and *B. Turtle,* J. Chem. Soc. Dalton Trans. *1974,* 139.
[47] *C. E. Jones, B. L. Shaw,* and *B. L. Turtle,* J. Chem. Soc. Dalton Trans. *1974,* 992.
[48] *R. L. Bennett, M. I. Bruce,* and *F. G. A. Stone,* J. Organomet. Chem. *94,* 65 (1975).
[49] *A. J. Cheney, B. E. Mann, B. L. Shaw,* and *R. M. Slade,* J. Chem. Soc. *A 1971,* 3833.
[50] *B. L. Shaw* and *R. E. Stainbank,* J. Chem. Soc. Dalton Trans. *1973,* 2394.
[51] *I. V. Barinov, T. I. Voevodskaya,* and *Y. A. Ustynyuk,* J. Organomet. Chem. *30,* C 28 (1971).
[52] *R. L. Bennett, M. I. Bruce, B. L. Goodall,* and *F. G. A. Stone,* Aust. J. Chem. *27,* 2131 (1974).
[53] *R. J. McKinney, G. Firestein,* and *H. D. Kaesz,* Inorg. Chem. *14,* 2057 (1975).
[54] *R. J. McKinney* and *H. D. Kaesz,* J. Am. Chem. Soc. *97,* 3066 (1975).
[55] *T. J. Giordano* and *P. G. Rasmussen,* Inorg. Chem. *14,* 1628 (1975).
[56] *S. S. Crawford, G. Firestein,* and *H. D. Kaesz,* J. Organomet. Chem. *91,* C 57 (1975).
[57] *J. C. Gaunt* and *B. L. Shaw,* J. Organomet. Chem. *102,* 511 (1975).
[58] *H. Alper,* J. Organomet. Chem. *80,* C 29 (1974).
[59] *R. Hoxmeier, B. Deubzer,* and *H. D. Kaesz,* J. Am. Chem. Soc. *93,* 536 (1971).
[60] *E. C. Baker, K. N. Raymond, T. J. Marks,* and *W. A. Wachter,* J. Am. Chem. Soc. *96,* 7586 (1974).
[61] *L. J. Guggenberger* and *F. N. Tebbe,* J. Am. Chem. Soc. *93,* 5924 (1971).
[62] *A. J. Cheney, W. S. McDonald, K. O'Flynn, B. L. Shaw,* and *B. L. Turtle,* J. Chem. Soc. Chem. Commun. *1973,* 128.
[63] *M. G. Clerici, B. L. Shaw,* and *B. Weeks,* J. Chem. Soc. Chem. Commun. *1973,* 516.
[64] *R. Mason, M. Textor, N. Al-Salem,* and *B. L. Shaw,* J. Chem. Soc. Chem. Commun. *1976,* 292.
[65] *V. I. Sokolov, T. A. Sorokina, L. L. Troitskaya, L. I. Solovieva,* and *O. A. Reutov,* J. Organomet. Chem. *36,* 389 (1972).
[66] *A. C. Cope, J. M. Kliegman,* and *E. C. Friedrich,* J. Am. Chem. Soc. *89,* 287 (1967); *J. M. Kleigman* and *A. C. Cope,* J. Organomet. Chem. *16,* 309 (1969).
[67] *R. S. Nyholm,* Pure Appl. Chem. *27,* 127 (1971).
[68] *M. A. Bennett, R. N. Johnson,* and *I. B. Tomkins,* J. Am. Chem. Soc. *96,* 61 (1974); and references cited therein.
[69] *F. N. Jones, M. F. Zinn,* and *C. R. Hauser,* J. Org. Chem. *28,* 663 (1963); *C. T. Viswanathan* and *C. A. Wilkie,* J. Organomet. Chem. *54,* 1 (1973).
[70] *D. W. Slocum* and *P. L. Gierer,* Chem. Commun. *1971,* 305.
[71] *D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett,* and *C. R. Hauser,* J. Org. Chem. *36,* 377 (1971).
[72] *M. Julia, M. Duteil,* and *J. Y. Lallemand,* J. Organomet. Chem. *102,* 239 (1975).
[73] *E. L. Hoel* and *M. F. Hawthorne,* J. Am. Chem. Soc. *97,* 6388 (1975).
[74] *R. Price* in *K. Venkataraman:* The Chemistry of Synthetic Dyes. Academic Press, New York 1970, Vol. 3, p. 303.
[75] *O. A. Dyachenko, L. O. Atovmyan,* and *S. M. Aldoshin,* J. Chem. Soc. Chem. Commun. *1975,* 105.
[76] *H. D. Empsall, E. M. Hyde,* and *B. L. Shaw,* J. Chem. Soc. Dalton Trans. *1975,* 1690.
[77] *K. W. Muir, R. Walker, J. Chatt, R. L. Richards,* and *G. H. D. Royston,* J. Organomet. Chem. *56,* C 30 (1973).
[78] *M. F. Lappert* and *P. L. Pye,* 7ICOMC, Venice, September 1975.
[79] *A. W. Parkins, E. O. Fischer, G. Huttner,* and *D. Regler,* Angew. Chem. *82,* 635 (1970); Angew. Chem. Int. Ed. Engl. 9, 633 (1970).
[80] *O. Gambino, M. Valle, S. Aime,* and *G. A. Vaglio,* Inorg. Chim. Acta *81,* 71 (1974); *M. Castiglioni, L. Milone, D. Osella, G. A. Vaglio,* and *M. Valle,* Inorg. Chem. *15,* 394 (1976).
[81] *M. I. Bruce, M. A. Cairns,* and *M. Green,* J. Chem. Soc. Dalton Trans. *1972,* 1293.
[82] *R. G. Little* and *R. J. Doedens,* Inorg. Chem. *12,* 840, 844 (1973).
[83] See, for example: *M. I. Bruce, R. C. F. Gardner,* and *F. G. A. Stone,* J. Chem. Soc. Dalton Trans. *1976,* 81.
[84] *E. W. Ainscough, T. A. James,* and *S. D. Robinson,* J. Chem. Soc. Dalton Trans. *1974,* 2384; and earlier papers cited therein.
[85] *M. Y. Darensbourg, D. J. Darensbourg,* and *D. Drew,* J. Organomet. Chem. *73,* C 25 (1974).
[86] *R. P. Stewart, J. J. Benedict, L. Isbrandt,* and *R. S. Ampulski,* Inorg. Chem. *14,* 2933 (1975).
[87] *L. W. Gosser,* Inorg. Chem. *14,* 1453 (1975).
[88] *M. A. Bennett* and *D. L. Milner,* J. Am. Chem. Soc. *91,* 6983 (1969).
[88a] *F. Hein* and *D. Tille,* Z. Anorg. Allg. Chem. *329,* 72 (1964).
[88b] *J. J. Daly, F. Sanz, R. P. A. Sneeden,* and *H. H. Zeiss,* Helv. Chim. Acta *57,* 1863 (1974).
[89] *H. Alper,* J. Organomet. Chem. *61,* C 62 (1973).
[90] *Y. Takahashi, A. Tokuda, S. Sakai,* and *Y. Ishii,* J. Organomet. Chem. *35,* 415 (1972).
[91] *R. L. Bennett, M. I. Bruce,* and *I. Matsuda,* Aust. J. Chem. *28,* 2307 (1975).
[92] *R. L. Bennett, M. I. Bruce, I. Matsuda, R. J. Doedens, R. G. Little,* and *J. T. Veal,* J. Organomet. Chem. *67,* C 72 (1974).
[93] *R. J. Doedens, J. T. Veal,* and *R. G. Little,* Inorg. Chem. *14,* 1138 (1975).
[94] *H. Alper,* Inorg. Chem. *15,* 962 (1976).
[95] *H. Alper* and *A. S. K. Chan,* J. Am. Chem. Soc. *95,* 4905 (1973).
[96] *G. LeBorgne* and *D. Grandjean,* J. Organomet. Chem. *92,* 381 (1975).
[97] *M. I. Bruce, J. Howard, I. W. Nowell, G. Shaw,* and *P. Woodward,* J. Chem. Soc. Chem. Commun. *1972,* 1041.
[98] *C. W. Bradford* and *R. S. Nyholm,* J. Chem. Soc. Dalton Trans. *1973,* 529.

[99] *M. I. Bruce, G. Shaw*, and *F. G. A. Stone*, J. Chem. Soc. Dalton Trans. *1972*, 2094.
[100] *A. J. Deeming, R. E. Kimber*, and *M. Underhill*, J. Chem. Soc. Dalton Trans. *1973*, 2589; *A. J. Deeming* and *M. Underhill, ibid. 1973*, 2727; *C. C. Yui* and *A. J. Deeming, ibid. 1974*, 1013; *1975*, 2091.
[101] *J. W. Rathke* and *E. L. Muetterties*, J. Am. Chem. Soc. *97*, 3272 (1975).
[102] *J. Chatt* and *J. N. Davidson*, J. Chem. Soc. *1965*, 843; *F. A. Cotton, D. L. Hunter*, and *B. A. Frenz*, Inorg. Chim. Acta *15*, 155 (1975).
[102a] *N. Bresciani, M. Calligaris, P. Delise, G. Nardin*, and *L. Randaccio*, J. Am. Chem. Soc. *96*, 5642 (1974).
[103] *N. D. Cameron* and *M. Kilner*, J. Chem. Soc. Chem. Commun. *1975*, 687.
[104] *R. F. Heck*, J. Am. Chem. Soc. *90*, 313 (1968).
[105] *P. V. Roling, J. L. Dill*, and *M. D. Rausch*, J. Organomet. Chem. *69*, C 33 (1974).
[106] *R. J. Cross* and *N. H. Tennent*, J. Organomet. Chem. *72*, 21 (1974).
[107] *A. C. Cope* and *R. N. Gourley*, J. Organomet. Chem. *8*, 527 (1967).
[108] *F.-W. Küpper*, J. Organomet. Chem. *13*, 219 (1968).
[109] *G. Longoni, P. Fantucci, P. Chini*, and *F. Canziani*, J. Organomet. Chem. *39*, 413 (1972).
[110] *G. Longoni, P. Chini, F. Canziani*, and *P. Fantucci*, J. Chem. Soc. Chem. Commun. *1971*, 470.
[111] *G. van Koten, A. J. Leusink*, and *J. G. Noltes*, Chem. Commun. *1970*, 1107; *G. van Koten* and *J. G. Noltes*, J. Chem. Soc. Chem. Commun. *1972*, 940; *A. J. Leusink, G. van Koten, J. W. Marsman*, and *J. G. Noltes*, J. Organomet. Chem. *55*, 419 (1973); *A. J. Leusink, G. van Koten*, and *J. G. Noltes, ibid. 56*, 379 (1973).
[112] *M. A. Bennett* and *R. Watt*, Chem. Commun. *1971*, 85; *M. A. Bennett, G. B. Robertson, R. Watt*, and *P. O. Whimp, ibid. 1971*, 752.
[113] *B. L. Booth* and *R. G. Hargreaves*, J. Chem. Soc. *A 1970*, 302.
[114] *M. Mickiewicz, K. P. Wainwright*, and *S. B. Wild*, J. Chem. Soc. Dalton Trans. *1976*, 262.
[115] *H. Brunner* and *J. Wachter*, J. Organomet. Chem. *107*, 307 (1976).
[116] *L. I. Zakharkin* and *A. I. Kovredov*, Zhur. Obshch. Khim. *44*, 1832 (1974).
[117] *B. Longato, F. Morandini*, and *S. Bresadola*, J. Organomet. Chem. *88*, C 7 (1975).
[118] *F. W. B. Einstein, A. B. Gilchrist, G. W. Rayner-Canham*, and *D. Sutton*, J. Am. Chem. Soc. *94*, 645 (1972).
[119] *P. L. Bellon, G. Caglio, M. Manassero*, and *M. Sansoni*, J. Chem. Soc. Dalton Trans. *1974*, 897.
[120] *M. I. Bruce, B. L. Goodall, B. J. Thomson*, and *F. G. A. Stone*, Aust. J. Chem. *27*, 2135 (1974).
[121] *D. M. Blake* and *C. J. Nyman*, Chem. Commun. *1969*, 483.
[121a] *A. J. Mukhedkar, M. Green*, and *F. G. A. Stone*, J. Chem. Soc. *A 1970*, 947.
[122] *H. C. Clark* and *K. E. Hine*, J. Organomet. Chem. *105*, C 32 (1976).
[123] *A. J. Cheney* and *B. L. Shaw*, J. Chem. Soc. Dalton Trans. *1972*, 754.
[124] *J. M. Duff* and *B. L. Shaw*, J. Chem. Soc. Dalton Trans. *1972*, 2219.
[125] *B. L. Shaw*, J. Am. Chem. Soc. *97*, 3856 (1975).
[126] *H. Takahashi* and *J. Tsuji*, J. Organomet. Chem. *10*, 511 (1967).
[127] *M. I. Bruce, B. L. Goodall*, and *F. G. A. Stone*, J. Chem. Soc. Chem. Commun. *1973*, 558.
[128] *M. I. Bruce, M. Z. Iqbal*, and *F. G. A. Stone*, J. Chem. Soc. *A 1971*, 2820.
[129] *R. W. Siekman* and *D. L. Weaver*, Chem. Commun. *1968*, 1021; *D. L. Weaver*, Inorg. Chem. *9*, 2250 (1970).
[130] *B. Crociani, T. Boschi, R. Pietropaolo*, and *U. Belluco*, J. Chem. Soc. *A 1970*, 531.
[131] *P. Braunstein, J. Dehand*, and *M. Pfeffer*, Inorg. Nucl. Chem. Lett. *10*, 581 (1974); *J. Dehand, J. Jordanov, M. Pfeffer*, and *M. Zinsius*, C. R. Acad. Sci. *C 281*, 651 (1975); *J. Dehand, M. Pfeffer*, and *M. Zinsius*, Inorg. Chim. Acta *13*, 229 (1975).
[132] *R. J. Cross* and *N. H. Tennent*, J. Chem. Soc. Dalton Trans. *1974*, 1444.
[133] *M. I. Bruce, M. Z. Iqbal*, and *F. G. A. Stone*, Chem. Commun. *1970*, 1325.
[134] *G. W. Parshall, W. H. Knoth*, and *R. A. Schunn*, J. Am. Chem. Soc. *91*, 4990 (1969).
[135] *H. Itatani* and *J. C. Bailar*, J. Am. Chem. Soc. *89*, 1600 (1967).
[136] *P. Abley* and *F. J. McQuillin*, Chem. Commun. *1969*, 1503.
[137] *S. Murahashi* and *S. Horiie*, J. Am. Chem. Soc. *78*, 4816 (1956); Bull. Chem. Soc. Jpn. *33*, 78, 88 (1960).
[138] *A. Rosenthal* and *I. Wender* in *I. Wender* and *P. Pino*: Organic Synthesis via Metal Carbonyls. Wiley, London 1968, p. 405.
[139] *A. Rosenthal, R. F. Astbury*, and *A. Hubscher*, J. Org. Chem. *22*, 1037 (1958); *A. Rosenthal* and *M. R. S. Weir, ibid. 28*, 3025 (1963).
[140] *T. Joh, N. Hagihara*, and *S. Murahashi*, Nippon Kagaku Zasshi *88*, 786 (1967).
[141] *Y. A. Ustynyuk* and *I. V. Barinov*, J. Organomet. Chem. *23*, 551 (1970).
[142] *M. I. Bruce, B. L. Goodall*, and *F. G. A. Stone*, J. Chem. Soc. Dalton Trans. *1975*, 1651.
[143] *D. R. Fahey*, J. Organomet. Chem. *27*, 283 (1971).
[144] *Y. Mori* and *J. Tsuji*, Tetrahedron *27*, 3811 (1971).
[145] *I. Rhee, Y. Hirota, M. Ryang*, and *S. Tsutsumi*, Bull. Chem. Soc. Jpn. *43*, 947 (1970).
[146] *J. Tsuji*, Acc. Chem. Res. *2*, 151 (1969).
[147] *M. Laing* and *P. M. Treichel*, J. Chem. Soc. Chem. Commun. *1975*, 746.
[148] *S. D. Robinson*, Chem. Commun. *1968*, 521.
[149] *J. S. Valentine*, J. Chem. Soc. Chem. Commun. *1973*, 857.
[150] *S. J. La Placa* and *J. A. Ibers*, Inorg. Chem. *4*, 778 (1965).
[151] *W. D. Bonds* and *J. A. Ibers*, J. Am. Chem. Soc. *94*, 3413 (1972).
[152] *A. P. Ginsberg* and *W. E. Lindsell*, Inorg. Chem. *12*, 1983 (1973).
[153] *V. G. Andrianov, Y. A. Chapovskii, V. A. Semion*, and *Y. T. Struchkov*, Chem. Commun. *1968*, 282.
[154] *M. I. Bruce, M. Z. Iqbal*, and *F. G. A. Stone*, J. Organomet. Chem. *31*, 275 (1971).
[155] *T. Joh, N. Hagihara*, and *S. Murahashi*, Bull. Chem. Soc. Jpn. *40*, 661 (1967).
[156] *M. I. Bruce, B. L. Goodall, M. Z. Iqbal*, and *F. G. A. Stone*, Chem. Commun. *1971*, 661.
[157] *I. Jardine* and *F. J. McQuillin*, Tetrahedron Lett. *1972*, 459.

Early History of the Quantum Mechanical Treatment of the Chemical Bond[**]

By Friedrich Hund[*]

Formulation of the Schrödinger equation (1926) laid the foundation for a theory of the electronic structure of molecules, and thus for a physically sound theory of the homopolar chemical bond. Physicists reached a qualitative understanding of the bond in diatomic molecules during the ensuing years 1927 to 1929, and of stereochemistry by 1931.

1. Survey

The history of a scientific discipline usually advances in a series of small steps. Any account of this history, however, must trace lines of development; their evaluation is subjective. Anybody who has been actively involved in such a history is in danger of presenting developments as he understood them at the time. It is hoped that trap has been largely avoided in the present article.

In the early days of "quantum chemistry" interest was focused not so much on calculation of physical quantities but rather on acquiring a qualitative understanding of chemical phenomena; that is, an understanding in terms of physical concepts. The topic of my account could equally well be: How did physicists understand chemistry? The chemist's idea of the atom, the periodic system, and rules for valence, saturation, bond angles were a challenge to physicists; the physicist's response was the quantum mechanics of atoms and molecules. If we regard quantum mechanics as the doctrine of mutual demarcation between a corpuscular and a wave or field view of matter, then the chemical bond appears as a manifestation of the field aspect of matter in the atomic shell, but the integral number laws as a manifestation of the corpuscular aspect, *i.e.* of electrons. Both aspects found expression in the Schrödinger equation formulated in 1926, even if this was only appreciated somewhat later. Although a "wave equation", it was also an equation for a system with one electron, with two electrons, *etc.*

The situation had been incompletely expressed in the provisional atomic dynamics developed between 1913 and 1924. It had led to an "Aufbauprinzip" for atoms, in which 1s, 2s, 2p, 3s, *etc.* electrons were consecutively added, their total number per "electron shell" being limited by a maximum eventually decided upon as 2, 6, 10... for s, p, d shells respectively. A vector model in which an angular momentum vector S (units: $h/2\pi$) of the total spin was combined with an angular momentum vector L of the orbits to give a resultant J, L being made up of the angular momentums $l_1, l_2 \ldots$ of the individual electrons, in conjunction with the Pauli exclusion principle permitted extensive understanding of atomic spectra. Attempts to treat molecular spectra in similar manner met with only partial success.

The formation of a molecule from (initially) two atoms could not be understood with these tools. An explanation of sorts was available for the rotational and vibrational components of the terms of molecular spectra. The "electronic terms" then had to correspond to states of the electron shell in the field of two atomic nuclei, and formation of a molecule from two atoms to the change in the ground state on transition from distant nuclei to proximate nuclei. A satisfactory treatment of such a system only became possible with the advent of the Schrödinger equation. Within a short time of its formulation, there began a rapid development of the theory of molecular structure and of interpretations of chemical valence, starting with diatomic molecules and progressing to polyatomic ones. The following steps are discerned with comparative ease: *molecular structure in analogy to atomic structure* (1925/26), *first understanding of the electronic structure of a diatomic molecule* (1926), *interpretations of valence (1927–1929)*, *understanding of stereochemistry* (1930/31). As already mentioned, this understanding was primarily qualitative. Those were the happy days in which "der Rahm noch nicht abgeschöpft war".

2. The Schrödinger Equation as a Tool

An essential requirement for any understanding of the chemical bond was that the structure of a molecule be understood. Prior to the formulation of the Schrödinger equation molecular structure was understood only fragmentarily in analogy with the contemporary understanding of atomic structure. The terms of atomic spectra exhibited "multiplicities"; these were even (doublets, quartets, *etc.*) for odd numbers of electrons, and odd (singlet, triplets, *etc.*) for even numbers of electrons. A similar situation was found in the electronic terms of diatomic molecules (*Mecke*, *Birge*, *Mulliken* 1924/25); analogous fundamental structures were also discovered in the electronic terms of molecules having the same number of electrons. Thus doublets resembling those for the Na atom were found in the series BO, CN, CO^+, N_2^+, and singlets and triplets like those for the Mg atom were found in the series CO, N_2, NO^+. *Mulliken* introduced a notation expressing these analogies: the form later adopted was: $^1\Sigma$, $^2\Sigma$, $^3\Sigma$, $^1\Pi$, $^2\Pi$, $^3\Pi$.

The vector model had to be modified to accommodate symmetry about the molecular axis instead of the spherical symmetry of the atom; the angular momentum quantum number L was replaced by the quantum number of the angular momentum about that axis, later to be called Λ. The combination of S and Λ with the angular momentum of rotation

[*] Prof. Dr. F. Hund
Charlottenburgerstrasse 19, D-3400 Göttingen (Germany)

[**] Based on a lecture delivered at the A-76 Conference: "Exploring the Chemical Bond—New Developments" held by the Chemical Physics Section of the Atomic Physics Division, European Physical Society at Amsterdam (August 30—September 1, 1976).

was newly introduced for the molecule. Depending upon the conditions, this led to different "coupling cases" (*Hund* 1926) which proved useful in distinguishing band types corresponding to the transitions later known as $\Sigma \rightarrow \Sigma$, $\Pi \rightarrow \Sigma$, and $\Pi \rightarrow \Pi$ transitions. While work was progressing on this "term zoology"—in which aspects of proven value in atomic spectra were applied to molecular spectra (*Mulliken* was particularly successful)—there was born the Schrödinger equation.

The equation appeared to be a reliable and, compared to the quantum mechanics developed by *Heisenberg*, *Born*, *Jordan*, and *Dirac* in 1925, conveniently manipulated basis for calculating the electronic states of a molecule, or more precisely the energies of electrons in the force field between two nuclei as a function of the distance between these nuclei. This energy function was then approximately the potential energy for the vibration of the nuclei. Immediately upon publication of the Schrödinger equation, *Burrau* performed an approximate calculation for the ground state of the simplest molecule H_2^+[1].

In general, the Schrödinger equation permitted a number of qualitative statements which were not forthcoming from the provisional atomic dynamics. Even in the simple case of a single electron in a one-dimensional potential $V(x)$ the "correspondence principle", *i. e.* the key concept of this provisional atomic dynamics, furnished approximate information about the energies $E(n)$ of the quantum states only for a relatively smooth function $V(x)$. It failed with potentials like that of Figure 1, the simplified model of a diatomic molecule.

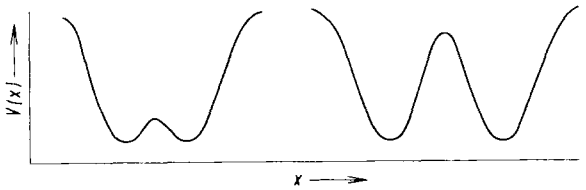


Fig. 1. Model of a diatomic molecule.

The Schrödinger equation, which is an ordinary differential equation in the one-dimensional case, is solvable (graphically for instance). Thus it was possible to interpolate between the case of widely separated potential troughs and the case of adjacent or united troughs. In particular, starting with equal troughs at a distance and bringing them together led to a splitting; considered in three dimensions, the splitting of an atomic term into two terms of the dinuclear system. In this way qualitative energy level schemes could be obtained for the H_2^+ molecule ion and the H_2 molecule as an interpolation between He^+ and $H+H^+$ and between He and H+H respectively[2]. Only later were these considerations utilized as a model of the chemical bond (although they might well have served as such).

The two new features of quantum mechanics, as compared with classical mechanics, *viz.* the indivisibility of the action quantum h (wave-particle dualism, uncertainty relation) and the indivisibility of elementary particles and indistinguishability of like elementary particles found characteristic and highly pictorial expression in the Schrödinger equation. It was the wave concept that was responsible for the wave function's bursting over the boundaries of classical motion. This feature was exploited in the interpolation between states of the two-center system with widely separated centers and with proximate centers, and provided the first instance of the tunnel effect. The indistinguishability of like elementary particles, initially electrons, was expressed by the symmetry properties of the wave function. Only those solutions of the Schrödinger equation corresponded to reality which were antisymmetrically dependent upon the coordinates of the electron. Thus in 1926 *Heisenberg* explained the singlet and triplet system (para- and ortho-system) of the He spectrum: in the former the spin component of the eigenfunction was antisymmetric but the orbit component symmetric; the situation was reversed in the latter case. Similar reasoning applied to the H_2 spectrum. Correspondingly, for like nuclei: assumption of a proton spin (1/2) and suitable spins for other nuclei explained the differences in intensity observed in the rotational bands of molecules with two identical nuclei.

This was all very useful in the interpretation of band spectra, which was diligently pursued at the time (1926/27). However, the first interpretation of the chemical bond was obtained in 1927 from a somewhat different application of the Schrödinger equation.

3. Interpretation of Valence

The inaugural step of "quantum chemistry" was made in 1927 when *Heitler* and *London* applied the Schrödinger equation and a seemingly very crude approximative procedure to the H_2 molecule[3]. They approximated the eigenfunction of the two electrons (1, 2) in the expression

$$u(1,2) = a(1)b(2) \pm b(1)a(2) \qquad \text{(I)}$$

by the eigenfunctions a, b of electrons in two H atoms. In the crudest approximation of the energy of the two states as a function of the internuclear distance r

$$E(r) = C(r) \pm A(r) \qquad \text{(II)}$$

the contribution $A(r)$ was understandable only in the light of the new quantum mechanics as the consequence of encroachment of the wave function of one atom on the other. A was negative; hence the combination with the plus sign was that of lower energy. A could now be regarded as a measure of the chemical bond. It was comforting for those physicists who initially felt this interpretation to be too formal that the shape of the eigenfunctions (I) qualitatively afforded the result (II) with $A<0$. As a one-dimensional reduction, the left-hand side of Figure 2 represents the lowest-lying states of the molecule and the right-hand side the eigenfunctions

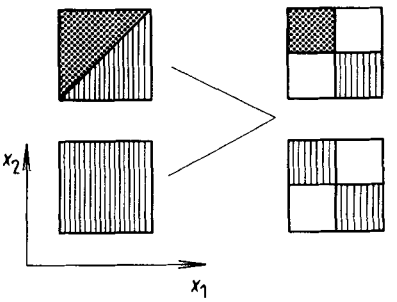


Fig. 2. One-dimensional model of the H_2 molecule.

for one electron each per atom in separate atoms, each belonging to the same lowest energy.

The procedure of *Heitler* and *London* was significant for two reasons: it led to a model of chemical valence and provided a pattern for similar crude approximations in which the eigenfunctions were approximated, not by a complete orthogonal system of functions, but by a very incomplete system of functions which were generally not orthogonal. Before long, physicists ventured to approximate functions of an electron in a symmetrical diatomic molecule in the form $a \pm b$ and to attempt a crude quantitative description of the splitting of an atomic term into two molecular terms mentioned in Section 2.

Heitler and *London* now framed a simplified model of chemical valence[4, 5]. In the case of H_2, a $^1\Sigma$ state of the molecule arose from the ^2S states of the H atoms with the plus sign in equation (I), and a higher, non-bonding $^3\Sigma$ state with the minus sign. Operation of the valence corresponded to the transition:

$$^1\Sigma \leftarrow {}^2S + {}^2S$$

and non-operation of the valence to:

$$^3\Sigma \leftarrow {}^2S + {}^2S.$$

No valence could operate on formation of a hypothetical HeH molecule:

$$^2\Sigma \leftarrow {}^2S + {}^1S.$$

In the ground state of the N_2 molecule

$$^1\Sigma \leftarrow {}^4S + {}^4S$$

three valences were saturated, and in higher states

$$^3\Sigma,\ ^5\Sigma,\ ^7\Sigma \leftarrow {}^4S + {}^4S$$

two, one, or none. Disregarding anything that happened in P, D,... Π... states, a simple scheme was available; in

$$^{m-n+1}\Sigma \leftarrow {}^{m+1}S + {}^{n+1}S; \quad m \geq n$$

one atom of valence m combines with one of valence n, with saturation of all n valences; in

$$^{m+n+1}\Sigma,\quad {}^{m+n-1}\Sigma,\quad {}^{m+n-3}\Sigma \ldots$$

0, 1, 2... valences are saturated.

This scheme conceived by *Heitler* and *London* in 1927/28 could also be applied to the combination of molecules with additional atoms. *It was a picture of the rules of chemistry concerning valence and saturation impressed upon expressions of quantum mechanics.* Hence it was a *model of valence*, albeit a greatly simplified model for it was overtaxed as soon as P, D... atomic terms occurred. Thus the true ground state of the O_2 molecule corresponded to the scheme

$$^3\Sigma \leftarrow {}^3P + {}^3P$$

According to the rules of the valence model this would mean saturation of only one valence for two divalent O atoms.

In 1929 *Heitler* introduced the designation "*orbit valence*" for the possibility of bonding relating to $L > 0$; its origin was elucidated two years later. The simple scheme shown above then corresponded to the "*spin valence*".

4. "Aufbau" Principle for Diatomic Molecules

The Schrödinger equation was used in the theory of molecular structure to develop a more exact idea about the relationship of rotation, vibration, and electron motion (*Born* and *Oppenheimer*, *Kronig* 1927). An understanding of electronic structure of diatomic molecules was sought with the aid of an Aufbau principle, resembling that used for atoms by *Bohr* to rationalize the periodic system of the elements. He had accomplished the conceptual jump from one atom to the next with an atomic number 1 unit higher by increasing the nuclear change by 1 and inserting one electron into an incomplete orbit, *i.e.* adding 1s, 2s, 2p, 3s, 3p, *etc.* electrons in turn. Corresponding to the symmetry about one axis diatomic molecules now required allocation of (in a later notation) σ, π, δ electrons, and a molecule with two identical nuclei σ_g, σ_u, π_u, π_g, electrons. In 1928 *Mulliken* deduced such an interpretation by states of individual electrons from the electronic term types ($\Sigma, \Pi, \ldots$) of the empirical molecular spectra of several molecules[6]. In so doing he noticed that on reducing the internuclear distance certain electronic states increased in energy—he called them "promoted electrons"—and thus did not contribute to bonding of the atoms.

Interpolation between the limiting case of proximate nuclei and the limiting case of distant nuclei held promise of revealing the energetic sequence in the addition of electrons, which was dependent upon the internuclear distance. There resulted, initially in tabular form, a kind of normal energy level scheme (*Hund* 1928[7])—nowadays known as a correlation diagram. For two identical nuclei it finally took the form shown in Figure 3.

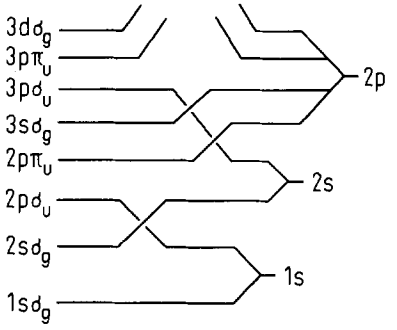


Fig. 3. Electronic states in a diatomic molecule having identical nuclei.

The diagrams of electronic energy levels which could be produced therefrom were not entirely unequivocal since it remained to be established whether, for variable internuclear distance, only the strictly fulfilled symmetries had to be considered or also the approximately fulfilled ones. *Herzberg* and *Lennard-Jones* showed in 1929 that the real conditions were best satisfied by the assignment which conserved all the symmetry quantum numbers of the individual electrons[8, 9].

These preliminary steps of a theory of the electronic structure of diatomic molecules also furnished aspects of the chemical bond complementing those put forward by *Heitler* and *London*. Introduction of an electron according to the Aufbau principle could strengthen or weaken the binding of the molecule. Thus interpolation along the series

$$\begin{array}{l} He^+ \text{ —— } H_2^+ \text{ —— } H + H^+ \\ He \text{ —— } H_2 \text{ —— } H + H \end{array}$$

showed that, owing to the high ionization energy of the atom, the ionization energy of H_2 was expected to be higher than that for H, *i.e.* the second electron in H_2 reinforces the bond already present in H_2^+. In contrast, the interpolations

$$\begin{array}{l} Li^+ \text{ —— } HeH^+ \text{ —— } He + H^+ \\ Li \text{ —— } HeH \text{ —— } He + H \end{array}$$

suggested a lower ionization energy for the hypothetical molecule HeH than for H, *i.e.* weakening of the bond possibly present in HeH^+[7]. The Aufbau principle of the molecule used by *Herzberg* in 1929 together with the interpolation of the states of the individual electrons led him to a very simple and convincing view of the chemical bond. On approach of two identical atoms the energies of the individual electrons split as shown in Figure 3. Occupation of a molecular state from the lower half of the resulting states by an electron strengthens a bond, while occupation of a state from the upper half weakens it. Its wave function has acquired a new nodal plane between the two atoms. On formation of N_2 from N + N just the states in the lower half (π_u, σ_g) are occupied: of the three p electrons belonging to each N atom, two go into the bonding π state and one into the bonding σ state, thus saturating three valences. On formation of O_2, a bond-weakening state (π_g) is also occupied; of the four p electrons belonging to each O atom, three enter bonding states and one enters a bond-weakening state, thus saturating two valences. *The valence of an atom is the number of electrons which can enter bonding states minus the number of electrons which have to enter bond-weakening states.* Similar arguments could be developed for molecules having non-identical atoms.

The relationship between the two interpretations of the chemical bond—the Heitler-London approach and that based upon the states of individual electrons—which had been rather poorly understood at the 1928 Bunsen Conference was soon to be better appreciated. If the lowest state σ_g of an individual electron of the H_2 molecule in the form $a+b$ is approximated by the states a, b in the atoms, then the expression for the ground state of the molecule

$$[a(1)+b(1)][a(2)+b(2)] = [a(1)b(2)+b(1)a(2)] + [a(1)a(2)+b(1)b(2)]$$

is seen to be a mixture of a state formed from atomic states according *Heitler* and *London* with a state arising from ionic states H^+ and H^-. Compared with reality, the contribution of the ions was overemphasized in the description by states of individual electrons of the molecules (soon to be called "molecular orbitals" by *Mulliken*); it was completely neglected by *Heitler* and *London*. Both procedures could be regarded as the starting point for a continuable approximation procedure. Their various aspects were complementary. The Heitler-London approach was certainly superior as an approximation for distant nuclei, *i.e.* for the transition to separated atoms, and hence for quantification of bonding. Perhaps the molecular

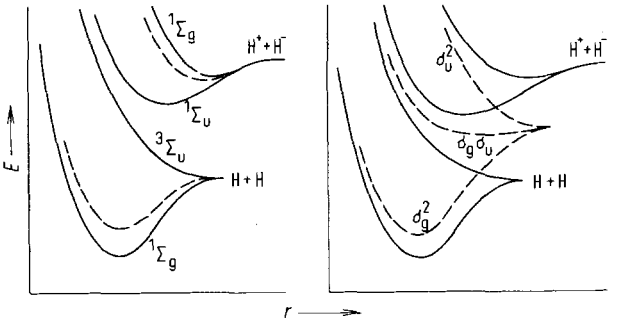


Fig. 4. H_2 molecule according to *Heitler-London* (left) and with states of individual electrons (right).

orbital approximation was better for proximate nuclei; the influence of interaction between electrons could easily be introduced in the same way as for atoms (in the case of $\sigma_g\sigma_u$ of H_2 as a splitting into a lower $^3\Sigma$ and an upper $^1\Sigma$ state). Figure 4 shows the qualitative course of the energy values as functions of the internuclear distance r—the Heitler-London procedure is shown on the left-hand side and the molecular orbital approach on the right (the first approximation is shown as a dashed curve in each case).

5. Stereochemistry

The tetravalence of carbon so important for chemistry could not be readily accommodated by either the Heitler-London scheme of spin valence or the Herzberg scheme of bonding and antibonding electrons. As early as 1928, however, *Pauling* suggested four electrons would become available for bonding if the energy gap between s and p electrons were regarded as small relative to the energy of a bond in a molecule[10].

Double bonds frequently occur in carbon compounds, *e.g.* in ethylene $H_2C{=}CH_2$. On replacement of one or more H atoms by another atom, then twisting about the double bond gives a molecule having different properties, whereas twisting about a single bond does not give a new isomer. Rotation is possible about a single bond, but not about multiple bonds. The reason was discovered by *Hückel* in 1930[11]. Single bonds are σ bonds (based on a bonding σ^2 state, two electrons in states whose eigenfunctions are symmetrical about the line joining the participating atoms). Double bonds contain a (somewhat stronger) σ bond and a (somewhat weaker) π bond; the eigenfunction of the two π electrons has a nodal plane containing the line joining the atoms. If the molecule has a distinct plane then twisting about the $\sigma\pi$ bond will require expenditure of energy.

Rules exist governing the bond angles, *e.g.* angle at the O atom, tetrahedral arrangement at the C atom, in polyatomic molecules. The explanation was found by *Slater*[12] and *Pauling*[13] in 1930/31: A strong bond is favored by pronounced overlapping of the eigenfunctions of the two participating atom electrons; if one atom supplies two p electrons they can contribute to two σ bonds if two mutually orthogonal p functions of this atom can engage in extensive overlapping,

i.e. the lines joining it to other atoms are roughly perpendicular to each other. The approximation procedure was worked out by *Slater*[12]: the eigenfunctions of the molecule were formed as a combination of products of functions of the individual electrons in the separate atoms, and of the many such combinations possible those were preferred for which the one-electron functions could overlap particularly effectively, *i.e.* which correspond to valence structures.

An understanding of the special situation in aromatic compounds, starting with benzene, was reached by *Hückel* in 1931[14] when he accommodated three of the four valence electrons of each C atom in σ bonds, and the fourth one for reasons of symmetry not in a π bond localized between two adjacent C atoms but in a state belonging to the whole ring. For this purpose *Hückel* employed two approximate procedures, *viz.* Slater-type combinations of eigenfunctions of individual electrons in separate atoms and Mulliken-type "Aufbau" from functions of individual electrons in the multicenter system.

Two starting points or procedures were now available for a qualitative explanation of the valence rules of organic chemistry, and their mutual relationship was appreciated. Thus it seemed an obvious step to classify the valences as s, p, p^2, p^3—on regarding the energy difference between s and p electrons as small, sp^2 and sp^3 valences were also available; an sp^3 valence led to a nonplanar system and an sp^2 valence to a planar one; p^4 and p^5 valences were similar to p^2 and p valences, respectively. Bonds were classified as σ, $\sigma\pi$, $\sigma\pi^2$ bonds (*e.g.* N_2), σ defect bonds (F_2), $\sigma\pi$ defect bonds (O_2) ("defect" meant an electron missing from a closed shell).

Apart from "spin valence", which was a very simple model of limited validity, *two concepts of the chemical bond* were also current for polyatomic molecules as from 1931. One of them corresponded to approximation of the eigenfunctions by functions of individual electrons in separate atoms, and hence took into account the interaction of the electrons at the same level of approximation as the effect of bonding to another atom. The other one corresponded to approximation by eigenfunctions of individual electrons in the multicenter system, and thus accounted primarily for the effect of bonding and relegated the interaction of the electrons to second place. The first concept is better suited for treating the transition from the molecule to separate atoms (in which the interaction of the electrons is particularly important, the difference between $H+H$ and $H^+ + H^-$ in the case of H_2 serves to illustrate this point). However, the second one is easier to manipulate and not inferior to the first when applied to the real interatomic distances encountered in a molecule. *Both concepts were known to be models* in the sense that effects were neglected not because they were small in magnitude but because they did not appear typical for the chemical bond. The models neglected these effects in different ways. Such was the vein of discussion about concepts of the chemical bond at the Physicist's Congress held at Bad Nauheim in 1932, and presumably also elsewhere in the world.

6. Conclusion

Meanwhile, highly sophisticated quantum mechanical techniques have grown up from the humble models of 1926 to 1931. The qualitative or crude quantitative beginnings nowadays appear fairly simple; after all, the convenient Schrödinger equation was available with the illustrative eigenfunctions. Let us briefly summarize those first steps:

1926: The Schrödinger equation permitted simple calculations and interpolation of molecular states between known atomic states.
1927: A simple interpretation of chemical valence appeared.
1928: The electronic structure of a diatomic molecule could be understood with the aid of an "Aufbau" principle.
1929: The chemical bond was also explained as contribution of the individual electrons.
1930: The special nature of the π bond was recognized.
1931: The valence rules of stereochemistry were understood.

Received: June 28, 1976 [A 147 IE]
German version: Angew. Chem. *89*, 89 (1977)

[1] *Ø. Burrau*, K. Dan. Vidensk. Selsk. Mat.-Fys. Medd. *7/14* (1927).
[2] *F. Hund*, Z. Phys. *40*, 742 (1927).
[3] *W. Heitler, F. London*, Z. Phys. *44*, 455 (1927).
[4] *W. Heitler*, Z. Phys. *46*, 49 (1928); *47*, 835 (1928).
[5] *F. London*, Z. Phys. *46*, 455 (1928); *50*, 24 (1928).
[6] *R. S. Mulliken*, Phys. Rev. *32*, 186, 761 (1928).
[7] *F. Hund*, Z. Phys. *51*, 759 (1928); Z. Elektrochem. *34*, 437 (1928).
[8] *G. Herzberg*, Z. Phys. *57*, 601 (1929).
[9] *J. E. Lennard-Jones*, Trans. Faraday Soc. *25*, 668 (1929).
[10] *L. Pauling*, Proc. Nat. Acad. Sci. U.S.A. *14*, 359 (1928).
[11] *E. Hückel*, Z. Phys. *60*, 423 (1930).
[12] *J. C. Slater*, Phys. Rev. *37*, 481 (1931); *38*, 1109 (1931).
[13] *L. Pauling*, J. Am. Chem. Soc. *53*, 1367, 3225 (1931).
[14] *E. Hückel*, Z. Phys. *70*, 204 (1931); *72*, 310 (1931).

The Surface Chemical Bond[**]

By Gabor A. Somorjai[*]

Adsorbed particles can be bound chemically to the surface of a solid (chemisorption). Modern variants of electron diffraction and electron spectroscopy now enable us to gain an insight into the nature of such surface chemical bonds, which play a key role in heterogenous catalysis and many other technically important phenomena such as adhesion, lubrication etc. Predominantly localized surface bonds can be compared to the covalent bonds in cluster compounds.

1. Introduction

The nature of the surface chemical bond that forms between adsorbed atoms and/or molecules on the surface of a solid has been the subject of extensive speculation over the past several decades. The formation and breaking of these bonds are controlling processes in heterogenous catalysis and play an important role in adhesion and lubrication, to name only a few of the many important phenomena that take place at surfaces. Only over the past decade have techniques become available that permit investigation of the surface bond on the molecular level: a) surface crystallography by low-energy electron diffraction (LEED), whereby the location, bond distance and bond angles of the adsorbates are determinable and b) electron spectroscopic techniques (ultraviolet photoelectron spectroscopy (UPS), X-ray photoelectron spectroscopy (XPS), and electron absorption spectroscopy), which permit studies of the electronic structure of the substrate and adsorbate and the vibrational frequencies associated with the various surface bonds. These techniques are still under development and have been applied to only a few adsorbate systems. Nevertheless, as a result of these few studies a model of the surface chemical bond emerges. It appears that the bonding in the solid surface-adsorbed molecule (atom) system is localized among a few neighboring atoms that can be viewed as a cluster. The adsorbed species are bound to one or several of the nearest surface atoms in well-defined configurations corresponding to maximized bond energy. Correlations between chemical bonding at the surface and bonding in multinuclear clusters of atoms have been found and will be discussed later.

In this paper we shall first discuss the structure and charge density of solid surfaces as revealed by low-energy electron diffraction and electron spectroscopic studies. These surface properties determine primarily the nature of the surface bond. We shall then review the adsorbate systems where information about the bonding has already become available.

2. Atomic Structure of Clean Solid Surfaces

Surface atoms are in an asymmetric environment. They are surrounded by atoms in and below the surface layer, but there are no atoms above them. This surface environment has also lower symmetry than that for atoms in the bulk. The structural asymmetry experienced by atoms at the surface can lead to surface reconstruction: atoms in the surface may move into new equilibrium positions that provide higher symmetry or greater overlap of available bonding orbitals.

2.1. Surface Reconstruction

There are several types of surface reconstruction observed for clean solid surfaces. Many surfaces have atomic structures that are different from that expected from the projection of the X-ray bulk unit cell. The surface atoms assume new equilibrium positions by out-of-plane buckling or by relaxing inward (contraction), which often results in entirely different ordered surface structures. An example of this is shown in Figure 1. The LEED pattern (a) and schematic representation (b) shown here are characteristic of the surface structure of the (100) crystal face of platinum. This surface exhibits the so-called (5×1) surface structure[1, 2]. There are two perpendicular domains of this structure and there are 1/5, 2/5, 3/5 and 4/5 order spots between the (00) and (10) diffraction beams.

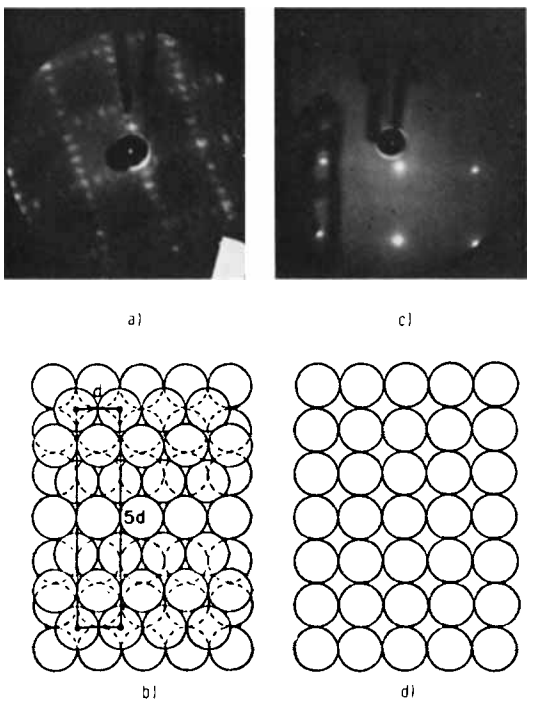


Fig. 1. a) Diffraction pattern of the Pt (100)-(5×1) structure; b) schematic representation of the (100) surface with a hexagonal overlayer; c) diffraction pattern of the Pt (100)-(1×1) structure; d) schematic representation of the (100) surface.

[*] Prof. Dr. G. A. Somorjai
Materials and Molecular Research Division,
Lawrence Berkeley Laboratory and
Department of Chemistry, University of California
Berkeley, California 94720 (USA)

[**] Based on a lecture delivered at the conference "A-76: Exploring the Chemical Bond—New Developments" of the Chemical Physics Section of the Atomic Physics Division, European Physical Society, Amsterdam (August 30—September 1, 1976).

The surface structure appears to be stable at all temperatures from 25 °C up to the melting point, although at elevated temperatures impurities from the bulk can come to the surface and cause a transformation of the structure into the impurity stabilized (1 × 1) surface structure (Fig. 1, c and d).

Preliminary calculations by *Clark et al.*[3] and in our laboratory favor a model for Pt (100) in which the surface atoms assume a distorted hexagonal configuration by out-of-plane buckling. The apparent (5 × 1) unit cell is then formed as a result of coincidence of the positions of the atoms in the surface, *i.e.* of the atoms in the distorted hexagonal layer with those in the undistorted second layer below. The (100) crystal faces of gold[4] and iridium[5], which are neighbors of platinum in the periodic table, exhibit the same surface reconstruction and the same surface structure as that of platinum (cf. Fig. 1). The (110) crystal faces of these three elements are also restructured[6] and exhibit different unit cells than that expected from the bulk x-ray structure. On the other hand, the (111) crystal faces of these three metals appear to have the same surface structure as that indicated by the bulk unit cell.

For semi-conductors, most crystal planes that have been studied show reconstruction[7]. Numerous monatomic and diatomic semi-conductor surfaces have already been investigated and surface reordering has been observed for most of them. Frequently there are changes of surface structure with temperature that are often irreversible.

For many metal surfaces, the distance between the uppermost two layers, *i.e.* the *z*-spacing, is equal to that of the bulk value to within the estimated accuracy of about five percent. However, the Al (110)[8], Mo (100)[9] and W (100)[10] surfaces seem to show substantial contraction in the upper layer *z*-spacing with respect to the bulk while retaining the (1 × 1) surface unit cell. A simple contraction or expansion of the interplanar *z*-spacing of this kind is usually termed a "relaxation".

For many binary solids non-stoichiometry occurs in the surface layer: the surface composition may be different from that in the bulk[7]. Non-stoichiometry is apparently a major contributary factor in the observed reconstruction of the polar faces of the 3B-5B semi-conductors such as gallium arsenide, GaAs. The (111) face, for example, would ideally have all gallium atoms at the surface bonded to arsenic atoms immediately beneath the surface while the reverse would be true of the $(\bar{1}\bar{1}\bar{1})$ face. However, the $(\bar{1}\bar{1}\bar{1})$ surface has been found to lose arsenic at elevated temperatures and this is associated with the appearance of a new surface structure, while at low temperature another surface structure is arsenic stabilized[11]. Similarly, phosphorus is found to preferentially desorb at high temperatures from the gallium phosphide's $(\bar{1}\bar{1}\bar{1})$ surface[12]. On the other hand, the gallium arsenide (110) surface, which contains an equal number of gallium and arsenic surface atoms, does not exhibit reconstruction. A number of studies have also pointed to possible non-stoichiometry in alkyli-metal halide crystal surfaces upon cleavage[13]. On oxide surfaces, such as aluminum oxide[14] and vanadium pentoxide[15], changes in chemical composition and valency of surface atoms have been related to the formation of new surface unit cells.

Molecular crystals constitute a large and important group of materials that include most organic solids, but only very recently have the surface structures of some of these materials been investigated on an atomic scale by low-energy electron diffraction. Ice and naphthalene crystals have been grown by vapor-phase deposition[16] and ordered surface structures of crystals of many other organic solids such as benzene, trioxane, *n*-octane, cyclohexene and methanol have been grown on metal substrates at low temperatures[17]. Phthalocyanine crystals have been grown from the vapor-phase on ordered metal surfaces[18]. These high molecular weight, large size organic crystals exhibit a different kind of surface reconstruction. When copper phthalocyanine was grown on the Cu (111) surface, the surface structure of the growing organic crystal layer did not resemble the structure of any of the simpler crystal planes in the bulk structure of the organic crystal. It appears that the ordered metal substrate predetermined the orientation and packing of the phthalocyanine monolayer, which in turn controlled the orientation and packing of the organic layer deposited on top of it. For large molecules, such as phthalocyanine, restructuring into a more stable crystallographic arrangement requires molecular rotation and diffusion processes that are too slow under conditions of crystal growth. Thus the molecules are frozen into a surface structure that is predetermined by the structure of the substrate and the first adsorbed organic monolayer.

2.2. Surface Irregularities

As shown schematically in Figure 2, the surfaces of real solids are atomically heterogeneous and not smooth. There are several atomic sites present simultaneously that are distinguishable by their number of nearest neighbors. The symmetry of these low coordination number sites and their charge density are different from that of the sites on the smooth surface and are different from each other. As a result, large variations in chemical bonding of adsorbates at these different sites could occur. Indeed, there is an increasing body of experimental evidence indicating that atomic steps and kinks behave as different chemical entities at transition metal[19, 20] and semi-conductor surfaces[21], forming chemical bonds of different strengths compared to those formed by atoms on the terraces.

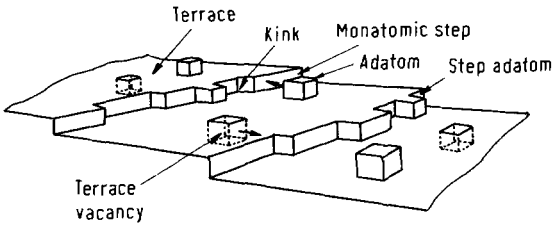


Fig. 2. Model of a solid surface on an atomic scale.

Surfaces with a large concentration of stable and ordered irregularities (steps and kinks) can be prepared by cutting crystal faces along directions having high Miller indices[22]. Stepped surfaces of metals[23], semi-conductors[24] and oxide surfaces[25] have been prepared in this way.

In order to study the surface chemical bond it is essential to carry out the investigation of structurally well-characterized solid surfaces. For this purpose single crystals of various orientations are used. Low Miller index crystal faces, *e.g.* the (111), (100) and (110) orientations of face-centered cubic metals, certainly have a high density of surface atoms and minimal

surface free energy. Under suitable conditions, these surfaces can be prepared in such a way that most of their atoms are terrace atoms. The density of steps or other irregularities are orders of magnitude lower than the total surface concentration (approximately 10^{15} atoms/cm^2). At the present stage of development, studies of adsorbate structure and bonding are carried out on atomically smooth and homogeneous surfaces such as are provided by the already mentioned low Miller index surfaces of cubic solids. One face of a single crystal of a clean solid provides the best surface to carry out these experiments. Hence, in this paper we shall not discuss the structural properties and adsorption characteristics of high Miller index surfaces that exhibit a large concentration of surface irregularities.

3. Charge Density at Clean Solid Surfaces

Let us consider an atomically smooth surface where each atom is in the same structural environment. The surface atoms have fewer nearest neighbors as compared to atoms in the bulk. As a result, electronic orbitals that participate in bonding of atoms in the crystal are available at the surface, where they give rise to increased charge density. These localized unsaturated bonding orbitals are frequently called dangling bonds and the angular distribution of their charge density largely depends on the structural arrangement (packing of atoms, orientation) at the surface. The excess free electron density at metal surfaces that is not localized on any particular atom gives rise to an induced surface dipole. The presence of this dipole is responsible for changes in the work function of metals from crystal face to crystal face. The formation of the surface dipole can be rationalized and demonstrated using the so-called jellium model. There are strong exchange correlation forces which act on the electrons in the solid due to many-body coulomb interactions. In the metal interior each electron lowers its energy by pushing others away to form an exchange-correlation "hole". This repulsive interaction is lost when the electron leaves the solid so there is a steep potential barrier at the surface. In the jellium model the positive charge density from the ion cores is smeared out over the atomic volume and the conduction electrons are free to respond to the surface barrier potential. At the surface, however, the electrons are not totally trapped and there is a small probability for them to leak out into the vacuum. Such a charge leakage creates a dipole effect which modifies the self-consistent surface barrier potential. This dipole creates an additional electrostatic barrier, V_{dipole}, for the electrons in the solid, so that the total barrier is, $V_{total} = V_{exchange} + V_{dipole}$. This gives the work function, $\phi = V_{exchange} + V_{dipole} - E_F$, where E_F is the energy at the Fermi level. Variations of the work function from crystal face to crystal face are well documented.

Surface irregularities, for example steps of atomic height, exhibit different work functions, as have recently been determined experimentally by *Wagner et al.*[26]. Theoretical studies provide firm foundation of the effect of surface heterogeneity and irregularities on the density of states at the Fermi level[27] and on the angular distribution of charge densities[28] at these low coordination number surface sites. Structural heterogeneity at the surface leads to chemical heterogeneity, *i.e.* the ability of the surface to carry out complex chemical rearrangements involving the simultaneous forming and breaking of surface bonds of varied strength at the various atomic surface sites.

4. Techniques for Studying the Surface Chemical Bond

4.1. Surface Crystallography by LEED Spectroscopy[29, 30]

A typical apparatus used for low-energy electron diffraction experiments is illustrated in Figure 3. Ultra-high vacuum conditions (base pressure approximately 10^{-9} torr) are maintained to ensure surface cleanliness. The backscattered electrons are post-accelerated onto a fluorescent screen and the diffraction pattern so produced is observed through a glass viewport. The condition of the surface under study is immediately apparent from the diffraction pattern. Sharp spots are indicative of long-range order (200 Å) on the surface. Diffuse and large spots probably signal poor ordering or the presence of adsorbed impurities. Extra diffraction spots, *i.e.* those not expected on the basis of simple termination of the bulk lattice structure along the surface plane, indicate either a reordering, reconstruction of the lattice in the surface region, or ordered structures of impurities. Electron spectroscopy—mainly Auger electron spectroscopy (see Section 4.2.1)—is routinely used to identify impurities that may be present in amounts of up to about one percent of a monolayer before, during and after low-energy electron diffraction studies.

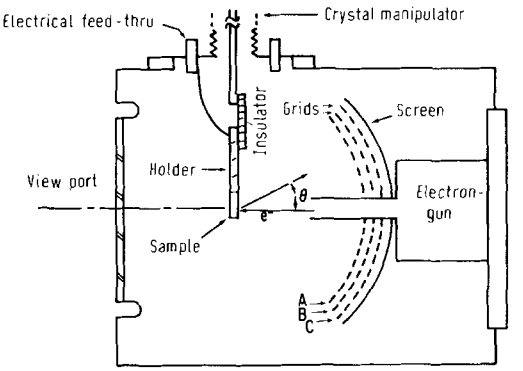


Fig. 3. A low-energy electron diffraction (LEED) apparatus of the post-acceleration type. Grids A and C are at ground potential for shielding purposes, and a voltage nearly equal to the gun accelerating potential is applied to grid B so that only the elastically backscattered electrons may pass through it. These electrons are then post-accelerated to a phosphor screen for observation through the viewport.

The electron energy range of 15 to 200 eV provides optimal surface sensitivity. Electrons of this energy range do not penetrate more than a few atomic layers before they undergo inelastic scattering events (absorption) and are lost from the diffracted (elastically backscattered) portion of the beam. Furthermore, they are rather strongly scattered in an elastic fashion by the attractive coulomb forces of the atomic nuclei and may traverse very complex trajectories (multiple or dynamical scattering) before leaving the crystal. These considerations are, or course, quite general and also have some bearing on the quantitative interpretation of various methods of electron spectroscopy.

As outlined above, the dimensions of the surface unit cell are readily found from observations of the diffraction pattern geometry. We cannot in this manner, however, discover the arrangement of atoms or molecules in the basis of the unit cell or obtain information concerning the spacings of atoms perpendicular to the surface plane. This essential information is obtained by analysis of the dependence of the intensity I of the diffraction spots on the incident beam energy V, from the so-called I/V profiles. These profiles exhibit pronounced peaks and valleys which are indicative of constructive and destructive interference of the electron waves scattered from planes parallel to the surface as the electron wavelength is varied. A rather complete quantum-mechanical description of this scattering has been achieved through the efforts of a number of theorists in recent years, but the details are outside the scope of this discussion. It suffices here to state that an accurate description of the I/V profiles generally requires consideration of several orders of multiple scattering and absorption due to inelastic events and vibrational effects. The diffraction beam intensities are measured by photographing the fluorescent screen or by using other means of detection of the elastically scattered electron flux[31]. The intensities are then calculated on the basis of a scattering model in which the essential parameter to be adjusted is the atomic geometry. The assumed geometry is varied until the best fit between theory and experiment is reached. Fortunately, the calculated I/V profiles are very sensitive to geometrical spacings, so that an accuracy of 0.1 Å in atomic positions have been obtained in the better calculations. This procedure has already been applied to numerous clean surfaces and has also provided quantitative information about bonding for atomic and molecular adsorbates. Alternates of this rather indirect method of analysis have not as yet proven viable.

4.2. Electron Spectroscopy Techniques

The methods of electron spectroscopy that are used to determine the surface composition and bonding may be divided into two groups: (i) The techniques of core-level electron spectroscopy, which enable chemical identification on the basis of the characteristic energies of atomic core states. Variations of surface chemical bonding are observed as chemical shifts of the core levels. (ii) The techniques of valence-level spectroscopy, which are also sensitive to chemical structure. Here an electron is excited from the valence band or the bonding orbital of the surface atom or adsorbate; from its energy, information can be obtained about chemical bonding and structure at surfaces.

4.2.1. Core-level Electron Spectroscopy

There are four processes involving core levels that are of importance in surface studies.

1. Incident X-rays excite electrons from a core level into a vacuum. The energy distribution of the emitted electrons is observed. This is the principle of *X-ray photoelectron spectroscopy* (XPS)[32].

2. Incident electrons cause electron excitation from a core level to a final level above the Fermi level and in so doing suffer a detectable loss in energy. The technique used for measurements in this case is called *energy-loss spectroscopy* (ELS)[33].

3. After initial excitation of the core level by incident X-rays, electrons, ions *etc.*, an Auger deexcitation process occurs. The core hole is filled by an electron transition from a higher occupied level and the transition energy is transferred to another electron (Auger electron) in the same atom or in a neighboring atom which is then emitted. In *Auger electron spectroscopy*, the energy distribution of emitted electrons is observed[34].

4. After excitation of an electron from a core level by an incident electron, the core hole is filled by a transition from a higher occupied level and X-rays or Auger electrons are emitted. In *appearance potential spectroscopy* (APS) the derivative of the intensity of emitted X-rays or Auger electrons is measured as a function of the incident electron energy[35]. At each threshold value of the incident electron energy, at which the energy is just sufficient to excite a core electron to vacant levels above the Fermi level (E_F), the intensity of emission suddenly increases. This is recorded as a peak in the derivative curve of the emission intensity.

4.2.2. Valence Electron Spectroscopy

In ultraviolet photoelectron spectroscopy (UPS)[36] an ultraviolet photon is absorbed by a valence electron whose energy is increased by $\hbar\omega$, making it possible for the excited electron to leave the crystal. The final state energy E_2 of the excited electron is measured, thus also enabling determination of the initial state energy E_1: $E_1 = E_2 - \hbar\omega$. Currently, surface studies are carried out at photon energies in the range of 10 to 45 eV.

4.2.3. Electron Absorption Spectroscopy[37]

In this technique the energy losses suffered by incident electrons of 1—10 eV energy are monitored with a resolution of ± 7 to 20 meV. Monochromatized incident electron beams and high energy resolution electron detectors are employed for such studies. Exploitation of the fact that the energy losses in this energy range are due to vibrational excitations of the surface bonds provided a means of detection and distinguishing C—C, C=C, C≡C, C—H and M—C bonds. Moreover, adsorbed hydrogen atoms, whose scattering cross sections are very small compared to those of other atoms and which are therefore not readily detectable by either electron spectroscopy or by LEED techniques, are detectable by electron absorption spectroscopy through their stretching and bending modes of vibration relative to the atoms in the solid surface (M—H). Recent investigations by *Ibach et al.* and by *Willis et al.* have illustrated the high sensitivity of this technique in the study of the surface chemical bond.

5. The Surface Crystallography of Adsorbed Monolayers of Atoms

The structural asymmetry and excess charge of the atoms at the surface have an important effect on the structure of the adsorbate/substrate system. In the presence of adsorbates, bonds are formed that make optimum use of the available bonding orbitals. For small adsorbed atoms and molecules

this often leads to the formation of a close-packed adsorbate structure in which the adsorbate occupies the high symmetry atomic sites that correspond to a continuation of the bulk structure. We shall review several examples of such chemisorbed structures below.

For most of the 200 and more surface structures of adsorbed monolayers that have been studied so far, only the two-dimensional symmetry of the diffraction pattern has been determined[29]. Hence, only the size and shape of the two-dimensional surface unit cell are known. Determination of the actual positions of the adsorbed atoms requires analysis of the intensity of the diffraction beam and has been performed only on a small number of systems—in almost all cases for atomic adsorption and low Miller index surfaces of face-centered cubic metals. The first of these analyses was carried out by *Anderson* and *Pendry*[38], who examined sodium adsorption on the nickel(100) crystal face and reported that the sodium atoms occupy fourfold coordinated sites at a distance of 0.87 Å above the topmost nickel layer. *Demuth et al.*[39] have examined the overlayer structures of oxygen, sulfur, selenium and tellurium on the nickel (100) surface, where each of the adsorbed atoms also occupy fourfold coordinated bonding sites; the displacements from the center of the top nickel layer are 0.9, 1.3, 1.45 and 1.9 Å, respectively. Results are also reported for the nickel (111) and nickel (110) surfaces. *Forstmann et al.*[40] reported iodine adsorbed on the Ag (111) surface to occupy threefold coordinated sites at a distance of 2.5 Å above the topmost layer. The adsorption of oxygen on tungsten[41] and of nitrogen on tungsten[42] and other body-centered cubic metals have also been studied.

Several general observations appear to be emerging from this work. Chemisorbed atoms seek an adsorption site which allows them to maximize their coordination. The substrate-adsorbate bond length, at least for the strongly chemisorbed systems studied thus far, can be reproduced rather well by adding the metallic radius of the substrate and the single bond covalent radius of the adsorbate. This is shown in Table 1, which lists the experimentally determined bond lengths and the predicted bond lengths obtained by summing the covalent radii. In most cases the difference is within the 0.1 Å accuracy claimed for the experimental determination, in no case is the discrepancy greater than ten percent. This result suggests that the chemisorption bond of the small adsorbate atoms studied so far is basically covalent in character, which means that theoretical treatment in terms of localized surface complexes and clusters should be applicable to their chemisorption.

Table 1. Adsorbate-substrate bond lengths [Å] determined by LEED.

Substrate	Adsorbate	Bond Length (experimental)	Ref.	Bond Length (predicted) [18]
Ni(001)	O	1.97	[a]	1.90
	S	2.18	[a]	2.28
	Se	2.27	[a]	2.41
	Te	2.58	[a]	2.61
	Na	3.37	[b]	3.10
Ni(110)	O	1.91	[c]	1.90
	S	2.17	[d]	2.28
Ni(111)	S	2.02	[d]	2.28
Ag(001)	Se	2.80	[e]	2.61
Ag(111)	I	2.75	[f]	2.77
Al(100)	Na	3.52	[g]	3.32
Mo(001)	N	2.02	[h]	2.08
W(110)	O	2.08	[i]	2.05

[a] *F. Forstmann, W. Berndt, P. Büttner*, Phys. Rev. Lett. *30*, 17 (1973).
[b] *J. E. Demuth, D. W. Jepsen, P. M. Marcus*, Phys. Rev. Lett. *32*, 1182 (1974).
[c] *B. M. Hutchins, T. N. Rhodin, J. E. Demuth*, Am. Phys. Soc. Meeting, Denver, Colorado, 1975.
[d] *M. Van Hove, S. Y. Tong*, Phys. Rev. Lett. *35*, 1092 (1975).
[e] *L. L. Kesmodel, P. C. Stair, G. A. Somorjai*, unpublished.
[f] *A. Ignatiev, F. Jona, D. W. Jepsen, P. M. Marcus*, Surface Sci. *49*, 189 (1975).
[g] *J. L. Gland, G. A. Somorjai*, Surf. Sci. *38*, 157 (1973); *41*, 387 (1974).
[h] *J. E. Demuth, D. W. Jepsen, P. M. Marcus*, Phys. Electronics Conf., State College, Pennsylvania, 1975.
[i] *L. Pauling*, The Chemical Bond, Cornell University Press, Ithaca, N. Y., 1967.

The small adsorbate atoms that are listed in Table 1 invariably occupy sites of the highest symmetry. These sites would also be the location of the next layer of metal atoms if we were to continue building up the solid layer by layer. The adsorbate-metal atom bond distance is equal, within the limits of experimental accuracy, to the sum of the covalent radii of the two atoms being bonded. There are other types of surface bonding, however, that are not readily rationalized using simple chemical arguments. Thus, in the case of oxygen on nickel (110), the best agreement with experiment is obtained if it is assumed that adsorbed oxygen atoms lie in a twofold bridge site between 1.41 and 1.51 Å above the nickel layer[43]. This is clearly not the highest coordination site on the surface. The fact that bridge bonding is preferred suggests that atomic oxygen is bonded *via* the p_x and p_y atomic orbitals to two adjacent nickel atoms. The bond angles and atomic distances are very close to what one would expect in compounds of the type X_2O, where X is the metal atom.

Another example of unusual bonding was recently discovered during studies on the adsorption of hydrogen to the nickel (110) surface. A new surface structure forms and surface crystallography studies indicated that this unit cell is a consequence of the restructuring of the nickel (110) surface as a result of hydrogen chemisorption and is not due to ordering of the hydrogen adsorbate[43]. The surface structure model giving the best fit to experimental data involves distorting the nickel surface atoms so as to produce the new (1×2) periodicity. This is achieved by simple depression or raising of every alternate row of nickel atoms in one direction, or a pair-wise distortion of every alternate row of nickel atoms in the plane of the surface. The optimal agreement with experimental curves is obtained by a 0.1 Å compression of the surface layer and a 0.1 Å alternate displacement of the rows of nickel atoms in the $[1\bar{1}0]$ direction.

Studies on the titanium/oxygen system also provided another example of unusual structure. It has recently been reported[44] that after chemisorption, oxygen atoms are located *below* the first layer of titanium atoms in the (0001) surface. There is little doubt that future studies will throw more light on the variety and complexity of surface bonding and will reveal many unexpected bonding configurations.

6. Studies on the Bonding of Hydrocarbons to Metal Surfaces

6.1. The Surface Crystallography of Acetylene on Pt(111)

Acetylene forms a (2×2) overlayer on the platinum (111) crystal surface. In recent experimental studies we have identified, on the basis of LEED I/V profiles for the platinum/acety-

lene system[45,46], two different (2 × 2) structures of adsorbed acetylene, which we refer to briefly as stable and metastable states. They have been interpreted as involving different chemical bonding. Exposure to small amounts [1 L (Langmuir) = 10^{-6} torr·sec) of C_2H_2 at room temperature leads initially to formation of the metastable (2 × 2) structure, which upon gentle heating (to 100°C, 1 h) is transformed into the stable (2 × 2) structure. Both structures are characterized by the same (2 × 2) surface unit cell and involve the same carbon coverage as determined by Auger electron spectroscopic analysis. However, they are readily distinguishable by their different *I/V* profiles.

Let us examine the various modes of bonding of acetylene to platinum in the context of high symmetry bonding sites available on the (111) face of a face-centered cubic crystal. As illustrated in Fig. 4, we distinguish four sites designated as: a) singly π-coordinated; b) doubly σ-bonded; c) μ_2-bridging; and d) μ_3-bridging (triangular complexes). For each site we have indicated only those surface metal atoms expected to have significant metal-carbon interaction. It is natural to discuss these surface geometries in terms of structural analogies to organometallic complexes. In these terms, the singly coordinated π complex (a) typically involves the interaction of one or both π orbitals of the acetylene molecule with a single metal surface atom. In the μ_2-bridging site (c) both π orbitals are utilized for bonding with two surface atoms. In principle, both (a) and (c) should entail little rehybridization of the C_2H_2 molecule since essentially undistorted π orbitals would be involved. On the other hand, the di-σ bond (b) implies sp→sp² rehybridization and the formation of two carbon-metal σ bonds accompanied by considerable bending of the CCH angle (*ca.* 120°, *cis*). This possibility has received serious consideration in the catalysis literature. Finally, the triangular structure (d), commonly found in trinuclear alkynemetal complexes, illustrates a mode of bonding loosely referred to in terms of both σ and μ bonds. We find this triangular geometry to be the favored arrangement in the (2 × 2) stable structure of acetylene on platinum (111).

In Table 2 are cited various organometallic compounds demonstrating the four geometries we have considered. It should be noted that we have examined only highly symmetric structures having the C-C axis parallel to the platinum surface. Large deviations from planarity, *e.g.* end-on bonding characteristic of metal carbonyls, are unlikely to occur in chemisorbed acetylene as they would lead to minimum overlap of bonding molecular orbitals. Furthermore, in previous work it was shown that a rather closely packed layer of planar acetylene molecules is consistent with the observed (2 × 2) unit cell. The possibility of dissociation of acetylene into CH fragments bound to the surface in a (2 × 2) configuration was ruled out on the basis of experimental findings.

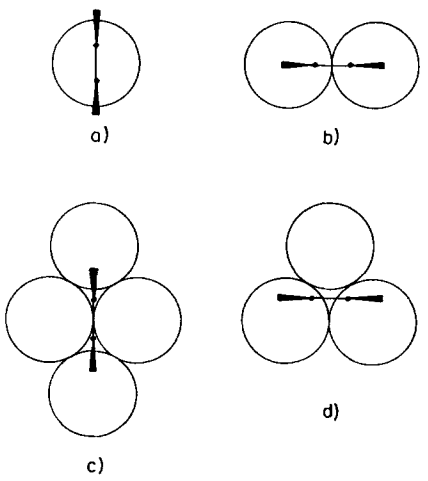


Fig. 4. Schematic diagram indicating various high-symmetry local bonding sites for acetylene on the (111) face of a face-centered cubic crystal: a) singly π-coordinated; b) doubly σ-bonded; c) μ_2-bridged; d) μ_3-bridged.

Table 2. Bonding structures and bond lengths in some transition-metal complexes with alkyne ligands RC≡CR.

Compound	Coordination geometry	M—C (Average) [Å]	C≡C [Å]
$(Ph_3P)_2Pt(C_2Ph_2)$ [a]	π (single)	2.04	1.32
$(CO)_6Co_2(C_2Ph_2)$ [b]	μ_2-bridge	1.97	1.46
$(\eta^5\text{-}C_5H_5)_2(CO)_2Rh_2(CF_3C_2CF_3)$ [c]	σ (double)	2.04	1.29
$(CO)_{10}Os_3(C_2Ph_2)$ [d]	μ_3-bridge	2.22	1.29

[a] *J. O. Glanville, J. M. Stewart, S. O. Grim*, J. Organometal. Chem. 7, P9 (1967).
[b] *W. G. Sly*, J. Am. Chem. Soc. *81*, 18 (1959).
[c] *R. S. Dickson, H. P. Kirsch, D. J. Lloyd*, J. Organometal. Chem. *101*, C48 (1975).
[d] *M. Tachikawa, J. R. Shapley, C. G. Pierpont*, J. Am. Chem. Soc. *97*, 7174 (1975).

In Figures 5 and 6 we compare selected results for di-σ, μ_2, and μ_3 structures. On the (111) surface of a face-centered cubic crystal (abc stacking) there are two inequivalent triangular sites distinguished by the presence or absence (hole site) of a second layer substrate atom located beneath the center of the triangle formed by substrate atoms in the topmost layer. The hole site corresponds to the site that would be filled in the formation of an additional substrate layer and

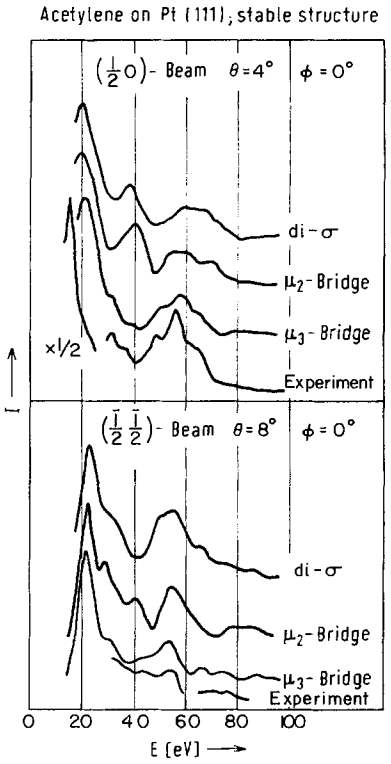


Fig. 5. Comparison of calculated *I/V* profiles for various model geometries ($z = 1.9$ Å) with experiment (stable acetylene overlayer) for two fractional-order beams.

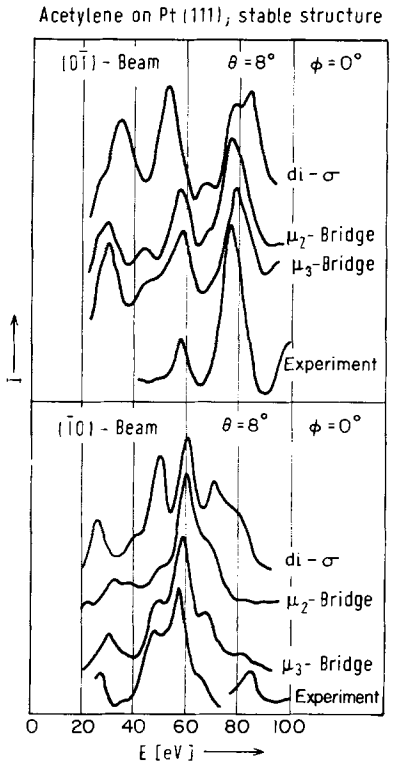


Fig. 6. Comparison of calculated I/V profiles for various model geometries ($z = 1.9$ Å) with experiment (stable acetylene overlayer) for two integral-order beams.

this is also found in the calculations to be the particular triangular site giving the optimum agreement for the location of C_2H_2 molecules in the acetylene overlayer. The z-distance of 1.9 Å employed in these comparisons was the optimum value to within ± 0.1 Å—for all three structures and all diffraction angles.

Analysis of Figures 5 and 6 shows that the triangular geometry gives consistently better agreement than either the μ_2-bridging or di-σ geometries. The singly coordinated π complex can be readily ruled out as well. We should also note the effects of scattering by the hydrogen atoms in a trial calculation for the μ_2-bridging structure at normal incidence.

The intensity profiles also indicate that no major $sp \rightarrow sp^2$ rehybridization of acetylene occurs. The CCH bond angle appears to be greater than 150° for acetylene in the adsorbed state; if rehybridization were to occur, a CCH bond angle of 120° would be expected. For a z-distance of 1.9 Å, the C—Pt distance is found to be 2.2 Å for C_2H_2 centered on the triangular site. This value is very close to the predicted covalent bond distance of 2.16 Å.

Using a dynamical analysis of low-energy electron diffraction intensity profiles we have been able to distinguish between various proposed bonding models for the chemisorption of acetylene on the Pt (111) surface. We have found that bonding of acetylene in a triangular site on the Pt (111) surface is the stable and preferred configuration. It is interesting to note that this same bonding geometry is exhibited in trinuclear alkynemetal clusters; moreover, the average C—Pt distance is similar to that determined for the corresponding distance in the trinuclear osmium cluster (Table 2), the covalent radius of osmium being only 0.04 Å shorter than that of platinum. Although we cannot detect a small change in C—C bond length we anticipate a C—C bond stretching of about 0.1 Å to occur for acetylene adsorption judging from the C—C length found in X-ray structure determinations on alkynemetal clusters.

We have also found encouraging evidence that bending of the CCH angle may be studied by such dynamical techniques despite the fact that electron scattering by hydrogen is relatively weak.

6.2. Studies of Other Hydrocarbons by Electron Spectroscopy

The bonding and composition of ethylene on the nickel (111) crystal face were studied by UPS[47]. At 100 K, the organic molecule adsorbs by bonding *via* its π orbitals to the metal surface. On heating to 230 K, C_2H_4 dehydrogenates to form C_2H_2 that is bound with even stronger π bonds to the nickel surface. With UPS the changes in bonding caused by the activated dehydrogenation that occurs could be monitored as a function of temperature. The chemisorption involved predominantly π-d bonding, so it would seem that rehybridization of the adsorbed molecule does not occur.

Similar studies carried out with C_2H_4 adsorbed on the W (110) crystal face have already been reported[48]. At 300 K, the adsorbate dehydrogenates to form C_2H_2 that π bonds to the metal. As the surface temperature is increased to 500 K, breaking of the carbon-hydrogen bond occurs and the C_2 fragments are identified by UPS by way of their C—C and C—W bonds. On heating to 1100 K, the C—C bond breaks and carbon atoms remain on the surface in a disordered state.

One of the striking features of the adsorption process is the existence of small (of the order of kT) activation energy barriers in the reaction paths leading to various bond breaking reactions. As a result an organic molecule may be adsorbed intact even on the most reactive metal surface at sufficiently low surface temperatures. On increasing the temperature electron spectroscopy can be used to identify the different bond breaking processes, which seem to occur in readily distinguishable steps.

6.3. Results of Electron Absorption Spectroscopy Studies

Surface vibrational modes have been detected in high-resolution energy spectra of backscattered low-energy electrons. In such an experiment, the energy loss of the incident electrons is determined by measuring the energy distribution of the electrons scattered from the surface or from the adsorbates. *Propst* and *Piper* observed characteristic energy losses due to adsorption of a number of simple gases on W (100)[49]. In their paper they list the vibrational bands observed for H_2, N_2, CO and H_2O. The energy resolution of 50 meV in these experiments did not permit the measurement of peak shift as a function of coverage. However, the authors concluded from the absence of molecular vibrational bands for strongly bound CO on tungsten (100) that this molecule undergoes dissociation.

More recently *Ibach et al.*[50, 51, 52] have developed a much more sensitive technique in which the energy resolution is ± 7 meV. They have confirmed that CO does in fact adsorb dissociatively on tungsten surfaces. They have also observed surface modes of lattice vibrations on both zinc oxide and silicon surfaces. In addition, vibrational modes of adsorbed oxygen were observed on silicon (111). Electron adsorption

studies were also carried out on platinum surfaces. Hydrogen was detected on metal surfaces by the stretching modes of vibration of its bonds to the metal atoms. This technique appears to be one of the most promising for studies on the surface chemical bonds of hydrogen, since it detects this atom in the adsorbate states very well indeed. Other techniques of electron scattering have failed to detect hydrogen directly because of its extremely small scattering cross section.

7. Studies on the Bonding of CO to Metal Surfaces

The chemisorption of carbon monoxide has been studied on several metal surfaces by electron spectroscopy. Using synchrotron radiation, *Shirley et al.* have found that CO adsorbs in a bridge structure bound through the carbon to the metal on the platinum (111) crystal face, while the oxygen end of the molecule points away from the surface[53]. Using the high Miller index (775) surface, which has a large concentration of kink atoms of low coordination number, *Mason et al.* found that CO dissociates at the kink sites[54], whereas it does not on atoms in terrace sites. These studies were carried out using UPS and XPS techniques. The concentration of carbidic carbon corresponded to the kink concentration and arose during the initial stages of CO chemisorption. It can be concluded therefore, that the adsorption of CO takes place first at kink sites, where the molecule dissociates. Once the kinks are blocked by carbon, CO further chemisorbs in the molecular state on other atomic sites of the heterogeneous platinum surface. CO adsorbs on tungsten crystal surfaces in several bonding sites, some of them molecular, some of them dissociated[55].

8. Conclusion

Several important findings have been made by LEED and electron spectroscopic studies on the chemical bonding of adsorbates on solid surfaces. Surface crystallography has revealed that many small atoms (O, S, Se, Na) occupy high symmetry surface sites at atomic distances characteristic of a covalent bond to the nearest neighbor metal atoms. Acetylene forms π-d bonds and occupies high symmetry sites at atomic distances that are similar to those found in organometallic cluster compounds. Surface irregularities, steps and kinks at surfaces of many solids display distinctly different bonding characteristics and chemical reactivities as compared to atoms on surface terraces. Both the bonding characteristics of adsorbates and the marked changes of chemical activity with coordination numbers of surface atoms, point to the predominance of localized bonding of adsorbates. The surface bond may be regarded as being localized between the adsorbed species and its nearest neighbor surface atoms and, to a first approximation, interactions with more distant metal atoms can be neglected. Adsorbed atoms or molecules can thus be looked upon as part of a surface molecule or surface cluster that forms between the adsorbed species and its nearest neighbor surface atoms. Consequently, good correlations between the chemistry of polynuclear clusters and that of adsorbed surface species are to be expected. Future studies will certainly verify the validity of this physical picture of the surface chemical bond.

Received: September 2, 1976 [A 151 IE]
German version: Angew. Chem. 89, 94 (1977)

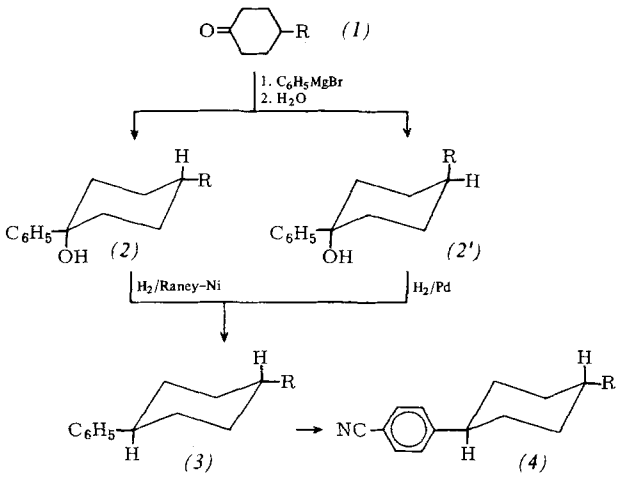
[1] *G. A. Somorjai, S. Hagstrom, H. B. Lyon*, Phys. Rev. Lett. *15*, 491 (1965).
[2] *G. A. Somorjai, A. E. Morgan*, Surf. Sci. *12*, 405 (1968); J. Chem. Phys. *51*, 3309 (1969).
[3] *T. A. Clark, R. Mason, M. Tescari*, Surf. Sci. *30*, 553 (1972).
[4] *D. G. Fedak, N. A. Gjostein*, Surf. Sci. *8*, 77 (1967).
[5] *J. T. Grant*, Surf. Sci. *18*, 228 (1969).
[6] *H. P. Bonzel, R. Ku*, J. Vac. Sci. Technol. *9*, 663 (1972).
[7] *L. L. Kesmodel, G. A. Somorjai*, Acc. Chem. Res., in press.
[8] *G. A. Somorjai, M. R. Martin*, Phys. Rev. *B7*, 3607 (1973).
[9] *J. A. Strozier, Jr., D. W. Jepsen, F. Jona* in *J. M. Blakely*: Surface Physics of Materials, Vol. I. Academic Press, New York 1975.
[10] *M. A. Van Hove, S. Y. Tong*, Surf. Sci. *54*, 91 (1976).
[11] *J. R. Arthur*, Surf. Sci. *43*, 449 (1974).
[12] *H. H. Brongersma, P. M. Mul*, Surf. Sci. *35*, 393 (1973).
[13] Cf. *e.g. T. E. Gallon, I. G. Higginbotham, M. Prutton, H. Tokutaka*, Surf. Sci. *21*, 224 (1970) and references cited therein.
[14] *G. A. Somorjai, T. M. French*, J. Phys. Chem. *74*, 2489 (1970).
[15] *L. Fiermans, J. Vennik*, Surf. Sci. *18*, 317 (1969).
[16] *L. E. Firment, G. A. Somorjai*, Surf. Sci. *55*, 413 (1976).
[17] *L. E. Firment, G. A. Somorjai*, J. Chem. Phys., in press.
[18] *J. Buchholz, G. A. Somorjai*, J. Chem. Phys., in press.
[19] *D. W. Blakely, G. A. Somorjai*, Nature *258*, 580 (1975).
[20] *G. A. Somorjai, S. L. Bernasek, W. J. Siekhaus*, Phys. Rev. Lett. *30*, 1202 (1973).
[21] *H. Ibach, K. Horn, R. Dorn, H. Lüth*, Surf. Sci. *38*, 433 (1973).
[22] *G. A. Somorjai, D. W. Blakely*, J. Catal. *42*, 181 (1976).
[23] *J. Perdereau, G. E. Rhead*, Surf. Sci. *24*, 555 (1971).
[24] *M. Henzler*, Surf. Sci. *19*, 159 (1970).
[25] *W. P. Ellis, R. L. Schwoebel*, Surf. Sci. *11*, 82 (1968).
[26] *B. Krahl-Urban, H. Wagner*, Phys. Electronics Conf., Madison, Wisconsin, 1976.
[27] *L. L. Kesmodel, L. M. Falicov*, Solid State Commun. *16*, 1201 (1975).
[28] *Y. W. Tsang, L. M. Falicov*, J. Phys. *C 9*, 51 (1976).
[29] *G. A. Somorjai, L. L. Kesmodel* in *M. Kerker*: International Review of Science, Phys. Chem. Ser. 2, Vol. 7, Surface Chemistry and Colloids. Butterworths, London 1975.
[30] *J. B. Pendry*, J. Phys. Chem. 2273 (1973); 2283 (1969).
[31] *P. C. Stair, T. J. Kaminska, L. L. Kesmodel, G. A. Somorjai*, Phys. Rev. *B11*, 623 (1975).
[32] *K. Siegbahn et al.*: ESCA-Atomic, Molecular and Solid State Structure Studied by Means of Electron Spectroscopy. Almqvist and Wiksells. Uppsala 1967.
[33] *E. G. McRae, H. D. Hagstrum* in *N. B. Hannay*: Treatise on Solid State Chemistry, Vol. 6A. Plenum Press, New York 1976.
[34] Cf. *e.g. C. C. Chang*, Surf. Sci. *25*, 53 (1971); *G. A. Somorjai, F. J. Szalkowski*, Adv. High Temp. Chem. *4*, 137 (1971).
[35] *R. L. Park, J. E. Houston*, J. Vac. Sci. Technol. *11*, 1 (1974).
[36] Cf. *e.g. D. E. Eastman* in *D. A. Shirley*: Electron Spectroscopy. North Holland, New York 1972.
[37] *H. Ibach*, J. Vac. Sci. Technol. *9*, 713 (1972).
[38] *S. Andersson, J. B. Pendry*, J. Phys. *C 5*, L 41 (1972).
[39] *J. E. Demuth, D. W. Jepsen, P. M. Marcus*, Phys. Rev. Lett. *31*, 540 (1973).
[40] *F. Forstmann, W. Berndt, P. Büttner*, Phys. Rev. Lett. *30*, 17 (1973).
[41] *M. Van Hove, S. Y. Tong*, Phys. Electronics Conf., State College, Pennsylvania, 1975; Phys. Rev. Lett. *35*, 1092 (1975).
[42] *A. Ignatiev, F. Jona, D. W. Jepsen, P. M. Marcus*, Surf. Sci. *49*, 189 (1975).
[43] *J. E. Demuth*, Progr. Colloid Surf. Sci., in press.
[44] *H. D. Shih, F. Jona, D. W. Jepsen, P. M. Marcus*, Phys. Rev. Lett. *36*, 14 (1976).
[45] *P. C. Stair, G. A. Somorjai*, Chem. Phys. Lett. *41*, 391 (1976).
[46] *L. L. Kesmodel, P. C. Stair, R. C. Baetzold, G. A. Somorjai*, Phys. Rev. Lett. *36*, 1316 (1976).
[47] *J. E. Demuth, D. E. Eastman*, Phys. Rev. *B13*, 1523 (1976).
[48] *E. W. Plummer, B. J. Waclawski, T. V. Vorburger*, Chem. Phys. Lett. *28*, 510 (1974).
[49] *F. M. Propst, T. C. Piper*, J. Vac. Sci. Technol. *4*, 53 (1967).
[50] *H. Frotzheim, H. Ibach, S. Lehwald*, "Surface Sites of H on W(100)", unpublished.
[51] *H. Frotzheim, H. Ibach, S. Lehwald*, "Surface Vibrations of CO on W(100)", unpublished.
[52] *H. Frotzheim, H. Ibach, S. Lehwald*, "Surface Vibrations of Oxygen on W(100)", unpublished.
[53] *D. A. Shirley et al.*, Phys. Rev. Lett., in press.
[54] *R. Mason, G. A. Somorjai*, J. Am. Chem. Soc., in press.
[55] *T. Yates, N. E. Erickson, S. D. Worley, T. E. Madey* in: The Physical Basis for Heterogeneous Catalysis. Plenum Press, New York 1975, p. 75.

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

Substituted Phenylcyclohexanes—A New Class of Liquid-Crystalline Compounds

By *Rudolf Eidenschink*, *Dietrich Erdmann*, *Joachim Krause*, and *Ludwig Pohl*[*]

We have found that 4-[*trans*-4-alkylcyclohexyl]benzonitriles *(4)* form nematic phases with higher clearing points and wider temperature intervals than those of the industrially important 4'-alkylbiphenyl-4-carbonitriles[1]. This means that the effect of a short-range order[2] of steric origin on the stability of nematic phases must be much greater than hitherto assumed.



Compounds *(4a)* to *(4e)* (Table 1) are obtained as follows: The *cis/trans* isomeric 4-alkyl-1-phenylcyclohexanols *(2)* and *(2')* formed in approximately equal amounts on reaction of 4-alkylcyclohexanone *(1)* with phenylmagnesium bromide in diethyl ether are separated on a column packed with silica gel (Kieselgel 60, Merck). Light petroleum (boiling range 50 to 70 °C) containing an amount of diethyl ether increasing up to 15 vol-% was used as solvent. *(2)* is hydrogenated with retention over Raney nickel in ethanol, and *(2')* with inversion over palladium/activated charcoal (10 % Pd) in ethanol. The nitrile group is introduced into the common product *(3)* in known manner (Friedel-Crafts acetylation, haloform reaction to give the carboxylic acid, conversion into the amide, and dehydration with $POCl_3$).

The structures of the products *(4a)* to *(4e)* are in accord with the results of elemental analysis and the IR and ^{13}C-NMR spectra. Since the formation of a nematic phase requires an elongated molecular shape[3], compound *(4)* probably exists in the equatorial *trans* form.

Table 1. Properties of compounds *(4)*.

	R	Yield [a] [%]	M.p. [°C]	Clearing point [°C]
(4a)	n-C_3H_7	36	36	46
(4b)	n-C_4H_9	30	41	41
(4c)	n-C_5H_{11}	42	31	55
(4d)	n-C_6H_{13}	25	42	47
(4e)	n-C_7H_{15}	38	30	59 [b]

[a] Based on amount of *(1)* weighed in.
[b] *(4e)* has a smectic-nematic transition at 17 °C.

Compounds *(4)* have viscosities of about 20 cP at 20 °C. These low values are advantageous for their application in electro-optical devices. The absorption maxima at 235 nm suggest use of eutectic mixtures as solvents in the study of anisotropic molecular properties. The optical anisotropy lies between 0.12 and 0.13, and the DC anisotropy is around +10.

Received: November 19, 1976 [Z 608 IE]
German version: Angew. Chem. *89*, 103 (1977)

CAS Registry numbers:
(1a), 40649-36-3; *(1b)*, 61203-82-5; *(1c)*, 61203-83-6; *(1d)*, 5441-57-6; *(1e)*, 16618-75-0; *(2a)*, 61203-84-7; *(2b)*, 61203-85-8; *(2c)*, 61203-86-9; *(2d)*, 61203-87-0; *(2e)*, 61203-88-1; *(2'a)*, 61203-89-2; *(2'b)*, 61203-90-5; *(2'c)*, 61203-91-6; *(2'd)*, 61203-92-7; *(2'e)*, 61203-93-8; *(3a)*, 61203-94-9; *(3b)*, 61203-95-0; *(3c)*, 61203-96-1; *(3d)*, 61203-97-2; *(3e)*, 61203-98-3; *(4a)*, 61203-99-4; *(4b)*, 61204-00-0; *(4c)*, 61204-01-1; *(4d)*, 61204-02-2; *(4e)*, 61204-03-3; phenyl bromide, 108-86-1

[1] *G. Gray*, *H. J. Harrison*, and *J. A. Nash*, Electron. Lett. *9*, 130 (1973).
[2] *W. Maier* and *A. Saupe*, Z. Naturforsch. *15a*, 287 (1960).
[3] *R. Steinsträsser* and *L. Pohl*, Angew. Chem. *85*, 706 (1973); Angew. Chem. Int. Ed. Engl. *12*, 617 (1973).

Assignment of Configuration of Olefins, Diols, and Epoxides. Quantitative Analysis of Their Stereoisomeric Mixtures

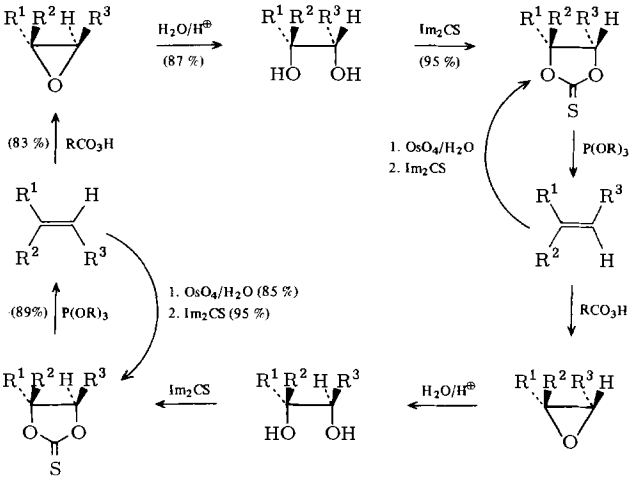
By *Alain Krief*, *László Hevesi*, *János B. Nagy*, and *Eric G. Derouane*[*]

We report here on a new method, extensively tested by us[1], for the assignment of the configuration of di- and trialkyl-substituted olefins, diols, and epoxides, as well as for

[*] Dr. R. Eidenschink [+], Dr. D. Erdmann, Dr. J. Krause, and Dr. L. Pohl
Zentrallaboratorium Industriechemikalien und Analytisches Zentrallaboratorium E. Merck
Frankfurter Strasse 250, D-6100 Darmstadt (Germany)
[+] To whom correspondence should be addressed.

[*] Prof. Dr. A. Krief [+], Prof. Dr. L. Hevesi, Dr. J. B. Nagy, Prof. Dr. E. G. Derouane
Facultés Universitaires de Namur
Département de Chimie
61, rue de Bruxelles, B-5000 Namur (Belgium)
[+] To whom correspondence should be addressed.

the quantitative analysis of mixtures of their stereoisomers. No simple general method has hitherto been available for these compounds[2].



Scheme 1. Stereospecific transformation of olefins into epoxides, diols, and thionocarbonates. The values in parentheses refer to approximate yields. Im = imidazolyl. Procedure: see ref. [6].

Our method is based on the ^{1}H-NMR chemical shift differences in stereoisomeric cyclic thionocarbonates[3], which are easily stereospecifically derived from the olefins[4] as described in Scheme 1. The significant chemical shift differences concern the proton or methyl substituents of the five-membered thionocarbonate ring. For example, the protons on the *cis (erythro)* disubstituted thionocarbonates generally appear at lower applied field ($\delta \approx 4.8$ to 4.9 ppm) than those on the corresponding *trans (threo)* isomer ($\delta \approx 4.4$ to 4.5 ppm)[5].

In the case of trisubstituted derivatives the differences are less pronounced (see Table 1). However, when a methyl substituent is present on the five-membered ring the corresponding shifts complement those of the ring protons. As a general rule, a methyl group *cis* to the hydrogen resonates at lower field ($\Delta \approx 0.1$ ppm). Consequently, in most cases a quantitative analysis can be carried out with NMR precision.

This is illustrated for two mixtures having known ratios of (*Z*)- and (*E*)-2-octene [*(1a)* and *(1b)*]. Mixture a [*Z*/*E* = 28.5/71.5] and mixture b [*Z*/*E* = 95.3/4.7] have been transformed into the corresponding mixtures of thionocarbonates according to the reaction sequence shown in Scheme 1 [1) OsO_4—H_2O/$NaHSO_3$; 2) thiocarbonyldiimidazole]. Integration of the ^{1}H-NMR signals centered at 4.84 and 4.39 gave *erythro/threo* ratios of a) 29/71 and b) 94.5/5.5 for the mixtures of thionocarbonates. Furthermore, pure *erythro*-thionocarbonate *(2b)* (ring protons at 4.84 ppm) and pure *threo*-thionocarbonate *(2c)* (ring protons at 4.39 ppm) have been mixed together in known proportions (*erythro/threo* = 9.4/90.6 and 49.6/50.4). NMR analyses of these mixtures were correct to within 1–2% error. Similar precision was obtained with mixtures of trisubstituted olefins [*(1q)* and *(1r)* in Table 1] when they were subjected to olefin → epoxide → diol → thionocarbonate transformation according to Scheme 1[3].

The interest of our method is further enhanced by the possibility of stereospecific synthesis of both thionocarbonate isomers from each of the two olefin isomers.

Received: September 6, 1976;
supplemented: November 11, 1976 [Z 605 IE]
German version: Angew. Chem. *89*, 103 (1977)

CAS Chemistry numbers:
(1a), 20063-97-2; *(1b)*, 7642-04-8; *(1c)*, 13389-42-9; *(1d)*, 7206-13-5; *(1e)*, 61140-71-4; *(1f)*, 1779-13-1; *(1g)*, 7206-25-9; *(1h)*, 61140-72-5; *(1i)*, 56847-01-9; *(1j)*, 57491-60-8; *(1k)*, 57491-59-5; *(1l)*, 616-12-6; *(1m)*, 922-62-3; *(1n)*, 36969-75-2; *(1o)*, 36969-74-1; *(1p)*, 768-49-0; *(1q)*, 39815-52-6; *(1r)*, 39815-48-0; *(2a)*, 61140-73-6; *(2b)*, 61140-74-7; *(2c)*, 61140-75-8; *(2d)*, 61140-76-9; *(2e)*, 61140-77-0; *(2f)*, 61140-78-1; *(2g)*, 61140-79-2; *(2h)*, 61140-80-5; *(2i)*, 61140-81-6; *(2j)*, 57491-58-4; *(2k)*, 57516-08-2; *(2l)*, 61140-82-7; *(2m)*, 61140-83-8; *(2n)*, 61140-84-9; *(2o)*, 61140-85-0; *(2p)*, 61140-86-1; *(2q)*, 39815-51-5; *(2r)*, 61140-87-2; *m*-chloroperoxybenzoic acid, 937-14-4; thiocarbonyldiimidazole, 6160-65-2; *cis*-2-decene epoxide, 61140-88-3; *trans*-2-decene epoxide, 54125-39-2; *cis*-2-octene epoxide, 23024-54-6; *trans*-2-octene epoxide, 28180-70-3; *cis*-2-dodecene epoxide, 61140-89-4; *trans*-2-dodecene epoxide 61140-90-7; *cis*-7-heptadecene epoxide, 61140-91-8; *trans*-7-heptade-

Table 1. ^{1}H-NMR signals of di- and trisubstituted olefins *(1)* and thionocarbonates *(2)* (δ values in ppm from TMS, solvent $CDCl_3$, $T = 25$ °C).

(1)  *(2)* 

	Substituents				Olefins *(1)*				Thionocarbonates *(2)*			
	R^1	R^2	R^3	R^4	R^1	R^2	R^3	R^4	R^1	R^2	R^3	R^4
a	H	CH_3	H	n-C_7H_{15}	5.48 [ab]	1.65 [b]	5.48 [ab]		4.48 [ab]	1.52 [b]	4.48 [ab]	
b	H	CH_3	n-C_5H_{11}	H	5.28 [ab]	1.58 [b]		5.28 [ab]	4.84 [ab]	1.36 [b]		4.84 [ab]
c	H	CH_3	H	n-C_5H_{11}	5.26 [ab]	1.61 [b]	5.26 [ab]		4.39 [ab]	1.49 [b]	4.39 [ab]	
d	H	CH_3	H	n-C_9H_{19}	5.39 [a]	1.63	5.39 [a]		4.45 [a]	1.51	4.45 [a]	
e	H	n-C_5H_{11}	H	n-$C_{10}H_{21}$	5.36 [b]		5.36 [b]		4.45 [b]		4.45 [b]	
f	H	n-C_8H_{17}	n-C_8H_{17}	H	5.35			5.35	4.83			4.83
g	H	n-C_8H_{17}	H	n-C_8H_{17}	5.35		5.35		4.46		4.46	
h	H	n-C_8H_{17}	$(CH_2)_8OCH_3$	H	5.32			5.32	4.80			4.80
i	H	n-C_8H_{17}	H	$(CH_2)_8OCH_3$	5.32		5.32		4.43		4.43	
j	H	$(CH_2)_6OAc$	$(CH_2)_7CO_2CH_3$	H	5.38			5.38	4.82			4.82
k	H	$(CH_2)_6OAc$	H	$(CH_2)_7CO_2CH$	5.48		5.48		4.48		4.48	
l	H	CH_3	CH_3	C_2H_5	5.21	1.57	1.59		4.75	1.43	1.39	
m	H	CH_3	C_2H_5	CH_3	5.10	1.54	1.64		4.71	1.43		1.51
n	H	n-C_6H_{13}	C_2H_5	CH_3	5.14			1.69	4.41			1.49
o	H	n-C_6H_{13}	CH_3	C_2H_5	5.29		1.65		4.64		1.43	
p	H	C_6H_5	CH_3	CH_3	6.27		1.86 (1.89)	1.89 (1.86)	5.52		1.07	1.71
q	H	$(CH_2)_2OAc$	CH_3	C_2H_5	5.10		1.62		4.68 [a]		1.42	
r	H	$(CH_2)_2OAc$	C_2H_5	CH_3	5.10			1.68	4.58 [a]			1.53

[a] Center of olefinic/ring proton multiplets.
[b] In CCl_4.

cene epoxide, 61140-92-9; *cis*-9-octadecene epoxide, 61140-93-0; *trans*-9-octadecene epoxide, 61140-94-1; *cis*-1-methoxy-3-dodecene epoxide, 61140-95-2; *trans*-1-methoxy-3-dodecene epoxide, 61178-30-1; *cis*-1-methoxy-9-octadecene epoxide, 61140-96-3; *trans*-1-methoxy-9-octadecene epoxide, 61140-97-4; *cis*-1-(acetyloxy)-15-(methoxycarbonyl)-7-pentadecene epoxide, 61140-98-5; *trans*-1-(acetyloxy)-15-(methoxycarbonyl)-7-pentadecene epoxide, 61140-99-6; *cis*-3-methyl-2-pentene epoxide, 59175-40-5; *trans*-3-methyl-2-pentene epoxide, 59175-39-2; *cis*-3-methyl-3-decene epoxide, 61141-00-2; *trans*-3-methyl-3-decene epoxide, 61141-01-3; 2-methyl-1-phenyl-1-propene epoxide, 10152-58-6; *cis*-1-(acetyloxy)-4-methyl-3-hexene epoxide, 39815-49-1; *trans*-1-(acetyloxy)-4-methyl-3-hexene epoxide, 61141-02-4; 2,3-decanediol isomer 1, 19721-81-4; 2,3-decanediol isomer 2, 19721-82-5; 2,3-octanediol isomer 1, 37163-98-7; 2,3-octanediol isomer 2, 37163-97-6; 2,3-dodecanediol isomer 1, 61141-03-5; 2,3-dodecanediol isomer 2, 61141-04-6; 6,7-heptadecanediol isomer 1, 61141-05-7; 6,7-heptadecanediol isomer 2, 61141-06-8; 9,10-octadecanediol isomer 1, 61177-05-7; 9,10-octadecanediol isomer 2, 61177-06-8; 1-methoxy-3,4-dodecanediol isomer 1, 61141-07-9; 1-methoxy-3,4-dodecanediol isomer 2, 61178-31-2; 1-methoxy-9,10-octadecanediol isomer 1, 61141-08-0; 1-methoxy-9,10-octadecanediol isomer 2, 61141-09-1; methyl-16-(acetyloxy)-9,10-dihydroxyhexadecanoicacid isomer 1, 57491-56-2; methyl-16-(acetyloxy)-9,10-dihydroxyhexadecanoic acid isomer 2, 57491-57-3; 3-methyl-2,3-pentanediol isomer 1, 38217-38-8; 3-methyl-2,3-pentanediol isomer 2, 38217-39-9; 3-methyl-3,4-decanediol isomer 1, 61141-10-4; 3-methyl-3,4-decanediol isomer 2, 61141-11-5; 1-phenyl-2-methyl-1,2-propanediol, 20907-13-5; 1-(acetyloxy)-4-methyl-3,4-hexanediol isomer 1, 61141-12-6; 1-(acetyloxy)-4-methyl-3,4-hexanediol isomer 2, 39815-50-4

[1] a) *L. Hevesi, J. Hontoy, A. Krief, J. Lubochinsky*, and *B. Lubochinsky*, Bull. Soc. Chim. Belg. *84*, 709 (1975); b) *D. Van Ende* and *A. Krief*, Tetrahedron Lett. *1975*, 2709; c) *A. M. Léonard-Coppens* and *A. Krief*, *ibid. 1976*, 3227; d) *J. Rémion* and *A. Krief*, *ibid. 1976*, 3743.

[2] The utility of VPC is limited by separation difficulties and the necessity for calibration by means of authentic samples. NMR has been already used as a powerful direct method on the olefins. Nevertheless, except for those carrying functional groups as substituents, this method is not easily applicable. For a review, see *G. J. Martin* and *M. L. Martin*, Progr. Nucl. Magn. Reson. Spectrosc. *8*, 163 (1972).

[3] *A. Krief*, C. R. Acad. Sci. Ser. C *275*, 459 (1972).

[4] *E. J. Corey* and *R. A. E. Winter*, J. Am. Chem. Soc. *85*, 2677 (1963); *E. J. Corey, F. A. Carey*, and *R. A. E. Winter*, *ibid. 87*, 934 (1965).

[5] All the ^{1}H-NMR measurements have been carried out on a routine MH100-JEOL 100 MHz instrument.

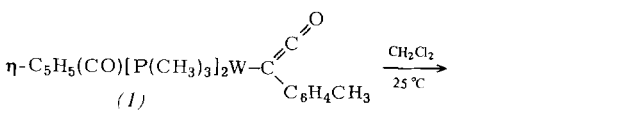
[6] The epoxides are prepared by rapid addition at 0°C (on a small scale) of a dichloromethane solution of the olefin to a solution of 1.2 equiv. of *m*-chloroperbenzoic acid in the same solvent. Diols are obtained by a) hydrolysis at room temperature of the epoxides in dimethoxyethane/water (2:1 v/v) catalyzed by $HClO_4$ (70% in water), or b) adding a slight excess (5%) of OsO_4 solution in anhydrous pyridine to a pyridine solution of the olefin at 10°C. After reaction for 4 h at room temperature, 10 equiv. of $NaHSO_3$ in water-pyridine (2:3 v/v) is added and reaction continued for 17 h.—The thionocarbonates [1a, 3, 4] are formed by heating 1 equiv. of diol with 2 equiv. thionocarbonyldiimidazole (Im_2CS) in dry toluene under N_2 at 100°C.—The conversion of thionocarbonates into olefins has been effected according to [4a]. In all the cases studied and especially for quantitative analysis of mixtures, care must be taken to conduct the reactions to completion (TLC monitoring) and not to remove one or part of one isomer if present.

p-Tolylketenyl as Novel *dihapto* 3-Electron Ligand[**]

By *Fritz R. Kreissl, Peter Friedrich*, and *Gottfried Huttner*[*]

Carbonyl(η-cyclopentadienyl)(*p*-tolylketenyl)bis(trimethylphosphane)tungsten *(1)*[1], formed by reaction of dicarbonyl(η-cyclopentadienyl)(*p*-tolylcarbyne)tungsten[2] with trimethylphosphane, rapidly liberates a phosphane ligand in solution at room temperature and forms a novel, stable ketenyl complex *(2)*.

(2) can also be prepared by direct reaction of η-$C_5H_5(CO)_2W{\equiv}C{-}C_6H_4CH_3$ with an equimolar amount of



(1) *(2)*

$P(CH_3)_3$ in dichloromethane; at low temperatures *(2)* adds a phosphane molecule and is reconverted into *(1)*[3].

The complex *(2)* can be isolated as brick-red crystals (m. p. 138°C) which are readily soluble in dichloromethane but insoluble in ether or pentane. Composition and structure of the ketene derivative[4] were confirmed by elemental analysis, molecular weight determination, IR, ^{1}H-, ^{13}C- and ^{31}P-NMR spectral data, and by an X-ray structure analysis.

The IR spectrum (KBr) shows two bands in the carbonyl region—one for the CO ligands (1878 cm^{-1}, vs) and one for the stretching vibration of the ketenyl group (1684 cm^{-1}, s).—The ^{1}H-NMR spectrum[5] (CD_2Cl_2) contains four signals of relative intensities 4:5:3:9, which are assigned to the aryl ($\delta = 7.75$ and 7.38 ppm), cyclopentadienyl (5.81), methyl (2.35), and *P*-methyl protons (1.43). The signals at 5.81 and 1.43 ppm are split into doublets as a result of spin-spin interaction with the phosphorus nucleus ($J = 1.2$ and 10.5 Hz, resp.).—The $\{^1H\}$-^{13}C-NMR spectrum[6] (CD_2Cl_2) shows the ten expected signals (chemical shifts rel. to $CD_2Cl_2 = 54.2$ ppm; ^{31}P-^{13}C coupling constants [Hz]): W—CO (229.6; 7.4), CO-ketene (203.7), C-ketene (197.6; 5.9), C_6H_4 (138.6, 138.4, 130.2, 126.7), C_5H_5 (93.3), CH_3 (21.9), and PCH_3 (21.6; 35.3).—The ^{31}P-NMR spectrum[6] contains a singlet accompanied by satellites at −13.0 ppm with $^1J(^{183}W$-$^{31}P) = 405.9$ Hz.

All spectral data of *(2)* are consistent with the results of an X-ray structure analysis[7] (Fig. 1).

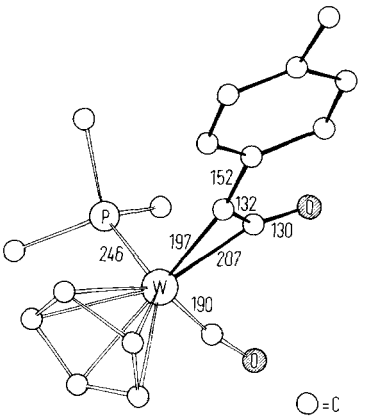


Fig. 1. Structure of the ketenyl complex *(2)* (distances in pm).

The ketenyl group, which is σ-bonded as a *monohapto* 1-electron ligand in *(1)*, has also 2 electrons of the C=C bond available for the metal in *(2)*; this π interaction leads to shortening of the distance between the metal atom and the σ-bonded carbon atom from 227(2) pm in *(1)* to 197(3) in *(2)*. The lengths of the C=C and C=O bonds increase from 124(3) and 121(3) pm, respectively, in *(1)* to 132(4) and 130(4) pm, respectively, in *(2)*. The length of the complexed double bond in *(2)* is consistent with the length of the corresponding bond in dicarbonyl(η-cyclopentadienyl)(diphenylketene)manganese (135 pm)[8].

Experimental:

All operations are carried out under nitrogen in dried (Na, P_4O_{10}) N_2-saturated solvents.—*(1)* (1.12 g, 2.0 mmol) is

[*] Dr. F. R. Kreissl [+], Dipl.-Chem. P. Friedrich, and Doz. Dr. G. Huttner
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[+] Author to whom correspondence should be addressed.

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

dissolved in dichloromethane (20 ml) at 25 °C, whereupon the color of the solution rapidly changes from yellow to dark red. Solvent and liberated trimethylphosphane are removed from the stirred solution in a vacuum. This procedure is repeated several times and the residue finally washed twice with 10 ml ether and then 10 ml pentane. After drying in a high vacuum, *(2)* is obtained as analytically pure, brick-red crystals; yield 0.80 g (83 %).

Received: November 12, 1976 [Z 602 IE]
German version: Angew. Chem. *89*, 110 (1977)

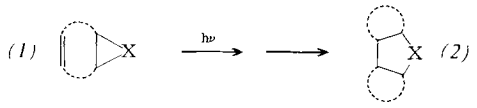
CAS Registry numbers:
(1), 60270-32-8; *(2)*, 61202-59-3; ^{31}P, 7723-14-0; ^{13}C, 14762-74-4

[1] *F. R. Kreissl, A. Frank, U. Schubert, T. L. Lindner*, and *G. Huttner*, Angew. Chem. *88*, 649 (1976); Angew. Chem. Int. Ed. Engl. *15*, 632 (1976).
[2] *E. O. Fischer, T. L. Lindner*, and *F. R. Kreissl*, J. Organomet. Chem. *112*, C27 (1976).
[3] *F. R. Kreissl, W. Uedelhoven*, and *K. Eberl*, Chem. Ber., in press.
[4] Analogous phenyl-, 4-methoxyphenyl-, mesityl-, and ferrocenyl-ketenes have also been prepared and characterized [3].
[5] Jeol C-60 HL.
[6] Bruker HFX 90, at 22.63 and 36.43 Hz.
[7] Syntex-$P2_1$: monoclinic, space group $P2_1/c$; $a=716.8$, $b=1879.2$, $c=1508.7$ pm, $\beta=115.5°$; 977 independent diffraction data ($I \geq 3\sigma$). Solution: Syntex-XTL, conventional, $R_1=0.06$.
[8] *A. D. Redhouse* and *W. A. Herrmann*, Angew. Chem. *88*, 652 (1976); Angew. Chem. Int. Ed. Engl. *15*, 615 (1976).

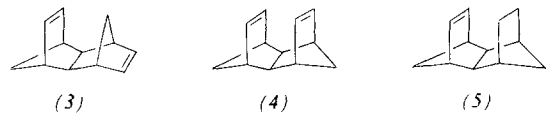
Geometrical Dependence of [2π+2σ]Photocycloaddition[**]

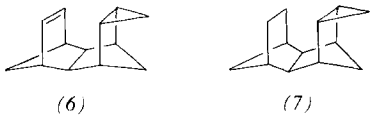
By *Horst Prinzbach, Gottfried Sedelmeier*, and *Hans-Dieter Martin*[*]

Photochemical cycloadditions of type *(1)* → *(2)* ([2π+2σ]) are even more dependent upon the relative orientation of the participating bonding orbitals than the analogous [2π+2π] reactions[1]. The β parameter as determined by



PE spectroscopy can be considered as an experimental criterion for the assessment of these geometrical requirements; the transannular overlap present in the "vertical" radical cations is assumed to be typical of the photoreactivity of the excited states. With this in mind we have investigated





[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. G. Sedelmeier
Lehrstuhl für Organische Chemie der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)
Prof. Dr. H.-D. Martin
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[**] Photochemical Transformations, Part 57. Part 56: *H. Prinzbach* and *H. Sauter*, Tetrahedron Lett. *1974*, 3049. Also: Small Rings, Part 21.—Part 20: *H.-D. Martin, C. Heller*, and *R. W. Hoffmann*, Chem. Ber., in press.

the correlation between β values and photochemistry in the cases of pentacyclo[6.3.1.1^{3,6}.0^{2,7}.0^{9,11}]tridec-4-ene *(6)*[2] and *endo*-tetracyclo[5.2.1.0^{2,6}.0^{3,5}]dec-8-ene[3].

The orbital energies ($\varepsilon=-IP_{i,v}$) shown in Figure 1 are derived, with the usual assumptions, from the vertical ionization potentials of *(3)*—*(7)* (Table 1). In the reference compound *(5)*, the transannular interaction (TAS = transannular strain) between the π- and C—H bonds lowers $IP_{1,v}$ by 0.3 eV (cf. $IP_{2,v}=8.90$ eV in *(3)*[4]). The β value in *(4)* (−0.45 eV)[4] hardly differs from that of norbornadiene (−0.4 eV)[5] and is lowered by a similarly small amount on replacement of a double bond by a three-membered ring (*(6)*: $\beta=-0.37$ eV; cf. *exo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene: $\beta=-0.3$ eV)[5]. A similar lowering by *ca.* 0.1 eV relative to the already smaller value of the corresponding diene *(8)* (−0.2 eV)[3] makes the β value of the homodiene *(9)* (−0.1 eV) very small.



Table 1. Vertical ionization potentials ($IP_{i,v}$ [eV]) of the hydrocarbons *(3)*—*(7)* (values rounded off to the nearest 0.05 eV).

	(3)	*(4)*	*(5)*	*(6)*	*(7)*
IP_1	8.45	8.10	8.60	8.80	9.45
IP_2	8.90	9.35	9.70	9.70	9.90
IP_3				10.00	

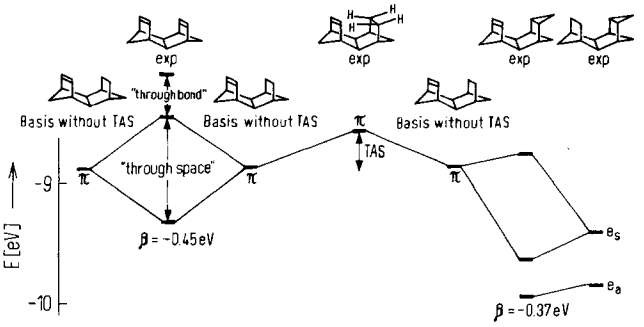
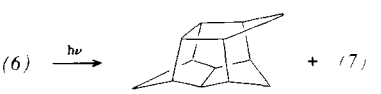


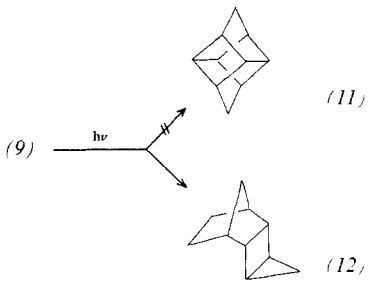
Fig. 1. Orbital correlation diagram for compounds *(4)*—*(7)*.

Direct irradiation of a *ca.* 3×10^{-3} M CH_3CN solution of *(6)* [$\varepsilon_{212\,nm}=2950$; −35 °C, 150 W Hg high pressure lamp, quartz vessel, 70 % conversion (96 h)] leads, according to GC, to a mixture (*ca.* 65 %) of hexacyclo[5.5.1.0^{2,6}.0^{3,11}.0^{5,9}.0^{8,12}]-tridecane *(10)* (colorless crystals, m.p. 222 to 223 °C)[6] and the hydrogenation product *(7)* (m.p. ≈ −20 °C) which was freed by chromatography (Al_2O_3, 20 % $AgNO_3$) from residual *(6)* and polymeric material and isolated by GC (SE 30/10 %, 100 °C; 27 and 23 % isolated, respectively, based on reacted *(6)*).



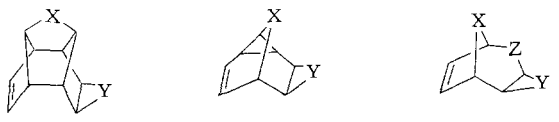
Under the same conditions, the conversion of *(9)* [$\varepsilon_{220}=700$] is comparably slow; in addition to polymeric product, TLC and GC give no indication of *(11)*[7] but only the progressive formation of the dihydro product *(12)*; the

latter is isolated in *ca.* 55 % yield after complete consumption of *(9)*.



The course of photolysis of *(6)* and *(9)* corresponds to expectation in that at the very short wavelength of excitation necessary $[2\pi+2\sigma]$ cycloaddition becomes effective against the major competing reaction, hydrogenation, only under very favorable overlap conditions, *i.e.* given a large β parameter.

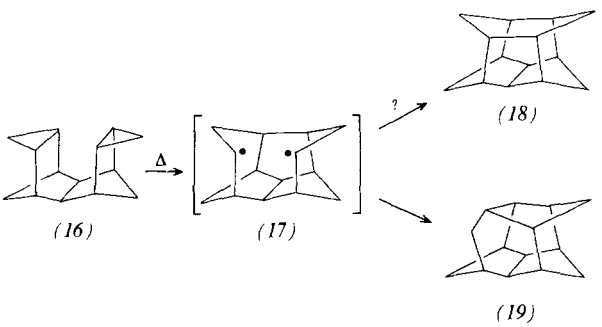
We expect to gain a more detailed insight from studies of homodienes of type *(13)*—*(15)* with systematic variations in distances and angles between the π/σ bonds.



(13) *(14)* *(15)*

X, Y, Z = $-(CH_2)_n-$, O, NR

In compound *(16)*[2] formed as co-product on preparation of *(6)* the stereochemistry is favorable for $[2\sigma+2\sigma]$ cycloaddition to form *(18)*, a reaction already attempted on earlier occasions. On gas phase pyrolysis, *(16)* is stable up to *ca.*



500 °C but polymerizes and chars above 750 °C. However, between 630 and 670 °C the reaction affords an hydrocarbon isomeric to *(16)* in 60—70 % yield together with a small amount of side products [*(18)*?]. According to spectroscopic data the hydrocarbon is not the highly symmetrical cycloadduct *(18)* but hexacyclo[6.5.1.$0^{2,6}$.$0^{3,12}$.$0^{5,10}$.$0^{9,13}$]tetradecane *(19)* (m.p. 199 to 200 °C)—probably formed from the intermediate *(17)* by hydrogen migration.

Received: November 2, 1976 [Z 604 IE]
German version: Angew. Chem. *89*, 111 (1977)

CAS Registry numbers:
(3), 15914-94-0; *(4)*, 1076-13-7; *(5)*, 1076-12-6; *(6)*, 61177-04-6; *(7)*, 61140-68-9; *(8)*, 15564-45-1; *(9)*, 30358-36-2; *(10)*, 24856-73-3; *(12)*, 53862-36-5; *(16)*, 61140-69-0; *(18)*, 61140-70-3; *(19)*, 61248-60-0

[1] *H. Prinzbach* and *D. Hunkler*, Chem. Ber. *106*, 1804 (1973); and references cited therein.

[2] Prepared by cyclopropanation of *(4)* [diazomethane, CuBr, ether; after total conversion 56% of *(6)* (m.p. ≈ 20 °C) and 35% of *(16)* (m.p. 78 °C); separation on Al_2O_3/20 % $AgNO_3$/*n*-pentane]. The structures of the new compounds *(6)*, *(7)*, *(16)*, and *(19)* are confirmed by elemental analysis and spectroscopic data (IR, UV, MS, ^{1}H- and ^{13}C-NMR).

[3] *H.-D. Martin, S. Kagabu*, and *R. Schwesinger*, Chem. Ber. *107*, 3130 (1974).

[4] *H.-D. Martin* and *R. Schwesinger*, Chem. Ber. *107*, 3143 (1974).

[5] *P. Bischof, E. Heilbronner, H. Prinzbach*, and *H.-D. Martin*, Helv. Chim. Acta *54*, 1072 (1971).

[6] *J. M. Brown*, J. Chem. Soc. *B 1969*, 868.

[7] *E. T. McBee, W. L. Dilling*, and *H. P. Braendlin*, J. Org. Chem. *27*, 2704 (1962).

[8] *H. Prinzbach* and *H.-D. Martin*, Helv. Chim. Acta *51*, 438 (1968); *A. Bruggink* and *H. Hogeveen*, Tetrahedron Lett. *1972*, 4961.

Unstable Intermediates in the Gaseous Phase[1]: The Thermal Decomposition of Alkyl Sulfides RS_nR[2]

By *Hans Bock* and *Shamsher Mohmand*[*]

Photoelectron spectrometers provide "finger prints" of molecules in the form of ionization band patterns. PE spectra are therefore especially suitable for the analysis of gaseous reaction products and, hence, for the optimization of gas-phase

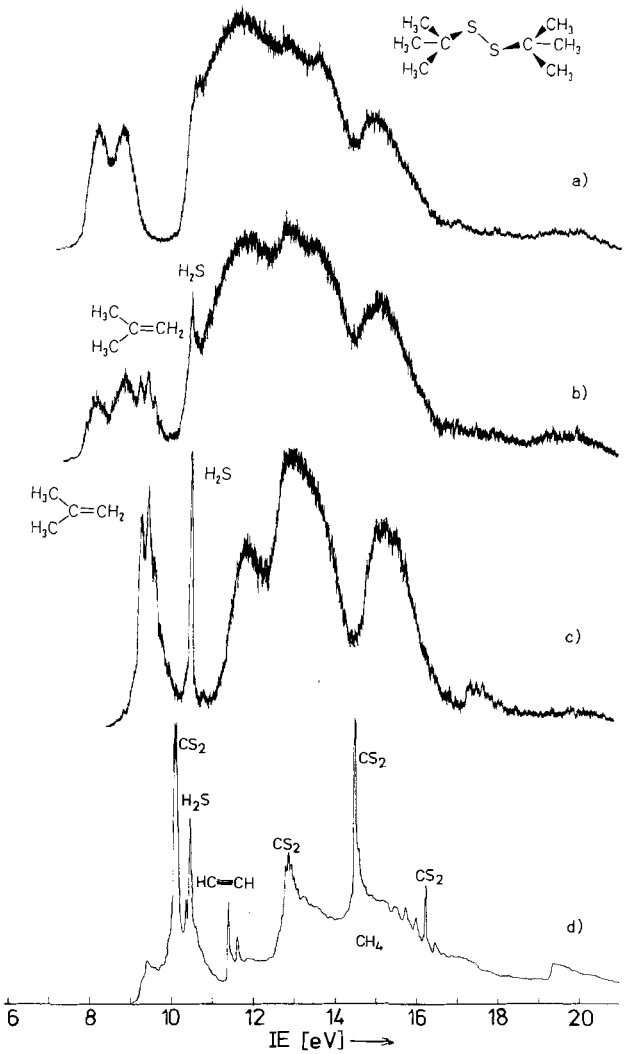


Fig. 1. PE spectra of di-*tert*-butyl sulfide (a) and its thermolysis products up to 690 K (b and c) and at 1400 K (d).

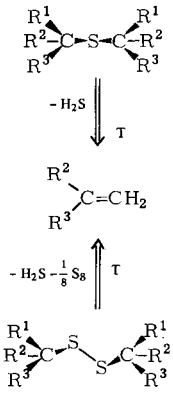
[*] Prof. Dr. H. Bock and Dipl.-Chem. S. Mohmand
Institut für Anorganische Chemie der Universität
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

reactions: With 100 to 200 mg of compound the temperature dependence of a reaction at 0.1 torr can be monitored, *e.g.*, between 300 K and 1500 K at intervals of 50 K within a day.

An example[3] is the pyrolysis of di-*tert*-butyl disulfide in a 0.5m-long, furnace-heated quartz tube: the continuously recorded PE spectra show that decomposition commences at 650 K (Fig. 1: a/b) and is complete at a furnace temperature of 690 K, and that H_2S[4] and isobutene[4] are the sole gaseous products formed (Fig. 1: c). In addition, sulfur is deposited on the tube wall outside of the furnace zone.

Like di-*tert*-butyl disulfide, numerous organic and inorganic compounds decompose under PE spectrometer conditions at relatively low temperatures *via* "reaction channels" which lead quantitatively to uniform reaction products (cf. Fig. 1: c). In most cases thermodynamically favorable "leaving molecules" such as hydrogen halides, nitrogen, hydrogen sulfide, sulfur dioxide, carbon monoxide, *etc.* are split off[1,3]. On the contrary, stronger "heating up" to higher temperature frequently leads to a "splattering" in fragments which are energetically favored under these conditions; thus the PE spectrum of the decomposition products of di-*tert*-butyl disulfide at 1400 K confirms the presence of species such as CS_2, H_2S, $HC{\equiv}CH$, CH_4, or H_2[4] (Fig. 1: d).

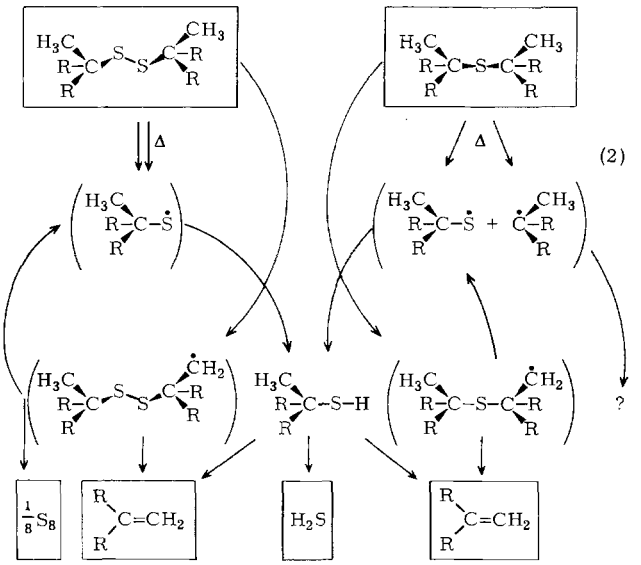
All the dialkyl sulfides or disulfides listed in (1) eliminate quantitatively hydrogen sulfide and, in the latter case, sulfur at 0.1 torr and at the given temperatures, forming the corresponding alkenes:



=	1090		970	920	[K]
	R^1	CH_3	CH_2CH_3	CH_3	CH_3
	R^2	H	H	CH_3	CH_3
	R^3	H	H	H	CH_3
=	840	790		770	690 [K]

(1)

Disulfides decompose at temperatures which are about 200 K lower than those for the sulfides; the decomposition temperature decreases further with increasing methyl substitution and increasing chain branching. The experimental results (1) are consistent *e.g.* with the expectation that a SS bond ($\Delta Hb \approx 226$ kJ/mol) ought to cleave more readily than a CS bond ($\Delta Hb \approx 272$ kJ/mol), and in part, suggest a common product formation scheme for the $(CH_3CR_2)_2S_n$ pyrolyses ($n=1, 2$; R = H, CH_3):



(2)

Assuming that a chain reaction proceeds *via* alkylthio radicals, the PE spectroscopically investigated thermolytic reactions of ethyl hydrosulfide and dimethyl sulfide[5]

$$H_3C{-}CH_2{-}SH \xrightarrow{820\ K} H_2C{=}CH_2 + H_2S \qquad (3)$$

$$H_3C{-}S{-}S{-}CH_3 \xrightarrow{890\ K} H_2C{=}S + H_3C{-}SH \qquad (4)$$

seem to support the hypothetical product formation scheme (2)[6].

Received: November 2, 1976 [Z 599a IE]
German version: Angew. Chem. *89*, 105 (1977)

CAS Registry numbers:
Ethyl sulfide, 352-93-2; propyl sulfide, 111-47-7; isopropyl sulfide, 625-80-9; *tert*-butyl sulfide, 107-47-1; ethyl disulfide, 110-81-6; propyl disulfide, 629-19-6; isopropyl disulfide, 4253-89-8; *tert*-butyl disulfide, 110-06-5; ethylene, 74-85-1; 1-propene, 115-07-1; 2-methyl-1-propene, 115-11-7; acetylene, 74-86-2

[1] Part 6.—Part 5: *H. Bock, B. Solouki, G. Bert*, and *P. Rosmus*, J. Am. Chem. Soc., in press. Also Part 66 of Photoelectron Spectra and Molecular Properties.—Part 65: *P. Rosmus, B. Solouki*, and *H. Bock*, Chem. Phys., in press.

[2] Diplomarbeit *S. Mohmand*, Universität Frankfurt 1976.

[3] *H. Bock, B. Solouki, S. Aygen, G. Bert, T. Hirabayashi, F. John, S. Mohmand, H. Müller, H. W. Rohwer, U. Stein, J. Wittmann*, and *H. Zacharias*, unpublished.

[4] Reference spectra necessary for the PE spectroscopic analysis are collected in books such as *D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy, Wiley-Interscience, London 1970, or summarized in reviews on definite classes of compounds. The expected PE band patterns can usually be estimated from the molecular symmetry using qualitative LCBO-MO models and/or checked with those of reference compounds, cf. *e.g. H. Bock*, Pure Appl. Chem. *44*, 343 (1975); and literature cited therein.

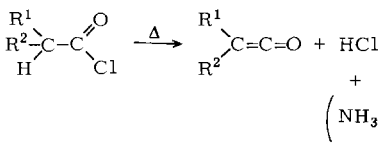
[5] Cf. also *H. W. Kroto* and *R. J. Suffolk*, Chem. Phys. Lett. *15*, 545 (1972).

[6] *Note added in proof:* According to *G. Martin* and *N. Barroeta*, J. Chem. Soc. Perkin II *1976*, 1421, thermal decomposition of di-*tert*-butyl disulfide proceeds *via* a first-order elimination of isobutane.

Unstable Intermediates in the Gaseous Phase[1]: The Thermal Decomposition of Acyl Chlorides RCOCl[2]

By *Hans Bock, Takakuni Hirabayashi, Shamsher Mohmand*, and *Bahman Solouki*[*]

Ketene is obtained on an industrial scale by thermal cleavage of water from acetic acid or by thermal removal of methane from acetone[3]; of the numerous laboratory methods[4] known, the one involving elimination of HCl from acyl chlorides is the most suitable for a PE spectroscopic analysis of ketene formation reactions in the gaseous phase.



(1)

[*] Prof. Dr. H. Bock, Dr. T. Hirabayashi, Dipl.-Chem. S. Mohmand, and Dr. B. Solouki
Institut für Anorganische Chemie der Universität
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

The hydrogen chloride formed shows a simple and strikingly characteristic PE spectrum[5] with two fine-structured vibrational bands at 12.8 and >16.2 eV, and can be removed from the reaction mixture by injection of ammonia gas[6] (Fig. 1).

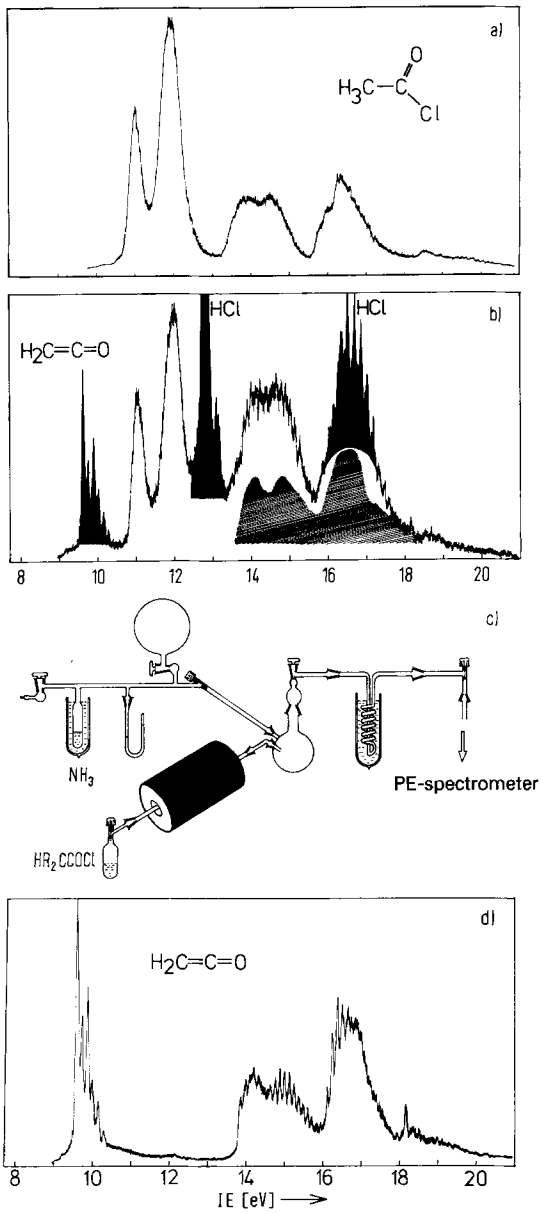
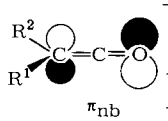


Fig. 1. PE spectra of acetyl chloride (a), of the pyrolysis mixture at 650 K (b), and, after injection of NH_3 (c) at 820 K (d). (H_3CCOCl, white; HCl, black; H_2CCO, hatched.)

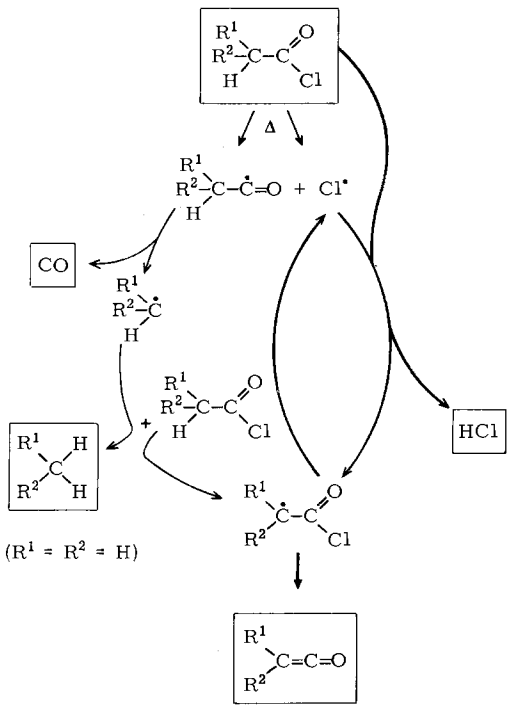
Numerous ketene derivatives can be generated in the gaseous phase at 0.1 torr from the corresponding substituted acyl chlorides according to (1) and characterized PE spectroscopically. The substituent-dependent changes enable assignment of the PE bands—*e.g.* the first ionization leads to a radical-cation state of type π_{nb}—and can be described within a MO model by hyperconjugative interaction.



	R^1	H[5]	CH_3	CH_3	C_6H_5	Cl
	R^2	H	H	CH_3	H	H
	IE_1 [eV]	9.60	8.95	8.38	8.17	9.35

(2)

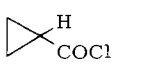
Indications of a possible reaction mechanism (3) for the smooth gas-phase elimination of HCl from acyl chlorides are given by a PE spectrum of the H_3CCOCl decomposition which was recorded after incorporation of a cold trap (−190 °C) between the furnace and PE spectrometer (Fig. 1: c), and from which the bands of CO and CH_4 in the unfrozen residual gas can be recognized.



(3)

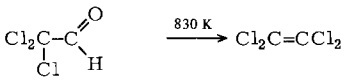
According to the hypothetical reaction scheme (3) the C—Cl bond is the weakest ($\Delta Hb \approx 327$ kJ/mol) and will presumably be cleaved first. This initiation reaction would yield Cl• atoms as radical chain carriers; the ketenes could be formed *via* $R_2\dot{C}COCl$ radicals.

Detailed PE spectroscopic investigations[7] show that the HCl elimination is often accompanied by loss of CO. Examples are:



(4)

$$H_2C{=}CH{-}COCl \xrightarrow{910\ K} HC{\equiv}CH + HCl + CO \quad (5)$$



(6)

On elimination of (HCl + CO) from trichloroacetaldehyde *(6)*, the major product of the pyrolysis is tetrachloroethylene—presumably formed by dimerization of dichlorocarbene.

Received: November 2, 1976 [Z 599b IE]
German version: Angew. Chem. 89, 106 (1977)

CAS Registry numbers:
Acetyl chloride, 75-36-5; propanoyl chloride, 79-03-8; 2-methylpropanoyl chloride, 79-30-1; benzeneacetyl chloride, 103-80-0; chloroacetyl chloride, 79-04-9; ketene, 463-51-4; methylketene, 6004-44-0; dimethylketene, 598-26-5; phenylketene, 3496-32-0; chloroketene, 29804-89-5; cyclopropanecarbonyl chloride, 4023-34-1; 2-propenoyl chloride, 814-68-6; trichloroacetaldehyde, 75-87-6; cyclopropene, 2781-85-3; acetylene, 74-86-2; tetrachloroethylene, 127-18-4

[1] Part 7.—Part 6: *H. Bock* and *S. Mohmand*, Angew. Chem. *89*, 105 (1977); Angew. Chem. Int. Ed. Engl. *16*, 104 (1977). Also Part 67 (and 66) of Photoelectron Spectra and Molecular Properties.
[2] In part from the Diplomarbeit *S. Mohmand*, Universität Frankfurt 1976.
[3] Cf. *K. Weissermel* and *H. J. Arpe:* Industrielle Organische Chemie. Verlag Chemie, Weinheim 1976, pp. 150ff.
[4] Cf. *D. Borrmann* in *Houben/Weyl:* Methoden der organischen Chemie, Vol. VII/4. Thieme, Stuttgart 1968, pp. 53ff.
[5] Cf. *D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle:* Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970.
[6] *B. Solouki, P. Rosmus*, and *H. Bock*, J. Am. Chem. Soc. *98*, 6054 (1976).
[7] *H. Bock, S. Aygen, T. Hirabayashi, S. Mohmand*, and *B. Solouki*, unpublished.

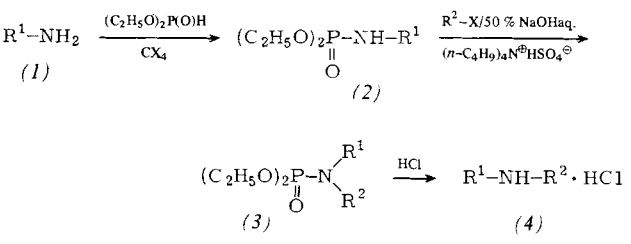
Alkylation of Diethyl Phosphoramidates – A Simple Route from Primary to Secondary Amines[**]

By *Andrzej Zwierzak* and *Janina Brylikowska-Piotrowicz*[*]

The methods commonly employed for the transformation of primary into secondary amines involve the synthesis and subsequent catalytic hydrogenation of the corresponding Schiff bases. Procedures for direct alkylation frequently afford mixtures of secondary and tertiary amines or necessitate the use of expensive and difficultly accessible reagents.

We have found that the diethyl esters *(2)* of the *N*-alkyl- or *N*-arylphosphoramidic acids, which are accessible in high yields from primary amines *(1)*[1] or their hydrochlorides, can be readily alkylated under the conditions of phase-transfer catalysis.

Applicability of this procedure is limited, however, to primary alkyl halides as alkylating agent. The protecting diethoxyphosphoryl group is removed from the alkylation product *(3)* by treatment of the latter with gaseous HCl in THF at room temperature[2].



Procedure:

A mixture of *(2)*[1] (0.05 mol), alkyl bromide (0.075—0.1 mol), toluene (30 ml), 50% aqueous solution of NaOH (25 ml), and tetra-*n*-butylammonium hydrogen sulfate (0.85 g, 5 mol%) was refluxed with vigorous stirring for 4 h. Toluene (50 ml) was then added, the organic layer separated, washed with water (20 ml), dried, and evaporated *in vacuo* to give crude *(3)* as an oil. For the degradation a solution of crude *(3)* (2.0 g) in THF (10 ml) was saturated with gaseous HCl and set aside at room temperature for 12 h. Solvent was then evaporated, the residue diluted with ether (15 ml), and refrigerated. The precipitated crystals of *(4)* were filtered off, washed with ether, and dried over P_2O_5.

Received: November 26, 1976 [Z 611 IE]
German version: Angew. Chem. *89*, 109 (1977)

CAS Registry numbers:
(1a): 75-04-7 / *(1f)*: 62-53-3 / *(1h)*: 100-46-9 / *(1j)*: 108-91-8 / *(2a)*: 1946-09-4 / *(2f)*: 1445-38-1 / *(2h)*: 53640-96-3 / *(2j)*: 32405-88-2 / *(3a)*: 53279-98-4 / *(3b)*: 3167-69-9 / *(3c)*: 61278-88-4 / *(3d)*: 61278-89-5 / *(3e)*: 61278-90-8 / *(3f)*: 25626-89-5 / *(3g)*: 61278-91-9 / *(3h)*: 61278-92-0 / *(3i)*: 61278-93-1 / *(3j)*: 61278-94-2 / *(3k)*: 61278-95-3 / *(4a)*: 624-60-2 / *(4b)*: 660-68-4 / *(4c)*: 36550-63-7 / *(4d)*: 61278-96-4 / *(4e)*: 61278-97-5 / *(4f)*: 4348-19-0 / *(4g)*: 2492-82-2 / *(4h)*: 18618-49-0 / *(4i)*: 23530-82-7 / *(4j)*: 61278-98-6 / *(4k)*: 61278-99-7 / diethyl phosphonate: 762-04-9 / methyl iodide: 74-88-4 / ethyl bromide: 74-96-4 / propyl bromide: 106-94-5 / butyl bromide: 109-65-9 / allyl bromide: 106-95-6

[1] *A. Zwierzak*, Synthesis *1975*, 507.
[2] *A. Zwierzak* and *K. Osowska*, Angew. Chem. *88*, 302 (1976); Angew. Chem. Int. Ed. Engl. *15*, 302 (1976).
[3] *O. Wallach*, Justus Liebigs Ann. Chem. *214*, 275 (1882).
[4] *K. N. Campbell, A. H. Sommers*, and *B. K. Campbell*, J. Am. Chem. Soc. *66*, 82 (1944).

Table 1. Yields and properties of compounds *(3)* and *(4)*. All yields are given for crude compounds. Crude compounds *(3)* were chromatographically pure after drying at 60°C/0.1 torr. Their ^{31}P-NMR spectra were compatible with the given structures.

	R^1	R^2	Yield [%]	*(3)* ^{31}P-NMR δ [ppm] against H_3PO_4	Yield [%]	*(4)* M.p. [°C] [d] [Lit.-m.p.]	Ref.
a	C_2H_5	CH_3	85 [a]	−10.1	87	[f]	
b	C_2H_5	C_2H_5	85 [b]	−10.0	94	223—224 (215–217)	[3]
c	C_2H_5	*n*-C_3H_7	67 [c]	−10.25	91	226—227 (223—224)	[4]
d	C_2H_5	*n*-C_4H_9	70 [c]	−10.3	88	195.5—196 (197)	[4]
e	C_2H_5	CH_2=CH−CH_2	93 [c]	− 9.75	90	180.5—181.5	
f	C_6H_5	C_2H_5	97 [b]	− 5.5	91	177.5 (176)	[5]
g	C_6H_5	*n*-C_4H_9	98.5 [c]	− 6.25	85	114 (114)	[6]
h	C_6H_5−CH_2	*n*-C_4H_9	97.5 [c]	−10.25	99.5	242 (242)	[7]
i	C_6H_5−CH_2	CH_2=CH−CH_2	85.5 [c]	− 9.75	97	[f]	
j	Cyclo-C_6H_{11}	C_2H_5 [e]	67 [b]	− 9.6	81.5	181—182 (182)	[8]
k	Cyclo-C_6H_{11}	*n*-C_4H_9 [e]	35 [c]	−10.25	83	290 (290)	[9]

[a] 2 mols CH_3I per mol of *(2)*.
[b] 2 mols alkyl bromide per mol of *(2)*.
[c] 1.5 mols of alkyl bromide per mol of *(2)*.
[d] Crude product dried *in vacuo* over P_2O_5.
[e] 10 Mol-% of catalyst, reaction time 6 h.
[f] Strongly hygroscopic. Structure confirmed by elemental analysis and ^{1}H-NMR spectrum.

[*] Prof. Dr. A. Zwierzak [+] and Dipl.-Chem. J. Brylikowska-Piotrowicz
Institute of Organic Chemistry, Technical University (Politechnika)
Zwirki 36, PL-90-924 Lodz 40 (Poland)
[+] Author to whom correspondence should be addressed.

[**] Organophosphorus Esters, Part 12. – Part 11: *A. Zwierzak* and *A. Sulewska*, Synthesis *1976*, 835.

[5] *C. A. Bischoff*, Ber. Dtsch. Chem. Ges. *30*, 3178 (1897).
[6] *J. V. Braun* and *R. Murjahn*, Ber. Dtsch. Chem. Ges. *59*, 1202 (1926).
[7] *A. R. Surrey* and *M. K. Rukwid*, J. Am. Chem. Soc. *77*, 3798 (1955).
[8] *A. N. Kost, A. P. Terent'ev*, and *G. A. Shvekhgeimer*, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk *1951*, 150.
[9] *A. Skita* and *G. Pfeil*, Justus Liebigs Ann. Chem. *485*, 152 (1931).

Isolation and Vibrational Spectra of Bond-Isomeric Hexakis(thiocyanato-isothiocyanato) Complexes of Ruthenium(III) and Osmium(III)

By *Hans-Joachim Schwerdtfeger* and *Wilhelm Preetz*[*]

Since the first preparation of $(TBA)_3[Ru(NCS)_6]$ and $(TBA)_3[Os(NCS)_6]$ (TBA^+ = tetrabutylammonium) it was doubtful whether the ambidentate SCN^- group is bonded as a "soft" ligand *via* S (thiocyanato) or as a "hard" ligand *via* N (isothiocyanato) to the trivalent central ion[1, 2]. IR spectra are compatible with both possibilities, and exchange reactions with $S^{14}CN^-$ yield evidence supporting both *N*-bonded and *S*-bonded groups[3]. Using high voltage electrophoresis[4] we have now been able to show unequivocally that both products are actually mixtures consisting of at least four or three, respectively, bond isomers of the type

$(TBA)_3[Ru(NCS)_n(SCN)_{6-n}]$, $n = 1, 2, 3, 4$

and

$(TBA)_3[Os(NCS)_n(SCN)_{6-n}]$, $n = 2, 3, 4$

Since the rate of migration of the complex anions in an electric field increases stepwise by 5—10% with increasing *n*, sharply separated zones of different colors are obtained. After elution the stable TBA salts are precipitated. They give distinctly different UV, VIS, IR, and Raman spectra, but identical analyses. They are therefore the first bond isomers to be isolated which have exclusively *N*- or *S*-bonded SCN ligands. All the isomers previously described contain other ligands in addition to one or two SCN groups[3]. Equilibration between several hexakis(thiocyanato-isothiocyanato) complexes shows that Ru^{III} and Os^{III} are borderline cases between hard and soft acids, and the kind of bonding of the ligand is therefore largely adopted at random.

In accord with data reported in the literature[5], the assignment of the individual species is based mainly upon the intensity ratios of the $\nu_{CS(N)}$, $\nu_{CS(S)}$, δ_{NCS}, δ_{SCN}, ν_{M-N}, and ν_{M-S} vibrations (Table 1). Interpretation of the vibrational spectra is difficult because the complexes having $n = 2, 3, 4$ are presumably mixtures of the two stereoisomeric forms.

Procedure

$(TBA)_3[Ru(NCS)_n(SCN)_{6-n}]$, $n = 1, 2, 3, 4$
$(TBA)_3[Os(NCS)_n(SCN)_{6-n}]$, $n = 2, 3, 4$:

$K_2[RuCl_6]$ (1 g) or $K_2[RuBr_5(OH)]$ (1 g) and KSCN (3 g) are dissolved in water (20 ml) and allowed to stand at room temperature for 4 d; $K_2[OsCl_6]$ (0.5 g) or $K_2[OsBr_6]$ (0.5 g) or $K_2[OsI_6]$ (0.5 g) and KSCN (6 g) are refluxed in water (30 ml) for 18 h. After centrifuging off the small amount of decomposition products formed in either case, the solutions are evaporated in a high vacuum at 0 °C. Extraction with ether/alcohol (1 : 1) furnishes, respectively, deep blue or orange solutions of the complex mixtures which contain only little KSCN. After removal of solvent in a rotary evaporator the residues are dissolved in a small volume of water and small portions subjected to high voltage electrophoresis[4]. The complexes eluted from the cut out zones with a small volume of ice-cold water can be isolated as voluminous precipitates with a few drops of 1 M (TBA)Br solution. The yields lie between 25 and 60 mg for each of the bond-isomeric complexes.

Received: November 8, 1976 [Z 606 IE]
German version: Angew. Chem. 89, 108 (1977)

CAS Registry numbers:
$(TBA)_3[Ru(NCS)_1(SCN)_5]$, 61202-48-0; $(TBA)_3[Ru(NCS)_2(SCN)_4]$, 61202-50-4; $(TBA)_3[Ru(NCS)_3(SCN)_3]$, 61247-56-1; $(TBA)_3[Ru(NCS)_4(SCN)_2]$, 61202-52-6; $(TBA)_3[Os(NCS)_2(SCN)_4]$, 61202-54-8; $(TBA)_3[Os(NCS)_3(SCN)_3]$, 61202-56-0; $(TBA)_3[Os(NCS)_4(SCN)_2]$, 61202-58-2

[1] *R. G. Pearson*, J. Am. Chem. Soc. *85*, 3533 (1963).
[2] *H.-H. Schmidtke* and *D. Garthoff*, Helv. Chim. Acta *50*, 1631 (1967); *R. A. Bailey, S. L. Kozak, T. W. Michelsen*, and *W. N. Mills*, Coord. Chem. Rev. *6*, 407 (1971).

Table 1. Colors, IR- [a] and Raman frequencies [b] in [cm^{-1}] of $(TBA)_3[Ru(NCS)_n(SCN)_{6-n}]$, $n = 1, 2, 3, 4$ and $(TBA)_3[Os(NCS)_n(SCN)_{6-n}]$, $n = 2, 3, 4$.

Complex	Color in soln.	ν_{CN}		$2\delta_{NCS}$	δ_{NCS}	δ_{SCN}	$\nu_{CS(N)}$		$\nu_{CS(S)}$		ν_{M-N}		ν_{M-S}	
		IR	Ra	Ra	Ra	Ra	IR	Ra	IR	Ra	IR	Ra	IR	Ra
Ru, $n=1$	blue-green	2110 vs	2118 m	948 w	475 m	431 w	817 w	825 m	698 vw	694 m	—	—	290 s, br	288 s, br
Ru, $n=2$	blue-violet	2110 vs	2127 s	951 w	476 s	429 w	818 w	841 sh 829 s	697 vw	696 m	312 w	309 sh	291 s 278 s 272 s	286 s, br
Ru, $n=3$	red-violet	2133 vs	2129 s	951 w	475 s	422 w	821 m	840 s 826 m	698 vw	693 m	317 m	302 m	298 s	284 s
Ru, $n=4$	red-violet	2128 vs	2145 vs 2118 s 2107 m	942 w	471 m	424 w	824 m	842 vs 826 sh	—	700 w	337 s 327 vs 309 m	318 w 302 w	—	275 s
Os, $n=2$	yellow-orange	2114 vs	2119 m 2102 m	957 w	478 m	432 w	828 m	842 s	—	697 w	277 m	319 w 293 w	263 s 260 s	263 s
Os, $n=3$	yellow-orange	2124 vs	2125 s 2099 s	952 m	477 s	428 w	830 m	851 s 838 vs	—	696 w	281 s	315 w 291 m	260 s	266 s 241 sh
Os, $n=4$	yellow	2132 vs 2117 vs	2130 s 2112 s 2091 s	954 m	476 s	427 w	829 s	853 vs 836 s	—	—	284 vs	315 m 281 s	256 w	265 s 243 m

[a] Pellet (*ca.* 7 mg complex in 2 g RbI) at 10 K, Beckman IR-9/11; [b] Pellet (1 mg complex in 50 mg KBr) at 77 K [6], Cary 82; $\nu_{CS(N)}$ = N-bound, $\nu_{CS(S)}$ ≈ S-bound, δ_{NCS} = N-bound, δ_{SCN} = S-bound.

[*] Prof. Dr. W. Preetz and Dipl.-Chem. H.-J. Schwerdtfeger
Institut für Anorganische Chemie der Universität
Olshausenstrasse 40—60, D-2300 Kiel (Germany)

[3] *S. Wajda* and *K. Rachlewicz*, Nukleonika *18*, 407 (1973); Proc. III. Int. Symp. Specific Interactions between Molecules or Ions, Karpacz 1976, p. 551.

[4] *W. Preetz*, Fortschr. Chem. Forsch. *11*, 375 (1969); *W. Preetz* and *H. Homborg*, Z. Anorg. Allg. Chem. *407*, 1 (1974).
[5] *J. Lewis, R. S. Nyholm*, and *P. W. Smith*, J. Chem. Soc. *1961*, 4590; *A. Turco* and *C. Pecile*, Nature *191*, 66 (1961); *D. Forster* and *D. M. L. Goodgame*, Inorg. Chem. *4*, 715 (1965); *A. Sabatini* and *I. Bertini*, *ibid. 4*, 959, 1665 (1965); *J. L. Burmeister* and *F. Basolo*, *ibid. 3*, 1587 (1964).
[6] *H. Homborg* and *W. Preetz*, Spectrochim. Acta *32 A*, 709 (1976).

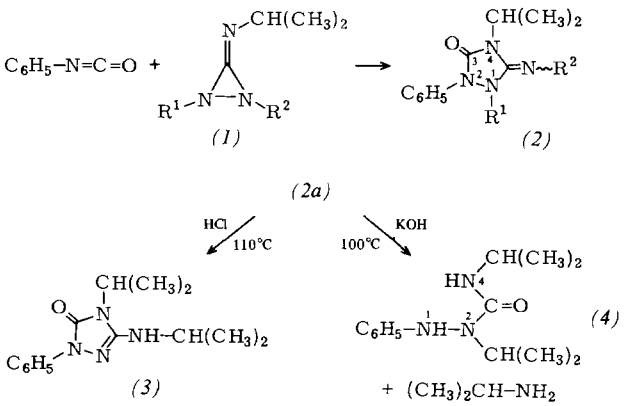
Cycloaddition of Phenyl Isocyanate to a Diaziridinimine[**]

By *Helmut Quast* and *Erwin Spiegel*[*]

Cycloadditions to hetero analogs of methylenecyclopropanes are steadily gaining in preparative and mechanistic importance. We now report the [3+2] cycloaddition of phenyl isocyanate to triisopropyldiaziridinimine *(1a)*[1].

Already at low temperature equimolar amounts of the two components react in ether to give a 1:1 adduct in 82% yield, which is shown by its spectra, degradation reactions, and independent synthesis from 1-anilino-1,2,3-triisopropylguanidine and phosgene to have the 1,2,4-triazolidine structure *(2a)*. The highly substituted triazolidine ring proved to be surprisingly stable. After refluxing in concentrated hydrochloric acid for 3d only the isopropyl group attached to C-1 had been lost. The triazolinone *(3)* isolated in 77% yield was obtained by an independent pathway from 1-anilino-2,3-diisopropylguanidine and phosgene. Only on prolonged heating of *(2a)* with KOH in water/methanol (1:1) in a sealed tube at 100°C does ring opening and hydrolysis occur to give isopropylamine (84% as the picrate) and 2,4-diisopropyl-1-phenylsemicarbazide *(4)* (yield 60%), which is readily accessible from 1-isopropyl-2-phenylhydrazine and isopropyl isocyanate.

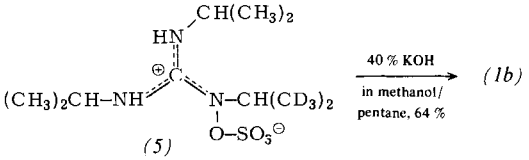
Like other guanidine derivatives[2] *(2a)* can exchange the imino group with an isocyanate. Heating of *(2a)* with phenyl isocyanate gives quantitative yields of isopropyl isocyanate and *(2d)*.



	R^1	R^2
(a)	$CH(CH_3)_2$	$CH(CH_3)_2$
(b)	$CH(\overset{*}{C}D_3)_2$ [a]	$CH(\overset{*}{C}D_3)_2$ [a]
(c)	$CH(\overset{*}{C}D_3)_2$ [a]	$CH(CH_3)_2$
(d)	$CH(CH_3)_2$	C_6H_5

[a] $CH(\overset{*}{C}D_3)_2$ corresponds to 50% deuterium labeling of the methyl groups.

In order to determine which N atoms are involved in the [3+2] cycloaddition of phenyl isocyanate *(1a)*, we synthesized the hydroxyguanidine-*O*-sulfonic acid *(5)* from [D_6]isopropylhydroxylamine-*O*-sulfonic acid and diisopropylcarbodiimide. In accord with the general diaziridinimine synthesis[1] the product of *(5)* was *(1b)*, in which only the two ring isopropyl groups were labeled (50% each).



^{1}H- and ^{13}C-NMR spectra of the adduct *(2)* formed from *(1b)* and phenyl isocyanate provided direct evidence that only two of the isopropyl groups were labeled, and thus ruled out mechanisms requiring symmetrization of the N atoms. However, which of the groups were labeled in the addition product could not be determined from the chemical shifts. On prolonged heating (2—3 weeks, 80°C) of the labeled adduct in an excess of isopropyl isocyanate one of the labeled isopropyl groups was exchanged in a reaction corresponding to that between *(2a)* and phenyl isocyanate. If both this product and the original adduct of *(1b)* and phenyl isocyanate are subjected to the degradation reactions described for *(2a)*, then unequivocal assignment of the structures *(2b)* and *(2c)* becomes possible.

Information about the course of hydrolysis of the triazolidines *(2)* could be obtained using *(2b)*. While *(2b)* remained completely unchanged after 10d at 80°C in [D_6]benzene or [D_4]methanol, the action of 2N KOH in methanol (3d, 90°C) led to exchange of the isopropyl group at N-4 and at the imino group, indicating reversible ring opening after addition of a nucleophile to C-3. The label of the iminoisopropyl group of *(2b)* is accordingly distributed evenly over the resulting isopropylamine and the isopropyl group at N-4 of the semicarbazide *(4)* on alkaline degradation.

1,2-Di-*tert*-butyldiaziridinone, which is related to the diaziridinimines, reacts in a completely different way with heterocumulenes[3]. The same is true of postulated ring-opened diaziridinimine equivalents[4]. The above cycloaddition of phenyl isocyanate can readily be applied to other diaziridinimines.

Procedure

Phenyl isocyanate (6.50 g, 54.6 mmol) is added at −78°C to *(1a)*[1] (10.0 g, 54.6 mmol) in anhydrous ether (15 ml). The mixture is allowed to warm to 20°C over a period of 15 h, the crystals filtered off under vacuum, and washed with pentane. Concentration of the mother liquor yields a second fraction of the same melting point. Yield: 13.5 g (82%) *(2a)* as colorless crystals of m.p. 89—90°C.

Received: November 11, 1976 [Z 603 IE]
German version: Angew. Chem. *89*, 112 (1977)

CAS Registry numbers:
(1a), 61193-67-7; *(1b)*, 61193-73-5; *(2a)*, 61193-68-8; *(2b)*, 61193-74-6; *(2d)*, 61193-69-9; *(3)*, 61193-70-2; *(4)*, 61193-71-3; *(5)*, 61193-72-4; phenyl isocyanate, 103-71-9; isopropylamine picrate, 61193-75-7; 1-isopropyl-2-phenylhydrazine, 5203-42-9; isopropyl isocyanate, 1795-48-8; [D_6]isopropylhydroxylamine-*O*-sulfonic acid, 61193-76-8; diisopropylcarbodiimide, 693-13-0

[*] Prof. Dr. H. Quast and Dipl.-Chem. E. Spiegel
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The results are taken from the projected thesis of *E. Spiegel*.

[1] *K.-H. Ross*, Dissertation, Universität Würzburg 1974; *H. Quast* and *K.-H. Ross*, to be published.
[2] *H. Ulrich*, Acc. Chem. Res. 2, 186 (1969).

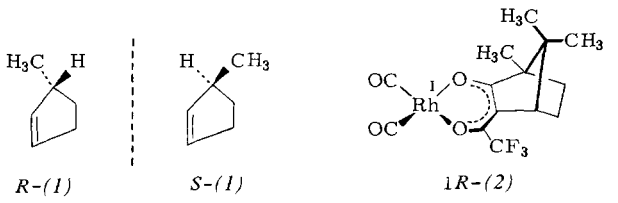
[3] *Y. Ohshiro, M. Komatsu, Y. Yamamoto, K. Takaki,* and *T. Agawa,* Chem. Lett. *1974,* 383; *C. A. Renner* and *F. D. Greene,* J. Org. Chem. *41,* 2813 (1976).
[4] *M. Komatsu, Y. Ohshiro, H. Hotta, M. Sato,* and *T. Agawa,* J. Org. Chem. *39,* 948 (1974).

Resolution of a Chiral Olefin by Complexation Chromatography on an Optically Active Rhodium(I) Complex[**]

By *Volker Schurig*[*]

Chromatographic resolution of racemic substrates on optically active stationary phases[1] is an elegant method for the absolute determination of chirooptical properties such as optical purity and optical rotation. While the resolution of racemic amino acid derivatives on optically active dipeptides[1] or host crown ethers[2] is attributed to diastereomeric interactions between hydrogen bonds and dipoles, that of the inherently asymmetric helicenes on optically active aromatic acceptor molecules[3] is due to selective diastereomeric charge-transfer complexation.

We have now accomplished the first gas chromatographic resolution of enantiomers on optically active metal complexes, postulated by *Gil-Av*[4], in an olefin/rhodium(I) system which commands interest in connection with asymmetric homogeneous catalysis.



R-(1) *S-(1)* *1R-(2)*

A high-resolution capillary column (200 m) was loaded with optically active dicarbonylrhodium(I) 3-trifluoroacetyl-(1*R*)-camphorate[6], *1R-(2)*, in squalane solution which is highly selective for alkenes[5a] and isotopically labeled ethylenes[5b]. Using this column, chiral 3-methylcyclopentene *(1)* was resolved quantitatively into its antipodes within 3 h at 22 °C (Fig. 1).

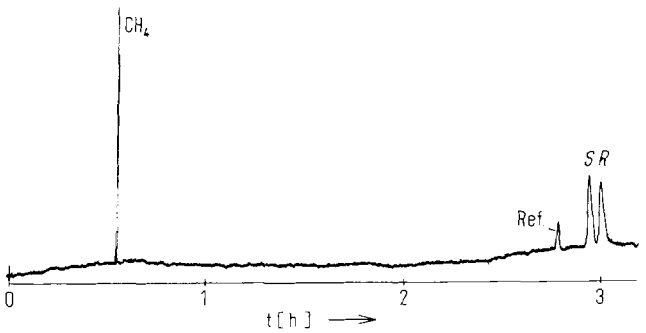


Fig. 1. Resolution of *(1)* by complexation gas chromatography on *1R-(2)* in squalane (0.15 m) at 22 °C; $\alpha = 1.025$, peak area ratio 1 : 1. For chromatographic conditions see ref. [5b]. Reference standard: methylcyclohexane [$r_R = 1.095$, $r_S = 1.07$, $r_{o(R,S)} = 0.26$ (pure squalane)].

[*] Univ.-Doz. Dr. V. Schurig
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen (Germany)

[**] This work, which was partly carried out at the Department of Chemistry, Weizmann Institute of Science, Rehovoth (Israel), was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Resolution is attributed to differences in π-complexation strength K between the enantiomers *R-(1)* and *S-(1)* with the rhodium complex *1R-(2)*. The difference in free energy of association $\Delta_{R,S}(\Delta G^0)$ calculated from the relation $Km_{Rh} = r/r_0 - 1$[5a] is −19 cal/mol (295 K).

The assignment of the antipodes (cf. Fig. 1) was deduced by preparation of enriched *R*-(+)-3-methylcyclopentene, *R-(1)* by acid dehydration of *R-cis,trans*-3-methylcyclopentanol which is accessible from *R*-3-methylcyclopentanone by reduction with $LiAlH_4$. Complexation chromatography of the olefin mixture permitted resolution of the positional isomers (1-methylcyclopentene, 15 %; 4-methylcyclopentene, 40 %) as well as determination of the optical purity of *R-(1)* (69 %)[7].

Unequivocal proof of the successful resolution of *(1)* is provided by use of the rhodium complex of opposite configuration, *1S-(2)*. Peak inversion was then observed for the olefin fraction *(1)* enriched in the *R* antipode. Moreover, peak coalescence was seen with the racemic complex *1S,1R-(2)*[8].

In principle the method described should be applicable to all conceivable ligand-metal interactions.

Received: December 6, 1976 [Z 619 IE]
German version: Angew. Chem. *89,* *113* (1977)

CAS Registry numbers:
R-(1), 39750-38-4; *S-(1)*, 39750-39-5; *1R-(2)*, 36654-16-7

[1] *E. Gil-Av, B. Feibush, R. Charles-Sigler* in *A. B. Littlewood:* Gas Chromatography 1966. Institute of Petroleum, London 1967, p. 227; and subsequent publications.
[2] *G. Dotsevi, Y. Sogah, D. J. Cram,* J. Amer. Chem. Soc. *97,* 1259 (1975); and subsequent publications.
[3] *F. Mikeš, G. Boshart, E. Gil-Av,* J. Chem. Soc. Chem. Commun. *1976,* 99.
[4] *E. Gil-Av,* personal communication.
[5] a) *V. Schurig, E. Gil-Av,* Chem. Commun. *1971,* 650; *E. Gil-Av, V. Schurig,* Anal. Chem. *43,* 2030 (1971); b) *V. Schurig,* Angew. Chem. *88,* 336 (1976); Angew. Chem. Int. Ed. Engl. *15,* 304 (1976).
[6] *V. Schurig,* Inorg. Chem. *11,* 736 (1972).
[7] Preliminary results indicate that the rotation given by *M. Mousseron et al.* for *R-(1)* (Bull. Soc. Chim. Fr. *1946,* 222), *i.e.* $[\alpha]_{597}$ +77.9°, is too low.
[8] Prepared according to ref. [6]. In contrast to *1R-(2)* and *1S-(2)* (yellow crystals) the racemic complex *1R, 1S-(2)* is dark red in the solid state. We call this interesting phenomenon "chirodichroism".

Through-Bond Interaction between Two Mutually Perpendicular π Systems—A New Possibility of Conjugation[**]

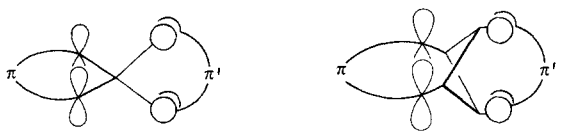
By *Peter Bischof, Rolf Gleiter,* and *Rudolf Haider*[*]

The physical and chemical properties of classically conjugated π systems can be explained by the concept of direct π-π interaction. In cases of homo- and spiro-conjugation, on the other hand, the interacting systems are separated by more than one C—C bond length. This leads to a smaller overlap integral and thus to a smaller interaction.

We shall now demonstrate that the interaction between two mutually perpendicular π systems linked by a spiro center *(1a)* becomes considerably stronger on replacing the spiro center by a four-membered ring *(1b)*. The spiro interaction between the two π systems is then replaced by a through-bond interaction[1]. The Walsh orbitals[2] of the four-membered ring act as a "relay".

[*] Prof. Dr. R. Gleiter, Dr. P. Bischof, and Dipl.-Ing. R. Haider
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)

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



(1a) (1b)

On comparing (1a) ($\pi=\pi'$, D_{2d}) with (1b) ($\pi=\pi'$, D_{2d}) we expect the following consequences[3] (see Table 1[4] and Fig. 1):

1) The splitting between the a_2 and b_1 orbitals should become larger.

2) The sequence of the a_2 and b_1 orbitals should be reversed.

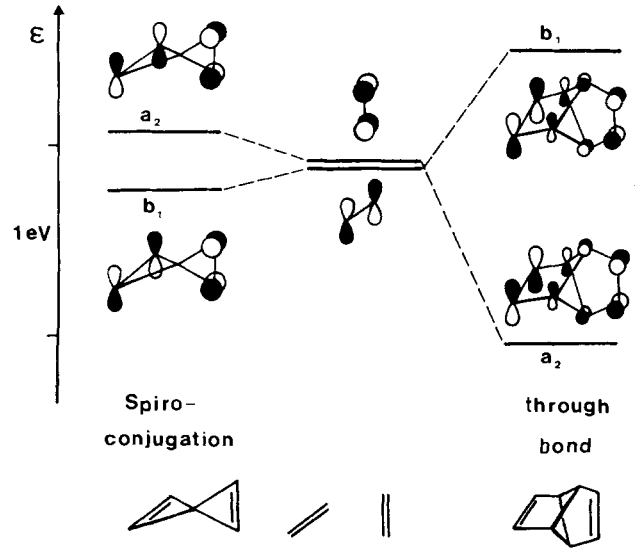


Fig. 1. Interaction diagram for two mutually perpendicular π* orbitals in spiropentadiene (left) and tricyclo[3.3.0.0^{2,6}]octa-3,7-diene (right). The π orbitals remain degenerate and are not shown.

We have calculated the orbital energy differences for the spiro compounds (2') to (6') and for the analogs (2) to

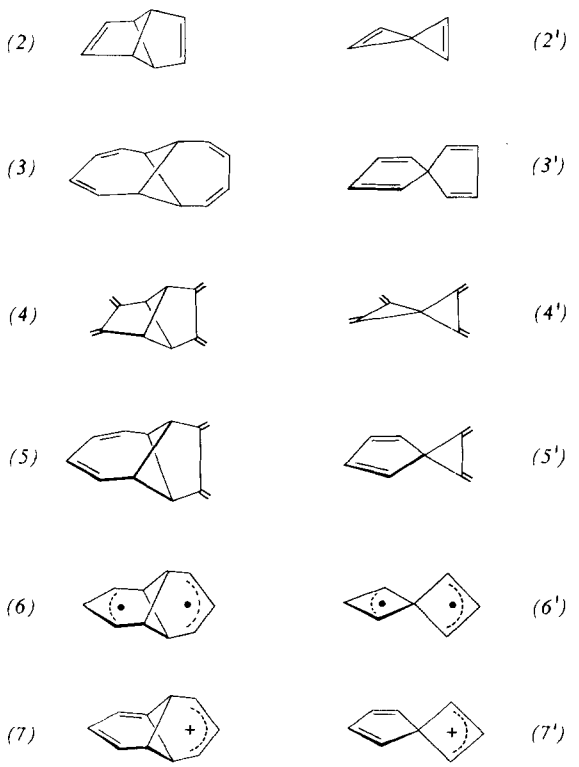
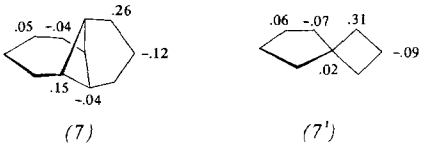


Table 1. Orbital energy differences, calculated by the MINDO/3 [5] and EH (extended Hückel) method [6].

Compound and symmetry	Energy difference of orbitals	Calculated by EH	Calculated by MINDO/3
(2), D_{2d}	$2b_1-1a_2$	1.59	1.06
(2'), D_{2d}	$1b_1-1a_2$	−0.32	−0.14
(3), D_{2d}	$2b_1-1a_2$	1.00	1.24
	$3b_1-2a_2$	0.81	0.23
(3'), D_{2d}	$1b_1-1a_2$	−0.55	−0.63
	$2b_1-1a_2$	−0.60	−0.25
(4), D_{2d}	$2b_1-1a_2$	0.45	0.77
	$3b_1-1a_2$	1.44	0.90
(4'), D_{2d}	$1b_1-1a_2$	−0.08	−0.08
	$2b_2-2a_2$	−0.31	−0.10
(5), C_{2v}	$3a_2-2a_2$	0.69	1.08
	$5a_2-4a_2$	1.07	0.76
(5'), C_{2v}	$2a_2-1a_2$	0.46	0.73
	$4a_2-3a_2$	0.84	0.24
(6), D_{2d}	$2b_1-1a_2$	1.71	6.23
(6'), D_{2d}	$1b_1-1a_2$	−0.66	−5.33

(6) with a four-membered ring. Comparison of the values in Table 1 confirms our hypothesis.

In contrast to the examples (2) to (5) we expect for (6) and (7) a stabilization of the ground state by the through bond interaction. This stabilization can be seen in the case of (6) from the large HOMO-LUMO splitting (see table). It is considerably larger than in (6'). In the case of (7) the distribution of the positive charge over the whole frame, as in (7') (see below), can be taken as an indication of its stabilization.



(7) (7')

Of the compounds listed in Table 1, (2)[7] and a tetramethyl derivative of (4)[8] are known. The unusual electronic spectrum of (2) suggests a strong interaction between the double bond and the four-membered ring[9]. Further confirmation of our hypothesis comes from recent photoelectron spectroscopic studies[10].

Received: November 1, 1976;
revised: November 29, 1976 [Z 612 IE]
German version: Angew. Chem. 89, 122 (1977)

CAS Registry numbers:
(2), 24079-76-3; (2'), 1727-65-7; (3), 61278-83-9; (3'), 14867-83-5; (4), 61278-84-0; (4'), 61278-85-1; (5), 61278-86-2; (5'), 61278-87-3; (6), 61348-41-2; (6'), 61348-40-1

[1] R. Hoffmann, A. Imamura, and W. J. Hehre, J. Am. Chem. Soc. 90, 1499 (1968); R. Gleiter, Angew. Chem. 86, 770 (1974); Angew. Chem. Int. Ed. Engl. 13, 696 (1974).

[2] R. Hoffmann and R. B. Davidson, J. Am. Chem. Soc. 93, 5699 (1971) and references cited therein; L. Salem and J. S. Wright, J. Am. Chem. Soc. 91, 5947 (1969).

[3] E. Heilbronner and H. Bock: Das HMO-Modell und seine Anwendung. Verlag Chemie, Weinheim 1970; M. J. S. Dewar: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[4] The geometry of the systems listed was calculated by the MINDO/3 method [5] (minimization of energy as a function of the bond lengths and bond angles). C_{2v} symmetry was assumed for (7) and (7'), otherwise D_{2d} symmetry.

[5] R. C. Bingham, M. J. S. Dewar, and D. H. Lo, J. Am. Chem. Soc. 97, 1285 (1975).

[6] R. Hoffmann, J. Chem. Phys. 39, 1397 (1963); R. Hoffmann and W. N. Lipscomb, J. Chem. Phys. 36, 2179, 3489 (1962); 37, 2872 (1962).

[7] *J. Meinwald* and *H. Tsuruta*, J. Am. Chem. Soc. *91*, 5877 (1969); *92*, 2579 (1970); *H. E. Zimmerman, J. D. Robbins*, and *J. Schantl*, J. Am. Chem. Soc. *91*, 5878 (1969).
[8] *W. T. Borden* and *A. Gold*, J. Am. Chem. Soc. *93*, 3830 (1971).
[9] *R. Gleiter* and *T. Kobayashi*, Helv. Chim. Acta *54*, 1081 (1973).
[10] *P. Bischof, R. Gleiter, M. J. Kukla*, and *L. A. Paquette*, J. Electron Spectrosc. Relat. Phenom. *4*, 177 (1974); *R. Gleiter, P. Bischof, W. E. Volz*, and *L. A. Paquette*, J. Am. Chem. Soc. *99*, 8 (1977).

Detection of S_6 and S_7 in Molten Cyclooctasulfur[1]

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

Despite numerous experimental and theoretical studies the molecular composition of molten cyclooctasulfur remains controversial. Some authors assume that not only S_8-rings (S_8^R) and (above 160°C) larger chain- or ring-molecules (S_μ) but also S_8-chains (S_8^C) or "complexes" between S_8^R and S_8^C ($S_8^C \cdot nS_8^R$) exist, others postulate a mixture of ring molecules S_6, S_7,...S_{30} or S_9, S_{10},...*etc.* Furthermore, S_3- and S_4-molecules of unknown structure are considered as being responsible for the change in color from yellow to dark red-brown observed on increasing the temperature.

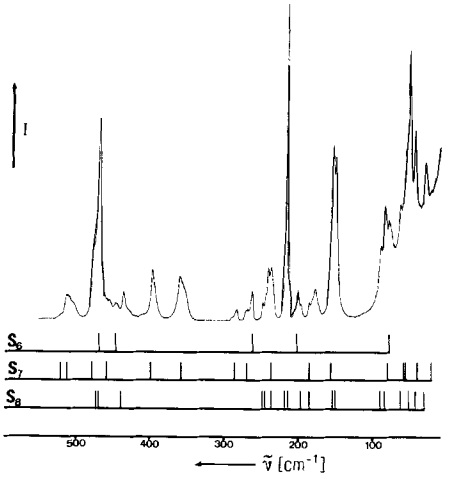
Since the IR and Raman spectra of S_6[2], S_7[3], S_8[4], S_{10}[3b], and S_{12}[5] rings and of the chain shaped polysulfide ions S_n^{2-} ($n=3$ to 8)[6] are known, all conditions are satisfied for qualitative analysis of the sulfur melt by vibrational spectroscopy.

We have examined the spectra of melts of ultrapure sulfur (S_8^R), which had been heated under nitrogen for 5 h at a constant temperature between 120–160°C in an aluminum vessel and then allowed to flow through a small hole in the bottom of the vessel into stirred liquid nitrogen and quenched within 1 to 2 s. These samples (A), which were handled only with cooling (< −50°C) and in the absence of light, were yellow powders having a maximum particle size of 1 mm at −196°C. Extraction of these samples at 25°C with CS_2 (intense yellow solution B) or *n*-pentane or *n*-hexane (light yellow solution C) afforded "π-sulfur solutions"[8]. The largest portion of S_8^R could be crystallized from B at −78°C (solution E remained). Freezing of C at −78°C or treatment of E with hexane until the onset of clouding at 25°C and cooling to −78°C afforded honey-like sulfur (D). Raman spectra of A, D, and E were recorded at −70 to −100°C with krypton laser excitation (647.1 nm), which does not destroy even unstable sulfur rings under these conditions. IR spectra (200 to 700 cm^{-1}) of D and E were recorded at 25°C[9].

Apart from S_8^R, S_6^R and S_7^R were detectable by the following IR absorptions or Raman lines:

S_6 IR: 313 (a_{2u}); Raman: 265 (a_{1g}), 203 (e_g) cm^{-1}
S_7 IR: 516, 481, 400, 270; Raman: 518, 481, 402, 360, 239 cm^{-1}

There is no interference of these frequencies by coincidences with bands due to S_8^R, a large excess of which is often present. With low S_8 contents, further S_6- and S_7-bands were found. Agreement of the wave numbers, of the relative intensities, and of the band shapes were taken into consideration on assignment of the spectra by comparison with those of the pure compounds. As Figure 1 shows, even Raman bands lying very close to each other can be resolved quite well at low temperature and small spectral slit widths (1.5 cm^{-1}), thus enabling detection of S_6 with its line-deficient spectrum.



S_6 and S_7 were detectable in all samples. In A their content referred to S_8 at a melt temperature of 160°C was greater than at 120°C and was estimated to be a few percent, in agreement with the value of 5.5% determined for the π-sulfur content from the melting point depression[8a].

Sulfur D, prepared by treatment of E with hexane, contained about equal amounts of S_7 and S_8 along with smaller amounts of S_6, as was shown by comparison with spectra of test mixtures from S_7 and S_8.

S_{10} and S_{12} were not detected in A (the region from 110 to 140 cm^{-1}, in which both exhibit stronger Raman lines, was free from any lines). The content of these rings in the melt at 120 to 160°C is thus estimated to be <0.2% in each case.

Several spectra contained IR absorptions at 265 and 250 cm^{-1} and Raman lines at 460, 188 and 117 cm^{-1} which are assigned to S_{12} and $S_{12} \cdot 2CS_2$, respectively. Since the average molecular mass of π-sulfur corresponds to *ca.* 8 atoms[8a], at least one larger ring must be present besides S_6, S_7, and S_8. There was no indication of S_8^C being present, which ought to show Raman active vibrations at 300 to 330 cm^{-1}[6] independent of the conformation.

According to these results numerous experimental and theoretical investigations on the problem of the composition of sulfur melts must be newly interpreted, since there is no more need for the assumption of S_8^C or $S_8^C \cdot nS_8^R$, and the concentration of small rings S_n ($n \neq 8$) is in no way negligibly small, as has been assumed on many occasions.

Received: November 22, 1976 [Z 613 IE]
revised: December 1, 1976
German version: Angew. Chem. *87*, 114 (1977)

CAS Registry numbers:
S_6, 13798-23-7; S_7, 21459-04-1

[*] Prof. Dr. R. Steudel, H.-J. Mäusle
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[1] Part 46 of Sulfur Compounds. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 45: *R. Steudel, T. Sandow*, Angew. Chem. *88*, 854 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976).
[2] *J. Berkowitz, W. A. Chupka, E. Bromels, R. L. Belford*, J. Chem. Phys. *47*, 4320 (1967); *L. A. Nimon, V. D. Neff, R. E. Cantley, R. O. Buttlar*, J. Mol. Spectrosc. *22*, 105 (1967); *26*, 175 (1968).
[3] a) *M. Gardner, A. Rogstad*, J. Chem. Soc. Dalton Trans. *1973*, 599; b) *R. Steudel, F. Schuster*, unpublished (*F. Schuster*, Diplomarbeit, Technische Universität Berlin 1976).

[4] *D. W. Scott, J. M. McCullough, F. H. Kruse*, J. Mol. Spectrosc. *13*, 313 (1964); *G. W. Chantry, A. Anderson, H. A. Gebbie*, Spectrochim. Acta *20*, 1223 (1964).
[5] *R. Steudel, M. Rebsch*, J. Mol. Spectrosc. *51*, 189 (1974); *R. Steudel, D. F. Eggers*, Spectrochim. Acta *31A*, 879 (1975).
[6] *R. Steudel*, J. Phys. Chem. *80*, 1516 (1976); *R. Steudel, F. Schuster*, Spectrochim. Acta, in press; *H. H. Eysel, G. Wieghardt, H. Kleinschmager, G. Weddigen*, Z. Naturforsch. *31b*, 415 (1976); *G. J. Janz et al.*, Inorg. Chem. *15*, 1751, 1755, 1759 (1976).
[7] The furnace was similar to that used by *P. W. Schenk* [Z. Anorg. Allg. Chem. *280*, 1 (1955)] and by *J. Ch. Koh* and *W. Klement* [J. Phys. Chem. *74*, 4280 (1970)].
[8] a) *P. W. Schenk, U. Thümmler*, Z. Elektrochem. *63*, 1002 (1959); Z. Anorg. Allg. Chem. *315*, 271 (1962); b) *A. H. W. Aten*, Z. Phys. Chem. *83*, 442 (1913); *86*, 1 (1914); *88*, 321 (1914).
[9] Perkin-Elmer IR spectrometer 325; Raman spectrometer Cary 82 with Varian triple monochromator.

Photochromism of Rhodamine Derivatives[**]

By *Karl-Heinz Knauer* and *Rolf Gleiter*[*]

The use of photochromic compounds, *e.g.* as photoswitches or in data processing technology depends upon the reversibility and magnitude of the photochromic effect[1].

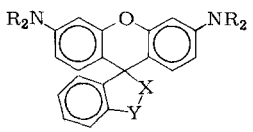
Although triarylmethyl cyanides ("leukonitriles") display a marked photochromic effect[2], the photoinduced reaction is not strictly reversible because the cyanide ion can be replaced by solvent.

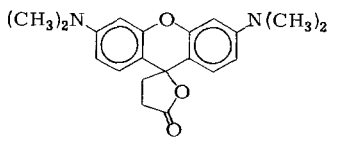
$$R_3CCN \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} R_3C^{\oplus} + CN^{\ominus} \qquad (1)$$

R = Aryl

This serious drawback is absent for geometrical reasons in the case of triarylmethane derivatives which have a spiro-type leuko form.

Flash photolysis of the colorless solutions of such rhodamine derivatives *(1a)* to *(4a)*[3] [*(1a)* in CH_3CN; $\lambda_{max}=314$ ($\log\varepsilon=4.11$), 274 (4.52), 239 (4.74) nm] in protic and aprotic solvents between 10 and 60°C reveals a transient having a maximum at $\lambda=558$ nm for *(1a)* and *(2a)*, 545 nm for *(3a)*, and 542 nm for *(4a)*.





(4a)

	R	X	Y
(1a)	C_2H_5	NC_6H_5	CO
(2a)	C_2H_5	*p*-NC_6H_4Br	CO
(3a)	CH_3	NH	SO_2

The absorption spectrum of the photoproduct of *(1a)* is identical with that of the corresponding protonated zwitterion *(1b)* obtained in acidic solution.

The activation parameters (Table 1) for the thermal reverse reaction of the photoproduct of *(1a)* are very similar to those of Malachite Green[4].

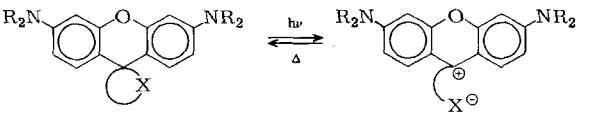
[*] Prof. Dr. R. Gleiter, Dr. K.-H. Knauer
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)

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

Table 1. Kinetic data for the thermal reverse reaction *(1b)*→*(1a)*.

Solvent	$k_{25°C}$ [s^{-1}]	$E^{\neq}$ [kcal·mol^{-1}]	$\Delta G^{\neq}_{25°C}$ [kcal·mol^{-1}]	$\Delta S^{\neq}_{25°C}$ [cal·mol^{-1} K^{-1}]
Ethanol	1.01	10.35	16.07	−21.16
Acetonitrile	$2{,}33\cdot10^{-3}$	13.89	21.02	−25.97

On the basis of these findings we deduced the following reaction sequence:



(1a)-(4a) *(1b)-(4b)* (2)

The half-reaction times for the thermal reverse reaction are listed in Table 2.

Table 2. Half-reaction times for the thermal reverse reaction *(2)*.

Compound	Solvent	T[°C]	$\tau_{1/2}$ [s]
(1b)	Acetonitrile	25	297
(1b)	Ethanol	25	0.067
(2b)	Acetonitrile	29	317
(3b)	Acetonitrile	25	1.7
(4b)	Ethanol	25	5.6

The relative quantum yield of *(1a)*→*(1b)* is independent of the oxygen concentration, but dependent upon the solvent: $\Phi_{rel}=1.0$ (dioxane), 0.88 (*n*-butyronitrile), 0.47 (acetonitrile), and 0.06 (ethanol). A similar solvent dependence is found for the fluorescence quantum yield of *(1a)*. In contrast, the phosphorescence quantum yield is independent of the solvent.

Hence we conclude that the photoreaction *(2)* proceeds from the singlet state (S_1). In the S_1 state the C—X bond is considerably weaker than in the S_0 or T_1 state[5].

Received: December 10, 1976 [Z 625 IE]
German version: Angew. Chem. *89*, 116 (1977)

[1] *R. C. Bertelson* in *G. H. Brown*: Techniques of Chemistry, Vol. III, Photochromism. Wiley-Interscience, New York 1971.
[2] *A. H. Sporer*, Trans. Faraday Soc. *57*, 983 (1961); *M. L. Herz*, J. Am. Chem. Soc. *97*, 6777 (1975).
[3] Farbwerke Hoechst AG, DRP 80153 (1893); *S. Dutt, J. F. Thorpe*, J. Chem. Soc. *125*, 2524 (1924).
[4] *M. L. Herz, D. Feldman, E. M. Healy*, J. Org. Chem. *41*, 221 (1976).
[5] *G. Porter* in *S. Claesson*: Fast Reactions and Primary Processes in Chemical Kinetics. Almqvist and Wiksell, Stockholm 1967.

Synthesis of Cyclodepsipeptides by Cyclooligomerization[**]

By *Manfred Rothe* and *Wolfgang Kreiss*[*]

A common feature of numerous biologically active cyclodepsipeptides is their repeating structure. Cyclooligomerization

[*] Prof. Dr. M. Rothe, Dr. W. Kreiss
Lehrstuhl Organische Chemie II der Universität
Oberer Eselsberg, D-7900 Ulm (Germany)

[**] Cyclic Peptides, Part 23. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF, Ludwigshafen.—Part 22: *M. Rothe, D. Mühlhausen*, Angew. Chem. *88*, 338 (1976); Angew. Chem. Int. Ed. Engl. *15*, 307 (1976).

of the basic repeating unit[1, 2] appears promising as a synthetic approach for these compounds since the laborious preparation of open chain precursors is then limited to that of subunits.

We have investigated the solvent-dependent formation of cyclic homologs of valinomycin. Cyclooligomerization was accomplished by the phosphite method[3].

Valinomycin partial sequences H(Val-D-Hyv-D-Val-Lac)$_n$OH[4], $n=1$, 2, and the complete sequence with $n=3$ served as linear subunits. The pronounced lipophilic character of these precursors permitted use of apolar solvents as well as the usual reaction medium diethyl phosphite. In the case of the tetradepsipeptide ($n=1$) cyclooligomerization was detectable up to the heptamer ($m=7$,84 ring atoms) by gel chromatography. The octadepsipeptide ($n=2$) gave di- and trimerization products ($m=4$ and 6, with 48 and 72 ring atoms, respectively) together with cyclic monomer, while the dodecadepsipeptide ($n=3$) yielded only the cyclic monomer (valinomycin, $m=3$). A significant influence of the solvent polarity was apparent in the relative amounts of the cyclic homologs obtained (Table 1).

Table 1. Solvent-dependent formation of cyclooligomers. DEP = diethyl phosphite, Tol = toluene.

H(Val-D-Hyv-D-Val-Lac)$_n$OH			cyclo(Val-D-Hyv-D-Val-Lac)$_m$ Yield [%]				
n	Solvent	c [mol/l]	$m=1$	2	3	4	6
1	DEP	0.05	48	14	2	—	—
1	Tol	0.05	4	13	7	2	—
2	DEP	0.01	—	30	—	4	1
2	Tol	0.01	—	23	—	10	2
3	DEP	0.001	—	—	24	—	—
3	Tol	0.001	—	—	56	—	—

Both partial sequences ($n=1$, 2) yielded greater amounts of the macrocyclic oligomers in the apolar reaction medium toluene. The large drop in intramolecular ring closure for the tetradepsipeptide in toluene is particularly striking. Possible explanations are loss of chain mobility of the linear monomer as a result of more extensive solvation as well as enhanced association. Association of the linear octa- and tetradepsipeptides in toluene could actually be detected by vapor pressure osmometry. However, it could not be correlated directly with the occurrence of cyclic oligomers.

The series of oligomeric cyclic peptides obtained could readily be interpreted as the result of linear polycondensations, which are concentration dependent. In this case cyclization is to be regarded as competing with chain growth.

Our attempts to oligomerize the aminoacyl hydroxy acids H-MeVal-D-Hyv-OH and H-D-Val-Hyv-OH to give higher-molecular members of the enniatin series led exclusively to cyclic monomers. The reason is to be seen in the marked formation tendency of the six-membered morpholinediones. The low solubility of the linear precursors precluded exploitation of the favorable influence of apolar solvents on oligomer formation observed in valinomycin series.

The preparative potential of cyclooligomerization is illustrated by the first synthesis of the macrocyclic valinomycin dimer [$m=6$, 72 ring atoms, molecular weight 2223 (mass spectrum)][5]. This depsipeptide is of significance as a model substance in studies on the ionic permeability of lipid membranes.

General procedure

The free linear depsipeptides were subjected to reaction under the usual conditions of phosphite cyclizations[3, 2]. The resulting reaction solutions were evaporated to dryness. On use of diethyl phosphite as reaction medium the residue was dissolved in dichloromethane and freed from acidic contaminants by extraction with $NaHCO_3$ solution. The crude products obtained in toluene were separated without further extractions by gel chromatography (Sephadex LH 20/methanol; 200 × 2.4 cm column; $EHTP_{acetone} = 0.0205$ cm).

Received: December 8, 1976 [Z 622 IE]
German version: Angew. Chem. 89, 117 (1977)

CAS Registry numbers:
H(Val-D-Hyv-D-Val-Lac)$_n$: $n=1$, 52545-11-6; $n=2$, 52545-12-7; $n=3$, 28531-95-5; cyclo(Val-D-Hyv-D-Val-Lac)$_m$: $m=1$, 52611-33-3; $m=2$, 14410-23-2; $m=3$, 2001-95-8; $m=4$, 14735-43-4; $m=6$, 61491-09-6

[1] *M. M. Shemyakin, E. I. Vinogradova, I. D. Ryabova, L. A. Fonina*, Zh. Obshch. Khim. *36*, 1391 (1966).
[2] *M. Rothe, W. Kreiss*, Angew. Chem. *85*, 1103 (1973); Angew. Chem. Int. Ed. Engl. *12*, 1012 (1973).
[3] *M. Rothe, I. Rothe, H. Brünig, K.-D. Schwenke*, Angew. Chem. *71*, 700 (1959).
[4] Abbreviations: Val = L-valine; D-Val = D-valine; Hyv = L-α-hydroxyisovaleric acid; D-Hyv = D-α-hydroxyisovaleric acid; Lac = L-lactic acid; MeVal = *N*-methyl-L-valine.
[5] The mass spectra were recorded by Dr. *I. Lüderwald*, Organisch-Chemisches Institut der Universität Mainz (Varian Mat 711 instrument).

Determination of Reaction Enthalpy in the Ion-Exchange of Chlorine Isotopes[**]

By *Klaus G. Heumann* and *Rainer Hoffmann*[*]

In a recent communication we reported on the chlorine isotope effect in ion-exchange chromatography[1]. We have now succeeded in determining the first set of thermodynamic data for an isotope exchange equilibrium of anions by measuring the temperature dependence of the chlorine isotope effect. Knowledge of such data is of fundamental importance for an understanding of isotope effects, in the development of chromatographic methods for the chemical enrichment of chlorine isotopes.

A column ($d=1.5$ cm, ht. of packing 80 cm) filled with the strongly basic anion exchanger AG1-X10 (NO_3^- form, 200—400 mesh, Bio-Rad) was used in the experiments. In each run 200 mg of chloride of natural isotopic composition was applied to the column in the form of NaCl and then eluted with 1 M $NaNO_3$ solution at an elution rate of *ca.* 0.35 ml/min. The temperature-dependence was determined by carrying out the runs at 0, 5, 7.5, 10, 15, 20, 30, 45, and 60 °C. The eluate was collected in fractions and the isotopic ratio $^{35}Cl/^{37}Cl$ determined by measurement of the negative thermions in a mass spectrometer.

The equilibrium constant K_c of the isotope exchange reaction

$$^{37}Cl(H_2O)_x^-R^+ + {}^{35}Cl(H_2O)_y^- \rightleftharpoons {}^{37}Cl(H_2O)_y^- + {}^{35}Cl(H_2O)_x^-R^+ \quad (1)$$

[R^+ = quaternary ammonium group of the anion exchanger]

can be determined according to a method described by *Glueckauf*[2]. The number of equilibrium steps in the column is determined from the elution curve, and the isotope effect ε of an equilibrium step ($K_c = 1+\varepsilon$) from the dependence

[*] Prof. Dr. K. G. Heumann, Dr. R. Hoffmann
Institut für Chemie der Universität
Universitätsstrasse 31, D-8400 Regensburg 1 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. *K. H. Lieser*, Technische Hochschule Darmstadt for allowing us to carry out the mass spectrometric measurements in his Institute.

of the measured isotopic ratio on the amount of eluted chloride. The elution curve must correspond to a Gaussian distribution, a prerequisite that is fulfilled on elution with 1 M $NaNO_3$ solution. K_c decreases with increasing temperature, thus indicating that the reaction from left to right in Eq. (1) is exothermic.

If the logarithm of K_c is plotted against the reciprocal of the absolute temperature, the reaction enthalpy can be determined according to the van't Hoff reaction isobar from the slope of the curve.

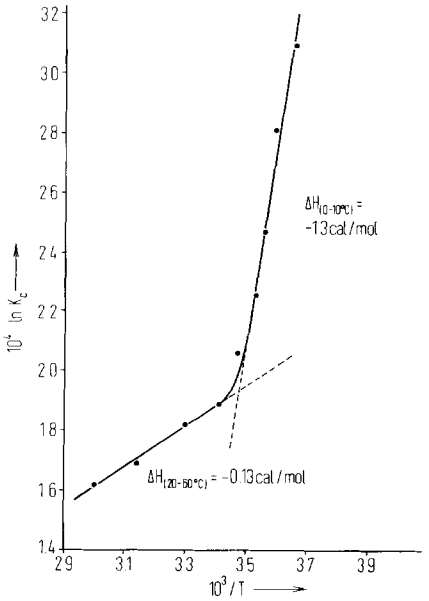


Fig. 1. Determination of ΔH for the Cl^- isotope exchange reaction from the temperature-dependence of the K_c value.

Figure 1 shows that two reaction enthalpies differing by one power of ten, $\Delta H(0—10\,°C) = -1.3$ and $\Delta H(20—60\,°C) = -0.13$ cal/mol are found in the temperature range investigated. Using these for the calculation of entropy values gives *e.g.* for 5 °C $\Delta S = -4.1 \times 10^{-3}$ cal/K·mol, and for 30 °C $\Delta S = -0.07 \times 10^{-3}$ cal/K·mol.

We interpret the unexpected change in the value of ΔH between 10 °C and 20 °C in terms of modification of the ionic structure of the reaction partners. Owing to partial dehydration of the ions on passage of the solution through the ion exchanger, $y > x$ for the hydration numbers in Eq. (1). Since changes of the ionic structure in such systems have hitherto not been observed in solution it would appear that the change of structure is due to either the Cl^- ions in the exchange resin or to the fixed ions of the exchanger. Such ion-exchange equilibria can therefore possibly serve as indicators for structural changes in ions of low energy.

So far reaction enthalpies for isotopic exchange reactions analogous to those studied by us have been determined only in the case of two isotopic pairs of cations in systems with a strongly acidic cation exchanger. Thus, *Glueckauf*[2] has obtained a value of $\Delta H(5.5—25\,°C) = -0.41$ cal/mol for $^{22}Na/^{24}Na$ using the experimental results of *Betts et al.*[3], whereas *Lee*[4] obtained $\Delta H(3—59\,°C) = -2.26$ cal/mol for $^6Li/^7Li$. Negative ΔS values were also calculated in both cases. Since the thermodynamic data for the $^{22}Na/^{24}Na$ pair were determined from only two measurements, really only the values for the lithium isotopes (four measurements) can be compared with our results: in contrast to Cl^-, in the case of Li^+ there is no change of ΔH value in the temperature range investigated. The enthalpy of $\Delta H(0—10\,°C) = -1.3$ cal/mol for the ion-exchange reaction of chloride agrees, within one order of magnitude, with that of lithium; the difference is probably due to the smaller difference in the ionic radii of the chloride isotopes[5].

Received: May 28, 1976 [Z 617 IE]
revised: November 18, 1976
German version: Angew. Chem. *89*, 118 (1977)

[1] *K. G. Heumann, R. Hoffmann*, Angew. Chem. *88*, 54 (1976); Angew. Chem. Int. Ed. Engl. *15*, 55 (1976).
[2] *E. Glueckauf*, Trans. Faraday Soc. *54*, 1203 (1958).
[3] *R. H. Betts, W. E. Harris, M. D. Stevenson*, Can. J. Chem. *34*, 65 (1956).
[4] *D. A. Lee*, J. Phys. Chem. *64*, 187 (1960).
[5] *D. N. Knyazev*, Russ. J. Phys. Chem. *35*, 298 (1961).

Serious Detonation during the Preparation of *tert*-Butyloxycarbonyl Azide (Boc-Azide)

By *Peter Feyen*[*]

tert-Butyloxycarbonyl azide (Boc-azide) is frequently employed as a reagent for the protection of amino groups. During its preparation we recently witnessed a serious explosion, which fortunately only resulted in damage to equipment.

Boc-azide was prepared by reaction of *tert*-$C_4H_9OCO—NH—NH_2$ with HNO_2 in ether according to the method described in Ref.[1]. The ether was distilled off at a water-bath temperature of 50 °C through a 30-cm Vigreux column. After about half of the ether had been distilled off, *i.e.* before actual distillation of the product, which normally occurs at 73 to 74 °C/70 torr and at a water-bath temperature of 90 to 95 °C, a detonation took place. According to Ref. [1] heavy metal azides may be responsible for the detonation, not Boc-azide itself. How this particular detonation could have arisen remains unanswered, since all the reagents and the ether employed were of proven high purity according to the manufacturer's analyses.

Differential thermal analysis[2] of the pure Boc-azide showed that practically no decomposition takes place on heating it in a closed glass vessel for 3 h at 80 to 90 °C. After 3 h at 100 °C the amount of decomposition had increased to about 50 %, and after 3 h at 110 °C it was almost complete. The heat of decomposition is 46 kcal/mol. At a heating rate of 5 °C/min maximum decomposition is reached at 138 °C.

Distillation of Boc-azide in ether containing 0.1 vol-% peroxides or additives such as Cu ions did not bring about premature detonation[3].

In view of this inexplicable incident and the fact that the Aldrich company has discontinued production of Boc-azide[4], it is urgently recommended that other reagents[5] be employed for introduction of the *tert*-butyloxycarbonyl protecting group.

Received: January 7, 1977 [Z 644 IE]
German version: Angew. Chem. *89*, 119 (1977)

[*] Dr. P. Feyen
Chemisch-wissenschaftliches Laboratorium Pharma
Forschungszentrum Aprath der Bayer AG
D-5600 Wuppertal-Elberfeld (Germany)

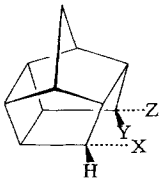
[1] *L. A. Carpino et al.*, Org. Synth. *44*, 15 (1964); Coll. Vol. V, 157 (1973).
[2] Investigation by Dr. *G. Hentze*, Ingenieurbereich AP Technische Physik, Bayer AG, Leverkusen (Germany)
[3] Investigation by Dr. *K. Schöller*, ZA Materialprüfung, Bayer AG, Leverkusen (Germany).
[4] *H. C. Koppel*, Chem. Eng. News *54* (39), 5 (1976).
[5] *T. Nagasawa et al.*, Bull. Chem. Soc. Jpn. *46*, 1269 (1973); *U. Ragnarson, S. M. Karlsson, B. E. Sandberg, L.-E. Sarsson*, Org. Synth. *53*, 25 (1973); *E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke, I. Ugi*, Angew. Chem. *80*, 396 (1968); Angew. Chem. Int. Ed. Engl. 7, 380 (1968); *E. Guibe-Jampel et al.*, Synth. Commun. *3* (2), 111 (1973); *G. Bram*, Tetrahedron Lett. *1973*, 469; Jap. Pat. 4862702 (December 4, 1971), Sankyo Co. Ltd.; *M. Itoh, D. Hagiwara, T. Hamuja*, Tetrahedron Lett. *1975*, 4393.

Synthesis and Absolute Configuration of Enantiomerically Pure D_3-Trishomocubanes (Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane) and Trishomocubanones[**]

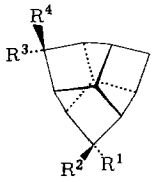
By *Günter Helmchen* and *Gerhard Staiger*[*]

Rigid chiral hydrocarbons and ketones are of special interest as test cases for chiroptic theories. Outstanding representatives are the enantiomeric trishomocubanes *(2f)* and *(3f)*, in that they are apparently the smallest stable organic molecules of the point symmetry group D_3[1].

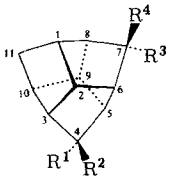
While racemic trishomocubane is very readily accessible *via* rearrangement of the alcohols *(1a)* and *(1b)* to the stereoisomeric 4,7-diiodotrishomocubanes with hydriodic acid and their subsequent reduction with zinc, only relatively tedious methods exist for the synthesis of derivatives appearing suitable for separation of the enantiomers[2]. We have how found that 4-hydroxy-7-iodotrishomocubanes are formed in good yields as intermediates in the first mentioned reaction and that these can be easily resolved into their enantiomers. The structures and properties of the new compounds are summarized in Table 1[3].



(1)



(2)



(3)

(a): X = Y = OH, Z = H
(b): X = Z = OH, Y = H
(c): X, Y = O, Z = H

Complete separation of the enantiomers *(2a)* and *(3a)* was achieved by liquid chromatography of their diastereomeric esters *(2c)* and *(3c)* with (−)-camphanic acid[4] [silica gel columns, petroleum ether/ethyl acetate (92:8), separation factor: 1.1]. Pure *(2c)* can also be obtained in 30% yield by crystallization of the mixture from ethyl acetate. Like the (−)-camphanic acid, which was prepared from natural (+)-camphor, *(2c)* and *(3c)* and their secondary products described below were enantiomerically pure. Reduction of *(2c)* with zinc/glacial acetic acid and hydrolysis of the product with ethanolic potassium hydroxide solution yielded (−)-4-trishomocubanol *(2d)*, which in turn furnished (−)-trishomocubanone *(2e)* by Jones-Kiliani oxidation (97% yield in each case). Wolff-Kishner reduction of *(2e)* afforded the readily volatile, camphor-like smelling (−)-trishomocubane *(2f)* in

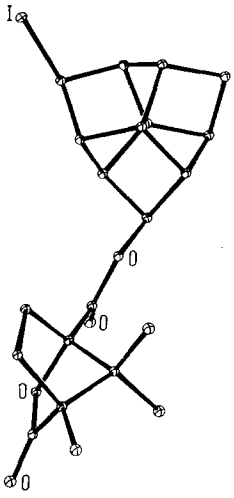


Fig. 1. Molecular structure of the ester *(2c)*.

Table 1. Configuration and physical properties of trishomocubane derivatives *(2)* and *(3)*.

	R^1	R^2	R^3	R^4	Abs. configuration [a] of *(2)*	M.p. [°C] *(2, 3)*	M.p. [°C] *(2)*	M.p. [°C] *(3)*	$[\alpha]_D^{20}$ [b] *(2)*	$[\alpha]_D^{20}$ [b] *(3)*	
(a)	H	OH	H	I	3*S*,4*R*,7*S*	132	116		− 65.4°		(*c*=2, ethanol)
(b)	H	OH	I	H		94					
(c)	H	$OCOR^5$ [c]	H	I	3*S*,4*R*,7*S*		162	138	− 21.8°	20.4°	(*c*=2, acetone)
(d)	H	OH	H	H	3*S*		166		−147°		(*c*=2, ethanol)
(e)	=O		H	H	3*S*		159		− 99.1°		(*c*=2, *c*-hexane)
(f)	H	H	H	H	3*S*		149		−164°		(*c*=1.3, *c*-hexane)
(g)	H	$OCOR^6$ [d]	H	I	3*S*,4*R*,7*S*						

[a] All the compounds have further chirality centers besides those specified; their configurations follow logically.
[b] Determined according to the Drude equation from measured values at 578 and 546 nm.
[c] R^5—COOH = (−)-camphanic acid.
[d] R^6—COOH = (+)-(*S*)-2-phenylbutyric acid.

Heating a mixture of the diols *(1a)* and *(1b)*[2] with concentrated hydriodic acid at 70°C (15 h) followed by chromatographic separation of the reaction products affords *(2, 3a)* and *(2, 3b)* in 54% and 13% yield, respectively. Assignment of configuration—confirmed in the case of *(2, 3a)* *(vide infra)*—was based on the fact that under the same conditions these compounds are also formed from the cyclic ether *(1c)* in a constant ratio of 6.5:1 independent of the reaction time and that *(2, 3a)* does not isomerize to *(2, 3b)*.

[*] Dr. G. Helmchen, G. Staiger
Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität
Pfaffenwaldring 55, D-7000 Stuttgart 80 (Germany)

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

80% yield. The compounds of the enantiomeric series were prepared analogously from *(3c)*.

An extraordinarily reliable and simple ^{1}H-NMR method recently developed by us[5] was used for determination of the absolute configuration: (−)-*(2a)*, obtained by hydrolysis of the ester *(2c)*, was esterified with (*S*)-2-phenylbutyryl chloride to give *(2g)*. The ^{1}H-NMR spectrum ($CDCl_3$) of this compound shows a signal at $\delta = 3.88$ ppm for 7-H. The corresponding signal of the (*R*)-2-phenyl butyrate occurs at $\delta = 3.82$ ppm, which was inferred from the spectrum of a mixture of the esters *(2g)* and *(3g)*. From these data it follows[5] that (−)-*(2a)* has the (3*S*,4*R*,7*S*) configuration. This result was confirmed by an X-ray structure analysis of *(2c)* (cf. Fig. 1)[6].

Received: November 30, 1976 [Z 614 IE]
German version: Angew. Chem. 89, 119 (1977)

[1] Review: *M. Farina, C. Morandi*, Tetrahedron *30*, 1819 (1974).
[2] Review: *C. W. Jefford*, J. Chem. Educ. *53*, 477 (1976).
[3] All the new compounds gave correct elemental analyses and spectral data. The absolute values of the optical rotations of enantiomers were in good agreement within the limits of experimental error.
[4] *H. Gerlach*, Helv. Chim. Acta *51*, 1587 (1968).
[5] *G. Helmchen*, Tetrahedron Lett. *1974*, 1527.
[6] *K. H. Jogun, J. J. Stezowski*, unpublished.

Synthetic Hemopolymers for Reversible Binding of Molecular Oxygen[**]

By *Ernst Bayer* and *Gunter Holzbach*[*]

Dedicated to Professor Hans-Joachim Bielig on his 65th birthday

Myoglobin and hemoglobin number among the most thoroughly studied biologically active proteins. Although the structure of these metalloproteins and their mode of action have been largely elucidated it has so far proved impossible to synthesize analogous heme complexes which reversibly bind oxygen under physiological conditions (20 to 40 °C; aqueous solution); such substance would play a very important role in the development of blood substitutes. Reversible oxygenation of model complexes containing heme has been observed only at low temperatures or in nonphysiological media[1]. Replacement of the protein component of an enzyme or an oxygen carrier appears to be difficult, even in well investigated biopolymers. Since protein synthesis is still too complicated or unreliable by presently available methods, and proteins are too unstable for practical use in catalyst systems, attention should be directed to synthetic polymers functionalized in suitable manner.

We have now synthesized heme-containing functionalized polymers for the reversible transport of oxygen which share the following properties with the natural oxygen carriers hemoglobin and myoglobin:

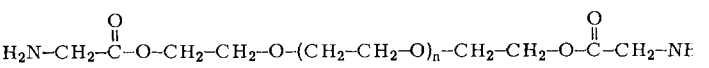
1) good solubility in water in order to achieve high concentrations of O_2;

2) hindrance of irreversible oxidation of the oxygen complex by the functionalized polymer;

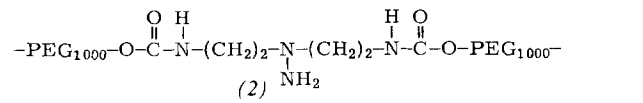
3) imitation of the distal imidazole.

Polyvinylpyrrolidinone, poly[ethylene glycol bis(glycine ester)][2a], *(1)*, and polyurethanes of structure *(2)* from polyethylene glycols (PEG) and diisocyanates[2b] were used as the basic polymers. Di-*tert*-butyloxycarbonylhistidine[3] is coupled to the free amino groups of polymers *(1)* and *(2)* in compliance with the procedures of liquid phase peptide synthesis with dicyclohexylcarbodiimide (DCCI)[4]. The amino protecting group of the histidine is then removed with trifluoroacetic acid/CH_2Cl_2 (1:1) and the amino group coupled with DCCI to a carboxy group of hemin. The hemin content of poly[ethylene glycol bis(glycylhistidylhemin)] *(3)* is 73 %, that of the histidylhemin derivative of the polymeric urethane *(4)* 100 %, based on the amino groups of the starting polymer *(1)* and *(2)*, respectively.

In the two functionalized polymers *(3)* and *(4)*, histidine is linked with the carboxy group of a propionic acid residue of hemin to form the amide. This arrangement prevents optimum coordinative fixation of the imidazole nitrogen of the histidine residue to the iron of heme for steric reasons. The histidine bound in this way can therefore be compared with



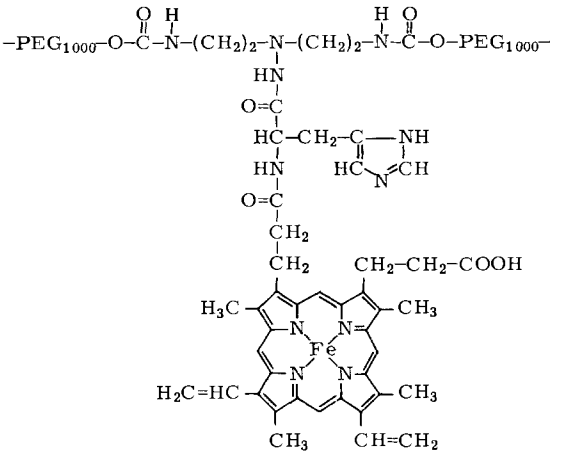
(1)



(2)

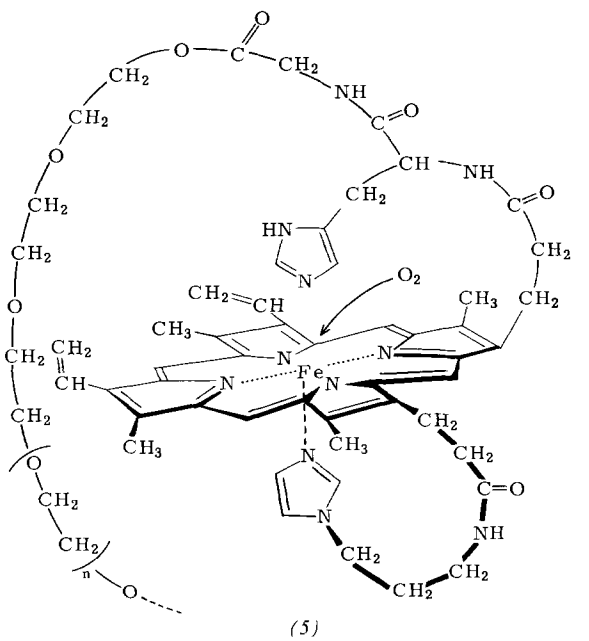
Heme–His–Gly–PEG–Gly–His–Heme

(3)



(4)

the distal histidine in myoglobin. The only other requirement for synthesis of an oxygen carrier is an imidazole ligand corresponding to the proximal histidine of natural oxygen carriers. This approach was adopted in the case of polymer *(4)* by addition and coordinative bonding of imidazole or imidazole derivatives. It is better however, to introduce an additional covalent bond between the proximal imidazole and the polymer. In the case of *(3)*, 3-(5-imidazolyl)propylamine[5] was therefore coupled to the second propionic acid group—once again using the methods of liquid phase peptide synthesis with DCCI/hydroxybenzotriazole. In the polymeric product *(5)* this imidazole group can undergo optimal coordination with the iron.



(5)

[*] Prof. Dr. E. Bayer, Dipl.-Biochem. G. Holzbach
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

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

The structural units of the active site of myoglobin or hemoglobin which are essential for binding oxygen are all present, albeit in a different arrangement, in the two polymers. The oxygen coordination site is shielded both by histidine and by the synthetic polymer. Nothing is known about the conformation of *(5)* in solution, especially in the vicinity of the active site. In the solid state, however, the hemin polymer *(5)* shows the same X-ray reflections ($d_1 = 3.794$ Å; $d_2 = 4.611$ Å) as are characteristic of the helix structure of poly(ethylene glycol) and poly(ethylene glycol peptide esters).

After synthesis the iron is present as Fe^{III} in both polymers *(4)* and *(5)*; they must therefore be reduced with sodium dithionite prior to oxygenation. An excess of reducing agent can be removed by chromatography on Sephadex. The O_2-free hemopolymers prepared in the above way are highly soluble in water. On oxygenation the typical spectral shifts occur (Table 1) which also accompany formation of the oxygen complexes of myoglobin and hemoglobin.

Table 1. Absorption maxima [nm] of various complex types of polymers *(4)* and *(5)*.

Polymer	Reduced	Oxygenated	Oxidized	CO complex
(4)	421	412	408	412
	529	526	540	537
	560	556		564
(5)	418	410	405	414
	527	524		535
	558	554		560

Oxygen can be reversibly removed from the dioxygen complexes, *e.g. in vacuo* (0.01 to 0.04 torr; 5 min). The process can be repeated several times. Addition of carbon monoxide to form a CO-hemopolymer is also possible (Fig. 1). The O_2 complex can be obtained therefrom by prolonged passage of oxygen. After repeated reversible oxygenation the complex shows increasing signs of irreversible oxidation to the hemin polymer, detected by the unstructured spectrum in VIS region and the shifts in the UV spectrum (Fig. 1). In the blood, the irreversibly oxidized hemoglobin which is also slowly formed is reduced to oxygenatable hemoglobin by an enzyme, *viz.* methemoglobin reductase[6]. The synthetic hemin polymers are also reduced to the Fe^{II} state by methemoglobin reductase and can then react once more with O_2 to form the oxygen complex.

The oxygen sorption curve for complex *(4)* is reproduced in Figure 2. The O_2 partial pressure for semi-saturation of our fully synthetic models [*(4)*, 0.21; *(5)*, 0.10 torr] is in good agreement with the values for myoglobin [0.2 to 1.2 torr[7]]. The sigmoid shape of the curve (Fig. 2) is indicative of a cooperative effect in oxygen binding, as in the case of hemoglobin[8].

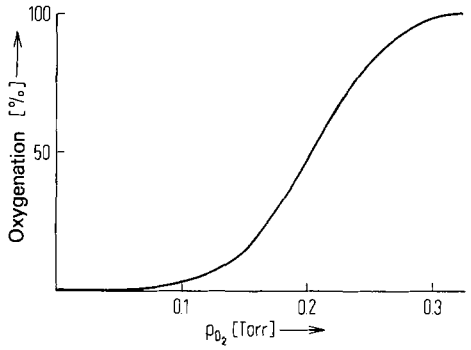


Fig. 2. Oxygen sorption curve of polymer *(4)* at 25 °C in 0.05 M phosphate buffer pH = 8.1.

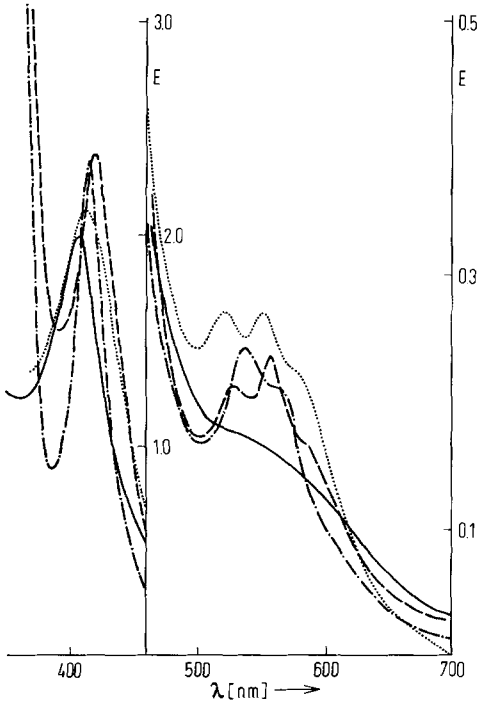


Fig. 1. Absorption spectra of polymer *(5)* in 0.05 M phosphate buffer pH = 7 (concentration: 4.5 ppm hemin iron): ..... oxygenated; ----- reduced; ——— oxidized; -·-·-·-CO complex.

The synthetic hemopolymers have properties closely resembling those of natural oxygen carriers, although the basic polymer is completely different. This demonstrates that specificity and reactivity are by no means privileges of naturally occurring polymers. This is confirmed for reactions of preparative and industrial interest by the development of homogeneous catalysts on the basis of synthetic, non-crosslinked polymers[9].

Received: November 4, 1976 [Z 616 IE]
German version: Angew. Chem. *89*, 120 (1977)

[1] *F. Basolo, B. M. Hoffman, J. A. Ibers*, Acc. Chem. Res. *8*, 384 (1975); *J. P. Collmann, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, W. T. Robinson*, J. Am. Chem Soc. *97*, 1427 (1975); *J. Geibel, C. K. Chang, T. G. Traylor, ibid. 97*, 5924 (1975); *E. Tsuchida, K. Honda, H. Sata*, Inorg. Chem. *15*, 352 (1976); and references cited therein.

[2] a) *M. Mutter, H. Hagenmaier, E. Bayer*, Angew. Chem. *83*, 883 (1971); Angew. Chem. Int. Ed. Engl. *10*, 811 (1971); b) *M. Mutter, I. Gatfield, E. Bayer*, unpublished.

[3] *C. H. Li, D. Yamashiro, S. Lemaire*, Biochemistry *14*, 953 (1975).

[4] *E. Bayer, M. Mutter*, Chem. Ber. *107*, 1344 (1974); *M. Mutter, R. Uhmann, E. Bayer*, Justus Liebigs Ann. Chem. *1975*, 901.

[5] *T. J. Schwan*, J. Heterocycl. Chem. *4*, 633 (1967).

[6] *E. Hegesh, M. Avron*, Biochim. Biophys. Acta *146*, 91, 397 (1967).

[7] *E. Antonini, M. Brunori*: Hemoglobin and Myoglobin and their Reactions with Ligands. North-Holland, Amsterdam 1971, p. 221.

[8] *E. N. Drake, S. J. Gill, M. Downing, C. P. Malone, Arch. Biochem. Biophys. 100*, 26 (1963).

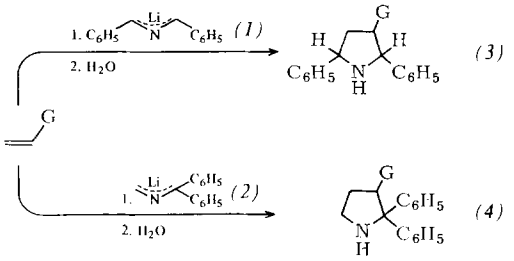
[9] *E. Bayer, V. Schurig*, Angew. Chem. *87*, 484 (1975); Angew. Chem. Int. Ed. Engl. *14*, 493 (1975); *V. Schurig, E. Bayer*, Chem. Technol. *6*, 212 (1976).

Extension of the Scope of Anionic Cycloadditions by Activating Organoelement Groups[**]

By *Thomas Kauffmann, Holger Ahlers, Angelika Hamsen, Herbert Schulz, Hans-Joachim Tilhard,* and *Annemarie Vahrenhorst*[*]

[$_\pi$2+$_\pi$4]-Cycloadditions to isolated unstrained CC double bonds usually require the presence of an activating group in the olefin. Carbonyl groups of proven value in Diels-Alder reactions and 1,3 dipolar cycloadditions are unsuitable for anionic 1,3 additions owing to the pronounced nucleophilic character of the anionic reagents; nor can cyano groups be used[1]. The choice was limited to aryl groups, *i.e.* to groups which are practically impossible to remove and hardly suitable for subsequent synthetic steps (CC linkages).

We have now found that S—C_6H_5, Se—C_6H_5, $P(C_6H_5)_2$, and $As(C_6H_5)_2$ groups permit the cycloaddition of 1,3-diphenyl-2-azaallyllithium *(1)* to a vinyl group (see reaction scheme and Table 1). The utility of $Si(C_6H_5)_3$ and $Si(CH_3)_3$ groups, which can be removed from sp^3 C atoms only with difficulty, for this purpose was already known[2]. With one exception, cycloadducts could also be obtained with 1,1-



diphenyl-2-azaallyllithium *(2)*. With *(2)* only one of the two possible regioisomeric cycloadducts could be detected in each case, *i.e.* structure *(4a)*. $P(O)(C_6H_5)_2$ and $P(S)(C_6H_5)_2$ do not act as activating groups; nor does $Sb(C_6H_5)_2$[3].

Since C—S, C—Se, and C—As bonds can be cleaved with relative ease and the $P(C_6H_5)_2$ should permit CC linkages to the cycloadducts after oxidation or quaternization, the scope of anionic 1,3-cycloadditions appears to have been considerably extended.

The structures of the newly prepared compounds are in accord with the results of elemental analysis and their spectra (MS, IR, ^{1}H-NMR). The stereochemistry at the chiral centers has not yet been elucidated.

Procedure:

Synthesis of *(3a)*: A solution of *cis*-2,3-diphenylaziridine (3.90 g, 20 mmol) in anhydrous THF (150 ml) is stirred under N_2 and treated at room temperature with an equimolar amount of *n*-butyllithium. The solution is heated under reflux for 2 h. The dark red reaction mixture is cooled to −60 °C and treated dropwise with phenyl vinyl sulfide (2.72 g, 20 mmol) in THF (20 ml), and then stirred for ½ h at −60 °C and 1 h at +20 °C. After addition of H_2O (20 ml) the mixture is extracted three times with $CHCl_3$ (3 × 100 ml). The oily residue obtained on evaporation of the dried organic phases crystallizes on addition of ether/light petroleum (30 to 60 °C) (1 : 2). Crystalline *(3a)* (4.5 g, 68 %) is obtained; its melting point does not increase on recrystallization from methanol.

Received: November 18, 1976 [Z 607 IE]
German version: Angew. Chem. 89, 107 (1977)

CAS Registry numbers:

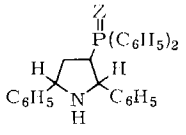
(1), 1605-06-7; *(2)*, 25564-63-0; *(3a)*, 61193-42-8; *(3b)*, 61193-44-0; *(3c)*, 61193-45-1; *(3d)*, 61193-46-2; *(4a)*, 61193-48-4; *(4b)*, 61193-50-8; *(4c)*, 61193-51-9; *(4d)*, 61193-52-0; *(5a)*, 61193-53-1; *(5b)*, 61193-54-2; *(6a)*, 61193-56-4; *(6b)*, 61193-51-5; *n*-butyllithium, 109-72-8; phenyl vinyl sulfide, 1822-73-7; phenyl vinyl selenide, 35167-28-3; diphenylvinylphosphane, 2155-96-6; diphenylvinylarsane, 61193-58-6; triphenylvinylsilane, 18666-68-7

Table 1. Cycloadditions in THF (molar ratios of starting compounds 1 : 1).

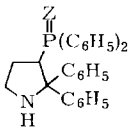
2-Aza-allyl cpd.	G	Reaction temp. [°C]	time [h]	Cyclo-adduct	Yield [%]	M.p. [°C]
(1)	—S—C_6H_5	−60 to +20	2	*(3a)*	68	70—72
(1)	—Se—C_6H_5	−40	22	*(3b)*	77	159—161 [a]
(1)	—$P(C_6H_5)_2$	0 to +20	24	*(3c)*	>42 [b]	—
(1)	—$As(C_6H_5)_2$	−40	48	*(3d)*	65	112—113
(2)	—S—C_6H_5	−60 to +20	24	*(4a)*	64	227—229 [c]
(2)	—Se—C_6H_5	−50 to −10	6	*(4b)*	42	198—200 [c]
(2)	—$P(C_6H_5)_2$	0 to +20	24	*(4c)*	>65 [b]	—
(2)	—$Si(C_6H_5)_3$	−80 to +20	20	*(4d)*	31	176—178

[a] M.p. of oxalate (free base is an oil).

[b] Not isolated but transformed into compounds *(5)* [from *(3c)*] or *(6)* [from *(4c)*] by air oxidation or reaction with the calculated amount of sulfur. Yield of *(5a)* and *(6a)* = minimum yield of cycloadduct.



(5a), Z = O, 42 %, m.p. 201 °C
(5b), Z = S, 34 %, m.p. 167—169 °C



(6a), Z = O, 65 %, picrate, m.p. 138 °C
(6b), Z = S, 39 %, m.p. 240 °C

[c] M.p. of picrate (free base is an oil).

[*] Prof. Dr. Th. Kauffmann, H. Ahlers, A. Hamsen, H. Schulz, Dipl.-Chem. H.-J. Tilhard, and A. Vahrenhorst
Organisch-Chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

[**] 1,3 Anionic Cycloadditions, Part 16. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 15: *Th. Kauffmann* and *R. Eidenschink*, Chem. Ber., in press.

[1] *A. Busch*, Dissertation, Universität Münster 1974.
[2] *E. Popowski*, Z. Chem. *14*, 360 (1974).
[3] The hitherto undescribed diphenyl(vinyl)stibane (oil, $n_D^{20} = 1.6559$) was obtained by reaction of diphenylstibane chloride with vinylmagnesium bromide in THF at −10 °C (yield 45 %).

Collision Activation Mass Spectrometry with Novel Analysis Technique

By *Richard Robbiani, Thomas Kuster,* and *Joseph Seibl*[*]

The analysis of collision induced degradation reactions of ions in the gas phase (CA-mass spectrometry[1]) has acquired increasing importance recently as a means for investigating ion structures. Ion cyclotron resonance (ICR) is preferably employed for such measurements, especially if ions of long lifetimes are the subject of interest. Otherwise double focusing mass spectrometers of Nier Johnson geometry are used in the so called DADI mode of operation[2], whereby the collision gas is admitted to the field free region between magnetic and electric sector. This mode of operation requires reversal of the instrument's conventional configuration, as the magnetic sector must precede the electric sector and therefore is not easily applicable to existing instrumentation. In addition under these conditions the principle of double focusing (mutual compensation of energy dispersion of electric and magnetic field) is not operative for ions generated in this region. The peaks appear broadened by collisional scattering and tend to overlap, often in a quite disturbing manner.

We would like to point out that collision induced degradations can be investigated with double focusing mass spectrometers in their usual configuration (the electric sector preceding the magnetic sector) while simultaneously avoiding the above mentioned drawbacks of the DADI method. If the collision gas is admitted to or just behind the ion source, the products formed by collisional processes in the first field free region can be analyzed by the newly established "linked scan technique"[3]. The operating principle of this method consists essentially of giving daughter ions m_2^+, m_3^+ ... arising from a freely selectable parent ion m_1^+ so much additional kinetic energy (velocity) that they acquire the same momentum as their precursor m_1^+. Having the same momentum they are recorded at the same place as m_1^+ at the collector site without altering the magnetic field. The required additional kinetic energy is imparted by increasing the accelerating voltage V. Thereby the ion trajectory in the electric sector is stretched and in order to focus the beam on to the intermediate slit the electric sector voltage E must be changed simultaneously ("linked") in such a way that E/V remains constant. A continuous linked scan of this sort produces a daughter ion spectrum of m_1^+ much like a DADI scan, save that now the principle of double focusing is operative. The signals are sharp and do not overlap. The measurement takes place earlier with respect to formation of the investigated ions than in the DADI configuration, reducing the probability of their isomerization before collision.

We tested the method by examining the ion $C_{12}H_{10}O^+$ (*m/e* 170) formed from diphenyl carbonate by decarboxylation under electron impact. *McLafferty et al.*[4] have determined the DADI-CA spectrum of this product and compared it with the spectra of diphenyl ether and the isomeric phenylphenols which were determined under identical conditions.

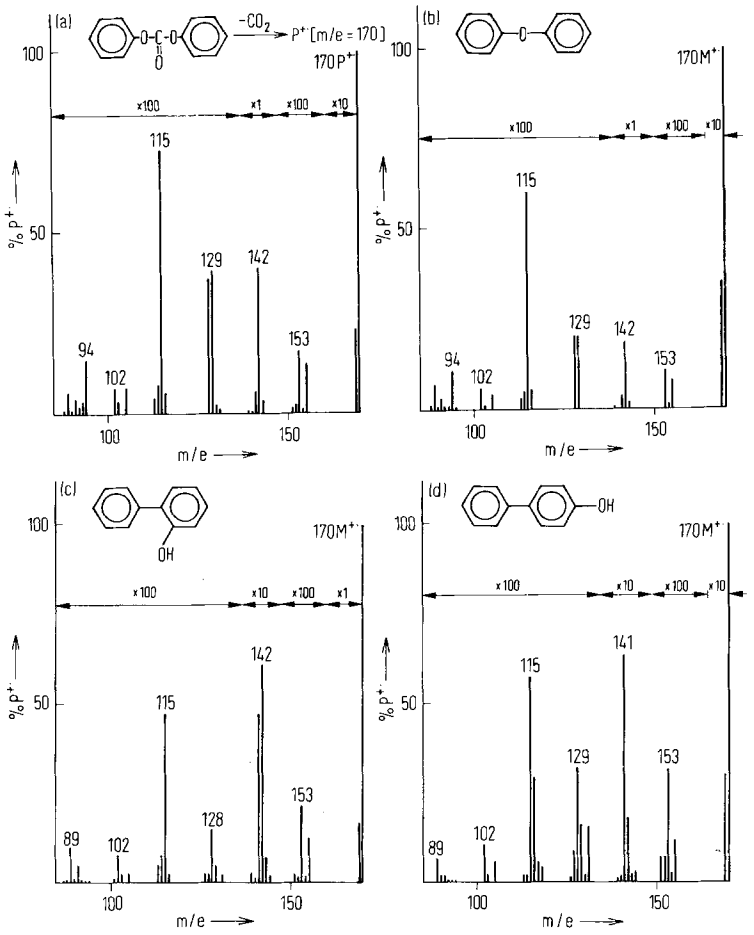


Fig. 1. Collision activation spectra of *m/e* = 170 from diphenyl carbonate (a), diphenyl ether (b), *o*-phenylphenol (c), and *p*-phenylphenol (d). Pure CA spectra, monomolecular components have been eliminated by substraction.

[*] Prof. Dr. J. Seibl, Dr. R. Robbiani, Dr. T. Kuster
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule
Universitätstrasse 16, CH-8092 Zürich (Switzerland)

The authors found that the decarboxylation product gave a spectrum similar to that of the diphenyl ether but different from those obtained from the phenylphenols and concluded, that a diphenyl ether structure must be attributed to the fragment of diphenyl carbonate. The conclusion is of course somewhat relativized by the statement that the spectra of the isomeric phenylphenols are mutually identical. Our LS-CA spectra of the diphenyl carbonate fragment, of diphenyl ether, and of two of the isomeric phenylphenols are shown in Figure 1. Corroborating the results reported in [4] the spectra of fragment (a) and diphenyl ether (b) are virtually identical and are taken to indicate identical structures. In accordance with expectation, it appears that differences in internal energy of the decomposing ions of different origin do not influence their behavior under CA conditions to any significant extent, at least not in this case. The spectra of the isomeric phenylphenols (c) and (d) are again different from (a) and (b), in line with the finding in [5], but in contrast to the DADI results they are by no means identical. The differences are absolutely sufficient for structural identification of the respective isomer. These opposing results of DADI-CA *versus* LS-CA suggests that the molecular ions of phenylphenols can isomerize completely to a common structure within the short period of time required to travel from the first to the second field-free region of the instrument. To move the observational window closer in time to the ion production process seems to be a suitable way for analyzing ion processes preceding the collisional activation step.

The described method is applicable to other modes of operation like linked scan of sector- and magnet field as well, and is suited for a further shift of the observational window to even shorter time lags between ion formation and collision process, as for example in combination with field-desorption ionization.

Received: November 4, 1976 [Z 615 IE]
German version: Angew. Chem. *89*, 115 (1977)

CAS Registry numbers:
Diphenyl carbonate, 109-09-0; diphenyl ether, 101-84-8; *o*-phenylphenol, 90-43-7; *p*-phenylphenol, 92-69-3

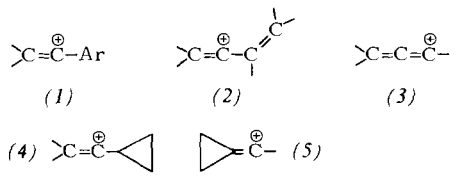
[1] *K. Levsen, H. Schwarz*, Angew. Chem. *88*, 589 (1976); Angew. Chem. Int. Ed. Engl. *15*, 509 (1976).
[2] *U. P. Schlunegger*, Angew. Chem. 87, 731 (1975); Angew. Chem. Int. Ed. Engl. *14*, 679 (1975).
[3] *A. F. Wesion, K. R. Jennings, S. Evans, R. M. Elliott*, Int. J. Mass Spectrom. Ion Phys. *20*, 317 (1976).
[4] *F. W. McLafferty, K. Levsen*, Org. Mass Spectrom. *8*, 355 (1974).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Stabilized vinyl cations are reviewed in article by *M. Hanack*. Classically stabilized cations of this type are α-arylvinyl *(1)*, dienyl *(2)*, and allenyl cations *(3)*; the nonclassically stabilized vinyl cations include cyclopropylvinyl *(4)* and cyclopropylidenemethyl cations *(5)*. Vinyl cations can be readily generated

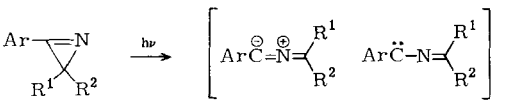


(1) *(2)* *(3)* *(4)* *(5)*

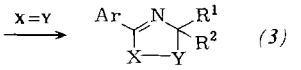
by solvolysis, particularly if the "super leaving groups" $F_3C-SO_3^{\ominus}$ and $F_9C_4-SO_3^{\ominus}$ are employed. The more stable the intermediary vinyl cation the less the rearrangement that takes place in the solvolysis. [Stabilized Vinyl Cations. Acc. Chem. Res. *9*, 364—371 (1976); 44 references]

[Rd 915 IE—L]

The photochemistry of 2*H*-azirines *(1)* is dealt with in an article by *A. Padwa*. 2*H*-Azirines—cyclic amines—are versatile substrates which can serve as precursors for other heterocycles. They react both with electrophiles as well as with nucleophiles and can participate as dienophiles or dipolarophiles in thermally allowed $[_4\pi_s + _2\pi_s]$ cycloadditions. On electronic excitation 2*H*-azirines undergo irreversible ring opening to give reactive nitrile ylides *(2a)* and/or *(2b)*, which react, for example, with dipolarophiles to form five-membered



(1) *(2a)* *(2b)*



(3)

heterocyclic compounds *(3)*. Further possible reactions of *(1)* include photochemical dimerization and intramolecular reactions, when R^1 = vinyl or allyl. [Azirine Photochemistry. Acc. Chem. Res. *9*, 371—378 (1976); 61 references]

[Rd 916 IE—L]

The biological activity of sesquiterpene lactones forms the theme of an article by *E. Rodriguez, G. H. N. Towers*, and *J. C. Mitchell*. These compounds are characteristic components of most Compositae, but are also occasionally found in other angiosperms and even in liverworts. The bitter substances often contain an α,β-unsaturated γ-lactone ring, which according to recent findings could be responsible for their activity towards tumors and microorganisms as well as their cyto- and phytotoxicity. Sesquiterpene lactones poison cattle, protect plants from being eaten by insects and in the case of man give rise to allergic dermatitis on contact. [Biological Activities of Sesquiterpene Lactones. Phytochemistry *15*, 1573—1580 (1976); 75 references]

[Rd 920 IE—R]

Fast reactions of carbanions and carbocations in solution are reported on by *L. M. Dorfman*, *R. J. Sujdak*, and *B. Bockrath*. These species can be generated and investigated by pulse radiolysis. Absolute rate constants were determined for a number of reactions. The benzyl anion ($PhCH_2^{\ominus}$) was prepared both unpaired and as the ion pair ($PhCH_2^{\ominus}$, $Na^{\oplus}$) in solvents such as tetrahydrofuran:

$$e_s^{\ominus} + (PhCH_2)_2Hg \rightarrow PhCH_2^{\ominus} + PhCH_2Hg^{\bullet}$$

The benzyl anion shows a UV band at 362 nm; the ion pair absorbs at 355 nm. The reactions of these species with alcohols were studied in detail. Carbocations, *e.g.* the benzyl cation ($PhCH_2^{\oplus}$), were obtained by pulse radiolysis in hydrocarbon halides:

$$e^{\ominus} + RCl \rightarrow RCl^{\bullet\ominus} + 2e^{\ominus}$$

$$RCl^{\bullet\ominus} + (PhCH_2)_2Hg \rightarrow RCl + PhCH_2^{\oplus} + PhCH_2^{\bullet} + Hg$$

The carbocation $PhCH_2^{\oplus}$ shows an absorption band at 363 nm. The lifetime of some of these cations is longer than 1 μs. Investigations were carried out, *inter alia*, on their reactions with halide ions and tertiary amines. [Fast Reactions of Carbanions and Carbocations in Solution. Acc. Chem. Res. *9*, 352—357 (1976); 42 references]

[Rd 914 IE—L]

The surface of titanium dioxide is the subject of a review by *G. D. Parfitt*. The rutile and anatase forms are considered separately; whenever possible the conditions of preparation and the origin of the samples are given. Most samples were obtained by oxidation or hydrolysis of titanium tetrachloride or by hydrolysis of titanium sulfate; the surface properties of the products depend strongly upon whether they still contain anions. Particle size must be taken into account. Particularly worthy of note is the comprehensive chapter on the hydroxylation of the surface. [The Surface of Titanium Dioxide. Progr. Surf. Membr. Sci. *11*, 181—226 (1976); 130 references]

[Rd 919 IE—F]

Elucidation of structure and specificity of chromatin by immunological methods is reported on by *M. Bustin*. Chromatin, a complex of DNA, RNA, histones and non-histone proteins, is responsible for regulation of the expression of the genetic information stored in the DNA. Studies on the individual chromosome proteins during the life of the cell suffer in that these proteins cannot be determined in a simple way. Antibodies that can be prepared for various components of the chromatin offer one possibility for specific detection. Unfortunately such determinations have so far not afforded any quantitative values; these are to be expected as soon as the methods for preparation of components of the nucleus have been refined. [Chromatin Structure and Specificity Revealed by Immunological Techniques. FEBS Lett. *70*, 1—10 (1976); 71 references]

[Rd 921 IE—R]

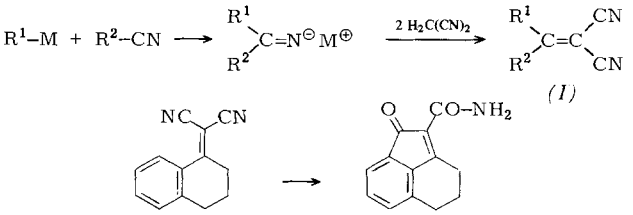
Pineal gland biorhythms form the theme of an article by *S. Binkley*. Particular emphasis is laid on the serotonin *N*-acetyltransferase which plays a role in the biosynthesis of melatonin from serotonin. This enzyme was investigated in chicken and rats. It is subject to circadian fluctuations, which are not only connected with the light-dark cycle but also persist in permanent darkness; however, on permanent illumination they disappear. In rats light reception is *via* the eyes, in chicken *via* extraretinal photoreceptors. [Pineal Gland Biorhythms: *N*-Acetyltransferase in Chicken and Rats. Fed. Proc. *35*, 2347—2352 (1976); 43 references]

[Rd 922 IE—R]

The synthesis and function of prostaglandins in the heart are reported on by *P. Needleman*. The isolated perfused heart of the rabbit can rapidly synthesize, liberate, and inactivate prostaglandins. Prostaglandins influence the resistance of the coronary vessels of the heart and thus the ability of the heart to work. The biosynthesis starts from arachidonic acid, which is converted into prostaglandin-like substances in a single passage through the heart. Arachidonic acid and bradykinin together effect a drop in resistance of the coronary vessels; this effect is directly connected with the synthesis and liberation of prostaglandin-like substances. The phenomenon can be increased by injection of a peptide type inhibitor of bradykinin degradation. Indomethacin, an inhibitor of prostaglandin biosynthesis, on the other hand, reduces the effect of bradykinin and arachidonic acid on the resistance of the coronary vessels. [The Synthesis and Function of Prostaglandins in the Heart. Fed. Proc. *35*, 2376—2391 (1976); 45 references]

[Rd 923 IE—R]

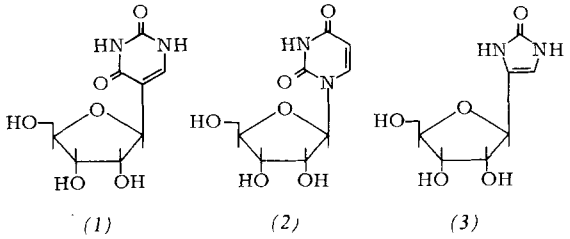
The use of malononitrile for annelation reactions *via* intermediary alkylidenemalononitriles *(1)* is dealt with in an article by *E. Campaigne* and *S. W. Schneller*. Compounds *(1)* can be prepared by base-catalyzed Knoevenagel condensation of carbonyl compounds and malononitrile or, much more advantageously, from an organometal compound, a nitrile, and malonitrile. The alkylidenemalonitriles *(1)* are a valuable system for the annelation of carbocyclic or heterocyclic rings, electronic effects and steric conditions decisively influencing



the reaction course. Five- or six-membered carbocycles (indenones, indanones, naphthalenes) or aromatic heterocycles (lactones, coumarins) can be obtained by cyclization in acid media. [Cyclization of Ylidenemalononitriles. Synthesis *1976*, 705—716; 32 references]

[Rd 912 IE—M]

The chemistry and biochemistry of C-nucleosides are reviewed by *G. D. Daves, Jr.* and *C. C. Cheng*. In the C-nucleosides, *e.g. (1)*, the carbohydrate component is linked to the base by a CC bond which is hydrolytically stable. Some C-nucleo-



sides can serve as enzyme substrates; thus pseudouridine *(1)* is recognized as uridine *(2)* at the nucleotide and polynucleotide level. In the meantime more than ten natural C-nucleosides

have been discovered; six of these, *e.g.* showdomycin *(3)*, are antibiotics. [The Chemistry and Biochemistry of C-Nucleosides. Progr. Med. Chem. *13*, 303—349 (1976); 265 references]

[Rd 918 IE—F]

Disguised chemical selectivities are the subject of a review article by P. Rys. That several chemical reactions can compete with one another is a well known phenomenon. Kinetic chemical selectivity is defined as the ratio of the rate constants of two competing reactions, and thermodynamic chemical selectivity as the ratio of their equilibrium constants. If diffusion or adsorption effects alter the rate of at least one of the reactions, the selectivity is disguised. In specific cases it can be shown that the product pattern depends *e.g.* on the precursor complexes of the reaction partners, the spatial orientation of the reaction partners in these complexes, or on the diffusion conditions. [Disguised Chemical Selectivities. Acc. Chem. Res. *9*, 345—351 (1976); 58 references]

[Rd 913 IE—L]

The influence of prostaglandins on the behavior of blood vessels is reported on by *J. C. McGiff, K. U. Malik*, and *N. A. Terragno*. Prostaglandins are tissue hormones which manifest their effect in the immediate neighborhood of the site of formation. Endogenous prostaglandins, *e.g.* PGE_2, counteract vasoconstriction and the anti-sodium diuretic activity of circulating, hypertensive hormones, and control the release of noradrenalin. This is demonstrated by the increased sensitivity of vessels having low or inhibited rates of prostaglandin synthesis to stimulation by hypertensive hormones and inhibition of the activity of these hormones by exogenous prostaglandin. [Prostaglandins as Determinants of Vascular Reactivity. Fed. Proc. *35*, 2382—2387 (1976); 53 references]

[Rd 924 IE—R]

BOOK REVIEWS

Grundlagen der analytischen Chemie. Unter besonderer Berücksichtigung der Chemie in wäßrigen Systemen. (Principles of Analytical Chemistry. With Special Reference to Chemistry in Aqueous Systems). By *F. Seel*. Verlag Chemie, Weinheim—New York 1976. 6th improved edit., 387 pp., 49 figs., 53 tables, bound, DM 42.—.

If we consider modern analytical chemistry to be a science whose aim is to provide correct information about chemical systems—a view generally accepted today in professional circles—then we must agree that it is impossible to write a textbook of 387 pages covering the "Principles of Analytical Chemistry" (chemical, physical, and biochemical analysis) with Prof. *Seel*'s specific extreme precision. Accordingly, the phrase "With Special Reference to Chemistry in Aqueous Systems" is an important part of the title of the "new Seel".

This was certainly the author's reasoning. In his own words, "The present book presents a collection of the most important principles of general chemistry insofar as these are relevant to the analytical work that the student carries out in his basic inorganic practicals". This presumably means "qualitative" and "quantitative" analysis in the classical sense. Opinion as to whether processes such as colorimetry, polarography, potentiometry with ion-selective electrodes, chromatography, statistical evaluation of the methods, and assessment of analytical methods and results should nowadays be included in these basic courses will not be discussed here.

What is certain is that the author intentionally rejected treatment of specialized processes on this occasion in order to be able, within the given limits, to describe the physicochemical principles of classical analytical chemistry in his usual demanding manner.

It should be emphasized that the book succeeds in the attempt to "derive the variety of analytically important (chemical) reactions from a very small number of fundamental reactions types (dissolution and precipitation processes, complexation, acid-base reactions, and redox reactions). It is repeatedly stated, and proved by the application of the law of mass action, that the course of many analytical reactions can be explained only by a combination of such fundamental model reaction types. Indication of the formal relationship between acid-base and redox reactions is also important for the student. The didactic value of the book is enhanced by the use of logarithmic diagrams for the description of dissociation equilibria in the basic chapters and by their application to practical problems in hydrogen sulfide separation processes.

Partly as an understatement and partly self-critically, the author claims that his work "... is no textbook of analytical chemistry". A better description would be "... an excellent textbook on special chapters in analytical chemistry". The author does not simplify but explains in detail and requires the reader's intelligent participation.

Robert Kellner [NB 358 IE]

Handbook of Analysis of Organic Solvents. By *V. Šedivec* and *J. Flek*. Ellis Horwood Ltd., Chichester 1976. 1st edit., 455 pp., various figs., numerous tables, bound, £ 18.00.

In this monograph the authors limit themselves mostly to "classical" analysis of solvents, whilst often admitting a very wide interpretation of what a solvent may be. Gas chromatography receives very brief mention and spectroscopic methods none at all. The first part gives general principles—sampling, determination of physical constants, separation, and quantitative analysis of two- and three-component systems; in the second part individual groups of compounds are discussed. However, alkyl aryl and diaryl ethers are not included among the ethers, nor are alkyl aryl ketones among the ketones. Among other shortcomings we may note: Peroxides and water can often be excellently removed by Al_2O_3 (pp. 16 and 20). There is no mention of the determination of water by *Karl Fischer*'s method (p. 18). Is not a sample for tasting superfluous (p. 32)? In the distillation of CS_2 there is no "Caution" notice (p. 41). Cumene and *p*-cymene form hydroperoxides very readily (p. 124). The expression "nascent hydrogen" should be finally allowed to die (pp. 286/287). As a whole, the book can be recommended, especially because of its numerous tables which make it superfluous to refer to the handbooks that often provide the information less readily. The book is suitable for the practising chemist but can also be used for teaching. The production is good.

Heinz Kropf [NB 360 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Anionic Surfactants, Part II. Edited by *W. M. Linfield*. Vol. 7 of the series "Surfactant Science Series". Edited by *M. J. Schick* and *F. M. Fowkes*. Marcel Dekker, New York 1976. xi, 674 pp., bound, SFrs. 130.—.—ISBN 0-8247-6159-6

Thermodynamics of Seawater as a Multicomponent Electrolyte Solution. Part 1: Entropy, Volume, Expansibility, Compressibility. By *J. V. Leyendekkers*. Vol. 3/1 of the series "Marine Science". Edited by *D. W. Hood*. Marcel Dekker, New York 1976. xi, 496 pp., bound, SFrs. 81.—.—ISBN 0-8247-6486-2

Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel. Band 3: Geschichte, Ökologie, Forschung, Tropenkrankheiten, Textilschutz, Insektizid-Resistenz, Materialschutz. Edited by *R. Wegler*. Springer-Verlag, Berlin 1976. xiii, 322 pp., bound, DM 136.—.—ISBN 3-540-07817-7

RKW-Handbuch Forschung, Entwicklung, Konstruktion (F+E). Ergänzbares Handbuch für Wissenschaft, Technik, Wirtschaft und Verwaltung. Edited by *H. Moll* and *H. J. Warnecke*. Erich Schmidt Verlag, Berlin 1976. Revisable edition including 2nd instalment, 430 pp., 1 foldout chart, DM 41.—, additional special file DM 9.80.

Molecular Connectivity in Chemistry and Drug Research. By *L. B. Kier*. Vol. 14 of the series "Medicinal Chemistry". Edited by *G. deStevens*. Academic Press, New York 1976. xiii, 257 pp., bound, $ 27.00.—ISBN 0-12-406560-0

Atmospheric Chemistry. By *J. Heicklen*. Academic Press, New York 1976. xiv, 406 pp., bound, $ 38.00.—ISBN 0-12-336740-9

Selected Papers on Chemical Engineering Science. By *D. W. van Krevelen*. Elsevier Scientific Publishing Company, Amsterdam 1976. xiv, 386 pp., bound, Dfl. 110.00.—ISBN 0-444-41529-7

Isoelectric Focusing. Edited by *N. Catsimpoolas*. Academic Press, New York 1976. xi, 265 pp., bound, $ 23.50.—ISBN 0-12-163950-9

Principles of Pyrometallurgy. By *C. B. Alcock*. Academic Press, New York 1976. xiii, 348 pp., bound, $ 19.25.—ISBN 0-12-048950-3

Irreducible Tensor Methods. An Introduction for Chemists. By *B. L. Silver*. Vol. 36 of the series "Physical Chemistry". Edited by *E. M. Loebl*. Academic Press, New York 1976. xvii, 226 pp., bound, $ 26.50.—ISBN 0-12-643650-9

Electrochemical Stripping Analysis. By *F. Vydra, K. Štulík*, and *E. Juláková*. From the series "Ellis Horwood Series in Analytical Chemistry". Edited by *R. A. Chalmers*. Ellis Horwood Ltd., Chichester/John Wiley & Sons, New York 1976. 283 pp., bound, $ 33.25.—ISBN 0-470-15131-5 (Halsted Press); 85312-017-X (Ellis Horwood)

Drug Design, Vol. VII. Edited by *E. J. Ariens*. Vol. 11/VII of the series "Medicinal Chemistry". Edited by *G. deStevens*. Academic Press, New York 1976. xv, 295 pp., bound, $ 30.00.—ISBN 0-12-060307-1

Silicate Science, Vol. VIII: Industrial Glass: Glazes and Enamels. By *W. Eitel*. Academic Press, New York 1976. xvi, 396 pp., bound, $ 39.00.—ISBN 0-12-236308-6

Thermal Uses and Properties of Carbohydrates and Lignins. Edited by *F. Shafizadeh, K. V. Sarkanen*, and *D. A. Tillman*. Academic Press, New York 1976. ix, 320 pp., bound, $ 15.00.—ISBN 0-12-637750-2

Peptides 1976. Edited by *A. Loffet*. Editions de l'Université de Bruxelles 1976. xxiii, 660 pp., bound.—Proceedings of the Fourteenth European Peptide Symposium, Wépion/Belgium, April 11—17, 1976.—ISBN 2-8004-0639-9

Gmelin Handbuch der Anorganischen Chemie. 8th edition. Springer-Verlag, Berlin 1976.

Main work, System No. 39: Seltenerdelemente, Part C: Die Verbindungen. 3rd instalment: Sc, Y, La und Lanthanide. Fluoride, Oxidfluoride und zugehörige Alkalidoppelverbindungen. xxxiv, 439 pp., bound, DM 794.—.—ISBN 3-540-93321-2

Main work, System No. 56: Mangan. Part C: Die Verbindungen. 6th instalment. Verbindungen mit Schwefel, Selen und Tellur. xxxviii, 360 pp., bound, DM 765.—.—ISBN 3-540-93325-5

Supplementary work, Vol. 38: Transurane. Part B 2: Binäre Legierungssysteme 1. xxiv, 241 pp., bound, DM 549.—.—ISBN 3-540-93327-1

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031. Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 3
March 1977
Pages 125 – 204

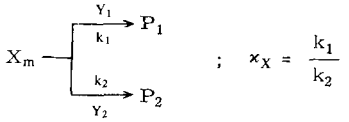
Basis and Limitations of the Reactivity-Selectivity Principle

By Bernd Giese[*]

The reactivity-selectivity principle (RSP), which describes a linear relationship between the decrease in selectivity and increase in reactivity of molecules X_m in their reactions with Y_1 and Y_2, has been much criticized during the last few years. The present paper shows the kind of reactions where the RSP does not hold and reveals how the individual types of reaction can be distinguished by varying the solvent. The dependence of molecule selectivity on temperature produces a further effect. An isoselective relationship (ISR) can be deduced when this dependence is taken into account. This relationship is not concerned with the connection between the temperature-dependent rate and competition constants, but with the connection existing between activation enthalpies and activation entropies, which are temperature-independent over wide ranges. The application of the ISR to different types of reactions makes it possible to characterize and distinguish between short-lived intermediates and underlines the significance of the isoselective temperature (T_{is}) in interpreting the reaction parameters of linear free energy relationships and in planning syntheses.

1. Introduction

The aim of preparative chemistry is quick and uniform synthesis of desired compounds. Formation of inconvenient side-products is caused by the ability of initial substances and/or intermediates X_m to react in different ways, *e.g.* with Y_1 and Y_2:



$$; \quad \varkappa_X = \frac{k_1}{k_2}$$

If the reactions proceed with the rate constants k_1 and k_2, the product ratio P_1/P_2 depends on the concentration of the reaction partners Y_1 and Y_2 and on the competition constant $\varkappa_X$. Thus, in planning a synthesis, competition constants of possible branched reaction pathways should be approximately known.

A different problem can arise in studies of reaction mechanisms: more often than not, it is impossible to identify postulated short-lived intermediates, *e.g.* X_m, by their physical properties. In many cases, however, such intermediates can be detected chemically by competitive trapping with suitable reaction partners, *e.g.* Y_1 and Y_2[1]. The reactivity-selectivity principle (RSP) is applied in order to obtain information on the rate constants of the intermediates k_1 and k_2 from the competition constants $\varkappa_X$:

If molecules X_1, X_2, X_3 ... X_m react with Y_1 and Y_2, selectivity ($\log \varkappa_X$)[2] decreases proportionally to increasing reactivity ($\log k_X$).

This linear relationship is described by proportionality relationship (a) or by equation (b).

$$\delta \log \varkappa_X \sim -\delta \log k_X \quad \text{(a)}$$
$$\log \varkappa_X = a - b \cdot \log k_X \quad \text{(b)}$$

[*] Priv.-Doz. Dr. B. Giese
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

The symbol δ indicates that only changes of reactivities and selectivities on varying molecules X_m of the reaction series in question are compared. The constants a and b, *i.e.* the intercept and the slope of linear equation (b), are larger than zero (cf. Section 3). The RSP can be checked graphically by a $\log\varkappa_X/\log k_X$ plot (Fig. 1).

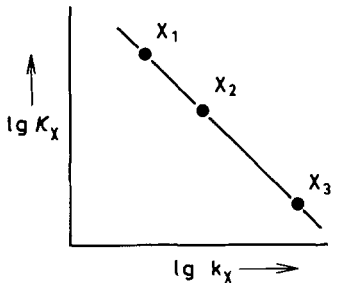


Fig. 1. Graphical check of the RSP [Eq. (a)] in a selectivity-reactivity plot.

If the various molecules X_m give a straight line with a negative slope as in Figure 1, the reaction complies with the RSP: in this case the more reactive molecule X_2 is less selective than molecule X_1.

2. Basis of the Reactivity-Selectivity Principle (RSP)

2.1. Variation of Substituents

The connection between changes in reactivity and changes in selectivity, which is supplied by the RSP, certainly appears plausible, for the differences in the free activation enthalpies $\Delta G_1^{\neq} - \Delta G_2^{\neq}$ are large in the case of large activation enthalpies of the individual reactions: when a less reactive molecule X_1 reacts with Y_1 or Y_2 it has to overcome a larger free activation enthalpy than the more reactive molecule X_2. Variation of the reaction partners (Y_1 and Y_2) has greater influence on the free activation enthalpy of the less reactive particle X_1, as can be shown by the Hammond postulate[3] according to which the slower reaction has a "later" transition state than the faster reaction. Reorientation of electron distribution and atom location is further advanced in a "late" transition state than in an "early" transition state (Fig. 2).

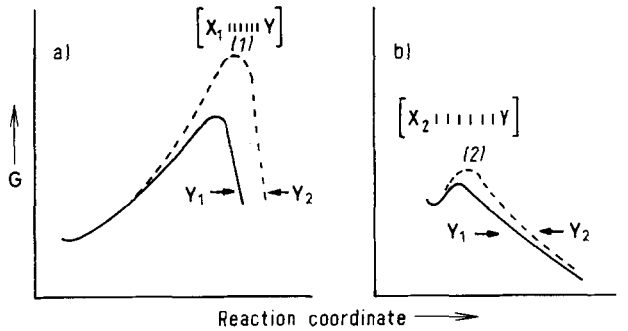
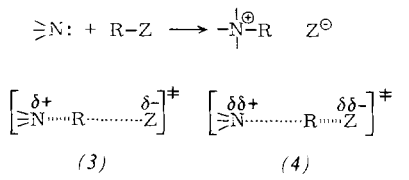


Fig. 2. Reaction profiles for reaction of Y_1 and Y_2 with a) less reactive molecule X_1 and b) more reactive molecule X_2.

Bond lengths and angles have changed to a greater extent in the activated complex *(1)* than in the activated complex *(2)*. Where partial charges occur at transition states, such as in amine alkylation, the charge separation is more advanced on the activated complex *(3)* of the slower reaction than on that of the faster reaction [*(4)*].



A change to a reaction partner which stabilizes or destabilizes charges has greater influence on transition state *(3)* than on transition state *(4)*, because formation of the charges is further advanced in *(3)* than in *(4)*. This is exemplified by the methylation of α-substituted pyridines *(5)*[4].

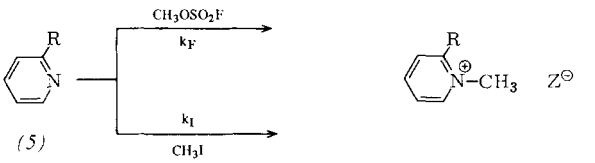


Figure 3 demonstrates how the selectivity of the competing reactions with methyl fluorosulfonate/methyl iodide decreases with increasing reactivity of the pyridine derivative *(5)* (varying substituents R). The fluorosulfate leaving group effects a better stabilization of the negative charge than iodide, and this is more noticeable in the "later" transition state of the slower reaction than in the "earlier" transition state of the faster reaction, where charge separation is comparatively small.

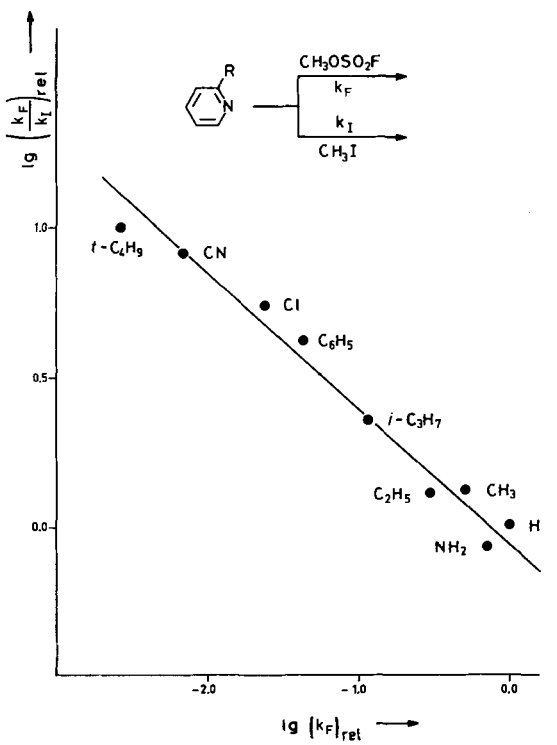


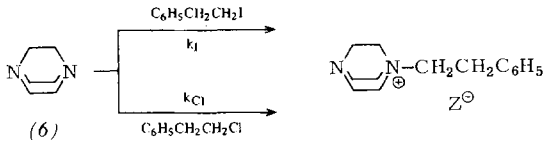
Fig. 3. Checking the reactivity-selectivity principle by reaction of various substituted pyridines *(5)* with methyl fluorosulfonate and methyl iodide in nitrobenzene at 30°C.

2.2. Variation of the Solvent

If the RSP holds, changing the solvent should have similar effects on reactivity and selectivity as varying substituents:

An increase in reactivity caused by changing the solvent is accompanied by a proportional decrease in selectivity of molecule X_m reacting with Y_1 and Y_2.

The oppositely directed influence of solvents on reactivity and selectivity can also be exemplified by the alkylation of tertiary amines.



(6)

Figure 4 demonstrates how the selectivity of 1,4-diazabicyclo[2.2.2]octane (6) decreases and the reactivity increases in the competition system phenethyl iodide/phenethyl chloride as the solvent is changed[5].

The considerable scatter of the experimental values in Figure 4 is typical of interaction between solvents and dissolved substances, which is dependent on several parameters[6]. Therefore, application of the selectivity principle is admissible only if the reaction is examined in a sufficient number of solvents. In spite of frequently poor correlations, a greater influence of the solvent is observed on slower reactions than on faster reactions[7] provided that similar reactions are considered.

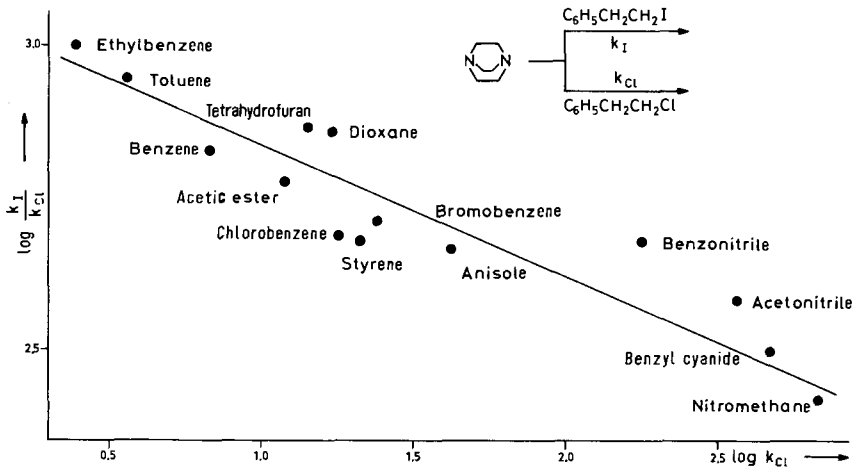


Fig. 4. Checking the reactivity-selectivity principle by reaction of tertiary amine (6) with 2-phenethyl iodide and 2-phenethyl chloride in various solvents at 54.4 °C.

3. Limitations of the Reactivity-Selectivity Principle

The connection between changes in reactivity and selectivity expressed in equation (b) can be reformulated as equation (c) on substituting competition constant $\varkappa_X$ by rate constants k_{X,Y_1} and k_{X,Y_2}.

$$\log \varkappa_X = \log k_{X,Y_1} - \log k_{X,Y_2} = a - b \cdot \log k_{X,Y_1} \quad \text{(b)}$$

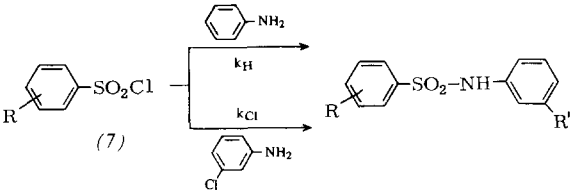
$$(b+1)\log k_{X,Y_1} = a + \log k_{X,Y_2} \quad \text{(c)}$$

Thus, the proportional connection between reactivity and selectivity is valid if a linear relationship exists between the reactivities of the individual reaction series. The selectivity principle therefore turns out to be a specific form of linear free energy relationship and therefore holds only for limited variations of molecules X_m and reaction partners Y_1 and Y_2[8]. The positive sign of b, a result of the application of the Hammond postulate (cf. Section 2.1), limits the validity range still further: only those linear free energy relationships in which variations of substituent and solvent exert a greater influence on the slower reaction series comply with the RSP.

When testing the reactivity-selectivity principle numerically or graphically, care must be taken that the competition constants are greater than unity, otherwise the sign of b must change for the RSP to remain valid. On the other hand, either k_{X,Y_1} or k_{X,Y_2} can be inserted, for the rate constants are related according to equation (c).

3.1. Opposing Influence of Substituents on Bond Cleavage and Bond Formation

In the last few years the RSP has been much criticized because there are reactions in which selectivity does not change in spite of increasing reactivity, or even increases proportionally to increasing reactivity[9]. One example is the reaction of arenesulfonyl chlorides (7) in the competition system aniline/3-chloroaniline.



The positive slope in a selectivity-reactivity plot of experimentally determined values[10] (Fig. 5) shows that the most reactive sulfonyl chloride, nitrobenzenesulfonyl chloride, is also the most selective in this particular competition system.

This finding is completely opposed to the prediction of the selectivity principle.

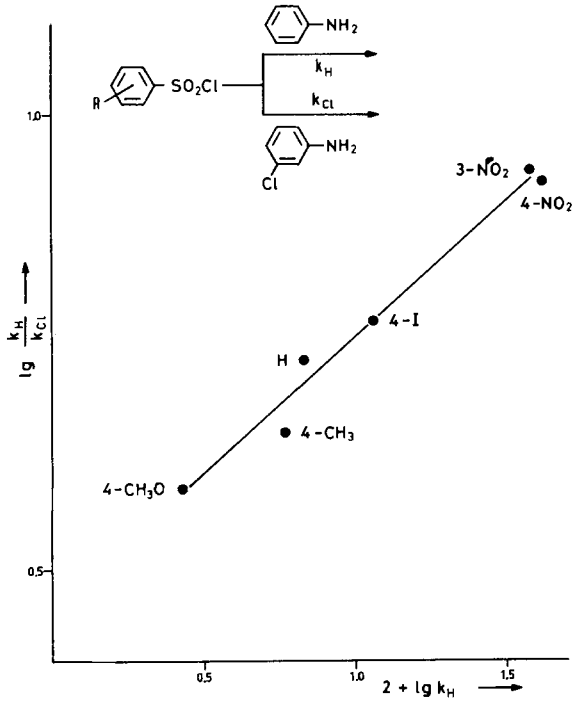


Fig. 5. Failure of the RSP for reaction of various substituted benzenesulfonyl chlorides *(7)* with aniline and 3-chloroaniline in methanol at 25 °C.

The influence of the solvent on the reaction of benzenesulfonyl chloride with aniline/3-chloroaniline, however, gives an entirely different picture from that of varying substituents. The selectivity is seen to fall and individual reaction rates to rise when the solvent is changed (Fig. 6)[11].

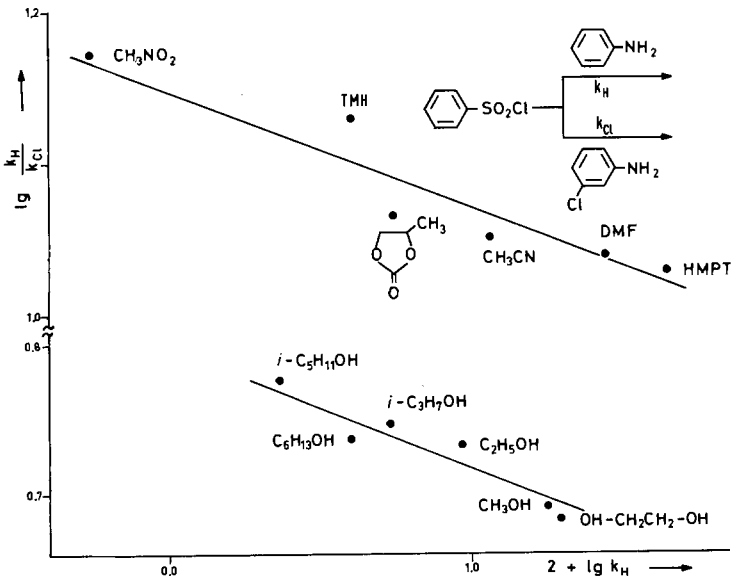


Fig. 6. Checking the RSP by reaction of benzenesulfonyl chloride with aniline and 3-chloroaniline in aprotic and protic solvents at 45 °C. TMH = tetramethylurea, DMF = dimethylformamide, HMPT = hexamethylphosphoramide.

Why should the reactivity-selectivity principle fail for substituent variation and yet remain valid for solvent variation?

This apparent discrepancy is resolved when the various types of interaction between substituents and individual atoms of reacting molecules are taken into consideration. Reactivity changes (that is, selectivity) estimated in a competition system when substituents are varied represent only a partial view of the entire reaction. If reaction of A with BC consists in bond formation A—B and bond cleavage B—C, the free energy of activation $\Delta G^{\neq}$ can be formally split up into two partial values, *viz.* for bond formation ($\Delta G^{\neq}_{AB}$) and bond cleavage ($\Delta G^{\neq}_{BC}$) in the transition state [Eq. (d)].

$$A + B{-}C \longrightarrow [A\cdots B\cdots C]^{\neq} \longrightarrow A{-}B + C$$

$$\Delta G^{\neq} = \Delta G^{\neq}_{AB} + \Delta G^{\neq}_{BC} \qquad (d)$$

Only if partial values $\Delta G^{\neq}_{AB}$ and $\Delta G^{\neq}_{BC}$ change proportionally to $\Delta G^{\neq}$ when substituents R are varied, does each of the formal "partial reactions" describe stereoelectronic reorientation of the entire reaction [Eq. (e)]. Relationships (f) and (g) are derived from (d) and (e). Equation (g) shows that proportional change of $\Delta G^{\neq}$, $\Delta G^{\neq}_{AB}$, and $\Delta G^{\neq}_{BC}$ is possible only if the ratio of bond formation and bond cleavage in the transition state of the reaction is independent of substituents R.

$$\Delta G^{\neq}_{R} \sim \Delta G^{\neq}_{AB,R} \sim \Delta G^{\neq}_{BC,R} \qquad (e)$$

$$\frac{\Delta G^{\neq}_{1}}{\Delta G^{\neq}_{2}} = \frac{\Delta G^{\neq}_{AB,1}}{\Delta G^{\neq}_{AB,2}} = \frac{\Delta G^{\neq}_{BC,1}}{\Delta G^{\neq}_{BC,2}} \qquad (f)$$

$$\frac{\Delta G^{\neq}_{AB,1}}{\Delta G^{\neq}_{BC,1}} = \frac{\Delta G^{\neq}_{AB,2}}{\Delta G^{\neq}_{BC,2}} \qquad (g)$$

This condition, a constant ratio of bond formation to bond cleavage, is met for reaction of α-substituted pyridines *(5)* with the competition system methyl fluorosulfonate/methyl iodide. If formation of a N—C bond is facilitated, as in the case of unsubstituted pyridine compared with the 2-*tert*-butyl derivative, the energy maximum (transition state of the reaction) is already reached while the C—Z bond (Z = OSO_2F, I) is only slightly stretched. Bond formation and bond cleavage are both slight in the transition state *(8)* but extensive in the transition state *(9)*. The ratio of bond formation and bond cleavage turns out to be almost independent of substituent variation in *(5)*.

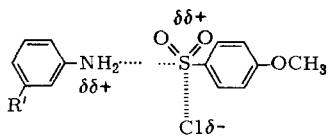


Slight bond formation | Slight bond cleavage | Extensive bond formation | Extensive bond cleavage

(8) (9)

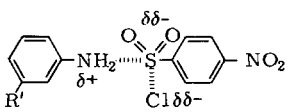
$$\frac{\text{bond formation}}{\text{bond cleavage}} \approx \text{const.}$$

On the other hand, the ratio of bond formation and bond cleavage is not constant when arenesulfonyl chlorides *(7)* react with an aniline/3-chloroaniline system, because substituent variation on sulfonyl chlorides influences bond formation and bond cleavage in opposite directions: a methoxy group at position 4 of the arenesulfonyl chloride impedes formation of a negative charge at the sulfur atom, but facilitates the expulsion of the chloride ion. A nitro group on *(7)*, however, promotes formation of the N—S bond and impedes cleavage of the S—Cl bond. The ratio of bond formation and bond cleavage is smaller in the transition state *(10)* than in the transition state *(11)*. Therefore, the nitrogen atom of *(11)* will bear a higher charge than that of *(10)*, so that the more reactive nitrobenzenesulfonyl chloride is more selective than the less reactive methoxybenzene sulfonyl chloride in the competition system aniline/3-chloroaniline (Fig. 5).



Slight bond formation | Extensive bond cleavage

(10)



Extensive bond formation | Slight bond cleavage

(11)

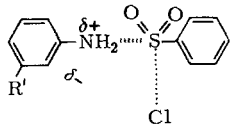
$$\frac{\text{Bond formation}}{\text{Bond cleavage}} = \text{variable}$$

The Hammond postulate indeed holds for these reactions (the faster reaction has an "earlier" transition state), but the RSP is not valid (the more reactive particle is also the more selective one).

Therefore, great care should be taken when interpreting competition measurements, if "central atom B" is varied. Only an analysis of the influence of substituents[12] on bond formation and bond cleavage[13] can supply information on selectivity behavior.

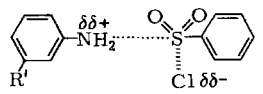
Compared with variation of substituents on arenesulfonyl chloride *(7)*, varying the solvent has quite a different effect on the reaction, because solvents stabilize both the positive charge on the aniline nitrogen and the negative charge on the leaving chloride ion. Transition state *(13)* is reached "earlier" in the more polar ethylene glycol than transition state *(12)* in less polar isoamyl alcohol because of favorable interaction between charges and ethylene glycol.

Isoamyl alcohol:



(12)

Ethylene glycol:



(13)

The RSP holds if varying the solvent influences bond formation and bond cleavage in the same direction: the selectivity of benzenesulfonyl chloride decreases as reactivity increases (Fig. 6).

3.2. Dominating Influence of Frontier-Orbital Interaction

With a number of reactions, however, it seems that other reasons are responsible for simultaneous increase of reactivity and selectivity: if reactions of molecules X_m and Y_n pass through "early" transition states, and energy differences E_I and E_{II} (Fig. 7) between the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) of the same symmetry are small, the course of the reaction can be described in a satisfactory manner by means of stabilization energies ΔE_I and ΔE_{II}[16]. The smaller the orbital differences E_I and E_{II}, the greater are the subsequent stabilizing interactions ΔE_I and ΔE_{II}, and the faster are such reactions. This point of view neglects, for instance, repulsive energy resulting from the mutual approach of molecules X_m and Y_n. Therefore, this model should only be applied to reactions with "early" transition states, in which reacting molecules are still comparatively far apart[16,17].

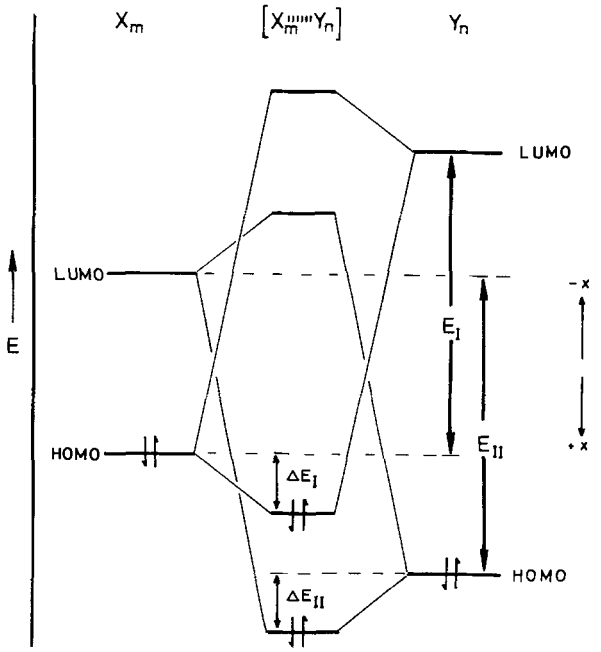


Fig. 7. Interaction between frontier orbitals (HOMO and LUMO) of reacting molecules X_m and Y_n.

Assuming that substituent variation on X_m and Y_n produces a greater effect on the position of frontier orbitals, and subsequently on stabilizing interaction, than on repulsive energy, relationship (h) was derived for cycloadditions[18].

$$\delta \log k = K \cdot \beta^2 \left[\frac{1}{E_I + x} + \frac{1}{E_{II} - x} \right] \qquad \text{(h)}$$

In equation (h), E_I and E_{II} are the differences between HOMO and LUMO (Fig. 7), x is the effect of the substituents on the frontier orbitals, energy-decreasing $(+x)$ and energy-increasing $(-x)$, respectively, β is the resonance integral and K specifies the products of the atomic orbital coefficients (β and K are assumed to be constant for this simplified consideration). The inversely proportional relationship between reactivity and frontier orbital differences shows that the influence of substituents is greater, the smaller the energy differences E_I and E_{II} of the reacting molecules. The selectivity increases with increasing reactivity of molecules X_m and Y_n[18,19].

According to equation (h), plotting reactivity against any parameter varying proportionally to the energy of the frontier orbitals, produces hyperbolas. If the frontier orbitals are arranged in a symmetrical manner, as in Figure 7, a point of intersection of two hyperbolas is obtained. This intersection is attained for the Diels-Alder reaction of bis(dimethylamino)-cyclopentadienone *(14)*, $X = N(CH_3)_2$, with unsubstituted styrene[20] (Fig. 8). Any substitution of styrene causes an increase in reactivity.

Like substituents, solvents influence the energy of the frontier orbitals[22], an effect due to the appropriate "donicity"[23] of the solvents. Thus, according to equation (h), selectivity

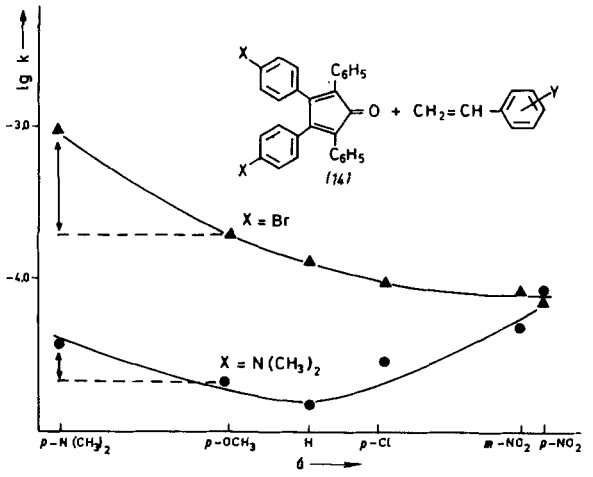


Fig. 8. Reactivities of cyclopentadienones *(14)*, $X = Br$, $N(CH_3)_2$, plotted against σ-parameters of styrene substituents Y.

should increase with increasing reactivity for such cycloadditions if the solvent is changed. This is indeed the case, as is shown by the solvent influence on reactivity values of some Diels-Alder reactions[24] and 1,3-dipolar cycloadditions[25]. A simultaneous increase of selectivity and reactivity was also observed in [2+2]-cycloadditions of diphenylketene and enol ethers (Fig. 9)[26].

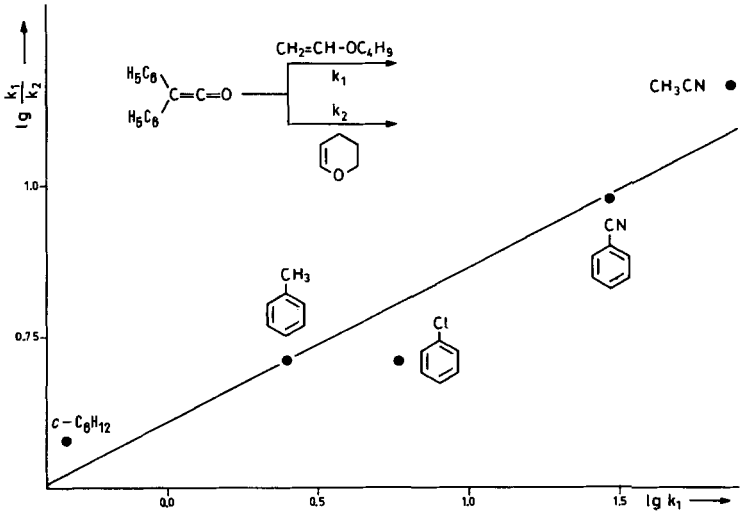


Fig. 9. Solvent influence on reactivity and selectivity of reaction of diphenylketene with butyl vinyl ether and 2,3-dihydropyran.

Varying the substituents on the diene shifts the minimum, according to equation (h). Dibromocyclopentadienone *(14)*, $X = Br$, with lower electron density, reaches minimum reactivity only with styrene derivatives of low electron density. In 4-dimethylaminostyrene/4-methoxystyrene as competition system, selectivity of the fast reacting dibromo compound *(14)* is higher, because reactivity is determined at a steeper part of the hyperbola[21] (Fig. 8).

On the other hand, reaction of tetracyanoethylene (TCNE) with the same competition system shows decreasing selectivity values on increasing reactivity of TCNE due to a change of solvent (Fig. 10)[27].

In contrast to the one-step cycloaddition of diphenylketene[26], tetracyanoethylene and enol ethers form zwitterionic intermediates[27], the formation rates of which are no longer governed by the stabilizing interaction of frontier orbitals.

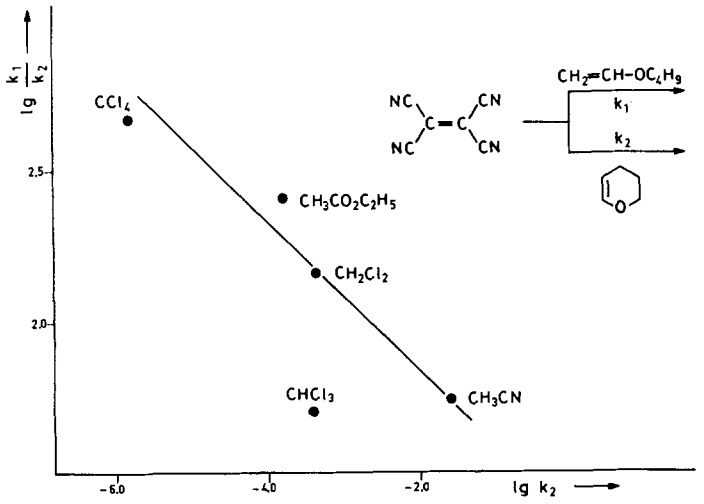


Fig. 10. Solvent influence on reactivity and selectivity of reaction of tetracyanoethylene with butyl vinyl ether and 2,3-dihydropropane.

Therefore, application of the reactivity-selectivity principle to solvent variations can help to distinguish between one-step reactions and formation of zwitterionic intermediates.

4. Dependence on Temperature

4.1. Temperature Dependence of Selectivity Values

Classification of chemical reactions according to the reactivity-selectivity principle as dealt with in Sections 2 and 3 completely ignores the temperature dependence of selectivity values.

However, the selectivity (that is, difference in reactivity[2]) will depend on temperature according to equation (i) if the competing reactions have different activation enthalpies.

$$\log\frac{k_1}{k_2}=\frac{\Delta H_2^{\ddagger}-\Delta H_1^{\ddagger}}{2.303\cdot RT}-\frac{\Delta S_2^{\ddagger}-\Delta S_1^{\ddagger}}{2.303\cdot R} \qquad \text{(i)}$$

Whereas the order of rate constants of reaction series does not change when the temperature is varied[28], the temperature has such a drastic influence on competition constants that selectivity values coincide within a narrow temperature range, the isoselective temperature T_{is}, and reverse their order above this temperature. Halide formation of alkyl radicals R· in the competition system $BrCCl_3/CCl_4$ was the first example of this selectivity behavior to be thoroughly examined[29]. Plotting radical selectivity measured between 0 and 130 °C against the reciprocal temperature produces straight lines as shown in Figure 11. Their position corresponds to the expected gradation of selectivity at 0 °C: the methyl radical, most reactive in CCl_4[30], is less selective than primary, secondary, and tertiary radicals; the most selective is the bulky *tert*-undecyl radical. Between 40 and 80 °C selectivities have similar values and above 80 °C the order is reversed. Thus at 130 °C the methyl radical is the most selective, while the *tert*-undecyl radical is the least selective. A further surprising result is the increase of selectivity differences with increasing temperature above the isoselective temperature (Fig. 11).

The methyl radical remains the most reactive radical in spite of reversal of selectivity, as shown in Figure 12, where

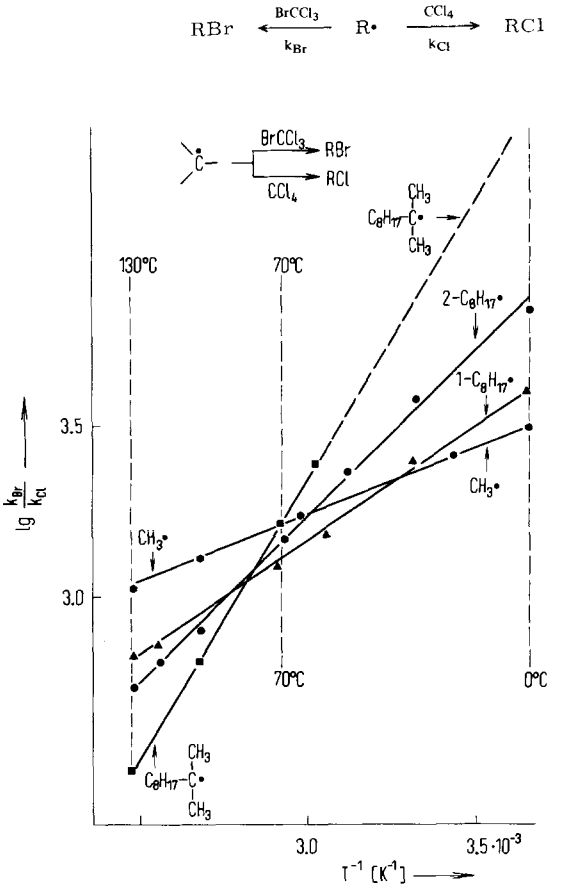


Fig. 11. Reaction of alkyl radicals (π-radicals) in the competition system $BrCCl_3/CCl_4$ between 0 and 130 °C.

selectivity[29] of halogen abstraction in competition system $BrCCl_3/CCl_4$ is plotted against reactivity[30] of chlorine abstraction in CCl_4 for methyl and cyclohexyl radical at various temperatures. Reversal of selectivity is not accompanied by reversal of reactivity.

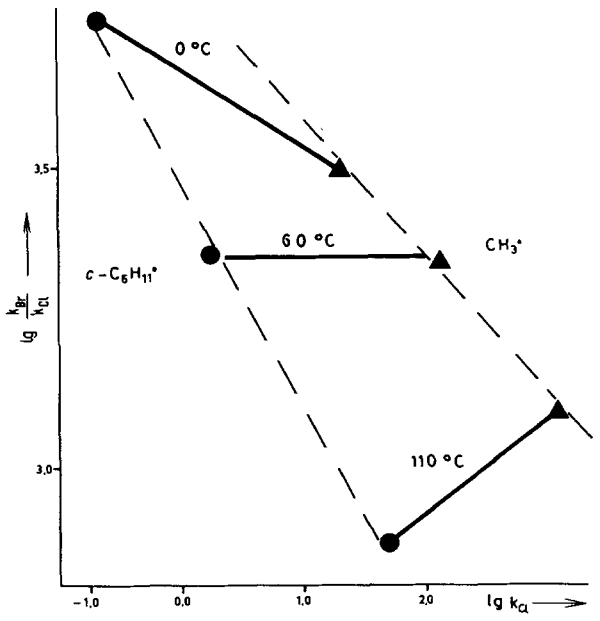


Fig. 12. Selectivity-reactivity plot for reaction of methyl and cyclohexyl radicals in the competition system $BrCCl_3/CCl_4$ at three temperatures.

Like π-radicals[31], σ-radicals also reverse their order[29] (Fig. 13). In this case T_{is} is in the region of 60 °C.

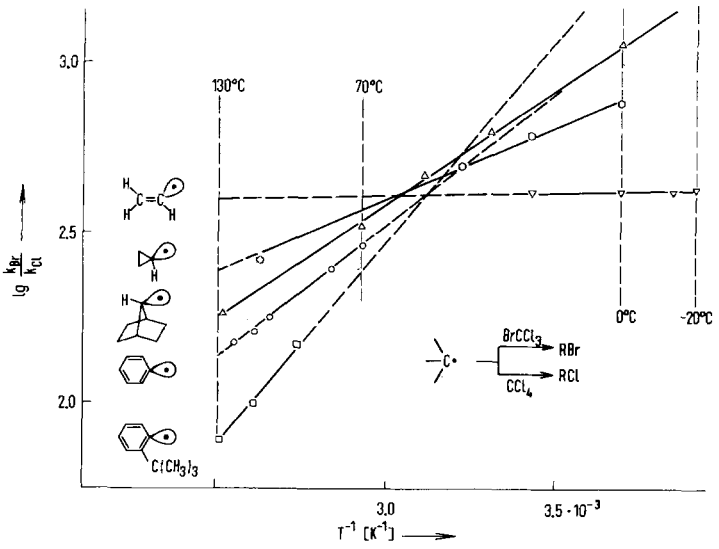


Fig. 13. Reaction of σ-radicals in competition system $BrCCl_3/CCl_4$ between −20 and +130 °C.

Temperature also has a pronounced influence on the selectivities of primary, secondary, and tertiary alkyl radicals in their addition reaction with the 3-chlorostyrene/4-methylstyrene competition system[32]. Distinct differences in selectivity exist at −20 °C, but at +40 °C the radicals have almost identical competition constants (Fig. 14).

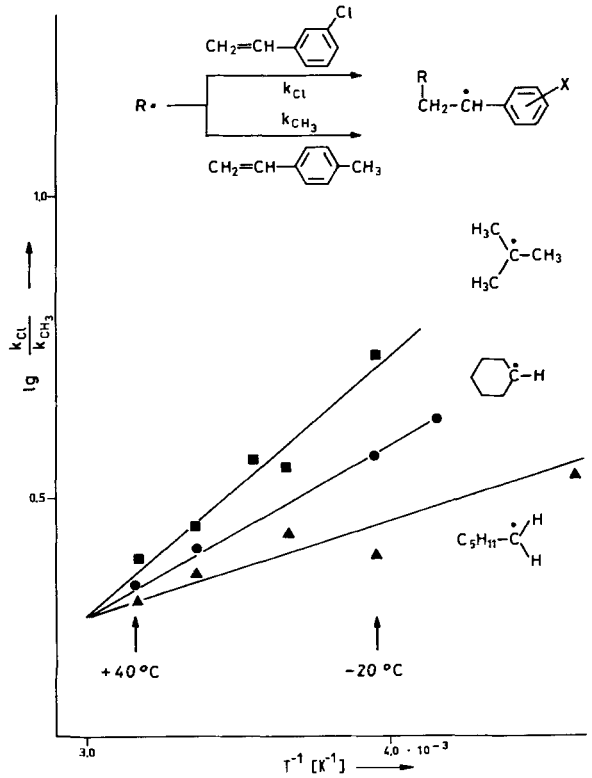


Fig. 14. Reaction of primary, secondary, and tertiary radicals with competition system 3-chlorostyrene/4-methylstyrene between −55 and +40 °C.

Diels-Alder reaction of substituted anthracenes with *N*-arylmaleimide[17] also shows a reversal of selectivity at about 110 °C (Fig. 15). As in radical halogen abstraction (Fig. 11 and 13) the more reactive anthracenes with higher electron density are more selective above the isoselective temperature than the less reactive anthracenes (with lower electron density).

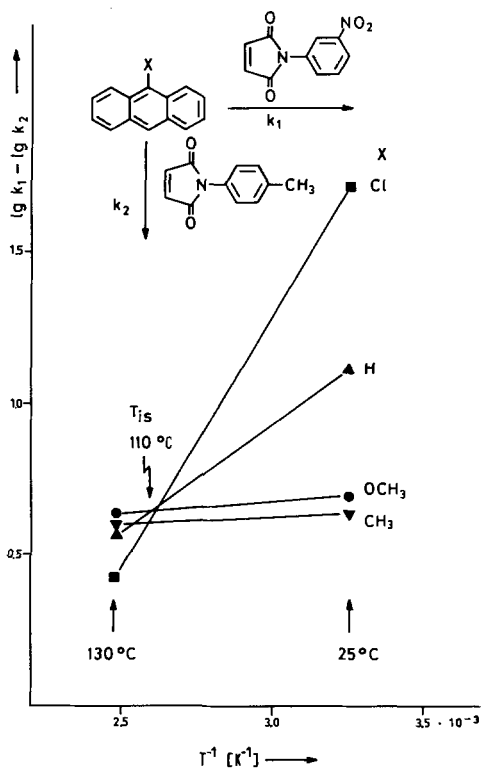


Fig. 15. Temperature dependence of selectivity of anthracene derivates reacting with the competition system *N*-(3-nitrophenyl)maleimide/*N*-(*p*-tolyl)maleimide between 25 and 130 °C.

These examples demonstrate how the temperature dependence of selectivity values may falsify discussions of competition data if T_{is} lies within or below the range of measurement.

4.2. Temperature Dependence of Reaction Parameters in Linear Free Energy Relationships

Equation (j) is the general form of a linear free energy relationship.

$$\log \frac{k_X}{k_0} = p_r \cdot p_s \qquad \text{(j)}$$

Linear free energy relationships describe the effect of substituents (variation of X) on the rate constant k_X of a reaction series. The substituent constants p_s determined in standard reactions and the experimentally determined reactivity differences ($\log k_X - \log k_0$) afford the characteristic reaction parameters, which are dependent on temperature, being typical selectivity values[34]. If variation of reactants X_m or their partners Y_n can be described by substituent parameters of linear free energy relationships, the reaction parameters of the individual series of reactions are essentially equal at the isoselective temperature (T_{is}). This temperature dependence of reaction parameters can be exemplified by the reactions discussed in Section 4.1.

The Taft-Hancock equation (k) has proved its value for halogen abstraction by π-radicals *(15)—(22)*[35]:

$$\log \frac{k_X}{k_{CH_3}} = \delta_X \cdot E_s^c \qquad (k)$$

where δ_X (X = Br, Cl) are the reaction parameters[36] and E_s^c the steric substituent constants[37].

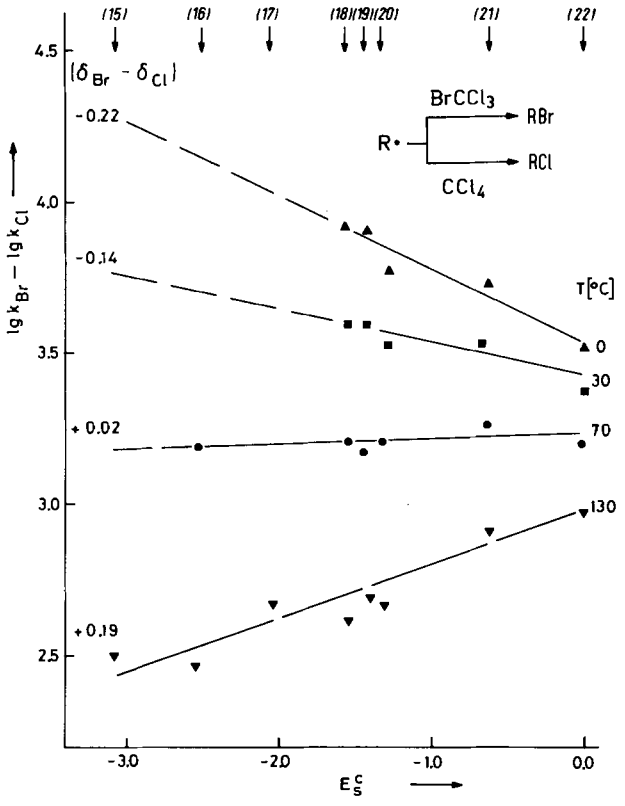


Fig. 16. Dependence of differences in reactivity ($\log k_{Br} - \log k_{Cl}$) for alkyl radicals *(15)—(22)* on steric E_s^c constants between 0 and 130°C. *(15)*, $CH_3\dot{C}(C_2H_5)_2$; *(16)*, $C_8H_{17}\dot{C}(CH_3)_2$; *(17)*, $C_4H_9C(CH_3)_2\dot{C}H_2$; *(18)*, *c*-$\dot{C}_7H_{13}$; *(19)*, *c*-$\dot{C}_6H_{11}$; *(20)*, 2-$\dot{C}_8H_{17}$; *(21)*, 1-$\dot{C}_7H_{15}$; *(22)*, $\dot{C}H_3$.

The various slopes of the straight lines in Figure 16 indicate that the differences of reaction parameters ($\delta_{Br} - \delta_{Cl}$) change their signs at about 60°C. This value accords with the isoselective temperature (Fig. 11). Plotting the differences ($\delta_{Br} - \delta_{Cl}$) directly against $1/T$ affords a straight line. ($\delta_{Br} - \delta_{Cl}$) becomes zero at the isoselective temperature (Fig. 17).

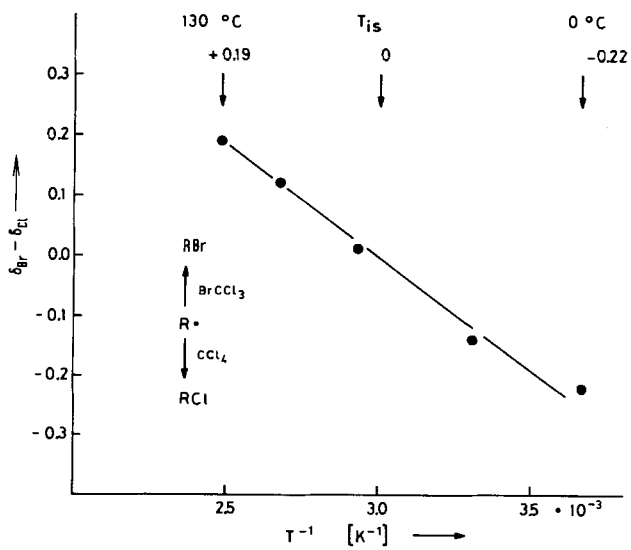


Fig. 17. Temperature dependence of reaction parameter differences ($\delta_{Br} - \delta_{Cl}$) for halogen abstraction by radicals *(15)—(22)* in the competition system $BrCCl_3/CCl_4$.

Addition of alkyl radicals to alkenes (Fig. 14)[32,38] and Diels-Alder reaction of anthracene derivatives with *N*-arylmaleimides[17] (Fig. 15) can be described by the Hammett relationship (l):

$$\log \frac{k_X}{k_H} = \rho \cdot \sigma \qquad (l)$$

In equation (l) the ρ-values are the temperature dependent reaction parameters, the σ-values are the substituent constants[39]. Plotting dienophile selectivity against σ_I-parameters affords almost straight lines, their slopes being of opposite sign at 25 and at 130°C (Fig. 18).

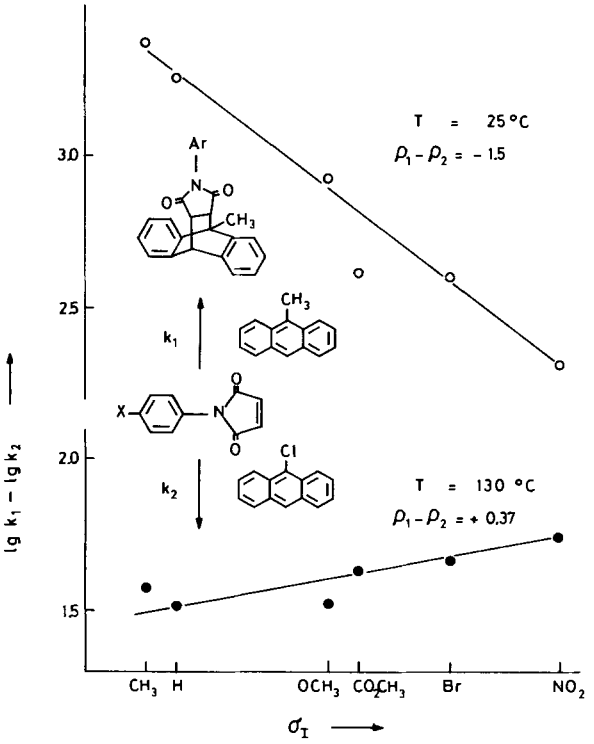


Fig. 18. Dependence of differences in reactivity ($\log k_1 - \log k_2$) on σ_I-parameters for reaction of substituted *N*-arylmaleimides with 9-methylanthracene and 9-chloroanthracene at 25 and 130°C.

This temperature dependence of reaction parameters makes it evident that comparative interpretation of linear free energy relationships is only possible with at least qualitative knowledge of their temperature dependence.

5. The Isoselective Relationship

5.1. Deduction of the Isoselective Relationship

The reactivity-selectivity principle (RSP) is applicable only above or below the isoselective temperature because of the temperature dependence of selectivity values. Which equation, then, is suitable for correct description of the behavior of molecules X_m reacting with Y_n over the entire temperature range?

The temperature dependence of selectivity for every individual particle X_m is described according to the Eyring relationship, equation (i). If boundary condition (m), accounting for coincidence of selectivity values within the immediate vicinity of T_{is}, is introduced, equation (n) evolves, which can be rewritten as the isoselective relationship (o)[40].

$$T_{is}\colon\ 0 \equiv \delta \log \frac{k_1}{k_2} \tag{m}$$

$$0 = \frac{\delta\Delta H_2^{\ddagger} - \delta\Delta H_1^{\ddagger}}{2.303 \cdot R\, T_{is}} - \frac{\delta\Delta S_2^{\ddagger} - \delta\Delta S_1^{\ddagger}}{2.303 \cdot R} \tag{n}$$

$$\delta(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}) = T_{is} \cdot \delta(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}) \tag{o}$$

The isoselective relationship (ISR) signifies the proportional alteration of the differences of activation parameters $\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ and $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$ when particles X_m are varied. δ indicates variation of molecules X_m, the isoselective temperature (T_{is}) is the proportionality factor of the ISR.

Equation (o) is formally very similar to the isokinetic relationship (p), derived from the temperature dependence of reactivity ($\log k$) of a series of reactions (varying X_m and constant Y)[41].

$$X_m \xrightarrow[k]{Y} P$$

$$\delta\Delta H^{\ddagger} = \beta \cdot \delta\Delta S^{\ddagger} \tag{p}$$

In contrast to selectivity, coincidence of reactivity values at a certain temperature (in this case the isokinetic temperature β) and reversal of order of reactivity above this temperature has not yet been observed unequivocally for simple series of reactions[42]. Statistically correct evaluation of results of measurement affords β-values as computational quantities, the physical significance of which is a matter of dispute[28, 43].

5.2. Application of the Isoselective Relationship to Elucidation of Reaction Mechanisms

The RSP relates temperature dependent reactivity and selectivity values, the ISR on the other hand compares activation enthalpies and activation entropies, which are temperature-independent over wide ranges. If, for instance as in the examples of Figures 16 to 18, the large temperature dependence of selectivity values makes interpretation of reaction parameters of linear free energy relationships dubious, the problem can be evaded by plotting differences of activation enthalpies against substituent parameters (Fig. 19).

In Figure 19 the reaction parameters of Taft-Hancock and Hammett relationships for radical halogen abstraction and Diels-Alder reaction are constant quantities with no temperature dependence over wide ranges.

A further application of the ISR makes it possible to distinguish between intermediates with different bonding properties. It was shown that π- and σ-radicals afford two straight lines in $\Delta\Delta H^{\ddagger}/\Delta\Delta S^{\ddagger}$ diagrams[40]. As activation enthalpy and activation entropy are evaluated from the same experiments according to the Eyring relationship and are thus mutually dependent[28, 43], the selectivity of π- and σ-radicals was plotted against $1/T$ in Figure 20. This representation

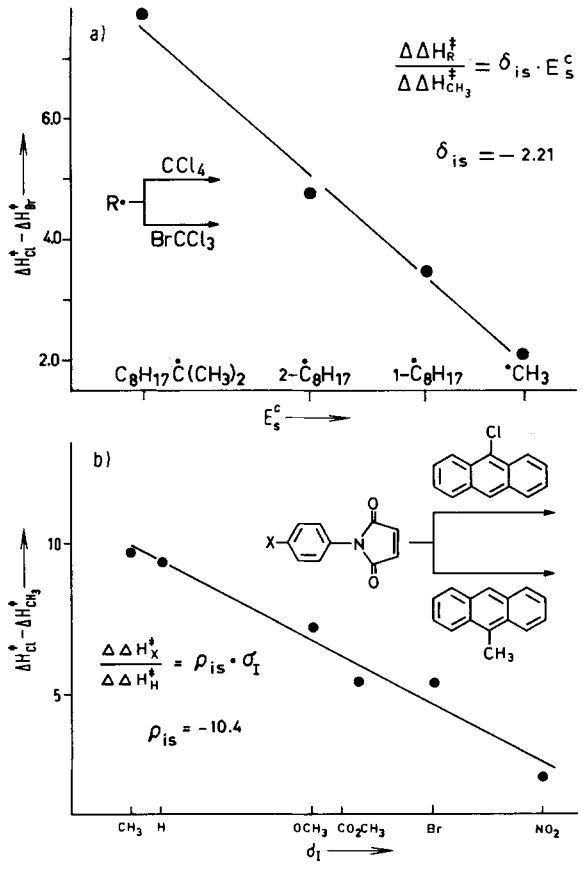


Fig. 19. Linear free energy relationships between activation enthalpy differences and substituent parameters for a) radical halogen abstraction, b) Diels-Alder reaction.

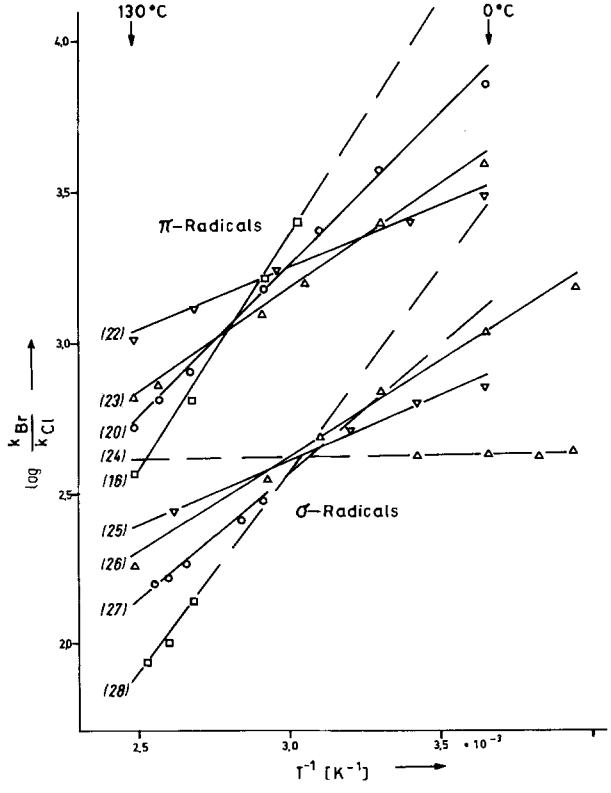


Fig. 20. Temperature dependence of selectivities of π- and σ-radicals for halogen abstraction in competition system $BrCCl_3/CCl_4$.
(23), 1-$\dot{C}_8H_{17}$; *(24)*, $CH_2{=}\dot{C}H$; *(25)*, c-$\dot{C}_3H_5$; *(26)*, 7-norbornyl; *(27)*, $\dot{C}_6H_5$; *(28)*, 2-*t*-$C_4H_9{-}\dot{C}_6H_4$.

is statistically sound, for selectivity and reaction temperature are independent variables[28]. The two fans of straight lines in Figure 20 confirm the existence of two separate isoselective relationships corresponding to π-radicals and σ-radicals, respectively. Thus estimation of competition constants in a $BrCCl_3/CCl_4$ system allows distinction of these types of radical[44].

Similarly, it was possible to distinguish[47] between different types of intermediate[46] occurring when halogens and benzenesulfonyl chlorides are added to alkenes. Figure 21 shows the different changes in selectivity for norbornene derivatives bridged by X=Cl, Br, I or by a phenylthiyl group for intramolecular *endo* trapping reactions with the adjacent ester groups, the temperature ranging from −60 to +60 °C[47].

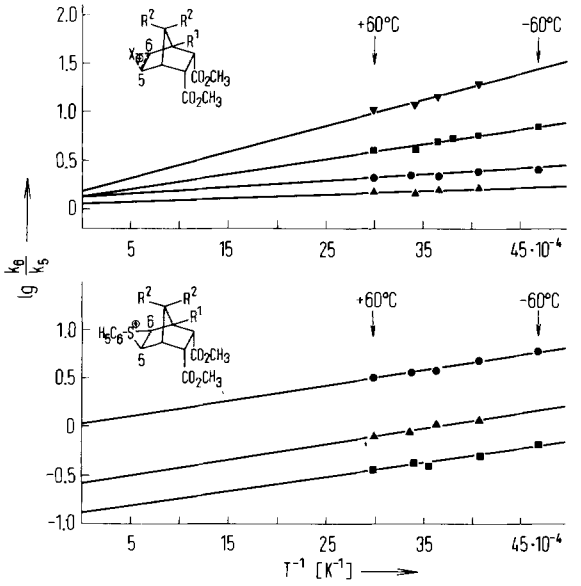
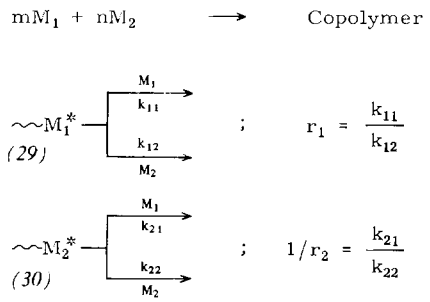


Fig. 21. Different dependence of selectivity of intermediates bridged by halogen (X=Cl, Br, I) or a phenylthiyl group for intramolecular trapping reaction with adjacent ester groups.

The ISR could develop into a diagnostic criterion for distinguishing between different structures of reactive intermediates.

5.3. Use of the Isoselective Relationship for Planning a Synthesis

When the occurrence of several intermediates leads to branching of reaction pathways, the different temperature dependence of selectivity values influences the yields and structures of reaction products. This is shown for example by copolymerization, an extremely important synthetic reaction: the structure of the polymer material is essentially dependent



on copolymerization parameters r_1 and r_2. The values of r_1 and r_2 describe the ability of growing nuclei *(29)* and *(30)* to react competitively with monomers M_1 and M_2[48].

Thus copolymerization parameters are competition constants. The course of copolymerization is specified by the absolute values of r_1 and r_2 and their product $(r_1 \cdot r_2)$. It has been shown for various radicals[32,38] how selectivities in olefin mixtures change to different extents when temperature is varied and become equal at relatively low temperatures (Fig. 14). In the case of radical copolymerization, therefore, copolymerization parameters are temperature-dependent to different extents[49]. Reaction behavior in the vicinity of the isoselective temperature where "ideal copolymerization"[48] is possible, should prove interesting.

6. Conclusion

The fact that the RSP does not hold for many series of reactions does not necessarily render the Hammond postulate useless, as frequently presumed[9,50]. If substituents influence bond cleavage as well as bond formation, a more reactive particle can be more selective than a less reactive molecule in spite of an "earlier" transition state (see Section 3.1). If the Hammond postulate is valid, the RSP is also not applicable at temperatures near or above the isoselective temperature (T_{is}) (see Section 4). This substituent and temperature dependence of selectivity values and reaction parameters must be taken into account when interpreting kinetic data and planning syntheses.

An unsolved problem is the question, for which series of reactions the isoselective temperature might lie within the range of measurement. According to equation (o), T_{is} is low if the activation entropies of reaction series $X_m + Y_1$ and $X_m + Y_2$ differ widely. It was concluded from studies on addition of carbenes to alkenes that variation of reactants in reactions with low activation enthalpies (slight mutual approach of molecules in the transition state) can have greater influence on activation entropy than on activation enthalpy[51]. Adopting this concept, low isoselective temperatures are to be expected in particular for reactions with "early" transition states. T_{is} is actually low for radical addition to styrenes (Fig. 14), for radical halogen abstraction in the competition system $BrCCl_3/CCl_4$ (Fig. 11 and 13), and for Diels-Alder reaction of anthracenes and maleimides (Fig. 15), *e.g.* between 40 and 110 °C; these are reactions with low activation enthalpies. However, temperature dependence of further series of reactions must be determined in order to allow reliable predictions of the types of reaction for which low isoselective temperatures are to be expected.

I wish to express my gratitude to my co-workers Dipl.-Chem. Klaus Heuck, Dipl.-Chem. Jürgen Meister, Dipl.-Chem. Joachim Stellmach, and Mrs. Karla Keller. I owe special thanks to my teacher Professor Rolf Huisgen and to Professor Christoph Rüchardt, whose advice and discussion contributions were of great assistance for this work. Our research was supported by the Deutsche Forschungsgemeinschaft.

Received: January 17, 1977 [A 157 IE]
German version: Angew. Chem. 89, 162 (1977)
Translated by *Robert Winiker*, Freiburg

[1] *R. Huisgen*, Angew. Chem. *82*, 783 (1970); Angew. Chem. Int. Ed. Engl. *9*, 751 (1970).
[2] Reactivity is defined $\log k$, selectivity indicates a difference in reactivity.
[3] *G. S. Hammond*, J. Am. Chem. Soc. *77*, 334 (1955).
[4] *U. Berg, R. Gallo, J. Metzger, M. Chanon*, J. Am. Chem. Soc. *98*, 1260 (1976).
[5] *M. Auriel, E. de Hoffmann*, J. Am. Chem. Soc. *97*, 7433 (1975).
[6] *I. A. Koppel, V. A. Palm* in *N. B. Chapman, J. Shorter:* Advances in Linear Free Energy Relationship. Plenum Press, London 1972, Chap. 5.
[7] Reactions exhibiting such solvent influence are described in a) *B. Giese, R. Huisgen*, Tetrahedron Lett. *1967*, 1889; b) *Y. Drougard, D. Decroocq*, Bull. Soc. Chim. Fr. *1969*, 2972; c) *A. Buckley, N. B. Chapman, M. R. J. Dack, J. Shorter, H. M. Wall*, J. Chem. Soc. *B1968*, 631.
[8] For an extensive discussion of linear "free energy" relationships see *N. B. Chapman, J. Shorter:* Advances in Linear Free Energy Relationships. Plenum Press, London 1972.
[9] *C. D. Johnson*, Chem. Rev. *75*, 755 (1975); and literature cited therein.
[10] *O. Rogne*, J. Chem. Soc. *B1971*, 1855.
[11] *B. Giese, K. Heuck*, unpublished work.
[12] *J. C. Harris, J. L. Kurz*, J. Am. Chem. Soc. *92*, 349 (1970); *E. R. Thornton, ibid. 89*, 2915 (1967).
[13] The necessary desolvation of ions in reaction of charged particles can also be regarded as bond cleavage. *Pross* [14] recently interpreted the surprising selectivity behavior of cations [15] by this means.
[14] *A. Pross*, J. Am. Chem. Soc. *98*, 776 (1976).
[15] *C. D. Ritchie, D. J. Wright, D. Huang, A. A. Kamego*, J. Am. Chem. Soc. *97*, 1163 (1975); and literature cited therein.
[16] *K. Fukui*, Fortschr. Chem. Forsch. *15*, 1 (1970).
[17] *A. I. Konovalov, B. N. Solomonov, A. N. Ustyugov*, Dokl. Akad. Nauk SSSR *213*, 349 (1973).
[18] *R. Sustmann, H. Trill*, Angew. Chem. *84*, 887 (1972); Angew. Chem. Int. Ed. Engl. *11*, 838 (1972); *R. Sustmann*, Pure Appl. Chem. *40*, 569 (1974); *K. N. Houk*, Acc. Chem. Res. *8*, 361 (1975).
[19] *A. I. Konovalov, B. N. Solomonov, A. N. Ustyugov*, Dokl. Akad. Nauk SSSR *211*, 102 (1973).
[20] *A. I. Konovalov, B. N. Solomonov, O. Y. Chertov*, Zh. Org. Khim. *11*, 106 (1975).
[21] Intersection of hyperbolas with opposite signs leads to a curve similar to a parabola, the minimum of which is reached when frontier orbitals are distributed symmetrically (Fig. 7). The smaller the energy differences E_I and E_{II}, the steeper are such parabolas [Eq. (h)].
[22] The influence of solvent on the energies of frontier orbitals can be shown, for instance, by UV spectroscopy; see *H. A. Staab:* Einführung in die theoretische organische Chemie, Verlag Chemie, Weinheim 1964, p. 385. Electrochemical redox reactions supply further information, as shown by unpublished work by *H. Baumgärtel*.
[23] *V. Gutmann*, Angew. Chem. *82*, 858 (1970); Angew. Chem. Int. Ed. Engl. *9*, 843 (1970).
[24] *M. E. Burrage, R. C. Cookson, S. S. Gypte, I. D. R. Stevens*, J. Chem. Soc. Perkin Trans. *1975*, 1325.
[25] *R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies, J. M. Vernon*, Chem. Ber. *98*, 3992 (1965).
[26] *R. Huissgen, L. A. Feiler*, Chem. Ber. *102*, 3444 (1969).
[27] *G. Steiner, R. Huisgen*, Tetrahedron Lett. *1973*, 3769.
[28] *O. Exner*, Prog. Phys. Org. Chem. *10*, 411 (1973).
[29] *B. Giese*, Angew. Chem. *88*, 159 (1976); Angew. Chem. Int. Ed. Engl. *15*, 173 (1976).—Earlier work on the dependence of selectivity on solvents also showed a reversal of the order of selectivity in a narrow temperature range: *H. Pracejus, A. Tille*, Chem. Ber. *96*, 854 (1963).
[30] *J. Currie, H. Sidebottom, J. Tedder*, Int. J. Chem. Kinet. *6*, 481 (1974).
[31] In π radicals a p orbital is occupied by a single electron, whereas in σ radicals the unpaired electron is located in a hybrid orbital. See also [44].
[32] *B. Giese, J. Meister*, unpublished work.
[33] Equilibrium constants can be treated in an analogous manner.
[34] *O. Exner*, Collect. Czech. Chem. Commun. *39*, 515 (1974).
[35] *B. Giese*, Angew. Chem. *88*, 723 (1976); Angew. Chem. Int. Ed. Engl. *15*, 688 (1976).
[36] *R. W. Taft* in *M. S. Newman:* Steric Effects in Organic Chemistry. Wiley, New York 1956, Chap. 13; *C. K. Hancock, E. A. Meyers, B. J. Yager*, J. Am. Chem. Soc. *83*, 4211 (1961).
[37] *T. Fujita, C. Takayama, M. Nakajima*, J. Org. Chem. *38*, 1622 (1973).
[38] *B. Giese, J. Meister*, Angew. Chem. *89*, 178 (1977); Angew. Chem. Int. Ed. Engl. *16*, 178 (1977).
[39] *L. P. Hammett:* Physikalische Organische Chemie. Verlag Chemie, Weinheim 1973.
[40] *B. Giese*, Angew. Chem. *88*, 161 (1976); Angew. Chem. Int. Ed. Engl. *15*, 174 (1976).
[41] *J. E. Leffler, E. Grunewald:* Rates and Equilibria of Organic Reactions. Wiley, New York 1963.
[42] For a discussion of experimental data indicating attainability of isokinetic temperature for certain series of reactions see [28] and [43].
[43] *O. Exner*, Collect. Czech. Chem. Commun. *40*, 2762 (1975).
[44] Distinction of π and σ radicals by different reaction behavior is very interesting because pyramidal structure of the *t*-butyl radical was derived from spectroscopical measurements [45].
[45] *T. Koenig, T. Balle, W. Snell*, J. Am. Chem. Soc. *97*, 662 (1975); *J. B. Lisle, L. F. Williams, D. E. Wood, ibid. 98*, 227 (1976); *D. J. Krusic, P. Meakin, ibid. 98*, 228 (1976).
[46] *B. Giese*, Chem. Ber. *108*, 2978 (1975).
[47] *B. Giese, J. Stellmach*, Angew. Chem. *88*, 258 (1976); Angew. Chem. Int. Ed. Engl. *15*, 237 (1976).
[48] *H.-G. Elias:* Makromoleküle. Hüthig and Wepf, Basel 1975.
[49] *F. M. Lewis, C. Walling, W. Cummings, E. R. Briggs, F. R. Mayo*, J. Am. Chem. Soc. *70*, 1519 (1948).
[50] *C. D. Johnson:* The Hammett-Equation. Cambridge University Press, Cambridge 1973, p. 152.
[51] *P. S. Skell, M. S. Cholod*, J. Am. Chem. Soc. *91*, 6035 (1969).

Organic Fluorescence Reagents in the Study of Enzymes and Proteins

By Yuichi Kanaoka[*]

Studies designed to elucidate life processes require close cooperation between various scientific disciplines. A pertinent example is seen in the application of fluorescence spectroscopy to biological studies, where biological sciences, physical and organic chemistry, and technical innovations complement one another. This report reviews the application of fluorescence probes which bind covalently to certain sites of proteins. The major organic fluorescence reagents used in this field are tabulated.

1. Introduction

Fluorescence probes have been defined by *Edelman* and *McClure*[1] as "small molecules which undergo changes in one or more of their fluorescence properties as a result of noncovalent interaction with a protein or other macromolecules." In general there are three types of fluorescent chromophores in proteins—intrinsic, coenzymic, and extrinsic. The side chains of aromatic amino acid residues are intrinsic chromophores. Studies on intrinsic and coenzymic chromophores have afforded important information about the structure and function of proteins. However, "Nature does not always provide the right chromophore at the right place in a protein" *(Stryer)*[2]. In fact, a variety of extrinsic fluorescence labels, now commonly referred to as fluorescence probes, have been devised and employed for the study of biopolymers. The relative merits and drawbacks of extrinsic labeling techniques, with covalent or noncovalent bonding, depend in complex fashion on the particular system being studied and the type of information desired.

In this article the discussion is mainly confined to the *extrinsic* fluorescence probes which *covalently* combine with enzymes and proteins, since studies with noncovalently bound and naturally occurring labels have been extensively reviewed elsewhere[3]. Instead of encyclopedic coverage of a large number of related papers, we attempt to focus our attention on surveying what fluorogenic groups are employed and what methodologies are applied, since we have been concerned with the development of new approaches in biological studies on the basis of novel organic fluorescence reagents. Our principal interest centers upon specific and preferential labeling of functional sites of proteins; however, some nonspecific and coenzymic examples are referred to where appropriate.

2. Basic Principles of Fluorescence[4–15]

Some of the basic concepts of fluorescence spectroscopy are briefly summarized in this Section. As shown in Figure 1, a molecule that has been excited to an upper singlet energy level (S_2) rapidly goes (in $<10^{-10}$ s) to the lowest excited state (S_1). From S_1 the molecule may go to any of the rotational and vibrational levels of the ground state (S_0), either by fluorescence or by internal conversion, or it may go to the triplet state (T_1) by nonradiative processes referred to as intersystem crossing. The lifetime of a molecule in S_1 may range between 0.1 and 100 nanoseconds (10^{-9} s) depending on the chromophore, seemingly short but still sufficiently long for a variety of chemical and physical interactions to take place, which include rotational motion, solvent reorientation, complex formation, proton transfer, and energy transfer. The processes important for fluorescence spectroscopy are those involving the S_1 state, for they determine the fluorescence spectrum as well as the quantum yield, lifetime, and polarization of

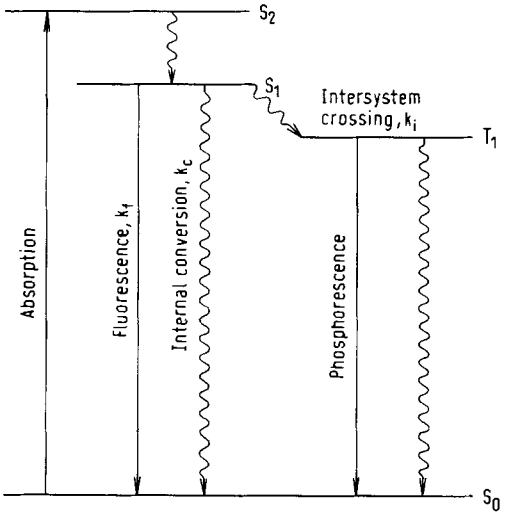


Fig. 1. Energy level diagram of a fluorophore, schematic (see text). Straight and wavy arrows denote radiative and nonradiative processes, respectively.

fluorescence. The fluorescence spectrum represents the intensity of fluorescence at different wave lengths. The fluorescence quantum yield Φ_f is the fraction of excited molecules which fluoresce; it is related to kinetic parameters by Eq. (a)

$$\Phi_f = \frac{k_f}{k_f + k_c + k_i} \qquad (a)$$

where k_f, k_c, and k_i represent the rate constants of fluorescence from S_1, of nonradiative energy loss from S_1, and of intersystem crossing, respectively (see Fig. 1). The fluorescence lifetime τ is defined by Eq. (b), which describes the decay

$$F(t) = F_0 e^{-t/\tau} \qquad (b)$$

of fluorescence intensity following excitation, and is the time required for the intensity F to decay to e^{-1} of its initial value F_0. Eqs. (c) and (d) hold. For a process to compete

[*] Prof. Dr. Y. Kanaoka
Faculty of Pharmaceutical Sciences
Hokkaido University
Sapporo, 060 (Japan)

$$1/\tau = k_f + k_c + k_i \quad (c)$$

$$\Phi_f = k_f \tau \quad (d)$$

effectively with the radiative processes, it must have a rate constant greater than the decay rate of the excited state from which it occurs as shown in Eq. (e), where k is the rate constant of the process.

$$k > 1/\tau \quad (e)$$

When a molecule absorbs plane-polarized light, the emitted light is also plane-polarized. For a randomly labeled, rigid ellipsoidal protein Eq. (f) is obtained, where P and P_0 are the polarization in the presence and absence of rotation, respectively, and ρ_h is the harmonic mean of the rotational relaxation times. It is desirable that 3τ and ρ_h be

$$\frac{1}{P} - \frac{1}{3} = \left(\frac{1}{P_0} - \frac{1}{3}\right)\left(1 + \frac{3\tau}{\rho_h}\right) \quad (f)$$

of similar magnitude. These spatial and polarization properties of emission, studied by fluorescence polarization techniques, allow the rotational motion of macromolecules to be measured in solution and hence permit studies of size, shape, and rigidity of proteins.

3. Molecular Structures and Fluorescence—Strategy of Designing Fluorescence Reagents

For fluorescence to dominate, the rate constant for the fluorescence transition (k_f) must be large relative to those for other competing processes. Strongly fluorescing molecules usually have the following characteristics: (a) The absorption transition of lowest energy is intense (large ε_{max}). Generally the fluorescence spectrum of ($S_1 \rightarrow S_0$) of a molecule is similar to the "mirror image" of its absorption spectrum ($S_0 \rightarrow S_1$). (b) The molecule should not contain structural features or functional groups that enhance the rates of radiationless transitions (k_c, k_i).

In solution, most unsubstituted arenes exhibit fluorescence for they possess low-lying π, π^* singlet states as a result of highly favored π, π^* transitions ($\varepsilon_{max} \approx 10^4$). In molecules with excitable nonbonding (n) electrons, the energy of the n,π^* transition will usually be lower than that of the π,π^* transition. Since n,π^* transitions are less intense ($\varepsilon \approx 10^2$) and have longer lifetimes, k_i is larger starting from an n,π^* state than from a π,π^* state. Generalizing, it may be said that *ortho-para*-directing substituents often enhance fluorescence, whereas *meta*-directing groups repress it[16]. Many of the common *meta*-directing substituents possess low-lying n,π^* states. For example, introduction of nitro groups usually leads to total quenching, while carbonyl substituents (ketone, aldehyde, carboxylic acid derivatives) repress fluorescence. By contrast, some *ortho-para*-directing substituents such as amino, hydroxy, or methoxy tend to enhance the fluorescence of arenes. The diminishing influence of heavy atoms such as bromo- and iodo-substituents is termed the "heavy-atom effect." Some unsaturated nitrogen heterocycles with a lowest n,π^* state do not fluoresce.

In addition, fluorescent properties are also sensitive to environmental factors including solvent, pH, and presence of other chemical species[4, 5]. Notably it is this sensitivity of the fluorescence parameters to the environment of the chromophore which makes the fluorescence labeling a useful tool in the study of conformation and dynamics.

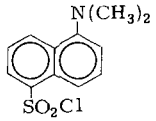
Although the principles of fluorescence of organic molecules outlined above are oversimplified, let us briefly consider the rational approaches to the design of a fluorescence probe (F)-X for proteins, where (F) and X represent a fluorophore (fluorescent chromophore) and a reactive group, respectively. The first requirement for the probes is that they have suitable fluorescent properties: Their emission maxima should be distinct from those of the proteins. The fluorescent characteristics should either be sensitive to the structures and dynamics of the environment if (F) is to be used as a reporter, or relatively insensitive to them if (F) is to serve as a tracer or marker, and as an analytical tool. Their fluorescence lifetimes should be sufficiently long for the proposed application. Secondly, the structure of the probe should allow covalent attachment to the protein at a unique location. Thirdly, it is generally desirable that the probe be soluble in water to some extent, since it is to act on aqueous solutions of protein. Finally, an "all or none" nature greatly facilitates spectroscopic determination, *i.e.* the probe should be nonfluorescent but the protein-conjugate fluorescent, or *vice versa*.

These criteria lead to the following strategy. (a) To compromise between the two contradictory requirements, namely aromatic and hence hydrophobic compounds on the one hand, and water-solubility on the other, aromatic systems having two or three rings are preferred as a fundamental fluorophore. (b) Auxiliary chromophores are necessary, *e.g.* heteroatoms in the ring. Such an addition of polar groups may also favor the solubility. (c) If a reporter is required, the fluorescent properties must be sensitive to polarity and other factors of the environment. (d) It may also be necessary to bear in mind that the absorption and emission maxima may be affected by donor-acceptor interactions with the other chromophores, including tryptophan residues in proteins. (e) For specific labeling, special structural characteristics (*e.g.*, substrate-like or hapten-like) must be present. (f) For covalent bonding suitable organic functional groups must be selected which can react by any mechanism, whether heterolytic, homolytic, or photochemical. (g) Since general rules are not available for the "all or none" nature or the structure-fluorescence lifetime relationship, systematic screening has to be undertaken.

4. Covalent and Random Fluorescence Labeling

If a fluorophore covalently attached to a protein is excited with a polarized light, the fluorescence will also be polarized to a degree that is inversely related to the amount of Brownian motion occurring during the interval between absorption and emission. Since *Weber*'s pioneering work[17], 5-(dimethylamino)-1-naphthalenesulfonyl chloride (DNS-Cl or dansyl chloride) (*1*) is the fluorophore of choice in most polarization studies. DNS-conjugates have usually been assumed to have fluorescence lifetimes τ of 11 to 14 ns regardless of the protein,

and to have a polarization P_0 of about 0.4[18]. Hence DNS-Cl *(1)* is well suited to the polarization studies of modified globular proteins that have hydrodynamic properties corresponding to those of rigid spherical particles with molecular weights of 10000 to 200000. Solvent effects on the fluorescence of DNS-OH and its derivatives have recently been reported[19].



(1), DNS-Cl (or dansyl chloride)

Polarization studies of proteins modified with *(1)* or other reagents have furnished considerable data on rotational motion and on mutual orientation of molecules, showing whether a given molecule is rigid or flexible and indicating its size and shape. Many procedures are available for covalent attachment of the probes[20, 21]. If the method is to be used on very large proteins with long relaxation times, then long fluorescence lifetimes τ are desirable. Anthracene-, pyrene-, and fluorene-conjugates were prepared and indeed shown to have greater τ values than derivatives of *(1)*. Unfortunately, however, the advantage is partly offset by their inherently lower P_0 values[18].

The use of Eq. (f) to determine the rotational relaxation time ρ_h is permissible assuming that fluorophores are randomly distributed on proteins and rigidly attached. In many cases, however, labeling reagents attach preferentially to particular sites. Moreover, the fluorophores may be in different microscopic environments, resulting in heterogeneous emission. Actually many observations suggest that side-chains are mobile, and flexible segments and subunits rotate. Fluorescence spectra, polarization, quantum yields, and lifetimes have been examined as a function of the degree of labeling and the kind of reagent using bovine serum albumin and γ-globulin[22].

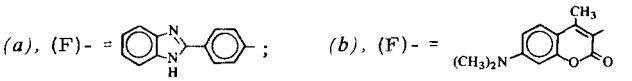
5. Preferential Fluorescence Labeling: Design of a Series of Maleimide Reagents for Thiols[23]

The thiol group is an exceedingly important functional center in biological systems. A wide range of biological phenomena is believed to be somehow dependent on thiols and thiol derivatives[25]; an extensive methodology has been developed for their study. Maleimides generally undergo facile addition to thiols. As thiols are chemically the most active groups found in cells, this reaction is expected to be preferential if not specific for thiols. In earlier work we had found that certain *N*-substituted maleimides *(2)* which are themselves nonfluorescent react readily with various thiols to form fluorescent addition products *(3)*[23a]. This finding led us to develop the reaction shown in Scheme 1 as an empirical "all or none" process[23d] for fluorometric studies on thiol groups.

After careful studies of the reactivity, hydrolytic behavior, and fluorescence properties of a series of maleimides and succinimides, which are their hydrogenation products[23p], we reached the conclusion that it is possible to design thiol reagents carrying a variety of fluorophores (F) yet having similar



(2) nonfluorescent — *(3)* fluorescent



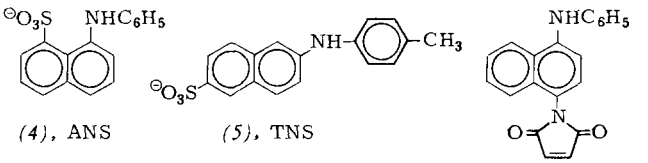
(a), (F)- = ; *(b)*, (F)- =

(2a), BIPM; *(2b)*, DACM

Scheme 1.

reactivities. A systematic search for fluorophores, starting from substituted naphthalenes as the smallest bicyclic system[23o], led us ultimately to *N*-(7-dimethylamino-4-methyl-2-oxo-3-chromenyl)maleimide (DACM) *(2b)*, as a promising reagent of this type which fluoresces at longer wavelengths and is more soluble in water than the others[23l]. In the design of DACM, solubility was enhanced by use of the polar auxochromes coumarinyl and dimethylamino.

Among the initially examined maleimides, *N*-[*p*-(2-benzimidazolyl)phenyl]maleimide (BIPM) *(2a)* turned out to be the first practical reagent in this series. Thus a very sensitive fluorometric determination of thiol compounds has been developed with *(2a)*[23f]. The detection limit is of the order of 0.01 μg of reduced glutathione. BIPM reacts specifically with thiol groups of egg albumin to give fluorescent adducts, confirming the suitability of this type of reagent for protein modification[23k]. On the basis of these results the reactivity of thiol groups in proteins was subjected to kinetic analysis. By comparing parameters for thiol groups in Takaamylase A and myosin A, the states of the thiol groups in the protein molecules were studied[23j]. BIPM inhibits cell-free synthesis of polyphenylalanine in a *E. coli* system, thus providing chemical proof of the involvement of thiol groups of the ribosomal protein[23e]. By virtue of its improved fluorescence properties, DACM is expected to find extensive application[23r].



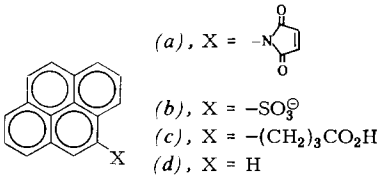
(4), ANS — *(5)*, TNS

(6), ANM

N-Arylaminonaphthalenesulfonates such as ANS *(4)* and TNS *(5)* are used as sensitive probes for the polarity of their environment because the quantum yield increases and the emission maximum shifts toward the blue as the environmental polarity decreases[1-3, 24]. The emission properties appear to be most strongly influenced by reorientation of the solvation sheath during the lifetime of the excited state. The relaxation process depends on the excited state dipole moments of these fluorophores which are large compared to the ground state dipoles, as well as the dipole moment and mobility of the solvent[3, 24]. One of the limitations of the use of hydrophobic probes which are not covalently bound to the protein is that it is often not possible to identify which sites are involved. A more useful approach may well be the

use of fluorophores which are covalently incorporated into the protein. Although chlorides of *(4)* and *(5)* may be such reagents, they are not specific and will react with all nucleophilic sites in a protein.

N-(4-Anilino-1-naphthyl)maleimide (ANM) *(6)* is a reagent which combines the selective reactivity of maleimide toward thiols with the spectral properties of arylaminonaphthalene[23g]. As expected, ANM is a useful hydrophobic probe for thiol groups in proteins. The remarkable solvent-dependence of the fluorescence spectra of the ANM-conjugates was described in terms of *Kosower*'s *Z* values. For example, the environmental hydrophobicity of the reactive thiol in egg albumin was estimated to be 74—79 *Z*[23g, 23p]. The differential hydrophobic nature of the thiols of the elongation factors in protein synthesis was elucidated by means of this reagent[26], while the calcium ion-induced conformational change in a muscle contraction system, *e.g.* the actin-tropomyosin-troponin complex, was analyzed by labeling F-actin or tropomyosin with ANM[23h, 23i, 23n]. A novel technique for the study of the orientation of proteins in membranes has been developed, in which analysis of angular distribution of polarization was applied to ANM-labeled samples of muscle membranes[23s].



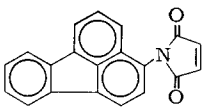
(a), X =

(b), X = $-SO_3^{\ominus}$

(c), X = $-(CH_2)_3CO_2H$

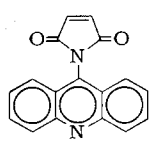
(d), X = H

(7)

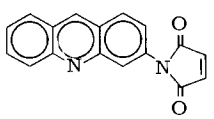


(8), FAM

The fluorescence lifetimes of the adducts of proteins with the above reagents are less than 10 ns, and are thus too short for studies of complex biological systems involving large proteins[23r]. On the basis of the empirical rule (see Section 5) *N*-(4-pyrenyl)maleimide *(7a)* was synthesized whose adducts with proteins had fluorescence lifetimes around 100 ns[28]. After screening polycondensed arenes, we have recently extended the list of reagents by a new "medium lifetime" clock, *N*-(4-fluoranthyl)maleimide (FAM) *(8)*, whose adducts display fluorescence lifetimes of around 20 ns[23m]. Efforts are still continuing to find useful fluorophores like the acridine derivatives *(9)* and *(10)*[23q, 27].

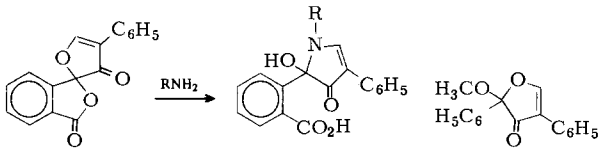


(9)



(10)

Notable advances have been recently made in the preferential labeling of amines. Nonfluorescent hydroxyfuranones react with amino groups to give the highly fluorescent pyrrolin-4-ones[29a, b] (Scheme 2). 4-Phenylspiro[furan-2,1′-phthalan]-3,3′-dione *(11)* has been successfully used for fluorometric assay of proteins in the nanogram range[29c] and sensitive amino acid analysis[29d, 29e], while *(11a)* was utilized for fluorescent labeling of proteins[29b].



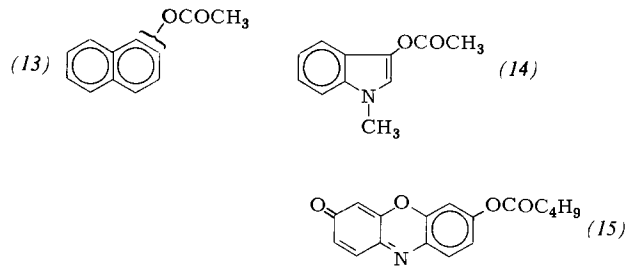
(11) nonfluorescent *(12)* fluorescent *(11a)*

Scheme 2.

6. Specific Fluorescence Labeling; Enzyme Assay

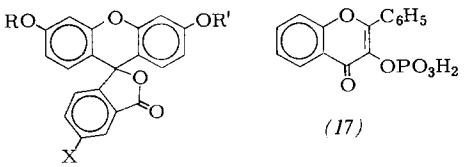
In fluorescent molecules for enzyme research (see Section 3), fluorophores must be introduced into substrate molecules without affecting the activity as substrates and the spectroscopic response. This is feasible: many enzymes can accommodate the extra bulk, without blocking the active site, which must satisfy specific structural requirements[30, 31]. Those substrates which react to form covalently bound intermediates, transient or long-lived, are mainly considered; in addition some of the fluorescent equilibrium inhibitors which exhibit noncovalent interaction are also briefly mentioned.

Because fluorometric methods are generally several orders of magnitude more sensitive than chromogenic ones, a large increase in the sensitivity of measurement is expected ($\approx 10^{-9}$ mol/l). Thus fluorometry has been successfully applied to many enzyme assays[32–35]. The all or none approach is particularly useful: fluorogenic substrates are nonfluorescent but are transformed by enzymatic action into a fluorescent product. Utilizing the enzyme-catalyzed hydrolysis of a nonfluorescent ester to a highly fluorescent alcohol, the method has been extensively



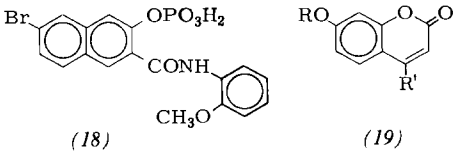
(13) *(14)* *(15)*

used for the determination of hydrolytic enzymes. For example, naphthyl acetates *(13)*[35a], *N*-methyl-3-indolyl acetate *(14)*[35a], and resorufin butyrate *(15)*[35a] were used for determination of cholinesterases. Dibutyrylfluorescein *(16a)*, R = R′ = butyryl, was used for lipases[35a, 36] while the bis(β-D-galactopyranoside)[37] and the 3-*O*-methyl phosphate[38, 39]



(16a), X = H
(16b), X = NCS

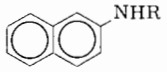
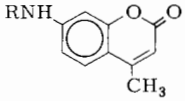
(17)



(18) *(19)*

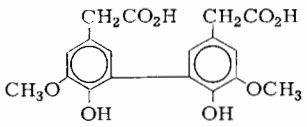
were used for galactosidase and phosphatases, respectively. The phosphates *(17)*[39] and *(18)*[35d] can also be used for determining phosphatases. Riboflavin 5-phosphate served the same purpose in a histochemical procedure[40].

Coumarin is one of the most versatile of the fundamental fluorophores. Thus esters of umbelliferone (7-hydroxycoumarin) *(19)* or its 4-methyl derivative *(19)*, $R'=CH_3$, are frequently employed as fluorogenic substrates for various hydrolytic enzymes. The phosphate[35f] is excellently suited for determination of phosphatases, and many other esters have been used for carbohydrate hydrolases[33-34]. Likewise, assays for peptidases and proteases make use of the similar fundamental fluorophores, naphthalene and coumarin. The β-naphthylamides *(20)* of phenylalanine[41], L-leucine[42], and cystine[42]

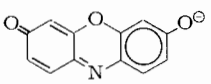
(20)   *(21)*

R = CO–CHR–NR_2

were used for aminopeptidase, leucineaminopeptidase, and oxytocinase, respectively. Assays for carboxypeptidase made use of *N*-(β-naphthyloxycarbonyl)phenylalanine[43,44]. We have recently found that the L-leucine derivative of *(21)* is the substrate of choice for leucineaminopeptidase[45]. The benzoyl-L-arginine derivative of *(20)* was used for trypsin[46a]. Further improvements are expected from corresponding derivatives having the coumarin skeleton [*(21)*][46b]. The following examples illustrate the applications to assays for oxidative enzymes. Nonfluorescent homovanillic acid was oxidized enzymatically to the fluorescent dimer *(22)*[35f]. Dehydrogenases can be determined on the basis of the conversion of resazurin (resorufin *N*-oxide) to the resorufin anion *(23)* with participation of the NAD-NADH or NADP-NADPH system[35a].



(22)

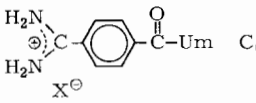


(23)

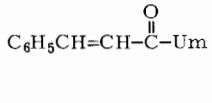
The typical reaction course of some hydrolytic enzymes (E) is formulated in terms of the acyl-enzyme model [Eq. (g)], where $X^{\ominus}$ is a leaving group and E—COR is the intermediate acylenzyme.

$$E + R{-}COX \underset{}{\overset{K_m}{\rightleftharpoons}} E{\cdot}R{-}COX \xrightarrow[-X^{\ominus}]{k_2} E{-}COR \xrightarrow[+H_2O]{k_3} E + R{-}CO_2H \quad (g)$$

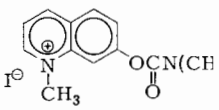
For quantitative enzyme studies the necessity of determining the concentration of active sites instead of using arbitrary activity units is becoming increasingly clear[47]. Important characteristics in assessing usefulness as a "titrant" are: large k_2, small k_3, and small K_m. In compound *(24)*, the protonated *p*-amidinobenzoyl moiety which has a strong affinity for the trypsin active site[48a] and a 4-methylumbelliferyl moiety are combined. The burst [formation of $X^{\ominus}$ in Eq. (g)] titration by fluorometry and the steady state kinetics revealed that *(24)* is a good fluorescent titrant for trypsin, while the cinnamic ester *(25)* can be used as a titrant for chymotrypsin[48b]. The analogous esters of protonated *p*-guanidinobenzoic acid



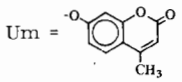
(24)



(25)



(26)

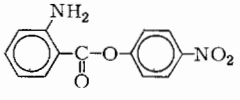


and *p*-trimethylaminocinnamic acid are titrants for trypsin and chymotrypsin, respectively[49]. (7-Dimethylcarbamoyloxy)-1-methylquinolinium iodide *(26)* was used for acetylcholinesterase[50].

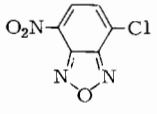
7. Studies on Enzyme Mechanisms

Conformational changes associated with proteolytic zymogen activation have been studied with DNS-substituted peptides [see *(1)*] for chymotrypsinogen[51], with 6-(*N*-methylanilino)-2-naphthalenesulfonyl-(MANS)-peptides for pepsinogen[52a,52b] and with fluorescein-labeled prothrombin[53]. It was suggested that the substrate-binding site is already present in chymotrypsinogen[51]. A change in the emission was observed when disulfide bonds of DNS-substituted Taka-amylase were reductively cleaved[54]. In trypsinogen an amino group was introduced into a tyrosine residue. After labeling with DNS-Cl, the activation process was examined by the fluorescence of DNS[55]. DNS-Cl was in turn an affinity label for the localization of the thyroxine binding site on prealbumin[56].

p-Nitrophenyl anthranilate *(27)* irreversibly inhibits α-chymotrypsin by reacting with the active site[57], while it does not react with chymotrypsinogen. The fluorescent spectra show that the environment of the active site is polar. A determination of the fluorescence polarization and emission kinetics in the nanosecond range indicated that the active site of the acylen-



(27)

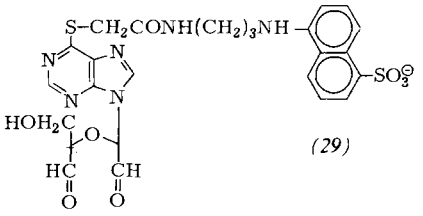


(28)

zyme is rigid and the chromophore has no independent rotational mobility[2,57]. 4-Chloro-7-nitro-2,1,3-benzooxadiazole *(28)*, a fluorescence reagent for thiol groups[58a,b], reacts with cysteine-25 at the active site of papain[59]. *(28)* was also employed as a probe for the coenzyme-induced structural changes in glyceraldehyde 3-phosphate dehydrogenase[58c]. We have recently found that certain esters possessing a cationic site in the leaving group are efficiently hydrolyzed by trypsin to form acyltrypsin[60a]. Using this "inverse substrate" technique, fluorescence reporters can be specifically introduced into the active site of trypsin[60b].

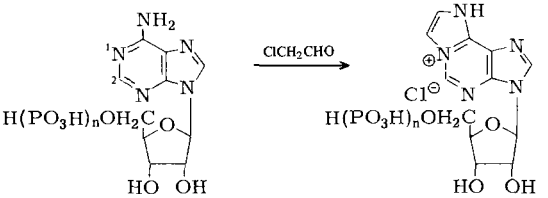
A fluorescent nucleotide analog having the partial structure *(29)* was used for affinity labeling of the initiation site of

E. coli ribonucleic acid polymerase, and covalently reacted with the β-subunit[61]. The inactive labeled enzyme still retains the ability to bind DNA and nucleoside triphosphates. Energy transfer measurements (see Section 8) indicate that initiation site and rifampicin binding site are at least 37 Å apart.



(29)

Possible methods of increasing the fluorescence of purines and pyrimidines consist in extending the conjugated system by addition of fused unsaturated rings and quaternization of heterocyclic nitrogen atoms (cf. Section 3). Fluorescent modification of nucleotide-containing coenzymes was thus performed as shown in the transformation (Scheme 3) of adenosine triphosphate (ATP) *(30)*, $n=3$[62a]. This finding made a set

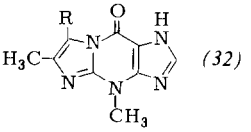


(30), ATP *(31)*

Scheme 3.

of coenzyme derivatives available for fluorescence studies. For example, ε-ATP *(31)*, $n=3$, was inactive as a substrate for firefly luciferase. However, chemically synthesized luciferyl-ε-AMP is oxidized by luciferase and light is emitted[62b]. Although ε-ATP binds to aspartate transcarbamylase, unlike ATP, it inhibits the enzyme suggesting that the N^1 in the purine ring is crucial for ATP activation[62c]. The adenylylation of a tyrosine residue in the subunits of glutamine synthetase plays an important role in regulation of this enzyme in *E. coli*. ε-Adenylylated glutamine synthetase served as an "internal" fluorescence probe for enzyme conformation and subunit interactions[63].

Kinetic methods[64] have found increasing application in fluorescence studies. Three "clocks" may be considered: electronic transitions (S_1 lifetimes), diffusion (rotational relaxation times), and chemical reaction (chemical relaxation times)[64a]. A compilation of reagents for fluorescent labeling has been attempted in Table 1 (Section 9); although noncovalent probes are not our major subject some recent examples are also mentioned in which stopped-flow ($>10^{-4}$ s) and temperature-jump ($>10^{-6}$ s) techniques are employed. The mode of binding to allosteric sites was examined in relation to enzyme regulation[65]. Observation of transient intermediates showed that NAD^+ binding to liver alcohol dehydrogenase causes a conformational change probably coupled with proton release[66]. By monitoring the fluorescence of naturally occurring Y-base *(32)*, the binding of $tRNA^{Phe}$ (yeast) to the cognate synthetase was studied[67]. The preequilibrium kinetics of L-isoleucine activation catalyzed by Ile-tRNA synthetase was analyzed



(32)

with TNS [see *(5)*]; of all the reactants isoleucine binds slowest to the enzyme[68]. The action of papain was examined with *N*-MANS-oligopeptides as fluorescent peptide substrates[52c] (MANS = 6-(*N*-methylanilino)-2-naphthalenesulfonyl). The observed biphasic reaction indicates that an initial enzyme-substrate complex is converted in a first-order process to another complex, which undergoes cleavage to form products.

8. Energy Transfer and Other Methods

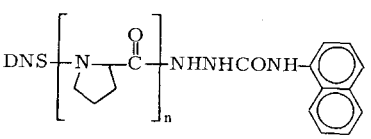
The use of long-range nonradiative transfer of excitation energy for the measurement of distance within molecules has attracted much attention in biopolymer studies. According to *Förster*, singlet-singlet transfer occurs by a resonance interaction of the dipole pair between the energy donor and acceptor chromophores[2, 6, 8, 13, 69]. The distance R_0 (at which transfer is 50 % efficient) is related to spectroscopic and geometric parameters and given by Eq. (h), where n is refractive index, k_f is the rate constant for fluorescence of donor [Eq. (c)], J is the spectral overlap integral, and τ_{D^0} is the lifetime of the donor in the absence of acceptor. K is an orientation factor of the donor and acceptor. A general requirement for excitation transfer is that the donor fluorescence spectrum overlaps the acceptor absorption spectrum, and Eq. (h) applies

$$R_0=(8.71\times10^{23}\,JK^2k_f\tau_{D^0}n^{-4})^{1/6}\ [\text{Å}] \qquad \text{(h)}$$

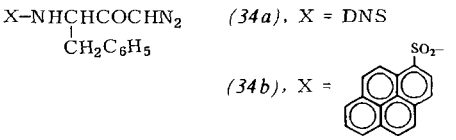
at distances of approximately 10 to 70 Å. The experimental determination of the parameters has been discussed elsewhere[8, 69]. The distance r between a donor and acceptor is given by Eq. (i) where E is the efficiency of transfer.

$$E=\frac{r^{-6}}{r^{-6}+R_0^{-6}} \qquad \text{(i)}$$

The validity of *Förster*'s theory has been well established. Several systems containing donor and acceptor pairs were synthesized and the distances estimated on the basis of the theory[70]. Flexible models with the indole group of tryptophan (Trp) as a donor and DNS as an acceptor were found in *N*-DNS—Trp[69b, 71] and DNS—$NH(CH_2)_nCO$—Trp ($n=1$ to 10)[71]. The distance r increased with n. Several experimental techniques were compared with DNS^{21}—ACTH(1—24)tetra-



(33)

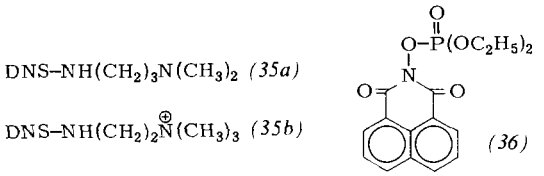


(34a), X = DNS

(34b), X =

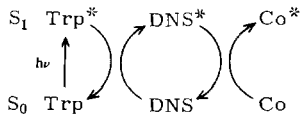
kosapeptide containing Trp in position 9[69b, 73]. Typically, oligomers of poly-L-proline *(33)* served as rigid spacers, in which a donor (α-naphthyl) and an acceptor (DNS) are separated by distances ranging from 12 to 46 Å[72]. The results were in excellent agreement with the r^{-6} dependence predicted by Eq. (i).

Pepsin substrate analogs such as *(34)*, which contain acceptor fluorophore, were covalently introduced into the active site[74] and the energy transfer phenomena were studied. *(35a)* was an active-site-directed, equilibrium probe for the anionic subsite of cholinesterase, while maretin *(36)* was a probe for the esteratic subsite. Kinetic and distance studies on the



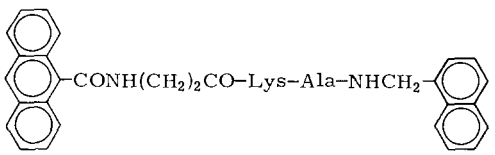
(36)

enzyme were conducted with these probes[75]. A three-component energy transfer relay system consisting of cobalt carboxypeptidase, its DNS-peptide substrates [DNS-(Gly)$_n$-Trp;



Scheme 4.

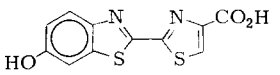
$n=1$ to 3], and tryptophan residues of the enzyme was devised[76]. As shown in Scheme 4, the DNS group served both as an acceptor of Trp excitation energy and as a donor to the cobalt atom. Energy transfer between Trp and DNS rapidly indicates the formation and breakdown of enzyme-substrate complexes; subsequent energy transfer from the bound DNS to the cobalt atom allows calculation of the distance between these moieties. This interesting system suggests far-reaching applications of energy transfer techniques to mechanistic studies of enzymes.



(37)

Tryptic digestion of *(37)* in which the Lys-Ala bond is cleaved was followed by monitoring the increase in fluorescence of a donor (naphthalene) since the transfer of energy to the acceptor (anthracene) is interrupted during the reaction[77]. Aspartate transcarbamylase is feedback regulated by nucleotides. The substrates bind to six catalytic sites and the nucleotide effectors bind to six regulatory sites per enzyme molecule. With the tryptophan residues on the catalytic subunit acting as donor groups, either pyridoxamine phosphate (covalently bound to an amino group at the active site) or ANS (noncovalently bound) is the acceptor[78b]. The pyridoxamine label serves in turn as a donor with mercurinitrophenol bound to the thiol of the catalytic subunit as the acceptor. The observed energy transfer was used to measure the distances between these specific sites.

Refinement of topological studies of proteins on the basis of energy transfer is still in progress[79]. Measurement of the decrease in depolarization during energy transfer to estimate K^2 [see Eq. (h)] values has been reviewed[80] (see Section 9). Circular polarization is related to conformational asymmetry of emitting molecules[81]. Furthermore, interactions of dehydrogenases with ε-ADP [cf. *(31)*] were investigated by the technique in order to analyze various structural changes occurring on coenzyme binding[81c, 81d]. One of the most fundamental as well as promising methods pertinent to fluorescence studies is the nanosecond time-resolved technique[13]. For example, a protein-dye complex of bovine serum albumin and TNS [see *(5)*] has been studied, as has a complex of cystathionase and its coenzyme with pyridoxylamino acids[82]. Decay of fluorescence anisotropy was recently reviewed[83]. The rates of excited state ionization can be directly measured



(38)

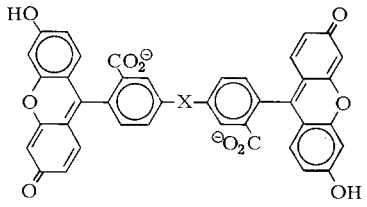
by the time-resolved method. Thus proton transfer rates of dehydroluciferin *(38)* and its complex with luciferase have been studied[84a]. Novel fluorescent probes which undergo excited state ionization have been suggested; they can be used both for the characterization of microenvironments and as sensitive detectors of conformational changes[84b].

9. Applications of Fluorescence Labeling to Studies on Antibodies, Membranes, and Other Complex Systems

Fluorometric techniques have been employed to interpret the immune reaction: quenching of antibody fluorescence by haptens, quenching or enhancement of hapten fluorescence by antibody, and polarization could be observed[81]. However, most of these studies on antibody-hapten interaction use the noncovalently bonded fluorescence reagents. For example anti-DNS antibodies were titrated with ε-DNS-Lys[85], and production of anti-MANS antibodies has recently been reported[86]. The potential scope of nanosecond time-resolved fluorescence spectroscopy in studies of large protein systems, was demonstrated by work on the DNS-Lys/anti-DNS-antibody complex[13, 87]. The emission anisotropy experiments of the DNS bound to the active site of immunoglobulin G (IgG) and to F(ab')^2 and Fab fragments showed that the antibody displays a discrete mode of flexibility consistent with the model of a flexible joint between the heavy chain and the Fab fragment[13, 87]. Circular and linear polarization investigations on a complex of DNS derivatives and anti-DNS antibodies indicated that the asymmetry is induced by complex formation[88]. Kinetic studies of reactions between fluorescein (FLC) and antifluorescein antibody were carried out utilizing polarization measurements in the static (≈ 5 s) and in the stopped-flow (≈ 5 ms) modes[89]. It is the rate of dissociation which largely determines the stability of the hapten complex.

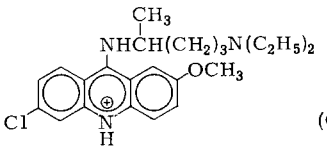
In order to study the shape of the IgG molecule in solution, a hybrid antibody was prepared in which one site specifically bound to the donor, ε-DNS-Lys, and the other site bound

to the acceptor, FLC[85b, 90]. On the basis of the energy transfer theory the distance between the two hapten binding sites as well as the angle between Fab moieties were estimated to reveal that the molecules have an open Y- or T-shaped configuration[90a]. Furthermore, the acceptor FLC was covalently attached by disulfide interchange with the FLC-cystine derivative *(39a)*[90a] to both of the thiols generated by selective reduction of the inter heavy-chain disulfide bond of whole anti-DNS antibody and the $(Fab')_2$ fragments, and of the light-heavy interchain disulfide bond of the Fab fragment. Distance measurements with these systems using nanosecond decay kinetics allowed location of these interchain disulfide bonds, ultimately giving a general idea of the dimensions of IgG.

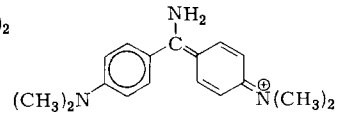


(39a), X = –NHCO–Cys–Cys–CONH–
(39b), X = $-NHCSNH(CH_2)_2S-S(CH_2)_2NHCSNH-$

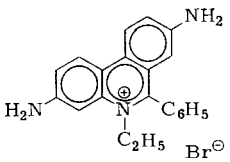
Although a number of fluorescent probes have been employed for studying membranes and macrostructures, the majority of them are noncovalently bound ones. Membranes are assemblies of highly complex chemical entities not confined to proteins. Since several reviews are available[3, 91], only typical fluorophores will be considered. Membrane surface charges were studied with anions; lipid components were examined with anions which are located in the lipid portion; organic anions such as ANS *(4)* and TNS *(5)*[92] and cations



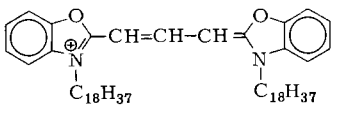
(40)



(41)



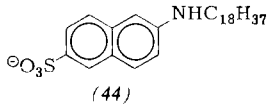
(42)



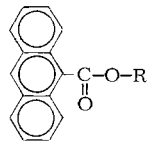
(43)

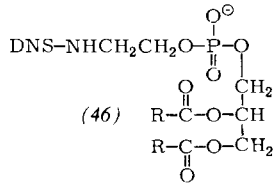
were employed as "energy probes" in excitable membranes. Compound *(35b)* was used for studying membrane-bound cholinergic receptor[93]. From the aminoacridines used, the quinacrine derivative *(40)*[94a] is shown. Other examples of cationic probes are auramin O *(41)*[94b], ethidium bromide *(42)*[95a], and the polymethine compound *(43)*[91c].

Examples of anions are: 6-(octadecylamino)-2-naphthalenesulfonate *(44)*[91b, 96], 12-(9-anthroyl)stearic acid

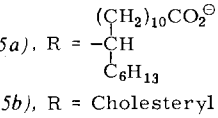


(44)



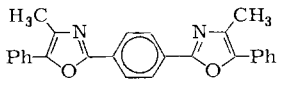


(46)

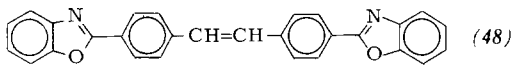


(45a), R =
(45b), R = Cholesteryl

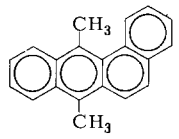
(45a)[91c, 91e, 96], *N*-DNS-phosphatidylethanolamine *(46)*[91b, 96], and 4-pyrenesulfonate *(7b)*[91d].



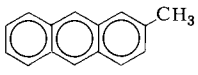
(47)



(48)



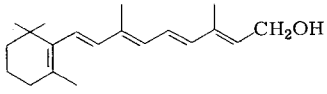
(49)



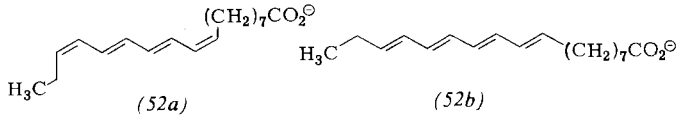
(50)

Neutral molecules are: *p*-bis(4-methyl-5-phenyl-2-oxazolyl)-benzene *(47)*[91c], the bisbenzoxazole derivative *(48)*[96], 7,12-dimethylbenz[*a*]anthracene *(49)*[97b], and 2-methylanthracene *(50)*[97a].

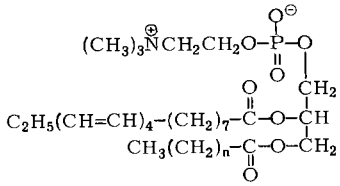
Fatty acid derivatives carrying a polyene fluorophore have also been employed: retinol *(51)*[91d], 9,11,13,15-octadecatetraenoic acids *(52a)* and *(52b)*[95c], and compound *(53)*, a lecithin-type derivative of *(52a)*[95c]. These various probes were chosen for their differences in charge, lipophilicity, rigidity, shape, and size. Pyrene excimer fluorescence was used as probe for micelles[98a] and vesicles[98b, 98c]. 5-(Iodoacetyl-



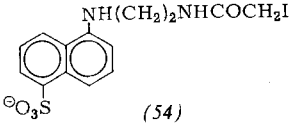
(51)



(52a) *(52b)*



(53)



(54)

$HO_2C-CH(NH-DNS)-CH_2-S-S-CH_2-CH(NH-DNS)-CO_2H$

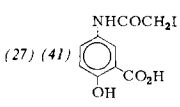
(55)

aminoethylamino)-1-naphthalenesulfonate *(54)*[99a, 99b] and *(28)*[78c] are examples of covalently bonding reagents used for membranes. Motion of proteins in excitable membranes was studied with covalently attached DNS by nanosecond anisotropy[100a], while interacting enzymes were also examined[100b]. A multienzyme complex was analyzed by the energy transfer method[78a]. Proximity relationships in rhodopsin were studied similarly with *(54)*, di-DNS-cystine *(55)*, and difluoresceinisothiocarbamidocystamine *(39b)* as covalently bound fluorophores, from which energy is transfered to retinal[101].

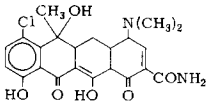
The structures of fluorescence reagents, including those not mentioned in the text, are compiled in Table 1.

Table 1. Reagents for fluorescence labeling.

Benzene derivatives



(27) (41)

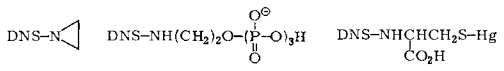


(56)[102a] *(57)*[102b, 102c]

3-Salicylate and 19-salicylhydrazone of strophanthidin [102d]

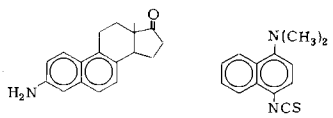
Naphthalene derivatives

(1) (4) (5) (6) (13) (18) (20) (29) (33) (34a) (35) (36) (44) (46) (54) (55)



(58)[103a] *(59)*[103b] *(60)*[103c]

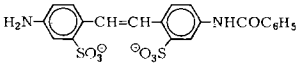
2-(*N*-DNS-Aminoethyl)-1-thio-β-D-galactopyranoside *(61a)* [104] and its 2-(*N*-DNS-aminohexyl) derivative *(61b)* [104]



(62)[96] *(63)*[104a]

Other arenes

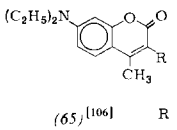
(7) (8) (22) (34b) (37) (45) (49) (50)



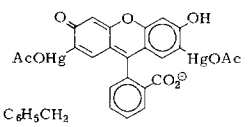
(64)[105]

Oxygen heterocycles

(2b) (16)[107] *(17) (19) (21) (24) (25) (39)*



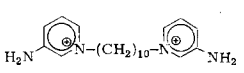
(65)[106] R = H, $C_6H_5CH_2$



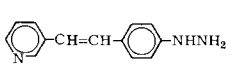
(66)[91c]

Nitrogen heterocycles

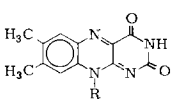
(2a) (9) (10) (11) (11a) (14) (15) (23) (26) (28) (31) (32) (38) (40) (42) (43) (47) (48)



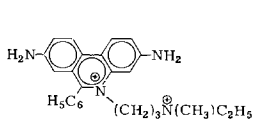
(67)[108a]



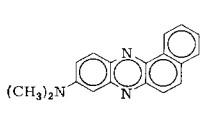
(68)[108b]



(69)[108c]



(70)[108d]



(71)[91d]

Polyenes

(51) (52) (53)

10. Closing Remarks

Fluorescent spectroscopy is among the most sensitive, and one of the most versatile of the methods available for studying structure and dynamics of macromolecules. Application of fluorescence probes to obtain a better understanding of a wide spectrum of biological systems is making rapid advances. In addition to steady-state techniques, advances in nanosecond fluorescence spectroscopy have made it possible to measure directly time-dependent phenomena which will provide a wealth of information about the structure and function of macromolecules. One of the important strategies will be to develop more useful fluorescence probes which can be directed at specific sites of proteins as desired and satisfy specific spectroscopic requirements. For example, there is a need for well-defined systems as appropriate donor-acceptor pairs, a range of compounds with desired gradations of excited-state lifetimes, reagents suitable for fluorescence microscopic use, multifunctional probes with the other kinds of reporters, and biosynthetically incorporated probes.

I am grateful to Professors T. Sekine and M. Machida and to other collaborators involved in our own work cited. Financial support of these studies by the Ministry of Education, Science and Culture, Japan, is gratefully acknowledged.

Received: July 29, 1976 [A 148 IE]
German version: Angew. Chem. *89*, 142 (1977)

[1] *G. M. Edelman* and *W. O. McClure*, Acc. Chem. Res. *1*, 65 (1968).
[2] *L. Stryer*, Science *162*, 526 (1968).
[3] *L. Brand* and *J. R. Gohlke*, Annu. Rev. Biochem. *41*, 843 (1972).
[4] *D. M. Hercules:* Fluorescence and Phosphorescence Analysis. Wiley, New York 1966.
[5] *R. S. Becker:* Theory and Interpretation of Fluorescence and Phosphorescence, Wiley-Interscience, New York 1969.
[6] a) *Y. Kanaoka, K. Shibata, T. Sekine*, and *T. Takagi:* Principles of Fluorescence Spectroscopy and The Application to Studies of Biological Systems (in Japanese). Kyōritsu-shuppan, Tokyo 1974; b) *S. Goto, ibid.* p. 180.
[7] For experimental details see, for example, refs. [6, 8—15].
[8] *L. Brand* and *B. Witholt*, Methods Enzymol. *11*, 776 (1967).
[9] *S. Udenfriend:* Fluorescence Assay in Biology and Medicine. Academic Press, New York 1962, Vol. 1; b) *ibid.* Vol. 2, 1969.
[10] *G. Weber*, Methods Enzymol. *16*, 380 (1969).
[11] *R. F. Chen, H. Edelhoch*, and *R. F. Steiner* in *S. J. Leach:* Physical Principles and Techniques of Protein Chemistry. Academic Press, New York 1965, Part A, Chap. 4.
[12] *C. R. Cantor* and *T. Tao* in *G. L. Cantoni* and *D. R. Davies:* Procedures in Nucleic Acid Research. Harper & Row, New York 1971, Vol. 2, p. 31.
[13] *J. Yguerabide*, Methods Enzymol. *26 C*, 498 (1972).
[14] *G. G. Guilbault:* Practical Fluorescence. Marcel Dekker, New York 1973.
[15] a) *R. F. Chen* and *H. Edelhoch:* Biochemical Fluorescence: Concepts. Marcel Dekker, New York 1975, Vol. 1; b) *R. F. Chen* and *H. Edelhoch, ibid.* Vol. 2, 1976.
[16] *E. L. Wehry* in ref. [14], Chap. 3.
[17] *G. Weber*, Biochem. J. *51*, 155 (1952); Adv. Protein Chem. *8*, 415 (1953).
[18] *R. F. Chen*, in ref. [14], Chap. 12.
[19] *Y.-H. Li, L.-M. Chan, L. Tyer, R. T. Moody, C. M. Himel*, and *D. M. Hercules*, J. Am. Chem. Soc. *97*, 3118 (1975).

[20] a) *H. R. Horton* and *D. E. Koshland Jr.*, Methods Enzymol. *11*, 856 (1967). b) *M. E. Kirtley* and *D. E. Koshland Jr.*, *ibid. 26C*, 578 (1972).
[21] *R. F. Steiner* and *H. Edelhoch*, Chem. Rev. *62*, 457 (1962).
[22] *R. F. Chen*, Arch. Biochem. Biophys. *128*, 163 (1968); *133*, 263 (1969).
[23] a) *Y. Kanaoka, T. Sekine, M. Machida, Y. Soma, K. Tanizawa*, and *Y. Ban*, Chem. Pharm. Bull. *12*, 127 (1964); b) *Y. Kanaoka, M. Machida, Y. Ban*, and *T. Sekine*, *ibid. 15*, 1738 (1967); c) *Y. Kanaoka, M. Machida, H. Kokubun*, and *T. Sekine*, *ibid. 16*, 1747 (1968); d) *Y. Kanaoka, M. Machida, K. Ando*, and *T. Sekine*, Biochim. Biophys. Acta *207*, 269 (1970); e) *K. Kimura, A. Watanabe, M. Machida* and *Y. Kanaoka*, Biochem. Biophys. Res. Comm. *43*, 882 (1971); f) *T. Sekine, K. Ando, M. Machida*, and *Y. Kanaoka*, Anal. Biochem. *48*, 557 (1972); g) *Y. Kanaoka, M. Machida, M. I. Machida*, and *T. Sekine*, Biochim. Biophys. Acta *317*, 563 (1973); h) *T. Sekine, T. Ohyashiki, M. Machida*, and *Y. Kanaoka*, *ibid. 351*, 205 (1974); i) *T. Ohyashiki, T. Sekine*, and *Y. Kanaoka*, *ibid. 351*, 214 (1974); j) *T. Sekine, K. A. Kato, K. Takamori, M. Machida*, and *Y. Kanaoka*, *ibid. 354*, 139 (1974); k) *M. Machida, T. Sekine*, and *Y. Kanaoka*, Chem. Pharm. Bull. *22*, 2642 (1974); l) *M. Machida, N. Ushijima, M. I. Machida*, and *Y. Kanaoka*, *ibid. 23*, 1385 (1975); m) *Y. Kanaoka, T. Takahashi, M. Machida, K. Yamamoto*, and *T. Sekine*, *ibid. 24*, 1417 (1976); n) *T. Ohyashiki, Y. Kanaoka*, and *T. Sekine*, Biochim. Biochim. Biophys. Acta *420*, 27 (1976); o) *M. Machida, M. Bando, Y. Migita, M. I. Machida*, and *Y. Kanaoka*, Chem. Pharm. Bull., in press; p) *M. I. Machida*, Thesis, Hokkaido University (1973); q) *M. Machida, T. Takahashi, K. Itoh*, and *Y. Kanaoka*, to be published; r) *K. Yamamoto, Y. Kanaoka*, and *T. Sekine*, to be published; s) *T. Sekine, K. Kato, Y. Nishijima*, and *Y. Kanaoka*, to be published; t) *Y. Kanaoka* in *M. Natsume:* Organic Reactions for Life Science, (In Japanese) Nankōdo, Tokyo 1976. p. 73.
[24] *C. J. Seliskar* and *L. Brand*, J. Am. Chem. Soc. *93*, 5404, 5414 (1971); Science *171*, 799 (1971).
[25] *P. C. Jocelyn:* Biochemistry of the SH Group. Academic Press, New York 1972; *M. Friedman:* The Chemistry and Biochemistry of the Sulfhydryl Group in Amino Acids, Peptides and Proteins. Pergamon Press, London 1973.
[26] *K. Arai, M. Kawakita*, and *Y. Kaziro*, J. Biochem. *77*, 1095 (1975).
[27] *Y. Nara* and *Y. Tsujimura*, Bunseki Kagaku *22*, 451 (1973).
[28] *J. K. Weltman, R. P. Szaro, A. R. Frackelton, R. M. Dowben, J. R. Bunting*, and *R. E. Cathou*, J. Biol. Chem. *248*, 3173 (1973).
[29] a) *M. Weigele, S. L. DeBernardo, J. P. Tengi*, and *W. Leimgruber*, J. Am. Chem. Soc. *94*, 5927 (1972); b) *M. Weigele, S. DeBernardo, W. Leimgruber, R. Cleeland*, and *E. Grunberg*, Biochem. Biophys. Res. Commun. *54*, 899 (1973); c) *P. Böhlen, S. Stein, W. Dairman*, and *S. Udenfriend*, Arch. Biochem. Biophys. *155*, 213 (1973); d) *S. Stein, P. Böhlen, J. Stone, W. Dairman*, and *S. Udenfriend*, *ibid. 155*, 202 (1973); e) *A. M. Felix* and *G. Terbeksen*, *ibid. 157*, 177 (1973).
[30] *B. R. Baker:* Design of Active-Site-Directed Irreversible Enzyme Inhibitors. Wiley, New York 1967, p. 18.
[31] *C. M. Himel* and *L.-M. Chan* in ref. [15b], Chap. 14.
[32] *G. G. Guilbault*, Anal. Chem. *38*, 537R (1966); *40*, 459R (1968); *42*, 334R (1970).
[33] *G. G. Guilbault*, Enzymatic Methods of Analysis, Pergamon Press, Oxford 1970.
[34] *G. G. Guilbault* in ref. [14], Chap. 8.
[35] a) *G. G. Guilbault* and *D. N. Kramer*, Anal. Chem. *35*, 588 (1963); *37*, 130, 1219 (1965); *38*, 1675 (1965); b) *G. G. Guilbault, M. H. Sadar, R. G. Kzer*, and *S. Skou*, Anal. Lett. *1*, 717 (1968); c) *M. H. Sadar, S. S. Kuan*, and *G. G. Guilbault*, Anal. Chem. *42*, 1770 (1970); d) *G. G. Guilbault* and *A. Vaughan*, *ibid. 43*, 721 (1971); Anal. Lett. *3*, 1 (1970); e) *G. G. Guilbault, S. H. Sadar, R. Glazer*, and *J. Haynes*, *ibid. 1*, 333 (1968); f) *G. G. Guilbault, D. N. Kramer*, and *E. Hackley*, Anal. Chem. *39*, 271 (1967).
[36] *M. Fleisher* and *M. K. Schwaitz*, Clin. Chem. *17*, 417 (1971).
[37] *B. Rotman, J. Zdevic*, and *M. Edelstein*, Proc. Natl. Acad. Sci. USA *50*, 1 (1963).
[38] *J. H. Tierney*, Fed. Proc. *23*, 2381 (1964).
[39] *D. B. Land* and *E. Jackim*, Anal. Biochem. *16*, 481 (1966).
[40] *T. Takeuchi* and *S. Nagami*, Acta Pathol. Japan *4*, 277 (1954).
[41] *L. J. Greenberg*, Biochem. Biophys. Res. Commun. *9*, 430 (1962).
[42] *M. Roth* in *R. Ruyssen* and *E. L. Vandenriesche:* Enzymes in Clinical Chemistry. Elsevier, Amsterdam 1965, p. 10.
[43] *H. A. Ravin* and *A. M. Seligman*, J. Biol. Chem. *190*, 391 (1951).
[44] *N. Lasser* and *J. Feitelson*, Biochemistry *10*, 307 (1971).
[45] *Y. Kanaoka, T. Takahashi*, and *H. Nakayama*, to be published.
[46] a) *M. Roth*, Clin. Chim. Acta *8*, 574 (1963); b) *M. Zimmerman, E. Yurewicz*, and *G. Patel*, Anal. Biochem. *70*, 258 (1976).
[47] *F. J. Kezdy* and *E. T. Kaiser*, Methods Enzymol. *19*, 3 (1970); *T. Chase* and *E. Shaw*, *ibid. 19*, 20 (1970).
[48] a) *K. Tanizawa, S. Ishii*, and *Y. Kanaoka*, Biochem. Biophys. Res. Commun. *32*, 893 (1968); b) *H. Nakayama* and *Y. Kanaoka*, Chem. Pharm. Bull. *21*, 2904 (1973).
[49] *G. W. Jameson, D. V. Roverts, R. W. Adams, W. S. A. Kyle*, and *D. T. Elmore*, Biochem. J. *131*, 107 (1973).
[50] *T. L. Rosenberry* and *S. A. Bernhard*, Biochemistry *10*, 4114 (1971).
[51] *D. A. Deranleau* and *H. Neurath*, Biochemistry *5*, 1413 (1966).
[52] a) *G. P. Sachdev, A. D. Brownstein*, and *J. S. Fruton*, J. Biol. Chem. *248*, 6192 (1973); b) *250*, 501 (1975); c) *J. A. Mattis* and *J. S. Fruton*, Biochemistry *15*, 2191 (1976).
[53] *D. N. Fass* and *K. G. Mann*, J. Biol. Chem. *248*, 3280 (1973).
[54] *T. Takagi, Y. Nakanishi, N. Okabe*, and *T. Isemura*, Biopolymers *5*, 627 (1967).
[55] *R. A. Kenner* and *H. Neurath*, Biochemistry *10*, 551 (1971); *R. A. Kenner*, *ibid. 10*, 545 (1971).
[56] *S.-Y. Cheng, H. J. Cahnmann, M. Wilchek*, and *R. N. Ferguson*, Biochemistry *14*, 4132 (1975).
[57] *R. P. Haugland* and *L. Stryer* in *G. N. Ramachandran:* Conformation of Biopolymers. Academic Press, New York 1967, Vol. 1, p. 321.
[58] a) *G. K. Radda*, Biochem. J. *122*, 385 (1971); b) *D. J. Birkett, N. C. Price, G. K. Radda*, and *A. G. Salmon*, FEBS Lett. *6*, 346 (1970); c) *N. C. Price* and *G. K. Radda*, Biochim. Biophys. Acta *371*, 102 (1974).
[59] *G. Allen* and *G. Lowe*, Biochem. J. *133*, 679 (1973).
[60] a) *K. Tanizawa* and *Y. Kanaoka*, to be published; b) *H. Nakayama, K. Tanizawa*, and *Y. Kanaoka*, unpublished data.
[61] *F. Y.-H. Wu* and *C.-W. Wu*, Biochemistry *13*, 2562 (1974).
[62] a) *J. A. Secrist III, J. R. Barrio, N. J. Leonard*, and *G. Weber*, Biochemistry *11*, 3499 (1972); b) *M. Deluca, N. J. Leonard, B. J. Gates*, and *W. D. McElroy*, Proc. Natl. Acad. Sci. USA *70*, 1664 (1973); c) *Y.-H. Chien* and *G. Weber*, Biochem. Biophys. Res. Commun. *50*, 538 (1973).
[63] *P. B. Chock, C. Y. Huan, R. B. Timmons* and *E. R. Stadtman*, Proc. Natl. Acad. Sci. USA *70*, 3134 (1973).
[64] *Q. H. Gibson*, Methods Enzymol. *16*, 187 (1969); *G. Gutfreund*, *ibid. 16*, 229 (1969); *G. Weber*, *ibid. 16*, 380 (1969); *H. Gutfreund*, Annu. Rev. Biochem. *40*, 315 (1971); *J. F. Kirsch*, *ibid. 42*, 205 (1973); a) *T. M. Jovin* in ref. [15a], Chap. 6.
[65] *G. von Ellenrieda, K. Kirshner*, and *I. Schuster*, Eur. J. Biochem. *26*, 220 (1972).
[66] *J. D. Shore, H. Gutfreund*, and *D. Yates*, J. Biol. Chem. *250*, 5276 (1975).
[67] *G. Krauss, R. Romer, D. Reisner*, and *G. Maass*, FEBS Lett. *30*, 6 (1973).
[68] *E. Holler* and *M. Calvin*, Biochemistry *11*, 3741 (1973).
[69] a) *A. A. Lamola* and *N. J. Turro* in *P. A. Leermakers* and *A. Weissberger:* Technique of Organic Chemistry. Wiley-Interscience, New York 1969, Vol. 14; b) *P. Schiller* in ref. [15a], Chap. 5; c) *I. Z. Steinberg*, Annu. Rev. Biochem. *40*, 83 (1971).
[70] *S. A. Latt, H. T. Cheung*, and *E. R. Blout*, J. Am. Chem. Soc. *87*, 995 (1965); *A. A. Lamola, P. A. Leermakers, G. W. Beyers*, and *G. S. Hammond*, *ibid. 87*, 2322 (1965); *R. D. Rauh, T. R. Evans*, and *P. A. Leermakers*, *ibid. 90*, 6897 (1968).
[71] *R. H. Conrad* and *L. Brand*, Biochemistry *7*, 777 (1968).
[72] *L. Stryer* and *R. P. Haugland*, Proc. Natl. Acad. Sci. USA *58*, 719 (1967).
[73] *P. W. Schiller*, Proc. Natl. Acad. Sci. USA *69*, 975 (1972).
[74] *R. A. Badley* and *F. W. J. Teale*, J. Mol. Biol. *44*, 71 (1969).
[75] a) *C. M. Himel, R. T. Mayer*, and *L. L. Cook*, J. Polymer Sci. A-1 *8*, 2219 (1970); b) *R. T. Mayer* and *C. M. Himel*, Biochemistry *11*, 2082 (1972); c) *L. M. Chan, C. M. Himel* and *A. R. Main*, *ibid. 13*, 86 (1974).
[76] *S. A. Latt, D. S. Auld*, and *B. L. Vallee*, Proc. Nat. Acad. Sci. USA *67*, 1383 (1970); Anal. Biochem. *50*, 56 (1972); Biochemistry *11*, 3015, 4994 (1972).
[77] *A. Carmel, M. Zur, A. Yaron*, and *E. Katchalski*, FEBS Letters *30*, 11 (1973).
[78] a) *O. A. Moe, D. A. Lerner*, and *G. G. Hammes*, Biochemistry *13*, 2552 (1974); b) *S. Matsumoto*, and *G. G. Hammes*, *ibid. 14*, 214 (1975); c) *L. C. Cantley Jr.* and *G. G. Hammes*, *ibid. 14*, 2976 (1975).
[79] *C. R. Cantor* and *P. Pechukas*, Proc. Natl. Acad. Sci. USA *68*, 2099 (1971); *A. Grinvald, E. Haas*, and *I. Z. Steinberg*, *ibid. 69*, 2273 (1972); *Z. Hillel* and *C.-W. Wu*, Biochemistry *15*, 2105 (1976).
[80] *R. Dale* and *J. Eisinger*, in ref. [15a], Chap. 4.
[81] a) *I. Z. Steinberg*, in ref. [15a], Chap. 3; b) *J. Schlessinger* and *I. Z. Steinberg*, Proc. Natl. Acad. Sci. USA *69*, 769 (1972); c) *J. Schlessinger* and *A. Levitzki*, J. Mol. Biol. *82*, 547 (1974); d) *J. Schlessinger, I. Z. Steinberg*, and *A. Levitzki*, *ibid. 91*, 523 (1975).
[82] a) *L. Brand* and *J. R. Gohlke*, J. Biol. Chem. *246*, 2317 (1971); b) *D. C. H. Yang, W. E. Gall*, and *G. E. Edelman*, *ibid. 249*, 7018 (1974); c) *J. E. Churchich, T. Buler*, and *K. J. Oh*, *ibid. 250*, 7722 (1975).
[83] *D. Wahl* in ref. [15b], Chap. 1.
[84] a) *M. Deluca, L. Brand, T. A. Cebula, H. H. Seliger*, and *A. F. Makula*, J. Biol. Chem. *246*, 6702 (1971); b) *M. R. Loken, J. W. Hayes, J. R. Gohlke*, and *L. Brand*, Biochemistry *25*, 4779 (1972).
[85] a) *W. T. Shearer* and *C. W. Parker* in ref. [15a], Chap. 21; b) *R. E. Cathou* and *J. R. Bunting*, *ibid.* Chap. 22; c) *T. J. Yoo*, *ibid.* Chap. 23.

[86] a) *M. Onodera* in ref. [6a], p. 189; b) *M. Onodera, H. Shiokawa,* and *T. Takagi*, J. Biochem. *79*, 195 (1976).

[87] *J. Yguerabide, H. F. Epstein,* and *L. Stryer*, J. Mol. Biol. *51*, 573 (1970).

[88] *J. Schlessinger* and *I. Z. Steinberg*, J. Mol. Biol. *87*, 725 (1974).

[89] *A. J. Portmann, S. A. Levison,* and *W. B. Dandliker*, Biochem. Biophys. Res. Commun. *43*, 207 (1971); *S. A. Levison, A. J. Portmann, F. Krieszenbaum,* and *W. B. Dandliker, ibid. 43*, 258 (1971); *S. A. Levison, A. N. Hicks, A. J. Portmann,* and *W. B. Dandliker*, Biochemistry *14*, 3778 (1975).

[90] a) *T. C. Werner, J. R. Bunting,* and *R. E. Cathou*, Proc. Natl. Acad. Sci. USA *69*, 795 (1972); b) *J. R. Bunting* and *R. E. Cathou*, J. Mol. Biol. *77*, 223 (1973); c) *87*, 329 (1974); d) *H. Kawauchi, K. Kadooka, M. Tanaka,* and *K. Tazimura*, Arg. Biol. Chem. *35*, 1720 (1971).

[91] a) *I. Tasaki, L. Carnay,* and *A. Watanabe*, Proc. Natl. Acad. Sci. USA *64*, 1362 (1969); b) *A. S. Waggoner* and *L. Stryer, ibid. 67*, 579 (1970); c) *J. Yguerabide* and *L. Stryer, ibid. 68*, 1217 (1971); d) *G. K. Radda*, Biochem. J. *122*, 385 (1971); e) *G. K. Radda* and *J. Vanderkooi*, Biochim. Biophys. Acta *265*, 509 (1972); f) *A. Azzi*, Methods Enzymol. *32*, 234 (1974); g) *J. Vanderkooi* and *McLaughlin*, in ref. [15b], Chap. 19; h) *R. Kraaynhof, J. R. Brocklehurst,* and *C.-P. Lee*, in ref. [15b], Chap. 20.

[92] a) *I. Tasaki, E. Carbone, K. Sisco,* and *I. Singer*, Biochim. Biophys. Acta *323*, 220 (1973); b) *I. Tasaki, M. Nallett,* and *E. Carbone*, J. Membr. Biol. *11*, 353 (1973); c) *A. Azzi, B. Chance, G. K. Radda,* and *C. P. Lee*, Proc. Natl. Acad. Sci. USA *62*, 612 (1969).

[93] a) *G. Weber, D. Borris, E. DeRobertis, F. Barrantes, J. La Torre,* and *M. De Carlin*, Mol. Pharmacol. *7*, 530 (1971); b) *J. B. Cohen* and *J.-P. Changeux*, Biochemistry *12*, 4855 (1973).

[94] a) *A. Azzi, A. Fabbro, M. Santano,* and *P. L. Gherardiri*, Eur. J. Biochem. *21*, 404 (1971); b) *A. Azzi*, Biochem. Biophys. Res. Commun. *37*, 254 (1969).

[95] a) *C. Gitler, B. Rubalcava,* and *A. Caswell*, Biochim. Biophys. Acta *193*, 479 (1969); b) *B. Rubalcava, D. M. de Muños,* and *C. Gitler*, Biochemistry *8*, 2742 (1969); c) *L. A. Sklar, B. S. Hudson,* and *R. D. Simoni*, Proc. Nat. Acad. Sci. USA *72*, 1649 (1975).

[96] *R. A. Badley, W. G. Martin,* and *H. Schneider*, Biochemistry *12*, 268 (1973).

[97] a) *M. Shinitzky, A.-C. Dianoux, C. Gitler,* and *G. Weber*, Biochemistry *10*, 2106 (1971); b) *M.-C. Postel-Vinay* and *B. T. SwisCocki*, Biochim. Biophys. Acta *332*, 156 (1974).

[98] a) *H. J. Pownall* and *L. C. Smith*, J. Am. Chem. Soc. *95*, 3136 (1973); b) *A. K. Soutar, H. J. Pownall, A. S. Hu,* and *L. C. Smith*, Biochemistry *13*, 2828 (1974); c) *S. Cheng, J. K. Thomas,* and *C. F. Kulpa, ibid. 13*, 1135 (1974).

[99] a) *E. N. Hudson* and *G. Weber*, Biochemistry *12*, 4154 (1973); b) *F. Y.-H. Wu, K. Nath,* and *C.-W. Wu, ibid. 13*, 2567 (1974).

[100] a) *P. Wahl, M. Kasai,* and *J.-P. Changeux*, Eur. J. Biochem. *18*, 332 (1971); b) *J. L. Churchich* and *Y.-H. Lee*, Biochem. Biophys. Res. Commun. *68*, 409 (1976).

[101] *C.-W. Wu* and *L. Stryer*, Proc. Natl. Acad. Sci. USA *69*, 1104 (1972).

[102] a) *A. D. B. Malcolm* and *G. K. Radda*, Eur. J. Biochem. *15*, 555 (1970); b) *A. H. Caswell* and *J. D. Hatchison*, Biochem. Biophys. Res. Commun. *42*, 43 (1971); c) *G. J. Brewer*, Biochemistry *13*, 5038 (1974); d) *F. Wesch, J. A. Waters, J. W. Daly,* and *B. Witkop*, J. Med. Chem. *15*, 757 (1972).

[103] a) *W. H. Scouten, R. Lubcher,* and *W. Baughman*, Biochim. Biophys. Acta *336*, 421 (1974); b) *M. Onodera* and *K. Yagi, ibid. 253*, 254 (1971); c) *P. C. Leavis* and *S. S. Lehrer*, Biochemistry *13*, 3042 (1974).

[104] *J. P. Reeves, E. Shechter, R. Weil,* and *H. R. Kaback*, Proc. Natl. Acad. Sci. USA *70*, 2722 (1973); *S. Schuldiner, R. Weil,* and *H. R. Kaback, ibid. 73*, 109 (1976); *S. Schuldiner, R. D. Spencer, G. Weber, R. Weil,* and *H. R. Kaback*, J. Biol. Chem. *250*, 8893 (1975); a) *H. Ichikawa, T. Tanimura, T. Nakajima,* and *Z. Tamura*, Chem. Pharm. Bull. *18*, 1493 (1970).

[105] *A. Kotani, M. Naoi, M. Harada,* and *K. Yagi*, J. Biochem. *65*, 835 (1969).

[106] *O. Takenaka, Y. Nishimura, A. Takenaka,* and *K. Shibata*, Biochim. Biophys. Acta *20*, 1 (1970); *Y. Nishimura, O. Takenaka,* and *K. Shibata*, J. Biochem. *20*, 293 (1971).

[107] *M. J. Lee, R. A. Harris,* and *D. E. Green*, Biochem. Biophys. Res. Commun. *36*, 937 (1969).

[108] a) *G. Mooser, H. Schulman,* and *D. S. Sigman*, Biochemistry *11*, 1595 (1972); b) *S. Mizutani, Y. Wakamura, N. Yoshida, T. Nakajima,* and *Z. Tamura*, Chem. Pharm. Bull. *17*, 2340 (1969); c) *K. Yagi*, in ref. [15b], Chap. 15; d) *P. Taylor* and *S. Lappi*, Biochemistry *14*, 1989 (1975).

Poly(organophosphazenes)—Unusual New High Polymers

By Harry R. Allcock[*]

An inorganic-backbone high polymer system based on alternating phosphorus and nitrogen atoms promises to solve many of the problems hitherto associated with conventional organic polymers. The chemistry, structure, biomedical, and technological aspects of these polymers are reviewed.

1. Introduction

Synthetic organic polymers are the basic raw materials for the manufacture of a vast range of articles used in technology and in ordinary daily life. Indeed, the multiplicity of organic polymers discovered in the last 40 years is responsible for much of the technical sophistication of modern life. However, in recent years there has been a decline in the number of new polymer systems used in technology. To a large degree this situation has arisen because new materials are now needed with properties that conventional organic polymers just cannot provide.

A few examples will illustrate this point. Most synthetic polymers burn. When used as textile fibers or as objects in the home, their flammability can only be corrected by the introduction of labile and sometimes toxic flame retardant compounds. Thus, a real need exists for synthetic polymers that are non-flammable and, ideally, will not decompose when heated to elevated temperatures.

Rubber and many synthetic elastomers harden and degrade in the atmosphere, swell and soften in contact with oils, hydrocarbon fuels, and solvents, and lose their elasticity when cooled below -20 or -30°C. A clear need exists for elastomers that do not possess these deficiencies.

In the biomedical field, the construction of replacement body organs, such as artificial heart pumps, replacement blood vessels, artificial skin, replacement tendons, *etc.* has been severely hampered by the incompatibility of many synthetic

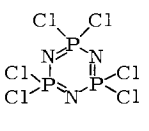
[*] Prof. Dr. H. R. Allcock
Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802 (USA)

polymers with body tissues, blood, and lymph. Also in the medical field, considerable advances in chemotherapy are envisaged if drug molecules could be bound to water-soluble macromolecules in order to bring about a slow, controlled release of the drug. Unfortunately, nearly all synthetic organic polymers are insoluble in water, and most of those that are soluble are also toxic or resistant to biodegradation.

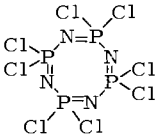
It was with these facts in mind that, several years ago, we undertook to design and synthesize a polymer system that could overcome many of these problems. The system chosen was one based on a polymer skeleton of alternating phosphorus and nitrogen atoms. These polymers are called polyphosphazenes. Only one other inorganic backbone system is currently in broad technological use—the silicone system. As will be illustrated, phosphazene high polymers are considerably more versatile from both a chemical and a potential applications point of view than are the silicones. Moreover, they show striking advantages over most organic polymer systems for the properties and applications mentioned above.

2. Background to Phosphazene Chemistry

The chemistry of *cyclic* (*i.e.* non-polymeric) phosphazenes has a long and distinguished history which extends back for over a hundred and forty years. *Liebig* and *Wöhler*[1] are usually credited with the first synthesis, in 1834, of hexachlorocyclotriphosphazene *(1)* [2,2,4,4,6,6-hexachlorotri(λ^5-phosphazene)] by the reaction of phosphorus pentachloride with ammonia.



(1)



(2)

By 1900 the cyclic tetrameric chlorophosphazene *(2)* had been isolated, the correct structure of *(1)* and *(2)* had been deduced[2–7], their hydrolytic behavior had been studied[8–13], and their thermal conversion to a hydrolytically unstable rubbery material, now known to be a crosslinked form of poly(dichlorophosphazene) *(3)* had been described[8–13]. An improved synthesis of *(1)* and *(2)* was described by *Schenck* and *Römer* in 1924, and this method remains today the basis of the modern manufacturing method[14].

The chemistry of the *cyclic* phosphazenes has been studied intensively since 1955, mainly in Britain, Germany, and the United States. Three main lines of research have been evident. Firstly, the direct synthesis of phosphazenes from halophosphoranes or halophosphanes has received considerable attention. Such reactions are summarized by equations (a)—(d).

$$PCl_5 + NH_4Cl \xrightarrow[-\ HCl]{} (NPCl_2)_{3\ to\ \approx\ 10} \quad [14\text{-}24]\ (a)$$

$$Ph_2PCl_3 + NH_4Cl \xrightarrow[-\ HCl]{} (NPPh_2)_{3\ or\ 4} \quad [25, 26]\ (b)$$

$$Ph_2PCl + NaN_3 \xrightarrow[-\ NaCl,\ -\ N_2]{} (NPPh_2)_{3\ or\ 4} \quad [27]\ (c)$$

$$Me_2\overset{\oplus}{P}(NH_2)_2Cl^{\ominus} \xrightarrow[-\ NH_4Cl]{} (NPMe_2)_{3\ or\ 4} \quad [28]\ (d)$$

It is important to note that none of these direct synthesis reactions yields high polymers. The products are low molecular weight cyclic species. The mechanisms of reactions of types (a) and (b) have been studied in detail[15–23], and it seems clear that the stepwise chain growth mechanism precludes the synthesis of long chains.

The second area of *cyclo*phosphazene research has attracted by far the most activity. It involves the nucleophilic and electrophilic replacement of halogen atoms in halocyclophosphazenes by organic residues, as illustrated by equations (e)—(g).

$$\underset{(1)}{(NPCl_2)_3} \xrightarrow[-\ NaCl]{NaOR} [NP(OR)_2]_3 \quad [29, 30]\ (e)$$

$$\underset{(2)}{(NPCl_2)_4} \xrightarrow[-\ NaCl]{H_2NR} [NP(NHR)_2]_4 \quad [31\text{-}33]\ (f)$$

$$\underset{(1)}{(NPCl_2)_3} \xrightarrow[-\ HCl]{C_6H_6/AlCl_3} (NPPh_2)_3 \quad [25, 34, 35]\ (g)$$

Considerable reaction mechanistic work has taken place, designed to elucidate the *cis/trans*, or geminal/non-geminal characteristics of the reactions.

Thirdly, single crystal X-ray and other techniques have been used extensively to determine the molecular parameters of the cyclic derivatives, mainly for the testing of alternative bonding theories. X-ray work has also been carried out on the clathrate inclusion adducts formed by some cyclotriphosphazenes. All these developments have been reviewed elsewhere[36–41].

Surprisingly, apart from the clathrate adducts[42] and a few cyclophosphazene flame retardant additives, relatively few practical or technological developments have emerged from this earlier research on *cyclic* phosphazenes. However, this work has provided a firm fundamental background for the current emergence of useful phosphazene high polymers. The rest of this review will be concerned exclusively with this polymeric aspect.

3. The Polymer Synthesis Route

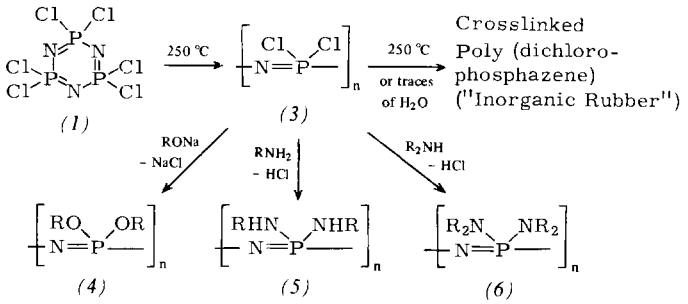
The thermal conversion of hexachlorocyclotriphosphazene *(1)* to the rubbery poly(dichlorophosphazene) has been known for over 80 years[11]. The high polymer is a transparent elastomeric material which has excellent stress-relaxation behavior. It is often called "inorganic rubber". Before 1965 a number of investigators had examined this material for possible use as a technological elastomer. In every case these investigations failed because the polymer is hydrolytically unstable. In contact with a moist atmosphere it degrades slowly to a crusty, crystalline conglomerate of ammonium chloride and ammonium phosphate, with the concurrent evolution of hydrogen chloride.

When we began our investigations, it seemed clear that this material could form the basis of a broad range of new and useful polymers if only the hydrolytic instability could be overcome. The rubbery elasticity of the material, in particular, provided the proof that an inorganic backbone could give rise to properties hitherto associated mainly with organic macromolecules.

In view of the fact that the cyclic trimers and tetramers, such as $(NPCl_2)_3$ *(1)* and $(NPCl_2)_4$ *(2)*, undergo nucleophilic substitution reactions with alkoxides or amines, our strategy was to attempt similar substitution reactions on the high polymer, $(NPCl_2)_n$. The initial experiments were disappointing. The poly(dichlorophosphazene) proved to be swellable, but insoluble, in all organic solvents. Even when the swollen polymer was emulsified in an organic solvent and then treated with nucleophiles, the halogen replacement was incomplete and the resultant polymers remained hydrolytically unstable.

A solution to this problem was provided by a fundamental study of the polymerization of $(NPCl_2)_3$ *(1)* carried out by *Allcock* and *Kugel*[43]. It was reasoned that a polymer which is swelled by but is nevertheless insoluble in a variety of solvents is probably crosslinked. It seemed plausible that the crosslinked modification could be formed from an uncrosslinked species which should be completely soluble in organic media. This was indeed found to be the case. A careful control of the reaction conditions allowed the uncrosslinked polymer to be isolated at an intermediate stage in the polymerization reaction. Subsequent reaction led to crosslinking.

The uncrosslinked poly(dichlorophosphazene) was soluble in benzene or tetrahydrofuran to form highly viscous solutions. *Allcock*, *Kugel*, and *Valan*[43-45] treated such solutions of the polymer with alkoxides, such as sodium methoxide, ethoxide, or phenoxide[43,44] or with amines, such as aniline, piperidine, or dimethylamine[45]. Complete halogen replacement occurred. The substituted products were hydrolytically stable elastomers or flexible thermoplastics. The physical properties changed with each different substituent group. It was clear even from the initial experiments that, given the broad range of available alcohols, phenols, and primary or secondary amines, the system provided a route to the synthesis of an almost unprecedented range of different high polymers. The over-all synthesis route is summarized in Scheme 1.

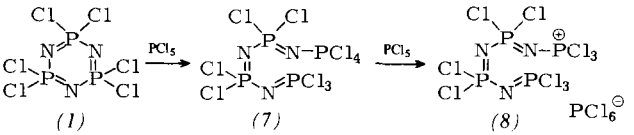


Scheme 1.

4. The $(NPCl_2)_3$ Polymerization Problem

With these facts in mind, it is instructive to ask why these developments did not take place earlier and why the crosslinked form of high polymeric poly(dichlorophosphazene) was apparently not isolated in the preceding 70 years. The answer lies in the complexity of the chlorophosphazene polymerization process. Unlike many organic polymerizations, this is a highly unpredictable reaction that is unusually sensitive to the presence of trace impurities. These function as accelerators, inhibitors, or crosslinking agents.

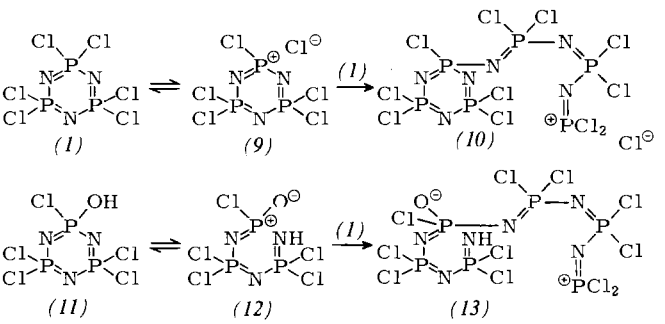
Two examples will illustrate this point. First, phosphorus pentachloride is a powerful polymerization inhibitor. It functions mainly by the cleavage of rings to give non-polymerizable, inhibitory chains[46-48] [see *(7)* and *(8)*] by the end-capping of active chain ends[46].



Since phosphorus pentachloride is a reagent for the synthesis of *(1)*, it can be carried through the trimer purification process in trace amounts sufficient to totally block polymerization.

Secondly, traces of water function as a catalyst at low concentrations (≈ 0.1 %) and as an inhibitor or crosslinking agent at higher concentrations[46]. Clearly, rigorous and standardized purification and polymerization procedures are needed before uncrosslinked polymer can be isolated. Even in the apparent absence of impurities, crosslinking of the polymer takes place after about 75 % of the trimer has been consumed[43,44].

The detailed mechanism of the polymerization is still not fully understood. It is known that the electrical conductivity of the molten trimer rises dramatically at temperatures where polymerization also takes place (>230 °C)[49]. This suggests that ionization of the phosphorus-chlorine bond occurs during initiation or propagation [see *(9)* and *(10)*]. The catalytic effect of water implies either that this reagent facilitates removal of chloride ion from phosphorus, or that hydroxyphosphazenes *(11)* are the true initiators [see *(12)* and *(13)*]. Speculative mechanisms based on these observations are shown in Scheme 2.



Scheme 2.

The mechanism of crosslinking is similarly complex. Traces of water can definitely crosslink the chains[46]. However, if an ionization of the type shown in *(9)* can occur, it seems probable that initiation of *branching* could take place at middle units of the polymer. It appears that non-hydrolytic crosslinking does not occur until a deficiency of trimer exists in the polymerization system. Hence, an attack by active chain ends on other chains would appear to provide a plausible crosslinking mechanism. Nevertheless, this remains an important area for future research.

5. Alkoxy- and Aryloxy-Substituted Polymers

In organic polymer chemistry the modification of existing polymers by substitution reactions can only rarely be used

as a synthesis route. The coiling of polymer chains in solution and the relatively low reactivity of, for example, halogen atoms bonded to a hydrocarbon-type chain, place severe limitations on the degree to which organic polymers can be modified. The same is true of methylsiloxane polymers. The methyl group cannot be replaced effectively by other ligands; hence, each polymer must be made by polymerization of the corresponding "monomers". Obviously, this is not the case with halophosphazene high polymers. The phosphorus-chlorine bond has a very high reactivity in nucleophilic substitution. Hence, the poly(organophosphazene) synthesis route makes use of a chemically unstable polymeric species as an intermediate for the preparation of a multiplicity of stable derivatives.

The introduction of alkoxy or aryloxy groups into a polyphosphazene structure can be performed quite readily. A solution of poly(dichlorophosphazene) *(3)* in benzene or tetrahydrofuran is added dropwise to a stirred solution of a slight excess of sodium alkoxide or aryloxide, usually in an ethereal solvent[43, 44]. After completion of the reaction, the polymer is freed from sodium chloride, reprecipitated, and usually solution-cast as a film, or solution-extruded into fibers.

With the exception of the methoxy- and ethoxy-derivatives, which are elastomers at 25 °C[43, 44], most known alkoxy- or aryloxyphosphazene high polymers are colorless, flexible, film-forming thermoplastics at room temperature[43, 44]. The properties of some typical homopolymers are listed in Table 1. It is important to note that some have very low glass transition temperatures (T_g), and many are microcrystalline materials. All are stable to moisture and, indeed, most can be stored in contact with strong aqueous base or aqueous acid without decomposition. Concentrated sulfuric acid is one of the few reagents that causes degradation[44]. Polymers that contain fluoroalkoxy side groups are also highly water- and oil-repellent. Very few of the polymers examined to date will burn, and many are flame-retardants for organic polymers, such as cotton.

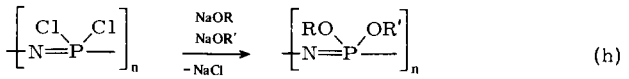
The high torsional mobility of the phosphazene backbone is indicated by the low T_g values. Low T_g values are often associated with elastomeric properties, but in most alkoxy- or aryloxyphosphazene homopolymers, the microcrystallites tend to function as labile "crosslink" sites that impart toughness to the polymer but prevent the facile molecular

Table 1. Properties of Selected Poly(organophosphazenes). T_g = glass transition temperature; T_m = microcrystalline melting point; T_l (in brackets) = additional melting point-like transitions; T_g temperatures quoted in brackets are approximate values or secondary transitions.

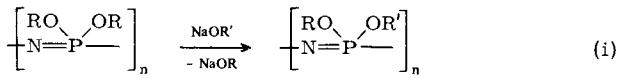
Polymer	T_g [°C]	T_m (or T_l) [°C]	Physical form at 25 °C	Solvent	Ref.
Poly(alkoxy- and poly(aryloxyphosphazenes) of type *(4)*					
$[NP(OMe)_2]_n$	− 76		elastomer	methanol	[43, 44]
$[NP(OEt)_2]_n$	− 84		elastomer	alcohols	[43, 44]
$[NP(OCH_2CF_3)_2]_n$	− 66	242	flexible, orientable thermoplastic	acetone, THF	[43, 44]
$[NP(OCH_2C_2F_5)_2]_n$	(− 25)		flexible thermoplastic	CF_3COOEt	[51]
$[NP(OCH_2CF_2CF_2H)_2]_n$			flexible thermoplastic	THF	[51]
$[NP(OCH_2C_3F_7)_2]_n$	− 65 (14)	100	thermoplastic	fluorocarbons	[51, 51a]
$[NP(OCH_2CF_3)(OCH_2C_3F_7)]_n$	− 77 (− 64)		elastomer	$C_2F_3Cl_3$-acetone	[50, 51a, 52]
$[NP(OCH_2C_2F_5)(OCH_2C_3F_7)]_n$			flexible thermoplastic		[52]
$[NP(OCH_2(CF_2)_6CF_3)_2]_n$	− 40				[53]
$[NP(OCH_2CF_2CF_2H)(OCH_2C_6F_{12}H)]_n$	− 60		elastomer	$C_2F_3Cl_3$-acetone	[52]
$[NP(OPh)_2]_n$	− 8	390 (160)	flexible film-forming thermoplastic	benzene	[43, 44, 54]
$[NP(OC_6H_4F\text{-}p)_2]_n$	− 14		flexible film-forming thermoplastic	THF	[53]
$[NP(OC_6H_4Cl\text{-}p)_2]_n$	4	365 (167)	flexible film-forming thermoplastic	THF	[54, 55, 55a]
$[NP(OC_6H_4Cl\text{-}m)_2]_n$	− 24	370 (66)	flexible film-forming thermoplastic	THF, $CHCl_3$	[54, 55]
$[NP(OC_6H_4Me\text{-}p)_2]_n$	0.3	340 (152)	flexible film-forming thermoplastic	THF, $CHCl_3$	[54, 55]
$[NP(OC_6H_4Me\text{-}m)_2]_n$	− 25	348 (90)	flexible film-forming thermoplastic	THF, $CHCl_3$	[54, 55]
$[NP(OC_6H_4CF_3\text{-}m)_2]_n$	− 35	330	flexible film-forming thermoplastic	THF	[53]
$[NP(OC_6H_4Et\text{-}p)_2]_n$	− 18	(43)	flexible film-forming thermoplastic		[54, 55]
$[NP(OC_6H_4C_6H_5)(OCH_2CF_3)]_n$	22	187		THF, DMSO	[56]
Poly(aminophosphazenes) of type *(5)* and *(6)*					
$[NP(NHMe)_2]_n$	14	140	flexible thermoplastic	water	[57]
$[NP(NHEt)_2]_n$	30		thermoplastic	aqueous acid	[45]
$[NP(NHPr^n)_2]_n$	(− 92)		flexible thermoplastic	CF_3CH_2OH	[57]
$[NP(NHBu^n)_2]_n$			flexible thermoplastic	CF_3CH_2OH	[57]
$[NP(NMe_2)_2]_n$	− 4		flexible thermoplastic	aqueous acid	[45]
$[NP(NC_5H_{10})_2]_n$	19		flexible thermoplastic	benzene	[45]
$[NP(NEt_2)Cl]_n$			elastomer	benzene	[57, 58]
$[NP(NEt_2)(NH_2)]_n$			glass	THF	[57, 58]
$[NP(NEt_2)(NHMe)]_n$	− 106		flexible thermoplastic	THF	[57, 58]
$[NP(NEt_2)(NHEt)]_n$	− 100		flexible thermoplastic	benzene	[57, 58]
$[NP(NEt_2)(NHPr^n)]_n$	< − 120		flexible thermoplastic	benzene	[57, 58]
$[NP(NEt_2)(NHBu^n)]_n$	< − 120		flexible thermoplastic	benzene	[57, 58]
$[NP(NHPh)_2]_n$	91—105		glass	benzene	[45, 59]
$[NP(NHC_6H_4F\text{-}p)_2]_n$			glass	benzene-THF	[59]
$[NP(NHC_6H_4F\text{-}m)_2]_n$	80		glass	benzene-THF	[59]
$[NP(NHC_6H_4Cl\text{-}p)_2]_n$	85		glass	THF	[59]
$[NP(NHC_6H_4Cl\text{-}m)_2]_n$	80		glass	acetone	[59]
$[NP(NHC_6H_4Me\text{-}p)_2]_n$	97		glass	benzene-THF	[59]
$[NP(NHC_6H_4Me\text{-}m)_2]_n$	76		glass	benzene-THF	[59]
$[NP(NHC_6H_4Et\text{-}p)_2]_n$	88		glass	benzene-THF	[59]
$[NP(NHC_6H_4Et\text{-}m)_2]_n$	61		glass	THF	[59]
$[NP(NHC_6H_4Bu^n\text{-}p)_2]_n$	53		glass	benzene-THF	[59]
$[NP(NHC_6H_4OMe\text{-}p)_2]_n$	92		glass	benzene-THF	[59]

conformation changes needed for elasticity. Microcrystallites are formed only if the symmetry and regularity of the chain geometry is high enough to allow adjacent chains to pack together in a regular manner. Hence, the introduction of asymmetry or irregularity should allow the elastomeric characteristics to emerge.

This can be accomplished by the *random* introduction of two or more different alkoxy or aryloxy substituent groups. Two methods are available to achieve this end. Firstly, as demonstrated by *Rose*[50], poly(dichlorophosphazene) can be allowed to react simultaneously with two or more different alkoxides [eq. (h)]. If the reactivities of the two nucleophiles are similar, their introduction into the polymer will be random. Mixed substituent polymers made in this way are essentially non-crystalline, and they form an unusual and valuable series of elastomers[50, 52, 54]. This process is now used on a manufacturing scale to produce technological elastomers[61-64] (see Section 13).



(h)



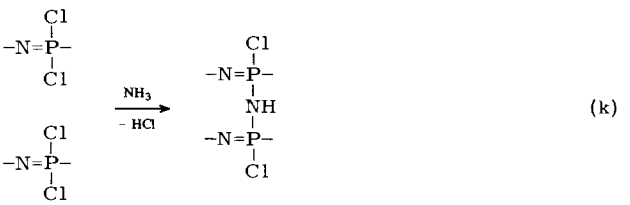
(i)

An alternative way to accomplish the same end is illustrated in equation (i). Treatment of an alkoxyphosphazene homopolymer with the alkali metal salt of a second nucleophile permits a metathetical ligand exchange process to take place[62]. Elastomers made in this way are similar to those prepared by the direct competition route.

Finally, it should be noted that poly(di*chloro*phosphazene) is not the only substrate that can be used to prepare alkoxy- or aryloxyphosphazene polymers. Similar polymers can be made from poly(difluorophosphazene)[65], and presumably poly(dibromophosphazene) behaves in the same way.

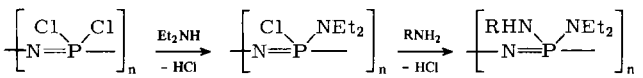
6. Aminophosphazene High Polymers

The aminolysis of poly(dichlorophosphazene) is usually accomplished in the presence of an excess of the amine, which functions both as a nucleophile and a hydrohalide acceptor[45, 57-59]. Completely substituted poly(aminophosphazenes) can be synthesized readily with the use of ethylamine, propylamine, butylamine, aniline, piperidine, dimethylamine, *etc.*[45, 57]. However, ammonia cannot be used as a nucleophile since this reagent crosslinks the chains [eq. (k)][45, 57], and the crosslinking process leads to insolubilization and incomplete substitution. Methylamine behaves similarly at room temperatures or above, but gives fully substituted linear polymers at low temperatures[57]. Obviously, the crosslinking reaction is retarded by increasing steric bulk in the amine.



(k)

However, beyond a certain size, the bulkiness of the *N*-substituent is disadvantageous. For example, *N*-methylaniline does not replace all the halogen atoms in poly(dichlorophosphazene)[57]. Diphenylamine causes decomposition rather than simple substitution. Diethylamine replaces exactly half of the available chlorine atoms[57, 58]. In fact, diethylamine replaces one chlorine atom on each phosphorus to yield a surprisingly stable elastomeric polymer *(14)*, which can itself be subjected to further nucleophilic substitution to yield mixed substituent derivatives *(15)*[57, 58]. These fully substituted polymers are non-crystalline, transparent, film-forming thermoplastics, very similar to cellophane in appearance.



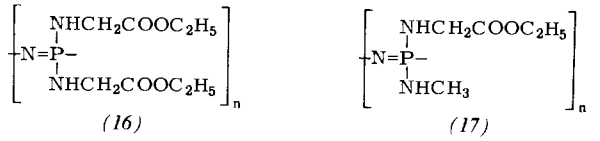
(3) *(14)* *(15)*

All the fully substituted aminophosphazene polymers are film-forming thermoplastics rather than elastomers. Their T_g values tend to be higher than those of related alkoxy- or aryloxy-derivatives, especially when primary amino residues are present. Presumably this reflects the influence of inter- and intramolecular hydrogen bonding in lowering the torsional mobility of the chains[45]. A second difference from alkoxy- or aryloxy-substituted polymers is found in the surface properties and solubility characteristics. Aminophosphazene polymers tend to be hydrophilic rather than hydrophobic, and some are soluble in aqueous rather than organic media. Again, these properties are probably connected with the ease of hydrogen bonding. Some of the properties of typical aminophosphazene polymers are summarized in Table 1.

7. Amino Acid Derivatives

As mentioned earlier, a need exists for polymers that will be either biocompatible or biodegradable to harmless, excretable or metabolizable small molecules. Biodegradable polymers could be used as surgical sutures, temporary tissue-reinforcement films or meshes, or as water-soluble or hydrolyzable carrier molecules for chemotherapeutic drugs or birth control agents.

With these applications in mind, a series of flexible polymers that contain amino acid ester units as substituent groups have recently been synthesized[60]. The amino acid residues are bound to the polymer through the amino component. Polymers have been made which contain either amino acid ester residues only, or both an amino acid ester and a second, water solubilizing group, such as methylamino. Two typical polymers are shown in formulas *(16)* and *(17)*. Other polymers have been prepared which contain esters of alanino, leucino, and phenylalanino groups as substituents on the polymer chain.



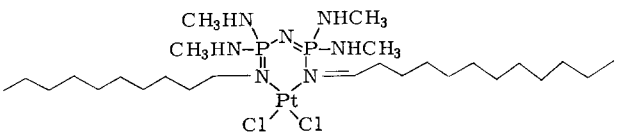
(16) *(17)*

Polymers of this type are designed to degrade hydrolytically to phosphate, ammonia, and the amino acid. This they do.

However, all the polymers synthesized to date also degrade by a second mechanism which causes spontaneous shortening of the chains by a depolymerization process. At temperatures between about 25° and 50°C, this chain shortening reaction leads to a loss of the polymeric properties over a period of days or weeks, depending on the amino acid ester group employed. The reaction can be inhibited by storage at low temperatures. Hence, polymers of this type would "self-destruct" in the body at a rate needed for the absorption of sutures or the release of chemotherapeutic reagents.

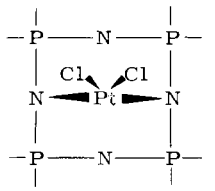
8. Platinum and Heme Complexes

Considerable recent interest has been generated by the use of square planar platinum complexes as anticancer drugs[66]. One problem with the chemotherapeutic use of these compounds is the rapidity with which they are excreted, and the consequent damage to the kidneys that results from this process. Water-soluble high polymers cannot pass through semi-permeable membranes. Hence, they would be expected to be retained within the circulatory system and not be excreted. A drug molecule bound to the polymer should be similarly retained until decomposition of the polymer permitted its slow controlled release. With this objective in mind, *Allcock, Allen* and *O'Brien* have prepared polymeric complexes of type *(18)*[67-69]; these have proved in initial tests to be



(18)

effective antitumor agents. Evidence that the platinum is bound to the *skeletal* atoms of the phosphazene chain comes from model compound studies with the cyclic tetramer, $[NP(NHCH_3)_2]_4$. This compound forms a complex of formula $[NP(NHCH_3)_2]_4PtCl_2$[68,69], which is also active in antitumor tests. An X-ray diffraction analysis of this complex indicates that the square planar platinum is bound to the skeletal atoms in a transannular fashion *(19)*[69]. Since complexes *(18)* and *(19)* have similar spectral properties, the binding of platinum to the polymer is believed to involve the skeletal rather than the side group nitrogen atoms.



(19)

A second utilization of water-soluble phosphazenes is as models for biological polymers, such as proteins. For example, it is well-known that the oxygen-carrying capability of hemoglobin and myoglobin in aqueous media depends on the presence of both the iron(II)-porphyrin component (heme) and the protein unit (globin). If the heme unit is separated from the protein, the Fe^{II} atom is irreversibly oxidized to Fe^{III} in the presence of oxygen. Some investigators have attempted to modify the porphyrin molecule itself to prevent oxidation[70-72]. We have used a polyphosphazene chain to achieve the same end. Strong evidence exists that at least one function of the protein is to separate porphyrin residues and to prevent μ-oxo-dimer formation[73,74], since dimerization is believed to facilitate oxidation. Polyaminophosphazenes contain coordination sites in the skeleton and in the side groups, and they form a logical class of compounds for the binding of heme units. If the heme concentration along each chain were sufficiently low, porphyrin dimerization should be inhibited. Hence, such complexes might form reversible oxygen binding systems, perhaps with long-range uses as blood transfusion substitutes.

Poly[bis(methylamino)phosphazene], $[NP(NHCH_3)_2]_n$, forms a complex with iron(III) porphyrin complexes, such as hemin chloride. Reduction of Fe^{III} to Fe^{II} yields complexes which, in concentrated solution or in thin films, will absorb and release oxygen[75].

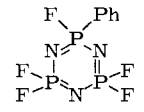
9. Polymerization and Ring-Ring Equilibration of Organocyclophosphazenes

The synthesis methods outlined earlier for the preparation of poly(organophosphazenes) from poly(dichlorophosphazene) are highly effective and permit an almost unparalleled range of different polymers to be made. Nevertheless, the prospect that poly(organophosphazenes) might be accessible by the *direct* polymerization of cyclic organophosphazene trimers and tetramers remains a tantalizing prospect. It is, therefore, instructive to examine the behavior of organo-substituted cyclic trimers at high temperatures with a view to establishing which factors inhibit or facilitate polymerization.

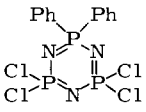
No conditions have yet been found which permit the homopolymerization of fully organic substituted cyclic trimers or tetramers. Although halogeno or pseudohalogeno derivatives, such as $(NPCl_2)_3$, $(NPF_2)_3$, $(NPBr_2)_3$, $[NP(NCS)_2]_3$ polymerize thermally to yield high polymers, compounds such as $[NP(CH_3)_2]_3$, $[NP(C_6H_5)_2]_3$, $[NP(OCH_2CF_3)_2]_3$, or $[NP(OC_6H_5)_2]_3$, do not. However, it is known that organic derivatives, such as these can equilibrate to yield species with large rings. For example, $[NP(CH_3)_2]_3$, when heated forms a mixture of the cyclic trimer and tetramer[76]. Similarly, the trifluoroethoxy derivative yields tetramer, pentamer, and higher cyclic compounds, but no high polymer[77]. Some evidence exists that $[NP(C_6H_5)_2]_3$ behaves in the same way[78]. The important point is that the *mechanism* of the equilibration is clearly accessible to these systems. If the mechanisms of ring-ring equilibration and chain propagation are similar (and this seems likely), the question remains of why chain propagation is inhibited when the organic substituent groups are present.

An attempt has been made to answer this question by the synthesis and attempted polymerization of phosphazene cyclic trimers that contain *both* halogen atoms and organic substituent groups. Two series of compounds have been examined—those in which phenyl groups were present[78], and those which contained trifluoroethoxy groups[77]. It was found that $N_3P_3F_5C_6H_5$ *(20)* polymerizes thermally, but derivatives *(21)* to *(26)* do not. However, compounds *(20)*—*(23)* form copolymers with $(NPCl_2)_3$, whereas species *(24)*—*(26)* do

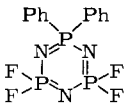
not. Hence, increasing numbers of phenyl groups lower the tendency for polymerization.



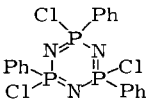
(20)



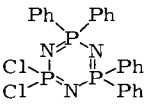
(21)



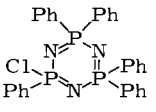
(22)



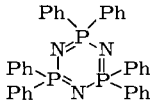
(23)



(24)

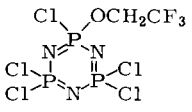


(25)

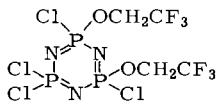


(26)

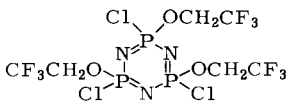
Similarly, compounds *(27)*—*(29)* polymerize at 200 °C to yield linear polymers, but derivatives *(30)*—*(32)* do not. At higher temperatures, side reactions result in the elimination of CF_3CH_2Cl from compounds *(27)*—*(31)*. Compound *(32)* copolymerizes with $(NPCl_2)_3$.



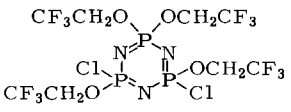
(27)



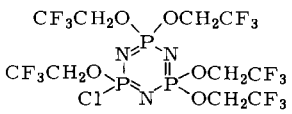
(28)



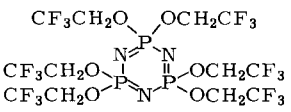
(29)



(30)



(31)



(32)

The progressive inhibitory effect of organic substituent groups probably results from a steric influence by these groups[36, 37, 79]. An open-chain phosphazene is subject to more severe side group-side group and side group-chain repulsions than is a cyclic trimer or tetramer. In a small ring cyclic phosphazene, the side groups point away from each other to minimize steric interactions. In a chain they do not. Hence, the steric influence of the side groups would be expected to be especially serious in the chain propagation steps[77–79]. The enthalpy of a chain species would be higher than that of a cyclic species, and cyclization would be preferred to linear chain propagation. Further evidence in favor of this viewpoint comes from polymer depolymerization studies[80, 81].

10. Polymer Decomposition and Depolymerization

Aminophosphazene polymers decompose at high temperatures to yield side group fragments, with concurrent crosslinking of the chains. Alkoxy- and aryloxy-substituted polymers behave differently. At elevated temperatures (especially above 250 °C) they *depolymerize* to yield small cyclic phosphazene molecules that have the same basic repeating structure as the high polymers[80, 81]. Poly(dichlorophosphazene) behaves similarly, but at higher temperatures (above 350 °C)[11, 13, 82–89].

Depolymerization is a response to thermodynamic influences. At high temperatures, the $T\Delta S$ term in the usual equation $\Delta G = \Delta H - T\Delta S$ becomes increasingly important, favoring systems in which many small molecules are formed at the expense of a few long chain molecules. This factor is responsible for the high temperature depolymerization of organic polymers, such as poly(methyl methacrylate), to their vinyl monomers. Poly(dimethylsiloxane) depolymerizes for the same reason.

However, in poly(organophosphazenes) an additional factor is superimposed onto the entropic influence. Bulky organic groups, when present as substituents on the polymer chain, can raise the enthalpy of the polymer relative to that of the cyclic trimer or tetramer. Hence, both the entropic and the enthalpic terms now favor depolymerization[79]. Presumably, the enthalpic term is so serious for some poly(organophosphazenes), (aryloxy derivatives, for example), that the polymers may be stable at moderate temperatures only because the mechanism of depolymerization is not accessible.

Figure 1 shows the behavior of $[NP(OCH_2CF_3)_2]_n$ after 30 h at various temperatures, as illustrated by gel permeation chromatography curves. The high molecular weight peak moves to progressively lower molecular weight values as thermal depolymerization proceeds[80].

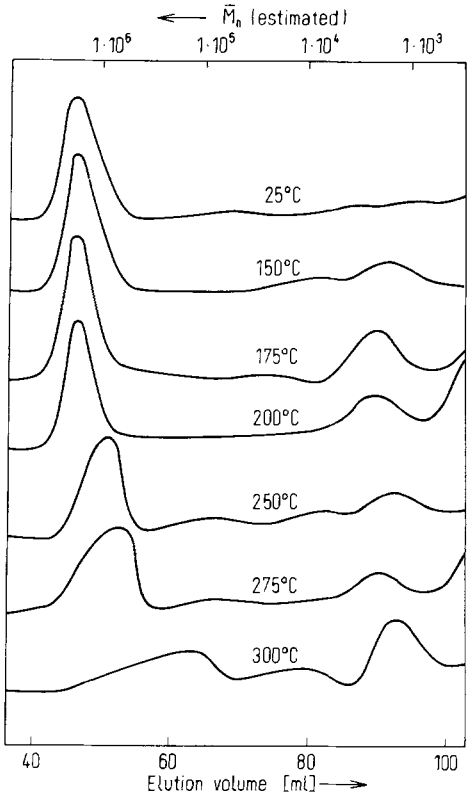


Fig. 1. Changes in the gel permeation chromatography curves of $[NP(OCH_2CF_3)_2]_n$ after heating of the polymer for 30 h at different temperatures.

In practice, this thermal instability is no worse than it is for silicones or most organic polymers. Moreover, crosslinking of the chains, or the introduction of discontinuities, such as phenyl substituents in an alkoxy or aryloxyphosphazene, serve to lower the "unzipping" chain length and raise the thermal stability.

11. X-Ray Structure Analysis of Polyphosphazenes

The rapid expansion of synthetic activity in polyphosphazene chemistry has naturally raised questions about the structure and conformational characteristics of these polymers. An early X-ray diffraction analysis of poly(dichlorophosphazene) by *Meyer, Lotmar*, and *Pankow*[90] indicated the presence of a chain structure, but the resolution of the data was insufficient to correctly deduce the chain conformation. Later work by *Giglio, Pompa*, and *Ripamonti*[91], using the optical transform technique, suggested a *cis-trans* planar conformation.

More recently, the structures of $(NPF_2)_n$, $(NPCl_2)_n$, $[NP(OCH_2CF_3)_2]_n$, and $[NP(OC_6H_5)_2]_n$ have been studied by *Allcock, Kugel, Stroh*, and *Arcus*, with the use of X-ray fiber diagram techniques[44, 92, 93]. Firstly, it was found that $(NPF_2)_n$ exists in two different microcrystalline modifications at temperatures below 25 °C. At temperatures near −56 °C,

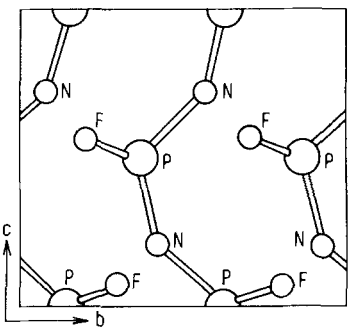


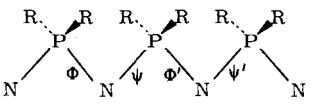
Fig. 2. Projection of the atoms in part of the unit cell of poly(difluorophosphazene) (conformer B), viewed down the *a* axis.

the structure is that of a *cis-trans*-planar chain (Fig. 2)[92], but above −36 °C the conformation apparently changes to that of a spiral helix. Secondly, it has been shown that $(NPCl_2)_n$ also assumes an almost *cis-trans* planar conformation when the elastomer is stretched at temperatures of 25 °C or below[93]. Thirdly, the fiber diagrams of $[NP(OCH_2CF_3)_2]_n$ and $[NP(OC_6H_5)_2]_n$ can also be interpreted in terms of a *cis-trans* planar chain[44]. Recently, the structure of $[NP(OC_6H_5{-}Cl\text{-}p)_2]_n$ has been examined, and the main chain conformation again appears to be *cis-trans*-planar[94].

Two questions arise from these results. Firstly, why do the chains assume a *cis-trans*-planar conformation? Secondly, what structural features of these molecules are responsible for the conformational mobility, especially at low temperatures? Attempts have been made to answer these questions by conformational analysis experiments as described in the next section.

12. Conformational Analysis

The chain conformation assumed by a microcrystalline polymer normally represents a minimum energy conformation in terms of the *intra*molecular non-bonding interactions. These interactions involve side group-side group and side group-chain repulsions and attractions. Inherent skeletal bond barriers may also influence the conformation, especially if double bonds are present. *Inter*molecular packing forces can also exert an influence on the conformation. However, in principle, it is possible to predict or rationalize the preferred chain conformations from calculations of the non-bonding intramolecular forces. The calculation of such energies for a long polymer molecule would be a formidable problem, and the simplified assumption is normally made that the conformation of a short chain segment, such as *(33)*, represents the conformation of the whole chain.



(33)

Once such calculations have been made, the results may be plotted as an energy surface, the coordinates of which represent the effects of 360° torsion of bonds φ and ψ in *(33)*. An energy surface of this type not only permits identification of energy minima, but also provides information about the barriers to torsion of individual skeletal bonds and the breadth of the principal energy wells. Such features can, in theory, be correlated with physical properties, such as skeletal flexibility, glass transitions, elasticity, *etc.*

Calculations of this type have been performed for a number of polyphosphazenes, including $(NPF_2)_n$, $(NPCl_2)_n$, $(NPBr_2)_n$, $[NP(OCH_3)_2]_n$, $[NP(OCH_2CF_3)_2]_n$, and $[NP(OC_6H_5)_2]_n$[95, 96]. Lennard-Jones 6:12-type energy potentials and a Coulombic term were used to calculate the energies of each interaction within the short chain segment for a wide range of different conformations. Typical energy surfaces are shown in Figure 3.

Firstly, the surfaces generate minima near the *cis-trans* planar conformations. ($\varphi = 0$, $\psi = 180$) detected for $(NPF_2)_n$, $(NPCl_2)_n$, $[NP(OCH_2CF_3)_2]_n$, and $[NP(OC_6H_5)_2]_n$ from the X-ray analysis. Secondly, the barriers to individual bond torsion are calculated to be surprisingly low for the polymers with the lowest glass transition temperatures, such as $(NPF_2)_n$, $(NPCl_2)_n$, $[NP(OCH_3)_2]_n$, $[NP(OC_2H_5)_2]_n$, and $[NP(OCH_2CF_3)_2]_n$. Thus, it appears that the low-temperature flexibilities of these polymers are a consequence of the absence of serious bon-bonding intramolecular interactions as the backbone bonds undergo broad torsional motions. Even for $[NP(OC_6H_5)_2]_n$, the bulky phenoxy residues can undergo subtle avoidance motions that permit a low energy pathway for backbone bond torsion.

It should be pointed out that these calculations did not take into account the possibility that an inherent barrier could exist in this system due to the presence of $d\pi$-$p\pi$ backbone bonding. However, the *experimental* evidence from X-ray diffraction work and spectroscopy with small phosphazene mole-

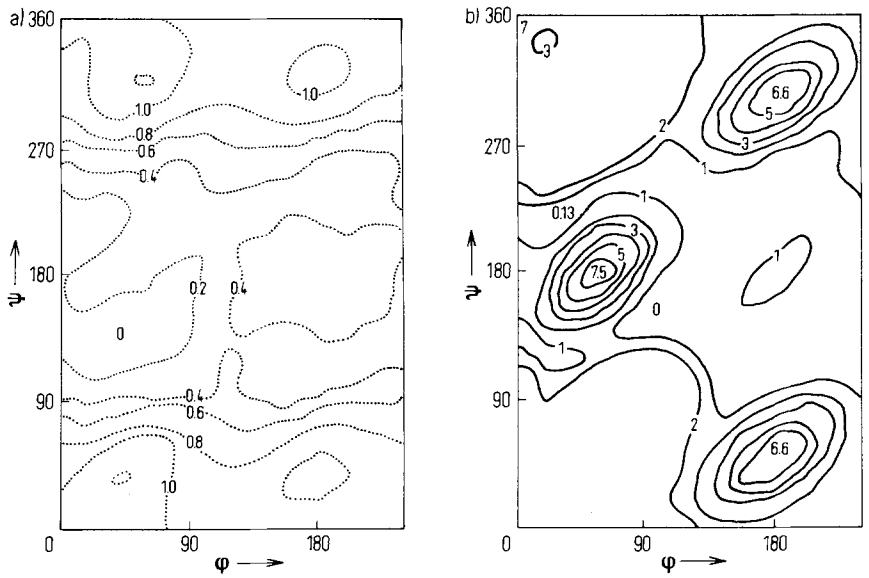


Fig. 3. Conformational energy surfaces calculated for (a) $(NPF_2)_n$ and (b) $(NPCl_2)_n$ [104]. The important features are the extreme flatness of the surface in (a), the low energy pathway for conformational changes in (b), and the presence of low energy minima near the *cis-trans* planar conformation ($\varphi = 0$, $\psi = 180$). The contour designations are in kcal/residue. For these calculations, bonds φ' and ψ' were allowed to assume minimum energy conformations as bonds φ and ψ were varied.

cules favors the view that such bonding, if it exists, exerts only a miniscule influence on the conformational behavior.

13. Possible Applications

The poly(organophosphazenes) that have been synthesized to date have generated considerable interest from an applications point of view. The following are the main areas of current interest and activity.

Firstly, most polyphosphazenes do not burn, and many are flame retardants for other polymers. Fabrication into fibers is relatively easy. Hence, textiles form a logical area for the future uses of polyphosphazenes. Added to this is the fact that specific polyphosphazenes (such as, $[NP(OCH_2CF_3)_2]_n$) are highly water- and oil-repellant and can be dyed or substituted with dye molecules. Thus, their long-range potential in textile technology becomes obvious. However, at the present time, polyphosphazenes are expensive, and the most logical initial developments are as fibers for fire-resistant fabrics or for co-weaving with conventional organic polymer fibers.

Secondly, as discussed in Section 5, mixed substituent poly(organophosphazenes) are elastomers, often with very low glass transition temperatures. It is these materials that have received the most intense technological attention as oil-resistant, low temperature elastomers for high performance applications in the aircraft, automobile, and oil technology areas[52, 55, 56, 62, 63]. One company in the United States[61] is currently producing seals, gaskets, flexible hoses, and expanded foams based on a variety of polyphosphazene formulations, and this area of application is expected to grow.

Thirdly, the film-forming polyphosphazenes offer some advantages over conventional organic films. Again, they are fire-resistant and can be carefully designed to have specific surface characteristics, adhesion properties, or solvent insolubility. Because the polyphosphazene backbone is essentially transparent to ultraviolet light at wavelengths longer than about 200 mμ, the weathering stability of some polyphosphazenes is expected to be higher than that of organic polymers. Other possibilities exist as electrical insulators or flexible wire coatings, but no actual products have yet been marketed in this area.

Finally, the strong possibility exists that polyphosphazenes will be used either to fabricate or to coat biomedical replacement devices, such as artificial heart pumps. The extreme water-repellency, coupled with high elasticity and low fat absorption that can be achieved with polyphosphazenes, makes them ideal candidates for this type of application. In initial *in vitro* blood compatability tests, they appear to be superior to silicone rubber or conventional organic polymers. From a long-range point of view, the water soluble polyphosphazenes may prove valuable as chemotherapeutic drug carrier molecules, and this aspect is receiving considerable attention in our own research group at the present time.

The polyphosphazene research in our group has been generously supported by grants from the U.S. Army Research Office, Office of Naval Research, N.A.S.A., The Firestone Tire and Rubber Company, and the National Heart and Lung Institute of N.I.H.

Received: July 29, 1976 [A 150 IE]
German version: Angew. Chem. *89*, 153 (1977)

[1] *J. Liebig*, Justus Liebigs Ann. Chem. *11*, 139 (1834).
[2] *C. Gerhardt*, Ann. Chim. Phys. [3] *18*, 188 (1846).
[3] *A. Laurent*, C. R. Acad. Sci. *31*, 356 (1850).
[4] *J. H. Gladstone, J. D. Holmes*, J. Chem. Soc. *17*, 225 (1864).
[5] *J. H. Gladstone, J. D. Holmes*, Ann. Chim. Phys. [4] *3*, 465 (1864).
[6] *J. H. Gladstone, J. D. Holmes*, Bull. Soc. Chim. Fr. [2] *3*, 113 (1865).
[7] *H. Wichelhaus*, Ber. Dtsch. Chem. Ges. *3*, 163 (1870).
[8] *H. N. Stokes*, Am. Chem. J. *17*, 275 (1895).
[9] *H. N. Stokes*, Ber. Dtsch. Chem. Ges. *28*, 437 (1895).
[10] *H. N. Stokes*, Am. Chem. J. *18*, 629, 780 (1896).
[11] *H. N. Stokes*, Am. Chem. J. *19*, 782 (1897).
[12] *H. N. Stokes*, Am. Chem. J. *20*, 740 (1898).

[13] *H. N. Stokes*, Z. Anorg. Chem. *19*, 36 (1899).
[14] *R. Schenck, G. Römer*, Ber. Dtsch. Chem. Ges. *57B*, 1343 (1924).
[15] *L. G. Lund, N. L. Paddock, J. E. Proctor, H. T. Searle*, J. Chem. Soc. *1960*, 2542.
[16] *M. Becke-Goehring, G. Koch*, Chem. Ber. *92*, 1188 (1959).
[17] *M. Becke-Goehring, E. Fluck*, Angew. Chem. *74*, 382 (1962); Angew. Chem. Int. Ed. Engl. *1*, 281 (1962).
[18] *M. Becke-Goehring, W. Lehr*, Z. Anorg. Allg. Chem. *327*, 128 (1964).
[19] *M. Becke-Goehring, W. Lehr*, Chem. Ber. *94*, 1591 (1961).
[20] *M. Becke-Goehring, E. Fluck, W. Lehr*, Z. Naturforsch. *17b*, 126 (1962).
[21] *M. Becke-Goehring, W. Lehr*, Z. Anorg. Allg. Chem. *325*, 287 (1963).
[22] *M. Becke-Goehring, B. Scharf*, Z. Anorg. Allg. Chem. *353*, 320 (1967).
[23] *J. Emsley, P. B. Udy*, J. Chem. Soc. *A 1971*, 768.
[24] *R. Steinman, F. B. Schirmer, L. F. Audrieth*, J. Am. Chem. Soc. *64*, 2377 (1942).
[25] *H. Bode, H. Bach*, Ber. Dtsch. Chem. Ges. *75B*, 215 (1942).
[26] *C. P. Haber, D. L. Herring, E. A. Lawton*, J. Am. Chem. Soc. *80*, 2116 (1958).
[27] *D. L. Herring*, Chem. Ind. (London) *1960*, 717.
[28] *H. H. Sisler, S. E. Frazier, R. G. Rice, M. G. Sanchez*, Inorg. Chem. *5*, 326 (1966).
[29] *E. T. McBee, H. R. Allcock, R. Caputo, A. Kalmus, C. W. Roberts*, U. S. Govt. Astia Rep. AD209,669 (1959).
[30] *R. Rätz, H. Schroeder, H. Ulrich, E. Kober, C. Grundmann*, J. Am. Chem. Soc. *84*, 551 (1962).
[31] *A. M. Ficquelmont*, C. R. Acad. Sci. *200*, 1045 (1935).
[32] *H. Bode, K. Bütow, G. Lienau*, Chem. Ber. *81*, 547 (1948).
[33] *R. Keat, R. A. Shaw*, Angew. Chem. *80*, 192 (1968); Angew. Chem. Int. Ed. Engl. *7*, 212 (1968), and references cited therein.
[34] *R. A. Shaw, F. G. B. Wells*, Chem. Ind. (London) *1959*, 1189.
[35] *K. G. Acock, R. A. Shaw, F. G. B. Wells*, J. Chem. Soc. *1964*, 121.
[36] *H. R. Allcock*: Phosphorus-Nitrogen Compounds. Academic Press, New York 1972.
[37] *H. R. Allcock*, Chem. Rev. *72*, 315 (1972).
[38] *S. Pantel, M. Becke-Goehring*: Six- and Eight-Membered Ring Systems in Phosphorus Nitrogen Chemistry. Springer, Berlin 1969.
[39] *R. A. Shaw, B. W. Fitzsimmons, B. C. Smith*, Chem. Rev. *62*, 247 (1962).
[40] *N. L. Paddock*, Quart. Rev. Chem. Soc. *18*, 168 (1964).
[41] *E. Fluck*, Top. Phosphorus Chem. *4*, 291 (1967).
[42] *H. R. Allcock, R. W. Allen, E. C. Bissell, L. A. Smeltz, M. Teeter-Stein*, J. Am. Chem. Soc., in press, and references cited therein.
[43] *H. R. Allcock, R. L. Kugel*, J. Am. Chem. Soc. *87*, 4216 (1965).
[44] *H. R. Allcock, R. L. Kugel, K. J. Valan*, Inorg. Chem. *5*, 1709 (1966).
[45] *H. R. Allcock, R. L. Kugel*, Inorg. Chem. *5*, 1716 (1966).
[46] *H. R. Allcock, J. E. Gardner, K. M. Smeltz*, Macromolecules *8*, 36 (1975).
[47] *E. Fluck*, Z. Anorg. Allg. Chem. *320*, 64 (1963).
[48] *E. F. Moran*, J. Inorg. Nucl. Chem. *30*, 1405 (1968).
[49] *H. R. Allcock, R. J. Best*, Can. J. Chem. *42*, 447 (1964).
[50] *S. H. Rose*, J. Polym. Sci., Part B *6*, 837 (1968).
[51] *H. R. Allcock, G. F. Konopski, W. J. Cook*, unpublished work (1973).
[51a] *T. M. Conelly, J. K. Gillham*, J. Appl. Polym. Sci. *20*, 473 (1976).
[52] *S. H. Rose, J. Cable, K. A. Reynard*, U. S. Mater. Mechan. Res. Rep. AD 693-289 (1969); AD 704-332, AD 720-215 (1970).
[53] *G. Allen, C. J. Lewis, S. M. Todd*, Polymer *11*, 31, 44 (1970).
[54] *R. E. Singler, G. L. Hagnauer, N. S. Schneider, B. R. LaLiberte, R. E. Sacher, R. W. Matton*, J. Polym. Sci., Polym. Chem. Ed. *12*, 433 (1974).
[55] *R. E. Singler, N. S. Schneider, G. L. Hagnauer*, Polym. Eng. Sci. *15*, 321 (1975).
[55a] *G. L. Hagnauer, B. R. LaLiberte*, J. Polym. Sci., Polym. Phys. Ed. *14*, 367 (1976).
[56] *G. Allen, R. M. Mortier*, Polymer *13*, 253 (1972).
[57] *H. R. Allcock, W. J. Cook, D. P. Mack*, Inorg. Chem. *11*, 2584 (1972).
[58] *H. R. Allcock, D. P. Mack*, Chem. Commun. *1970*, 685.
[59] *J. E. White, R. E. Singler, S. A. Leone*, J. Polym. Sci., Polym. Chem. Ed. *13*, 2531 (1975).
[60] *H. R. Allcock, T. Fuller, D. P. Mack, K. Matsumura, K. M. Smeltz*, unpublished work (1971–1976).
[61] The Firestone Tire and Rubber Company, Akron, Ohio.
[62] *G. S. Kyker, T. A. Antkowiak*, Rubber Chem. Technol. *47*, 32 (1974).
[63] *D. P. Tate*, J. Polym. Sci., Polym. Symp. *48*, 33 (1974).
[64] *H. R. Allcock, G. Y. Moore*, Macromolecules *5*, 231 (1972).
[65] *H. R. Allcock, D. B. Patterson*, unpublished work (1975).
[66] *B. Rosenberg, L. Van Camp, J. E. Trosko, V. H. Mansour*, Nature *222*, 385 (1969).
[67] *H. R. Allcock, R. W. Allen, J. P. O'Brien*, J. Chem. Soc. Chem. Commun. *1976*, 717.
[68] *H. R. Allcock, R. W. Allen, J. P. O'Brien*, J. Am. Chem. Soc., in press.
[69] *R. W. Allen, J. P. O'Brien*, J. Am. Chem. Soc., in press.
[70] *J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, W. T. Robinson*, J. Am. Chem. Soc. *97*, 1427 (1975).
[71] *J. Almog, J. E. Baldwin, J. Huff*, J. Am. Chem. Soc. *97*, 226 (1975).
[72] *C. K. Chang, T. G. Traylor*, Proc. Natl. Acad. Sci. USA *72*, 1166 (1975).
[73] *O. Leal, D. L. Anderson, R. G. Bowman, F. Basolo, R. L. Burwell*, J. Am. Chem. Soc. *97*, 5125 (1975).
[74] *J. H. Wang*, J. Am. Chem. Soc. *80*, 3168 (1958).
[75] *H. R. Allcock, J. E. Gardner, P. P. Greigger, J. L. Schmutz, S. D. Wright*, unpublished results.
[76] *H. R. Allcock, D. B. Patterson*, Macromolecules, in press.
[77] *H. R. Allcock, J. L. Schmutz*, J. Am. Chem. Soc., in press.
[78] *H. R. Allcock, G. Y. Moore*, Macromolecules *8*, 377 (1975).
[79] *H. R. Allcock*, J. Macromol. Sci. Rev. Macromol. Chem. *4*, 149 (1970).
[80] *H. R. Allcock, W. J. Cook*, Macromolecules *7*, 284 (1974).
[81] *H. R. Allcock, G. Y. Moore, W. J. Cook*, Macromolecules *7*, 571 (1974).
[82] *A. M. de Fiquelmont*, C. R. Acad. Sci. *204*, 689, 867 (1937).
[83] *F. Patat, K. Frombling*, Monatsh. Chem. *86*, 718 (1955).
[84] *F. Patat, P. Derst*, Angew. Chem. *71*, 105 (1959).
[85] *J. R. MacCallum, J. Tanner*, J. Macromol. Sci. Chem. *4*, 481 (1970).
[86] *J. R. MacCallum*, J. Macromol. Sci. Chem. *5*, 653 (1971).
[87] *O. Schmitz-DuMont*, Z. Elektrochem. *45*, 651 (1939).
[88] *O. Schmitz-DuMont*, Angew. Chem. *52*, 498 (1939).
[89] *J. R. Soulen, M. S. Silverman*, J. Polym. Sci., Part A *1*, 823 (1963).
[90] *K. H. Meyer, W. Lotmar, G. W. Pankow*, Helv. Chim. Acta *19*, 930 (1936).
[91] *E. Giglio, F. Pompa, A. Ripamonti*, J. Polym. Sci. *59*, 293 (1962).
[92] *H. R. Allcock, R. L. Kugel, E. G. Stroh*, Inorg. Chem. *11*, 1120 (1972).
[93] *H. R. Allcock, R. A. Arcus, E. G. Stroh*, unpublished work (1972–1976).
[94] *S. M. Bishop, I. H. Hall*, Br. Polym. J. *6*, 193 (1974).
[95] *H. R. Allcock, R. W. Allen, J. J. Meister*, Macromolecules *9*, 950 (1976).
[96] *R. W. Allen, H. R. Allcock*, Macromolecules *9*, 956 (1976).

Fully Automatic Potentiometric Titrations

New analytical methods (9)

By Siegfried Ebel and Angelika Seuring[*]

Fully automatic titration systems consist of at least two units: the sample-changing system and the measuring system, the latter including addition of the reagent. These systems are preferably coupled to a computer. The possibilities of fully automatic titration can be best utilized if the sources of error are taken into account and the evaluation procedure optimal for the specific analysis is selected.

1. Introduction

Potentiometric titrations are nowadays used routinely in many laboratories for the control of raw materials, intermediates, and end products. Whereas until a few years ago their range of application was restricted mainly to acid/base, redox, and a few precipitation reactions, the introduction of ion-sensitive electrodes has enabled this range to be greatly extended. From a historical point of view, purely manual titration with color indicators was followed by potentiometrically indicated titrations in which the measurements were made stepwise and noted individually, later there came automatic recording by potentiographs, and finally digital potentiometric titrations with on-line coupled computer systems. Further, the use of sample changers made it possible to provide fully automatic procedures, except for preparation of the sample.

At first sight each improvement in apparatus appears to be accompanied by an increase in accuracy and reproducibility, but in reality typical systematic errors arise with each new development. In the present review we shall look critically at current possibilities afforded by automated titration with potentiometric indication of the end point, attention being directed mainly at the sources of error and the evaluation. So far as is necessary for an understanding of systematic errors we shall make some remarks on the problems of measurement and on the general character of titration curves.

Since in most cases only commercially available titration systems will be of interest to the reader, we have intentionally refrained from reporting on special apparatus described in the literature[1–5]. Moreover, only the potentiometric end-point indication will be discussed, despite considerable interest in colorimetric titration because of its use on a microscale[6] and despite the development of computer-controlled systems[7]. The theoretical principles, general outlines, and literature reviews of the fields of potentiometry, potentiometric titrations, and automation are provided in the cited monographs [5, 8–19] and review articles[20–23].

2. Problems of Measurement

In manual titrations the operator can interfere at any time in the analytical procedure and prevent mistakes or compensate for interference; very often this is done unconsciously. In fully automatic systems, however, any disturbances or even conditions that could lead to systematic errors must be recognized in advance and removed. We shall therefore discuss here some general problems of measurement. In some cases further interferences can occur, including in particular changes of the potential difference of the measuring circuits due to the "matrix"[*].

The potential difference ΔE between an indicator electrode and a reference electrode, which depends on the volume of reagent added, is the measured quantity that constitutes the basis of all potentiometric titration curves. In most measuring circuits the reference electrode is separated by a diaphragm from the solution being measured. According to the Nernst equation, there is a direct relationship between the potential of the measuring electrode and the logarithm of the activity a_x of the ion to be determined. The overall valid relationship is given by equation (1), which includes the constant potential of the reference electrode $E^{\ominus}_{Ref}$ and the diffusion potential E_j at the diaphragm, the latter being often responsible for major disturbances.

$$\Delta E = -\frac{RT}{nF} \ln a_x + E_j + E^{\ominus}_{Ref} \qquad (1)$$

If the activity of the ion to be measured is changed by the addition of a further definite amount of this ion (the standard addition method, especially with ion-selective electrodes) or by reaction with the added reagent (titration), then the potential difference of the measurement circuit will also change. Important problems arise at this point: all time-dependent phenomena falsify the course of the titration curve from that expected on the basis of thermodynamic constants (acidity constant, solubility product, *etc.*). There are six main points that warrant special attention in automated titrations.

2.1. Mixing Effects

Provided that stirring is vigorous no difficulty worth mentioning arises when titrations are carried out with solvents of low viscosity, with large volumes of the solution under analysis, and with none to great a difference in concentration between this solution and the reagent. However, in solvents such as nitrobenzene, chlorobenzene, and methylcellosolve the mixing times can be considerable. With rapidly responding electrodes this can result in increased noise, which may upset the end-point titration, or—at least shortly before reaching

[*] Prof. Dr. S. Ebel, A. Seuring
Fachbereich Pharmazie und Lebensmittelchemie der Universität
Marbacher Weg 6, D-3550 Marburg (Germany)

[*] By "matrix" is meant all the accompanying components of the sample under analysis.

the equivalence point—in extreme cases in "overshooting" of the electrode potential (cf. Fig. 8).

2.2. Kinetics of the Chemical Reaction

Acid-base reactions occur so fast that kinetically-determined effects should have no influence on their course. However, in precipitation reactions, especially in highly dilute solutions, considerable systematic errors can arise. Supersaturation effects appear in the early part of the titration, and there follows a region where supersaturation recedes. Near the equivalence point adsorption phenomena can lead to additional errors. The kinetics of precipitate formation[24, 25] are not yet understood in all their details. Appreciable errors due to kinetics can also arise in the titration of organic substances; examples are the determination of primary aromatic amines by diazotization, titanometric titration of nitro groups, and bromometric determination of aromatic compounds, where accurate matching of the rate of titration to the specific analytical problem is essential.

2.3. Response Time of the Measurement Electrode

In aqueous solutions glass electrodes usually have a very short response time. Appreciably longer response times are, however, found in mixed solvent systems (*e.g.* methanol/water), in protic solvents (*e.g.* alcohols, glacial acetic acid) and above all in aprotic solvents (*e.g.* dioxane, sulfolane)[26, 27]. These longer times cause a noticeable flattening of the titration curves, and thus lead to excessive consumption of reagent. Particular attention must be paid to relaxation effects due to concentration differences when working with ion-selective electrodes. The response of such electrodes has been studied in detail[28–31]; in particular, in the case of liquid-exchanger and gas-sensitive electrodes the response times are usually appreciably lengthened owing to the phase transitions occurring before establishment of the potential.

2.4. Diffusion Potential Relaxation

The reference electrode is always in a solution of constant defined composition and thus does not give rise to time-dependent phenomena. However, diffusion phenomena can alter the diffusion potential at the diaphragm and thus lead to systematic errors (Fig. 1). In view of the large throughput of samples to be analyzed, *i.e.* short times of analysis, sought for in automatic titration systems, this source of error should never be completely neglected.

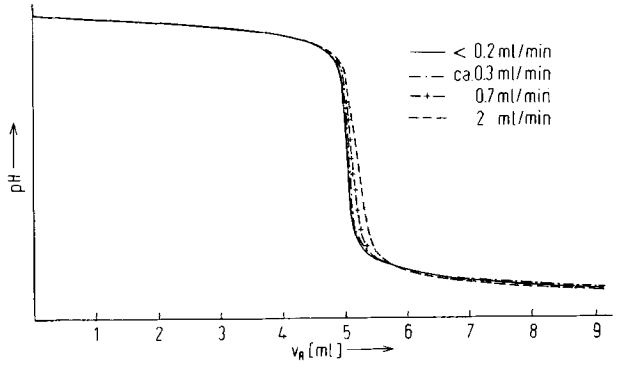


Fig. 1. Influence of the diffusion potential at a combined glass electrode on a titration curve [32]. The rate of addition of a strong acid to base is shown. v_R = reagent volume.

2.5. Potential Drifts

Over longer periods of time the potential difference of a measuring system can be affected by external influences. Such potential drifts may not only be in one direction but also fluctuate about some mean value. For example, glass electrodes in aqueous and above all in nonaqueous solvent systems may show potential drifts caused by changes in the gel structure of the swollen outer layer; here reconditioning in water may prove helpful. With ion-selective electrodes potential drifts are sometimes caused by the matrix. Finally, with platinum electrodes uncontrolled changes in the potential difference may occur; these are often caused by oxidative processes or adsorption phenomena.

It should also be noted that the potential of the Ag/AgCl reference electrode depends measurably on the intensity of the light; this effect is seldom of importance in the case of normal titrations, but it may cause serious disturbances during prolonged operation of fully automatic sample changers, particularly when reducing substances can diffuse into the reference electrode system (SO_2 electrodes[33]).

2.6. Electrostatic Charges

In solvents of low dielectric constant charged particles are present mainly as ion pairs and not in free form. Such solutions are thus very poor conductors of electricity. As a further consequence, occasional electrostatic charges cannot drain fast enough from the reference electrode that is at zero potential. The result is a change in the potential difference of the measurement circuit, which under certain circumstances may only slowly regain the value determined solely by the electrochemical reaction. Taking data for the potential recorded at the moment where an electrostatic potential is superimposed on the measurement potential, will in many cases (*e.g.* end-point titration) lead to faulty analysis.

3. Titration Curves[15, 35–41]

Potentiometric titration curves give the relationship between the potential difference ΔE of the measurement circuit and the added volume v_R of the reagent. The following definitions are of importance regarding the evaluation of titration curves.

Equivalence point: This is defined by the stoichiometry of the chemical reaction forming the basis of the titration and by the initial and the reagent concentrations (c_A, c_R).

Point of inflection: On a typical potentiometric titration curve there is usually a point of inflection in the vicinity of the equivalence point. This point can be calculated from the fundamental set of equations of the titration curve.

End point: Evaluation of a titration curve leads to an end point subject to random and synthetic errors and dependent on the method employed.

In this review we shall not go further into the theory of titration curves, but it must be noted that in volumetry there

is not a single case of a symmetrical titration curve. Even the titration curves of strong acids or bases or of isovalent precipitations show at least slight asymmetry. This is also immediately apparent from the set of equations for the titration curve (the fundamental set of equations; here for the titration of a strong acid with a strong base):

$$a_{H_3O} \cdot a_{OH} = K_w \tag{2}$$

$$[H_3O^+] + c_T = [OH^-] + c_B \tag{3}$$

$$c_T = \frac{c_R \cdot v_R}{v_A + v_R} \tag{4}$$

$$c_B = \frac{c_A \cdot v_A}{v_A + v_R} \tag{5}$$

c_A initial concentration, c_R concentration of reagent, v_A initial volume, v_R volume of reagent

Apart from the fact that the mean activity coefficient $f_\pm$ and thus the combination of $[H_3O^+]$ and a_{H_3O} (and of $[OH^-]$ and a_{OH}) changes during the titration, the asymmetry of the titration curve is caused mainly by the change in volume. Moreover, eq. (3) is not symmetrical with respect to $[H_3O^+]$ and $[OH^-]$. Consequently, the equivalence point and the point of inflection cannot be identical, as was already demonstrated by *Roller*[34] as early as 1928. However, the steeper the titration curve in the vicinity of the equivalence point, the smaller is the error if the point of inflection is regarded as the end point of the titration. The error can be considerable ($> 1\ \%$) in strongly asymmetric titrations (heterovalent redox or precipitation titrations).

4. Sample Changer

The phrase "automatic titration" has changed its meaning appreciably in recent years. Whereas about 15 years ago a potentiograph with automatic cut-off at the equivalence point was regarded as an automatic titrator[5, 19], today it is expected that at least sample transport and delivery of reagents be fully automated. Ideally the mechanization should go so far as to include automation of sample preparation and treatment (*e.g.* warming, boiling under reflux); this is quite possible in industrial automatic systems, but no laboratory device of this kind that functions on a really routine basis has as yet been described.

At least a certain degree of flexibility is required of automated laboratory systems, *i.e.* they should be designed for use on a multipurpose basis. Two variants of such systems can be employed. In one of them a large number of samples are processed simultaneously, *i.e.* for each individual sample there must be a mechanical buret[1]; the mechanical demand is enormous, since each sample also requires its own electrode; and further problems arise with the multiple high-impedance changeover switches. In the second type the sample is transported to the titration site; for this purpose a transport system such as is used for column chromatography suffices[3]. A disadvantage of such sample changers (and of commercial systems with exclusively linear sample transport) is that strictly speaking only one definite working position is available, and thus no mechanizable step can be carried out before the actual titration. Magazine changers are much more versatile (cf. Fig. 2)[42, 43]. Each magazine contains a definite number

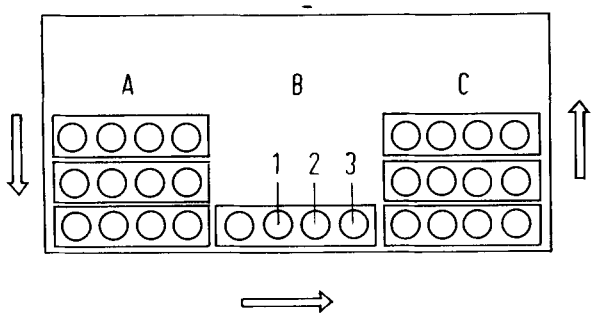


Fig. 2. Principle of Metrohm E 503 sample changer [42, 43]. A: magazines awaiting use; B: magazine in use; 1 addition of auxiliary solutions, covering of titration vessel, *etc.*, 2 delivery of solutions in back-titration; 3 titration; C: magazine previously used. Arrows indicate the direction of movement of the magazine.

of samples forming one mechanical unit. Thus, the samples can be prepared individually or together at a determined place in the sample changer. Moreover, such a system enables additional manipulations to be effected before the titration (addition of auxiliary solutions, *e.g.* TISAB solution when working with ion-sensitive electrodes, or buffer solutions in complexometric titrations; addition of standard solutions in back-titration).

Furthermore, all sample-changing systems should be so designed that rinsing processes can be incorporated in the system, so that memory effects can be reduced to a minimum.

At the Achema 1976 exhibition a further very interesting possibility was demonstrated: a sample-changing system with a multiburet titrator. The individual titration vessels are transported under computer control to their appropriate places preselected for a particular titration process. Here, addition of auxiliary reagents and the actual titration can be carried out. It is thus possible to automate small series of analyses or even repeated successive single analyses[44].

In the simplest set up the sample is identified by its serial number, but systems involving active sample identification by magnetic or optical coding of the magazine are also available[43, 44]. Weighing of the sample can also be incorporated in the system by way of an electronic digital balance with identification of the individual samples[45].

5. Fully Automatic Titration Systems

By fully automatic titration systems we mean here those apparatus that automatically titrate a certain number of samples. Other operations (*e.g.* dilution, addition of auxiliary solutions) may be integrated within the system. Selection and treatment of the sample are generally not included in the automation. In this section we shall try, on admittedly subjective examples, to describe the various types of fully automated titration systems. Such systems must fulfil all the demands—instrumentally or electronically—arising from the problems outlined in Sections 2 and 3.

5.1. Automatic Analog Recording Systems

In the simplest case with fully automatic titration systems one can start with the analog recording titration curves and evaluate them manually by one of the known graphical methods[46] (tangent method[47], Tubbs' circle method[48], intersection method[49]). It follows that the control unit then has to deal only with sample transport and the actual titrator (Fig. 3). Such a system may at first sight seem antiquated in this era of digital readouts and computerization, but it has two advantages that should not be overlooked. In the first place, when the titration is complete the whole titration

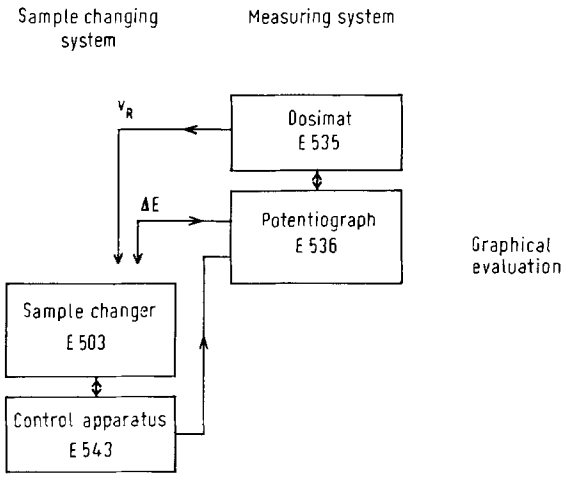


Fig. 3. Block diagram of the Metrohm fully automatic analog recording titration system E 553/12.

curve is available as a record from which an experienced analyst can deduce more information than, for example, just

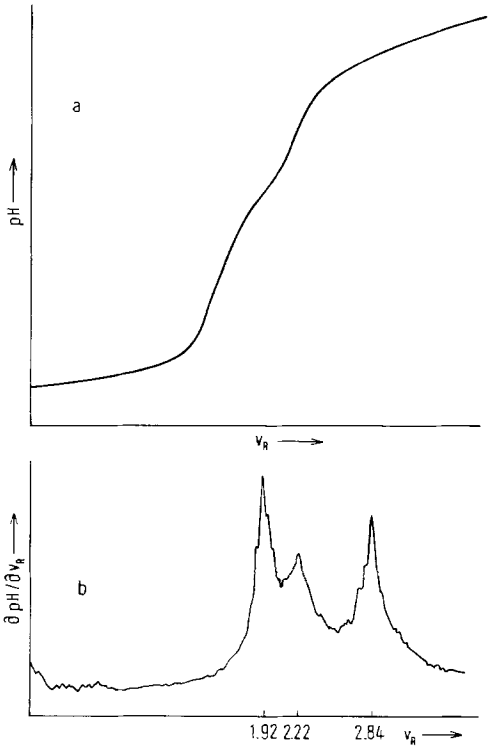


Fig. 4. Titration curve of an acidimetric simultaneous titration: HCl ($c_A = 0.01$ mol/liter), acetic acid ($pK_a = 4.75$, $c_A = 0.033$ mol/liter), and 4-nitrophenol ($pK_a = 7.15$, $c_A = 0.017$ mol/liter); titration with 0.1 N NaOH; Metrohm E 536 potentiograph; combined glass electrode. a) Normal titration curve, b) differentiated titration curve.

the end point. The second advantage is that direct recording of titration curves differentiated with respect to the reagent volume can now be simply effected, the volume of reagent added being matched to the change in potential difference, *i.e.* time-dependent phenomena can be largely eliminated from differentiated titration curves. In complicated titrations, *e.g.* in the simultaneous determination of similar components (Fig. 4) or of components present in very different concentrations (Fig. 5), evaluations can often be made only from the differentiated titration curve.

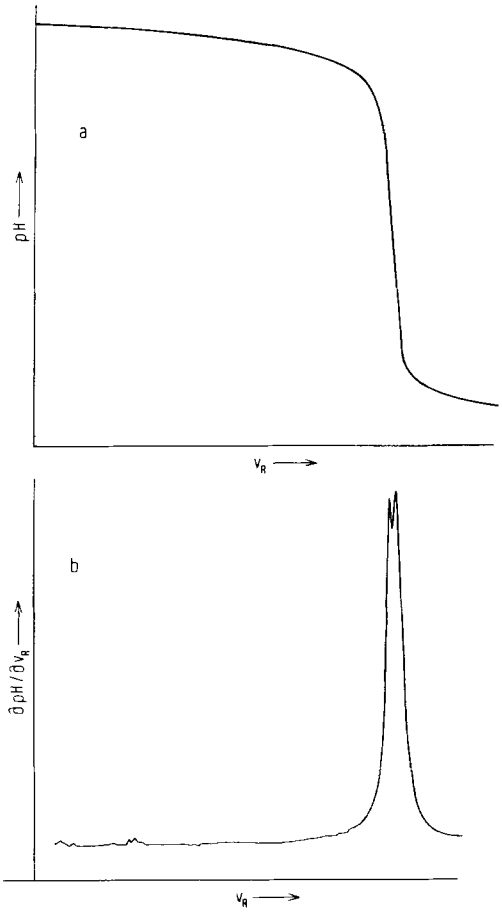


Fig. 5. Titration curve for 0.1 N NaOH containing carbonate *vs.* 0.1 N HCl. Metrohm E 536 potentiograph; combined glass electrode. a) Normal titration curve, b) differentiated titration curve. Both titration curves with the addition of reagent matched to the change of potential difference.

5.2. End-point Titrators

In routine analyses titrations are often carried out up to a prescribed potential difference in the measurement circuit, *i.e.* subject to certain criteria the control mechanism adds reagent solution until this specified value has been reached. Such titration systems with corresponding sample changers for fully automatic operation with a prescribed number of samples are available from several different manufacturers (Metrohm, Herisau/Switzerland (Fig. 6); Mettler, Greifensee (Fig. 7); Radiometer, Copenhagen).

Any deviation of the true end-point potential of the titration from the preselected end-point potential involves an error that is the greater the flatter is the titration curve in the vicinity of the end point. The errors caused by such deviations can be calculated[50–56], but they can also be very simply

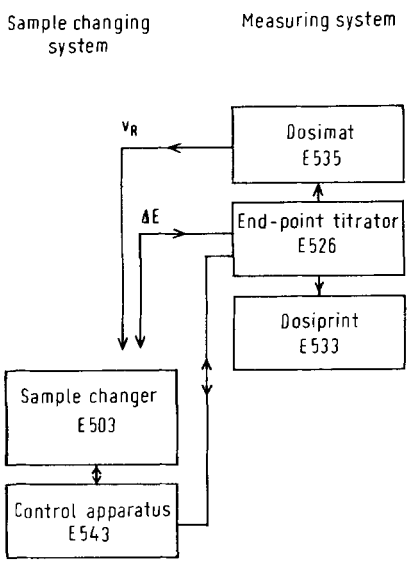


Fig. 6. Block diagram of the Metrohm end-point titrator E 553/9 (without data processing). The result of the titrations can be printed out.

determined by experiment: one first titrates to a defined potential (deviating *e.g.* −10 mV from the theoretical value) and then continues titrating, after alteration of the pre-selected end-point potential, up to the theoretically correct value; the error can be easily determined from the respective amounts of reagent consumed on these two occasions.

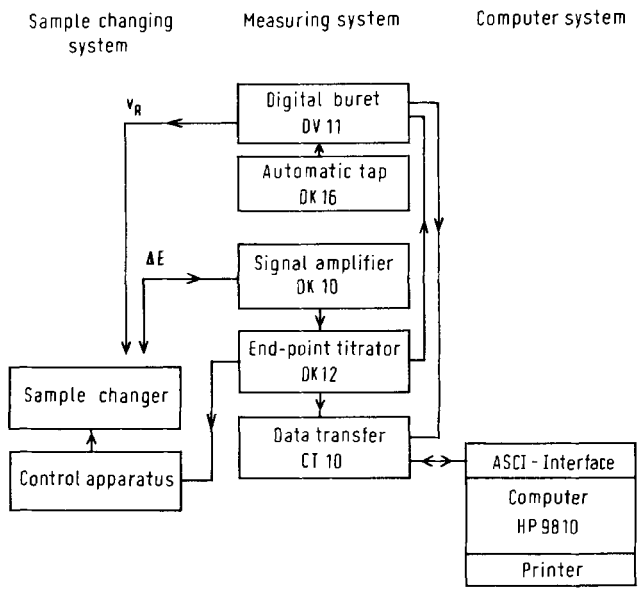


Fig. 7. Block diagram of the Mettler end-point titrator (with on-line data processing).

Errors due to potential drift (cf. Section 2) become very evident with end-point titrations. Potential drift can readily occur in long series of measurements, particularly with fully automatic sample exchange, and thus leads to a systematic succession of errors. In addition, changes arise in the real end point owing to temperature differences (particularly during overnight operation) or to evaporation of solvent and absorption of CO_2 during long intervals between sample preparation and titration if the sample containers are not closed (remedy: penetrable foils or stoppers, removable caps).

Furthermore, the end-point potential depends not only on the substance to be determined and on the reagent but also on the total matrix. In this respect special mention should be made of the influence of foreign salts on the activity coefficients and the alteration of thermodynamic parameters by high concentrations of inert substances. The almost uncontrollable influence of the diffusion potential at the diaphragm of the reference electrode should also be noted. It is therefore absolutely essential to determine the end-point potential with a sample that is identical with or at least very similar to those to be analyzed; it is also advisable to use the same end-point titrator for this determination and all subsequent analyses, since no additional parameter due to a different instrument can then interfere[57].

It is very important to match the rate of addition of the reagent to the course of the titration curve; if the titration is too fast, there is a danger of overtitrating, especially when the curve is very steep; on the other hand, the analysis time should be as short as possible, especially when working with sample changers. Several solutions to these problems have been described.

In the simplest case the difference between the actual and the true value can be used to match the pulse repetition frequency of a variable-speed motor-driven piston buret to the titration curve; or the analog-produced derivative of the potential curve can be used to control the buret. In addition, good commercial systems have reversible matching stages which facilitate optimum adjustment of the control mechanism to suit the titration.

For slow redox titrations (*e.g.* diazotization, reduction by $TiCl_3$) a special regulatory mechanism was proposed[58] and has been realized commercially (Redoxomat; Colera, Lorch). The typical potential/time relationship of incremental redox titrations exhibits the following peculiarity: after addition of reagent the potential at first changes more than would correspond to the actual course of the reaction and then, after consumption of an intermediary excess of reagent, readjusts itself to the true value.

This secondary potential change is utilized for addition of the reagent by means of a relay system. At the end point there is no further change of potential, no more reagent is added, and after a certain delay time the titration is broken off. Thus, the relay system takes over both matching the rate of the titration and recognition of the end point. Since the potential behavior of platinum electrodes is not always completely reproducible, this system should in some cases be superior to end-point titration.

We should, however, mention one essential disadvantage of all end-point titrators: the result is, after all, just one single value, namely the volume v_E of reagent needed to reach a prescribed end point. This provides no possibility of drawing conclusions about interferences or any properties of the sample or about the cause of a deviation.

5.3. Digital Titration Systems

In automatic titration systems titration curves or titration data are generally obtained digitally, *i.e.* one obtains a series of measurements from data on the volume of reagent added and the corresponding potential difference of the measuring circuit employed. In principle, all the commercial systems operate in such a way that the volume of reagent dispensed

increases by constant predetermined amounts. The principal elements of the digital titrator are the buret unit for reagent addition and the control unit that supervises the system and at the same time, as its most important function, takes over the elimination of time-dependent phenomena. The control unit for the sample changer is separate. In all cases the digital titration data must be evaluated by computer, *i. e.* fully automatic digital titration systems with sample changers are whenever possible, connected on-line to a computer.

5.3.1. Reagent Addition

Most of the modern titration systems, whether commercially available or described in the literature (see *e.g.*[59]) make use of variable-speed motor-driven piston burets. Delivery of the exact amount of titrant with defined volume increments is considerably simpler with this driving system than with piston burets operated by a synchronous motor or mechanically—the latter have now been largely abandoned. A further advantage is the easy digitalization by means of counters. Addition of the reagent is probably the part of the whole system that leads to the smallest number of errors in analysis. The usual commercial piston burets (*e.g.* Metrohm Dosimat E 535) attain reproducibilities of $<0.01\,\%$ and accuracies of $<0.04\,\%$[60] ($<0.01\,\%$[61]).

One other, very unconventional, method of adding the reagent should be mentioned: micro drops are produced by means of a micromagnetic valve and a mechanical chopper; these drops are controlled by strong electric fields and finally counted[2, 62–64]. However, calibration is rather troublesome, so that this method of adding the reagent is hardly likely to be suitable for routine operation.

5.3.2. Exclusion of Time-dependent Phenomena

Time-dependent phenomena can falsify a titration curve and thus lead to considerable systematic errors. Several technical possibilities have been proposed for excluding these effects to the maximum possible extent. In the simplest case one can operate with a time control, as in the Metrohm Titroprint E 475[64]. A delay time between addition of the reagent and measurement of the result is pre-set on the apparatus; this interval must be adjusted to suit the titration at hand. A disadvantage of this method is that the same interval must be retained throughout the whole titration, whereas the potential is set up at rates that vary during a titration—here we need only mention the longer times for the establishment of the potential near the equivalence point.

Another possibility is to use the variation of electrode signal with time after addition of the reagent to decide the moment when data shall be recorded. In the simplest case the analog produced derivative of the change in potential (Fig. 8) is used to control the data rate: transfer of the measurement to the read-out unit (computer, punched paper tape, print-out device) is carried out when the variation rate is smaller than a set threshold (*e.g.* 1 mV/min). One then waits until the chemical and thus also the electrode equilibrium has been established (to within a small error of time) (Mettler Equilibrium Titrator DK/DV system[65]). A similar system was used by *Boldt* and *Lackner* in 1963[66] for very slow redox titrations, for which a relay-controlled analog memory was used. In computer-controlled titration systems the computer

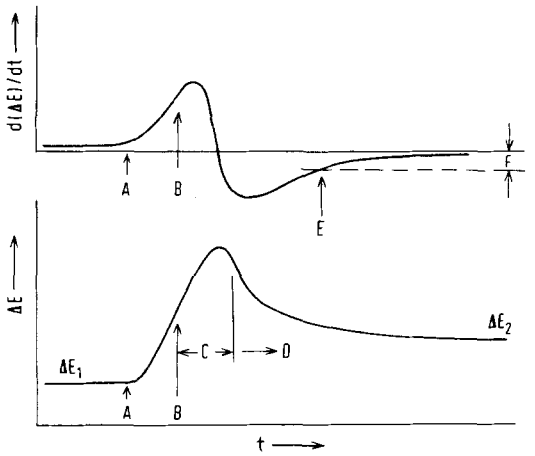


Fig. 8. Time-dependence of the potential in discontinuous titrations. Bottom: normal signal; top: signal differentiated with respect to time. A Beginning of addition, B end of addition, C overshooting of the cell potential (does not occur in all types of titration); waiting time to avoid incorporation of false potential, D adjustment phase of the cell potential (and its registration) on the equilibrium potential, E transfer of the potential to the computer or memory, F switch threshold, ΔE_1 equilibrium potential before reagent addition, ΔE_2 equilibrium potential after reagent addition.

can also take over the function of equilibrium titrator. *Anfält* and *Jagner*[1] described such a system, in which appropriate averaging leads to a decrease in statistical fluctuations and an improvement in the signal-to-noise ratio. In our experience such systems are especially useful when working with ion-selective electrodes[67]. Fig. 9 shows the block diagram of a system

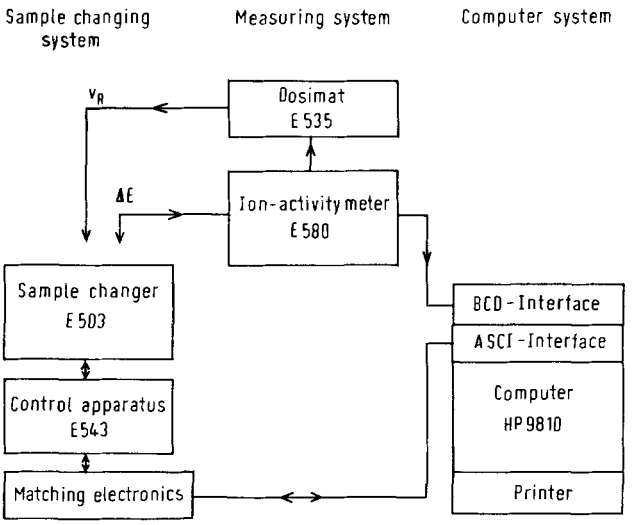


Fig. 9. Block diagram of a fully automatic system, made up of commercially available components, for direct potentiometry with ion-selective electrodes [69].

constructed almost wholly of commercially available units (only logic matching of computer pulse to input signal of controller is required[68]).

5.3.3. Data Processing

Digital titrations require numerical calculation of the end point. With fully automatic titration systems the output of data is so large that data processing is essential. It has long been a subject of dispute, or rather of philosophy, whether to work with an on-line computer or first transfer all the data onto an intermediate tape or punched cards. From the

point of view of the price/performance ratio direct data processing with a very efficient desk calculator (*e.g.* Hewlett-Packard HP 9810, 9815, 9830) is considered optimal, since a calculator with the necessary interface costs almost exactly as much as a punched paper tape or even magnetic tape unit with the necessary interface. The block diagrams in Figs. 10 and 11 show fully automatic digital titration systems built up exclusively of commercially available components and which have proved satisfactory in our laboratory.

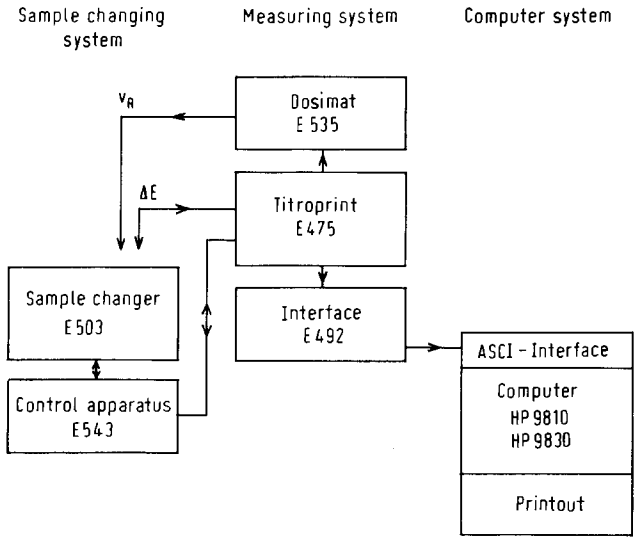


Fig. 10. Block diagram of a fully automatic digital titration system based on the Metrohm Titroprint E 475.

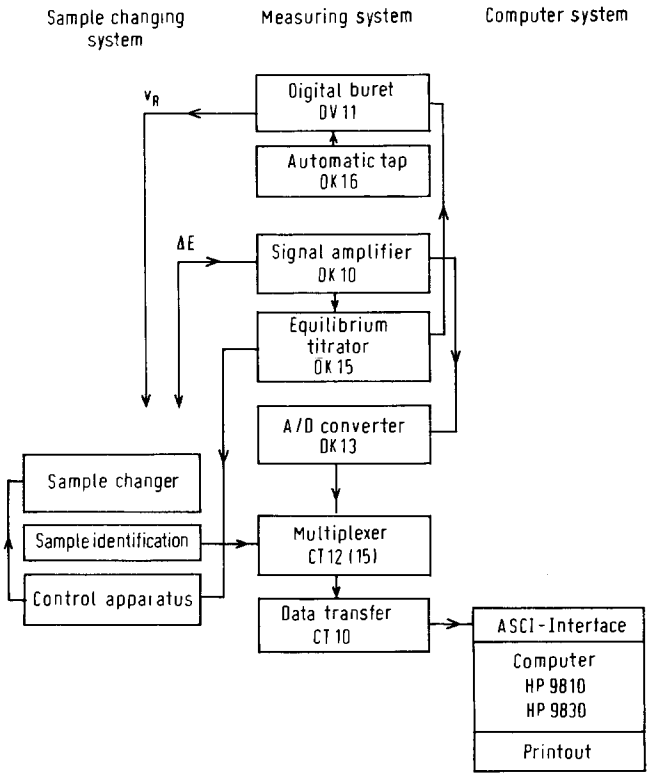


Fig. 11. Block diagram of a fully automatic digital titration system based on the Mettler equilibrium titrator (DK/DV system).

5.4. Systems Controlled by a Microprocessor

In 1976 the Radiometer company introduced a titration system controlled by a microprocessor[70]. In this system five collected values are averaged (digital suppression of noise), and the mean is recognized as a measured point if the potential change is less than 0.4 mV/s or if 45 s have elapsed since the last addition of reagent. The magnitude of the next volume increment is calculated according to eq. (7) from the titration curve differentiated with respect to reagent volume

$$\frac{\partial \Delta E}{\partial v_{R(n,n-1)}} \approx \frac{|\Delta E_n - \Delta E_{n-1}|}{\Delta v_{R(n,n-1)}} \tag{6}$$

$$\Delta v_{R(n,n+1)} = \frac{a}{b + \frac{2\partial \Delta E}{\partial v_{R(n,n-1)}} - \frac{\partial \Delta E}{\partial v_{R(n,n-2)}}} + c \tag{7}$$

a, b, c are empirically derived constants.

Furthermore, after each addition of reagent a test is carried out to see whether an inflection point in the titration curve has been passed through. If so, the inflection point is calculated by *Hahn-Weiler* or *Kolthoff-Furmann* procedures, modified to account for unequal increments in volume of reagent. The titration curve may show several inflection points, *i.e.* simultaneous titrations can also be carried out.

6. Evaluation of Digital Titrations[71]

Many processes have been described for the determination of the end point of a digital titration; they can be divided into three groups:

1. Simple approximation methods. These generally use only three points near the equivalence point.
2. Mathematical methods. These use all the measurements and require knowledge of the mathematical course of the titration curve.
3. Exhaustive approximation methods. These use all the measurements, approximate the titration curve by a selected function, and determine the inflection point.

This classification gives no indication of the accuracy attainable, the liability of the method to occasional error, or the sensitivity to time-dependent phenomena.

6.1. Simple Approximation Methods

The first methods for the evaluation of digital titrations were described as early as 1926. This is not surprising, since potentiometric titration curves initially had to be recorded manually and stepwise. *Hahn* and *Weiler*[72] started from the crude simplification that the equivalence point and the inflection point coincide, *i.e.* that the titration curve is symmetrical up to that point. In a further simplification difference quotients were used in place of the differentiated titration curve to determine the inflection point. The same procedure was described by *Kolthoff* and *Furmann*[73] in a more general formulation.

On the basis of experimental work and theoretical considerations, *Hahn*[15, 74] arrived at some improved methods. The starting point of his considerations was that the "outer zone" of the titration shows only slight potential change, while the "inner zone" harbors nearly all of the potential jump. The

nomogram method described by *Hahn*[75] as early as 1928 is the most interesting; it was later published again by *Fortuin*[76] in similar form and in fact only then became well known. Numerous variations based on it have been published by *Wolf*[77] and by *Keller* and *Richter*[78] for use with automated titrations. The last-named procedure in particular, which was based on systematic considerations of approximations[79], yields exceptionally good results without involving very much mathematical effort. Error simulation calculations show that it is far superior to all other simple approximation methods[80–82] and often even more reliable than the considerably more demanding mathematical procedure. It should also be mentioned that all simple approximation methods are actually valid only for titrations of strong acids or for isovalent precipitation titrations, although they can be readily used also for titrations of weak acids or titrations in anhydrous glacial acetic acid[77, 83]. Unsymmetrical titration curves (from, *e.g.* heterovalent precipitation titrations) can be evaluated if the asymmetry is taken into account by heterovalence equalization arising directly from the stoichiometry[84].

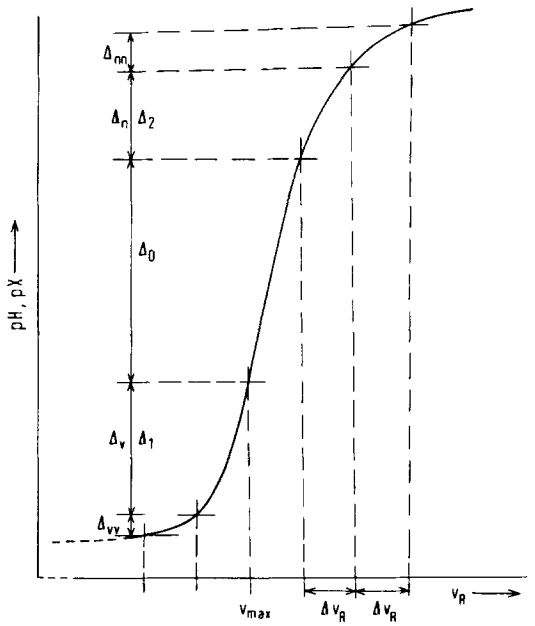


Fig. 12. Evaluation of digital potentiometric titrations by the simple approximation method. The indices v and n refer to volume increments respectively before and after the largest potential jump. $\Delta_0 > \Delta_1 > \Delta_2$.

All simple approximation methods for the evaluation of digital potentiometric titrations use only the three largest potential steps and assume constant increments of the reagent volume. With the aid of the factor ρ [see eqs. (11) to (17)] the end point can be calculated for all procedures by means of eq. (8) (for explanation of the symbols see Fig. 12; v_E is the volume of reagent required to reach the equivalence point).

$$v_E = v_{max} + a\Delta v_R + b \cdot \rho \cdot \Delta v_R \quad (8)$$

$$a = \begin{cases} 0 \text{ for } \Delta_v > \Delta_n;\ \Delta_1 \text{ before } \Delta_0 \\ 1 \text{ for } \Delta_v < \Delta_n;\ \Delta_1 \text{ after } \Delta_0 \end{cases} \quad (9)$$

$$b = \begin{cases} +1 \text{ for } \Delta_v > \Delta_n;\ \Delta_1 \text{ before } \Delta_0 \\ -1 \text{ for } \Delta_v < \Delta_n;\ \Delta_1 \text{ after } \Delta_0 \end{cases} \quad (10)$$

$$\rho = \frac{\Delta_0 - \Delta_1}{2\Delta_0 - \Delta_1 - \Delta_2} \quad [72, 73] \quad (11)$$

$$\rho = \frac{\Delta_2}{2\Delta_1} \quad [15, 74] \quad (12)$$

conditions: $\Delta_1 \leq 2\Delta_2;\ \rho \geq \frac{\Delta_1}{\Delta_0};\ \rho \geq 0.3$

$$\rho = 1.58 \cdot \lg \frac{\Delta_2}{\Delta_3} \quad [15, 74] \quad (13)$$

conditions: $\Delta_2 < 1.5\Delta_3$ [a]

$$\rho = \frac{\Delta_2}{2\Delta_1} - 0.35 \cdot \left(0.3 - \frac{\Delta_2}{2\Delta_1}\right) \quad [15, 74] \quad (14)$$

conditions: $0.3 \geq \frac{\Delta_2}{2\Delta_1} \geq 0.15$

$$\rho = 0.5 \cdot R_2 - 0.2 \cdot R_1^2 \quad [75, 76] \quad (15)$$

$$\rho = [0.5 \cdot R_2 - 0.3 \cdot R_1^2(1 - R_2)](1 - R_1^6) \quad [77] \quad (16)$$

$$\rho = \frac{18R_2 - 5R_2^2 - 10R_1^2R_2 - 3}{20 - 20R_1^2R_2} \quad [78] \quad (17)$$

conditions: $\rho \geq 0.1$

$$R_1 = \frac{\Delta_1}{\Delta_0};\ R_2 = \frac{\Delta_2}{\Delta_1}$$

[a] Δ_3 is defined in analogy to Δ_1, Δ_2 as the fourth largest potential step.

Some methods are applicable only under certain conditions; if these are not fulfilled, the desired result can be achieved by combining two potential steps, so that $\Delta_0 + \Delta_1$ becomes the new Δ_0.

A disadvantage of all simple approximation methods is that only three measured points near the equivalence point are used for the evaluation. Precisely these points however, are liable to be subject to errors due to the time-dependent phenomena mentioned above (adjustment of electrode potential, kinetics of the titration reaction, time constant of the measuring system, *etc.*). The error in the analytical result due to these causes can be estimated[80, 81] (cf. Fig. 13). It

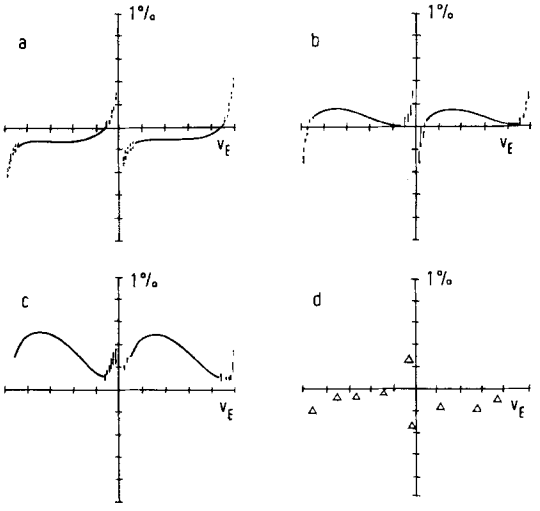


Fig. 13. Error of the *Keller-Richter* numerical version [78] of the *Hahn-Fortuin* [75, 76] simple approximation method for different magnitudes of the potential transfer error caused by time-dependent phenomena [80, 81], and practical results [86]. a) Without time-dependent error, b) potential recording 98% of the theoretical value, c) potential recording 95% of the theoretical value, d) practical results. Titration of a weak acid: $c_A \approx 0.02$ mol/liter, $c_R \approx 0.1$ mol/liter, $pK_a \approx 6$.

can then be seen that a potential transfer error of, *e.g.*, 1 or 2 % can occur precisely at the end point, *i.e.* the largest potential difference becomes too small by this amount. This difference then appears in the next potential difference as a positive systematic error. It is, however, also possible to calculate titrations carrying time constants[85] and to determine the evaluation error therefrom.

6.2. Mathematical Methods

This general heading is intended to cover all methods of evaluation that start directly from the mathematical expression for the titration curve. Here must be noted on the one hand the methods based on *Gran*'s work[87,88] and on the other the nonlinear regression or multiparametric curve fitting calculations. The calculation involved is often a formidable task, but the advantage is that the individual measurement points are weighted differently according to their susceptibility to error. Furthermore, in these methods it is the equivalence point and not the inflection point of the titration curve that is determined. A disadvantage is that the fundamental mathematics of the titration curve to be evaluated must be known, and that each type of titration must be handled differently.

In 1952 *Gran*[88] published a graphical method for the determination of the equivalence points of potentiometric titrations; this depended on a linearization of the titration curve. The formulas given [eq. (18)—(22)] in Table 1 are, however, only approximate expressions; these were later improved[60,89,90]. The main error in an evaluation by *Gran*'s method is the assumption that the resulting function is linear. Since all multiplicative factors (slope of the electrode characteristic, activity coefficient) produce a slight curvature[60,91], attempts have been made to eliminate these factors by iterative calculation[92,93].

In titrations of weak acids some authors merely evaluate partial regions, which may be suitably linear[94] or carry only small errors of measurement[32]; in these cases the first measured points and those in the immediate neighborhood of the equivalence point are not included. Others have suggested linear adjustment of observations (based on simple expressions)[95–97] or linear adjustment with systematic testing for a linear relationship[40], as well as adjustment by means of polynomials[60,92] (orthogonal polynomials[98] of the 3rd and 4th order).

Whereas the *Gran* method for acidimetric titrations can be handled with precision starting from the law of mass action, from the condition of electroneutrality, and from equilibrium constants[60,89,92], this has not yet been demonstrated in practice for other types of titrations. It is true that the complete formula for isovalent precipitation titrations has been de-

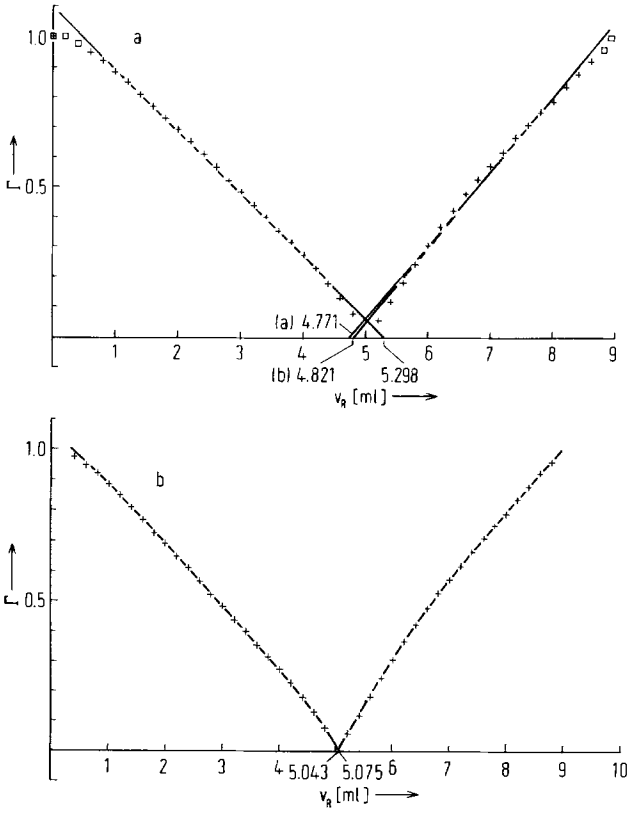


Fig. 14. *Gran* function Γ of an isovalent precipitation titration ($AgNO_3$ + NaCl). a) Iterative procedure according to [93], b) approximated by orthogonal polynomials [100]. $AgNO_3$, $c_A = 0.0168$ mol/liter, $v_A = 30.0$ ml; titration with 0.1 N NaCl.

Table 1. Calculation of the Gran function Γ for various types of titration. σ "electrode steepness" (correction factor), $f_\pm$ activity coefficient, K_L solubility product, K_w ionic product of water, K_a acidity constant, x stoichiometric factor, k selected favorable arbitrary constant for the evaluation.

	Approximate formula [a]		Exact formula [b]	
Titration of a strong acid	$\Gamma = \frac{v_A + v_R}{c_R} \cdot 10^{-pH}$	(18)	$\Gamma = \frac{v_A + v_R}{c_R}\left[\frac{1}{f_\pm} \cdot 10^{-pH} - \frac{K_\omega}{F_\pm} \cdot 10^{pH}\right]$	(23)
$H_3O^+ \xrightarrow{OH^-} H_2O$	$\Gamma = \frac{v_A + v_R}{c_R} \cdot K_\omega \cdot 10^{pH}$	(19)		
Titration of a weak acid	$\Gamma = \frac{v_R}{K_a} \cdot 10^{-pH}$	(20)	$\Gamma = \frac{v_R}{K_a} \cdot 10^{-pH} + \frac{v_A + v_R}{c_R \cdot K_a}\{10^{-pH} + K_a \cdot 10^{-pH} + K_\omega \cdot K_a \cdot 10^{pH} - K_\omega\}$	(24)
$HAc \xrightarrow{OH^-} H_2O + Ac^-$	$\Gamma = \frac{v_A + v_R}{c_R} \cdot K_\omega \cdot 10^{pH}$	(19)		
Precipitation titration	$\Gamma = (v_A + v_R) \cdot 10^{\{(x/\sigma)\cdot(\Delta E - k)\}}$	(21)	$\Gamma = (v_A + v_R)\left[x \cdot \frac{a_x}{f_x} - x \cdot \frac{1}{f_A} \cdot \left(\frac{K_L}{a_x}\right)^{\frac{1}{x}}\right]$	(25)
$xA^{a\pm} \xrightarrow{aX^{x\pm}} A_xX_a$	$\Gamma = (v_A + v_R) \cdot 10^{\{(x/a)\cdot(x/\sigma)\cdot(k - \Delta E)\}}$	(22)	with $a_x = 10^{\{-(x/\sigma)(\Delta E - E^\ominus)\}}$	(26)

[a] In each case the upper formula refers to the front branch and the lower formula to the back branch of the titration curve.
[b] A single formula describes the whole course of the titration curve.

scribed[93], and that there should be a linear connection when activity coefficients are used in the calculation, but real titration curves almost invariably give slightly curved *Gran* functions[99, 100] (cf. Fig. 14).

No systematic study of redox titrations has yet been made. Here linearization may be beset above all with problems concerning the indicator electrode.

Acidimetric titrations in mixed solvent systems and titrations of weak bases in anhydrous glacial acetic acid with 0.1 N $HClO_4$ can be evaluated by modified *Gran* functions[83, 101] and adjustment by polynomials.

Nonlinear regression analysis or multiparametric curve fitting also starts from the mathematical expression of the titration curve. The object of the numerical process is to determine a function $Y_{calc.}$ in dependence on several parameters P_i (*e.g.* for acid/base titrations, c_A, K_a, $E_*^\ominus$) from experimental data Y_i, in such a way that the sum S of the squared errors is a minimum.

$$Y_{calc} = f(p_1, p_2, p_3 \ldots x) \tag{27}$$

$$S = \sum (Y_i - Y_{calc})^2 \stackrel{!}{=} \min \tag{28}$$

Methods of this kind have been described for the determination of the stability constants of mixed complexes (Legatrop computer program[102]) and have also been used for the evaluation of titration curves[103]. *Meites* has also published programs (Curfit[104], CFT3[105]) that can be applied to the evaluation of titration curves[106]. An alternative approach to these more general methods of curve fitting involves methods of calculation employing truncated Taylor series and partial differentiation of the equation of the curve with respect to all the parameters (for a general introduction see, *e.g.*, [107]). This approach has been described for multiple standard mixing methods with ion-selective electrodes[108], for acidimetric titrations[100, 109], for precipitation titrations[100], and for titrations in anhydrous glacial acetic acid[83].

6.3. Exhaustive Approximation Methods

A middle role is played by the evaluation methods that can be collected under the heading of Exhaustive Approximation Methods. Like the simple approximation methods, these do not start with a mathematical equation for the titration curve, *i.e.* they are independent of the type of titration and thus determine not the equivalence point but the point of inflection. On the other hand, like the mathematical methods in principle, they utilize all the measured points in the evaluation and thus do not depend so heavily on the potential transfer errors in the vicinity of the end point. Here the first citation should be of a graphical method going back to *Kohn* and *Zitko*[110], which was later elaborated for digital titrations[111]. In this method the end point v_E is obtained when the surface area of the trapezium F_T equals the area F_P of the polygon series (see Fig. 15). The evaluation can be improved, especially for slightly unsymmetrical titration curves, because it is easy to incorporate an asymmetry correction[83, 112]. The method is thus particularly suitable for titrations in anhydrous glacial acetic acid.

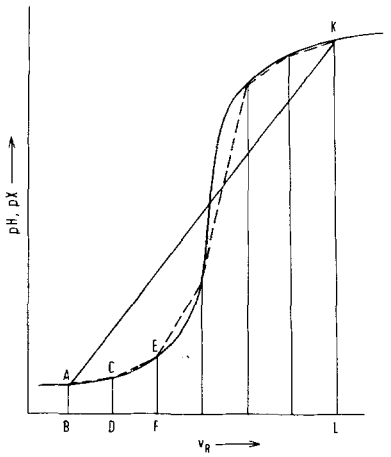


Fig. 15. Principle of the evaluation of digital potentiometric titrations by *Kohn-Zitko*'s method [110] (according to [111, 112]). v_E is defined as: $F_T = F_P$, Area of trapezium F_T: ABLK, Polygon series area F_P: Sum of the trapeziums ABCD, CDFE *etc.*

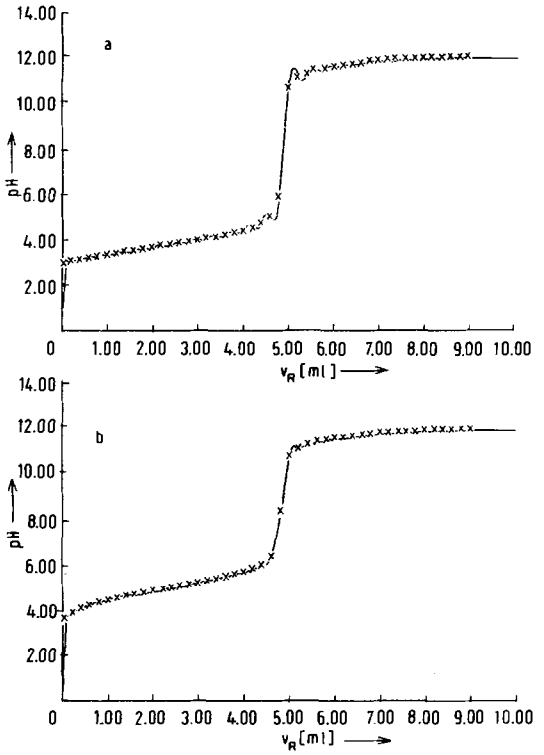


Fig. 16. Fourier approximation of a digital potentiometric titration curve [113]. a) No supporting point near the equivalence point, b) supporting point near the equivalence point. Solutions: a) ≈ 25 ml of 0.02 N mandelic acid, b) ≈ 25 ml of 0.02 N acetic acid.

Evaluation of digital potentiometric titration curves by Fourier series seems very promising[113]. The end point is obtained from the point of inflection with maximum slope (cf. Fig. 16). The error depends on the magnitude of the reagent volume increment.

7. Examples of Application

7.1. Direct Potentiometry

A series of analytical problems is solved relatively easily by means of ion-selective electrodes[114]. If the whole response range of such electrodes must be used, it is still best to determine the calibration function for the electrode under defined

conditions and to analyze the sample under conditions as similar as possible. In a fully automatic system (Fig. 9) the calibration plot is first established with *e.g.* four samples (*e.g.* $c_A = 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}$); then several analyses follow. Because of potential drift it is advisable (depending on the nature of the analysis and on the electrode) to repeat the calibration after a certain number of analyses[69]. The computer must know the positions of the standard solutions in the sample changer. Such self-calibration systems operate with fairly high sample frequencies (*e.g.* for the determination of chloride in drinking water and service water: about 40 samples/hour[115]). By extension of the system (a second operational stage on the sample changer with an attached Dosimat) the TISAB solution (Total Ionic Strength Adjustment Buffer) can be added immediately before the measurement (important *e.g.* for the determination of Na^+ by means of nitrilotriethanol because of the absorption of CO_2 from the air) (cf. Fig. 17).

7.2. Simple Standard Addition Method

The standard addition method[116, 117] is often used in work with ion-selective electrodes. In this method the concentration of the ion to be measured is changed by adding defined quantities of that ion. The systems shown in Figures 9 and 10 are suitable for this method of measurement. Only two points, at $v_R = 0.0$ and, *e.g.*, $v_R = 10.0$ ml, are used for the evaluation; all other measurements are rejected by the computer. There is no need for a calibration function for the evaluation, but instead the electrode slope σ must be known. Potential drift is little in evidence, since the standard potential of the measuring cell employed need not be known. The potential difference $\Delta(\Delta E)$ between the two selected points affords the required concentration c_x in the volume v_x from the concentration c_s and the volume v_s of the standard solution added:

$$c_x = c_s \cdot v_s \cdot \frac{\beta}{v_x + v_s + v_x \cdot \beta} \tag{29}$$

$$\beta = 10\uparrow\left\{-\frac{\Delta(\Delta E)}{\sigma}\right\} \tag{30}$$

A TISAB solution must be added to ensure that the conditions (pH, ionic strength) remain constant during the measurement. The accuracy of the method is determined mainly by the accuracy of the measurement; the errors are acceptable only within limited concentration ranges (for consideration of the error see, *e.g.*, [118]).

7.3. Multiple Standard Addition Method

In the simple standard addition method every error in the determination of potential is carried directly into the result. Proposals have therefore been made to monitor a series of measurement points and to determine the desired concentration by a balancing calculation. The following relationship between the cell potential and the concentration of the potential-determining ion is valid for every measurement point (provided that here too the analysis is carried out at constant ionic strength):

$$\Delta E_i = E_*^{\ominus} + \sigma \cdot \lg\left\{\frac{c_x v_x + c_s v_s}{v_x + v_s}\right\} \tag{31}$$

The problem of evaluation can be solved by nonlinear regression analysis (multiparametric curve fitting)[108] or by transformation and linearization[119] with subsequent adjustment of the straight lines (cf. also [120]). The programmable desk calculators shown in the block diagrams (Hewlett-Packard 9810 and 9830) work so fast that a fully automatic arrangement is justified and the time between two samples suffices for the evaluation.

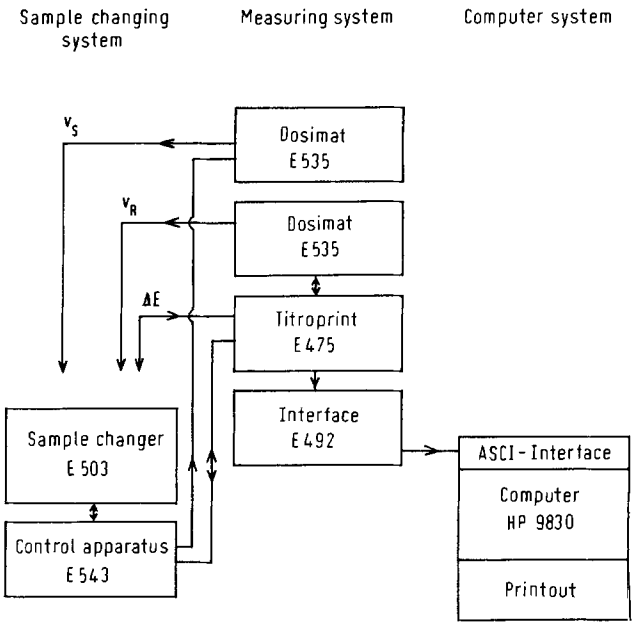


Fig. 17. Fully automatic system for indirect determination [69]: the upper Dosimat adds an excess of reagent at the first transport station, this excess being back-titrated at the second transport station. The system is also suitable for indirect determinations with ion-selective electrodes.

If the system shown in Figure 10 is slightly modified (Fig. 17) indirect determinations can also be carried out. For example, sulfate can be determined by adding a definite volume of a lead salt solution at the first transport station, thus precipitating the sulfate; the excess of lead is then determined by one of the two methods of evaluation described, involving the multiple standard addition method; the standard solution is added at the second transport station.

Rather large deviations must be expected in the multiple standard addition method if the concentration of the reagent used is not optimal for the concentration of the ion to be determined[115, 121].

7.4. End-point Titrations

In end-point titrations involving fully automatic methods (particularly in precipitation titrations), it should be noted that, in addition to the problems mentioned in Section 5.2, a systematic error can occur that is dependent on the consumption of the reagent. Under certain circumstances this error is reproducible and can be accounted for in the evaluation. We investigated this problem in the determination of chloride in drinking water and service water[115].

7.5. Digital Titrations

The problems of evaluation were outlined in Section 5.3. The methods mentioned are suitable for acidimetric titrations

(also when glacial acetic acid is employed as the solvent), for precipitation titrations, and for some redox titrations. In this last case it is particularly important that the methodology should be well planned out for fully automatic systems. Some demanding evaluation procedures (*e. g.* nonlinear regression analysis, *Gran* procedure with optimization calculations) require long calculation times with desk calculators. The calculation time is, however, limited by the time required by the control mechanism of the sample changer between two samples (the system in Fig. 10 has only passive data transfer). Nevertheless, as it is not the interface that transmits the data but the computer that calls the data from the interface (Fig. 11), in systems involving active data transfer the time between samples does not play the primary role[122, 123].

We are indebted to the Deutsche Forschungsgemeinschaft for supporting our work as reported in this review by material and personal means, to the Fonds der chemischen Industrie for materials, to instrument manufacturers for provision of apparatus, and in particular to U. Bethge, Dr. A. Binder, Dr. C. P. Christiansen, E. Glaser, Dr. S. Kalb, E. Koch, Dr. R. Krömmelbein, Dr. W. Parzefall, and P. Surmann for their fruitful collaboration in the field of evaluation and automation of electroanalytical processes.

Received: August 26, 1976 [A 152 IE]
German version: Angew. Chem. *89*, 129 (1977)
Translated by Express Translation Service, London

[1] *T. Anfält, D. Jagner*, Anal. Chim. Acta *57*, 177 (1971).
[2] *T. W. Hunter, J. T. Sinnamon, G. Hieftje*, Anal. Chem. *47*, 497 (1975).
[3] *A. Johansson, L. Pehrsson*, Analyst *95*, 652 (1970).
[4] *J. J. Kankare, P. O. Kosonen, P. O. Vihera*, Anal. Chem. *46*, 1362 (1974).
[5] *J. P. Philips:* Automatic Titrators. Academic Press, London 1954.
[6] *J. Slanina* et al., Z. Anal. Chem. *260*, 354 (1972).
[7] *K. A. Mueller, M. F. Burke*, Anal. Chem. *43*, 641 (1971).
[8] *R. G. Bates:* Determination of pH. Wiley, New York 1964.
[9] *K. Cammann:* Das Arbeiten mit ionensensitiven Elektroden. Springer, Berlin 1973.
[10] *R. A. Durst:* Ion-selective electrodes. NBS Spec. Publ. 314, Washington 1969.
[11] *S. Ebel, W. Parzefall:* Experimentelle Einführung in die Potentiometrie. Verlag Chemie, Weinheim 1975.
[12] *G. Eisenmann:* Glass Electrodes for Hydrogen and other Cations. Dekker, New York 1967.
[13] *J. K. Foreman, P. B. Stockwell:* Automatic Chemical Analysis. Ellis Horwood/Wiley, New York 1975.
[14] *I. Gyenes:* Titrationen in nichtwäßrigen Lösungsmitteln. Enke, Stuttgart 1970.
[15] *F. L. Hahn:* pH und potentiometrische Titrierungen. Akadem. Verlagsges., Frankfurt 1964.
[16] *D. J. G. Ives, G. J. Janz:* Reference Electrodes. Academic Press, New York 1969.
[17] *H. L. Kies:* Rev. Anal. Chem. *2*, 9 (1974).
[18] *G. Kraft, J. Fischer:* Indikation von Titrationen. de Gruyter, Berlin 1972.
[19] *D. C. M. Squirrel:* Automatic Methods in Volumetric Analysis. Hilger Watts, London 1964.
[20] *D. K. Roe*, Anal. Chem. *38*, 416R (1966).
[21] *E. C. Toren*, Anal. Chem. *40*, 402R (1968).
[22] *E. C. Toren, P. M. Gross, R. P. Buck*, Anal. Chem. *42*, 284R (1970).
[23] *R. P. Buck*, Anal. Chem. *44*, 270R (1972); *46*, 28R (1974); *48*, 23R (1976).
[24] *A. E. Nielsen:* Kinetics of Precipitation. Pergamon Press, Oxford 1964.
[25] *A. G. Walton:* Formation and Properties of Precipitates. Chemical Analysis Vol. 23. Interscience, New York 1967.
[26] *B. Karlberg, G. Johansson*, Talanta *16*, 1545 (1969).
[27] *B. Karlberg*, Anal. Chim. Acta *66*, 93 (1973).
[28] *M. Mascini, A. Napoli*, Anal. Chem. *46*, 447 (1974).
[29] *G. J. Moody, J. D. R. Thomas*, Lab. Pract. *23*, 475 (1974).
[30] *B. Fleet, T. H. Ryan, M. J. D. Brand*, Anal. Chem. *46*, 12 (1974).
[31] *J. Mertens, P. van den Winkel, D. L. Massart*, Anal. Chem. *48*, 272 (1976).
[32] *S. Ebel, R. Krömmelbein*, Z. Anal. Chem. *256*, 28 (1971).
[33] *A. Binder, S. Ebel, M. Kaal, T. Thron*, Dtsch. Lebensm. Rundsch. *71*, 246 (1975).
[34] *P. S. Roller*, J. Am. Chem. Soc. *50*, 1 (1928); *54*, 3485 (1932); *57*, 98 (1935).
[35] *G. M. Fleck:* Equilibria in Solution. Holt Rinehart & Winston, New York 1966.
[36] *I. M. Kolthoff, P. J. Elving:* Treatise on Analytical Chemistry. Vol. I, 1, p. 243ff.; Intersci. Encyclopediae, New York 1959.
[37] *F. Seel:* Grundlagen der analytischen Chemie. 6th edit. Verlag Chemie, Weinheim 1976.
[38] *S. Ebel*, Z. Anal. Chem. *245*, 353 (1969).
[39] *S. Ebel*, Arch. Pharm. *302*, 856 (1969).
[40] *D. Dryssen, D. Jagner, F. Wengelin:* Computer Calculation of Ionic Equilibria and Titration Procedures. Wiley, New York 1968.
[41] p. 65ff. in [11].
[42] *H. J. Keller*, Neue Tech. A *1972* (2), 2.
[43] *H. J. Keller*, Chem. Rundsch. *25*, 815 (1972).
[44] *R. W. Arndt*, Achema lecture, Frankfurt 1976.
[45] *W. Rellstab*, Achema lecture, Frankfurt 1973.
[46] p. 77ff. in [11].
[47] p. 123 in [18].
[48] *C. F. Tubbs*, Anal. Chem. *26*, 1670 (1954).
[49] *S. Ebel*, Z. Anal. Chem. *245*, 108 (1969).
[50] *J. Butcher, Q. Fernando*, J. Chem. Educ. *43*, 546 (1966).
[51] *Q. Fernando, J. Butcher*, J. Chem. Educ. *44*, 166 (1967).
[52] *J. N. Butler*, J. Chem. Educ. *40*, 66 (1963).
[53] *H. L. Christopherson*, J. Chem. Educ. *40*, 63 (1963).
[54] *L. Erdey, G. Svehla*, Anal. Chim. Acta *40*, 473 (1968).
[55] *A. Ringbom:* Complexation in Analytical Chemistry. Wiley, New York 1963.
[56] *S. Schwarzenbach:* Die komplexometrische Titration. Enke, Stuttgart 1957.
[57] p. 106 in [11].
[58] *G. Halfter, G. Köhler*, Chem. Ing. Tech. *30*, 340 (1958).
[59] *J. J. Kankare, P. O. Kosonen, P. O. Vihera*, Anal. Chem. *46*, 1362 (1974).
[60] *R. Krömmelbein*, Dissertation, Universität Marburg 1973.
[61] *D. Jagner*, Anal. Chim. Acta *50*, 15 (1970).
[62] *G. M. Hieftje, B. M. Manadarano*, Anal. Chem. *44*, 1616 (1972).
[63] *D. G. Mitchell, K. M. Aldous*, Analyst *98*, 580 (1973).
[64] *S. Wolf*, Chem. Ztg. Chem. Appar. *93*, 676 (1969).
[65] *W. Rellstab*, Chem. Rundsch. *25*, 1571 (1972).
[66] *P. Boldt, H. Lackner*, Chem. Ing. Tech. *35*, 707 (1963).
[67] *S. Ebel, A. Seuring*, unpublished work.
[68] *S. Ebel, J. Hocke*, unpublished work.
[69] *U. Bethge, S. Ebel, H. Mohr, A. Seuring*, Unterlagen zu einem Kurs "Vollautomatische Titrationssysteme". Stuttgart-Filderstadt 1976.
[70] *H. Malmvig*, Achema lecture, Frankfurt 1976.
[71] p. 112ff. in [11].
[72] *F. L. Hahn, G. Weiler*, Z. Anal. Chem. *69*, 417 (1926).
[73] *I. M. Kolthoff, N. H. Furmann:* Potentiometric Titrations. Wiley, New York 1949.
[74] *F. L. Hahn*, Z. Anal. Chem. *163*, 169 (1958).
[75] *F. L. Hahn, M. Frommer, R. Schulze*, Z. Phys. Chem. *133*, 390 (1928).
[76] *J. M. H. Fortuin*, Anal. Chim. Acta *24*, 175 (1961).
[77] *S. Wolf*, Z. Anal. Chem. *250*, 13 (1970).
[78] *H. J. Keller, W. Richter*, Metrohm Bull. *2*, 173 (1971).
[79] *H. Kobler, W. Richter*, private communication.
[80] *S. Ebel, S. Kalb*, Z. Anal. Chem. *278*, 105 (1976).
[81] *S. Kalb*, Dissertation, Universität Marburg 1975.
[82] *S. Ebel, S. Kalb*, Metrohm Monographien Band 2, publication planned for 1977.
[83] *C. P. Christiansen*, Dissertation, Universität Marburg 1975.
[84] *S. Ebel, S. Kalb*, Z. Anal. Chem. *278*, 109 (1976).
[85] *S. Ebel, J. Hocke*, unpublished work.
[86] Results from GDCh-Fortbildungskurs "Vollautomatische Titrationen" (cf. [69]).
[87] *G. Gran*, Acta Chem. Scand. *4*, 559 (1950).
[88] *G. Gran*, Analyst *77*, 661 (1952).
[89] *F. Ingman, E. Still*, Talanta *13*, 1431 (1966).
[90] *A. Johansson*, Analyst *95*, 535 (1970).
[91] *S. Ebel, R. Krömmelbein*, Z. Anal. Chem. *256*, 31 (1971).
[92] *S. Ebel, R. Krömmelbein*, Z. Anal. Chem. *264*, 342 (1973).
[93] *C. McCallum, D. Midgley*, Anal. Chim. Acta *65*, 155 (1973).
[94] *A. Ivaska, E. Wänninen*, Anal. Lett. *6*, 961 (1973).
[95] *T. Anfält, D. Jagner*, Anal. Chim. Acta *57*, 165 (1971).
[96] *T. Anfält, D. Dryssen, D. Jagner*, Anal. Chim. Acta *43*, 478 (1968).
[97] *D. Jagner, K. Aren*, Anal. Chim. Acta *52*, 491 (1970).
[98] *R. Ludwig:* Methoden der Fehler- und Ausgleichsrechnung. Vieweg, Braunschweig 1969.
[99] *C. McCallum, D. Midgley*, Talanta *21*, 723 (1974).

[100] W. Parzefall, Dissertation, Universität Marburg 1976.
[101] S. Ebel, Chem. Ing. Tech. 46, 811 (1974).
[102] L. G. Sillen, Acta Chem. Scand. 16, 159, 173 (1962); 18, 1085 (1964).
[103] p. 211 in [40].
[104] T. Meites, M. Meites, Talanta 19, 1131 (1972).
[105] L. Meites: The General Multiparametric Curve Fitting Program CFT 3. Computing Laboratory, Potsdam, N. Y. 1973.
[106] D. M. Barry, L. Meites, Anal. Chim. Acta 68, 435 (1974).
[107] W. E. Wentworth, J. Chem. Educ. 42, 97, 162 (1965).
[108] M. J. D. Brand, G. A. Rechnitz, Anal. Chem. 42, 1172 (1970).
[109] K. Waldmeier, R. Rellstab, Z. Anal. Chem. 264, 337 (1973).
[110] R. Kohn, V. Zitko, Chem. Zvesti 12, 261 (1958).
[111] D. C. Cörmös, I. Marusciac, Stud. Univ. Babes-Bolyai, Ser. Chem. 16, 27 (1971).
[112] C. P. Christiansen, S. Ebel, Z. Anal. Chem., in press.
[113] P. Surman, Diplomarbeit, Universität Marburg 1974.
[114] Cf. e.g. p. 34 in [11].
[115] A. Seuring, planned Dissertation, Universität Marburg.
[116] R. A. Durst in [12].
[117] Orion-Newsletters 1, 9 (1969); 2, 5 (1970).
[118] p. 39ff. in [11].
[119] A. Liberti, M. Mascini, Anal. Chem. 41, 676 (1969).
[120] p. 44ff. in [11].
[121] I. Buffle, N. Parthasarathy, D. Monnier, Anal. Chim. Acta 59, 427 (1972).
[122] I. Buffle, Anal. Chim. Acta 59, 439 (1972).
[123] N. Parthasarathy, I. Buffle, D. Monnier, Anal. Chim. Acta 59, 447 (1972).

COMMUNICATIONS

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

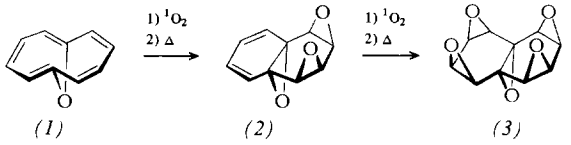
Synthesis and Structure Analysis of a Naphthalene Pentoxide

By *Emanuel Vogel, Arthur Breuer, Claus-Dieter Sommerfeld, Raymond E. Davis,* and *Ling-Kang Liu*[*]

Photooxidation of 1,6-bridged [10]annulenes with oxygen ($^1O_2$) affords 1,4-endoperoxides, which can be readily isomerized thermally to *syn*-diepoxides[1]. In the case of the 1,6-imino[10]annulene this reaction sequence has proved to be synthetically very useful, for it opens a simple route to *syn*-1,2;3,4-naphthalene dioxide[2].

We have now found that 1,6-epoxy[10]annulene can be converted into a naphthalene pentoxide by two successive $^1O_2$-addition/thermolysis sequences.

On irradiation with a sodium-vapor lamp in the presence of methylene blue and oxygen (methylene chloride; 10 to 15°C) 1,6-epoxy[10]annulene *(1)* shows little tendency to take up $^1O_2$[3]; the 1,2;3,4;9,10-naphthalene trioxide *(2)* [m.p. 119—120°C (needles from ethyl acetate); NMR ($CDCl_3$): sing-

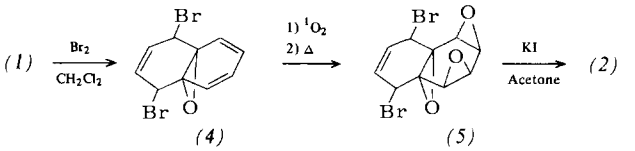


(1) *(2)* *(3)*

let (degenerate AA'BB' system) at τ=3.50 (olefin protons) and AA'BB' system centered at τ=6.49 (epoxide protons); UV (acetonitrile): λ_{max}=265 nm (ε=3200)], originating from a labile 1,4-endoperoxide, can be isolated in only *ca.* 1% yield, even after 120 h[4].

That the trioxide has the *anti* configuration *(2)*, and that, accordingly, attack of the singlet oxygen proceeds from the side of the molecule opposite to the oxygen bridge, could only be clarified later by an X-ray structure analysis of the pentoxide *(3) (vide infra)*.

In order to obtain *(2)* on a preparative scale it is advantageous not to photooxidize the annulene *(1)* itself, but rather its dibromo adduct *(4)*[5] (reaction with $^1O_2$ complete within 1 h). Photooxidation of *(4)* leads smoothly *via* an unstable 1,4-endoperoxide to the trioxide *(5)* [m.p. 189 to 190°C (dec); NMR ($CDCl_3$): singlets at τ=4.2 (olefin protons) and 5.0 (CHBr protons) and AA'BB' system at τ=6.35 (epoxide protons)], which on treatment with potassium iodide in acetone (40°C; 20 h) furnishes *(2)* in 50% yield. In contrast to *(1)*, compound *(2)* reacts relatively readily with $^1O_2$ (complete conversion after 120 h) with formation of a non-peroxidic oxidation product having the molecular composition $C_{10}H_8O_5$ [m.p. 280°C (dec); colorless platelets (from acetonitrile); yield 55%; 100-MHz ^{1}H-NMR (CD_3CN): AA'BB' system at τ=6.55 (H_1,H_4 / H_5,H_8) and 6.62 (H_2,H_3 / H_6,H_7); $J_{1,2}$=3.78 Hz, $J_{2,3}$=3.69 Hz, $J_{1,3}$=0.15 Hz, $J_{1,4}$=−0.15 Hz; ^{13}C-NMR (CD_3CN, TMS): δ(C_9/C_{10})=61.5, δ(C_1,C_4 / C_5,C_8)=50.2, δ(C_2,C_3 / C_6,C_7)=48.0].



The NMR spectra of this compound are consistent with the presence of a sterically uniform naphthalene pentoxide. It follows from the ^{1}H-NMR spectrum and the 3-line ^{13}C-NMR spectrum that the pentoxide is symmetrical with respect to the central epoxide ring (C_{2v} symmetry). The stereochemistry has been elucidated by X-ray structure analysis carried out by the American co-authors[6].

[*] Prof. Dr. E. Vogel [**], Dr. A. Breuer, Dr. C.-D. Sommerfeld
Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)
Prof. Dr. R. E. Davis, L.-K. Liu
Department of Chemistry
The University of Texas at Austin
Austin, Texas 78712 (USA)

[**] *E. Vogel* thanks the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen for support of this work. *R. E. Davis* is grateful to the R. A. Welch Foundation for financial support.

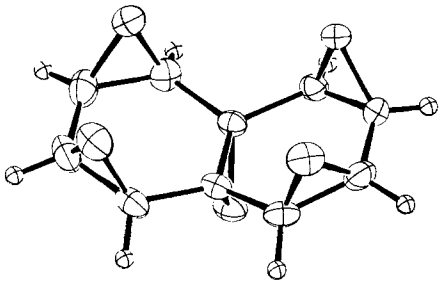


Fig. 1. *syn,syn,syn,syn*-1,2;3,4;5,6;7,8-*anti*-9,10-naphthalene pentoxide *(3)*, computer drawing.

The investigations showed that the naphthalene pentoxide has almost unperturbed C_{2v} symmetry in the crystal and that the compound has the *syn,syn,syn,syn*-1,2; 3,4; 5,6; 7,8-*anti*-9,10 configuration *(3)* (Fig. 1). The bond lengths and some of the angles are given in Figure 2. Each of the two "cyclohexane rings", *i.e.* C(1) to C(4), C(9), C(10) and C(5) to C(10), is planar (maximum deviation of the C atoms from planarity ±0.02 Å); the dihedral angle between the ring planes is 155.6°.

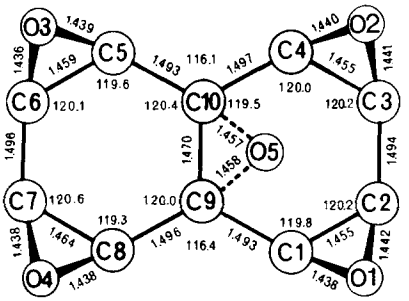


Fig. 2. Bond lengths [Å] and bond angles [°] in *syn,syn,syn,syn*-1,2; 3,4; 5,6; 7,8-*anti*-9,10-naphthalene pentoxide *(3)*. Maximum error ±0.003 Å and ±0.2°, respectively.

The angles between the central epoxide ring and the planes of the two six-membered rings are 102.3° and 102.1°, while the four outer epoxide rings form angles of 106.7°, 105.6°, 103.6° and 106.3° (counting according to Figure 2), respectively, with "their" six-membered rings. In the light of the molecular structure of *syn*-benzene trioxide, recently reported by *Littke* and *Drück*[7], the data found for *(3)* are consistent with expectation.

Received: September 9, 1976 [Z 610a IE]
German version: Angew. Chem. *89*, 175 (1977)

CAS Registry numbers:
(1), 4759-11-9; *(2)*, 61247-62-9; *(3)*, 58692-22-1; *(4)*, 5904-81-4; *(5)*, 61218-71-1

[1] *E. Vogel, A. Alscher*, and *K. Wilms*, Angew. Chem. *86*, 407 (1974); Angew. Chem. Int. Ed. Engl. *13*, 398 (1974); *M. Schäfer-Ridder, U. Brocker*, and *E. Vogel*, Angew. Chem. *88*, 262 (1976); Angew. Chem. Int. Ed. Engl. *15*, 228 (1976).

[2] *E. Vogel, H.-H. Klug*, and *M. Schäfer-Ridder*, Angew. Chem. *88*, 268 (1976); Angew. Chem. Int. Ed. Engl. *15*, 229 (1976); *syn*-1,2;3,4-naphthalene dioxide has in the meantime also been obtained by thermolysis of the 11,11-difluoro-1,6-methano[10]annulene 2,3;4,5-dioxide (from 11,11-difluoro-1,6-methano[10]annulene and $^1O_2$)—unpublished work carried out with *R. Müller*.

[3] The resistance of *(1)* toward attack by singlet oxygen might mainly be due to the (−*I*) effect of the bridge oxygen atom. This explanation is further supported by the observation that 1,6-methano[10]annulenes containing electronegative bridge substituents, particularly 11,11-difluoro-1,6-methano[10]annulene, undergo photooxidation only very slowly.

[4] The major proportion of *(1)* employed is recovered unchanged.

[5] *E. Vogel, W. A. Böll*, and *M. Biskup*, Tetrahedron Lett. *1966*, 1569.

[6] The crystals of naphthalene pentoxide are orthorhombic; $a = 9.466(8)$, $b = 15.810(8)$, $c = 11.281(5)$ Å; space group Pbca (No. 61) $d_{calc} = 1.61$ g/cm³ for $Z = 8$, $d_{exp} = 1.62$ g/cm³. 1942 independent reflections ($4° \leq 2\theta \leq 55°$) were recorded with MoKα radiation on a single crystal at −35°C using an automatic Syntex $P2_1$ diffractometer and the reflections with $I_0 \leq 3\sigma(I_0)$ used for the analysis and refinement. The use of direct methods enabled the positions of all the atoms except hydrogen to be determined. After these parameters had been refined to an *R* value of 0.10 the hydrogen atoms could be located by difference Fourier synthesis. Further refinement of the position parameters using the method of least squares led to a final *R* value of 0.037.

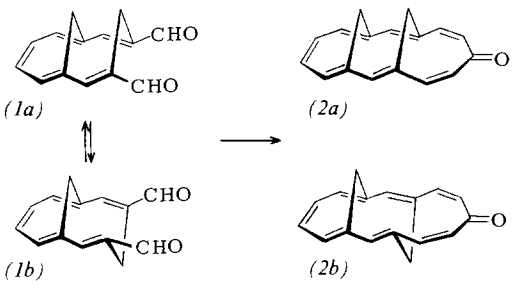
[7] *W. Littke* and *U. Drück*, Angew. Chem. *86*, 557 (1974); Angew. Chem. Int. Ed. Engl. *13*, 539 (1974).

syn-4,13;6,11-Dimethano[15]annulenone, a 14π-Analog of Tropone—Synthesis and X-Ray Structure Analysis

By *Wolfgang Wagemann, Klaus Müllen, Emanuel Vogel, Tullio Pilati*, and *Massimo Simonetta*[*]

The recently reported[1] bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene-3,5-dicarbaldehyde, for which an equilibrium between *syn* and *anti* conformers *(1a)* and *(1b)* is to be assumed, ought to undergo a Knoevenagel condensation with acetone dicarboxylic ester to give the 4,13;6,11-dimethano[15]annulenone as *syn* and/or *anti* stereoisomers *(2a)* and *(2b)*.

Prediction of which of the two [15]annulenone isomers is preferentially formed is difficult. The dialdehyde is surely present almost entirely as the conformer *(1a)* capable of more effective conjugation; but it cannot be ruled out that *(1a)* undergoes ring closure slower than *(1b)* for steric reasons (increase in the conformational strain of the internal CH_2 hydrogen atoms) and thus that *(2b)* is preferentially formed.



Condensation of *(1)* with dimethyl acetonedicarboxylate in benzene in presence of piperidineacetate as catalyst (3 h, 80°C) leads, as expected, to dimethyl 2-oxo-5,14;7,12-dimethano[15]annulene-1,3-dicarboxylate, which can be readily separated as a sterically uniform compound by chromatography on alumina (ether) [orange prisms (from chloroform/ether), m.p. 244 to 245°C, yield 28%]. Treatment of the diester with 10% methanolic potassium hydroxide (reflux, 1 h) and subsequent heating of the crude dicarboxylic acid liberated on acidification with HCl in boiling dimethylformamide (30 min) furnishes the 4,13;6,11-dimethano[15]annulenone [air-stable, red rhombic crystals (from chloroform/*n*-hexane), m.p. 235 to 236°C, yield 80%] sterically corresponding to the diester.

[*] Dr. W. Wagemann, Prof. Dr. E. Vogel
Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)
Dr. K. Müllen
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule
Universitätsstrasse 6/8, CH-8006 Zürich (Switzerland)
Dr. T. Pilati, Prof. Dr. M. Simonetta
Istituto di Chimica Fisica
Università di Milano
Via Golgi, 19, I-20133 Milano (Italy)

The 360-MHz ^{1}H-NMR spectrum[2] (CD_2Cl_2) of the 4,13;6,11-dimethano[15]annulenone led to the following assignments: $\tau = 2.59$ and 2.65 (H_8,H_9 and H_7,H_{10}, resp.; AA'BB' system with $J_{7,8} = 7.5$ and $J_{8,9} = 9.2$ Hz), 2.61 (H_5,H_{12}; s), 2.79 and 3.85 (H_3,H_{14} and H_2,H_{15}; AB system with $J_{2,3} = 12.3$ Hz), 7.28 and 8.31 ($H_{16\,endo}$ and $H_{16\,exo}$; AB system with $J = 15.8$ Hz), 7.64 and 10.92 ($H_{17\,endo}$ and $H_{17\,exo}$; AB system with $J = 13.0$ Hz).

On recording the spectrum in CF_3COOH the signals of the annulenone- and bridge-protons experience drastic down- and up-field shifts, respectively, from which it can be concluded that protonation to a delocalized 13-hydroxy-1,10;3,8-dimethano[15]annulenium ion has taken place. Also consistent with formation of the annulenium ion are the changes in the UV spectrum on going from ethanol to ethanol/perchloric acid as solvent, and the relatively high pK_a value of the annulenone of -0.4 ± 0.2 (tropone: $pK_a = -0.6 \pm 0.3$).

These findings prove the 4,13;6,11-dimethano[15]annulenone stereoisomer to be a 14-π analog of tropone and of the 4,9-methano[11]annulenone[3]. This makes the presence of *(2a)* likely, for *(2b)* could hardly be capable of forming a delocalized annulenium ion for steric reasons[4]. Final clarification of the stereochemistry was possible from an X-ray structure analysis carried out by our Italian colleagues[5].

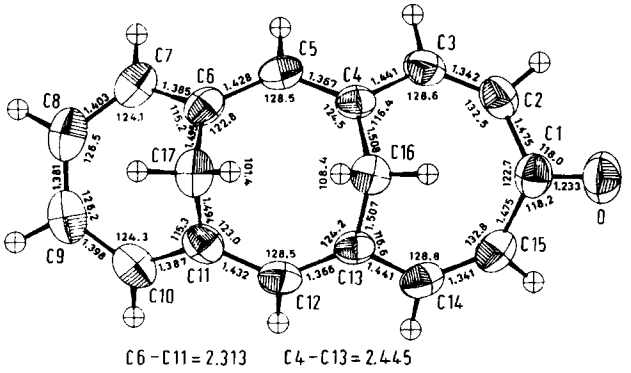


Fig. 1. Bond lengths [Å] and bond angles [°] in the *syn*-4,13;6,11-dimethano[15]annulenone *(2a)*. Maximum error ±0.003 Å and ±0.2°, respectively.

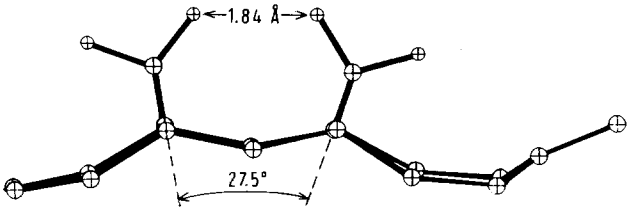


Fig. 2. Side view of *syn*-4,13;6,11-dimethano[15]annulenone *(2a)*

The analysis confirmed the assumption that the 4,13;6,11-dimethano[15]annulenone stereoisomer has the *syn* configuration *(2a)*. More detailed information about the molecular structure is given in Figures 1 and 2. It follows, in particular from the side view of the molecule shown in Fig. 2, that the internal bridge hydrogen atoms are relatively strongly compressed, and that the bending of the annulenone ring is thus limited. Interestingly, according to Fig. 1 the degree of alternation of single and double bonds decreases with increasing distance of the bonds from the CO group[7]. The cause of this, which is also reflected in a certain equalizing of the vicinal coupling constants of the ring protons H(7) to H(10), is currently under investigation.

Received: September 9, 1976 [Z 610b IE]
German version: Angew. Chem. 89, 176 (1977)

CAS Registry numbers:
(1), 55759-42-7; *(2a)*, 61232-09-5; dimethyl acetonedicarboxylate, 1830-54-2; dimethyl 2-oxo-5,14;7,12-dimethano[15]annulene-1,3-dicarboxylate, 61232-10-8; 2-oxo-5,14;7,12-dimethano[15]annulene-1,3-dicarboxylate, 61232-11-9

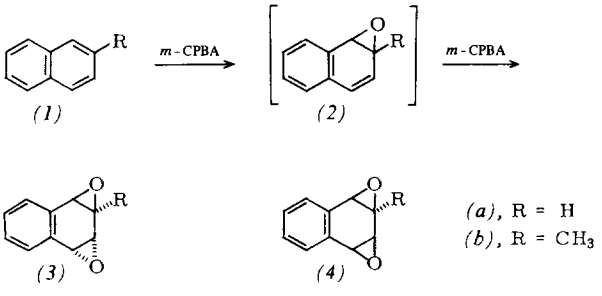
[1] *E. Vogel, J. Sombroek*, and *W. Wagemann*, Angew. Chem. *87*, 591 (1975); Angew. Chem. Int. Ed. Engl. *14*, 564 (1975).
[2] We thank Prof. *K. Wüthrich* and Ms *A. Frey*, ETH Zürich for recording the 360-MHz spectrum.
[3] *W. Grimme, J. Reisdorff, W. Jünemann*, and *E. Vogel*, J. Am. Chem. Soc. *92*, 6335 (1970).
[4] *Cf.* the difference in the properties of *syn*- and *anti*-1,6;8,13-dimethano[14]annulene: *E. Vogel, U. Haberland*, and *H. Günther*, Angew. Chem. *82*, 510 (1970); Angew. Chem. Int. Ed. Engl. *9*, 513 (1970).
[5] The 4,13;6,11-dimethano[15]annulenone stereoisomer crystallizes monoclinically (four molecules per unit cell) in the space group $P2_1/n$, lattice constants $a = 9.854(2)$, $b = 10.903(2)$, $c = 11.259(2)$ Å; $\beta = 92.42(2)°$; $d_{calc} = 1.288$, $d_{exp} = 1.287$ g/cm^3. 2784 symmetry independent reflections ($2\theta_{max} = 54.9°$) were measured on a Syntex $P\bar{1}$ diffractometer with MoKα radiation. The structure was determined by direct methods on the basis of 275 reflections with $E > 1.65$ [6] and refined by the method of least squares. In the final refinement cycle the coordinates of all atoms were included, anisotropic temperature factors for the 18 heavy atoms and isotropic B values for the 14 hydrogen atoms. The resulting R factor (for 2549 reflections with $I > 0$) was 0.054, the weighted factor R ($= R_w$) 0.046. A final difference map showed a maximum value of 0.25 e/Å^3.
[6] *R. E. Long*, Thesis, University of California, Los Angeles 1965.
[7] The same trend, albeit in weaker form, is observed in the case of 4,9-methano[11]annulenone: *D. W. Hudson* and *O. S. Mills*, Chem. Commun. *1971*, 153.

A Complementary Route to *anti*-1,2:3,4-Naphthalene Dioxide; Direct Oxidation of Arenes with *m*-Chloroperbenzoic Acid[**]

By *K. Ishikawa* and *G. W. Griffin*[*]

Widespread attention has recently focused on arene oxides and particularly epoxy diols related to arene dioxides as the possible ultimate mutagens and/or carcinogens[1]. Such metabolites of exogenous aromatic hydrocarbons have been found to interact with cell nucleophiles and produce malignant transformations of cells *in vitro*. Some time ago the synthesis of benzene dioxide was reported by *Vogel et al.*[2] and its possible significance from a biochemical standpoint became evident when shortly thereafter *Borders et al.*[3] found that a naturally occurring substance with antibiotic properties incorporates a benzene dioxide moiety.

As a consequence of our continuing interest in arene oxides[4] and in particular the *direct* epoxidation of polycyclic hydrocarbons[5] we have investigated the oxidation of naph-



[*] Prof. Dr. G. W. Griffin and Dr. K. Ishikawa
Department of Chemistry, University of New Orleans
Lake Front, New Orleans, Louisiana 70122 (USA)

[**] This investigation was supported by Grant Number 1-RO1-CA-18346-01, awarded by the National Cancer Institute, DHEW, and also by Grant Number MPS75-14831, awarded by the National Science Foundation, which the authors wish to acknowledge. We also wish to thank Dr. *E. Elder* and Ms. *J. Thompson* for assistance in the preparation of the manuscript.

thalene *(1a)* with *m*-chloroperbenzoic acid (*m*-CPBA). Under carefully controlled reaction conditions and workup procedures it has been possible to achieve the direct synthesis and isolation of *anti*-1,2:3,4-naphthalene dioxide *(3a)*[6] using *m*-CPBA in the presence of water as the oxidant.

A solution of *(1a)* (0.04 M) in methylene chloride containing *m*-CPBA (2.25 equiv.) was stirred with saturated sodium bicarbonate at 25°C for 14 h and the organic phase washed with aqueous sodium thiosulfate to remove excess *m*-CPBA. The organic phase is dried over anhydrous sodium sulfate, concentrated and chromatographed on a column packed with silica gel which has been previously deactivated by stirring with ethanol[7]. The elution was conducted with benzene-hexane (0—40%). The *anti*-dioxide *(3a)* (15—20%) emerges after *(1a)* and is followed by a by-product whose structure remains to be established, although it is not the *syn* isomer *(4a)* or a trioxide or diol epoxide, as evidenced by NMR analysis. The melting point (99–100°C) and spectral data for *(3a)* compare favorably with that described by *Vogel et al.*[6]. The NMR spectrum exhibits the complicated pair of AA'BB' signals at $\tau = 6.0$—6.5 ($CDCl_3$) reported previously for *(3a)*. It is of interest that *(3a)* is not deoxygenated with thiourea in methanol, which is generally effective in reducing K-region arene oxides[8].

It is important to note that the concentration of *(1a)* and *m*-CPBA be maintained at a low level and the isolation procedures used for *(3a)* are critical. For example, if the concentration of *(1a)* is increased to 0.2 M, by-product formation increases to the point where isolation of *(3a)* is difficult.

That the technique has general application is apparent from the fact that 2-methylnaphthalene *(1b)* also undergoes oxidation under conditions similar to those described for *(1a)*, albeit at a faster rate (3 h); however, in this case both the *anti* and *syn* isomers [*(3b)* and *(4b)*, respectively] are obtained, presumably because initial oxidation occurs at the activated 1,2-bond to give *(2b)*, and the differential steric factors responsible for the stereocontrol observed in the subsequent step in the comparative oxidation of *(2a)* are reduced. Techniques similar to those used with *(3a)* were employed for the isolation of the unstable dioxides (40%) and also partial separation of the two stereoisomers *(3b)* and *(4b)*. Assignment of stereochemistry in the case of *(3b)* and *(4b)* is complicated by the absence of a proton at C-2 precluding utilization of the $J_{2,3}$ coupling constant which provides the sole method reported to date for the differentiation of *(3a)* and *(4a)*[6]. The NMR spectra of *(3b)* and *(4b)* are nearly identical and bear an obvious resemblance to those of *(3a)* and *(4a)* [$\tau = 8.33$ s, (CH_3); 6.50 br s (H^1); 6.27 dd (H^3, H^4) ($CDCl_3$)]. The major isomer after recrystallization from CH_2Cl_2/hexane melts at 67—68°C, with partial decomposition.

As expected, anthracene upon treatment with *m*-CPBA in the manner described gives primarily anthraquinone. If, however, positions 9 and 10 are blocked by aryl substituents, as is the case in 9,10-diphenylanthracene, oxidation occurs to give a dioxide. The oxidation in this case was conducted most efficiently by adding 4 equiv. of *m*-CPBA in two equal portions during a twelve hour period. In this manner the resulting dioxide, m.p. 188—190°C (dec), $M^+ = 362$, was obtained in 16% yield. The NMR spectrum [$\tau = 6.39$, 6.14 AA'BB' m] is very similar to that of *(3a)*; by analogy with the oxidation of naphthalene *(1a)* the oxidation of 9,10-diphenylanthracene should lead to the 9,10-diphenyl-1,2:3,4-anthracene dioxide, which is probably in the *anti* configuration.

Received: December 13, 1976 [Z 633 IE]
German version: Angew. Chem. *89*, 181 (1977)

CAS Registry numbers:
(1a), 91-20-3; *(1b)*, 91-57-6; *(3a)*, 58717-74-1; *(3b)*, 61477-29-0; *(4a)*, 58692-14-1; *(4b)*, 61520-79-4; *m*-CPBA, 937-14-4; 9,10-diphenylanthracene, 1499-10-1; 9,10-diphenyl-1,2;3,4-anthracene dioxide, 61477-30-3

[1] *I. B. Weinstein, A. M. Jeffrey, K. W. Jennette, S. H. Blobstein, R. G. Harvey, C. Harris, H. Autrup, H. Kasai, K. Nakanishi*, Science *193*, 592 (1976); *A. M. Jeffrey, K. W. Jennette, S. H. Blobstein, I. B. Weinstein, F. A. Beland, R. G. Harvey, H. Kasai, I. Miura, K. Nakanishi*, J. Am. Chem. Soc. *98*, 5714 (1976); *M. Koreeda, P. D. Moore, H. Yagi, H. J. C. Yeh, D. M. Jerina*, ibid. *98*, 6720 (1976); *A. M. Wood, W. Levin, A. Y. H. Lu, D. Ryan, S. B. West, Re. E. Lehr, M. Schäfer-Ridder, D. M. Jerina, A. H. Conney*, ibid., in press.

[2] *H.-J. Altenbach, E. Vogel*, Angew. Chem. *84*, 985 (1972); Angew. Chem. Int. Ed. Engl. *11*, 937 (1972); see also *E. Vogel, N.-J. Altenbach*, and *E. Schmidbauer*, Angew. Chem. *85*, 862 (1973); Angew. Chem. Int. Ed. Engl. *12*, 838 (1973); *C. H. Foster, G. A. Berchtold*, J. Org. Chem. *40*, 3743 (1975).

[3] *D. B. Borders, P. Shu, J. E. Lancaster*, J. Am. Chem. Soc. *94*, 2540 (1972); *D. B. Borders, J. E. Lancaster*, J. Org. Chem. *39*, 435 (1974); US-Pat. 3770773 (1973).

[4] *N. E. Brightwell, G. W. Griffin*, J. Chem. Soc. Chem. Commun. *1973*, 37; *B. J. Dowty, N. E. Brightwell, J. L. Laseter, G. W. Griffin*, Biochem. Biophys. Res. Commun. *57*, 452 (1974); *G. W. Griffin, S. K. Satra, N. E. Brightwell, K. Ishikawa, N. S. Bhacca*, Tetrahedron Lett. *1976*, 1239.

[5] *K. Ishikawa, H. C. Charles, G. W. Griffin*, Tetrahedron Lett., in press.

[6] Elegant, albeit multistep, procedures have very recently been reported by *Vogel et al.* for the synthesis of the diastereomeric dioxides *(3a)* and *(4a)*. While synthesis of the *syn* isomer *(4a)* was achieved in high yield (50%) from naphthalene-1,4-endoperoxide, the *anti* isomer, was obtained in only 1–2%; the procedure described herein is thus complementary. See *E. Vogel, H.-H. Klug, M. Schäfer-Ridder*, Angew. Chem. *88*, 268 (1976); Angew. Chem. Int. Ed. Engl. *15*, 229 (1976). We are indebted to Prof. *Vogel* for a spectrum of *(3a)*, contained in the doctoral thesis of *H.-H. Kluge* (Universität Köln, Germany, 1976) for purposes of comparison.

[7] See for example *E. H. Mosbach, M. Nierenberg, F. E. Kendall*, J. Am. Chem. Soc. *75*, 2358 (1953) and *E. R. Katzenellenbogen, K. Dobriner, T. H. Kritchevsky*, J. Biol. Chem. *207*, 315 (1954).

[8] *G. W. Griffin, K. Ishikawa, S. K. Satra*, J. Heterocycl. Chem. *13*, 1369 (1976).

Partial Nitrosylation of Dicarbonyl(η-cyclopentadienyl)cobalt[**]

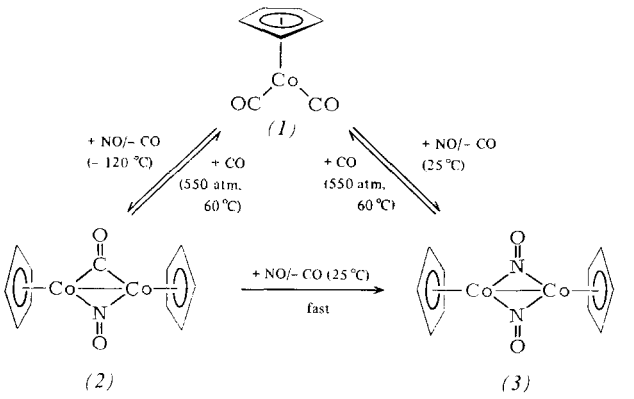
By *Wolfgang A. Herrmann* and *Ivan Bernal*[*]

Dicarbonyl(η-cyclopentadienyl)cobalt *(1)* reacts at room temperature with nitrogen monoxide with complete substitution of CO; apart from the stable dinuclear complex $(\eta\text{-}C_5H_5CoNO)_2$ *(3)* no other products are isolated[1].

Partial nitrosylation of *(1)* has now been accomplished by drastically reducing the reaction temperature or by using organic NO-transfer agents: Rapid formation of μ-carbonyl-μ-nitrosyl-bis(η-cyclopentadienylcobalt) *(Co—Co)* *(2)*[2] takes place on treating an *n*-pentane solution of *(1)* for a short period of time with NO gas at −120°C. With an excess of NO, *(2)* is converted slowly at −120°C, and quantitatively within a few seconds at room temperature, into the dinitrosyl complex *(3)*. From this finding we conclude that *(2)* is an intermediate in the synthesis of *(3)*[1]. Both compounds can be recarbonylated under pressure (550 atm, 60°C, 3 h in THF) to the mononuclear starting complex *(1)*.

[*] Dr. W. A. Herrmann
Chemisches Institut der Universität
Universitätsstrasse 31, D-8400 Regensburg 1 (Germany)
Prof. Dr. I. Bernal
Chemistry Department, University of Houston
Houston, Texas 77004 (USA)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Alexander-von-Humboldt Stifting, the Welch Foundation, and the US National Science Foundation.



paramagnetic

ν_{NO}: 1543 cm^{-1};
ν_{CO}: 1819 cm^{-1}(KBr)

diamagnetic

ν_{NO}: 1585,
1525 cm^{-1}(KBr)

N-Methyl- and *N*-ethyl-*N*-nitrosourea react with *(1)* in boiling benzene to give exclusively the partially nitrosylated product *(2)*, even when used in twofold excess. This large difference in reactivity in comparison to NO underlines the preparative importance of these two nitrosourea derivatives as very mild nitrosylating reagents for metal carbonyls. They are readily accessible and thermally relatively stable (m.p./dec >100 °C). This also applies for *N*-nitroso-*p*-toluenesulfonamide, which is employed for a similar purpose in complex chemistry; its use in the case described here, however, leads only to mixtures of the difficultly separable complexes *(2)* and *(3)*.

The structure of *(2)*, confirmed by an X-ray structure analysis to be a dinuclear complex containing a Co—Co single bond[3], is consistent with its paramagnetism (1.86 μ_B[2]), which we were also able to detect ESR spectroscopically. The 15-line system ($a_{Co}=47.4$, $a_N \leq 14$ Oe; *g*-factor 2.0539) evidences uniform charge distribution over both Co nuclei ($I=7/2$); were the unpaired electron to reside preferentially on the bridge ligand, as in the μ-peroxobis(pentamminecobalt) ion[4], a_{Co} would be much smaller.

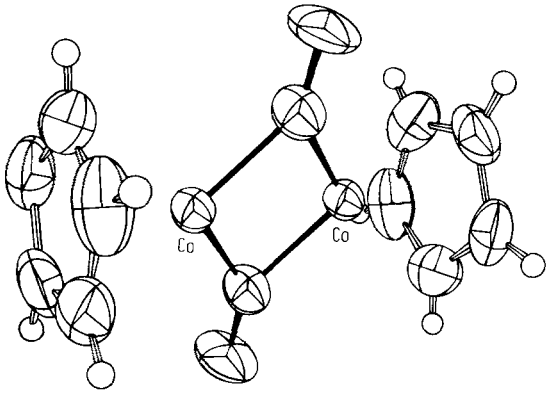


Fig. 1. ORTEP diagram of *(2)*. The $Co_2(NO)(CO)$ fragment is coplanar (max. deviation from the plane ±0.4 pm). Bond lengths: Co—Co 237.0 pm (single bond), Co—Co = Co—NO 182.9 pm; angle CoNCo (= ∢CoCCo) 80.7°.

Experimental[5]:

a) Nitrogen monoxide variant: A slow stream (0.5 mm capillary) of dry NO gas is passed through a magnetically stirred solution of *(1)*[6] (1.80 g, 10 mmol) in *n*-pentane (100 ml) at −120 °C. After 10 minutes, the solvent is first removed under high vacuum at −40 °C and then any unconsumed *(1)* at room temperature. The brown residue crystallizes from diethyl ether/methylene chloride (2:1, −35 °C); yield 410 mg (27 %) of *(2)*.

b) *N*-Alkyl-*N*-nitrosourea variant: A mixture of *(1)* (1.80 g, 10 mmol) and *N*-methyl-[7a] or *N*-ethyl-*N*-nitrosourea[7b] (15 mmol, 1.55 and 1.76 g resp.) in benzene (40 ml) is heated under reflux for 8 h. The solution is evaporated down in a high vacuum and the residue chromatographed (20 × 3 cm column; +15 °C) with benzene on silica gel (0.063—0.200 mm, Act. II—III). Recrystallization (diethyl ether/methylene chloride 2:1; −35 °C) of the substance obtained from the brown zone yields 918 g (61 %) of analytically pure *(2)*.

Received: November 30, 1976 [Z 618 IE]
revised: December 3, 1976
German version: Angew. Chem. *89*, 186 (1977)

CAS Registry numbers:
(1), 12078-23-8; *(2)*, 58071-48-0; *(3)*, 51862-20-5; *N*-methyl-*N*-nitrosourea, 684-93-5; *N*-ethyl-*N*-nitrosourea, 759-73-9

[1] *H. Brunner*, J. Organomet. Chem. *12*, 517 (1968).
[2] *(2)* was first obtained by photoinduced reaction of *(3)* with *(1)*: *J. Müller, S. Schmitt*, J. Organomet. Chem. *97*, C 54 (1975).
[3] *(2)* crystallizes monoclinically; space group $P2_1/c$, $Z=2$. For a detailed description of the structure of *(2)*, see *I. Bernal, J. Korb, M. G. Reisner, W. A. Herrmann*, J. Organomet. Chem., in press.
[4] *I. Bernal, E. A. V. Ebsworth, J. A. Weil*, Proc. Chem. Soc. London *1959*, 57; *J. A. Weil, J. K. Kinnaird*, J. Phys. Chem. *71*, 3341 (1967).
[5] All work carried out under nitrogen and in the absence of moisture.
[6] Prepared according to *M. D. Rausch, R. A. Genetti*, J. Org. Chem. *35*, 3888 (1970).
[7] a) Organikum, 12th edit., VEB Deutscher Verlag der Wissenschaften Berlin 1973, p. 584; b) Reagent from Fluka-Feinchemikalien.—The acetic acid added for stabilization is removed by washing with water. The compound can be stored for several months at 35 °C.

Isolation of Halohydroborates of Type $[B_{10}H_{10-n}X_n]^{2-}$

By *Klaus-Georg Bührens* and *Wilhelm Preetz*[*]

Electrophilic substitution reactions on hydrodecaborate ions *(1)* with chlorine, bromine, or iodine in aqueous or alcoholic solution lead to the corresponding halohydroborates *(2)*[1].

$$\underset{(1)}{B_{10}H_{10}^{2-}} + nX_2 \longrightarrow \underset{(2)}{B_{10}H_{10-n}X_n^{2-}} + nHX$$

X = Cl, Br, I; n = 1-9,10

Only the terminal members ($n=10$) of the three homologous series *(2)* have as yet been confirmed, while it was not ruled out for the few intermediates isolated—*e.g.* $B_{10}H_2Cl_8^{2-}$, $B_{10}H_3Br_7^{2-}$, $B_{10}H_8I_2^{2-}$[1]—that mixtures of several of the very similar species had actually been obtained.

By means of electrophoresis[2] we have now detected all the substituted species *(2)*, of which the compounds listed in Table 1 were isolated in pure form. They were characterized by elemental analysis and vibrational spectra of the sparingly soluble tetramethylammonium salts.

[*] Prof. Dr. W. Preetz, Dr. K.-G. Bührens
Institut für Anorganische Chemie der Universität
Olshausenstrasse 40—60, D-2300 Kiel (Germany)

Table 1. Characteristic IR frequencies [cm^{-1}] of the isolated halohydroborates.

$[(CH_3)_4N]_2B_{10}H_9Cl$	2535 sh, 2515 sh, 2495 vs, 1125 sh, 1105 s, 1010 w, 880 w, 820 w, 800 w
$[(CH_3)_4N]_2B_{10}H_8Cl_2$	2520 vs, 1180 vw, 1070 m, 1020 m, 870 m, 835 m, 805 s, 725 m
$[(CH_3)_4N]_2B_{10}H_7Cl_3$	2540 sh, 2505 vs, 1175 w, 1075 m, 1030 m, 885 m, 830 s, 820 s, 735 s
$[(CH_3)_4N]_2B_{10}H_6Cl_4$	2530 vs, 2510 vs, 2485 sh, 1100 s, 1075 sh, 1035 s, 895 m, 875 m, 845 s, 755 s
$[(CH_3)_4N]_2B_{10}H_5Cl_5$	2560 sh, 2540 vs, 1140 sh, 1095 s, 1035 s, 860 s, br, 780 sh, 760 s
$[(CH_3)_4N]_2B_{10}H_4Cl_6$	2555 s, 1150 sh, 1095 s, 1040 s, 875 s, br, 780 m, 760 sh
$[(CH_3)_4N]_2B_{10}H_9Br$	2515 sh, 2505 vs, 2465 vs, 1125 sh, 1105 m, 1010 w, 880 w, 840 sh, 820 m, 790 m
$[(CH_3)_4N]_2B_{10}H_8Br_2$	2520 sh, 2495 vs, 1175 vw, 1100 s, 1075 m, 1035 w, 875 w, 850 sh, 830 m, 790 s
$[(CH_3)_4N]_2B_{10}H_7Br_3$	2520 sh, 2510 sh, 2495 vs, 1100 s, 1070 m, 1020 m, 870 m, 850 m, 830 sh, 800 s
$[(CH_3)_4N]_2B_{10}H_6Br_4$	2525 s, 1120 w, br, 1070 m, 1020 m, 870 w, 820 m, 810 m, 795 m
$[(CH_3)_4N]_2B_{10}H_5Br_5$	2525 s, 1130 sh, 1110 m, 1070 w, 1010 m, 870 sh, 825 s, 810 sh, 805 sh
$[(CH_3)_4N]_2B_{10}H_4Br_6$	2530 s, 1150 sh, 1110 m, 1005 m, 870 w, 810 s
$[(CH_3)_4N]_2B_{10}H_9I$	2510 s, 2485 vs, 2475 sh, 1100 w, 1010 m, 840 w, 810 m, 785 m, 770 m, 720 m
$[(CH_3)_4N]_2B_{10}H_8I_2$	2510 sh, 2490 vs, 2470 sh, 1175 w, 1100 s, 1070 m, 875 m, 830 w, 780 s, 765 sh
$[(CH_3)_4N]_2B_{10}H_7I_3$	2545 sh, 2530 s, 2495 s, 1030 m, br, 1100 s, 860 m, 802 m, 785 s, 770 s
$[(CH_3)_4N]_2B_{10}H_6I_4$	2540 s, 2516 s, 1120 sh, 1115 m, 1020 w, 860 m, 840 sh, 805 m, 790 m, 725 m

The rate of reaction decreases along the series $Cl_2 > Br_2 > I_2$. It is very high for the initial reaction steps and diminishes with increasing degree of halogenation. The solutions invariably contain 3 to 5 successive components, of which those in the middle are present in the highest concentration. The maximum shifts systematically towards higher values of n as the halogenation time increases. The ion mobilities decrease with increasing degree of halogenation. The difference in mobility therefore becomes progressively smaller and the ions having $n > 6$ can no longer be completely separated. The pherogram of a mixture of all radioactively labeled chlorohydroborates and the relevant activity profile are shown in Figure 1.

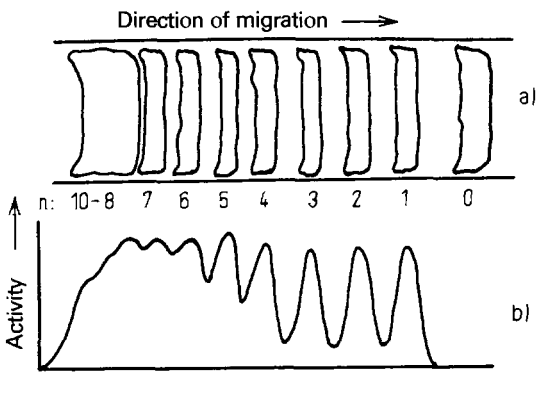


Fig. 1. a) Pherogram and b) activity profile of compounds $B_{10}H_{10-n}Cl_n^{2-}$ labeled with ^{36}Cl.

In the vibrational spectra, the BH stretching frequencies are seen in the 2470—2560 cm^{-1} region, the skeletal frequencies in the 1000—1300 cm^{-1} region, and the B—X stretching frequencies in the 700–895 cm^{-1} region. In the more extensively halogenated species in particular, characteristic splitting patterns are observed which are especially pronounced in the Raman spectra recorded on saturated acetonitrile solutions. Presumably, several geometrical isomers coexist in the solutions. The intensity of the BH stretching vibrations steadily diminishes with increasing halogenation while the center of gravity of the bands shifts to higher frequencies. The increase in strength of the BH bond manifested in this shift is paralleled by an increase in stability of the products.

Procedure:

A current of N_2 carrying a very small amount of Cl_2 or Br_2 is passed through ice-cooled solutions of $(NH_4)_2B_{10}H_{10}$ (1.5 g, 0.01 mol) in water (50 ml) (only a few minutes for preparation of species with $n < 3$, and up to an hour for more highly halogenated compounds). Iodination is performed by shaking the aqueous solution with a few ml of CCl_4 in which iodine is dissolved until the iodine color disappears, the procedure being repeated if necessary. After filtering off resinous side-products the mixtures *(2)* are precipitated from the aqueous solutions as the tetramethylammonium salts which are recrystallized from acetonitrile/water. They are treated with a cation exchanger to give the more soluble NH_4^+ or Na^+ salts, which are subjected to high voltage electrophoresis. On spraying of the pherograms with a dilute acridine hydrochloride solution the separated colorless halohydroborates give yellow zones which are cut out, collected, and eluted with 0.01 M NaOH. After concentration the ions *(2)* can be precipitated with tetramethylammonium chloride. Recrystallization from water/alcohol (almost pure alcohol for $n = 1$, almost pure water for $n = 6$) gives the colorless finely crystalline salts $[(CH_3)_4N]_2B_{10}H_{10-n}X_n$ in yields between 20 and 60 mg.

Received: December 3, 1976;
supplemented: December 21, 1976 [Z 637 IE]
German version: Angew. Chem. 89, 195 (1977)

CAS Registry numbers
$(NH_4)_2B_{10}H_{10}$, 12008-61-6; $[(CH_3)_4N]_2B_{10}H_9Cl$, 61617-71-8; $[(CH_3)_4N]_2B_{10}H_8Cl_2$, 51668-03-2; $[(CH_3)_4N]_2B_{10}H_7Cl_3$, 57594-30-6; $[(CH_3)_4N]_2B_{10}H_6Cl_4$, 61617-72-9; $[(CH_3)_4N]_2B_{10}H_5Cl_5$, 52655-96-6; $[(CH_3)_4N]_2B_{10}H_4Cl_6$, 51745-61-0; $[(CH_3)_4N]_2B_{10}H_9Br$, 61617-73-0; $[(CH_3)_4N]_2B_{10}H_8Br_2$, 61617-74-1; $[(CH_3)_4N]_2B_{10}H_7Br_3$, 61617-75-2; $[(CH_3)_4N]_2B_{10}H_6Br_4$, 61617-76-3; $[(CH_3)_4N]_2B_{10}H_5Br_5$, 61617-77-4; $[(CH_3)_4N]_2B_{10}H_4Br_6$, 61617-78-5; $[(CH_3)_4N]_2B_{10}H_9I$, 61491-42-7; $[(CH_3)_4N]_2B_{10}H_8I_2$, 61617-79-6; $[(CH_3)_4N]_2B_{10}H_7I_3$, 61617-80-9; $[(CH_3)_4N]_2B_{10}H_6I_4$, 61617-81-0

[1] *W. H. Knoth, H. C. Miller, J. C. Sauer, J. H. Balthis, Y. T. Chia, E. L. Muetterties*, Inorg. Chem. *3*, 159 (1964).
[2] *W. Preetz*, Fortschr. Chem. Forsch. *11*, 375 (1969); *K.-G. Bührens, W. Preetz*, J. Chromatogr., in press.

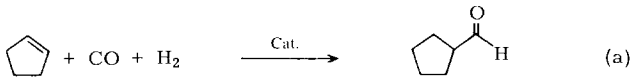
The Reaction of Olefins with Silane and Carbon Monoxide Catalyzed by $Co_2(CO)_8$[1]

By *Yoshio Seki, Akihiko Hidaka, Shinji Murai*, and *Noboru Sonoda*[*]

Hydrosilylation, the catalyzed addition of $R_3Si—H$ to an olefin, is formally analogous to catalytic hydrogenation. The well-known hydroformylation reaction involves addition of hydrogen and carbon monoxide to olefins [Reaction (a)]. Addition of a silane and carbon monoxide to olefins, however, has not been reported apart from in a very complex reaction described almost a decade ago[2].

[*] Y. Seki, A. Hidaka, Prof. Dr. S. Murai [+], and Prof. Dr. N. Sonoda
Department of Petroleum Chemistry, Faculty of Engineering, Osaka University
Suita, Osaka 565 (Japan)
[+] Author to whom correspondence should be addressed.

We have studied the reaction of olefins (cyclopentene, cyclohexene, cycloheptene, and cyclooctene) with diethyl(methyl)silane *(1)* and carbon monoxide in the presence of $Co_2(CO)_8$. Instead of the products of type *(2)*, expected by direct formal analogy with hydroformylation, the enol silyl ethers *(3)* were obtained. The yields were: *(3a)* 48 %, *(3b)* 71 %, *(3c)* 74 %, *(3d)* 69 %. Isomeric products were not formed.



(a)

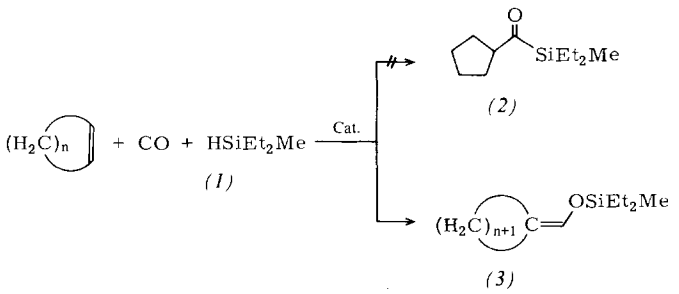


Table 1. Physical properties of the compounds *(3a)* to *(3d)*.

	n	B.p. [°C/Torr]	IR [a] (C=C) $\tilde{\nu}$ [cm^{-1}]	^{1}H-NMR [b] (s, HC=C) δ [ppm]
(3a)	3	98—100/15	1685	6.04
(3b)	4	130—138/28	1680	5.88
(3c)	5	155—165/50	1660	5.92
(3d)	6	126—135/25	1660	5.94

[a] Without solvent. [b] In CCl_4.

Numerous synthetic reactions are known in which enol silyl ethers are used as starting materials and in which these substances are prepared from carbonyl compounds[3]. The reaction described here affords direct access to enol silyl ethers from olefins. Its scope and limitation is at present under investigation.

The reaction does not proceed *via* aldehydes or acylsilanes as intermediates, for reaction of these compounds with *(1)* does not lead to enol silyl ethers.

Experimental:

Synthesis of *(3b)*: A solution of 2.52 g (30 mmol) of cyclohexene, 1.02 g (10 mmol) of diethyl(methyl)silane, and 0.068 g (0.2 mmol) of $Co_2(CO)_8$ in 20 ml of benzene was placed in a 100 ml stainless steel autoclave. The autoclave was flushed with N_2 (80 kg/cm^2) and CO (50 kg/cm^2), then charged with CO (80 kg/cm^2) and heated at 140 °C with stirring. After 20 h, the autoclave was cooled and depressurized. Distillation of the cooled reaction mixture furnished pure *(3b)*.

Received: December 28, 1976 [Z 639 IE]
German version: Angew. Chem. 89, 196 (1977)

CAS Registry numbers:
(1), 760-32-7; *(3a)*, 61490-90-2; *(3b)*, 61490-91-3; *(3c)*, 61490-92-4; *(3d)*, 61490-93-5; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; $Co_2(CO)_8$, 10210-68-1; carbon monoxide, 630-08-0

[1] Catalyzed reactions of silanes in the presence of carbon monoxide, Part 1.—Parts of this work were presented at the 24th Symposium on Organometallic Chemistry of The Chemical Society of Japan, Kyoto, October 13—15, 1976 (Abstracts 116B).—We thank Shin-Etsu Industry Co., Ltd. for the supply of organosilanes.

[2] *A. J. Chalk* and *J. F. Harrod*, J. Am. Chem. Soc. *89*, 1640 (1967); Adv. Organomet. Chem. *6*, 119 (1968), reported the reaction of ethylene, 1-pentene, and cyclohexene with Et_3SiH and CO in the presence of $CO_2(CO)_8$. The results were so complex that almost none of the products were characterized. Only in the case of ethylene was the mixture of products shown to contain unsaturated alkoxysilanes of the composition $C_3H_5OSiEt_3$.

[3] *J. K. Rasmussen*, Synthesis, in press.

Synthesis and Stereochemistry of Strained Naphthalenophanes[**]

By *Wolfgang Bieber* and *Fritz Vögtle*[*]

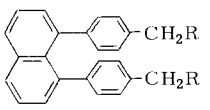
Deformed benzene rings and transannular electronic effects between spatially interpenetrating π-electron clouds can best be studied on helicenes and phanes. While numerous publications are concerned with the extreme [2.2]paracyclophane system[1a], the naphthalenoparacyclophanes *(1)* and *(2)*, which are hardly less strained, have not hitherto been reported. Related to the [3.2]paracyclophane system yet containing additional stiffening, they are profitable synthetic objectives on account of the particular features of steric interactions in the *peri* position of the naphthalene system[2] and the parallel and orthogonal orientations of the π systems. Moreover, they also offer an opportunity of studying additional effects due to bracketing in isolation, since the two phenylene rings are already in a "face-to-face"[3] arrangement in the open-chain precursor *(3)*.



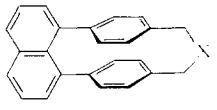
(1) *(2)*

Synthesis: Reaction of di-*p*-tolyllithium cuprate with 1,8-diiodonaphthalene leads to 1,8-di-*p*-tolylnaphthalene *(3)*[4], which affords *(4)* in 80 % yield on NBS bromination in CH_2Cl_2[5]. Intramolecular ring closure to give the phane *(1)* occurs in 65 % yield on treatment with phenyllithium in THF, being favored by the rigid structure.

The geometry of the 1,8-diarylnaphthalenes also facilitates the alternative synthesis of *(1)* *via* desulfuration of the sulfide *(5)*, which is obtained on reaction of *(4)* with Na_2S in *tert*-butanol/benzene. The corresponding sulfone *(6)* (H_2O_2 oxidation of *(5)* in glacial acetic acid/benzene) transforms spontaneously and practically quantitatively into the hydrocarbon *(1)* with elimination of SO_2 above its melting point (317 °C)[6].



(3), R = H
(4), R = Br

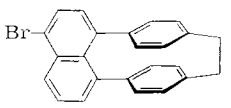


(5), X = S
(6), X = SO_2

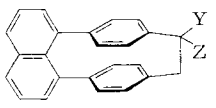
NBS bromination of *(1)* displays a remarkable solvent dependence: in CH_2Cl_2 bromination occurs exclusively in the aromatic ring to form the phane *(7)*, while in CCl_4 the monobromide *(8)* required for preparation of *(2)* is formed alongside the *gem*-dibromide *(9)*. Elimination of HBr from *(8)* with *tert*-butoxide in THF gives *(2)* in 55 % yield.

[*] Prof. Dr. F. Vögtle, Dipl.-Chem. W. Bieber
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

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



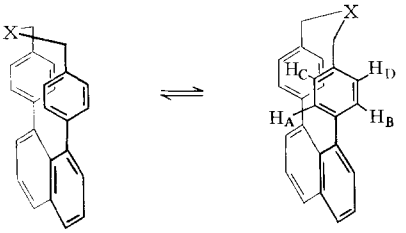
(7)



(8), Y = H, Z = Br
(9), Y = Z = Br

Stereochemistry: Comparison of ^{1}H-NMR absorptions (Table 1) shows that a characteristic *upfield shift* of 0.2 ppm occurs on going from the open-chain species *(3)* to the bracketed compound *(1)*; the shift is attributed to enhancement of the anisotropic effect by the forced mutual approach of the *p*-phenylene rings.

Low temperature ^{1}H-NMR spectra [90 MHz; in CD_2Cl_2/D_6-acetone/$CFCl_3$ (1:5:5)] show the 14-membered rings of the sulfide *(5)* and the sulfone *(6)* to possess a conformational mobility (shown by models to be hindered mainly by ring strain) which is reminiscent of ring topomerization in the cyclohexane system:



(A) (B)

The conformations *(A)* and *(B)* interconvert rapidly at room temperature on the NMR time scale: the *p*-phenylene protons give a time-averaged AA'BB' system. Below the coalescence points of −75 °C and −65 °C, respectively, an ABCD system (A ≈ B) is observed for the sulfide and the sulfone. In the sulfone the singlet of the bridge CH_2 protons splits to give the AB system ($T_c = -65$ °C), while in the sulfide only a broadening of the methylene singlet is observed down to −140 °C. $\Delta G_c^{\neq}$ for ring inversion is about 9.6 kcal/mol (40.2 kJ/mol) for *(5)*, and 10.0 kcal/mol (41.9 kJ/mol) for *(6)*.

Table 1. Melting points and ^{1}H-NMR data of the new naphthalenophanes [a]; the data for [2.2]- *(11)* and [3.2]paracyclophane *(13)* [1b] are given for sake of comparison.

Cpd.	M.p. [°C]	CH (bridge) [b]	CH (phenylene) [b]
(1)	245—246	3.07	6.51
(2)	249—251	7.35	6.69
(3)	179—179.5	2.15	6.72
(5)	215—218.5	3.84	6.70
(6)	317	4.46	6.98
(11)	285—287	3.05	6.37
(13)	148—149	2.10 2.71 2.97	6.48

[a] Correct elemental analyses and mass spectra were obtained for all compounds.
[b] ^{1}H-NMR (90 MHz; in $CDCl_3$): δ-values [ppm].

While the NMR data reveal additional transannular π interactions between the phenylene rings for *(1)*, interpretation of the UV absorptions (Fig. 1) is impeded by conjugation which still comes about in spite of the near orthogonality of the naphthalene and phenylene rings[7]. The red shift of the maximum lying at shorter wavelength on going from the cyclic systems to the open one *(3)* is striking; it can be interpreted in terms of the greater mobility of the non-bracketed phenylene rings which facilitate conjugation with the naphthalene nucleus. In analogy to the [2.2]paracyclophane system a diminution of intensity of the shorter wavelength maxima is observed for the olefin *(2)*.

The red shift of *ca.* 15 nm observed in the UV spectra of the *tetracyanoethylene adducts* on going from the monoarylated naphthalene[8] to the 1,8-ditolylnaphthalene adduct would correspond to an increase in the π basicity in the open chain system[9a]. Interpretation[9b] of the short wave absorptions of the TCNE adducts of *(1)*, *(2)*, and *(5)* is not easy because the role of the naphthalene nucleus as π base in the phanes is difficult to estimate.

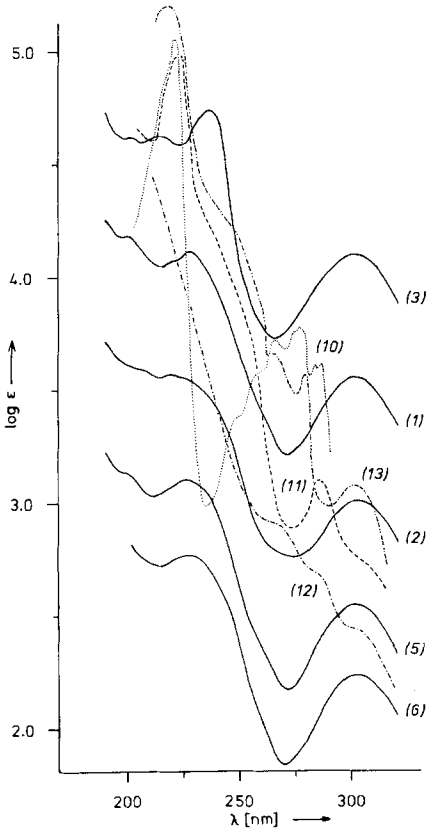


Fig. 1. UV spectra of the compounds *(1)*, *(2)*, *(3)*, *(5)*, and *(6)* (in cyclohexane); the spectra of naphthalene *(10)*, [2,2]paracyclophane *(11)* and its diene *(12)* [10a], and [3.2]paracyclophane *(13)* [10b] (in ethanol) are given for comparison. Compounds *(1)*, *(2)*, *(5)*, and *(6)* are progressively displaced downwards by 0.5 ordinate units (log ε) compared to *(3)*, and *(11)* and *(13)* upwards compared to *(10)* and *(12)*.

The similarity of the UV spectra of the cyclized and noncyclic 1,8-diarylnaphthalenes, which is striking in view of the significant difference in the ^{1}H-NMR results indeed shows the open chain system to be more closely related to the bracketed one than in other examples reported so far: 1,8-diarylnaphthalenes can be described as "open-chain cyclophanes"—a consequence of the stereochemical peculiarity of the *peri*-position.

Received: December 13, 1976 [Z 627 IE]
German version: Angew. Chem. 89, 199 (1977)

CAS Registry numbers:
(1), 61491-12-1; *(2)*, 61491-13-2; *(3)*, 58541-18-7; *(4)*, 61491-14-3; *(5)*, 61491-15-4; *(6)*, 61491-16-5; *(7)*, 61491-17-6; *(8)*, 61491-18-7; *(9)*, 61491-19-8; di-*p*-tolyllithium cuprate, 54747-02-3; 1,8-diiodonaphthalene, 1730-04-7; NBS, 128-08-5

[1] Review: a) *F. Vögtle, P. Neumann*, Synthesis *1973*, 85; b) Top. Curr. Chem. *48*, 67 (1974).
[2] *V. Balasubramaniyan*, Chem. Rev. *66*, 567 (1966).
[3] *D. J. Cram, H. Steinberg*, J. Am. Chem. Soc. *73*, 5691 (1951).

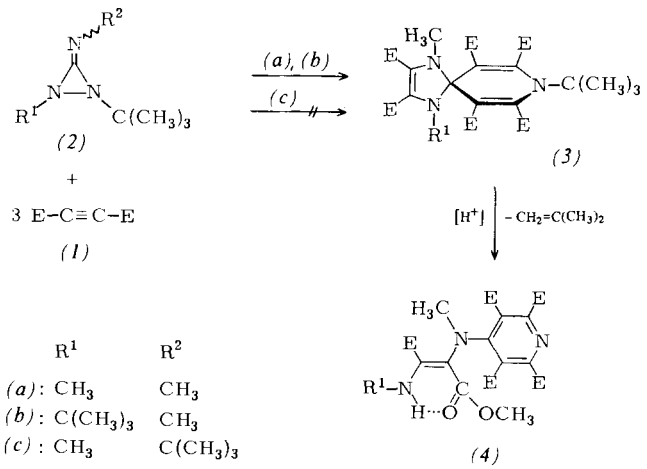
[4] In analogy with the synthesis of 1,8-diphenylnaphthalene by *H. O. House, D. G. Koepsell, W. J. Campbell*, J. Org. Chem. *37*, 1003 (1972). After completion of our studies *R. L. Clough, P. Mison, J. D. Roberts*, J. Org. Chem. *41*, 2252 (1976) reported another preparation for the then unknown 1,8-di-*p*-tolylnaphthalene.
[5] In CCl_4 the yield was only 50—60%.
[6] *F. Vögtle, J. Grütze*, Angew. Chem. *87*, 543 (1975); Angew. Chem. Int. Ed. Engl. *14*, 559 (1975); *J. Grütze, F. Vögtle*, Chem. Ber., in press.
[7] *H. O. House, R. W. Magin, H. W. Thompson*, J. Org. Chem. *28*, 2403 (1963).
[8] We thank *R. Wingen* for preparing the hitherto unknown 1-(3',5'-dimethylphenyl)naphthalene.
[9] a) *M. Sheehan, D. J. Cram*, J. Am. Chem. Soc. *91*, 3553 (1969); b) cf. *E. Langer, H. Lehner*, Tetrahedron *29*, 375 (1973).
[10] a) *K. C. Dewhirst, D. J. Cram*, J. Am. Chem. Soc. *80*, 3115 (1958); b) *D. J. Cram, N. L. Allinger, H. Steinberg, ibid. 76*, 6132 (1954).

Spiro Compounds Having a Nonplanar 1,4-Dihydropyridine Ring from Diaziridinimines and Dimethyl Acetylenedicarboxylate[**]

By *Helmut Quast, Karl-Heinz Ross, Erwin Spiegel, Karl Peters*, and *Hans Georg von Schnering*[*]

The pronounced reactivity and versatility of dimethyl acetylenedicarboxylate *(1)* make it an interesting but frequently unpredictable reagent[1]. This is seen in the number of its products whose structure could only be elucidated by X-ray structure analysis. We have discovered further examples in our studies on the cycloadditions of diaziridinimines[2].

Reaction of the diaziridinimine *(2a)* and *(1)* at 20°C in benzene/pentane produces the 1:3 adduct *(3a)* as deep red crystals (yield 27%). The two isomers *(2b)* and *(2c)*[3] behave differently when subjected to the same reaction: While *(2b)* and *(1)* give a 1:3 adduct resembling *(3a)* in its properties, reaction of *(2c)* with *(1)* affords only a 1:2 adduct of unknown structure in 4% yield.



	R^1	R^2
(a):	CH_3	CH_3
(b):	$C(CH_3)_3$	CH_3
(c):	CH_3	$C(CH_3)_3$

E = CO_2CH_3

The 270 MHz ^{1}H-NMR spectrum[4] and the ^{13}C-NMR spectra of the adduct of *(2a)* recorded in [D_6]benzene[4] and in [D]chloroform[5] indicate a symmetrical molecule. On cooling, however, all the ^{1}H-NMR signals undergo broadening which in the case of the NCH_3 signal leads to coalescence and splitting at −60°C [CD_2Cl_2, 60 MHz, $\Delta\nu = 13.5$ Hz (−88°C), $\Delta G_c^{\neq} = 10.8$ kcal/mol]. The symmetry observed at room temperature and the ^{13}C-NMR signal of a quaternary C atom at 86.0 ppm suggest structure *(3a)* having a nonplanar, flexible 1,4-dihydropyridine ring[6]. Final proof was provided by X-ray structure analysis, which showed *(3a)* to crystallize monoclinically in $P2_1/n$ (No. 14) with $a = 16.304(3)$, $b = 13.334(3)$, $c = 13.109(3)$ Å; $\beta = 99.02(2)°$; $Z = 4$. The structure was solved by direct methods and refined to $R = 0.096$ for 3066 reflections with $I > 2\sigma(I)$ [SYNTEX P$\bar{1}$ diffractometer; $Cu_{K\alpha}$; ω scan; $2\theta \leq 110°$; extended SYNTEX XTL system; MULTAN[7]; 40 independent atoms C, N, O with anisotropic B_{ij}; calculation neglecting the 33 H atoms].

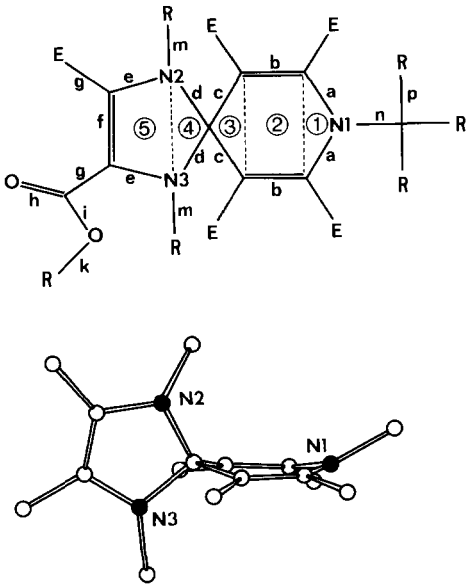


Fig. 1. Top: Designation of bonds and planes (numbers in circles) in *(3a)*. The designations g to k apply to all ester groups E.—Bottom: Spiro system of *(3a)*. Only the atom attached directly to the ring is shown for each of the substituents.

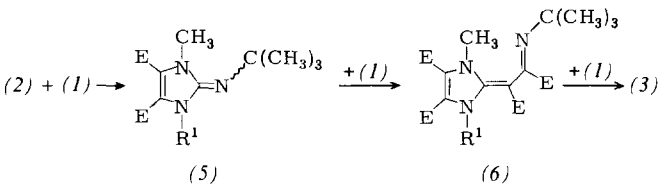
Figure 1 shows the structure of *(3a)*. The 1,4-dihydropyridine ring is distinctly bent; the planes 1 and 2 as well as 2 and 3 are mutually inclined by 11.3 and 15.0°, respectively. The double bonds b do not lie exactly in plane 2, as in a twisted boat. In the five-membered ring the planes 4 and 5 are mutually inclined by 4.4°; the planes 3 and 4 enclose an angle of 87.6°. The average bond lengths are (Å): a = 1.393, b = 1.358, c = 1.513, d = 1.480, e = 1.396, f = 1.337, g = 1.486, h = 1.200, i = 1.326, k = 1.469, m = 1.463, n = 1.554, p = 1.549; (σ = 0.009). Marked deviations from the average values occur only in d and e (different orientation of N-2 and N-3 to the six-membered ring). The lengths of c and d correspond to single bonds. The lengths a and b as well as e and f indicate extensive conjugation of the bonds in the two rings. Except for N-1, N-2, and the spiro C atom, the atoms of both rings lie in the plane defined by their three neighboring atoms. N-1 and N-2 project from this plane by 0.2 Å. The ester groups are practically identical, the average value of the angle between g and i being 111.8°.

The adducts *(3a)* and *(3b)* liberate isobutene very readily in the presence of traces of acid. The structure *(4)* of the yellow products formed in quantitative yield is based on ^{1}H-

[*] Prof. Dr. H. Quast, Dr. K.-H. Ross, Dipl.-Chem. E. Spiegel
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)
Dr. K. Peters, Prof. Dr. H. G. v. Schnering
Max-Planck-Institut für Festkörperforschung
Büsnauer Strasse 171, D-7000 Stuttgart 80 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The results are in part taken from the thesis of *K.-H. Ross*, Universität Würzburg 1974, and the projected thesis of *E. Spiegel*.

NMR, ^{13}C-NMR, and IR spectra. The IR absorption at 3320 cm^{-1}, which is independent of the state of aggregation, solvent, and concentration, indicates an intramolecular hydrogen bond.



(5) *(6)*

The unexpected formation of *(3)* can be rationalized in terms of a primary [3+2] cycloaddition of *(1)* to *(2)*, giving *(5)*, a [2+2] cycloaddition of *(1)* to the C=N bond of *(5)*, subsequent opening of the azetine ring to give *(6)*, and a [4+2] cycloaddition of *(1)* to *(6)*. Analogous spirodihydropyridines were accordingly also obtained from other heterocyclic imines and guanidine derivatives[8]. A reaction corresponding to *(6)*+*(1)*→*(3)* has recently been observed on formation of similar spirodihydropyridines from benzothiazoletriazenes[9].

Received: December 27, 1976 [Z 638 IE]
German version: Angew. Chem. 89, 202 (1977)

CAS Registry numbers:
(1), 762-42-5; *(2a)*, 61483-94-1; *(2b)*, 28231-54-1; *(2c)*, 61483-95-2; *(3a)*, 61483-96-3; *(3b)*, 61483-97-4; *(4a)*, 61483-98-5; *(4b)*, 61483-99-6

[1] *T. Wagner-Jauregg*, Synthesis *1976*, 349; *M. V. George, S. K. Khetan, R. K. Gupta*, Adv. Heterocycl. Chem. *19*, 279 (1976) *R. M. Acheson*, Khim. Geterotsikl. Soedin *1976*, 1101.
[2] *H. Quast, E. Spiegel*, Angew. Chem. *89*, 112 (1977); Angew. Chem. Int. Ed. Engl. *16*, 109 (1977).
[3] *H. Quast, E. Schmitt*, Chem. Ber. *103*, 1234 (1970).
[4] We are grateful to Dr. *D. F. Hillenbrand*, University of Wisconsin, Madison, Wis. (USA), for recording these spectra.
[5] We are grateful to Dr. *M. A. R. Smith*, Bruker-Physik AG, Karlsruhe (Germany), for recording and interpreting this spectrum in terms of structure *(3a)*.
[6] The 1,4-dihydropyridines studied previously have planar structures: *U. Eisner, J. Kuthan*, Chem. Rev. *72*, 1 (1972).
[7] *G. Germain, P. Main, M. M. Woolfson*, Acta Crystallogr. *A 27*, 368 (1971).
[8] *H. Quast, E. Spiegel*, Tetrahedron Lett. *1977*, in preparation.
[9] *E. Fanghänel, R. Ebisch, P. Niedermeyer*, Z. Chem. *15*, 143 (1975).

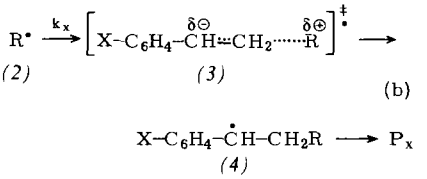
Polar Effects in the Addition of Alkyl Radicals to Olefins[**]

By *Bernd Giese* and *Jürgen Meister*[*]

Alkyl radicals *(2)* add faster to electron-deficient olefins[1a] and aromatic compounds[1b] than to electron-rich π systems. These differences in reactivity have been interpreted in terms of stabilization of the transition states due to polar effects[1c]. Experimental determination of the Hammett ϱ values[2] represents a quantitative method of establishing the extent of charge separation in *(3)*.

$$\log(k_X/k_0) = \varrho \cdot \sigma \qquad \text{(a)}$$

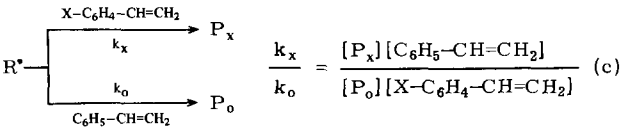
According to eq. (a) the reaction parameter ϱ reproduces the effect of the substituent X on the rate constant k_X in eq. (b). k_0 applies to X=H.



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

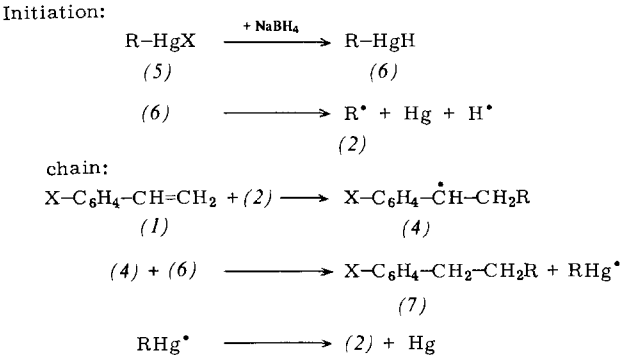
(4)

If the subsequent reactions of the adduct radicals *(4)* can be quantitatively determined (formation of products P_X), then the selectivity values ($\log k_X - \log k_0$) can be calculated according to eq. (c) on working in an excess of *(1)*[3].

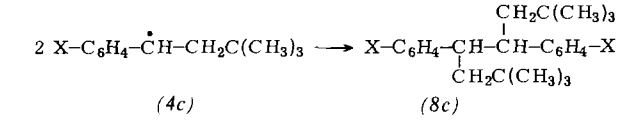


(c)

A suitable method for generating the radicals *(2)* and for trapping the adduct radicals *(4)* consists in the reaction of organomercury salts *(5)* with $NaBH_4$ in the presence of substituted styrenes *(1)*[4a]. The hydrides *(6)* should act as radical generators[4a,4b]. The resulting radicals *(2)*, which can undergo typical radical reactions[4], add to the olfins *(1)*. Subsequent H capture leads to the 1:1 adducts *(7)*.



Product analysis by gas chromatography showed that on reaction of ethanolic solutions of 1-hexyl- *(5a)* and of cyclohexylmercury acetate *(5b)* with $NaBH_4$ in the presence of the styrenes *(1)*, the 1:1 adducts *(7)* are formed as secondary products of *(4)*. Only *tert*-butylmercury chloride *(5c)* gave the dimer *(8c)* from the adduct radicals *(4c)*, alongside *(7c)*, in yields exceeding 5%. No disproportionation products could be detected[5].



(4c) *(8c)*

Plotting of the relative reactivities ($k_{styrene} \equiv 1$) of 4-chloro- *(1a)*, 3-chloro- *(1b)*, 4-methyl- *(1c)*, and 4-methoxystyrene *(1d)* *versus* the σ^+ parameters[6] for 14 reaction series gave straight lines each having a correlation coefficient *r* of about 0.95. The positive reaction parameters ϱ obtained for primary, secondary, and tertiary radicals *(2)* between −56 and +42 °C

[*] Priv.-Doz. Dr. B. Giese, Dipl.-Chem. J. Meister
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

(Fig. 1) establish the presence of a negative partial charge on the benzylic carbon atom in the transition state *(3)*. Thus, as in H abstractions from toluene derivatives[7], the alkyl radicals display nucleophilic properties in additions to olefins.

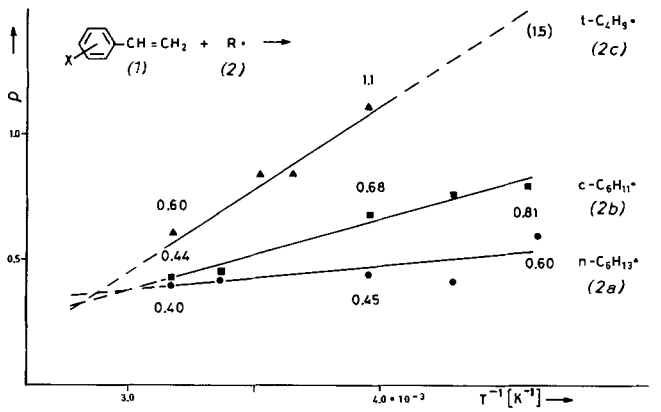


Fig. 1. Temperature dependence of the ϱ values (−56 to +42 °C) for the addition of alkyl radicals *(2a)*—*(2c)* to the styrenes *(1a)*—*(1d)* in ethanol.

The gradation of ϱ values for tertiary, secondary, and primary radicals warrants interest: The *tert*-butyl radical *(2c)* has a much larger ϱ value (1.1) at −20 °C than the cyclohexyl radical *(2b)* ($\varrho = 0.68$) and the 1-hexyl radical *(2a)* ($\varrho = 0.45$). In contrast, the values hardly differ from one another at +42 °C (0.60, 0.44, and 0.40, respectively) (Fig. 1). The reaction parameter of 0.51 determined for benzylic radicals at +60 °C in copolymerizations[8] is in good agreement with these results.

Like the steric reaction parameters for radical halogen abstractions[9] the values for additions of radicals to olefins are highly dependent upon temperature.

Received: December 13, 1976 [Z 630 IE]
German version: Angew. Chem. *89*, 178 (1977)

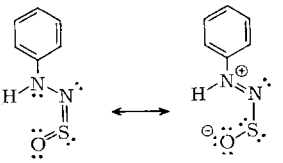
CAS Registry numbers:
(1a), 1073-67-2; *(1b)*, 2039-85-2; *(1c)*, 622-97-9; *(1d)*, 637-69-4; *(2a)*, 2679-29-0; *(2b)*, 3170-58-9; *(2c)*, 1605-73-8; *(5a)*, 2654-49-1; *(5b)*, 10341-90-9; *(5c)*, 543-63-5

[1] a) *P. I. Abell* in *C. H. Bamford, C. F. H. Tipper:* Comprehensive Chemical Kinetics. Vol. 18, Elsevier, Amsterdam 1976; b) *F. Minisci*, Top. Curr. Chem. *62*, 1 (1976); c) *P. I. Abell* in *J. K. Kochi:* Free Radicals Vol. 2, Wiley, New York 1973; *G. A. Russell* in *ibid.* Vol. 1.
[2] *L. P. Hammett:* Physikalische Organische Chemie. Verlag Chemie, Weinheim 1973.
[3] *K. Schwetlick:* Kinetische Methoden zur Untersuchung von Reaktionsmechanismen. VEB Deutscher Verlag der Wissenschaften, Berlin 1971.
[4] a) *B. Giese, J. Meister*, Chem. Ber., in press; b) *C. L. Hill, G. M. Whitesides*, J. Am. Chem. Soc. *96*, 870 (1974); c) *B. Giese*, Angew. Chem. *88*, 159 (1976); Angew. Chem. Int. Ed. Engl. *15*, 173 (1976); *A. J. Bloodworth, G. S. Bylina*, J. Chem. Soc. Perkin Trans. I, *1972*, 2433; *V. M. A. Chambers, W. R. Jackson, G. W. Young*, Chem. Commun. *1970*, 2433
[5] For benzyl radicals the recombination rate is 10 times higher than the disproportion rate. *M. J. Gibian, R. C. Corbey*, J. Am. Chem. Soc. *94*, 4178 (1972).
[6] *N. B. Chapman, J. Shorter*, Advances in Linear Free Energy Relationships. Plenum Press, London 1972.
[7] *R. W. Henderson, R. D. Ward*, J. Am. Chem. Soc. *96*, 7556 (1974); *W. A. Pryor, W. H. Davies, ibid. 96*, 7557 (1974); *A. A. Zavitsas, G. M. Hanna*, J. Org. Chem. *40*, 3782 (1975).
[8] *C. Walling, E. R. Briggs, K. B. Wolfstirn, F. R. Mayo*, J. Am. Chem. Soc. *70*, 1537 (1948).
[9] *B. Giese*, Angew. Chem. *88*, 723 (1976); Angew. Chem. Int. Ed. Engl. *15*, 688 (1976).

X-Ray Structure Analysis of *N*-Phenyl-*N'*-sulfinylhydrazine

By *Alfred Gieren* and *Bernhard Dederer*[*]

In order to gain further insight into the nature of the S=N double bond of tetravalent sulfur with the coordination number 2, having already solved the structure of sulfur diimides of the type RN=S=NR[1], we have performed to our knowledge the first X-ray structure analysis of an isoelectronic compound of the type RN=S=O. The compound investigated, *N*-phenyl-*N'*-sulfinylhydrazine *(1)*[2], crystallizes from



(1a) *(1b)*

anhydrous ethanol in the monoclinic space group $P2_1/a$ with eight molecules in the unit cell (2 molecules per asymmetric unit). Lattice constants: $a = 10.50_5$, $b = 15.75_1$, $c = 8.45_9$ Å, $\beta = 94.4_9°$; $d_{calc} = 1.47$, $d_{exp} = 1.45\ g \cdot cm^{-3}$. Using an automatic single crystal diffractometer 2642 independent reflections were recorded with Cu-K_α radiation (5 point measurement, $\theta/2\theta$ scan); 300 reflections were unobserved ($I \leq 2\sigma_I$). The structure was solved by direct methods. Least squares refinement (H atoms with isotropic temperature parameters, all other atoms with anisotropic ones) converged at an R value of 4.2 % (observed reflections). All the hydrogen atoms were located in a difference Fourier synthesis at $R = 8.5$ %.

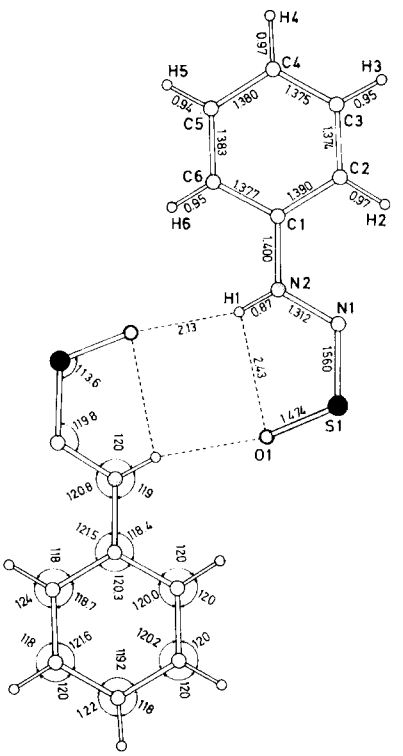


Fig. 1. Structure of dimeric *N*-phenyl-*N'*-sulfinylhydrazine. The bond lengths and angles are averaged over the two molecules. The mean standard deviations of the non-averaged values are 0.006 Å for the bond lengths (except C—H and N—H: 0.05 Å), and 0.4° for the angles (except those including H: 3°).

[*] Dr. habil. A. Gieren, Dipl.-Chem. B. Dederer
Max-Planck-Institut für Biochemie, Abt. Strukturforschung I
Am Klopferspitz, D-8033 Martinsried (Germany)

Compound *(1)* is roughly planar and in the crystalline state forms a dimer with approximate 2/m symmetry: the two molecules of the dimer (asymmetric unit) are linked by two (N)—H···O=(S) hydrogen bonds (2.13 Å). In addition, *(1)* contains an intramolecular bridge of the same kind (H···O 2.43 Å). Hence the hydrogen and the oxygen atom function as twofold donor and acceptor, respectively (Fig. 1).

The S=N bond length is 1.56 Å, and the S=O bond length 1.47 Å. Both bonds are thus significantly longer than the corresponding S^{IV}=N distances in sulfur diimides (*ca.* 1.53 Å)[1] and 2,5-diphenyl-1-phenylimino-1λ^4,2,5-thiadiazolidine-3,4-dione (1.51 Å)[3] on the one hand, and the S^{IV}=O distance in sulfur dioxide (1.43 Å)[4], on the other. The N—N bond length indicates a significant double bond character (N=N double bond length 1.24 Å[5]). Both nitrogen atoms are sp^2 hybridized, as shown by the bond angles at N-1 and N-2 and by the trigonal-planar configuration at N-2. The formal S=N double bond is *cis*-configurated, this being favored by formation of the H-chelate ring.

It may be deduced from the bond lengths and the sp^2 hybridization of N-2 that the mesoionic resonance formula *(1b)* makes a considerable contribution to the ground state. The formation of hydrogen bonds also evidences *(1b)* since the acidity of the NH proton and the basicity of the sulfinyl oxygen are thus enhanced.

Received: December 6, 1976 [Z 620 IE]
German version: Angew. Chem. *89*, 190 (1977)

CAS Registry numbers:
(1a), 112-83-4

[1] *A. Gieren, F. Pertlik*, Angew. Chem. *88*, 852 (1976); Angew. Chem. Int. Ed. Engl. *15*, 782 (1976); *A. Gieren, B. Dederer, H. W. Roesky, E. Janssen, ibid. 88*, 853 (1976) and *15*, 783 (1976), resp.
[2] *D. Klamann, U. Krämer, P. Weyerstahl*, Chem. Ber. *95*, 2694 (1962).—We thank Professor *G. Kresze* and Dipl.-Chem. *M. Rössert* for this substance.
[3] *R. Neidlein, P. Leinberger, A. Gieren, B. Dederer*, Chem. Ber., in press.
[4] *D. Kivelson*, J. Chem. Phys. *22*, 904 (1954).
[5] *A. Gieren*, Chem. Ber. *106*, 288 (1973).

(Chloromethylene)triphenylphosphorane

By *Rolf Appel* and *Wolfgang Morbach*[*]

Having recently isolated (dichloromethylene)triphenylphosphorane *(3c)*[2], a reactive compound fittingly described as "moderated"[1] we have attempted to synthesize (chloromethylene)triphenylphosphorane which is to be assigned an intermediate position between methylenetriphenylphosphorane *(3a)* and *(3c)*. The first indication of the existence of this ylide was provided by dehydrochlorination experiments on (chloromethyl)triphenylphosphonium chloride *(1b)* with

$$\underset{(1b)}{[Ph_3P{-}CH_2Cl]^{\oplus}Cl^{\ominus}} + \underset{(2)}{C(=PPh_3)_2} \rightleftharpoons \underset{(3b)}{Ph_3P{=}CHCl} + \underset{(4)}{[Ph_3P{=}C(H){=}PPh_3]^{\oplus}Cl^{\ominus}} \quad (a)$$

$$\underset{(1c)}{[Ph_3P{-}CHCl_2]^{\oplus}Cl^{\ominus}} + \underset{(5)}{P[N(CH_3)_2]_3} \longrightarrow \underset{(3b)}{Ph_3P{=}CHCl} + \underset{(6)}{PCl_2[N(CH_3)_2]_3} \quad (b)$$

[*] Prof. Dr. R. Appel, Dipl.-Chem. W. Morbach
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

bis(triphenylphosphoranylidene)methane *(2)*[2a]; however, the ylide could not be obtained on a preparative scale according to eq. (a) owing to an inadequate difference in basicity between the two ylide systems. Dechlorination of (trichloromethyl)-triphenylphosphonium chloride with tri(dimethylamino)phosphane which was successful in the case of *(3c)* failed to give a uniform product on application to *(1c)* according to equation (b) because dechlorination is accompanied by dehydrochlorination, thus precluding isolation of a pure product.

We have now succeeded in isolating pure *(3b)* by a systematic application of the reaction termed transylidation by *Bestmann*[3], which is based on the graduated basicity of the ylide systems *(3a—c)*. If the phosphonium salts *(1a—c)* are regarded as Brønstedt acids and the corresponding alkylenephosphoranes as bases, then the strengths of the corresponding acid/base pairs will depend upon the number of H and Cl atoms attached to the ylidic C atom.

Acidity:

$$\underset{(1a)}{[Ph_3PCH_3]^{\oplus}Cl^{\ominus}} < \underset{(1b)}{[Ph_3PCH_2Cl]^{\oplus}Cl^{\ominus}} < \underset{(1c)}{[Ph_3PCHCl_2]^{\oplus}Cl^{\ominus}}$$

Basicity:

$$\underset{(3a)}{Ph_3PCH_2} > \underset{(3b)}{Ph_3PCHCl} > \underset{(3c)}{Ph_3PCCl_2}$$

The electron-withdrawing effect of chlorine enhances the acidity of the phosphonium salts proceeding from *(1a)* to *(1c)*, while the basicity increases in the opposite direction from *(3c)* to *(3a)*. Owing to the considerable differences in the basicity of the ylides *(3a—c)* "transylidations" according to eqs. (c) to (e) proceed smoothly and adequately to permit isolation of the missing member in the series *(3b)* in good yield.

$$Ph_3PCH_2 + [Ph_3PCH_2Cl]^{\oplus}Cl^{\ominus} \longrightarrow [Ph_3PCH_3]^{\oplus}Cl^{\ominus} + Ph_3P{=}CHCl \quad (c)$$

$$Ph_3PCH_2 + [Ph_3PCHCl_2]^{\oplus}Cl^{\ominus} \longrightarrow [Ph_3PCH_3]^{\oplus}Cl^{\ominus} + Ph_3P{=}CCl_2 \quad (d)$$

$$Ph_3PCHCl + [Ph_3PCHCl_2]^{\oplus}Cl^{\ominus} \longrightarrow [Ph_3PCH_2Cl]^{\oplus}Cl^{\ominus} + Ph_3P{=}CCl_2 \quad (e)$$

(Chloromethylene)triphenylphosphorane (3b):

Compound *(3a)* (13.8 g, 0.05 mol)[4] is added to *(1b)* (21 g, 0.06 mol) in anhydrous THF (300 ml). After stirring for 20 to 30 min the precipitated salt *(1a)* and excess *(1b)* are filtered from the ylide present in solution. The initial crystal deposit obtained on concentrating the orange solution is dried in a high vacuum; further yields are purified by recrystallization from THF. Yield 10.9 g (70 %) of analytically pure yellow substance, decomp. 95 to 98 °C. ^{31}P-NMR: $\delta_{(THF)} = 14.3$ ppm (85 % H_3PO_4 as ext. standard); ^{1}H-NMR $\delta_{([D_8]THF)} = 2.64$ ppm (doublet, TMS int. standard, $J_{PCH} = 24$ Hz); ^{13}C-NMR: $\delta_{(C_6D_6)} = 25.73$ ppm (doublet, TMS int. standard, $J_{PC} = 64.4$ Hz).

Received: December 10, 1976 [Z 624 IE]
German version: Angew. Chem. *89*, 203 (1977)

CAS Registry numbers:
(1b), 5293-84-5; *(3a)*, 3487-44-3; *(3b)*, 29949-92-6

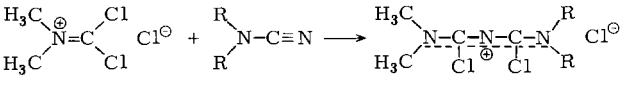
[1] Cf. *M. Schlosser* in: Methodicum Chimicum, Vol. VII, p. 530. Thieme, Stuttgart 1976.

[2] a) *R. Appel, F. Knoll, H. Veltmann*, Angew. Chem. *88*, 340 (1976); Angew. Chem. Int. Ed. Engl. *15*, 315 (1976); b) *R. Appel, H. Veltmann*, Tetrahedron Lett., in press.
[3] *H. J. Bestmann*, Angew. Chem. *77*, 609 (1965); Angew. Chem. Int. Ed. Engl. *4*, 583 (1965); Chem. Ber. *95*, 58 (1962).
[4] *H. Schmidbaur, H. Stühler, W. Vornberger*, Chem. Ber. *105*, 1084 (1972).

New Reagents for Synthesis of Heterocyclics from Carbodiimides and Phosgeniminium Salts[1]

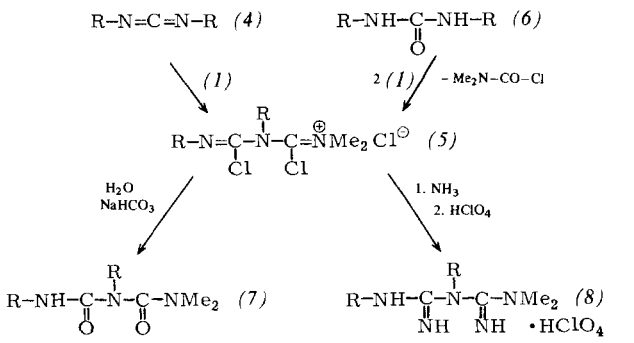
By *Asher Elgavi* and *Heinz Günter Viehe*[*]

(Dichloromethylene)dimethylammonium salts ("phosgeniminium salts") *(1)* are stable electrophilic reagents of the Mannich-Böhme and Vilsmeier-Haack-Arnold type[2]. These salts add readily to electron rich multiple bonds: with cyanamide *(2)*, for example, they yield the versatile azatrimethinecyanine *(3)*[3].



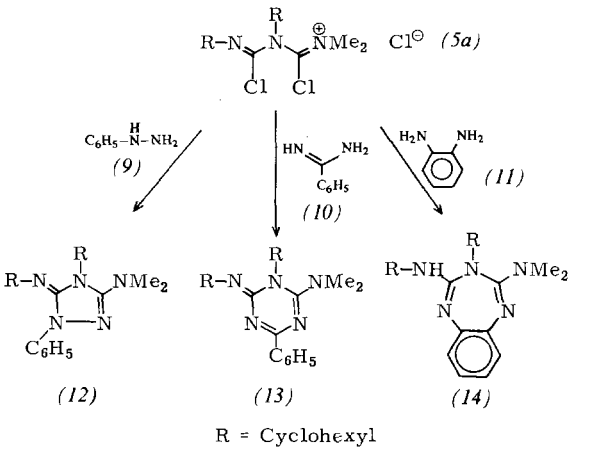
(1) *(2)* *(3)*

It is now found that carbodiimides *(4)* form the adducts *(5)* with *(1)*. The same products arise also from *(1)* and *N,N'*-disubstituted ureas *(6)*. Biselectrophiles *(5)* being isomeric with *(3)* are in fact trichlorides of 1,1,3,5-tetrasubstituted biurets *(7)*, which they yield upon hydrolysis. Aminolysis or ammonolysis of *(5)* afford the corresponding biguanides *(8)* (Table 1).



(a), R = Cyclohexyl; *(b)*, R = CH_3

The synthetic potential of (1,3-dichloro-2,4-dicyclohexyl-2,4-diaza-3-butenylidene)dimethylammonium chloride *(5a)* in heterocyclization reactions is demonstrated by the synthesis of triazolinimine *(12)*, triazinimine *(13)*, and benzotriazepine *(14)* (see Table 1).



R = Cyclohexyl

Procedures:

(5a): A mixture of dicyclohexylcarbodiimide *(4a)* and *(1)* (molar ratio 1 : 1) in chloroform is stirred at room temperature until *(1)* has dissolved. The solvent is partially evaporated and ether is added to precipitate *(5a)* as a white hygroscopic solid.

(5b): 1,3-Dimethylurea *(6b)* and *(1)* (molar ratio 1 : 2) are refluxed in chloroform for about 1 h until all *(1)* has dissolved; work-up is the same as for *(5a)*.

(14): A refluxing mixture of *(5a)* (3.68 g) and *o*-phenylenediamine *(11)* (10.8 g) in methylene chloride (40 ml) is stirred overnight. The solution is then concentrated and dry ether is added to precipitate the hydrochloride of *(14)* (4.6 g, 87 %). The free base *(14)* is obtained by treatment with concentrated KOH at 0 °C, and recrystallization from ethanol/water.—Compounds *(12)* and *(13)* were prepared analogously.

Table 1. Properties of the new compounds.

Cpd.	R	Yield [%]	M.p. [°C]	IR [cm^{-1}] (in $CHCl_3$)	^{1}H-NMR (δ values) [a]
(5a)	C_6H_{11}	95	95	2940, 2860, 1720, 1650, 1620	1.0—2.5 (20 H, m), 3.5 (2 H, m), 3.8 (6 H, s)
(5b)	CH_3	94	Oil	2960, 2700, 1720, 1655	3.2—3.4 (m)
(7a)	C_6H_{11}	95	154	3000, 2940, 2880, 1640, 1500	1.0—2.0 (20 H, m), 2.95 (6 H, s), 3.5—3.8 (2 H, m), 5.0 (1 H, d, J = 7.5 Hz) [b]
(8a)·$HClO_4$	C_6H_{11}	80	190	3440, 3360, 2930, 2850, 1595, 1565, 1500, 1100	1.0—2.1 (20 H, m), 3.05 (6 H, s), 3.3—3.5 (2 H, m), 5.3—5.7 (4 H, br.) [b]
(12)	C_6H_{11}	30	92	2930, 2860, 1630, 1580	1.0—2.0 (20 H, m), 2.70 (6 H, s), 2.8 (2 H, m), 7.3 (5 H, m)
(13)	C_6H_{11}	72	154	2925, 2850, 1635, 1590, 1535	1.2—1.9 (18 H, m), 2.6 (2 H, m), 3.07 (6 H, s), 3.5 (1 H, m), 4.2 (1 H, m), 7.4 (3 H, m), 8.3 (2 H, m)
(13)·HCl [c]	C_6H_{11}	80	140	2930, 2850, 1635, 1585, 1538, 1492	1.3—2.0 (20 H, m), 3.44 (6 H, s), 4.1—4.2 (2 H, m), 7.5 (3 H, m), 8.42 (2 H, m), 10.2 (1 H, d, J = 7 Hz) [b]
(14)	C_6H_{11}	70	142	3440, 3030, 2930	1.0—1.9 (18 H, m), 2.3 (2 H, m), 3.13 (6 H, s), 3.5 and 3.74 (2 H, m), 4.20 (1 H, m), 6.9—7.1 (4 H, m)

[a] In $CDCl_3$, TMS = 0.
[b] NH protons, exchangeable with $F_3C—CO_2D$.
[c] Protonation at the exocyclic imino nitrogen since CH—NH coupling can be observed.

[*] Dr. A. Elgavi
Bar Ilan University
Ramat-Gan (Israel)
Prof. Dr. H. G. Viehe
Laboratoire de Chimie Organique
Université de Louvain
Place Louis Pasteur, 1
B-1348 Louvain-la-Neuve (Belgium)

Received: January 20, 1977 [Z 653a IE]
German version: Angew. Chem. *89*, 188 (1977)

CAS Registry numbers:
(1), 33842-02-3; *(4a)*, 538-75-0; *(4b)*, 4852-30-6; *(5a)*, 61740-88-3; *(5b)*, 61740-89-4; *(6b)*, 96-31-1; *(7a)*, 61740-90-7; *(8a)*, 61740-92-9; *(9)*, 100-63-0; *(10)*, 618-39-3; *(11)*, 95-54-5; *(12)*, 61740-93-0; *(13)*, 61740-94-1; *(13)*·HCl, 61740-95-2; *(14)*, 61740-96-3; *(14)*·HCl, 61740-97-4

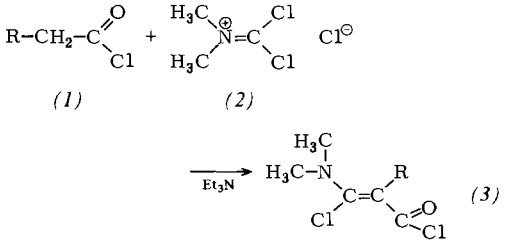
[1] Iminium Chemistry, Part 16.—Part 15: *B. Caillaux, P. George, F. Tatar-uch, Z. Janousek, H. G. Viehe*, Chimia *30*, 387 (1976).
[2] For reviews see *H. Böhme, H. G. Viehe*: Iminium Salts in Organic Chemistry. Wiley, New York 1976.
[3] *Z. Janousek, H. G. Viehe*, Angew. Chem. *85*, 90 (1973); Angew. Chem. Int. Ed. Engl. *12*, 74 (1973).

Reactions of Acyl Chlorides/Triethylamine or Ketenes with Phosgeniminium Salts[1]

By *Heinz Günter Viehe, Brigitte Le Clef*, and *Asher Elgavi*[*]

α-Chloro-β-(chlorocarbonyl)enamines *(3)* are known to arise from the addition of phosgene to ynamines[2] or from the condensation of phosgene with monosubstituted acetamides in the presence of bases[3, 4].

We have now found that *(3)* can be obtained in good yields from the reaction of monosubstituted acetyl chlorides and (dichloromethylene)dimethylammonium salts ("phosgeniminium salts") *(2)*[5] (Table 1).



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

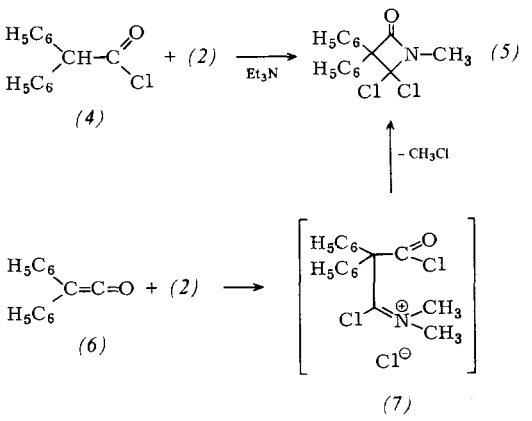
Table 1. α-Substituted β-chloro-β-(dimethylamino)acryloyl chlorides *(3)*.

Cpd.	R	Yield [%]	B.p. [°C/torr]	IR [cm^{-1}] (in $CHCl_3$)	^{1}H-NMR (δ value) [a]
(3a)	C_6H_5	70	dec.	1700, 1555	3.18 (6H, s), 7.32 (5H, s)
(3b)	Cl	75	70—75/0.1	1685, 1550	3.17 (s)
(3c)	CH_3	70	70—74/0.1	1715, 1555	2.20 (3H, s), 3.10 (6H, s)
(3d)	C_2H_5	60	75—80/0.3	1710, 1550	1.14 (3H, t), 2.60 (2H, q), 3.08 (6H, t)

[a] In $CDCl_3$, TMS = 0.

Thus phenylacetyl chloride *(1a)* condenses with *(2)* in the presence of triethylamine to yield *(3a)*. No reaction occurs in the absence of a base, which indicates that either phenylketene, the corresponding acylammonium salt, or the acyl chloride enolate[6] is the reactive intermediate.

If the starting material is diphenylacetyl chloride *(4)*, the new dichloro β-lactam *(5)* is obtained instead of the adduct *(3)*. This heterocycle arises alternatively and equally well from diphenylketene *(6)* and *(2)*.



(4) *(5)* *(6)* *(7)*

The intermediate *(7)* can be detected by NMR spectroscopy. When diphenylketene *(6)* and *(2)* are heated to 45 °C, broad peaks appear at δ = 4.25 and 7.45 ppm which correspond most probably to the *N*-dimethyl and phenyl signals. These absorptions disappear on the formation of *(5)*.

Compounds *(3)*, being reactive derivatives of malonamic acid, are well established reagents, particularly for the synthesis of heterocycles[4, 7]. *(5)* as the first representative of the reactive class of 4,4-dichloroazetidin-2-one merits further synthetic interest[8].

Experimental:

(3a): Triethylamine (2.02 g, 0.02 mol) is added dropwise at room temperature to a stirred suspension of *(2)* (1.65 g, 0.02 mol) in a dry chloroform solution containing phenylacetyl chloride (1.54 g, 0.02 mol). Stirring is continued until *(2)* is completely dissolved. The solvent is then evaporated and the product is extracted with refluxing ether. After filtration and evaporation of the solvent *(3a)* is recrystallized from ether/petroleum ether.

(5): Compounds *(2)* (1.62 g, 0.01 mol) and *(6)* (1.94 g, 0.02 mol) are added to dry chloroform (30 ml). The stirred solution is refluxed until *(2)* has completely disappeared. The solvent is evaporated and *(5)* is recrystallized from cyclohexane [colorless needles, m.p. 152—153 °C, yield 72%; IR ($CHCl_3$) 1775 cm^{-1} (C=O); NMR ($CDCl_3$/TMS = 0): δ = 3.0 (3H, s), 7.1—7.75 ppm (10H, m)]. The *N*-ethyl analog of *(5)* was obtained analogously [m.p. 138—139 °C, yield 73%; IR ($CHCl_3$): 1775 cm^{-1}; NMR ($CDCl_3$/TMS = 0): δ = 1.4 ppm (3H, t), 3.45 (2H, q), 7.1—7.7 (10H, m)].

Received: January 20, 1977 [Z 653b IE]
German version: Angew. Chem. *89*, 189 (1977)

CAS Registry numbers:
(1a), 103-80-0; *(1b)*, 79-04-9; *(1c)*, 79-03-8; *(1d)*, 141-75-3; *(2)*, 33842-02-3; *(3a)*, 57243-90-0; *(3b)*, 57243-88-6; *(3c)*, 57243-87-5; *(3d)*, 19698-31-8; *(4)*, 1871-76-7; *(5)*, 61741-05-7; *(5)* *N*-Et analog, 61741-06-8; *(6)*, 525-06-4

[*] Prof. Dr. H. G. Viehe, Dr. B. Le Clef
Université de Louvain, Laboratoire de Chimie Organique
Place L. Pasteur, 1
B-1348 Louvain-la-Neuve (Belgium)
Dr. A. Elgavi
Bar Ilan University
Ramat-Gan (Israel)

[1] Phosgeniminium Chemistry, Part 23.—Part 22: *B. Stelander, H. G. Viehe*, Angew. Chem. *89*, 182 (1977); Angew. Chem. Int. Ed. Engl. *16*, 189 (1977).
[2] *R. Buyle, H. G. Viehe*, Tetrahedron *24*, 3987 (1968).
[3] *R. Buyle, H. G. Viehe*, Tetrahedron *24*, 4217 (1968); *L. Ghosez, J. Marchand-Brynaert* in *H. Böhme, H. G. Viehe*: Iminium Salts in Organic Chemistry. Wiley-Interscience, New York 1976.
[4] *G. Winters, N. Dimola, E. Oppici, G. Nathansohn*, Farmaco Ed. Sci. *30*, 620 (1975).
[5] *Z. Janousek, H. G. Viehe* in *H. Böhme, H. G. Viehe*: Iminium Salts in Organic Chemistry. Wiley-Interscience, New York 1976.
[6] *R. Giger, R. Allain, M. Rey, A. S. Dreiding*, Helv. Chim. Acta *53*, 120 (1970); *W. T. Brady, G. A. Scherubel*, J. Org. Chem. *39*, 3790 (1974).
[7] *R. Buyle, H. G. Viehe*, Tetrahedron *25*, 3447, 3453 (1969).
[8] *J. P. Declercq, G. Germain, M. Van Meerssche*, to be published.

Halogenonitrosylmolybdates—Simple, Monomeric Mo^{II} Complexes

By *Sabyasachi Sarkar* and *Achim Müller*[*]

In general the complexes of bivalent molybdenum are still poorly understood[1]. It is assumed that several strong π-acceptors as ligands are necessary to stabilize the Mo^{II}-d^4-system (as *e.g.*, in $[Mo(CO)_2(diars)I_2]$ or $[Mo(diars)_2Cl_2]$[1,2]. Classical mononuclear coordination compounds with simple ligands (as in Cr^{II}) were hitherto unknown[3]. We report here on the first of such complexes, which can also be used for the preparation of other molybdenum(II) complexes.

The complexes $Cs_2[Mo(NO)Cl_5]$ *(1)* (orange) and $Cs_2[Mo(NO)Br_5]$ *(2)* (deep red) as well as $[(C_6H_5)_4P][Mo(NO)Cl_4]$ *(3)* (yellow) and $[(C_6H_5)_4P][Mo(NO)Br_4]$ *(4)* (red) can be isolated as diamagnetic and stable crystals at room temperature. They were characterized by elemental analysis, molecular weight measurements [*(3)* and *(4)* in CH_2Cl_2], magnetic measurements as well as by X-ray powder diffraction diagrams (for the interconversion of *(1)* to *(3)* and of *(2)* to *(4)* see experimental part). *(1)* and *(2)* as well as *(3)* and *(4)* are isostructural, respectively. The magnetic properties and vibrational spectra proved the existence of monomeric complex anions (C_{4v}-symmetry) with d^4-configuration of the central atom (four electrons in two d(e)-orbitals)[4]. All vibrational frequencies lie in the expected region. Accurate measurements of ν(NO) and ν(MoN) showed (Table 1) that the π-backbonding effect of NO in the chloro complex *(1)* is smaller than that in the bromo complex *(2)*; this can be explained by the higher electronegativity of the halogen ligand in the *trans* position in *(1)*. The *trans*-effect of the NO-group in *(1)* and *(2)* gave $\nu(MoX_4) > \nu(MoX)_{trans}$.

hydrochloric acid *in air* for *ca.* 2 h to get a clear solution. After addition of 2 g of CsCl, dissolved in 20 ml concentrated hydrochloric acid, *(1)* precipitated as orange crystals which were filtered, washed several times with concentrated hydrochloric acid and dried in a vacuum over KOH. The preparation of *(2)* (HBr and CsBr), *(3)* (HCl and $[(C_6H_5)_4P]Cl$) and of *(4)* (HBr and $[(C_6H_5)_4P]Br$) was carried out analogously. *(1)* and *(3)* are interconvertible in hydrochloric acid according to the following equation (see[6]):

$$Cs_2[Mo(NO)Cl_5] \underset{CsCl}{\overset{[(C_6H_5)_4P]^+}{\rightleftharpoons}} [(C_6H_5)_4P][Mo(NO)Cl_4]$$

The corresponding equation is valid for *(2)* and *(4)*.

Received: December 9, 1976 [Z 623 IE]
German version: Angew. Chem. *89*, 189 (1977)

CAS Registry numbers:
(1), 61505-69-9; *(2)*, 61505-70-2; *(3)*, 61505-72-4; *(4)*, 61505-74-6; $K_4[Mo(NO)(CN)_5]$, 20861-57-8

[1] a) *S. A. Cotton, F. A. Hart:* The Heavy Transition Elements. Macmillan Press, London 1975; *F. A. Cotton, G. Wilkinson:* Advanced Inorganic Chemistry. Wiley-Interscience, New York 1972; b) *D. L. Kepert:* The Early Transition Elements. Academic Press, London 1972.
[2] In polynuclear halogenocomplexes (as *e. g.*, $[Cl_4MoMoCl_4]^{4-}$, $[Mo_6Cl_8]^{4+}$) the stablization is achieved by electron delocalization through Mo-Mo-bonding[1].
[3] The isolation of one unstable compound "$K_4Mo(CN)_6$" of unknown structure has been reported from the reduction of $K_4[Mo(CN)_8]$ in a H_2-stream at 390°C: *J. S. Yoo, E. Griswold, J. Kleinberg*, Inorg. Chem. *4*, 365 (1965).
[4] Cf. *H. B. Gray, P. T. Manoharan, J. Pearlman, R. F. Riley*, Chem. Commun., *1965*, 62.
[5] *W. Hieber, R. Nast, G. Gehring*, Z. Anorg. Allg. Chem. *256*, 169 (1948).
[6] *W. P. Griffith, D. Pawson*, J. Chem. Soc. Dalton, *1973*, 1315.

Table 1. Vibrational frequencies of the new Mo^{II} complexes *(1)*–*(4)* (IR solid state spectra in nujol; [cm^{-1}]).

	ν(NO)	ν(MoN)	δ(NO)	$\nu_{as}(MoX_4)$	$\nu_s(MoX_4)$	$\nu(MoX)_{trans}$
(1)	1676±2(vs)	579±1(w)	608.5±2(w)	*ca.* 320*br*(vs)	[a]	262(m)
(2)	1680±2(vs)	568±1(w)	607.5±2(w)	*ca.* 235*br*(vs)	210(sh)	177(m)
(3)	1694.5±2(vs)	616±1(w)	638±2(w)	323*br*(s)	[a]	—
(4)	1691.5±2(vs)	615±1(w)	640±2(w)	230*br*(s)	[a]	—
	A_1	A_1	E	E	A_1	A_1

[a] overlapped by $\nu_{as}(MoX_4)$.

The MoNO moiety is so stable (the π-accepting ability of one NO ligand is large enough to stabilize the Mo-d^4-system!) that in the case of addition of other ligands, *e.g.*, CN^- or OH^-, only an exchange of Cl^- and Br^- is observed. Therefore, the complexes *(1)*–*(4)* can be used to synthesize other Mo^{II} complexes and also to study the ligand exchange reactions on Mo^{II} systems.

Experimental:

A saturated solution of 2 g $K_4[Mo(NO)(CN)_5]\cdot 2H_2O$[5] in water was refluxed after addition of 30 ml concentrated

[*] Prof. Dr. A. Müller, Dr. S. Sarkar[**]
Institut für Chemie der Universität
Postfach 500500, D-4600 Dortmund 50 (Germany)
[**] Alexander-von-Humboldt Foundation Fellow.

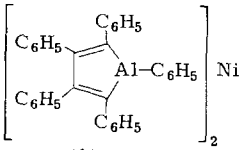
Novel Organonickel Compounds from (Pentaphenyl)aluminacyclopentadiene

By *Heinz Hoberg*[*] and *Reinhild Krause-Göing* and *Carl Krüger*[**] and *Janine C. Sekutowski*[***]

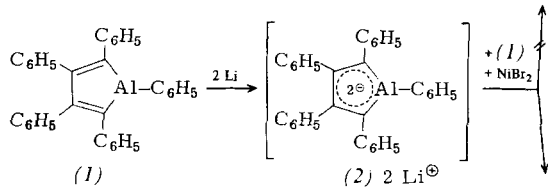
Acting as a cyclic diene, (pentaphenyl)aluminacyclopentadiene *(1)*[1] forms olefin complexes with transition metals. We have obtained a 1:1 complex from *(1)* and $(COD)_2Ni$[2]. The hitherto unknown 2:1 compound *(3)* should be accessible

[*] Priv.-Doz. Dr. H. Hoberg, Dipl.-Chem. R. Krause-Göing, Dr. C. Krüger, Dr. J. C. Sekutowski
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim (Germany)
[**] X-ray structure analysis.
[***] We are grateful to the Deutsche Forschungsgemeinschaft for support of this work.

by reduction of $NiBr_2$ with the dilithiated Al-five-membered ring *(2)* in the presence of *(1)*.



(3)



(1) *(2)* 2 $Li^{\oplus}$

$C_5(C_6H_5)_5NiC_3(C_6H_5)_3NiC_4(C_6H_5)_4$

(4)

+

$C_4(C_6H_5)_4NiC_4(C_6H_5)_4$

(5)

However, on performing the reaction of $NiBr_2$ with *(2)* in the presence of *(1)* in the molar ratio 1:1:1 we did not obtain compound *(3)* but instead the Al-free Ni complexes *(4)* and *(5)*.

IR and ^{1}H-NMR analyses reveal only phenyl groups. The mass spectrum of the deep violet compound *(4)* contained both the molecular ion and characteristics ions of the ligands at *m/e* 1184 $[C_{12}(C_6H_5)_{12}Ni_2]$, 446 $[C_5(C_6H_5)_5H]$, 356 $[C_4(C_6H_5)_4]$, 268 $[C_3(C_6H_5)_3H]$.

The structure of *(4)* could be established by X-ray analysis[3]. Cell data: $a=13.253(1)$, $b=21.310(1)$, $c=23.4775$ (6) Å, space group $P2_12_12_1$, $Z=4$, $R=0.075$ for 4473 reflections, of which 1378 were unobserved ($I \leq 2\sigma I$). The molecule (see Fig. 1 and 2) contains two non-identical nickel atoms, of which one (Ni-2) is complexed to pentaphenylcyclopentadiene, and the other one to a tetraphenylcyclobutadiene unit. Ni-1 and Ni-2 are bridged by a 1,2,3-triphenylallyl unit, which bonds as a π-allyl group to Ni-1[4] and *via* two σ bonds to Ni-2. The distance Ni-2—C-6 is 2.44(2) Å. Both nickel atoms achieve a stable 18-electron configuration by forming an additional Ni—Ni single bond[5]. Thus compound *(4)* is characterized both by an unusual mode of synthesis and by a remarkable structure, in which three dissimilar olefinic ligands are bonded to a Ni—Ni system and the bridging C_3 unit engages in both σ and π bonding.

It cannot yet be decided whether the $C_3(C_6H_5)_3$ and $C_5(C_6H_5)_5$ units present in *(4)* have arisen from the $C_4(C_6H_5)_4$ group of the Al-five-membered ring *(1)* as a result of a dichotomy[6].

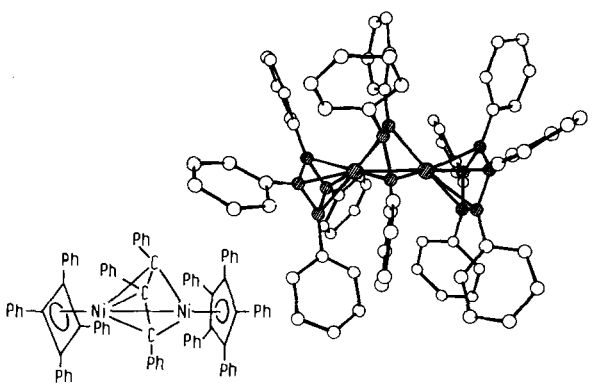


Fig. 1. Complete molecular structure of *(4)*.

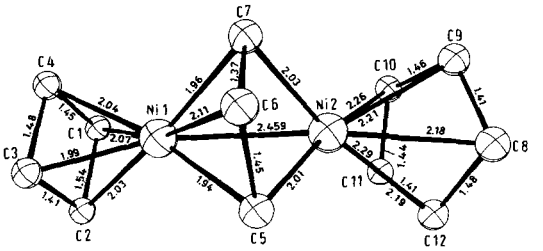


Fig. 2. Molecular structure of *(4)* and numbering of the atoms. The 12 phenyl groups have been omitted for the sake of clarity.

Elemental and MS analyses of *(5)* provide evidence that it is a compound in which two $C_4(C_6H_5)_4$ units are bonded to a nickel atom, *i.e.* possibly a derivative of the hitherto unknown bis(cyclobutadiene)nickel. Further studies, and in particular X-ray structure analysis, should substantiate this conclusion.

Procedure:

A suspension of $C_4(C_6H_5)_5Al \cdot O(C_2H_5)_2$ *(1)* (4.83 g, 9.0 mmol) and Li powder (73 mg, 10.5 mmol) in diethyl ether (350 ml) is stirred for 4 d at 20°C. The resulting red mixture is filtered and the filtrate allowed to react at −10°C with $NiBr_2$ (1.0 g, 4.6 mmol). The temperature of the stirred mixture is permitted to rise to 20°C, and after standing for *ca.* 48 h a gray precipitate is filtered off (*ca.* 0.4 g). From the intensely green filtrate fractional crystallization gives *(5)* (0.15 g, 4.2%; blue crystals, m.p. >300°C) and *(4)* (0.19 g, 7%; m.p. 270°C (dec.)). The yields are based on $NiBr_2$.

Received: December 22, 1976 [Z 631 IE]
German version: Angew. Chem. *89*, 179 (1977)

CAS Registry numbers:
(1), 61477-83-6; *(4)*, 61483-83-8; *(5)*, 61483-84-9

[1] *H. Holberg* and *R. Krause-Göing*, J. Organomet. Chem., in press.
[2] *H. Holberg* and *R. Krause-Göing*, to be published.
[3] For data collection and calculation see *inter alia*, *D. J. Brauer*, *C. Krüger*, *P. J. Roberts*, and *Y.-H. Tsay*, Chem. Ber. *107*, 3706 (1974).
[4] *B. L. Barnett* and *C. Krüger*, J. Organomet. Chem. *77*, 407 (1974).
[5] *C. Krüger*, Angew. Chem. *81*, 708 (1969); Angew. Chem. Int. Ed. Engl. *8*, 678 (1969); *K. Jonas*, *D. J. Brauer*, *C. Krüber*, *P. J. Roberts*, and *Y.-H. Tsay*, J. Am. Chem. Soc. *98*, 74 (1976); *B. L. Barnett*, and *C. Krüger*, Cryst. Struct. Commun. *2*, 85 (1973).
[6] *H. Benn*, *G. Wilke*, and *D. Henneberg*, Angew. Chem. *85*, 1052 (1973); Angew. Chem. Int. Ed. Engl. *12*, 1001 (1973).

Quantitative Field Desorption Mass Spectrometry; Stable Isotope Dilution and Cationization[**]

By *W. D. Lehmann* and *H.-R. Schulten*[*]

Field desorption mass spectrometry (FD-MS) has been used for the qualitative analysis of polar organic and inorganic compounds[1]. One of the principal applications is the determination of the molecular ion $[M]^{\ddagger}$. In FD-MS attachment of a cation $[Cat]^+$ to a neutral molecule M (cationization)[2] leads to particularly stable ions of the type $[M+Cat]^+$ which can be utilized in molecular weight determinations[3]. Quantitative FD-MS with ions of type $[M]^{\ddagger}$ has already been de-

[*] Dr. W. D. Lehmann, Dr. H.-R. Schulten[+]
Institut für Physikalische Chemie der Universität
Wegelerstrasse 12, D-5300 Bonn (Germany)
[**] Quantitative Field Desorption Mass Spectrometry, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Ministry of Science and Research of North Rhine-Westphalia.—Ref. [4] is to be regarded as Part 2.
[+] To whom correspondence should be addressed.

scribed[4]. We now report the first quantitative results of FD-MS obtained by exploiting cationization.

Field desorption mass spectrometry and similar mass spectrometric methods give spectra for numerous organic compounds which consist predominantly of the ion $[M]^{\ddagger}$ or $[M+Cat]^+$. These methods are particularly suitable for quantitative determinations because:
structurally significant fragments are not required,
interference due to impurities in the sample is reduced, and
the molecular ion or the cationized molecule carries almost the entire ion current, thus leading to maximum possible sensitivity.

A drawback of the FD-MS method is that it gives lower ion currents showing greater fluctuations than electron impact and chemical ionization. For this reason
the sensitivity was increased by cationization with alkali metal cations,
the precision improved by an isotopically labeled internal standard, and
the value determined for $[M+Cat]^+$ was averaged over a large number of repetitive scans.

Figure 1 shows a section of five scans recorded in the quantitative determination of a non-derivatized monosaccharide, glucose, on a microgram scale.

The extent of labeling of the internal standard [1-^{13}C]-glucose was determined by comparison of the attachment-FD spectra A and B (Table 1). Taking account of the intensity of the peak at *m/e* 202 of unlabeled glucose, it was calculated that C-1 of the [^{13}C]-glucose is 86.7% ^{13}C. Use of monoisotopic $[^{23}Na]^+$ for cationization greatly simplifies quantitative evaluation of the spectra. The quantitative data obtained are supported by determination of the intensity distribution of the $[M+H]^+$ group by the normal field desorption procedure (spectrum D, Table 1).

The spectra were evaluated by making the simplifying assumption that only $[M+Na]^+$ and $[M+H]^+$ ions are formed. For spectrum C($[M+Na]^+$ group) a molar ratio

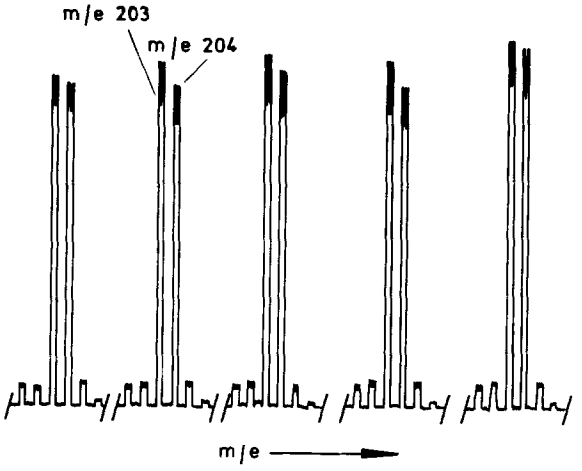


Fig. 1. Five scans from a series of measurements comprising 105 consecutive FD scans over the $[M+Na]^+$ group of a mixture of glucose and [1-^{13}C]-glucose (86.7% ^{13}C) in the presence of $[Na]^+$. According to the amount of sample weighed out the molar ratio was 1:1.17. Cationization was ensured by dissolution of glucose and NaI in the approximate molar ratio 1:1 in water. The solution was applied to a high-temperature activated FD emitter with a microliter syringe. The emitter heating current was about 10 mA while the spectrum was being recorded. The spectra were recorded at low resolution (plateau peaks) by variation of the accelerating potential with a Varian MAT 731 mass spectrometer (see also Table 1, spectrum C).

of 1:1.184 (error +1.1%) was obtained, and for spectrum D ($[M+H]^+$ group) a molar ratio of 1:1.191 (error + 1.7%).

Table 1. Relative intensities of the $[M+Na]^+$ group (spectra A to C) and the $[M+H]^+$ group (spectrum D) in the FD mass spectrum of glucose in the presence and absence, respectively, of $[Na]^+$. In order to record the sodium attachment spectra the sample was dissolved together with NaI in the approximate molar ratio of 1:1 in H_2O; for recording the normal FD mass spectrum pure H_2O was used as solvent. The amounts of sample applied were in the microgram range.

m/e	202	203	204	205
	Relative intensity [%]			
Spectrum A	2.3	100	8.9	
Spectrum B		17.5	100	6.3
Spectrum C	3.4	100	96.1	7.1
m/e	180	181	182	183
	Relative intensity [%]			
Spectrum D	10.5	100	96.5	9.8

Spectrum A: $[M+Na]^+$ group of glucose + NaI, 60 consecutive scans, 5 mA emitter heating current.
Spectrum B: $[M+Na]^+$ group of [1-^{13}C]-glucose (86.7% ^{13}C) + NaI, 60 consecutive scans, 10 to 15 mA emitter current.
Spectrum C: $[M+Na]^+$ group of a mixture of glucose and [1-^{13}C]-glucose (molar ratio 1:1.17) + NaI, 105 consecutive scans, 10 to 15 mA emitter heating current, mean error of the individual measurements of relative intensity of *m/e* 204: ±7.2%; mean error of average value: ±0.7% (see also Fig. 1).
Spectrum D: $[M+H]^+$ group of a mixture of glucose and [1-^{13}C]-glucose (molar ratio 1:1.17), 210 consecutive scans, 18 to 20 mA emitter heating current, mean error of the individual measurements of the relative intensity of *m/e* 182: ±6.8%; mean error of the average value: ±0.47%.

In the quantitative determination of glucose by field desorption mass spectrometry the mean error of the individual measurement is about 7%. On evaluation of 100 scans the mean error of the average value is ±0.7%, and this value decreases accordingly as more scans are recorded. No isotope effects were observed in these series of measurements. Our investigations show that field desorption mass spectrometry in conjunction with the isotopic dilution method possesses good sensitivity and precision for quantitative analysis and can be regarded as a promising method for biochemical and medical analysis (*e.g.* pharmakokinetic studies).

Received: December 16, 1976 [Z 632 IE]
German version: Angew. Chem. *89*, 180 (1977)

CAS Registry number:
Glucose, 50-99-7

[1] *H. D. Beckey, H.-R. Schulten*, Angew. Chem. *87*, 425 (1975); Angew. Chem. Int. Ed. Engl. *14*, 403 (1975); *H.-R. Schulten, F. W. Röllgen*, Angew. Chem. *87*, 544 (1975); Angew. Chem. Int. Ed. Engl. *14*, 561 (1975).
[2] *H.-R. Schulten, H. D. Beckey*, Org. Mass Spectrom. *6*, 885 (1972); *7*, 861 (1973).
[3] *F. W. Röllgen, H.-R. Schulten*, Org. Mass. Spectrom. *10*, 660 (1975); *H.-R. Schulten, F. W. Röllgen, ibid. 10*, 649 (1975); cf. *H. J. Veith*, Angew. Chem. *88*, 762 (1976); Angew. Chem. Int. Ed. Engl. *15*, 695 (1976).
[4] *S. Pfeifer, H. D. Beckey, H.-R. Schulten*, Z. Anal. Chem. *284*, 193 (1977), and references cited therein.

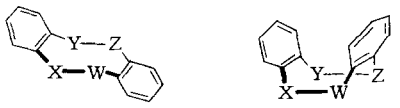
Chair and Boat: Stable Conformers of an Eight-Membered Ring System[**]

By *Rolf W. Saalfrank*[*]

Eight-membered ring systems of type *(1)* can in principle assume a rigid chair-like conformation or a flexible boat-like

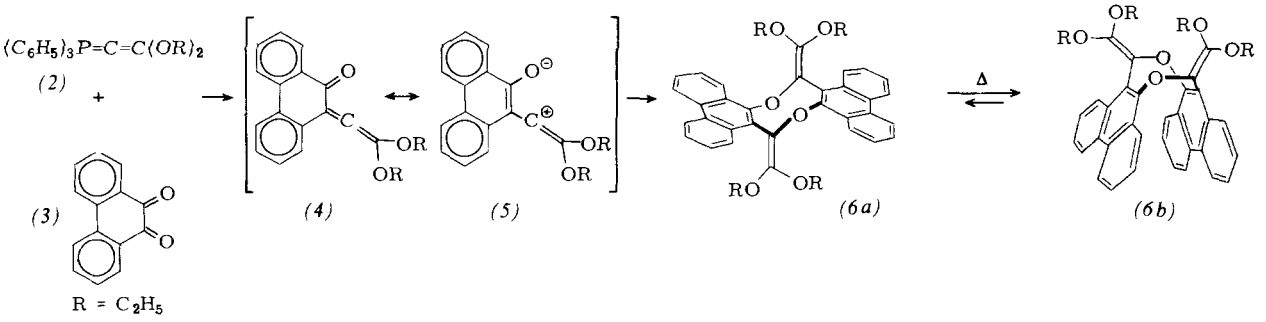
[*] Priv.-Doz. Dr. R. W. Saalfrank
Institut für Organische Chemie der Universität
Erlangen-Nürnberg (Germany)
[**] Based on a lecture delivered at the V. International Conference of Organic Chemistry, Gdansk (Poland), September 1974.

conformation[1]. α-Disalicylide [*(1)*, X=Z=O; Y=W=CO] exists exclusively in the boat conformation[2]. In the case of 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene [*(1)*, X=Z=Y=W=CH_2], however, both the chair and the boat conformations are present in almost equal proportions in solution[3], whereas in the crystalline state only the chair conformation is known[4]. In the following communication the synthesis and isolation of the chair and boat conformers of an eight-membered ring system is reported for the first time.



(1)

Wittig reaction of the (2,2-diethoxyvinylidene)triphenylphosphorane *(2)* with 9,10-phenanthrenequinone *(3)* leads, probably *via* [4+4] cycloaddition[6] of the 1,4-dipole *(5)* and the "*o*-quinonoid" allene *(4)*[5], to the cyclooctane derivative *(6)*, whose chair and boat conformers *(6a)* and *(6b)* can be separated by fractional crystallization.



Identification of the conformers follows from the temperature dependent ^{1}H-NMR and ^{13}C-NMR spectra (Table 1).

On the basis of their molecular symmetry [C_i for *(6a)*, C_2 for *(6b)*] one would expect the ^{1}H-NMR spectra of both conformers at room temperature to show two triplets for the methyl groups together with a multiplet, since the methylene protons in both molecules are diastereotopic. A molecular model shows that in the chair conformers *(6a)* two ethoxy groups are more remote from the phenanthrene residues than the other two. Hence two CH_3 groups are more strongly shielded and, as a consequence, their signals appear at higher field in the ^{1}H-NMR spectrum. In the flexible boat conformer *(6b)*, on the other hand, no ethoxy group is outstandingly oriented. Hence the two CH_3 triplets differ only slightly in their chemical shift.

Heating of the chair boat conformer in 1,2-dichlorobenzene leads to an equilibrium mixture. The position of the equilibrium (chair : boat ≈ 1 : 2) is practically independent of temperature between 30 and 90°C.

All conformers of the boat family are chiral. Their racemization ensues by flipping of the eight-membered rings. As shown by the multiplet of the diastereotopic methylene protons, the racemization at room temperature is slow with respect to the ^{1}H-NMR scale. With increasing temperature it becomes more rapid, and at about 100°C the methylene protons are magnetically equivalent.

The temperature dependence of the ^{1}H-NMR spectra of the chair conformer *(6a)* is surprising: Above 120°C its CH_3 triplets begin to broaden, at about 160°C they coalesce, and at 180°C a new triplet of double intensity appears exactly in the middle of the two original triplets[7]. This would indicate that free rotation about the exocyclic C=C double bond is possible in the chair conformer under these conditions[8].

Evidence for the isolated substances being conformers is also provided by the fact that the differences between corresponding ^{13}C-NMR signals do not exceed 1.5 ppm (see Table 1).

Experimental:

A hot benzene solution of 8.3 g (40 mmol) 9,10-phenanthrenequinone is added with vigorous stirring under nitrogen to a benzene solution of (2,2-diethoxyvinylidene)triphenylphosphorane *(2)*, prepared from 18.0 g (40 mmol) (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate[9]. The mixture is allowed to stand overnight; the solvent is then removed by evaporation and the residue treated with methanol. After 2 to 3 hours the precipitate (yellow crystals) is filtered off and dried (orange-red crystals). Recrystallization from methylene chloride/methanol (1 : 10) affords the boat conformer *(6b)* in the form of shiny-red platelets. The mother liquor is allowed to stand for 2 to 3 days at room temperature. The precipitated yellow chair conformer *(6a)* is recrystallized as above (yellow

Table 1. Physical properties of the conformers *(6a)* and *(6b)*.

	Yield [%] [a]	M.p. [°C]	IR (KBr) [cm^{-1}]	UV (C_2H_5OH) λ_{max} [nm] (log ε)	^{1}H-NMR (60 MHz, $CDCl_3$, TMS intern) τ	^{13}C-NMR [e] (25.15 MHz, $CDCl_3$, TMS intern) δ [ppm]
(6a)	9.8	190 [b]	1621; 1592	415; 437 (je 4.58)	9.70 (6H, t); 8.72 (6H, t); 7.1 bis 5.8 (8H, m) [c]; 2.9 bis 0.8 (16H, m)	−154.38; −132.33; −130.72; −129.99; −121.43; −116.16; −61.19; −59.13; −15.17; −13.92
(6b)	52	245 dec.	1613; 1585	450 (4.56)	8.77 (6H, t); 8.60 (6H, t); 6.04 (4H, q), 5.92 (4H, q) [d]; 3.7 bis 1.3 (16H, m)	−155.75; −132.81; −129.75; −128.69; −121.38; −115.25; −61.64; −59.34; −15.59; −15.26

[a] Referred to amount of (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate used.
[b] Transformation point of the yellow chair-conformer into the orange-red boat-conformer.
[c] Diastereotopic methylene protons.
[d] In 1,2-dichlorobenzene the diastereotopic methylene protons in this conformer also show the expected splitting pattern.
[e] In each case ten of the total of twenty ^{13}C-NMR signals.

needles on rapid crystallization, yellow platelets on slow crystallization).

Received: December 22, 1976 [Z 642 IE]
revised: January 4, 1977
German version: Angew. Chem. 89, 184 (1977)

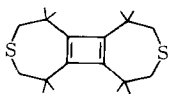
CAS Registry numbers:
(2), 21882-77-9; *(3)*, 84-11-7; *(4)*, 61544-07-8; *(6)*, 61544-08-9

[1] *W. D. Ollis, J. F. Stoddart, I. O. Sutherland*, Tetrahedron *30*, 1903 (1974).
[2] *P. G. Edgerley, L. E. Sutton*, J. Chem. Soc. *1951*, 1069.
[3] *R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis, I. O. Sutherland*, J. Chem. Soc. *1973*, 205.
[4] *W. Baker, R. Banks, D. R. Lyon, F. G. Mann*, J. Chem. Soc. *1945*, 27.
[5] *R. W. Saalfrank*, Angew. Chem. *86*, 162 (1974); Angew. Chem. Int. Ed. Engl. *13*, 143 (1974); Tetrahedron Lett. *1975*, 4405.
[6] *R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. Int. Ed. Engl. *8*, 312 (1969).
[7] The transformation is reversible.
[8] I am indebted to Priv. Doz. *F. Dickert* for stimulating discussions; cf. *L. M. Jackmann* in *L. M. Jackmann, F. A. Cotton:* Dynamic Nuclear Magnetic Resonace Spectroscopy. Academic Press, New York 1975, p. 203.
[9] *H. J. Bestmann, R. W. Saalfrank, J. P. Snyder*, Chem. Ber. *106*, 2601 (1973).

Observed and Calculated Electron-Density Distribution in the Bonds of a Rectangular Cyclobutadiene[**]

By *Hermann Irngartinger, Hans-Lothar Hase, Karl-Wilhelm Schulte*, and *Armin Schweig*[*]

According to the results of photoelectron spectroscopy[1a] and X-ray structure analysis[1b] the cyclobutadiene derivative *(1)*[1c] has a rectangular four-membered ring structure and a singlet ground state. In order to study the distribution of the bonding electrons for this structure and this state we have determined the difference electron density[2,3] for *(1)*



(1)

from the experimental X-ray data (4615 reflections up to $\sin\theta/\lambda = 0.663$ Å^{-1}; Mo-K_α radiation) and we have theoretically calculated the static ("double-ζ"[4] *ab initio*[5] quality) and dynamic (by a newly developed method[6]) difference electron densities for cyclobutadiene[7]. Figure 1 shows three sections through each of the resulting densities (*stat* = static, *dyn* = dynamic, *exp* = experimental density). Section *A* is in the plane of the four-membered ring, *B* at right angles through the center of the double bonds, and *C* is analogous but through the center of the single bonds).

As shown by the diagram, the density maxima (and minima) of the dynamic densities are considerably reduced (by about 70% for the C=C bond, and by about 60% for the C—C bond) relative to the maxima of the static densities. Therefore

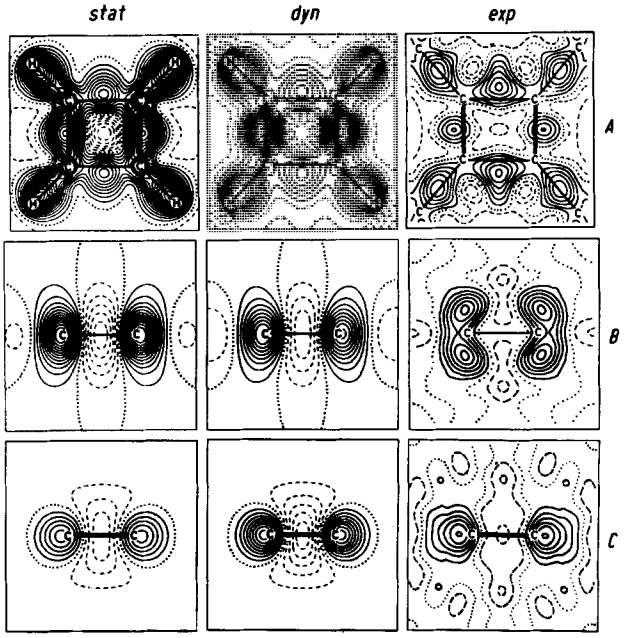


Fig. 1. Calculated static (*stat*), dynamic (*dyn*), and experimental (*exp*) difference electron densities in the four-membered ring of the cyclobutadiene system in three planes: *A*, section within the plane of the four-membered ring; *B*, section perpendicular to the plane of the four-membered ring through the centers of the double bonds; and *C*, section perpendicular to the four-membered ring through the centers of the single bonds. In all cases the contours indicate differences of 0.04 e/Å^3. The zero contour is dotted, the positive (negative) values being shown as solid (dashed) lines. The calculated densities were obtained for cyclobutadiene and the measured ones for *(1)*. In the *B* sections the line of view is parallel to the C=C bonds in the direction of a C—C bond and *vice versa* in the *C* sections.

the calculated dynamic densities are now in general agreement with the experimentally determined densities. It is particularly remarkable that both theory and experiment give density maxima for the four-membered ring compound which lie significantly off the lines joining the C atoms. Thus bent bonds are to be assumed for the four-membered ring of *(1)*, and also for cyclobutadiene, such as are known for three-membered rings[8] and have recently also been found for cyclobutane[9]. In contrast, the density maxima of the exocyclic C—C bonds of *(1)* and C—H bonds of cyclobutadiene lie in the center of the bond axes. The sections perpendicular to the bonds clearly show the elongation of the electron distribution in the π bonds, whereas the density distribution in the σ bonds is axially symmetric. More precise quantitative statements will require low temperature measurements and extension of the basis set in the calculations[10].

Received: December 3, 1976;
abridged: December 20, 1977 [Z 636 IE]
German version: Angew. Chem. 89, 194 (1977)

CAS Registry number:
(1), 40219-42-9

[*] Doz. Dr. H. Irngartinger
Institut für Organische Chemie der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg (Germany)
Prof. Dr. A. Schweig, Dr. H.-L. Hase, Dipl.-Chem. K.-W. Schulte
Fachbereich Physikalische Chemie der Universität
Auf den Lahnbergen, D-3550 Marburg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The studies performed at Heidelberg are part of the series "Electron Density Distribution in Chemical Bonds", Part 2.—Part 1: *H. Irngartinger, H.-U. Jäger*, Angew. Chem. *88*, 615 (1976); Angew. Chem. Int. Ed. Engl. *15*, 562 (1976). The work performed at Marburg was part of the investigations performed within the framework of DFG-Sonderforschungsbereich 127 ("Crystal Structure and Chemical Bonding"), Project H.

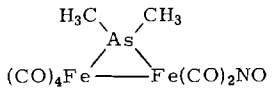
[1] a) *G. Lauer, C. Müller, K.-W. Schulte, A. Schweig, A. Krebs*, Angew. Chem. *86*, 597 (1974); Angew. Chem. Int. Ed. Engl. *13*, 544 (1974); *G. Lauer, C. Müller, K.-W. Schulte, A. Schweig, G. Maier, A. Alzérreca, ibid. 87*, 194 (1975) and *14*, 172 (1975); resp. b) *H. Irngartinger, H. Rodewald, ibid. 86*, 783 (1974) and *13*, 740 (1974) resp.; c) *H. Kimling, A. Krebs, ibid. 84*, 952 (1972) and *11*, 932 (1972), resp.
[2] The difference electron density of a molecule is defined as the difference between the total molecular electron density and the superposed atomic densities of the atoms of which the model considered is composed.
[3] The experimental difference densities have been averaged over the two independent molecules (space group P $\bar{1}$; $Z = 2$; molecular symmetry C$_i$ ($\bar{1}$)) and over chemically equivalent regions in accord with D_{2h} symmetry.

[4] *H. Basch, M. B. Robin, N. A. Kuebler*, J. Chem. Phys. *47*, 1201 (1967).
[5] The total electron density was calculated with the SCF part of the POLYATOM program system (obtainable from Quantum Chemistry Program Exchange, Indiana University, No. 199). The atomic densities were determined by the RHF program section using the same basis [4].
[6] *H.-L. Hase, H. Reitz, A. Schweig*, Chem. Phys. Lett. *39*, 157 (1976).
[7] The geometry of unsubstituted cyclobutadiene optimized by the CNDO/S procedure (bond lengths: C=C 1.349, C—C 1.515, C—H 1.083 Å; *G. Lauer, K.-W. Schulte, A. Schweig*, unpublished results) was used in the quantum chemical calculations. In order to determine the dynamic density a cubic pseudo-unit cell was constructed with the dimensions $a=b=c=4$ Å into which a molecule of cyclobutadiene just fits. Temperature factors measured for *(1)* are used for the carbon atoms, and it is further assumed that the temperature factors of the hydrogen atoms of cyclobutadiene have the same value as the experimentally accessible temperature factors of the corresponding carbon atoms in *(1)*.
[8] *C. J. Fritchie Jr.*, Acta Crystallogr. *20*, 27 (1966); *A. Hartmann, F. L. Hirshfeld, ibid 20*, 80 (1966); *D. A. Matthews, G. D. Stucky*, J. Am. Chem. Soc. *93*, 5954 (1971); *T. Ito, T. Sakurai*, Acta Crystallogr. *B29*, 1594 (1974).
[9] *M. Harel, F. L. Hirshfeld*, Acta Crystallogr. *B 31*, 162 (1975).
[10] The experimental results of Figure 1 were derived from a conventionally refined structure analysis at room temperature. The resulting possible errors in the atomic parameters (positional and temperature factors) and scale factor can lead to inaccuracies of the derived experimental difference electron densities. A theoretical estimate of the inaccuracies by conventional temperature factors in the case of tetracyanoethylene (TCNE) showed that they do not exceed 0.1 e/Å^3 in this system. Moreover, an exact comparison between calculated and measured difference electron densities for TCNE and smaller model systems has also shown that the difference densities calculated in "double ζ" quality are not falsified by more than 0.15 to 0.2 e/Å^3 (*H.-L. Hase, K.-W. Schulte, A. Schweig*, unpublished results). These experiments suggest that the observed and calculated results are already essentially correct.

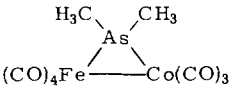
Catalytic Activity by Opening of Metal-Metal Bonds[**]

By *Hans Joachim Langenbach, Egbert Keller*, and *Heinrich Vahrenkamp*[*]

The metal-metal bonds in complexes *(1)* and *(2)* are so reactive that they are readily opened by phosphanes at room temperature[1]. Compounds *(1)* and *(2)* may therefore be regarded as complexes having latent free coordination sites capable of being exploited for catalytic reactions.

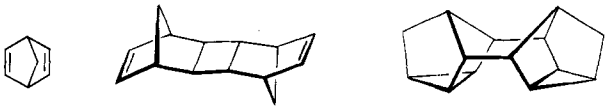


(1)



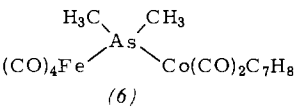
(2)

As an example of such a reaction we describe here the catalyzed dimerization of norbornadiene *(3)* with *(1)* and *(2)* which permitted the first characterization of a catalytically active intermediate formed by opening of a metal-metal bond of a polynuclear complex. Norbornadiene *(3)* is converted exclusively into the *exo-trans-exo* dimer *(4)* on reaction with *(1)* in benzene at 60°C, whereas reaction with *(2)* at 80°C leads to a 1:1 mixture of *(4)* and the dimer *(5)*. If the reaction with *(1)* or *(2)* is carried out unter milder conditions (CH_2Cl_2, room temperature) using equimolar amounts of catalyst and BF_3-etherate, very rapid and exclusive formation of *(5)* takes place. Compounds *(1)* and *(2)* surpass other catalysts[2] for the dimerization of norbornadiene in their accelerating effect on the reaction. Moreover, unlike *(1)*, other catalysts afford the dimer *(4)* always in admixture with other dimers[3].



(3) *(4)* *(5)*

Reaction of norbornadiene with *(2)* in benzene at 55°C affords the isolable complex *(6)*, which directly catalyzes the same reactions as *(2)* without any induction period. The structure of *(6)* has been determined by X-ray crystallography[4]. It confirms the opening of the metal-metal bond and loss of a CO group at cobalt as the activating step (Fig. 1).



(6)

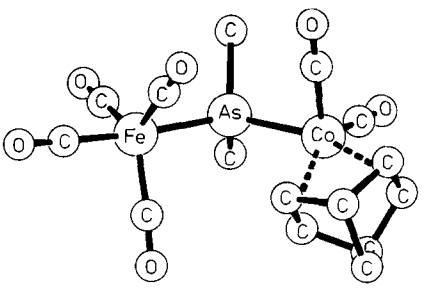


Fig. 1. Molecular structure of complex *(6)*. Important parameters: Fe—As=2.385 (1) Å, Co—As=2.379 (1) Å, Co—C (norbornadiene)=2.09, 2.10, 2.17, and 2.18 (1) Å.

In our opinion only one of the metal atoms of *(1)* and *(2)* can be considered as the catalytically active center of the reaction. The unaltered presence of the $(CO)_4Fe—As(CH_3)_2$ group in *(6)* and the inertness of $(CO)_4Fe—L$ complexes toward CO substitution, rule out participation of this part of the molecule in the dimerizing process. It would appear, therefore, despite the use of dinuclear complexes, that the monomolecular mechanism *via* a metallacyclic intermediate[5] is favored over the π-complex multicenter mechanism[1]. Accordingly, like *(1)*, $Fe(CO)_2(NO)_2$ preferably dimerizes norbornadiene to *(4)*[3], and formation of *(5)* is mainly achieved with cobalt catalysts[6,7]. Thus the essential property of the complexes *(1)* and *(2)* is not their polynuclear character but the functionality of their metal-metal bonds.

Experimental:

Synthesis of *(6)*: A mixture of *(2)* (930 mg, 2.0 mmol) and norbornadiene (2.00 g, 22 mmol) in benzene (15 ml) is stirred for 48 h at 55°C under nitrogen. After removal of all volatile components in a vacuum the residue is taken up in 1 ml of benzene. Dropwise addition of 10 ml hexane affords *(6)* as a brown-violet, air-sensitive precipitate [270 mg (27%), m.p. 89—90°C], which is washed with a little hexane and dried in a vacuum.

Received: December 22, 1976 [Z 640 IE]
German version: Angew. Chem. *89*, 197 (1977)

[*] Prof. Dr. H. Vahrenkamp, Dipl.-Chem. H. J. Langenbach, Dipl.-Chem. E. Keller
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

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

[1] *H. J. Langenbach, H. Vahrenkamp*. Chem. Ber., in press.
[2] *G. N. Schrauzer*, Adv. Catal. *18*, 373 (1968).
[3] *P. W. Jolly, F. G. A. Stone, K. MacKenzie*, J. Chem. Soc. *1965*, 6416; *D. R. Arnold, D. J. Trecker, E. B. Whipple*, J. Am. Chem. Soc. *87*, 2596 (1965).

[4] Monoclinic, $P2_1/c$; $a=7.289$ (2), $b=12.134$ (1), $c=21.040$ (3) Å. $\beta=107.78$ (2)°. Nonius-CAD4 diffractometer, 2650 reflections, $R=0.040$.
[5] *A. R. Fraser, P. H. Bird, S. A. Bezman, J. R. Shapley, R. White, J. A. Osborn*, J. Am. Chem. Soc. *95*, 597 (1973).
[6] *G. N. Schrauzer, B. N. Bastian, G. A. Fosselius*, J. Am. Chem. Soc. *88*, 4890 (1966).
[7] *M. Ennis, A. R. Manning*, J. Organomet. Chem. *116*, C 31 (1976).

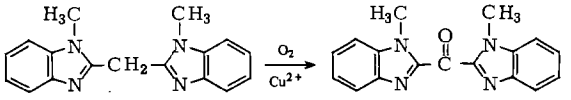
A Model of Internal Monooxygenase Catalyzed Reactions: Copper-Catalyzed Autoxidation of Bis(1-methylbenzimidazol-2-yl)methane[**]

By *Charles A. Sprecher* and *Andreas D. Zuberbühler*[*]

While dioxygenase activity, *e.g.* the oxidative cleavage of aromatic rings, can be mimicked closely in low molecular weight systems[1], no model studies seem to have been reported for internal monooxygenases[2], a group of enzymes catalyzing the four electron oxidation (a) of organic substrates.

$$RH_2+O_2\rightarrow RO+H_2O \qquad (a)$$

Here we wish to present evidence for internal monooxygenase behavior in the copper catalyzed autoxidation of bis(1-methylbenzimidazol-2-yl)methane *(1)* to bis(1-methylbenzimidazol-2-yl)ketone *(2)*.



(1) *(2)* + H_2O

Compound *(1)* (m.p. 211—213 °C from methanol), was obtained by condensation of 1-amino-2-(methylamino)benzene with diethyl malonate[3]. Copper(II) perchlorate (8 μmol) was added to a solution of *(1)* (3.6 mmol) in 200 ml anhydrous ethanol and the solution stirred for 30 min at room temperature and atmospheric pressure under pure O_2. An O_2 uptake of 81 ml (3.3 mmol) indicated a 1:1 substrate to O_2 stoichiometry, as required by eq. (a). On addition of H_2O containing some EDTA to complex Cu^{2+}, *(2)* was precipitated in nearly quantitative yield [m.p. 191—192 °C (from CH_3CN); NMR: loss of methylene protons at 4.65 ppm relative to TMS in $CDCl_3$); IR: carbonyl stretching at 1649 cm^{-1}; mass spectrum: molecular ion at $m/e=290$].

The redox stoichiometry was checked using an oxygen-analyzer. In 10 runs under different conditions the consumption of O_2 was 90±2% of the theoretical value. The origin of the carbonyl oxygen was tested with $D_2{}^{18}O$. The methylene compound was oxidized in the presence of an 80-fold excess of 64% $D_2{}^{18}O$ and *(2)* isolated immediately after completion of the reaction. Only a slight increase (8%) of the (M^++2) peak, corresponding to 13% exchange, was observed in the mass spectrum, excluding water as the source of the carbonyl oxygen. A considerable exchange (43%) is observed only if *(2)* is treated with $D_2{}^{18}O$ for 3 weeks. The concomitant shift of the carbonyl frequency by 28 cm^{-1} compares well with the shift of 29 cm^{-1} for the ^{16}O-^{18}O exchange in benzophenone[4].

The autoxidation of *(1)* is absolutely dependent on metal ion impurities. In commercial *p.a.* ethanol, $CHCl_3$, or acetonitrile a slow, irreproducible uptake of dioxygen takes place. This uptake is completely blocked by traces of strong chelators like dithizone or EDTA. Equimolar amounts of acid (H_2SO_4) or base (NaOH), and surprisingly, excess Cu^{2+} strongly inhibit the reaction. In 60% ethanol with dilute acetate buffer ($[CH_3COOH]=[CH_3COO^-]=0.0005$ mol/liter) at an ionic strength of 0.1 ($NaNO_3$) the rate of the reaction is first order with respect to $[O_2]$ and $[Cu^{2+}_{tot}]$ and independent of the substrate concentration, so long as $[substrate]/[Cu^{2+}_{tot}]>3$. According to potentiometric measurements, the formation of a partially deprotonated species $[CuL\cdot(L-H^+)]^+$ with $L=$ *(1)* is essentially complete under these conditions. *(1)* is probably deprotonated at the methylene group before reaction with the oxygen sets in.

Of the other metal ions tested, only Co^{2+} showed catalytic activity comparable to Cu^{2+}; Fe^{2+}, Fe^{3+}, Ni^{2+}, Zn^{2+}, and Mg^{2+} did not significantly increase the rate of dioxygen uptake. Methyl 2-(1-methylbenzimidazol-2-yl)acetate and 2-(1-methylbenzimidazol-2-yl)acetonitrile are oxidized at rates comparable to those found with *(1)* in the presence of Cu^{2+}. With the second substrate and using ethanol as the solvent, one of the carbon atoms is lost in the process. 1,2-Dimethylbenzimidazole and higher bis(1-methylbenzimidazol-2-yl)alkanes, do not show any reactivity. We therefore suggest that the sequence —N=C—CH_2—X (X indicating an unsaturated, electron-withdrawing group) may be essential for the catalyzed autoxidation.

The system described here fulfils all the basic requirements for internal monooxygenase activity: Dioxygen is used as an oxidant, one atom of O_2 is incorporated into the substrate, no external reducing agent is needed, and the oxidation is absolutely dependent on the presence of a suitable catalyst.

Received: December 27, 1976 [Z 643 IE]
German version: Angew. Chem. *89*, 185 (1977)

CAS Registry numbers:
(1), 55514-10-8; *(2)*, 61650-33-7; 1-amino-2-(methylamino)benzene, 4760-34-3; diethyl malonate, 105-53-3; copper(II) perchlorate, 13770-18-8

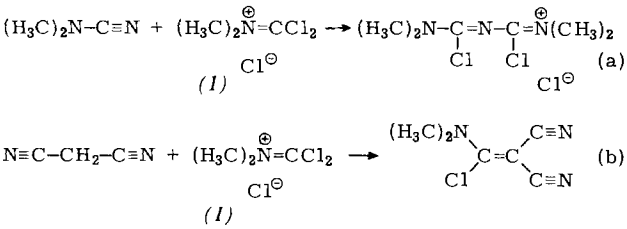
[1] *J. Tsuji, H. Takayanagi*, Tetrahedron Lett. *1976*, 1365.
[2] *O. Hayaishi*, Molecular Mechanisms of Oxygen Activation. Academic Press, New York 1974. p. 8.
[3] US-Pat. 3337578; Chem. Abstr. *68*, P95820h (1968).
[4] *M. Halman, S. Pinchas*, J. Chem. Soc. *1958*, 1703.

[*] Dipl.-Chem. C. A. Sprecher and Priv.-Doz. Dr. A. D. Zuberbühler
Institut für Anorganische Chemie der Universität
CH-4056 Basel, Spitalstrasse 51 (Switzerland)
[**] We thank the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (grant No. 2.0500.73) for financial support.

Reactions of Phosgeniminium Salts with Nitriles, Imino Ethers and Imidoyl Chlorides—Synthesis of 4,6-Dichloro-2-(dialkylamino)pyrimidines[1]

By *Bernard Stelander* and *Heinz Günter Viehe*[*]

Phosgeniminium salts *(1)* react with nitriles, depending on their substituents, either by addition to the CN triple bond [Equation (a)][2,3] or by condensation with the CH_2 group alpha to the CN group, if this is activated by a further substituent [Equation (b)][3]. Thus, acetonitrile *(2a)* does not condense with *(1)*, even in the presence of bases such as tertiary amines.

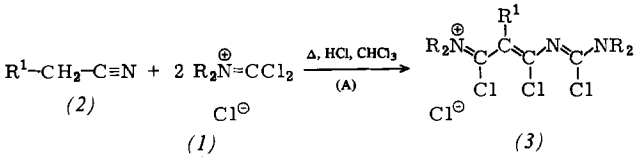


[*] B. Stelander, lic. chimie and Prof. Dr. H. G. Viehe,
Laboratoire de Chimie Organique de l'Université de Louvain
Lavoisier C3, Place L. Pasteur, 1
B – 1348 Louvain-la-Neuve (Belgium)

Table 2. Physical properties of compounds *(7)*.

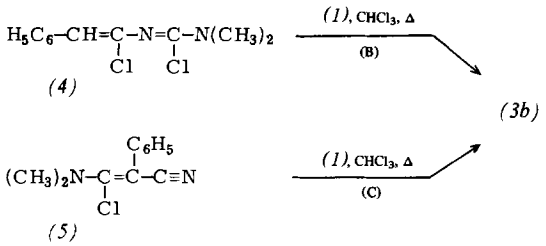
	R	R^1	Yield [%]	M.p. [°C] (b.p. [°C/torr])	^{1}H-NMR ($CDCl_3$) TMS = 0 δ[ppm]	UV (CH_2Cl_2) λ_{max} [nm]
(7a)	CH_3	H	33	53	3.33 (6H, s), 6.78 (1H, s)	246, 249, 308
(7b)	CH_3	C_6H_5	90	82—83	3.17 (6H, s), 7.18 (5H, m)	254, 260, 319
(7c)	CH_3	CH_3	84	60—61	3.10 (6H, s), 2.25 (3H, s)	246, 250, 320
(7d)	C_2H_5	C_6H_5	61	(115/0.1)	1.23 (6H, t), 3.60 (4H, q), 7.25 (5H, m)	259, 320

We have now found that acetonitrile, like its monoalkyl and monoaryl derivatives, reacts with two mols of *(1)* in the presence of hydrogen chloride to give the new 2,4,6-trichloro-1,3,7-triazaheptatrienium chlorides *(3)*[4] (Table 1).



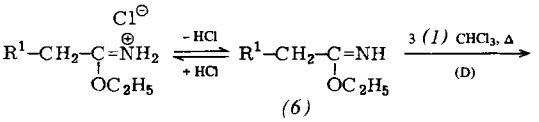
(2) *(1)* *(3)*

Compound *(3b)* is also formed in 95% and 85% yield, respectively, on reaction of *(1)* with compounds *(4)*[5] or *(5)*[6], thus suggesting the possible intermediacy of the latter in the synthesis of *(3)* from *(2)* and *(1)*.



(4) *(3b)* *(5)*

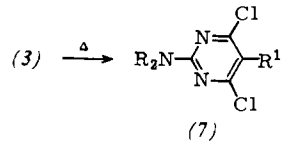
The imino ethers *(6)* react with *(1)* much faster than the nitriles *(2)*, forming compounds *(3)* in excellent yields (see Table 1).



(6)

(3) + $(H_3C)_2N$–COCl + C_2H_5Cl

The 2,4,6-trichloro-1,3,7-triazaheptatrienium chlorides *(3)* are hygroscopic solids, stable in a dry atmosphere, soluble in dichloromethane and chloroform, and insoluble in ether. They are characterized by their spectral data (Table 1) and by their pyrolysis to 4,6-dichloro-2-(dialkylamino)pyrimidines *(7)*. In each case only the symmetric isomer *(7)* is formed (see Table 2).



(7)

We have confirmed the structures of the products by two alternative unambiguous syntheses[6]. To our knowledge, only one representative *(7a)* of this class of pyrimidines is known[7]. Compounds *(7)* are chemically characterized by the two reactive chlorine atoms. Hydrolysis or aminolysis leads to barbituric acid derivatives[6].

Table 1. Physical properties of compounds *(3)*.

	R	R^1	Method	Time [h]	Yield [%]	^{1}H-NMR ($CDCl_3$) δ[ppm] (TMS = 0)	UV (CH_2Cl_2) λ_{max} [nm]
(3a)	CH_3	H	A	72	40—70	3.47 (6H, s), 3.72 (6H, s), 6.00 (1H, s)	232, 386
			D	3	85		
(3b)	CH_3	C_6H_5	A	24	40—60	3.31 (6H, s), 4.21 (6H, s), 7.43 (5H, s)	230, 278, 372
			B	3	95		
			C	3	85		
(3c)	CH_3	CH_3	A	24	40—70	2.30 (3H, s), 3.47 (6H, s), 4.17 (6H, s)	245, 365
			D	4	87		
(3d)	C_2H_5	C_6H_5	A	24	40—80	1.06—1.66 (12H, m), 3.60 (4H, q), 4.53 (4H, q), 7.43 (5H, s)	232, 276, 398
(3e)	C_2H_5	CH_3	A	24	30—57	1.27 (6H, t), 1.65 (6H, t), 2.10 (3H, s), 3.53 (4H, q), 4.37 (4H, q)	236, 370

Experimental:

Synthesis of *(3)* according to method A: 0.01 mol of *(1)* and 0.02 mols of *(2)* (excess) are refluxed in dry chloroform under a stream of gaseous hydrogen chloride until complete disappearance of *(1)* (24—72 h). The yellow solution is then concentrated in a vacuum and the residue washed three times with dry ether. The yellow solid *(3)* thus obtained is practically pure.

Synthesis of *(3)* according to methods B and C: 0.01 mol of *(1)* and 0.01 mol of *(4)* or *(5)* are refluxed in dry chloroform for three hours. Work-up is identical as for method A.

Synthesis of *(3)* according to method D: 0.03 mol of *(1)* and 0.01 mol of *(6)* are refluxed in dry chloroform for 3—4 hours. The work-up is identical as for method A.

Synthesis of *(7)*: 0.01 mol of *(3)* is heated in a bulb tube at 100—160 °C/0.1—0.01 torr. An oil is formed which readily solidifies [*(7d)* excepted]. The solid mass is recrystallized from aqueous methanol. *(7d)* can be further purified either by distillation or by column chromatography (silica gel 60/benzene).

Received: December 29, 1976 [Z 641 IE]
German version: Angew. Chem. 89, 182 (1977)

CAS Registry numbers:
(1a), 33842-02-3; *(1d)*, 59533-02-1; *(2a)*, 75-05-8; *(2b)*, 140-29-4; *(2c)*, 107-12-0; *(3a)*, 61769-93-5; *(3b)*, 61769-94-6; *(3c)*, 61769-95-7; *(3d)*, 61769-

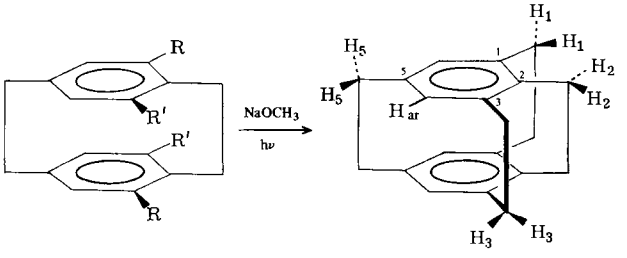
96-8; *(3e)*, 61846-69-3; *(4)*, 61769-97-9; *(5)*, 61769-98-0; *(7a)*, 5734-68-9; *(7b)*, 61769-99-1; *(7c)*, 61770-00-1; *(7d)*, 61770-01-2

[1] Phosgeniminium Chemistry Part 22.—Part 21: *M. Huys-Francotte, Z. Janousek, H. G. Viehe*, J. Chem. Res., in press.
[2] *Z. Janousek, H. G. Viehe*, Angew. Chem. *85*, 90 (1973); Angew. Chem. Int. Ed. Engl. *12*, 74 (1973); *C. Humblet*, Memoire de Licence, Université de Louvain 1972.
[3] *H. G. Viehe, Z. Janousek*, Angew. Chem. *85*, 837 (1973); Angew. Chem. Int. Ed. Engl. *12*, 806 (1973).
[4] Independent Vilsmeier reactions have recently led to analogous results: *J. Liebscher, H. Hartmann*, Collect. Czech. Chem. Commun. *41*, 1565 (1976).
[5] *E. Goffin*, Dissertation, Université de Louvain 1974.
[6] *B. Stelander*, Dissertation, Université de Louvain, planned for 1977.
[7] *W. R. Boon*, J. Chem. Soc. *1952*, 1532.

[2.2.2.2](1,2,3,5)Cyclophane[1]

By *Walter Gilb, Klaus Menke*, and *Henning Hopf*[*]

Boekelheide and *Gray* recently described[2] the synthesis of [2.2.2.2](1,2,4,5)cyclophane, the first phane in which two benzene rings are linked by four ethano bridges. Using an analogous method we have now prepared an isomer, the hydrocarbon[2.2.2.2](1,2,3,5)cyclophane *(6)*, the first cyclophane to have a consecutive arrangement of three ethano bridges. Multiply bridged cyclophanes are of interest because they should display a stronger transannular π-electron interaction than [2.2]paracyclophane. Such an enhancement of π-electron interaction should manifest itself in modified chemical and spectroscopic properties. Moreover, the geometry of the (non-planar) benzene rings should also be influenced by additional bridges, especially if they are directly adjacent to one another.



(1), R = $COOCH_3$, R' = H — *(6)*
(2), R = $COOCH_3$, R' = CH_2Cl (62%)
(3), R = CH_2OH, R' = CH_3 (42%)
(4), R = CHO, R' = CH_3 (82%)
(5), R = CH=NNHTs, R' = CH_3

The diester *(1)*[3] was alkylated with chloromethyl ethyl ether/aluminum trichloride at 70°C to give the dichloride *(2)*[4] (colorless platelets from chloroform/ether, m.p. 142°C), which was reduced with diisobutylhydridoaluminum in benzene at room temperature to the diol *(3)*[5] (colorless prisms from ethyl acetate, m.p. 197°C). Compound *(3)* was subsequently oxidized with activated manganese dioxide[6] in chloroform at room temperature to the dialdehyde *(4)*[4] (colorless prisms from carbon tetrachloride, m.p. 188°C). In a one-pot reaction, *(4)* was first transformed by treatment with tosyl hydrazide in tetrahydrofuran in the presence of catalytic amounts of hydrochloric acid into the bis-tosylhydrazone *(5)*, the sodium salt of which (addition of sodium methoxide to the reaction solution) could be directly converted into *(6)* by 22 hours' irradiation with a daylight lamp (Osram Vitalux, 300 W). Column chromatography on neutral silica gel and recrystallization from chloroform/carbon tetrachloride afforded analytically pure *(6)* (overall yield of cyclization reaction 35%) as platelets having a silky luster (m.p. 286°C, sealed tube)[4].

In its ^{1}H-NMR spectrum ($CDCl_3$/int. TMS) [2.2.2.2](1,2,3,5)cyclophane *(6)* gives sharp singlets for the bridge protons H_2 at $\delta = 2.67$ (4H) and H_5 at $\delta = 2.88$ (4H), whereas the protons of the "flanking" bridges (H_1 and H_3) give rise to an AA'BB' multiplet (8H) between $\delta = 3.33$ and 2.55. The signal of the aromatic protons H_{ar} ($\delta = 5.96$, 4H, s) corresponds to that for the 1,2,4,5 isomer[2], but is shifted upfield relative to the H_{ar} signals of [2.2]paracyclophane ($\delta = 6.46$) and [2.2.2](1,2,4)-cyclophane ($\delta = 6.41$ to 6.08)[1]. Whether it is permitted to conclude that *(6)* possesses stronger cyclohexatriene character on the basis of these findings can only be decided after study of the chemical behavior of *(6)*. The cyclophane strongly resembles the 1,2,4,5 isomer in its vibrational [KBr; 3020 (w), 2955 (s), 2926 (s), 2890 (s), 2857 (s), 900 (m), 626 (m), and 610 cm^{-1} (m)] and electronic spectrum [ethanol; $\lambda_{max} = 308$ ($\varepsilon = 195$) 287 (sh, 370), 248 (sh, 2030), 222 (sh, 14100), and 207 nm (71300)][2,7].

Received: December 10, 1876 [Z 629 IE]
German version: Angew. Chem. *89*, 177 (1977)

CAS Registry numbers:
(1), 53922-65-9; *(2)*, 61477-00-7; *(3)*, 61477-01-8; *(4)*, 61477-02-9; *(5)*, 61477-03-0; *(5)*, disodium salt, 61520-78-3; *(6)*, 61477-04-1; chloromethyl methyl ether, 107-30-2; tosyl hydrazide, 1576-35-8; sodium methoxide, 124-41-4

[*] Prof. Dr. H. Hopf, Dipl.-Chem. K. Menke, W. Gilb
Institut für Organische Chemie der Universität
Am Hubland, D-7800 Würzburg (Germany)

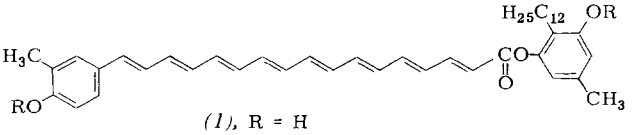
[1] Cyclophanes, Part 5. This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft, and performed in part at the Institut für Organische Chemie der Universität Karlsruhe.—Part 4: *S. Trampe, K. Menke, H. Hopf*, Chem. Ber. *110*, 371 (1977).

[2] *R. Gray, V. Boekelheide*, Angew. Chem. *87*, 138 (1975); Angew. Chem. Int. Ed. Engl. *14*, 107 (1975).
[3] *H. Hopf, F. Th. Lenich*, Chem. Ber. *107*, 1891 (1974).
[4] The new substances gave correct elemental analyses; their structural assignment is based on NMR, IR, UV, and mass spectra.
[5] During this reaction isobutyl groups are also transferred of the original chloromethyl substituent.
[6] *J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, T. Walker*, J. Chem. Soc. *1952*, 1094.
[7] We are grateful to Prof. *V. Boekelheide* for kindly supplying spectra for comparison, communicating experimental details, and numerous discussions.

Total Synthesis of Flexirubin Dimethyl Ether[**]

By *Hans Achenbach* and *Joachim Witzke*[*]

Flexirubin *(1)* the pigment of the "gliding bacterium" *Flexibacter elegans*, which was formely regarded as having a carotenoid structure, is the first member of a new class of bacterical pigments[1] which have meanwhile also been detected in the related genus *Cytophaga*[2]. The structure of the flexirubins is characterized by non-isoprenoid ω-phenylpolyenecarboxylic acids in ester type linkage with dialkylated resorcinols[3].



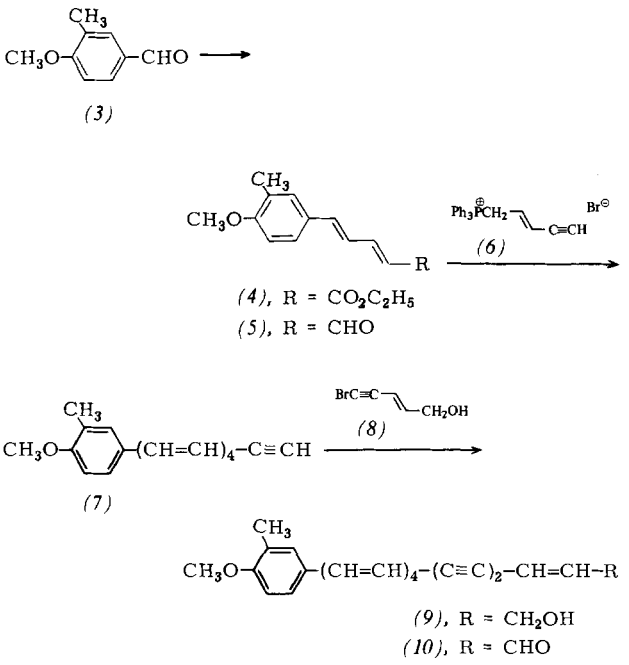
(1), R = H
(2), R = CH_3

[*] Prof. Dr. H. Achenbach, Dipl.-Chem. J. Witzke
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

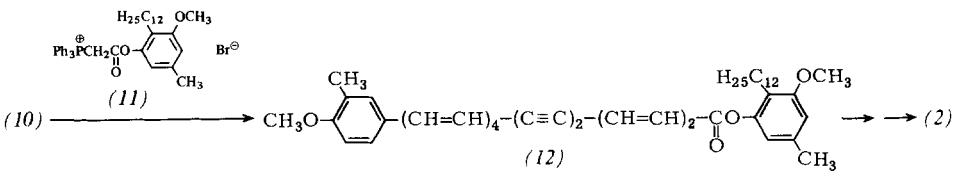
[**] Studies on the Metabolic Products of Microorganisms, Part 14. This work was supported by the Fonds der Chemischen Industrie.—Part 13: ref. [3c].

In particular, the fact that structurally similar ω-phenyl-analogous polyenoic acids of the vitamin A series display anti-tumor activity[4] prompted us to undertake the total synthesis of flexirubin dimethyl ether *(2)*.

Starting from 4-methoxy-3-methylbenzaldehyde[5] *(3)*, Wittig reaction with the phosphonium salt prepared from ethyl γ-bromocrotonate[6] initially gave the pentadienoic ester *(4)* [m.p. 92—94 °C; lit.[5] 91—93 °C] which was transformed by reduction ($LiAlH_4$) and oxidation (MnO_2) into the aldehyde *(5)* [m.p. 69—70 °C; λ_{max} 354 nm (EtOH)]. A second Wittig reaction with the phosphonium salt *(6)* derived from 1-bromo-2-penten-4-yne (from 2-penten-4-yn-1-ol[7] and Ph_3PBr_2) provides access to the decatetraenyne *(7)* [m.p. 76—79 °C; M^+ 250.1365; λ_{max} 370 nm (hexane)] which we have converted by Chodkiewicz coupling with *(8)* (from penten-4-yn-1-ol and NaOBr) into the diyne *(9)* [m.p. 158—163 °C; M^+ 330.1617; λ_{max} 397 nm (hexane); ^{1}H-NMR (180 MHz): $\delta = 2.22$ ppm (3H, s), 3.83 (3H, s), 4.2 (2H, br), 5.5—7.5 (13H, m)].



Wittig reaction of the aldehyde *(10)* [M^+ 328.1451; λ_{max} 419 nm (hexane)] (from *(9)* and MnO_2) with the phosphonium salt *(11)* yielded *(12)* [mixture of isomers: M^+ 658.4032; λ_{max} 411 nm (hexane)], thus completing the carbon skeleton of flexirubin. Compound *(11)* is accessible by esterification of bromoacetic acid with the sodium salt of the previously described compound 2-dodecyl-3-methoxy-5-methylphenol[3b] and subsequent reaction with triphenylphosphane. Catalytic



hydrogenation of *(12)* over a Lindlar catalyst and isomerization with iodine led to *(2)*[3b].

Received: January 11, 1977 [Z 647 IE]
German version: Angew. Chem. *89*, 198 (1977)

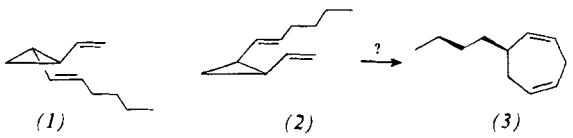
CAS Registry numbers:
(2), 60488-42-8; *(3)*, 32723-67-4; *(4)*, 61665-55-2; *(5)*, 61665-56-3; *(6)*, 61665-57-4; *(7)*, 61665-58-5; *(8)*, 52551-93-6; *(9)*, 61665-59-6; *(10)*, 61665-60-9; *(11)*, 61665-61-0; *(12)*, 61665-62-1; ethyl γ-bromocrotonate, 6065-32-3; 2-penten-4-yn-1-ol, 5557-88-0

[1] *H. Reichenbach, H. Kleinig, H. Achenbach*, Arch. Microbiol. *101*, 131 (1974).
[2] *H. Achenbach, W. Kohl, H. Reichenbach*, Arch. Microbiol., in press.
[3] a) *H. Achenbach, W. Kohl, H. Reichenbach*, Tetrahedron Lett. *1974*, 2555; b) Chem. Ber. *109*, 2490 (1976); c) Justus Liebigs Ann. Chem. *1977*, 1.
[4] *W. Bollag, H. Ruegg, G. Ryser*, DOS 2.414.619; Chem. Abstr. *82*, 111778 (1975).
[5] *A. Barns, N. Gerber*, J. Org. Chem. *26*, 4540 (1961).
[6] *F. Bohlmann*, Chem. Ber. *90*, 1519 (1957).
[7] *L. J. Haynes, I. Heilbron, E. R. H. Jones, F. Sondheimer*, J. Chem. Soc. *1947*, 1583.

Models for the Biosynthesis of Naturally Occurring Divinylcyclopropanes and Cycloheptadienes[**]

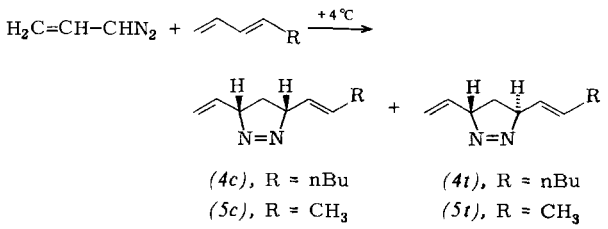
By *Manfred Schneider* and *Angelika Erben*[*]

Dictyopterenes A *(1)* and C′ *(3)* were isolated from the gametes of brown algae (Dictyopteris)[1]. The biosynthesis of *(3)* presumably proceeds *via* the *cis*-divinylcyclopropane *(2)*, which does not occur in nature. *(1)* and *(2)* are probably



formed by introduction of a methylene group from active methyl (*S*-adenosylmethionine)[2] into the corresponding 1,3,5-decatriene (from fatty acids), *(2)* being then converted by Cope rearrangement into *(3)* under the conditions of the biosynthesis (*ca.* +15 °C). *(1)* cannot be the precursor of *(3)* since it is thermally stable up to 150 °C[3].

Like *(1)* and *(3)*, monosubstituted *cis*-divinylcyclopropanes of type *(2)* ought to be readily accessible by decomposition of suitably substituted 3,5-divinyl-1-pyrazolines[4]. Participation of the Cope rearrangement in the biosynthesis of *(3)* could thus be studied on a model.



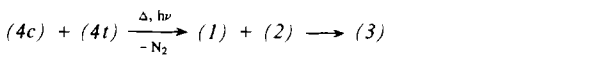
The 1,3-dipolar cycloaddition of 3-diazo-1-propene to *trans*-1,3-octadiene[5] affords the *cis*- and *trans*-3-(*trans*-1-hexenyl)-5-vinyl-1-pyrazolines *(4c)* and *(4t)*. The *cis*- and *trans*-3-(*trans*-1-propenyl)-5-vinyl-1-pyrazolines *(5c)* and *(5t)* are formed

[*] Dr. M. Schneider, A. Erben
Institut für Chemie der Universität Hohenheim
Postfach 106, 7000 Stuttgart 70 (Germany)

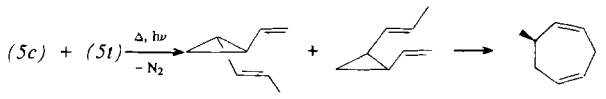
[**] We thank Dr. *W. Pickenhagen* (Firmenich & Cie., Geneva) for the spectra of *(1)* and *(3)*.—This work was supported by the Deutsche Forschungsgemeinschaft.

analogously by addition to *trans*-1,3-pentadiene. The cycloaddition proceeds exclusively as shown below, affording the 1-pyrazolines in the isomeric ratio 1:1 (NMR integration).

(4c) and *(4t)* decompose thermally (30—60 °C) and photochemically (0 °C, *n*-pentane, Pyrex filter, Hanau TQ 150) with formation of *trans*-1-(*trans*-1-hexenyl)-2-vinylcyclopropane *(1)* and 6-butyl-1,4-cycloheptadiene *(3)*. *trans*-1-(*trans*-1-Propenyl)-2-vinylcyclopropane *(1a)* and 6-methyl-1,4-cycloheptadiene *(3a)* are obtained in an analogous way from *(5c)* and *(5t)*.



Δ	41.5%	58.5%
hν	55.5%	44.5%



	(1a)	*(2a)*	*(3a)*
Δ	35%		65%
hν	60%		40%

All spectroscopic data of the natural products *(1)* and *(3)*, readily accessible in this way, were identical with those of the compounds isolated and obtained by multistep synthesis[6,7]. *(1a)* and *(3a)* have been unequivocally identified[4]. Low-temperature photolysis of *(4c)*+*(4t)* at −45 °C[7] affords exclusively *(1)* and *cis*-1-(*trans*-1-hexenyl)-2-vinylcyclopropane *(2)*. In an analogous way the low-temperature photolysis of *(5c)*+*(5t)* leads to *(1a)* and *cis*-1-(*trans*-1-propenyl)-2-vinylcyclopropane *(2a)*. The novel compounds *(2)* and *(2a)* are stable for several hours up to −20 °C, and rearrange quantitatively at 0—20 °C into the 1,4-cycloheptadienes *(3)* and *(3a)*, respectively. Both reactions can be followed directly by ^{1}H-NMR spectroscopy by observing the allylic protons of *(3)* (δ=2.18 and 2.86 ppm) and *(3a)* (δ=2.25 and 2.83 ppm).

Experimental:

A solution of *N*-allyl-*N*-nitrosourea *(6g)* in triethylene glycol (50 ml) is added dropwise with stirring at 20 °C and 15 torr to a solution of sodium *(6g)* in triethylene glycol (100 ml). The 3-diazo-1-propene that is formed (*ca.* 10 mmol, 0.7 g) is condensed at −78 °C in a cold trap containing 30 mmol *trans*-1,3-octadiene or -pentadiene. The resulting deep-red mixture is stored at +4 °C until completely decolorized (*ca.* 4 days), taken up in *n*-pentane and washed with ice-water to remove the pyrazole. After drying, all volatile components are distilled off at 0 °C/15 torr. The pyrazolines *(4c)*+*(4t)* (1.5 mmol) or *(5c)*+*(5t)* (1.4 mmol) so obtained are photolyzed at 0 °C without further purification in a forced circulator (Hanau T 150, pyrex filter) or thermolyzed in *n*-heptane at 30—60 °C. After distillation, the products *(1)* and *(3)*, or *(1a)* and *(3a)*, are isolated by gas chromatography (3 m 10% OV17 on Chromosorb W).

Received: January 17, 1977 [Z 651 IE]
German version: Angew. Chem. 89, 187 (1977)

CAS Registry numbers:
(1), 50265-47-9; *(1a)*, 61649-93-2; *(2)*, 50265-49-1; *(2a)*, 61688-32-2; *(3)*, 22735-58-6; *(3a)*, 61689-14-3; *(4c)*, 61649-94-3; *(4t)*, 61688-33-3; *(5c)*, 61649-95-4; *(5t)*, 61688-34-4; 3-diazo-1-propane, 2032-04-4; *trans*-1,3-octadiene, 39491-65-1; *trans*-1,3-pentadiene, 2004-70-8

[1] *L. Jaenicke, D. G. Müller*, Fortschr. Chem. Org. Naturst. *30*, 61 (1973).
[2] *J. H. Law*, Acc. Chem. Res. *4*, 199 (1971).
[3] The transformation can be achieved photochemically only by photosensitized irradiation with short-wave UV: *W. Pickenhagen, F. Näf, G. Ohloff, P. Müller, J.-C. Perlberger*, Helv. Chim. Acta *56*, 1868 (1973).
[4] *M. Schneider, J. Rebell*, J. Chem. Soc. Chem. Commun. *1975*, 283; *M. Schneider*, Angew. Chem. *87*, 717 (1975); Angew. Chem. Int. Ed. Engl. *14*, 707 (1975).
[5] Prepared by dehydration ($KHSO_4$, 160 °C) of 3-octen-1-ol (from acrolein and *n*-pentylmagnesium bromide) and subsequent fractional distillation. Small amounts of the *cis* form are isomerized to the *trans* form by I_2-catalyzed irradiation.
[6] *R. E. Moore, J. A. Pettus, Jr., J. Mistysyn*, J. Org. Chem. *39*, 2201 (1974); *G. Ohloff, W. Pickenhagen*, Helv. Chim. Acta *52*, 880 (1969).
[7] The irradiation was carried out directly in the NMR apparatus (Bruker HX 90 R with modified probe) using a quartz light guide; lamp: Philips SP1000W; filter UG1.

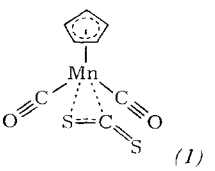
Intramolecular Mobility in CS_2 Complexes of Manganese[**]

By *Max Herberhold, Margot Süss-Fink*, and *Cornelius G. Kreiter*[*]

Considerable speculation still surrounds the coordinative bonding of carbon disulfide in transition metal complexes[1] since the structures of only few molecules are known. We have made the surprising observation that the two cyclopentadienylmanganese complexes $CpMn(CO)_2(CS_2)$ *(1)* and $[CpMn(CO)_2]_2(CS_2)$ *(2)* give temperature-dependent NMR spectra. Thence it is concluded that:

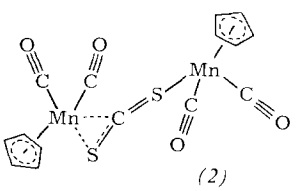
1) The mononuclear complex *(1)* possesses an η^2-coordinated CS_2 ligand which undergoes hindered motion in solution.

2) The dinuclear complex *(2)* contains a new kind of CS_2 bridge and is a fluxional molecule.



(1)

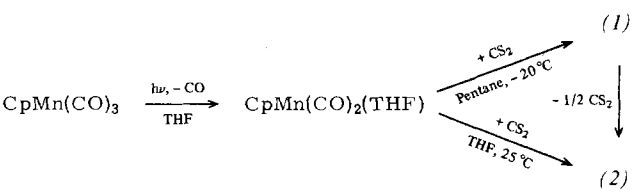
ν(C≡O) 2012,1957 cm^{-1} (THF)



(2)

ν(C≡O) 2021,1969; 1928,1871 cm^{-1} (THF)

Compounds *(1)* and *(2)* can be prepared by photolysis of $CpMn(CO_3)$ in tetrahydrofuran solution (THF) and subsequent reaction of the labile THF complex $CpMn(CO)_2(THF)$ with CS_2[2]:



In solution *(1)* slowly loses CS_2 to form *(2)*. Contrary to earlier reports[3], we were unable to observe the reverse reaction.

The compositions of *(1)* and *(2)* are confirmed by elemental analysis and mass spectra. Their structures follow from NMR

[*] Doz. Dr. M. Herberhold, Dipl.-Chem. M. Süss-Fink, Doz. Dr. C. G. Kreiter
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *M. Süss-Fink* is indebted to the Cusanus Foundation for a graduate study grant.

and IR spectra, which indicate a pronounced acceptor capacity of the CS_2 ligand[4]. We assume that CS_2 is coordinated like an olefin *via* a C=S double bond in *(1)*; on complexation, the molecule which is linear in the free state should experience bending, such as has been detected by X-ray analysis of $(Ph_3P)_2M(CS_2)$ (M = Pt, Pd)[5].

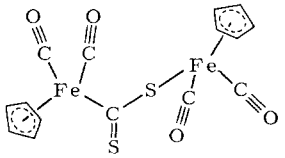
Table 1. ^{1}H- and ^{13}C-NMR spectra of the CS_2 complexes *(1)* and *(2)*.

Complex	T[K]	^{1}H-NMR [a] δ(Cp)	^{13}C-NMR [a] δ(Cp)	δ(CO)	δ(CS_2)
(1)	310	5.10			
	231		92.5	229.3	252.7
	169		92.6	228.4 (π)	254.1
				230.2 (π)	
(2)	310	4.89	87.9	231.5	
	210	5.33, 3.74			
	179 [b]		83.6, 92.7	228.1 (π)	251.5
				229.0 (π)	
				234.4 (σ)	

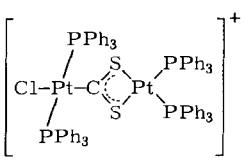
[a] In [D_6]-acetone; δ values [ppm] *vs.* TMS int.
[b] In [D_6]-acetone/THF.

A rigid molecule having the structure *(1)* must contain two non-equivalent CO ligands; however, only one CO signal is observed down to 220 K in the ^{13}C-NMR spectrum. The expected signal splitting confirming structure *(1)* is not observed until below *ca.* 200 K. This reversible splitting can be explained in terms of a hindered rotation of the CS_2 ligand about the axis of the coordinative bond which becomes slower with decreasing temperature ($\Delta G^{\ddagger}_{190} = 9.5 \pm 0.1$ kcal/mol; $\Delta G^{\ddagger}$ values of 8 to 12 kcal/mol are characteristic for the analogous rotation of monoolefin ligands in $CpMn(CO)_2L$ complexes[6]).

In addition to two C≡O bands which are shifted slightly relative to those of *(1)*, the IR spectrum of the dinuclear complex *(2)* contains two additional C≡O stretching absorptions. It may be deduced from their relatively low frequency that *(1)* is bonded as a donor ligand *via* a lone pair of the non-coordinated sulfur atom to another $[CpMn(CO)_2]$ fragment. In contrast to the dithiocarboxylato-bridged complexes *(3)*[7a] and *(4)*[7b], *(2)* appears to contain a true carbon disulfide bridge.



(3)



(4)

At room temperature the two differently coordinated $[CpMn(CO)_2]$ moieties cannot be distinguished in the ^{1}H- and ^{13}C-NMR spectra of *(2)*: only one signal each is registered for the Cp and CO ligands (Table 1). An intramolecular motion is clearly taking place in which the two $[CpMn(CO)_2]$ fragments rapidly exchange their sites and functions. This "degenerate σ/π bond isomerization" is completely frozen at 210 K, and line shape analysis of the ^{1}H-NMR cyclopentadienyl signals affords $\Delta G^{\ddagger}_{250} = 12.4 \pm 0.1$ kcal/mol. At even lower temperature (*ca.* 180 K) the rotation of the $CpMn(CO)_2(CS_2)$ "ligand" is also seen to be frozen in the ^{13}C-NMR spectrum, only the CO signal of the $CpMn(CO)_2$ fragment engaged in olefinic complexation undergoing splitting.

In contrast to *(2)*, the iron complex *(3)* does not give a temperature-dependent ^{1}H-NMR spectrum. Two cyclopentadienyl signals are always observed, until the complex decomposes into $[CpFe(CO)_2]_2$ and CS_2 at *ca.* 370 K.

Procedure[8]:

(Carbon disulfide)dicarbonyl(η-cyclopentadienyl)manganese (1)[2]:

To $CpMn(CO)_2(THF)$[9] (1.5 mmol) at −20°C is added cooled pentane (80 ml). After addition of CS_2 (2 ml) the solution is slowly warmed to room temperature and stirred for 5 min. The solvent is drawn off at −20°C and $CpMn(CO)_3$ sublimed off at room temperature under high vacuum. The residue is taken up in cooled pentane; after filtration (G3 frit) the solvent is drawn off at −20°C and compound *(1)* dried *in vacuo* at −10°C. Orange-red crystals, dec. at *ca.* 65°C (under argon); yield 0.10 g (27%).

(μ-Carbon disulfide)bis[dicarbonyl(η-cyclopentadienyl)manganese] (2)[2]:

CS_2 (2 ml) is added to the red solution of $CpMn(CO)_2(THF)$ formed on photolysis of $CpMn(CO)_3$ (0.306 g, 1.5 mmol) in THF and the mixture stirred for 2 h. $CpMn(CO)_3$ and *(1)* are washed out of the residue of the reaction solution. Recrystallization from ether gives dark red *(2)*, dec. at *ca.* 118°C (under argon): yield 0.13 g (40%).

Received: December 13, 1976 [Z 634a IE]
German version: Angew. Chem. *89*, 191 (1977)

CAS Registry numbers:
(1), 49716-49-6; *(2)*, 61483-85-0; $CpMn(CO)_2(THF)$, 12093-26-4; ^{13}C, 14762-74-4

[1] Review: *I. S. Butler, A. E. Fenster*, J. Organomet. Chem. *66*, 161 (1974).
[2] Both *(1)* and *(2)* were first observed in the reaction of the cyclooctene complex $CpMn(CO)_2(C_8H_{14})$ [9] with CS_2 and characterized by their IR solution spectra (in CS_2) [3]. However, *(1)* could not be isolated; *(2)* was formed in only minute amounts and was mistaken for a dimer of *(1)*.
[3] *A. E. Fenster, I. S. Butler*, Inorg. Chem. *13*, 915 (1974).
[4] *M. Herberhold, M. Süss-Fink*, Angew. Chem. *89*, 192 (1977); Angew. Chem. Int. Ed. Engl. *16*, 194 (1977).
[5] *R. Mason, A. I. M. Rae*, J. Chem. Soc. *A 1970*, 1767; *T. Kashiwagi, N. Yasuoka, T. Ueki, N. Kasai, M. Kakudo, S. Takahashi, N. Hagihara*, Bull. Chem. Soc. Jpn. *41*, 296 (1968).
[6] *H. Alt, M. Herberhold, C. G. Kreiter, H. Strack*, J. Organomet. Chem. *102*, 491 (1975); and references cited therein.
[7] a) *J. E. Ellis, R. W. Fennell, E. A. Flom*, Inorg. Chem. *15*, 2031 (1976); b) *J. M. Lisy, E. D. Dobrzynski, R. J. Angelici, J. Clardy*, J. Am. Chem. Soc. *97*, 656 (1975).
[8] All operations performed under argon. A mercury vapor lamp (Q 700, Quarzlampengesellschaft Hanau) was used for the photolysis of $CpMn(CO)_3$. Yields not optimized.
[9] *E. O. Fischer, M. Herberhold*, Experientia Suppl. *IX*, 259 (1964).

Acceptor Function of η^2-Bonded CS_2 Ligands[**]

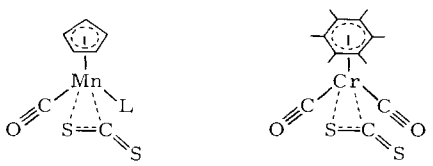
By *Max Herberhold* and *Margot Süss-Fink*[*]

Carbon monoxide is regarded as the prototype of all "acceptor ligands". There are only few two-electron ligands which surpass CO in its ability to withdraw charge from a central metal; apart from CS and PF_3 these also include dienophilic olefins such as tetracyanoethylene (TCNE) and maleic anhydride (MA). We have now discovered that η^2-coordinated carbon disulfide is also a stronger acceptor than CO. This follows from the IR and ^{1}H-NMR spectra of the cyclopentadienylmanganese complexes $CpMn(CO)_2(CS_2)$ *(1)*[1],

[*] Doz. Dr. M. Herberhold, Dipl.-Chem. M. Süss-Fink
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *M. Süss-Fink* is indebted to the Cusanus Foundation for a graduate study grant.

$[CpMn(CO)_2]_2(CS_2)$ *(2)*[11], $CpMn(CO)(PMe_3)(CS_2)$ *(3)*, and the arenechromium complexes $(ar)Cr(CO)_2(CS_2)$ *(4)* and *(5)*.



(1), L = CO
(3), L = $P(CH_3)_3$

(4), ar = Hexamethylbenzene
(5), ar = Mesitylene

The IR spectra of the complexes *(1)*—*(5)* (Table 1) display a characteristic $\nu(C{=}S)$ absorption of the CS_2 ligand in the region from 1150 to 1220 cm^{-1} (cf.[12]). The frequency of this band is significantly lower than that of the $\nu(C{\equiv}S)$ absorption of the thiocarbonyl complexes formed from *(1)* and *(3)*—*(5)* by desulfuration with a tertiary phosphane[13] (PPh_3, PMe_3).

Procedure[8]:

(Carbon disulfide)carbonyl(η-cyclopentadienyl)trimethylphosphanemanganese (3): A solution of $CpMn(CO)_2(PMe_3)$[9] (0.25 g, 1 mmol) and CS_2 (2 ml) in pentane (80 ml) is irradiated for 1 h. The crude product *(3)* is recrystallized from THF/hexane. Red-brown crystals, dec. 132 °C (under argon); yield 0.045 g (15%).

Arene(carbon disulfide)dicarbonylchromium (4) and (5): Several hours' irradiation of a pentane solution (100 ml) of arenetricarbonylchromium (1.5 mmol) and cyclooctene (2 ml) affords the intermediate complex $(ar)Cr(CO)_2(C_8H_{14})$. After addition of CS_2 (2 ml) the mixture is stirred until $(ar)Cr(CO)_2(CS_2)$ is deposited as a sparingly soluble precipitate. Recrystallization from THF/hexane furnishes $(C_6Me_6)Cr(CO)_2(CS_2)$, *(4)*, rust-colored crystals, dec. 140 °C (under argon); yield 0.06 g (12%), or $(C_6H_3Me_3)Cr(CO)_2(CS_2)$, *(5)*, dark brown, dec. 101 °C (under argon), yield 0.19 g (40%).

Received: December 13, 1976 [Z 634b IE]
German version: Angew. Chem. 89, 192 (1977)

Table 1. IR and ^{1}H-NMR data of the CS_2 complexes *(1)*—*(5)* and related compounds.

Complex	IR			^{1}H-NMR [d]	
	ν(CO) [a] [cm^{-1}]	k(CO) [b] [mdyn/Å]	ν(CS) [c] [cm^{-1}]	δ(Ring) [ppm]	δ(Me) [ppm]
$CpMn(CO)_3$	2018 1931	15.52		4.96	
$CpMn(CO)_2(CS_2)$ *(1)*	2012 1957	15.87	1215	5.10	
$[CpMn(CO)_2]_2(CS_2)$ *(2)*	2021 1969	16.08	1182	4.89	
	1928 1871	(14.57)			
$CpMn(CO)_2(CS)$	2003 1947	15.76	1266 [e]		
$CpMn(CO)_2(PMe_3)$	1922 1858	14.43		4.48 [f]	1.44 [g]
$CpMn(CO)(PMe_3)(CS_2)$ *(3)*	1914	14.80	1152	4.72 [h]	1.74 [i]
$[C_6Me_6]Cr(CO)_3$	1944 1864	14.44		—	2.23
$[C_6Me_6]Cr(CO)_2(CS_2)$ *(4)*	1944 1889	14.84	1150	—	2.26
$[C_6H_3Me_3]Cr(CO)_3$	1955 1878	14.64		5.17	2.21
$[C_6H_3Me_3]Cr(CO)_2(CS_2)$ *(5)*	1956 1901	15.02	1150	5.77	2.26
$[C_6H_3Me_3]Cr(CO)_2(CS)$	1950 1900	14.97	1188	5.40	2.24

[a] In THF solution, calibration with polystyrene film.
[b] Cotton-Kraihanzel force constant [4], calculated from the CO stretching frequencies in THF solution.
[c] In KBr.
[d] In $[D_6]$-acetone, *vs.* TMS int.; JEOL C-60 HL, range 1080 Hz.
[e] In CS_2 solution [3].
[f] $^3J(P,H)$ 2.2 Hz.
[g] $^2J(P,H)$ 8.9 Hz.
[h] $^3J(P,H)$ 1.9 Hz.
[i] $^2J(P,H)$ 10.1 Hz.

The expected number of C≡O stretching vibrations is observed in each case. However, comparison of the force constants[14] k(C≡O) shows that replacement of a CO ligand by CS_2 always leads to an increase of the k(C≡O) values of the remaining CO ligands. This means that CS_2 withdraws more charge from the metal than the originally coordinated CO group. A further criterion for the greater acceptor capacity of the CS_2 ligand relative to CO is provided by the ^{1}H-NMR spectrum: the singlet of the aromatic ring protons experiences a downfield shift on replacement of a CO ligand by CS_2. This effect can be explained by assuming that CS_2 reduces the charge density between the metal and the π-bonded ring. Thus CS_2 is a better acceptor ligand than CO, and in this respect proves to be comparable, for instance, with the ligands L=CS[3], PF_3[5], TCNE[6], or MA[7] in the series of $CpMn(CO)_2L$ complexes.

The pronounced acceptor strength of the CS_2 ligand in *(1)* to *(5)* is a convincing argument in favor of η^2-olefin-type coordination of CS_2 *via* a C=S double bond (cf.[11]).

CAS Registry numbers:
(1), 49716-49-6; *(2)*, 61483-85-0; *(3)*, 61483-86-1; *(4)*, 61505-86-0; *(5)*, 61483-87-2; $CpMn(CO)_3$, 12079-65-1; $CpMn(CO)_2(CS)$, 31741-76-1; $CpMn(CO)_2(PMe_3)$, 12276-09-4; $[C_6Me_6]Cr(CO)_3$ 12088-11-8; $[C_6H_3Me_3]Cr(CO)_3$, 12129-67-8; $[C_6H_3Me_3]Cr(CO)_2(CS)$, 61483-88-3

[1] *M. Herberhold, M. Süss-Fink, C. G. Kreiter*, Angew. Chem. *89*, 191 (1977); Angew. Chem. Int. Ed. Engl. *16*, 193 (1977).
[2] *I. S. Butler, A. E. Fenster*, J. Organomet. Chem. *66*, 161 (1974).
[3] *A. E. Fenster, I. S. Butler*, Inorg. Chem. *13*, 915 (1974).
[4] *F. A. Cotton, C. S. Kraihanzel*, J. Am. Chem. Soc. *84*, 4432 (1962).
[5] Cf. *J. Müller, K. Fenderl, B. Mertschenk*, Chem. Ber. *104*, 700 (1971); *Th. Kruck, V. Krause*, Z. Naturforsch. *27b*, 302 (1972).
[6] *M. Herberhold*, Angew. Chem. *80*, 314 (1968); Angew. Chem. Int. Ed. Engl. *7*, 305 (1968).
[7] *M. Herberhold, C. R. Jablonski*, J. Organomet. Chem. *14*, 457 (1968); Chem. Ber. *102*, 778 (1969).
[8] All operations performed under argon. A mercury vapor lamp (Q 700, Quarzlampengesellschaft Hanau) was used for the photoreactions. The yields are not optimized.
[9] Cf. *W. Strohmeier, F.-J. Müller*, Chem. Ber. *100*, 2812 (1967).

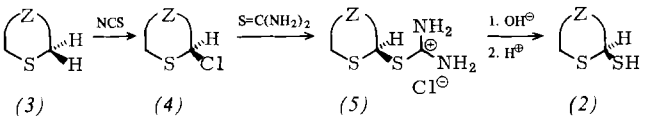
Cyclic Dithiohemiacetals—Synthesis and Properties[**]

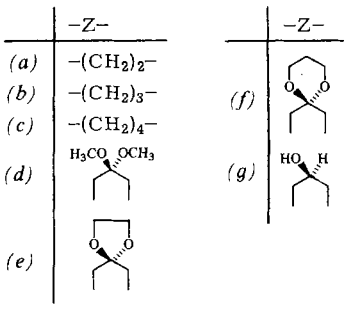
By *Hans-Joachim Gais*[*]

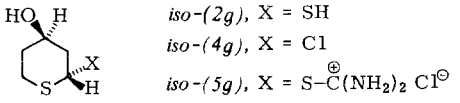
Whereas ring-chain tautomerism and the anomeric effect in cyclic hemiacetals *(1)* have long been recognized as fundamental phenomena—*e.g.* in carbohydrate chemistry[1]—nothing has yet been reported about the behavior of the sulfur analogs of *(1)*, the cyclic dithiohemiacetals *(2)*[2].



We report here on the synthesis and properties of the cyclic dithiohemiacetals *(2a)* to *(2g)* and *iso-(2g)*. They are the first representatives of this new class of compounds[3], for whose synthesis the reaction sequence *(3)*→*(4)*→*(5)*→*(2)* has proven the most advantageous.







iso-(2g), X = SH
iso-(4g), X = Cl
iso-(5g), X = S–C(NH$_2$)$_2$ Cl$^\ominus$

The α-chlorosulfides *(4a)* to *(4g)* and *iso-(4g)*, which are readily accessible from the sulfides *(3a)* to *(3g)* by reaction with *N*-chlorosuccinimide (NCS) in carbon tetrachloride[4,5], are converted by thiourea into the stable isothiouronium salts *(5a)* to *(5g)* and *iso-(5g)*. From these the dithiohemiacetals *(2a)* to *(2g)* and *iso-(2g)* can be obtained in satisfactory yields (Table 1) as colorless, liquid or crystalline compounds having a characteristic odor; they are stable over prolonged periods of time, both in substance and in solution, and only slightly sensitive to oxidation[6].

The ^{1}H-NMR spectra (Table 1), providing proof of the cyclic structure of the dithiohemiacetals *(2)*, give no indication of a ring-chain tautomerism with the open-chain mercaptothioaldehyde- *(6)* and mercaptovinylthiol-form *(7)*.

[*] Dr. H.-J. Gais
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. These investigations were carried out in part at the Department of Chemistry at Harvard University (Prof. *R. B. Woodward*).

Table 1. Cyclic dithiohemiacetals *(2a)* to *(2g)* and *iso-(2g)* [a].

(2a): Yield 41%; b.p. 135°C/15 torr; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.80$—2.45 (m, 4H), 2.38 (d, $J = 6.5$ Hz, 1H), 2.55—3.20 (m, 2H), 4.60 (sm, 1H); MS: M^+ 120(28), 87(100), 85(20), 59(17), 58(10), 53(15), 45(56).

(2b): Yield 56%; b.p. 65°C/0.1 torr; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.45$—2.40 (m, 6H), 2.11 (d, $J = 7$ Hz, 1H), 2.55—2.85 (m, 2H), 4.00 (ddd, $J_{AX} + J_{BX} = 12$ Hz, $J_{SH} = 7$ Hz, 1H); MS: M^+ 134 (27), 101 (100), 85 (17), 67 (40), 59 (30), 55 (12), 47 (12), 45 (38).

(2c): Yield 53%; b.p. 75°C/0.01 torr; ^{1}H-NMR (100 MHz, $CDCl_3$): $\delta = 1.40$—2.10 (m, 8H), 2.26 (d, $J = 6$ Hz, 1H), 2.30—3.10 (m, 2H), 4.24 (sm, 1H); MS: M^+ 148 (21), 115 (100), 87 (11), 81 (36), 73 (14), 61 (33), 60 (11), 59 (13), 55 (15), 47 (12), 45 (28).

(2d): Yield: 38%; b.p. 125°C/0.2 torr; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.30$—3.00 (m, 6H), 2.15 (d, $J = 9.5$ Hz, 1H), 3.12 (s, 3H), 3.20 (s, 3H), 3.95 (ddd, $J_{AX} + J_{BX} = 14.5$ Hz, $J_{SH} = 9.5$ Hz, 1H); MS: M^+ 194 (7), 163 (27), 162 (100), 133 (38), 129 (96), 128 (95), 127 (24), 103 (27), 101 (60), 97 (48), 88 (12), 87 (11), 86 (10), 85 (55), 75 (18), 74 (16), 73 (100), 59 (53), 58 (15), 57 (20), 55 (29), 45 (58).

(2e): Yield 69%; m.p. 55—56°C (benzene/ether); ^{1}H-NMR (100 MHz, C_6D_6): $\delta = 1.55$—1.85 (m, 3H), 197 (d, $J = 9.3$ Hz, 1H), 2.11—2.57 (m, 2H), 2.83 (ddd, 1H), 3.56 (sm, 4H), 3.92 (ddd, $J_{AX} + J_{BX} = 14.5$ Hz, $J_{SH} = 9.3$ Hz, 1H); MS: M^+ 192 (27), 159 (72), 132 (15), 131 (25), 130 (12), 99 (100), 87 (11), 86 (22), 72 (20), 59 (11).

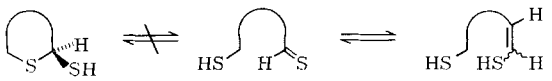
(2f): Yield 41%; m.p. 80°C (ether); ^{1}H-NMR (60 MHz, C_6D_6): $\delta = 1.05$—2.40 (m, 6H), 2.04 (d, $J = 10$ Hz, 1H), 2.60—3.20 (m, 2H), 3.50 (sm, 4H), 4.05 (ddd, $J_{AX} + J_{BX} = 14.5$ Hz, $J_{SH} = 10$ Hz, 1H); MS: M^+ 206 (33), 173 (78), 172 (35), 146 (45), 145 (50), 144 (16), 115 (60), 113 (100), 100 (29), 85 (50), 86 (22), 73 (30), 71 (10), 59 (30), 58 (17), 55 (43), 45 (35).

(2g): Yield 28%; b.p. 120°C/0.3 torr; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.29$—2.90 (m, 6H), 2.26 (d, $J = 9$ Hz, 1H), 3.36 (s, 1H), 3.57 (tt, 1H), 3.86 (ddd, $J_{AX} + J_{BX} = 14.8$ Hz, $J_{SH} = 9$ Hz, 1H); MS: M^+ 150 (25), 117 (100), 99 (15), 97 (10), 89 (25), 88 (10), 87 (10), 75 (40), 73 (55), 61 (15), 60 (15), 59 (15), 58 (11), 57 (15), 45 (25); IR (CCl_4): 3500, 3595 cm^{-1}.

iso-(2a): Yield 41%; b.p. 120°C/0.3 torr; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.70$—3.20 (m, 6H), 2.18 (d, $J = 8$ Hz, 1H), 3.00 (s, 1H), 4.15 (sm, 1H), 4.42 (sm, 1H); MS: M^+ 150 (4), 117 (100), 99 (10), 89 (25), 75 (32), 73 (63), 61 (15), 59 (15), 58 (10), 45 (30); IR (CCl_4): 3500, 3595 cm^{-1}.

[a] Yields w. r. t. *(3a)* to *(3g)*; b.p. on bulb-tube distillation; mass spectra: relative intensity in %.

In accordance with this finding, and in contrast to *(1)*, the diastereomeric 2-mercapto-1-thia-4-cyclohexanols *(2g)*



and *iso-(2g)* are configurationally stable[7] and do not undergo mutual transformation, even in the presence of acids or bases. Preliminary ^{1}H-NMR investigations of the conformational equilibrium in *(2a)* to *(2g)* and *iso-(2g)* provide evidence of an anomeric effect comparable in magnitude to that found in cyclic dithioacetals[8]. Interestingly, however, *(2d)* to *(2g)* exist almost exclusively in the conformation with equatorial arrangement of the mercapto group.

Experimental:

(2e): *N*-Chlorosuccinimide (0.17 mol) is added with stirring to a solution of *(3e)* (0.16 mol) in carbon tetrachloride (400 ml) at 0°C. After 2 h at 0°C—a ^{1}H-NMR spectrum of the reaction solution indicates the almost quantitative formation of *(4e)* [(60 MHz, CCl_4): $\delta = 1.74$–2.40 (m, 4H), 2.56–3.00 (m, 2H), 3.96 (s, 4H), 4.98 (dd, $J_{AX} + J_{BX} = 14$ Hz, 1H)]—the reaction mixture is filtered and treated at 0°C with a solution of thiourea (0.17 mol) in anhydrous acetone (300 ml). Filtration and washing with acetone yields 34.1 g (79%) of crystalline *(5e)*, m.p. 115–116°C, which is dissolved in 100 ml water and treated dropwise at 0°C with a solution of sodium hydroxide (0.36 mol) in water (80 ml). After 2 h at 0°C the solution is acidified with ice-cold 2 N sulfuric acid, extracted with di-

chloromethane, and the organic phase washed with saturated $NaHCO_3$ solution and evaporated to dryness. The residue is dissolved in a little dichloromethane and filtered with dichloromethane/*n*-hexane (1:1) over silica gel 60 (Merck). Evaporation to dryness and recrystallization of the residue from benzene/ether affords 21 g (87%) of colorless crystals, m.p. 55—56 °C.

Received: December 9, 1976 [Z 628 IE]
German version: Angew. Chem. 89, 201 (1977)

CAS Registry numbers:
(2a), 61477-08-5; *(2b)*, 61477-09-6; *(2c)*, 61477-10-9; *(2d)*, 61477-11-0; *(2e)*, 61477-12-1; *(2f)*, 61477-13-2; *(2g)*, 61477-14-3; *iso-(2g)*, 61477-15-4; *(3a)*, 110-01-0; *(3b)*, 1613-51-0; *(3c)*, 4753-80-4; *(3d)*, 61477-16-5; *(3e)*, 42850-68-0; *(3f)*, 61010-86-4; *(3g)*, 29683-23-6; *(4a)*, 22342-03-6; *(4b)*, 22342-04-7; *(4c)*, 22342-10-5; *(4d)*, 61477-17-6; *(4e)*, 61477-18-7; *(4f)*, 61477-19-8; *(4g)*, 61477-20-1; *iso-(4g)*, 61477-21-2; *(5a)*, 61477-22-3; *(5b)*, 61477-23-4; *(5c)*, 61477-24-5; *(5d)*, 61477-25-6; *(5e)*, 61477-26-7; *(5f)*, 61491-11-0; *(5g)*, 61477-27-8; *iso-(5g)*, 61477-28-9; *N*-chlorosuccinimide, 128-09-6; thiourea, 62-56-6

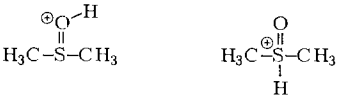
[1] *J. F. Stoddart*: Stereochemistry of Carbohydrates. Wiley-Interscience, New York 1971.
[2] Little is known about the behavior of cyclic monothiohemiacetals. Cf. *T. Sheradsky* in *S. Patai*: The Chemistry of the Thiol Group. Wiley, London 1974, Vol. 2, p. 685 and literature cited therein; *M. G. Missakian, R. Ketcham, A. R. Martin*, J. Org. Chem. *39*, 2010 (1974).
[3] For the synthesis of acyclic dithiohemiacetals, cf. *H. G. Peer, A. van der Heijden, S. B. Tjan, T. L. von Orden*, Synth. Commun. *1*, 277 (1971) and literature cited therein.
[4] *D. L. Tuleen, R. H. Bennett*, J. Heterocycl. Chem. *6*, 115 (1969).
[5] The acetate of *(3g)* was used as starting material for the synthesis of *(2g)* and *iso-(2g)*.
[6] Correct elemental analyses were recorded for *(2a)* to *(2g)* and *iso-(2g)*.
[7] The diastereoisomeric (7-mercapto-1,5-dioxa-8-thiaspiro[5.5]undec-10-yl)methanols are also configurationally stable. *K. Tatsuta*, Keiso University, Hiyushi, Yokohama (Japan), private communication.
[8] *N. S. Zefirov, V. S. Blagoveshchenskii, I. V. Kazimirchik, O. P. Yakovleva*, J. Org. Chem. (USSR) *7*, 599 (1971); *M. Oki, T. Sugawara, H. Iwamura*, Bull. Chem. Soc. Jpn. *47*, 2457 (1974).

Site of Protonation of Dimethyl Sulfoxide.—Raman Spectroscopic Data[**]

By *Manfred Spiekermann* and *Bernhard Schrader*[*]

To understand the mechanism of acid catalyzed reactions of sulfoxides, both the position of the acid-base equilibrium as well as the location of the proton in the first step of the reaction must be known[1].

Dimethyl sulfoxide *(1)* contains two potentially basic centers in the S=O group. Consequently a protonation of the oxygen atom *(1a)* or the sulfur atom *(1b)* would be possible:



(1a) *(1b)*

Investigations into the actual location of the proton in protonated *(1)* with the aid of NMR spectroscopy have led to contradictory findings[2,3].

Analysis of the vibrational spectra ought to further clarify the problem. IR spectroscopy would be better suited for the detection of OH groups and Raman spectroscopy for the detection of SH groups[4]. Great experimental difficulties are met with in recording the IR spectra of superacids; added to this the superacid itself contains OH groups.

We have investigated the Raman spectra of *ca.* 30 mol% solutions of *(1)* and of dimethyl sulfide *(2)* in 100% magic acid (HSO_3F—SbF_5, 1:1) (Raman spectrometer Coderg PHO with low-temperature measuring cell, −40 to +20 °C, argon-ion laser 5145 Å[5]). The spectra of the protonated species show new bands and/or band shifts compared to those of the pure compounds *(1)* and *(2)* and those of the pure superacid (Fig. 1). Their interpretation in the region of the skeletal vibrations below 1500 cm^{-1} is rendered difficult, since the signals of the protonated species in this region are superposed by bands of the pure superacid and of the complex ions in solutions of this type[6]. For compounds with SH groups the signal of the S—H stretching vibration appears above 1500 cm^{-1} at 2550 to 2600 cm^{-1}.

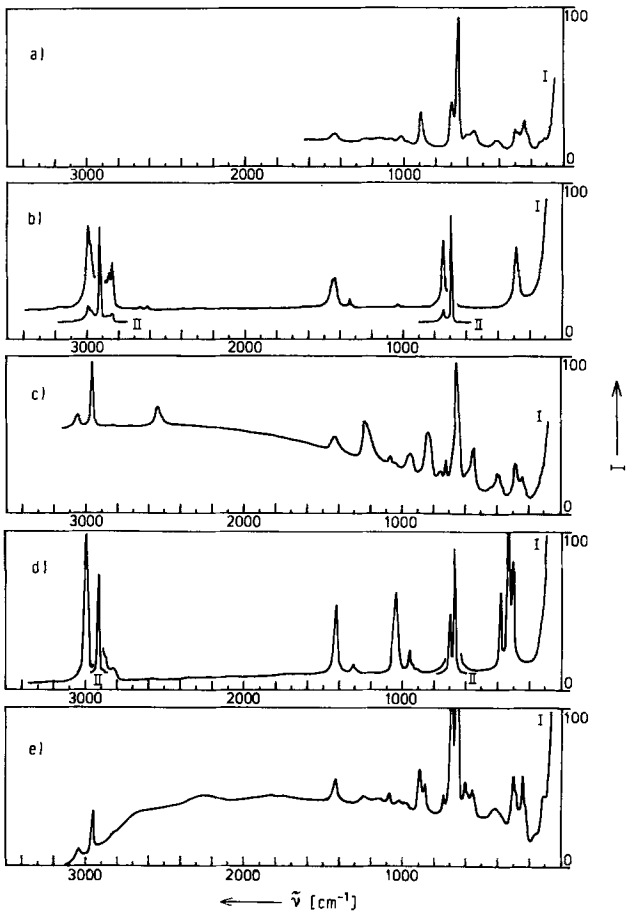


Fig. 1. Raman spectra of a) magic acid (MA), HSO_3F (100%); b) $(CH_3)_2S$ *(2)*; c) 30 mol% *(2)* in MA; d) $(CH_3)_2S{=}O$ *(1)*; e) 30 mol% *(1)* in MA [I = amplification × 1; II = amplification × 0.2].

In the spectrum of the protonated sulfide *(2)* the band is observed quite clearly at 2550 cm^{-1} (Fig. 1c), whereas in the spectrum of the protonated sulfoxide *(1)* this region is free of bands (Fig. 1e). In our opinion this affords a sure indication of the absence of SH groups in the protonated dimethyl sulfoxide and thus proof of the structure *(1a)*.

Received: January 7, 1977 [Z 646 IE]
German version: Angew. Chem. 89, 200 (1977)

[*] Prof. Dr. B. Schrader, Dipl.-Chem. M. Spiekermann
Abteilung Theoretische Organische Chemie der Universität
Postfach 500500, D-4600 Dortmund 50 (Germany)
New address: Teilbereich Physikalische und Theoretische Chemie der Universität-Gesamthochschule
Universitätsstrasse 2, D-4300 Essen 1 (Germany)
[**] This work was supported by the Fonds der Chemischen Industrie. We thank Prof. *Modena*, Padua, and Prof. *Kresze*, München, for introducing us to the problem.

[1] G. Modena, Int. J. Sulfur Chem. C 7, 95 (1972).
[2] Pro (1b): a) G. A. Olah, A. T. Ku, J. A. Olah, J. Org. Chem. 35, 3904 (1970); b) G. A. Olah, A. M. White, D. H. O'Brien, Chem. Rev. 70, 561 (1970).
[3] Pro (1a): Q. Appleton, L. Bernander, G. Olofsson, Tetrahedron 27, 5921 (1971); G. Gatti, A. Levi, V. Lucchini, G. Modena, G. Scorrano, J. Chem. Soc. Chem. Commun. 1973, 251; cf. also [1].
[4] B. Schrader, Angew. Chem. 85, 925 (1973); Angew. Chem. Int. Ed. Engl. 12, 884 (1973).
[5] M. Spiekermann, Diplomarbeit, Universität Dortmund 1975.
[6] F. A. Cotton, G. Wilkinson, Advanced Inorganic Chemistry. Wiley-Interscience, New York 1972.

2,3:6,7-Dioxa-bis-σ-homotropones. Synthesis and *cis*⇄*trans*-Isomerization[**]

By *Horst Prinzbach*, *Wolfgang Seppelt*, and *Hans Fritz*[*]

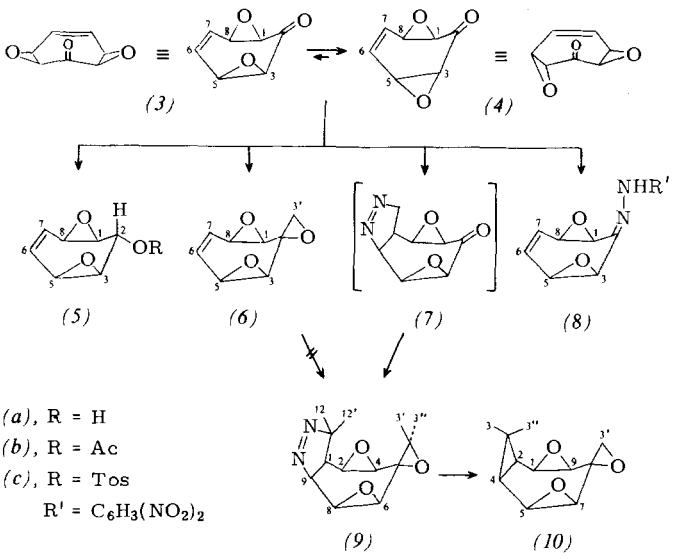
Substituted hetero-bis- *(1)* and hetero-tris-σ-homotropilidenes *(2)* are of interest as homologous hetero-σ-homobenzenes[1]—and, in this connection, also as intermediates in the preparative route to polyfunctional cycloheptanes[2] and to potential heteroaromatic cations. Since all attempts to substitute the methylene groups of tropilidene oxides *(1)* and *(2)* (X,Y,Z = O, R = H) and to epoxidize 7-hydroxytropilidene derivatives[3] have so far failed, the synthesis and *cis*⇄*trans*-isomerization of the tropone dioxides *(3)*/*(4)* described here constitute a versatile entry to compounds of type *(1)*[4] and possibly also *(2)*.



(1) X, Y, Z = CR'_2, O, NR' *(2)*

The acid-sensitive tropone reacts in alkaline medium with excess hydrogen peroxide (*e.g.* 2.0 g, 90 ml methanol, 5.6 ml 8% aqueous NaOH, 5 ml 85% aqueous H_2O_2, 3 h, 5°C, conditions not optimized), reaction terminating after *ca.* 70% conversion. According to TLC and ^{1}H-NMR investigations the crude product contains 45—50% of a chromatographically [ethyl acetate/CCl_4 (1:1)] isolable mixture of *(3)* and *(4)*, whose initial 1:1 composition continually changes in favor of *(4)*. After brief warming of a mixture of *(3)*/*(4)* in acetone or acetonitrile [$t_{1/2}$ (50°C) *ca.* 40 min] *(3)* is no longer chromatographically detectable alongside *(4)*. Compounds *(3)* and *(4)* are sparingly soluble in apolar solvents. According to ^{1}H-NMR analysis of the components separated by fractional crystallization *(3)* [$J_{5,6} \approx 0$ Hz, $\nu_{C=O} = 1688$ cm^{-1}] has a comparatively rigid open-boat configuration (C_s), *(4)* [m.p. 105°C, $(J_{5,6} + J_{5,7}) = 6.3$ Hz, $\nu_{C=O} = 1684$ cm^{-1}] a very flexible boat configuration (C_2).

Reversal of the *cis*→*trans* isomerization *(3)*→*(4)* cannot be observed ^{1}H- and ^{13}C-NMR spectroscopically on account of the strong thermodynamic disadvantage of *(3)*, but appears likely on the basis of the following experiments designed to utilize the kinetic preference of *(3)*. Reaction of the *trans*-dioxide *(4)* with $NaBH_4$ (ethanol, 0°C) affords exclusively the *cis*-alcohol *(5a)* [m.p. 102°C, $J_{5,6} \approx 0$ Hz, acetate *(5b)*: m.p. 120°C, tosylate *(5c)*: m.p. 93°C], with diazomethane



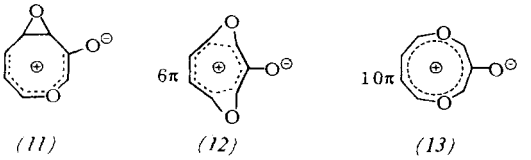
(a), R = H
(b), R = Ac
(c), R = Tos
R' = $C_6H_3(NO_2)_2$

(9) *(10)*

(*ca.* 5 equiv., ether/THF, −15°C, 50 h) a mixture (90%, *ca.* 1:1) of the *cis*-products *(6)* (m.p. 127°C, $J_{5,6} \approx 0$ Hz) and *(9)* (m.p. 90°C, $J_{1,2} = J_{8,9} = 4.5$ Hz), and with 2,4-dinitrophenylhydrazine only the *cis*-hydrazone *(8)* (>146°C dec., $J_{5,6} \approx 0$ Hz). The easier accessibility of the *endo* side in *(3)*, possibly supported by a *cis*-directing effect of the oxirane oxygen[5], as cause for the overwhelming kinetic preference is reflected in the stereochemistry of *(5)*, *(6)*, and *(9)*. Characteristic for *(5)* is the $J_{1,2}$-value (6.3 Hz), for *(6)* the [J(C-3', 1-H) + J(C-3', 3-H)]-coupling (5 Hz) and the relatively high chemical shift of the CH_2 protons [$\tau_{3'-H} = 7.17$ ($CDCl_3$); cf. $\tau_{3'-H(3''-H)}$ in *(16)*], and for *(9)*, in addition, the $J_{1,2}$- and $J_{8,9}$-coupling. Further structural information is provided by *(10)* [97%, m.p. 98°C, $\tau_{3'-H} = 6.91$ ($CDCl_3$), (C_s)], obtained from *(9)* by direct irradiation (CH_3CN, ether, 0°C, Pyrex filter), whose H,H couplings [*inter alia* $(J_{1,2} + J_{1,4}) = 5.2$ Hz] are in good agreement with those of two well known compounds, which according to X-ray structural analysis are *cis*-tris-σ-homotropilidenes[3].

Compounds *(3)* to *(6)* are of limited preparative utility for syntheses in the series *(2)*: the C=C double bond is shielded so effectively that it does not undergo addition with a variety of partners (*inter alia* CH_2N_2, peracids). Consequently *(6)* is not a precursor of *(9)*; the likely intermediate is *(7)*, but this cannot be enriched even in the presence of a substoichiometric amount of CH_2N_2.

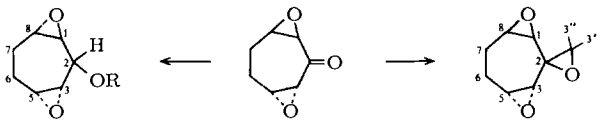
Mechanistically, the equilibrium *(3)*⇄*(4)* is noteworthy in connection with the role of heteroatoms in the [$\pi 2_s + \sigma 2_s + \sigma 2_s$]- and [$\sigma 2_s + \sigma 2_s + \sigma 2_s$]-cycloreversions of *cis*-hetero-bis- and *cis*-hetero-tris-σ-homobenzenes[1]. In both directions—insofar as catalysis is excluded—the activation barrier for cleavage of the C—C bond in the oxirane ring is remarkably low[6]. This situation most closely resembles the valence tautomerism between highly-substituted cyclopentadienone oxides and pyrylium 3-oxides[7]. Thus, several delocalized ylide intermediates are conceivable, *e.g.* *(11)* to *(13)*; however, we have so far failed to trap any one of them with methyl acetylenedicarboxylate (20—140°C, up to 5 d), tetra-



(11) *(12)* *(13)*

[*] Prof. Dr. H. Prinzbach, Dipl.-Chem. W. Seppelt, Dr. H. Fritz
Lehrstuhl für Organische Chemie der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

cyanoethylene (20—60 °C), or *N*-phenyltriazolinedione (20—40 °C). Observations favoring delocalized ylide intermediates are the steric integrity of the *cis/trans*-tropilidene dioxides *(1)* (X=Y=O, R=H)[3] and of the *cis*-hydrazone *(8)*, as well as the finding that *trans*-dioxide *(15)* ($\nu_{C=O}$ = 1713 cm^{-1}) reacts with $NaBH_4$ and with diazomethane without *trans*→*cis* isomerization to give the alcohol *(14a)* [acetate *(14b)*: m.p. *ca.* 20 °C, τ_{2-H} = 4.69; $J_{1,2}$ = 4.6; $J_{2,3} \approx 0$ Hz] and *(16)* [m.p. 34 °C, $\tau_{3'-H}$ = 6.87; $\tau_{3''-H}$ = 7.11], respectively.



(14a), R = H
(14b), R = Ac

(15)

(16)

The structures of the new compounds *(3)* to *(6)*, *(8)* to *(10)*, and *(14)* to *(16)* have been confirmed by elemental analyses and by UV, IR, MS, ^{1}H-NMR, and ^{13}C-NMR data.

Received: December 3, 1976 [Z 621 IE]
German version: Angew. Chem. *89*, 174 (1977)

CAS Registry numbers:
(3), 61520-91-0; *(4)*, 61463-44-3; *(5a)*, 61463-45-4; *(5b)*, 61463-46-5; *(5c)*, 61463-47-6; *(6)*, 61463-48-7; *(8)*, 61463-49-8; *(9)*, 61463-50-1; *(10)*, 61477-76-1; *(14a)*, 61463-51-2; *(14b)*, 61463-52-3; *(15)*, 61463-53-4; *(16)*, 61463-54-5; diazomethane, 334-88-3; 2,4-dinitrophenylhydrazine, 119-26-6

[1] *H. Prinzbach, D. Stusche, J. Markert, H. H. Limbach*, Chem. Ber. *109*, 3505 (1976), and literature cited therein.
[2] Examples are homologs of streptamine and deoxystreptamine: *H. Prinzbach, R. Keller, R. Schwesinger*, Angew. Chem. *87*, 626 (1975); Angew. Chem. Int. Ed. Engl. *14*, 632 (1975), and literature cited therein.
[3] *H. Prinzbach, C. Rücker*, Angew. Chem. *88*, 611 (1976); Angew. Chem. Int. Ed. Engl. *15*, 559 (1976).
[4] The synthesis of the two tropone monoxides (2,3-oxide: 25%; 4,5-oxide: 4%) from tropone and $^1O_2$ has been described by *Mukai et al.* (Tetrahedron Lett. *1975*, 891), and that of the *trans*-4,5-oxa-2,3-bis-σ-homotropone (12%) from 2,3-homotropone and $^1O_2$ by *Kitahara et al.* (Tetrahedron Lett. *1975*, 239).
[5] *H. Prinzbach, D. Stusche*, Angew. Chem. *82*, 836 (1970); Angew. Chem. Int. Ed. Engl. *9*, 799 (1970); *H.-J. Altenbach, E. Vogel, ibid. 84*, 985 (1972) bzw. *11*, 937 (1972).
[6] *R. Huisgen*, Pure Appl. Chem. *23*, 175 (1971); *W. Eberbach, B. Burchardt*, Tetrahedron Lett. *1976*, 3887, and literature cited therein.
[7] *E. F. Ullman, J. E. Milks*, J. Am. Chem. Soc. *84*, 1315 (1962).

Demonstration of the Ionic Structure of the Intercalation Compound $TaS_2 \cdot NH_3$

By *Robert Schöllhorn* and *Hans-Dieter Zagefka*[*]

Intercalation compounds of layer chalcogenides MX_2 (M = transition metal, X = S, Se) with neutral molecules have acquired increasing interest on account of their marked structural anisotropy and consequent special chemical and physical properties; the nature of the host lattice-guest molecule interaction, however, is still largely unclear even in the case of simple guest molecules. *Gamble et al.*[1] were recently able to demonstrate by ^{1}H-NMR measurements that the three-fold symmetry axis of the NH_3 molecule in the superconducting compound $TaS_2 \cdot NH_3$ is, contrary to previous assumptions, oriented parallel to the MX_2 layer plane; they postulated a charge-transfer interaction $NH_3 \rightarrow MX_2$, even though the position of the lone-pair orbital is unfavorable.

We have now found that the MX_2 layers act as oxidizing agent in the reaction of ammonia with 2H-TaS_2 (25 °C) and part of the NH_3 is oxidized to elemental nitrogen; N_2 could be detected both gas-chromatographically and mass-spectrometrically (using $^{15}NH_3$). The ratio Ta:N reached a value of 18 to 20. Only small amounts of H_2 are formed in the reaction, so that a catalytic decomposition, as is known for metal interfaces, can be ruled out. If the electrons liberated during N_2 formation according to eq. (1) are taken up by the conduction band of the TaS_2 layer [eq. (2)], then

$$2\,NH_3 \longrightarrow N_2 + 6\,H^+ + 6e^- \quad (1)$$

$$xe^- + TaS_2 \longrightarrow [TaS_2]^{x-} \quad (2)$$

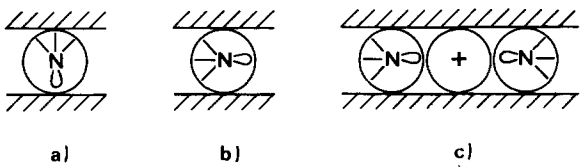
$$H^+ + NH_3 \longrightarrow NH_4^+ \quad (3)$$

the concomitant protons can be transferred to NH_3 molecules [eq. (3)]; the composition of the solid phase would thus be $(NH_4^+)_x(NH_3)_{1-x}[TaS_2]^{x-}$. In analogy with the reactions of solvated ternary compounds[2] detection of NH_4^+ ions ought to be possible by exchange in electrolyte solutions. In ion exchange reactions of $TaS_2 \cdot NH_3$ with KBr in liquid ammonia (—40 °C) we obtained, after careful washing with NH_3, the bromide-free potassium compound *(1)*: determination of the potassium content of this phase, which agreed with the content of nitrogen found in the extracted salt (NH_4Br), gave the value $x = 0.1$; the value of x calculated from the Ta/N ratio is likewise *ca.* 0.1.

$$(NH_4^+)_x(NH_3)_{1-x}[TaS_2]^{x-} + K^+ \longrightarrow (K^+)_x(NH_3)_{1-x}[TaS_2]^{x-} + NH_4^+ \quad (4)$$

(1)

The formation of $TaS_2 \cdot NH_3$ is thus coupled with a redox reaction in which a part of the guest molecules is chemically modified. The resulting compound $(NH_4^+)_x(NH_3)_{1-x}[TaS_2]^{x-}$ is to be regarded as a polyelectrolyte system consisting of $[TaS_2]^{x-}$ layers with delocalized negative charges; the interlayer spacings are populated by readily mobile and exchangeable NH_4^+ cations solvated by NH_3 molecules.



a) b) c)

Fig. 1. Models of the arrangement of the NH_3 molecules between the metal sulfide layers in $TaS_2 \cdot NH_3$: a) C_3 axis perpendicular to layers, b) C_3 axis parallel to the layers, c) ionic model.

This ionic structural model provides a simple explanation of the unusual arrangement of the NH_3 molecule (C_3 axis parallel to the layer)[1]. With a ratio of $NH_4^+/NH_3 = 1:9$, each NH_4^+ aquires a complete two-dimensional solvation sphere: the solvate molecules must—as is known from crystal structure investigations on ammonium halide-ammoniates[3]—be arranged with the lone pair directed to the positive charge centers (Fig. 1c); the isometric NH_4^+ ions themselves cannot contribute to the observed anisotropic effect of the spin-lattice relaxation. The X-ray crystallographic result[4] that the center of gravity of the N atoms lies in a plane midway between

[*] Prof. Dr. R. Schöllhorn, Dipl.-Chem. H. D. Zagefka
Anorganisch-chemisches Institut der Universität
Gievenbecker Weg 9, D-4400 Münster (Germany)

the layers is also in agreement with this model. The host lattice-guest phase bonding is therefore largely due to electrostatic interaction between the solvated NH_4^+ ions and the negatively charged layers. Measurements on the H/D exchange in the system $TaS_2 \cdot ND_3/NH_3$ at 25 °C[5] can now be explained in terms of a rapid proton transfer between NH_3 and NH_4^+ ions, resulting in a dynamic reorientation of the solvate molecules. The redox reaction also explains the kinetic results of *Dines et al.*[6]: only solvate molecules can be easily and reversibly removed from the lattice; above *ca.* 100 °C an irreversible decomposition of the NH_4^+ ions takes place, similarly as in layer silicates[7]. The sigmoidal shape of the initial intercalation curve and the temperature dependence can be interpreted by adsorption- and redox-equilibria.

N_2 formation was also demonstrated in the reaction of NbS_2 or $TaSe_2$ with NH_3. From the above observations and our earlier investigations on ion formation[2] it can be concluded that intercalation reactions of layer chalcogenides are fundamentally connected with redox reactions and ion formation. These conclusions also explain the NH_3-analogous position of pyridine in $TaS_2 \cdot (py)_{0.5}$[8]. Demonstration of the presence of discrete cations in intercalation compounds $MX_2 \cdot B_y$ is of considerable importance for interpretation of the physical properties of these phases, particularly of superconducting phenomena.

Received: December 13, 1976 [Z 635 IE]
German version: Angew. Chem. *89*, 193 (1977)

CAS Registry numbers:
$TaS_2 \cdot NH_3$, 34312-63-5; NH_4^+, 14798-03-9

[1] *F. R. Gamble, B. G. Silbernagel*, J. Chem. Phys. *63*, 2544 (1975); *B. G. Silbernagel, M. B. Dines, F. R. Gamble, L. A. Gebhard, M. S. Whittingham, ibid. 65*, 1906 (1976).
[2] *R. Schöllhorn, E. Sick, A. Lerf*, Mater. Res. Bull. *10*, 1005 (1975); *R. Schöllhorn, H. Meyer, ibid. 9*, 1237 (1974).
[3] *I. Olovson*, Acta Chem. Scand. *14*, 1453, 1466 (1960).
[4] *R. R. Chianelli, J. C. Scanlon, M. S. Whittingham, F. R. Gamble*, Inorg. Chem. *14*, 1693 (1975).
[5] *C. Riekel, R. Schöllhorn*, Mater. Res. Bull. *11*, 369 (1976).
[6] *M. B. Dines, R. Levy*, J. Phys. Chem. *79*, 1979 (1975).
[7] *R. E. Grim*, Clay Mineralogy. MacGraw-Hill, New York 1968.
[8] *C. Riekel, D. Hohlwein, R. Schöllhorn*, J. Chem. Soc. Chem. Commun. *1976*, 863.

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Aspects of the photochemistry of organo-transition metal compounds are reviewed in an article by *E. A. Koerner von Gustorf, L. H. G. Leenders, I. Fischler*, and *R. N. Perutz*. The authors deal *inter alia*, with, the methods of photochemical generation and characterization of unstable short-lived intermediates, photosynthesis of novel organometal compounds, photochemical rearrangements of organic compounds on metal templates, mechanistic studies by photochemical methods, and the use of photoreactions of organometal compounds as models for biological processes. [Aspects of Organo-Transition-Metal Photochemistry and Their Biological Implications. Adv. Inorg. Chem. Radiochem. *19*, 65—183 (1976); 632 references]

[Rd 929 IE—F]

The dependence of translation on the 5′-terminal methylation of m-RNA is dealt with in an article by *A. J. Shatkin, A. K. Banerjee, G. W. Both, Y. Furuichi*, and *S. Muthukrishnan*. The m-RNAs of numerous animal viruses and of eukaryotes have methylated 5′-terminal groups. Only methylated m-RNA allows a translation, unmethylated m-RNA is inactive. It can however be methylated by *S*-adenosylmethionine and wheat germ extract and thus become capable of translation. This reaction is inhibited by *S*-adenosylhomocysteine. The binding of the m-RNA to ribosomes depends on the methylation. [Dependence of Translation on 5′-Terminal Methylation of m-RNA. Fed. Proc. *35*, 2214–2217 (1976); 17 references]

[Rd 925 IE—R]

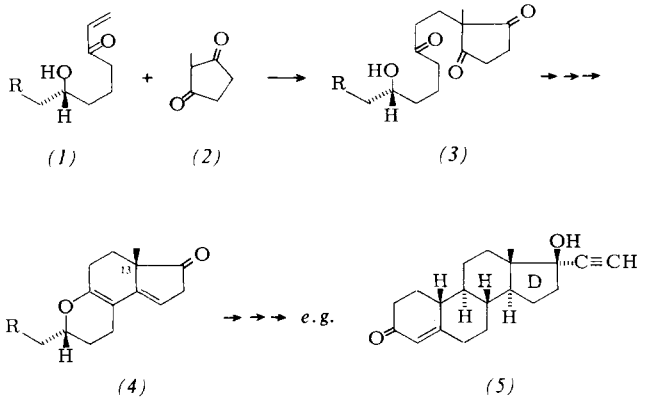
The effect of vitamins on drug metabolism is the subject of a report by *V. G. Zannoni* and *P. H. Sato*. There is mounting evidence that the enzyme system of drug metabolism in liver microsomes is influenced by the vitamins ascorbic acid, riboflavin, and tocopherol. In the case of ascorbic acid deficiency lower cytochrome P-450, NAPDH-cytochrome and other enzyme activities are found. After administration of ascorbic acid it takes 3 to 7 days for the enzyme activity to readjust to its original level. Cytochrome P-450 can also be readjusted to its normal level by administration of δ-aminolevulinic acid, a precursor in heme synthesis. Riboflavin deficiency is effective only in adult animals after prolonged periods of time; the recuperation time is 10 to 15 days after administration of riboflavin. Tocopherol deficiency affects only the *N*-demethylase; an effect on cytochrome P-450 is still controversial. [The Effect of Certain Vitamin Deficiencies on Hepatic Drug Metabolism. Fed. Proc. *35*, 2464—2469 (1976); 36 references]

[Rd 931 IE—R]

The role of hemin in the regulation of protein synthesis in erythroid cells is the subject of a review by *I. M. London, M. J. Clemens, R. S. Ranu, D. H. Levin, L. F. Cherbas*, and *V. Ernst*. It has long been known that iron ions promote heme synthesis, serving not only as substrate but also as cofactor in the synthesis of δ-aminolevulinic acid. Heme itself inhibits its own synthesis by feedback but simulates the synthesis of globin. Since this synthesis takes place in the reticulocytes which contain no nucleus stimulation must act at the translation level. The globin synthesis is inhibited by a high-molecular protein which impairs the binding of met-t-RNA_F to the 40S subunits of the ribosomes. [The Role of Hemin in the Regulation of Protein Synthesis in Erythroid Cells. Fed. Proc. *35*, 2218—2222 (1976); 37 references]

[Rd 926 IE—R]

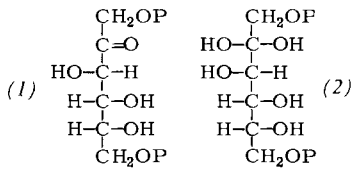
Asymmetric induction in the total synthesis of 19-norsteroids such as *(5)* is the subject of a report by *N. Cohen.* It is known that the useful biological properties of most steroids are confined to only one enantiomer; however, resort to classical resolution procedures ought to be avoided wherever possible. Many syntheses of 19-norsteroids start from prochiral precursors of ring D, *e.g. (2).* This is allowed to react with chiral compounds such as *(1)* (which are later transformed into

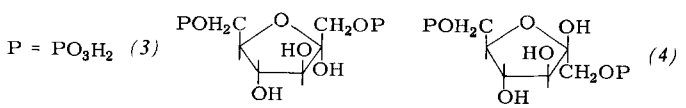


the rings A and B); ring closure of the intermediate *(3)* affords optically active products having wholly, [like *(4)*], or partly the required 13β configuration. Besides this intramolecular induction of chirality an intermolecular variant (with amino like acids) is also known. [Asymmetric Induction in 19-Norsteroid Total Synthesis. Acc. Chem. Res. *9*, 412—417 (1976); 38 references]

[Rd 927 IE—L]

The structure of ketones and their biologically important phosphate esters in solution is reported on by *G. R. Gray.* Is, for example, D-fructose-1,6-biphosphate present in the acyclic keto form *(1)*, as its hydrate *(2)*, in the cyclic α- *(3)* or





β-furanose form *(4)* or also in the corresponding furanose form? In solution the biphosphate is present in amounts of up to 1.7% (IR; 25°C) in form *(1)*, 18% in form *(3)*, and 80% (both ^{13}C-NMR, 30°C) in form *(4)*. Such findings are interesting as regards the question of whether enzymes can utilize all or only specific forms of the sugar. [Solution Structures of the Keto Sugars and Their Biologically Important Phosphate Esters. Acc. Chem. Res. *9*, 418—424 (1976); references]

[Rd 928 IE—L]

The drug-metabolizing enzyme systems of liver microsomes are reported on by *A. Y. H. Lu.* These enzyme systems consist of the protein components cytochrome P-450 and NADPH-cytochrome-c reductase and a phospholipid. Cytochrome P-450 binds oxygen and substrate, the reductase transfers electrons from NADPH to the cytochrome. Electron transfer is facilitated by the phospholipid. Numerous cytochromes P-450, exhibiting different spectral, catalytic, and immunological properties and different molecular weights, have been isolated. This variety probably accounts for the differences in drug metabolism found in various species, tissues, sexes, age groups, and under differing induction and dietary conditions. [Liver Microsomal Drug Metabolizing Enzyme System: Functional Components and Their Properties. Fed. Proc. *35*, 2460—2463 (1976); 56 references]

[Rd 930 IE—R]

The effect of dietary lipids on drug metabolizing enzymes forms the theme of a review by *A. E. Wade* and *W. P. Norred.* Rats fed on a diet of corn oil metabolize hexobarbital, aniline, and heptachlor more rapidly than do control animals. In particular, the activity of cytochrome P-450 is increased. Besides these quantitative changes, there would appear to be qualitative changes in the enzyme system by dietary lipids. [Effect of Dietary Lipid on Drug-Metabolizing Enzymes Fed. Proc. *35*, 2475—2479 (1976); 44 references]

[Rd 932 IE—R]

Structure-activity relations of antagonists of the renin-angiotensin system are reviewed in an article by *G. R. Marshall.* The inhibition of renin and renin-forming enzyme (a dipeptidyl carboxypeptidase) and suppression of renin-receptor interaction are considered from the mechanistic point of view. In addition questions bearing upon the future synthetic strategies for inhibitors are discussed. [Structure-Activity Relations of Antagonists of the Renin-Angiotensin System. Fed. Proc. *35*, 2494—2501 (1976); 68 references]

[Rd 933 IE—R]

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (dec.), and *W. M. Weigert*. Volume 11: Erdöl und Erdgas bis Formazanfarbstoffe. Verlag Chemie, Weinheim 1976. 4th edit., xvi, 718 pp., 307 figs., 212 tables, half-linen, subscription price DM 345.—; final price DM 385.—.

This volume continues the alphabetical series of volumes in the new edition of Ullmann[*]. A large part of the volume (219 pp.) is taken up by the major heading Fibers [Fasern, with entries on Structure, General Production methods, Individual Synthetic (Organic, Inorganic) Fibers, Testing and Analysis, and including a highly instructive tabular comparison of fiber properties. Another special commercial form of polymers is described under Films [Folien] (14 pp.). Under Synthetic Dyes [Synthetische Farbstoffe] (10 pp.) the reader finds useful reviews of the classification of dyes and the various steps generally used in dye manufacture, with data on production quantities and values together with export and import figures for various countries. A further general entry covers the Investigation of Dyes, including color measurement and calculation of formulations (48 pp.). The individual dye classes are treated under their own keywords, *e.g.* in this volume under Natural Dyes [Natürliche Farbstoffe] (36 pp.) and Formazan Dyes [Formazanfarbstoffe] (8 pp.). Entries on petroleum formation, exploration, occurrence and production (40 pp.) supplement those on Natural Gas [Erdgas] and Petroleum [Erdöl] which were dealt with largely in the preceding volume. Mention must also be made of Natural Fats and Oils [Natürliche Fette und Öle] (70 pp.), Fatty Acids [Fettsäuren] (24 pp.), Aliphatic Alcohols [Fettalkohole] (19 pp.), Aliphatic Amines [Fettamine] (6 pp.), Acetic Acid and Vinegar [Essigsäure und Essig] (34 pp.), Formaldehyde [Formaldehyd] (16 pp.), Formamide [Formamid] (8 pp.), Fluorine and Inorganic Fluorine Compounds [Fluor und anorganische Fluorverbindungen] (44 pp.), and Organic Fluorine Compounds [Organische Fluorverbindungen] (26 pp.). Entries covering applied fields occur also in this volume, *e.g.* Ferroelectrics [Ferroelektrika] (11 pp.), Flameproofing [Feuerfeste Erzeugnisse] (17 pp.), Fire Extinguishers [Feuerlöschmittel] (9 pp.), and Liquid Crystals [Flüssigkristalle] (15 pp.).

About the present volume we need only say that its quality matches that of the previous volumes in every respect. Thus, the extensive sections, like the 200 plus pages devoted to Fibers, are so concentrated as to be complete monographs standing up to comparison with separate specialist works. This over-all impression is not diminished by occasional unevenness (*e.g.* a somewhat more detailed description of the methods of preparation of organic fluorine compounds would be welcome, though it is realized that the size of the whole work and thus also of the individual sections is necessarily limited). As regards this last point, some space could have been saved if the vapor-liquid equilibria (*e.g.* for acetic acid/acetic anhydride) had been presented as tables rather than as diagrams, and thus even more informatively.

As far as new developments are concerned one of the most outstanding sections in this volume is that on Liquid Crystals, where the majority of the references are to publications from 1970 onward. Clearly, this volume can only enhance Ullmann's reputation, not only as a valuable source of information for practically-oriented scientists working in the chemical and allied industries but also as an excellent work of reference providing the chemist with reviews of important new developments. The work is a must for all chemical libraries.

Ulfert Onken [NB 362 IE]

[*] Cf. Angew. Chem. Int. Ed. Engl. *16*, 62 (1977).

Die Giftliste (List of Poisons). By *L. Roth*. Verlag Moderne Industrie, Munich 1976. 1st edit., 347 pp., ring-bound, DM 148.—.

The author, already known from his "Sicherheitsfibel Chemie" (Chemical Safety Primer), has now completed the laborious task of collecting information about the nearly 7000 substances that are poisonous, corrosive, irritant, or otherwise dangerous to health, insofar as they are contained in the German or Swiss Poisons Lists, the EEC guidelines for the labeling of dangerous materials, or the German MAK list.

Tables occupying 291 pages contain the details of labeling directions taken from the above-named regulations and guidelines. Particularly valuable is the inclusion of data from the Swiss Poisons List, as these are little known in Germany. Further indications of the special dangers in handling these materials or destroying them are collected under specially worked out codes. However, the "Immission Classes" listed for several substances in column 1 could lead to misunderstandings, because this refers to the classes in the Technical Guide for Cleanliness of the Air of 28. 8. 1974 for limiting *emissions* from industrial plants, controlled by § 4 of the Federal Immission Protection Law (previously § 16 of the Trade Order).

The introductory text gives not only explanations for the tables but also a literal transcription of the law on poisons and plant protection agents of the Land Baden-Württemberg, the law on dangerous working materials of 8. 9. 75, and a list of occupational diseases. There is also a table of radioactive nuclides. The section on first aid in cases of poisoning and the provision of the addresses of Poison Information Centers in the German Federal Republic and in other European countries will be found to be particularly valuable.

E. Quellmalz [NB 369 IE]

Angewandte Elektrochemie. Grundlagen der elektrolytischen Produktionsverfahren. (Applied Electrochemistry. Principles of Electrolytic Production Processes.) By *A. Schmidt*. Verlag Chemie, Weinheim—New York 1976. 1st edit., xv, 322 pp., 135 figs., 72 tables, bound, DM 98.—.

The most recent comprehensive standard work on electrochemistry in the German language appeared in 1933, edited by *Engelmann* in collaboration with numerous electrochemists.

After many years' activity in industry, *Alfred Schmidt* has now undertaken the task of writing a book on "Applied Electrochemistry" in line with the current state of knowledge and providing both the student and the specialist with a comprehensive review of the whole field in clear and modern form. In doing so the author supplements technical details with a treatment of economic aspects.

Section 1 presents the fundamental concepts and principles of electrochemical processes. After an introduction into the structure of matter and the problems of current conduction and distribution, electrode processes are treated in detail. Brief but clear definitions of the concepts customary in modern electrochemistry will be useful to students and above all to the practical worker.

In Section 2, dealing with the principles of industrial electrolytic processes, the apparatus and materials used in industry

are described, *e.g.* electrolysis cells, electrodes, electrolytes, cell connections, and power distribution. The latest knowledge about bipolar cells, coated titanium anodes, and the importance of regular current distribution is presented. Description of the generation of direct current is followed by a discussion of the economic principles involved: here the important questions of current yield, specific power consumption, and optimization of electrolysis plant are treated with reference to the increasing shortage of raw materials and increasing energy costs.

Presentation of the advantages and disadvantages of electrochemical processes, not given previously, enables these processes to be compared critically with other methods of industrial production. Ecological problems and the environment are also not forgotten.

In the section on industrial production processes considerable space is devoted to the electrolysis of water and to the preparation of chlorine and chlorine-oxygen compounds. The industrially less important products, peroxo compounds, permanganate, manganese dioxide, chromic acid, and fluorine are treated more briefly.

The production of metals by electrolysis of aqueous solutions and by fusion electrolysis is described in detail. A section on organic electrochemistry has been added, the importance of this field being expected to increase in the future.

Carefully chosen references at the end of each chapter, together with a collection of important bibliographies, facilitate ready reference to specific problems. Numerous surveys and tables in the appendix make this volume an important handbook not only for electrochemists but also for all who are concerned with electrochemical processes, and thus especially for engineers in many sectors of industry.

Karl Hass [NB 359 IE]

Lehrprogramm Statistik. Mit Beispielen und Ausgaben aus den Naturwissenschaften (Teaching Program Statistics. With Examples and Problems from the Natural Sciences). (Pocketbook 46) By *W. Schmidt*. Verlag Chemie/Physik Verlag, Weinheim 1976. 1st edit., vii, 137 pp., 51 figs., 1 table, paperback. DM 18.80.

This book arose from the material accompanying the practical course for physics students in their fourth semester.

The aim of the first three chapters is to provide sufficient grounding for further study of user-oriented specialist works on statistics. Starting from the basic principles of probability calculus, the author describes normal, binomial and Poisson distributions, treating in the third chapter simple statistical processes for the evaluation of experiments, *e.g.* formation of the mean or calculation of the standard deviation. The fourth chapter concerns some applications in the field of natural sciences.

For physics students conversant with the theory of sets and its symbolism the book provides a valuable extension of the practical work and the lectures. The interaction between the material learnt on the one hand and the questions, exercises, and problems on the other is very successful, the latter closing each teaching section; the reader can thus run a continuous check on his progress. The whole is supported by illustrations which in many cases make the point clear without any need to study the text. Since in spite of its extensions the book retains its character as an auxiliary aid to a lecture course, it is not especially suited for independent study without subsidiary material explaining the most commonly used symbols, abbreviations, and signs (no table of these is included). Furthermore, there are no literature references.

Karl Hans Simmrock [NB 364 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Ullmanns Encyklopädie der technischen Chemie, Band 12: Fungizide bis Holzwerkstoffe. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (dec.), and *W. M. Weigert* (dec.). Verlag Chemie, Weinheim 1976. 4th revised and expanded edition. xv, 727 pp., bound, DM 430.—.—ISBN 3-527-20012-6

DMS Raman/IR Atlas organischer Verbindungen, 3. Lieferung. Edited for the Institut für Spektrochemie und Angewandte Spektroskopie, Dortmund, by *B. Schrader* and *W. Meier*. Verlag Chemie, Weinheim 1977. Loose-leaf collection DM 265.—.—ISBN 3-527-25542-7

Handbuch der Textilhilfsmittel. Edited by *A. Chwala* (dec.) and *V. Anger* in collaboration with *Ch. Chwala*. Verlag Chemie, Weinheim 1977. xxiv, 1374 pp., bound, DM 440.—.—ISBN 3-527-25367-X

Atomic Absorption Spectroscopy. By *B. Welz*. Verlag Chemie, Weinheim 1976. xii, 267 pp., bound, DM 68.—.—ISBN 3-527-25668-7

Coordination and Catalysis. By *G. Henrici-Olivé* and *S. Olivé*. Vol. 9 of "Monographs in Modern Chemistry". Edited by *H. F. Ebel*. Verlag Chemie, Weinheim 1977. xii, 310 pp., bound, DM 98.—.—ISBN 3-527-25686-5

Praktische Nomographie. By *C. Bliefert, G. Dehms*, and *G. Morawietz*. Verlag Chemie, Weinheim 1977. x, 204 pp., paperback, DM 42.—.—ISBN 3-527-25685-7

Vom Wasser, Band 47, 1976. Lectures presented at the 1976 Anniversary Conference of the Fachgruppe Wasserchemie at Kiel. Issued by the Fachgruppe Wasserchemie in the Gesellschaft Deutscher Chemiker. Responsible for text: *W. Husmann*. Verlag Chemie, Weinheim 1976. viii, 484 pp., bound, DM 144.—.—ISBN 3-527-25668-7

Molekül-Reaktionen und Photochemie. By *C. H. DePuy* and *O. L. Chapman*. Verlag Chemie, Weinheim 1977. ix, 165 pp., paperback, DM 33.—.—ISBN 3-527-25648-2

Rückstandsanalytik von Pflanzenschutzmitteln. Mitteilung VI der Senatskommission für Pflanzenschutz-, Pflanzenbehandlungs- und Vorratsschutzmittel. Methodensammlung der Arbeitsgruppe "Analytik". 4. Lieferung 1976. Verlag Chemie, Weinheim 1977. Loose-leaf collection DM 87.—.—ISBN 3-527-25681-4

Modern Three-Hadron Physics. Edited by *A. W. Thomas*. Vol. 2 of the series "Topics in Current Physics". Founded by *H. K. V. Lotsch*. Springer-Verlag, Berlin 1977. xi, 250 pp., bound, DM 69.—.—ISBN 3-540-07950-5

Glass Structure by Spectroscopy. By *J. Wong* and *C. A. Angell*. Marcel Dekker, New York 1976. xv, 864 pp., bound, SFrs. 145.00.—ISBN 0-8247-6468-4

Theory of Simple Liquids. By *J. P. Hansen* and *I. R. McDonald*. Academic Press, London 1976. xv, 395 pp., bound, £ 14.00.—ISBN 0-12-323850-1

Carbon Dioxide. International Thermodynamic Tables of the Fluid State—3. Compiled by *S. Angus*, *B. Armstrong*, and *K. M. de Reuck*. IUPAC Division of Physical Chemistry, Commission on Thermodynamics and Thermochemistry. Pergamon Press, Oxford 1976. xxviii, 385 pp., bound, DM 175.—.—ISBN 0-08-020924-6

Fundamentals of Integrated GC-MS, Part II: Mass Spectrometry. By *B. J. Gudzinowicz*, *M. J. Gudzinowicz*, and *H. F. Martin*. Vol. 7 of the series "Chromatographic Science Series". Marcel Dekker, New York 1976. vii, 326 pp., bound, SFrs. 117.—.—ISBN 0-8247-6430-7

Organic Electronic Spectral Data, Vol. XII, 1970. Edited by *J. P. Phillips*, *H. Feuer*, and *B. S. Thyagarajan*. John Wiley & Sons, New York 1976. xiii, 1138 pp., bound, $ 57.00.—ISBN 0-471-02305-1

Colour and Constitution of Organic Molecules. By *J. Griffiths*. Academic Press, New York 1976. ix, 281 pp., bound, $ 20.75.—ISBN 0-12-303550-3

Radiationless Processes in Molecules and Condensed Phases. By *F. K. Fong*. Vol. 15 of the series "Topics in Applied Physics". Founded by *H. K. V. Lotsch*. Springer-Verlag, Berlin 1976. xi, 360 pp., bound, DM 97.—.—ISBN 3-540-07830-4

Colloid and Interface Science. Edited by *M. Kerker*. Academic Press, New York 1976.
Vol. II: Aerosols, Emulsions, and Surfactants. xx, 481 pp., bound, $ 21.00.—ISBN 0-12-404502-2
Vol. III: Adsorption, Catalysis, Solid Surfaces, Wetting, Surface Tension, and Water. xx, 548 pp., bound, $ 22.50.—ISBN 0-12-404503-0
Vol. IV: Hydrosols and Rheology. xviii, 587 pp., bound, $ 22.00.—ISBN 0-12-404504-9
Vol. V: Biocolloids, Polymers, Monolayers, Membranes, and General Papers. xvi, 507 pp., bound, $ 22.00.—ISBN 0-12-404505-7

An Introduction to the Chemistry of Heterocyclic Compounds. By *R. M. Acheson*. John Wiley & Sons, New York 1976. 3rd Edit., xvii, 501 pp., bound, $ 28.70.—ISBN 0-471-00268-2

Topics in Enzyme and Fermentation Biotechnology 1. Edited by *A. Wiseman*. Ellis Horwood, Chichester/John Wiley & Sons, New York 1977. 191 pp., bound, £ 10.50.—ISBN 0-470-98896-7 (Halsted Press); 85312-051-X (Ellis Horwood)

Die Chemische Industrie und ihre Helfer Ausgabe 1976/77. Edition Selka. Industrieschau-Verlagsgesellschaft, Darmstadt. 600 pp., paper, DM 38.—.—ISBN 3-7790-0066-X

Electrostatic Hazards. Their Evaluation and Control. By *H. Haase*. Verlag Chemie, Weinheim 1977. x, 124 pp., paper, DM 24.—.—ISBN 3-527-25684-9

Topics in Current Chemistry—Fortschritte der chemischen Forschung. Edited by *M. J. S. Dewar*, *K. Hafner*, *E. Heilbronner*, *S. Itô*, *J. M. Lehn*, *K. Niedenzu*, *K. Schäfer*, and *G. Wittig*. Managing Editor: *F. L. Boschke*. Springer-Verlag, Berlin 1976.
Vol. 67: Preparative Organic Chemistry. iv, 136 pp., bound, DM 52.—.—ISBN 3-540-07900-9
Vol. 68: Theory. iv, 156 pp., bound, DM 54.—.—ISBN 3-540-07932-7

Fundamentals of Integrated GC-MS. Part I: Gas Chromatography. By *B. J. Gudzinowicz*, *M. J. Gudzinowicz*, and *H. F. Martin*. Vol. 7 of the series "Chromatographic Science". Marcel Dekker, New York 1976. vii, 382 pp., bound, SFrs. 124.—.—ISBN 0-8247-6365-3

Reaktionsverhalten und Syntheseprinzipien. By *K.-H. Thiele*, *K. Jacob*, *H. Lettan*, *H.-J. Lunk*, *H. Meinert*, *H.-G. Müller*, *H. Paul*, *M. Schönherr*, *W. Schwartz*, *H.-J. Timpe*, and *H. Wegwart*. Arbeitsbuch 7 of the series "Fachstudium Chemie". Verlag Chemie, Weinheim 1977. 262 pp., stitched, DM 36.—.—ISBN 3-527-25672-5

Structure and Bonding. Edited by *J. D. Dunitz*, *P. Hemmerich*, *J. A. Ibers*, *C. K. Jørgensen*, *J. B. Neilands*, *D. Reinen*, and *R. J. P. Williams*. Vol. 31: Bonding and Compounds of Less Abundant Metals. Springer-Verlag, Berlin 1976. iv, 111 pp., bound, DM 42.—.—ISBN 3-540-07964-5

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. - Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany. Telephone 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031. Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 4
April 1977
Pages 205–272

Utilization of Microbes—Modern Developments in Biological Technology[**]

By Paul Präve[*]

Until recently microbiology had found use only in the foodstuffs sector and in the production of antibiotics; however, the production of biomass should be regarded as the key development of the new science of biotechnology. The biomass consists of fatty and protein-rich microorganisms that can be used for example in animal feeds. The microorganisms grow not only on cellulose waste and other biological substrates but also, for example, on petroleum and methanol. Their energy demand is comparatively low. It is being realized more and more that inflexible technologies pose problems for our civilization and that biotechnology, which utilizes the cyclic metabolic pathways of microorganisms and often recycles waste materials, shows great promise for the future.

1. Introduction

Microbiology is a relatively young science; it is concerned with small living organisms whose size lies in the micrometer region. Although man has used microorganisms for thousands of years it was only about a hundred years ago that he recognized them as capable of encroaching upon his life by causing disease or damaging crops. Names such as *Koch*, *Pasteur*, *Ehrlich*, and *Behring* are connected with extraordinary advances in our knowledge of the actions of harmful and often deadly microorganisms.

Almost simultaneously, however, it was realized that Nature's cycle could not be maintained without the participation of microorganisms, and slowly it became clear that microorganisms take part in a host of processes. Man uses them directly, *e.g.* in the production of foodstuffs.

In recent years the term biotechnology has come increasingly into use to denote applied microbiology; it denotes that biological reactions have been carried out by "technical" processes—a combination of biology and technology[1–3]. The underlying basis of biotechnology is microbiology, for microorganisms are used in all these processes. Biotechnology occupies a key position in the present spectrum of disciplines; one of its chief aims is to conduct the reactions of microorganisms under the conditions prevailing in reactors in such a way that the natural process can be carried out and the desired product obtained.

2. Biotechnology

Microorganisms are the small forms of life ranging from bacteria through yeasts and fungi to algae. Work with such "material" requires many specialized laboratory methods, technical processing methods, and large-scale industrial plant. Many different types of reactors or fermenters have been introduced, and stirring techniques, aeration, separation, drying, extraction, and other methods have been applied. Special technologies have been further developed for specific purposes.

Microbiological processes have a long history. In the first place, developments in other scientific disciplines, *e.g.* microscopy or the determination of biochemical metabolic pathways, led to the elucidation of processes that had previously been

[*] Dr. P. Präve
Hoechst AG, Pharma Biochemie und Mikrobiologie
Postfach 800320, D-6230 Frankfurt (M)-Höchst (Germany)

[**] Based on a lecture given at the 109th Meeting of the Gesellschaft Deutscher Naturforscher und Ärzte, on September 21, 1976, in Stuttgart, Germany.

used on an empirical basis. Even today use is made of some processes whose scientific foundations are still unknown.

One could philosophize as to which were the first biotechnological processes. Accident certainly played a decisive role. It can be assumed that microbiological transformations of foods were utilized very early. Man also knew that food could be preserved, *e.g.* when dried. It would also be worth considering whether partial predigestion did not play a part even before the use of fire; it would have been advantageous for natural selection to provide protein in a more readily digestible form.

The preparation of mead, bread, wine, sauerkraut, cheese, and other dairy products covers a group of microbiological processes that have been known from antiquity.

Unlike most modern technologies, which start from natural raw materials and finally produce waste, biotechnology can often bring a waste product back into the natural cycle. For example, biological purification of waste water is often the decisive method by which a water system is brought back to a natural state. Furthermore, many examples of fermentation (as the principal process of biotechnology is called) use mainly surplus products of agriculture or the food industry.

The value of the cyclic metabolic processes occurring in the microorganisms themselves is supplemented by the advantages of the industrial technology. For example, biotechnological processes occupy little space, are often independent of climate, and can be carried out either where the substrate occurs or where the product is used; they thus fulfil present and future needs.

3. Microbiological Processes—Survey of the Most Important Processes[4, 5]

3.1. Production of Foodstuffs

The classical use of microorganisms is for the production of foodstuffs. Processes of this type convert the available starting substrates into an edible, stable form that tastes well and/or can be readily digested.

A selection of such processes is shown in Table 1. The ripening of cheese can be used to illustrate the potency of microbial processes. The action of the microorganisms taking part includes the oxidation of lactose, lactic acid, other acids, alcohols, and ketones; the proteins present in the milk are converted by hydrolysis into peptides and amino acids; fats are hydrolyzed to fatty acids. These very diverse processes can at the moment be carried out only by using the enzyme systems present in microorganisms.

Similar reactions occur in the production of alcohol, involving processes that are inconceivable without the aid of microorganisms. They are a good example of age-old processes that yield first-class products only through the experience of the brewer or winemaker.

In Asia there are special foods that are hardly known in the rest of the world, although they play a major role in their homelands. In their preparation the substrates are so improved that products of high value are obtained. Such enrichment is a strong motive for many microbiological processes.

Table 1. Selected microbiological processes—production of foodstuffs.

Products	Microorganisms
Milk products	
Yoghurt	*Streptococcus thermophilus*
Kephir	*Streptococcus lactis*
Rocquefort cheese	*Penicillium rocquefortii*
Gouda cheese	*Bacterium sp.*
Tilsiter cheese	*Bacterium sp.*
Alcoholic products	
Beer	*Saccharomyces cerevisiae* *Saccharomyces carlsbergensis*
Rum	*Saccharomyces cerevisiae* yeasts
Whisky	*Saccharomyces cerevisiae*
Wine	*Saccharomyces ellipsoideus*
Soya (also wheat)	*Aspergillus oryzae* (koji mold),
Miso, tofu	also yeasts and bacteria
Fatty and proteinaceous products (biomass)	
Fat	Algae
Protein	Yeasts, bacteria
Agricultural processes (silage, rotting)	
Silage for feed	Lactobacteria
Flax	Decomposing bacteria

The direct production of fat or protein (biomass) by means of microorganisms is a development of the last few decades (see Section 4.1).

Silage plays a large part in agriculture: fresh greenstuffs are subjected to a souring process with lactobacteria and can then be stored and used as feed throughout the year.

The actual course of the reactions always starts from two components—microorganisms and substrate—and leads to three products—microorganisms, residual substrate, and product. The reactions are usually carried out in vats, tanks, or fermenters. The processes discussed in this section normally require only very simple reactors, such as simple wooden vessels, fermentation vats, or stainless steel stirred-tank fermenters. Centrifugation, distillation, and precipitation are among the methods used for isolation of the product.

3.2. Preparation of the Primary Metabolites

Among the products obtained from the metabolism of microorganisms are vitamins and ethanol, amino acids, and solvents. Microbiological processes have for some decades provided an important method of preparing a number of solvents such as acetone, butanol, acetic acid, and glycerol. Since the starting substrates have always been materials that are renewable, *e.g.* molasses, wood, and grain, an industrial process was in principle simply tacked onto the end of the agricultural process, so that a final utilization of the residual, intermediate, or waste product was achieved. Under special conditions (*e.g.* high price of oil) such processes could stage a comeback.

Thus, production of ethanol at economic prices is today possible in many countries because these countries produce the initial substrate at a low cost. Together with a few specialities, this is one of the few important processes of foodstuff production that is carried out microbiologically at the present time.

Table 2 lists further products, among which citric acid occupies a special position. This is used for many purposes,

Table 2. Selected microbiological processes—primary metabolites.

Products	Microorganisms	Uses
2,3-Butanediol	*Bacillus polymyxa*	Solvent
Ethanol	*Saccharomyces cerevisiae*	Beverages, solvent
Citric acid	*Aspergillus spp.*	Food, beverages
Lysine	*Micrococcus glutamicus*	Food and feed additives
Vitamin B_{12}	*Propionibacterium freudenreichii*	Food and feed additives

e.g. as an additive to lemonades, fruit juices, sweets, jellies, ice cream, auxiliary baking materials, as a complex-former in the fats industry, as a pH regulator, as a polishing and etching material, and for removing calcium carbonate deposits. Citric acid production from molasses or *n*-paraffin[6] cannot only compete with agricultural production but moreover is independent of the available land and of climate and is thus a good example of the advantages of specialized biotechnology.

The possibility of preparing natural amino acids is a development of the last twenty years; thanks especially to Japanese work almost any desired amino acid can today be synthesized by microorganisms. This is achieved in particular by the use of mutant strains, but often the desired L-amino acid is produced in a two-stage process using two different microorganisms.

From the wealth of other possibilities we shall mention here only the preparation of vitamins. These are already very complicated substances, but they can often be easily produced by biotechnological processes. An important future field of application will certainly be the biosynthesis of larger and more complicated molecules, whose chemical production would be accompanied by many difficulties.

Most of the processes described in this section require a developed biotechnology in which the stirred-tank fermenter is used as a reactor. In the production of the substances, refinement is also very demanding, since the desired product must be removed from the viscous and chemically complex nutrient solution used to maintain the microorganism.

In modern processes the various procedures are carefully controlled so as to keep, *e.g.*, the pH constant throughout the reaction.

3.3. Preparation of Secondary Metabolites

Secondary metabolites are substances formed by microorganisms under special conditions. These metabolites are rarely essential for normal industrial use or for intracellular processes. There are indications that the production of such substances is one method of removing waste material from the cells.

Table 3. Selected microbiological processes—secondary metabolites.

Products	Microorganisms	Uses
Amylase	*Bacillus subtilis*	Textile smoothing
Dextran	*Leuconostoc mesenteroides*	Plasma expanders
Protein-toxin	*Bacillus thuringiensis*	Insecticide
Penicillin	*Penicillium chrysogenum*	Drugs

Some selected products including enzymes, are listed in Table 3. Most of these are used on an industrial scale, as additives to washing powders, as smoothing materials, as digestion aids, for the clarification of fruit juices, *etc.* These exoenzymes are amylases, proteases, hemicellulases, pectinases, invertases, *etc.* None of them requires a coenzyme. They are not the enzymes of normal metabolism, which play a special role in the fine chemicals sector, although they are also obtained by biotechnological processes.

Furthermore, biopolymers are prepared by biotechnological processes and have special possible fields of application in chemistry and medicine (*e.g.* dextran).

Antibiotics constitute the best known and the most important group. Today it is inconceivable that we should have to treat infectious diseases without the help of antibiotics. Research in this area still leads to interesting products. They are all prepared from streptomycetes, molds, or bacteria in batches in aerated stirred-tank fermenters. The reactor size may exceed $100\,m^3$. Recently the precursors for antibiotics have also been prepared, *e.g.* 6-aminopenicillanic acid, and from these, special antibiotics have been synthesized that are active against some resistant strains.

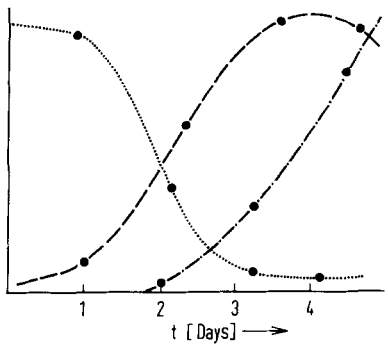


Fig. 1. Production of an antibiotic (schematic). – – – Cell growth (increase in the dry substance of the cell mass), ... Concentration of the carbon source in the nutrient medium, –·–·– Concentration of the antibiotic.

Taking antibiotic production as an example of a biotechnological process, the principle underlying a typical batchwise fermentation (Fig. 1) can be illustrated. The S-shaped curve of cell growth, with its lag, its logarithmic, and its stationary phase corresponds to an inverse of the concentration of the carbon source in the nutrient medium. Synthesis of the desired antibiotic starts at the end of the logarithmic phase of growth.

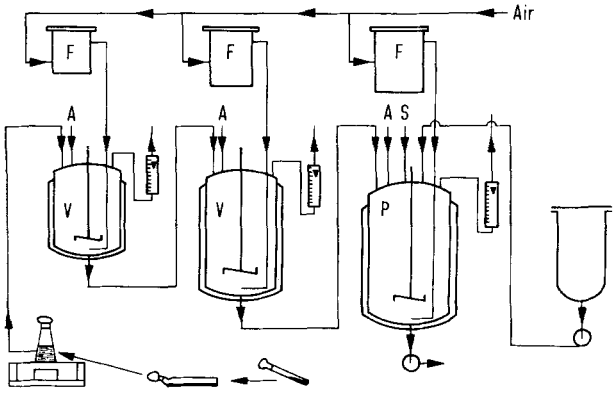


Fig. 2. Scale-up of the fermentation (slant culture—shaking culture—fermenter). A = antifoaming agent; F = filter; P = production fermenter; S = substrate; V = prefermenter; storage vessel on extreme right. For reaction route see text.

The first step of submerged fermentation is the transfer of the organism from an agar slant to a shake-culture in a conical flask (Fig. 2). The culture is then inoculated into a small prefermenter (*e.g.* 20 l). It is customary at this stage and on transfer to a second prefermenter (200 l) to arrange the growth times in such a way that the inoculation occurs during the logarithmic growth phase. In the present example, therefore, the production fermenter must contain 2000 l. This scale-up of about 1 : 10 is typical of the processes under consideration.

The preparation of *Bacillus thuringiensis* spores gives a product not considered harmful to the environment. These spores are sprayed onto cabbage plants and are eaten by pests, in particular by caterpillars. In the caterpillars a toxic product is liberated by the spores. The result of this method is a correction of the mass of special bacilli in the soil; it regenerates the balance that has been disturbed by monoculture.

3.4. Conversion Reactions

Apart from the fact that all the processes described above are conversions of substrates, particular importance must be paid to "biotransformations". Many microorganisms can act as biocatalysts for one-stage reactions of specific substances, thus effecting, *e.g.* an oxidation, methylation, or decarboxylation. These microbial intermediate syntheses are used especially in steroid chemistry to avoid difficult and demanding chemical operations.

3.5. The Economic Importance of Microbiological Processes

For a correct assessment of the importance of biotechnology it is necessary to examine the economic significance of some types of reactions.

Thus, 556000 tons of fresh cheese, in addition to hard, sliced, and soft cheese, with a value of 1.98 thousand million DM, was prepared in 1974 in West Germany alone; in addition, 178000 tons was imported (value 0.936 thousand million DM). In Germany in 1972 breweries and malthouses employed 95000 people in 756 establishments and had a turnover of 9.9 thousand million DM[7]. From the primary metabolites more than 200000 tons of citric acid were prepared worldwide by fermentation (excluding the socialist countries)[8]. Antibiotics are prepared in large quantities; the production of penicillin in the USA rose from 75 tons in 1949 to *ca.* 4500 tons in 1975; the present-day world production is estimated at 10000 tons p.a., the production of all antibiotics totalling 25000 tons p.a.

4. Recent Developments of Biotechnological Processes

Living things are subject to selection and mutation, *i.e.* to evolution. In microorganisms the changes can already be directed to some extent: for example, the yield of an antibiotic can be increased or the microorganisms can be adapted to a different substrate.

Microbiological-biochemical-genetic development work of this type often has sufficient technical consequences to cause economic changes. Antibiotics are a well known example, having been first prepared in small glass vessels they are now produced in highly specialized fermenters; antibiotics were once expensive luxuries, now they are accessible to everyone.

There are also many interesting possibilities from the industrial point of view. New fermenters have come to take their place besides the old types: according to *Rehm*[2, 9] three groups can be distinguished—stirred-tank fermenters (*e.g.* suitable for multiphase fermentation as required for *n*-paraffin substrates), airlift reactors (no mechanical stirring needed), and special types of reactors. This last group includes reactors in which explosive gas mixtures are handled, as is necessary for microorganisms utilizing oxyhydrogen or methane; also, among others, falling-film, fluidized-bed, multistage, and surface reactors[10].

4.1. Biomass Production

Production of biomass is one of the key developments in the whole of biotechnology. This term denotes the production of a mass of cells of microorganisms.

4.1.1. The Substrate

Like other living cells, microorganisms as a rule require a source of carbon and nitrogen for growth, and in addition phosphate and other salts must be present.

Organic compounds serve as a source of carbon and often of nitrogen too. This means that many microbiological processes are based on primary or secondary products of agriculture: milk in the production of yoghurt, barley in brewing, molasses in the production of citric acid, soya in production of antibiotics. A further possibility is to use waste products from human civilization: industrial plants for biological purification of sewage are already indispensable.

There are many substances besides those just mentioned that can act as substrates for the growth of microorganisms, although they appear to be unrelated to life and some of them are even poisonous to cells. Oil, natural gas, *n*-paraffin, methanol, CO_2, CO, and also cellulose are such substances. From the point of view of evolution it is difficult to understand why some bacteria and fungi can use methanol as a source of carbon, and yet can be isolated from soil and water or from flowers and fruits. An explanation could be the presence of pectinesterases[11], which liberate methanol from pectin. It is easier to understand that molds can decompose cellulose, although special species are required for this.

The normal annual growth of cellulose throughout the world is of the order of 10^8 tons; one could not imagine the world situation with respect to cellulose without the activity of microorganisms.

Methanol and cellulose are two very different carbon substrates. Methanol can be obtained from coal, natural gas, or oil and will very probably be one of the most important and cheapest raw materials for chemistry in the future. Cellulose, on the other hand, is a basic material for human civilization (heating, building of ships and houses), and moreover it is renewable. Both substrates are available for biotechnological processes. Some culture media for bacteria which utilize methanol or cellulose[12] are shown in Table 4.

Table 4. Nutrient media for bacteria using methanol and cellulose [12].

Methanol	Added continuously
NH_4OH (25 % soln.)	Initially 2.8 ml/l
H_3PO_4 (85 % soln.)	Initially 2.0 ml/l
$MgSO_4 \cdot 7H_2O$	0.9 g/l
Na_2SO_4	0.24 g/l
$Fe_2(SO_4)_3 \cdot 3H_2O$	85 mg/l
$CaCO_3$	0.14 g/l
and tap water	
Cellulose	5 %
KH_2PO_4	1 %
NaCl	0.1 %
$(NH_4)_2SO_4$	1 %
$MgSO_4 \cdot 7H_2O$	0.3 %
$CaCl_2$	0.1 %
Trace elements and water	

Conversion of methanol into biomass is occurs in a wholly synthetic culture medium, *i.e.* here the microorganisms are in the position that plants occupy in the natural life cycle. Processes based on cellulose accelerate the very slow decomposition of cellulose which takes place in nature. In both cases biomass is produced by a fermentation process from readily accessible raw materials. This biomass consists of cells that often exceed standards, *e.g.* for protein content, for animal feeds or human consumption.

4.1.2. Biotechnology

A characteristic feature of biotechnological processes is that they work batchwise; each batch requires hours, days, or perhaps weeks for completion. After the harvest a new batch is started. In contrast, biomass production is continuous; this means that biomass can be continually removed from the reaction vessel over a period of weeks, months or longer; at the same time fresh supplies of the nutrient medium must be added. The course of such a process, which is a common one in chemical technology, can be changed, by *e.g.* genetic changes in the cells, but it has many advantages (*e.g.* economic).

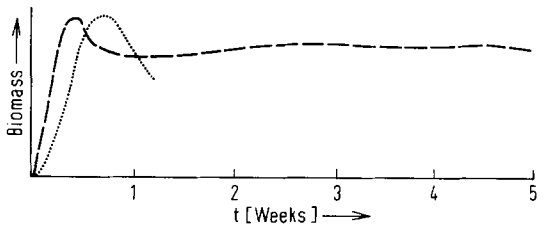


Fig. 3. Growth curves in batch (·····) and continuous (– – –) culture.

In Figure 3 a batch process for the production of biomass from methanol is compared with a continuous process. This refers to a process developed by Hoechst-Uhde and based on methanol, using bacteria of a *Methylomonas* sp.[13], which is obligatorily methylotropic. A fully synthetic medium and modern reactors are used.

Figure 4 shows a representative of the old generation of fermenters together with a new type. The route from the rotting of flax in a cool shelter *via* a fermenting vessel or a cabbage tub led by way of the continuously stirred and aerated tank fermenter to a number of new systems[10, 14–16] that were often influenced by highly developed chemical process technology. The basis of this development can be seen in Table 5.

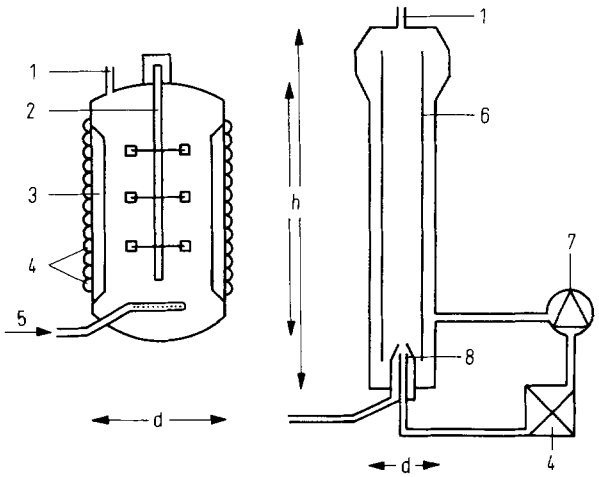


Fig. 4. Comparison of a small classical stirred-tank (left) and a modern injection nozzle loop reactor (right). 1 = Exhaust gas; 2 = multivane paddle; 3 = baffle plate; 4 = cooling; 5 = air; 6 = insertion tube; 7 = circulating pump; 8 = jet.

Table 5. Comparison of reactors (example: production of biomass).

Conventional stirred vessels	Modern loop reactor
High energy costs	Low energy costs
10 kW/m³	2 kW/m³
Internal cooling (jacket)	External cooling (plate exchanger)
Limited scale-up	Unlimited scale-up
Indefinite mixing—	Defined mixing—
irregular residence times	regular residence times
Large air demand	Low air demand
10—20 % oxygen yield	40—50 % oxygen yield
Batch operation	Continuous operation

A comparison of the data, in particular the energy consumption, shows what advantages can be obtained by optimization of the reaction vessel.

In this connection attention should be drawn to the gathering of data during the course of a reaction or cell growth in the fermenter. The computer displays very clearly the wealth of biological data and assists in the choice of appropriate biological developments, provided that two prerequisites are achieved: One is that the data measured must refer to the process in the fermenter, which is relatively easy with synthetic nutrient media but much harder to achieve with complex organic media. The second is that the metabolic state of the microorganism must be known. On this basis we can now begin to arrange for biological processes to take place optimally[3].

4.1.3. Economics

Economic considerations are an important factor in industrial processes. As a rule it is not sufficient to make a new product in a new way. The process as a whole must be able to compete with others and originality is often an insufficient advantage—the old process may provide almost the same product at a lower price.

The fate of new biological and technological developments also depends on economic considerations. However, the processes described here for biomass production have so many

advantages that at least a part of the new biotechnology will probably find application in large-scale practice.

Emphasis should first be placed on the continuous nature of the process. With this method fermentation plants can be designed to be smaller, or with larger vessels they can produce more product than those of batch operation. In a highly automated plant the personnel requirements are also lower. The economical output of plants which produce biomass is around 60000 to 100000 tons p.a.; this quantity of biomass or SCP (Single Cell Protein) can be produced by about 100 men.

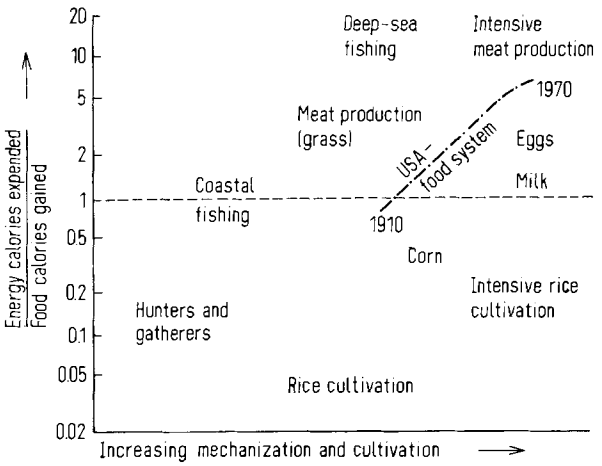


Fig. 5. Energy demand for food production (after [20, 21]). The ratio of energy calories to nutritional calories is shown.

In addition, SCP manufacture requires little land (*ca.* 1000 m^2), is independent of climate, and gives a product that always has the same composition. This product can be prepared almost anywhere in the world in the same quality. If one adds that many countries are greatly dependent on imports of soya and grain, it is clear that some hundred thousand tons of SCP will be produced every year. Such products may also affect the price of protein[17]. A considerably more important aspect of this biotechnology is, however, the energy demand.

Even before that great increase in the cost of energy it had been realized that the costs of power are of decisive importance for any process. This knowledge was, however, not considered seriously because primary energy was so cheap. Only the shock effect of publications about a possible collapse of world resources[18, 19], followed by the price rise, made a critical review of the whole situation imperative.

Thinking in terms of energy consumption there is a disquieting trend especially when one considers food production. A human requires *ca.* 1 million kcal p.a.; from this energetic viewpoint the world harvest ought to be sufficient to supply the requirements of 5.6 billion people p.a. However, 50—90% of the energy in grain is lost if carbohydrates are used for the animal feeds. Moreover, up to 34% of the world harvest is spoilt. On the other hand, the seas are still full of promise—at present only 1% of its potential is utilized. Figure 5 shows how many calories must be expended to provide one nutritional calorie.

One starts with a ratio of 1.0 for coastal fishing *i.e.* 1 calorie of energy is required to obtain 1 calorie of food. Our ancestors, the hunters and gatherers, lived energetically more favorably; with a ratio of 0.1 to 0.05 simple rice culture is in the same region. The modern methods of obtaining or producing food are much more energy-demanding: for normal production of meat or eggs 2—5 calories of energy must be provided, for intensive meat production 10 calories, and for fish caught in the open sea 20 calories or even more. Since biomass from microorganisms is characterized especially by its high protein content—of the same order as that of the richest protein sources—it is not surprising that SCP processes are being developed throughout the world. Presuma-

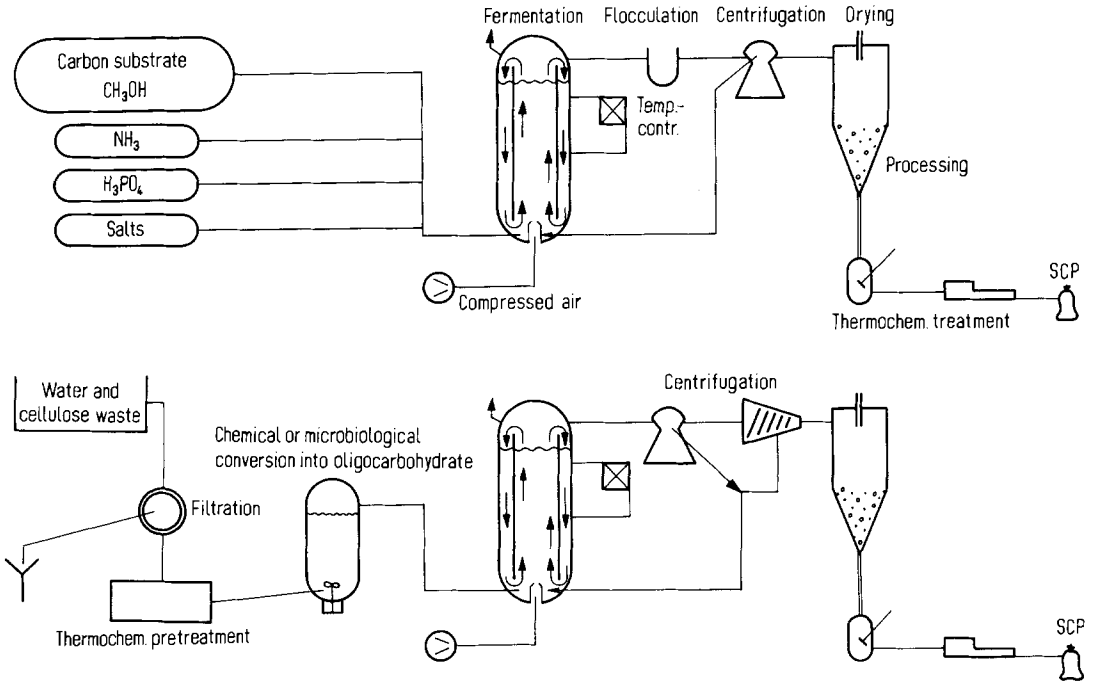


Fig. 6. Two SCP (single cell protein) processes, top for a methanol, bottom for a cellulose substrate [3].

bly such products will in the not too distant future be processed into human food, since the route *via* animals results in an average energy loss of 85 %[22]. A different calculation[23] starts from the fact that 4000 kg of grain are harvested from 1 hectare, and that such a crop used as animal feed yields 85 kg of protein (beef); fermentative utilization of the grain would, in contrast, yield 680 kg of protein!

4.1.4. Biomass Processes

Out of the many processes for the production of biomass two will be considered here from the aspect of their possible utilization. Figure 6 illustrates one process based on methanol and one based on cellulose.

Much interest attaches to use of a symbiotic mixed culture in a process starting from cellulose[25]; in this process a type of population such as occurs in nature is used for inoculation. Utilization of this substrate will certainly be locally restricted; in contrast, processes based on methanol can be used globally. The quality of the product is also an important positive argument (Table 6).

Table 6. Composition of some protein sources.

	FAO Standard [24]	Soya meal [24]	SCP yeast [24]	SCP bacterium [13]
Crude protein content [%]		45	60—62	80—85
Essential amino acids [g/16 g N]				
Ile	4.2	4.8	5.3	4.3
Leu	4.8	6.1	7.8	7.4
Lys	4.2	6.1	7.8	6.5
Met + Cys	4.2	2.9	2.5	2.5
Phe + Tyr	5.6	8.4	8.8	7.1
Thr	2.8	4.0	5.4	4.6
Val	4.2	5.0	5.8	5.6
Trp	1.4	1.3	1.3	1.5

4.2. Other Types of Processes

4.2.1. Enzymes

The step from the production of cells to their content is a short one. Enzymes may well be one of the most interesting groups among the cell constituents; they are biological catalysts that play a key role in the biosynthesis of, *e.g.* carbohydrates, proteins, fats, and steroids.

The major industrial users of enzymes are the starch, leather, foodstuffs, and detergent industries and medicine, but enzymes also play a part in the fine chemicals sector.

Enzymes produced by microorganisms have achieved great importance in the last few decades. For example, microbiological production of the rennin enzymes has already been developed, since it is difficult in certain countries to obtain rennin in amounts sufficient for cheesemaking. The most interesting development is, however, that of immobilized enzymes[26, 27]. Enzymes can be immobilized in water-insoluble material without any loss of their catalytic activity. Their uses are obvious and there are already many processes for this purpose; for example penicillin-cleaving amidases immobilized in a column or in a reactor yield 6-aminopenicillanic acid, the starting point for many important semisynthetic penicillins.

The food and beverage industries are also users of such enzyme preparations, and in the technical field enzyme treatment is especially valuable for making waste waters harmless.

4.2.2. Secondary Metabolites

Among the secondary metabolites we find, for example, new antibiotics, substances with pharmacological activity, and other natural products. The microbiological preparations of food colors, insecticides, and inhibitors are other interesting developments.

Here too belong biopolymers such as the dextrans. The future of this group seems very promising. As auxiliaries in drilling they confer on the drilling mud the viscosity needed for transporting rock. The properties of these natural but fermentatively prepared polymers for special purposes are very favorable[17].

4.2.3. Leaching

The capabilities of microorganisms can also be exploited for metal extraction. Thus, in leaching processes crystalline copper sulfide or uranium compounds can be solubilized by bacteria. It has long been known that microorganisms take part in weathering, soil formation, mineral deposition, *etc.*, but it is still astonishing to find that toxic heavy metal compounds can be dissolved by special microorganisms such as *Thiobacillus* and *Ferrobacillus* species. In this way it becomes possible to rework old mine dumps, and in a few cases the process is already used on a large scale (Sweden, Canada) to enrich low-grade ores.

4.2.4. Waste Disposal

Our industrial society must be concerned more with the problems posed by residues and wastes.

Waste water usually requires biological purification. Biotechnology is also used in the removal of refuse tips; in more recent processes the material is mixed with waste water and composted. Processes of this kind must be suited to the type of waste arising from a specific town, industry, or agricultural system, and thus a large field of work can be envisaged for the future. Only the microorganisms made available by mutation and adaptation and a corresponding advanced technology will finally enable the waste materials to be recycled.

There are processes by which waste is retransformed into basic raw materials. Thus, in many large towns methane is produced from waste in fermentation or decomposition towers with the aid of microorganisms. This methane is fed into the town's gas distribution network, burnt in small power plants, or used in the operation of the decomposition towers. The process is anaerobic, the organic material being first converted into hydrogen and fatty acids which are then decomposed by Methanobacteria into methane and CO_2.

4.2.5. Other Possibilities of Using Microorganisms

Nitrogen fixation by microorganisms for agricultural purposes cannot yet be exploited at will. Bacteria exist which can fix atmospheric nitrogen by means of a nitrogenase (*e.g.*

Clostridium, Azotobacter); in these organisms N_2 is converted by way of NH_3 into amino acids and proteins. The old three-field crop rotation system was based partly on nitrogen enrichment of the land by N_2-fixing microorganisms. Symbionts should also be cited; nodules on the roots of leguminous plants in particular contain bacteria (*Rhizobium* species) that bind molecular nitrogen during symbiosis; in this way some 100—200 kg of nitrogen are bound per hectare each year. The current manufacture of fertilizers by the Haber-Bosch process is essential to our civilization but requires a large expenditure of energy. Since there are other microorganisms that bind atmospheric nitrogen, there is a prospect that this economical energy-saving process will one day find greater application.

Another group of microorganisms must also be mentioned, namely those that react with inorganic compounds (the leaching process has been discussed in Section 4.2.3 above). *Desulfovibrio*, for example, forms acetic acid and hydrogen sulfide from sulfate and hydrogen; denitrifiers reduce NO_3 and NO_2, for example, liberating N_2 and water. For many microorganisms the energy source is light, required for example so that H_2S can be used as an H-donor. These phototrophic and many C-autotrophic microorganisms require carbon, but this carbon is derived from atmospheric CO_2 and not from carbohydrates, fats, or proteins. This carbon autotrophy shows the relationship between the microorganisms and plants. Utilization of these possibilities by biotechnology is only just beginning; but, for example, foul-smelling gases that also contain CO_2 can be subjected to fermentation in which the microorganisms transform the harmful material, use the CO_2 as a source of carbon, and in so doing also provide biomass.

Possibilities of a very different kind should now be added to the above examples. A wide variety of starting materials for chemical reactions can be prepared microbiologically: acetone, butanol, isopropanol, ethanol, glycerol, acetic acid, and many others can be produced by special microorganisms on media that are usually substrates of vegetable origin. Such substrates are renewable. Processes of this kind are not generally economic, but in the developing countries a given process may serve as the sole source of material; for example, ethanol production from sulfite lye, maize, whey, molasses, and nearly all fruits and grains is widely practised in the developing countries and to some extent also in the industrialized world. The use of such processes is likely to increase greatly in the future, when other starting materials become either unavailable or too expensive.

5. Cycles and Adaptation—Biotechnological Possibilities

5.1. Utilization of Natural Cycles

Looking at the carbon cycle[28] in Figure 7 makes it clear that the processes used today for treating dumps and purifying waste water are only a beginning. Microorganisms play a role in the essential synthetic and degradative processes taking place in the biosphere and cells of microorganisms and in

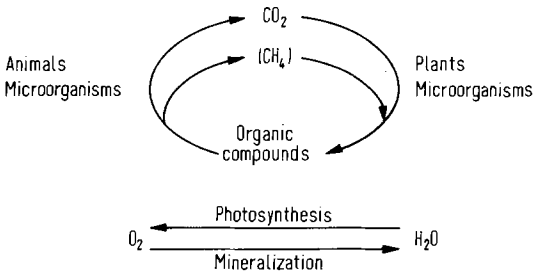


Fig. 7. The carbon cycle [28].

biotechnology. *Cramer*[29] compared biological metabolism with a cyclic function to cultural metabolism with a linear function; it became clear that exponential growth of one parameter in a closed system rapidly leads to stagnation values; any growth curve, whether of microorganisms or of man, confirms this conclusion, which is not contradicted by the statement that "growth is the sole proof of life" (Cardinal *Newman* 1864[30]). Biological reactions are balanced processes, which have a high degree of efficiency. This high efficiency is achieved through evolution. The performance of muscle cells is an example: it is believed that their efficiency averages 60%. Combustion engines reach maximum values of 30% or more, but the average is a bare 10%. Intensive animal breeding, deep-sea fishing, and intensive grain production have efficiencies between 5 and 20%. The biotechnological process for the production of biomass reaches 20% or more (see Fig. 5), so that it would seem wise to include such processes in considerations of how to remove waste and produce food or, in general, how to introduce biological cycles in place of the linear consumption processes.

5.2. Adapted Processes

Large-scale biotechnological processes require much capital, extensive know-how, and a highly skilled labor force, but

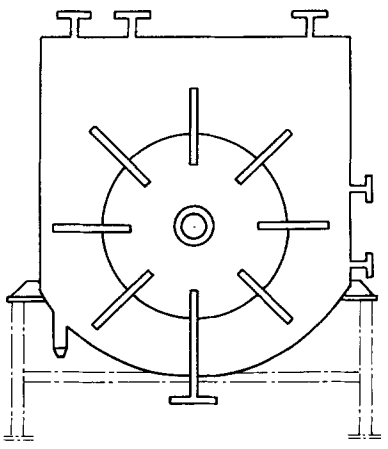


Fig. 8. Paddle wheel reactor for the production of biomass on a small scale.

they could be supplemented by small-scale processes that function with little capital, little know-how, and a relatively

untrained labor force. Biotechnological processes in particular must often be adapted to serve specific localities. The waste water of a town in Central Europe must be handled differently from ditch water in Africa. Processes for the production of biomass can be run in special small plants which provide a small population with biomass for use, *e.g.* as a component of animal feeds[31]. Figure 8 shows such a reactor[34]. An area with many intensive animal feeding units must, however, be served by a large plant.

However, it is not only a question of large plants—plants can be adapted to special needs. The basis for this lies in the possibility of cell adaptation: mutation, selection, or merely the suitability of the substrate may enable a particular problem to be solved. In this way, for example, application of the astonishing results coming from molecular biology in the last 15 years has started: by plasmid transfer the degradative metabolic route characteristic of one bacterium was transferred to another where it was, so to speak, collected, and the resulting "supermicrobe"[32, 33] could then degrade compounds such as camphor, octane, salicylate, and naphthalene. Biotechnological processes are important in that it may be possible to bring our civilization back into equilibrium with their aid.

6. Conclusion

The microbial cell had hitherto been utilized only accidentally and sporadically. In the past its possibilities were often neglected in favor of more economic processes. Today we have become aware of the darker side of our civilization, but microbiology and technology offer a possible way out. Microbiology brings with it the natural principle of cyclic processes, the simplest of cells are capable of many varied tasks, and the opportunities for these smallest of living forms include all the reactions known in the living organism. The technology of today is highly developed and offers a wealth of processes for which we can thank our level of civilization. *Claude*[35] speaks of the coming age of the cell; *Spinks*[23] puts his trust in technology but is politically and economically pessimistic.

It seems reasonable to except the union of biology and technology that we call biotechnology to play a decisive role in the future.

Received: September 14, 1976 [A 153 IE]
German version: Angew. Chem. *89*, 211 (1977)
Translated by Express Translation Service, London

[1] *H. Weide*, Monatsh. Veterinärmed. *29*, 704 (1974).
[2] *H.-J. Rehm:* Industrielle Mikrobiologie. Springer, Berlin 1967.
[3] *P. Präve, D. A. Sukatsch, U. Faust*, Interdisc. Sci. Rev. *1*, 85 (1976).
[4] *S. C. Prescott, C. G. Dunn:* Industrial Microbiology. McGraw-Hill, New York 1959.
[5] *M. J. Pelczar jr., R. D. Reil:* Microbiology. McGraw-Hill, New York 1972.
[6] DOS 2212929 (1972), Benckiser GmbH.
[7] Statistisches Jahrbuch für die Bundesrepublik Deutschland 1975. Stat. Bundesamt/Wiesbaden. Verlag Kohlhammer, Stuttgart 1976.
[8] *G. Schulz, J. Rausch* in: Ullmans Encyklopädie der technischen Chemie. 4th Edit. Verlag Chemie, Weinheim 1975, Vol. 9, pp. 624ff.
[9] *H.-J. Rehm*, Chem. Ind. (Düsseldorf) *27*, 373 (1975).
[10] *W. Sittig, H. Heine*, Lecture delivered at Achema 1976.
[11] *R. K. Finn*, personal communication.
[12] *S. Schmid, M. T. Bomar*, Alimenta *14*, 185 (1975).
[13] *U. Faust, B. Dorsemagen, P. Präve, D. A. Sukatsch, K. H. Zepf* in *H. Dellweg:* 5. Internationales Fermentations-Symposium, Berlin 1976. Verlag Versuchs- und Lehranstalt für Spiritusfabrikation und Fermentationstechnologie, Berlin 1976, p. 203.
[14] *A. Prokof, J. Votrula*, Folia Microbiol. *21*, 185 (1976).
[15] *V. Oels, K. Schügerl, J. Todt*, Chem. Ing. Tech. *48*, 73 (1976).
[16] *A. Einsele, A. Fiechter*, Chem. Anlagen Verfahren April 1973, p. 57.
[17] *C. S. Barnes*, Food Technol. Aust. Febr. 1976, p. 55.
[18] *D. L. Meadows et al.:* The Dynamics of Growth in an Finite World. Wright-Allen Press, Cambridge 1973.
[19] Futures *1* (Feb.) 1973, Guildford Surrey.
[20] *J. S. Steinhart, C. E. Steinhart*, Science *184*, 307 (1974).
[21] *A. L. Johnson jr.*, Astronaut. Aeronaut. Nov. 1974, p. 64.
[22] *D. Pimentel, L. E. Hurd, A. C. Bellotti, M. J. Forster, I. N. Oka, O. D. Choles, R. J. Whitman*, Science *182*, 443 (1973).
[23] *A. Spinks*, Proc. Roy. Soc. Med. *67*, 969 (1974).
[24] *H. G. de Pontanel:* Proteins from Hydrocarbons. Academic Press, London 1972.
[25] *R. K. Finn, A. L. Tannahill*, Biotechnol. Bioeng. *15*, 413 (1973).
[26] *H. H. Weetall*, Process Biochem. July/Aug. 1975, p. 3.
[27] *W. R. Vieth, K. Venkatasubramanian*, Chem. Technol., Jan. 1974, S. 47.
[28] *W. C. Evans*, Biochem. Soc. Trans. *7*, 433 (1976).
[29] *F. Cramer:* Fortschritt durch Verzicht. Nymphenburger Verlagshandlung, München 1975.
[30] *H. G. Stever*, Interdisc. Sci. Rev. *1*, 1 (1976).
[31] *R. Knecht, U. Faust*, UNIDO, Draft Report of the Exper. Group Meeting, Vienna, Oct. 1973, ID/WG. 164/29.
[32] *A. M. Chakrabarty, D. A. Friello*, US-Pat. 3923603 (1974), General Electric Company.
[33] Processing, Feb. 1976, p. 7.
[34] *U. Faust, R. Knecht, W. Wengeler*, DOS 2454443 (1976), F. Uhde GmbH.
[35] *A. Claude*, Science *189*, 433 (1975).

Secondary and Tertiary Structure of Polysaccharides in Solutions and Gels

By David A. Rees and E. Jane Welsh[*]

Many polysaccharide chains can adopt ordered helical and ribbon-like secondary structures. It seems however that these chains are often so stiff and extended that the cooperative interactions necessary for stability in the solvent environment can only be achieved when inter-chain as well as intra-chain interactions are favorable. Hence we commonly find two- or more-stranded associations of helices, of ribbons, or of helices with ribbons. These can be regarded as tertiary and higher levels of structure. The ordered secondary structure characteristically requires a regular repeating sequence of sugar residues, and the termination of this sequence by insertion of a residue of different type may also terminate the secondary structure and hence the association in which it is involved. This is the mechanism by which native polysaccharides may link up to form three dimensional networks, or gels, in which state they perform their natural roles in maintaining the hydration and integrity of biological tissues. For several polysaccharides there is evidence that the mechanism of biological control over the fine topology and properties of the gel network is mediated by enzymes which modify sugar residues at the polymer level to change the pattern of "interrupting" sugar residues.

1. Introduction

The idea of primary, secondary, and tertiary structure has essentially the same meaning for polysaccharides as for proteins and other biopolymers; it provides a convenient way of distinguishing different levels of structural organization. The primary structure describes the covalent sequence of monomer residues in the chain; the secondary structure defines any geometrically regular arrangement in space that this sequence might adopt; and the tertiary structure defines the way in which these arrangements pack together in a compact whole. In polypeptides and proteins, the α-helix and the β-sheet structure are familiar examples of secondary structure, whereas the tertiary structure is, for example, the overall form of a globular subunit. Similarly, various helical and ribbon-like secondary structures of polysaccharides are known and some of these are described later in this article. They can pack in more elaborate arrangements such as double helices and aggregates of helices and ribbons, which we can regard as tertiary and higher levels of structure.

In this article, we shall focus attention on structure in solution because this is usually expected to be most relevant to the understanding of physical and biological properties. However, the characterization of solution conformations does ultimately depend on comparison with ordered structures defined in the condensed phase by X-ray diffraction. Very many solid state conformations have been elucidated in the last five years—far more than have so far been studied in solution—but we do not have space to describe and discuss them systematically here.

In any discussion of polymers in solution, we cannot of course take it for granted that conformations are necessarily ordered. In all polymer systems there is an entropic drive to the disordered (random coil) state, which must be outweighed by sufficiently favorable non-bonded interactions before an ordered form can be adopted. For polysaccharides, the relevant interactions are hydrogen bonding, dipole and ionic interactions, and solvation terms. Contributions from hydrophobic and charge transfer interactions, which are so important for proteins and nucleic acids, probably have little relevance here. The secondary interactions are individually so weak that conformational stability can be achieved only when a large number of them is simultaneously favorable—that is, when they act cooperatively. In polysaccharides it rarely seems to be possible for such stabilization to exist within a single chain; on the contrary, it requires the alignment and interaction of two or more chain segments, usually with long regions of regular covalent sequence. Often, such regions are terminated by changes in sequence which are incompatible with the ordered association. There are obvious analogies here with helix-breaking residues, such as proline, in proteins. The interruptions can be provided by the introduction of one or more different sugar units, by chain branching, or other altered substitution.

A further important consequence of interruptions in secondary and tertiary structure of polysaccharides is that a single chain can pass through several regions of tertiary structure, that is through several chain associations, each involving a different partner with the result that a three-dimensional network, or gel structure, is set up. In such systems, the interruptions clearly have an important function in controlling the density and distribution of cross-linking and hence the hydration and detailed pore structure of the gel. These features seem to be under enzymic control at a late stage in polysaccharide biosynthesis; after polymerization, the regions of regular chain-associating residues are "unmasked" in ways that will be described for several examples, inviting analogy with the secretion of many proteins in an inactive form which is later converted by covalent modification to an active form.

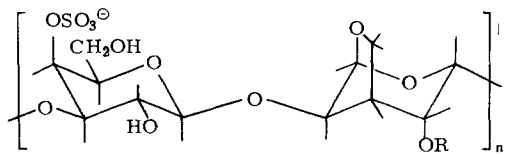
[*] Dr. D. A. Rees, Mrs. E. J. Welsh
Biosciences Division, Unilever Research
Colworth House
Sharnbrook, Bedford MK44 1LQ (England)

Other aspects of this subject, including solid state conformations and the implications of conformation for binding, were reviewed in 1973[1].

2. Double Helices in Solutions and Gels

2.1. Double Helices in Solution: Carrageenans and Agarose

Double helix conformations have been characterized in the solid state[2,3] for a number of algal polysaccharides of types



1,3-linked β-D-galactose — 1,4-linked 3,6-anhydro-D-galactose

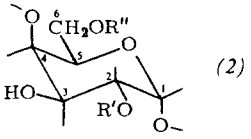
(1a), R = $SO_3^{\ominus}$: ι-carrageenan
(1b), R = H: κ-carrageenan

(1) and *(3)* (see Section 2.1.3). These are alternating copolymers of 1,3-linked β-D-galactose and 1,4-linked 3,6-anhydro-D- or L-galactose[4–7]. Individual members of the family carry different amounts of sulfate ester and/or other substituent groups. It appears that the polysaccharides containing 3,6-anhydro-D-galactose form threefold right handed helices whereas those containing 3,6-anhydro-L-galactose form threefold left handed helices.

2.1.1. ι-Carrageenan

ι-Carrageenan *(1a)* is the most highly sulfated member of the double helix-forming polysaccharide family and it is also the member for which the double helix conformation is most thoroughly characterized, both in the solid state and in solution. One influence that stabilizes the double helix is a hydrogen bond between O-2 and O-6 of D-galactose residues on different strands. It will be observed that these two positions represent the only unsubstituted hydroxy groups in the covalent structure and therefore that this one hydrogen bond, repeated along the chain by helical symmetry, provides a fully hydrogen bonded structure.

Native ι-carrageenan does not consists entirely of a regular, alternating sequence of sugar residues; interruptions exist at various points in the chain and appear to terminate the double helical regions. We shall first describe the properties of ι-carrageenan after processing to remove these interruptions which are of the types shown in formula *(2)*.



(2)

R' = H: split by periodate
R' = H, R'' = $SO_3^{\ominus}$ } undergo reaction with $NaBH_4$
R' = R'' = $SO_3^{\ominus}$ }

This is achieved by using the Smith periodate degradation sequence[8] to split the 4-linked residues in the C1 chair form that are not 2-sulfated, then converting the other residues into 3,6-anhydride with $NaBH_4$[9]. The result is that the native, long chains with interrupted sequence are converted to short chains of regular sequence which we call "ι-carrageenan segments".

That the ι-carrageenan segments can exist in the double helical conformation in solution, is supported by a variety of measurements on the reversible "melting" of this structure. Light-scattering and osmometry measurements show that the expected change by a factor of two occurs in the molecular weight[10]. The accompanying optical rotation change[11] shows (at constant temperature and pressure) a concentration-dependence which corresponds to a dimerization process[12] (see Fig. 2).

The sign and magnitude of this shift can be related by a semi-empirical treatment of optical activity to the conformation angles of the polysaccharide backbone[13]; it emerges that there is excellent agreement with the sign and magnitude to be expected from the double helix geometry shown to exist in the solid state[14]. In addition corroborative evidence of an order-disorder transition has been obtained by high resolution and relaxation NMR techniques. ^{13}C-NMR studies have shown that, as expected, the mobility of residues in the form believed to be the helix is severely restricted since a marked decrease occurs in the spin-spin relaxation times (T_2) for the carbon nuclei (Fig. 1).

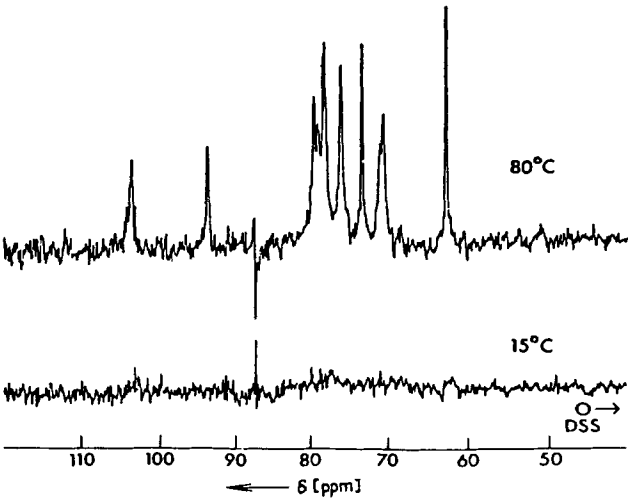


Fig. 1. Comparison of ^{13}C-NMR spectra for ι-carrageenan segments at 80°C (upper spectrum) and 15°C (lower spectrum). Concentration 6 % (w/v); solvent 0.1 M sodium chloride; standard DSS (DSS = sodium 2,2-dimethyl-2-silapentane-5-sulfonate).

This results in linewidth broadening to such an extent that the peaks are lost from the high resolution spectrum[15]. A similar progressive disappearance of intensity without other changes in the high resolution spectrum has been seen with ^{1}H-NMR spectra and has been interpreted in essentially the same way. The changes are paralleled by the appearance of a microsecond T_2 component in the pulse spectrometer concomitant with the optical rotation change.

A thermodynamic description has been obtained by determination of the enthalpy of the transition by calorimetry and from the van't Hoff isochore[16]. Again the model accounts adequately for the observations and the results show further that the interconversion is two state all or none. Finally,

small angle X-ray scattering shows rod-like molecules in solution with dimensions which correspond to the double helix.

2.1.2. Other Carrageenans

κ-carrageenan *(1b)* has essentially the same covalent structure as ι-carrageenan except that only one sulfate group is present on each disaccharide repeating unit, this being on O-4 of the D-galactose residue[17]. This change modifies not only the conformation in the solid state but also the solution properties. Although the X-ray diffraction evidence is not as well defined as ι-carrageenan, it has been interpreted in terms of a right handed three-fold double helix with the pitch somewhat shortened and the relative positions of chains shifted[2].

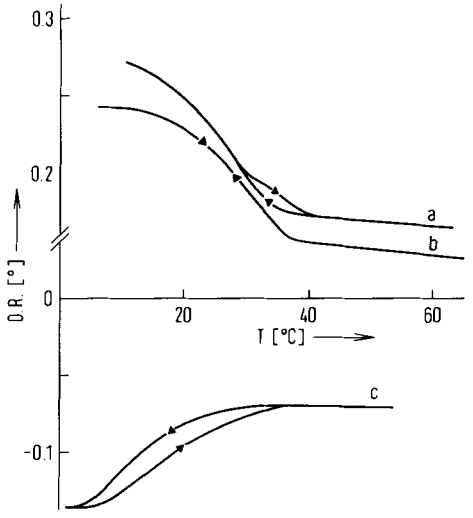


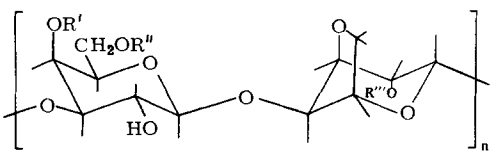
Fig. 2. Comparison of the optical rotation variations with temperature for segments of (a) κ-carrageenan, (b) ι-carrageenan, and (c) agarose sulfate. Heating and cooling curves are distinguished by arrows. $\lambda = 546$ nm; concentration 3 % (w/v); solvent distilled water.

Short chains of regular sequence can be obtained from κ-carrageenan in the same manner as described for ι-carrageenan. Optical rotation measurements on this product show a concentration-dependent, temperature-induced cooperative transition which provides good evidence that the double helix can persist in solution[18,19]. The curve shows hysteresis in formation and "melting" of the ordered conformation which is enhanced by the addition of univalent salt (Fig. 2, curve a). The extent of this effect appears to parallel the extent of aggregation of the double helices—hence its enhancement in salt solution when electrostatic repulsions are screened. The high charge density of the ι-carrageenan double helix limits aggregation and hence hysteresis is not observed in that system (Fig. 2, curve b).

Furcellaran, a third member of the carrageenan family, has an even lower content of sulfate ester with only 40 % of the 3-linked residues being substituted. Less is known about its solid state and solution conformations but the optical rotation and other properties strongly suggest analogous behavior[20]. As we would expect from its lower charge density, aggregation and hysteresis effects are still more pronounced than for κ-carrageenan.

2.1.3. Agarose and Derivatives

A recent X-ray diffraction investigation on fibers of agarose and a number of derivatives of type *(3)* (Table 1) from natural sources and chemical modification, has led to a family of related double helical models[3]. As mentioned earlier, the presence of the anhydro sugar in the L-configuration reverses the screw sense of the helix but still retains the threefold symmetry. The pitch of the helix (1.96 nm) is still shorter than for ι-carrageenan (2.66 nm) and κ-carrageenan (2.46 nm), following the trend of changing sulfate content. Within the agarose series the helix geometry is not fundamentally altered by introduction of substituents on O-2 of the 3,6-anhydride and on O-4 and O-6 of the D-galactose residue. This changed substitution does however alter the stability of the solution tertiary structure, particularly where aggregation of these helices is pronounced.



(3)

1,3-linked β-D-galactose

1,4-linked 3,6-anhydro-L-galactose

Table 1. Compilation of substituted agaroses of type *(3)*.

Name	R'	R''	R'''
Native agarose	H	H	H
Naturally occurring *O*-methylated agaroses	H	50—75 % H 25—50 % CH_3	H
	H	H	50 % H 50 % CH_3
Chemically hydroxyethylated agarose	CH_2CH_2OH, partially and irregularly substituted on all positions		
Naturally occurring agarose sulfate (used in optical rotation studies)	H	13 % CH_3 87 % $SO_3^{\ominus}$	80 % H 17 % $SO_3^{\ominus}$, 3 % CH_3
Agarose sulfate, also naturally occurring	H	$SO_3^{\ominus}$	80 % H 20 % $SO_3^{\ominus}$
Agarose naturally substituted with pyruvic acid	*ca.* 12 % 4,6-*O*-carboxyethylidene		H

As with carrageenan, the disaccharide repeating unit represents an idealized extreme of primary structure, because interruptions usually exist along the chain. Again these are helix-incompatible and can be modified to yield a structurally regular polysaccharide product. Unfortunately, it is not possible to follow the complete order-disorder transition with this product because the segments associate and separate rapidly from solution at the onset of helix formation[19]. This behavior is to be expected for a chain molecule which is not solubilized by ionic substituents because much of the drive to solution is associated with conformational entropy and this is lost when the molecule becomes conformationally rigid. Agarose segments substituted with sulfate ester on C-6 of the 3-linked sugar and partially on C-2 of the anhydride do remain in solution after formation of the ordered state. The optical rotation behavior is then consistent with double helix formation and, like κ-carrageenan, shows a hysteresis loop on heating and cooling[21] (Fig. 2, curve c).

2.2. Double Helices in Gels

As we indicated in the introduction, one consequence of interruptions in the covalent sequences in polysaccharides which undergo chain association is that individual polysaccharide chains are forced to combine with a large number of partners and, if the resulting complex is hydrophilic, the result is a swollen gel. This is shown schematically for ι-carrageenan in Figure 3.

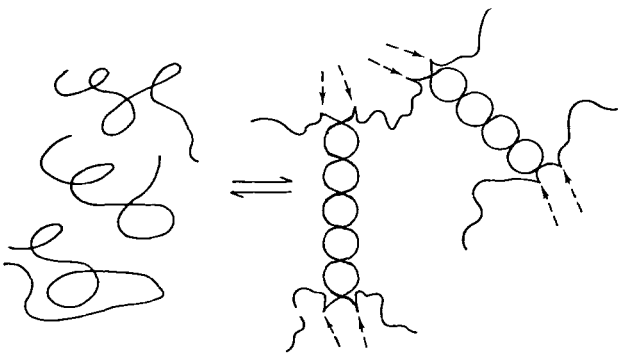


Fig. 3. Model for the molecular basis of gel formation by ι-carrageenan: The helix-breaking kinks are shown by arrows.

These gels show optical rotation changes analogous to those that accompany double helix formation and melting in the segments, and the midpoint for the transition is usually close to the temperature for sol-gel conversion[19]. This remains true even when the transition temperature is altered by changing the concentration of polysaccharide or salt, and in systems which show hysteresis in the heating and cooling curves. All this provides good evidence that the chain association in helix formation is the actual mechanism of cross-linking in the gel network.

The mechanism of gelation is further substantiated by competitive inhibition studies[22]. Introduction of ι-carrageenan segments into an ι-carrageenan gel is expected to lead to double helix formation between short and long chains which will be unproductive from the point of view of cross-linking into a continuous network. In contrast, in systems in which the double helices aggregate when formed as in κ-carrageenan, incorporation of segments should no longer prevent cross-linking (Fig. 4).

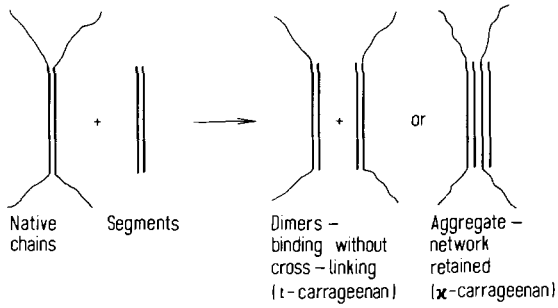


Fig. 4. Incorporation of segments into the gel network—proposed molecular interpretation.

These effects are indeed seen in gel strength measurements where incorporation of segments markedly decreases ι-carrageenan gel strength and κ-carrageenan gel strength is actually enhanced by addition of the corresponding segments. This competitive inhibition method therefore distinguishes between chain association by dimerization and chain association which involves the formation of larger aggregates.

Calorimetry[16] and optical rotation[15] measurements indicate that the extent of helix formation is as high as 80% of the theoretical maximum, or even higher, in carrageenan and agarose gels. This is surprising when we consider the topological constraints that must exist on the formation of double helices in these highly tangled systems.

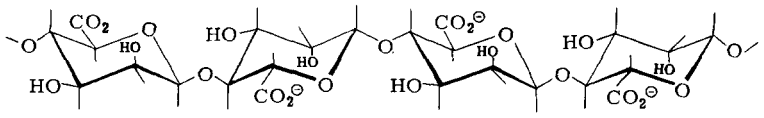
The detailed pore structure of the gel is evidently a consequence of the number and distribution of double helical sections which is in turn determined by the extent to which the covalent structure contains regular alternating sequences longer than the critical size for double helix formation. The knowledge we have of biosynthesis of these polysaccharides, suggests that these variables are under control through regulation of appropriate enzyme levels. As in the biosynthesis of most other polysaccharide types, these carbohydrate chains appear to be built up by transfer of glycosyl residues from nucleotide disphosphate donors. Very probably the sugar residues are polymerized in their unsubstituted form and then modified afterwards by the introduction of sulfate ester and the formation of anhydride and other derivatives. Very little detailed information is available on these stages but, in the agarose series, it seems likely that the nucleotides involved are uridine diphosphate D-galactose and guanosine diphosphate L-galactose[23].

For both the agarose series and the carrageenan series an enzyme has been detected in the parent alga which will convert 4-linked 6-sulfated residues to anhydride at the polymer level[24, 25]. This is presumed to represent a stage in natural biosynthesis, a view that is supported by the identification of precursor residues and in some cases precursor polysaccharide fractions; in principle these are convertible to agarose, κ-carrageenan, or ι-carrageenan respectively by the action of the appropriate enzyme. Because the stereochemical influence of an isolated 4-linked 6-sulfated residue in a chain otherwise composed of alternating 3-linked β-D-galactose and 4-linked 3,6-anhydride residues is to introduce a "kink", this enzyme can be considered to "de-kink" the chain and it has accordingly been given the trivial name "dekinkase".

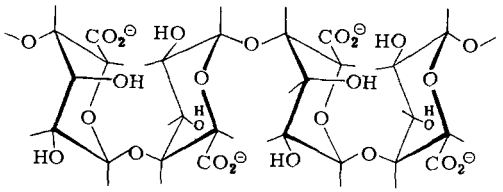
3. Ordered Ribbons in Solution and Gels: Alginates and Pectins

3.1. Alginates

Another group of algal polysaccharides which can adopt ordered solution conformations, primarily by a dimerization process, are the alginates. These are linear polymers of 1,4-linked β-D-mannopyranosyluronate residues and 1,4-linked α-L-gulopyranosyluronate residues, containing homopolymeric sequences[26,27,28] and also regions in which the two sugars alternate although perhaps not in strictly regular fashion[29,30]. The relative proportions of these types of sequence, or "blocks", alters with the botanical source, with the state of maturation of the plant, and with the morphological origin of the polysaccharide within it. It is possible to obtain naturally occurring polymers consisting almost exclusively of polymannuronate sequences and others in which guluronate represents over 70% of the residues present.



1,4-linked β-D-mannuronate



1,4-linked α-L-mannuronate

Fiber diffraction studies on alginate samples of these two extremes have given insight into conformations of two of the individual blocks. In the solid state polymannuronic acid adopts a flat ribbon-like twofold conformation[31] similar to that of other β-1,4 di-equatorially linked hexosans, such as cellulose, chitin, and mannan. In the salt form the helix can be modified to a threefold conformation[32] which is still extended and ribbon-like. In polyguluronic acid[33], as a consequence of the residues being linked di-axially and 1,4-, rotation about the glycosidic bonds is even more restricted and a buckled twofold conformation is adopted which is maintained in all the salt forms so far studied[32].

To study the ability of the various block structures to maintain secondary and tertiary structure in solution it is possible to split out the three types of sequence by partial acid hydrolysis[27,28]. Polyguluronate segments show an enhanced and at first unexpected Ca^{2+}-binding property when the chain length exceeds a critical value of 20 or so residues[34,35]. This observation of a threshold for strong calcium binding suggests a cooperative mechanism. Such effects are not seen for the corresponding polymannuronate oligomers. By other criteria also, it can be shown that polyguluronate sequences show cooperativity in their calcium binding behavior, whereas polymannuronate and the alternating sequences do not[34]. Such cooperativity implies that the binding of each ion facilitates the binding of the next, *i.e.* that these sites exist in ordered arrays which, in view of the stiff and extended nature of the chain (see above), are formed between chains rather than within an isolated chain. Physical and mathematical model building[36] using criteria based on crystal structures of analogous salts including calcium sodium D-galacturonate[37] and the strontium salt of a disaccharide derived from pectic acid[38], leads to a plausible model in which the chain conformation is similar to that already characterized by fiber diffraction for polyguluronic acid. The array of co-ordination sites is formed by the alignment of two polyguluronate chains; because of the buckled shape of these chains, cavities remain between them which happen to be of the right size to accommodate a calcium ion and moreover are lined with carboxylate and other electronegative oxygen atoms which are favorable ligands. For obvious reasons this model (Fig. 5) is known as the "egg-box model"[36].

A further distinctive feature of the calcium binding behavior of polyguluronate sequences is that large circular dichroism changes are seen when this occurs. A much smaller change is observed for alternating sequences with virtually no effect for polymannuronate blocks. The change is confined to the $n\rightarrow\pi^*$ transition region of the carboxylate spectrum, consistent with the n orbitals in the polyguluronate sequences being specifically involved in the chelation of calcium ions. The egg-box model provides a convincing basis for explanation of these changes because it places the ion in the correct position for coordination by carboxylate n-orbitals and in the same region of symmetry space as O-4 and O-5 which normally determine the sign of the $n\rightarrow\pi^*$ band.

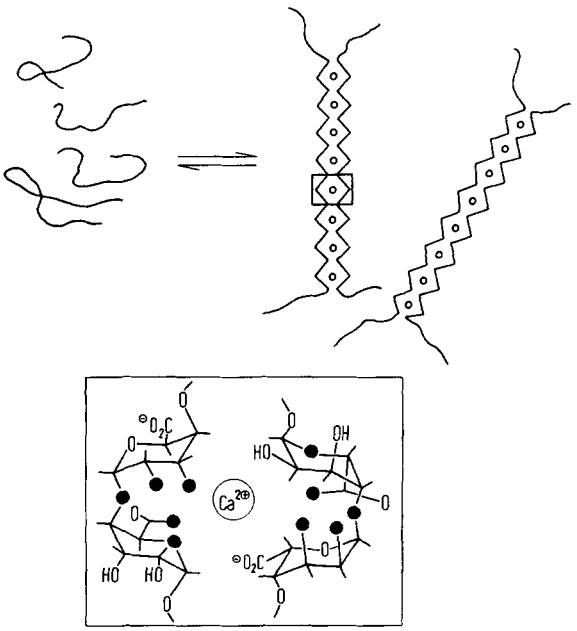


Fig. 5. Schematic representation of association of polyguluronate sequences by chelation of Ca^{2+}: "egg-box model". Below: Section; oxygen atoms coordinated to calcium are shown as filled circles.

This association of polyguluronate sequences by cation binding is believed to be the principal mechanism of cross-linking in alginate gelation. The characteristic CD spectral changes on gelation, particularly for alginates rich in polyguluronate

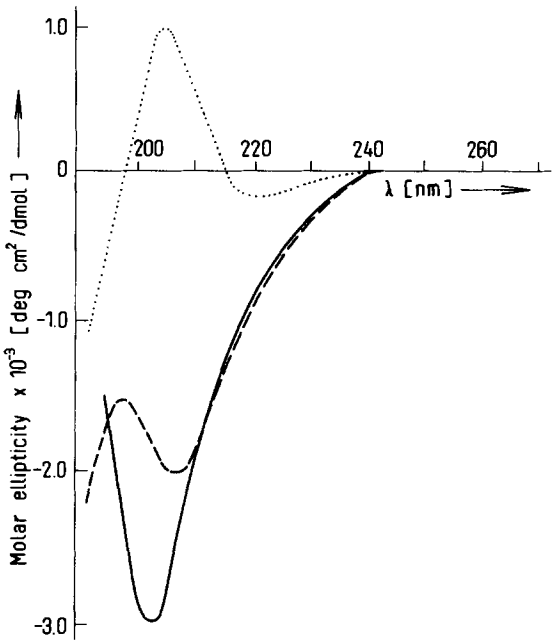


Fig. 6. Characterization of calcium binding to alginate by circular dichroism. Spectral changes with the diffusion of Ca^{2+} to a final concentration of 6 mmol into a solution of alginate (0.1 %) having mannuronate and guluronate residues in the ratio 29:71. Broken and dotted lines show spectra before and after this process, and the full line shows the difference spectrum.

sequences (Fig. 6) provide the same confirmation that this is so[39]. At first sight, there might seem no reason why the egg-box structures should not be layered structures involving many chains. However, the stoichiometry of binding as studied by equilibrium dialysis[40] and also by reinterpretation of earlier binding studies by a cation exchange method[41] points quite clearly to dimerization. By both approaches, it is found that competitive inhibition is observed at all, points to a dimeri-calcium ion for every four guluronate residues as expected on a dimerization model, rather than to one calcium ion for every two guluronate residues as would be expected on an infinite sheet model. The reason why the process tends to stop at the dimer may be that much of the electrostatic driving force for association has been neutralized by this stage: this would be analogous to the reasons why dibasic acids usually have two separate dissociation constants. It may also be that the polyguluronate chain undergoes the conformational adaptation to optimize coordination of the first set of calcium ions in a way that inhibits further associations.

Competitive inhibition studies[22] in which the influence of added "blocks" was studied on the bulk properties of alginate gels provide further confirmatory evidence. The fact that competitive inhibition is observed at all, points to a dimerization mechanism (compare with evidence of the same type discussed above for carrageenans). They also confirm that polyguluronate sequences rather than either of the other two types are mainly involved in the cross-linking mechanism. A marked decrease is seen in gel strength when polyguluronate blocks are added, less change with alternating blocks, and virtually no effect with the polymannuronate. These results are entirely consistent with the spectroscopic evidence and ion binding studies.

The extent to which ordered solution conformation can occur, and hence gelation, is therefore limited by the number and length of polyguluronate sequences. Biosynthetic studies suggest that, as for analogous features in agar and carrageenans, these are under enzymic control at the polymer level. Original studies with bacterial alginates (*Azotobacter vinelandii*) showed that the polymer chains were synthesized first as polymannuronate sequences, and that guluronate residues were introduced subsequently by epimerization at C-5[42,43]. Similar epimerase activities have now been demonstrated in brown algae, capable of producing regions of alternating sequence and of polyguluronate[44]. Work with algae has also suggested that the nucleotide precursor is guanosine diphosphate mannuronate[45].

3.2. Pectin

Pectin is a major constituent of the cell wall of higher plants, and like alginate is involved in the maintenance of structural integrity. It again illustrates how stiff, buckled chains can pack together under conditions of extensive hydration. It occurs naturally as the partial methyl ester of 1,4-linked poly-(α-D-galacturonic acid)[46,47]. These chains are geometrically similar to polyguluronate blocks in alginates in that the sugar residues are linked di-axially. In pectin, the polygalacturonate sequences are interrupted by 1,2-linked L-rhamnose residues which can introduce a severe kink into the backbone geometry[48]. Unlike alginate, pectin usually contains a proportion of branch chains which are composed mostly of various neutral sugar residues and which are expected to limit possible chain associations. Different types of chain associations occur depending on whether the chains are methyl-esterified and to what extent. These various modifications offer mechanisms of biological control over the secondary and tertiary structures that will be discussed later.

Fiber diffraction studies have shown that 1,4-linked polygalacturonate chains show a similar projected residue rise as polyguluronate, although the sodium salt which is the only form to have been examined experimentally in any detail does appear to be threefold in contrast to the twofold symmetry of polyguluronate[49]. We conclude that the stereochemical analogies between polygalacturonate and polyguluronate, like the covalent analogies, are close but limited.

The calcium binding behavior of (de-esterified) polygalacturonate chains shows strong similarities to that of polyguluronate. Binding is greatly enhanced at chain lengths above a critical value of around 20 residues[41], and large circular dichroism changes occur in the $n \rightarrow \pi^*$ region of the same type as with polyguluronate[36]. Moreover there are similarities in cation exchange behavior. All this leads us to expect that gelation and calcium binding by pectins of low methyl ester content will proceed by an "egg-box" mechanism which is broadly similar to that which we have described for polyguluronate. Differences in detail include the fact that these regions of ordered association are terminated by covalent features of a different character.

For pectins with higher degrees of methyl esterification, interactions with cations are relatively weak because the chains are uncharged and hence gelation does not occur under the same conditions as for the polyanion. However pectin can be induced to gel by addition of a large amount of a cosolute such as sucrose to lower the water activity and hence to favor polymer-polymer interaction rather than polymer-solvent interaction[47]. For samples which are incompletely esterified, chain association is further facilitated by a low pH to suppress residual ionized residues and thus to minimize electrostatic repulsion between chains. This gelation is accompanied by an *increase* in amplitude of the $n \rightarrow \pi^*$ band in the circular dichroism, greater than that over the same temperature range for solutions of nongelling polysaccharide[36]. Thus pectin has two very different mechanisms for chain association depending on the extent of methyl esterification and on the aqueous environment. In natural situations, it is to be expected that both of these mechanisms will occur to relative extents that depend on the amount and distribution of methyl ester as well as on other covalent features.

The extent and distribution of methyl esterification in native pectins would appear to be under enzymic control at the polymer level, although the relative importance of control at the esterification step relative to the de-esterification step is not clear. It would appear that polygalacturonate chains are synthesized by polymerization from uridine diphosphate D-galacturonate which is then esterified by transfer of the methyl group from *S*-adenosyl-L-methionine[50, 51]. Subsequently, de-esterification may occur under the influence of pectin esterase[52], the action pattern of which is such as to generate consecutive sequences of de-esterified galacturonate residues—in contrast to chemical treatments which cause de-esterification in a more irregular way[53].

Some of the natural differences in pectin covalent structure in the plant cell walls may correlate with stages in cell growth. In tissues having a potential for rapid growth there appears to be a high proportion of L-rhamnose residues to prevent alignment of chains and hence gelation[54, 55]. Regular packing may be further limited by side-chains typically based on β-D-galactopyranose and/or α-L-arabinofuranose. The combined effect on physical and mechanical properties of the cell wall may then be to facilitate stretching and hence cell elongation.

4. Native Order in Solution: Xanthan

Xanthan, the extracellular polysaccharide from *Xanthomonas campestris*, has a pentasaccharide repeating unit[56, 57] in which trisaccharide side chains occur on alternate glucose residues of a cellulose-like backbone, giving rise to a highly branched molecule of type *(4)*. All the sugar residues are present in the pyranose form.

Actually the structure may not be quite as regular as depicted here; pyruvate substitution, which occurs in less than stoichiometric proportions, could be distributed irregularly or according to some type of regular pattern. Some departure from a strict alternating pattern of side-chain distribution is also possible in principle, although the evidence available from chemical degradation studies does not support this at present.

X-ray diffraction studies on oriented xanthan fibers[58] have shown that the chain describes a fivefold helix with a pitch of

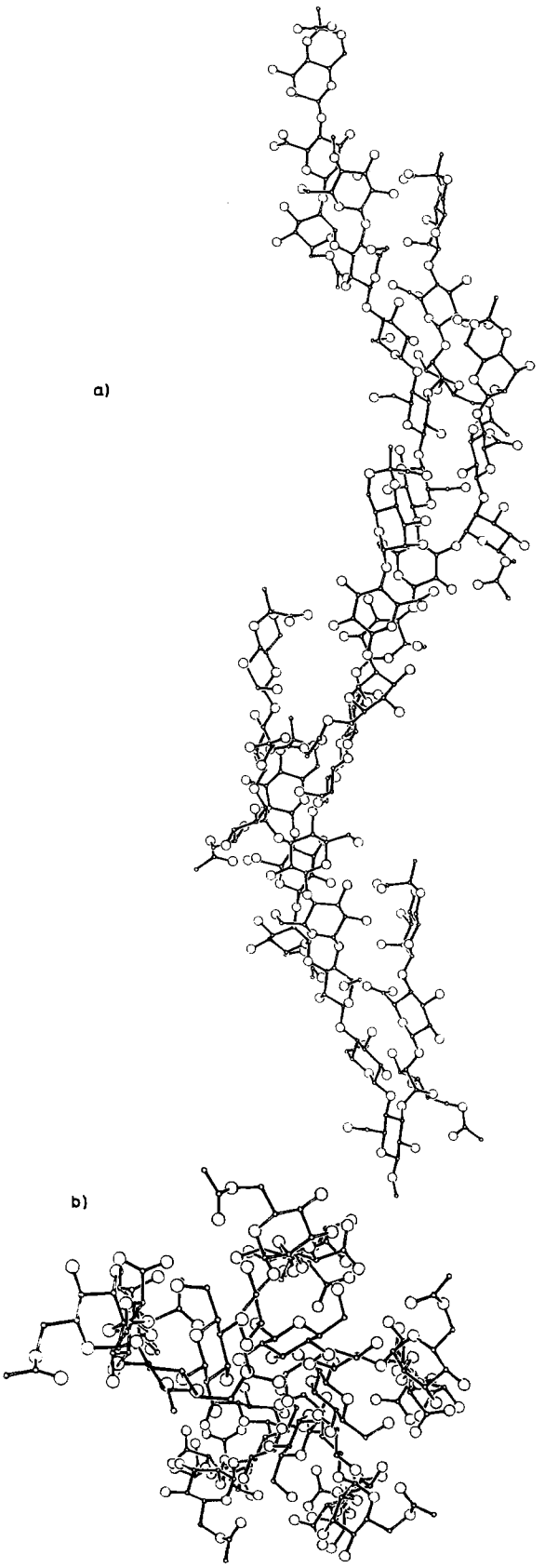
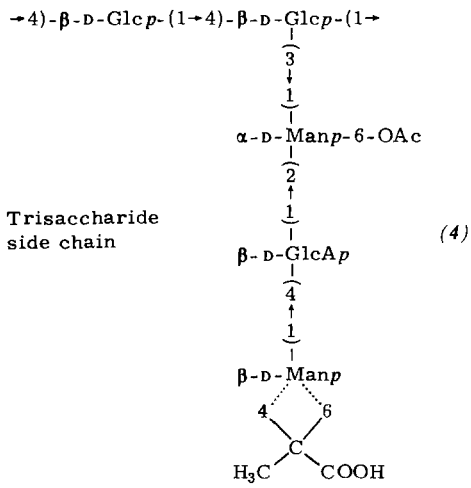


Fig. 7. Xanthan fivefold helix; computer generated diagram showing a likely interpretation of present X-ray diffraction evidence. a) Projection perpendicular to the helix axis; b) projection along the helix axis.

Cellulose-type backbone



Trisaccharide side chain

(4)

about 50 Å. Several alternative models can be built; a very likely possibility is shown in Figure 7. In this single helical conformation the trisaccharide side-chains fold down to align with the main chain and form noncovalent interactions which presumably stabilize the overall conformation. Evidence for the existence of an ordered form in solution has come from a variety of physical measurements[59, 60]. Optical rotation, NMR relaxation measurements, and low shear viscosity measurements each show a sigmoidal change with temperature (Fig. 8). Analogous results are found in circular dichroism studies on the carboxylate chromophore[59]. The temperature of the order-disorder transition is found to be independent of polysaccharide concentration at constant ionic strength. Since the transition is too broad to indicate a highly cooperative phase change, this concentration independence is taken as evidence for a unimolecular reaction which implies a coil to single helix transition. It seems likely that the xanthan single helix is stabilized in solution by associations between the side chain and the backbone similar to those in the model (Fig. 7) for the solid state. This is the first example of secondary structure stabilized within a single polysaccharide chain, and can be considered to be analogous to the α-helix in polypeptides and proteins.

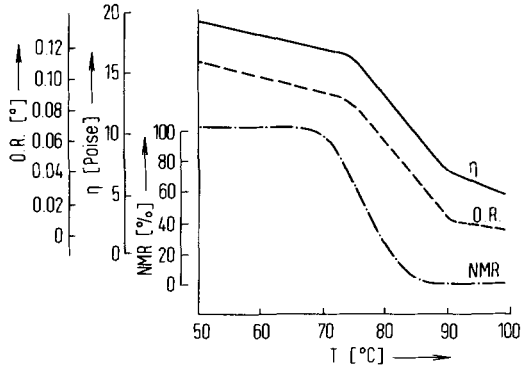


Fig. 8. Influence of temperature on optical rotation (O.R.), slow shear ($\dot{\gamma} = 14\ s^{-1}$) viscosity ($\eta$), and high resolution nuclear magnetic resonance relaxation (NMR) for 1% (w/v) aqueous solutions of *Xanthomonas* polysaccharide.

5. Helix-Ribbon Associations

Although xanthan adopts an ordered conformation in solution, it does not gel; this is of course expected if the order-disorder transition does not require the cross-linking of chains. However, a rubbery gel can be formed by addition of certain β-1,4-linked polysaccharides of a type which normally exist in solution as random coils and in the condensed phase as stiff, extended ribbons[61]. This gelling interaction implies a cross-linking between the unlike polysaccharide chains. The gel-sol transition is sharp enough to indicate cooperative character—that is, that the two polysaccharides interact in ordered conformations.

One example of this gelling interaction is between xanthan and the galactomannan from *Ceratonia siliqua* (also known as locust bean gum or carob gum). Analogous behavior is seen in mixtures of this and certain other galactomannans when mixed with the double helical algal polysaccharides. For example, concentrations of κ-carrageenan or agarose that are too low to gel alone will gel in the presence of this galactomannan[19]. Likewise the short chain segments derived from these polysaccharides and which will not gel alone, will do so in mixtures with galactomannan. All these mixed gels show sharp melting and setting behavior consistent with cooperative transitions and hence the networks would appear to be cross-linked by ordered non-covalent associations. Comparison of the gelling interactions of galactomannans with different degrees of substitution would suggest that the unsubstituted mannose residues are the effective ones in binding. In view of the chemical evidence[62] that these can occur in long consecutive "blocks", the likely mechanism for cross-linking involves helix-ribbon associations of the type shown schematically in Figure 9. The stoichiometry of this association, and whether it exists only as a subunit of some larger aggregate, remains to be determined.

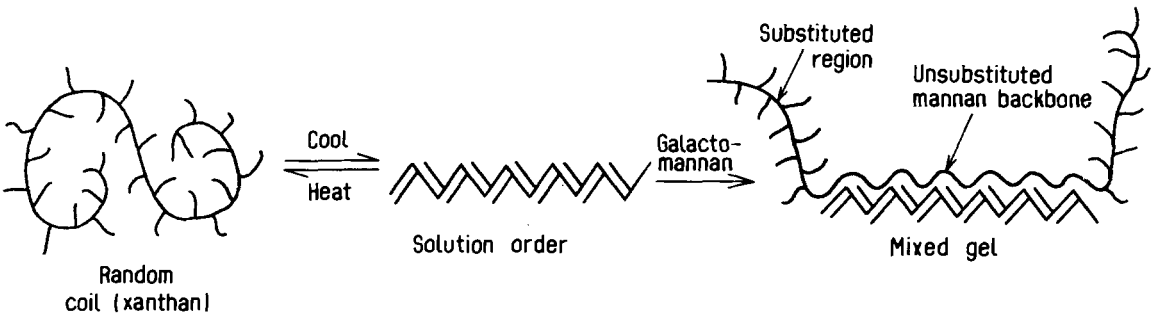


Fig. 9. Model proposed for the interaction between the xanthan helix and the unsubstituted backbone regions of galactomannans. (By courtesy of Dr. *E. R. Morris.*) Similar models in which galactomannan-double helix interactions occur have been proposed for interactions involving agarose and carrageenan[19].

The general features of this model are confirmed by optical rotation measurements[19]. The helix-coil transition for κ-carrageenan segments is perturbed by galactomannan, confirming an interaction between the two polysaccharides (Fig. 10). The cooling transition is shifted in a way that suggests that nucleation of the carrageenan double helix is facilitated by this interaction—that is, presumably by binding of the galactomannan. Likewise, on the heating curve the helix melts at higher temperature pointing to its stabilization by binding.

The optical rotation behavior of agarose in the presence of galactomannan can be interpreted in similar terms, although some of the observations are actually different. Once again, the cooling transition is shifted to slightly higher temperature

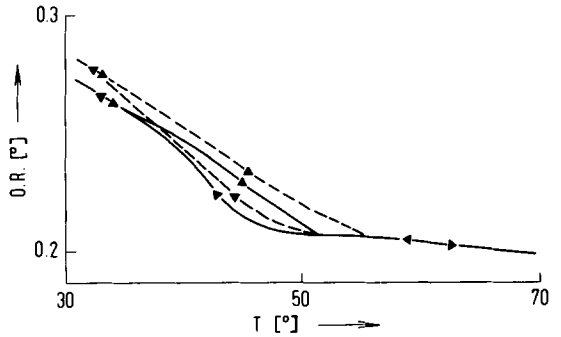


Fig. 10. Comparison of the variations in optical rotation (O.R.) with temperature for segmented κ-carrageenan (——) and a mixture of segmented κ-carrageenan and galactomannan from *Ceratonia siliqua* (– – –). Concentration of κ-carrageen and galactomannan 4 % and 1 %, respectively.

indicating an involvement of galactomannan in the nucleation event. On heating however, the optical rotation changes follow a complex form which strongly indicates that the galactomannan can be removed from its association before the double helix itself melts (Fig. 11). This dissociation of the galactomannan shows as a sigmoidal optical rotation change pointing to a cooperative process and hence confirming that the galactomannan chain is itself present in an ordered conformation in the bound state.

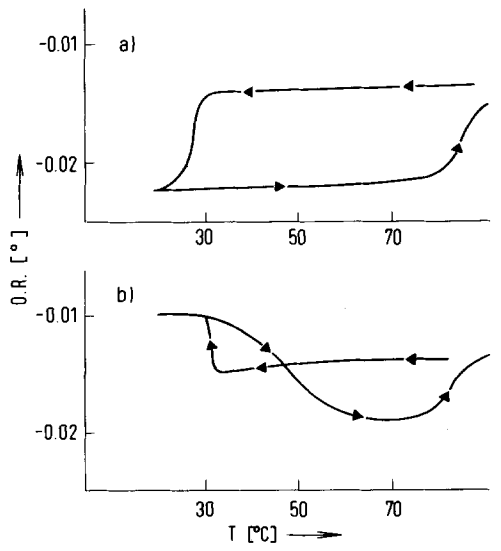
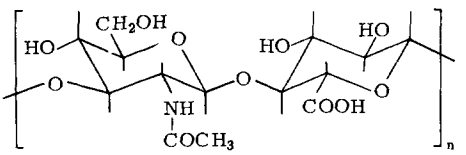


Fig. 11. Comparison of the variations in optical rotation (O.R.) with temperature a) for agarose and b) for a mixture of agarose and galactomannan from *Ceratonia siliqua*. Concentration of agarose and galactomannan 0.05 % and 0.1 %, respectively.

To varying extents, xanthan, agarose, and κ-carrageenan interact with other β-1,4-linked ribbon-like polysaccharides such as cellulose derivatives, xylans and glucomannans[61,63]. These interactions can be considered to be analogous to quaternary structure in proteins, and the specificity of interactions of this sort may well be important in the structural integrity of plant tissues. For the particular instance of xanthan, it might be significant that the bacterial species from which this polysaccharide derives is a pathogen which colonizes plant tissue by invasion through intercellular regions. Possibly the polysaccharide-polysaccharide interactions which we describe could play a role in host-pathogen recognition.

6. Animal Polysaccharides: Glycosaminoglycans

The glycosaminoglycans are matrix polysaccharides of animal origin. Most of them are alternating copolymers of type *(5)* formed from β-1,4-linked uronic acid and β-1,3-linked *N*-acetylhexosamine, and either residue may carry sulfate ester groups[64]. *(5)* is hyaluronic acid. An exception is keratan sulfate[65] in which the 4-linked residue is *N*-acetyl D-glucosamine and the 3-linked residue is D-galactose. Heparin is also different from other members of this group of polysaccharides[66]; although its structure has an alternating arrangement of uronic acid and *N*-acetylhexosamine residues, there are major differences in the configurations and positions of linkage.



(5)

1,3-linked *N*-acetyl-D-glucosamine — 1,4-linked D-glucuronic acid

Those polysaccharides which have an alternating arrangement of 1,3 and 1,4 linkages could be considered to be analogous to the agarose and carrageenan family in their general backbone stereochemistry [compare *(1)* and *(5)*] and also in that the 4-linked residue occurs naturally in both possible ring chair conformations. In glycosaminoglycans this residue may be D-glucuronate in the Reeves C1 conformation or L-iduronate which, at least in solution, exists in the Reeves 1C conformation[67]; in the agarose-carrageenan series, the analogous residue may be 3,6-anhydrogalactose or galactose 6-sulfate. Interconversion of the alternate forms would appear to occur at the polymer level in biosynthesis of glycosaminoglycans[66,68,69], just as (see above) the corresponding transformation exists in the agarose and carrageenan series.

In recent years, glycosaminoglycans have been very extensively studied by X-ray diffraction of oriented fibers and a variety of single-helical conformations have been characterized. All of these appear to be left-handed helices which differ in their states of extension. The threefold helices are most common[70–73], but fourfold forms are known for hyaluronic acid[74,75], twofold forms for keratan sulfate[76] and for some other polysaccharides in the acid form, and 8_5 helices for chondroitin 6-sulfate[77] and dermatan sulfate[78]. Although

the stereochemical analogies with agarose and carrageenans might lead us to expect the existence of double helical conformations, such forms have not yet been authenticated.

The polysaccharide of this family whose solution conformation has been most fully investigated is hyaluronic acid *(5)*. Many hydrodynamic studies have shown that, to a good first approximation, the molecule can be described as a random coil[79–81]. At the same time, however, evidence exists for intermolecular interactions which are difficult to explain merely in terms of entanglements of flexible chains[82, 83]. Hyaluronate solutions show coupling of coil domains at a concentration that is an order of magnitude lower than would be necessary for entanglement of most polymers—that is, hyaluronate molecules "stick" where they touch[84]. Further, hyaluronate behavior is untypical of random coil polysaccharides when the hydroxy groups are ionized by exposure to high pH; a random coil is expected to expand with consequent increase in molecular rigidity and solution viscosity. Both NMR relaxation studies[85] and viscosity measurements[86] show that sodium hyaluronate becomes more flexible and compact at high pH suggesting a reversible disruption of some form of association whose precise molecular origin is as yet unknown.

The inter-chain association of hyaluronate can be enhanced by diminishing the electrostatic charge by adjusting to pH 2.5; under these conditions and in the presence of a lower concentration of sodium chloride, the solution shows pronounced elastic character even at low polysaccharide concentration[81]. It is not strictly a gel because the inter-molecular contacts break and reform (*e.g.* when the material is cut, it "heals") indicating a fleeting association of chain segments in a state of dynamic equilibrium. The material has therefore been called a "viscoelastic putty". The properties become still more elastic when the water activity is reduced, for example by dialysis against a low concentration of ethanol. All these phenomena invite analogy with the systems discussed earlier in the article, where ordered polysaccharide secondary and tertiary structures were involved in cross-linking processes. However, the molecular origin of the effects for hyaluronate has still to be characterized.

7. Conclusions

The polysaccharide systems described in this review show enough common features to suggest general principles in the formation and interactions of secondary and tertiary structures in solutions and gels.

In all known examples, ordered conformations in polysaccharides require long regions of regular repeating covalent structure. When the regular covalent pattern is interrupted, the conformational ordering is usually (though not invariably) terminated. This terminating influence of changed sequence is more pronounced than it is in proteins and nucleic acids because the typical, natural variations in covalent structures of polysaccharides are more fundamental in their stereochemical implications. The polypeptide or polynucleotide backbone is not altered in general contour when one monomer residue is exchanged for another; whereas substitution of one sugar residue for another in a polysaccharide can involve change of glycosidic configuration, of position and configuration of the aglycon linkage and even of the sugar ring conformation. Hence an α-helical or β-sheet region in a globular protein may incorporate amino acid residues of a number of different types and, similarly, all four types of nucleotide residues can be accommodated within a single double helical region in a nucleic acid. In a polysaccharide helix or ribbon however, the insertion of a new sugar residue often introduces a sharp kink or at least changed packing requirements.

A further difference between polysaccharide and other biopolymer chains is that model building calculations[1] show that polysaccharides are much stiffer structures. Chain folding within a confined volume as seen in globular proteins does not generally occur for polysaccharides and many polysaccharides are extended ribbons or helices which need inter-chain packing to accumulate enough favorable non-bonded interactions for stability. In this article, we have given examples of this in two-stranded helical structures, two-stranded ribbon-ribbon associations, and multi-stranded helix-ribbon associations. We know only one example of a structure which may be stabilized intramolecularly, namely xanthan. Actually, even the model described, being highly branched, combines a number of separate strands within the same molecule so that the conformation can be considered to be intramolecularly multi-stranded.

We suggest two main conclusions about the relation between polysaccharide secondary and tertiary structure and biological function. Firstly, the formation of ordered conformations, even in very highly hydrated environments, usually involves intermolecular associations; no doubt this reflects the biological function of polysaccharides in structural integrity at the outer surfaces of cells and in the organization of cells into tissues. Secondly, these ordered states and hence their associations are often under the fine control of enzymes which modify sugar residues at the polymer level.

We are grateful to Dr. E. R. Morris for valuable discussions during the writing of this article.

Received: August 9, 1976 [A 156 IE]
German version: Angew. Chem. *89*, 228 (1977)

[1] *D. A. Rees:* M. T. P. International Review of Science, Organic Chemistry Series One, Vol. 7, Carbohydrates. Butterworths, London 1973, p. 251; *ibid.* Biochemistry Series One, Vol. 5, Biochemistry of Carbohydrates. Butterworths, London 1975, p. 1.
[2] *N. S. Anderson, J. W. Campbell, M. M. Harding, D. A. Rees, J. W. B. Samuel,* J. Mol. Biol. *45*, 85 (1969); *S. Arnott, W. E. Scott, D. A. Rees, C. G. A. McNab, ibid. 90*, 253 (1974).
[3] *S. Arnott, A. Fulmer, W. E. Scott, I. C. M. Dea, R. Moorhouse, D. A. Rees,* J. Mol. Biol. 90, 269 (1974).
[4] *N. S. Anderson, T. C. S. Dolan, A. Penman, D. A. Rees, G. P. Mueller, D. J. Stancioff, N. F. Stanley,* J. Chem. Soc. *C 1968*, 602.
[5] *N. S. Anderson, T. C. S. Dolan, D. A. Rees,* J. Chem. Soc. *C 1968*, 596.
[6] *C. Araki, K. Arai,* Bull. Chem. Soc. Jpn. *40*, 1452 (1967).
[7] *M. Duckworth, W. Yaphe,* Carbohydr. Res. *18*, 1 (1971).
[8] *I. J. Goldstein, G. W. Hay, B. A. Lewis, F. Smith:* Methods in Carbohydrate Chemistry. Vol. 5. Academic Press, New York 1965, p. 361.
[9] *D. A. Rees,* J. Chem. Soc. *1961*, 5168; *1963*, 1812.
[10] *R. A. Jones, E. J. Staples, A. Penman,* J. Chem. Soc. Perkin Trans. II *1973*, 1608.
[11] *A. A. McKinnon, D. A. Rees, F. B. Williamson,* Chem. Commun. *1969*, 701.
[12] *T. A. Bryce, D. A. Rees, D. S. Reid, A. H. Clark,* to be published.
[13] *D. A. Rees,* J. Chem. Soc. *B 1970*, 877.
[14] *D. A. Rees, W. E. Scott, F. B. Williamson,* Nature *227*, 390 (1970).
[15] *T. A. Bryce, A. A. McKinnon, E. R. Morris, D. A. Rees, D. Thom,* Faraday Discuss. Chem. Soc. No. 57, 221 (1974).

[16] *D. S. Reid, T. A. Bryce, A. H. Clark, D. A. Rees*, Faraday Discuss. Chem. Soc. Nr. 57, 230 (1974).
[17] *N. S. Anderson, T. C. S. Dolan, D. A. Rees*, J. Chem. Soc. *C1968*, 596.
[18] *A. A. McKinnon*, PhD Thesis, Edinburgh 1973.
[19] *I. C. M. Dea, A. A. McKinnon, D. A. Rees*, J. Mol. Biol. *68*, 153 (1972).
[20] *I. C. M. Dea, R. Moorhouse, D. A. Rees*, unpublished data.
[21] *I. C. M. Dea, D. A. Rees, E. J. Welsh*, unpublished data.
[22] *E. R. Morris, D. A. Rees, G. Young*, to be published.
[23] *J. C. Su, W. Z. Hassid*, Biochemistry *1*, 468 (1962).
[24] *D. A. Rees*, Biochem. J. *81*, 347 (1961).
[25] *C. J. Lawson, D. A. Rees*, Nature *227*, 392 (1970).
[26] *A. Haug, B. Larsen, O. Smidsrød*, Acta Chem. Scand. *21*, 691 (1967).
[27] *A. Haug, B. Larsen, O. Smidsrød*, Acta Chem. Scand. *20*, 183 (1966).
[28] *A. Haug, B. Larsen:* Proceedings of the Vth International Seaweed Symposium. Pergamon Press, Oxford 1966, p. 271.
[29] *A. Haug, B. Larsen, O. Smidsrød, T. Painter*, Acta Chem. Scand. *23*, 2955 (1969).
[30] *J. Boyd*, PhD Thesis, University College of North Wales, Bangor 1975.
[31] *E. D. T. Atkins, I. A. Niedusynski, W. Mackie, K. D. Parker, E. E. Smolko*, Biopolymers *12*, 1865 (1973).
[32] *W. Mackie*, Biochem. J. *125*, 89P (1971).
[33] *E. D. T. Atkins, I. A. Niedusynski, W. Mackie, K. D. Parker, E. E. Smolko*, Biopolymers *12*, 1879 (1973).
[34] *R. Kohn, B. Larsen*, Acta Chem. Scand. *26*, 2455 (1972).
[35] *R. Kohn*, Pure Appl. Chem. *42*, 371 (1975).
[36] *G. T. Grant, E. R. Morris, D. A. Rees, P. J. C. Smith, D. Thom*, FEBS Lett. *32*, 195 (1973).
[37] *R. O. Gould, S. E. B. Gould, D. A. Rees, W. E. Scott*, J. Chem. Soc. Perkin Trans. II *1976*, 237.
[38] *S. E. B. Gould, R. O. Gould, D. A. Rees, A. W. Wight*, J. Chem. Soc. Perkin Trans. II *1976*, 392.
[39] *E. R. Morris, D. A. Rees, D. Thom*, J. Chem. Soc. Chem. Commun. *1973*, 245.
[40] *J. Boyd, E. R. Morris, D. A. Rees, D. Thom, J. R. Turvey*, to be published.
[41] *O. Smidsrød, A. Haug*, Acta Chem. Scand. *26*, 2063 (1972).
[42] *B. Larsen, A. Haug*, Carbohydr. Res. *17*, 287 (1971).
[43] *A. Haug, B. Larsen*, Carbohydr. Res. *17*, 297 (1971).
[44] *J. Madgwick, A. Haug, B. Larsen*, Acta Chem. Scand. *27*, 3592 (1973).
[45] *T.-Y. Lin, W. Z. Hassid*, J. Biol. Chem. *241*, 3282 (1966).
[46] *H. Deuel, E. Stutz*, Adv. Enzymol. *20*, 341 (1968).
[47] *D. A. Rees*, Adv. Carbohydr. Chem. Biochem. *24*, 267 (1969).
[48] *D. A. Rees, A. W. Wight*, J. Chem. Soc. *B1971*, 1366.
[49] *K. J. Palmer, M. B. Hartzog*, J. Am. Chem. Soc. *67*, 2122 (1949); *K. J. Palmer, R. C. Merrill, H. S. Owens, M. Ballantyne*, J. Phys. Chem. *51*, 710 (1947).
[50] *H. Kauss, A. L. Swanson, W. Z. Hassid*, Biochem. Biophys. Res. Commun. *26*, 234 (1967).
[51] *H. Kauss, W. Z. Hassid*, J. Biol. Chem. *242*, 3449 (1967).
[52] *R. Kohn, I. Furda, Z. Kopec*, Collect. Czech. Chem. Commun. *33*, 264 (1968).
[53] *R. Kohn, I. Furda*, Collect. Czech. Chem. Commun. *34*, 641 (1969).
[54] *G. O. Aspinall, I. W. Cottrell, S. V. Egan, I. M. Morrison, J. N. C. White*, J. Chem. Soc. *C1967*, 1071.
[55] *S. E. B. Gould, D. A. Rees, N. G. Richardson, I. W. Steele*, Nature *208*, 876 (1965).
[56] *P. Jansson, L. Kenne, B. Lindberg*, Carbohydr. Res. *45*, 275 (1975).
[57] *L. D. Melton, L. Mindt, D. A. Rees, G. R. Sanderson*, Carbohydr. Res. *46*, 245 (1976).
[58] *S. Arnott, R. Moorhouse, D. A. Rees*, unpublished data.
[59] *E. R. Morris, D. A. Rees, G. Young, A. Darke, M. D. Walkinshaw*, J. Mol. Biol., *110*, 1 (1977).
[60] *A. Jeannes, J. E. Pittsley, F. R. Senti*, J. Appl. Polym. Sci. *17*, 519 (1961).
[61] *I. C. M. Dea, A. Morrison*, Adv. Carbohydr. Chem. Biochem. *31*, 241 (1975).
[62] *C. A. Baker, R. L. Whistler*, Carbohydr. Res. *45*, 237 (1975).
[63] *I. C. M. Dea, A. A. McKinnon, D. A. Rees, E. J. Welsh*, unpublished data.
[64] *E. A. Balazs:* Chemistry and Molecular Biology of the Intercellular Matrix. Vol. 2. Academic Press, London 1970.
[65] *M. B. Mathews, J. A. Cifonelli*, J. Biol. Chem. *240*, 4140 (1965); *V. P. Bhavanandan, K. Meyer, ibid. 243*, 1052 (1968).
[66] *U. Lindahl:* M. T. P. International Review of Science, Organic Chemistry Series 2, Vol. 7, Carbohydrates. Butterworths, London 1976, p. 283.
[67] *A. S. Perlin, B. Casu, G. R. Sanderson, J. Tse*, Carbohydr. Res. *21*, 123 (1972).
[68] *U. Lindahl, G. Bäckström, A. Malmström, L. A. Fransson*, Biochem. Biophys. Res. Commun. *46*, 985 (1972).
[69] *M. Höök, U. Lindahl, G. Bäckström, A. Malmström, L. A. Fransson*, J. Biol. Chem. *249*, 3908 (1974).
[70] *J. K. Sheehan, E. D. T. Atkins, I. A. Nieduszynski*, J. Mol. Biol. *91*, 153 (1975).
[71] *S. Arnott, J. M. Guss, D. W. L. Hukins, M. B. Mathews*, Science *180*, 743 (1973).
[72] *D. H. Isaac, E. D. T. Atkins*, Nature New Biol. *244*, 252 (1973).
[73] *E. D. T. Atkins, D. H. Isaac*, J. Mol. Biol. *80*, 773 (1973).
[74] *J. M. Guss, D. W. L. Hukins, P. J. Smith, W. T. Winter, S. Arnott, R. Moorhouse, D. A. Rees*, J. Mol. Biol. *95*, 359 (1975).
[75] *E. D. T. Atkins, J. K. Sheehan*, Science *179*, 562 (1973).
[76] *S. Arnott, J. M. Guss, D. W. L. Hukins, I. C. M. Dea, D. A. Rees*, J. Mol. Biol. *88*, 175 (1974).
[77] *E. D. T. Atkins, R. Gaussen, D. H. Isaac, V. Nandanwar, J. K. Sheehan*, J. Polym. Sci. *B10*, 863 (1972).
[78] *S. Arnott, J. M. Guss, D. W. L. Hukins, M. B. Mathews*, Biochem. Biophys. Res. Commun. *54*, 1377 (1973).
[79] *T. C. Laurent*, Fed. Proc. *25*, 1037 (1966).
[80] *A. G. Ogston, J. E. Stanier*, Biochem. J. *49*, 585 (1951).
[81] *E. A. Balazs*, Fed. Proc. *25*, 1817 (1966).
[82] *B. N. Preston, M. Davies, A. G. Ogston*, Biochem. J. *96*, 449 (1965).
[83] *D. A. Gibbs, E. W. Merrill, K. A. Smith, E. A. Balazs*, Biopolymers *6*, 777 (1968).
[84] *D. A. Gibbs, E. A. Balazs*, personal communication.
[85] *A. Darke, E. G. Finer, R. Moorhouse, D. A. Rees*, J. Mol. Biol. *99*, 477 (1975).
[86] *M. B. Mathews*, personal communication (see also ref. [64], p. 747); *E. R. Morris, E. J. Welsh*, unpublished data.

Analytical Applications of Chemiluminescence

By G. D. Mendenhall[*]

Most organic compounds react very slowly with atmospheric oxygen at room temperature. The weak chemiluminescence accompanying this autoxidation can be amplified and measured by sensitive instruments. Emission of light from many materials can also be induced mechanically and photochemically. The intensity-time curves are so characteristic that they can be used to establish whether the composition and history of two samples are identical. Moreover, numerous physical properties can be correlated with emission and thus measured.

1. Introduction

Chemiluminescence, light emitted from a chemical reaction, was first observed in biological sources such as the firefly and luminescent bacteria and marine organisms[1]. In 1727, *Swift* described a fictional, 16-year effort in one laboratory to isolate sunbeams from cucumbers[2]. The recognition of the advantages of a controlled source of light other than fire thus anticipated the progress of science and technology by a considerable margin.

There were in fact a number of attempts to use luminescent bacteria for lighting purposes from the Middle Ages up into the present century. In recent decades a number of intense sources of chemiluminescence have been discovered, and some of them indeed have been modified to provide useful lighting devices (*e.g.* the Cyalume® light marker developed by *Rauhut*[3]), and for more specialized purposes as described below.

It is not widely appreciated, however, that chemiluminescence is a virtually universal property of oxidizable organic substances. This discovery was made only after the advent of photomultipliers that were sufficiently sensitive to detect the faint emission from papers, plastics, rubber, edible materials, resins, cloth, and most articles of nonmetallic nature that undergo some degree of oxidative decay. If the emission from a reprint of a recent article in Angewandte Chemie is representative, for instance, the page on which this article appears is emitting about 10^2 photons per second at room temperature. The light is probably associated with the dynamic changes that contribute to the disintegration of the paper over the span of decades to centuries. The most extensive studies to date of faint chemiluminescence of this sort have been carried out by *Vassil'ev* and *Shlyapintokh*[4].

2. Instrumentation and the Nature of Measurements

Compared with many other spectral techniques, the apparatus for measurement of chemiluminescence is relatively simple. A sample container must eliminate background sources of light and not chemiluminescence itself. Usually provision is made for temperature and atmosphere control. The detected light must be recorded in some convenient way, either with a strip chart or by computerized data collection. Spectral distributions may be measured with cut-off or interference filters, or with conventional grating or prism dispersion. The former methods are more suitable with faint chemiluminescence from natural sources and have been included in an apparatus constructed at Battelle-Columbus (Fig. 1). Less sensitive equipment is available commercially, including fluorimeters that can be operated purely in the emission mode.

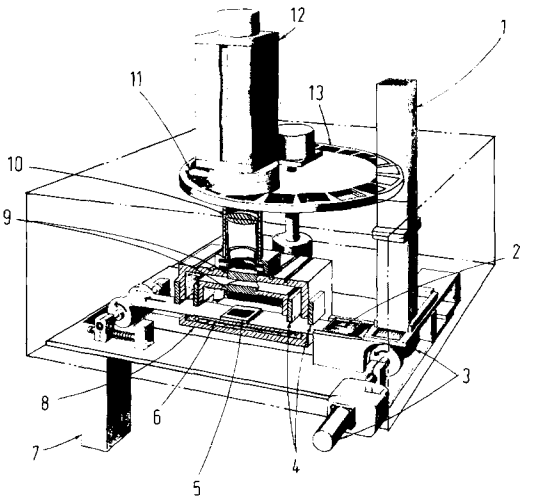


Fig. 1. Apparatus constructed at Battelle-Columbus (Ohio, USA) for measuring chemiluminescence. 1, sample bank and charger; 2, liquid sample; 3, sample conveyor and drive; 4, automatic doors; 5, solid samples (external dimensions *ca.* 50 × 50 mm²); 6, sample oven; 7, sample bank; 8, water-cooled oven shield; 9, quartz windows; 10, collector lens; 11, manually operated shutter; 12, photomultiplier; 13, filter wheel with 20 filters.

The apparatus depicted in Figure 1 is particularly suited for examination of thin sheets of material at elevated temperatures. The samples are mounted on glass or aluminum backing onto 35-mm aluminum slide holders, which ensure that a constant surface area is exposed to the photomultiplier. The samples are carried on a conveyer belt into an inner, heated compartment; a second compartment surrounding the first is water-cooled to avoid heating the entire apparatus, which is enclosed with 1/4-inch aluminum panels. The temperature, atmosphere, and position of the filter wheel in the apparatus are controlled from an adjacent room where the recording facilities are also located.

When emission from a sample is low (10—10^3 counts/s), a correction is made by subtracting the counting rate observed from the oven without the sample. Noise in the associated electronics, small sources of emission in the oven compartment, and cosmic radiation contribute to this background, which is temperature-dependent but rarely exceeds 10^3 counts/s with our particular apparatus.

[*] Dr. G. D. Mendenhall
Organic and Structural Chemistry Section
Battelle-Columbus Laboratories
505 King Avenue, Columbus, Ohio 43201 (USA)

At a given instant, the chemiluminescence from a sample is defined by an intensity and an energy (spectral) distribution. One usually measures these parameters *versus* time, temperature, composition, or other variables. In some cases the quantity of interest is the integrated intensity, *i.e.*, the total chemiluminescence emission, or still more complicated functions of the intensity (see, *e.g.* Section 9).

3. Chemiluminescence for Analysis of Trace Materials

One way that chemiluminescence analysis can be made particularly useful is by modification of a *highly efficient* light-producing reaction so that one reagent is rate limiting. Trace amounts of the reagent then can be determined in samples once the proportionality between chemiluminescence and its concentration has been established. This method has been applied to the determination of trace metals in solution by their catalytic effect on the rate of luminol oxidation[5, 6], and for measurement of the concentration of atmospheric hydrocarbons by their chemiluminescent reaction with oxygen atoms[7], among other examples.

Another approach along these lines involves the use of coupled enzymatic reactions to produce light. In one such example, low concentrations of lactic dehydrogenase (LDH) can be measured from the chemiluminescence emitted from the following reaction sequence[8]:

$$CH_3CH(OH)COOH + NAD \xrightarrow{LDH} NADH + CH_3COCOOH \quad (1)$$

$$O_2 + NADH + FMN + RCHO \xrightarrow{Luciferase} FMNH + RCOOH + NAD + Light \quad (2)$$

There are a number of ways in which such sequential reactions have been carried out. For detection of a small amount of substrate (here lactic acid), for instance, the sample may be passed through a column containing bound enzyme, and converted entirely into products [eq. (1)] that subsequently undergo reaction according to eq. (2) with luminescence.

Another variation of this method involves the use of classes of enzymes which oxidize substrates with concomitant formation of hydrogen peroxide. The latter can be detected, *e.g.*, by its chemiluminescent reaction with oxalate esters [eqs. (3) and (4)]. (Fl. is a fluorescing compound.)

$$Glucose + O_2 \xrightarrow{Glucose\ oxidase} \longrightarrow H_2O_2 \quad (3)$$

$$H_2O_2 + ROCOCOOR \longrightarrow \xrightarrow{Fl.} 2\ ROH + 2\ CO_2 + Light \quad (4)$$

Two reviews of the rather extensive analytical applications of these types of reactions are available[9].

4. Chemiluminescence from Autoxidation

A very different approach to the utilization of chemiluminescence takes advantage of the weak light emission that accompanies the autoxidation of organic materials. The autoxidation sequence is presented in Scheme 1 (eqs. (5) to (12)] in a somewhat simplified form that neglects β-scission of alkoxy groups, induced decomposition, cage recombination of radicals, and the relatively slow terminations involving tertiary peroxy radicals. The species P* is a ketone in an excited singlet or triplet state. We assume activity coefficients of unity for all species.

From the kinetic evidence and on thermodynamic grounds, it is believed that the electronic excitation occurs in the termination step [eq. (9)] which produces a small proportion of excited states [eq. (10)]. In most simple hydrocarbons and derivatives, one photon is emitted per 10^8 to 10^{10} terminations[10]. This inefficiency arises in part because the excited ketones P* are usually quenched by oxygen and other solutes before they can emit.

$$\left.\begin{array}{l} \text{a) ROOR} \\ \text{or b) ROOH + Catalyst} \\ \text{or c) RH + } [O_2]_{const.} \end{array}\right\} \xrightarrow{2\ R'H} 2\ R'^{\bullet} \quad (5)$$

$$\text{or } 2\ ROOH \longrightarrow RO^{\bullet} + RO_2^{\bullet} + H_2O \xrightarrow{2\ R'H} 2\ R'^{\bullet} \quad (6)$$

$$R'^{\bullet} + O_2 \longrightarrow R'O_2^{\bullet} \quad (7)$$

$$\left.\begin{array}{l} R'O_2^{\bullet} + R'H \longrightarrow R'^{\bullet} + ROOH \\ \text{or } R'O_2 + R'H \longrightarrow\longrightarrow ROOR + R'^{\bullet} \end{array}\right\} \quad (8)$$

$$2\ R'O_2^{\bullet} \longrightarrow R'OH + R''_2C{=}O + O_2 \quad (9)$$

$$2\ R'O_2^{\bullet} \longrightarrow P^* \quad (10)$$

$$P^* + Q \longrightarrow P + Q \quad (11)$$

$$P^* \longrightarrow P + h\nu \quad (12)$$

Scheme 1. R = alkyl site on polymer chain, lipid, hydrocarbon, *etc.*; R'H = olefin; P* = electronically excited state of ketone; Q = quenching species, *e.g.* oxygen.

The detectable chemiluminescence is reduced further by self-absorption in opaque materials, and by a geometrical factor $f_{geom} = A/4\pi r^2$, where r is the distance from the sample to the photomultiplier, and A is the effective area of the sensing head. For $r = 20$ cm and $A = 4$ cm^2, for instance, $f_{geom} \approx 10^{-3}$. These factors do not present a particular handicap in most measurements, since photomultipliers are available which respond even to single photon events. A modest counting rate of $1000\,s^{-1}$ from a sample, for instance, corresponds to about 10^{12} terminations per second, or to an initiation rate of 10^{-11} mol/s.

The mathematical treatment of the set of reaction in Scheme 1 is rather complicated, although a number of equations have been derived based on certain initial conditions. At temperatures below about 50°C, for instance, the oxidation of most materials is sufficiently slow that the concentrations of all species remain essentially constant during times adequate to measure the chemiluminescence emission. In this low-temperature case,

$$v_{init} = k_{init}[Initiator] = v_{term} \approx \text{constant} \quad (13)$$

For initiation according to (5)

$$d(h\nu)/dt = k_{12}[P^*] = \frac{k_{10}k_{12}k_{init}[Initiator]}{k_9(k_{12} + k_{11}[Q])} \quad (14)$$

Usually $k_{11}[Q] \gg k_{12}$, so that

$$d(h\nu)/dt = \frac{k_{10}k_{12}k_{init}}{k_9k_{11}[Q]}[Initiator] \quad (15)$$

The activation energy for chemiluminescence is then

$$E_I \approx E_{10} + E_{12} + E_{init} - E_9 - E_{11} \tag{16}$$

If $E_9 \approx E_{10}$, then $E_I \approx E_{init}$, since the other terms are usually small. The quantum yield, Φ_{CL}, per radical chain is

$$\Phi_{CL} = \frac{d(h\nu)}{d[\text{Initiator}]} = \frac{k_{10}k_{12}}{k_9(k_{12}+k_{11}[Q])} \tag{17}$$

For a bimolecular mode of initiation according to eq. (6), the expression corresponding to eq. (15) is

$$d(h\nu)/dt = \frac{k_{10}k_{12}k_6[\text{ROOH}]^2}{k_9(k_{12}+k_{11}[Q])}, \tag{18}$$

$$\text{with } E_I \approx E_{10} + E_{12} + E_6 - E_9 - E_{11} \approx E_6 \tag{19}$$

Another set of equations can be derived to predict the chemiluminescence from a sample during the *autocatalytic period* of oxidation when the rates of oxygen uptake and light emission both increase rapidly. If the initiation is first-order or pseudo-first order, the doubling time for the chemiluminescence intensity is given by eq. (20):

$$t_{1/n} - t_{1/2n} = \frac{2}{k_{init}} \ln \frac{n^{1/2} - (1/2)^{1/2}}{n^{1/2} - 1} \qquad (n > 1) \tag{20}$$

where $t_{1/n}$ refers to the time required to reach $1/n$ of maximum chemiluminescence (I_{max}) in the sample. In this derivation the maximum chemiluminescence is assumed to correspond to a chain length of unity.

At low degrees of conversion (large n), the doubling time for the unimolecular case approaches zero.

If the autocatalytic buildup occurs with bimolecular initiation [eq. (2)], the doubling time for the chemiluminescence is given by a more complicated function:

$$t_{1/n} - t_{1/2n} = \left(\frac{k_9}{k_6}\right)^{1/2} \frac{1}{k_8[\text{R'H}]} \left[\ln \frac{n^{1/2} - (1/2)^{1/2}}{n^{1/2} - 1} + 1/2 \ln 2\right] \tag{21}$$

At very low conversions the doubling time from eq. (21) is predicted to become independent of n and approach a constant value of $0.347\, k_9^{1/2}/(k_6^{1/2} k_8[\text{R'H}])$.

A third set of equations apply when a steady-state rate of oxidation has been achieved, the radical chain length is unity, and a *limiting rate* of oxygen uptake obtains[11]. Under these conditions

$$2k_8[\text{R'O}_2^\cdot][\text{R'H}] = k_{init}[\text{Initiator}] \text{ (unimolecular)} \tag{22}$$

$$2k_8[\text{R'O}_2^\cdot][\text{R'H}] = k_6[\text{ROOH}]^2 \text{ (bimolecular)} \tag{23}$$

$$\text{and } I_{max} = \frac{k_8^2 k_{10} k_{12}[\text{R'H}]^2}{k_9(k_{12}+k_{11}[Q])} \text{ (unimolecular)} \tag{24}$$

In the bimolecular case, eq. (24) applies with an additional factor of four. The activation energy $E_{I_{max}}$ obtained from an Arrhenius plot of I_{max} is represented as follows:

$$E_{I_{max}} \approx 2E_8 + E_{10} + E_{12} - E_{11} - 2E_9 \approx 2E_8 - E_9 \tag{25}$$

The basic form of these expressions is not altered by the presence of fluorescers that may accept energy from P*, (within limits) by specifying the precise origin or fate of P*, or (within limits) by inclusion of mechanistic details described above. The general mechanism for the autoxidation sequence shown is widely accepted[4, 11, 12], although the nature(s) of the individual species clearly will depend on the substrate and individual rate constants will be influenced by medium effects.

In many materials, particularly in fabricated mixtures, a substantial effort would be required to elucidate the detailed steps of the autoxidation and chemiluminescence emission, even in simple systems. We emphasize, therefore, that there is rarely any rigorous justification for applying these equations in any given case, and the examples presented here are simply an attempt to treat the subject from a basis beyond mere empiricism. As progress is made in understanding both autoxidation and chemiluminescence, our approach may become more sophisticated. At the same time, the reader should not be intimidated by this mathematical format into abandoning an empirical approach in the application of this technique, which is often quite fruitful.

5. Oxidation of Simple Hydrocarbons

Lundeen and *Livingston*[13], as well as *Nathan* and *Mendenhall*[14, 15] have applied some of the above equations to the chemiluminescence arising from hydrocarbon oxidation. The light emission from tetralin containing 9,10-diphenylanthracene, for instance, rose from zero at the beginning of an oxidation to a constant rate, at which point the rate of O_2

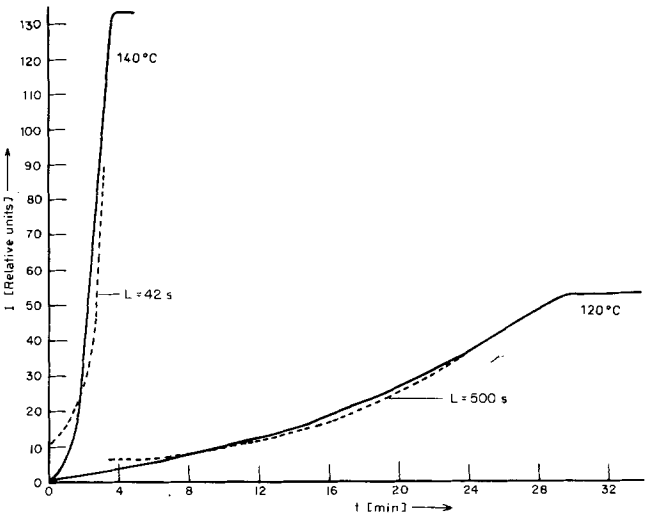


Fig. 2. Chemiluminescence from autoxidation of tetralin in the presence of 10^{-3} mol/l of 9,10-diphenylanthracene. (——) experimental curve, (– – –) curve calculated according to eq. (21).

uptake was also approximately constant (Fig. 2). Treatment of the data[15] according to eqs. (20) and (21) gave plots shown in Figure 3. The quantity L is defined as follows:

$$L \equiv (t_{1/n} - t_{1/2n}) \left[\ln \frac{n^{1/2} - (1/2)^{1/2}}{n^{1/2} - 1} + 1/2 \ln 2\right]^{-1} \tag{26}$$

There is excellent agreement of the data with the equations based on bimolecular initiation [eq. (21)], although studies of this system by other workers indicate that the oxidation

products include phenolic inhibitors[16], and that the maximum rate of oxygen absorption is far less than that predicted from other experimental evidence[17]. Even if the system is considerably more complicated than suggested by our reaction scheme, the shape of the chemiluminescence *versus* time plot at a given temperature can be described quite well over a limited range by a single parameter (Fig. 2).

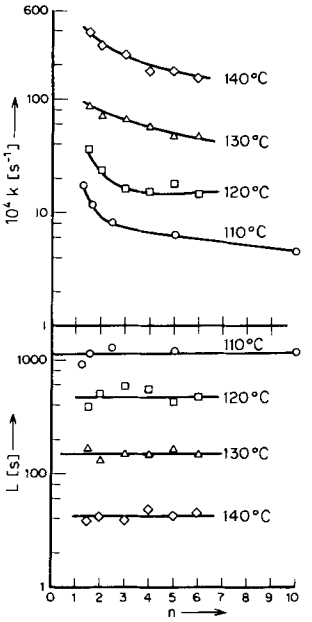


Fig. 3. Test for molecularity of the initiation step in the autoxidation of tetralin according to eqs. (20) and (21). L is defined by eq. (26).

For tetralin $E_{I_{max}}$ [eq. (24)] has been measured as 20.8[13] and 22.7[14] kcal/mol. These values are reasonable, since under these conditions $E_{I_{max}} \approx 2E_8 - E_9$, and from other studies[18, 19] $E_8 \approx 12$ kcal/mol and $E_9 \approx 3$ kcal/mol. The chemiluminescence from films of purified *cis*-1,4-polyisoprene and related elastomers in oxygen has also been studied in these laboratories[20]. In the initial stages eq. (21) describes the chemiluminescence from polyisoprene fairly well, although a plot of $f(\lambda)$ values,

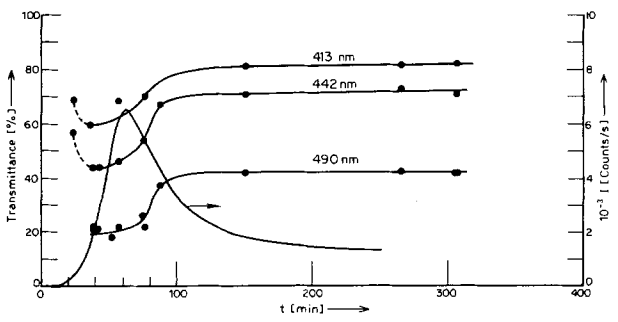


Fig. 4. Chemiluminescence (right-hand ordinate) and $f(\lambda)$ values (left-hand ordinate) from *cis*-1,4-polyisopropene in oxygen at 116°C. The $f(\lambda)$ values were determined by measuring the chemiluminescence after passage through filters which were opaque to light of shorter wavelengths than those given.

the fractions of chemiluminescence transmitted through a filter eliminating wavelengths shorter than λ, show that the nature of the emitting state changes as oxidation proceeds (Fig. 4).

At elevated temperatures the oxidation of a number of straight-chain hydrocarbons shows nonlinear behavior in a plot of I_{max} *versus* $1/T$ (*e.g.* Fig. 5). This result indicates a

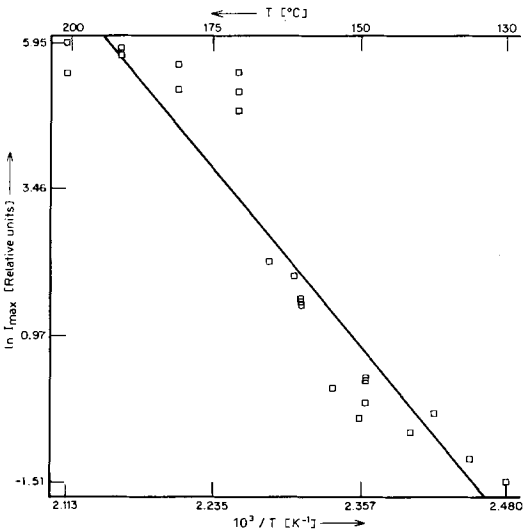


Fig. 5. Arrhenius plot of maximum chemiluminescence on autoxidation of *n*-dodecane containing 10^{-3} mol/l of 9,10-diphenylanthracene in oxygen.

change in the mechanism for producing chemiluminescence at the temperature corresponding to the change in slope, and the experiment was suggested to bear on the validity of accelerated aging tests carried out at high temperatures with hydrocarbons such as jet fuels[14].

6. Chemiluminescence Studies of Complicated Materials

Most nonmetallic materials that are of practical significance do not have a simple composition. The chemiluminescent behavior of such materials, on the other hand, often is surprisingly simple and a sensitive indicator of subtle changes in the samples.

At moderate temperatures up to 45°C two samples of a well-known breakfast cereal gave fairly linear Arrhenius plots

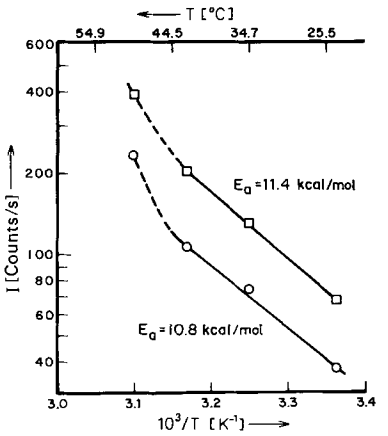


Fig. 6. Arrhenius plot of chemiluminescence from samples of two breakfast cereals in oxygen. □, laboratory cereal; ○, plant cereal; E_a activation energy.

of chemiluminescence emission up to about 45°C, but measurements at a higher temperature gave values that did not fall on the line determined by the other three points (Fig. 6).

Although the result is complicated by an enhanced chemiluminescence from the effects of room lights, the shape of the plot is consistent with the manufacturer's experience that accelerated aging tests carried out above 45 °C did not give valid results. The lab-prepared cereal was known also to be much less stable than the plant product. All other factors being equal, one expects a faster rate of initiation to produce a proportionately higher chemiluminescence intensity [eq. (19)].

On the other hand, linear activation energies have been found for chemiluminescence emission from most commercial polymers in oxygen between 25 and 100 °C or higher. Whether this result validates accelerated aging tests on these materials remains to be seen.

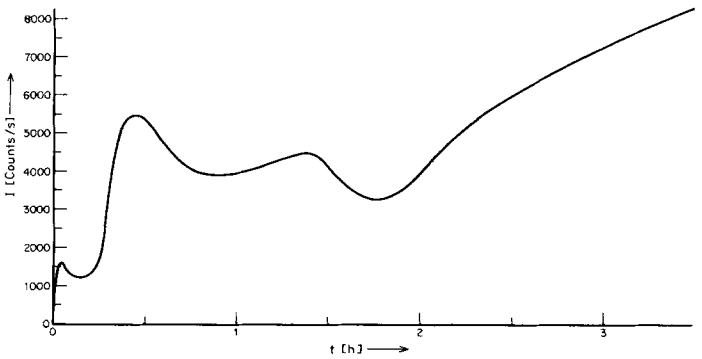


Fig. 7. Chemiluminescence from edible oil sample at 118 °C in oxygen.

Many materials do show complicated chemiluminescent behavior that cannot be related to the limiting cases for which we have semiempirical equations. One such example, which is typical of edible oils, is shown in Figure 7. The curve is interesting, although the oscillatory behavior may result from a number of possible changes in the material, whose nature might be elucidated only with other techniques. Complicated curves such as these are useful, however, for assessing uniformity among samples of material because the time *versus* intensity plots are highly reproducible. In one study at Battelle, for instance, we received two allegedly identical samples of an uncured potting compound. The products made from the two compounds did not show similar long-term stability, however, and this difference apparently was reflected in the markedly different chemiluminescence spectra (Fig. 8). The problem was later traced to a deficiency of one component in the material which showed less chemiluminescence.

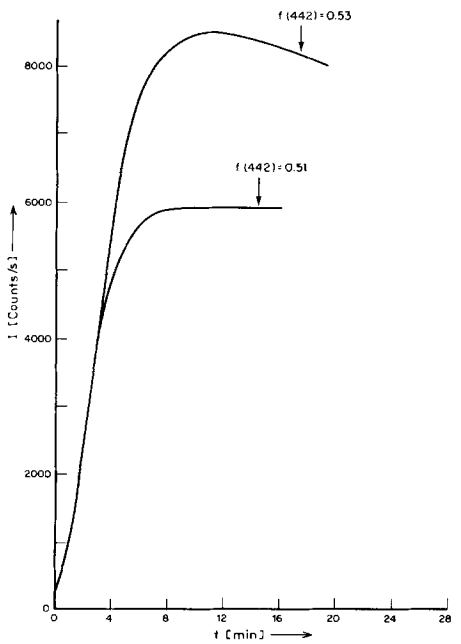


Fig. 8. Chemiluminescence from two potting compound samples at 80 °C in oxygen.

Simplified chemiluminescence spectra can be obtained by measuring the emission in an inert atmosphere. Under these circumstances the light probably results from preformed peroxides and hydroperoxides, whose decomposition gives radicals which can terminate to give excited states in the same way as they do in the presence of oxygen. Chemiluminescence from an edible oil under argon at 155 °C is shown in Figure 9, along with the enhancement brought about by addition of 9,10-diphenylanthracene. Such a procedure can detect peroxidic materials below the limits of conventional methods for their measurement.

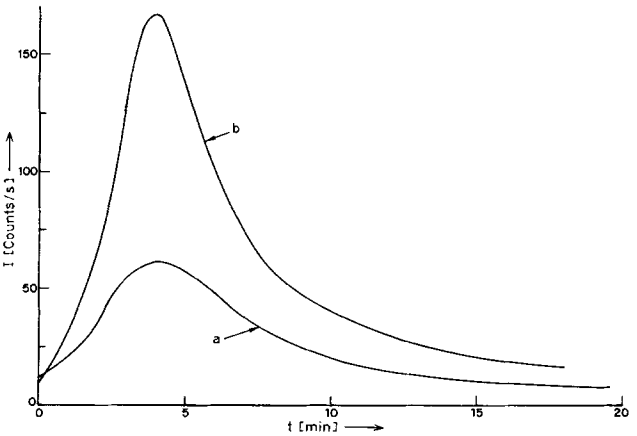


Fig. 9. Chemiluminescence from edible oil under argon at 155 °C. The oil had been aged for five weeks in air. a) pure oil; b) with addition of 0.6 mg of 9,10-diphenylanthracene/ml.

Another method of extracting useful information about a sample is to calibrate the chemiluminescence by dispersing in it a measured amount of free-radical initiator. The enhancement of the chemiluminescence is predicted to be proportional to the added initiator according to eq. (27), where v_0 is the initiation rate in the pure material. Preliminary results with a small sample of an edible oil were encouraging (Fig. 10), although the conditions of the experiment were not optimal.

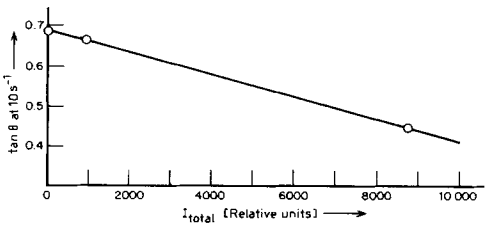


Fig. 10. The added-initiator technique. Example: addition of azoisobutyronitrile (AIBN) to edible oil at 55 °C.

$$\frac{d(h\nu)}{dt} = \frac{k_{10}k_{12}}{k_9(k_{12}+k_{11}[Q])}[v_0 + k_{init}[Initiator]] \quad (27)$$

In some cases we have used chemiluminescence techniques to measure changes in a material that are brought about by nonoxidative reactions. In Figure 11 emission curves are

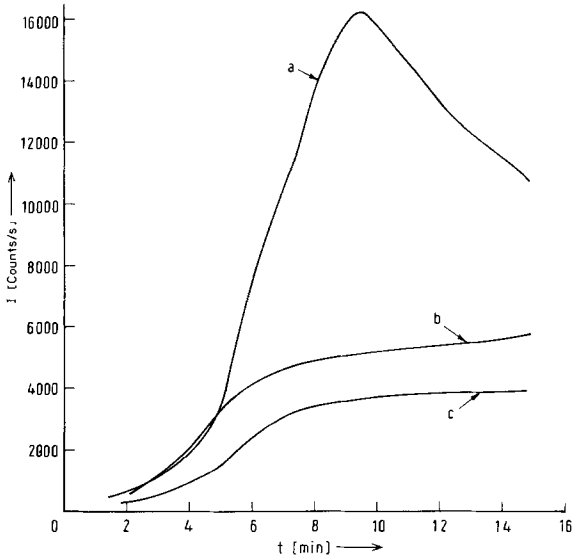


Fig. 11. Effect of curing time on chemiluminescence from an epoxy coating on steel. The samples were examined in an oxygen atmosphere at 200 °C. a) undercured (2.5 min at 246 °C); cured normally (5 min at 246 °C); overcured (10 min at 274 °C).

given for samples of steel bearing a protective epoxy coating that has been cured at high temperature for different times in each sample. A much smaller total emission was observed in properly cured material, although the curing reactions are almost certainly ionic in nature. In a related study of photoinduced degradation, we found that samples of polyethylene pipe showed twice as much chemiluminescence from the outer surface after outdoor exposure of the pipe for several months. Both inner and outer surfaces of unweathered pipe gave identical results under these conditions.

7. Effect of Antioxidants

In an early classic paper on polymers, *Ashby*[21] pointed out the progressive decrease of chemiluminescence from polypropylene with increasing antioxidant concentrations. Figure 12 reproduces the results from his study of synergism between two antioxidants. We and others have repeated *Ashby*'s experiment with other systems; however, the shape of the chemiluminescence *versus* time curves have been found to depend on the particular polymer-antioxidant combination. In preliminary experiments we have shown results similar to those in Figure 12 with antioxidant-edible oil combinations.

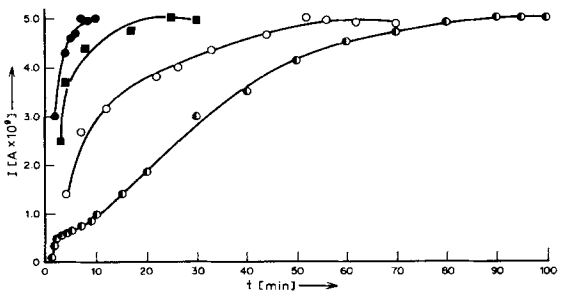


Fig. 12. Illustration of synergistic effects of antioxidants in polypropylene (Hercules 6501) at 143 °C by chemiluminescence emission (from *Ashby* [21]). ●, without antioxidant; ■, with dilauryl-3,3'-thiodipropionate (0.01 %); ○, with 6,6'-di-*tert*-butyl-4,4'-thiodi(*o*-cresol) (0.01 %); ◐, with dilauryl-3,3'-thiodipropionate (0.01 %) plus 6,6'-di-*tert*-butyl-4,4'-thiodi(*o*-cresol) (0.01 %). Reprinted with permission of the author and publisher.

In general terms, the reduced emission in the presence of antioxidants can result principally from: 1) quenching of the excited states (P*); 2) alternate termination pathways involving the antioxidant that compete with formation of P*; and 3) reduction of the number and length of free-radical chains through destruction of initiators and peroxy radicals, which then prevents autocatalysis. A number of techniques for determining inhibitor efficiencies in fluid solutions have been described[4f].

8. Mechanically and Photochemically Induced Chemiluminescence

It is well known among polymer chemists that mechanical damage to rubbers and other materials results in bond scission and free-radical reactions. We were not surprised to find that increased chemiluminescence from many polymers results from abrading or beating them, or from milling. *Grabec*[22] recently reported emission of light on stretching of a sample of a polymer, although the phenomenon was ascribed to triboluminescence rather than to oxidation reactions.

During our studies we noticed that room lights caused an enhanced luminescence emission from edible oils, cereals, and resins, among other materials. The decay of chemilumines-

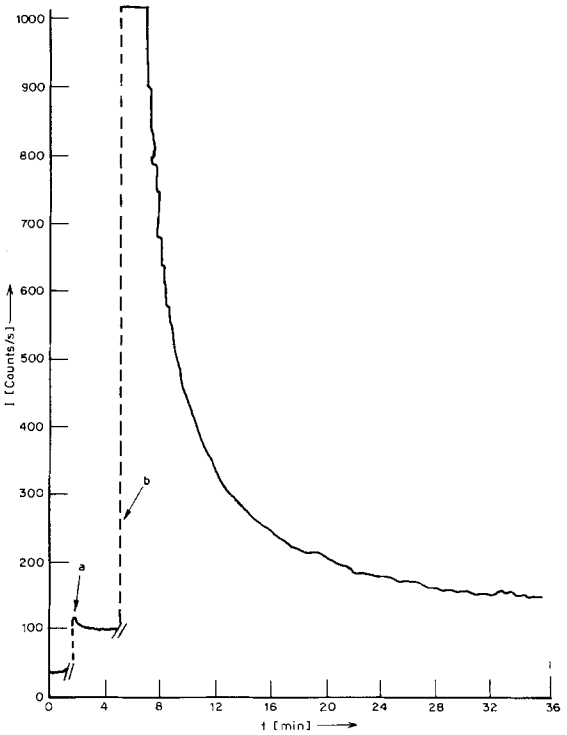


Fig. 13. Light-induced chemiluminescence from a soda cracker at 25 °C in air. a) sample introduced into apparatus; b) sample irradiated.

cence from a soda cracker is typical and is shown in Figure 13. The cracker was irradiated by means of a photographer's flashbulb immediately before examination. The light probably causes bond scission in some components of the samples and results in a free-radical chain reaction as in Scheme 1. In terms of this scheme, the decay curve for chemiluminescence arising from momentary light or mechanical action is described by eqs. (28) and (29) if the emission falls from an initial (I_0) to a constant value (I_∞) after irradiation[4f]. The final value is assumed to result from residual initiators in the sample. Equation (29) describes curves such as the one in Figure 13 fairly well in the later stages of decay, although in deriving this expression we assumed that the radicals are dispersed homogeneously in the portion of the sample from which we can detect light.

$$\frac{d(RO_2^\bullet)}{dt} = -2k_9(RO_2^\bullet)^2 + 2k_5[\text{Initiator}] \tag{28}$$

$$t = \frac{1}{4k_9k_5[\text{Initiator}]} \ln \frac{(I_\infty^{1/2} + I^{1/2})(I_\infty^{1/2} - I_0^{1/2})}{(I_\infty^{1/2} - I^{1/2})(I_\infty^{1/2} + I_0^{1/2})} \tag{29}$$

9. Correlations of Chemiluminescence with Physical Properties; Service Life Predictions

The importance of methods for determining the useful service life of fabricated materials has increased rapidly in recent years, due partly to the growing numbers and variety of synthetic products on the market. In many cases the new synthetic material or formulation is preferred on economic grounds over the product currently in use, although there is an associated risk on replacement because the behavior of the new product over long periods is not known. A large number of empirical tests have evolved throughout the manufacturing industry to determine long-term properties of new items, and of products made routinely by batch processes. Many of these tests are not entirely satisfactory, even though decisions of enormous economic significance sometimes must be based on their outcome.

One way in which such tests themselves may benefit from chemiluminescence is through Arrhenius plots that can reveal discontinuities between the service and the accelerated aging temperatures. This was known in advance of our study of the breakfast cereal (Figure 6), although our results were obtained more conveniently and in far less time. Uniformity among a collection of samples undergoing an aging test, on the other hand, can be studied by monitoring the chemiluminescence during the test itself. Batch-to-batch differences, including uniformity of product processing (Figures 8 and 11) can be revealed after short observation times in many cases.

A different approach, on the other hand, was adopted in experiments at Battelle with use of chemiluminescence to study degradation of a polyurethane sample. We assumed that a bimolecular mode of initiation [eq. (6)] occurred, that the effective concentration of abstractable hydrogens remained constant in the polymer, and that autoxidation products did not interfere. Rewriting eq. (18), we obtain

$$[\text{ROOH}] = (k_9 I)^{1/2}/(q_1 k_6)^{1/2}, \text{ where } q_1 = k_{10}k_{12}/(k_{12} + k_{11}[Q]) \tag{30}$$

From steady-state relations we can shown that

$$-d[O_2]/dt \equiv v_{O_2} = k_8(k_6/k_9)^{1/2}[\text{ROOH}][R'H] \tag{31}$$

and from (18), (30), and (31) we obtain

$$v_{O_2}/v_{hv} = \frac{k_8(k_9/k_6)^{1/2}[R'H]}{q_1[\text{ROOH}]} = \frac{k_8[R'H]}{q_1^{1/2} I^{1/2}} \tag{32}$$

$$\text{or } v_{O_2} = \frac{k_8[R'H] I^{1/2}}{q_1^{1/2}} = q_2 I^{1/2} \tag{33}$$

For a constant value of I

$$E_a(v_{O_2}/v_{hv}) \approx E_8 - 1/2\, E_{q_1} \tag{34}$$

This equation allows us to correct chemiluminescence data obtained at different temperatures for differences in radical chain length. We estimate $E_8 \approx 12 \pm 1$ kcal/mol and $E_{q_1} \approx 0$ kcal/mol, which give $E_a(v_{O_2}/v_{hv}) \approx 12$ kcal/mol.

Since oxygen uptake was calculated to depend on $I^{1/2}$, we plotted this value as a function of time over several days' accelerated aging at 60°C (Fig. 14). At 40°C, I_0 was 6.5 ± 1 counts/s, and from the chemiluminescence behavior at higher temperatures we inferred that this value was relatively constant for long periods. The area under the 60°C curve (for 7d) in Figure 14 was 39 (relative units). This value corresponds

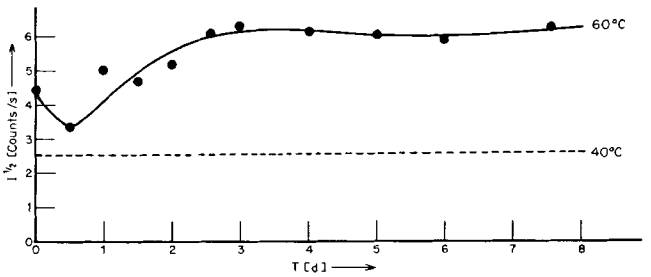


Fig. 14. Chemiluminescence (given as $I^{1/2}$) from a polyurethane sample in air at 40 and 60°C.

to 124 units at 40°C [after correction for the activation energy according to eq. (34)]. An equivalent area under the curve of a plot of $I^{1/2}$ *versus* time is realized at 40°C after

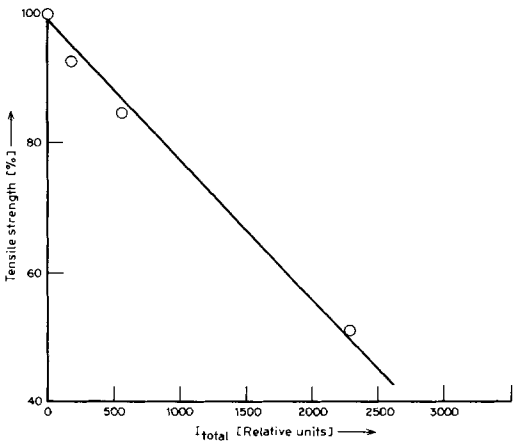


Fig. 15. Demonstration of proportionality between chemiluminescence and tensile strength of Malaysian natural rubber at 125°C. The aging data were kindly provided by *S. C. Teo*. The samples were examined at 70°C after 0, 6, 24, and 48 h at 125°C. I_{total} is total chemiluminescence emission.

$124/(6.5\pm1)^{1.2}=49\pm4$ days. That is, our treatment predicts that the same extent of oxygen uptake occurs in 7 days at 60 °C as in 49 days at 40 °C. We should emphasize, however, that this approach involves a number of assumptions about the oxidation mechanism that remain unproven.

We have carried out preliminary studies also to correlate physical properties of polymers with chemiluminescence emission. The oxidation of many polymeric materials is accompanied by both cross-linking and chain scission. The extent of either is proportional to the number of free-radical chains, and hence to the total chemiluminescence emission from the sample. This approach ignores completely the detailed morphological changes that can be observed by other techniques, but under certain conditions (Figs. 15 and 16) smooth relationships are observed between total chemiluminescence and physical changes in the sample that are probably caused by free-radical reactions.

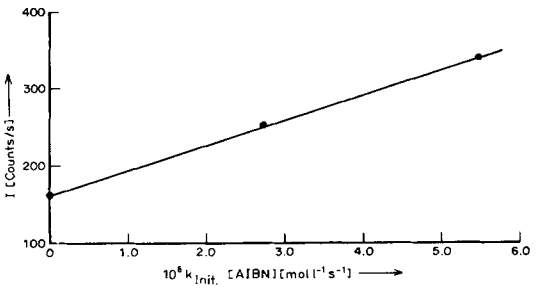


Fig. 16. Correlation between chemiluminescence emission and loss factor ($\tan\delta$) of General Electric Silicone W-96. Points correspond to aging in oxygen at 193 °C for 0, 0.45, and 6 h. I_{total} is total chemiluminescence emission.

10. Summary

The wide versatility of chemiluminescence techniques can readily be seen from the rather limited number of examples we have presented. The instrumentation for chemiluminescence is relatively simple and reliable, highly sensitive, precise over many orders of magnitude, and there is generally no associated art of sample preparation. The technique can be applied with equal success as a sophisticated research tool for mechanistic studies or for quality control of fabricated products in a nondestructive manner.

The application of chemiluminescence to the study of changes in materials (polymer degradation, flavor reversion, *etc.*) is largely a matter of discovering conditions under which the light emission will relate to properties of interest. This discovery is often done in a highly empirical way, aided by reasonable assumptions about the nature and behavior of the material under investigation. In spite of the limitations frequently imposed by a lack of detail about a given sample, the results of chemiluminescence studies of this sort have usually exceeded our expectations.

The Battelle chemiluminescence program has been assisted during the past five years by support from the Battelle Institute Program, the National Aeronautics and Space Administration, the Naval Air Systems Command, and from numerous industrial firms, some of whom gave permission to disclose details of current and past projects. Individuals at Battelle during this time who have made principal contributions in this effort include Dr. Albert H. Adelman, Dr. Gerald W. Lundeen, and Dr. Richard A. Nathan.

Received: May 24, 1976;
revised: September 1, 1976 [A 159 IE]
German version: Angew. Chem. 89, 220 (1977)

[1] For a recent review of bioluminescence, see: *F. McCapra*, Acc. Chem. Res. 9, 201 (1976).
[2] *J. Swift:* Gulliver's Travels; Voyage to Laputa. Signet Classic, New Amsterdam Library, New York 1960, Chap. 5, p. 197.
[3] *M. M. Rauhut*, Acc. Chem. Res. 2, 80 (1969).
[4] a) *V. Ya. Shlyapintokh*, Russ. Chem. Rev. 35, 292 (1966); b) *R. F. Vassil'ev*, Sov. Phys. Usp. 9, 504 (1967); c) Prog. React. Kinet. 4, 305 (1967); d) Russ. Chem. Rev. 39, 529 (1970); e) *E. Schröder, K. Thinius, L. Weissmann*, Plaste Kautsch. 17, 387 (1970); f) *V. Ya. Shlyapintokh, O. N. Karpukhin, L. M. Postnikov, V. F. Tsepalov, A. A. Vichutinskii, I. V. Zakharov:* Chemiluminescence Techniques in Chemical Reactions. Consultants Bureau, New York 1968.
[5] *N. M. Lukovskaya, A. V. Terletskaya, T. A. Bogoslavskaya*, Zh. Anal. Khim. 29, 2268 (1977), and references cited therein.
[6] *W. R. Seitz, D. M. Hercules* in *M. J. Cormier, D. M. Hercules, J. Lee:* Chemiluminescence and Bioluminescence. Plenum Press, New York 1973, p. 427.
[7] *A. Fontijn, R. Ellison*, Environ. Sci. Technol. 9, 1157 (1975).
[8] a) *S. E. Brolin, E. Borglund, L. Tegner, G. Wettermark*, Anal. Biochem. 42, 124 (1971); b) *M. J. Cormier*, unpublished results; c) *D. Knowlton*, unpublished results
[9] a) *W. R. Seitz, M. P. Neary*, Methods Biochem. Anal. 23, 180 (1976); b) *B. L. Strehler*, ibid. 16, 99 (1968).
[10] a) *R. E. Kellogg*, J. Am. Chem. Soc. 91, 5433 (1969); b) *J. Beutel*, ibid. 93, 2615 (1971).
[11] *C. Walling*, J. Am. Chem. Soc. 91, 7590 (1969).
[12] a) *B. Ranby, J. F. Rabek:* Photodegradation, Photooxidation, and Photostabilization of Polymers. Wiley, New York 1975; b) *C. Walling:* Free Radicals in Solution. Wiley, New York 1957, Chap. 9; c) *K. U. Ingold*, Acc. Chem. Res. 2, 1 (1969); *J. A. Howard* in *J. K. Kochi:* Free Radicals. Wiley-Interscience, New York 1973, Vol. III, p. 3.
[13] *G. Lundeen, R. Livingstone*, Photochem. Photobiol. 4, 1085 (1965).
[14] *R. A. Nathan:* Chemiluminescence for the Determination of the Kinetics and Mechanism of Jet Fuel Oxidative Degradation. Naval Air Systems Command, Contract N00019-73-C-0360 (March, 1974).
[15] *G. D. Mendenhall, R. A. Nathan*, unpublished results.
[16] *A. Robertson, W. A. Waters*, J. Chem. Soc. 1948, 1574.
[17] *A. E. Woodward, R. B. Mesrobian*, J. Am. Chem. Soc. 75, 6189 (1953).
[18] See [12c] and references cited therein.
[19] *J. A. Howard, J. E. Bennett*, Can. J. Chem. 50, 2374 (1972).
[20] *G. D. Mendenhall, T. B. Stanford, R. A. Nathan:* Chemiluminescence Study on Aircraft Tire Rubber Thermal Degradation. NASA-Ames Research Center Contract NAS2-3195 (March 1976).
[21] *G. E. Ashby*, J. Polym. Sci. 50, 99 (1961).
[22] *I. Grabec*, J. Polym. Sci., Polym. Lett. Ed. 12, 573 (1974).

New Developments in the Field of Vitamin B_{12}: Enzymatic Reactions Dependent upon Corrins and Coenzyme B_{12}

By G. N. Schrauzer[*]

Simple corrins such as vitamin B_{12} and vitamin B_{12} coenzyme catalyze a variety of unusual enzymatic reactions of which some are still without analogy in organic or organometallic chemistry. The mechanisms of these reactions are currently the subject of lively discussion. The present review focuses attention on new ideas about the mode of action of vitamin B_{12} coenzymes in enzymatic reactions.

1. Introduction

The first article of the present series described some of the more important reactions of the cobalt atom in corrins and in vitamin B_{12} model compounds[1]. In this article we shall discuss corrin-dependent enzymatic reactions with particular emphasis on questions concerning the mechanism of action of corrinoid coenzymes. Details dealing with the biological sources, properties, and isolation of the respective enzymes will not be given, nor will we mention purely medical aspects such as vitamin B_{12} deficiency syndromes, physiological transport mechanisms and the like, as these topics are adequately treated elsewhere[2, 3]. Moreover, the complexity of the corrin-dependent enzymatic reactions necessitated further limitations of coverage, as it turned out to be impossible to discuss all enzymatic reactions in full detail and to include historical developments within the available space. The view can be taken that proposed mechanisms of enzymatic reactions can be considered as valid only after they have been simulated, at least in principle, in suitable model systems under nonenzymatic conditions. Following the discovery of vitamin B_{12} model compounds in our laboratory, we as well as other workers have attempted to elucidate the mechanisms of corrin-dependent enzymatic reactions along these lines. In spite of considerable effort, there is still much controversy and uncertainty concerning the mode of action of corrinoid coenzymes. I believe that this is in part a consequence of insufficient communication between the workers in this highly interdisciplinary field. Moreover, new results of enzymological studies continue to appear in the biochemical literature, which in part necessitate a modification of current mechanistic ideas. It is therefore important to summarize the present status of this intriguing area of research.

1.1. Outline

The known corrin-dependent enzymes may be placed in two major groups. The first group comprises enzymes in which simple corrins, *e.g.* vitamin B_{12} itself, are utilized as cofactors. These are shown in Table 1. Enzymes which require vitamin B_{12} coenzymes such as 5'-deoxyadenosylcobalamin as cofactors fall into the second group (see Table 2). It is therefore reasonable to treat the reactions of the enzymes of the two groups separately.

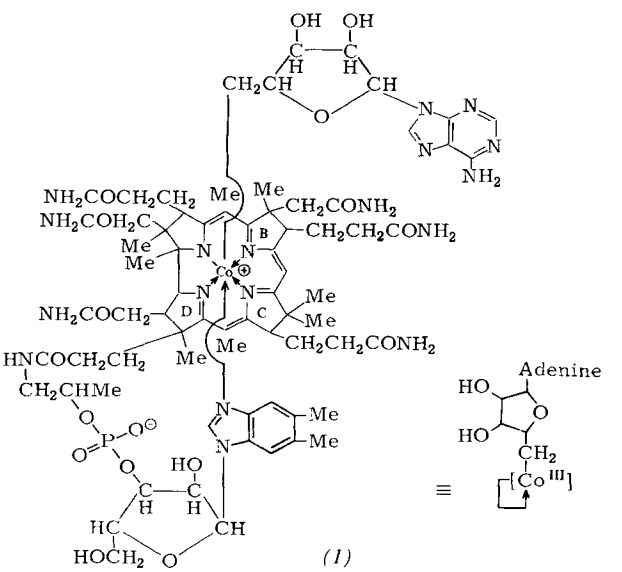
Table 1. Enzymes dependent on simple corrins [4].

Enzyme	Source(s)	Reaction catalyzed [a]	Cofactors
Methane synthetase	*e.g. Methanosarcina barkeri, Methanobacterium M. o. H.*	$C_1 \longrightarrow CH_4$	Reductant (H_2) (ATP, H_2, "coenzyme M")
Methylarsane synthetase	*Methanobacterium M. o. H.*	$C_1 \xrightarrow{+As^{3+}} AsH_{3-n}(CH_3)_n$	ATP, H_2, "coenzyme M" (?)
Acetate synthetase	*Clostridium thermoaceticum*	$C_1 + CO_2 \longrightarrow CH_3CO_2^{\ominus}$	Reductant
Methionine synthetase	*Escherichia coli*	5-CH_3-THFA + Homocysteine $\longrightarrow$ THFA + Methionine	Adenosylmethionine (reducing conditions)

[a] C_1 denotes one-carbon precursors of the methyl group, also including compounds which already possess a reactive methyl group, *e.g.* 5-CH_3-THFA [=5-methyltetrahydrofolic acid, see eq. (k) for formula].

1.2. Nomenclature

We shall use the same abbreviated nomenclature as outlined in Ref. [1]. 5'-Deoxyadenosylcobalamin *(1)* (Fig. 1) is simply



(1)

Fig. 1. Structure of coenzyme B_{12} *(1)* [43, 44]. In place of the 5'-deoxyadenosyl group, vitamin B_{12} bears a cyano group at the cobalt atom and vitamin B_{12a} a hydroxyl group.

[*] Prof. Dr. G. N. Schrauzer
University of California at San Diego, Revelle College
La Jolla, Calif. 92093 (USA)

Table 2. Coenzyme B_{12}-dependent enzymes [4].

Enzyme	Source(s)	Reaction catalyzed		Mol. Wt.	Cofactors
Dioldehydrase	*Aerobacter aerogenes*	$CH_3CH(OH)CH_2OH \longrightarrow CH_3CH_2CHO + H_2O$		?	$K^{\oplus}(NH_4^{\oplus})$
Glyceroldehydrase	*Lactobacillus sp.*	$CH_2(OH)CH(OH)CH_2OH \longrightarrow CH_2(OH)CH_2CHO + H_2O$		188000	$K^{\oplus}(NH_4^{\oplus})$
Ethanolamine deaminase	*Clostridium sp.*	$CH_2(NH_2)CH_2OH \longrightarrow CH_3CHO + NH_3$		520000	$K^{\oplus}(NH_4^{\oplus}, Rb^{\oplus})$
Ribonucleotide reductase	*e.g. Lactobacillus leichmannii*	$R(SH)_2 + GTP \longrightarrow R(S_2) + dGTP + H_2O$		70000	Effector (*e.g.* dGTP)
Methylmalonyl-CoA mutase	*Propionibacterium shermanii*	$HO_2CCH(CH_3)COCoA \rightleftharpoons HO_2CCH_2CH_2COCoA$		56000	
	Sheep liver			165000	
Glutamate mutase	*e.g. Clostridium tetranomorphum*	$HO_2C(CH_2)_2\overset{\oplus}{C}HCO_2H \rightleftharpoons HO_2C\overset{\oplus}{C}H{-}CHCO_2H$ (NH_3; CH_3, NH_3)		17000	
α-Methyleneglutarate mutase	*Clostridium barkeri*	$HO_2C(CH_2)_2\overset{CH_2}{\overset{\|}{C}}{-}CO_2H \rightleftharpoons HO_2C\overset{CH_3}{\overset{\|}{C}}H{-}\overset{CH_2}{\overset{\|}{C}}{-}CO_2H$		*ca.* 170000	
L-β-lysine aminomutase	*Clostridium sticklandii*	$\overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3 \rightleftharpoons \overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3$ ($CH_2(CH_2)_2\overset{\ominus}{C}HCH_2CO_2^{\ominus} \rightleftharpoons CH_3{-}\overset{\oplus}{C}HCH_2\overset{\oplus}{C}HCH_2CO_2$)	(I) (II)	*ca.* 60000 [a] 160000	$K^{\oplus}(Rb^{\oplus})$, $Mg^{2\oplus}(Mn^{2\oplus})$. ATP, pyruvate
D-α-lysine aminomutase	*Clostridium sticklandii*	$\overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3 \rightleftharpoons \overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3$ ($CH_2(CH_2)_3\overset{\ominus}{C}HCO_2^{\ominus} \rightleftharpoons CH_3{-}\overset{\oplus}{C}H(CH_2)_2\overset{\oplus}{C}HCO_2$)	(I) (II)	*ca.* 60000 160000	$K^{\oplus}(Rb^{\oplus})$, $Mg^{2\oplus}(Mn^{2\oplus})$. ATP, pyridoxal phosphate
Ornithine aminomutase	*Clostridium sticklandii*	$\overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3 \rightleftharpoons \overset{\oplus}{N}H_3\ \overset{\oplus}{N}H_3$ ($CH_2(CH_2)_2\overset{\ominus}{C}HCO_2^{\ominus} \rightleftharpoons CH_3{-}\overset{\oplus}{C}HCH_2\overset{\oplus}{C}HCO_2$)	(I) (II)	*ca.* 60000 160000	none (?)

[a] Two components; protein II binds coenzyme B_{12}.

denoted as "coenzyme B_{12}". All other abbreviations are either readily understood or explained in the text. The typical vitamin B_{12} model compounds are called cobaloximes.

2. Enzymatic Reactions Dependent on Simple Corrins

The enzymes listed in Table 1 occur in the presence of simple corrins such as *e.g.* vitamin B_{12a} (hydroxocobalamin). Certain methane-producing bacteria utilize corrin derivatives in which bases other than 5,6-dimethylbenzimidazole are present in the molecule, *e.g.* "Factor III", which contains 5-hydroxybenzimidazole, or corrins in which no axial base is present, *e.g.* "Factor B" (cobinamide)[5]. The formation of methylarsanes presumably does not require an independent enzyme and may be considered as a by-product of methanogenesis in the presence of added arsenic.

2.1. Methane Biosynthesis

A number of bacterial species produce methane as the terminal product of the metabolism of cellulose, sugars, fatty acids, alcohols, formaldehyde, serine, but also from CO_2. These organisms are as a rule difficult to cultivate. Among the best-known are *Methanosarcina barkeri* and *Methanobacterium M. o. H.* Other methane-producing bacteria that may be mentioned in this context are those of the genus *Methanococcus* as well as *Methanobacterium ruminantium*, *Methanospirillium*, and *Methanobacterium formicium*. To illustrate the difficulties of isolation and cultivation of some of these organisms we quote the example of *Methanococcus vanneillii*, which was isolated from San Francisco Bay sludge but subsequently became lost. A deep-frozen tube of cells, stored for over 12 years was still available, however, from which *Stadtman* was able to obtain viable cells for renewed cultivation[5].

Considerable amounts of methane are produced from sewage sludge, a source of combustible gas that could in future become commercially interesting. Prior to World-War II, 2×10^6 cubic meters of methane were collected per year in the disposal plant of Stuttgart, Germany. This amount was sufficient to provide fuel for 110 municipal motor vehicles[6]. Methane is also formed in the rumen of cows and other animals. A fully grown cow may generate as much as 200 liters of methane per day[5]. This is considered to be an undesirable side-reaction during the digestive process as it lowers the feed-efficiency. Methane is produced in the human intestine too, in amounts which depend on the type and quantity of food ingested.

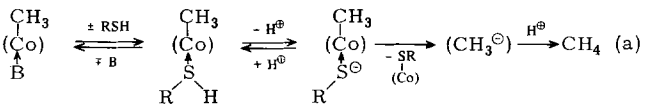
2.2. Methane-Biosynthesis *in Vitro*

Methane bacteria can be cultivated in media containing ammonia as the source of nitrogen; B-vitamins as well as rumen fluid are added to promote growth. CO_2, methanol, ethanol, formate, or acetate can be employed as sources of C_1, while hydrogen is commonly used as the reducing agent. The pure methane synthetases have not yet been isolated; they appear to be extremely sensitive, and most of the available information on methanogenesis *in vitro* was obtained from experiments with intact cells or cell-free extracts[5]. A variety of compounds contain reactive methyl groups or precursors of the methyl group for methane production. These include: serine, pyruvate, 5-methyltetrahydrofolic acid (5-CH_3-THFA), 5,10-methylene-tetrahydrofolic acid, methylcobalamin, other co-methylated corrins and even methyl-derivatives of vitamin B_{12} model compounds[7]. Extracts from *Methanobacterium M. o. H.* require catalytic amounts of ATP for methane production. Additional cofactors are presumably also necessary; most interestingly, 2-mercaptoethylsulfonate, $HS{-}CH_2CH_2SO_3^-$, has been found to be one such factor. This compound was shown by *Wolfe et al.*[8] to possess the properties of a coenzyme and was for this reason named "coenzyme M". In the absence of ATP, this compound is *S*-methylated by methylcobalamin; the product is reductively demethylated by a different enzyme

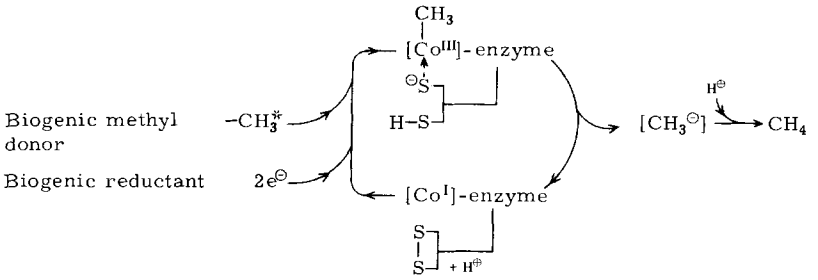
to yield methane. The reductive demethylation, which regenerates coenzyme M, is inhibited by tripolyphosphate[8]. It is not yet known if methane is formed exclusively *via* methylated coenzyme M or whether the *S*-methylation-demethylation is not a side-reaction. On the other hand, there can be no doubt that methylated corrins are formed in the terminal stages of methanogenesis. A corrin-containing protein present in cell-extracts of *Methanobacterium omelianskii*, which is actually a symbiotic association of *Methanobacterium M. o. H.* with a hydrogen-producing organism[9], can be converted into a propylated derivative on reaction with propyl iodide. This causes inhibition of methane formation, but exposure of the protein to light restores activity. It thus may be assumed that the enzyme-bound corrin is converted into the *n*-propyl-derivative and that the Co—C bond in the latter is cleaved on irradiation with light. Methanogenesis is also inhibited by a variety of halogenated hydrocarbons, including freon and DDT[10–12]. Chloromethylcobalamins act as competitive inhibitors of methane formation. How methane is produced from the methylated corrin cofactor does not follow clearly from any of these experiments. It was assumed for some time that the reaction occurs *via* free methyl radicals[13], but such a mechanism must now be considered as unlikely.

2.3. Mechanism of Methane Synthesis

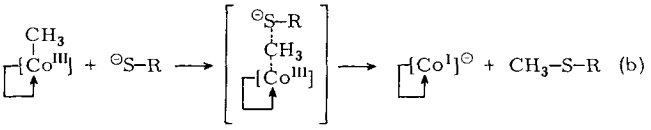
Scheme 1 surveys the most important reactions which occur in cell extracts of methane-producing bacteria. A fully satisfying mechanism of methanogenesis cannot be formulated on the basis of the available enzymological evidence. We considered the possibility that methane is formed from the methylated corrin through the reductive cleavage of the Co—C bond[14]. This reaction occurs readily under nonenzymatic conditions; thiols and dithiols are some of the reductants that can be used for this purpose (see [1]). The reaction occurs as shown in eq. (a), it thus involves an axial attack of cobalt by the thiol:



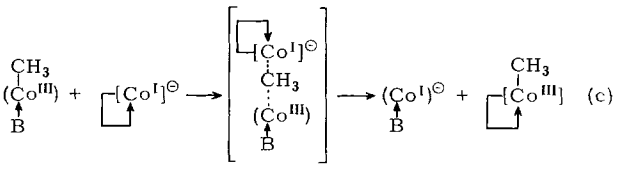
A mechanism of enzymatic methane production was formulated along these lines and is schematically represented in Scheme 2[14]. At the time of this proposal, little was known about coenzyme M. Since coenzyme M is a thiol, we expected it to react with methylcobalamin according to eq. (a). This has since been confirmed[15], but we cannot say, of course, whether coenzyme M reacts in this manner under enzymatic conditions as well.



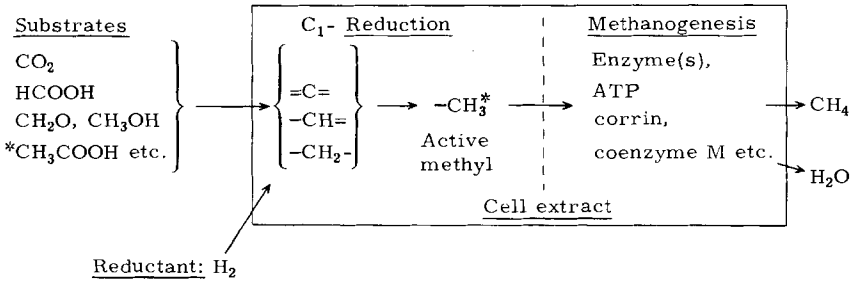
Scheme 2. Proposed mechanism of methane biosynthesis.



The *S*-methylation of coenzyme M, which has been observed under enzymatic conditions, can also be formulated, as methylcobalt complexes react with thiolate ions according to eq. (b)[1].



Eq. (b) could thus be considered as an acceptable model of the enzymatic demethylation of methylcobalamin by coenzyme M.



Scheme 1. Enzymatic methane synthesis.

The fact that methylcobaloximes are demethylated to yield methane in functional cell-extracts of *Methanobacterium M. o. H.* is of considerable interest. Methane is produced under these conditions only if catalytic amounts of a corrin and ATP are added[7]. This suggested a mechanism in which the

cobaloxime-bound methyl group is first transferred to the corrin cofactor, followed by the actual enzymatic demethylation process. A reversible exchange of methyl groups in terms of eq. (c) occurs readily under nonenzymatic conditions[16].

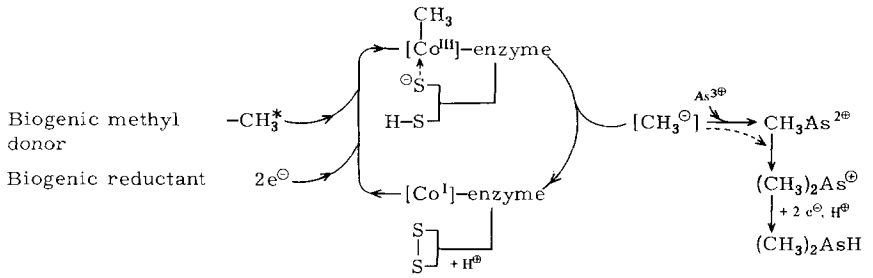
However, this interpretation leads to mechanistic difficulties. Thus, if a transfer of the methyl group were the main reaction, the rates of methane evolution from different methylcobaloxime substrates should either all be the same or should at least be related to the relative tendency of methylcobaloximes to undergo transfer of the methyl group according to eq. (c). However, this is not the case. It was observed instead that the relative rates of methane production depend on the nature of the axial bases. Other authors suggested that this was mainly due to differences in the solubilities of the different cobaloximes studied[17], *but a more detailed comparison of the solubilities of the model compounds in polar solvents did not reveal any significant correlation with the rates of methane production*[16]. A statistically significant *direct association* ($P=0.05$) between the relative rates of enzymatic methane production and the nonenzymatic reaction according to eq. (a) was observed using experimental data for 13 different compounds. The linear correlation coefficient increases to $r=0.87$ ($P<0.01$), if the calculations are restricted to methylcobalamin and methylcobaloximes (7 data points)[18]. These results suggest that methane may well arise from methylcobalamin after the manner of Scheme 2 and that methylcobaloximes are reductively demethylated under the enzymatic conditions by way of a reaction which occurs with a displacement of the axial base by a biogenic reductant, possibly a thiol or dithiol.

Thus methane biosynthesis is seen to be a relatively complicated process. It at least seems clear why corrins are utilized for such a comparatively simple biochemical reaction: It is now well established that the Co(I) supernucleophiles of vitamin B_{12} (vitamin B_{12s}) are perhaps the most effective scavengers of activated methyl groups in nature. On the other hand, corrin-independent mechanisms of methanogenesis may exist as well, as is suggested by the reductive demethylation of methylated coenzyme M[19], but these processes are not yet understood. Further details of methane biosynthesis will not be discussed, particularly those concerning the reduction of CO_2 to active methyl groups. Such reactions are part of the metabolism of C_1-compounds and are corrin-independent processes.

2.4. Methylarsane Biosynthesis

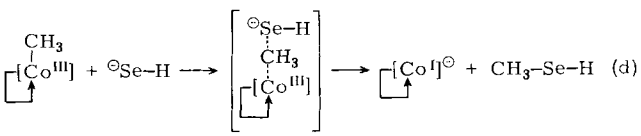
The addition of arsenate to cell extracts of *Methanobacterium M. o. H.* yields derivatives of methylarsanes, *i.e.* $AsH(CH_3)_2$ and $AsH_2(CH_3)$[20]. The methylation of arsenic was also observed with intact cells of this organism under conditions of methanogenesis. The reaction is inhibited by added selenite. Methylcobalamin acts as the donor of the methyl group[20], and obviously has little if anything in common with the methylation of arsenic by certain fungi, *e.g. Penicillium glaucum.* The corrin-dependent formation of methylarsanes must be closely related with methane biosynthesis, as methane is always formed as well. Methylcobalamin and methylcobaloximes methylate arsenic under the conditions of reductive Co—C bond cleavage[16]. The reaction is inhibited by selenite, but the latter is of course reduced to selenide and ultimately forms methyl selenide. Ethylcobalamin, on the other hand, does not give rise to ethylarsane, under neither enzymatic[20] nor nonenzymatic conditions[16].

With ethylcobaloximes, only traces of ethylarsane are formed[16]. There thus exist plausible model reactions for methylarsane biosynthesis as represented in Scheme 3.



Scheme 3. Postulated mechanism of enzymatic methylarsane synthesis.

The inhibitory effect of selenide on arsenic methylation is attributed to a competition between the methylation of arsenic and a nucleophilic displacement of the cobalt-bound methyl group in terms of eq. (d).



The conversion of arsenic to methylarsanes under conditions of methanogenesis may be regarded as a bacterial detoxification process. The observed *methylation of mercuric ion* should also be mentioned in this context. Hg^{2+} ion reacts with methylcobalamin rapidly to produce $Hg(CH_3)^+$[21–23], a process which may have some toxicological significance[24].

2.5. Acetate Biosynthesis

Acetate (or acetic acid) is formed as terminal product of the fermentation of glucose, cellulose, *etc.* by *Clostridium thermoaceticum*[25]. The net reactions which occur are summarized in eqs. (e) to (g)[26].

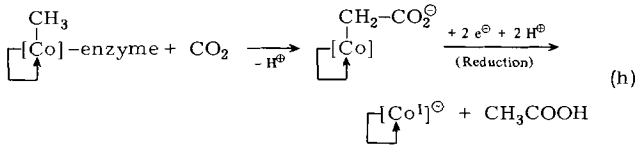
$$C_6H_{12}O_6 + 2\ H_2O \longrightarrow 2\ CH_3COOH + 2\ CO_2 + 8\ H \quad (e)$$

$$8\ H + 2\ CO_2 \longrightarrow CH_3COOH + 2\ H_2O \quad (f)$$

$$C_6H_{12}O_6 \longrightarrow 3\ CH_3COOH \quad (g)$$

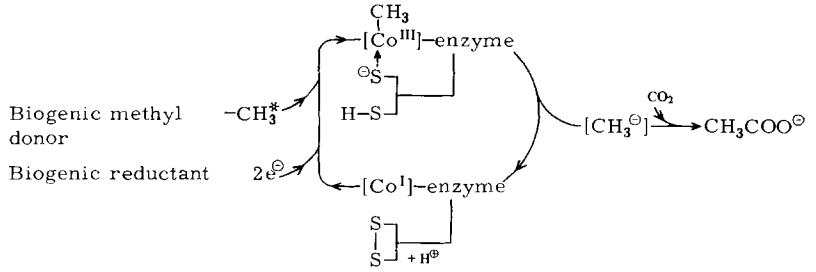
Cell-free extracts of *Cl. thermoaceticum* convert the methyl group of added methylcobalamin to acetate *as a whole, i.e.* the reaction occurs without loss or exchange of hydrogen atoms of the methyl group[27]. This reaction thus represents

a rare example of a bacterial CO_2 assimilation. It occurs under reducing conditions and is inhibited by SH-blocking reagents. The conversion of methylcobalamin to acetate was first assumed to occur as shown in eq. (h)[28].



(h)

However, a reaction of this type is unlikely as it assumes the removal of a proton from the cobalt-bound methyl group, in contrast to the observations mentioned above. A methylation of CO_2 by methylcobalamin in analogy to known reactions of Grignard reagent also does not occur, since methylcobalamin or related organocobalt complexes are insufficiently reactive. However, the formation of acetate from methylcobalt complexes was demonstrated under conditions of reductive Co—C bond cleavage. This led to the proposal of acetate biosynthesis shown in Scheme 4[16,29].

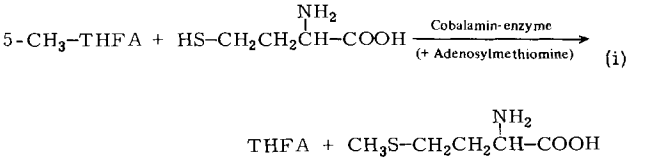


Scheme 4. Postulated mechanism of acetate biosynthesis from methylcobalamin.

Hence, acetate biosynthesis, the enzymatic methylation of arsenic, and methanogenesis appear to be closely related reactions. The reaction of CO_2 with CH_3^- must occur in an essentially proton-free enzymic environment, for otherwise methane would be formed preferentially. It would be of interest to examine if *Cl. thermoaceticum* methylates arsenic or produces methane under certain conditions.

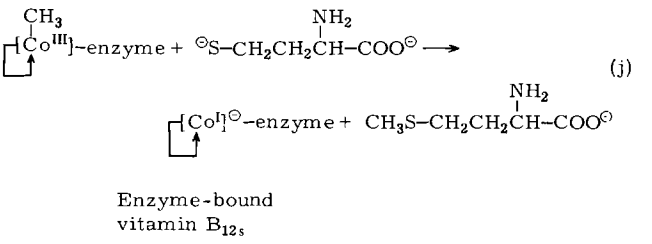
2.6. Methionine Synthesis by *Escherichia coli*

E. coli contains an enzyme which transfers the methyl group from 5-methyltetrahydrofolic acid (5-CH_3-THFA) to homocysteine according to eq. (i)[30–36].



(i)

Corrin-dependent methionine synthesis also occurs in animal tissues but not in plants. *S*-Adenosylmethionine (AMe) also appears to be a cofactor and was shown to methylate enzyme-bound vitamin B_{12s} more rapidly than 5-CH_3-THFA. The terminal step of methionine biosynthesis is assumed to occur according to eq. (j), a reaction which has also been simulated under nonenzymatic conditions using methylcobaloxime as the donor of the methyl group.



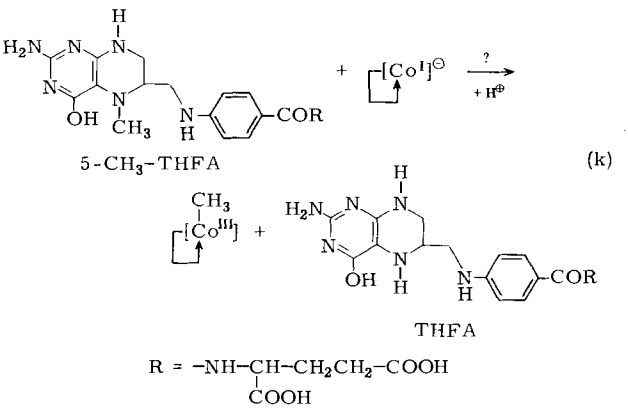
(j)

Enzyme-bound vitamin B_{12s}

Alkaline conditions are required for the nonenzymatic synthesis of methionine from methylcobaloxime and homocysteine, since a nucleophilic displacement according to eq. (j) occurs only in the presence of the homocysteinyl dianion. In neutral solution, homocysteine causes reductive cleavage of the Co—C bond [see eqs. (a) and (b)].

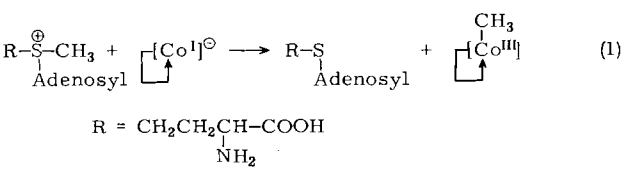
On the other hand, attempts to demonstrate the formation of methylcobalamin from 5-CH_3-THFA and vitamin B_{12r} or B_{12s} have thus far not been successful under nonenzymatic conditions [eq. (k)].

It must be assumed that reaction according to eq. (k) can only occur after a specific activation of the 5-CH_3 group,



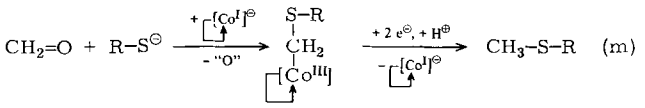
(k)

or that the methylation of the enzyme-bound corrin by 5-CH_3-THFA is an indirect reaction. The question how reaction (k) occurs is one of the unresolved problems in all corrin-dependent methyl group transfer reactions. The role of adenosylmethionine in methionine biosynthesis has also not been fully elucidated, even though reaction (l) occurs nonenzymatically with no difficulty.



(l)

It should be mentioned in passing that thiols are reductively methylated on reaction with formaldehyde in the presence of catalytic amounts of vitamin B_{12s} [eq. (m)][37,38].



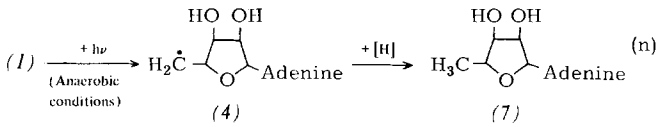
(m)

It would be of interest to demonstrate a corrin-dependent enzymatic methylation of homocysteine in analogy to eq. (m), utilizing substrates such as 5,10-methylene-tetrahydrofolic acid, which contains the C_1-unit at the oxidation level of formaldehyde.

3. Coenzyme B_{12}-Dependent Enzymatic Reactions

3.1. Properties and Reactions of Coenzyme B_{12}

At least nine enzymes are presently known in which coenzyme B_{12} is a required cofactor (see Table 2). The structure of the coenzyme (see Fig. 1) does not provide any clue as to how it functions in enzymatic reactions. It is commonly assumed that a cleavage of the Co—C bond occurs if the coenzyme is bound to the apoenzymes, but how this activation takes place is a matter of controversy. Coenzyme B_{12} or 5'-deoxyadenosylcobalamin *(1)* is stable in the solid state and in neutral aqueous solution. An irreversible decomposition into hydroxocobalamin (vitamin B_{12a}), adenine, and D-*erythro*-2,3-dihydroxypent-4-enal *(2)* occurs on reaction with acids[39]. In alkaline solution, the Co—C bond is cleaved by way of an elimination reaction, giving rise to the formation of vitamin B_{12s} and of 4',5'-anhydroadenosine *(3)*[40]. On irradiation, vitamin B_{12r} and the 5'-deoxyadenosyl radical *(4)* are formed, indicating that the Co—C bond is cleaved homolytically. The radical *(4)* terminates under anaerobic conditions to yield the cyclic adenosinoid *(5)*[41]. In the presence of air, *(4)* is oxidized primarily to *(6)*[42]. A reductive cleavage of the Co—C bond on reaction of *(1)* with thiols or dithiols, gives



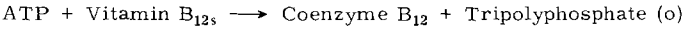
(n)

rise to 5'deoxyadenosine *(7)* (see Scheme 5)[16]. The same compound *(7)* can also be formed from *(4)* in solvents containing labile hydrogen atoms, *e.g.* in alcohols [eq. (n)].

Coenzyme B_{12} is also decomposed by alkaline cyanide. Most Co—C bond cleavage reactions of *(1)* are irreversible, except the recombination of vitamin B_{12r} with *(4)* and, possibly, the base-induced elimination to give vitamin B_{12s} and *(3)*[40].

3.2. Coenzyme B_{12} Biosynthesis

Coenzyme B_{12} *(1)* is synthesized by a variety of microorganisms and was first isolated by *Barker et al.* from extracts of *Cl. tetanomorphum*[41,42]. In the terminal step of the biosynthesis of *(1)*, the adenosyl residue from ATP is transferred to the cobalt atom under reducing conditions with attendant formation of tripolyphosphate [eq. (o)][45,46].

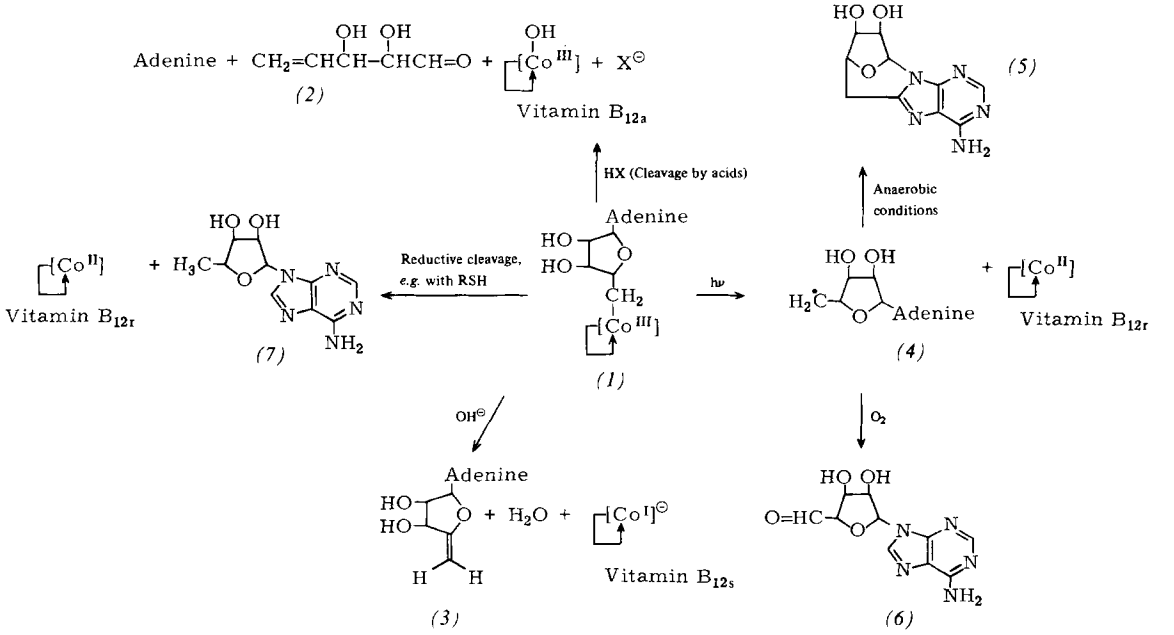


(o)

Reaction according to eq. (o) could not yet be verified under nonenzymatic conditions. The enzymatic reaction presumably involves a specific activation of the C—O—P bond of ATP. In laboratory syntheses of *(1)*, vitamin B_{12s} is reacted with 2',3'-protected derivatives of adenosine, usually the tosylates and the protecting groups are subsequently removed under mildly acidic conditions.

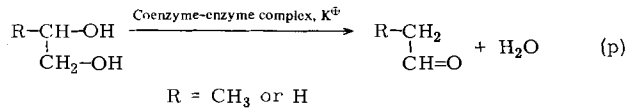
3.3. Dioldehydrases

In cell extracts of *Aerobacter aerogenes* an enzyme was discovered by *Abeles et al.*[47] which catalyzes the conversion



Scheme 5. Reactions of coenzyme B_{12} *(1)* (see also Fig. 1).

of D,L-1,2-propanediol and of ethylene glycol to propionaldehyde and acetaldehyde, respectively [eq. (p)].

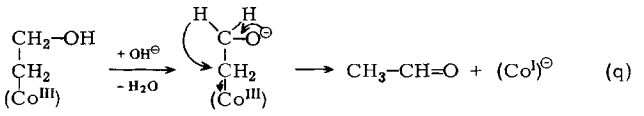


(p)

A *Lactobacillus* contains a related enzyme which causes the conversion of glycerol into hydroxypropionaldehyde[48]. This reaction may occur during alcohol fermentation and is undesirable as it gives rise to the formation of acrolein on subsequent distillation. Dioldehydrase from *A. aerogenes* has since been isolated in relatively pure form. The apoenzyme is known to contain thiol groups, some of which are presumably located in the vicinity of the coenzyme binding site. It was observed only a short time ago, however, that the enzyme also converts 1,2-butanediol into butyraldehyde and 2,3-butanediol into 2-butanone, for example[49]; these substrates were previously considered to be inhibitors. The functional holoenzyme is inactivated by oxygen. The relative oxygen-sensitivity depends on the pretreatment of the apoenzyme. If solutions of the apoenzyme are prepared and stored under careful exclusion of oxygen, more highly oxygen-sensitive holoenzyme samples are obtained than when the apoenzyme is dissolved and maintained aerobically. We assume[50] that the apoenzyme can exist in at least two active modifications, which differ from each other in their content of free SH groups. Exposure of the apoenzyme to air seems to cause an oxidation of free SH groups to disulfide, giving rise to the formation of a the less oxygen-sensitive holoenzyme. This view is supported by the fact that the oxidized modification may be in part converted back into the reduced form on reaction with mild reducing agents[50].

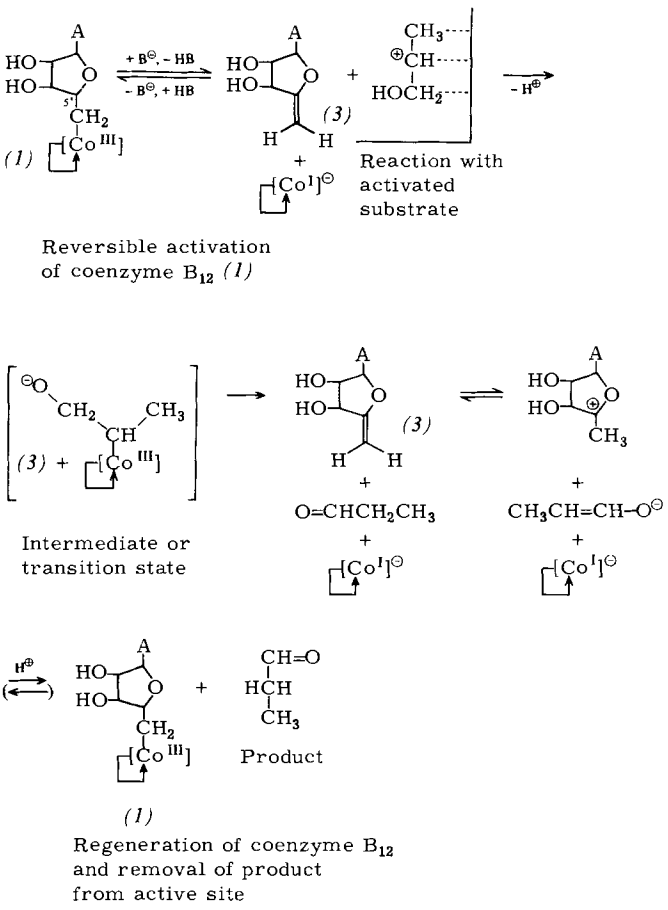
3.3.1. Mechanism of Enzymatic Dehydration of Diols

1,2-Diols can be converted into aldehydes or ketones quite easily on reaction with acids. Thus, phenylglycol is converted to phenylacetaldehyde simply by steam-distillation of a solution of the diol in 12% aqueous H_2SO_4. But what is the mechanism of the coenzyme B_{12}-catalyzed dehydration of glycol to acetaldehyde? β-Hydroxyethylcobaloximes were found to decompose into acetaldehyde and cobaloxime(I) in alkaline solution. This led us 10 years ago to propose that an analogous reaction occurs in the enzymatic dehydration of diols [see eq. (q)][51].



(q)

Since glycols as such do not react with vitamin B_{12s} or cobaloximes(I), the assumption was made that the diol substrates are specifically activated on interaction with the enzyme[29]. We furthermore suggested that enzyme-bound vitamin B_{12s} is generated from coenzyme B_{12} by way of a base-induced elimination. The 4′,5′-anhydroadenosine *(3)* formed during this activation of the coenzyme was assumed to remain in the vicinity of the active site. To explain the demonstrated exchange of substrate protons with the hydrogen atoms at the 5′-position of the coenzyme, we proposed that the product aldehyde exchanges protons with the enzyme-bound *(3)* as shown in Scheme 6. According to this mechanism, the coenzyme-substrate hydrogen exchange is thus considered to be



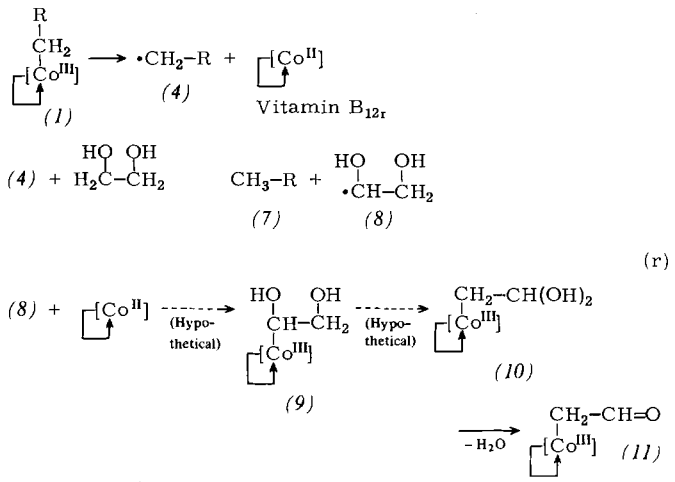
Scheme 6. Suggested mechanism for enzymatic conversion of D,L-1,2-propanediol into propionaldehyde [29].

independent of the actual catalytic conversion of diols to aldehydes and is instead assumed to occur between the 4′-protons of *(3)* and the labile β-protons of the product aldehyde generated at the active site. Such ionic proton-exchange reactions can be readily simulated in model systems[29]. In Section 3.3.2 we shall discuss an alternative mechanistic proposal in which the same processes are formulated *via free radicals.*

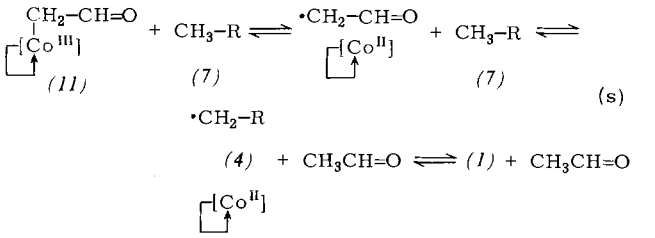
The mechanism in Scheme 6 is supported by the fact that the oxygen-sensitive modification of dioldehydrase-holoenzyme is inactivated by N_2O almost as efficiently as by O_2[50]. In the first part of this series, we already pointed out that N_2O is a specific oxidant of vitamin B_{12s}. Thus, the inactivation of the holoenzyme by N_2O demonstrates the presence of enzyme-bound vitamin B_{12s}. We recently also obtained evidence for the presence of *(3)* in the functional holoenzyme[52]. In spite of these observations, the proposed mechanism in Scheme 6 has thus far not been accepted by other workers in the field. It has been argued, that our mechanism does not fully explain the observed hydrogen-isotope exchange effects[53], but these and other objections will not be discussed here in view of more extensive counterarguments presented in Ref. [54]. We still consider the mechanism in Scheme 6 to be correct *in principle*, but since an alternative mechanism has been proposed which is based on different assumptions, we shall discuss this mechanism as well.

3.3.2. Alternative Mechanism

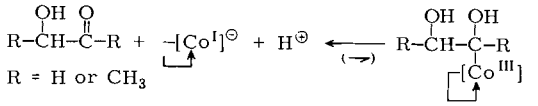
Abeles and other workers believe that the diol dehydration occurs by way of free radicals[55]. The assumption is made that coenzyme B_{12} *(1)* is converted into the active form by *homolysis* of the Co—C bond. The resulting 5′-deoxyadenosyl radical *(4)* in turn abstracts a hydrogen atom from the glycol substrate and is converted into 5′-deoxyadenosine *(7)*. The glycol radical *(8)* is subsequently assumed to react with vitamin B_{12r} to yield 1,2-di-hydroxyethylcobalamin *(9)*, an intermediate which is postulated to rearrange into the hydrate of formylmethylcobalamin *(10)* or formylmethylcobalamin *(11)*, respectively [eq. (r). The enzyme has been omitted from the formulas].



In the terminal step of the reaction, formylmethylcobalamin *(11)* was suggested to yield acetaldehyde by a reaction involving *homolysis* of the Co—C bond and a hydrogen abstraction reaction between the resulting acetaldehyde radical and a 5′-hydrogen atom of 5′-deoxyadenosine *(7)*. This hypothetical reaction sequence is outlined in eq. (s).



This radical mechanism was assumed in order to explain the observed appearance of ^3H-labeled acetaldehyde in the reaction of unlabeled glycol with the holoenzyme containing ^3H in the 5′-position of the coenzyme[56]. If the view is taken, that this exchange of hydrogen involves the coenzyme and the *substrate* glycol, it would indeed be necessary to consider radical reactions of the type shown in eq. (r) or (s). However, there is in fact evidence that ^3H-exchange reactions also occur between enzyme-bound coenzyme and *product* aldehyde. This would mean that the hydrogen-exchange reactions are reversible even though the glycol dehydration is irreversible. Attempts to verify the hypothetical reactions (r) and (s) met with little success. Model experiments indicated that compounds of type *(9)* are either extremely unstable or incapable of existence; the postulated rearrangement of *(9)* into *(10)* thus could not be demonstrated. Compound *(9)* could be regarded as a "*corrinohydrin*" of glycolaldehyde. However, we have previously shown that the equilibrium in reaction (t) is far on the left side, over a wide pH range[57a].

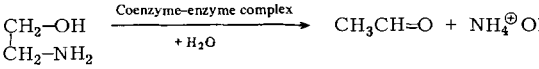


Glycol radicals generated by a radiolysis reaction of glycols were in addition shown to have no tendency to form *(9)* on reaction with vitamin B_{12r}[57b]. Another argument against the free-radical mechanism of glycol dehydration was obtained in attempts to verify reaction eq. (s). Formylmethylcobalamin *(11)* decomposes thermally as well as on irradiation in solution to yield acetaldehyde and hydroxocobalamin *without the intermediate appearance of vitamin* B_{12r}[58] [see eq. (q) in the first part of this series]. Thus it is not possible to support this alternative mechanism of enzymatic diol dehydration by means of direct experimental studies. This is not to say that free-radical rearrangements of glycol radicals to acetaldehyde radicals cannot occur. Acetaldehyde is formed, for example, in the reaction of glycol with Fenton's reagent. It has also been reported that traces of acetaldehyde are generated if methylcobaloxime is photolyzed in the presence of glycol, provided that the reaction is performed in acidic solution[59]. We studied the same reaction in neutral media. Under these conditions, the glycol radicals generated seem to dimerize to yield erythritol and related compounds[57a]. Since a homolysis of the Co—C bond of coenzyme B_{12} was considered to represent the mechanism of its enzymatic activation, it should also be pointed out that such a process is improbable for energetic reasons. Traces of *(7)* have been detected after the work-up of enzyme solutions incubated with radioactively labeled *(1)*. This was interpreted to suggest that *(7)* participates in the catalytic process of glycol dehydration. However, since the same compound is formed as the product of a reductive cleavage of the Co—C bond of *(1)* and dioldehydrase contains thiol groups, *(7)* may also be the by-product of a side-reaction rather than a catalytic intermediate [see eq. (n) and Scheme 5].

ESR measurements, finally, have been performed on functional dioldehydrase. Under certain experimental conditions, paramagnetic species were observed, but the signals are not very characteristic and could not be identified unambiguously.

3.4. Ethanolamine-Deaminase (Ethanolamine-Ammonia Lyase)

An enzyme which catalyzes the conversion of ethanolamine into acetaldehyde and ammonia [eq. (u)] was discovered in *Clostridium sp.*[60] and shown to require *(1)* for activity. The

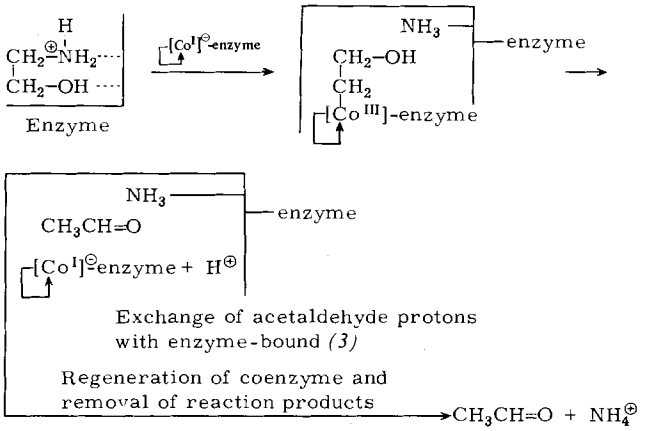


enzyme was studied in detail by *Babior*[61]. The apoprotein has a MW of 520000 and on treatment with 5 M guanidinium hydrochloride is cleaved into inactive subunits of MW 51000. The oxygen atom of ethanolamine becomes the oxygen atom of product acetaldehyde and remains associated with the same carbon atom. The enzyme appears to be related to some

extent with dioldehydrase, especially since glycol can function as a stoichiometric substrate. If [^{3}H]-2-aminoethanol is employed as the substrate, ^{3}H enters into the 5'-position of the coenzyme. For reaction (u), both ionic and free-radical mechanisms were therefore postulated as will be outlined below.

3.4.1. Mechanism of Enzymatic Deamination of Aminoethanol

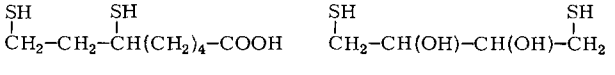
We found in our laboratory[62] that ethanolamine-ammonia lyase is inactivated by oxygen as well as by N_2O, and hence concluded that the active enzyme contains a bound Co(I)-corrin. Using ^{14}C-labeled coenzyme B_{12} we were also able to detect traces of labeled *(3)* on careful work-up of preparations of the functional holoenzyme, while *(7)* could not be seen. Accordingly, a mechanism was postulated for the enzymatic reaction which is shown in Scheme 7[62]. We see no possibility to support a free-radical mechanism on the basis of model experiments.



Scheme 7. Proposed ionic mechanism of enzymatic deamination of ethanolamine by ethanolamine deaminase (abbreviated version)[62].

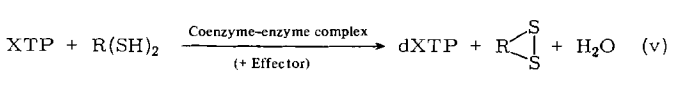
3.5. Ribonucleotide Reductase

An enzyme in *Lactobacillus leichmannii* catalyzes the reduction of ribonucleotides to deoxyribonucleotides[63, 64]. 5'-



(12) *(13)*

Deoxyadenosylcobalamin is the coenzyme, a thioredoxin-system the reductant, but for *in vitro* experiments, the latter may be replaced by dithiols such as dihydrolipoic acid *(12)* or dithioerythritol *(13)* [eq. (v)].

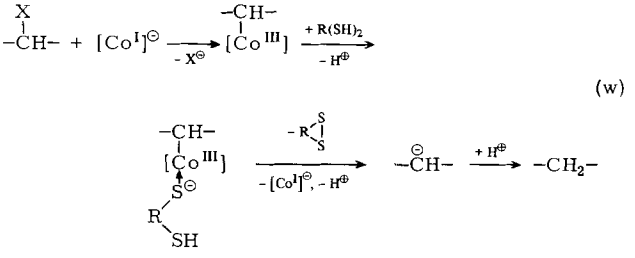


(v)

Certain deoxyribonucleotides accelerate the reduction of the substrates and are for this reason considered to act as effectors. A similar enzyme was detected in *Lactobacillus acidophilus* and *Rhizobium melioti*; it is possibly also present in a variety of other organisms[65, 66]. The enzyme is non-specific with respect to the nucleotide base component. However, minor modifications of the ribose moiety have a pronounced effect on the ability of the substrates to be reduced. The added effector is assumed to be bound by the apoenzyme but probably not in the vicinity of the active site. It is believed to induce a conformational change of the protein which in turn enhances substrate binding and/or reduction. Incubation of the enzyme with 5'-^{3}H-labeled coenzyme B_{12} causes the appearance of tritium in the water solvent during substrate reduction[67]. At low enzyme concentrations the amount of tritium released is proportional to the yields of reduced product. If the reaction is carried out in ^3H_2O, tritium is found both in the enzyme-bound *(1)* as well as in the product deoxyribonucleotide. The displacement of the OH group by H in the C'-2 position of the ribose moiety occurs with net retention of configuration. The apoprotein appears to contain thiol groups in the vicinity of the coenzyme binding site. Vitamin B_{12a} does not exhibit coenzyme activity but is reduced to vitamin B_{12r} upon the addition of a thiol and an effector. The resulting solution shows ESR signals of vitamin B_{12r} with highly resolved ^{14}N-superhyperfine splitting[68], indicating that the 5,6-dimethylbenzimidazole remains attached to cobalt under these conditions. In functional ribonucleotide reductase holoenzyme ESR-acetive species have been observed as well[69]. The signals show a certain degree of similarity to those observed in other coenzyme B_{12}-dependent enzymes but could not yet be identified.

3.5.1. Mechanism of Enzymatic Reduction of Ribonucleotides

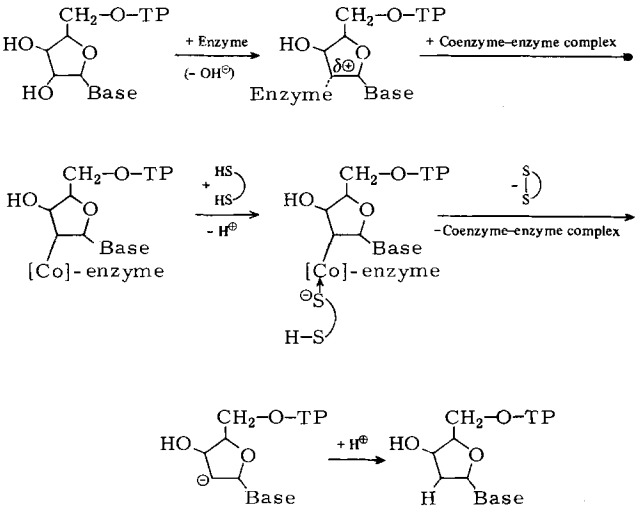
For the mechanism of ribonucleotide reduction, schemes have been put forward which involve free radicals [*e.g. (4)*] and in which 5'-deoxyadenosine *(7)* is assumed to be an intermediate carrier of hydrogen. It has been suggested, for example, as a working hypothesis, that *(4)* abstracts a hydrogen atom from the dithiol reductant[64], but since thiols are known to be efficient scavengers of radicals it would seem to be unlikely that such mechanisms can be part of the catalytic process. An ionic mechanism was proposed on the basis of our own experiments[16], however, which appears to be in accord with most of the available experimental evidence. This mechanism was deduced from observations made in the study of the reductive cleavage of alkylcobalt complexes by thiols and dithiols[16]. These reactions may be regarded as prototypes of corrin-catalyzed reductions of substrates [eq. (w)].



(w)

Along these lines, the mechanism given in Scheme 8 was proposed. It has not been possible as yet to demonstrate the presence of enzyme-bound vitamin B_{12s} in the functional holoenzyme[70] using N_2O, since the enzymatic reduction of ribonucleotides is also not greatly inhibited by oxygen. However, a surprising observation was made in a subsequent study

on the effects of buffers in reductive Co—C bond cleavage reactions. *Jacobsen* and *Huennekens* reported in 1969 that the rate of enzymatic ribonucleotide reduction is dependent on the type and concentrations of the buffers employed[71]. The authors interpreted their results by assuming chaotropic effects of the buffer anions on the enzyme protein. We in turn investigated the effects of buffer-type and -concentration on the rates of methane production from methylcobaloxime in the presence of dithioerythritol *(13)* and dihydrolipoate *(12)*. *A surprising similarity between the nonenzymatic rates of methane production and the enzymatic rates of ribonucleotide reduction was observed*[16], the results are shown in Figure



Scheme 8. Postulated mechanism of enzymatic ribonucleotide reduction [16]. TP = triphosphate.

2. The observed relative rates of the reductions occurring in both systems are directly and significantly correlated [$r = 0.71, P < 0.01$][18]. This remarkable similarity between two reactions which cannot be immediately recognized as having

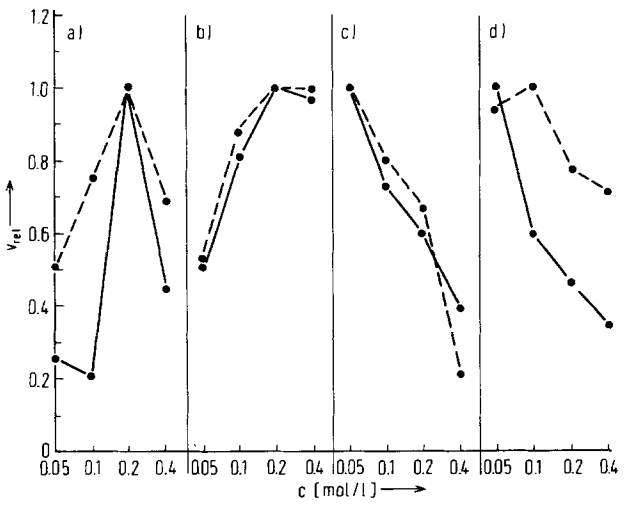


Fig. 2. Relative rate profiles of enzymatic reduction of ribonucleotide (----) and of methane formation from methyl(aquo)cobaloxide (——) in tris and phosphate buffer with dithioerythritol *(13)* and dihydrolipoic acid *(12)* as reductant [16]. v_{rel}, relative reaction rate; c, concentration of buffer. a) Tris buffer + *(13)*; b) phosphate buffer + *(13)*; c) tris buffer + *(12)*; d) phosphate buffer + *(12)*. Kind of ribonucleotide: GTP; amount of thiols 0.17 M.

anything in common becomes plausible if it is assumed that the same processes are rate-determining in both systems. Presumably, the axial coordination of the thiols is a concentration- and buffer-dependent step and responsible for the observed results. We again assume that the activation occurs by way of a β-elimination to yield enzyme-bound vitamin B_{12s} and *(3)*, respectively, although direct evidence is not yet available.

3.6. Coenzyme B_{12}-Dependent Mutase Reactions

The presently known coenzyme B_{12}-dependent mutases[72–81] are shown in Table 2. They exhibit high substrate-specificity, the reactions are reversible and take place without proton-exchange with the solvent. However, an exchange between protons of the substrate and hydrogen at the 5'-position of the coenzyme has been demonstrated. It has also been shown that hydrogen migrates between two neighboring carbon atoms, and all reactions may be *formally* considered to involve the reversible removal and attachment of a substituent R to positions 3 and 2 of propionic acid [eq. (x)].

$$\underset{\text{R}}{\text{CH}_2\text{–CH}_2\text{–COOH}} \rightleftharpoons\rightleftharpoons\rightleftharpoons \underset{\text{R}}{\text{CH}_3\text{–CH–COOH}} \qquad \text{(x)}$$

R = –CO–CoA, –CH(NH_2)COOH, CH_2=C(–)–COOH etc.

We considered a mechanism in which an organocobalt intermediate undergoes isomerization according to eq. (y)[4] as a part of the overall rearrangement process.

$$\underset{[\text{Co}^{\text{III}}]}{\text{CH}_2\text{–CH}_2\text{–R'}} \rightleftharpoons\rightleftharpoons\rightleftharpoons \underset{[\text{Co}^{\text{III}}]}{\text{CH}_3\text{–CH–R'}} \qquad \text{(y)}$$

Reactions of this type have been observed in model systems [see eq. (h) in the first article]. However, it would have to be assumed that C—C bonds of the substrates are reversibly broken or at least labilized to yield complexes of the type assumed in eq. (y), and no good examples are known to date for such reactions. As early as 1964 *Ingraham* considered that the rearrangement of methylmalonyl-CoA occurs *via* organocobalt intermediates of type *(14)*[82]. We studied complexes of type *(15)* as possible models for the reverse conversion of succinyl-CoA into methylmalonyl-CoA but were unable to observe a reaction of this type [eq. (z)][83, 83a]

$$\underset{[\text{Co}^{\text{III}}]}{\text{CH}_2\text{–CH(–C(=O)–CoA)–COOH}} \;\not\rightleftharpoons\; \underset{[\text{Co}^{\text{III}}]}{\text{CoA–C(=O)–CH–CH}_2\text{–COOH}} \qquad \text{(z)}$$

(14) *(15)*

Lowe and *Ingraham* succeeded in 1971 in performing at least one reaction which could be considered a possible model for the rearrangement of *(14)* to *(15)*[84]; however, even this reaction cannot be fully compared with enzymatic process (see, *e.g.*[4]). It is particularly difficult to formulate a mechanism for the reverse reactions, *i.e.* the conversion of succinyl-CoA into methylmalonyl-CoA. In spite of more recent encouraging reports from other workers[85, 86], it is necessary to treat all attempts to explain the mechanisms of these intriguing reac-

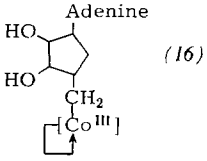
tions with caution, until more evidence becomes available and the role of the enzyme in the reactions is better known.

3.7. Aminomutases

Extracts of *Cl. sticklandii* catalyze the reversible conversion of α-lysine into β-lysine. Analogous isomerizations were observed with arginine and ornithine. In all reactions an amino group and a hydrogen atom appear to migrate simultaneously between two carbon atoms. All known aminomutases consist of two protein components (see Table 2). In some cases, enhanced activity is observed upon the addition of bivalent metal cations, *e.g.* Mg^{2+} or Mn^{2+}, or by catalytic amounts of ATP. At least one aminomutase also requires pyridoxal phosphate as cofactor. In view of the complexity of these enzymes, possible mechanisms will not be discussed.

3.8. Coenzyme B_{12} Analogs

It is obvious that our understanding of the mechanism of action of coenzyme B_{12} *(1)* is closely linked to the question of how the coenzyme is activated by the enzyme. Only two alternatives remain to be considered: Does the activation occur *via* a homolytic or heterolytic cleavage of the cobalt-carbon bond? To obtain additional experimental information that might prove useful toward the solution of this problem various analogs of coenzyme B_{12} have been synthesized[87] and tested for coenzyme activity. It was soon found that even minor modifications of the structure of *(1)* cause a loss or diminution of activity. The behavior of only one coenzyme B_{12} analog, *(16)*, will be described here. The substitution of the ribose oxygen by a CH_2 group causes a significant diminution of coenzyme activity in the dioldehydrase system[53], which has been attributed to the greater stability of the Co—C bond in *(16)* as compared to *(1)*. However, *(16)* also undergoes Co—C bond cleavage on reaction with strong bases[88].



(16)

We have recently observed that the activity of *(16)* in dioldehydrase can be increased by exposing the pseudoholoenzyme to light[88]. The effect was attributed to a light-induced heterolytic cleavage of the Co—C bond of enzyme-bound *(16)*. In alkaline aqueous solution, *(16)* was found to yield vitamin B_{12s}[89] on irradiation with strict exclusion of air. We suggested that the Co—C bond of the coenzyme in dioldehydrase is not necessarily closed after each substrate turnover[88], in accord with the general features of the mechanism in Scheme 6.

4. Concluding Remarks

This review shows that we may eventually come to understand all the details of the mechanism of action of vitamin B_{12} coenzymes in enzymatic reactions. It also indicates, however, that serious problems remain to be solved even in the simpler systems. Although model studies seem to lead in the right direction, it cannot be denied that there are still wide gaps between the current biochemical and organometallic interpretations of the available experimental data. The most important difference of opinion concerns the function of coenzyme B_{12} itself: The biochemical studies led to the conclusion that the coenzyme promotes free-radical reactions of the substrates and that its adenosyl moiety acts as an intermediate carrier of substrate hydrogen. Model work, as performed by the author, has produced mechanistic proposals in which free radicals are avoided and the hydrogen-exchange phenomena are formulated as ionic processes which are not directly associated with the actual conversion of the substrates to the products. A decision between the two divergent views is left to the reader.

This review was prepared with support by National Science Foundation Grant CHE 76-10890.

Received: August 9, 1976 [A 155 IE]
German version: Angew. Chem. *89*, 239 (1977)

[1] *G. N. Schrauzer*, Angew. Chem. *88*, 465 (1976); Angew. Chem. Int. Ed. Engl. *15*, 417 (1976).
[2] *E. L. Smith:* Vitamin B_{12}. 3rd Edit., Methuen, London 1965.
[3] a) *H. A. Whipple:* Vitamin B_{12} Coenzymes. Ann. N. Y. Acad. Sci. *112*, 2 (1964); b) Vitamin B_{12} and Intrinsic Factor. 1st European Symposium. Enke, Stuttgart 1962; c) *R. Ammon, W. Dirscherl:* Vitamin B_{12} und verwandte Corrinoide. Thieme, Stuttgart 1975.
[4] *G. N. Schrauzer*, Fortschr. Chem. Org. Naturst. *31*, 593 (1974).
[5] *R. S. Wolfe*, Adv. Microb. Physiol. *6*, 107 (1971) and references cited therein.
[6] Cf. *H. Kluth:* Wunder des Fortschritts. A. Scherl-Verlag, Berlin 1939, p. 91.
[7] *B. C. McBride, J. M. Wood, J. W. Sibert, G. N. Schrauzer*, J. Am. Chem. Soc. *90*, 5276 (1968).
[8] *C. D. Taylor, D. Craig, R. S. Wolfe*, J. Biol. Chem. *249*, 4879 (1974).
[9] *M. P. Bryant, E. A. Wolin, M. J. Wolin, R. S. Wolfe*, Arch. Microbiol. *59*, 20 (1967).
[10] *T. Bauchop*, J. Bacteriol. *94*, 171 (1967).
[11] *J. M. Wood, F. S. Kennedy, R. S. Wolfe*, Biochemistry *7*, 1707 (1968).
[12] *B. C. McBride, R. S. Wolfe*, Nature *234*, 551 (1971).
[13] *M. W. Penley, J. M. Wood*, Biochim. Biophys. Acta *273*, 265 (1972).
[14] *J. W. Sibert, G. N. Schrauzer*, J. Am. Chem. Soc. *92*, 1421 (1970).
[15] Unpublished experiments with *J. H. Grate.*
[16] *G. N. Schrauzer, J. A. Seck, R. J. Holland, T. M. Beckham, E. A. Rubin, J. W. Sibert*, Bioinorg. Chem. *2*, 93 (1973).
[17] *M. W. Penley, D. G. Brown, J. M. Wood*, Biochemistry *9*, 4203 (1970).
[18] The statistical calculations were performed using the method of linear regression; *G. N. Schrauzer*, unpublished work.
[19] a) *C. D. Taylor, R. S. Wolfe*, J. Biol. Chem. *249*, 4879 (1974); b) *249*, 4886 (1974).
[20] *B. C. McBride, R. S. Wolfe*, Biochemistry *10*, 4312 (1971).
[21] *J. M. Wood, F. S. Kennedy, C. G. Rosen*, Nature *220*, 123 (1968).
[22] *H. A. O. Hill, J. M. Pratt, S. Ridsdale, F. R. Williams, R. J. P. Williams*, Chem. Commun. *1970*, 341.
[23] *G. N. Schrauzer, J. H. Weber, T. M. Beckham, R. K. Y. Ho*, Tetrahedron Lett. *1971*, 275.
[24] *J. M. Wood*, Naturwissenschaften *62*, 1 (1975).
[25] *H. A. Barker, M. D. Kamen*, Proc. Natl. Acad. Sci. USA *31*, 219 (1945).
[26] *J. M. Poston, K. Kuratomi, E. R. Stadtman*, Ann. N. Y. Acad. Sci. *112*, 804 (1964).
[27] *D. J. Parker, H. G. Wood, R. K. Ghambeer, L. G. Ljungdahl*, Biochemistry *11*, 3074 (1974).
[28] *L. G. Ljungdahl, H. G. Wood*, Annu. Rev. Microbiol. *23*, 515 (1970).
[29] *G. N. Schrauzer, J. W. Sibert*, J. Am. Chem. Soc. *92*, 3509 (1970).
[30] *J. M. Buchanan, H. L. Elford, R. E. Loughlin, B. M. McDougall, S. Rosenthal*, Ann. N. Y. Acad. Sci. *112*, 756 (1964).
[31] *J. R. Guest, S. Friedman, M. J. Dilworth, D. D. Woods*, Ann. N. Y. Acad. Sci. *112*, 774 (1964).
[32] *H. W. Dickerman, B. G. Redfield, J. G. Bieri, H. Weissbach*, Ann. N. Y. Acad. Sci. *112*, 791 (1964).

[33] *A. R. Larrabee, S. Rosenthal, R. E. Cathou, J. M. Buchanan*, J. Am. Chem. Soc. *83*, 4094 (1961).
[34] *R. T. Taylor, H. Weissbach*, J. Biol. Chem. *242*, 1502 (1967).
[35] *R. L. Blakley*: The Biochemistry of Folic Acid and Related Pteridines. North Holland Publ. Co., Amsterdam 1969, Chap. 9, p. 332.
[36] *H. Weissbach, R. T. Taylor*, Vitam. Horm. *28*, 415 (1970).
[37] *G. N. Schrauzer, R. J. Windgassen*, J. Am. Chem. Soc. *89*, 3607 (1967).
[38] *G. N. Schrauzer, R. J. Windgassen*, Nature *214*, 492 (1967).
[39] *D. A. Dolphin, A. W. Johnson, R. Rodrigo*, Ann. N. Y. Acad. Sci. *112*, 590 (1964).
[40] *G. N. Schrauzer, J. W. Sibert*, J. Am. Chem. Soc. *92*, 1022 (1970).
[41] *H. P. C. Hogenkamp, H. A. Barker*, Fed. Proc. *21*, 470 (1962).
[42] *H. A. Barker, R. D. Smyth, H. Weissbach, J. I. Toohey, J. N. Ladd, B. E. Volcani*, J. Biol. Chem. *235*, 480 (1960).
[43] *P. G. Lenhert, D. Crowfoot-Hodgkin*, Nature *192*, 937 (1961).
[44] *P. G. Lenhert*, Proc. Roy. Soc. *A 303*, 45 (1968).
[45] *A. Peterkofsky, H. Weissbach*, Ann. N. Y. Acad. Sci. *112*, 622 (1964).
[46] *J. B. Pawelkiewicz, B. Bartosinski, W. Walerych*, Ann. N. Y. Acad. Sci. *112*, 638 (1964).
[47] *R. H. Abeles, H. A. Lee, Jr.*, J. Biol. Chem. *238*, 2367 (1963).
[48] *K. L. Smiley, M. Sobolov*, Arch. Biochem. Biophys. *97*, 538 (1962).
[49] *T. Toraya, T. Shirakashi, T. Kosuga, S. Fukui*, Biochem. Biophys. Res. Commun. *69*, 475 (1976).
[50] *G. N. Schrauzer, J. Seck, R. J. Holland*, Z. Naturforsch. *28c*, 1 (1973).
[51] *G. N. Schrauzer, R. J. Windgassen*, J. Am. Chem. Soc. *89*, 143 (1967).
[52] *R. N. Katz, T. M. Vickrey, G. N. Schrauzer*, Angew. Chem. *88*, 583 (1976); Angew. Chem. Int. Ed. Engl. *15*, 542 (1976).
[53] *R. H. Abeles*, Adv. Chem. Ser. *100*, 346 (1971).
[54] *G. N. Schrauzer*, Adv. Chem. Ser. *100*, 1 (1971).
[55] *R. H. Abeles, D. A. Dolphin*, Acc. Chem. Res. *9*, 114 (1976) and references cited therein.
[56] *P. A. Frey, M. K. Essenberg, R. H. Abeles*, J. Biol. Chem. *242*, 5369 (1967).
[57] a) *G. N. Schrauzer, W. J. Michaely, R. J. Holland*, J. Am. Chem. Soc. *95*, 2024 (1973); b) *R. Blackburn, M. Kyaw, G. O. Phillips, A. L. Swallow*, Trans. Faraday Soc. *1975*, 2277.
[58] *T. M. Vickrey, R. N. Katz, G. N. Schrauzer*, J. Am. Chem. Soc. *97*, 7248 (1975).
[59] *B. T. Golding, T. J. Kemp, E. Nocchi, W. P. Watson*, Angew. Chem. *87*, 841 (1975); Angew. Chem. Int. Ed. Engl. *14*, 813 (1975).
[60] *C. Bradbeer*, J. Biol. Chem. *240*, 4669, 4675 (1965).
[61] *B. M. Babior*, Acc. Chem. Res. *8*, 376 (1975) and references cited therein.
[62] *G. N. Schrauzer, E. A. Stadlbauer*, Bioinorg. Chem. *4*, 185 (1975).
[63] *R. L. Blakley*, J. Biol. Chem. *240*, 2173 (1965).
[64] *H. P. C. Hogenkamp, G. N. Sando*, Struct. Bonding *20*, 23 (1975) and references cited therein.
[65] *R. L. Blakley, R. K. Ghambeer, P. F. Nixon, E. Vitols*, Biochem. Biophys. Res. Commun. *20*, 439 (1965).
[66] *F. K. Gleason, H. P. C. Hogenkamp*, J. Biol. Chem. *245*, 4894 (1970).
[67] a) *R. H. Abeles, W. S. Beck*, J. Biol. Chem. *242*, 186 (1971); b) *W. S. Beck, R. H. Abeles, W. G. Robinson*, Biochem. Biophys. Res. Commun. *25*, 421 (1966).
[68] *J. A. Hamilton, R. Yamada, R. L. Blakley, H. P. C. Hogenkamp, F. D. Looney, M. E. Winfield*, Biochemistry *10*, 347 (1971).
[69] *W. H. Orme-Johnson, H. Beinert, R. L. Blakley*, J. Biol. Chem. *249*, 2338 (1974).
[70] The detection of vitamin B_{12s} or of Co(I) derivatives of the model compounds in the presence of thiols is difficult due to the formation of thiolates of cobalamins or cobaloximes. These cobalt-sulfur compounds can be regarded as cobalt(I) nucleophiles *in situ*, for the cobalt atom is easily alkylated in complexes of this type even if the nucleophilic Co(I) derivatives are not detectable spectroscopically.
[71] *D. W. Jacobsen, F. M. Huennekens*, Biochem. Biophys. Res. Commun. *37*, 793 (1969).
[72] *R. Stjernholm, H. G. Wood*, Proc. Natl. Acad. Sci. USA *47*, 303 (1961).
[73] *H. Eggerer, E. R. Stadtman, P. Overath, F. Lynen*, Biochem. Z. *333*, 1 (1960).
[74] *R. W. Kellermeyer, H. G. Wood*, Biochemistry *1*, 1124 (1962).
[75] *W. W. Miller, J. H. Richards*, J. Am. Chem. Soc. *91*, 1498 (1969).
[76] *H. F. Kung, S. Cederbaum, L. Tsai, T. C. Stadtman*, Proc. Natl. Acad. Sci. USA *65*, 978 (1970).
[77] *H. F. Kung, T. C. Stadtman*, J. Biol. Chem. *246*, 3378 (1971).
[78] *H. F. Kung, L. Tsai*, J. Biol. Chem. *246*, 6436 (1971).
[79] *H. A. Barker, V. Rooze, F. Suzuki, A. A. Iodice*, J. Biol. Chem. *239*, 3260 (1964).
[80] *A. A. Iodice, H. A. Barker*, J. Biol. Chem. *238*, 2094 (1963).
[81] *R. G. Eagar, Jr., B. G. Baltimore, M. M. Herbst, H. A. Barker, J. H. Richards*, Biochemistry *11*, 253 (1972).
[82] *L. L. Ingraham*, Ann. N. Y. Acad. Sci. *112*, 713 (1964).
[83] *G. N. Schrauzer, R. J. Windgassen*, J. Am. Chem. Soc. *89*, 1999 (1967).
[83a] *Note added in proof*: A thioester migration in a complex related to *(14)* to yield a rearranged product has been reported by *A. I. Scott* and *K. Kang* [J. Am. Chem. Soc. *99*, 1997 (1977)].
[84] *J. N. Lowe, L. L. Ingraham*, J. Am. Chem. Soc. *93*, 3801 (1971).
[85] *G. Bidlingmaier, H. Flohr, U. M. Kempe, T. Krebs, J. Retey*, Angew. Chem. *87*, 877 (1975); Angew. Chem. Int. Ed. Engl. *14*, 822 (1975).
[86] *P. Dowd, M. Shapiro, K. Kang*, J. Am. Chem. Soc. *97*, 4754 (1975).
[87] *H. P. C. Hogenkamp*, Biochemistry *13*, 2736 (1974).
[88] *G. N. Schrauzer, R. N. Katz, J. H. Grate, T. M. Vickrey*, Angew. Chem. *88*, 186 (1976); Angew. Chem. Int. Ed. Engl. *15*, 170 (1976).
[89] In addition to vitamin B_{12s}, vitamin B_{12r} is formed in the photolysis of *(16)*; the photolysis must be performed in specially vacuum-degassed cuvettes to eliminate traces of oxygen. If this is done carefully, the major photolysis product is vitamin B_{12s}. The photolysis of diolde-hydrase incubated with *(1)* does not produce any stimulation, but instead a slight diminution of enzymatic activity. The irradiation experiments with the enzyme must also be conducted as strictly anaerobically as possible [88].

COMMUNICATIONS

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

Synthesis of Thiol and Selenol Esters from Carboxylic Acids and Thiols or Selenols, respectively[**]

By *Hans-Joachim Gais*[*]

Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday

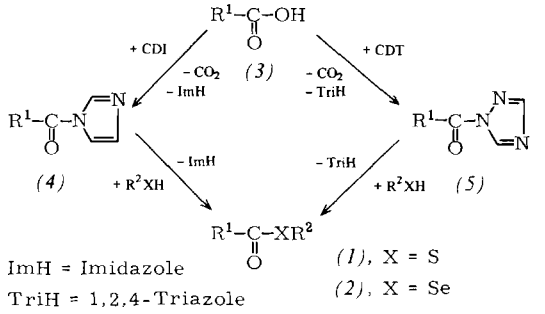
In contrast to their O-analogs, thiol esters *(1)* and selenol esters *(2)* frequently exhibit toward nucleophiles a higher and more selective reactivity, which is enhanced even further by activation with heavy metal ions or oxidizing agents. These properties make *(1)* and *(2)* valuable acyl transfer agents and permit selective transformations in complex molecules.

[*] Dr. H.-J. Gais
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)

[**] Support of this work by Professor *K. Hafner* is gratefully acknowledged.

In particular, the total synthesis of macrolide antibiotics and cytochalasanes and the synthesis of acyl-coenzyme A demand simple, mild and general methods for the preparation of *(1)* and *(2)*.

Carboxylic acid-imidazolides *(4)* or -1,2,4-triazolides *(5)* are accessible in almost quantitative yields from carboxylic acids *(3)* and carbonyl di-imidazole (CDI) or -1,2,4-triazole (CDT)[1], respectively. We have found that *(4)* and *(5)* react with aliphatic[2] and aromatic thiols or selenols to give *(1)* and *(2)* in excellent yields (Tables 1 and 2)[3].



The activation of *(3)* with CDI or CDT and acylation of the thiols or selenols are carried out without isolation of *(4)* or *(5)* in inert anhydrous solvents at or below room temperature under almost neutral reaction conditions. In the case of aromatic thiols and selenols the reactions are complete within a few minutes, and in the case of aliphatic thiols within a few hours. The imidazole or 1,2,4-triazole formed along with *(1)* or *(2)* is readily removed by extraction with water. In the case of *N*-benzyloxycarbonyl-L-phenylalanine, activation and acylation are accompanied by only very slight racemization (Table 2).

The selective activation of carboxyl groups with CDI[4] important for synthesis of a macrocyclic lactone from thiol esters of ω-hydroxycarboxylic acids is demonstrated by the formation of *(1ag)*, *(1ah)*, and *(1ai)* from ricinelaidic acid (Table 1).

Experimental

N-Benzyloxycarbonyl-L-phenylalanine phenylthiol ester *(1aj)*: A mixture of CDI (1.71 g, 10.5 mmol) and *N*-benzyloxycarbonyl-L-phenylalanine (2.99 g, 10.0 mmol) in anhydrous DMF (50 ml) is stirred for 2 h at −10 °C under exclusion of moisture (evolution of CO_2!). The reaction mixture is then treated with thiophenol (1.08 ml, 10.5 mmol) and stirred for 30 minutes at −10 °C. After addition of ethyl acetate (50 ml) the mixture is washed with saturated NaCl solution, dried over $MgSO_4$, and the solvents evaporated *in vacuo*. The crystalline residue is chromatographed on silica gel 60 (Merck) with CH_2Cl_2/*n*-hexane (3 : 1). Yield of crude product 3.71 g (95 %). Recrystallization from ethyl acetate/*n*-hexane furnishes 3.48 g (89 %) of colorless needles. Evaporation of the aqueous phase *in vacuo* and extraction of the residue with hot ethyl acetate affords

Table 1. Synthesized thiol esters *(1)* and selenol esters *(2)*.

	R^1	R^2	Yield [%] [a]
(1a)	C_6H_5	C_6H_5	97
(1b)		C_2H_5	89
(1c)		$CH(CH_3)_2$	95
(1d)		$C(CH_3)_3$	92
(1e)		CH_2COOH	91
(1f)		$(CH_2)_2COOH$	84
(1g)		2-C_5H_4N	86 [b]
(1h)		$(CH_2)_2OH$	89
(2a)		C_6H_5	92 [b]
(1i)	$(CH_3)_3C$	C_6H_5	92
(1j)		C_2H_5	93
(1k)		$CH(CH_3)_2$	86
(1l)		$C(CH_3)_3$	86
(2b)		C_6H_5	90 [b]
(1m)	cyclohexyl	C_6H_5	94
(1n)		C_2H_5	90
(1o)		$CH(CH_3)_2$	92
(1p)		$C(CH_3)_3$	93
(2c)		C_6H_5	94 [b]
(1q)	$R^2S-CO-(CH_2)_4$	C_6H_5	83 [d]
(1r)		C_2H_5	87 [d]
(1s)		$CH(CH_3)_2$	81 [d]
(1t)	$CH_3-(CH_2)_{16}-$	C_6H_5	94
(1u)		C_2H_5	86
(1v)		$CH(CH_3)_2$	92
(1w)		$C(CH_3)_3$	88
(2d)		C_6H_5	94 [b]
(1x)	6,8-dimethylazulen-4-ylmethyl	C_6H_5	91
(1y)		C_2H_5	86
(1z)		$CH(CH_3)_2$	89
(2e)		C_6H_5	94 [b]
(1aa)	*trans*-8-heptadecenyl	C_6H_5	91
(1ab)		C_2H_5	86
(1ac)		$CH(CH_3)_2$	91
(1ad)		$C(CH_3)_3$	84
(2f)		C_6H_5	88 [b]
(1ae)	$H_3CS-CH=C(SCH_3)-$ *c*	1,5-dioxa-9-thiaspiro[5.5]-undec-8-yl	87
(1af)		4-hydroxy-1-thia-cyclohex-2-yl	71 [c]
(1ag)	11-hydroxy-*trans*-8-heptadecenyl	C_6H_5	83
(1ah)		C_2H_5	81
(1ai)		$CH(CH_3)_2$	84

[a] Yield of analytically pure compound; [b] from *(5)*; [c] mixture of two diastereoisomers in the ratio 1 : 1; [d] starting from adipic acid.

Table 2. Thiol esters *(1)* and selenol esters *(2)* from *N*-benzyloxycarbonyl-L-phenylalanine [a].

	R^2	Yield [%] [b]	M.p. [°C] (Lit. [°C])	$[\alpha]_D^T$ [°] (Lit. $[\alpha]_D^T$)	Ref.
(1aj)	C_6H_5	89 (95) [c]	115—116 (117—118)	−77.9 (−77.5) [d]	[5a]
(1ak)	C_2H_5	91 (96)	65.5—66.5	−61.6 [e]	—
(1al)	$CH(CH_3)_2$	92 (97)	69—70	−61.0 [e]	—
(2g)	C_6H_5	89 (95) [c,f]	107—108 (112—113)	−81.5 (−70) [g]	[5b]

[a] In DMF at −10 °C; [b] Yield of recrystallized, analytically pure compound. In brackets: Yields of analytically and spectroscopically pure crude compound; [c] Optical purity of the analytically spectroscopically pure crude product >96 %; [d] $c=2$ in DMF, $T=25$ °C; [e] $c=2$ in ethyl acetate, $T=26$ °C; [f] from *(5)*; [g] $c=4$ in DMF, $T=24$ °C.

the imidazole, which can be recovered almost quantitatively and reused for the preparation of CDI.

Received: September 13, 1976 [Z 556 IE]
German version: Angew. Chem. 89, 251 (1977)
Publication delayed at Author's request

CAS Registry numbers:
(1a), 884-09-3; *(1b)*, 1484-17-9; *(1c)*, 13291-41-3; *(1d)*, 13291-44-6; *(1e)*, 6398-74-9; *(1f)*, 60718-18-5; *(1g)*, 10002-30-9; *(1h)*, 52772-11-9; *(1i)*, 60718-19-6; *(1j)*, 22872-50-0; *(1k)*, 60718-20-9; *(1l)*, 28058-96-0; *(1m)*, 58587-03-4; *(1n)*, 10035-86-6; *(1o)*, 54829-35-5; *(1p)*, 54829-37-7; *(1t)*, 4222-48-4; *(1u)*, 60718-24-3; *(1v)*, 60718-25-4; *(1w)*, 33563-87-0; *(1x)*, 60718-26-5; *(1y)*, 60718-27-6; *(1z)*, 60718-28-7; *(1aa)*, 60718-29-8; *(1ab)*, 60718-30-1; *(1ac)*, 60718-31-2; *(1ad)*, 60718-32-3; *(1ae)*, 60718-33-4; *(1af)* (isomer 1), 60718-34-5; *(1af)* (isomer 2), 60761-39-9; *(1ag)*, 60718-35-6; *(1ah)*, 60718-36-7; *(1ai)*, 60718-37-8; *(1aj)*, 2075-55-0; *(1ak)*, 60718-38-9; *(1al)*, 60718-39-0; *(2a)*, 38447-68-6; *(2b)*, 60718-40-3; *(2c)*, 60718-41-4; *(2d)*, 60718-42-5; *(2e)*, 60718-43-6; *(2f)*, 60718-44-7; *(2g)*, 60746-24-9; *(3)* ($R^1 = C_6H_5$), 65-85-0; *(3)* ($R^1 = (CH_3)_3C$), 75-98-9; *(3)* (R^1 = cyclohexyl), 98-89-5; *(3)* ($R^1 = CH_3-(CH_2)_{16}$), 57-11-4; *(3)* (R^1 = 6,8-dimethylazulen-4-ylmethyl), 26157-14-2; *(3)* (R^1 = *trans*-8-heptadecenyl), 112-79-8; *(3)* ($R^1 = H_3CS-CH=C(SCH_3)-$), 10500-00-2; *(3)* (R^1 = 11-hydroxy-*trans*-8-heptadecenyl), 540-12-5; *(4)* ($R^1 = C_6H_5$), 10364-94-0; *(4)* ($R^1 = (CH_3)_3C$), 4195-19-1; *(4)* (R^1 = cyclohexyl), 60718-45-8; *(4)* ($R^1 = CH_3-(CH_2)_{16}$), 17450-32-7; *(4)* (R^1 = dimethylazulen-4-ylmethyl), 60718-47-0; *(4)* (R^1 = *trans*-8-heptadecenyl, 60718-48-1; *(4)* ($R^1 = H_3CS-CH=C(SCH_3)$), 60718-49-2; *(4)* (R^1 = 11-hydroxy-*trans*-8-heptadecenyl), 60718-50-5; *(5)* ($R^1 = C_6H_5$), 60718-51-6; *(5)* ($R^1 = (CH_3)_3C$), 60718-52-7; *(5)* (R^1 = cyclohexyl), 60718-53-8; *(5)* ($R^1 = CH_3-(CH_2)_{16}$), 60718-55-0; *(5)* (R^1 = 6,8-dimethylazulen-4-ylmethyl), 60718-56-1; *(5)* (R^1 = *trans*-8-heptadecenyl), 60718-57-2; *(5)* ($R^1 = H_3CS-CH=C(SCH_3)$), 60718-58-3; *(5)* (R^1 = 11-hydroxy-*trans*-8-heptadecenyl), 60746-23-8; CDI, 530-62-1; CDT, 41864-22-6; benzenethiol, 108-98-5; ethanethiol, 75-08-1; 2-propanethiol, 75-33-2; 2-methyl-2-propanethiol, 75-66-1; mercaptoacetic acid, 68-11-1; 3-mercaptopropanoic acid, 107-96-0; 2-pyridinethiol, 2637-34-5; 2-mercaptoethanol, 60-24-2; benzeneselenol, 645-96-5; *N*-benzyloxycarbonyl-L-phenylalanine, 1161-13-3

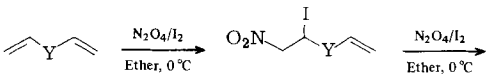
Selective Monofunctionalization of Non-Conjugated Dienes by Nitrogen Dioxide/Iodine Monoaddition[**]

By *Volker Jäger* and *Hans Jürgen Günther*[*]

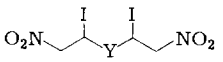
Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday

The selective transformation of one of two or more identical functional groups that are separated by two or more saturated carbon atoms represents a synthetic problem which is generally solved statistically[1] or by carrying out heterogeneous reactions[2], or circumvented[1].

In the case of simple 1,5-, 1,6- and 1,7-dienes selective monofunctionalization can be effected by reaction with stoichiometric amounts of dinitrogen tetroxide in the presence of iodine[3]. In this way the unsymmetrical monoadducts *(2)* are obtained selectively from symmetrical dienes *(1)*[4]. The bis-adducts *(3)* are formed in minor amounts only[4a] (see Table 1).



(1) *(2)*



(3)

Table 1. NO_2/iodine adducts from 1,*n*-dienes [4b].

Educt	—Y—	NO_2/I [equiv.]	*(2)* Crude yield [%] (content [%]) [a]	*(3)* Crude yield [%] (content [%]) [a]
(1a)	$-(CH_2)_2-$	1.10/1.25	99.5 [b]	(<5) [d, e]
(1b)	*cis*-Cyclohexan-1,2-diyl	1.04/1.22	86.5 [c]	(<5)
(1c)	$-(CH_2)_3-$	1.11/1.25	95.5	(<5)
(1d)	$-CH_2-C(CH_3)_2-CH_2-$	1.09/1.65 2.54/2.54	96 (<5)	(<5) 90.5 [d]
(1e)	$-(CH_2)_4-$	1.00/1.00 [g] 1.05/1.12 [h]	81 93	9.7 [f] 5.8 [f]

[a] Determined by NMR spectroscopy and by elemental analysis of the crude product.
[b] B.p. ≈55°C/0.05 torr.
[c] B.p. ≈80°C/0.005 torr.
[d] The compound can be isolated using an excess of NO_2/I, longer reaction time, and warming (0→20°C; 12 h)
[e] M.p. 111°C.
[f] M.p. 92°C (dec.)
[g] 0.24 mol *(1)*, 0.51 ether, addition period 6.5 h.
[h] 0.7 mol *(1)*, 1.51 ether, addition period 7 h.

Steric effects[5] or the transmission of inductive (polar) effects[6] especially of the nitro group through the carbon chain should hardly be responsible for the reduced reactivity of the remaining C=C double bond. Possible intramolecular interactions of the iodine/nitro function with the C=C double bond or with intermediates have yet to be clarified.

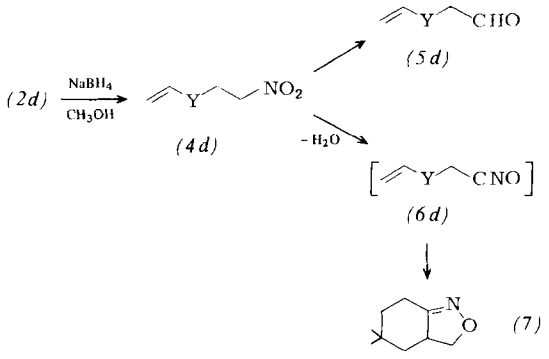
ω-Nitroalkenes *(4)*, ω-unsaturated aldehydes *(5)*, and ω-unsaturated nitrile oxides *(6)* are readily accessible (the latter *in situ*) from compounds *(2)* by modifications of known procedures. These products are of interest, *e.g.*, as starting materials for intramolecular 1,3-dipolar cycloadditions[7]. The inherent preparative possibilities are illustrated by some reactions start-

[1] *H. A. Staab, W. Rohr* in *W. Foerst:* Neuere Methoden der präparativen Organischen Chemie. Verlag Chemie, Weinheim 1967, Vol. V, p. 53, and literature cited therein.
[2] Aliphatic thiolesters *(1)* are prepared from *(4)* in THF by addition of imidazole or from *(4)* or *(5)* in DMF without addition of imidazole; cf. *W. P. Jencks, K. Salvesen*, J. Am. Chem. Soc. *99*, 1419 (1971).
[3] Satisfactory elemental analyses and spectroscopic data have been obtained for all the compounds.
[4] a) *D. Scherling, I. Csendes, Ch. Tamm*, Helv. Chim. Acta *59*, 914 (1976); b) *E. W. Colvin, T. A. Purcell, R. A. Raphael*, J. Chem. Soc. Chem. Commun. *1972*, 1031.
[5] a) *H. C. Beyerman, W. M. van der Brink, F. Weygand, A. Prox, W. König, L. Schmidhammer, E. Nintz*, Rec. Trav. Chim. Pays-Bas *84*, 213 (1965); b) *H.-D. Jakubke*, Chem. Ber. *97*, 2816 (1964).

[*] Dr. V. Jäger, Dipl.-Chem. H. J. Günther
Institut für Organische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

[**] Part of the planned dissertation by *H. J. Günther*.—This work was supported by the Deutsche Forschungsgemeinschaft.

ing with *(2d)*[4b]: Reaction of *(2d)* with sodium borohydride in methanol at 0 to 20°C affords 4,4-dimethyl-7-nitro-1-heptene *(4d)* in 72% yield; *(4d)* is then converted in a modified Nef reaction[8] into the aldehyde *(5d)* (77% yield, b.p. 80°C/15 torr). Dehydration of *(4d)* with phenyl isocyanate/triethylamine/benzene under reflux[9] in a dilution set-up furnishes [*via* the ω-unsaturated nitrile oxide *(6d)*] the cycloadduct *(7)* (91% yield, m.p. 61°C).



Experimental

NO_2/iodine addition to 1,*n*-dienes[3]: A solution of the diene and iodine in ether (0.15 to 0.6 mol diene/l ether) is prepared at 0°C in a three-necked flask (acetone/dry-ice condenser, gas inlet tube, magnetic stirrer). Dinitrogen tetroxide (dried with P_2O_5, weighed after cooling in a sealable cold trap) is then transferred into the flask by means of an argon stream at a rate of 0.01 to 0.05 mol (0.9 to 4.6 g) per hour. The reaction mixture is then extracted [in the case of *(1e)* after filtering off the precipitated bis-adduct *(3e)*] with 10% sodium thiosulfate solution until disappearance of the iodine color, washed with sodium hydrogen carbonate solution and water, and dried over $CaCl_2$. Solvent and any residual diene are then removed in a rotary evaporator (oil-pump vacuum at the end). The remaining yellow to brown liquids are not very stable at room temperature and should be stored at −20°C (Care: skin irritants).—Spectral data for *(2a)*: ^{1}H-NMR (CCl_4): δ = 6.2—5.4 (1H, m, —CH=), 5.3—4.2 ppm (5H, $=CH_2$, —CHI—CH_2NO_2); IR (film): ν_{NO_2} = 1560, 1375 cm^{-1}.

Received: January 25, 1977 [Z 664 IE]
revised: January 31, 1977
German version: Angew. Chem. 89, 253 (1977)

CAS Registry numbers:
(1a), 592-42-7; *(1b)*, 1004-84-8; *(1c)*, 3070-53-9; *(1d)*, 22146-18-5; *(1e)*, 3710-30-3; *(2a)*, 61846-88-6; *(2b)*, 61846-89-7; *(2c)*, 61846-90-0; *(2d)*, 61846-91-1; *(2e)*, 61846-92-2; *(3a)*, 61846-93-3; *(3b)*, 61846-94-4; *(3c)*, 61846-95-5; *(3d)*, 61846-96-6; *(3e)*, 61846-97-7; *(4d)*, 61846-98-8; *(5d)*, 61846-99-9; *(6d)*, 61847-00-5; *(7)*, 61847-01-6; N_2O_4, 10544-72-6; I_2, 7553-56-2

[1] An example is ester differentiation in the synthesis of vitamin B_{12}: *R. B. Woodward*, Pure Appl. Chem. *33*, 145 (1973), and literature cited therein.
[2] *E.g.* by means of solid-phase reagents: *C. C. Leznoff*, Chem. Soc. Rev. *3*, 65 (1974), and literature cited therein.
[3] With monoalkenes or alkynes: *T. E. Stevens, W. D. Emmons*, J. Am. Chem. Soc. *80*, 338 (1956); *V. Jäger*, Dissertation, Universität Erlangen-Nürnberg, 1970; *V. Jäger, H. G. Viehe*, Angew. Chem. *81*, 259 (1969); Angew. Chem. Int. Ed. Engl. *8*, 273 (1969).
[4a] With irreversible consecutive 2nd order reactions and equal C=C-reactivity in *(1)* and *(2)* one expects a mono-/bis-adduct ratio of ≈ 30:67 at 97% conversion (!): *W. G. McMillan*, J. Am. Chem. Soc. 79, 4838 (1957).
[4b] The structures of the compounds prepared are confirmed by IR, ^{1}H-, and (in most cases) ^{13}C-NMR spectra and by correct elemental analyses [exception: *(1b)*, deviations up to 0.6%].
[5] *M. Charton*, J. Am. Chem. Soc. *97*, 1552, 3691, 3694 (1975), and literature cited therein.
[6] *P. E. Peterson, D. M. Chevli*, J. Org. Chem. *39*, 3684 (1974), and literature cited therein.
[7] Reviews: *A. Padwa*, Angew. Chem. *88*, 131 (1976); Angew. Chem. Int. Ed. Engl. *15*, 123 (1976); *W. Oppolzer*, Angew. Chem. *89*, 10 (1977); Angew. Chem. Int. Ed. Engl. *16*, 10 (1977).
[8] Cf. *R. M. Jacobson*, Tetrahedron Lett. *1974*, 3215.
[9] *T. Mukaiyama, T. Hoshino*, J. Am. Chem. Soc. *82*, 5339 (1960).

Bis(trimethylsilyl)magnesium—The First Organosilylmagnesium Compound Isolated[**]

By *Lutz Rösch*[*]

Reaction of cyclohexylmagnesium bromide and triphenylchlorosilane affords hexaphenyldisilane whose formation is explained in terms of the intermediacy of an organosilylmagnesium compound[1]. Other reactions involving silyl transfer in the presence of magnesium are also assumed to proceed *via* organosilylmagnesium compounds as intermediates[2], and evidence has recently been obtained for their existence in solution[3].

We have now been able to isolate the first representative of this class of compounds, *viz.* bis(trimethylsilyl)magnesium, and thus to prove the existence of organosilylmagnesium compounds. Stirring of bis(trimethylsilyl)mercury with an excess of magnesium powder in dimethoxyethane (DME) at room temperature furnishes an intensely wine-red solution within a few hours. The red color disappears in the course of several days and a dark-colored reaction mixture is obtained. Filtration, removal of volatile components, and sublimation of the residue gives a colorless substance which ignites spontaneously on exposure to air. Well defined colorless needles are obtained on recrystallization from pentane. In the ^{1}H-NMR spectrum recorded in benzene the signals of coordinated dimethoxyethane are accompanied by just one sharp signal in the vicinity of TMS. Decomposition of the compound with water or D_2O gives trimethylsilane or trimethyldeuteriosilane. Elemental analysis indicates the composition

$$Mg[Si(CH_3)_3]_2 \cdot C_4H_{10}O_2 \quad (1)$$

Conclusive proof of this composition is provided by the mass spectrum, which displays the molecular peak $[(Me_3Si)_2Mg \cdot DME]^+$ with the expected isotope splitting, and signals for the expected fragmentation products. Decomposition occurred only at 80°C on determination of the melting point.

Procedure

All operations were carried out with rigorous exclusion of air and moisture under argon as protective gas. Sublimed $(Me_3Si)_2Hg$ (8 g) is dissolved in dry DME (30 ml) and stirred with magnesium powder (10 g) until the initial red coloration has disappeared (*ca.* 8 d). The solution is filtered through a glass frit, volatile constituents removed at oil-pump vacuum and room temperature, and the residue sublimed at 50°C/10^{-5}

[*] Dr. L. Rösch
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. I am grateful to Prof. *J. Müller* for recording the mass spectrum, and to Prof. *H. Schumann* for his interest in this work.

torr. About 1 g of $(Me_3Si)_2M \cdot DME$ is obtained as a white crystalline powder, m.p. *ca.* 80°C (dec.).

Received: November 22, 1976 [Z 609 IE]
German version: Angew. Chem. *89*, 257 (1977)
Publication delayed at author's request

CAS Registry numbers:
$(Me_3Si)_2Mg$, 61218-55-1; $(Me_3Si)_2Hg$, 4656-04-6

[1] *T. G. Selin* and *R. West*, Tetrahedron *5*, 97 (1959).
[2] *M. W. George*, *D. J. Peterson*, and *H. Gilman*, J. Am. Chem. Soc. *82*, 403 (1960); *J. Dunogues*, *R. Calas*, *M. Bolourtchian*, *C. Biran*, and *N. Duffaut*, J. Organomet. Chem. *55*, 257 (1973); *H. Schumann* and *L. Rösch*, Chem. Ber. *107*, 854 (1974).
[3] *L. Rösch*, *W. Erb*, and *H. Müller*, Z. Naturforsch. *31b*, 281 (1976); *E. Colomer* and *R. Corriu*, J. Chem. Soc. Chem. Commun. *1976*, 176.

A Novel 3z-2e Bond System[**]

By *Joseph Grobe*, *Roland Martin*, and *Uwe Möller*[*]

Investigations on the M→L back-bonding in transition metal complexes have indicated a Fe→Si interaction in the case of the carbonyliron derivatives $Fe(CO)_4[PMe_2CH_2CH_2SiX_3]$ (X=F, Cl)[1]. For the d^8 electron configuration of Fe^0 this effect is most simply described in terms of a Lewis base-acid interaction with $Fe(CO)_4PMe_2CH_2$ as base and the CH_2SiX_3 moiety as acid. It is still uncertain, however, whether such a σ back-bonding is reinforced by (d-d)π back bonding.

Transition metal compounds having Lewis base properties are already known. Thus, for example, the anion $[Mn(CO)_5]^-$ isoelectronically related to $Fe(CO)_5$ forms an adduct with "BH_3"[2]. This tendency is even more strongly pronounced in planar d^8 systems, as demonstrated by the existence of $(Ph_3P)_2Rh(CO)Cl \cdot BX_3$ (X=Cl, Br)[3] and $(Ph_3P)_2Ir(CO)Cl \cdot nBF_3$ ($n=1, 2$)[4]. Corresponding adducts of d^{10} complexes with Lewis acids are also known; *e.g.*, $(Ph_3P)_2Pt \cdot 2BX_3$ (X=F, Cl) or $(Ph_3P)_2Pt \cdot SiF_4$[5].

We have now made attempts to exploit the pronounced basicity of planar d^8 systems for a more accurate study of M→Si interaction. Reaction of bis(benzonitrile)dichloropalladium(II) *(1)* with the oligomeric donor-acceptor ligand *(2)* ($n \approx 6$)[1b, 6] in benzene afforded the yellow-orange complex *(3)* in quantitative yield; on the basis of spectroscopic findings, *(3)* was assigned the structure *(A)* (see Fig. 1).

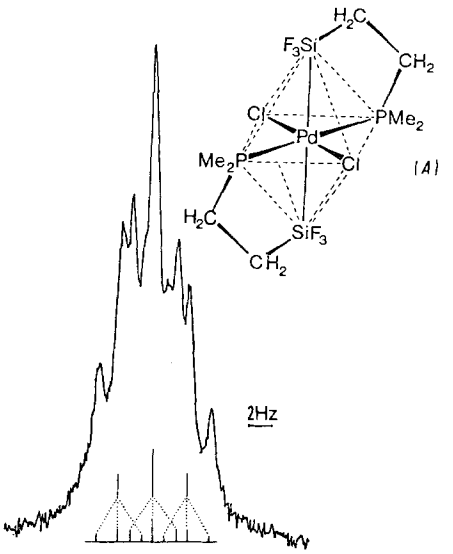
$$\underset{(1)}{trans\text{-}(PhCN)_2PdCl_2} + \frac{2}{n}\underset{(2)}{(Me_2PCH_2CH_2SiF_3)_n} \rightarrow$$

$$\underset{(3)}{(F_3SiCH_2CH_2PMe_2)_2PdCl_2} + 2\ PhCN$$

The composition and molecular size of the new compound follow from the mass spectrum ($M^+=526$ for ^{108}Pd and ^{35}Cl). The spectroscopic investigations were rendered difficult by the sparing solubility of *(3)* in inert organic solvents and the alteration of the complex in the dissolved and in the solid state.

A planar arrangement of the two chlorine and the two phosphane ligands in the *trans*-position seems plausible:
1) The complex is formed from *trans*-$(PhCN)_2PdCl_2$.
2) In the ^1H-NMR spectrum of *(3)*, the "triplet" with broadened inner signal typical for *trans*-isomers is found for the methyl groups on phosphorus. It is a higher order spectrum of type $X_6AA'X'_6$[7] with large AA' coupling, from which only the signal position $\tau=9.05$ ppm and the magnitude $|^2J_{PH}+{}^4J_{PH}|$ can be taken exactly as the distance between the two outer lines with 7.0 Hz. This value is comparable with that for *trans*-$PdCl_2(PMe_3)_2$ (7.4 Hz) and suggests $^2J_{PP'}$ and $^4J_{PH}$ couplings of about 600 and 3 Hz, respectively, as were determined for *trans*-$PdX_2(PMe_3)_2$ complexes[8].

This necessitates the *trans* arrangement for the two SiF_3 groups if they are included in the coordination sphere of the palladium. The bonding Pd→Si interaction responsible for the formulation *(A)* can be recognized in the ^{19}F-NMR spectrum (Fig. 1). It shows a strong coupling with two equivalent ^{31}P- and two ^1H nuclei (CH_2 group bound to Si) [$^3J_{PF}=1.88$ Hz; $^3J_{HF}=2.88$ Hz] and can be characterized as a triplet of triplets. Assignment of the couplings is confirmed by double resonance experiments.



(A)

Fig. 1. ^{19}F-NMR spectrum and constitution of the complex *(3)* (FT spectrum at 84.66 MHz, 1000 scans).

If strong fixation is assumed for the coordination of the SiF_3 groups to the palladium, a distorted trigonal-bipyramidal environment of three fluorine atoms, one carbon atom and one palladium atom is expected. Such structures have very low pseudorotation barriers, even on incorporation of two atoms into a ring system[9]. The equivalence of the fluorine atoms observed in the ^{19}F-NMR spectrum of *(3)* is thus understandable; the mobility of the system is so great that the equivalence is still preserved at −60°C.

For interpretation of the bonding in complex *(3)* we presuppose that the $4d_{x^2-y^2}$, 5s, $5p_x$, $5p_y$ orbitals of the palladium participate in the planar unit $PdCl_2P_2$. Only one electron pair of the Pd center is available for the bonding of the two SiF_3 groups *via* the $4d_{z^2}$ or a $(4d_{z^2}-5p_z)$ hybrid orbital. Each Pd—Si bond is thus formally effected by only one electron, which in our opinion can best be described by a "coordinative 3z-2e bond".

Received: January 10, 1977 [Z 645 IE]
German version: Angew. Chem. *89*, 257 (1977)

CAS Registry numbers:
(1), 15617-18-2; *(2)*, 33845-46-4; *(3)*, 62126-13-0

[*] Prof. Dr. J. Grobe, R. Martin, Dr. U. Möller
Eduard Zintl-Institut der Technischen Hochschule
Hochschulstrasse 4, D-6100 Darmstadt (Germany)

[**] Part 6 of Alternative Ligands. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: *J. Grobe*, *J. Hendriock*, J. Organomet. Chem., in press.

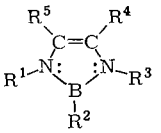
[1] a) *J. Grobe*, *U. Möller*, J. Organomet. Chem. *36*, 335 (1972); b) *J. Grobe*, *A. Walter*, *ibid.*, in press.

[2] G. W. Parshall, J. Am. Chem. Soc. 86, 361 (1964).
[3] H. Nöth, P. Powell, Chem. Commun. 1966, 637.
[4] R. N. Scott, D. F. Shriver, L. Vaska, J. Am. Chem. Soc. 90, 1079 (1968); R. N. Scott, D. F. Shriver, D. D. Lehman, Inorg. Chim. Acta 4, 73 (1970).
[5] T. R. Durkin, E. P. Schram, Inorg. Chem. 11, 1054 (1972); M. Fishwick, H. Nöth, W. Petz, M. G. H. Wallbridge, ibid. 15, 490 (1976).
[6] J. Grobe, U. Möller, J. Organomet. Chem. 31, 157 (1971).
[7] R. K. Harris, Can. J. Chem. 42, 2275 (1964).
[8] D. A. Duddell, J. G. Evans, P. L. Goggin, R. J. Goodfellow, A. J. Rest, J. G. Smith, J. Chem. Soc. A 1969, 2134; R. J. Goodfellow, B. F. Taylor, J. Chem. Soc. Dalton 1974, 1676.
[9] M. Eisenhut, R. Schmutzler, Chem. Commun. 1971, 1452.

Δ^4-1,3,2-Diazaborolines as Complex Ligands

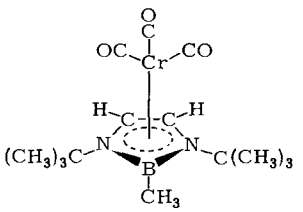
By *Günter Schmid* and *Joachim Schulze*[*]

Diazoborolines of type *(1)*, accessible by dehydrogenation of diazoborolidines[1a] or from α,β-diimines and haloboranes[1b], are isoelectronic with the cyclopentadienide ion and should therefore also have good ligand properties. This assumption is further supported by ^{11}B- and ^{14}N-NMR, UV, and photoelectron spectroscopic investigations[1,2], which provide evidence for a delocalized 6π-electron system.



(1a), $R^1 = R^3 = C(CH_3)_3$, $R^2 = CH_3$, $R^4 = R^5 = H$

We have now been able to isolate the tricarbonylchromium complex *(2)* as the first coordination compound containing such a heterocyclic ligand, namely 1,3-di-*tert*-butyl-2-methyl-Δ^4-1,3,2-diazaboroline *(1a)*.



(2)

Reaction of *(1a)* with $(CH_3CN)_3Cr(CO)_3$ in dioxane at 85 °C affords *(2)* in 91 % yield; *(1a)* can also be used in excess without solvent, but without any increase in the yield of product. *(2)* crystallizes as yellow needles which are soluble in various ethers. The air-stable crystals decompose above *ca.* 170 °C.

The mass spectrum of *(2)* shows the molecular ion at $m/e = 330$ (I_{rel} 14.5 %) along with $LCrCO^+$ (7.2) [L = *(1a)*], LCr^+ (100) and the free heterocycle itself (21.4) as characteristic fragments. The stability of the completely decarbonylated fragment LCr^+ seems surprising. In accord with the local C_{3v} symmetry of the $Cr(CO)_3$ group the IR spectrum of *(2)* displays two very strong νCO bands at 1929 and 1813 cm^{-1}, thus showing the diazaboroline *(1a)* to be a very strong donor ligand. The vibrations of the coordinated and of the free diazoboroline do not differ very largely from each other; only the band at 1628 cm^{-1} to be assigned to the C=C double bond in *(1a)* is no longer observed in *(2)*. In accord with the finding that increasing donor ability of the aromatic ligand in (ar)$Cr(CO)_3$ effects strong deshielding of the C-atoms in the carbonyl groups[3], in *(2)* $\delta^{13}C(CO)$ (234.6 ppm, Table 1) is shifted noticeably downfield as compared to $Cr(CO)_6$ (212.5 ppm)[3]. Thus the ligand strength of *(1a)* corresponds to that of the mesitylene in (π-mesitylene)$Cr(CO)_3$ with $\delta^{13}C(CO) = 235.1$ ppm[4].

Table 1. NMR-spectroscopic data [a] of *(1a)* and *(2)*.

	(1a)	*(2)*
^{11}B-NMR, δ [ppm] *vs.* $BF_3 \cdot OEt_2$ (in $CDCl_3$)		
	26.2	18.3 [5]
^{1}H-NMR, δ [ppm] *vs.* TMS (in $CDCl_3$)		
CH	6.16 (2)	6.05 (2)
*t*Bu	1.43 (18)	1.46 (18)
Me	0.73 (3)	1.10 (3) [6]
^{13}C-NMR, δ [ppm] *vs.* TMS (in $CDCl_3$)		
C(Ring)	111.5	89.8
$C(CH_3)_3$	52.5	56.9
$C(CH_3)_3$	22	31
CO	—	234.6

[a] Positive signs signify downfield shifts compared to the standard.

(1,3-Di-tert-butyl-2-methyl-Δ^4-1,3,2-diazaboroline)tricarbonylchromium (2)

A mixture of $(CH_3CN)_3Cr(CO)_3$ (2.26 g, 8.7 mmol) and *(1a)* (5.82 g, 30.0 mmol) in dry dioxane saturated with nitrogen is heated in the absence of air for 6 h at 85 °C. Liberated acetonitrile is repeatedly removed from the equilibrium by suction into a cold trap. The brown-yellow reaction solution is filtered hot and cooled to 10 °C. The resulting precipitate is separated by filtration and washed with petroleum ether (b.p. 40—60 °C). Extraction with ether affords additional *(2)*; total yield 2.56 g (91 %). The composition of the product was confirmed by elemental analysis and molecular weight determination.

Received: January 13, 1977 [Z 648 IE]
German version: Angew. Chem. 89, 258 (1977)

CAS Registry numbers:
(1a), 62085-92-1; *(2)*, 62126-02-7; ^{13}C, 14762-74-4

[1] a) J. S. Merriam, K. Niedenzu, J. Organomet. Chem. 51, C1 (1973); b) L. Weber, G. Schmid, Angew. Chem. 86, 519 (1974); Angew. Chem. Int. Ed. Engl. 13, 467 (1974); G. Schmid, J. Schulze, Chem. Ber., in press.
[2] J. Kroner, H. Nöth, J. Organomet. Chem. 71, 165 (1974); K. Niedenzu, J. S. Merriam, Z. Anorg. Allg. Chem. 406, 251 (1974).
[3] G. M. Bodner, L. J. Todd, Inorg. Chem. 13, 1335 (1974).
[4] B. E. Mann, J. Chem. Soc. Dalton 1973, 2012.
[5] Cf. G. Schmid, Chem. Ber. 103, 528 (1970); H. Werner, R. Prinz, E. Deckelmann, ibid. 102, 95 (1969); H. Nöth, W. Regnet, Z. Anorg. Allg. Chem. 352, 1 (1967).
[6] Cf. W. Siebert, K. Kinberger, Angew. Chem. 88, 451 (1976); Angew. Chem. Int. Ed. Engl. 15, 434 (1976).

[*] Prof. Dr. G. Schmid, Dipl.-Chem. J. Schulze
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

Palladium(0)-Catalyzed [2σ+2π] Cycloadditions of Methylenecyclopropane to Alkenes

By *Paul Binger* and *Ulf Schuchardt*[*]

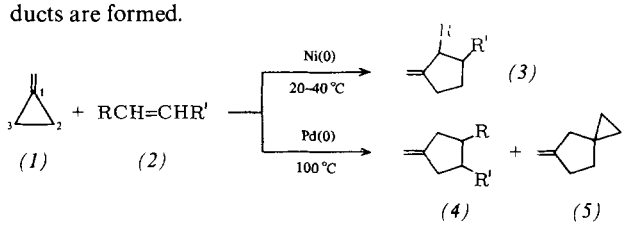
Catalyzed codimerizations of methylenecyclopropane *(1)* with alkenes to give [2π+2π] and [2σ+2π] cycloadducts has hitherto been accomplished only with nickel(0) compounds[1,2]. Besides cyclobutane derivatives[2] methylenecy-

[*] Dr. P. Binger, Dr. U. Schuchardt
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim-Ruhr (Germany)

clopentane derivatives of type *(3)*[1] are formed with opening of the three-membered ring in the neighborhood of the double bond.

Exclusive $[2\sigma+2\pi]$ cycloaddition of *(1)* with alkenes *(2)* has now been found on palladium(0) catalysts, where, in contrast to the nickel(0) catalyzed reactions, the three-membered ring is opened between C-2 and C-3.

At 100—115 °C the methylenecyclopentane derivatives *(4)* are obtained (cf. Table 1), up to 300 mol *(1)* being converted per 1 mol Pd. The codimerization always has to compete with cyclodimerization of *(1)*, which affords the 5-methylenespiro[2.4]heptane *(5)*. Only negligible amounts of other products are formed.



Methylenecyclopentane (4c)

(1) (40 g, 0.74 mol) is added to a solution of bis(pentanedionato)palladium (0.61 g, 2 mmol), triisopropylphosphane (0.32 g, 2 mmol), and ethoxydiethylaluminum (0.52 g, 4 mmol) in benzene (20 ml) in a 200 ml-V2A steel autoclave at −78 °C. Ethylene *(2c)* (120 atm) is fed into the autoclave at room temperature. After 6 hours' shaking the pressure drops from a maximum of 630 atm to 380 atm. 29 liters of excess ethylene (GC) is drawn off and the content of the autoclave distilled. 55.3 g of a colorless liquid of b.p. up to 25 °C/14 torr is obtained; GC analysis: 29.6 % benzene, 22.6 % *(4c)*, 46.4 % *(5)*, 3.3 g black viscous residue.

Dimethyl cis- and trans-4-methylene-1,2-cyclopentanecarboxylate (4f)

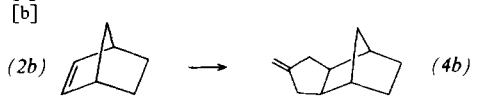
(1) (6.5 g, 0.12 mol) is added to a solution of bis(pentanedionato)palladium (0.3 g, 1 mmol), triisopropylphosphane (0.16 g, 1 mmol), and ethoxydiethylaluminum (0.26 g, 2 mmol) in dimethyl maleate *(2f)* (17.25 g, 0.12 mol) at −78 °C in a bomb-tube fitted with a threaded seal. The sealed bomb-tube is then heated to 100 °C for 18 h, whereupon a contraction in volume of 4 ml occurs. The bomb-tube is opened at −78 °C and the content (24.5 g yellow solution) fractionally distilled. This affords 1.7 g of a fraction of b.p. up to 25 °C/0.02 torr with (GC) 73.8 % *(5)* and 17.6 % *(2f)* [residue (8.8 %), seven unknown peaks] and 18.7 g of a fraction of b.p. 51—55 °C/0.02 torr with (GC) 5.6 % *(2f)*, 51.1 % *trans-(4f)* and 33.7 % *cis-(4f)* [residue (9.6 %), ten unknown peaks].

Table 1. Palladium(0)-catalyzed $[2\sigma+2\pi]$ cycloadditions of *(1)* to alkenes *(2)* to give methylenecyclopentane derivatives *(4)*, 5-methylenespiro[2.4]heptane *(5)*, and oligomers. The catalyst was prepared from bis(pentanedionato)palladium, triisopropylphosphane and ethoxydiethylaluminum (1 : 1 : 2) in benzene *(a—d)* or in the alkene concerned *(e—g)*. Experiments were carried out in a bomb-tube [molar ratio of *(1)* : *(2)* = 1 : 1]; conversion of *(1)*: > 90 %.

	(2) R	R'	Reaction Temp. [°C]	Time [h]	Rel. Yield [%] *(4)* [a]	*(5)*	Oligomer	Remarks
a	*(2a)* ≡ *(1)*		100	4	—	94	6	
b	[b]		100	1	78	21	1	*(4b)*: only *exo*
c	H	H [c]	115	≈ 6	23	72	5	
d	H	CO_2CH_3 [d]	100	3	51	3	46	
e	CH_3	CO_2CH_3 *trans*	100	18	43	50	7	*(4e)*: probably *trans*
f	CO_2CH_3	CO_2CH_3 *cis*	100	18	77	23	—	*(4f)*: 60 % *trans*, 40 % *cis*
g	$CO_2C_2H_5$	$CO_2C_2H_5$ *trans*	100	18	88	4	—	*(4g)*: 88 % *trans*, 12 % *cis*

[a] All codimers *(4)* were identified spectroscopically (MS, IR, ^{1}H-NMR).

[b]



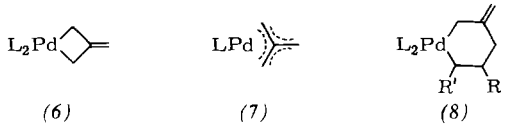
[c] With excess ethylene in a 200 ml V2A steel autoclave.

[d] Terminated after 20 % conversion of *(1)*, since *(2d)* polymerizes.

1- or 2-Alkenes (with the exception of ethylene) and cycloalkenes not containing a strained double bond, *e.g.* cyclopentene, are not suitable for this new codimerization with *(1)*.

Besides 1 : 1 mixtures of bis(dibenzylideneacetone)palladium[3] and a trialkylphosphane, especially triisopropylphosphane, palladium(0) compounds obtained *in situ* are particularly suitable as palladium(0) catalysts (see Table 1).

The catalytic cycloadditions described here might proceed *via* palladacyclobutanes of type *(6)*[4] and palladacyclohexanes of type *(8)*.



As experiments with 1-methyl-2-methylenecyclopropane have shown, *(6)* is transformed at a detectable rate into a complex of type *(7)* at 120 °C. Only above this temperature are methylene and ethylidenecyclopentane derivatives formed[5].

Received: April 12, 1976 [Z 476 IE]
German version: Angew. Chem. 89, 254 (1977)
Publication delayed at authors' request

[1] *R. Noyori, T. Odagi, H. Takaya*, J. Am. Chem. Soc. *92*, 5780 (1970); *R. Noyori, Y. Kumgai, I. Umeda, H. Takaya, ibid. 94*, 4018 (1972).

[2] *P. Binger*, Angew. Chem. *84*, 352 (1972); Angew. Chem. Int. Ed. Engl. *11*, 309 (1972); Synthesis *1973*, 427; *R. Noyori, T. Ishigami, N. Hayashi, H. Takaya*, J. Am. Chem. Soc. *95*, 1674 (1973).

[3] a) *Y. Takahashi, T. Ito, S. Sakai, Y. Ishii*, J. Chem. Soc. *D 1970*, 1065; b) *T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers*, J. Organomet. Chem. *65*, 253 (1974).

[4] *A. C. Day, J. T. Powell*, Chem. Commun. *1968*, 1241.

[5] *P. Binger, U. Schuchardt*, unpublished work.

N-(Trimethylsilyl)amino Acid Trimethylsilyl Esters as Reagents for Directed Self-Condensation of Methyl Ketones under Mild Conditions[**]

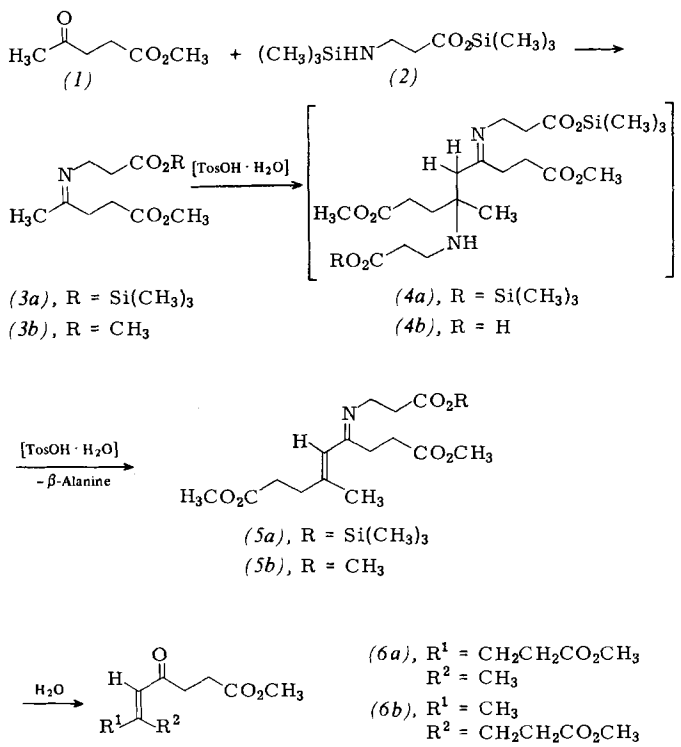
By *Günter Schulz* and *Wolfgang Steglich*[*]

Self-condensation of methyl ketones to α,β-unsaturated dimers generally requires strongly alkaline or acid conditions[1]. On use of secondary amines several days' boiling in benzene is necessary even with *n*-alkyl methyl ketones[2]. We have found that the reaction proceeds under extremely mild conditions with *N*-(trimethylsilyl)amino acid trimethyl silyl esters.

On addition of *N*-(trimethylsilyl)-β-alanine trimethylsilyl ester *(2)*[3] (1.5 equiv.) and a few grains of *p*-toluenesulfonic acid monohydrate to methyl levulinate *(1)*, β-alanine (0.5 equiv.) is soon precipitated in an exothermic reaction. According to the ^{1}H-NMR spectrum quantitative formation of the ketimine *(3a)*[4] also takes place [in CCl_4: $\delta = 0.26$ ppm (s, 9H); 1.86 (s, 3H); 2.47 (s, 4H); 2.53 (t, 2H); 3.40 (t, 2H); 3.58 (s, 3H)].

If *p*-toluenesulfonic acid monohydrate (0.1 equiv.) is now added and the mixture heated to 80 °C for 5 h the signals of unreacted *(3a)* and hexamethyldisiloxane are accompanied only by those of the condensation product *(5a)* [in CCl_4 $\delta = 1.63$ ppm (s, 3H) and 5.63 (broad s, 1H) are characteristic for *(5a)*].

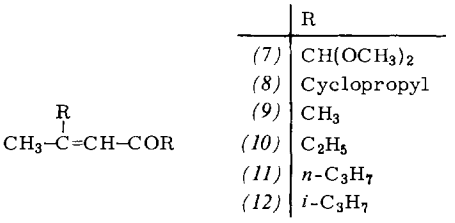
After stirring with water the α,β-unsaturated ketone can be isolated as a 4:1 mixture of the stereoisomers *(6a)* and *(6b)* in 58% yield [b.p. 140 °C/0.05 torr (bulb-tube distillation); IR (CCl_4): 1740 (broad), 1695, 1630 cm^{-1}; ^{1}H-NMR (CCl_4) of (a): $\delta = 2.14$ ppm (d, 3H); 2.78 (s, 4H); 2.81 (dd, 2H); 3.01 (dd, 2H); 3.64 (s, 6H); 6.07 (broad s, 1H); ^{1}H-NMR (CCl_4) of *(6b)*: $\delta = 1.91$ ppm (d, 3H) instead of 2.14 (d, 3H) as for *(6a)*].



The reaction proceeds in regioselective manner and with exclusive participation of the acetyl group. In contrast, the ester group of *(1)* reacts with basic condensation reagents such as sodium methoxide[5].

The above self-condensation is not the result of a simple acid-catalyzed ketimine dimerization[2] since protonation of the ketimine *(3a)* with anhydrous *p*-toluenesulfonic acid, which can be reversed with triethylamine, does not lead to the condensation product *(5a)*. Apparently, expulsion of the silyl group from *(4a)* to form *(4b)* is of importance since the amine component required for condensation can subsequently be released as a low energy betaine. This concept finds support in the reaction of *(1)* with *N*-(trimethylsilyl)-β-alanine methyl ester to form the ketimine *(3b)*, which also shows no tendency to form the dimer *(5b)* in the presence of *p*-toluenesulfonic acid monohydrate.

Methylglyoxal dimethyl acetal and cyclopropyl methyl ketone can also be condensed to form the unsaturated ketones *(7)* and *(8)* respectively in 49 and 23% yield with the aid of *(2)*. The ratios of (*Z*) and (*E*) isomers are 1:20 and 1:3. The condensation can also be accomplished with pertrimethylsilylated α-amino acids[6]. Thus *N*-(trimethylsilyl)glycine trimethylsilyl ester yields exclusively the α,β-unsaturated ketones *(9)* to *(12)* in yields of 30 to 70% (not optimized) with acetone, methyl ethyl ketone, methyl *n*-propyl ketone, and methyl isopropyl ketone; the (*E*) isomer always predominates in the product.



	R
(7)	$CH(OCH_3)_2$
(8)	Cyclopropyl
(9)	CH_3
(10)	C_2H_5
(11)	n-C_3H_7
(12)	i-C_3H_7

Procedure

Synthesis of *(7)*: Methylglyoxal dimethyl acetal (2.03 g) is stirred with *(2)* (6.00 g) in anhydrous $CHCl_3$ (5 ml). Within a short time the mixture warms and β-alanine precipitates. After 5 min, *p*-toluenesulfonic acid monohydrate (0.14 g) is added and the mixture heated to 85 °C (bath temperature) for 3 h. After partitioning between water and CH_2Cl_2 the dehydrated organic phase is evaporated down and the residue distilled in a bulb-tube (110 °C/0.05 torr). Yield 0.92 g (49%), colorless oil; IR (CCl_4): 1705, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$), (*E*)-*(7)*: $\delta = 2.12$ ppm (d, $J = 2$ Hz, 3H); 3.31 (*s*, 6H); 3.43 (s, 6H); 4.52 (s, 1H); 4.64 (broad s, 1H); 6.68 (quintuplet, $J = 2$ Hz, 1H); (*Z*)-*(7)*: $\delta = 1.92$ ppm (d, $J = 2$ Hz, 3H) instead of 2.12 (d, $J = 2$ Hz, 3H).

Received: October 28, 1976 [Z 596a IE]
German version: Angew. Chem. *89*, 255 (1977)
Publication delayed at Authors' request

CAS Registry numbers:
(1), 624-45-3; *(2)*, 17891-06-0; *(3a)*, 61010-40-0; *(3b)*, 61010-41-1; *(5a)*, 61010-42-2; *(6a)*, 61010-43-3; *(6b)*, 61010-44-4; *(Z)*-*(7)*, 61010-45-5; *(E)*-*(7)*, 61010-46-6; *(Z)*-*(8)*, 37714-95-7; *(E)*-*(8)*, 37715-04-1; *(9)*, 141-79-7; *(10)*, 20685-44-3; *(11)*, 22287-10-1; *(12)*, 61010-47-7; *p*-toluenesulfonic acid, 104-15-4; *N*-(trimethylsilyl)-β-alanine methyl ester, 61010-48-8; methylglyoxal dimethyl acetal, 6342-56-9; cyclopropyl methyl ketone, 765-43-5; *N*-(trimethylsilyl)glycine trimethylsilyl ester, 7364-42-3; acetone, 67-64-1; methyl ethyl ketone, 78-93-3; methyl *n*-propyl ketone, 107-87-9; methyl isopropyl ketone, 563-80-4

[*] Dipl.-Chem. G. Schulz, Prof. Dr. W. Steglich
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

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

[1] *H. O. House:* Modern Synthetic Reactions. 2nd Edit., Benjamin, Menlo Park, Calif. 1972, pp. 629ff.; *J. Mathieu, J. Weill-Raynal:* Formation of C—C Bonds. Thieme, Stuttgart 1975, Vol. II, p. 542.

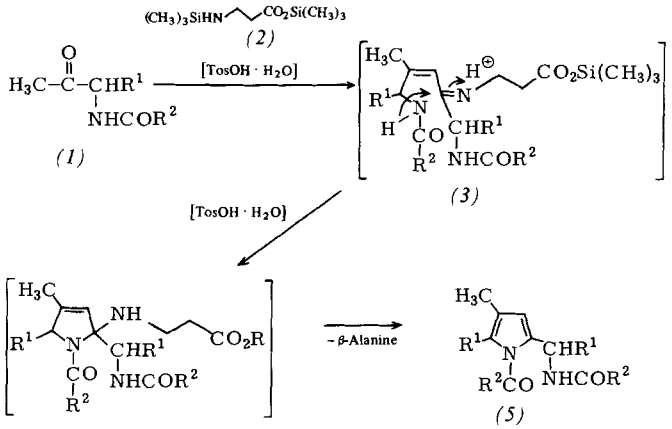
[2] *P. Madsen, S.-O. Lawesson*, Rec. Trav. Chim. Pays-Bas *85*, 753 (1966).
[3] *H. R. Kricheldorf, M. Fehrle*, Synthesis *1974*, 420.
[4] *R. Comi, R. W. Franck, R. Reitano, S. Weinreb*, Tetrahedron Lett. *1973*, 3107. The stoichiometry of ketimine formation obeys the equation: *(1)* + 1.5 *(2)* → *(3)* + 0.5 $H_3N^+CH_2CH_2CO_2^-$ + $[(CH_3)_3Si]_2O$.
[5] *R. P. Evstigneeva, V. A. Glybina, E. V. Okart, N. A. Preobrazhenskii*, Zh. Obshch. Khim. *30*, 2261 (1960); *N. V. Zotchik, L. D. Miroshnichenko, R. P. Evstigneeva, N. A. Preobrazhenskii, ibid. 32*, 2823 (1962).
[6] *L. Birkhofer, A. Ritter*, Chem. Ber. *93*, 424 (1960).

Condensation of α-Acylaminoalkyl Methyl Ketones to Give *N*-Acylpyrroles[**]

By *Günter Schulz* and *Wolfgang Steglich*[*]

We have reported *N*-(trimethylsilyl)-β-alanine trimethylsilyl ester *(2)* as a novel reagent for the self-condensation of methyl ketones[1]. We have now also established that this reagent is suitable for preparation of *N*-acylpyrroles from α-acylaminoalkyl methyl ketones *(1)* which are readily accessible from α-amino acids with acetic anhydride/4-(dimethylamino)-pyridine[2].

Compound *(1)* is suspended in *(2)* (1.5 equiv.) and a catalytic amount of *p*-toluenesulfonic acid monohydrate is added. After brief warming *(1)* goes into solution and β-alanine is precipitated. Further *p*-toluenesulfonic acid monohydrate is added and the mixture heated to 80 °C for several hours[1]. The resulting *N*-acylpyrroles *(5)* are freed from unreacted starting material by filtration over silica gel.



(4a), R = $Si(CH_3)_3$
(4b), R = H

	R^1	R^2	Yield [%]	M.p. [°C]
(5a)[4]	H	CH_3	55	95
(5b)	CH_3	CH_3	60	139
(5c)	CH_3	C_6H_5	75	121
(5d)	i-C_3H_7	CH_3	40	oil

The constitution of the acylpyrroles *(5)* follows from elemental analyses, mass spectra, and the IR and ^{1}H-NMR spectra [IR in KBr[3]: ν_{CO} = 1700—1690 and 1640—1630 cm^{-1}, ν_{NH} = 3280—3260 cm^{-1}; ^{1}H-NMR ($CDCl_3$) of *(5a)*: δ = 1.94 ppm (s, 3H); 2.03 (s, 3H); 2.51 (s, 3H); 4.47 (d, J = 6 Hz, 1H); 6.13 (broad s, 1H); 6.4—6.9 (broad, 1H); 6.79 (broad s, 1H).

The acetyl group can be removed from the pyrrole nucleus by hydrolysis with 2 N NaOH (1 h, room temperature).

Procedure:

Synthesis of *(5b)*: 3-Acetylaminobutan-2-one (1.11 g) and *(2)* (3.00 g) are united in an argon-purged flask and warmed with stirring to 80 to 90 °C (bath temperature), the acetylamino ketone being dissolved. β-Alanine is precipitated within a few minutes of adding a catalytic amount of *p*-toluenesulfonic acid monohydrate. Further *p*-toluenesulfonic acid monohydrate (0.1 equiv.) is added and the mixture diluted with anhydrous $CHCl_3$ (1 ml). After 24 h, the mixture is stirred with CH_2Cl_2, β-alanine is filtered off, the filtrate evaporated down, and the residue recrystallized from ether or sublimed *in vacuo*. Yield: 0.57 g (60 %) of colorless crystals; m.p. 139 °C; IR (KBr): 3260, 1692, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.39 ppm (d, J = 6.5 Hz, 3H); 1.93 (s, 6H); 2.29 (broad s, 3H); 2.58 (s, 3H); 5.43 (broad m, 1H); 6.07 (broad s, 1H); 6.67 (very broad d, J = 9 Hz, 1H).

Received: October 28, 1976 [Z 596b IE]
German version: Angew. Chem. *89*, 256 (1977)
Publication delayed at Authors' request

CAS Registry numbers:
(1a), 7737-16-8; *(1b)*, 6628-81-5; *(1c)*, 18227-62-8; *(1d)*, 40689-12-1; *(2)*, 17891-86-0; *(5a)*, 38120-89-7; *(5b)*, 61009-71-0; *(5c)*, 61009-72-1; *(5d)*, 61009-73-2; *p*-toluenesulfonic acid, 104-15-4

[1] *G. Schulz, W. Steglich*, Angew. Chem. *89*, 255 (1977); Angew. Chem. Int. Ed. Engl. *16*, 251 (1977).
[2] *W. Steglich, G. Höfle*, Angew. Chem. *81*, 1001 (1969); Angew. Chem. Int. Ed. Engl. *8*, 981 (1969).
[3] *(5d)* in CCl_4: ν_{CO} = 1710, 1670 cm^{-1}, ν_{NH} = 3415 cm^{-1}.
[4] *S. I. Zavyalov, N. I. Aronova, I. F. Mustafaeva*, Izv. Akad. Nauk SSSR, Ser. Khim. *1972*, 1625.

Control of the Direction of Addition in the Nickel-Catalyzed 2:1-Cooligomerization of Butadiene with Monoolefins by Perturbation of the Monoolefin[**]

By *Paul Heimbach, Achim Roloff*, and *Hartmut Schenkluhn*[*]

It has often been observed that the formation of different products in metal-catalyzed reactions depends on the nature of the ligand on the catalyst (ligand control), *e. g.* in the cyclooligomerization of butadiene[1], in the dimerization of propene on Ni catalysts[2], and in the oxo synthesis on Rh catalysts[3]. In order to investigate the corresponding substrate control, systems are required which are not subject to ligand control. In the cooligomerization of butadiene with propylene on nickel catalysts[4], we found that the direction of addition during the insertion of the monoolefin into the metal-allyl bond is independent of the nature of additional ligands[5]. However,

[*] Dipl.-Chem. G. Schulz, Prof. Dr. W. Steglich
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

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

[*] Prof. Dr. P. Heimbach [+], Dr. A. Roloff, Dr. H. Schenkluhn
Universität Essen—Gesamthochschule, Fachbereich Chemie
Postfach 6843, D-4300 Essen 1 (Germany)
and
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim (Germany)
[+] To whom correspondence should be addressed.

[**] Control of Metal-Catalyzed Reactions, Part 2—Part 1: *F. Brille, P. Heimbach, H. Schenkluhn*, unpublished.
This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

the direction of addition is influenced by a perturbation (St) of the monoolefin in which either a substituent is introduced *(1)* or a sp^2-carbon atom is replaced by nitrogen *(2)* (Fig. 1).



(1a)

LUMO	-0.4812	0.3388
HOMO	0.4868	0.3177



(1b)

LUMO	0.6819	-0.7180
HOMO	0.7145	0.6298



(1c)

LUMO	-0.6584	0.5387
HOMO	-0.6654	-0.5857



(2)

LUMO	0.7491	-0.6214
HOMO	0.5572	0.7054

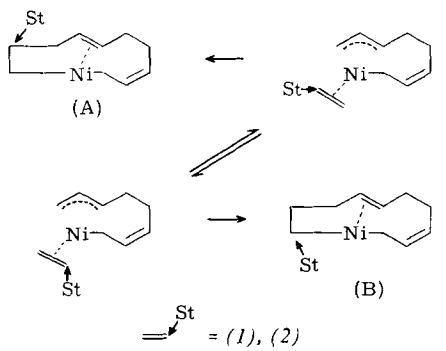


Fig. 1. Insertion of *(1)* or *(2)* into the metal-allyl bond in the cooligomerization of *(1)* or *(2)* with butadiene. The preferred direction of addition (A) or (B), is determined by the electron densities in the LUMOs of the atoms of *(1)* and *(2)* which participate in the double bond (see Table 1). The orbital coefficients [7] are given below the formulas.

We have used the monoolefin substrates listed in Figure 1 as reactants for butadiene. It can be seen from Table 1 that the direction of addition depends on the nature of the perturbation. Indeed exclusive addition in either one of the two directions can be achieved.

Table 1. Dependence of the direction of addition on the nature of the modification of the olefin (cf. Fig. 1). Reaction temperature: 40 °C.

Olefin	Direction of addition	Type of addition [a]
(1a)	B	100 % M→C^s
(1b)	A	76 % M→C^p
	B	24 % M→C^s
(1c)	B	100 % M→C^t
(2)	B	100 % M→N

[a] M→C^p = Addition of the metal to the primary C atom of the olefin.
M→C^s = Addition of the metal to the secondary C atom of the olefin.
M→C^t = Addition of the metal to the tertiary C atom of the olefin.
M→N = Addition of the metal to the N atom of the azaolefin.

The reaction step shown in Figure 1 proceeds irreversibly. Changing the solvent does not have any significant effect on the reaction rate. It should therefore be possible to establish rules for the substrate control of the insertion step similar to those already discussed for concerted reactions[6] (*e.g.* Diels-Alder and ring-closure reactions).

We found that the predominant directions of addition of all four compounds listed in Table 1 could be explained by assuming interaction to take place between the lowest unoccupied molecular orbital of the olefin and the highest occupied molecular orbital (ψ_2) of the allyl group. The terminal C-atom of the allyl group then bonds with the center of highest electron deficiency in the monoolefin. Figure 1 shows the orbital coefficients of the frontier orbitals of compounds *(1)* and *(2)*; the squares of these coefficients are measures of electron density. It can be seen from Figure 1 and Table 1 that in each case, the C atom of *(1)* or *(2)* which reacts predominantly with the terminal C atom of the allyl group is the one which has a larger absolute orbital coefficient in the LUMO.

Received: September 14, 1976
revised: December 27, 1976 [Z 652a IE]
German version: Angew. Chem. *89*, 260 (1977)

CAS Registry numbers:
(1a), 100-42-5; *(1b)*, 115-07-1; *(1c)*, 79-41-4; *(2)*, 6407-34-7; nickel, 7440-02-0; butadiene, 106-99-0

[1] *W. Brenner, P. Heimbach, H.-J. Hey, E. W. Müller, G. Wilke*, Justus Liebigs Ann. Chem. *727*, 161 (1969).
[2] *B. Bogdanovic, G. Wilke:* Proceedings of the VIIth World Petroleum Congress. Elsevier, Amsterdam 1967, Vol. 5, page 351.
[3] *J. Falbe:* Carbon Monoxide in Organic Synthesis. Springer, Berlin 1970.
[4] *F. Brille, P. Heimbach, H. Schenkluhn*, unpublished.
[5] We found that the direction of addition in the other cooligomerizations listed in Table 1 was also uninfluenced by additional ligands on the nickel. The monoolefin probably occupies the place of the ligand in the fundamental step of the reaction (Fig. 1).
[6] *K. N. Houk*, J. Am. Chem. Soc. *95*, 4092 (1973); Acc. Chem. Res. *8*, 361 (1975).
[7] We are grateful to Dr. *F. Mark* for the calculations by a variant of the CNDO treatment.

Control of the Nickel-Catalyzed Cooligomerization of Butadiene with Schiff Bases by Cocatalysts[**]

By *Paul Heimbach, Bernard Hugelin, Erich F. Nabbefeld, Dieter Reinehr, Achim Roloff*, and *Eduard Troxler*[*]

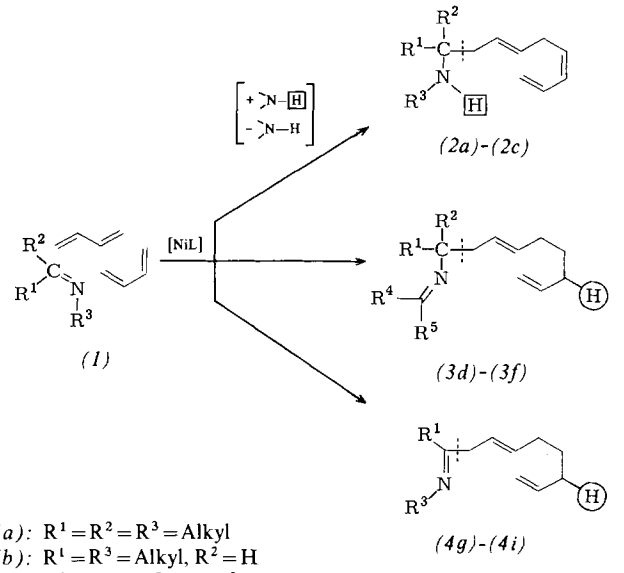
Di- and trisubstituted Schiff bases *(1)* can, like ethylene[1,2], be converted with butadiene into 2:1 adducts on Ni-ligand catalysts[3,4]. Three 2:1 adducts [*(2)* to *(4)*] can be formed with yields of up to 88 % [based on *(1)*].

Octadienylated Schiff bases of types *(3)* and *(4)* are only formed if very pure reactants are used. Type *(4)* Schiff bases are produced if the substituent R^3 in the α-position with respect to nitrogen does not contain hydrogen and if $R^2 = H$. If a hydrogen atom is in the α-position in R^3, then a type *(3)* Schiff base can be synthesized. Addition of very weak

[*] Prof. Dr. P. Heimbach [+], E. F. Nabbefeld, Dr. A. Roloff
Universität Essen—Gesamthochschule, Fachbereich Chemie
Postfach 6843, D-4300 Essen 1 (Germany)
and
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim (Germany)
Dr. B. Hugelin, Dr. D. Reinehr, Dr. E. Troxler
Zentrale Forschungslaboratorien der Ciba-Geigy AG
CH-4000 Basel (Switzerland)
[+] To whom correspondence should be addressed.

[**] Control of Metal-Catalyzed Reactions, Part 3.—Part 2: *P. Heimbach, A. Roloff, H. Schenkluhn*, Angew. Chem. *89*, 260 (1977); Angew. Chem. Int. Ed. Engl. *16*, 252 (1977).

protic compounds (primary and secondary amines or phosphanes, alcohols, weak organic acids, water) leads to the formation of octatrienylated amines of type *(2)*[4]. Figure 1 shows



(a): $R^1=R^2=R^3=$Alkyl
(b): $R^1=R^3=$Alkyl, $R^2=H$
(c): $R^1=$Aryl, $R^2=H$, $R^3=$Alkyl
(d): $R^1=R^2=$Alkyl, $R^3=CHR^4R^5$
(e): $R^1=$Alkyl, $R^2=H$, $R^3=CHR^4R^5$
(f): $R^1=$Aryl, $R^2=H$, $R^3=CHR^4R^5$
(g): $R^1=$Aryl, Alkyl, $R^2=H$, $R^3=N(CH_3)_2$
(h): $R^1=$Aryl, $R^2=H$, $R^3=C(CH_3)_3$
(i): $R^1=$Alkyl, $R^2=H$, $R^3=$Aryl

amines of type *(2)* are not nearly so effective for this switch-over as morpholine. Nevertheless, an auto-cocatalysis must also be taken into consideration.

We think that the intermediates important for the branching of the reaction can be described by structures *(5)* and *(6)*[7]. The C=N double bond of *(1)* is inserted into one of the nickel-allyl bonds of the C_8-chain formed from two butadiene molecules. Migration of hydrogen from one of the two positions which are α with respect to the nitrogen, to the 3-position of the second allyl group leads to the formation of *(3)* or *(4)*. Association of an amine permits transfer of a hydrogen atom to the amide nitrogen [see *(6)*]. The subsequent β-elimination of a hydrogen atom from the diene chain with regeneration of the amine >N—H leads to compound *(2)*.

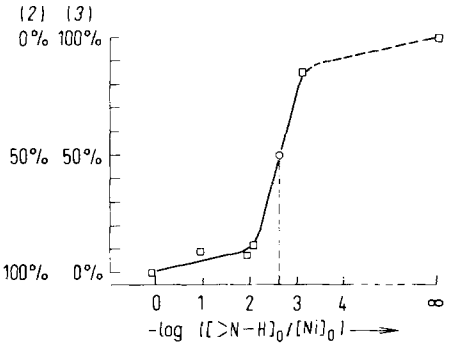


Fig. 1. Products of the catalyzed cooligomerization of *N*-(benzylidene)propylamine with butadiene as a function of the negative logarithm of the molar ratio morpholine : nickel. The sum of the type *(2)* and *(3)* isomers was taken as 100%; molar ratio nickel : Schiff base = 1:50; molar ratio Schiff base : butadiene = 1:2; reaction temperature 40°C [5].

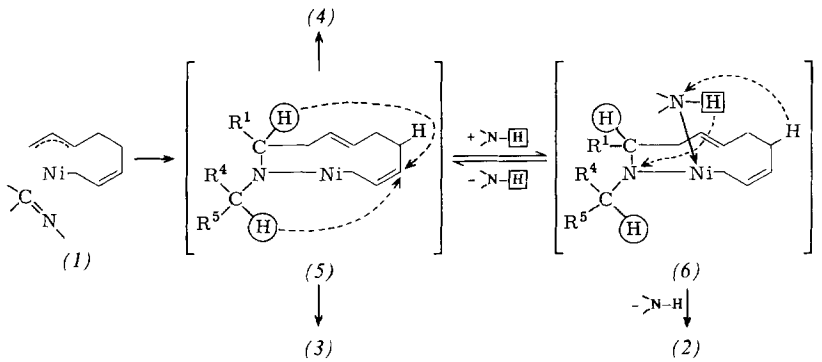


Table 1. Yields and properties of some type *(2)* and *(4)* products. Reaction conditions: 40°C; molar ratio $Ni^{(0)}$: triphenylphosphane = 1:1; butadiene : Schiff base *(1)* = 2:1; Ni : Schiff base *(1)* = 1:50.

	R^1	R^2	R^3	Yield [a] [%]	B.p. [°C/torr]	n_D^{20} (Purity)
(2a)	CH_3	CH_3	*i*-C_3H_7	76	$58/10^{-4}$	1.4932 (94%)
(2b)	C_3H_7	H	C_3H_7	88	$54/10^{-4}$	1.4760 (92%)
(2c)	C_6H_5	H	C_4H_9	65	$95/10^{-4}$	1.5262 (98%)
(3d)	$-(CH_2)_5-$		*i*-C_3H_7	52	$73/10^{-4}$	1.4862 (95%)
(3f)	C_6H_5	H	*s*-C_4H_9	60	$81/10^{-4}$	1.5114 (97%)
(4g)	C_6H_5	H	$N(CH_3)_2$	42	$72/10^{-4}$	1.5272 (94%)

[a] Based on converted Schiff base (conversion is 80 to 100%). The yields have not been optimized. If the conversion is high then type *(2)* products (as 1,3-dienes) and type *(3)* and *(4)* products (as Schiff bases) can react further.

that the reaction changes over from the synthesis of a Schiff base *(3f)* to the synthesis of an amine *(2c)* (cooligomerization of *N*-(benzylidene)propylamine with butadiene) and also demonstrates the dependence of this change-over on the morpholine concentration. Surprisingly, just a few ppm of morpholine can cause this switch[6]; the resulting octatrienylated

Some of the compounds synthesized are compiled in Table 1. The experimental conditions are as described in [8].

Received: December 27, 1976 [Z 652b IE]
German version: Angew. Chem. 89, 261 (1977)

CAS Registry numbers:
(1a), 3332-08-9; *(1b)*, 7707-71-3; *(1c)*, 1077-18-5; *(1d)*, 13652-31-8; *(1f)*, 40051-50-1; *(1g)*, 1075-70-3; *(2a)*, 61701-86-8; *(2b)*, 61701-87-9; *(2c)*, 61701-88-0; *(3d)*, 61701-89-1; *(3f)*, 61701-90-4; *(4g)*, 61701-91-5; butadiene, 106-99-0; nickel, 7740-02-0

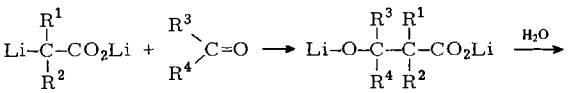
[1] *P. Heimbach, G. Wilke*, Justus Liebigs Ann. Chem. *727*, 183 (1969).
[2] The perturbation [(−I) effect] caused by the introduction of the nitrogen is compensated by the alkyl substituents [(+I) effect]; compensation of this perturbation results in a behavior analogous to that of the unperturbed system (ethylene).
[3] *A. Roloff*, Dissertation, Universität Bochum 1976; *D. Reinehr, B. Hugelin, E. Troxler*, DOS 2507007 (Sep. 4, 1975) Ciba-Geigy AG, Basel (Switzerland).
[4] *P. Heimbach, E. F. Nabbefeld, A. Roloff*, unpublished.
[5] The curve was derived using an unpublished method of *J. Kluth* and *H. Schenkluhn*.
[6] An extremely pure Schiff base is necessary if octadienylated Schiff bases of types *(3)* and *(4)* are to be synthesized, as traces of water or primary amines present in the preparation can act as cocatalysts.
[7] These hydrogen transfer reactions are probably sigmatropic rearrangements and not the consequence of β-elimination and -addition steps.
[8] *W. Brenner, P. Heimbach, G. Wilke*, Justus Liebigs Ann. Chem. *727*, 194 (1969); *K.-J. Ploner, P. Heimbach, ibid. 1976*, 54.

Decarboxylative Dehydration of β-Hydroxycarboxylic Acids by Redox Condensation: A Novel Olefin Synthesis

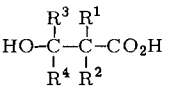
By *Johann Mulzer* and *Gisela Brüntrup*[*]

By addition of carbonyl compounds to the dilithium salts of carboxylic acids a wide variety of β-hydroxycarboxylic acids *(1)* can be obtained in good yields[1]. The decarboxylative dehydration of *(1)* according to eq. (B) leads to the olefins *(2)*, the combination of (A) and (B) being an attractive alternative to the Wittig reaction.

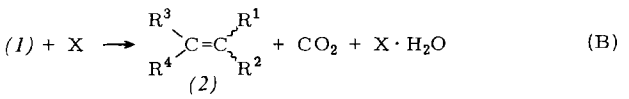
Depending on the nature of the dehydrating reagent X eq. (B) can be realized in two variations I or II. Thus, with X = dimethylformamide acetal, for example, olefin formation and elimination of H_2O and CO_2 proceeds in *one* step (variation I[2]). Alternatively, if X = arenesulfonyl chloride, *(1)* is first converted into its β-lactone, from which *(2)* is subsequently obtained by thermal elimination of CO_2 (variation II[3]). We report here on a novel method for variation I utilizing the principle of the redox condensation[4]. The reagent X we use is the adduct of triphenylphosphane and ethyl azodicarboxylate[5]. This adduct is capable of binding the H_2O which is formed according to eq. (B) in an exergonic process [eq. (C)].



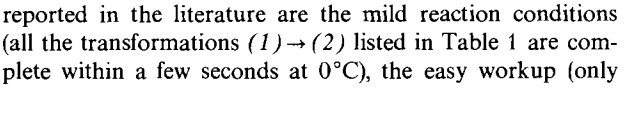
(A)



(1)



(B)



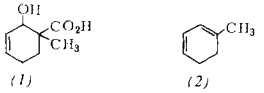
(C)

The advantages the new method has over those already reported in the literature are the mild reaction conditions (all the transformations *(1)* → *(2)* listed in Table 1 are complete within a few seconds at 0°C), the easy workup (only nonvolatile and hence easily separable byproducts are formed), and the low cost of the reagents employed (azodicarboxylate can be readily prepared on a large scale from hydrazine, chloroformates and an oxidizing agent[6]). The full scope, the stereochemistry and the mechanism of the reaction are currently under investigation.

Experimental:

To a stirred solution of *(1a)* (3.0 mmol) in anhydrous THF (3 ml) is added a solution of $P(C_6H_5)_3$ (3.0 mmol) in THF (2 ml) under a nitrogen atmosphere. The resulting mixture is treated dropwise with a solution of 3.0 mmol of ethyl azodicarboxylate in THF (2 ml). The rapid progress of the reaction is indicated by the slight warming of the mixture and the instantaneous decoloration of the azoester. After the evolution of CO_2 has ceased, the resulting mixture is stirred for an additional 10 min. The solvent is then evaporated under reduced pressure and the residue triturated with ether/pentane. The triphenylphosphane oxide and the hydrazoester crystallize and are removed by filtration. The filtrate, after stripping

Table 1. Examples of β-hydroxycarboxylic acids *(1)* prepared according to Eq. (A) and of olefins *(2)* prepared according to Eq. (B/C).

		(1)		*(2)*	
		M.p. [°C]	Yield [%]	B.p. [°C/torr]	Yield [%]
(a):	$R^1=R^2=R^3=H$, $R^4=C_6H_5$	90—91	70	60—70/10	70
(b):	$R^1=R^2=R^3=H$, $R^4=p$-C_6H_4Cl	92—94	70	60—70/10	65
(c):	$R^1=R^2=R^3=H$, $R^4=p$-$C_6H_4CH_3$	94—95	75	60—70/10	70
(d):	$R^1=R^2=R^3=H$, $R^4=$*trans*-$CH=CHC_6H_5$	77—78	80	80—90/10	65
(e):	$R^1=R^2=R^3=H$, $R^4=CH_2C_6H_5$	90—91	30	65—75/10	60
(f):	$R^1=R^3=H$, $R^2=CH_3$, R^4=2,2-diphenylcyclopropyl	oil	50 [a]	110—120/5·10^{-4}	75 [b]
(g):	 *(1)* *(2)*	oil	[a, c]		55 [d]

[a] Diastereomeric mixture. [b] *cis-trans* Mixture. [c] *(1g)* was obtained in 40% yield by Diels-Alder addition of 1-acetoxybutadiene to methacrylic acid and base-catalyzed hydrolysis. [d] Isolated and characterized (NMR, IR) as the TCNE adduct (dec. > 200°C).

[*] Dr. J. Mulzer, G. Brüntrup
Institut für Organische Chemie der Universität
Karlstrasse 23, D-8000 München 2 (Germany)

off the solvent, is distilled at 10 torr. Spectroscopically and analytically pure *(2a)* is obtained in 70 % yield.

Received: January 12, 1977 [Z 657 IE]
German version: Angew. Chem. *89*, 265 (1977)

CAS Registry numbers:
(1a), 156-05-8; *(1b)*, 25209-46-5; *(1c)*, 61752-37-2; *(1d)*, 61752-38-3; *(1e)*, 6828-41-7; *(1f)*, 61752-39-4; *(1g)*, 61752-40-7; *(2a)*, 100-42-5; *(2b)*, 1073-67-2; *(2c)*, 622-97-9; *(2d)*, 16939-57-4; *(2e)*, 300-57-2; *Z-(2f)*, 61752-41-8; *E-(2f)*, 61752-42-9; *(2g)*, 61752-43-0; $P(C_6H_5)_3$, 603-35-0; diethyl azodicarboxylate, 1972-28-7; 1-acetoxybutadiene, 1515-76-0; methacrylic acid, 79-41-4

[1] *G. W. Moersch, A. R. Burkett*, J. Org. Chem. *36*, 1149 (1971); *A. P. Krapcho, E. G. E. Jahngen Jr., ibid. 39*, 1650 (1974).
[2] *S. Hara, H. Taguchi, H. Yamamoto, H. Nozaki*, Tetrahedron Lett. *1975*, 1545; *A. Rüttimann, A. Wick, A. Eschenmoser*, Helv. Chim. Acta *58*, 1450 (1975).
[3] *W. Adam, J. Baeza, J.-C. Liu*, J. Am. Chem. Soc. *94*, 2000 (1972).
[4] *T. Mukaiyama*, Angew. Chem. *88*, 111 (1976); Angew. Chem. Int. Ed. Engl. *15*, 94 (1976).
[5] *E. Brunn, R. Huisgen*, Angew. Chem. *81*, 534 (1969); Angew. Chem. Int. Ed. Engl. *8*, 513 (1969); *O. Mitsunobu, M. Eguchi*, Bull. Chem. Soc. Jpn. *44*, 3427 (1971); *A. K. Bose, B. Lal, W. A. Hoffman, M. S. Manhas*, Tetrahedron Lett. *1973*, 1619.
[6] *N. Rabjohn*, Org. Synth. Coll. Vol. *3*, 375 (1955); *J. C. Kauer, ibid. 4*, 411 (1963).

Ionization Barrier of Trityl Chloride in Sulfur Dioxide[1]

By *Martin Feigel* and *Horst Kessler*[*]

Rate constants for ionization and dissociation of a compound RX *via* ion pairs into free ions according to the following simplified Winstein scheme

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underbrace{R^{\oplus}X^{\ominus}}_{\text{ion pair}} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underbrace{R^{\oplus} + X^{\ominus}}_{\text{free ions}}$$

have so far been studied by two different methods: (i) determination of the solvolytic behavior of RX[2] and (ii) examination of the kinetics of recombination of $R^{\oplus}$ and $X^{\ominus}$ by flow methods[3a] or relaxation techniques[3b]. All these methods use time-dependent changes in concentrations in order to determine kinetic parameters. We now report a study of the ionization kinetics of triphenylmethyl chloride in SO_2 under equilibrium conditions by NMR spectroscopy.

When a solution of trityl chloride in SO_2 is cooled down, the center of gravity of the ^{1}H-NMR signals migrates downfield, indicating a shift of the equilibrium from covalent to ionic species. In addition, the signals exhibit broadening below -40 °C and ultimately split into a spectrum of ionic and covalent trityl chloride. In order to allow a quantitative evaluation of the ^{1}H-NMR spectra we used trityl chloride deuterated in the *ortho* and *para* positions[4] which at low temperatures only gives rise to singlets at $\delta = 7.37$ (covalent trityl chloride) and 7.93 ppm (all ionic forms). Line shape analysis of the coalescence of these two signals (Fig. 1) results in temperature-dependent values of the average lifetimes τ_{ion} (all ions) and τ_{cov} (covalent form). The rate constant k_1 can easily be calculated from τ_{cov} according to

$$k_1 = \frac{1}{\tau_{cov}}; \quad k_{-1} = \frac{1}{\tau_{ion}}\left(1 + \frac{k_2}{k_{-2}\, a_{Cl^{\ominus}}}\right)$$

$a_{Cl^{\ominus}}$: activity of free chloride ions

[*] Prof. Dr. H. Kessler, Dipl.-Chem. M. Feigel
Institut für Organische Chemie der Universität, Laboratorium Niederrad
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

Since the calculation of k_{-1} requires knowledge of the equillibrium constant of dissociation, only the temperature dependence of $k'_{-1} = 1/\tau_{ion}$ (the reciprocal lifetime of all ionic forms) was considered in the compilation of kinetic data (Table 1) for recombination.

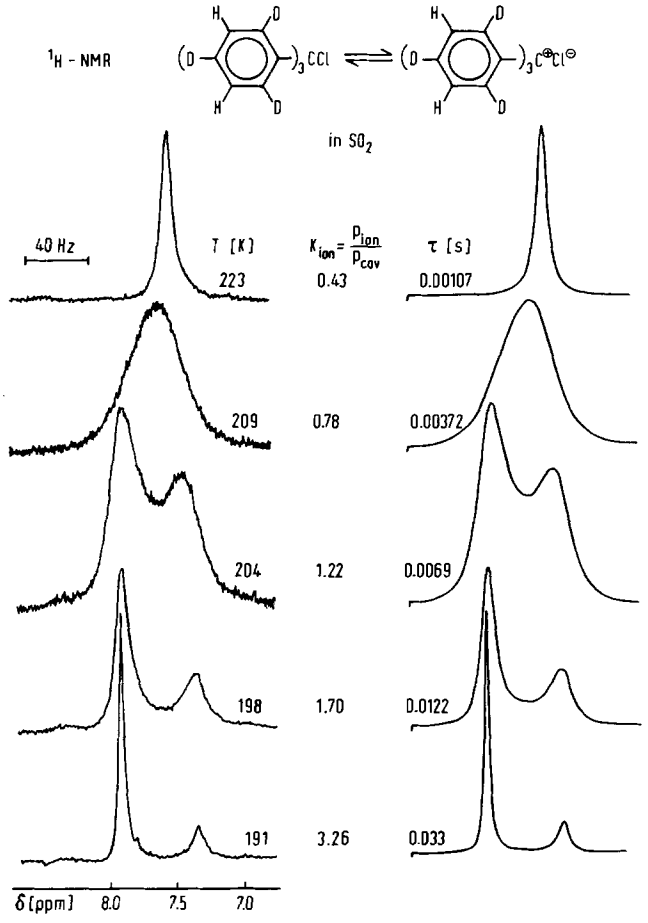


Fig. 1. Line shape analysis (right) of the FT-^{1}H-NMR spectra (left) of nonadeuteriotrityl chloride in SO_2 (0.1 M). The individual mean lifetimes of the ionic and covalent species are given by $\tau_{ion} = \tau/p_{cov}$ and $\tau_{cov} = \tau/p_{ion}$; p_s = population of the species S; $K_{ion} = p_{ion}/p_{cov}$.

Table 1. Activation parameters for trityl chloride in SO_2 (0.1 M).

	Ionization (k_1)	Recombination (k'_{-1}) [a]
$\Delta G^{\neq}_{209}$ [kcal/mol]	10.12 ± 0.05	10.06 ± 0.05
$\Delta H^{\neq}$ [kcal/mol]	5.34 ± 0.5	10.6 ± 0.5
$\Delta S^{\neq}$ [cal/mol·K]	−22.9 ± 3	+ 2.6 ± 3

[a] Recombination pseudo first order, see text.

Whereas enthalpy contributions are mainly responsible for the recombination barrier, the ionization barrier is largely determined by the strong negative activation entropy (Table 1). The higher order of the solvent molecules around the ions than around covalent RX lowers the entropy. It follows from our data that in the transition state the solvation is comparable with that of ion pairs[5].

Regarding the results obtained in less polar solvents the value of $\Delta G^{\neq}_1$ in SO_2 appears high. For example the barrier was estimated to be lower than 4 kcal/mol from S_N1 reactions of trityl chloride in benzene[7]. Furthermore, in dichloroethane the recombination of trityl cations with chloride anions is diffusion controlled[3b]. Since the population of ions and covalent compound are similar in SO_2 (measureable populations p_s are an essential condition for kinetic NMR measurements

at equilibrium; cf. Fig. 1), according to the Hammond postulate the transition state in our case is more similar to the covalent compound than on collapse of the high-energy system of dissociated ions in dichloroethane[8]. Dynamic NMR measurements therefore permit the study of barriers of ionization equilibria, and should thus provide a deeper insight into the transition state of ion recombinations in solution.

Received: January 18, 1977 [Z 658 IE]
German version: Angew. Chem. 89, 266 (1977)

CAS Registry numbers:
Trityl chloride, 76-83-5

[1] NMR Spectroscopic Studies on Kinetics and Thermodynamics of Reversible Dissociation Reactions, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 2: *M. Feigel, H. Kessler*, Tetrahedron *32*, 1575 (1976).

[2] *D. J. Raber, J. M. Harris, P. v. R. Schleyer* in *M. Szwarc*: Ions and Ion-pairs in Organic Reactions, Vol. II. Wiley, New York 1974, pp. 247—374.

[3] a) *C. D. Ritchie*, Acc. Chem. Res. *5*, 348 (1972); b) *L. M. Dorfmann, R. J. Sujdak, B. Bockrath, ibid. 9*, 352 (1976).

[4] *J. I. Brauman, W. C. Archie*, J. Am. Chem. Soc. *92*, 5981 (1970).

[5] The entropy of trityl chloride ion pairs in SO_2 is not known exactly. While K_1 has been determined as 0.014 at 0 °C [6a], a value of $K_1 = 0.0025$ can be calculated from the results of temperature-dependent conductivity measurements [6b]. In [6b] ΔS_1^0 was determined as −34.5 e.u. Our own concentration-dependent NMR measurements give $\Delta S_1^0 = -37.5$ e.u. for the deuterated compound, but a value of $K_1 = 0.0044$ on extrapolation to 0 °C.

[6] a) *N. N. Lichtin*, Prog. Phys. Org. Chem. *1*, 75 (1963); b) *E. Clougherty*, Ph. D. Boston University 1966, Diss. Abstr. B *27*, 1438.

[7] *E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, Y. Pocker*, J. Chem. Soc. *1975*, 1265.

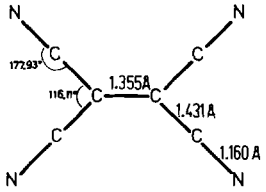
[8] A recombination barrier of $\Delta G^{\ddagger}_{217} = 8.1$ kcal mol was determined by an indirect method for tri-*p*-tolylmethyl chloride in methylene chloride [9a]; no change in line shape has been reported on direct measurement of the ionization of this compound in SO_2/CD_2Cl_2 [9b].

[9] a) *H. H. Freedman, A. E. Young, V. R. Sandel*, J. Am. Chem. Soc. *86*, 4722 (1964); b) *M. Nojima, M. Ishiyama, N. Tokura*, Kogyo Kagaku Zasshi *73*, 2306 (1970).

Comparison of Calculated and Experimental Electron Difference Densities of Tetracyanoethylene[**]

By *Hans-Lothar Hase, Karl-Wilhelm Schulte*, and *Armin Schweig*[*]

It is assumed[1] that electron difference densities[2] in the region of chemical bonds can be determined with an accuracy[3] of 0.05 e/Å^3. We now report quantum chemical *ab initio* results which cast doubt upon this expectation[4] for the standard example tetracyanoethylene (TCNE)[5].



For this purpose the static and dynamic electron difference densities were calculated in "4—31 G" quality[6]. Figure 1 shows sections through the resulting static *(stat)* and dynamic *(dyn)* densities and also through the experimental *(exp)* densities [in the molecular plane *(A)*, perpendicular thereto through the C=C *(B)*, C—C *(C)*, and C≡N bonds *(D)*]. As shown by the figure, overall agreement between the calculated and the experimental difference densities is surprisingly good. However, some considerable discrepancies (0.5 e/Å^3 for C≡N and 0.4 e/Å^3 for C—C) are found for the difference densities in the bonds (Table 1).

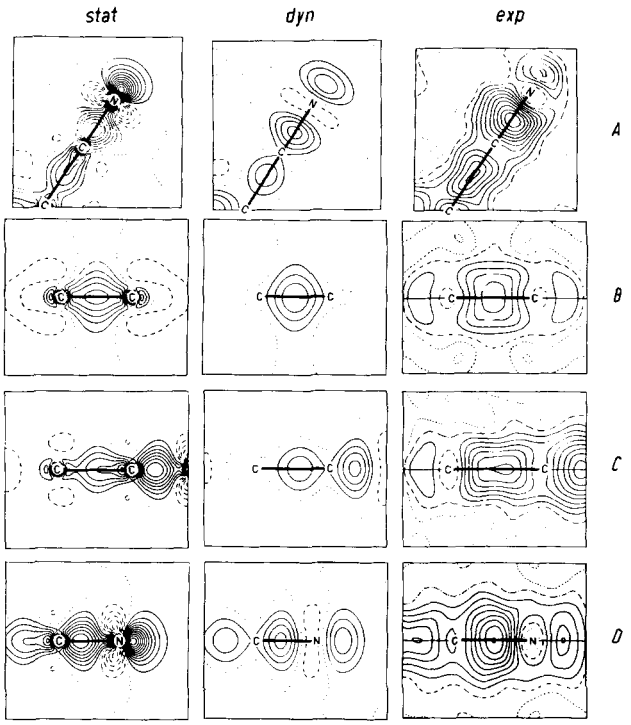


Fig. 1. Calculated ("4—31 G" basis) static *(stat)* and dynamic *(dyn)* and experimental *(exp)* electron difference densities in the molecular plane *(A)* and perpendicular to the molecular plane through the C=C *(B)*, C—C *(C)*, and C≡N bonds *(D)* of tetracyanoethylene (TCNE). The contour lines mark differences of 0.1 e/Å^3 in all cases; positive lines (——), negative lines (– – –), zero line (···· calculated and ·–·– experimental).

The deviations of the calculated values to be expected as a result of using the incomplete "4—31 G" basis have been estimated for the model compound cyanogen (NCCN). For

Table 1. Peak heights in the difference densities of tetracyanoethylene (TCNE).

Difference density type		Peak heights in the difference densities [e/Å^3]			
		C≡N	C=C	C—C	lone pair
4—31 G	static	0.7	0.5	0.6	1.1
	dynamic	0.4	0.3	0.2	0.3
experimental	dynamic	0.9	0.4	0.6	0.4

Table 2. Peak heights in the difference densities of cyanogen (NCCN).

Difference density type		Peak heights in the difference densities [e/Å^3]		
		C≡N	C—C	lone pair
DZ+P (near HF)	static	1.0	0.6	1.1
	dynamic	0.65	0.4	0.35
4—31 G	static	0.8	0.4	1.1
	dynamic	0.47	0.24	0.40

[*] Prof. Dr. A. Schweig, Dr. H.-L. Hase, Dipl.-Chem. K.-W. Schulte
Fachbereich Physikalische Chemie der Universität
Auf den Lahnbergen, D-3550 Marburg (Germany)

[**] Part 3 of "Comparison of Observed and Calculated Electron Densities", DFG-Sonderforschungsbereich 127 ("Crystal Structure and Chemical Bonding"). Presented in part at the "Sagamore V" conference, Killjava (Finland), August 16—20, 1976.—Part 2: *H. Irngartinger, H. L. Hase, K.-W. Schulte, A. Schweig*, Angew. Chem. *89*, 194 (1977); Angew. Chem. Int. Ed. Engl. *16*, 187 (1977).

this molecule the static difference density is known in "near HF" quality[7]. As shown by comparison of the corresponding dynamic difference densities in the bonds with the corresponding "4—31 G" values[8] (Table 2) the mutual deviation between the two calculations does not exceed 0.16 (C—C) or 0.18 e/Å^3 (C≡N). "4—31 G" calculations thus prove to be surprisingly reliable for calculations of difference densities.

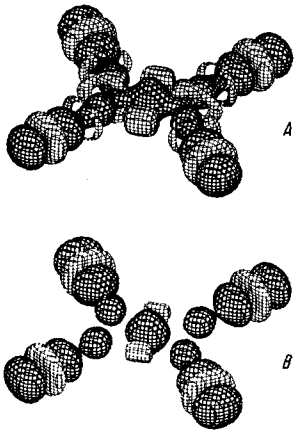


Fig. 2. Perspective representation of the three-dimensional static *(A)* and dynamic *(B)* "4—31 G" difference electron densities of tetracyanoethylene (TCNE) for the values 0.1 e/Å^3 (——) and −0.1 e/Å^3 (——).

These results suggest that the "4—31 G" bond difference densities of Table 1 are falsified by no more than 0.2 e/Å^3 in the critical bonds C≡N and C—C. Thus, the corresponding experimental densities are probably more erroneous than hitherto assumed (0.07 e/Å^3). The large experimental values may possibly be explicable in terms of erroneous scaling[8].

Our results pose the challenge to compare calculated and experimental difference electron densities for other compounds in order to better appreciate their accuracy. The present demonstration of the very good (if not yet optimum) quality of the "4—31 G" difference densities attainable with reasonable effort is an encouraging step in this direction. These densities (static and dynamic) are shown in perspective[9] for TCNE in Figure 2. Corresponding representations of experimental difference densities have not so far been employed in any case.

Received: January 20, 1977 [Z 655a IE]
German version: Angew. Chem. 89, 263 (1977)

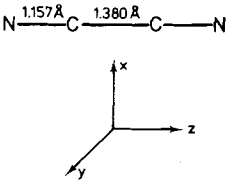
CAS Registry number:
Tetracyanoethylene, 670-54-2

[1] *P. Coppens*, Acta Crystallogr. *A 31*, S218 (1975).
[2] The electron difference density of a molecule is defined as the difference between the total molecular electron density and the superposed atomic densities of the atoms of which the molecule considered is composed.
[3] Standard deviation in the electron difference densities resulting from statistical errors (in the structure factors, the positional and temperature factors of the atoms, and in the scale factor). Systematic errors (due to approximation corrections of the experimental values or to crystal forces) are not considered.
[4] A somewhat greater standard deviation (0.07 e/Å^3) was estimated for TCNE [5].
[5] *P. Becker, P. Coppens, F. K. Ross*, J. Am. Chem. Soc. *95*, 7604 (1973).
[6] *R. Ditchfield, W. J. Hehre, J. A. Pople*, J. Chem. Phys. *54*, 724 (1971). The total static electron density was calculated with the POLYATOM program system (QCPE, No. 199) on the basis of the experimental geometry [5]. The atomic densities were determined with the RHF program section using the same basis set. In order to determine the dynamic difference electron density according to *H.-L. Hase, H. Reitz*, and *A. Schweig*, Chem. Phys. Lett. *39*, 157 (1976), an orthorhombic unit cell was constructed with the dimensions $a=8$, $b=9$, $c=5$ Å, into which a molecule of TCNE just fits. The temperature factors obtained by neutron diffraction were used [5].
[7] *A. D. McLean, M. Yoshimine*: Tables of Linear Molecule Wave Functions, IBM 1967; *F. L. Hirshfeld*, Acta Crystallogr. *B 27*, 769 (1971).
[8] *P. Coppens*, Acta Crystallogr. *B 30*, 255 (1974). According to this method the maximum bond densities in NCCN are represented by a Gaussian function $\rho = A\exp(-\alpha r^2)$ perpendicular to the bonds and subsequently "smeared out" in simple manner. Our "4—31 G" difference densities give $A=0.8$, 0.4, and 1.1 e/Å^3 and $\alpha=6.365$, 7.354, and 12.237 Å^{-2} for C≡N, C—C, and the lone pair, respectively.
[9] *J. Radloff*, Elektron. Rechenanl. *16*, 18 (1974).

An Economic Basis for Electron Difference Density Calculations[**]

By *Hans-Lothar Hase* and *Armin Schweig*[*]

Experimental electron difference densities are already available for large polyatomic molecules. RHF (Restricted Hartree-Fock) calculations have so far proved impossible for such systems, and calculations with drastically limited basis sets are therefore unavoidable. In this communication we propose such a basis which leads to results of "near RHF" quality and therefore appears very promising for difference density calculations on large molecules.



As shown by a comparison[1], the "4—31 G"[2] difference densities of cyanogen (NCCN) are of surprisingly high quality relative to the "near RHF" densities[3]. However, discrepancies do occur in the peak heights in the difference densities (0.2 e/Å^3) and in the detailed shape of the densities (cf. Fig. 1). As a corrective measure we have tentatively extended the "4—31 G" basis by admixture of limited sets of atomic or bond polarization functions (henceforth abbreviated as AP or BP). Four basis sets were tested explicitly: STO-3G[4] *(A)*; 4—31 G *(B)*; 4—31 G+AP [AP: six d functions at each atom[5]] *(C)*; and 4—31 G+BP [BP: one s and two p functions in the middle of each bond][5] *(D)*.

Table 1. Peak heights in the difference densities of cyanogen (NCCN).

Basis sets		Peak heights in the difference densities [e/Å^3]		
		C≡N	C—C	lone pair
A	STO-3 G	0.1	0.1	1.0
B	4—31 G	0.8	0.4	1.1
C	4—31 G+AP	0.9	0.5	1.1
D	4—31 G+BP	1.1	0.6	1.1
E	DZ+AP	1.0	0.6	1.1

Sections through the resulting static electron difference densities *A*—*D* are shown in Figure 1 and through the corresponding "near RHF" density *(E)* for comparison. Table 1 contains the maximum difference densities in the bonding

[*] Prof. Dr. A. Schweig, Dr. H.-L. Hase
Fachbereich Physikalische Chemie der Universität
Auf den Lahnbergen, D-3550 Marburg (Germany)

[**] Part 4 of "Comparison of Observed and Calculated Electron Densities", DFG-Sonderforschungsbereich 127 ("Crystal Structure and Chemical Bonding").—Part 3: ref. [1].

and lone pair regions. Thus the "4—31 G + BP" and the "near RHF" results are practically identical. It is particularly noteworthy that the high quality difference densities are obtained

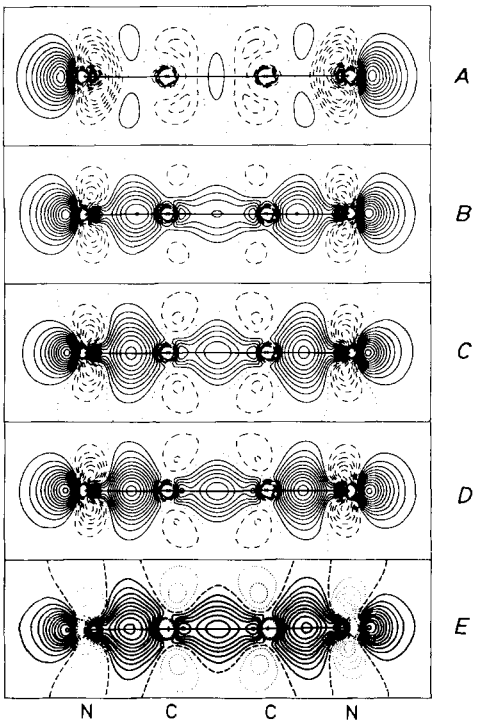


Fig. 1. Calculated electron difference densities of cyanogen (NCCN) for five different basis sets: STO-3G *(A)*, 4—31G *(B)*, 4—31G + AP *(C)*, 4—31G + BP *(D)*, DZ + AP *(E)* [3]. Contours indicate differences of 0.1 e/Å^3; positive lines (——), negative lines (– – – – for *A* to *D* and ····· for *E*), zero line (····· for *A* to *D* and – – – – for *E*).

with only 45 basis functions instead of 60 as in the case of the "4—31 G + AP" basis *(C)*[6]. These results would indicate that it is much more economical and useful to employ polarization functions of bond type (BP) instead of atomic type (AP) for difference density calculations if densities of high quality are to be determined for large molecules.

Received: January 20, 1977 [Z 655b IE]
German version: Angew. Chem. *89*, 264 (1977)

CAS Registry numbers:
Cyanogen, 460-19-5

[1] *H.-L. Hase, K.-W. Schulte, A. Schweig*, Angew. Chem. *89*, 263 (1977); Angew. **Chem. Int. Ed. Engl.** *16*, 257 (1977).
[2] *R. Ditchfield, W. J. Hehre, J. A. Pople*, J. Chem. Phys. *54*, 724 (1971).
[3] *A. D. McLean, M. Yoshimine:* Tables of Linear Molecule Wave Functions, IBM 1967; *F. L. Hirshfeld*, Acta Crystallogr. *B 27*, 769 (1971).
[4] *W. J. Hehre, R. F. Stewart, J. A. Pople*, J. Chem. Phys. *51*, 2657 (1969).
[5] The set of six d functions (d_{xx}, d_{yy}, d_{zz}, d_{xy}, d_{xz} and d_{yz}) contains only five actual d functions, the sixth one ($d_{xx}+d_{yy}+d_{zz}$) being an additional s function. The exponents were taken from a publication by *B. Roos* and *P. Siegbahn*, Theor. Chim. Acta *17*, 199 (1970).—The two p functions used are the p_x and the p_y function. The exponents of the CC bond functions originate from a publication by *R. J. Buenker* and *S. D. Peyerimhoff*, Chem. Phys. 9, 75 (1975). The exponents of the CN bond functions were estimated on the basis of the CC exponents and the average 2s- or 2p carbon α(C) and -nitrogen exponents α(N) according to α(CN) = [α(CC) + α(NN)]/2 and α(NN) = [α(N)/α(C)] · α(CC).—All calculations were performed with the POLYATOM program system (QCPE, No. 199) using the experimental geometry [*C. K. Moller, J. P. Stoicheff*, Can. J. Phys. *82*, 635 (1954)]. We gratefully acknowledge mention of the utility of bond polarization functions by Prof. *W. H. E. Schwarz*, Bonn.
[6] The basis sets *A*, *B*, *C*, *D* contain 60 (20), 80 (36), 104 (60), 89 Gaussian functions (contracted to 45 basis functions).

Isocyanide Synthesis with Diphosgene[**]

By *Giselher Skorna* and *Ivar Ugi*[*]

Elimination of water from *N*-alkyl- or *N*-arylformamides *(1)* is the method of choice for preparation of isocyanides *(3)*[1]. Phosgene in the presence of tertiary amines has proved particularly effective as dehydrating agent[1, 2]. In general, higher yields of isocyanides are obtained with phosgene than with other dehydrating agents; however, phosgene is volatile and highly toxic. Outside production plants, phosgene is no longer readily available owing to the safety legislation concerning its transport. Hence a dehydrating agent is required which is as effective as phosgene in the isocyanide synthesis and yet less dangerous to handle.

We have found that isocyanides *(3)* can be prepared in excellent yields from *N*-monosubstituted formamides *(1)* with diphosgene [perchloro(methyl formate)] *(2)*[3] as dehydrating agent (cf. Table 1).

$$\underset{(1)}{2\,R{-}NH{-}CHO} + \underset{(2)}{Cl{-}CO{-}O{-}CCl_3} + 4\,NEt_3 \rightarrow$$

$$\underset{(3)}{2\,R{-}N{\equiv}C} + 2\,CO_2 + 4\,NEt_3 \cdot HCl$$

Table 1. Synthesis of isocyanides *(3)* with diphosgene *(2)*.

Isocyanide *(3)*	Yield [%] with *(2)*	Yield [%] with $COCl_2$
(3a) Methyl isocyanide [a]	47	37 [1]
(3b) *tert*-Butyl isocyanide [b]	97	82 [1]
(3c) Cyclohexyl isocyanide	98	88 [1]
(3d) Benzyl isocyanide	95	82 [1]
(3e) *p*-Methoxyphenyl isocyanide	95	64 [4]
(3f) Methyl isocyanoacetate	82	47 [5]
(3g) *N*-(L-α-Isocyano-β-phenylpropionyl)-L-phenylalanine methyl ester [c]	75	51 [6]

[a] Tri-*n*-butylamine is used as base and *o*-dichlorobenzene as solvent. On completion of the reaction dry NH_3 is passed through the mixture. Crude *(3a)* is distilled at *ca.* 150 torr/50 °C bath temperature into traps cooled with Dry Ice (cf. [1]).
[b] *o*-Dichlorobenzene is used as solvent. On work-up the mixture is extracted with a phosphate buffer (pH *ca.* 5) and then with 0.5 N NaOH solution.
[c] Reaction performed at −30 °C with *N*-methylmorpholine as base.

Diphosgene has a good chance of becoming the reagent of choice for the synthesis of isocyanides for it is easier to handle and gives higher yields than phosgene. The two-phase phosgene method[8] was found to be more productive only in the synthesis of isocyanomethylpolystyrene[7].

General procedure:

N-Monosubstituted formamide *(1)* (0.10 mol), anhydrous triethylamine (29.0 ml, 21.3 g, 0.21 mol), and anhydrous CH_2Cl_2 (100 ml) are introduced into a three-necked flask fitted with a reflux condenser maintained at −30 °C. Diphosgene *(2)* (6.03 ml, 9.69 g, 0.05 mol) dissolved in anhydrous CH_2Cl_2 is added with stirring at 0 °C over one hour. After stirring for 25—30 min, the temperature is allowed to rise to *ca.* 20 °C and the solution extracted with water (50 ml) and 7.5 % $NaHCO_3$ solution. The organic phase is separated and dried over a 4-Å molecular sieve. The solvent is evaporated *in*

[*] Dipl.-Chem. G. Skorna, Prof. Dr. I. Ugi,
Organisch-Chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

vacuo and the crude isocyanide *(3)* purified by distillation or recrystallization.

Received: January 27, 1977 [Z 659 IE]
German version: Angew. Chem. *89*, 267 (1977)

CAS Registry numbers:
(1a), 123-39-7; *(1b)*, 2425-74-3; *(1c)*, 766-93-8; *(1d)*, 6343-54-0; *(1e)*, 5470-34-8; *(1f)*, 3154-54-9; *(1g)*, 59490-41-4; *(2)*, 503-38-8; *(3a)*, 593-75-9; *(3b)*, 7188-38-7; *(3c)*, 931-53-3; *(3d)*, 10340-91-7; *(3e)*, 10349-38-9; *(3f)*, 39687-95-1; *(3g)*, 61752-36-1

[1] Review: *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann*, Angew. Chem. *77*, 492 (1965); Angew. Chem. Int. Ed. Engl. *4*, 472 (1965).
[2] *I. Ugi, W. Betz, U. Fetzer, K. Offermann*, Chem. Ber. *94*, 2814 (1961); *P. Hoffmann, G. Gokel, D. Marquarding, I. Ugi* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971, p. 9.
[3] *H. C. Ramsperger, G. Waddington*, J. Am. Chem. Soc. *55*, 214 (1933).
[4] *K. Meyr, I. Ugi*, Chem. Ber. *93*, 239 (1960).
[5] *D. Marquarding, P. Seidel*, unpublished result.
[6] *R. Urban, D. Marquarding, P. Seidel, A. Weinelt, I. Ugi*, Chem. Ber., in press; see also *R. Urban*, Dissertation, Technische Universität München 1975.
[7] *G. Skorna, I. Ugi*, Tetrahedron Lett., in press.
[8] *D. Arlt, H. Hagemann, P. Hoffmann, I. Ugi*, DAS 1 668 100 (1968), Farbenfabriken Bayer.

Diastereoisomers with Differing Bond Lengths: Structure Analysis of the Diastereomeric Forms of μ-(1,2-Dichloro-1,2-diphenyldiphosphane)bis(pentacarbonylchromium)[**]

By *Gottfried Huttner, Peter Friedrich, Heinrich Willenberg,* and *Hans-Dieter Müller*[*]

The distances between covalently bonded phosphorus atoms deviate only slightly from an average value of 222 pm, regardless of the nature of the substituents attached to the phosphorus and its formal charge[1]. It therefore appears surprising that the P—P distance in P_2F_4 has recently been determined as 228.1(6) pm[2]. We have now found even longer P—P distances in transition metal complexes of 1,2-dichloro-1,2-diphenyldiphosphane, which can be interpreted at least in part as the result of steric interactions, as demonstrated by structural comparison of two diastereomeric diphosphane complexes.

The symmetrically substituted diphosphane $Ph_2P_2Cl_2$ forms the dinuclear complexes *(1)* with $(CO)_5Cr$[3]. The structures of the *meso* form *(1a)* and of the racemate *(1b)* were determined by X-ray analyses[4] (Fig. 1).

The P—P distance in the *meso* form *(1a)* is 229.0(1) pm and thus lies at the upper limit of the range hitherto observed for the P—P bond lengths of diphosphanes[2, 5] and their complexes[6].

In the racemic form *(1b)* the P—P distance is increased by 3.7 pm to 232.7(6) pm; thus *(1b)* exhibits the longest P—P distance so far reported for diphosphanes.

Since *(1a)* and *(1b)* bear the same substituents at the phosphorus, the difference in the P—P bond lengths can only arise from steric interactions between the substituents which have to adopt a less favorable arrangement in the racemate *(1b)* (C_2 symmetry) than in the centrosymmetric *meso* form *(1a)* (Fig. 1).

To our knowledge the compounds *(1a)* and *(1b)* constitute the first pair of diastereoisomers for which significant differences have been observed in the central bond lengths.

Received: December 1, 1976;
revised: January 28, 1977 [Z 661 IE]
German version: Angew. Chem. *89*, 268 (1977)

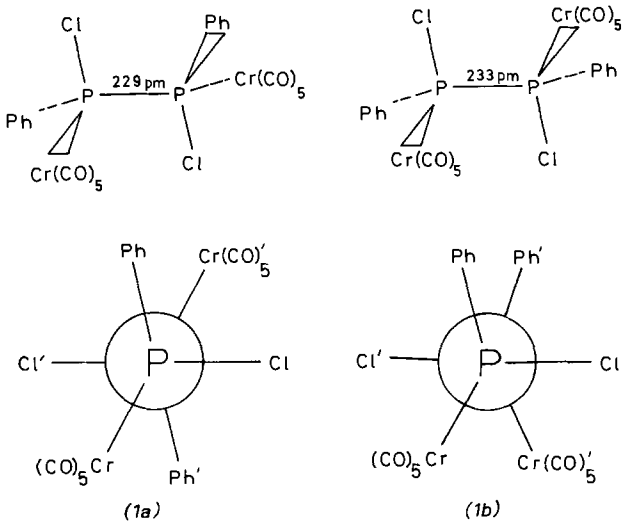


Fig. 1. Schematic representation of the diastereomeric diphosphane complexes *(1a)* and *(1b)*.

[*] Doz. Dr. G. Huttner, Dipl.-Chem. P. Friedrich, Dipl.-Chem. H. Willenberg, Dr. H.-D. Müller
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

[1] *D. E. C. Corbridge*: The Structural Chemistry of Phosphorus. Elsevier, Amsterdam 1974.
[2] *H. L. Hodges, L. S. Su, L. S. Bartell*, Inorg. Chem. *14*, 599 (1975).
[3] *G. Huttner, H. Willenberg, H.-D. Müller*, unpublished.
[4] Measurement: SYNTEX-$P2_1$; solution: SYNTEX-XTL; *(1a)*: space group $P\bar{1}$, $Z=1$, 1379 independent reflections ($I \geq 3\sigma$), $T=183$ K, $R_1=0.037$; *(1b)*: space group C2/c, $Z=4$, 633 independent reflections ($I \geq 3\sigma$), $T=298$ K, $R_1=0.062$.
[5] A survey is given in [1] and in Annu. Rep. Prog. Chem. Sect. A *72*, 129 (1976).
[6] *G. Huttner, H.-D. Müller, V. Bejenke, O. Orama*, Z. Naturforsch. *31b*, 1166 (1976); *J. A. J. Jarvis, R. H. B. Mais, P. G. Owston, D. T. Thompson*, J. Chem. Soc. *A 1968*, 622, and references cited therein.

A Monothiooxalato-*O,S*-oxo Complex of Molybdenum Containing Two S_2^{2-} Ligands

By *Karl Mennemann* and *Rainer Mattes*[*]

During studies on the reactivity of mono- and dinuclear halogeno- and oxalato-oxomolybdates(V) towards thiooxalates[1] we isolated from aqueous solution dark red crystals of a molybdenum compound having an unexpectedly high sulfur content. The IR spectrum revealed the presence of *O,S*-coordinated monothiooxalate[2] and of terminal oxygen [ν(MoO): 930 cm^{-1}]; a band at 530 cm^{-1} could not initially be assigned.

X-Ray structure analysis[3] showed the molybdenum atom to be heptacoordinated in the form of a pentagonal bipyramid (cf. Fig. 1): the equatorial plane contains only sulfur atoms, *viz.* the S atom of the monothiooxalate ligand [*d*(MoS): 253(2) pm] and, surprisingly, two S_2 groups with a mean Mo—S distance of 238(2) pm and an S—S distance of 203(2) pm; a terminal oxygen atom and an O atom belonging to the carboxyl group of the monothiooxalate form the two apices of the bipyramid [*d*(MoO): 170(4) and 231(4) pm]. Thus the geometry

[*] Prof. Dr. R. Mattes, Dipl.-Chem. K. Mennemann
Anorganisch-chemisches Institut der Universität
Gievenbecker Weg 9, D-4400 Münster (Germany)

is analogous to that of the sulfur-free peroxo complex $K_2[MoO(O_2)_2(C_2O_4)]$[4].

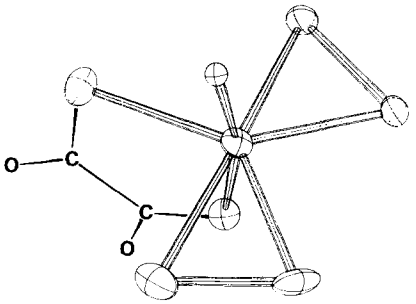


Fig. 1. Structure of the complex anion in cesium bis(disulfido)monothiooxalato-*O,S*-oxomolybdate(VI) *(1)*.

Compounds containing S_2 groups as ligands have hitherto only been found in the case of iridium and rhodium[5], niobium[6], *e.g.* $(\eta^5\text{-}C_5H_5)_2Nb(S_2)X$ with X=Cl, Br, I, SCN, and molybdenum[7], *e.g.* $MoO(S_2)[S_2CN(C_3H_7)_2]_2$. In all cases the IR spectrum contains a band at 520 to 560 cm^{-1} which, as for the new molybdenum complex *(1)*, is to be assigned to an S—S stretching frequency. In the earlier publications cited it is emphasized that the S_2 molecule is bound to the metal center and the metal atom is assigned the resulting oxidation number (*e.g.* Nb^{III}, Mo^{IV}). We are not of this opinion and consider that the niobium and molybdenum compounds, including *(1)*, are better formulated as disulfido complexes (with S_2^{2-} ligands), *i.e.* as sulfur analogs of the peroxo complexes of niobium(V) and molybdenum(VI)[8]. Our reasons are as follows: the structure of the anion of *(1)* corresponds to that of a diperoxomolybdate(VI)[4]; assumption of neutral S_2 ligands would lead to an oxidation number of +2 for molybdenum; however, reduction of Mo^{V} to Mo^{II} is impossible under our reaction conditions. Passage of O_2 through the solution during the reaction actually increases the yield of $Cs_2[MoO(S_2)_2(COS—CO_2)]$. A terminal Mo—O bond with double bond character is not to be expected for Mo^{II}[9].

Procedure:

$Cs_2[Mo_2O_4(C_2O_4)_2(H_2O)_2]\cdot 2H_2O$ (3 g) is dissolved in H_2O (80 ml) and $Cs_2(C_2O_2S_2\text{-}1,2)$ (6.05 g) is added portionwise to the hot solution. On passage of O_2 it rapidly changes color from dark red *via* dark green to blue. After removal of a yellowish green crystalline precipitate (*ca.* 2 g) which also contains a few red crystals and a red amorphous precipitate, the solution once again turns red. $Cs_2[MoO(S_2)_2(COS—CO_2)]$ precipitates in the cold as dark red to black crystals; yield 350 mg.

Identification of the other products provides important clues about the reaction path; thus the yellowish green crystals are shown by analysis and structural elucidation to be $Cs_2[Mo_2O_2(\mu\text{-}S)_2(C_2O_2S_2\text{-}1,2)_2]$ and the remaining products are likewise sulfur- or oxygen-bridged dimeric dithiooxalato-oxo complexes of molybdenum(V)[10].

Received: February 2, 1977 [Z 666 IE]
German version: Angew. Chem. *89*, 269 (1977)

CAS Registry numbers:
$Cs_2[MoO(S_2)_2(COS—CO_2)]$, 61951-17-5;
$Cs_2[Mo_2O_4(C_2O_4)_2(H_2O)_2]$, 61951-18-6;
$Cs_2[Mo_2O_2(\mu\text{-}S)_2(C_2O_2S_2\text{-}1,2)_2]$, 62005-76-9

[1] *W. Stork, R. Mattes*, Angew. Chem. *87*, 452 (1975); Angew. Chem. Int. Ed. Engl. *14*, 436 (1975).
[2] *R. Mattes, W. Stork, J. Kahlenberg*, Spectrochim. Acta, in press.
[3] $a=1183(2)$, $b=1141(3)$, $c=916.7(1)$ pm; space group $Pna2_1$; $Z=4$. Pailred data; 584 reflections with $F_o \geq 4\sigma(F_o)$; $R=0.059$.
[4] *R. Stomberg*, Acta Chem. Scand. *24*, 2024 (1970).
[5] Cf. *W. D. Bonds, J. A. Ibers*, J. Am. Chem. Soc. *94*, 3413 (1972); references cited therein.
[6] *P. M. Treichel, G. P. Werber*, J. Am. Chem. Soc. *90*, 1753 (1968).
[7] *J. Dirand, L. Ricard, R. Weiss*, Inorg. Nucl. Chem. Lett. *11*, 661 (1975).
[8] The opinion of the referees mentioned in a footnote belonging to ref. [6] is in agreement with our view. The structure elucidation performed by *L. F. Dahl*, which has [according to *L. F. Dahl* and *R. Parry*] afforded an S—S bond length of *ca.* 170 pm (!), has not yet been published.
[9] Cf. *K. Mennemann, R. Mattes*, Angew. Chem. *88*, 92 (1976); Angew. Chem. Int. Ed. Engl. *15*, 118 (1976).
[10] *K. Mennemann*, unpublished.

Asymmetrical Bridge Complexes of Type $\eta^3\text{-}C_7H_7(CO)_2Mo(OR)_3Mo\text{-}\eta^7\text{-}C_7H_7$ with Two Mo Centers of Different Oxidation Number[**]

By *Basil Kanellakopulos, Dietrich Nöthe, Klaus Weidenhammer, Henning Wienand*, and *Manfred L. Ziegler*[*]

The symmetrical dinuclear complexes $(\eta^7\text{-}C_7H_7)\text{-}MoX_3Mo(\eta^7\text{-}C_7H_7)$ *(1)* with X=Cl, Br, I, OCH_3 were recently synthesized[1] and characterized on the basis of NIR and ESCA investigations as "mixed-valence" compounds[2].

We have now prepared the complexes $(\eta^3\text{-}C_7H_7)(CO)_2Mo\text{-}(OR)_3Mo(\eta^7\text{-}C_7H_7)$ *(2)* [R=CH_3 *(2a)*, C_2H_5 *(2b)*, C_6H_5 *(2c)*, $C_6H_4CH_3$ *(2d)*, C_6H_4Cl *(2e)*][3] by reaction of $(\pi\text{-}C_7H_7)Mo(CO)_2Br$ with sodium alkoxides or phenoxides. Compounds *(2)*—to our knowledge the first asymmetric "mixed-valence" complexes having π-acids as ligands—were identified by elemental analysis, IR and mass spectra, ESR measurements, and by an X-ray structural analysis[4] on *(2a)*. It follows from Figure 1 that the compounds are dinuclear complexes in which the two Mo centers are coupled by three OR bridges; one Mo atom is completely coordinated by a 1—3-η-cycloheptatrienyl and two carbonyl ligands, the second by a 1—7-η-cycloheptatrienyl ligand.

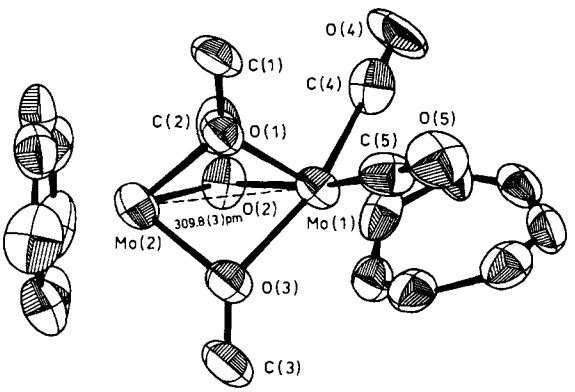


Fig. 1. ORTEP plot of a molecule *(2a)*. The thermal ellipsoids correspond to a probability of 50%; all atoms are drawn true to scale.

As expected, the IR bands in the CO stretching vibration region are shifted to lower wavelengths as compared to the

[*] Prof. Dr. B. Kanellakopulos
Kernforschungszentrum Karlsruhe—Institut für Heisse Chemie
Postfach 3640, D-7500 Karlsruhe (Germany)
Dr. D. Nöthe, Dipl.-Chem. K. Weidenhammer, Dipl.-Chem. H. Wienand, Prof. Dr. M. L. Ziegler [+]
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1 (Germany)
[+] Author to whom correspondence should be addressed.

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

mononuclear bromide[5]. In the mass spectrum (Varian MAT CH7, 70 eV, ion source 150 °C, vaporization temperature: 175 *(2a)*, 145 *(2b)*, 185 *(2c)*, 198 *(2d)*, 185 °C *(2e)*) only the molecular ion (M^+) can be observed in the case of alkyl derivatives; in the aryl derivatives the lines of highest mass correspond to the fragment ions ($M^+ - 2CO$).

Since no utilizable ^{1}H-NMR spectra of compounds *(2)* could be obtained, ESR investigations were carried out on *(2a)*, *(2b)* and *(2e)*. The species prove to be paramagnetic. Susceptibility measurements (Faraday method) at room temperature yielded a value of $\mu_{eff} = 1.735\,\mu_B$, corresponding to one unpaired electron. The paramagnetic susceptibility remains field-independent from 4.2 up to 300 K for six magnetic fields (between 3.50 and 13.1 kG) and obeys the Curie-Weiss law ($C = 5$ K).

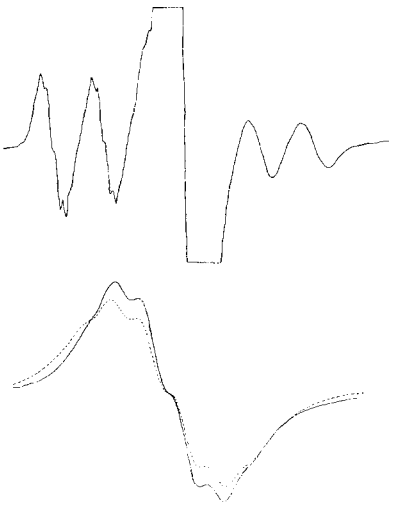


Fig. 2. (Above) ESR total spectrum of *(2a)*. (Below) central line (—— measured, ---- simulated).

As Figure 2 shows, the unpaired electron is located at only one molybdenum nucleus (^{92,94,96,98,100}Mo (75 %), $I = 0$ and ^{95,97}Mo (25 %), $I = 5/2$), otherwise an 11-line spectrum should occur in the case of equivalent Mo atoms, a 36-line spectrum in the case of non-equivalence. The superhyperfine structure points to additional interaction of the electron with magnetically active nuclei; the number of lines and intensity ratios prove the presence of seven magnetically equivalent protons ($a_H = 5.2$ G). No interaction with the bridge ligands is detectable, since there is no alteration in the spectrum on substitution of OCH_3 by OC_2H_5 and OC_6H_4Cl ($g = 1.9537$, $a_{Mo} = 46.4$ G *(2a)*; $g = 1.9529$, $a_{Mo} = 46.7$ G *(2b)*; $g = 1.9530$, $a_{Mo} = 48$ G *(2e)*).

Experimental:

To a solution of π-$C_7H_7Mo(CO)_2Br$ (1.6 g, 5 mmol) in methanol (150 ml) is added 5 mmol $NaOCH_3$ at room temperature. After 48 h the initial green, later yellow-green, solution is evaporated to dryness, the residue taken up in 30 ml CH_2Cl and treated with pentane/petroleum ether (300 ml, 1 : 1). *(2a)* remains in solution and can be isolated as black crystals on removal of solvent by evaporation.

Received: Februar 2, 1977 [Z 667 IE]
German version: Angew. Chem. 89, 271 (1977)

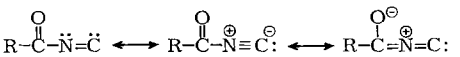
CAS Registry numbers:
(2a), 62005-82-7; *(2b)*, 62005-83-8; *(2c)*, 62005-85-0; *(2d)*, 62005-86-1; *(2e)*, 62005-84-9; π-$C_7H_7Mo(CO)_2Br$, 53556-07-3

[1] *M. Bochmann, M. Cooke, M. Green, H. P. Kirsch, F. G. A. Stone, A. J. Welch*, J. Chem. Soc. Chem. Commun. *1976*, 381.
[2] *G. C. Allen, M. Green, B. J. Lee, H. P. Kirsch, F. G. A. Stone*, J. Chem. Soc. Chem. Commun. *1976*, 794.
[3] *D. Mohr, H. Wienand, M. L. Ziegler*, unpublished work.
[4] The compound *(2a)* can be obtained in crystalline form from CH_2Cl_2/*n*-pentane (1 : 1) by slow removal of solvent without supplying energy. It crystallizes in the triclinic space group $P\bar{1}$-C_i^1 with $a = 958.9(3)$, $b = 1049.8(4)$, $c = 2002.5(5)$ pm; $\alpha = 92.76(2)$, $\beta = 99.64(2)$, $\gamma = 95.53(2)°$; $Z = 4$. 5830 independent reflections differing from 0 were recorded with an automatic single crystal diffractometer (Siemens AED) and corrected in the usual way; $R = 7.5$ %.
[5] ν_{CO} (CH_2Cl_2; cm^{-1}: *(2a)* 1935 (vs), 1845 (s); *(2b)* 1930 (vs), 1845 (vs); *(2c)* 1990 (s), 1948 (vs), 1855 (vs); *(2d)* 1990 (vs), 1940 (vs), 1890 (vs), 1860 (vs); *(2e)* 1980 (w), 1935 (vs), 1855 (vs).

N-Acyl Isocyanides[**]

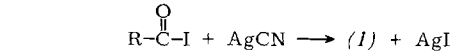
By *Gerhard Höfle* and *Bernd Lange*[*]

Whereas acyl cyanides were first reported as long ago as 1832 and have since been thoroughly investigated[2], the isomeric *N*-acyl isocyanides *(1)* have so far been neither detected nor synthesized[3]. These compounds should—in contrast to the alkyl and aryl isocyanides—be also capable of reacting as electrophilic carbenes, which would make them attractive reaction partners in cycloadditions.



(1)

We have now succeeded in preparing aliphatic and aromatic compounds of the type *(1)* in a surprisingly simple way by reaction of carboxylic acid iodides with silver cyanide.



R = Aryl, Alkyl

If secondary reactions of *(1)* are interrupted immediately after consumption of the acid iodide by cooling to *ca.* −30 °C then *e.g. N*-benzoyl *(1a)* and *N*-pivaloyl isocyanide *(1b)* can be detected in solution by IR and ^{13}C-NMR spectroscopy. In $CHCl_3$, both compounds show an intense isocyanide band at 2100 cm^{-1} and carbonyl bands at 1738 cm^{-1} [*(1a)*] and 1758 cm^{-1} [*(1b)*]. The ^{13}C-NMR spectrum[4] of *(1a)* shows a carbonyl signal at 154.8 ppm and a signal for the isocyanide group at 165.0 ppm. This finding and the coupling constants $^1J_{^{13}CO,\,^{14}N} = 6$ Hz and $^2J_{^{13}CO\,^{13}CN} = 7$ Hz confirm the postulated structure. It follows by comparison with spectroscopic data of other isocyanides[5] that the acyl moiety in *(1)*, contrary to expectation, only slightly influences the electron distribution in the isocyanide group.

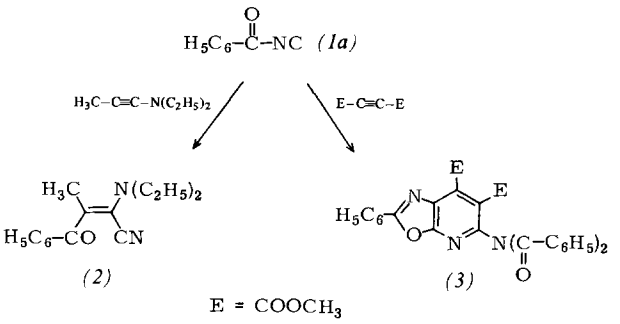
Isolation of *(1a)* is best achieved by low-temperature sublimation in a high vacuum; colorless crystals having a distinct odor of isocyanide are obtained in 73 % yield. *(1a)* is transformed within a few minutes at its melting point of 14 °C into the well-known trimer[6], but is capable of existing for several hours in very dilute solutions[7].

Reaction with methanol gives methyl benzoate in good yield, while reaction with dilute HCl yields benzoic acid and

[*] Priv.-Doz. Dr. G. Höfle, Dipl.-Chem. B. Lange
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[**] Reaction of Organic Halogeno Compounds with Silver Cyanide. Part 3. This work was supported by the Deutsche Forschungsgemeinschaft. Part 2: Ref. [1].

N-formylbenzamide. The high carbonyl activation also manifests itself in the rapid rearrangement into benzoyl cyanide with the acyl transferring agent 4-pyrrolidinopyridine[8] and the acylation of 1-diethylaminopropyne to *(2)*. With electron-deficient acetylenedicarboxylates on the other hand the tendency to undergo cycloadditions comes into play. The 1:3 adduct *(3)* is formed in a multistep reaction[3].



Experimental:

Synthesis of *(1a)*: Benzoyl iodide (1.2 g, 5.2 mmol) is added to a solution of AgCN (1.7 g, 12.7 mmol) (precipitated from aqueous solutions of $AgNO_3$ and KCN, washed with methanol and ether without pressing, and dried at 110 °C over P_2O_5) in 25 ml anhydrous CH_2Cl_2. After ten minutes' stirring at 20 °C the silver salts are rapidly separated and the solvent removed by evaporation at −35 °C/0.1 torr. On slowly warming the residue to 0 °C at 10^{-4} torr *(1a)* sublimes and is collected on a cold finger cooled with liquid N_2; yield 0.50 g (73 %), m.p. 14 °C.

Received: February 8, 1977 [Z 669 IE]
German version: Angew. Chem. *89*, 272 (1977)

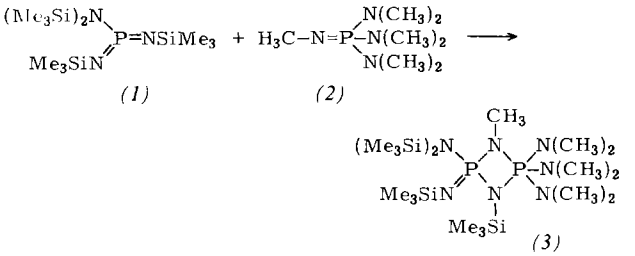
CAS Registry numbers:
(1a), 21445-20-5; *(1b)*, 61915-49-9; *(2)*, 61915-50-2; *(3)*, 61915-51-3; 1-diethylaminopropyne, 4231-35-0; dimethyl acetylenedicarboxylate, 762-42-5; AgCN, 506-64-9; benzoyl iodide, 618-32-8; pivaloyl iodide, 61915-52-4

[1] *G. Höfle*, Angew. Chem. *86*, 679 (1974); Angew. Chem. Int. Ed. Engl. *13*, 676 (1974). To be considered as Part 1: *G. Höfle*, Tetrahedron Lett. *1974*, 347.
[2] For a review see *e.g.*: *J. Thesing, D. Witzel, A. Brehm*, Angew. Chem. 68, 425 (1956).
[3] *G. Höfle*, Habilitationsschrift, Technische Universität Berlin 1975.
[4] Bruker WHO 270 at 67.88 MHz; the enrichment in isocyanide and carbonyl group was 90 % ^{13}C. Owing to quadrupole relaxation the triplet of the carbonyl group was broadened and the signal of the isocyanide group appeared as a broad singlet with a half-width of 8 Hz.
[5] Cf. *e.g. R. W. Stephany, M. J. A. de Bie, W. Drenth*, Org. Magn. Reson. *1974*, 45.
[6] *J. U. Nef*, Justus Liebigs Ann. Chem. *287*, 303 (1895).
[7] As shown by preliminary studies, this apparently paradoxical behavior arises as a result of the third order kinetics of the trimerization.
[8] *G. Höfle, W. Steglich*, Synthesis *1972*, 619.

A Diazadiphosphetidine with Ring-Stabilized "Pentaamidophosphorus"[1]

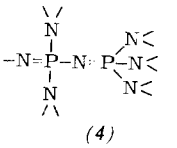
By *Rolf Appel* and *Mechthild Halstenberg*[*]

The cycloaddition of aminobis(imino)phosphorane *(1)*[2] to methyliminotriphenylphosphorane[3] can be applied to numerous other alkyl- and silyl-substituted iminophosphoranes[4]. Of particular interest is the reaction of *(1)* with tris(dimethylamino)methyliminophosphorane *(2)*. The phosphanimide *(2)* contains a phosphorus atom already bonded to four nitrogen atoms. During addition of *(1)* it increases its coordination number and is ultimately surrounded by five nitrogen ligands.



To our knowledge the only phosphorus compound hitherto found to contain a PN_5 unit is the azide $P(N_3)_5$ which was understandably not isolated[5]. In spite of its very modest stability, however, compound *(3)* can be isolated in good yield.

The composition and molecular size of *(3)* have been established by elemental analysis and molecular weight determination. The structure proposed is in accord with ^1H-, ^{13}C-, and ^{31}P-NMR and IR data. The chemical shift of the pentacoordinated phosphorus atom in *(3)* which at −38.3 ppm lies outside the upfield region typical of many pentavalent phosphorus compounds could initially be interpreted as indicating a linear structure *(4)* resulting from silyl group migration.



However, the ^1H-NMR spectrum of *(3)* opposes this alternative: the dimethylamino protons appear as a doublet but an *N*-methyl group as a double doublet. Such strong coupling with the two phosphorus atoms is not to be expected for the linear isomer but is compatible with the cyclic structure *(3)*[9]. Isolation of the PN_5 derivative in this case is probably made possible by the pronounced tendency to form diazadiphosphetidines.

Tris(dimethylamino)methyliminophosphorane (2)[6]:

A solution of hexachloroethane (71.1 g, 300 mmol) in CH_2Cl_2 (200 ml) is added dropwise over a period of 2 h to a stirred solution of tris(dimethylamino)phosphane (48.9 g, 300 mmol) in CH_2Cl_2 (250 ml) at room temperature. Stirring is continued for 2 h and a solution of methylamine (23.3 g, 750 mmol) in CH_2Cl_2 (100 ml) is added dropwise, also over 2 h at room temperature. Stirring, filtration to remove precipitated methylamine hydrochloride, and removal of solvent affords an oil which crystallizes within a day at room temperature. The crude product is digested in ether (500 ml) with exclusion of moisture and after vacuum filtration freed from traces of solvent. The spectroscopically pure[7] solid (69.0 g, 300 mmol = 100 %) is added portionwise at −40 °C to a suspension of sodamide in liquid ammonia prepared from 6.9 g (300 mmol) of sodium. After stirring for 1 h the mixture is allowed to warm to room temperature and the NH_3 evaporated off completely. The residue is taken up in ether (250 ml). Filtration to remove NaCl, concentration of the filtrate, and

[*] Prof. Dr. R. Appel, Dipl.-Chem. M. Halstenberg
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

vacuum distillation with exclusion of moisture affords 41.5 g (72 %) of *(2)*, b.p. 55 °C/0.3 torr.

1-Methyl-2-bis(trimethylsilyl)amino-2-trimethylsilylimino-3-trimethylsilyl-4-tris(dimethylamino)-1,3,2λ⁵,4λ⁵-diazadiphosphetidine (3):

Compound *(2)* (1.92 g, 10 mmol) is added dropwise to a stirred solution of *(1)*[2] (3.66 g, 10 mmol) in *n*-pentane (15 ml). After 3 h precipitated *(3)* is filtered off and briefly dried *in vacuo*. Yield 4.52 g (81 %) of *(3)*, m.p. 72 °C (dec.)[8].

Received: January 27, 1977 [Z 660 IE]
German version: Angew. Chem. 89, 268 (1977)

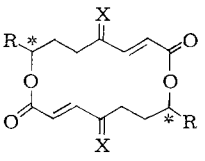
CAS Registry numbers:
(1), 52111-28-1; *(2)*, 49778-04-3; *(3)*, 61752-01-0; tris(dimethylamino)phosphane, 1608-26-0; methylamine, 74-89-5

[1] Nonmetallic Imine Compounds, Part 80.—Part 79: *R. Appel, J. R. Lundehn*, Chem. Ber., in press.
[2] *E. Niecke, W. Flick*, Angew. Chem. *86*, 128 (1974); Angew. Chem. Int. Ed. Engl. *13*, 134 (1974); *O. J. Scherer, N. Kuhn*, Chem. Ber. *107*, 2123 (1974).
[3] *R. Appel, M. Halstenberg*, Angew. Chem. *87*, 810 (1975); Angew. Chem. Int. Ed. Engl. *14*, 768 (1975).
[4] *R. Appel, M. Halstenberg*, unpublished.
[5] *W. Buder, A. Schmidt*, Z. Anorg. Allg. Chem. *415*, 263 (1975).
[6] *P. Haasemann, J. Goubeau*, Z. Anorg. Allg. Chem. *408*, 293 (1974); *H. Goldwhite, P. Gysegem, S. Schow, C. Swyke*, J. Chem. Soc. Dalton *1974*, 16. In order to avoid the reaction of tris(dimethylamino)phosphane with methyl azide described in the literature we prepared *(2)* by deprotonation of the corresponding aminophosphonium chloride with sodamide.
[7] ^{31}P-NMR (CH_2Cl_2): $\delta = -39.8$ ppm.
[8] ^{31}P-NMR (C_6H_6): $\delta = +5.4$ (d, tetracoord. P), -38.3 ppm (d, pentacoord. P); $^2J_{PNP} = 8$ Hz. ^{1}H-NMR (C_6D_6): $\delta = -0.4$ (s, $Si(CH_3)_3$), -2.3 (d, $N(CH_3)_2$: $^3J_{PNCH} = 10$ Hz), -2.7 ppm (dd, NCH_3: $^3J_{PNCH} = 9$ Hz, $^3J_{PNCH} = 11$ Hz).
[9] Spectroscopic investigations on the substance labeled with ^{15}N in the ring also indicate heterocyclic *(3)* on the basis of the NMR coupling pattern. *R. Appel, F. Knoll, M. Halstenberg*, unpublished results.

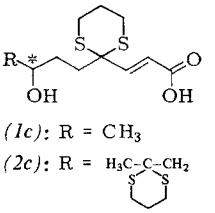
Synthesis and Determination of the Absolute Configuration of Pyrenophorin and Vermiculin[**]

By *Dieter Seebach, Bernhard Seuring, Hans-Otto Kalinowski, Winfried Lubosch*, and *Bernd Renger*[*]

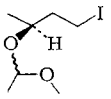
(−)-Pyrenophorin *(1a)* (fungicidal)[1] and (−)-vermiculin *(2a)* (antibiotic)[2] are two simple macrocyclic dilactides ("dilides") with cytotoxic activity. Both have already been synthesized as *d,l* compounds[3]; the absolute configurations (*R,R* or *S,S*) at the C atoms marked with an asterisk in the formulas are so far unknown. We report here on alternative productive syntheses of these two natural products. The starting materials are the optically active building blocks *(S)-(3)* and *S-(4)*[4], from which the hydroxy acids *(1c)* and *(2c)*, respectively, are synthesized. "Dimerizing cyclization" leads respectively to *(1b)* and *(2b)*, which on hydrolysis afford the enantiomerically pure pyrenophorin *(1a)* and vermiculin *(2a)*, respectively. Since the chiral educts were prepared from β-hydroxybutyrate [→ *(3)*] and malic acid [→ *(4)*] ("chiral pool"[5]) of known absolute configuration[4] and since the stereochemistry of the synthesic step at the asymmetric center is known *(vide infra)*, the total syntheses described here also permit assignment of the absolute configurations of the natural products.



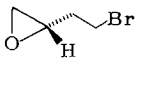
(1a): R = CH_3, X = O
(1b): R = CH_3, X = $-S(CH_2)_3S-$
(2a): R = $CH_3-CO-CH_2$, X = O
(2b): R =  , X = $-S(CH_2)_3S-$



(1c): R = CH_3
(2c): R =



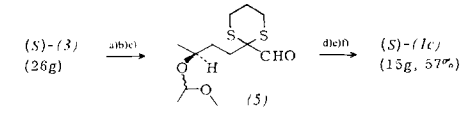
(S)-(3)



(S)-(4)

"Semipyrenophorin" derivative (1c) (cf. Scheme 1): C—C coupling of acetal-protected iodoalcohol *(3)* by the dithiane method in a one-pot reaction affords the aldehyde *(5)*[6], which is transformed by a Wittig reaction into the α,β-unsaturated ester; hydrolysis of the acetal and ester groups furnishes *(1c)*.

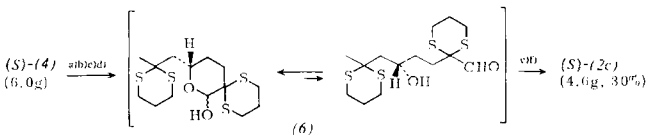
Scheme 1. Synthesis of the hydroxy acid *(1c)*.



a) Addition of *(3)* (opt. purity 90 %) to 2-Li-1,3-dithiane in THF at −100 °C, warmed within 3 h to −78 °C, then within 12 h to +10 °C;
b) *n*-BuLi addition (−40 °C), 30 h at −25 °C (freezer);
c) Addition of dimethylformamide at −78 °C, addition to NaCl solution after warming to −20 °C.
d) Crude product *(5)* heated under reflux with $Ph_3P{=}CH{-}CO_2Me$ in benzene for 30 h, filtration over SiO_2;
e) $HCl/H_2O/THF$, 3 h, room temperature;
f) $LiOH/CH_3OH/H_2O$, 5 h, room temperature, washing of alkaline phase, then $H_2O/H^{\oplus}$, extraction and crystallization of *(1c)*

"Semivermiculin" derivative (2c) (cf. Scheme 2): Three successive C—C coupling reactions by the dithiane method are also carried out here in a one-pot process without workup[6].

Scheme 2. Synthesis of the hydroxy acid *(2c)*.



a) Addition of *(4)* ($[\alpha]_D = -23.9°$ ($c = 4.8$; $CHCl_3$), >95 % opt. purity) to 2-Li-dithiane in THF, 2 d between −78 and −5 °C;
b) 2-Li-2-methyl-1,3-dithiane solution, 1 d between −30 and 0 °C;
c) Metalation with *n*-BuLi/TMEDA; 1 d at −20 °C;
d) Addition of dimethylformamide at −70 °C, warming to −10 °C, workup and isolation of *(6)*.
e) Olefination of crude product *(6)* with $PH_3P{=}CH{-}CO_2Me$, dioxane, 50 h reflux;
f) $LiOH/CH_3OH/H_2O$ analogous to Scheme 1.

[*] Prof. Dr. D. Seebach [+], Dipl.-Chem. B. Seuring, Dr. H.-O. Kalinowski, Dipl.-Chem. W. Lubosch, Dipl.-Chem. B. Renger
Institut für Organische Chemie der Universität Giessen
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

[+] Author to whom all correspondence should be addressed; new address:
Laboratorium für Organische Chemie,
Eidgenössische Hochschule
Universitätsstr. 16, CH-8092 Zürich (Switzerland)

[**] Part of the planned dissertation by *B. Seuring*, Universität Giessen. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Dr. *H. Gerlach* (ETH Zürich) and Dr. *J. Fuska* (University of Bratislava) for samples.

At low temperature the difunctional electrophile *(4)* reacts only at the "bromine end" with Li-dithiane; subsequent opening of the epoxide with methyldithiane anion and formylation at the initially introduced dithiane center affords the aldehyde *(6)*, which is present almost exclusively as the cyclic semiacetal. The subsequent steps are once again a Wittig reaction with methoxycarbonylmethylenephosphorane and hydrolysis of the resulting ester to the acid *(2c)*, which crystallizes after extractive purification.

Owing to the high yields of all steps and the high stability of the dithiane group towards acids, bases, and strong nucleophiles no workup and/or purification is needed in either synthesis up to the stage where the crystalline 7-hydroxy acid *(1c)* or *(2c)* is obtained (cf. Table 1)[6] and—as can be seen from Schemes 1 and 2—large amounts can be readily synthesized. This demonstrates the advantage of employing 1,3-dithianes for the C—C coupling and nucleophilic acylation, particularly in multistep syntheses.

The only method we have so far used successfully for dimerizing cyclization of *(1c)* and *(2c)* to the dithiane derivatives *(1b)* and *(2b)* of the desired molecules is the azodicarboxylate/triphenylphosphane method[7] [10^{-2} M, toluene, 2d, −25 to +20°C; 60% *(1b)* and 25% *(2b)*, respectively, after preparative thin-layer chromatography, cf. Table 1]. In this reaction—as in intermolecular esterifications[8a]—inversion occurs at the carbinol C-atom[8b]. Hence the "dilides" *(1b)* and *(2b)* and also the samples of (−)-pyrenophorin *(1a)* and (+)-vermiculin *(2a)* (70 and 60% resp.) obtained from them by hydrolysis of the dithiane groups with HgO/$BF_3 \cdot Et_2O$[9] must be (*R*,*R*) configurated and not (*S*) configurated like the precursor. This means that the natural product pyrenophorin has the (*R*,*R*) configuration and natural vermiculin the (*S*,*S*) configuration.

Table 1. Physical and/or spectroscopic data of compounds *(1)* and *(2)*.

(1a)	m.p. 175°C [a]; $[\alpha]_D = -54.5°$ (c=0.48, acetone) [a, b]
(1b)	$[\alpha]_D = -109°$ (c=0.36, $CHCl_3$); ^{13}C-NMR ($CDCl_3$): δ=164.6, 149.1, 124.5, 68.9, 52.9, 34.6, 28.0, 27.4, 26.7, 25.0, 17.5 ppm [b]
(1c)	m.p. 83 to 84°C; $[\alpha]_D = +6.1°$ (c=1, $CHCl_3$)
(2a)	m.p. 174°C (dec.); $[\alpha]_D = +11.7°$ (c=0.3, $CHCl_3$) [c, d]
(2b)	m.p. 207 to 208°C (dec.); $[\alpha]_D = +66.8°$ (c=1.5, $CDCl_3$)
(2c)	$[\alpha]_D = +25.8°$ (c=0.9, $CHCl_3$); ^{13}C-NMR ($CDCl_3$): δ=170.9, 152.3, 122.8, 68.7, 53.3, 47.5, 37.4, 31.8, 28.5, 27.2, 26.8, 26.6, 25.0, 24.6 ppm

[a] Ref. [1]: m.p. 175°C; $[\alpha]_D = -50°$.
[b] ^{1}H-NMR identical with that quoted in Ref. [3a].
[c] Ref. [2]: m.p. 175—177°C (dec.); $[\alpha]_D = -12.5°$ (c=0.2, $CHCl_3$); the ^{13}C-NMR spectrum is identical with that of an authentic sample of the natural product.
[d] ^{1}H-NMR identical with that quoted in Ref. [3b].

Received: January 31, 1977 [Z 663 IE]
German version: Angew. Chem. 89, 270 (1977)

CAS Registry numbers:
(1a), 5739-85-5; *(1b)*, 61989-64-8; *(1c)*, 61847-04-9; (−)-*(2a)*, 37244-00-1; (+)-*(2a)*, 61847-02-7; *(2b)*, 61847-03-8; *(2c)*, 61847-05-0; *(3)*, 61847-06-1; *(4)*, 61847-07-2; *(5)*, 61847-08-3; *(6)*, 61847-09-4; 2-Li-1,3-dithiane, 36049-90-8; $PH_3P{=}CH{-}CO_2Me$, 15677-02-8

[1] *S. Nozoe, K. Hirai, K. Tsuda, K. Ishibashi, M. Shirasaka, J. F. Grove*, Tetrahedron Lett. *1965*, 4675; *J. F. Grove*, J. Chem. Soc. *C 1971*, 2261, and literature cited therein.
[2] *J. Fuska et al.*, J. Antibiot. *25*, 208 (1972); *27*, 141 (1974); Antibiotiki (Moscow) *19*, 890 (1974); *R. K. Boeckmann, jr., J. Fayos, J. Clardy*, J. Am. Chem. Soc. *96*, 5954 (1974).
[3] a) *E. W. Colvin, T. A. Purcell, R. A. Raphael*, J. Chem. Soc. Perkin I, *1976*, 1718; J. C. S. Chem. Commun. *1972*, 1031; *H. Gerlach*, private communication; b) *E. J. Corey, K. C. Nicolaou, T. Toru*, J. Am. Chem. Soc. *97*, 2287 (1975). Note added in proof: *dl*-vermiculin has just been synthesized from "Hagemann" ester: *Y. Fukuyama, C. L. Kirkemo, J. D. White*, J. Am. Chem. Soc. *99*, 646 (1977).
[4] *B. Seuring, D. Seebach*, Helv. Chim. Acta, in press.
[5] *D. Seebach, H.-O. Kalinowski*, Nachr. Chem. Tech. *24*, 415 (1976).
[6] All intermediate products have also been isolated and fully characterized.
[7] *T. Kurihara, Y. Nakajima, O. Mitsunobu*, Tetrahedron Lett. *1976*, 2455.
[8] a) *H. Loibner, E. Zbiral*, Helv. Chim. Acta *59*, 2100 (1976), and literature cited therein; exception: *G. Grynkiewicz*, Rocz. Chem. *50*, 1449 (1976).—b) We have proven on model systems [methyl esters of *(1c)* and *(2c)*/cinnamic acid and (+)-(*E*,*R*)-12-hydroxy-9-octadecenic acid. cf. *H. Gerlach, K. Oertle, A. Thalman*, Helv. Chim. Acta *59*, 755 (1976)] that our intermediates react intermolecularly (corresponding to step 1 of the dimerizing cyclization) and a chiral hydroxy acid intramolecularly (corresponding to step 2 of the dimerizing cyclization) with inversion at the carbinol center.
[9] *E. Vedejs, P. L. Fuchs*, J. Org. Chem. *36*, 366 (1971).

$[Zn_2Cr(OH)_6]X \cdot 2H_2O$, New Layer Compounds Capable of Anion Exchange and Intracrystalline Swelling

By *Hanns-Peter Boehm, Johann Steinle*, and *Carmen Vieweger*[*]

Layer structures with negatively charged layers and intercalated exchangeable cations are well known. They frequently exhibit unidimensional intracrystalline swelling[1]. In contrast, apart from graphite salts, compounds having cationic layers and exchangeable anions have rarely been described[2]. The inadequate interpretation of the observation[3] that zinc oxide turns pink on spraying with an alcoholic solution of chromium(III) nitrate prompted us to study the reaction of ZnO with solutions of Cr^{III} salts. In so doing we obtained a new layer compound in which exchangeable anions are intercalated between brucite-type layers.

ZnO reacts with aqueous solutions of hexaaquachromium(III) or tetraaquadichlorochromium(III) ions at room temperature within several days, and at 60 to 80°C within a few hours, to form a voluminous gray- to pink-violet precipitate which gave a characteristic X-ray powder photograph. Using an excess of chromium, the reflections due to ZnO can no longer be recognized after completion of the reaction.

Analysis of the products dried at 110°C indicated the empirical formula $Zn_2CrO_3X \cdot 5H_2O$ ($X = Cl^-$, NO_3^-, or $^1/_2 SO_4^{2-}$). Since the occurrence of O^{2-} is unlikely under the reaction conditions, we assign the new compounds the formula $[Zn_2Cr(OH)_6]^+X^- \cdot 2H_2O$ by analogy with $[Ca_2Al(OH)_6]^+X^- \cdot 2H_2O$[2a]. Their gray-violet color is compatible with an octahedral arrangement of OH^- ions surrounding the Cr^{3+} ions in brucite-type layers. The coordination number of 7 found for the Ca ions in $[Ca_2Al(OH)_6]^+$ compounds[4] appears unlikely for the smaller Zn ions, which presumably occupy octahedral or tetrahedral sites in the hydroxide double layers.

The reflections observed in the relatively simple X-ray powder diagram (Cu-Kα radiation) could be interpreted as (00*l*) reflections and broadened two-dimensional (*hk*) reflections of a turbostratically perturbed layer lattice. The basal spacings (in the *c* direction) depend upon the kind of anion intercalated (cf. Table 1). The (*hk*) reflections were indexed as (11), (20), (30), and (22) of a two-dimensional lattice of hexagonal symmetry with $a_0 = 0.536$ nm. This corresponds to the diameters of two OH^- in a dense triangular packing. The equivalent area per unit layer charge of 0.249 nm^2 is very similar to that in micas. Some samples exhibited weak

[*] Prof. Dr. H. P. Boehm, C. Vieweger
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)
Dr. J. Steinle
Present address: AEG-Telefunken AG, D-4788 Warstein 2 (Germany)

and diffuse (*hkl*) reflections. The densities determined by pyknometry indicate the presence of one formula unit per unit cell, which contains in the *c* direction two hydroxide layers and one anion layer. The X-ray densities are only slightly lower than those calculated from *Biltz* spatial increments[5] for the components. All attempts to age the finely divided precipitates (specific surface area 5 to 22 m^2/g) to give better crystallized substances were unsuccessful.

The chloride initially dried at room temperature had a slightly greater basal spacing (0.776 nm) which fell irreversibly at 110°C to the value given in Table 1 (weight loss 11.49% corresponding to 2.27 H_2O per formula unit). No change in basal separation was observed on drying of the nitrate, although it irreversibly lost 4.32 H_2O per formula unit at 110°C.

The X^- anions of the compounds are exchangeable. Thus after the action of 2 M $NaNO_3$ solution on the chloride for 1 h the Cl^- could be detected quantitatively in the solution (after 15 min at 60°C); the layer separation of the reaction product corresponds to that of the directly synthesized nitrate. Complete exchange was also accomplished with solutions of NaF, $NaHCO_3$, and Na_2SO_4; with $NaClO_4$ only 50% of the anions were exchanged in the first step. Likewise, only 90% exchange took place in the first step between the nitrate and 1 M NaCl solution, only 52% with bromide solution, and only 41% with iodide. Especially large basal separations were measured after treatment with sodium alkyl sulfates (Table 1). Deviations in the last decimal place of the given values were observed on repeating the experiments. This phenomenon, which may be due to additional inclusion of water or to irregularities in the conformation of the alkyl chains[6], was also observed with *n*-alkylammonium layer silicates[7].

Table 1. Basal spacing in compounds $[Zn_2Cr(OH)_6]^+X^- \cdot 2H_2O$.

X^-	*d* [nm]	X^-	*d* [nm]
F^-	0.751	*n*-$C_8H_{17}SO_4^-$	2.11$_1$
Cl^-	0.773	*n*-$C_{10}H_{21}SO_4^-$	2.37$_7$
Br^-	0.785	*n*-$C_{12}H_{25}SO_4^-$	2.615
I^-	0.840	*n*-$C_{14}H_{29}SO_4^-$	2.80
N_3^-	0.762	*n*-$C_{16}H_{33}SO_4^-$	2.89
NO_3^-	0.888	*n*-$C_{18}H_{37}SO_4^-$	3.26
ClO_4^-	1.180		
$^1/_2\,SO_4^{2-}$	1.180		
$^1/_2\,HPO_4^{2-}$	1.090		

The compounds having inorganic anions in the intercalated layers do not display unidimensional swelling in water or other polar solvents. In contrast, we found the compounds with X^- = alkyl sulfate to undergo unidimensional swelling under *n*-alkyl alcohols or *n*-alkylamines (Table 2). This behavior is analogous to that of alkylammonium layer silicates[1, 7]; the basal spacing after inclusion of dodecyl sulfate and dodecanol corresponds very closely to the value calculated for alkyl double layers (4.13 nm).

Experiments designed to prepare similar layer compounds of the same type in which Zn^{2+} and Cr^{3+} are replaced by other di- and trivalent cations have so far only been successful in the CuO/Cr^{III} salt system.

Table 2. Swelling of $[Zn_2Cr(OH)_6]^+C_{12}H_{25}SO_4^- \cdot nH_2O$ in *n*-alkanols and *n*-dodecylamine.

Swelling agent	*d* [nm]	Swelling agent	*d* [nm]
C_3H_7OH	2.83	$C_{12}H_{25}OH$	4.11
C_4H_9OH	2.92	$C_{14}H_{29}OH$	4.24
$C_6H_{13}OH$	3.08	$C_{16}H_{33}OH$	4.49
$C_8H_{17}OH$	3.37	$C_{12}H_{25}NH_2$	4.17
$C_{10}H_{21}OH$	3.82		

Procedures:

ZnO (2 to 3 g) is stirred with a little water to give a smooth suspension to which is added a *ca.* 1 M solution of a chromium salt (10 ml; pH ≈ 4). The decolorized solution is replaced by fresh solution after 1 d. After repeating the procedure twice the solution is no longer decolorized even after 14 d. The isolated precipitate is washed with water and dried at 110°C.

In order to perform ion exchange, the Cl^- or NO_3^--containing substance (250 mg) is shaken with a 1 N, 2 N, or 5 N solution of alkali metal salt (10 ml). After a given time halide is determined by potentiometric titration of aliquot portions of the solution. The exchange solution is renewed if necessary.

Received: January 19, 1977 [Z 654 IE]
German version: Angew. Chem. *89*, 259 (1977)

CAS Registry numbers:
$[Zn_2Cr(OH)_6]^+F^-$, 61950-97-8; $[Zn_2Cr(OH)_6]^+Cl^-$, 61950-96-7; $[Zn_2Cr(OH)_6]^+Br^-$, 61950-95-6; $[Zn_2Cr(OH)_6]^+I^-$, 61950-98-9; $[Zn_2Cr(OH)_6]^+N_3^-$, 61900-05-8; $[Zn_2Cr(OH)_6]^+NO_3^-$, 61900-06-9; $[Zn_2Cr(OH)_6]^+ClO_4^-$, 61900-07-0; $[Zn_2Cr(OH)_6]^+ \cdot {}^1/_2SO_4^{2-}$, 61900-08-1; $[Zn_2Cr(OH)_6]^+ \cdot {}^1/_2HPO_4^{2-}$, 61900-09-2; $[Zn_2Cr(OH)_6]^+$*n*-$C_8H_{17}SO_4^-$, 61900-10-5; $[Zn_2Cr(OH)_6]^+$*n*-$C_{10}H_{21}SO_4^-$, 61900-11-6; $[Zn_2Cr(OH)_6]^+$*n*-$C_{12}H_{25}SO_4^-$, 61900-12-7; $[Zn_2Cr(OH)_6]^+$*n*-$C_{14}H_{29}SO_4^-$, 61900-13-8; $[Zn_2Cr(OH)_6]^+$*n*-$C_{16}H_{33}SO_4^-$, 61900-14-9; $[Zn_2Cr(OH)_6]^+$*n*-$C_{18}H_{37}SO_4^-$, 61900-15-0

[1] *Ar. Weiss*, Angew. Chem. *75*, 113 (1963); Angew. Chem. Int. Ed. Engl. *2*, 134 (1963); Clays Clay Miner. *10*, 191 (1963).
[2] a) *W. Feitknecht, H. W. Buser*, Helv. Chim. Acta *34*, 128 (1951); b) *R. Allmann*, Chimia *24*, 99 (1970).
[3] *S. R. Morrison, J.-P. Bonelle*, J. Catal. *25*, 416 (1972).
[4] *R. Allmann*, Neues Jahrb. Mineral., Monatsh. *1968*, 140.
[5] *W. Biltz:* Raumchemie der festen Stoffe. L. Voss, Leipzig 1934.
[6] *G. Lagaly, Ar. Weiss*, Angew. Chem. *83*, 580 (1971); Angew. Chem. Int. Ed. Engl. *10*, 558 (1971); *G. Lagaly, S. Fitz, Ar. Weiss*, Clays Clay Miner. *23*, 45 (1975).
[7] *Ar. Weiss, G. Lagaly*, Kolloid-Z. Z. Polym. *216/217*, 356 (1967); *G. Lagaly*, Angew. Chem. *88*, 628 (1976); Angew. Chem. Int. Ed. Engl. *15*, 575 (1976).

Synthesis of Substituted *p*-Aminophenols from *p*-Phenylenediamines[**]

By *Ulrich Nickel* and *Klaus Kemnitz*[*]

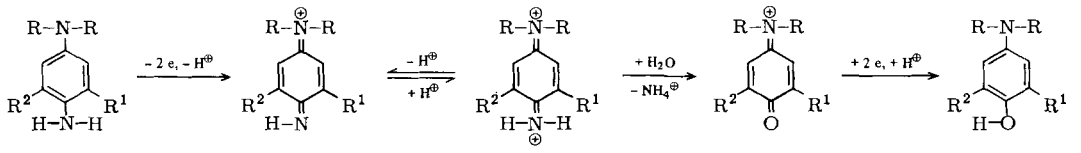
In connection with studies on the mechanism of oxidation of *p*-phenylenediamine derivatives[1] we have also investigated the deamination of the oxidation products. It was found that the unsubstituted imino group is cleaved from oxidation products of type *(2)* at pH ≤ 6 with formation of substituted *p*-quinonemonoimines *(3)*[2].

This reaction offers a facile entry to the often difficultly accessible *N*-substituted *p*-aminophenols from the corresponding derivatives of the *p*-phenylenediamine *(1)*. These must be oxidized rapidly and quantitatively to the quinonediimines *(2)* and then, after a time interval at pH ≤ 2 which is sufficient for complete conversion of the quinonediimine into the quinonemonoimine *(3)*, reduced once again.

In order to avoid side reactions the oxidizing agent must be added before the oxidation, the reducing agent before the reduction. After reduction of *(3)* the pH value is increased

[*] Dr. U. Nickel, Dipl.-Chem. K. Kemnitz
Institut für Physikalische und Theoretische Chemie der Universität Erlangen-Nürnberg
Egerlandstrasse 3, D-8520 Erlangen (Germany)

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



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

(4a): R = C_2H_5, R^1 = R^2 = H
(4b): R = C_2H_5, R^1 = CH_3, R^2 = H
(4c): R = CH_3, R^1 = R^2 = H
(4d): R = R^1 = R^2 = CH_3

for formation of the free *p*-aminophenol *(4)*, which is extracted from the aqueous phase with a suitable solvent.

So far the *p*-aminophenols *(4a)* to *(4d)* have been prepared (as hydrochlorides) in yields of at least 80% and identified on the basis of their UV, NMR, and IR spectra.

$Ce(SO_4)_2$ and iodine are suitable oxidizing agents, and $SnCl_2$ or iodide can be used as reducing agent; so there are several variants for the preparation.

Experimental:

1. *(4a)*, *(4b)*, *(4c)*, *(4d)*: An aqueous solution of *(1)* (10 mmol)[3] is added with vigorous stirring to a solution of $Ce(SO_4)_2$ (22 mmol) in approximately 1 N H_2SO_4 and the mixture poured after *ca.* 5 seconds into an acidified solution of $SnCl_2$ (12 mmol). Cerium and zinc are precipitated as the hydroxides with NaOH, the pH of the filtrate adjusted to about 8 and the resulting solution extracted three times with *n*-amyl alcohol or diethyl ether. The extract is dried over Na_2SO_4 and then evaporated down. The product *(4a)* can be precipitated as the hydrochloride. A slight red coloration of the solution after addition of alkali is due to partial oxidation of the *p*-aminophenol by atmospheric oxygen; this can be avoided by working under nitrogen.
2. *(4a)*, *(4c)*: Oxidation is carried out as described under 1, but after *ca.* 5 seconds the reaction mixture added to an aqueous solution of about 60 mmol KI. The iodine formed is reduced with thiosulfate, the pH adjusted to 8 and the solution then treated as described under 1. This procedure involves one more working step, but less hydroxide is precipitated. Part of the iodine can be recovered by extraction with CCl_4 before the reduction with thiosulfate.
3. *(4d)*, *(4c)*: A particularly elegant procedure is oxidation with iodine[1, 4] and subsequent reduction with the iodide formed, but this is only applicable in dilute solutions: A solution of *(1)* (2 mmol) in semi-concentrated phosphate buffer (about 100 ml) is oxidized with 2.1 to 2.2 mmol KI_3 in H_2O (about 100 ml). The solution is poured after about 30 seconds into 50 ml *ca.* 1 N HCl, whereupon the quinonemonoimine *(3)* is reduced by the iodide formed during the oxidation to the *p*-aminophenol, the iodine being recovered. The solution is then worked up as described under 2.
4. *(4b)*, *(4d)*: If the *p*-phenylenediamine derivatives *(1)* must be first prepared *via* the corresponding *p*-nitroso compounds they need not be isolated. All that is necessary is to reduce the nitroso compound, *e.g.* with hydrazine hydrochloride in the presence of Raney nickel, pour the reaction solution after separation from solid phase directly into the acidic solution of the oxidizing agent, and then continue as in 1.

Received: January 25, 1977 [Z 670 IE]
revised: February 10, 1977
German version: Angew. Chem. 89, 273 (1977)

CAS Registry numbers:
(1a), 93-05-0; *(1b)*, 148-71-0; *(1c)* 99-98-9; *(1d)*, 27746-08-3; *(4a)*, 27822-92-0; *(4b)*, 27822-93-1; *(4c)*, 5882-48-4; *(4d)*, 27982-26-9

[1] *M. Borchardt, W. Jaenicke, G. Loos, U. Nickel*, unpublished work; *M. Borchardt*, Dissertation, Universität Erlangen 1976.
[2] *U. Nickel, K. Kemnitz, W. Jaenicke*, unpublished work; *J. F. Corbett*, J. Chem. Soc. *B 1969*, 213.
[3] *A. Tockstein, V. Dlask*, Collect. Czech. Chem. Commun. *36*, 1090 (1971); *M. Schellenberg, H. Mollet*, Helv. Chim. Acta *54*, 2431 (1971).
[4] *U. Nickel, G. Loos, W. Jaenicke*, Ber. Bunsenges. Phys. Chem. *78*, 1271 (1974).

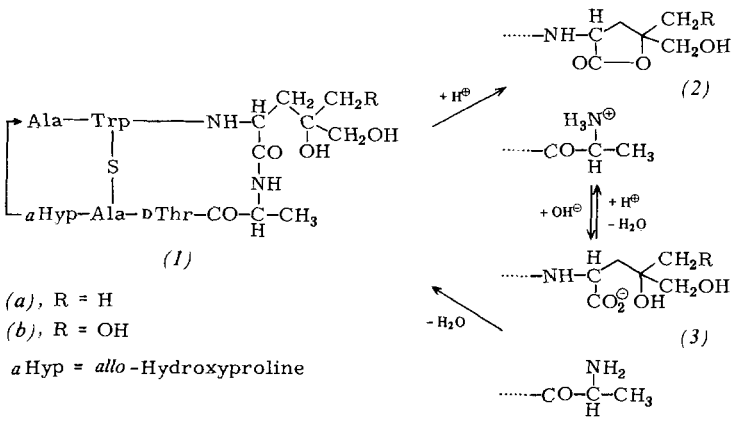
Resynthesis of Phalloidin and Phallisin from the Seco-Compounds[1]

By *Eisuke Munekata, Heinz Faulstich*, and *Theodor Wieland*[*]

The peptide bond between the dihydroxy amino acid and alanine of phalloidin *(1a)* and phallisin *(1b)*, two constituents of the green deathcup toadstool *Amanita phalloides*[2], can be cleaved by relatively mild proton catalysis owing to the neighboring group effect of the γ-hydroxyl group. There result the nontoxic seco-compounds which appear as lactones *(2a)* and *(2b)*, respectively. They are transformed into the anions *(3a)* and *(3b)* by hydroxide ions. We regard the resynthesis of the toxins *(1a)* and *(1b)* from *(3a)* and *(3b)*, respectively, as a key reaction since (i) it could represent the final step of the total synthesis of the natural phallotoxins and (ii) it would provide an entry to analogs if the N-terminal alanine of *(2a)* were removed in an Edman degradation step and replaced by any desired amino acid. Internal peptide linkage is unsuccessful with slowly acting methods (azide-, carbodiimide-, and imidazolide method, as well as activated ester methods) because they regenerate the lactone ring. Nor did we succeed in producing quantities of *(1a)* detectable by paper chromatography from a sample of *(3a)* obtained on an earlier occasion, even upon use of the rapidly acting method of mixed anhydrides which proved successful in the case of secoketophalloidin[3].

We have now found a particularly mild method of executing the hydrolytic cleavage of *(2a)* and *(2b)* and obtaining the anions *(3a)* and *(3b)* in extremely pure form. To this end we ran a solution of *(2a)* or *(2b)* in 4×10^{-3} N aqueous NH_4OH (in which hydrolysis proceeds very slowly) through a column packed with Sephadex LH-20. Compound *(3a)* or *(3b)* appearing as a sharp fraction could be cyclized by the method of mixed anhydrides (cf. [4]). *(1a)* or *(1b)* could be isolated in about 10% yield from the reaction mixture.

[*] Dr. E. Munekata [**], Priv.-Doz. Dr. H. Faulstich, Prof. Dr. Th. Wieland [†]
Max-Planck-Institut für medizinische Forschung,
Abteilung Naturstoff-Chemie
Jahnstrasse 29, D-6900 Heidelberg (Germany)
[†] To whom correspondence should be addressed.
[**] Alexander-von-Humboldt Fellow (1974–1976).



(1)

(a), R = H
(b), R = OH

aHyp = *allo*-Hydroxyproline

(2)

(3)

Both the resynthesized toxins were identical with the starting compounds *(1a)* and *(1b)* in all the properties examined: CD spectra as in [5], R_F [TLC on Merck 60 F_{254} silica gel plates in chloroform/methanol/water (65:25:4 v/v)]: *(1a)* = 0.31, *(1b)* = 0.24, UV difference spectra in the presence of actin as in [6], toxicity in white mouse (LD_{50}) of *(1a)*: 2 mg/kg, and of *(1b)* 2.5 mg/mg[2].

Procedures:

Production of *(2a)* and *(3a)* from *(1a)*: A solution of *(1a)* (1.0 g, 1.27 mmol) in trifluoroacetic acid (250 ml) + water (250 ml) is stirred for 15 h at 20 °C and then evaporated down *in vacuo*. The residue is chromatographed on Sephadex G-15 (column 5.5 × 184 cm) with 0.1 N acetic acid. Of the 27.0 ml fractions, Nos. 118—190 afford 780 mg (78 %) of the trifluoroacetate of *(2a)*. No *(1a)* could be detected with cinnamaldehyde-HCl in the TL chromatogram of a sample applied in concentrated form. Conversion into *(3a)* was accomplished by passing *(2a)*-trifluoroacetate (500 mg, 0.63 mmol) dissolved in 0.004 N ammonium hydroxide through Sephadex LH-20 (column 2.2 × 245 cm). On elution with the same solvent *(3a)* appears in Nos. 33—80 of the 6.5 ml fractions; evaporation *in vacuo* affords *(3a)* (418 mg, 82 %) which is homogeneous on electrophoresis.

Cyclization of *(3a)*: To a stirred solution of *(3a)* (390 mg, 0.48 mmol) in dimethylformamide (DMF) (51 ml) + tetrahydrofuran (THF) (38 ml) at −10 °C are added a 1 % solution of trifluoroacetic acid in THF (3.51 ml) and 5 min later a 1 % solution of isobutyloxycarbonyl chloride in THF (6.63 ml). After 25 min the solution is rapidly poured into a mixture of DMF (194 ml) and a 1 % solution of *N*-methylmorpholine in THF (13.3 ml) cooled to 0 °C. The mixture is stirred for 2 h at 0 °C and for 12 h at 20 °C. After evaporation *in vacuo* the residue is chromatographed with 0.2 % NH_4OH on Sephadex LH-20 (column 2.2 × 245 cm) with collection of 6.0 ml fractions. The last third of the first UV absorbing peak (Nos. 121—170) is chromatographed once more on Sephadex LH-20 (column 1.8 × 147 cm) in the same solvent. Compound *(1a)* (33 mg = 8.7 %) appears in Nos. 38—54 of the 7.3 ml fractions; it is identical with the original sample of *(1a)* in each of the above-mentioned properties.—Both procedures can be applied to the phallisin series.

Received: February 15, 1977 [Z 677 IE]
German version: Angew. Chem. *89*, 274 (1977)

CAS Registry numbers:
(1a), 17466-45-4; *(1b)*, 19774-69-7; *(2a)*, 62015-97-8; *(2b)*, 62015-99-0; *(3a)*, 35222-17-4; *(3b)*, 62046-08-6

[1] Constituents of the Green Deathcup Toodstool, Part 52.—Part 51: *A. Gauhe, Th. Wieland*, Justus Liebigs Ann. Chem. *1977*, in press.

[2] *Th. Wieland*, Science *159*, 946 (1968).

[3] *Th. Wieland, I. Sangl*, Justus Liebigs Ann. Chem. *671*, 160 (1964).

[4] *F. Fahrenholz, H. Faulstich, Th. Wieland*, Justus Liebigs Ann. Chem. *743*, 83 (1971); *H. Faulstich, E. Nebelin, Th. Wieland, ibid. 1973*, 50; *H. Heber, H. Faulstich, Th. Wieland*, Int. J. Pept. Protein Res. *6*, 381 (1974).

[5] *H. Faulstich, Th. Wieland*, Europ. J. Biochem. *22*, 79 (1971).

[6] *Th. Wieland, J. X. de Vries, A. Schäfer, H. Faulstich*, FEBS-Lett. *54*, 73 (1975).

Dimers of Ketenylidene- and *N*-Phenylketeniminylidene-triphenylphosphorane

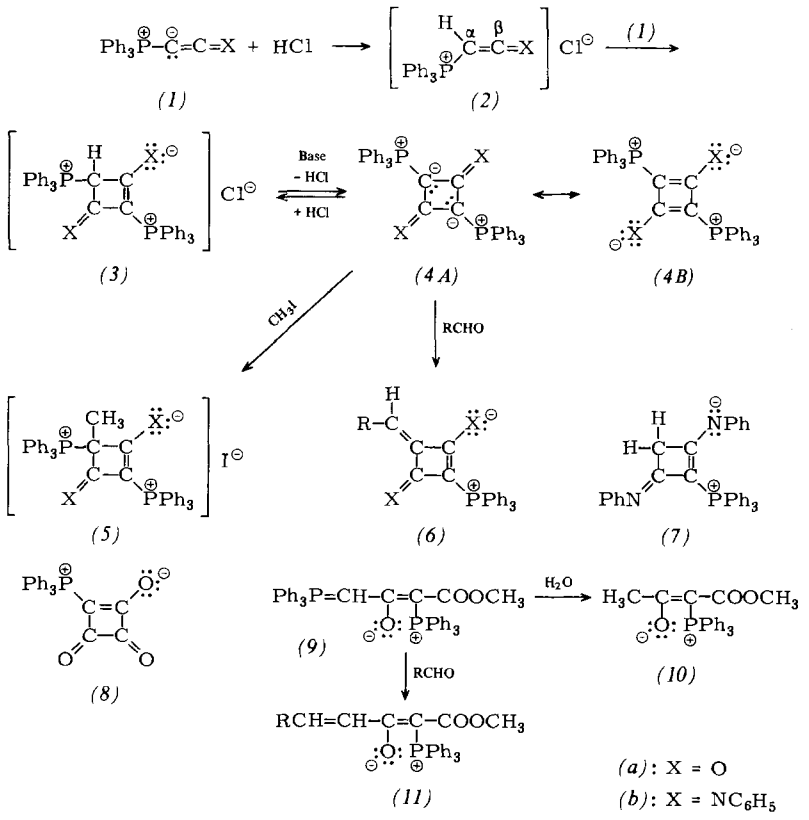
By *Hans Jürgen Bestmann, Günter Schmid, Dieter Sandmeier*, and *Lothar Kisielowski*[*]

Ketenylidenetriphenylphosphorane *(1a)* and the *N*-phenylketeniminylidenetriphenylphosphorane *(1b)* are monomeric[1], strongly nucleophilic ketene derivatives that do not dimerize. Their dimers *(4)*, which can be described by the resonance formulas *(4A)* ↔ *(4B)*, are therefore of interest, since their mesomeric form *(4B)* represents yet another type of "push-pull" cyclobutadiene[2]. We have been able to synthesize the compounds *(4)* *via* the route shown in the following reaction scheme.

Slow addition of ½ equivalent of HCl to a solution of the heterocumulene ylides *(1a)* or *(1b)* leads *via* protonation at the ylidic C-atom to their transformation into the phosphonium salts *(2a)* or *(2b)*, which are now "real" ketenes or ketenimines having ambident dipolar character, *i.e.* nucleophilic at C_α and electrophilic at C_β[3]. They undergo spontaneous cycloaddition with non-protonated *(1)* to give the 1,3-cyclobutanedione derivatives *(3a)* and *(3b)*, respectively[4]. *(3a)*: m.p. 270 °C (sinters); ^{1}H-NMR[5] ($CDCl_3$): τ = 3.85 (d, J_{PH} = 8 Hz, $P^\oplus$−CH); ^{31}P-NMR[5] ($CDCl_3$): δ = −18.95 (d, $P^\oplus$−CH), +1.36 ppm (d, $P^\oplus$−C<, J_{pp} = 5.72 Hz); IR: 1760, 1645 cm^{-1} (CO); yield 96 %. *(3b)*: m.p. 236 to 238 °C; ^{31}P-NMR[5] (d_6-DMSO): δ = −22.04 (d, $P^\oplus$−CH, J_{pp} = 5 Hz), +4.08 ppm (broad s, $P^\oplus$−C<); IR: 1608, 1572 cm^{-1} (C=N); yield 82 %.

Reaction of the phosphonium salts *(3)* with bases, particularly sodium bis(trimethylsilyl)amide[6], leads to the bisylides *(4)*, which can be regarded as dimers of *(1)*. Evidence of participation of the cyclobutadiene resonance formula *(4B)* is afforded by the position of the CO frequencies in the IR spectrum of *(4a)* at 1650 and 1610 cm^{-1} and that of the C=N bands of *(4b)* at 1563 and 1527 cm^{-1}.

[*] Prof. Dr. H. J. Bestmann, Dr. G. Schmid, Dipl.-Chem. D. Sandmeier, Dipl.-Chem. L. Kisielowski
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestr. 42, D-8520 Erlangen (Germany)



(4a): yellow crystalline powder, m.p. 278 to 280 °C (charring) ^{31}P-NMR[5] ($CDCl_3$): $\delta = +9.48$ ppm (s); yield 83 %. *(4b)*: yellow crystalline powder, m.p. 178 °C (dec.); MS: $m/e = 754$ (M^+), 492 [$M^+ - 262$ (Ph_3P)]; yield 63 %.

The following, in part preparatively useful reactions confirm the structure of the compounds *(4)*: Reaction with HCl regenerates the phosphonium salts *(3)*. Reaction of *(4a)* and *(4b)* with methyl iodide affords the known phosphonium salts *(5a)* and *(5b)*[7a]. On reaction of *(4a)* and *(4b)* with *p*-nitrobenzaldehyde the phosphoranes *(6a)*[7a] and *(6b)*[7b] are formed (R = *p*-$NO_2C_6H_4$). Hydrolysis of *(4b)*[8a] in aqueous methanol affords the monoylide *(7)* [m.p. 221 °C, ^{1}H-NMR (d_5-pyridine): $\tau = 8.18$ (s, CH_2); MS: $m/e = 494$ (M^+); yield 52 %]. Oxidation of *(4a)* with the adduct of ozone and triphenylphosphite[8b] leads to the cyclobutanetrione derivative *(8)* [m.p. 258 °C (dec.); ^{31}P-NMR[5] ($CDCl_3$): $\delta = -7.60$ ppm (s), IR: 1769, 1651, 1629 cm^{-1} (CO)], which reacts with benzylidenetriphenylphosphorane to give *(6)*, R = C_6H_5, [m.p. 192 °C; ^{31}P-NMR[5] ($CDCl_3$): $\delta = -0.43$ ppm]. *(4a)* reacts with methanol with ring opening to give the bisylide *(9)*[9] [m.p. 247 °C; yield 79 %], whose two ylide functions differ in reactivity. *(9)* is hydrolyzed by water to the acetylmethoxycarbonylmethylenetriphenylphosphorane *(10)*[10] and reacts with *p*-nitrobenzaldehyde to give the phosphorane *(11)* (R = *p*-$NO_2C_6H_4$) [m.p. 205 °C; yield 69 %].

Received: February 3, 1977 [Z 676 IE]
German version: Angew. Chem. *89*, 275 (1977)

CAS Registry numbers:
(1a), 15596-07-3; *(1b)*, 21385-80-8; *(2a)*, 62126-70-9; *(2b)*, 62085-93-2; *(3a)*, 62085-94-3; *(3b)*, 62085-95-4; *(4a)*, 62085-96-5; *(4b)*, 62085-97-6; *(7)*, 62085-98-7; *(8)*, 62085-99-8; *(9)*, 4895-59-4; *(11)*, 62086-00-4

[1] Crystal structure of *(1a)*: *J. J. Daly, P. Wheatley*, J. Chem. Soc. *A 1966*, 1703; of *(1b)*: *H. Burzlaff, E. Wilhelm, H. J. Bestmann*, Chem. Ber., in press.

[2] *R. Gompper, G. Seybold*, Angew. Chem. *80*, 804 (1968); Angew. Chem. Int. Ed. Engl. *7*, 824 (1968); *R. Gompper, S. Mensch, G. Seybold, ibid. 87*, 711 (1975) and *14*, 704 (1975), resp.; *R. Gompper, J. Kroner, G. Seybold, H.-U. Wagner*, Tetrahedron *32*, 629 (1976) and literature cited therein.

[3] Cf. *L. Ghosez, M. J. O'Donnel* in *Marchand, Lehr*: Pericyclic Reactions, Vol. II. Academic Press, New York 1977, in press.

[4] In the Scheme we have given the betaine form for compounds *(3)* and *(5)—(11)* since this is the most likely mesomeric form according to IR spectroscopic findings.

[5] 100 MHz, PFT-Technique, H_3PO_4 as external standard.

[6] Cf. *H. J. Bestmann, W. Stransky, O. Vostrowsky*, Chem. Ber. *109*, 1694 (1976).

[7] a) *G. H. Birum, C. N. Matthews*, J. Am. Chem. Soc. *90*, 3842 (1968); *H. J. Bestmann, R. Besold, D. Sandmeier*, Tetrahedron Lett. *1975*, 2293; b) *H. J. Bestmann, G. Schmid*, Angew. Chem. *86*, 479 (1974); Angew. Chem. Int. Ed. Engl. *13*, 473 (1974).

[8] a) For hydrolysis of phosphorylidenes cf. *H. J. Bestmann*, Angew. Chem. *77*, 609, 651, 850 (1965); Angew. Chem. Int. Ed. Engl. *4*, 583, 645, 830 (1955); b) *H. J. Bestmann, L. Kisielowski, W. Distler, ibid. 88*, 297 (1976) and *15*, 298 (1976).

[9] *P. A. Chopard*, J. Org. Chem. *31*, 107 (1966).

[10] *G. Märkl*, Chem. Ber. *94*, 3005 (1961).

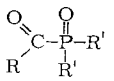
Synthesis of Acyldiarylphosphane Oxides—Key Compounds in the Oxidation of Acyldiarylphosphanes with Molecular Oxygen[**]

By *Ekkehard Lindner, Hans-Dieter Ebert, Hans Lesiecki*, and *Gottfried Vordermaier*[*]

By slow oxidation of the acylphosphane $RC(O)P(C_6H_5)_2$ with O_2 under rigorous exclusion of water we have been able to isolate for the first time the previously only postulated[1] or unsatisfactorily described[2] acyldiarylphosphane oxides *(1)*.

[*] Prof. Dr. E. Lindner, Dr. H.-D. Ebert, Dipl.-Chem. H. Lesiecki, Dipl.-Chem. G. Vordermaier
Institut für Anorganische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

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



(1a), R = CH_3, R' = C_6H_5
(1b), R = CF_3, R' = C_6H_5

In contrast to the known, relatively stable acyl-phosphonates and -dialkylphosphane oxides[2], compounds *(1)* are extremely sensitive towards nucleophiles, especially water. *(1a)* and *(1b)*, which can be stabilized by small amounts of $(CF_3CO_2)O$, are also obtained according to

$$(RCO)_2O + HP(O)R'_2 \longrightarrow \underset{(2)}{(1a, b)} + RCO_2H$$

as colorless oils that decompose with loss of CO above 120 and 80 °C, respectively. They were characterized by elemental analysis, IR(phase: film), ^{31}P-NMR (in C_2Cl_4), and mass spectra (Table 1).

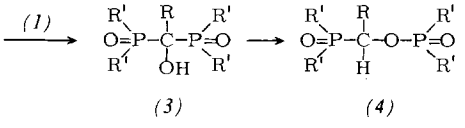
Table 1. IR [cm^{-1}], ^{31}P-NMR (rel. 85% H_3PO_4 ext.) and MS data of the acyldiphenylphosphane oxides *(1)*.

	ν(>C=O)	ν(P=O)	δ^{31}P [ppm]	*m/e* (M^+)
(1a)	1720 s	1200 vs	−21.1	244
(1b)	1781 vs	1215 vs [+ν(CF_3)]	−30.4	298

In comparison with the acyldiarylphosphanes $RC(O)PR'_2$, in *(1)* ν(>C=O) is shifted by *ca.* 45 [*(a)*] and 80 cm^{-1} [*(b)*] to shorter wavelengths. In the $^{31}P\{^1H\}$-NMR spectra only one singlet occurs in each case, as in $CH_3C(O)P(C_6H_5)_2$ ($\delta = -16.6$ ppm; CCl_4); in the spectrum of $CF_3C(O)P(C_6H_5)_2$, on the other hand, a quartet occurs at $\delta = -17.6$ ppm ($J_{PCCF} = 16$ Hz).

With the isolation of the phosphane oxide *(1)* we are now able to explain completely the course of the oxidation of acyldiarylphosphanes[3] to [1-diarylphosphoryl-1-H(perfluoro)alkyl]diaryl phosphinates *(4)*:

$$RC(O)PR'_2 \xrightarrow{O_2} (1) \xrightarrow[-RCO_2H]{H_2O(D_2O,\ H_2{}^{18}O)} (2)$$



(3) *(4)*

The initially formed acylphosphane oxide *(1)* is very readily hydrolyzed to phosphane oxide *(2)* and the free acid RCO_2H. *(2)* reacts with excess *(1)* to give the alcohol *(3)*, which rearranges irreversibly into the thermodynamically more stable phosphinate *(4)*. The hydrogen atom in *(2)*, *(3)* and at the chirality center of *(4)* can be exchanged quantitatively for deuterium by employment of D_2O. It can be shown with $H_2{}^{18}O$ that the ^{18}O isotope is situated as expected in carboxylic acid after the transformation step *(1)* → *(2)*. The elimination of CO_2 and CF_3H observed earlier[4] in the oxidation of $CF_3C(O)P(C_6H_5)_2$ is due to a competing reaction, which predominates on rapid introduction of O_2 into an ethereal solution of the acylphosphane.

Experimental:

(1a,b): The reaction vessel is first treated with $(CH_3)_3SiCl$ to render its surface hydrophobic. Dry oxygen is passed into a solution of acyldiphenylphosphane (16 mmol) in diethyl ether (50 ml) until decoloration of the solution. Introduction of gas must be so regulated that the oxygen is completely absorbed. After removal of the solvent in a high vacuum *(1a,b)* remains behind in quantitative yield.

(3a,b): An ethereal solution (100 ml) of water (5 mmol D_2O or $H_2{}^{18}O$) is added to a solution of *(1a)* or *(1b)* (10 mmol) in anhydrous diethyl ether (100 ml) at room temperature. After a few minutes *(3a,b)* separates out as a colorless precipitate; this is filtered and dried in a high vacuum. Yield *ca.* 85%.

Received: February 3, 1977 [Z 668 IE]
German version: Angew. Chem. 89, 276 (1977)

CAS Registry numbers:
(1a), 27384-09-4; *(1b)*, 52101-96-9; *(2)*, 24630-80-6; *(3a)*, 18629-56-6; *(3b)*, 58052-37-7; *(4a)*, 21416-24-0; *(4b)*, 27501-29-7; $(CH_3CO)_2O$, 108-24-7; $(CF_3CO)_2O$, 407-25-0

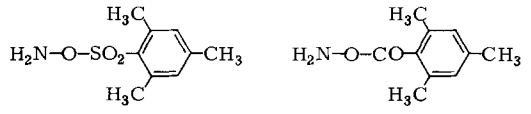
[1] *D. J. H. Smith, S. Trippett*, J. Chem. Soc. Perkin Trans. I *1975*, 963; *P. Sartori, R. H. Hochleitner, G. Hägele*, Z. Naturforsch. *31b*, 76 (1976).
[2] *A. N. Pudovik, T. M. Sudakova*, Dokl. Akad. Nauk SSSR *190*, 1121 (1970); Chem. Abstr. *72*, 132877n (1970); *E. A. Ishmaeva, M. G. Zimin, R. M. Galeeva, A. N. Pudovik*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 538; Chem. Abstr. *75*, 76925z (1971).
[3] *E. Lindner, H.-D. Ebert, H. Lesiecki*, Angew. Chem. *88*, 25 (1976); Angew. Chem. Int. Ed. Engl. *15*, 41 (1976).
[4] *E. Lindner, H.-D. Ebert*, Angew. Chem. *83*, 587 (1971); Angew. Chem. Int. Ed. Engl. *10*, 565 (1971).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

***O*-Mesitylenesulfonylhydroxylamine *(1a)* and related aminating reagents** such as *(1b)* and *(1c)* are summarized in a review by *Y. Tamura, J. Minamikawa*, and *M. Ikeda*. Reaction of *(1a)* with the —N= group of nucleophilic heteroaromatic tertiary amines leads under mild conditions to formation of salts of type *(2)* in good yield. With tertiary amines hydrazinium salts are formed, whereas secondary amines react less smoothly. Anionic N-systems such as amides, imides, and pyrroles can be *N*-aminated with *(1)*. *S*-Aminosulfonium salts, valuable intermediates for organic syntheses, are readily accessible directly from *(1a)* and sulfides. Phosphane reacts with the *O*-substituted hydroxylamines *(1)* to give *P*-aminophosphonium salts. Some carbanions are aminated by *(1a)* or *(1c)* to primary amines. On reaction with electrophiles aldehydes and acetones give the *O*-substituted oximes, which are useful for characterization and for further reactions. *(1a)* reacts with Schiff bases to give diaziridines, with acylating



(1a) (1b)

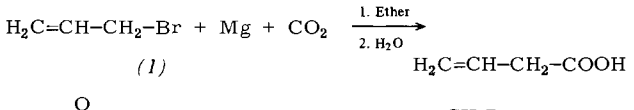


(1c) (2)

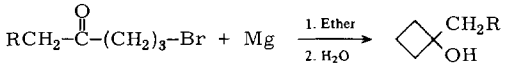
reagents to give *N*-acyl derivatives, and with organoboranes to give primary amines. [*O*-Mesitylenesulfonylhydroxylamine and Related Compounds—Powerful Aminating Reagents. Synthesis *1977*, 1—17; 107 references]

[Rd 934 IE—M]

The Barbier reaction—a one-step alternative for syntheses *via* organomagnesium compounds—is dealt with in an article by *C. Blomberg* and *F. A. Hartog*. In contrast to the two-step Grignard reaction it consists in reaction of organic halides with Mg, in some cases also with Zn, Ca, or Li, in the presence



(1) $H_2C{=}CH{-}CH_2{-}COOH$

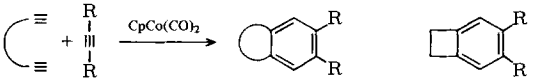


(2)

of a substrate in a suitable solvent. Sometimes the Barbier reaction is superior to the Grignard reaction, *e.g.* in the case of allyl halides *(1)*. With CO_2 in ether (preferably with addition of hydrocarbon) they form carboxylic acids, with aldehydes and ketones secondary and tertiary alcohols, respectively. Other aliphatic halides, *e.g.* (substituted) 1-bromo-4-pentanones *(2)*, 5-iodopentane nitriles and 6-iodohexane nitriles may also be employed, whereupon cyclobutanols, cyclopentanones, and cyclohexanones, respectively, are formed. Benzyl halides also undergo the Barbier reaction. Reaction of diiodomethane with carbonyl compounds in the presence of Mg-amalgam affords unsaturated hydrocarbons, *e.g.* cyclohexanone → methylenecyclohexane, *p*-chlorobenzaldehyde → *p*-chlorostyrene. Spirosilanes can be prepared by reaction of butadiene with Mg and a halosilane. [The Barbier Reaction—A One-Step Alternative for Syntheses *via* Organomagnesium Compounds. Synthesis *1977*, 18—30; 80 references]

[Rd 935 IE—M]

Transition metal-catalyzed cyclizations of acetylenes form the theme of a report by *K. P. C. Vollhardt*. Indanes and tetralins, for example, can be synthesized from 1,6-heptadiynes or 1,7-octadiynes and monoacetylenes according to the scheme *(1)* + *(2)* → *(3)*. $CpCo(CO)_2$ has proved useful as catalyst. In addition, strongly strained molecules of type *(4)*, anthraquinones, *etc.* are also accessible according to this scheme.

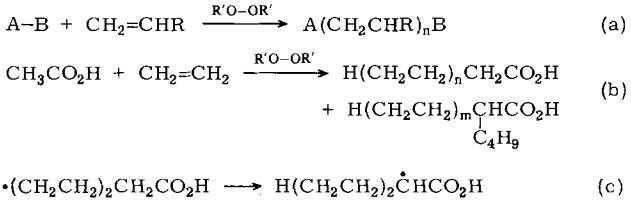


(1) (2) (3) (4)

Compound *(2)*, $R=(CH_3)_3Si$, affords trimethylsilyl-substituted products *(3)* and *(4)*, which can be converted into numerous other compounds. Polycycles and heterocycles are likewise obtainable from *(1)* and *(2)* by cooligomerization. [Transition-Metal-Catalyzed Acetylene Cyclizations in Organic Synthesis. Acc. Chem. Res. *10*, 1—8 (1977); 54 references]

[Rd 936 IE—L]

Free-radical rearrangements in telomerization forms the subject of a report by *R. Kh. Freidlina* and *A. B. Terent'ev*. Telomerization can formally be described by equation (a). However, products are also observed [see *e.g.* reaction (b)], which arise from hydrogen shifts in the growing chain [equation (c)].



(a)

(b)

(c)

α,α-Dialkylcarboxylic acids are accessible by a related one-step reaction from unbranched acids. These products are of interest in the varnish industry. [Free-Radical Rearrangements in Telomerization. Acc. Chem. Res. *10*, 9—15 (1977); 48 references]

[Rd 937 IE—F]

Recent developments in heterogeneous catalysis, especially catalysis by metals, are summarized in a review by *J. H. Sinfelt*. An outline of the progress made in the characterization of the degree of dispersion of a metal catalyst on a carrier material is followed by an account of the catalytic activity of a metal in the hydrogenolysis of ethane in relation to its position in the periodic system. The review concludes with a report on catalysis with alloys and related bimetallic clusters. Such clusters are prepared by impregnating a carrier with aqueous solutions of salts of the two metals and reducing the salts with hydrogen. These clusters are often distinguished by their increased catalytic selectivity. [Heterogeneous Catalysis: Some Recent Developments. Science *195*, 641—646 (1977); 38 references]

[Rd 938 IE—F]

BOOK REVIEWS

Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe (Analytical Methods for the Testing of Hazardous Working Materials). Edited by *D. Henschler*. Verlag Chemie, Weinheim 1976. Vol. 1: Luftanalysen. 1st edit., xiii, 515 pp., 163 figs., loose-leaf edit., DM 124.—. Vol. 2: Analysen im biologischen Material. 1st edit., xiii. 378 pp., 99 figs. Loose-leaf edit., DM 104.—.

The Deutsche Forschungsgemeinschaft, through its Senate Commission for the Testing of Hazardous Materials, has published, in loose-leaf format, two sets of recommendations for

the determination of harmful materials present in industrial premises (MAK values), namely those in the atmosphere and in biological materials. In the selection of methods for such determinations it is important to have a representative understanding of the action profile, and in this connection special attention is paid to the labor-medicine relevance. The more laborious methods are also recommended when necessary.

The two volumes are structured strictly according to the same scheme. Following an explanation of the basic analytical concepts such as the material to be measured, the measurement quantities, sampling, sample preparation, analytical procedures, single- or multicomponent determinations, attainment and quality (accuracy) of the analytical result, detection limits, specificity, *etc.*, the application and performance of general analytical methods are discussed. The latter are the spectroscopic methods, in particular atomic absorption spectroscopy, gas chromatography, and the electrochemical methods in which ion-selective electrodes are used. The volume on air analyses contains preliminary remarks about the specific sampling methods for this type of work.

About two-thirds of each volume then deals with the specific methods recommended. All those proposed have been carefully checked, especially ones taken from the literature. Where no satisfactory methods had been known, new methods were worked out and were then recommended if they passed experimental testing in an independent laboratory. Particular emphasis is placed on the following features: evaluation of the analytical method, statistical testing of the results, specificity, and detection limits.

The two volumes are perfect examples of careful preparation and recommendation of analytical methods for industrial analyses of materials in air and in biological materials. They constitute a worthwhile enrichment of collected methods, stimulate comparable analytical exercises, and can be recommended without any qualification.

Hermann Kienitz [NB 365 IE]

Einführung in die Chemie und Technologie der Kunststoffe (Introduction to the Chemistry and Technology of Plastics). By *F. Runge* and *E. Taeger*. Akademie-Verlag, Berlin 1976. 4th revised and expanded edition, xiv, 682 pp., 91 figs., 70 tables, 4 charts, bound, *ca.* DM 88.—.

Comparison of the first (1952) with the present fourth edition of this work shows merely by the almost fourfold increase in size the rapid strides that have been made in macromolecular chemistry and its practical applications. There is thus certainly a need for a modern introduction into this academically and industrially important field. Since this is a textbook for a deeper study of the subject, there is a very broad general discussion of the principles of synthesis and states of polymers. The description of the syntheses is based on division into chain and step polymerizations—a principle not yet in general use, but nevertheless a very practical one and into which not merely the classical polycondensations and polyadditions but also the newer "nonclassical" polyreactions such as radical coupling can be readily fitted in. This part of the book provides an excellent introduction into the synthetic methods of macromolecular chemistry. However, the subsequent section on the solid state of polymers and its dependence on structure is distinctly less successful; it is largely restricted to a general discussion of questions connected with properties of direct importance for industrial application.

The chapters "From polymers to industrial materials" and "processing of plastics" are relatively short and purely qualitative; it is true that they contain much about the most important processes and the necessary auxiliary materials, but there is no mention of *e. g.* the methods of testing or of the quantities important for industrial applications and their determination; the elasticity modulus is only very briefly mentioned, and important concepts such as bending strength, elongation, or melt viscosity are completely absent.

The special part of the book is concerned with the most important aspects of industrial polymerization and with the raw materials, manufacturing processes, and the processing of plastics produced industrially. The subdivision is based largely on the structure of the basic skeleton (carbon chains, chains with heteroatoms *etc.*); the individual sections differ greatly from one another in arrangement and depth. The literature references and the tradenames mentioned are also often chosen rather arbitrarily, but to be fair it must be remembered that an introduction of this kind to high-polymeric materials always requires a certain amount of selection, and this naturally emphasizes the authors' point of view more than does treatment of general chemical principles. It should be noted that new developments are covered extensively.

A broad presentation of this kind of an area of chemistry so diverse in raw materials and industrial applications cannot be free from simplifications, but in some places a more precise formulation would have been desirable (for example on page 81, in the treatment of the relationships between the polymerization rate and conversion, where Fig. A 6 is certainly not correct in the general form given); in a later edition at least a few references to further comprehensive works should be added to the general section. In spite of a certain imbalance between the general and the special parts, the book can be recommended as an introduction into the chemical principles of plastics, particularly as hardly anything comparable is available in this form in German-language literature; for information about the actual raw materials the reader must, however, turn to an additional textbook.

Dietrich Braun [NB 363 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*) Pappelallee 3, P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 5
May 1977
Pages 273–338

The Biochemistry of Sphingolipid Storage Diseases

By Konrad Sandhoff[*]

Sphingolipids are components of animal membranes that are made up of a hydrophobic ceramide and a hydrophilic moiety (phosphorylcholine, oligosaccharides or their derivatives). Several enzymes are required for the step-by-step degradation of the sphingolipids. If one of these enzymes is deficient or totally lacking, then its substrates accumulate in the body and cause severe damage, especially when storage occurs in the nervous system. The enzyme defects are inherited in a recessive manner.

1. Introduction

Up until 1975 over 2300 human hereditary disorders had been described[1]. As early as 1909 it was suggested by *Garrod*[2] that "inborn errors of metabolism" were responsible for these diseases but biochemical lesions have as yet been demonstrated for only 176 of them[1]. If the activity of an enzyme is greatly diminished or totally absent, then the normal flow of metabolism is interrupted at a certain point. If biosynthesis continues uninhibited up to the point of biochemical lesion a pathological accumulation of the substrate of the defective enzyme can result; such accumulations are observed in disorders of numerous metabolic pathways (*e.g.* in the degradation of glycogen, mucopolysaccharides, amino acids, and sphingolipids). Various pathological symptoms, often including mental and neurological disturbances, are observed depending on the nature and importance of the accumulated substances. Unfortunately, in most cases the precise relationship between the biochemical causes and the neurological effects has not yet been elucidated. A connection between the accumulation of a substance and the resulting neuropathological changes can, however, be recognized in the sphingolipid storage diseases which primarily affect the central nervous system. Clinically, the course of several of these disorders is very similar, and it is only as a result of the analysis of the pathologically increased sphingolipids and the identification of the specific enzyme defects that it is possible to distinguish clearly between the individual diseases.

[*] Priv.-Doz. Dr. K. Sandhoff
Max-Planck-Institut für Psychiatrie, Neurochemische Abteilung
Kraepelinstrasse 2, D-8000 München 40 (Germany)

2. Sphingolipids

The membrane-forming lipids of mammals are essentially glycerol phosphatides, cholesterol, and sphingolipids. Although the glycerol phosphatides are the most important quantitatively, no disease is known which is caused by a primary storage of such a phosphatide. It is remarkable however, that almost every sphingolipid can be accumulated pathologically in humans; these storage diseases are called the sphingolipidoses. Historically speaking, the investigation of these diseases led to the discovery of several sphingolipids such as the gangliosides[3–9] and glucocerebroside, also known as glucosylceramide[10].

Ceramide, the hydrophobic part of the molecule, is characteristic of all the sphingolipids: it consists of sphingosine (*trans*-(2*S*,3*R*)-2-amino-4-octadecene-1,3-diol) or a sphingosine analog as base with a fatty acid moiety bound to its amino group (Fig. 1). The sphingolipids are differentiated by the nature of their hydrophilic groups which are bound to the primary hydroxyl group of the sphingosine. In the case of

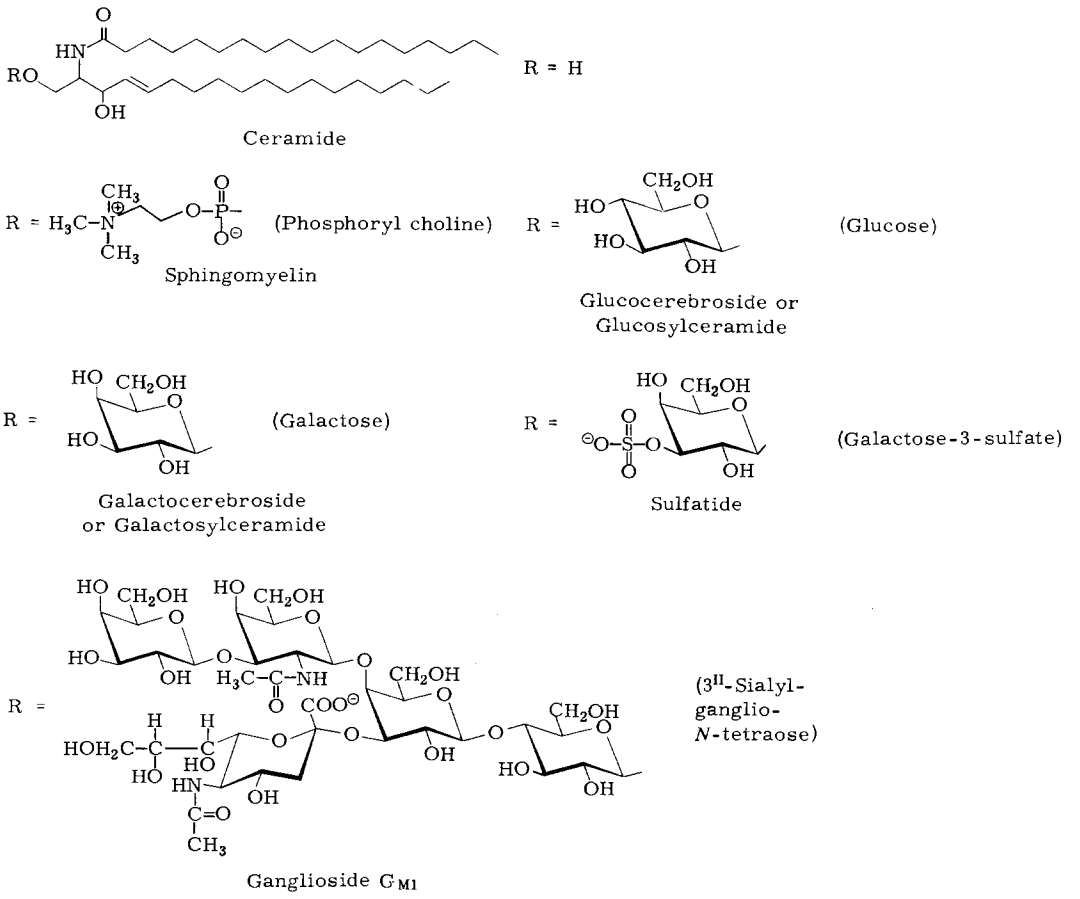


Fig. 1. Structure of some sphingolipid storage substances.

the most common sphingolipid, sphingomyelin, the hydrophilic component is phosphorylcholine. In the glycosphingolipids the hydrophilic component is either a sugar residue, as in the cerebrosides, or an oligosaccharide chain which, in the case of the gangliosides, contains sialic acid (*N*-acylneuraminic acid) as a characteristic structural unit[11]. The "pure" sphingolipids which have so far been prepared are rarely homogeneous in terms of their hydrophobic components, but contain only one type of hydrophilic residue. It is the latter which is mainly responsible for the different chemical and physiological behaviors of the complex lipids. Variations in the hydrophobic ceramide component play only a minor role in large molecules such as the gangliosides. In addition to sphingosine, dihydrosphingosine and a sphingosine analog with 20 instead of 18 carbon atoms are also found[11,12]. The fatty acid component of the ceramide is also heterogeneous; one fatty acid is always found in especially high concentrations (*e.g.* stearic acid in brain gangliosides) but its nature depends on the source of the ganglioside.

3. Localization and Function of the Sphingolipids

Sphingolipids, in particular the glycosphingolipids, are constituents of cell membranes[13]. The glycosphingolipids, in contrast to the ubiquitous sphingomyelin, are found predominantly as membrane components in nervous tissue. The neuronal plasma membrane is especially rich in gangliosides[14] whereas galactocerebrosides and sulfatides are mainly present as structural components of myelin (*i.e.* in the white matter of the brain)[15]. However, sphingolipids are also found in all other animal tissues although in smaller quantities than in nervous tissue. The comparative studies of *Klenk* and *Yamakawa* on erythrocyte membranes have led to the present concept that every animal cell type can have a specific glycosphingolipid pattern which exhibits species differences (cf.[16,17]). Differentiated cells exhibit a more complex pattern than undifferentiated cells. Thus a simplification of the glycosphingolipid pattern is also observed in cells which have been transformed by virus infection (cf. [13]).

These findings indicate that glycosphingolipids play a specific role in the formation of individual cell types but little is known about their function. Their oligosaccharide residues and those of the glycoproteins influence the properties of the cell surface. In addition, the gangliosides create negative charges on the cell membrane and serve as receptors for numerous substances (*e.g.* cholera toxin[18–23], enterotoxin[24,25], α-toxin[26–28], interferon[29], thyrotropin[30], and possibly tetanus toxin[31,32]). According to *Roseman*[33,34], the glycosphingolipids might be important for the mutual recognition and adhesion of cells.

4. Formation and Degradation of the Sphingolipids

The biosynthesis of the sphingolipids always begins with the formation of their hydrophobic component, the ceramide. The structural units of the hydrophilic component are then attached step by step to the primary hydroxyl group[33,35–39]. Each monosaccharide is transferred onto the end of the grow-

ing oligosaccharide chain from an activated form, a sugar nucleotide, depending on the specificity of cell-specific transferases (Fig. 2). For the formation of the sulfatides, sulfate is transferred from 3′-phosphoadenosine 5′-phosphosulfate to a galactocerebroside. In the case of sphingomyelin synthesis, phosphorylcholine is transferred from cytidine diphosphate choline or phosphatidylcholine[40] to a ceramide.

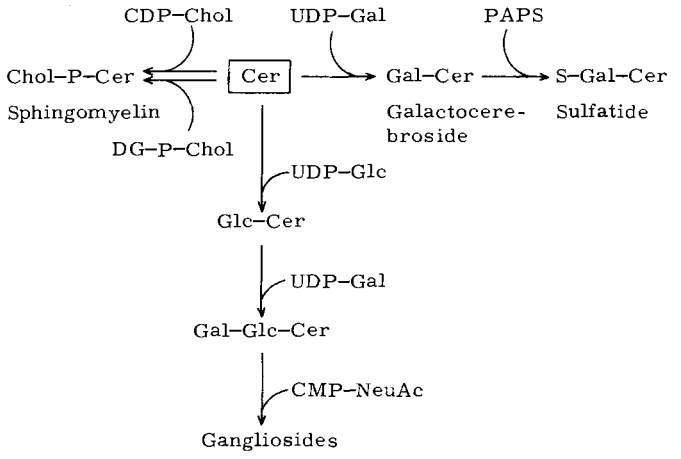


Fig. 2. Biosynthesis of sphingolipids. Abbreviations: CDP = cytidine diphosphate, Cer = ceramide, Chol = choline, CMP = cytidine monophosphate, DG = diacylglycerol, Gal = D-galactose, Glc = D-glucose, NeuAc = *N*-acetylneuraminic acid, P = phosphate, PAPS = 3′-phosphoadenosine 5′-phosphosulfate, UDP = uridine diphosphate, S = sulfate.

The biological degradation of the sphingolipids is catalyzed by hydrolases[12,37] which display their optimal activities in the acid pH range. They are stored intracellularly in membrane-bound sacs, the lysosomes, and are thus separated from the cytosol of the cell. In general, their specifity is directed towards certain types of bonds rather than towards individual substrates. Together, they can cleave a range of macromolecules (*e.g.* proteins, nucleic acids, polysaccharides, and complex lipids) into their structural units. The degradation of sphingolipids (Fig. 3 and Table 1) begins at the hydrophilic end of the molecule. The oligosaccharide chain is shortened step-by-step by removal of the terminal residues. Sphingomyelin is split up directly into phosphorylcholine and a ceramide which is subsequently cleaved to give sphingosine and a fatty acid. The question of how the sphingolipids are enclosed within the lysosomes is still largely unexplained.

5. Disorders of Degradation

Inherited disorders of sphingolipid metabolism have so far been observed almost exclusively in their degradation[41–44]. The resulting accumulation of lipids shortens the lives of the patients to a greater or lesser extent. In contrast, only one case is known of a possible hereditary disorder of sphingolipid synthesis (cf. Section 10.6). It seems reasonable to assume that genetically linked disorders of synthesis and the associated deficiencies in certain sphingolipids and their functions are

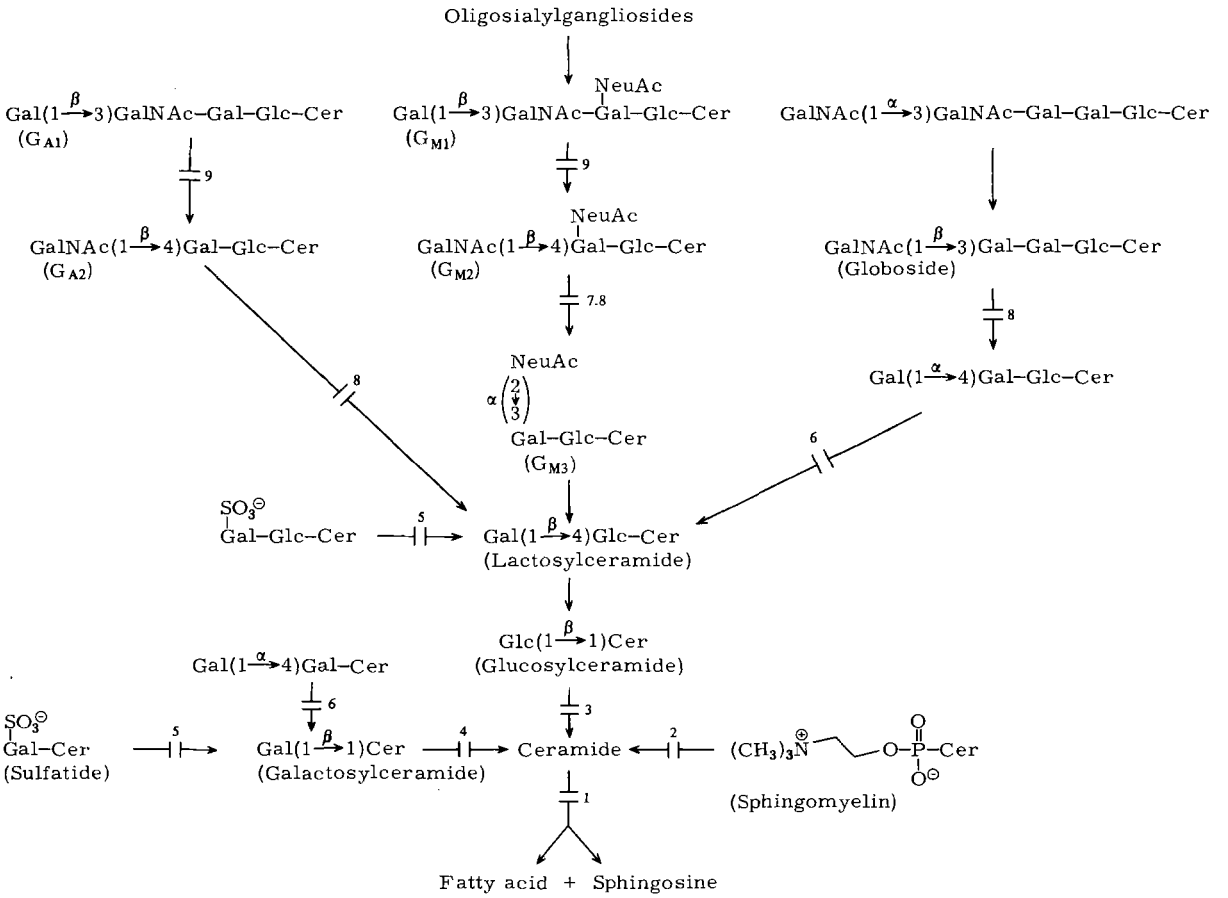


Fig. 3. Degradation of sphingolipids. The positions at which the degradation is interrupted by hereditary enzyme deficiencies are indicated by numbers which correspond to those in Table 1.

Table 1. Degradation of sphingolipids. The numbers in Fig. 1 refer to inherited enzyme defects leading to the storage diseases named.

No.	Disease	Defective enzyme	Stored substance; principal storage site
1	Farber's disease (ceramidosis)	Ceramidase	Ceramide; viscera and brain
2	Niemann-Pick s disease (sphingomyelinosis)	Sphingomyelinase	Sphingomyelin; viscera and brain in Type A
3	Gaucher's disease (glucocerebrosidosis)	Glucocerebroside β-glucosidase (glucosylceramide β-glucosidase)	Glucosylceramide; viscera and brain in infantile form
4	Krabbe's disease (galactocerebrosidosis)	Galactocerebroside β-galactosidase	Galactosylceramide; brain (white matter)
5	Metachromatic leucodystrophy (sulfatidosis) and Austin's disease	Sulfatide sulfatase (arylsulfatase A)	Sulfatides; brain and kidney
6	Fabry's disease	α-Galactosidase A	α-Galactosylgalactosylceramide and α-galactosyllactosylceramide; visceral organs
7	G_{M2} gangliosidosis, variant B (Tay-Sachs' disease)	Hexosaminidase A	Ganglioside G_{M2}; brain (gray matter)
8	G_{M2} gangliosidosis, variant 0	Hexosaminidases A and B	Gangliosides G_{M2} and G_{A2}; brain Globoside; viscera
9	G_{M1} gangliosidosis	Ganglioside G_{M1} β-galactosidase	Ganglioside G_{M1}; brain Keratan sulfate [a]; visceral organs

[a] Keratan sulfate is a linear mucopolysaccharide containing the disaccharide unit: [D-galactopyranosyl(β1→4)2-acetamido-2-deoxyglucopyranosyl 6-sulfate (β1→3)].

much more detrimental to life than the storage of these substances in disorders of degradation. Almost every step in degradation can be inhibited by an enzyme deficiency. These enzyme defects, which are schematically represented in Figure 3, are passed on in a recessive manner according to the laws of Mendelian genetics.

Usually, every cell of the human body has two allelic genes at each locus which code for the synthesis of a peptide chain—one gene is from the father and one is from the mother. If one of these genes has mutated and then produces a functionally inactive polypeptide chain or no polypeptide chain at all, this defect is usually not detrimental to the health of the carrier; this is because the second allelic gene synthesizes functional gene products although in only half the normal amount. A person can thus be a carrier of a mutated allele without suffering any damage to his health. A disease is, however, observed if two carriers of a defective allele pass this on to their child; the child therefore has a locus with two defective alleles which do not code for a functional enzyme protein.

The genetically controlled defects of sphingolipid hydrolases occur very rarely with a gene frequency of approximately 0.002 *i.e.* from 1000 genes in the average population which code for an enzyme, two are mutants. In certain population groups much higher values are observed, *e.g.* Tay-Sachs disease has a gene frequency of approximately 0.01 among Jews of East European origin (Ashkenazi)[45].

The lack of an enzyme activity in the lysosomes leads to an intralysosomal build-up of all its substrates[46]; an increase in concentration of more than a hundred-fold is no exception. Storage granules are formed in the cell cytoplasm: these are pathologically transformed lysosomes which are no longer able to digest their contents.

The enzyme defects shown in Figure 3 and Table 1 which block the normal degradation of sphingolipids, occur in all tissues and body fluids which contain lysosomal enzymes—thus they are also found in leucocytes, cultured fibroblasts, and amniotic cells. However, storage only takes place in the tissues in which the lipid substrates of the deficient enzyme are also synthesized. The accumulation of sulfatides in metachromatic leucodystrophy is thus seen mainly in the brain and kidney. In the brain this leads to the destruction of the white matter whereas storage in the kidney is tolerated without any significant injury. In gangliosidoses, the gangliosides G_{M1} and G_{M2}, typical of nervous tissue, are mainly stored in the neurons. Multilaminated bodies containing, in addition to gangliosides, phospholipids, and proteins are found in the cytoplasm of these cells (Fig. 4)[47,48]. The enormous deposition of lipids leads to balloon-like swelling of the nerve cells and ultimately to their destruction.

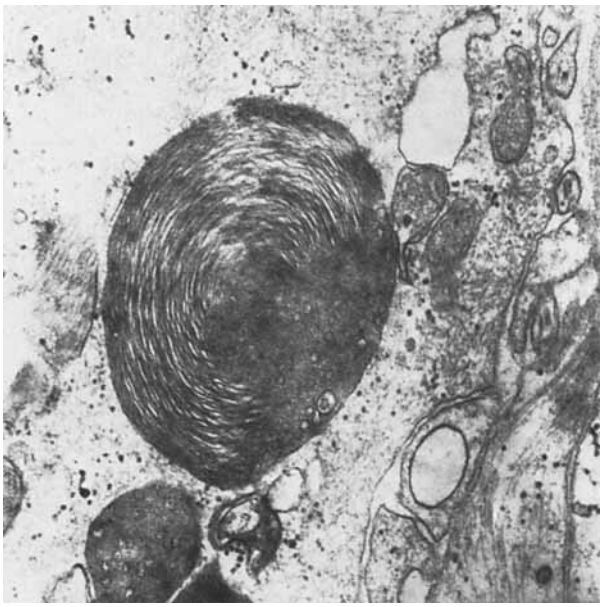


Fig. 4. Multilaminated bodies (MCB) in the cytoplasm of a nerve cell from a Tay-Sachs patient. (Magnification × 54000: micrograph by *E. Sluga*, Wien).

6. Measurement of Sphingolipid Hydrolases

The identification of the relevant enzyme defect is critical for the diagnosis of the storage diseases. Since the lysosomal hydrolases usually have only a low substrate specificity, their activity can be measured not only with natural substrates but also with synthetic, water-soluble substrates. The activity of these enzymes can be most simply determined with fluoro-

genic or chromogenic substrates. 4-Methylumbelliferyl (Fig. 5) and *p*-nitrophenyl derivatives are widely used[49]. In the investigation of tissue extracts with synthetic substrates it often remains uncertain whether it is really only the activity of the enzyme catalyzing the degradation of the relevant, natural lipid that is being measured. Investigation with the natural substrate is therefore often necessary for diagnostic purposes.

Sphingolipids are cleaved very slowly by hydrolases *in vitro*, and it is only when detergents or natural activators are added that easily measured reaction rates are obtained. The inert behavior of these lipids is due to their characteristic solubility properties in aqueous media. They dissolve in a monodisperse form only below a certain concentration known as the critical micelle concentration (CMC). Above the CMC they form micelles (like gangliosides and many detergents) or liposomes which are made up of multilamellated double layers (like the sphingomyelins). Micelles and liposomes are attacked only very slowly or not at all by the hydrolases *in vitro*. The addition of a detergent, usually in concentrations above the CMC, leads to the formation of mixed detergent-lipid micelles; in such a complex the substrate can react with the enzyme.

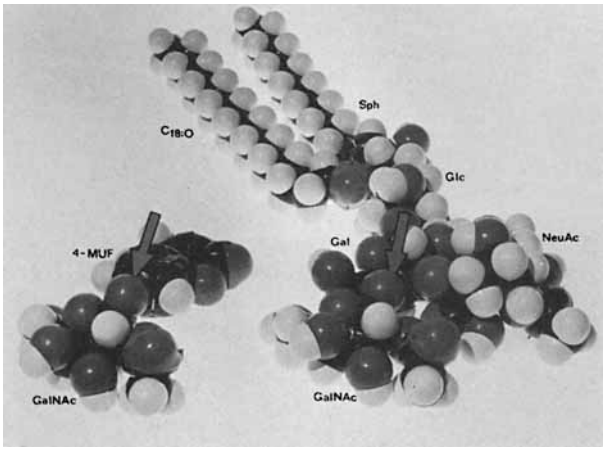
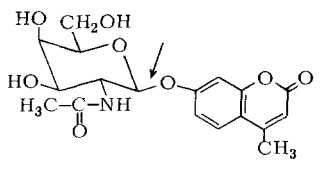
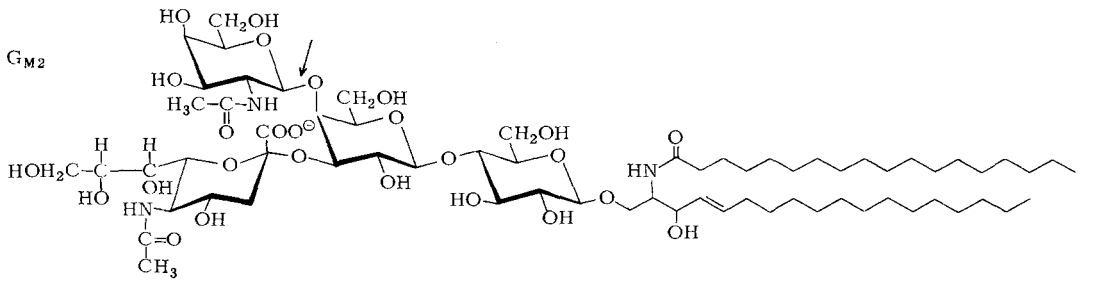


Fig. 5. Comparison between the synthetic and natural substrates of hexosaminidase A (cf. Fig. 3 and Table 1, No. 7), 4-methylumbelliferyl-β-*N*-acetyl-D-galactosaminide (4-MUF-GalNAc) and ganglioside G_{M2}. The β-glycosidic bonds split by the enzyme are indicated by arrows.

4-MUF–GalNAc



G_{M2}



However, the nature of the interaction between lipid, detergent, and enzyme and hence the true substrate concentration remain unknown, and the specification of kinetic parameters (*e.g.* apparent Michaelis constants) is therefore of only limited value.

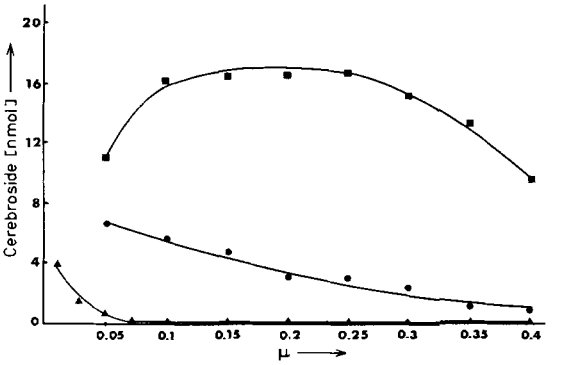


Fig. 6. Influence of ionic strength (μ) and addition of sodium taurodeoxycholate or protein activator on the activity of arylsulfatase A (cf. Fig. 3 and Table 1, No. 5). The samples contained 20 nmol of sulfatide and sodium acetate buffer (pH 4.8) at the given ionic strength in a volume of 100 μl. Additions: 0.1 unit sulfatase A (▲—▲); 0.1 unit sulfatase A and 11 μg (≙0.55 nmol) protein activator (●···●); 0.025 unit sulfatase A and 200 nmol sodium taurodeoxycholate (■—■). The samples containing sodium taurodeoxycholate were incubated for 15 min at 37 °C, the others for 60 min at 37 °C. The liberated cerebroside was then determined (*G. Fischer* and *H. Jatzkewitz*, unpublished). The ionic strength $\mu = \frac{1}{2}\sum c_i \cdot z_i^2$ is given in ½ mol of monovalent ions/l (c_i = concentration of the ion i; z_i = charge of the ion i).

The enzymatic cleavage of sphingolipids can also be accelerated in the absence of detergents by natural protein activators. The addition of an acid, low molecular weight protein (MW 22000) from liver stimulates the enzymatic degradation of sulfatides (Fig. 6)[50, 51]. According to the investigations of *Fischer* and *Jatzkewitz*[52], activator and sulfatide form a complex in a molar ratio of 1:1 and it is probably in this form that the lipid acts as a substrate for hydrolysis *in vivo*.

A similar protein activator (MW 22000) stimulates the splitting of gangliosides by hexosaminidase and β-galactosidase by an as yet unknown mechanism[53–55]. The requirement for the activator suggests that there is also an interaction between lipid and activator in these cases. On the other hand, the activator (MW 22000) for the cleavage of glucocerebroside forms an active complex with the enzyme glucocerebrosidase[56–61].

The physiological role of the protein activators is still unexplained. Changes in their concentrations could, for example, regulate the activity of the hydrolases in the lysosome. An activator deficiency disease has not yet been described. The sphingolipidoses which have so far been biochemically characterized are caused by deficiencies in enzyme activities. The most thoroughly investigated enzyme deficiencies (*i.e.* in β-galactosidase, arylsulfatase, and hexosaminidase) will now be considered in more detail.

7. β-Galactosidase Deficiencies

β-Galactosidase deficiencies are responsible for two completely different hereditary disorders. G_{M1}-Gangliosidosis is primarily a disease of the grey matter of the brain while Krabbe's disease leads to damage of the white matter.

7.1. G_{M1}-Gangliosidosis

G_{M1}-Gangliosidosis (cf. Fig. 3 and Table 1, No. 9) occurs as a result of a β-galactosidase deficiency which can be demonstrated with synthetic substrates[62]. The natural substrate of this enzyme and thus the main storage substance of this disease, is the ganglioside G_{M1}[63,64]. The ganglioside-G_{M1} β-galactosidase (a monomeric protein of molecular weight 72000) splits, in addition to the ganglioside, other β-galactosides—the sialic acid free residue of ganglioside G_{M1}, called G_{A1}[65], and a range of glycoproteins and mucopolysaccharides containing a terminal galactose bound by a β-glycosidic bond[66,67]. All these substrates are deposited in different organs depending on their site of synthesis. The enormous storage of gangliosides in the neurons leads to progressive damage of the nervous system while the deposition of acidic mucopolysaccharides[68–73] in the cells of the reticuloendothelial system[*] causes an enlargement of the liver and spleen and also changes in the bones.

Clinically, several forms of the disease can be distinguished. In Type 1, generalized G_{M1}-gangliosidosis, the symptoms of the disease appear within the first six months of life and lead to death after about two years with progressive mental and physical deterioration[62]. Type 2, the late infantile form[62,74], with slight disturbance of bone growth, and the adult forms[62,74–76] are milder in comparison. Cerebral symptoms become apparent after the first year of life at the earliest. In the late infantile form death occurs at about ten years of age. Intermediate types have also been described[67].

In neither the infantile nor the late infantile diseases is the lack of enzyme activity due to a disappearance of the enzyme protein; this can be immunologically detected in approximately normal quantities in both forms of the disease[77], *i.e.* a defective enzyme with very low activity is present in each case. The fact that the residual activity in Type 2 is higher than in Type 1 could be the reason for the considerably milder course of Type 2. In a Type 2 patient, a change in the electrophoretic mobility of the enzyme and an increase in its Michaelis constants for 4-methylumbelliferyl-β-D-galactoside and ganglioside G_{M1} have been demonstrated[77] (see also Fig. 5). Similar changes in the electrophoretic and kinetic properties of the residual β-galactosidase were also observed in Type 1[78]. These observations speak in favor of a mutation in the structural gene of the enzyme.

7.2. Krabbe's Disease

Globoid cell leucodystrophy or Krabbe's disease (cf. Fig. 3 and Table 1, No. 4) primarily attacks the white matter of the central nervous system. Early clinical symptoms are seen in the first year of life. As a result of progressive psychomotor deterioration, overexcitability to external stimuli, increasing spastic paralysis, convulsions, blindness and deafness the patients seldom survive beyond the age of two years[79].

This disease is caused by the lack of the enzyme, galactosylceramide β-galactosidase[80–82], which can be distinguished from ganglioside-G_{M1} β-galactosidase since it does not precipitate with antibodies against the latter, it remains active in G_{M1}-gangliosidosis and shows a different substrate specificity. In addition to galactocerebrosides, this enzyme can also split galactosylsphingosine, lactosylceramide, and monogalactosyldiglyceride[82–87]. Strictly speaking Krabbe's disease is not a storage disease. In the degenerating white matter of the brain only a slight increase of the undegradable metabolite, galactosylceramide, is found[88,89]. The population of cerebroside- and myelin-synthesizing cells (the oligodendroglia) declines sharply[79]. Multinuclear globoid cells (macrophages—migratory cells—of mesodermal origin) infiltrate the white matter and take up the storage material (Fig. 7). Toxic galactosylsphingosine (psychosine) resulting from the enzyme defect could play a pathogenetic role[90].

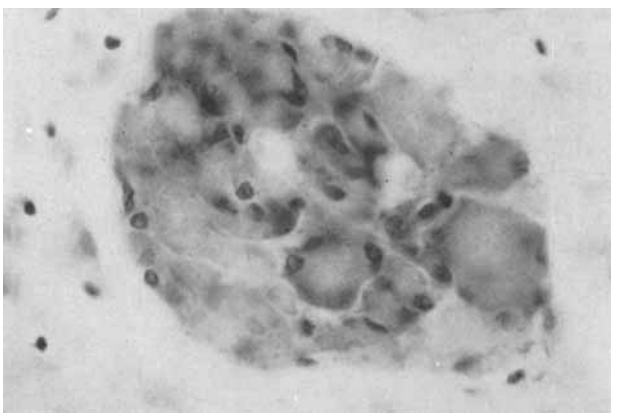


Fig. 7. In Krabbe's disease numerous, usually multinucleated, globoid cells are seen under the light microscope in the white matter of the brain; they are frequently most abundant around the blood vessels. These macrophages (migratory cells) of mesodermal origin take up the lipids (Nissl staining; magnification approximately × 250; photograph: *P. Mehraein*, München).

8. Arylsulfatase Deficiencies

Arylsulfatase deficiencies are responsible for metachromatic leucodystrophy, Austin's disease, and the Maroteaux-Lamy

[*] A functional unit of biologically very active mesenchymal cells characterized by phagocytosis, storage, and antibody production which form, as it were, the resorbing inner surface of the body (*Pschyrembel:* Klinisches Wörterbuch, de Gruyter, Berlin 1972).

syndrome (cf. Fig. 3 and Table 1, No. 5). In the Maroteaux-Lamy syndrome defects in arylsulfatase B[91-93] and *N*-acetylgalactosamine sulfatase[94,95] activities have been demonstrated; both activities are probably associated with the same enzyme. As the Maroteaux-Lamy syndrome belongs to the mucopolysaccharidoses it will not be discussed further here.

8.1. Metachromatic Leucodystrophy

The storage of sulfatides[96,97]—typical structural units of myelin in nervous tissue—in metachromatic leucodystrophy is correlated with a deficiency of cerebroside sulfatase[98,99] and arylsulfatase A (Fig. 3)[98,100,101] activities. Cerebroside sulfatase can be determined by the hydrolysis of cerebroside sulfate in the presence of a natural protein activator[51,102] or taurodeoxycholate[51] (Fig. 6); arylsulfatase activity is measured by the hydrolysis of nitrocatechol sulfate[103] or 4-methylumbelliferyl sulfate[104]. Both activities have been recognized as being properties of the same enzyme[50,105-107] and have very low values in all organs of patients with metachromatic leucodystrophy. An enzyme protein of very low activity can be identified; its kinetic and antigenic properties appear to be abnormal[108,109].

Human arylsulfatase A has a molecular weight of 107000 and consists of two subunits of approximately 50000[110]. At low pH values and high ionic strengths it forms dimers and tetramers. In addition to the sulfate esters of cerebrosides, the enzyme cleaves other sulfated lipids such as lactosylsulfatide[111] (which is also found in slightly increased amounts in metachromatic leucodystrophy[112]), psychosine sulfate[113], sulfogalactoglycerol lipid[114], and seminolipid[115,116].

Metachromatic leucodystrophy is, above all, a demyelinating disease of the central nervous system[117]. As a result of the cerebroside sulfatase deficiency, sulfatides and other sulfated lipids are stored, not only in nervous tissue, but also in the kidney. However, the neurological symptoms are clinically predominant and kidney function is only slightly impaired. The first difficulties in walking are seen at the age of 1 to $1\frac{1}{2}$ years in the late infantile form of the illness. Hypotonicity, deterioration of the reflexes, mental deficiency, failing sight, convulsions, and deficiencies in the motor system set in and lead to death within ten years[118]. Morphologically, a pathological degradation of the myelinated fibers in the nervous tissue is found. The small amount of myelin still detectable has an abnormal lipid composition with an especially high sulfatide content[119,120]. The juvenile and adult forms of the disease take a milder course[118]; here the severity of the course of the disease can be correlated with the extent of the enzyme defect, as *Kihara et al.* have demonstrated with cultured fibroblasts[121,122]. These cells incorporated the natural substrate, ^{35}S-sulfatide, from the medium and the rate of degradation of the labeled sulfatide decreased with the severity of the disease.

8.2. Austin's Disease

Austin's disease is a variant of metachromatic leucodystrophy[118,123,124] in which several sulfatases are deficient—the lysosomal arylsulfatases A and B[118], microsomal arylsulfatase[118], steroid sulfatase[125], heparan N-sulfatase[126], and iduronate sulfatase[126]. In this variant, sulfatide storage in the nervous tissue is also of greatest importance. However, increases in the amounts of mucopolysaccharides and sulfated steroids are also observed in the organs due to the multiple sulfatase deficiencies. In one case of the disease normal quantities of the arylsulfatase A protein were detected immunologically but in an enzymatically inactive form[127]. The reason for the common deficiency of the, in some aspects, very different lysosomal and microsomal sulfatases remains unknown. This multienzyme deficiency suggests that all the affected sulfatases have a common feature; a common subunit or factor necessary for the activity or biosynthesis of all these sulfatases could, for example, be missing or defective.

9. Hexosaminidase Deficiencies (G_{M2}-Gangliosidoses)

In 1881 *Warren Tay*[128] was the first to draw attention to the clinical characteristics of infantile amaurotic idiocy when he observed a cherry-red spot in the eye-ground region of most acute vision of a one year old child. The blood vessels become visible through the degenerating layer of ganglion cells and increasingly weak vision ends in blindness. The children suffering from this disease develop normally at first but lose abilities such as grasping and sitting up which they had already learned in their first months of life. Paralysis of the limbs, epileptic fits and convulsions set in. The disease leads to death within two to three years with progressive mental and physical deterioration[45,129,130]. Morphologically, a characteristic change in the ganglion cells of the nervous system is found. The cytoplasm of the cells is severely swollen, the cells are enlarged severalfold and their dendrites are distended. Under the electron microscope many oval, multilaminated granules can be seen in the cytoplasm of the neurons (cf. Fig. 4)[47] (as is also observed in G_{M1}-gangliosidosis). These granules contain the storage substance of this disease[48]—the ganglioside G_{M2}[131,132] (cf. Fig. 3 and Table 1, Nos. 7 and 8); the disease is therfore referred to as G_{M2}-gangliosidosis. Whereas ganglioside G_{M2} only occurs in traces as an interme-

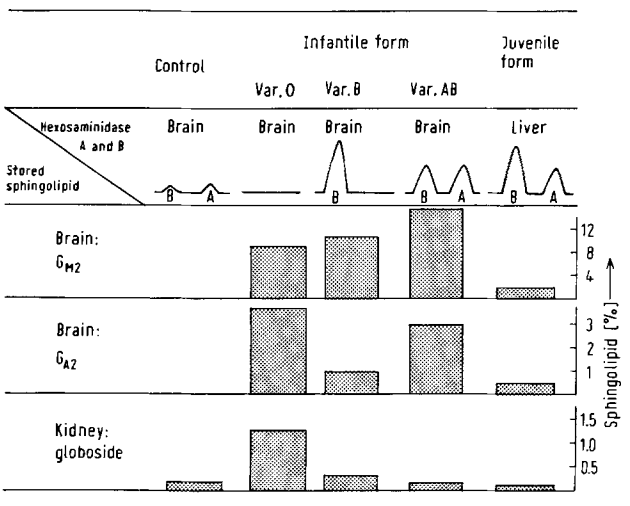


Fig. 8. Storage of glycolipids and hexosaminidase pattern in G_{M2}-gangliosidosis (infantile form with variants 0, B, and AB and juvenile form). The pattern of hexosaminidase activities was measured with synthetic substrates after the isoelectric separation of isoenzymes A and B. The quantities of the stored sphingolipids are given as percentages of the dry weight of the storage organ [134].—In the juvenile form of G_{M2}-gangliosidosis the level of hexosaminidase B in the liver is normal whereas the activity of hexosaminidase A only amounts to 50% of the normal value.

Table 2. Comparison of *N*-acetyl-β-D-hexosaminidases A and B.

Property	Hexosaminidase A		Hexosaminidase B		Ref.
Isoelectric point	5.0		7.3		[137]
Stability at 50 °C	−		+		[129]
Precipitation with antibodies to hexosaminidase B	+		+		[143, 145, 146]
Precipitation with antibodies to hexosaminidase A	+		+		[143, 145, 146]
Precipitation with specific antibodies to hexosaminidase A [a]	+		−		[145, 146]
Molecular weight	100000		100000		[160]
Proposed composition	$\alpha_2\beta_2$		$\beta_2\beta_2$		[160]
Activity in variant 0	−		−		[130, 133, 134]
Activity in variant B	−		+		[135, 141, 142]
Hydrolysis of ganglioside G_{M2} [μmol h^{-1} mg^{-1}] [b]	0.25		0.04		[159]
Hydrolysis of	K_m [mmol/l]	V_{max} [μmol $min^{-1} \cdot mg^{-1}$]	K_m [mmol/l]	V_{max} [μmol $min^{-1} \cdot mg^{-1}$]	
4-MUF-β-D-GalNAc [c]	0.09	14	0.05	35	[159]
4-MUF-β-D-GlcNAc [c]	0.8	160	0.6	280	[159]
Asialoganglioside G_{A2} [b]	0.05	0.15	0.03	0.65	[159]
Globoside [b]	0.20	1.1	0.26	4.7	[159]

[a] Antibodies to hexosaminidase A are freed from cross-reacting material by absorption with Sepharose-loaded hexosaminidase B.
[b] Hexosaminidases purified from human autopsy liver and tested in the presence of 2 mmol/l of sodium taurodeoxycholate.
[c] 4-MUF = 4-methylumbelliferyl.

diate product in healthy brain tissue, it forms about 6—12 % of the dry brain weight of patients with this disease[133, 134].

The enormous increase in ganglioside G_{M2} leads to the destruction of the nerve cells and therefore to myelin degeneration. The demyelinization is reflected in the lipid content of the diseased nervous tissue[134]. A drastic decrease of all typical myelin lipids such as cerebrosides, sulfatides, and C_{24}-sphingomyelin is observed. Similar secondary changes also occur in G_{M1}-gangliosidosis.

Three enzymatic variants of G_{M2}-gangliosidosis can be identified (Fig. 8)[135]. Defective isoenzymes of *N*-acetyl-β-D-hexosaminidase can cause the storage of glycosphingolipids. In human tissues mainly hexosaminidases A and B are found[136, 137]; both of them cleave β-*N*-acetylglucosaminides and β-*N*-acetylgalactosaminides as well as ganglioside G_{M2} and its sialic acid-free residue G_{A2} in the presence of detergent (Table 2)[138–140]. However, when the detergent is substituted by natural activator proteins, the ganglioside G_{M2} is hydrolyzed only by hexosaminidase A[159].

Tay-Sachs disease, which has been known for a long time, is caused by a complete lack of the hexosaminidase A enzyme[135, 141, 142]; inactive enzyme protein cannot be detected immunologically[143–146]. In contrast, the activity of the B enzyme is normal in most organs and in nervous tissue is even increased by as much as six-fold[133, 134, 141]. This disease is systematically denoted as variant B of infantile G_{M2}-gangliosidosis (Fig. 8).

A deficiency in both isoenzymes A and B is responsible for the occurrence of variant 0 of infantile G_{M2}-gangliosidosis[130, 133]. Inactive enzyme proteins have been immunologically detected in only one case[143, 144]. The additional storage of globoside in internal organs and the increase of glycosphingolipid G_{A2} in nervous tissue are typical in this form of the disease (Figs. 3 and 8)[130, 133, 134, 147–150].

It is also worth noting the rare variant AB in which an enormous storage of ganglioside G_{M2} and its sialic acid-free residue G_{A2} occurs although no enzyme deficiency can be detected with artificial substrates[134, 135, 151, 152]. However, the activity of the A enzyme towards the main storage substance, ganglioside G_{M2}, appears to be reduced *in vitro*[134]. The disorder in this form of the disease still remains to be elucidated. Is an activator, necessary for the degradation of ganglioside G_{M2}, missing or is there an abnormal hexosaminidase with an altered substrate specificity? A disorder in the organization of the lysosome, which prevents an ordered interaction between the lipid and the enzyme must also be considered.

In the juvenile form of G_{M2}-gangliosidosis (Fig. 8) it is possible that a hexosaminidase A with an altered substrate specificity is present. This form of the disease can be considered as a milder type of Tay-Sachs disease[129, 151, 153–156]. This is consistent with the fact that much less ganglioside G_{M2} is stored in the nervous tissue than is observed in the infantile form. With synthetic substrates, hexosaminidase A activity still amounts to 15 to 60 % of the normal level[129, 157]; with natural lipid substrates however, considerably lower activities have been found in the one case so far investigated[158].

Geiger and *Arnon*[160] have isolated the subunits of hexosaminidase A and B and proposed a model for the structure of the enzymes. According to this model, hexosaminidase A consists of two subunits, α_2 and β_2 (cf. Table 2) in each of which two peptide chains are linked by a disulfide bridge. The B enzyme is a homopolymer of composition $\beta_2\beta_2$. The common β_2 subunit of enzymes A and B could be changed or lacking in the 0 variant whilst the defect in the B variant would be in the α_2 subunit. The model explains why the trace enzyme S, which is made up of α_2 subunits, is only missing in the B variant[134, 145, 161, 162]. It also explains why hexosaminidase A ($\alpha_2\beta_2$) reappears in hybrids of skin cells of 0 and B variants[163–167] in which the A enzyme is missing; the cells must synthesize intact α_2 (variant 0) or β_2 (variant B) subunits which combine in the hybrids to form the A enzyme. The gene loci for the α and β chains lie on different chromosomes[168–171].

10. Further Enzyme Defects in Sphingolipid Metabolism

10.1. Fabry's Disease

Fabry's disease (cf. Fig. 3 and Table 1, No. 6) is a disorder of sphingolipid metabolism which does not primarily affect

the nervous system. In this disease the deposition of lipids leads to the appearance of skin eruptions (angiokeratoma), pains in the extremities, and renal failure which is often the cause of death in elderly patients. Lipids with terminal galactose residues bound by α-glycosidic bonds are stored—trihexosylceramide, digalactosylceramide (Fig. 3), and a complex lipid with blood group B specificity[172,173]. The cause is a deficiency in α-galactosidase A which, *in vitro*, cleaves the stored di- and trihexosylceramides[174-178]. In the patients examined so far, no immunologically crossreacting material has been found[178,179]. However, residual activity with synthetic substrates such as 4-methylumbelliferyl- and *p*-nitrophenyl-α-galactoside could still be detected. This residual activity can be attributed to another enzyme, α-galactosidase B, which is not deficient in patients with Fabry's disease and is immunologically unrelated to the A enzyme[178-182].

10.2. Gaucher's Disease

The storage of glucocerebroside (glucosylceramide) (Fig. 1), above all in the cells of the reticuloendothelial system, is characteristic of Gaucher's disease (cf. Fig. 3 and Table 1, No. 3). These storage cells (Gaucher cells) colonize spleen, liver, and lymph nodes and cause, in addition to bony changes, an enormous enlargement of these organs. The storage is due to a deficiency in β-glucosidase[183,184] which normally splits off the sugar residue from the storage substance, its fatty acid-free residue (*i.e.* β-glucosylsphingosine), and also from synthetic β-glucosides[185]. In the various forms of Gaucher's disease (infantile, juvenile, and adult), different degrees of deficiency in glucocerebrosidase activity have been observed[184]. The milder and more slowly progressing forms are reported to show higher residual activities than the infantile form in which neurological symptoms cause additional complications.

10.3. Niemann-Pick's Disease

It is striking that, in the course of the various forms of Niemann-Pick's disease (cf. Fig. 3 and Table 1, No. 2), the nervous system can be affected very differently. Recessively inherited sphingomyelinase defects give rise to storage of sphingomyelin in the infantile type A with neurological symptoms and in the juvenile type B without any effect on the brain[186-188]. According to *Callahan*[189,190] the lysosomal enzyme has several isoenzymes; in the juvenile type C, displaying neurological symptoms, one of these is reported to be missing. It still has to be explained why, in the juvenile and adult types D and E in which no enzyme defect has so far been found, sphingomyelin is stored. In addition to the lysosomal sphingomyelinase, a microsomal sphingomyelinase could be of importance, which is especially active in brain tissue[187,191]. It remains to be explained what role this enzyme might play in the different types of Niemann-Pick's disease, in particular to what extent it might be responsible for the quite different neurological symptoms observed in the various forms.

10.4. Fucosidosis

Fucosidosis is due to a deficiency in lysosomal α-fucosidase which leads to the storage of fucose-containing glycoproteins and glycolipids[192-197]. Enzyme protein could not be immunologically detected in a patient with the infantile form of the disease[198]. Lack of enzyme activity is also observed in the protracted, adult form of the disease[199]. α-Fucosidase shows a wide polymorphism[200,201]; the enzyme occurs in six forms which can be separated from one another[198,200,202] and which are all lacking in this disease.

10.5. Farber's Disease

Until now, Farber's lipogranulomatosis has been very rarely diagnosed (cf. Fig. 3 and Table 1, No. 1). According to *Sugita et al.*[203-205] a deficiency in ceramidase which, in acid solution, should split ceramides into sphingosine and fatty acids, is the cause of the observed storage of ceramide in several organs.

10.6. G_{M3}-Gangliosidosis

As has been described in the previous sections, hereditary defects of almost all sphingolipid hydrolases have been discovered in the last ten years. Until recently the exception was neuraminidase. In contrast to the other lysosomal sphingolipid hydrolases, this enzyme is found in the brain predominantly in the neuronal plasma membrane[206,207]. The enzyme releases sialic acid from its membrane-bound ganglioside substrates. The activity of neuraminidase (in this case probably of lysosomal origin) has now been reported to be considerably decreased in leucocytes or cultured fibroblasts from patients suffering from mucolipidoses, types I, II, and III[207a,207b,207c]. However, the chemical nature of the storage material has not yet been elucidated.

Storage of a neuraminidase substrate, ganglioside G_{M3}, has as yet only been observed in two patients. In the first patient the enzyme defect could not be identified as only formalin-fixed tissue was available for examination[208]. In the second patient *Brady et al.*[209,210] observed that, in addition to an increase in ganglioside G_{M3}, there was a lack of all the tetrasaccharide gangliosides present in healthy brain tissue. This abnormal ganglioside pattern is apparently not due to a disorder of degradation but of biosynthesis; whereas the neuraminidase activity in this patient appeared to be normal, the activity of *N*-acetylgalactosaminyl transferase, which extends ganglioside G_{M3} by one amino sugar and thus converts it to ganglioside G_{M2}, was greatly reduced[210].

11. Diagnosis of Homozygotes and Heterozygotes

On the basis of biochemical findings, the diagnosis of sphingolipidoses can now be obtained from a lipid analysis of the affected tissue or by measuring the enzyme defect in tissues or body fluids. The enzymatic analyses are used more widely as they can be carried out, not only with organ extracts, but also with extracts of leucocytes, cultured fibroblasts, or amniotic cells[45,49]. In addition, enzymatic analysis permits the identification of heterozygotes whose levels of enzyme activity usually lie between those of controls and patients[45,49,211-219]. The identification of disease carriers is a prerequisite for genetic counselling of affected families.

Enzyme analyses have confirmed the recessive mode of inheritance of the storage diseases. However, uncertainties arise in the diagnostic measurement of enzyme activities in cell cultures. The levels of activity of lysosomal enzymes from cultured cells of normal individuals vary widely and the activity also depends on the phase of the cell cycle[220]. Nevertheless, since there is no causal therapy for the sphingolipidoses, the enzyme analyses are of great importance, especially for prenatal diagnosis. Fetal cells taken from the amniotic fluid and maintained in culture contain a set of lysosomal enzymes which is very similar to that of cultured skin fibroblasts from children and adults[221-231]. These cells can therefore be used for prenatal diagnosis.

As a rule, enzyme measurements are carried out with synthetic substrates[49, 211-231]. Galactocerebroside β-galactosidase is an exception since its activity is measured towards radioactively labeled galactosylceramide[79].

The determination of specific enzyme defects in cultured amniotic cells and, in some cases, in the amniotic fluid itself allows in principle the prenatal diagnosis of all lipidoses with known enzyme defects. However, it remains questionable whether the identification of an enzyme defect with synthetic substrates is adequate as a diagnosis for a lipidosis. With synthetic substrates, the combined activities of several enzymes are often recorded which makes interpretation of the results difficult. As long as the enzyme deficiency is due to the absence of enzyme protein in the patient, it is also possible to use radioimmunological procedures for the diagnosis of the disease. This method has already been developed for Tay-Sachs disease by *Arnon et al.*[146].

12. Therapeutic Studies

The investigations carried out so far have supported the hypothesis that lipid storage in sphingolipidoses is caused by different deficiencies of degradative enzymes. It could thus be shown in model experiments that uptake of active enzymes by defective cells led to the degradation of the storage material. Defective fibroblasts take up lysosomal enzymes from the culture medium; the enzymes can have a considerable stability in the cells, with half lives of between a few days and several weeks[43, 44, 121]. On the basis of these experiments extremely pure enzymes have been infused into patients[44, 232, 233]. Encouraging short-term success was obtained, especially in forms of the disease which do not significantly affect the brain. The trihexosylceramide content of the plasma of patients with Fabry's disease decreased temporarily after the injection of ceramide trihexosidase; the glucocerebroside level in the erythrocytes of patients with Gaucher's disease falls after the injection of β-glucosidase[232]. Temporary improvements were also observed in patients with Fabry's disease after the transplantation of a healthy kidney which acts as a permanent source of the lacking enzyme, releasing it into the circulation[234-236]. However, in the case of lipidoses which mainly affect the brain therapeutic experiments have so far been unsuccessful[232, 233].

The infused enzyme is mainly taken up by the liver and degraded; it is apparently unable to penetrate the blood-brain barrier and reach the nervous tissue. Before enzyme replacement can be clinically used several problems still have to be solved. Since the infused enzyme is inactivated too quickly and eliminated from the organism, repeated doses are necessary; this can, in return, cause an undesirable immune response. These fundamental difficulties will not be overcome by methods in which the stability of the enzyme is increased by chemical modification[237, 238] or packing in the immunologically neutral erythrocyte ghosts[239, 240] or leucocytes[241] of the patient.

Theoretically there should be other means of therapy besides enzyme replacement. Among other methods which should be considered is the transfer of the genetic information for the defective or missing enzyme protein to the diseased organism by means of viral vectors. *Horst et al.*[242] recently reported an experiment with cell cultures which can be regarded as a model of this approach. They succeeded in transferring the genetic information for β-galactosidase from *E. coli* to cultured fibroblasts from a patient with G_{M1}-gangliosidosis by using the phage λ plac. At the moment, however, there is no evidence that such "genetic engineering" might be employed in the treatment of inherited illnesses.

13. Final Remarks

The biochemical investigation of sphingolipidoses has led to the identification of storage substances and enzyme deficiencies in most forms of these diseases. The gene mutations causing them can, however, only be determined when the protein chemistry of the enzymes involved is further advanced. The physiological function of the sphingolipids, above all in cell membranes, should also be more closely studied in order to obtain a better understanding of the pathogenesis of these diseases.

Received: July 8, 1976;
in shortened form: October 4, 1976 [A 158 IE]
German version: Angew. Chem. 89, 283 (1977)
Translated by: Dr. *Gail Schulz*, Göttingen

[1] *V. A. McKusick:* Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes. 4th Edit. Johns Hopkins Press, Baltimore 1975.
[2] *A. E. Garrod:* Inborn Errors of Metabolism. Oxford University Press, London 1923.
[3] *E. Klenk*, Hoppe-Seylers Z. Physiol. Chem. *262*, 128 (1939).
[4] *E. Klenk*, Hoppe-Seylers Z. Physiol. Chem. *267*, 128 (1941).
[5] *E. Klenk*, Hoppe-Seylers Z. Physiol. Chem. *268*, 50 (1941).
[6] *E. Klenk*, Hoppe-Seylers Z. Physiol. Chem. *273*, 76 (1942).
[7] *E. Klenk*, Ber. Dtsch. Chem. Ges. *75*, 1632 (1942).
[8] *E. Klenk, H. Langerbeins*, Hoppe-Seylers Z. Physiol. Chem. *270*, 185 (1941).
[9] *E. Klenk, F. Rennkamp*, Hoppe-Seylers Z. Physiol. Chem. *273*, 253 (1942).
[10] *A. Aghion:* La maladie de Gaucher dans l'enfance. Thèse, Université de Paris 1934.
[11] *H. Wiegandt*, Angew. Chem. *80*, 89 (1968); Angew. Chem. Int. Ed. Engl. *7*, 87 (1968).
[12] *R. W. Ledeen, R. K. Yu* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases, Academic Press, New York 1973, pp. 105f.
[13] *S. I. Hakamori*, Biochim. Biophys. Acta *417*, 55 (1975).
[14] *H. Wiegandt*, J. Neurochem. *14*, 671 (1967).
[15] *W. T. Norton* in *R. W. Albers*, G. J. Siegel, R. Katzman, B. W. Agranoff: Basic Neurochemistry. Little, Brown and Co., Boston 1972, pp. 365f.
[16] *S. Hakamori* in *R. Jeanloz, P. Balasz:* The Aminosugars. Bd. II-A. Academic Press, New York 1965, pp. 353f.
[17] *T. Yamakawa* in *E. Schütte:* Lipoide. 16. Colloquium der Gesellschaft Physiolog. Chemie, Mosbach. Springer, Berlin 1966, pp. 87f.
[18] *C. A. King, W. E. van Heyningen*, J. Infect. Dis. *127*, 639 (1973).
[19] *J. Holmgren, I. Lonnroth, L. Svennerholm*, Scand. J. Infect. Dis. *5*, 77 (1973).

[20] *P. Cuatrecasas*, Biochemistry *12*, 3547 (1973).
[21] *S. W. Craig, P. Cuatrecasas*, Proc. Natl. Acad. Sci. USA *72*, 3844 (1975).
[22] *T. Révész, M. Greaves*, Nature *257*, 103 (1975).
[23] *H. H. Sedlacek, J. Stärk, F. R. Seiler, W. Ziegler, H. Wiegandt*, FEBS Lett. *61*, 272 (1976).
[24] *J. Holmgren*, Infect. Immun. *8*, 851 (1973).
[25] *S. T. Donta, J. P. Viner*, Infect. Immun. *11*, 982 (1975).
[26] *Y. Takeda, T. Takeda, T. Honda, J. Sakurai, N. Ohtomo, T. Miwatani*, Infect. Immun. *12*, 931 (1975).
[27] *T. Honda, K. Goshima, Y. Takeda, Y. Sugino, T. Miwatani*, Infect. Immun. *13*, 163 (1976).
[28] *T. Honda, S. Taga, T. Takeda, M. A. Hasibuan, Y. Takeda, T. Miwatani*, Infect. Immun. *13*, 133 (1976).
[29] *F. Besancon, H. Ankel*, Nature *252*, 478 (1974).
[30] *B. R. Mullin, P. H. Fishman, G. Lee, S. M. Aloj, F. D. Ledley, R. J. Winand, L. D. Kohn, R. O. Brady*, Proc. Natl. Acad. Sci. USA *73*, 842 (1976).
[31] *W. E. van Heyningen*, J. Gen. Microbiol. *31*, 375 (1963).
[32] *W. E. van Heyningen, J. Mellanby*, J. Gen. Microbiol. *52*, 447 (1968).
[33] *S. Roseman*, Chem. Phys. Lipids *5*, 270 (1970).
[34] *S. Chipowsky, Y. C. Lee, S. Roseman*, Proc. Natl. Acad. Sci. USA *70*, 2309 (1973).
[35] *W. Stoffel*, Chem. Phys. Lipids *11*, 318 (1973).
[36] *P. Morell, P. Braun*, J. Lipid Res. *13*, 293 (1972).
[37] *S. Gatt, Y. Barenholz*, Annu. Rev. Biochem. *42*, 61 (1973).
[38] *J. C. Steigerwald, S. Basu, B. Kaufman, S. Roseman*, J. Biol. Chem. *250*, 6727 (1975).
[39] *H. J. Maccioni, A. Arce, R. Caputto*, Biochem. J. *125*, 1131 (1971).
[40] *W. D. Marggraf, F. A. Anderer*, Hoppe-Seylers Z. Physiol. Chem. *355*, 803 (1974).
[41] *B. W. Volk, S. M. Aronson:* Sphingolipids, Sphingolipidoses and Allied Disorders. Plenum, New York 1972.
[42] *H. Jatzkewitz*, Dtsch. Med. Wochenschr. *95*, 131 (1970).
[43] *R. O. Brady*, Angew. Chem. *85*, 28 (1973); Angew. Chem. Int. Ed. Engl. *12*, 1 (1973).
[44] *E. Neufeld, T. W. Lim, L. J. Shapiro*, Annu. Rev. Biochem. *44*, 357 (1975).
[45] *B. W. Volk, L. Schneck:* The Gangliosidoses. Plenum, New York 1975.
[46] *H. G. Hers* in *H. G. Hers, F. van Hoff:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 147f.
[47] *R. D. Terry, M. Weiss*, J. Neuropathol. Exp. Neurol. *22*, 18 (1963).
[48] *S. Samuels, S. R. Korey, J. Gonatas, R. D. Terry, M. Weiss*, J. Neuropathol. Exp. Neurol. *22*, 81 (1963).
[49] *M. M. Kaback, R. R. Howell* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 599f.
[50] *E. Mehl, H. Jatzkewitz*, Biochim. Biophys. Acta *151*, 619 (1968).
[51] *G. Fischer, H. Jatzkewitz*, Hoppe-Seylers Z. Physiol. Chem. *356*, 605 (1975).
[52] *G. Fischer, H. Jatzkewitz*, personal communication.
[53] *Y. T. Li, M. Y. Mazzotta, C. C. Wan, R. Orth, S. C. Li*, J. Biol. Chem. *248*, 7512 (1973).
[54] *S. C. Li, C. C. Wan, M. Y. Mazzotta, Y. T. Li*, Carbohydr. Res. *34*, 180 (1974).
[55] *S. C. Li, Y. T. Li*, J. Biol. Chem. *251*, 1159 (1976).
[56] *M. W. Ho, J. S. O'Brien*, Proc. Natl. Acad. Sci. USA *68*, 2810 (1971).
[57] *M. W. Ho, J. S. O'Brien, N. S. Radin, J. S. Erickson*, Biochem. J. *131*, 173 (1973).
[58] *M. W. Ho*, FEBS Lett. *53*, 243 (1975).
[59] *M. W. Ho, N. D. Light*, Biochem. J. *136*, 821 (1973).
[60] *M. W. Ho* in *J. M. Tager, G. J. M. Hooghwinkel, W. Th. Daems:* Enzyme Therapy in Lysosomal Storage Diseases. Elsevier, Amsterdam 1974, pp. 239f.
[61] *M. W. Ho, M. Rigby*, Biochim. Biophys. Acta *397*, 267 (1975).
[62] *F. van Hoof* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 305f.
[63] *H. Jatzkewitz, K. Sandhoff*, Biochim. Biophys. Acta *70*, 354 (1963).
[64] *K. Suzuki, G. C. Chen*, J. Lipid Res. *8*, 105 (1967).
[65] *Y. Suzuki, K. Suzuki*, J. Biol. Chem. *249*, 2113 (1974).
[66] *A. G. W. Norden, L. L. Tennant, J. S. O'Brien*, J. Biol. Chem. *249*, 7969 (1974).
[67] *J. S. O'Brien*, Clin. Genet. *8*, 303 (1975).
[68] *K. Suzuki*, Science *159*, 1471 (1968).
[69] *K. Suzuki, K. Suzuki, S. Kamoshita*, J. Neuropathol. Exp. Neurol. *28*, 25 (1969).
[70] *J. W. Callahan, L. S. Wolfe*, Biochim. Biophys. Acta *215*, 527 (1970).
[71] *G. C. Tsay, G. Dawson*, Biochem. Biophys. Res. Commun. *52*, 759 (1973).
[72] *L. S. Wolfe, R. G. Senior, N. M. K. Ng Ying Kin*, J. Biol. Chem. *249*, 1828 (1974).
[73] *N. M. K. Ng Ying Kin, L. S. Wolfe*, Biochem. Biophys. Res. Commun. *66*, 123 (1975).
[74] *E. F. Gilbert, J. Varakis, J. M. Opitz, G. M. Zu Rhein, R. Ware, C. Viseskul, E. G. Kaveggia, H. A. Hartmann*, Z. Kinderheilkd. *120*, 151 (1975).
[75] *L. Pinsky, J. Miller, B. Shanfield, G. Watters, L. S. Wolfe*, Am. J. Hum. Genet. *26*, 563 (1974).
[76] *M. C. B. Loonen, L. v. d. Lugt, C. L. Franke*, Lancet II, 785 (1974).
[77] *A. G. W. Norden, J. S. O'Brien*, Proc. Natl. Acad. Sci. USA *72*, 240 (1975).
[78] *L. Chou, C. I. Kaye, H. L. Nadler*, Pediatr. Res. *8*, 120 (1974).
[79] *K. Suzuki, K. Suzuki* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 395f.
[80] *K. Suzuki, Y. Suzuki*, Proc. Natl. Acad. Sci. USA *66*, 302 (1970).
[81] *Y. Suzuki, K. Suzuki*, Science *171*, 73 (1971).
[82] *T. Miyatake, K. Suzuki*, J. Biol. Chem. *247*, 5398 (1972).
[83] *T. Miyatake, K. Suzuki*, Biochem. Biophys. Res. Commun. *48*, 538 (1972).
[84] *T. Miyataka, K. Suzuki*, J. Neurochem. *22*, 231 (1974).
[85] *D. A. Wenger, M. Sattler, S. P. Markey*, Biochem. Biophys. Res. Commun. *53*, 680 (1973).
[86] *D. A. Wenger, M. Sattler, W. Hiatt*, Proc. Natl. Acad. Sci. USA *71*, 854 (1974).
[87] *D. A. Wenger, M. Sattler, C. Clark, H. McKelvey*, Clin. Chim. Acta *56*, 199 (1974).
[88] *J. Austin*, Arch. Neurol. (Chicago) *9*, 207 (1963).
[89] *L. Svennerholm* in *J. Folch-Pi, H. Bauer:* Brain Lipids and Lipoproteins, and the Leucocodystrophies. Elsevier, Amsterdam 1963, pp. 104f.
[90] *M. T. Vanier, L. Svennerholm*, Acta Paediatr. Scand. *64*, 641 (1975).
[91] *D. A. Stumpf, J. H. Austin*, Trans. Am. Neurol. Assoc. *97*, 29 (1972).
[92] *D. A. Stumpf, J. H. Austin, A. C. Crocker, M. La France*, Am. J. Dis. Child. *126*, 747 (1973).
[93] *A. L. Fluharty, R. L. Stevens, D. L. Sanders, H. Kihara*, Biochem. Biophys. Res. Commun. *59*, 455 (1974).
[94] *J. W. Spranger, M. R. Wiedemann*, Humangenetik *9*, 113 (1970).
[95] *J. F. O'Brien, M. Cantz, J. Spranger*, Biochem. Biophys. Res. Commun. *60*, 1170 (1974).
[96] *H. Jatzkewitz*, Hoppe-Seylers Z. Physiol. Chem. *311*, 279 (1958).
[97] *J. H. Austin*, Proc. Soc. Exp. Biol. Med. *100*, 361 (1959).
[98] *E. Mehl, H. Jatzkewitz*, Hoppe-Seylers Z. Physiol. Chem. *339*, 260 (1964).
[99] *E. Mehl, H. Jatzkewitz*, Biochem. Biophys. Res. Commun. *19*, 407 (1965).
[100] *J. H. Austin, A. S. Balasubramanian, T. N. Pattabiraman, S. Saraswathi, D. K. Basu, B. K. Bachhawat*, J. Neurochem. *10*, 805 (1963).
[101] *J. Austin, D. McAfee, L. Shearer*, Arch. Neurol. (Chicago) *12*, 447 (1965).
[102] *H. Jatzkewitz, K. Stinshoff*, FEBS Lett. *32*, 129 (1973).
[103] *H. Baum, K. S. Dodgson, B. Spencer*, Clin. Chim. Acta *4*, 453 (1959).
[104] *B. C. Harinath, E. Robins*, J. Neurochem. *18*, 245 (1971).
[105] *H. Jatzkewitz, E. Mehl*, J. Neurochem. *16*, 19 (1969).
[106] *A. Jerfy, A. B. Roy*, Biochim. Biophys. Acta *293*, 178 (1973).
[107] *K. Harzer, K. Stinshoff, W. Mraz, H. Jatzkewitz*, J. Neurochem. *20*, 279 (1973).
[108] *E. Neuwelt, D. Stumpf, J. Austin, P. Kohler*, Biochim. Biophys. Acta *236*, 333 (1971).
[109] *E. Neuwelt, P. F. Kohler, J. Austin*, Immunochemistry *10*, 767 (1973).
[110] *R. L. Stevens, A. L. Fluharty, M. H. Skokut, H. Kihara*, J. Biol. Chem. *250*, 2495 (1975).
[111] *K. Harzer, H. U. Benz*, Hoppe-Seylers Z. Physiol. Chem. *355*, 744 (1974).
[112] *M. Sugita, J. T. Dulaney, H. W. Moser*, J. Lipid Res. *15*, 227 (1974).
[113] *Y. Eto, U. Wiesmann, N. N. Herschkowitz*, J. Biol. Chem. *249*, 4955 (1974).
[114] *A. L. Fluharty, R. L. Stevens, R. T. Miller, H. Kihara*, Biochem. Biophys. Res. Commun. *61*, 348 (1974).
[115] *K. Yamato, S. Handa, T. Yamakawa*, J. Biochem. (Tokyo) *75*, 1241 (1974).
[116] *S. Yamaguchi, K. Aoki, S. Handa, T. Yamakawa*, J. Neurochem. *24*, 1087 (1975).
[117] *W. Scholz*, Z. Gesamte Neurol. Psychiatr. *99*, 651 (1925).
[118] *J. Austin* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 411f.
[119] *J. S. O'Brien, E. L. Sampson*, Science *150*, 1613 (1965).
[120] *K. Suzuki, K. Suzuki, G. Chen*, Science *151*, 1231 (1966).
[121] *H. Kihara, M. T. Porter, A. L. Fluharty*, Birth Defects. Orig. Artic. Ser. *9*, 19 (1973).
[122] *M. T. Porter, A. L. Fluharty, J. Trammell, H. Kihara*, Biochem. Biophys. Res. Commun. *44*, 660 (1971).
[123] *J. Austin*, Trans. Am. Neurol. Assoc. *83*, 149 (1958).
[124] *J. Austin*, Res. Publ. Assoc. Res. Nerv. Ment. Dis. *40*, 189 (1960).
[125] *J. V. Murphy, H. J. Wolfe, E. A. Balazs, H. W. Moser* in *J. Bernsohn, H. J. Grossman:* Lipid Storage Diseases. Academic Press, New York 1971, pp. 67f.

[126] *Y. Eto, U. N. Wiesmann, J. H. Carson, N. N. Herschkowitz*, Arch. Neurol. (Chicago) *30*, 153 (1974).
[127] *D. Stumpf, E. Neuwelt, J. Austin, P. Kohler*, Arch. Neurol. (Chicago) *25*, 427 (1971).
[128] *W. Tay*, Trans. Ophthalmol. Soc. U. K. *1*, 55 (1881).
[129] *J. S. O'Brien* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 323f.
[130] *K. Sandhoff, K. Harzer* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 345f.
[131] *L. Svennerholm*, Biochem. Biophys. Res. Commun. *9*, 436 (1962).
[132] *R. Ledeen, K. Salsman*, Biochemistry *4*, 2225 (1965).
[133] *K. Sandhoff, U. Andreae, H. Jatzkewitz*, Pathol. Eur. *3*, 278 (1968).
[134] *K. Sandhoff, K. Harzer, W. Wässle, H. Jatzkewitz*, J. Neurochem. *18*, 2469 (1971).
[135] *K. Sandhoff*, FEBS Lett. *4*, 351 (1969).
[136] *D. Robinson, J. L. Stirling*, Biochem. J. *107*, 321 (1968).
[137] *K. Sandhoff*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1095 (1968).
[138] *K. Sandhoff, W. Wässle*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1119 (1971).
[139] *K. Sandhoff*, FEBS Lett. *11*, 342 (1970).
[140] *J. F. Tallman, R. O. Brady, M. V. Quirk, M. Villalba, A. E. Gal*, J. Biol. Chem. *249*, 3489 (1974).
[141] *S. Okada, J. S. O'Brien*, Science *165*, 698 (1969).
[142] *B. Hultberg*, Lancet II, 1195 (1969).
[143] *M. Carroll, D. Robinson*, Biochem. J. *131*, 91 (1973).
[144] *S. K. Srivastava, E. Beutler*, J. Biol. Chem. *249*, 2054 (1974).
[145] *E. Beutler, W. Kuhl*, Nature *258*, 262 (1975).
[146] *B. Geiger, R. Navon, Y. Ben-Yoseph, R. Arnon*, Eur. J. Biochem. *56*, 311 (1975).
[147] *P. D. Snyder Jr., W. Krivit, C. C. Sweeley*, J. Lipid Res. *13*, 128 (1972).
[148] *W. Krivit, R. J. Desnick, J. Lee, J. Moller, F. Wright, C. C. Sweeley, P. D. Snyder, H. L. Sharp*, Am. J. Med. *52*, 763 (1972).
[149] *S. Okada, M. McCrea, J. S. O'Brien*, Pediatr. Res. *6*, 606 (1972).
[150] *Y. Suzuki, J. C. Jacob, K. Suzuki, K. M. Kutty, K. Suzuki*, Neurology *21*, 313 (1971).
[151] *E. M. Brett, R. B. Ellis, L. Haas, J. U. Ikonne, B. D. Lake, A. D. Patrick, R. Stephens*, Arch. Dis. Child. *48*, 775 (1973).
[152] *C. M. de Baecque, K. Suzuki, I. Rapin, A. B. Johnson, D. L. Whethers, K. Suzuki*, Acta Neuropathol. *33*, 207 (1975).
[153] *H. Bernheimer, F. Seitelberger*, Wiener Klin. Wochenschr. *80*, 163 (1968).
[154] *K. Suzuki, K. Suzuki, I. Rapin, Y. Suzuki, N. Ishii*, Neurology *20*, 190 (1970).
[155] *S. Okada, M. L. Veath, J. S. O'Brien*, J. Pediatr. *77*, 1063 (1970).
[156] *I. Rapin, K. Suzuki, K. Suzuki, M. P. Valsamis*, Arch. Neurol. (Chicago) *33*, 120 (1976).
[157] *Y. Suzuki, K. Suzuki*, Neurology *20*, 848 (1970).
[158] *J. Zerfowski, K. Sandhoff*, Acta Neuropathol. *27*, 225 (1974).
[159] *K. Sandhoff, E. C. Conzelmann, H. Nehrkorn*, Hoppe Seylers Z. Physiol. Chem., in press (1977).
[160] *B. Geiger, R. Arnon*, Biochemistry *15*, 3484 (1976).
[161] *E. Beutler, W. Kuhl, D. Comings*, Am. J. Hum. Genet. *27*, 628 (1975).
[162] *J. U. Ikonne, M. C. Ratazzi, R. J. Desnick*, Am. J. Hum. Genet. *27*, 639 (1975).
[163] *G. H. Thomas, H. A. Taylor Jr., C. S. Miller, J. Axelman, B. R. Migeon*, Nature *250*, 580 (1974).
[164] *H. Galjaard, A. Hoogeveen, H. A. de Wit-Verbeek, A. J. J. Reuser, W. Keijzer, A. Westerveld, D. Bootsma*, Exp. Cell Res. *87*, 444 (1974).
[165] *H. H. Ropers, K. H. Grzeschik, E. Bühler*, Humangenetik *26*, 117 (1975).
[166] *M. C. Rattazzi, J. A. Brown, R. G. Davidson, T. B. Shows*, Cytogenet. Cell Genet. *14*, 232 (1975).
[167] *N. van Cong, D. Weil, R. Rebourcet, C. Pangalos, J. Frézal*, Cytogenet. Cell Genet. *14*, 272 (1975).
[168] *H. van Someren, H. Beijersbergen van Henegouwen*, Humangenetik *18*, 171 (1973).
[169] *T. A. Tedesco, C. Croce, H. Boedecker*, Am. J. Hum. Genet. *25*, 78a (1973).
[170] *P. A. Lalley, M. C. Rattazzi, T. B. Shows*, Proc. Natl. Acad. Sci. USA *71*, 1569 (1974).
[171] *F. Gilbert, R. Kucherlapati, R. P. Creagan, M. J. Murnane, G. J. Darlington, F. H. Ruddle*, Proc. Natl. Acad. Sci. USA *72*, 263 (1975).
[172] *J. A. Kint, D. Carton* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973. pp. 357f.
[173] *J. R. Wherrett, S. I. Hakamori*, J. Biol. Chem. *248*, 3046 (1973).
[174] *E. Beutler, W. Kuhl*, Am. J. Hum. Genet. *24*, 237 (1972).
[175] *S. Wood, H. L. Nadler*, Am. J. Hum. Genet. *24*, 250 (1972).
[176] *R. O. Brady, A. E. Gal, R. M. Bradley, E. Martensson*, J. Biol. Chem. *243*, 1021 (1967).
[177] *J. A. Kint*, Science *167*, 1268 (1970).
[178] *P. J. G. M. Rietra, J. L. Molenaar, M. N. Hamers, J. M. Tager, P. Borst*, Eur. J. Biochem. *46*, 89 (1974).
[179] *E. Beutler, W. Kuhl*, N. Engl. J. Med. *289*, 694 (1973).
[180] *E. Beutler, W. Kuhl*, J. Biol. Chem. *247*, 7195 (1972).
[181] *I. Kano, T. Yamakawa*, Chem. Phys. Lipids *13*, 283 (1974).
[182] *P. J. G. M. Rietra, F. A. J. T. M. van den Bergh, J. M. Tager*, Clin. Chim. Acta *62*, 401 (1975).
[183] *R. O. Brady, J. N. Kanfer, D. Shapiro*, Biochem. Biophys. Res. Commun. *18*, 221 (1965).
[184] *R. O. Brady, J. N. Kanfer, R. M. Bradley, D. Shapiro*, J. Clin. Invest. *45*, 1112 (1966).
[185] *P. G. Pentchev, R. O. Brady, S. R. Hibbert, A. E. Gal, D. Shapiro*, J. Biol. Chem. *248*, 5256 (1973).
[186] *R. O. Brady, J. N. Kanfer, M. B. Mock, D. S. Fredrickson*, Proc. Natl. Acad. Sci. USA *55*, 366 (1966).
[187] *P. B. Schneider, E. P. Kennedy*, J. Lipid Res. *8*, 202 (1967).
[188] *R. O. Brady, F. M. King* in *H. G. Hers, F. van Hoof:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 439f.
[189] *J. W. Callahan, M. Khalil, J. Gerrie*, Biochem. Biophys. Res. Commun. *58*, 384 (1974).
[190] *J. W. Callahan, M. Khalil, M. Philippart*, Pediatr. Res. *9*, 908 (1975).
[191] *S. Gatt*, Biochem. Biophys. Res. Commun. *68*, 235 (1976).
[192] *F. van Hoof, H. G. Hers*, Eur. J. Biochem. *7*, 34 (1968).
[193] *P. Durand, C. Borrone, G. Della Cella*, J. Pediatr. *75*, 665 (1969).
[194] *V. Patel, I. Watanabe, W. Zeman*, Science *176*, 426 (1972).
[195] *F. van Hoof in H. G. Hers, F. van Hoff:* Lysosomes and Storage Diseases. Academic Press, New York 1973, pp. 277f.
[196] *C. Borrone, R. Gatti, X. Trias, P. Durand*, J. Pediatr. *84*, 727 (1974).
[197] *G. Dawson, J. W. Spranger*, N. Engl. J. Med. *285*, 122 (1971).
[198] *J. A. Alhadeff, A. L. Miller, H. Wenaas, T. Vedvick, J. S. O'Brien*, J. Biol. Chem. *250*, 7106 (1975).
[199] *B. G. Kouseff, N. G. Beratis, L. Strauss, P. W. Brill, R. E. Rosenfield, B. Kaplan, K. Hirschhorn*, Pediatrics *57*, 205 (1976).
[200] *B. M. Turner, V. S. Turner, N. G. Beratis, K. Hirschhorn*, Am. J. Hum. Genet. *27*, 651 (1975).
[201] *B. M. Turner, N. G. Beratis, V. S. Turner, K. Hirschhorn*, Nature *257*, 391 (1975).
[202] *R. Thorpe, D. Robinson*, FEBS Lett. *54*, 89 (1975).
[203] *M. Sugita, J. T. Dulaney, H. W. Moser*, Science *178*, 1100 (1972).
[204] *M. Sugita, M. Iwamori, J. Evans, R. H. McCluer, J. T. Dulaney, H. W. Moser*, J. Lipid Res. *15*, 223 (1974).
[205] *M. Sugita, M. Williams, J. T. Dulaney, H. W. Moser*, Biochim. Biophys. Acta *398*, 125 (1975).
[206] *C. L. Schengrund, A. Rosenberg*, J. Biol. Chem. *245*, 6196 (1970).
[207] *G. Tettamanti, I. G. Morgan, G. Gombos, G. Vincendon, P. Mandel*, Brain Res. *47*, 515 (1972).
[207a] *M. Cantz, J. Gehler, J. Spranger*, Biochem. Biophys. Res. Commun. *74*, 732 (1977).
[207b] *G. H. Thomas, G. E. Tiller, L. W. Reynolds, C. S. Miller, J. W. Bace*, Biochem. Biophys. Res. Commun. *71*, 188 (1976).
[207c] *G. Strecker, J. C. Michalski, J. Montreuil, J. P. Farriaux*, Biomedicine *25*, 238 (1976).
[208] *H. Pilz, K. Sandhoff, H. Jatzkewitz*, J. Neurochem. *13*, 1273 (1966).
[209] *S. R. Max, N. K. Maclaren, R. O. Brady, R. M. Bradley, M. B. Rennels, J. Tanaka, J. H. Garcia, M. Cornblath*, N. Engl. J. Med. *291*, 929 (1974).
[210] *P. H. Fishman, S. R. Max, J. F. Tallman, R. O. Brady, N. K. Maclaren, M. Cornblath*, Science *187*, 68 (1975).
[211] *D. L. Johnson, M. A. del Monte, E. Cotlier, R. J. Desnick*, Clin. Chim. Acta *63*, 81 (1975).
[212] *A. Saifer, G. Perle, C. Valenti, L. Schneck* in *B. W. Volk, S. M. Aronson:* Sphingolipids, Sphingolipidoses and Allied Disorders. Plenum Press, New York 1972, pp. 599f.
[213] *J. S. O'Brien, M. W. Ho, S. Okada, K. Zielke, M. L. Veath, L. Tennant* in *B. W. Volk, S. M. Aronson:* Sphingolipids, Sphingolipidoses and Allied Disorders, Plenum Press, New York 1972, pp. 581f.
[214] *K. Zielke, M. L. Veath, J. S. O'Brien*, J. Exp. Med. *136*, 197 (1972).
[215] *C. W. Hall, E. F. Neufeld*, Arch. Biochem. Biophys. *158*, 817 (1973).
[216] *K. Harzer*, Humangenetik *20*, 9 (1973).
[217] *K. Harzer, H. U. Benz*, J. Neurochem. *21*, 999 (1973).
[218] *K. Harzer, K. Sandhoff, H. Schall, F. Kollmann*, Klin. Wochenschr. *49*, 1189 (1971).
[219] *M. M. Kaback, J. S. O'Brien*, Hosp. Pract. *8*, 107 (1973).
[220] *S. Chatterjee, L. F. Velicer, C. C. Sweeley*, J. Biol. Chem. *250*, 4972 (1975).
[221] *A. Milunsky, J. W. Littlefield, J. N. Kanfer, E. H. Kolodny, V. E. Shih, L. Atkins*, N. Engl. J. Med. *283*, 1370 (1970).
[222] *A. Milunsky, J. W. Littlefield, J. N. Kanfer, E. H. Koldny, V. E. Shih, L. Atkins*, N. Engl. J. Med. *283*, 1441 (1970).
[223] *A. Milunsky, J. W. Littlefield, J. N. Kanfer, E. H. Kolodny, V. E. Shih, L. Atkins*, N. Engl. J. Med. *283*, 1498 (1970).
[224] *B. K. Burton, A. B. Gerbie, H. L. Nadler*, Am. J. Obstet. Gynecol. *118*, 718 (1974).
[225] *P. S. Harper, K. M. Laurence, A. Parkes, F. S. Wusteman, H. Kresse, K. v. Figura, M. A. Ferguson-Smith, D. M. Duncan, R. W. Logan, F. Hall, P. Whiteman*, J. Med. Genet. *11*, 123 (1974).

[226] *R. J. Desnick, W. Krivit, H. L. Sharp*, Biochem. Biophys. Res. Commun. *51*, 20 (1973).
[227] *R. C. A. Sengers, K. J. B. Lamers, J. A. J. M. Bakkeren, E. D. A. M. Schretlen, J. M. F. Trijbels*, Neuropaediatrie *6*, 377 (1975).
[228] *H. Galjaard, A. Hoogeveen, W. Keijzer, E. de Wit-Verbeek, C. Vlek-Noot*, Histochem. J. *6*, 491 (1974).
[229] *M. F. Niermeijer, W. J. Kleijer, M. Jahodova, E. S. Sachs, H. Galjaard*, J. Genet. Hum. *23*, 123 (1975).
[230] *A. E. Gal, R. O. Brady, S. R. Hibbert, P. G. Pentchev*, N. Engl. J. Med. *293*, 632 (1975).
[231] *A. Scharfman, N. Houdret, P. Roussel, G. Biserte, C. Aerts, A. B. Tonnel, C. Voisin*, Clin. Chim. Acta *63*, 369 (1975).
[232] *P. G. Pentchev, R. O. Brady, A. E. Gal, S. R. Hibbert*, J. Mol. Med. *1*, 73 (1975).
[233] *J. F. Tallman, P. G. Pentchev, R. O. Brady*, Enzyme *18*, 136 (1974).
[234] *M. Phillippart, S. S. Franklin, A. Gordon*, Ann. Intern. Med. *77*, 195 (1972).
[235] *M. Phillippart*, Birth Defects, Orig. Artic. Ser. *9*, 81 (1973).
[236] *R. J. Desnick, K. Y. Allen, R. L. Simmons, J. E. Woods, C. F. Anderson, J. S. Najarian, W. Krivit*, Birth Defects, Orig. Artic. Ser. *9*, 88 (1973).
[237] *P. D. Snyder Jr., F. Wold, R. W. Bernlohr, C. Dullum, R. J. Desnick, W. Krivit, R. C. Condie*, Biochim. Biophys. Acta *350*, 432 (1974).
[238] *B. Geiger, B. U. v. Specht, R. Arnon*, Eur. J. Biochem. *73*, 144 (1977).
[239] *G. M. Ihler, R. H. Glew, F. W. Schnurre*, Proc. Natl. Acad. Sci. USA *70*, 2663 (1973).
[240] *M. B. Fiddler, S. R. Thorpe, R. J. Desnick*, Am. J. Hum. Genet. *26*, 30a (1974).
[241] *C. M. Cohen, G. Weissmann, S. Hoffstein, Y. C. Awasthi, S. K. Srivastava*, Biochemistry *15*, 452 (1976).
[242] *J. Horst, F. Kluge, K. Beyreuther, W. Gerok*, Proc. Natl. Acad. Sci. USA *72*, 3531 (1975).

Efficiency and Evolution of Enzyme Catalysis

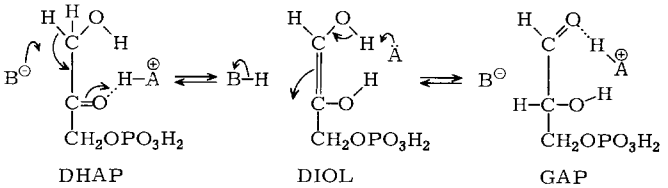
By W. John Albery and Jeremy R. Knowles[*]

A new function derived from kinetic data, the efficiency function, can be used to quantify the efficiency of a catalyst. For freely diffusing species the maximum efficiency is unity. The enzyme triose phosphate isomerase has an efficiency of 0.6 and is thus almost a perfect catalyst. The efficiency of the acetate ion as catalyst for the same reaction is 2.5×10^{-11}. This increase in catalytic efficiency is discussed in terms of three types of evolutionary improvement: the uniform binding of the substrate to the enzyme, changes in the internal thermodynamics of the bound states, and more effective catalysis of elementary steps. These concepts are illustrated for triose phosphate isomerase.

1. Introduction

Chemical kinetics without catalysis is like skiing without skis. Enzymes are nature's catalysts and every living system depends on the efficiency with which they mediate the flow of energy and material through the organism. During the last 10^9 years (1 G year) the different species have evolved in response to environmental pressures. Likewise we may expect that enzymes have improved and become better catalysts as a result of the pressures that select those organisms possessing a more efficient flow of energy and material.

For instance, the glycolytic enzyme triose phosphate isomerase catalyzes the reaction shown in Scheme 1 some 10^{10} times more effectively than does a simple catalyst like acetate ion[1].



Scheme 1. Isomerization of dihydroxyacetone phosphate (DHAP) *via* enediol (DIOL) to D-glyceraldehyde 3-phosphate (GAP). This reaction is catalyzed by triose phosphate isomerase.

We should not be too surprised that the enzyme is a far more efficient catalyst than the simple functional groups that comprise it. Clearly in order to control the flow of energy and material through the living system it is essential that the desired processes should take place much more rapidly than the random thermal reactions of the different metabolites. Hence there has to be a large difference in catalytic efficiency between the simple catalysts and the enzymes. Can we quantify this difference, and is there any limit to how efficient a catalyst can be? Is there such a thing as a "perfect" catalyst? The answer to both these questions is yes, and the first part of this paper is concerned with describing an "efficiency function" for catalyzed reactions in solution; in the second part the function will be applied to triose phosphate isomerase.

2. The Efficiency Function

Although the concepts presented below are general ones, in order to avoid too much algebra, we will apply them to the simple reaction shown in Scheme 2.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EP \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E + P \qquad K$$

Scheme 2. E = catalyst, S = substrate, P = product.

[*] Dr. W. J. Albery
Physical Chemistry Laboratory
South Parks Road, Oxford, OX1 3QZ (Great Britain)
Prof. J. R. Knowles
Department of Chemistry, Harvard University
12, Oxford St., Cambridge, Mass. 02138 (USA)

This reaction involves a single substrate, a single product, a single step for their interconversion, and has an overall equilibrium constant

$$K=[P]_{eq}/[S]_{eq}$$

Although the letter E suggests an enzyme, Scheme 2 simply describes the interconversion of S and P in solution effected by *any* catalyst E. In this paper, however, we will refer to E as the enzyme, recognizing that this dignifies simple organic catalysts with a title they do not deserve.

The reaction in Scheme 2 may take place under "irreversible" or "reversible" conditions. Under "irreversible" conditions the back reaction of P to S does not take place to any significant extent. This may be because P is thermodynamically so stable that its chances of return are negligible, or it may be that P is removed by some subsequent reaction that is sufficiently rapid to prevent its return to S. Under "reversible" conditions, the net flux of material from S to P is small enough for the concentrations of S and P to be close to their equilibrium values. This would occur if the reaction catalyzed by E is flanked by two relatively slow processes:

$$\xrightarrow{\text{slow}} S+E \overset{\text{fast}}{\rightleftharpoons} E+P \xrightarrow{\text{slow}}$$

In an ordered sequence of enzyme-catalyzed reactions one step often controls the flux through the whole sequence. This step has to be an irreversible step. Control cannot be exercised through a reversible step, because the transition state between S and P is then of such low free energy that it does not influence the flux through either the earlier or the later steps. On the other hand it is much more efficient for steps which are *not* control steps to operate reversibly rather than irreversibly. This is because for a given flux less entropy is created under reversible conditions.

Now, let us propose a function, y, that measures the efficiency of a catalyst[2]:

$$y=\frac{[E]_0(1-[P]/K[S])}{\vec{v}} \tag{1}$$

where $[E]_0$ is the total concentration of the enzyme and $\vec{v}$ is the velocity of the reaction from left to right. Under irreversible conditions $[P] \ll K[S]$ and y is then $[E]_0/\vec{v}$, which is simply the reciprocal of the turnover number of the enzyme. The term in brackets describes how far the system is perturbed from equilibrium and modifies the turnover number to cover the reversible cases.

How does y vary with each of the variables on the right hand side of equation (1)? First, if all the concentrations are held constant and the velocity of reaction, $\vec{v}$, is increased, y decreases. Secondly, if the velocity of reaction, [P], and [S] are all held constant, but the concentration of enzyme is decreased, y decreases. Thirdly, if for the same concentration of enzyme and the same velocity of reaction the perturbation of [S] and [P] from their equilibrium values is decreased, y decreases. All these three changes therefore lead to a decrease in y, but they are all changes in which the enzyme has become a more efficient catalyst. In the first case the velocity of reaction is larger; in the second the same velocity is maintained with less enzyme and in the third the same velocity is maintained closer to reversible conditions and with more product and/or less substrate present. In a metabolic pathway this is an advantage because S is itself a product and P a substrate for other enzyme-catalyzed reactions in the sequence. A lower concentration of S decreases the rate of the back reaction through the previous step or steps and a higher concentration of P increases the forward rate through the subsequent step or steps. Furthermore, the more reversible is the system the more efficient it is.

Table 1. Variation of y in equation (1).

	Less Enzyme $[E]_0$	Greater Flux $\vec{v}$	More Reversible $(1-[P]/K[S])$
Improved efficiency	↓	↑	↓
Change in y	↓	↓	↓

These arguments are summarized in Table 1. *Hence we can conclude that the lower the value of y the more efficient is the enzyme or catalyst.* This will be true whether we are concerned with maximizing the velocity of the reaction, or achieving a given velocity with as little catalyst as possible, or perturbing the system as little as possible from equilibrium. It is important to have such a general function, since in the biochemical environment the enzyme may operate under conditions of constant flux, or of constant metabolite pool concentrations, or neither.

We next find how the velocity of the reaction, $\vec{v}$, depends on the rate constants of Scheme 2, and so obtain

$$y=a/[S]+b+\theta c \tag{2}$$

where

$$a=\frac{\vec{K}_m}{\vec{k}_{cat}}=\frac{1}{k_1}+\frac{k_{-1}}{k_1k_2}+\frac{k_{-1}k_{-2}}{k_1k_2k_3} \tag{3}$$

$$b=\frac{1}{\vec{k}_{cat}}=\frac{1}{k_2}+\frac{k_{-2}}{k_2k_3}+\frac{1}{k_3} \tag{4}$$

$$c=\frac{1}{\overleftarrow{k}_{cat}}=\frac{1}{k_{-2}}+\frac{k_2}{k_{-1}k_{-2}}+\frac{1}{k_{-1}} \tag{5}$$

The value of θ is zero for the irreversible case and is unity for the reversible case; $\vec{K}_m$ is the Michaelis constant for the irreversible reaction from left to right. These equations describe how the function y is related to the free energy profile of the reaction. Each individual term in the expressions for a, b, and c is associated with a single free energy difference, as shown in Figure 1.

Under irreversible conditions ($\theta=0$) the c terms describing $\overleftarrow{k}_{cat}$ for the back reaction are not included in y at all [equation (2)]. The a and b terms between them describe every possible rate-limiting barrier that the system has to surmount in going from left to right. Under reversible conditions ($\theta=1$) we have in addition the c terms which 'mirror' the b terms for the back reaction. The a terms are not 'mirrored' in this way.

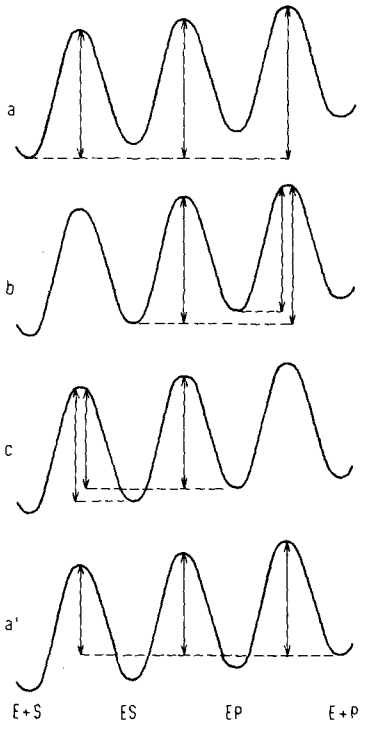


Fig. 1. The free energy differences associated with each term in the expressions for a, b, c, and a' in equations (3) to (6). Note that the k_{cat} terms in b and c involve the bound states ES and EP while the a terms and a' terms relate all three transition states to E+S and E+P respectively.

This is because the Haldane relation holds. This relation states that the overall equilibrium constant:

$$K = \frac{[P]_{eq}}{[S]_{eq}} = \frac{a'}{a}$$

where

$$a' = \frac{\overleftarrow{K}_m}{\overleftarrow{k}_{cat}} = \frac{1}{k_{-3}} + \frac{k_3}{k_{-2}k_{-3}} + \frac{k_2 k_3}{k_{-1}k_{-2}k_{-3}} \qquad (6)$$

$\overleftarrow{K}_m$ is the Michaelis constant for the irreversible reaction from right to left. The a' terms are also illustrated in Figure 1.

It can be seen that under reversible conditions

$$\frac{a}{[S]_{eq}} = \frac{a'}{[P]_{eq}}$$

and the *same* value of y will be obtained whether one considers the reaction to go left to right ($a/[S]_{eq}$) or right to left ($a'/[P]_{eq}$). Figure 1 shows that the only difference in the free energies of the a and a' terms lies in the base line from which they are measured.

Equation (2) and Figure 1 therefore allow us to see how the efficiency of a catalyst is related to the free energy profile of the catalyzed reaction.

While the right hand side of equation (2) contains lots of rate constants it also contains one variable; the concentration of S. This is inevitable since the steps E+S and E+P are second order reactions while the remaining steps are all first order reactions and so the free energy profile for the reaction must depend on the concentration of S.

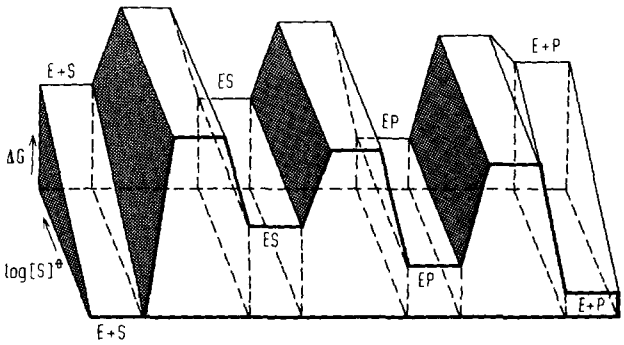


Fig. 2. Effect on the free energy profile of the choice of the standard concentration for the substrate, $[S]^\ominus$. The greater the $[S]^\ominus$ the greater the free energy of E+S and E+P with respect to the other states.

Figure 2 illustrates the effect of varying the concentrations of S and P on the free energy profile. At the back of the diagram the concentrations of S and P are high and ES and EP are more stable than E+S and E+P. Under these conditions the enzyme is saturated and the function y is dominated by the k_{cat} terms b and c. At the front of the diagram the concentrations of S and P are low, ES and EP are less stable than the unbound states and the function y is dominated by the $\vec{K}_m/\vec{k}_{cat}$ term, a.

If we followed the normal chemist's convention we would choose the slice of Figure 2 corresponding to $[S] \approx 1$ mol/liter. But this choice depends on Napoleon, the CGS system, and other historical accidents. The free energy profile at 1 mol/liter is *not* informative about what happens in the living cell, and if we wish to take a slice that is relevant to the *in vivo* situation then we must choose the same concentration of S, $[S]^\ominus$, as the enzyme actually experiences. This choice of S will serve for any sequence of reversible enzyme-catalyzed reactions and one could construct a single free energy profile for the whole sequence. After each irreversible reaction the product concentration is not related by thermodynamics to the substrate concentration and so a new standard state must be taken for the next sequence of reversible reactions.

Now physical organic chemists may say "but we can measure catalytic efficiency for Scheme 2 by means of the overall second order rate constant, k_{obs}. For instance, we plot these rate constants as measures of catalytic effectiveness in a Brønsted catalysis plot. Why do we need this function y?" The answer is that in catalysis by simple organic molecules the states EP and ES represent the caged reactants and products and are of higher free energy than E+S (or E+P) at the concentrations of S usually used. So for simple systems, the $[S]^{-1}$ term dominates the other terms in equation (2) and

$$y \approx \frac{a}{[S]} \approx \frac{1}{k_{obs}[S]}$$

Thus, as long as the free energy of the catalyst-substrate and catalyst-product complexes are high, one can measure catalytic efficiency with k_{obs}. But as soon as the free energies of ES and EP become relevant then we need the more general function y.

We have seen that as a catalyst becomes more efficient y decreases. Hence evolutionary pressure on an enzyme always

acts to reduce y. Just as Gibbs free energy is a measure of the approach to chemical equilibrium, so we can use y as a measure of the evolutionary improvement in catalytic efficiency. At chemical equilibrium the Gibbs free energy is at a minimum and we may ask, is there a minimum value of y which describes the perfect catalyst?

Returning to Figure 1 and equation (2) we can see that y will be reduced if the free energy barriers are reduced till they become kinetically insignificant. (The concept of kinetic significance was introduced by *Richard Noyes*. A kinetically insignificant transition state is one of such low free energy that it is in no way rate limiting for the overall process. Similarly a kinetically insignificant intermediate is one of such high free energy that, compared to the reactants or other more stable intermediates, very little material accumulates in the insignificant state.)

Which free energy barriers can the enzyme alter? It cannot change the outside levels (E+S and E+P) since these are fixed by the thermodynamics of the S-P system. It also cannot alter the rates (k_1 and k_{-3}) at which S+E and P+E find each other in the solution. The largest possible values of k_1 and k_{-3} are those corresponding to the diffusion controlled limit, and diffusion coefficients do not vary greatly with molecular structure. The free energies of these "external" states (E+S, E+P and transition states 1 and 3) cannot therefore be altered by the enzyme. By contrast, the "internal" states (ES, EP and transition state 2) will depend on how tightly the enzyme binds S and P and how well it catalyzes

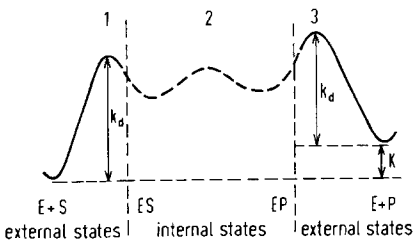


Fig. 3. The free energy profile for a perfect catalyst. The enzyme cannot improve the relative free energies of the external states, since they are fixed by thermodynamics (K) or by the rate at which molecules diffuse in solution (k_D). For the perfect catalyst all the other states, the internal states, are kinetically insignificant.

the reaction. If all these internal states become kinetically insignificant, the rate of the catalyzed reaction will reach a maximum and the free energy profile corresponding to the perfect catalyst will therefore have the form shown in Figure 3. The expression for y will then contain just two terms from a:

$$y_{min} = \frac{1}{k_D[S]} + \frac{1}{K k_D[S]}$$

where k_D is the diffusion controlled rate constant for E+S and E+P. The reaction catalyzed by the perfect catalyst is therefore limited only by the diffusion of the substrate *on* for a downhill reaction or by the diffusion of the product *off* for an uphill reaction. Since we now have a definition for y_{min}, we can define an efficiency function E_f which compares the efficiency of any catalyst to that of the perfect catalyst:

$$E_f = \frac{y_{min}}{y} = \frac{k_D^{-1}(1+K^{-1})}{a+[S](b+\theta c)} \tag{7}$$

For simple organic reactions we see that:

$$E_f = \frac{k_{obs}(1+K^{-1})}{k_D} \tag{8}$$

For an enzyme-catalyzed reaction, E_f can be written in terms of the usual Michaelis Menten parameters:

$$E_f = \frac{k_D^{-1}(1+K)}{\vec{K}_m/\vec{k}_{cat} + [S](\vec{k}_{cat}^{-1} + \theta\overleftarrow{k}_{cat}^{-1})} \tag{9}$$

When $\theta = 1$ for the reversible system the same value of E_f is obtained in terms of the product P:

$$E_f = \frac{k_D^{-1}(1+K)}{\overleftarrow{K}_m/\overleftarrow{k}_{cat} + [P](\vec{k}_{cat}^{-1} + \overleftarrow{k}_{cat}^{-1})}$$

3. Application to Triose Phosphate Isomerase

The free energy profile for the catalysis of the reaction in Scheme 1 by the enzyme triose phosphate isomerase is now largely known[3] and the non-enzymatic catalysis of the reaction has also been studied. So we can compare the values of the efficiency functions E_f for catalysis by the enzyme, and catalysis before the Garden of Eden by a base such as acetate ion. For the reasons discussed above we choose a concentration of S for the calculation of y corresponding to the *in vivo* concentration of triose phosphates in muscle, which is about 40 μmol/liter[4]. The results for E_f[2] are:

Triose Phosphate Isomerase: $E_f = 0.6$

Acetate Ion: $E_f = 2.5 \times 10^{-11}$

Since E_f for the perfect catalyst is unity, it is evident that triose phosphate isomerase is almost perfect. The free energy profiles for the reaction catalyzed by the enzyme and catalyzed by acetate are shown in Figure 4. The highest transition

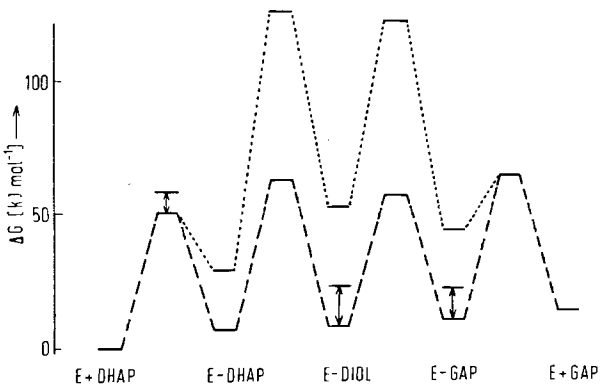


Fig. 4. The free energy profile for the reaction in Scheme 1 catalyzed by acetate ion (dotted line) and by the enzyme, triose phosphate isomerase (broken line). The vertical arrows indicate where the free energy profile for the enzyme is somewhat uncertain.

state for the enzyme reaction (going left to right) is diffusion *off* of the product and this is why the enzyme is almost perfect. How has the enzyme achieved this remarkable improvement?

3.1. Uniform Binding

The simplest answer to this question might be that, whereas for the simple organic catalyst ES and EP are only caged reactants and products, the enzyme binds the substrates, intermediates and transition states more tightly and the lower free energy of the transition states results in a faster reaction.

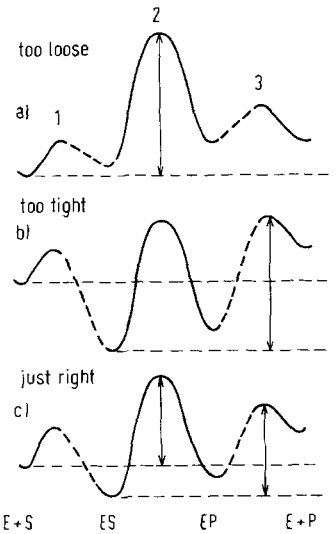


Fig. 5. The effect on the free energy profile of "uniform binding" of the substrate and product to the enzyme. In a) There is too little binding and transition state 2 is too "high"; in b) there is too much uniform binding and intermediate ES is too "low"; in c) the optimum profile is shown.

The effect of binding the internal states is shown in Figure 5. In Figure 5a we have the profile for a simple catalyst. In Figure 5b the catalyst binds S and P so tightly that transition state 2 now lies below transition state 3. Have we therefore already developed the perfect catalyst? Unfortunately the answer is no, because now the intermediates ES and EP are so stable that most of the enzyme becomes trapped in the ES valley. The dominant terms in y for the profiles in Figures 5a and 5b are shown. By differentiation one can prove that the *optimum condition* (*i.e.* the minimum value of y) *is when these two terms in y are equal.* This is shown in Figure 5c.

In making the changes in Figure 5 we moved *all* the internal states (ES, EP and transition state 2) up and down as a single block with respect to the external states. If we consider what changes random point mutations would cause in the free energy profile for an enzyme-catalyzed reaction, it is reasonable to suggest that those changes which do not discriminate amongst different internal states and which can use a variety of different interactions will occur more often than those changes which do discriminate and which require more particular and subtle alterations in enzyme structure. Thus the type of change considered in Figure 5 can arise from interactions with parts of the substrate molecule remote from the reaction center and by a variety of mechanisms such as hydrophobic interactions, hydrogen bonding, electrostatic interactions, and the rest. Changes in binding interactions some way from the reaction center will not discriminate significantly between the different bound states and we may expect the binding of all such states to be changed equally. Since for most enzyme substrates the reaction center is a relatively small part of the molecule, the random mutations that alter the binding are more likely to do it in a uniform fashion rather than discriminating (say) between ES and EP. Because changes in uniform binding are relatively the easiest type of change, we may expect that many enzymes will have achieved optimum profiles in this respect. As shown in Figure 6, triose phosphate isomerase is very close to the optimum condition illustrated in Figure 5c.

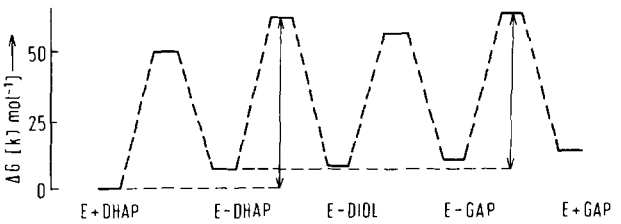


Fig. 6. The free energy profile for the triose phosphate isomerase catalyzed reaction in Scheme 1. It almost satisfies the optimum condition of uniform binding.

Now we may ask "Has triose phosphate isomerase achieved its high efficiency compared to acetate ion merely by using uniform binding?" Figure 7 shows the profile that one would obtain if one altered the acetate profile so as to optimize the uniform binding. The efficiency function for this profile has a value of $E_f = 3 \times 10^{-6}$. This is five orders of magnitude better than the simple acetate catalyst but it is still much less than the enzyme's actual value of 0.6.

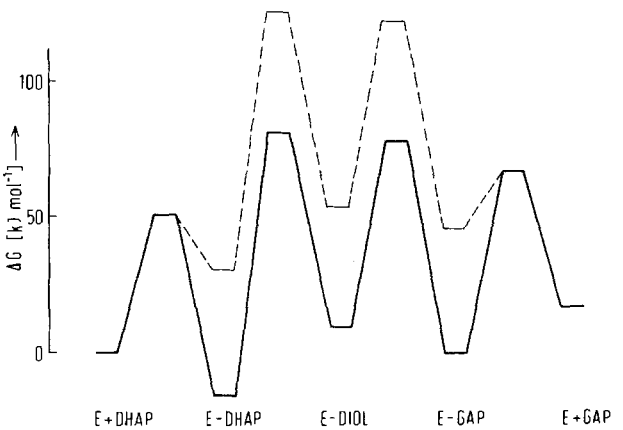


Fig. 7. The free energy profile for the reaction in Scheme 1 catalyzed by acetate ion (broken line) and the improved profile obtained after optimizing the uniform binding (full line). The relative free energies of all the internal states (E:DHAP to E:GAP) are the same in both profiles.

3.2. Differential Binding

We propose that the next easiest change the enzyme can make is to alter the internal thermodynamics of the bound intermediates. For instance, the optimized acetate profile (Figure 7) can be further improved if the enediol is bound more tightly compared to DHAP. This lowering of the free

energy of the enzyme : enediol complex will drive the proton abstraction from DHAP that much harder and hence improve the efficiency. To effect this change the enzyme has to discriminate in its binding of DHAP and of the enediol. There are still a number of mechanisms, *e.g.* hydrogen bonding, whereby this can be done, but this change is more localized and more specific; the enzyme must obviously interact discriminately with the substrate near the reaction center. Figure 8 shows the profile for the reaction where the internal thermodynamics has been optimized *and* the uniform binding readjusted to accommodate the new internal levels. Notice that the internal thermodynamics are optimized when DHAP and the enediol have the *same* free energy. This is because if one tries to drive the proton abstraction any harder by further lowering the enzyme:enediol complex then the efficiency drops because the enzyme : enediol complex is becoming too stable. The value of the efficiency function for this profile (Figure 8) is $E_f = 1.5 \times 10^{-4}$. The optimization of the internal thermodynamics has produced a smaller but still significant improvement.

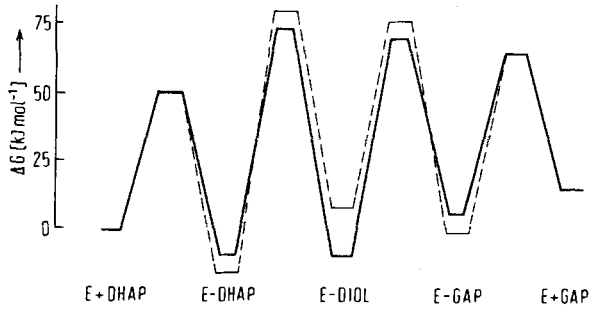


Fig. 8. The profile in Fig. 7 (broken line) is further improved (full line) by equalizing the free energies of the E : DHAP and E : DIOL complexes and then once again optimizing the uniform binding.

3.3. Catalysis of Elementary Steps

Having optimized both the uniform binding and the internal thermodynamics the only possible further improvement is to lower the free energies of the kinetically significant transition states *with respect to* the kinetically significant intermediates. That is, the free energy difference between the highest hill and the lowest valley must be reduced. Many wise angels have argued on the head of a pin whether this is done by binding the transition state more tightly with respect to the intermediates or by destabilizing the intermediates with respect to the transition state. We regard this distinction as irrelevant since after an improvement in the catalysis of a particular step, changes in uniform binding will optimize the level of the internal states with respect to the external states. As shown in Figures 6 and 8 this has happened for triose phosphate isomerase. The mechanism by which the catalysis of particular elementary steps can be improved must be the most subtle of all, since there are very few amino acid replacements that will result in a more rapid execution of the required covalency changes. As an example of such an improvement the enzyme might develop bifunctional rather than monofunctional catalysis. Indeed, triose phosphate isomerase seems to use an electrophilic group at the active site to polarize the carbonyl group of the substrate[5], thereby facilitating the abstraction of the enolate hydrogen by the active site base (Figure 9).

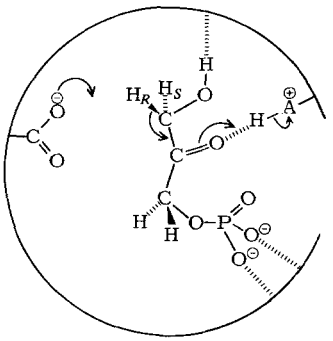


Fig. 9. Putative complex of dihydroxyacetone phosphate with triose phosphate isomerase. The carboxylate group of glutamic acid 165 abstracts the pro-*R* hydrogen assisted by an electrophilic group HA [5].

We cannot generalize about the ways in which the catalysis of individual steps of an enzyme reaction is improved. However, by using the efficiency function we can quantify *how much* of the improved performance of the enzyme is due to the relatively unsophisticated binding of the substrates and how much is due to the catalysis of elementary steps.

3.4. Variation of Efficiency with Substrate Concentration

In our discussion of triose phosphate isomerase we took the *in vivo* substrate concentration as our value of [S] in the calculation of the efficiency function. It is interesting to plot E_f for triose phosphate isomerase as a function of the substrate concentration according to equation (7). This is done in Figure 10. We find the enzyme on the edge of the plateau of perfection.

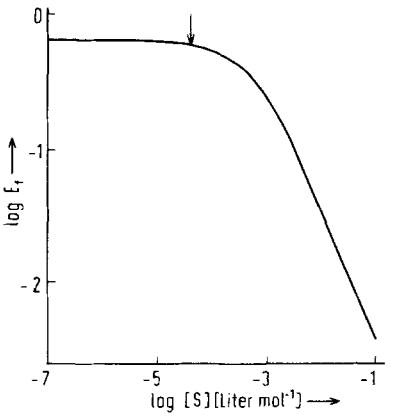


Fig. 10. Variation of efficiency function for triose phosphate isomerase with [S] according to equation (7). The arrow indicates the *in vivo* substrate concentration.

This is to be expected, since we have seen that the free energy profile of the enzyme is well tuned to the ambient substrate concentration. The enzyme has climbed out of the pit of the simple catalysts and has reached the plateau where there can be no further significant improvement in its catalytic effectiveness.

4. The Efficiency Surface

So far we have discussed separately the variation of efficiency with substrate concentration and with uniform binding. But uniform binding and substrate concentration are related, since uniform binding will be optimized for a particular ambient substrate concentration. To illustrate this behavior we can calculate a surface for the efficiency function. In order to construct a diagram that will fit into three dimensions we first assume that the E + S steps and the E + P steps are diffusion controlled:

$$k_1 = k_{-3} = k_D$$

Secondly, we describe the variation of uniform binding by the parameter β, where

$$\beta = \frac{k_2}{k_{-1}} + \frac{k_{-2}}{k_3} \tag{10}$$

Changing the uniform binding causes the same proportionate change in k_{-1} and k_3 while k_2 and k_{-2} remain constant. Increasing the binding of the internal states decreases k_{-1} and k_3 and increases β.

Most of the rest of the rate constants in the efficiency function can then be collected into a parameter γ where

$$\gamma = \frac{y_{min}}{k_2^{-1} + \theta k_{-2}^{-1}} = \frac{1 + K^{-1}}{k_D(k_2^{-1} + \theta k_{-2}^{-1})} \tag{11}$$

Thus γ is unaffected by changes in uniform binding, but any improvement resulting from changes in internal thermodynamics *or* in the catalysis of single steps that lead to larger values of k_2 or k_{-2}, will give a larger value of γ.

Then we obtain for the efficiency function:

$$E_f \approx \frac{1}{1 + \beta^{-1} + (1+\beta)[S]/\gamma} \tag{12}$$

This relation holds[*] for all reversible systems ($\theta = 1$), for all simple systems ($k_2/k_{-2} \approx K$), and all "uphill" systems ($k_2/k_{-2} \approx K \ll 1$). A slightly different expression is found for irreversible systems ($\theta = 0$) which are "downhill" ($K \gg 1$) and where the internal thermodynamics is more balanced than the external ($k_2/k_{-2} \ll K$):

$$E_f \approx \frac{1}{1 + \beta^{-1} + [S]/\gamma} \tag{13}$$

The difference is only the extra β/γ term in equation (12). Since equation (12) applies to a larger number of cases including the more efficient reversible systems we concentrate on equation (12).

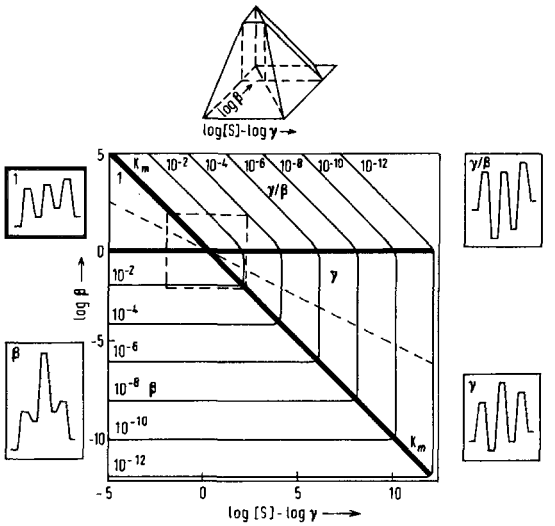


Fig. 11. Contour diagram showing the variation of the efficiency function from equation (12) with the uniform binding parameter β [eq. (10)] and the substrate concentration divided by γ [eq. (11)]. The shape of the surface is shown in the top inset. The other insets show typical free energy profiles for the four planes in the diagram. The line labeled K_m [eq. (15)] gives the [S] when the enzyme is half saturated. The broken line indicates the optimum value of β (see Fig. 5c). The area inside the broken square is shown in Fig. 12.

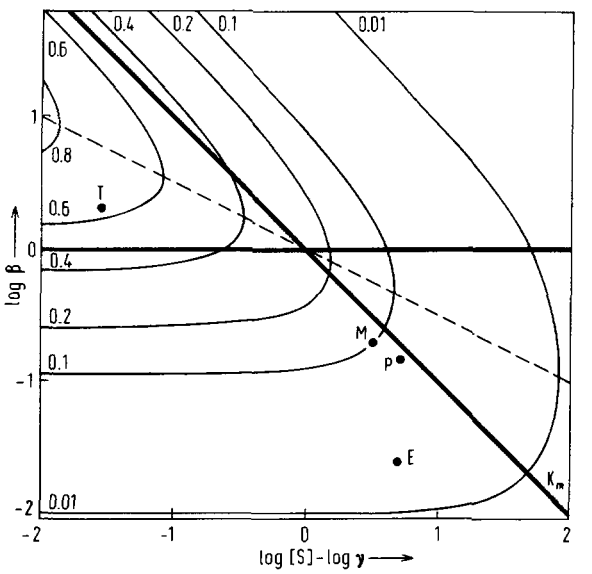


Fig. 12. The area near the origin in Fig. 11. The points T, M, P and E are the locations on the diagram for four glycolytic enzymes: T, triose phosphate isomerase; M, phosphoglycerate mutase; P, phosphoglucose isomerase; E, enolase.

Now since E_f depends on β and $[S]/\gamma$ we can plot equation (12) for E_f in the contour diagrams shown in Figures 11 and 12; Figure 12 shows the area around (0,0) in more detail. Depending on which term is dominant in the denominator of equation (12) we find four different planes in Figure 11. In the top left corner we have the "plateau of perfection", where E_f tends to unity. At the bottom of the diagram we have the β plane where $E_f \approx \beta$. On this plane the uniform binding is too weak and transition state 2 is always rate limiting. On both of these planes the efficiency function is

[*] The full expression for E_f is

$$E_f = \frac{1}{1 + \beta^{-1} + [1 + (1+\rho)\beta][S]/\gamma}$$

where

$$\rho = \frac{(k_2/k_{-2} - K)(1-\theta)}{(1+K)(1+\theta k_2/k_{-2})}$$

The parameter $\rho \approx 0$ for the systems discussed under equation (12) and $\rho \approx -1$ for the system discussed under equation (13).

independent of substrate concentration. Here the catalyst is unsaturated and the kinetic rate law has the form

$$v = k[S][E]$$

By contrast, when the other two terms in equation (12) are dominant, the efficiency function is inversely proportional to [S]. The efficiency falls off with increasing [S] and the rate law has the form

$$v = k[E]$$

These systems are saturated.

We now introduce a third Michaelis constant $K_{m,eq}$ (in addition to $\vec{K}_m$ and $\overleftarrow{K}_m$) which is appropriate for reversible systems reacting close to equilibrium conditions:

$$K_{m,eq} = \frac{\vec{K}_m}{1+\vec{k}_{cat}/\overleftarrow{k}_{cat}} = \frac{\overleftarrow{K}_m K^{-1}}{1+\overleftarrow{k}_{cat}/\vec{k}_{cat}} \qquad (14)$$

These systems become half saturated, when

$$[S] \approx [P]K^{-1} \approx K_{m,eq}.$$

To cover both reversible and irreversible cases we write

$$K_m = \frac{\gamma}{\beta} = \vec{K}_m/(1+\theta\vec{k}_{cat}/\overleftarrow{k}_{cat}) \qquad (15)$$

where K_m reduces to $\vec{K}_m$ for $\theta=0$ and to $K_{m,eq}$ for $\theta=1$[*].

This constant K_m defines the dividing line labeled K_m in Figure 11. Systems which cross this line as the substrate concentration is varied obey Michaelis Menten kinetics. To the right of the β plane we have the γ plane. Here the efficiency does not depend much on the uniform binding parameter because the main rate limiting process is the decomposition of a relatively stable ES or EP intermediate over transition state 2. Finally in the top right-hand corner we have the γ/β plane. Here the binding is too tight, and the rate limiting transition state for the decomposition of ES and EP is transition state 1 or 3. In the case of the downhill irreversible reaction where equation (15) holds, this plane is missing. It can be seen that the efficiency function can be applied to systems regardless of whether their biological role requires them to work under saturated or unsaturated conditions.

Having described the surfaces we can locate the area where simple systems are found. From equation (10):

$$\beta \approx \frac{k_2}{k_{-1}} = \frac{k_{obs}}{k_D} = E_f \approx 10^{-10}$$

and from equation (11)

$$\gamma \approx \frac{k_2}{k_D} = \frac{k_{obs}k_{-D}}{k_D^2} = \frac{\beta k_{-D}}{k_D} = 10\beta \approx 10^{-9}\ \text{mol/liter}$$

for a typical k_{obs} of 1 liter mol^{-1} s^{-1}, and $k_D/k_{-D}=0.1$ liter mol^{-1}. (The last quantity describes a typical association equilibrium constant for caged catalyst reactant or catalyst product pairs. In the absence of any specific interaction one can calculate such a constant for ES and EP from the chances of the two molecules, E and S or P, being nearest neighbors.) In Figure 13 we have therefore plotted the area in which the simple systems are found. They do not exhibit Michaelis Menten kinetics and the concentration of substrate is not large enough to take them across the dividing line between the β and γ planes.

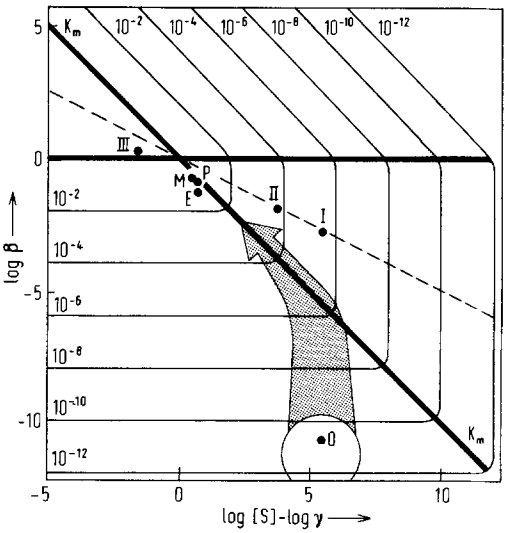


Fig. 13. The location of different systems on the efficiency surface. The circle indicates the area where simple organic systems are found and the point 0 is reaction 1 catalyzed by acetate ion. Points I and II are the same reaction after optimization of uniform binding with the profile (Fig. 7) and improvement in differential binding with the profile (Fig. 8). Point III is the location of triose phosphate isomerase. Three other glycolytic enzymes are shown by the points M, P and E: M, phosphoglycerate mutase, P, phosphoglucose isomerase and E, enolase.

The pressures of natural selection will first drive the evolving enzyme up towards the γ plane, since, as discussed above, there are many ways of adjusting uniform binding (*i. e.* increasing β). Once close to the K_m line further optimization of uniform binding is not too critical and catalytic efficiency now has to be improved by increasing k_2 or k_{-2} (*i. e.* increasing γ). Eventually the enzyme may cross the origin on to the plateau of perfection. We have shown in Figure 13 these steps for triose phosphate isomerase.

The enzyme will not move far onto the plateau of perfection. The reason for this is that the enzyme requires constant evolutionary pressure to maintain its foothold on the plateau. Most mutations will be disadvantageous to the enzyme and will tend to sweep it back down the hill. There can be no evolutionary pressure on the flat part of the plateau. Imagine an enzyme which by some good chance did become "super-perfect" with a very low transition state 2 as shown in Figure 3. The high

[*] The full expression for K_m is

$$K_m = \frac{\gamma/\beta}{1+\rho(1+\beta)^{-1}}$$

where ρ is defined in the previous footnote. Equation (15) holds when $\rho=0$ and equation (12) holds, or when $\beta \gg 1$.

proportion of disadvantageous mutations would undo the good work until transition state 2 was again partly rate limiting. Once this has occurred natural selection would then prevent further deterioration. For this reason we expect to find enzymes clinging to the edge of the plateau. The most accessible part of the plateau is near the origin and this is the region where we should find the enzymes. The conditions for the origin are $\beta=1$ and $\gamma=[S]^{\theta}$, where $[S]^{\theta}$ is the *in vivo* concentration of the substrate. Several authors[6-8] have suggested that for an efficient enzyme the Michaelis constant should match the ambient substrate concentration. We agree with this conclusion, since at the origin:

$$K_m=\gamma/\beta=[S]^{\theta},$$

but care must be taken about the reversibility of the system and K_m must be defined by equation (15). In addition, we can also describe the profile at the origin. As discussed there are some reasons for thinking that catalysis will be improved if $k_2\approx k_{-2}$. Assuming this equality and that $[S]=[S]^{\theta}$ we obtain the profile shown in Figure 14. It can be seen that

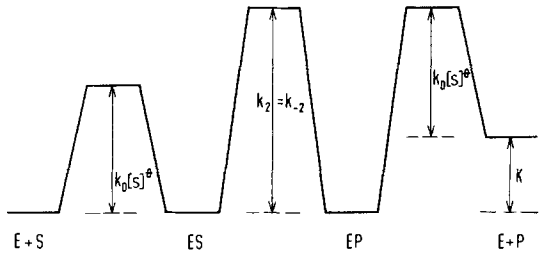


Fig. 14. The free energy profile for the almost perfect enzyme that is close to the origin in Figures 11, 12 and 13.

transition state 2 and transition state 3 are of equal free energy. This is because if transition state 2 were above 3 the enzyme would be inefficient and if it were much below 3 then there would be no evolutionary pressure to maintain an unnecessarily fast interconversion of ES and EP. We therefore expect that for enzymes on the edge of the plateau several transition states will be partly rate limiting. As in geological erosion the high peaks are worn away leaving a range of smooth hills.

Returning to Figure 14 we find that the intermediates ES and EP are of almost the same free energy as E+S. If the free energy of the intermediates were far below E+S, the enzyme would be inefficient, the catalyst being bogged down in the ES valley. But there is no evolutionary pressure to maintain the free energy of ES much above E+S. We therefore expect that the free energy profile for an enzyme will have several intermediates of much the same free energy as E+S when $[S]=[S]^{\theta}$ the ambient substrate concentration. For reversible downhill systems the relevant level will be E+P since it is of lower free energy than E+S.

Throughout this paper triose phosphate isomerase has been used as an example because we have a detailed knowledge of its free energy profile. However, we can plot other enzymes on our diagram using published values of k_{cat} and K_m. The relation between our variables and k_{cat} and K_m are:

$$\beta^{-1}\approx\frac{\vec{K}_m k_D}{\vec{k}_{cat}(1+K^{-1})}-1 \tag{16}$$

and

$$\gamma^{-1}\approx\frac{k_D(\vec{k}_{cat}^{-1}+\theta\overleftarrow{k}_{cat}^{-1})}{1+K^{-1}}-(1+\rho)K_m^{-1} \tag{17}$$

In Figure 13 we have plotted points for three other glycolytic enzymes for which data on k_{cat}, K_m, K and $[S]^{\theta}$ are available; these are the data required to calculate E_f, β and γ for a reversible system (for which $\rho=0$). These three enzymes (enolase, phosphoglucose isomerase and phosphoglycerate mutase) have no control function in glycolysis and it is gratifying to find them in Figures 12 and 13 close to the origin and close to the K_m line[*].

5. Conclusion

Finally we summarize our conclusions.

1. Our proposed efficiency function quantifies the efficiency of any catalyst for a reaction in solution under both reversible and irreversible conditions.
2. For freely diffusing species the maximum efficiency is unity.
3. We expect and find enzymes to have an efficiency somewhat less than unity (≈ 0.1).
4. Simple organic systems have efficiencies of very roughly 10^{-11}.
5. For triose phosphate isomerase about half the improvement in enzyme efficiency comes from binding the substrates, intermediates, and transition states by a non-discriminating interaction and about half by improved catalysis of covalency changes.
6. For an almost perfect enzyme the Michaelis constant matches the *in vivo* substrate concentration.
7. In the free energy profile of an almost perfect enzyme there will be several transition states that are partly rate limiting and several intermediates of comparable free energy to the free energy of free enzyme plus substrate or product.

Received: September 30, 1976 [A 163 IE]
German version: Angew. Chem. *89*, 295 (1977)

[1] *A. Hall, J. R. Knowles*, Biochemistry *14*, 4348 (1975).
[2] *W. J. Albery, J. R. Knowles*, Biochemistry *15*, 5631 (1976).
[3] *W. J. Albery, J. R. Knowles*, Biochemistry *15*, 5627 (1976).
[4] *J. R. Williamson*, J. Biol. Chem. *240*, 2308 (1964).
[5] *M. R. Webb, J. R. Knowles*, Biochemistry *14*, 4692 (1975).
[6] *A. R. Fersht*, Proc. Roy. Soc. B *187*, 397 (1974).
[7] *P. H. Crowley*, J. Chem. Biol. *50*, 461 (1975).
[8] *A. Cornish-Bowden*, J. Mol. Biol. *101*, 1 (1976).

[*] The values of k_{cat}, K_m and K_{eq} required for the calculation of E_f were taken from the following sources: phosphoglycerate mutase [from rabbit muscle: *H. G. Britton, J. B. Clarke*, Biochem. J. *130*, 397 (1972). It was assumed that the concentration of the cofactor 2,3 bisphosphoglycerate ($K_m=0.28$ μmol/liter) was optimal]; enolase [from rabbit muscle: *R. P. Cory, F. Wold*, Biochemistry *5*, 3131 (1966); *F. Wold* in *P. Boyer:* The Enzymes, Academic Press, New York 1971, Vol. 5, p. 499. It was assumed that the magnesium concentration was optimal at about 1 mmol/liter]; phosphoglucose isomerase [from rabbit muscle: *E. A. Noltmann* in *P. Boyer:* The Enzymes, Academic Press, New York 1972, Vol. 6, p. 271; assuming that the α-forms are the preferred substrates; *K. J. Schray, S. J. Benkovic, P. A. Benkovic, I. A. Rose*, J. Biol. Chem. *248*, 2219 (1973)]. *In vivo* concentration levels of substrates were taken from *J. R. Williamson*, J. Biol. Chem. *240*, 2308 (1965); *H. J. Hororst, M. Reim, H. Bartels*, Biochem. Biophys. Res. Commun. *7*, 137 (1962).

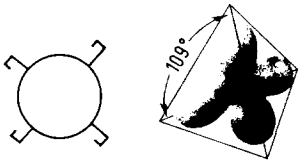
The Pauli Principle and Chemical Bonding in Molecules and Solids[**]

By Laurens Jansen and Ruud Block[*]

The starting point of this contribution is a discussion of the concept of exchange interactions and its relation to chemical bonding and valence. Then, a class of phenomena characterized by weak chemical bonding ($\lesssim 1$ eV) in solids and molecules is analyzed in more detail, with "superexchange" in insulating solids with paramagnetic 3d-cations serving as prototype. A model of "effective electrons" is developed for weak bonding on the basis of exchange perturbation theory, taking full account of the Pauli principle. The model is applied to: i) magnetic interactions in solids (interaction energy 10^{-2} to 10^{-4} eV); ii) stability of noble-gas halides (binding energy ≈ 1 eV); and iii) rotational barriers in simple molecules (barrier heights of several 0.1 eV).

1. Introduction

Although the concept of a *chemical bond* between two atoms, A and B, denoted by A—B in the chemist's symbolism, is an old one, it is safe to say that, in spite of fifty years of quantum mechanics, we still do not know precisely what is meant by this concept. *Gassendi*, is his oeuvre "Syntagma Philosophicum" (1658), suggested that atoms could attach themselves to each other by means of "hooks" on their surface *(a)*; the number of hooks constituting what we call the "maximum valency" of the atom.



(a): 1658 *(b)*: 1931

For two-and-a-half centuries after *Gassendi*, no progress whatsoever was made in understanding the chemical bond; even in the era of *Kekulé*, towards the end of the nineteenth century, the picture of an atom still largely resembled a billiard ball with a certain number of fixed knobs on the surface, by means of which other atoms could be attached.

As we know, *Kossel* and *Lewis* in 1916 put an end to this romantic period by giving some structure to the bar between the atoms A and B. They implied that atoms strive towards attaining a noble-gas configuration for their electrons. This can be accomplished, energy permitting, either by transferring electrons from one atom to the other (as in Na^+Cl^-) or by "sharing" (as in H:H). In the first case we obtain the ionic bond *(Kossel)*, in the second case the homopolar electron-pair bond *(Lewis)*. The homopolar bond seemed to be vindicated as the archtype of chemical bonding through *Heitler* and *London*'s calculation[1] on the hydrogen molecule in 1927; instead of *Lewis*' naive electron sharing a complex chain of concepts emerged. The bonding in H_2 is the result of *exchange interactions* between the atoms. These, in turn, arise as a result of the Pauli principle, *i.e.*, the wave function describing the system must change its sign if any two electrons are interchanged.

As this is not readily formulated in terms of chemical concepts, however, chemists continued writing bars between atoms and kept on interpreting them in terms of electron-pair bonds. If the ground-state electron configuration of an atom could not account for a given number of pair bonds in molecules, then "valence structures" were constructed to explain observed facts. A highlight was *Pauling*'s sp^3-hybridization scheme[2] *(b)* for the carbon atom (1931). This, in fact, is *Gassendi* all over again, now with "lobes" of unpaired-electron density instead of the "hooks" of three centuries earlier.

Ingenious schemes of pair bonding are found in modern inorganic complex chemistry as well as in solid state chemistry; in the latter case, so-called "dangling bonds" are also implied at surfaces where complete saturation cannot occur. It should be realized that the interpretation of chemical bonding in terms of pairs of electrons with opposite spins has no direct connection with concepts of quantum mechanics. In fact, in this description quantum mechanics is essentially short-circuited and replaced by "chemical intuition" formulated as a number of *ad hoc* rules of assumed general validity, which live "their own lives", regardless of what quantum-mechanical theory can tell us.

The "message" of this article is, nevertheless, not that this is too primitive and that the only sensible alternative is to solve the Schrödinger equation exactly for a system of interacting atoms. What we do want to demonstrate is that the pair-bonding scheme, applied to a number of selected, yet simple, problems leads either to incorrect results, or, worse still, to no result at all. Instead, these problems can be dealt with effectively, without increasing their complexity, if one takes the Pauli principle really seriously and does not reduce it to a pairing principle. The problems selected all concern what may be called "weak chemical bonding", which we define to comprise phenomena with binding energies of about 1 eV or less. This limitation renders the use of perturbation techniques, starting from non-interacting atoms, plausible in principle. We will now discuss: i) magnetic interactions in 3d-solids (binding energies 10^{-2} to 10^{-4} eV); ii) stability of noble-gas halides such as XeF_2 and XeF_4 (binding energies about 1 eV per bond); and iii) rotational barriers in simple molecules (barrier heights of several 0.1 eV).

[*] Prof. Dr. L. Jansen, Dr. R. Block
Institute of Theoretical Chemistry, University of Amsterdam
170, Nieuwe Achtergracht, Amsterdam-C (The Netherlands)

[**] Based on a lecture delivered at the Conference "A 76: Exploring the Chemical Bond—New Developments" held by the Chemical Physics Section of the Atomic Physics Division, European Physical Society, in Amsterdam (August 30—September 1, 1976).

2. Effective-Electron Model for Weak Chemical Bonding

The model to be discussed for weak chemical bonding (weak exchange interactions) was first designed in order to analyze phenomena of coupling between electrons with unpaired spins on different paramagnetic 3d-cations in insulating solids such as solid MnS. The Mn^{2+} ion has a half-filled 3d-shell and the O^{2-} ion is diamagnetic. Let us consider the coupling between unpaired electrons on *two* neighboring Mn^{2+} ions in the presence of *one* O^{2-} ion. The reason why we must consider also at least one anion is that the distance between even nearest-neighbor cations is too large to explain the observed phenomena of *magnetic ordering* at low temperatures in such solids, *i.e.* the spins on different cations are all arranged in a certain pattern if the temperature is sufficiently reduced (below a few hundred K, depending upon the substance). It has become clear that the coupling arises through the anion; we call this phenomenon "indirect exchange", or "superexchange", a much studied subject in solid-state physics.

One remark before we come to the analysis of the phenomena under study. The Pauli principle is a *symmetry condition* on the wave function describing a system of an arbitrary number of electrons: if one *permutes* the labels of any two electrons, then the wave function must change its sign. Of course, there are in general many more conditions imposed by symmetries of a type different from permutations, namely rotations, reflections, translations (in a solid), *etc.* However, in order to avoid burdening the reader with abstract concepts, we shall refrain from a general discussion of the concept of symmetry; for this, the interested reader is referred to the literature[3].

Next, we discuss the assumptions of the model used in numerical calculations. First of all, we limit ourselves to phenomena of weak chemical bonding, implying that we may start from noninteracting atoms, ions, or molecules and may calculate their interaction as a perturbation of the initial state. Secondly, as stated earlier, we will consider the consequences of the Pauli principle as applied to the total system, not only to two electrons at a time on one-electron orbitals. We do, however, use localized orbitals for the description of the system, *i.e.* we do not smear out these orbitals over all atoms involved, as is the case in the "molecular orbital" method.

Perturbation theories taking into account the Pauli principle for interacting atoms (exchange perturbation theories), ions, or molecules have been developed in different versions; we here select a Rayleigh-Schrödinger type[4], most directly connected with standard perturbation theory in which effects of the Pauli principle on interactions are neglected. The usual treatment of van der Waals forces is an example of this latter category.

Let us now state explicitly the assumptions of the model. The validity of these assumptions is partly hypothetical, partly empirical; it must be ultimately established by comparison with experimental facts.

A) Weak exchange interactions may be evaluated by using perturbation methods, starting from free-ion wave functions.

B) The Pauli principle as applied to the whole system determines the essential characteristics of (weak) exchange interactions.

C) Properties of (weak) exchange interactions are not primarily dependent upon the number of unpaired electrons per atom or ion. As a consequence, we may replace, on each paramagnetic cation, its unpaired electrons by one "effective electron". The number of unpaired electrons is reflected indirectly in the "magnetic size" of the orbital of the effective electron.

Assumptions (A) and (B) have already been discussed. Assumption (C) may be made less *ad hoc* by observing that the stable magnetic patterns of insulating solids with 3d-cations are all antiferromagnetic; moreover, for solids with the B1 (NaCl) structure the patterns are all of the so-called second kind (except for CrN). In addition, the orders of magnitude of their Néel temperatures are the same (of the order of 100 K). Since the 3d-cations involved (Ni, Co, Mn, Fe, *etc.*) have varying numbers of unpaired electrons, this experimental fact indicates that the essential aspects of magnetic ordering may be described by assuming *one* "effective" unpaired electron per cation. In accordance with this assumption, we replace the electrons of the anion by *two*, spin-paired, effective electrons. For the simplest system affording superexchange of two cations and one anion, this then leads to the so-called "three-center, four-electron model" proposed by *Kramers*[5] as early as 1934. We note that the zero-order, free-ion, wave functions are necessarily *not orthogonal* to each other.

3. Applications of the Model

3.1. Indirect Exchange Interactions in Solids Containing Cations with an Incomplete 3d Electron Shell

Since the model adopted for weak chemical bonding has been devised to describe magnetic coupling in insulating solids, its first application[6, 7] must obviously deal with this class of phenomena. Consider two paramagnetic cations A and B, each with one effective electron, and one diamagnetic anion, C, with two spin-paired effective electrons. We start from an assignment of electrons 1, 2, 3, and 4 in which electron 1 is on cation A, 2 on cation B, and the electrons 3, 4 on anion C. Then, following standard methods, it is easy to construct a wave function for the state of three non-interacting ions which satisfies the Pauli principle. Note that there are two such functions, one for the case where the spins of the two unpaired electrons are parallel, one for the case where these spins are antiparallel. Next, the interactions between electrons on different ions are considered in first, second, *etc.* order of perturbation theory, very similar to a usual Rayleigh-Schrödinger perturbation analysis without exchange (*i.e.* neglecting the Pauli principle). An *ad hoc* assumption is here that we do not have to go beyond interactions of second order.

In view of the fact that there are only two unpaired electrons, the first-order interaction energy becomes particularly simple. It is, of course, different for the two spins of the unpaired electrons on the two cations parallel or antiparallel. This interaction energy $E^{(1)}$ can be written as

$$E^{(1)} = M + N \cdot \begin{cases} +\frac{1}{4} \text{ for parallel spins} \\ -\frac{3}{4} \text{ for antiparallel spins} \end{cases} \quad (1)$$

where M and N are spin-independent. We have evaluated (1) for Slater functions $r^{n-1}\exp(-pr)$ on each of the centers A, B, and C[8]. Actually, it turns out that the results are

very similar for $n=1$, 2, 3, and 4, so that we limit ourselves to 1s-functions ($n=1$). We only consider configurations of A, B, and C for which the distances AC and BC are the same. The opening angle θ at the anion C is varied from $\theta=40°$ to 180°; the choice of parameters is $p_A=p_B=1\,au^{-1}$,

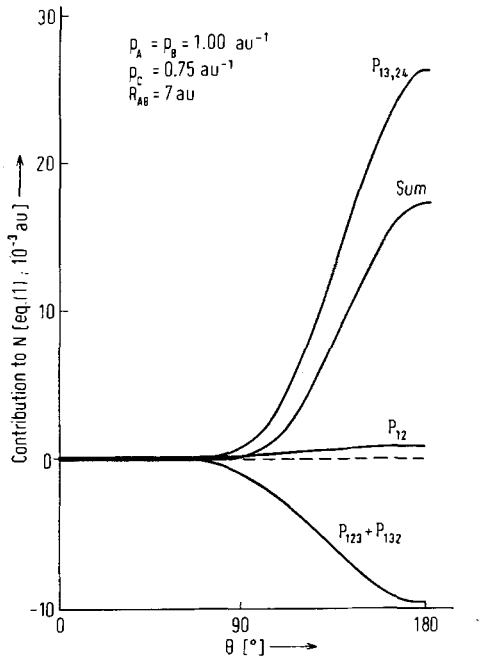


Fig. 1. Contributions to singlet-triplet splitting in the three-center, four-electron model, from permutations involving both electrons with unpaired spin (1, 2), as well as their sum, as a function of the opening angle θ at the anion. Parameters p_A, p_B (cations) and p_C (anion) of the 1s Slater orbitals are given. The unit of energy is 10^{-3} au (1 au $\approx 0.3\times10^6\,kT$). Positive values indicate singlet, negative values triplet stability.

$p_C=0.75\,au^{-1}$, $R_{AB}=7$ au. The results are given in Figure 1; from (1) we note that a positive contribution to N implies that the antiparallel (singlet) configuration is more stable, whereas negative contributions imply higher stability for parallel spins (triplet). The unit of energy is 10^{-3} au (1 au $\approx 0.3\times10^6\,kT$; T is given in K, k is Boltzmann's constant).

We see that first-order exchange favors antiparallel coupling of the cation spins, except for a region of weak ferromagnetic alignment around $\theta=80°$. The permutations $P_{13,14}$ and P_{12} always lead to antiferromagnetism, whereas $P_{123}=P_{132}$ always favors parallel spins. For large openings θ the coupling is strongly antiferromagnetic, in agreement with experiment.

Of particular interest for comparison with experiment is the narrow θ-range of weak ferromagnetic (*i.e.* parallel) coupling. Considering, in particular, the results for $\theta=85°$ (-0.078×10^{-3} au) and for $\theta=95°$ ($+0.178\times10^{-3}$ au) we see that in the first case the coupling is weakly ferromagnetic, in the second case weakly antiferromagnetic (*i.e.* antiparallel). Experimentally, it is known that the type of coupling does indeed sensitively depend on the opening θ just in this region. Note that the angle dependence of the exchange is due solely to the Pauli principle applied to a system of spherically symmetric atomic wave functions.

On the basis of the above simple model, 180°-indirect exchange in solids of composition XMF_3 and X_2MF_4 (X = K, Rb, Tl; M = Mn, Co, Ni) has been evaluated[9] and compared with experimental results. The available data show that the "exchange constants" $\mathcal{J}/k$ [where $\mathcal{J}$ is the same as $-N/2$ of eq. (1) and k is the Boltzmann constant] for Mn^{2+}, Co^{2+}, and Ni^{2+} are in the ratio 1:3.6:7.7 interpolated at the same distance $R=4.074$ au, and that they depend on R (cation-cation) as $|\mathcal{J}/k|\approx R^{-n}$, with $n\approx12$. Determining the values of the Slater p parameter for these cations from existing SCF calculations and diamagnetic susceptibilities, the effective-electron model yields 1:3.3:7.6 for this ratio and a value of n indeed close to 12. Very recent results for a number of other compounds, *e.g.* Cl in place of F, and also including the compound with M = Fe, are given in Table 1.

Table 1. Exchange constants $\mathcal{J}/k$ for 180°-superexchange in a number of compounds as predicted by the effective-electron model and compared with experiment. The numbers in parenthesis indicate experimental accuracy; R is the cation-cation nearest-neighbor distance. Note that in the first compound the anion is Cl^- and in the last compound the cation is Fe^{2+}.

Compound	R [Å]	$\mathcal{J}/k$ calculated	$\mathcal{J}/k$ experimental
Cs_2MnCl_4	5.130	− 5.0	− 5.0 (2)
$TlMnF_3$	4.250	− 3.1	− 3.0 (3)
$KCoF_3$	4.058	−17.6	−19.2 (20)
K_2NiF_4	3.992	−50	−51.5 (3)
Rb_2FeF_4	4.214	− 6.1	− 6.5 (15)

The results for 180°-superexchange are very much better than those produced by any other theoretical model. We have also applied[7] the effective-electron model to the three modifications of manganese(II) sulfide [B1 (NaCl lattice), B3 (sphalerite lattice), and B4 (wurtzite lattice)]. All three modifications are antiferromagnetically ordered at low temperatures, but of different kind. It is often supposed in the literature that different *covalent* character of the Mn—S bond is responsible for the different ordering. Application of the effective-electron model shows that *ionic* Mn—S bonding accounts very well for the phenomena if we take the differences in three-ion exchange properly into account.

3.2. Stability of Noble-Gas Halides: A Case of Selective Valence

Results bearing more directly on the concept of valence are obtained from applications of the model to bonding in molecules. We select the noble-gas halides as prime example, because their very existence seems to invalidate *Lewis'* octet rule and thus to attack the traditional interpretation of "valence" at one of its principal roots.

Since 1962 it has been known that XeF_2, XeF_4, XeF_6, KrF_2, and KrF_4 are stable molecules, with binding energies of about 30 kcal/mol for the Xe compounds, about 15 kcal/mol for the Kr compounds. Extensive first-principle theoretical analyses have not been very successful: an electron-pair description of bonding is practically hopeless from the outset since in the Xe compounds more and more electrons must be promoted from inner shells. Application of the molecular-orbital method does lead to stable molecules, but theoretical selectivity regarding stable geometric configurations is much too low to be convincing. In particular, it is difficult to explain why XeF_4 is square-planar and not tetrahedral, and why noble-gas compounds with Cl instead of F do not exist.

The three-atom exchange model used for the analysis of magnetic ordering in solids is also applicable[10, 11] to these molecules. A halogen atom has an open p shell of electrons

and spin 1/2, represented in the model by one effective electron. The rare-gas atom has closed shells, replaced by two spin-paired effective electrons. A complex XRX, with X a halogen atom, R a noble-gas atom, is then represented by the same three-center, four-electron model as we have already applied in the discussion of magnetic ordering. The extension to molecules RX_n with $n>2$, is straightforward. For the orbital parts of the effective-electron wave functions we chose a simple Gaussian form[12]:

$$\phi(r)=(\beta/\pi^{1/2})^{3/2}\exp(-\beta^2 r^2/2)$$

where r is the distance from the effective electron to its nucleus and β is a parameter characteristic for the size of the atom. If we denote the parameter for the noble-gas atom by β, that for the halogen atom by β', then $\gamma=(\beta'/\beta)^2$ is a measure for their relative size; for $\gamma<1$ the halogen atom is larger than the rare-gas atom, whereas for $\gamma>1$ the situation is reversed. The interaction energy for a complex XRX is evaluated in first- and second-order Rayleigh-Schrödinger type exchange perturbation theory[4]. In Figure 2 we demonstrate the selectivity of these three-atom exchange interactions. In the figure, the calculated binding energy (per bond) for linear symmetric noble-gas halides in the singlet state is plotted as a function of the relative-size parameter γ, for a value of the dimensionless parameter $\beta R_0=1.1$, where R_0 is the noble-gas-halogen atom distance. Estimated values[10] for γ are ≈ 2.5 for XeF_2, ≈ 1.8 for KrF_2, and ≈ 1 for $XeCl_2$. For other halides the γ values are still lower.

The curve agrees strikingly well with experimental findings in predicting XeF_2 and KrF_2 to be stable, $XeCl_2$ to be unstable, and other halides incapable of existence. Also, the binding

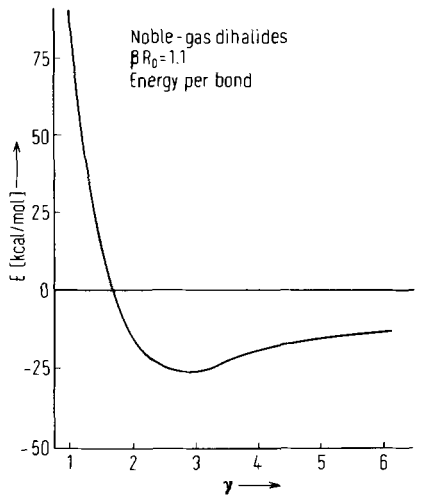


Fig. 2. Sum of first- and second-order interaction energies for xenon dihalides, as a function of the relative size γ of the xenon and the halogen atoms.

energy in KrF_2 is considerably lower than in XeF_2, again in agreement with experiment. The binding is found to be very stereospecific in that a XeF_2-molecule with a 90°-opening at the xenon atom exhibits no bonding at all. All dihalides are unstable in the triplet state.

In order to examine the configurations of noble-gas halides with coordination numbers >2, we carried out the calculations[11] for XeF_4 in both a square-planar and a tetrahedral geometry. Here, we have different states of total spin to consider; these are indexed in Figures 3 and 4 by different values of total spin S. Figure 3 gives the result for the square-planar, Figure 4 for the tetrahedral arrangement; the value of βR_0 is approximately 1.15.

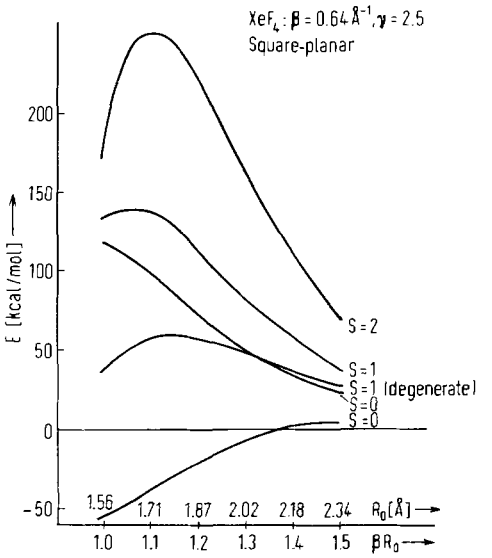


Fig. 3. Calculated energy per bond of the square-planar configuration for the molecule XeF_4, as a function of the dimensionless parameter βR_0, where R_0 is the Xe—F distance.

The results are seen to be in very good agreement with experiment, with regard both to stereospecificity and to binding energy (exp. ≈ 30 kcal/mol per bond). The introduction of a relative-size parameter as an important quantity in determining the possibility of chemical bonding is an old idea.

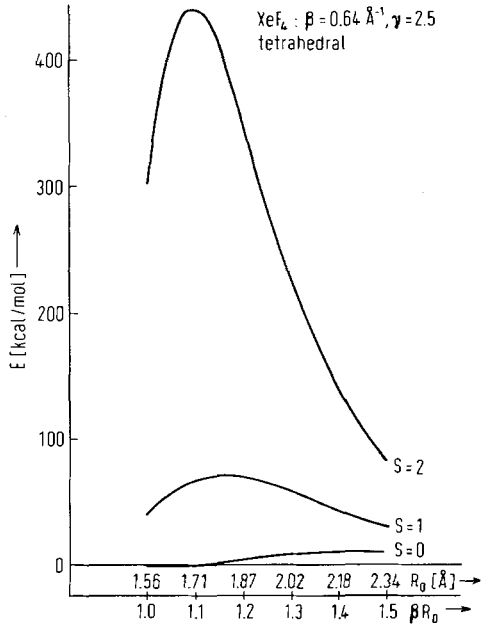


Fig. 4. Calculated energy per bond of the tetrahedral configuration for the molecule XeF_4, as a function of the dimensionless parameter βR_0 (see Fig. 3).

Stability of ionic crystals in the Goldschmidt model (1927) depends sensitively on the ratio R_+/R_- of cation and anion radii, the ions being considered as rigid spheres. This size

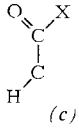
concept was also used extensively by *van Arkel* and collaborators in an analysis of properties of inorganic molecules and solids[13]. In a sense, therefore, introduction of three-atom exchange interactions seems to re-establish the significance of some old ideas regarding chemical bonding and valence.

3.3 Rotational Barriers in Simple Molecules

A last type of application of many-atom exchange interactions in the above model formalism concerns the evaluation of rotational barriers in simple organic and inorganic molecules. The subject of rotational barriers dates back to the early days of stereochemistry and to *Van 'tHoff* (1874); he postulated that rotation about a C—C single bond should be free, that around a C=C double bond should be restricted. Now, 100 years later, it can only be stated that these early views have been confirmed to a substantial extent by a great many experiments. Specifically, we now know that rotation around a carbon-carbon single bond, while not completely free, is hampered by a barrier of only a few kcal/mol, whereas the rotational barrier in *e.g.* ethylene is much higher, namely about 65 kcal/mol. Promising theoretical approaches date only from 1963, when *Pitzer* and *Lipscomb*[14] calculated a barrier in ethane of 3.3 kcal/mol, compared with an experimental value of 2.8 kcal/mol. *Pitzer, Kern, et al.* obtained interesting results for ethane[15] (1968) and methanol[16] (1974) on the basis of a bond-orbital concept, showing that exchange interactions are essentially responsible for the barrier. If the wave function is not antisymmetrized, then the barrier has the wrong sign.

We have carried out a model calculation of rotational barriers in about 40 simple molecules[17] including ethane, its halogen derivatives, as well as inorganic molecules such as B_2Cl_4, Si_2H_6, *etc.* The influence of the atoms on the axis of rotation was neglected. The electrons of the remaining atoms (H, or halogen) were replaced by one effective electron each, with parallel spins. The results are generally in good agreement with experiment; they will, however, not be reported here because in all these cases we have to do with so-called "repulsive dominant" barriers, *i.e.* the stable configuration is determined by a minimum in repulsive interactions between groups of atoms on different side of the axis of rotation.

Very different, and intriguing, are the phenomena involving barriers in molecules which contain a C=O double bond, of which the simplest representative is acetaldehyde. Acetyl halides were also considered[18]. The most stable molecular geometry is the *trans* configuration *(c)*, in which C—X is *trans*



(c)

to C—H, and C—X, C=O, and one C—H lie in the same plane. This preference cannot be explained on the basis of repulsive interactions between non-bonded atoms; thus, we speak here of an "attractive dominant" barrier. Attractive many-body exchange interactions, needed to explain the particular stability of the conformation *(c)*, can be taken over from the phenomenon of superexchange in insulating solids (cf. Section 3.1): the C=O bond replaces the diamagnetic anion, the atoms H and X (halogen) the two cations. We use again simple Gaussian functions for the orbitals of the four effective electrons, with β_{db} as characteristic parameter for the double bond.

We find, first of all, that the barrier is indeed sensitive to variations in β_{db}, and that it has the correct sign. For a series of molecules H_3C—COX (X=H, F, Cl, Br, I) the "best" value of β_{db} varies very little from molecule to molecule

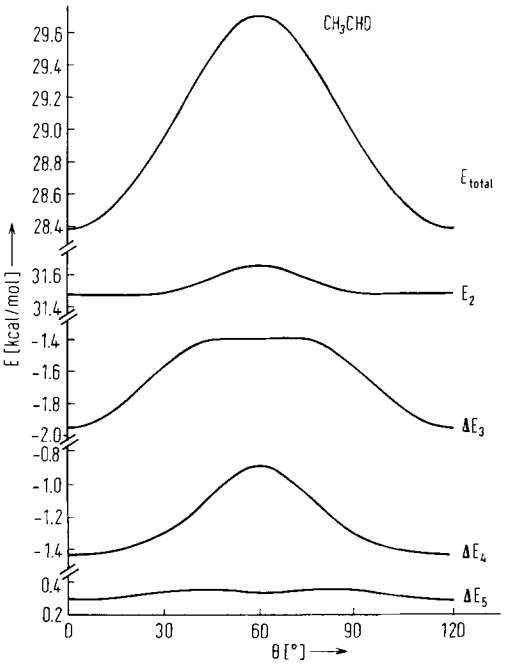


Fig. 5. Cluster expansion of the first-order energy for the molecule CH_3COH in terms of two-atom interactions (E_2), simultaneous interactions between three (ΔE_3), four (ΔE_4) and five atoms (ΔE_5), as a function of the dihedral angle θ (at $\theta=0°$ the C=O double bond eclipses one of the C—H bonds of the methyl group). Note the change of scale for each curve.

and gives good agreement with experiment (barrier 1—2 kcal/mol). Also, we undertook a cluster expansion of the first-order energy, *i.e.* we have split this energy into contributions due to interactions between two centers (E_2), three centers (ΔE_3), and, in order to include the methyl group, between four (ΔE_4) and five centers (ΔE_5). In Figure 5, these results are given as function of the angle of rotation θ ($\theta=0°$ denotes *cis* arrangement of C=O and C—H).

From the figure we see that E_2 is repulsive and varies little with θ; ΔE_3 is negative and most attractive at $\theta=0°$; the same applies to ΔE_4. The five-center interaction, ΔE_5, is very small and practically independent of θ. Further, we have found that ΔE_3 is indeed due to superexchange in the HC—COX unit.

All three examples we have analyzed can, therefore, be understood quantitatively in terms of a simple model in which the consequences of permutation symmetry of the wave function, *i.e.* the Pauli principle, are rigorously taken into account and in which no space-oriented one-electron orbitals and no covalency effects play a role.

Received: August 23, 1976;
revised: December 27, 1976 [A 164 IE]
German version: Angew. Chem. *89*, 317 (1977)

[1] *W. Heitler, F. London*, Z. Phys. *44*, 455 (1927).
[2] *L. Pauling*, J. Am. Chem. Soc. *53*, 1367 (1931).
[3] See, *e.g., L. Jansen, M. H. Boon*: Theory of Finite Groups—Applications to Physics. North-Holland, Amsterdam 1967. Chapter III.
[4] *L. Jansen*, Phys. Rev. *162*, 63 (1967); *W. Byers Brown*, Chem. Phys. Lett. *2*, 105 (1968); *D. S. Farberov, V. Ya. Mitrofanov, A. N. Men*, Int. J. Quantum Chem. *6*, 1057 (1972).
[5] *H. A. Kramers*, Physica (Utrecht) *1*, 182 (1934).
[6] *R. Ritter, L. Jansen, E. Lombardi*, Phys. Rev. *B8*, 2139 (1973).
[7] *L. Jansen, R. Ritter, E. Lombardi*, Physica (Utrecht) *71*, 425 (1974).
[8] *R. Block, L. Jansen* in *J. L. Calais, J. Linderberg, O. Goscinski, Y. Ohrn*: Quantum Science: Methods and Structure. Plenum, New York 1976, p. 123.
[9] *L. J. de Jongh, R. Block*, Physica (Utrecht) *79B*, 568 (1975).
[10] *E. Lombardi, R. Ritter, L. Jansen*, Int. J. Quantum Chem. *7*, 155 (1973).
[11] *E. Lombardi, L. Pirola, G. Tarantini, L. Jansen, R. Ritter*, Int. J. Quantum Chem. *8*, 335 (1974).
[12] These calculations were carried out in Geneva with computer programs for Gaussian functions. Later checks for different problems revealed no qualitative difference when Slater functions are used instead.
[13] See, *e.g., A. E. van Arkel, J. H. de Boer*: Chemische Bindung als elektrostatische Erscheinung. Hirzel, Leipzig 1931.
[14] *R. M. Pitzer, W. N. Lipscomb*, J. Chem. Phys. *39*, 1995 (1963).
[15] *O. J. Sovers, C. W. Kern, R. M. Pitzer, M. Karplus*, J. Chem. Phys. *49*, 2592 (1968).
[16] *C. W. Kern, R. M. Pitzer, O. J. Sovers*, J. Chem. Phys. *60*, 3538 (1974).
[17] *E. Lombardi, G. Tarantini, L. Pirola, L. Jansen, R. Ritter*, J. Chem. Phys. *61*, 894 (1974).
[18] *E. Lombardi, G. Tarantini, L. Pirola, R. Ritter*, J. Chem. Phys. *63*, 2553 (1975).

Synthetic and Mechanistic Aspects of Inorganic Insertion Reactions. Insertion of Carbon Monoxide

By Fausto Calderazzo[*]

The synthetic potential and the mechanistic aspects of inorganic insertion reactions of carbon monoxide, especially into metal-carbon σ-bonds, are considered. Reactions of this type are encountered among most 3d, 4d, and 5d elements. In one case it has been demonstrated that the CO insertion proceeds by alkyl migration; this is likely to be a general feature of all such reactions. If an alkyl migration takes place, then insertion of CO into the M—C bond is governed kinetically by the cleavage of that bond. CO abstraction from RCO—M bonds most commonly proceeds by rate-determining vacation of a coordination position. Both CO insertion and abstraction are usually highly stereospecific.

1. Introduction

It is advantageous to define an insertion reaction in coordination chemistry solely on the basis of its stoichiometric result. For a metal complex M—L, therefore, we speak of an insertion reaction if the stoichiometric product results from the formation of new bonds by X to both the metal M and

$$X + M—L \rightarrow M—X—L \quad (1)$$

the ligand L [eq. (1)]. The classical example of an insertion reaction is the carbonylation of alkyl(pentacarbonyl)manganese by carbon monoxide, discovered almost twenty years ago [eq. (2)][11].

$$R—Mn(CO)_5 + CO \rightleftarrows R—CO—Mn(CO)_5 \quad (2)$$

The mechanism of inorganic insertion reactions is known in only few instances. In the great majority of cases the reaction mechanism is extrapolated from the experimental data (usually reaction kinetics or stereochemistry of reaction products) because no other necessary and complementary information is available.

[*] Prof. Dr. Fausto Calderazzo
University of Pisa
Istituto Chimica Generale
Via Risorgimento 35
I-56100 Pisa (Italy)

The demands made of reagents M—L and X in eq. (1) can now be discussed. The species X to be inserted into the M—L bond is by definition "coordinatively unsaturated", since it increases its coordination number on forming new bonds. Its unsaturation is usually of the $p_\pi - p_\pi$ type (CO, SO_2, CO_2, *etc.*). Table 1 defines the insertion reactions which have been observed or may, at least in principle, become observable. The inserted group X can function in the end product as a monoatomic (C̲O, C̲NR, S̲nCl$_2$), a diatomic (>C=C<, —C≡C—, O_2), a triatomic (CS_2), or a polyatomic (S_n) bridge. Some of the groups X may be bidentate, *e.g.* CO_2 and CS_2 which insert into M—NR_2 bonds to give dialkylcarbamato- and dialkyldithiocarbamato complexes, respectively. Insertion of $SnCl_2$[21] is illustrated in eq. (3).

Table 1. Experimentally detected and theoretically possible insertions reactions.

Metal-ligand bond	Group inserted
M—C	CO, CNR, CR_2, >C=C<, —C≡C—, CO_2, O_2, SO_2, S_n, $SnCl_2$
M—H	CO_2, CNR, >C=C<, RNCO
M—N	CO_2, CS_2
M—O	RNCO, SO_2
M—S	CS_2
M—Cl	CNR, CR_2, $SnCl_2$
M—M	$SnCl_2$

$$CpFe(CO)_2Cl + SnCl_2 \rightarrow CpFe(CO)_2SnCl_3 \quad (3)$$
Cp = cyclopentadienyl

The present article will deal exclusively with insertions of carbon monoxide into transition metal compounds. (For insertions into compounds of nontransition elements see [3].) The most widely studied reaction is the insertion of CO into metal-carbon σ-bonds. An exhaustive and excellent review article was written on this subject four years ago[4]. However, considerable advances have been achieved since then.

The interest in carbon monoxide insertion reactions resides in the scope they offer for functionalizing hydrocarbons and other substrates to give more valuable organic compounds, such as aldehydes, acids, and esters. Catalytic reactions of this kind are hydroformylation[5], the reaction of methanol with CO to give acetic acid[6], the double insertion of CO and olefins within the coordination sphere of a metal to give acids or esters in the presence of water or alcohols[7], the synthesis of hydroquinone by carbonylation of acetylene in the presence of ruthenium catalysts[8], the synthesis of acrylic acid from acetylene in the presence of nickel catalysts[9] (catalytic aspects of carbon monoxide insertion are to be found in [10, 11]).

Also the Fischer-Tropsch reaction and its modifications[12], which amounts to a catalytic hydrogenation of carbon monoxide, has again attracted attention[13] as a tool for exploiting coal reserves.

It is interesting to note the case of a metal complex which is inserted into the X—Y bond of a covalent molecule (X—Y = H_2, alkyl halide, acyl halide) [eq. (4)][14, 15]. The reactions

$$L\text{–}M + X\text{–}Y \rightleftharpoons L\text{–}M\begin{matrix}X\\Y\end{matrix} \quad (4)$$

typified by eq. (4) are usually termed oxidative additions; the coordination number and oxidation number of the metal increase by two units. In insertion reactions of the classical type [eq. (1)] the metal alters neither its coordination nor its oxidation number. For example, in eq. (2) the manganese of the insertion product maintains its coordination number 6 and its oxidation state I. Accordingly, the stereochemical and electronic demands of the metal are seen to be less stringent in insertion reactions than in oxidative additions. Thus, it is not surprising that insertion reactions can be observed for nearly all transition elements.

2. General Considerations

The shaded areas of Figure 1 represent those transition elements for which carbon monoxide insertion reactions into σ-bonds have been reported. Generally speaking, an insertion reaction of this type is regarded as known when any one of the following stoichiometric reactions (or the reverse reactions) has been fully characterized:

$$R\text{—}M + CO \rightarrow RCO\text{—}M \quad (5)$$
$$R\text{—}M(CO) \rightarrow RCO\text{—}M \quad (6)$$
$$R\text{—}M(CO) + L \rightarrow RCO\text{—}M(L) \quad (7)$$
L = two-electron donor

Equations (5) to (7) specify three types of CO insertion reactions:

1) CO insertion into the metal-carbon σ-bond of a metal complex which may or may not contain coordinated carbonyl groups;

2) conversion of a coordinated CO group into an acyl (or aroyl) group (the reverse of this reaction has been observed, see Section 4);

3) CO insertion into a metal carbonyl complex promoted by a Lewis base L.

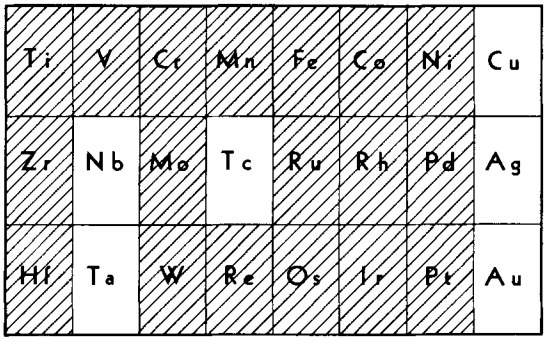


Fig. 1. CO insertion into transition metal-carbon σ-bonds. The hatched areas mean that CO insertions are known for the metal concerned. References: titanium [20], zirconium [21], hafnium [22], vanadium [23], chromium [24], molybdenum [25], tungsten [26], manganese [27], rhenium [28], iron [29], ruthenium [30], osmium [31], cobalt [32], rhodium [33], iridium [34], nickel [35], palladium [36], platinum [36a, 37].

The data of Figure 1 will now be considered. Only few metals are not yet known to give insertions of carbon monoxide into metal-carbon bonds. In the case of technetium, radioactive decay has probably discouraged an extensive research effort. However, CO insertion into a Tc—OR bond to give an alkoxycarbonyl compound has been reported[16].

The discovery of CO insertions also appears likely for other metals, especially considering that ethylene insertion is already known for niobium[17], that tetrafluoroethylene has been reported[18] to insert into the gold-methyl bond, and that isocyanides insert into copper-aryl bonds[19].

An important general observation is that relatively few kinetically stable CO inserted products are known for ruthenium, cobalt, rhodium, nickel and palladium. This is understandable in view of the comparatively low stability of both alkyl-(aryl-) and acyl (aroyl) derivatives of these metals. It is therefore not surprising to find that these metals are usually effective catalysts for the carbonylation of organic substrates.

A further point of interest comes from the observation *(vide infra)* that 5d metals are usually less inclined to undergo CO insertion reactions than the 3d and 4d metals of the same subgroup. It is now becoming plausible that the lower reactivity of 5d transition elements might be related to the higher strength of the metal-carbon bond.

Some thermochemically measured element-carbon bond dissociation energies are collected in Table 2. From these data it may be provisionally concluded that metal-carbon σ-bonds to alkyl and aryl groups are by no means weak bonds, and from the comparison between the manganese-methyl and the rhenium-methyl systems[40], it is evident that the 5d element forms stronger bonds to carbon then its 3d analog.

Since metal-carbon bond breaking is definitely an important step in carbonylation reactions, this may result in a slower

Table 2. Dissociation energies of some element-carbon σ-bonds. Cp = cyclopentadienyl, Et = ethyl, Me = methyl, Ph = phenyl.

Bond	Compound	Dissociation energy [kcal/mol]	Ref.
Ti—Me	$TiCp_2Me_2$	60 [a]	[38]
Ti—Ph	$TiCp_2Ph_2$	84 [a]	[38]
Ta—Me	$TaMe_5$	62 [a]	[39]
W—Me	WMe_6	38 [a]	[39]
Mn—Me	$MeMn(CO)_5$	27.9 (30.9)	[40]
Re—Me	$MeRe(CO)_5$	53.2	[40]
Pt—Ph	*trans*-$Pt(PEt_3)_2Ph_2$	60 [a]	[41]
Zn—Me	[b]	42 [a]	[42]
Cd—Me	[b]	33 [a]	[42]
Hg—Me	[b]	29 [a]	[42]
B—Me	[b]	87 [a]	[42]
Al—Me	[b]	66 [a]	[42]
Ga—Me	[b]	59 [a]	[42]

[a] Mean bond dissociation energy.
[b] For $M(Me)_n$ compounds.

carbonylation of $Me—Re(CO)_5$ compared with $Me—Mn(CO)_5$. Unfortunately no quantitative data are yet available. In this connection it is, however, important to note that a considerable decrease in rates was found for the tungsten complex in the following reaction[26]:

$$R—MCp(CO)_3 + L \rightarrow RCO—MCp(CO)_2L \quad (8)$$
$$M = Cr, Mo, W;\ L = PR_3$$

Carbon monoxide insertion reactions are still unknown for organolanthanides[43] and organoactinides[44]. However, this may simply be due to the infancy of the chemistry of σ-alkyls and aryls of 4f and 5f elements.

3. Kinetic Studies on Manganese Compounds

Mechanistically speaking, insertion reactions have many points in common, independently of the metal to which the alkyl (or aryl group) is bonded. The kinetic and mechanistic results obtained for manganese will be discussed first, and then it will be indicated whether and how they can be applied to other systems.

The kinetic data for the CO insertion [eq. (2)] into $Me—Mn(CO)_5$[27a] and $Ph—Mn(CO)_5$[45] can be accommodated[27b] by a mechanism involving the formation of an acyl(tetracarbonyl) intermediate [eq. (9)].

$$R—Mn(CO)_5 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [RCO—Mn(CO)_4] \underset{k_{-2}(-L)}{\overset{k_2(+L)}{\rightleftharpoons}} \begin{matrix} RCO—Mn(CO)_4L \\ L = CO \end{matrix} \quad (9)$$

This intermediate is suggested to be formed by alkyl migration in the original alkyl derivative to one of the terminal CO groups. This is in agreement with the mechanism of methyl migration found[27c] to be operative in the $Me—Mn(CO)_5/^{13}CO$ system by infrared spectroscopic methods. The acyl(tetracarbonyl) intermediate may be solvated, especially in solvents of high coordinating power. However, the structure of the intermediate is a difficult question to answer (see Section 4).

By applying the steady state approximation to the kinetic scheme [eq. (9)], and under the reasonable assumption that the term k_{-2} is comparatively small, the following kinetic equations are obtained [eqs. (10) and (11)].

$$k_{obs} = \frac{k_1 k_2 [L]}{k_{-1} + k_2 [L]} \quad (10)$$

$$1/k_{obs} = \frac{k_{-1}}{k_1 k_2 [L]} + \frac{1}{k_1} \quad (11)$$

The kinetic expression (10) predicts that when the term $k_2[L]$ is small (for example at atmospheric and lower pressure of carbon monoxide), the term k_{-1} may not be negligible, so that k_{obs} is finally a function of [L].

In contrast, at elevated CO pressure, under conditions such that k_{-1} may be small compared with $k_2[L]$, k_{obs} can become practically identical to k_1. The latter, within the validity of the assumptions, is the rate constant for the formation of the acyl(tetracarbonyl) intermediate.

The reaction of $Me—Mn(CO)_5$ with CO is first-order with respect to the metal complex, and dependent on the concentration of CO at atmospheric and lower pressure[27a]. On the other hand, the reaction of $Ph—Mn(CO)_5$ is independent of CO concentration[45] at the same CO pressure. Moreover, the rate of carbonylation of $Me—Mn(CO)_5$ becomes independent[27d,46] of CO concentration above 15 atm. In agreement with the kinetic expression (11), a good linear plot of $1/k_{obs}$ *vs.* 1/[CO] was obtained for the $Me—Mn(CO)_5$/CO system. From the intercept of the linear plot, k_1 can be calculated (see Table 3). Insertion of CO into the Me—Mn bond of $Me—Mn(CO)_5$ involving nucleophiles other than CO [eq. (12)] is found in several instances to be first order in metal complex concentration and independent of [L]. The kinetic scheme [eq. (9)] can also be applied to those cases.

$$Me—Mn(CO)_5 + L \rightarrow MeCO—Mn(CO)_4L \quad (12)$$

Table 3. Rate constants for the formation of the proposed acetyl(tetracarbonyl) intermediate from $Me—Mn(CO)_5$ and a ligand L [eqs. (9) and (12)].

Ligand L	$k_1 \times 10^4$ [s^{-1}]	Ref.
$P(OPh)_3$	9.9 [a]	[27b]
PPh_3	4.0 [b]	[27b]
$c\text{-}C_6H_{11}NH_2$	3.7 [b]	[27b]
PPh_3	6.6 [c]	[47]
CO	≈8	[46]

[a] In tetrahydrofuran at 25.5 °C.
[b] In 2,2'-diethoxydiethyl ether at 25.5 °C.
[c] In 2,2'-diethoxydiethyl ether at 30 °C.

The validity of the experimental results is confirmed by the observation (see Table 3) that the rate constant k_1 for the $Me—Mn(CO)_5$/CO system is in satisfactory agreement with the $k_{obs} \approx k_1$ found for the $Me—Mn(CO)_5/PPh_3$ system under the same experimental conditions.

Since the rate for the carbonylation of $Ph—Mn(CO)_5$ by CO was found[45] to be independent of [CO], k_{obs} in this case is practically equal to the rate constant for the formation of the benzoyl(tetracarbonyl) intermediate.

The data for the reaction

$$R—Mn(CO)_5 + CO \rightleftarrows RCO—Mn(CO)_5$$

at 30°C in 2,2'-diethoxydiethyl ether, *i.e.* $10^4 \times k_1 = ca.$ 8 (R = Me) and 1.0 s^{-1} (R = Ph), lead to the conclusion that the Me—Mn bond is kinetically more labile than the Ph—Mn bond. These are believed to be the first comparative kinetic data available for transition elements. Phenyl derivatives are usually thermally more stable than the methyl ones[48]. Assuming other transition elements to resemble manganese, an order of magnitude difference between the kinetic lability of the two M—R bonds may well explain the empirical observations. Whether this is ultimately a purely kinetic effect or has its origin in thermodynamic stabilization of the aryl derivative is still an open question[49].

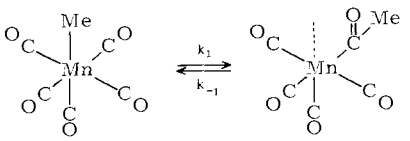
To conclude this section, mention should be made of a recent experiment[50] showing that acetyl migration, rather than methyl migration, is not a kinetically important pathway. Pyruvoyl(pentacarbonyl)manganese was synthesized by the conventional method [eq. (13)] and fully characterized (by X-ray analysis, too).

$$[Mn(CO)_5]^- + MeCOCOCl \rightarrow MeCOCO{-}Mn(CO)_5 + Cl^- \quad (13)$$

The pyruvoyl complex was shown to decarbonylate at a much slower rate than MeCO—$Mn(CO)_5$, thus excluding its intermediacy in CO abstraction from MeCO—$Mn(CO)_5$.

4. Mechanistic and Stereochemical Studies

It is now possible to specify the nature of the intermediate. If methyl migration is the mechanism of formation of acetyl(pentacarbonyl)manganese[27c], the rate constant k_1 refers to the process shown in eq. (14).



(14)

The vacant position may be occupied by the solvent. Considerable solvent effects were found for the reaction of Me—$Mn(CO)_5$ with CO[27a], Me—$FeCp(CO)_2$ with PPh_3[25a], and Me—$MoCp(CO)_3$ with PR_3 and $P(OR)_3$[25a]. In neat tetrahydrofuran (THF) Me—$Mn(CO)_5$ generates a band at about 1650 cm^{-1}[27a], suggestive of an adduct MeCO—$Mn(CO)_4$(THF). Dissolution of $PhCH_2$—$FeCp(CO)_2$ in dimethyl sulfoxide (DMSO) was reported[51] to result in a color change and the appearance in solution of a new band at 1600 cm^{-1}, suggesting the presence of $PhCH_2CO$—FeCp(DMSO)CO.

The kinetics of the carbonylation of d^6 iridium(III)[34a] and d^8 platinum(II)[37a] were interpreted as involving only little solvent assistance if any, although an acyl intermediate was considered to be operative also in these cases [eqs. (15) and (16)].

$$R{-}IrCl_2(CO)_2L + L' \rightarrow RCO{-}IrCl_2(CO)LL' \quad (15)$$

$$Et{-}PtCl(CO)L + L \rightarrow EtCO{-}PtClL_2 \quad (16)$$

No assistance by the solvent and the intermediacy of an acyl species were suggested by *Craig* and *Green*[25b, 25c] for CO insertion into some alkyl derivatives of d^4 molybdenum(II) complexes:

$$R{-}MoCp(CO)_3 + L \rightarrow RCO{-}MoCp(CO)_2L \quad (17)$$

L = PPh, $P(OR)_3$; R = Me, Et, σ-C_3H_5

It does not necessarily follow from the lack of kinetic evidence for solvent assistance that a coordinatively unsaturated, presumably highly energetic, complex is formed during these carbonylation reactions. It has recently been found[21] that the acetyl group of MeCO—$ZrCp_2Me$, obtained by carbonylation of Me_2—$ZrCp_2$ [eq. (18)], is bonded to zirconium through

$$Me_2{-}ZrCp_2 + CO \rightarrow MeCO{-}ZrCp_2Me \quad (18)$$

both the carbon and the oxygen atoms (see Fig. 2). The acetyl group in this zirconium(IV) complex of d^0 configuration can best be described as a four-electron donor, by which the central metal atom assumes the Xe inert gas electronic configuration.

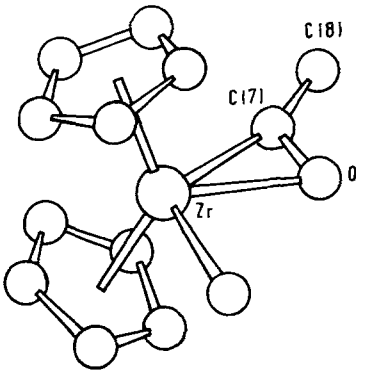
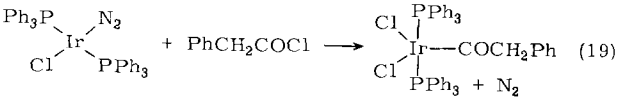


Fig. 2. Molecular structure of MeCO—$ZrCp_2Me$ [21]. Bond distances: Zr—C(7), 2.197(6); Zr—O, 2.290(4); C(7)—O, 1.211(8); C(7)—C(8), 1.492(10).

"Side-on" coordination of the acyl group to a transition element had been postulated[52a] for d^6 ruthenium(II) complexes of formula RCO—$RuCl(CO)(PPh_3)_2$ mainly on the basis of infrared spectroscopic results [ν_{CO}(acyl) = 1505—1510 cm^{-1}]. "Side-on" coordination of CO in dinuclear manganese complexes is also of interest in this connection[52b, 52c].

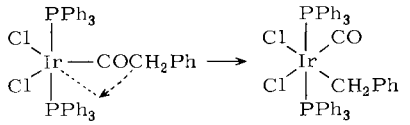
We shall now consider the ground-state structural features of alkyl- and acyl derivatives of transition elements, and it will be shown that the molecular arrangement found for the acetylzirconium complex does not represent an isolated example. The type of molecular arrangement found for the zirconium complex could, in certain cases, be close to the structure of the intermediate. The new finding shows that the metal may satisfy its electronic and stereochemical demands by binding the acyl group in a way different from that known *(vide infra)* in most acyl derivatives of transition elements. The acyl group is normally *C*-bonded to the metal ("end-on") with long nonbonding metal-O distances.

An important contribution to the problem of the nature of the intermediate in carbon monoxide insertion reactions has been provided by *Kubota et al.*[34b, 53]. Oxidative addition of phenylacetyl chloride to a dinitrogen complex of iridium(I) according to eq. (19) afforded an acyl derivative of iridium(III)[53a] (cf. also[53b]).



(19)

The phenylacetyl complex is monomeric in solution and probably has a trigonal-bipyramidal structure. Whatever may be the reason for the stabilization of this apparently coordinatively unsaturated species, its isolation and thermal transformation into the alkyl compound [eq. (20)] are very relevant experimental facts in connection with CO insertion. The acyl-



(20)

alkyl conversion may be assumed to take place *via* the rate-determining migration of the CH_2Ph group to give the stable hexacoordinate iridium(III) complex. The rate constants for the conversion have been determined[34b] for some *p*-substituted phenylacetyl derivatives (with R in place of Ph) at 30 °C in benzene:

R	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	*p*-$O_2NC_6H_4$
$10^4 \times k(s^{-1})$	9.2	8.35	3.9

According to the assumption indicated in eq. (20), these are the rate constants corresponding to the cleavage of the C—C bond in the acyl group. The results found by *Kubota et al.* show that for iridium(III) complexes, and possibly for others too, alkyl migration from an acyl group to a vacant coordination site on the metal is not a particularly fast process. This is an interesting result because for manganese it was not possible to directly measure the same kind of process [*i.e.* k_{-1} of the kinetic scheme (9)]. The rate constant k_1 in Table 3 for $Me—Mn(CO)_5$ is that for methyl migration from the metal. We can only estimate k_{-1} by studying the process of CO abstraction from $MeCO—Mn(CO)_5$ to give $Me—Mn(CO)_5$ [reverse of equation (2), R = Me]. By the principle of microscopic reversibility both processes should have the same intermediate indicated in eq. (9) as $RCO—Mn(CO)_4$. The rates of CO abstraction from $RCO—Mn(CO)_5$ at 30 °C in 2,2′-diethoxydiethyl ether are[54]:

R	*n*-Pr	Et	Me	$PhCH_2$
$10^5 \times k(s^{-1})$	5.2	3.7	2.8	2.3

The observed differences are small, which is understandable only by assuming that these values are a measure of the rate of formation of the intermediate by CO dissociation from the metal.

To summarize the situation, and referring to the kinetic scheme (9) (R = Me), we can say that we know the rate constants for the formation of the intermediate $MeCO—Mn(CO)_4$ from $MeCO—Mn(CO)_5$ (k_{-2}) and from $Me—Mn(CO)_5$ (k_1), but we can only guess that k_{-1} (*i.e.* the rate constant corresponding to the cleavage of the C—C bond of the acetyl group) is larger than k_{-2}.

That $Me—Mn(CO)_5$ is formed from $MeCO—Mn(CO)_5$ by a relatively slow, rate-determining CO dissociation from the metal is supported by the results[27d] obtained in the reaction of PPh_3 with ^{13}C-labeled acetyl(pentacarbonyl)manganese [eq. (21)].

$$Me^{13}CO—Mn(CO)_5 + PPh_3 \rightarrow CO + Me^{13}CO—Mn(CO)_4PPh_3 \quad (21)$$

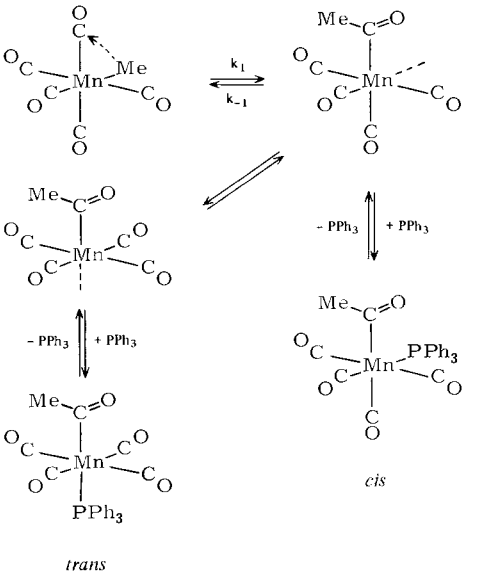
It is interesting to note that an acetyl iron system gives similar and complementary results[55]. ^{13}C-Labeled acetyl(dicarbonyl)cyclopentadienyliron(II) was photolyzed with a mercury lamp in heptane [eq. (22)] and the product of the reaction analysed by mass spectrometry. The labeling was found to be maintained in the product obtained, thus complementing the previous results for ^{14}C-[56] and ^{13}C-labeled $MeCO—Mn(CO)_5$[27c]. Moreover, photolyses of $Me^{13}CO—FeCp(CO)_2$ carried out in the presence of PPh_3 resulted in the formation of $Me^{13}CO—FeCp(CO)PPh_3$. It is reasonable to assume that the intermediate has originated from a Fe—CO bond fission. The competitive experiment with PPh_3 then shows that addition of PPh_3 is faster than methyl migration from the acetyl group to the metal.

$$Me^{13}CO—FeCp(CO)_2 \xrightarrow{h\nu} Me—FeCp(^{13}CO)(CO) + CO \quad (22)$$

$$Me^{13}CO—FeCp(CO)_2 \xrightarrow{h\nu} CO + [Me^{13}CO—FeCp(CO)] \quad (23)$$

$$Me—Mn(CO)_5 + PPh_3 \rightarrow \underset{cis + trans}{MeCO\quad Mn(CO)_4PPh_3} \quad (24)$$

Some additional details can be given concerning the acyl intermediate $MeCO—Mn(CO)_4$ in the manganese case. The reaction of $Me—Mn(CO)_5$ and PPh_3 [eq. (24)] has been found[27d] to give initially the *cis* isomer, which subsequently transforms into the *trans* isomer (Scheme 1).

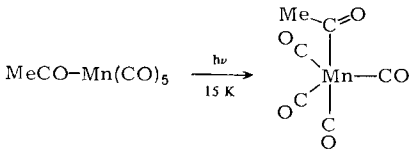


Scheme 1

Scheme 1 contains a further relevant suggestion about the nature of the acyl intermediate, *i.e.* that it may exist in two different structures, which have been tentatively indicated to approximate a trigonal bipyramid and a square pyramid. Interconversion between the two structures does not appear to arise from Me migration. The existence of two different intermediates interconverting with an energy barrier between them is required by the observation[27d] that the two geometrical isomers arising from reaction (24) are not initially present in the final equilibrium ratio, as would be the case if they

originated from a common intermediate or from two rapidly interconverting intermediates.

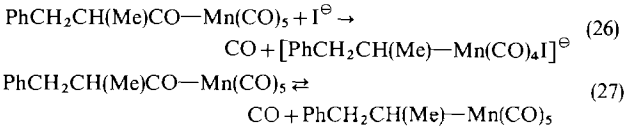
Relevant to this point is the recent[57] photolysis of MeCO—$Mn(CO)_5$[57], which produced, *inter alia*, a species suggested to be a trigonal bipyramidal MeCO—$Mn(CO)_4$ on the basis of infrared spectroscopic results [eq. (25)].



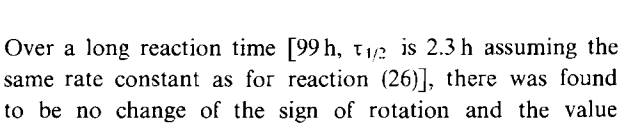
(25)

CO insertions into metal-carbon σ-bonds and related reactions are highly stereospecific, both at carbon and at the metal. The following preliminary experiments have been carried out[58]:

1) Reaction of an optically active acyl(pentacarbonyl)manganese with $I^{\ominus}$ (at 30.0°C in 2,2'-diethoxydiethyl ether, $k = 8.5 \times 10^{-5}\,s^{-1}$) [eq. (26)], and 2) thermal treatment of the same acyl complex to give the equilibrium mixture with the corresponding alkyl [eq. (27)].



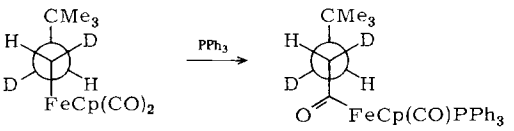
(26)



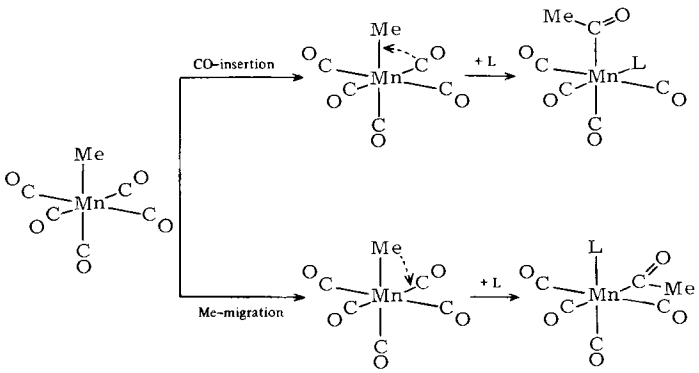
(27)

Over a long reaction time [99 h, $\tau_{1/2}$ is 2.3 h assuming the same rate constant as for reaction (26)], there was found to be no change of the sign of rotation and the value of the specific rotation changed slightly after a conversion of about 10%. Despite the low conversion, the experiment shows that the equilibrium is maintained under highly stereospecific conditions, although it was not possible to establish whether there was retention or inversion at the carbon.

More recent work[59a, 59b] on the reaction of *threo*-$Me_3CCHDCHD$—$FeCp(CO)_2$ with PPh_3 has established that the *threo*-acyl derivative is formed with more than 95% retention of configuration.



High stereospecificity was also found at iron[29, 60–62].



Scheme 2

To conclude this section, it should be recalled that alkyl migration to form an acyl group has been demonstrated in the case of the Me—$Mn(CO)_5$/CO system[27c]. Scheme 2 shows that both possible mechanisms, *i.e.* insertion of a coordinated CO group into the M—Me bond or alkyl migration, would give stereochemically equivalent, although not identical, products.

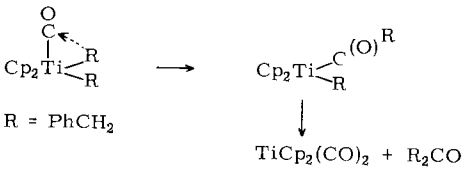
5. Studies on Titanium, Zirconium, Hafnium, and Vanadium Compounds

Having discussed the kinetic and mechanistic work which has been carried out mainly on manganese and iron, we now wish to consider CO insertion reactions of titanium, zirconium, hafnium, and vanadium compounds.

$(PhCH_2)_2TiCp_2$ reacts with carbon monoxide to give dibenzyl ketone [eq. (28)][63].

$$(PhCH_2)_2TiCp_2 + 3\,CO \rightarrow TiCp_2(CO)_2 + (PhCH_2)_2CO \qquad (28)$$

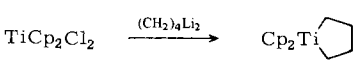
This reaction may be regarded as a reductive elimination assisted by carbon monoxide and provides an alternative route to $TiCp_2(CO)_2$[64–66]. It was suggested[63] that ketone formation, which requires a CO insertion into the benzyl-titanium bond, could take place *via* precoordination of CO to titanium, followed by benzyl migration (assumed) to form the unstable acyl intermediate [eq. (29)].



(29)

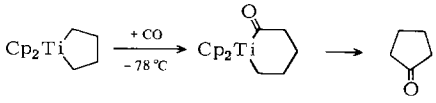
Precoordination of CO to titanium(IV) is regarded as a necessary reaction step. It is important to note in this connection that formation of ketone was predominant in heptane[63], whereas in the weakly basic benzene extensive thermal decomposition took place. Binding of CO to titanium(IV) is presumably very weak and competition by the solvent may easily occur. (Coordination of CO to other Group IVB elements in the oxidation state IV has been discussed[67].)

A thermally unstable metallocyclic titanium(IV) derivative was obtained[68] by reaction (30).



(30)

The cyclic derivative is stable at low temperature only [in contrast to the moderate stability of the dibenzyl compound, see eq. (29)] and reacts with CO to give cyclopentanone through the probable intermediacy of a metallocyclic acyl derivative [eq. (31)].



(31)

The possibility of inserting CO into a titanium-carbon σ-bond was definitely confirmed by the reaction of CO with alkyltitanium(IV) halides under ambient conditions in hydrocarbon solvents[20]:

$$R{-}TiCp_2X + CO \rightarrow RCO{-}TiCp_2X \quad (32)$$
$$X = Cl,\ R = Me,\ Et,\ CH_2Ph;\ X = I,\ R = Et$$

The complexes are characterized by strikingly low ν values for the acyl CO stretching vibration, thus suggesting a change of structural arrangement with respect to the known bonding situations for other transition elements. An X-ray investigation[69] of MeCO—$TiCp_2Cl$ shows that the "side-on" arrangement of the acetyl group already encountered for the zirconium derivative MeCO—$ZrCp_2Me$[21] is not an isolated case and may be much more common than previously thought, at least in this area of the Periodic Table (cf. Fig. 3).

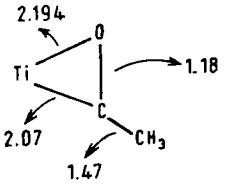


Fig. 3. Section of structure of MeCO—$TiCp_2Cl$, schematic. Bond lengths in Å [69].

Structural data for numerous acyl-(aroyl-) and alkyl-(aryl-) derivatives of transition elements are compiled in Table 4. The (O)C—C distances in the acetyl derivatives of titanium(IV) and zirconium(IV) are remarkably short, which may be an additional reason for the stability of these compounds. It has also been noted that the Fe—C distances in an acetyl[80] and in a benzoyl derivative[79] are somewhat shorter than in a corresponding phenyl-iron derivative[74], thus suggesting some kind of metal-carbon interaction in the benzoyl (and acetyl) complex. Of particular importance is the structure determination of $[cis\text{-}(MeCO)(PhCO){-}Mn(CO)_4]^{\ominus}$[77], which provides an opportunity of comparing structural parameters for two different RCO groups in the same molecule (see Section 6).

Like the titanium analogs [eq. (31)] alkylzirconium halides undergo CO insertion[82] [eq. (33)].

$$Me(CH_2)_5{-}ZrCp_2Cl + CO \rightarrow Me(CH_2)_5CO{-}ZrCp_2Cl \quad (33)$$

Acyl derivatives of zirconium(IV)[21] and hafnium(IV)[22] have been characterized only very recently [eq. (34)]:

$$R_2MCp_2 + CO \rightleftarrows RCO{-}MCp_2R \quad (34)$$

Isolation of the carbonylated products was possible for M = Zr, R = Me, CH_2Ph, Ph and for M = Hf, R = Ph; in addition, gas-volumetric and spectral data established that carbonylation also takes place similarly for M = Hf, R = Me, CH_2Ph. Moreover, in these latter cases, the position of the equilibrium was such that gas-volumetric measurements permitted determination of the formation constants and some thermodynamic parameters. ^{1}H-NMR and IR measurements established conclusively that only one R group was involved in CO insertion. The thermodynamic parameters for carbonylation of the hafnium complexes and some R—$Mn(CO)_5$ complexes are listed in Table 5[53]. These thermodynamic data may be considered assuming that the other bonds in the molecule are not affected by the insertion and that the ΔH^0 and ΔS^0 values predominantly reflect modifications occurring in the metal-carbon bond region. One point deserves special comment in connection with the data for the methyl derivatives Me—$HfCp_2Me$ and Me—$Mn(CO)_5$, which are particularly reliable. The ΔH^0 values are substantially identical, despite the considerable difference in bonding presumably existing in the two cases. The structure of the acetyl-hafnium species is not known, but the zirconium and hafnium species MeCO—MCp_2Me have substantially identical ν_{CO}(acetyl) values [1540 and

Table 4. Bond lengths in alkyl-, aryl-, and aroyl complexes of transition metals.

Compound	M—C [Å]	C—O [Å]	(O)C—C [Å]	Ref.
Alkyl- and aryl complexes				
Me—$TiIndenyl_2Me$	2.21(2)	—	—	[70]
Me—$ZrCp_2COMe$	2.336(7)	—	—	[21]
Me—$ZrIndenyl_2Me$	2.251(6)	—	—	[70]
Me—$HfIndenyl_2Me$	2.332(12)	—	—	[70]
Ph—$WCp(CO)_3$	2.32	—	—	[71]
Me—$Mn(CO)_5$	2.185(11) [a]	—	—	[72]
Me—$ReCpBr(CO)_2$	2.32	—	—	[73]
Ph—$FeCp(CO)PPh_3$	2.11	—	—	[74]
Acyl- and aroyl complexes				
MeCO—$TiCp_2Cl$	2.07(2)	1.18(2)	1.47(3)	[69]
MeCO—$ZrCp_2Me$	2.197(6)	1.211(8)	1.492(10)	[21]
$H_2NCH_2CH_2CO{-}MoCp(CO)_2$	2.22(2)	1.20(3)	1.56(3) [b]	[75]
MeCO—$MoCp(CO)_2PPh_3$	2.264(14)	1.211(16)	1.550(20)	[76]
$[cis\text{-}(MeCO)(PhCO){-}Mn(CO)_4]^{\ominus}$	Me: 2.045(11)	1.203(13)	1.512(16)	[77]
	Ph: 2.091(11)	1.218(13)	1.510(14)	
$p\text{-}ClC_6H_4CO{-}Re(CO)_5$	2.22	1.16	1.45	[78]
PhCO—$FeCp(CO)PPh_3$	1.97	1.22	1.49	[79]
MeCO—$Fe(CO)_2$(Tri-1-pyrazolylborato)	1.968(5)	1.193(6)	1.522(8)	[80]
trans-MeCO—$NiClPMe_3$	1.84(1)	1.20(1)	1.57(2)	[81]

[a] Determined by electron diffraction.
[b] The acyl carbon atom is part of a bidentate ligand.

Table 5. Thermodynamic parameters for CO insertion into metal-carbon σ-bonds.

R—M + CO ⇄ RCO—M

R—M	RCO—M	Solvent [a]	K [l/mol]	T[K]	ΔH^0 [kcal/mol]	ΔS^0 [cal K^{-1} mol^{-1}]	Ref.
Me—$HfCp_2Me$	MeCO—$HfCp_2Me$	T.	149	297.4	−12.7	−33.0	[22]
$PhCH_2$—$HfCp_2CH_2Ph$	$PhCH_2CO$—$HfCp_2CH_2Ph$	T.	156	297.4	−11.5	−28.7	[22]
n-Pr—$Mn(CO)_5$	n-PrCO—$Mn(CO)_5$	D.	2700	303.2	− 7.5	− 8.9	[54]
Et—$Mn(CO)_5$	EtCO—$Mn(CO)_5$	D.	3300	303.2	− 9.6	−15.5	[54]
Me—$Mn(CO)_5$	MeCO—$Mn(CO)_5$	D.	366	303.2	−12.6	−30.0	[54]
Ph—$Mn(CO)_5$	PhCO—$Mn(CO)_5$	D.	66	303.2	−10.8	−27.4	[54]
$PhCH_2$—$Mn(CO)_5$	$PhCH_2CO$—$Mn(CO)_5$	D.	very small	303.2	—	—	[54]

[a] T. = toluene, D. = 2,2'-diethoxydiethyl ether.

1550 cm^{-1} in CH_2Cl_2 solution, respectively, to be compared with the value of 1664 cm^{-1} known[83] for the acetyl group in MeCO—$Mn(CO)_5$]. Similar structures are therefore assumed. It is to be noted, however, that the thermodynamic parameters for the two Me—Zr/MeCO—Zr and Me—Hf/MeCO—Hf systems may be sensitive to solvent and they are therefore not directly comparable. The larger K value for the manganese complex is to be attributed, in view of the similar value of ΔH^0, to a less unfavorable entropy effect.

CO insertion into vanadium-carbon σ-bonds is also a recent achievement. VCp_2I reacts with CO to give an equilibrium mixture with $VCp_2I(CO)$ [eq. (35)][84] ($\Delta H^0 = -13.1$ kcal/mol, $\Delta S^0 = -34.6$ eu). The system does not evolve further, although one might expect a species such as $VCp_2(COI)CO$ to have a sufficient stability.

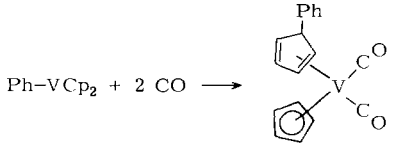
$$VCp_2I + CO \rightleftarrows VCp_2I(CO) \qquad (35)$$

Having established the possibility of labile coordination by CO to the coordination sphere of vanadium(III), the conditions necessary for CO insertion were determined. Alkylbis(cyclopentadienyl)vanadium(III) complexes were then shown[23] to react with CO to give acyl derivatives.

$$R—VCp_2 + 2CO \rightarrow RCO—VCp_2(CO) \qquad (36)$$
$$R = Me,\ CH_2Ph$$

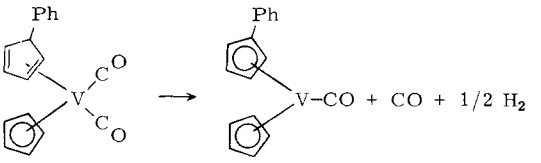
Both complexes obtained by reaction (36) show rather low ν_{CO}(acyl) values (R = Me: 1605 cm^{-1}; CH_2Ph: 1615 cm^{-1}), similar to those of the acyl derivatives of zirconium and hafnium. This may suggest that the acylvanadium(III) complexes have an unusual type of acyl coordination to the metal.

A completely different reactivity was observed[23] with the phenyl derivative [eq. (37)].



(37)

The diolefinic derivative of vanadium(I), which clearly originates from phenyl migration to the cyclopentadienyl ring, could be isolated. However, the complex decomposes according to eq. (38), both in the solid state and in solution to give CO, H_2, and a phenyl-substituted bis(cyclopentadienyl)-vanadium(II) derivative.



(38)

There is no obvious explanation for such a dramatic effect of the group R on this CO insertion reaction. The decision between insertion into the Ph—V bond to give the still hypothetical PhCO—VCp_2 or migration to the cyclopentadienyl ring to give the observed reaction product must be the result of a very delicate balance of bond energies, the latter being dependent on the nature of R in a way which is still very difficult to predict.

6. Studies on Compounds of Other Transition Elements

A comparative study was reported of CO insertions and CO abstractions for the metals of the chromium triad[26].

$$Me—MCp(CO)_3 + PR_3 \rightarrow MeCO—MCp(CO)_2PPh_3 \qquad (39)$$
$$M = Cr,\ Mo,\ W$$

Tungsten is reluctant to undergo either reaction (39) or CO abstraction [eq. (40)].

$$MeCO—WCp(CO)_2PPh_3 \rightarrow CO + Me—WCp(CO)_2PPh_3 \qquad (40)$$

Assuming a kinetic behavior similar to that encountered with manganese, it may be suggested for reactions (39) and (40) that a decisive factor is the strength of the W—Me and W—CO bonds, respectively. In the $M(CO)_6/^{14}CO$ exchange process[85] tungsten has a much higher activation energy (40.4 kcal/mol) than the molybdenum compound (30.8 kcal/mol).

CO abstraction from acyl derivatives of molybdenum and iron has been carried out[86] with $RhCl(PPh_3)_3$ as decarbonylating agent. In the reaction of the trifluoroacetyl-molybdenum complex

$$CF_3CO—MoCp(CO)_3 \xrightarrow{RhCl(PPh_3)_3} CF_3CO—MoCp(CO)_2PPh_3 + CF_3—MoCp(CO)_3 \qquad (41)$$

the trifluoroacetyl product was predominant, suggesting that CF_3 migration occurs more slowly than addition of PPh_3.

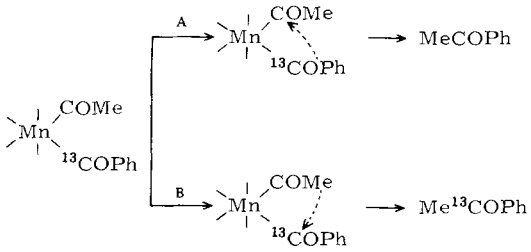
Similar to the attack by methyllithium on a terminal CO group of $W(CO)_6$ to give the $[MeCO—W(CO)_5]^{\ominus}$ anion[87], PhCO—$Mn(CO)_5$ was found[77] to be methylated at one of the terminal carbonyl groups. The bis(acyl) anion [eq. (42)],

$$PhCO—Mn(CO)_5 + Me^{\ominus} \rightarrow [cis\text{-}(PhCO)(MeCO)—Mn(CO)_4]^{\ominus} \quad (42)$$

was isolated as the tetramethylammonium salt. This anion has some peculiar features. It is the first bis(acyl) derivative carrying two different acyl groups. Only two other examples of kinetically stable, isolable bis(acyl) complexes are known, namely the complexes *cis*-$(EtCO)_2Os(CO)_4$[31] and $[cis\text{-}(MeCO)_2Mn(CO)_4]^{\ominus}$[88]. The X-ray investigation of the dianion obtained by reaction (42) (see also Table 4) has shown that the Mn—$C_{benzoyl}$ distance is 2.091 Å, and Mn—C_{acetyl} 2.045 Å. Hence the acetyl group is bonded much more strongly. This is consistent with the data of Table 5, which shows that the formation constant for MeCO—$Mn(CO)_5$ is larger than for PhCO—$Mn(CO)_5$ and that insertion into Me—$Mn(CO)_5$ is more exothermic than into Ph—$Mn(CO)_5$. In agreement with this is the observation that thermal decomposition of the anion ^{13}C-labeled at the benzoyl position gives unlabeled acetophenone [eq. (43)].

$$NMe_4^{\oplus}[cis\text{-}(Ph^{13}CO)(MeCO)—Mn(CO)_4]^{\ominus} \rightarrow MeCOPh \quad (43)$$

This experiment shows that phenyl migration to the coordinated MeCO group occurs more rapidly than methyl migration to the coordinated PhCO group.



(44)

In eq. (44), phenyl migration is faster than methyl migration in step A, while the situation is reversed in step B. There appears to be no necessity for R migration in a coordinatively unsaturated species resulting from loss of a terminal CO group, as implied in reference[77]. The reaction sequence (44) predicts the formation of the $[Mn(CO)_5]^{\ominus}$ anion: unfortunately no details about the fate of manganese were reported. This study is very important because is the only one existing in the literature establishing the relative rates of R migration from coordinated RCO groups in a truly competitive experiment. The reader may recall that the rate of methyl migration from manganese is greater than that of phenyl.

Moreover it was shown[77] that the results of the thermal decomposition [eq. (43)] were strongly affected by the nature of the counterion: the $Li^{\oplus}$ derivative gave some ^{13}C-enriched acetophenone. This was suggested to be due to specific coordination of $Li^{\oplus}$ to the acyl oxygens. Binding of alkali metals to oxygen atoms of coordinated structures is now a well established fact. It has been found between $Na^{\oplus}$ and Schiff base metal complexes[89] and, more recently[90], even terminal carbonyl groups have been found to interact with $Na^{\oplus}$ in $Na_2Fe(CO)_4 \cdot 1.5$ dioxane.

Nucleophilic attack by methyllithium on a terminal carbonyl group of MeCO—$Mn(CO)_5$ was also reported by *Lukehart et al.*[88], according to a reaction similar to (42). Treatment of the resulting bis(acetyl)anion, $[cis\text{-}(MeCO)_2Mn(CO)_4]^{\ominus}$ with anhydrous $AlCl_3$ gave a neutral derivative of formula $[Mn(CO)_4(COMe)_2]_3Al$.

CO insertions into rhenium-carbon bonds have been comparatively little studied. Several CO abstractions, usually occurring at temperatures higher than those employed for the corresponding manganese complexes, have been reported. For example, acetyl- and benzoyl(pentacarbonyl)rhenium were decarbonylated[28] according to eq. (45).

$$RCO—Re(CO)_5 \rightarrow CO + R—Re(CO)_5 \quad (45)$$
$$R = Me,\ T \geq 80°C;\ R = Ph,\ T = 120°C$$

However, no quantitative data on these systems are available.

Manganese and iron have much in common, as far as CO insertions are concerned. An ion-pair effect, similar to that reported[77] by *Casey* and *Bunnell*, has been found for the reaction of acyliron anions with tertiary phosphanes[91]. Small cations such as $Li^{\oplus}$ and $Na^{\oplus}$ favor the formation of the acyl derivative.

$$M[R—Fe(CO)_4] + PR_3 \rightarrow M[RCO—Fe(CO)_3PR_3] \quad (46)$$
$$M = Li^{\oplus},\ Na^{\oplus},\ \text{and others}$$

Synthetic applications of reactions possibly related to carbon monoxide insertions have been reported, aimed at the preparation of aldehydes[92], ketones[93–95], carboxylic acids, esters and amides[96], by making use of the $[Fe(CO)_4]^{2\ominus}$ anion as carbonylating agent.

In contrast to iron, only few CO insertions are known for ruthenium. This is certainly connected with the enhanced kinetic lability of ruthenium-carbon σ-bonds in general. In this respect the iron subgroup metals probably resemble the chromium triad. The 4d element ruthenium is generally speaking more reactive than osmium *(vide infra)*. Acyl derivatives of ruthenium(II) have been obtained[97] by the usual method of treating the alkyl derivatives with tertiary phosphanes, *e.g.* according to eq. (47). Protonation of the acetyl group afforded salts of the $[MeC(OH)RuCp(CO)PR_3]^{\oplus}$ cations, to which a carbene-like type of structure was assigned.

$$Me—RuCp(CO)_2 + PR_3 \rightarrow MeCO—RuCp(CO)PR_3 \quad (47)$$

Kinetic evidence for the formation of the protonated intermediate $[MeC(OH)Mn(CO)_5]^{\oplus}$ was gathered in studies[98] of acid-catalyzed solvolysis of the acetyl-manganese complex.

Insertions into alkyl-osmium bonds have also been reported[31]. The dialkyl derivatives $R_2—Os(CO)_4$ (R = Me, Et) are stable compounds at room temperature, which is very surprising for dialkyl derivatives of the iron triad.

$$[Os(CO)_4]^{2\ominus} + 2RI \rightarrow cis\text{-}R_2—Os(CO)_4 + 2I^{\ominus} \quad (48)$$

The dimethyl derivative, a colorless solid sublimable at room temperature, decomposes at 120°C to ethane and $Os(CO)_5$ in the presence of CO, with no indication of insertion products.

$$Me_2Os(CO)_4 + CO \xrightarrow{THF} Os(CO)_5 + C_2H_6 \quad (49)$$

The diethyl derivative, on the other hand, undergoes carbonylation, the main product of the reaction being *cis*-$(EtCO)_2Os(CO)_4$, identified spectroscopically in solution [eq. (50)].

$$cis\text{-}Et_2Os(CO)_4 + 2CO \xrightarrow[100\,atm]{110\,^\circ C,\ C_6H_6} cis\text{-}(EtCO)_2{-}Os(CO)_4 \quad (50)$$

This is the first case of double insertion into a dialkyl derivative.

Similar to the reactions mentioned earlier with PhCO—$Mn(CO)_5$[77] and $W(CO)_6$[87], *cis*-$OsBr_2(CO)_4$ undergoes methylation by methylmagnesium bromide at the terminal carbonyl groups[99].

$$cis\text{-}OsBr_2(CO)_4 + 2Me^{\ominus} \rightarrow [(MeCO)_2OsBr_2(CO)_2]^{2\ominus} \quad (51)$$

According to spectroscopic data, the anion has the all-*cis* stereochemistry.

CO insertions into alkyl(tetracarbonyl)cobalt compounds (or corresponding rhodium compounds) are important, being related to the hydroformylation reaction[100]. The most commonly accepted mechanism for this reaction requires: i) reaction of a metal hydride with an olefin to give the appropriate alkylmetal complex; ii) CO insertion; and iii) hydrogenolysis of the acyl derivative to give the aldehyde. Applied to ethylene this can be outlined as follows:

i) $L_nM{-}H + C_2H_4 \rightarrow L_nM{-}Et$
ii) $L_nM{-}Et + CO \rightarrow L_nM{-}COEt$
iii) $L_nM{-}COEt + H_2 \rightarrow L_nM{-}H + EtCHO$

In hydroformylations with 1-octene, infrared spectra typical of $C_8H_{17}CO{-}Co(CO)_4$ and $Co_2(CO)_8$[101] were recorded. In contrast, spectra measured during hydroformylation of diisobutylene (2,4,4-trimethyl-1- and -2-pentene) or cyclohexene show the presence of $H{-}Co(CO)_4$ and $Co_2(CO)_8$, thus suggesting that a relatively slow addition of olefins to the hydride takes place in this case.

Both $R{-}Co(CO)_4$ and $RCO{-}Co(CO)_4$ are unstable species thermally but they become more stable on substitution with a tertiary phosphane. CO insertion into such substituted compounds has been reported [eq. (52)][32b].

$$Me{-}Co(CO)_3P(n\text{-}Bu)_3 + CO \rightarrow MeCO{-}Co(CO)_3P(n\text{-}Bu)_3 \quad (52)$$

A benzyl derivative has been treated[32c] with labeled CO.

$$PhCH_2{-}Co(CO)_3PPh_3 + {}^{13}CO \rightarrow PhCH_2CO{-}Co({}^{13}CO)(CO)_2PPh_3 \quad (53)$$

This confirms the labeling experiments mentioned earlier and suggests that the mechanism of formation of the acyl could be alkyl migration.

Heck[32a] has studied the decarbonylation of acyl(tetracarbonyl)cobalt compounds by triphenylphosphane.

$$RCO{-}Co(CO)_4 + PPh_3 \rightarrow CO + RCO{-}Co(CO)_3PPh_3 \quad (54)$$

The reactions were found to be zero-order in tertiary phosphane concentration and first-order in cobalt complex concentration, thus suggesting dissociation of a terminal CO group to be rate-determining, as in the manganese system (cf. Section 4). For selected groups R in eq. (54) one obtains the following rate constants:

R	*n*-C_5H_{11}	Me	$PhCH_2$
$10^3 \times k[s^{-1}]$	1.07	0.97	1.32

Within the range of alkyl groups indicated, the effect is small, as expected. All the aroyl systems react much faster[32a].

In the course of the stoichiometric reaction of $Rh_4(CO)_{12}$ with olefins to give aldehydes [eq. (55)], *Chini et al.*[33b] have isolated anionic acyl cluster compounds of formula $[RCO{-}Rh_6(CO)_{15}]^{\ominus}$. This appears to be the sole example of an acyl-metal group in a metal cluster[102].

$$3Rh_4(CO)_{12} + 4MeCH{=}CH_2 + 4H_2 \rightarrow 2MeCH_2CH_2CHO + 2Me_2CHCHO + 2Rh_6(CO)_{16} \quad (55)$$

Oxidative addition of acyl- or aroyl halides to $RhCl(PPh_3)_3$ yields RCO complexes of rhodium(III)[33a].

$$RhCl(PPh_3)_3 + RCOCl \rightarrow PPh_3 + RCO{-}RhCl_2(PPh_3)_2 \quad (56)$$

Like the iridium(III) complexes reported by *Kubota*[53], these rhodium(III) complexes readily convert thermally into the corresponding alkyl or aryl derivatives of hexacoordinated rhodium(III).

$$RCO{-}RhCl_2(PPh_3)_2 \rightleftharpoons R{-}RhCl_2(CO)(PPh_3)_2 \quad (57)$$

Carbonyliridium complexes are less reactive than rhodium and cobalt analogues. *Whyman*[105] studied the behavior of the hydride $H{-}Ir(CO)_3P(i\text{-}Pr)_3$[103,104] towards ethylene, CO, and H_2 [eq. (58)].

$$H{-}Ir(CO)_3P(i\text{-}Pr)_3 + C_2H_4 \xrightarrow[14\,atm]{50\,^\circ C} Et{-}Ir(CO)_3P(i\text{-}Pr)_3 \quad (58)$$

On replacing ethylene with CO, an infrared spectrum consistent with the formation of an acyl derivative was measured, whereas substituting H_2 for ethylene yielded an infrared band assignable to the aldehyde. The experimental evidence supports the hydroformylation scheme also in the case of iridium.

Isolable products arising from the CO insertion into nickel-carbon σ-bonds have been reported only recently[35a,35b]

$$trans\text{-}Me{-}NiX(PMe_3)_2 + CO \rightarrow trans\text{-}MeCO{-}NiX(PMe_3)_2 \quad (59)$$
X = Cl, Br, I, O_2CMe

The complexes have one strong infrared absorption at 1635—1650 cm^{-1}, depending on the halogen.

Palladium(II) and platinum(II) complexes likewise undergo carbon monoxide insertion[36a].

$$trans\text{-}R{-}PdX(PEt_3)_2 + CO \rightarrow trans\text{-}RCO{-}PdX(PEt_3)_2 \quad (60)$$
X = Cl, Br, I; R = Me

$$trans\text{-}R{-}PtX(PEt_3)_2 + CO \rightarrow trans\text{-}RCO{-}PtX(PEt_3)_2 \quad (61)$$
X = Cl, Br, I; R = Me, Ph

$$Me{-}Pt(PP)Me + CO \rightarrow MeCO{-}Pt(PP)Me \quad (62)$$
PP = $Et_2PCH_2CH_2PEt_2$

Reaction (62) is one of the few examples of CO insertion into dialkyl (or diaryl) complexes of transition metals. Single insertion of CO takes place in this case, similar to the zirconium and hafnium cases[22] and contrary to the osmium case[31].

A coordination position of the RCO derivative must be vacated to initiate the CO abstraction (with retention of both R and CO in the coordination sphere of the metal). This can be accomplished photolytically as mentioned earlier[55,57], and also chemically[106]. Expulsion of Cl from the coordination sphere of RCO-platinum(II) derivatives was carried out with silver ions.

$$RCO{-}PtCl(PPh_3)_2 + Ag^{\oplus} \rightarrow AgCl + [R{-}Pt(CO)(PPh_3)_2]^{\oplus} \quad (63)$$
$$R = Me, Et, Ph, Me_2CH, p\text{-}XC_6H_4$$

Reaction (63) was observed in acetone, whereas in the effective donor acetonitrile isolable RCO-complexes of formula $[RCO{-}Pt(PPh_3)_2(NCMe)]^{\oplus}$ were isolated.

Although CO insertion reactions into copper-carbon σ-bonds are still unknown, there is experimental evidence available that suggests the intermediacy of acyl-copper derivatives[107]. Ketones have in fact been obtained by treatment of $[Bu_2Cu]^{\ominus}$ with CO.

7. CO Insertions into Other Metal-Ligand Bonds

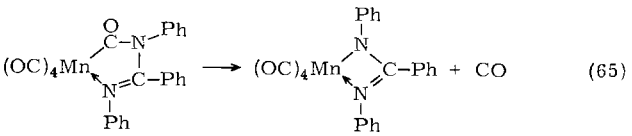
The possibility of isolating products of CO insertions into a metal-ligand bond M—L is bound closely with the thermodynamic stability of the M—CO—L system *vs.* M—L + CO (L = H, NR_2, OR, SR, Cl, Br, I). In many cases, we are dealing with a less favorable thermodynamic situation, compared to acyl- or aroyl compounds, as far as the C(O)—L bond is concerned. On the other hand, several compounds containing the M—$CONR_2$ or M—COOR groupings as obtained by preparative methods other than the CO insertion, have been described as kinetically stable substances. It should also be mentioned that reaction paths are known that require or suggest the transient formation of M—CO—L bonds. This kind of CO insertion plays a very important role in catalytic carbonylations of organic substrates[108].

Despite considerable research efforts, CO insertion into M—H bonds still appears an elusive reaction. Pentacarbonyl(hydrido)manganese does not react appreciably with carbon monoxide under conditions suitable for the formation of the acyl derivatives from the corresponding alkyls[45]. This is consistent with the observation that no formyl groups were detected spectroscopically during photolytic treatment[109] of $H{-}Mn(CO)_5$ in an argon matrix.

On the other hand, an anionic formyl derivative of iron has been prepared from formic acetic anhydride, and reported[110] to undergo slow decomposition to the corresponding hydride.

$$(MeCO)(HCO)O + [Fe(CO)_4]^{2\ominus} \rightarrow [HCO{-}Fe(CO)_4]^{\ominus} + MeCOO^{\ominus} \quad (64)$$

The problem of CO insertions into metal-nitrogen bonds has been recently reviewed[111]. The complexes $MCpX(CO)_2$ [M = Mo, W; X = —N=CR_2, —$N(CR_2)_2$, —N(R)C(=N)—R'] did not give CO insertion products. On the other hand, thermal



(65)

treatment of a carbamoylmanganese complex resulted in the carbonyl abstraction product [eq. (65)], which however, failed to regenerate the starting material on treatment with CO under drastic conditions (125 °C, $p_{CO} = 200$ atm).

$$M{-}NR_2 + CO \rightleftharpoons MCONR_2 \quad (66)$$

Although CO insertion into metal-nitrogen bonds, for example into metal-dialkylamide bonds [eq. (67)], is not known as yet, carbamoyl complexes[112] are believed to be intermediates in some metal-catalyzed carbonylations of amines[113] and in reactions of CO with nitrogen-containing compounds in general[114].

1,1-Diphenylurea exchanges with ^{14}CO in the presence of $Co_2(CO)_8$ at elevated temperature[114]. This may suggest the transitory formation of Co—NPh_2 and Co—$CONPh_2$ bonds.

For an example of CO insertion into a metal-alkoxide bond, see reference [16].

A reaction which does not appear to have been reported as yet for a kinetically stable isolable complex is CO insertion into a metal-halogen bond. However, evidence does exist for the transitory formation of M—CO—X bonds in transition metal carbonyl chemistry. Some years ago *Noack*[115] used low temperature infrared spectroscopic methods to study the reaction between $Fe(CO)_5$ and Br_2 and I_2. In $CHCl_3/CH_2Cl_2$ a band was observed at about 1650 cm^{-1}, which was attributed to an intermediate species $FeBr(CO)_4(COBr)$ that rapidly collapses to $Fe(CO)_4Br_2$ on increasing the temperature. No acyl bands could be detected in CH_2Cl_2[116].

M—CO—Cl species are important intermediates for the reduction of anhydrous metal halides by CO. Anhydrous gold(III) chloride, prepared from tetrachloroauric acid in thionyl chloride[117], reacts further with CO in the same solvent to give almost quantitative yields of AuCl(CO) [eq. (67)].

$$\tfrac{1}{2}\,Au_2Cl_6 + 2CO \rightarrow COCl_2 + AuCl(CO) \quad (67)$$

A systematic investigation of the reaction between anhydrous gold(III) chloride and AuCl(CO) under nitrogen or argon has revealed[118] the existence of a soluble unstable carbonyl derivative of gold, characterized by $\nu_{CO} = 2180\ cm^{-1}$. This is higher than the carbonyl stretching vibration of AuCl(CO) in the same solvent (2162 cm^{-1}). In addition, a black moisture-sensitive substance of analytical composition $AuCl_2$ was isolated, whose yield was optimized when the $AuCl_3$: AuCl(CO) molar ratio was 3 : 1. No evolution of carbon monoxide was observed in any of the reactions and it was established spectroscopically that the CO initially coordinated to gold(I) in AuCl(CO) was transformed into $COCl_2$. The molecular structure of the analytical product $AuCl_2$ has now been established by X-ray analysis[119]. The structure is that of a covalently bonded gold(III)-gold(I) mixed-valence compound of formula Au_4Cl_8. Within the molecule the two gold(III) centers and the two gold(I) centers have the expected planar and linear coordinations, respectively. The existence of a compound of composition

$AuCl_2$ was a subject of considerable dispute in the literature[120].

Au_4Cl_8 reacts very rapidly with CO, even in the solid state, to give AuCl(CO). The soluble transient carbonyl species (ν_{CO} at 2180 cm^{-1}) of probable formula $Au_2Cl_4(CO)$, similar to the mixed-valence olefin complexes described by *Hüttel et al.*[121], plays an important role in the formation of Au_4Cl_8. Since the fate of coordinated CO is known, the formation of Au_4Cl_8 can best be represented by eq. (68).

$$Au_2Cl_4(CO) + Au_2Cl_6 \rightarrow Au_4Cl_8 + COCl_2 \quad (68)$$

Transfer of chlorine from Au_2Cl_6 to coordinated CO, and hence formation of kinetically unstable Au—CO—Cl bonds, are required by the results obtained in this study.

The author wishes to thank the National Research Council (C.N.R.), Rome, and Snam-Progetti S.p.A., Milan, for support of the work carried out at the University of Pisa, and to express his gratitude to all his past and present collaborators.

Received: August 6, 1976 [A 160 IE]
German version: Angew. Chem. *89*, 305 (1977)

[1] *T. H. Coffield, J. Kozikowski, R. D. Closson*, J. Org. Chem. *22*, 598 (1957).
[2] *F. Bonati, G. Wilkinson*, J. Chem. Soc. *1964*, 179.
[3] Übersicht: *M. F. Lappert, B. Prokai*, Adv. Organomet. Chem. *5*, 225 (1967).
[4] *A. Wojcicki*, Adv. Organomet. Chem. *11*, 87 (1973).
[5] *J. Falbe*: Synthesen mit Kohlenmonoxid. Springer, Berlin 1967.
[6] *D. Forster*, J. Am. Chem. Soc. *98*, 846 (1976), and references therein.
[7] *G. P. Chiusoli*, Acc. Chem. Res. *6*, 422 (1973).
[8] *P. Pino, G. Braca, G. Sbrana, A. Cuccuru*, Chem. Ind. (London) *1968*, 1732.
[9] *C. W. Bird*, Chem. Rev. *62*, 283 (1962), and references therein.
[10] *J. Tsuji*: Organic Syntheses by Means of Transition Metal Complexes. Springer, Berlin 1975.
[11] *R. F. Heck*: Organotransition Metal Chemistry. Academic Press, New York 1974.
[12] *H. Storch, N. Golumbr, R. Anderson*: The Fischer-Tropsch and Related Syntheses. Wiley, New York 1951.
[13] *M. G. Thomas, B. F. Beier, E. L. Muetterties*, J. Am. Chem. Soc. *98*, 1296 (1976).
[14] *J. Halpern*, Acc. Chem. Res. *3*, 386 (1970).
[15] *J. P. Collman, W. R. Roper*, Adv. Organomet. Chem. *7*, 53 (1968).
[16] *W. Hieber, F. Lux, C. Herget*, Z. Naturforsch. *20b*, 1159 (1965).
[17] *F. N. Tebbe, G. W. Parshall*, J. Am. Chem. Soc. *93*, 3793 (1971).
[18] a) *C. M. Mitchell, F. G. A. Stone*, J. Chem. Soc. Dalton *1972*, 102; b) *A. Johnson, R. J. Puddephatt, J. L. Quirk*, J. Chem. Soc. Chem. Commun. *1972*, 938.
[19] *G. van Koten, J. G. Noltes*, J. Chem. Soc. Chem. Commun. *1972*, 59.
[20] *G. Fachinetti, C. Floriani*, J. Organomet. Chem. *71*, C5 (1974).
[21] *G. Fachinetti, C. Floriani, F. Marchetti, S. Merlino*, J. Chem. Soc. Chem. Commun. *1976*, 522.
[22] *G. Fachinetti, G. Fochi, C. Floriani*, J. Chem. Soc. Dalton, in press.
[23] a) *G. Fachinetti, C. Floriani*, J. Chem. Soc. Chem. Commun. *1974*, 516; b) *G. Fachinetti, S. Del Nero, C. Floriani*, J. Chem. Soc. Dalton *1976*, 203.
[24] *K. W. Barnett, D. L. Beach, T. G. Pollmann*, Inorg. Nucl. Chem. Lett. *9*, 131 (1973).
[25] a) *I. S. Butler, F. Basolo, R. G. Pearson*, Inorg. Chem. *6*, 2074 (1967); b) *P. J. Craig, M. Green*, J. Chem. Soc. *A 1968*, 1978; c) *ibid. 1969*, 157.
[26] *K. W. Barnett, D. L. Beach, S. P. Gaydos, T. G. Pollmann*, J. Organomet. Chem. *69*, 121 (1974).
[27] a) *F. Calderazzo, F. A. Cotton*, Inorg. Chem. *1*, 30 (1962); b) *R. J. Mawby, F. Basolo, R. G. Pearson*, J. Am. Chem. Soc. *86*, 3994 (1964); c) *K. Noack, F. Calderazzo*, J. Organomet. Chem. *10*, 101 (1967); d) *K. Noack, M. Ruch, F. Calderazzo*, Inorg. Chem. *7*, 345 (1968).
[28] *W. Hieber, G. Braun, W. Beck*, Chem. Ber. *93*, 901 (1960).
[29] *P. Reich-Rohrwig, A. Wojcicki*, Inorg. Chem. *13*, 2457 (1974).
[30] *G. Sbrana, G. Braca, E. Benedetti*, J. Chem. Soc. Dalton *1975*, 754.
[31] *F. L'Eplattenier, C. Pélichet*, Helv. Chim. Acta *53*, 1091 (1970).
[32] a) *R. F. Heck*, J. Am. Chem. Soc. *85*, 651 (1963); b) *F. Piacenti, M. Bianchi, E. Benedetti*, Chim. Ind. (Milano) *49*, 245 (1967); c) *Z. Nagy-Magos, G. Bor, L. Markó*, J. Organomet. Chem. *14*, 205 (1968).
[33] a) *M. C. Baird, J. T. Mague, J. A. Osborn, G. Wilkinson*, J. Chem. Soc. A *1967*, 1347; b) *P. Chini, S. Martinengo, G. Garlaschelli*, J. Chem. Soc. Chem. Commun. *1972*, 709.
[34] a) *R. W. Glyde, R. J. Mawby*, Inorg. Chem. Acta *4*, 331 (1970); b) *M. Kubota, D. M. Blake, S. A. Smith*, Inorg. Chem. *10*, 1430 (1971).
[35] a) *H.-F. Klein*, Angew. Chem. *85*, 403 (1973); Angew. Chem. Int. Ed. Engl. *12*, 402 (1973); b) *H.-F. Klein, H. H. Karsch*, Chem. Ber. *109*, 2524 (1976); c) *S. Otsuka, A. Nakamura, T. Yoshida, M. Naruto, K. Ataka*, J. Am. Chem. Soc. *95*, 3180 (1973).
[36] a) *G. Booth, J. Chatt*, J. Chem. Soc. *A 1966*, 634; b) *K. Kudo, M. Sato, M. Hidai, Y. Uchida*, Bull. Chem. Soc. Jpn. *46*, 2820 (1973); c) *L. S. Hegedus, K. Siirala-Hansén*, J. Am. Chem. Soc. *97*, 1184 (1975).
[37] a) *R. W. Glyde, R. J. Mawby*, Inorg. Chem. *10*, 854 (1971); b) *C. J. Wilson, M. Green, R. J. Mawby*, J. Chem. Soc. Dalton *1974*, 421.
[38] *V. I. Telnoi, I. B. Rabinovic, V. D. Tikhonov, V. I. Latyaeva, L. I. Vishinskaia, G. A. Razuvaev*, Dokl. Akad. Nauk SSSR *174*, 1374 (1967); Chem. Abstr. *68*, 43809s (1968).
[39] *F. A. Adedeji, J. A. Connor, H. A. Skinner, L. Galyer, G. Wilkinson*, J. Chem. Soc. Chem. Commun. *1976*, 159.
[40] *D. L. S. Brown, J. A. Connor, H. A. Skinner*, J. Organomet. Chem. *81*, 403 (1974).
[41] *S. J. Ashcroft, C. T. Mortimer*, J. Chem. Soc. *A 1967*, 930.
[42] *H. A. Skinner*, Adv. Organomet. Chem. *2*, 49 (1964).
[43] *M. Tsutsui, N. M. Ely*, J. Am. Chem. Soc. *97*, 1280 (1975).
[44] a) *E. Cernia, A. Mazzei*, Inorg. Chim. Acta *10*, 239 (1974), and references therein; b) *T. J. Marks, A. M. Seyam, J. R. Kolb*, J. Am. Chem. Soc. *95*, 5529 (1973); c) *M. Tsutsui, N. Ely, A. Gebala*, Inorg. Chem. *14*, 78 (1975).
[45] *F. Calderazzo*, unpublished results.
[46] *K. Noack, F. Calderazzo*, unpublished results.
[47] *F. Calderazzo, F. A. Cotton*, Chim. Ind. (Milano) *46*, 1165 (1964).
[48] *P. J. Davidson, M. F. Lappert, R. Pearce*, Chem. Rev. *76*, 219 (1976).
[49] *R. P. Stewart, P. M. Treichel*, J. Am. Chem. Soc. *92*, 2710 (1970).
[50] *C. P. Casey, C. A. Bunnell, J. C. Calabrese*, J. Am. Chem. Soc. *98*, 1166 (1976).
[51] *K. Nicholas, S. Raghu, M. Rosenblum*, J. Organomet. Chem. *78*, 133 (1974).
[52] a) *R. R. Hitch, S. K. Gondal, C. T. Sears*, Chem. Commun. *1971*, 777; b) *R. Colton, C. J. Common*, Aust. J. Chem. *28*, 1673 (1975); c) *K. G. Caulton, P. Adair*, J. Organomet. Chem. *114*, C11 (1976).
[53] a) *M. Kubota, D. M. Blake*, J. Am. Chem. Soc. *93*, 1368 (1971); b) cf. also *D. Eggleston, M. C. Baird*, J. Organomet. Chem. *113*, C25 (1976).
[54] *F. Calderazzo, F. A. Cotton*, Abstr. Papers, 7th I.C.C.C., June 1962, Stockholm, Paper 6H7.
[55] *J. J. Alexander*, J. Am. Chem. Soc. *97*, 1729 (1975).
[56] *T. H. Coffield, J. Kozikowski, R. D. Closson*, Abstr. Papers, I.C.C.C. London 1959, Paper 26.
[57] *A. J. Rest*, J. Organomet. Chem. *25*, C30 (1970).
[58] *F. Calderazzo, K. Noack*, Organomet. Chem. Rev. *1*, 118 (1966).
[59] a) *G. M. Whitesides, D. J. Boschetto*, J. Am. Chem. Soc. *91*, 4313 (1969); b) *P. L. Bock, D. J. Boschetto, J. R. Rasmussen, J. P. Demers, G. M. Whitesides*, *ibid. 96*, 2814 (1974).
[60] *T. G. Attig, A. Wojcicki*, J. Organomet. Chem. *82*, 397 (1974).
[61] *A. Davison, N. Martinez*, J. Organomet. Chem. *74*, C17 (1974).
[62] *H. Brunner, J. Strutz*, Z. Naturforsch. *29b*, 446 (1974).
[63] *G. Fachinetti, C. Floriani*, J. Chem. Soc. Chem. Commun. *1972*, 654.
[64] *J. G. Murray*, J. Am. Chem. Soc. *83*, 1287 (1961).
[65] *B. Demerseman, G. Bouquet, M. Bigorgne*, J. Organomet. Chem. *101*, C24 (1975).
[66] *B. Demerseman, G. Bouquet, M. Bigorgne*, J. Organomet. Chem. *93*, 199 (1975).
[67] *J. W. Lauher, R. Hoffmann*, J. Am. Chem. Soc. *98*, 1729 (1976).
[68] *J. X. McDermott, G. M. Whitesides*, J. Am. Chem. Soc. *96*, 947 (1974).
[69] *H. Stoeckli-Evans, G. Fachinetti, C. Floriani*, J. Chem. Soc. Dalton, in press.
[70] *J. L. Atwood, W. E. Hunter, D. C. Hrncir, E. Samuel, H. Alt, M. D. Rausch*, Inorg. Chem. *14*, 1757 (1975).
[71] *V. A. Semion, Yu. T. Struchkov*, Zh. Strukt. Khim. *9*, 1046 (1968); Chem. Abstr. *70*, 71713r (1969).
[72] *H. M. Seip, R. Seip*, Acta Chem. Scand. *24*, 3431 (1970).
[73] *G. G. Aleksandrov, Yu. T. Struchkov, Yu. V. Makarov*, Zh. Strukt. Khim. *14*, 98 (1973); Chem. Abstr. *78*, 116315w (1973).
[74] *V. A. Semion, Yu. T. Struchkov*, Zh. Strukt. Khim. *10*, 88 (1969); Chem. Abstr. *70*, 109823s (1969).
[75] *G. A. Jones, L. J. Guggenberger*, Acta Crystallogr. *B31*, 900 (1975).
[76] *M. R. Churchill, J. P. Fennessey*, Inorg. Chem. *7*, 953 (1968).
[77] *C. P. Casey, C. A. Bunnell*, J. Am. Chem. Soc. *98*, 436 (1976).
[78] *I. S. Astakhova, V. A. Semion, Yu. T. Struchkov*, Zh. Strukt. Khim. *10*, 508 (1969).

[79] V. A. Semion, Yu. T. Struchkov, Zh. Strukt. Khim. 10, 664 (1969); Chem. Abstr. 71, 117377k (1969).
[80] F. A. Cotton, B. A. Frenz, A. Shaver, Inorg. Chim. Acta 7, 161 (1973).
[81] G. Huttner, O. Orama, V. Bejenke, Chem. Ber. 109, 2533 (1976).
[82] C. A. Bertelo, J. Schwartz, J. Am. Chem. Soc. 97, 228 (1975).
[83] K. Noack, U. Schaerer, F. Calderazzo, J. Organomet. Chem. 8, 517 (1967).
[84] F. Calderazzo, G. Fachinetti, C. Floriani, J. Am. Chem. Soc. 96, 3695 (1974).
[85] F. Calderazzo, R. Ercoli, G. Natta in P. Pino, I. Wender: Metal Carbonyls: Preparations, Structure and Properties. Wiley, New York 1968.
[86] J. J. Alexander, A. Wojcicki, Inorg. Chem. 12, 74 (1973).
[87] E. O. Fischer, A. Massböl, Chem. Ber. 100, 2445 (1967).
[88] C. M. Lukehart, G. P. Torrence, J. V. Zeile, J. Am. Chem. Soc. 97, 6903 (1975).
[89] C. Floriani, F. Calderazzo, L. Randaccio, J. Chem. Soc. Chem. Commun. 1973, 384.
[90] H. B. Chin, R. Bau, J. Am. Chem. Soc. 98, 2434 (1976).
[91] J. P. Collman, J. N. Cawse, J. I. Brauman, J. Am. Chem. Soc. 94, 5905 (1972).
[92] M. P. Cooke, J. Am. Chem. Soc. 92, 6080 (1970).
[93] J. P. Collman, S. R. Winter, D. R. Clark, J. Am. Chem. Soc. 94, 1788 (1972).
[94] M. P. Cooke, R. M. Parlman, J. Am. Chem. Soc. 97, 6863 (1975).
[95] J. P. Collman, N. W. Hoffman, J. Am. Chem. Soc. 95, 2689 (1973).
[96] J. P. Collman, S. R. Winter, R. G. Komoto, J. Am. Chem. Soc. 95, 249 (1973).
[97] M. L. H. Green, L. C. Mitchard, M. G. Swanwick, J. Chem. Soc. A 1971, 794.
[98] R. W. Johnson, R. G. Pearson, Inorg. Chem. 10, 2091 (1971).
[99] F. L'Eplattenier, Inorg. Chem. 8, 965 (1969).
[100] D. T. Thompson, R. Whyman in G. N. Schrauzer: Transition Metals in Homogeneous Catalysis. Dekker, New York 1971; cf. also G. Henrici-Olivé, S. Olivé, Transition Met. Chem. 1, 77 (1976).
[101] R. Whyman, J. Organomet. Chem. 81, 97 (1974).
[102] P. Chini, G. Longoni, V. G. Albano, Adv. Organomet. Chem. 14, 285 (1976).
[103] L. Malatesta, M. Angoletta, F. Conti, J. Organomet. Chem. 33, C43 (1971).
[104] A. J. Drakesmith, R. Whyman, J. Chem. Soc. Dalton 1973, 362.
[105] R. Whyman, J. Organomet. Chem. 94, 303 (1975).
[106] M. Kubota, R. K. Rothrock, J. Geibel, J. Chem. Soc. Dalton 1973, 1267.
[107] J. Schwartz, Tetrahedron Lett. 1972, 2803, and references therein.
[108] a) M. I. Bruce, J. Organomet. Chem. 44, 209 (1972); b) D. M. Fenton, P. J. Steinwand, J. Org. Chem. 39, 701 (1974); c) T. Saegusa, T. Tsuda, K. Isayama, ibid. 35, 2976 (1970); d) P. Koch, E. Perrotti, J. Organomet. Chem. 81, 111 (1974).
[109] A. J. Rest, J. J. Turner, J. Chem. Soc. Chem. Commun. 1969, 375.
[110] J. P. Collman, S. R. Winter, J. Am. Chem. Soc. 95, 4089 (1973).
[111] a) T. Inglis, M. Kilner, J. Chem. Soc. Dalton 1976, 562; b) T. Inglis, M. Kilner, T. Reynoldson, E. E. Robertson, ibid. 1975, 924.
[112] W. Jetz, R. J. Angelici, J. Am. Chem. Soc. 94, 3799 (1972).
[113] F. Calderazzo, Inorg. Chem. 4, 293 (1965).
[114] A. Rosenthal, I. Wender in I. Wender, P. Pino: Organic Syntheses via Metal Carbonyls. Wiley, New York 1968.
[115] K. Noack, J. Organomet. Chem. 13, 411 (1968).
[116] M. F. Farona, G. R. Camp, Inorg. Chim. Acta 3, 395 (1969).
[117] D. Belli Dell'Amico, F. Calderazzo, Gazz. Chim. Ital. 103, 1099 (1973).
[118] D. Belli Dell'Amico, F. Calderazzo, F. Marchetti, J. Chem. Soc. Dalton, 1976, 1829.
[119] D. Belli Dell'Amico, F. Calderazzo, F. Marchetti, S. Merlino, G. Perego, J. Chem. Soc. Chem. Commun. 1977, 31.
[120] J. D. Corbett, L. F. Druding, J. Inorg. Nucl. Chem. 11, 20 (1959), and references therein.
[121] R. Hüttel, H. Reinheimer, K. Nowak, Chem. Ber. 101, 3761 (1968).

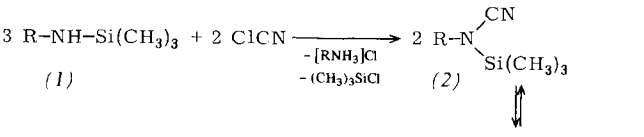
COMMUNICATIONS

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

Silatautomeric Organylcarbodiimides/Cyanamides

By *Ingo Ruppert*[*]

Various reports have recently been published about the synthesis of *tert*-butyl-[1a] and phenyl-substituted[1b] monosilylcarbodiimides, which can be employed not only for a variety of addition reactions[2a] but also for condensations involving elimination of halosilane[2b]. A particularly facile entry to these compounds with free choice of organyl substituent is provided by the action of cyanogen chloride on secondary silylamines[3].



R = CH_3 *(a)*, C_2H_5 *(b)*, $(CH_3)_2CH$ *(c)*, $(CH_3)_3C$ *(d)*, C_6H_5 *(e)*

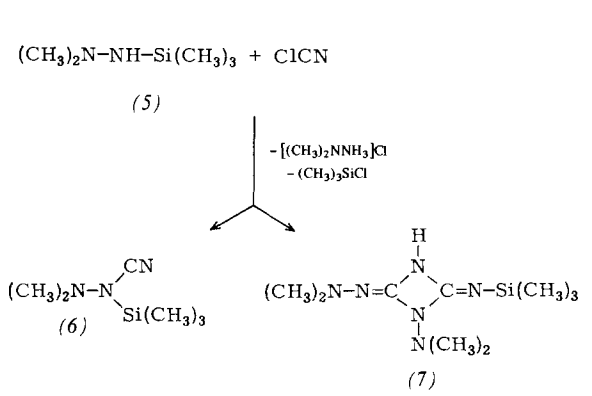
If a slight excess of ClCN is passed into an ethereal solution of the silylamines *(1a—e)* the progress of the reaction can be followed by observing the amount of amine hydrochloride precipitated. Prior metalation of the silylamines[4] with butyllithium did not raise the yield of organylsilylcarbodiimides *(3a—e)*. In contrast, the disilylated amine *(4)*, unfortunately readily accessible only as the methyl derivative[5], can be used to advantage for condensation.

$$CH_3–N[Si(CH_3)_3]_2 + ClCN \longrightarrow (3a) + (CH_3)_3SiCl$$
(4)

Attempts to prepare an amino-substituted carbodiimide by using *N,N*-dimethyl-*N'*-trimethylsilylhydrazine *(5)* as amine component were unsuccessful.

Instead only the cyanohydrazine *(6)*, an aminocyanamide isomeric to the corresponding carbodiimide, could be isolated

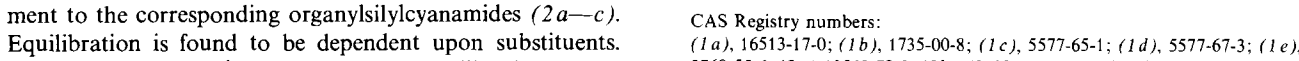
[*] Dr. I. Ruppert
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)



as a by-product. The major reaction product is *(7)*, which is assigned the structure of a 1,3-diazetidine on the basis of analytical and spectroscopic data. Its formation *via* [2+2]-cycloaddition of an NH- and a silyl-functional carbodiimide appears reasonable to say the least.

Whereas freshly distilled samples of *(3a—c)* give only NMR signals specific for silylcarbodiimides with largely constant chemical shifts (*e.g.* about −130 ppm for the central ^{13}C atom[6]) the stored substance exhibited a slow doubling of all signals at the expense of the original intensities both in ^1H- and $^{29}Si\{^1H\}$- and in the $^{13}C\{^1H\}$-NMR spectrum; the changes occur much faster on dilution with $CDCl_3$. In particular, the ^{13}C study reveals a new singlet in the range of chemical shifts characteristic of cyanamides[7]. No change in average molecular weight determined by osmometry could be detected, thus ruling out oligomerization.

These results can only be explained by a silatropic rearrangement to the corresponding organylsilylcyanamides *(2a—c)*. Equilibration is found to be dependent upon substituents. As follows from the ^1H-NMR spectra, equilibration (25 °C) in $CDCl_3$ solution is complete for *(3a)* [*(b)*, *(c)*] within *ca.* 7 h (3, 4 d) at 62 (45, 31) mol-% of *(2a)* [*(b)*, *(c)*]. Fresh distillation leaving practically no residue again yields the pure carbodiimides. For this reason an attempted separation of isomers by gas chromatography failed. The fact that only the carbodiimide isomer is observed even after several months' storage of the *tert*-butyl and phenyl derivatives *(3d)* and *(3e)* can be explained, at least in the former case, by the unfavorable accumulation of bulky groups on the cyanamide nitrogen in *(2d)*. Further evidence for the stability of *(3e)* comes from the observation that even mild silylation of the corresponding phenylcyanamide with trimethylchlorosilane/triethylamine leads only to the rearrangement product *(3e)*.



The joint appearance and interconversion of the two constitutional isomers in the carbodiimide/cyanamide system could be established for the first time with the above silatautomers[8].

Procedure:

N-Organyl-N'-trimethylsilylcarbodiimides (3a—e) and organyltrimethylsilylcyanamides (2a—c): Cyanogen chloride (*ca.* 6.2 g, 100 mmol) which has been precondensed in a cold trap is slowly passed into a solution of silylamine (100 mmol) in ether (75 ml) with magnetic stirring in a closed apparatus (Hg pressure valve). The reaction temperature is −20 °C only in the case of *(1a)*; compounds *(1b—d)* are treated at room temperature, and *(1e)* at 50 °C in an autoclave. When precipitation is complete the mixture is filtered, solvent and trimethylchlorosilane are distilled off at normal pressure, and the product fractionated in the absence of moisture *in vacuo* (cf. Table 1).

Received: January 13, 1977 [Z 649 IE]
German version: Angew. Chem. *89*, 336 (1977)

CAS Registry numbers:
(1a), 16513-17-0; *(1b)*, 1735-00-8; *(1c)*, 5577-65-1; *(1d)*, 5577-67-3; *(1e)*, 3768-55-6; *(2a)*, 10568-78-2; *(2b)*, 62139-66-6; *(2c)*, 62139-67-7; *(3a)*, 62139-68-8; *(3b)*, 62139-69-9; *(3c)*, 62139-70-2; *(3d)*, 52399-88-9; *(3e)*, 30543-46-5; *(4)*, 920-70-7; *(5)*, 13271-94-8; *(6)*, 62139-71-3; *(7)*, 62139-72-4; ^{13}C, 14762-74-4; ClCN, 506-77-4

[1] a) *I. Matsuda, K. Itoh, Y. Ishii*, J. Organomet. Chem. *69*, 353 (1974); *I. Ruppert, V. Bastian, R. Appel*, Chem. Ber. *108*, 2329 (1975); b) *K. Itoh, M. Okamura, Y. Ishii*, J. Organomet. Chem. *65*, 327 (1974).

Table 1. Preparative and spectroscopic data of the compounds prepared [a].

	Yield [%]	B.p. [°C/torr]		$^{13}C\{^1H\}$-NMR [b]		$^{29}Si\{^1H\}$-NMR [b]
(2a)			+1.9 ($SiCH_3$)	− 34.4 (NCH_3)	−118.1 (N—C≡N)	− 1.9
(3a)	56 (78)	36/14	−0.9 ($SiCH_3$)	− 31.1 (NCH_3)	−130.3 (N=C=N) [c]	−18.5
(2b)			+1.4 ($SiCH_3$)	− 15.1 (CH_3)	−117.0 (N—C≡N)	− 2.1
				− 42.2 (NCH_2)		
(3b)	65	47/14	−0.8 ($SiCH_3$)	− 17.3 (CH_3)	−131.3 (N=C=N)	−17.4
				− 40.2 (NCH_2)		
(2c)			+1.2 ($SiCH_3$)	− 22.4 (CH_3)	−115.0 (N—C≡N)	− 2.2
				− 48.3 (NCH)		
(3c)	68	48/14	−0.8 ($SiCH_3$)	− 25.1 (CH_3)	−130.5 (N=C=N)	−16.2
				− 48.0 (NCH)		
(3d)	89	53/14	−0.8 ($SiCH_3$)	− 31.8 (CH_3)	−130.7 (N=C=N)	− 2.1
				− 54.3 (NC)		
(3e)	36	55/0.01	−0.8 ($SiCH_3$)	−123.1 (C^2-Ph) [d]	−128.3 (N=C=N)	− 4.0
				−123.2 (C^4-Ph)		
				−129.3 (C^3-Ph) [d]		
				−141.1 (C^1-Ph)		
(6)		59 [e]	+1.9 ($SiCH_3$)	− 46.2 (NCH_3)	−111.5 (N—C≡N)	
(7)		131 [e]	+0.2 ($SiCH_3$)	− 47.3 (NCH_3)	−166.2 (C=N)	
				− 54.6 (NCH_3)	−172.5 (C=N)	

[a] All substances (mixtures of isomers) gave correct elemental analyses; their IR, ^1H-NMR, and mass spectra are in accord with the structural assignment.
[b] The $^{13}C\{^1H\}$- (15.1 MHz) and $^{29}Si\{^1H\}$-PFT spectra (17.9 MHz) were recorded *vs.* int. TMS in *ca.* 50% $CDCl_3$ solution (downfield shifts ppm with negative sign).
[c] Strongly broadened in contrast to the ^{13}C signal of the corresponding cyanamide.
[d] The C^2 and C^3 carbon of the phenyl group were assigned by comparison with the known ^{13}C spectrum of Ph—NCO.
[e] M.p. [°C].

[2] a) *R. Appel, M. Halstenberg*, J. Organomet. Chem. *99*, C25 (1975); b) *R. Appel, M. Montenarh*, Z. Naturforsch. *B30*, 847 (1975).
[3] Concerning the comparable preparation of bis(trimethylsilyl)carbodiimide from cyanogen halide and silyl derivatives of ammonia, see: *I. Hundeck*, Angew. Chem. 77, 729 (1965); Angew. Chem. Int. Ed. Engl. 4, 704 (1965).
[4] *L. Birkofer, A. Ritter, P. Richter*, Tetrahedron Lett. *1962*, 195.
[5] *U. Wannagat, H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).
[6] For comparison, the carbodiimide carbon atom of analogous representatives of this class of substances exhibits the following chemical shifts: Me_3Si—NCN—$SiMe_3$ −124.5, *t*Bu—NCN—Ph −136.1, Ph—NCN—Ph −135.1 ppm (in $CDCl_3$ *vs.* internal TMS).
[7] ^{13}C-NMR measurements on authentic samples gave the following shifts for the cyanamide carbon: PhNH—CN −112.5, Et_2N—CN −117.3, Ph_2N—CN −112.4 ppm.
[8] Review: *F. Kurzer, K. Douraghi-Zadeh*, Chem. Rev. 67, 107 (1967); cf. also: *N. Wiberg, G. Hübler*, Z. Naturforsch. *B31*, 1317 (1976).

Crystal Structure of B_2S_3: Four-Membered B_2S_2 Rings and Six-Membered B_3S_3 Rings[**]

By *Harald Diercks* and *Bernt Krebs*[*]

Characterization of boron chalcogenides runs into the obstacle that crystalline phases are difficult to prepare. Crystalline B_2S_3 has been available since 1962 by a variety of methods[1]; however, the quality of the crystalline material was in no case sufficient for a structure determination. The same applies to all other binary boron chalcogenides.

According to a preliminary report by *Chen, Conard*, and *Gilles*[2] B_2S_3 forms monoclinic crystals (C2, Cm, or C2/m) with $a=4.048$, $b=37.09$, $c=10.73$ Å, $\beta=90.0°$, $Z=14.1$; an attempted complete structure analysis was unsuccessful.

During studies on the synthesis of heavy metal thioborates we obtained single crystals of B_2S_3 suitable for X-ray structure determination by thermal decomposition of ternary phases (cf. also [1b]). For example, if the stoichiometric reaction mixture for preparation of $Ag_3B_5S_9$[3] (closed graphite crucible in an evacuated sealed quartz glass tube) is subjected to a temperature gradient of 800 to 600°C for *ca.* 10d, then apart from silver thioborate the extremely moisture sensitive colorless compound B_2S_3 is obtained as 0.3 mm long column shaped single crystals which are microtwinned [B:S = 1:1.49(2); monoclinic ($P2_1/c$) with $a=4.039(1)$, $b=10.722(2)$, $c=18.620(4)$ Å, $\beta=96.23(3)°$, $Z=8$, $V=801.6$ Å^3; $d_{calc}=1.952$, $d_{exp}=1.93(3)$ g/cm^3]. The crystal structure was determined for a twin along ($\bar{2}01$) from four-circle diffractometer data[4] and refined to $R=5.7\%$.

The structure is made up of planar B_3S_3 six-membered rings and B_2S_2 four-membered rings linked by S bridges to almost planar infinite two-dimensional high-polymer layers. The projection of two unit cells perpendicular to the plane of the layer is depicted in Figure 1. Zig-zag chains of six-membered rings run through the layers parallel to *b*; each six-membered ring is bonded *via* a four-membered ring (situated at an inversion center) to a six-membered ring of the adjacent chain. All the boron atoms exhibit trigonal-planar coordination. While the B_3S_3 ring corresponds to those of trimeric metathioboric acid $(BSSH)_3$ and its alkali salts in structure and bonding[3, 5], the 1,3,2,4-dithiadiboretane ring is of particular interest because the four-membered ring skeletons of $[BSN(C_2H_5)_2]_2$[6], $(BSSH)_2$, and $(BSSC_2H_5)_2$[7] could not previously be characterized structurally or spectroscopically. The very short transannular B...B (2.237 Å) and S...S distances (2.878 Å) in the strained four-membered ring warrant attention; the average B—S bond length (1.823 Å) differs but slightly from the average value taken over all B—S bonds in the structure (1.808 Å).

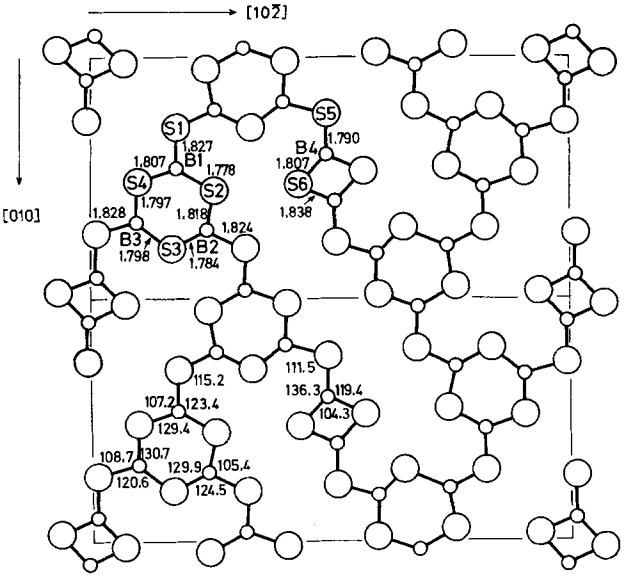


Fig. 1. Layer structure of B_2S_3 with bond lengths [Å] and angles [°].

Only van der Waals forces act between the $(B_2S_3)_n$ layers (S...S distances $\geq 3.814(2)$ Å); the perpendicular interlayer spacing is 3.55 Å. Overall, the packing of the S atoms can be regarded formally as a distorted ..ABAB.. closest packing. The extensive angular distortions in the trigonal-planar BS_3 groups (Fig. 1) are mainly due to the influence of S...S repulsive forces within the layers (shortest S...S distances within the BS_3 groups: S1...S2 2.898, S1...S4 2.926, S4...S5 2.945(2) Å; between S atoms within the layers not belonging to the same BS_3 polyhedron: S2...S3 3.194, S3...S6 3.256(2) Å).

The structure of B_2S_3 bears no resemblance to the three-dimensionally linked B_2O_3 crystal structure[8].

Received: February 9, 1977 [Z 672 IE]
German version: Angew. Chem. 89, 327 (1977)

CAS Registry numbers:
B_2S_3, 12007-33-9

[*] Prof. Dr. B. Krebs, Dr. H. Diercks
Anorganisch-chemisches Institut der Universität
Gievenbecker Weg 9, D-4400 Münster (Germany)

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

[1] a) *P. Hagenmüller, F. Chopin*, C. R. Acad. Sci. *255*, 2259 (1962); b) *P. Hagenmüller, F. Chopin, R. Castagna, ibid. C 262*, 418 (1966); c) *E. G. Zhukov, Ya. Kh. Grinberg*, Izv. Akad. Nauk SSSR, Neorg. Mater. *1969*, 1646; d) *H.-Y. Chen, P. W. Gilles*, J. Am. Chem. Soc. *92*, 2309 (1970).
[2] *H.-Y. Chen, B. R. Conard, P. W. Gilles*, Inorg. Chem. 9, 1776 (1970).
[3] *B. Krebs, H. Diercks*, X. Int. Congr. Crystallogr., Amsterdam, August 1975; Acta Crystallogr. *A31*, S66 (1975); in part unpublished work.
[4] The hitherto unrecognized twinning leads to complete coincidence of the *hkl* reflections of one individual with $hk(-h-l)$ of the other. Relation of the correct (I) cell to that (II) reported by *Chen et al.*: $a(I)=a(II)$, $b(I)=c(II)$, $c(I)=b(II)/2\sin\beta(II)$.
[5] *W. Schwarz, H. D. Hausen, H. Hess, J. Mandt, W. Schmelzer, B. Krebs*, Acta Crystallogr. *B29*, 2029 (1973); *F. Chopin, G. Turrell*, J. Mol. Struct. 3, 57 (1969).
[6] *J. A. Forstner, E. L. Muetterties*, Inorg. Chem. 5, 164 (1966).
[7] *E. Wiberg, W. Sturm*, Z. Naturforsch. *8b*, 530 (1953); *10b*, 114 (1955); Angew. Chem. 67, 483 (1955).
[8] *G. E. Gurr, P. W. Montgomery, C. D. Knutson, B. T. Gorres*, Acta Crystallogr. *B26*, 906 (1970).

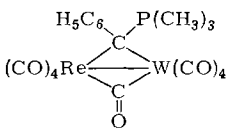
Phenyl(trimethylphosphonio)methanidyl, A Novel 3-Electron Bridge Ligand[**]

By *Fritz R. Kreissl, Peter Friedrich, Tassilo L. Lindner*, and *Gottfried Huttner*[*]

Reaction of trimethylphosphane with *trans*-halogenotetracarbonylcarbyne complexes of chromium and tungsten leads to metal-substituted ylides[1], whereas reaction with dicarbonyl(η-cyclopentadienyl)arylcarbyne complexes of tungsten affords metal-substituted ketenes[2a,c] and η^2-ketenyl complexes[2b,c]. A novel reaction behavior has been observed on treatment of pentacarbonylrheniotetracarbonyl(phenylcarbyne)tungsten *(1)*[3] with trimethylphosphane. μ-Carbonyl-μ-phenyl(trimethylphosphonio)methanidyltetracarbonylrheniotetracarbonyltungsten *(2)* could be isolated as a yellow, diamagnetic crystalline product. *(2)* is soluble in dichloromethane

$$(CO)_5Re{-}(CO)_4W{\equiv}C{-}C_6H_5 + P(CH_3)_3 \xrightarrow{Et_2O}$$

(1)



(2)

and acetone, but not in ether or *n*-pentane. Composition and structure of the ylide derivative were confirmed by IR and ^{1}H-, ^{13}C-, ^{31}P-NMR spectra and by an X-ray structure analysis.

The IR spectrum (KBr) of *(2)* shows seven bands in the carbonyl region for the terminal CO ligands (2092 s, 2042 s, 2003 s, 1960 vs, 1945 sh, 1930 s, 1920 sh cm^{-1}); we assign the absorption at 1842 s cm^{-1} to the bridge CO group. The ^{1}H-NMR spectrum (CD_2Cl_2) exhibits two multiplets at δ = 7.60 and 7.25 ppm for the phenyl group and a doublet at δ = 1.64 ppm, which is assigned to the *P*-methyl protons. The PCH_3 signal with a coupling of $^2J_{PH} = 11.3$ Hz proves the presence of a fourfold coordinated phosphorus atom with positive charge[4]. The $\{^1H\}$-^{13}C-NMR spectrum [CD_2Cl_2; δ values rel. to CD_2Cl_2 = 54.2 ppm (J_{PC} [Hz])] displays the eleven signals expected for *(2)*: CO 199.48, 197.86, 193.00, 191.49, 187.39; C_6H_5 158.37, 139.66 (7.3), 128.06 (4.9), 126.98 (4.9); W—C 80.37 (9.8); PCH_3 18.83 (56.2). Chemical shifts and coupling constants of the ylide-C and *P*-methyl signals agree with the values observed for ylide complexes[5]. The $\{^1H\}$-^{31}P-NMR spectrum shows a sharp singlet at δ = 41.3 ppm.

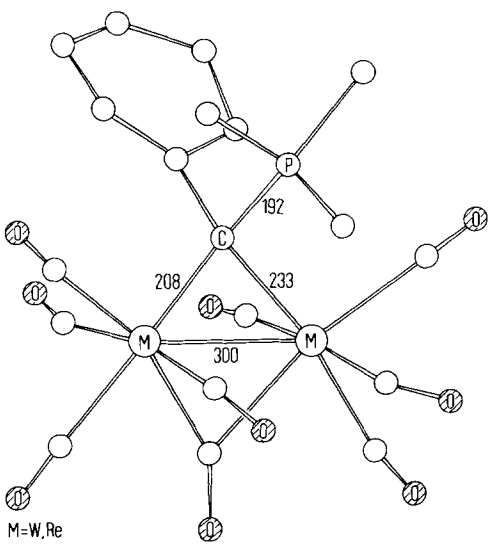


Fig. 1. Structure of the ylide bridge complex *(2)* (bond lengths in pm).

The constitution of *(2)* derived from spectroscopic data was confirmed by an X-ray structure analysis[6] (Fig. 1).

According to the noble gas rule complex *(2)* ought to possess a metal-metal bond; the W—Re distance of 300 pm complies with this assumption. The metal atoms W and Re cannot be distinguished by X-ray analysis owing to the small difference in their scattering power. However, the structure shows no pseudosymmetry[7].

The distances of the bridge C atoms of the methanidyl ligand from the two metal centers are markedly different, having values of 208 and 133 pm. It is suggested that the shorter distance be assigned to the tungsten-carbon bond of the carbyne complex component and that the bridge lacks symmetry due to the tendency towards charge delocalization between the metals[8].

Experimental

All operations should be carried out under nitrogen in dry (Na, P_4O_{10}) and N_2-saturated solvents.—Trimethylphosphane (0.1 g, 1.32 mmol) is added with stirring to a solution of *(1)* (0.71 g, 0.1 mmol) in diethyl ether (50 ml) at −60 °C. After 5 hours' further stirring the supernatant liquor is decanted off and the residue washed 5 times with 10 ml pentane. After drying in a high vacuum at −30 °C, *(2)* is obtained analytically pure as yellow crystals; yield 85 %.

Received: February 15, 1977 [Z 673 IE]
German version: Angew. Chem. *89*, 325 (1977)

CAS Registry numbers:
(1), 62126-55-0; *(2)*, 62126-54-9; $P(CH_3)_3$, 594-09-2; ^{13}C, 14762-74-4

[1] *F. R. Kreissl*, J. Organomet. Chem. *99*, 305 (1975); *F. R. Kreissl, W. Uedelhoven, A. Ruhs, ibid. 113*, C55 (1976); *E. O. Fischer, A. Ruhs, F. R. Kreissl*, Chem. Ber. *110*, 805 (1977).

[2] a) *F. R. Kreissl, A. Frank, U. Schubert, T. L. Lindner, G. Huttner*, Angew. Chem. *88*, 649 (1976); Angew. Chem. Int. Ed. Engl. *15*, 632 (1976); b) *F. R. Kreissl, P. Friedrich, G. Huttner, ibid. 89*, 110 (1977) and *16*, 102 (1977); c) *F. R. Kreissl, K. Eberl, W. Uedelhoven*, Chem. Ber., in press.

[3] *E. O. Fischer, T. L. Lindner, F. R. Kreissl, P. Braunstein*, Chem. Ber., in press.

[4] *H. Dreeskamp, H. Elser, C. Schumann*, Ber. Bunsenges. Phys. Chem. *70*, 751 (1966).

[5] *F. R. Kreissl, W. Held*, Chem. Ber. *110*, 799 (1977).

[6] $a = 1487(2)$, $b = 1712(2)$, $c = 1809(3)$ pm, space group Aba 2, $Z = 8$, 856 independent diffraction data ($I \geq 3\sigma$); $R_1 = 0.074$. Measurements: Syntex-$P2_1$, solution: Syntex-XTL.

[7] *H. Vahrenkamp*, Chem. Ber. *106*, 2570 (1973).

[8] For charge delocalization *via* bridge ligands see: *F. A. Cotton*, Progr. Inorg. Chem. *21*, 1 (1976).

[*] Dr. F. R. Kreissl [+], Dipl.-Chem. P. Friedrich, Dr. T. L. Lindner, Doz. Dr. G. Huttner
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[+] Author to whom correspondence should be addressed.

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

Crystal Structure of As_2O_5

By *Martin Jansen*[*]

Although As_2O_5 numbers among the longest known oxides[1], its crystal structure is still unknown. Attempts to

[*] Dr. M. Jansen
Institut für Anorganische und Analytische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

grow single crystals suitable for X-ray structure analysis have hitherto been thwarted by the poor thermal stability (loss of oxygen and sublimation of As_4O_6 above 300°C) and the ease of hydrolysis of As_2O_5.

Single crystals of this arsenic oxide have now been obtained by annealing of amorphous As_2O_5 under positive oxygen pressure with careful exclusion of moisture. Space group: $P2_12_12_1$ with $a = 8.64_6$, $b = 8.45_0$, $c = 4.62_6$ Å; $Z = 4$[2]. For the structure analysis, 1085 symmetry-independent reflections were measured (Philips PW 1100 automatic four-circle diffractometer, MoK_α, graphite monochromator, $\omega/2\theta$ scan). The structure was solved with Patterson and Fourier syntheses[3]; refinement of the positional and anisotropic temperature factors converged at an R value of 5.3 %. The positional parameters and the AsO bond lengths are shown in Table 1.

Table 1. Positional parameters of As_2O_5 and AsO bond lengths.

	x	y	z
As(1)	0.1515	0.4025	0.1284
As(2)	0.5336	0.7826	0.1340
O(1)	0.2903	0.4334	0.8451
O(2)	0.4953	0.1439	0.6171
O(3)	0.5824	0.2655	0.0817
O(4)	0.4990	0.4757	0.4612
O(5)	0.2757	0.2561	0.3000

As(1) – [O(1), O(1), O(2), O(3), O(4), O(5)] = (1.78, 1.80, 1.83, 1.82, 1.83, 1.82 Å)
As(2) – [O(2), O(3), O(4), O(5)] = (1.67, 1.66, 1.71, 1.69 Å)

The structure of As_2O_5 resembles that of β-Ga_2O_3[4] in that the two oxides both exhibit cations in adjacent tetrahedral and octahedral oxygen environments (ratio 1:1). The composition M_2O_5 which for exclusively octahedral coordination can only be attained by edge and corner linking of the octahedra is achieved in As_2O_5 by equal contributions of the coordination and linkage principles of ReO_3 and the SiO_2 modifications stable under normal pressure, as expressed in the formula $(AsO_{6/2})(AsO_{4/2})$.

Thus all the polyhedra are linked by corners: along [001] there are strands of octahedra which are linked by tetrahedra in such a way that tubular cavities are formed in the direction of [001].

The strongly crosslinked crystal structure explains the crystal form and is in agreement with the findings of *Thilo* and *Winkler* that only half the As can be replaced at most by P and Sb, respectively, on formation of mixed crystals of As_2O_5 with P_2O_5 and Sb_2O_5[5]. It could also account for the reluctance of the compound to crystallize.

Experimental:

H_3AsO_4, prepared from sublimed As_4O_6[6], is completely dehydrated first in a dessicator and then in high vacuum. The finely powdered As_2O_5 is placed in a steel autoclave under protective gas (corundum crucible, loosely closed with a corundum stopper). The autoclave (volume 14 ml, sample volume including corundum crucible 5 ml) is charged with 5 ml of liquid oxygen and heated to 600°C for 4 weeks. After prolonged cooling down (50°C/h) the sample was isolated, once again with careful exclusion of moisture. In this way As_2O_5 is obtained as homogeneous glass clear, largely agglomerated crystalline needles; maximum dimensions: 0.2 × 0.05 × 0.03 mm.

Received: February 16, 1977 [Z 674 IE]
German version: Angew. Chem. 89, 326 (1977)

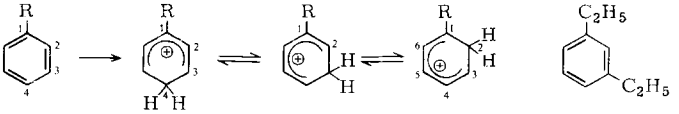
CAS Registry number:
As_2O_5, 1303-28-2

[1] *T. Bergman:* De Arsenico. Altenburg 1777 (nach Gmelins Handbuch der anorganischen Chemie, 8th Edit. System-No. 17. Verlag Chemie, Weinheim 1952).
[2] Cf. *J. W. Visser*, J. Appl. Crystallogr. *2*, 89 (1969): Using the method of *Ito-de Wolff* the values $a = 8.645$, $b = 8.454$, $c = 4.629$ Å were determined from powder data.
[3] SHEL-X program system (*G. Sheldrick*, unpublished) modified for CDC 3300. *A. Hohenester* and *M. Jansen.*
[4] *S. Geller*, J. Chem. Phys. *33*, 676 (1960).
[5] *A. Winkler, E. Thilo*, Z. Anorg. Allg. Chem. *339*, 71 (1965); *A. Winkler, ibid. 350*, 320 (1967).
[6] *G. Brauer:* Handbuch der Präparativen Anorganischen Chemie, Bd. I. F. Enke Verlag, Stuttgart 1975.

Ortho-para Protonation of Toluene and Ethylbenzene in Super Acids

By *Dan Fărcaşiu, M. T. Melchior*, and *Lynne Craine*[*]

Reports on the protonation of monoalkylbenzenes *(1)* in super acids indicate an overwhelming preference for *para* protonation to *(2)*[1]. Fast intramolecular exchange of the aromatic hydrogens implied a small equilibrium concentration of *meta* and *ortho* protonated isomers *(2)*⇌*(3)*⇌*(4)*[1a, 2]. On cooling below −97°C only the ^{1}H-NMR spectrum of the *para* protonated isomer was "frozen out" in each case[1a, b]; no detectable amount of *ortho* protonated species *(4)* in equilibrium with *2* was evidenced. On the other hand, a study of the protonation of alkylbenzenes in the gas phase[3] indicates that a measurable amount of *(4)* should be present in the mixture. We report here a reinvestigation of the protonation of toluene *(1a)* and ethylbenzene *(1b)* in two super acid media [acid A: HF-SbF_5 (1:1) containing SO_2FCl; acid B HF-TaF_5 (30:1)], by ^{13}C-NMR spectroscopy[4].



(1) *(2)* *(3)* *(4)* *(5)*

(a), R = CH_3; *(b)*, R = $^{\gamma}CH_2$–$^{\beta}CH_3$

Solutions of ethylbenzene *(1b)* in both acids at low temperature exhibited the spectrum expected[1a, c] for *para* protonation to *(2b)*. However, the spectrum in acid A exhibited also the signals of *ortho* protonated ethylbenzene *(4b)* at the locations to be expected on the basis of spectra of *(2b)* and of protonated *m*-diethylbenzene *(5)*[1c] (Table 1 and Fig. 1).

Characteristic changes of the spectrum were observed on warming in either acid. The pattern of change, as well as the fact that very similar chemical shifts were recorded at the same temperature in both acids of significantly different strength[5], unambiguously established the interconversion of *para (2b)* and *ortho* protonated *(4b)* isomers as the source

[*] Dr. D. Fărcaşiu [+] and Dipl.-Chem. L. Craine
Corporate Research Laboratories
Exxon Research and Engineering Company
P. O. Box 45, Linden, N. J. 07036 (USA)
Dr. M. T. Melchior
Analytical and Information Division
Exxon Research and Engineering Co.
[+] Author to whom all correspondence should be addressed.

Table 1. Chemical shifts in the ^{13}C-NMR spectrum of alkylbenzenes in super acids [4]. The carbon atoms are numbered as in the formulas. br. = broad.

Precursor	Solvent [a]	T [°C]	^{13}C-NMR (δ values in ppm) [b] C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β
Toluene	A	− 70	200.9 [1a]	136.5	178.0	46.4			27.9	
(1a)	A	− 10	br.	128.9	178.0	66.6			28.6	
	A	10	br.	126.6	176.8	66.0			27.2	
	B	0	202.4	126.4	177.7	67.5			27.2	
Ethylbenzene	A	−100	204.6 [c]	136.0	179.4	47.3			36.0	11.7
(1b)			215.0 [d]	52.1	177.9 [e]	133.2 [f]	173.9 [e]	134.3 [f]	34.4	11.7
	A	0	br.	126.9	178.3	br.			36.2	(11.7) [g]
	A	10	207.8 br.	125.9	178.4	68.0 br.			36.5	(11.7) [g]
	B	− 75	204.2 [c] 214 br. [d]	135.6	179.1	47.0			35.6	11.1
	B	− 60	204.5 br.	135.5 br.	177.9	br.			35.1	10.9
	B	− 30	206.7 br.	126.6 br.	178.1	66.6 br.			35.3	(11.1) [g]
	B	0	207.3	125.4	178.3	69.0			35.2	(11.1) [g]
	B	10	207.6	124.4	178.5	70.5			35.2	(11.1) [g]
m-Diethylbenzene	A [1c]	− 65	200.5	133.5 [f]	207.0	48.5	172.8	133.9 [f]	35.1	12.0
(5)									34.4	12.4

[a] Acid A: $HF/SbF_5/ArH$, 7/7/1, with 1.5 vol. SO_2FCl per vol. of acid; acid B: $HF/TaF_5/ArH$, 30/1/0.33. [b] From external (co-axial) TMS. [c] Values for *(2b)*. [d] Values for *(4b)*. [e] Assignment based on the observation that the ring carbon atoms *ortho* to the CH_2 group resonate generally at lower field than the ring atoms *para* to the CH_2 group. [f] Assignment might be reversed. [g] The spectra at higher temperature were measured from the signal for C-β, assumed of constant chemical shift.

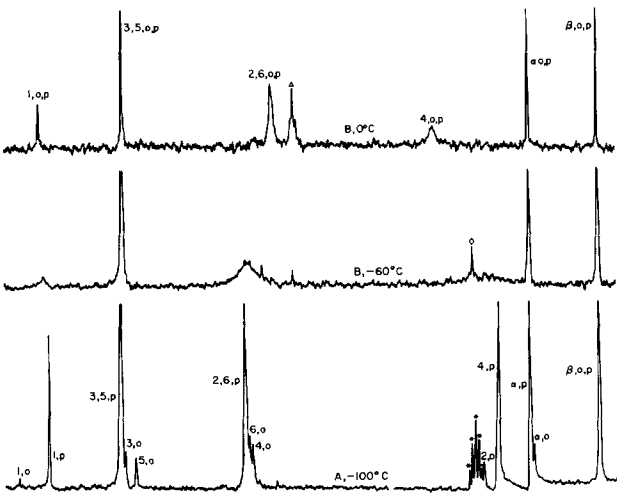


Fig. 1. ^{13}C-NMR spectra of protonated ethylbenzene. A: acid A; B: acid B. External standard: * $CDCl_2$; ◇ CH_2Cl_2; △ CD_3CN. The numbers on the signals signify carbon atoms, o and p indicate *ortho*- *(4b)* and *para*-protonated isomer *(2b)*.

of the observed exchange process, which was reversible on cooling. In the weaker acid B, the peaks are still somewhat broadened at the lowest temperature which could be attained (−75 °C)[6], but the signal for C-1 in *(4b)* could be seen (Table 1). In this acid the peaks for C-2 and C-4 disappear around −50 °C and the coalesced peaks can be observed above −30 °C. Interestingly, the coalescence temperature is about 30 °C higher in acid A[7], thus indicating that isomer interconversion *(2b)*⇌*(4b)* is faster in the weaker acid. The intramolecular hydrogen shift *(2)*⇌*(3)*⇌*(4)* should have the same rate in both cases. On the other hand, the published ^{1}H-NMR study of toluene *(1a)* in $DF-SbF_5-SO_2FCl$[1a] indicated that the concurrent proton exchange with the solvent is slow in that system. It appears then that the mechanism of isomerization *(2)*⇌*(4)* involves an intermolecular proton transfer from the protonated to the unprotonated alkylbenzene (*i.e.* *(1)*+*(2)*⇌*(4)*+*(1)*)[2a, c]. Alternatively, the exchange might occur by different mechanisms in the two media: intramolecular in acid A and intermolecular in acid B. It must be noted that within the detection limits of the ^{13}C-NMR method, protonation is virtually complete in the $HF-TaF_5$ acid system (B) as well. This leads to the possibility that the exchange process observed for a protonated aromatic substrate less basic than *(1)* (*e.g.* benzene[1a, 2e]) might occur intermolecularly even in $HF-SbF_5$.

The equilibrium ratio *(2b)*/*(4b)* could be determined by the integration of the low temperature spectra (*ca.* 6 % *(4b)* in acid A at −100 °C, 14 % *(4b)* in acid B at −75 °C), and from the chemical shifts measured for C-2 and C-4 in the region of fast exchange (0 °C to 10 °C for acid A[7], −30 °C to 10 °C for acid B) giving the values of $\Delta H^0 = -1.3$ kcal/mol, $\Delta S^0 = -2.7$ cal K^{-1} mol^{-1}. The equilibrium constant at 0 °C, calculated from the regression line is 3.0 [25 % *(4b)*]. All the values are approximate, in view of errors in the measurement of chemical shifts and especially in determining and maintaining constant the temperature during the long intervals required for spectra accumulation. (Discarding the experimental value obtained at −100 °C results in values $\Delta H^0 = -0.9$ kcal/mol, $\Delta S^0 = -1.0$ cal K^{-1} mol.) In any event, the ΔH^0 value is very close to that reported for toluene [*(2a)*⇌*(4a)*] in the gas phase[3] and somewhat lower than the result of *ab initio* calculations[3].

For protonated toluene the same behavior was seen (Table 1), but the poorer solubility in acid B limited the scope of investigation. Nevertheless, an estimate of the *para*/*ortho* protonation equilibrium constant *(2a)*/*(4a)* could be made from the chemical shifts for C-2 and C-4 at −10 to +10 °C[6, 7], using chemical shifts for the *ortho* protonated isomer *(4a)* calculated from those of *(4b)* and *(2a)*. The value [20—25 % *(4a)* in the mixture at 0 °C) is very similar to that found for ethylbenzene.

Received: December 6, 1976 [Z 650 IE]
In abbreviated form: January 14, 1977
German version: Angew. Chem. 89, 323 (1977)

CAS Registry numbers:
(1a), 108-88-3; *(1b)*, 100-41-4; *(2b)*, 36510-22-2; *(4b)*, 61650-32-6; *(5)*, 141-93-5

[1] a) *G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, G. D. Mateescu*, J. Am. Chem. Soc. *94*, 2034 (1972); b) *I. B. Repinskaya, A. I. Rezvukhin, V. A. Koptyug*, Zh. Org. Khim. *8*, 1965 (1972); c) *G. A. Olah, R. J. Spear, G. Messina, P. W. Westerman*, J. Am. Chem. Soc. *97*, 4051 (1975).

[2] a) C. MacLean, E. L. Mackor, Discuss. Faraday Soc. 34, 165 (1962); b) E. L. Mackor, C. MacLean, Pure Appl. Chem. 8, 393 (1964); c) D. M. Brouwer, C. MacLean, E. L. Mackor, Discuss. Faraday Soc. 39, 121 (1965); d) T. Birchall, R. J. Gillespie, Can. J. Chem. 42, 502 (1964); e) G. A. Olah, R. H. Schlosberg, D. P. Kelly, G. D. Mateescu, J. Am. Chem. Soc. 92, 2546 (1970).
[3] J. L. Devlin, III, J. F. Wolf, R. W. Taft, W. J. Hehre, J. Am. Chem. Soc. 98, 1990 (1976). Additivity of alkyl substituent effects was assumed in that work.
[4] The NMR spectra were obtained in the Fourier transform mode, at 25.2 MHz, using a Varian XL-100 instrument with a variable temperature probe.
[5] Acid A is well over 10^3 times stronger than acid B.
[6] The solution in acid B partially froze at lower temperature.
[7] The peaks are still broad in acid A at +10°C.

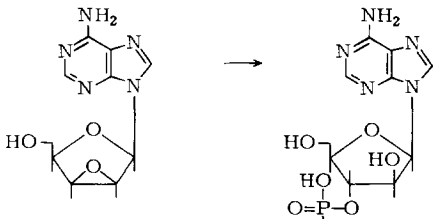
Facile Synthesis of Arabinoadenosine 3'-Phosphate[**]

By *Rudolf Mengel* and *Harald Wiedner*[*]

Only few examples of oxirane ring opening by phosphate ions are known in nucleoside chemistry[1]. We demonstrated that adenosine can be transformed into its lyxo-epoxide *(1)*[2] and that this product can be opened with mineral acid or alkali halide in the presence of boron trifluoride-etherate to give predominantly 3'-substituted halonucleosides[3].

We have now examined the cleavage of the oxirane ring of *(1)* with phosphoric acid in hexamethylphosphoric triamide. Fourteen hours' heating to 100°C affords arabinoadenosine 3'-phosphate *(2)* which can be precipitated as the barium salt. On electrophoresis[4a] and chromatography[4b] the salt behaves in a manner resembling adenosine 5'-monophosphate and is cleaved by alkaline phosphatase[5a] to arabinoadenosine together with traces of xyloadenosine[4c]. After reprecipitation of the salt and treatment with phosphatase, xyloadenosine can no longer be detected. Treatment with 5'-nucleotidase[5b] (18 h) has no effect on *(2)*, while 3'-nucleotidase[5c] cleaves the compound to the extent of 90% within 18 h.

The 90 MHz ^{1}H-NMR spectrum of *(2)* was measured against sodium 2,2-dimethyl-2-silapentanesulfonate as internal standard in D_2O to which had been added one drop of trifluoroacetic acid (to shift the HOD signal away from the signals due to the sugar protons). It showed signals at



(1) *(2)*

$\delta = 8.6$ (s, 1, H_8), 8.46 (s, 1, H_2), 6.5 (d, $J_{1'-2'} = 5.2$ Hz, 1, $H_{1'}$), 4.86 (m, 1, $H_{3'}$), 4.74 (q, $J_{2'-3'} = 4$ Hz, 1, $H_{2'}$), 4.29 (quart, 1, $H_{4'}$), 3.95 ppm ("d", 2H, $H_{5'a}$, $H_{5'b}$). The chemical shift of the H atom attached to C-3' (shifted downfield by 0.5 ppm relative to adenosine) and the coupling constant between ^{31}P and 3'-H, show the phosphate group to be located in position 3'.

Arabinoadenosine 3'-phosphate *(2)* could serve as an "arabino" building block in oligonucleotide synthesis and as starting material for the synthesis of arabino-cAMP[6]. Compound *(2)* also warrants interest in connection with the fact that arabinoadenosine has an inhibitory action on DNA polymerase, ribonucleotide reductase, adenyl cyclase, various viruses, and various animal tumors.

Procedure

A solution of adenosine lyxoepoxide *(1)* (100 mg, 0.4 mmol) and phosphoric acid (crystalline, 98%; 200 mg, 1.7 mmol) in hexamethylphosphoric triamide (2 ml) is stirred for 14 h at 100°C. After neutralization with conc. ammonia most of the solvent is removed *in vacuo* at 100°C. After addition of 10% barium acetate solution (6 ml), triethylamine (0.4 ml), and ethanol (12 ml) a precipitate is formed. The mixture is allowed to stand for 12 h at 4°C and then centrifuged; the residue is washed with ethanol (3 × 10 ml), and then with water (7 × 10 ml). The combined aqueous extracts are evaporated to 10 ml, treated with ethanol (10 ml), and left to stand for 10 h at 4°C. The precipitate formed is filtered off and applied to a Sephadex DEAE A 25 column (2.3 cm × 35 cm). Elution is performed with a gradient of triethylammonium hydrogen carbonate (0.05 to 0.2 M; 2 liter); 25-ml fractions are collected. Fractions 33 to 47 contain 0.153 mmol of *(2)* (yield 38%). They are concentrated and freeze dried.

Received: February 17, 1977 [Z 678 IE]
German version: Angew. Chem. 89, 328 (1977)

CAS Registry numbers:
(1), 40110-98-3; *(2)*, 54621-41-9

[1] W. E. Harvey, J. J. Michalsky, A. R. Todd, J. Chem. Soc. 1951, 2271; K. Tadashi, A. Mituse, J. Motonobu, N. Tokuro, Japan. Patent Kokai 74, 18879 (CI. 16E 461) 1974; Chem. Abstr. 80, 121290e (1974).
[2] M. J. Robins, Y. Fouron, R. Mengel, J. Org. Chem. 39, 1564 (1974).
[3] R. Mengel, H. Wiedner, Chem. Ber. 109, 1395 (1976).
[4] a) Triethylammonium hydrogen carbonate, pH = 7.5, 1000 V; b) on PEI cellulose with 1 N NH_4OAc/ethanol (1:1); c) xyloadenosine and arabinoadenosine can be separated by electrophoresis in borate buffer (pH = 9) at 1000 V.
[5] a) Boehringer (Mannheim); b) [E.C. 3.1.3.5], Sigma Comp.; c) [E.C. 3.1.3.6], Sigma Comp.
[6] T. A. Khwaja, R. Harris, R. K. Robins, Tetrahedron Lett. 1972, 4681, and references cited therein.—Cf. the analogous synthesis of 9-β-D-arabinofuranosylcytosine 3',5'-cyclophosphate: R. A. Long, G. L. Szekeres, T. A. Khwaja, R. W. Sidwell, L. N. Simon, R. K. Robins, J. Med. Chem. 15, 1215 (1972).

Side Reactions in Peptide Synthesis: *tert*-Butylation of Tryptophan

By *Erich Wünsch*, *Ernst Jaeger*, *Lajos Kisfaludy*, and *Miklos Löw*[*]

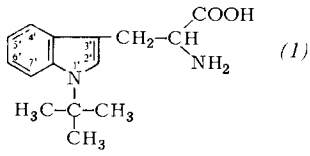
Indole and its derivatives are known to be very reactive. The amino acid tryptophan contains an indole ring as a third function, thus incorporating a relatively reactive moiety into the peptide chain. Side reactions due to indole have been described and postulated in peptide chemistry, *e.g.* also under conditions of acidolytic removal of protective groups from

[*] Priv.-Doz. Dr. R. Mengel, H. Wiedner
Fachbereich Chemie der Universität
Postfach 7733, D-7750 Konstanz (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and represents part of the Doctoral Dissertation by *H. Wiedner* (Universität Konstanz, 1976).

[*] Prof. Dr. E. Wünsch, Dr. E. Jaeger
Max-Planck-Institut für Biochemie, Abteilung für Peptidchemie
Schillerstrasse 42, D-8000 München 2 (Germany)
Dr. L. Kisfaludy, Dr. M. Löw
Forschungslaboratorium der Chemischen Werke Gedeon Richter AG
H-1475 Budapest X, Pf. 27 (Hungary)

synthetic peptide derivatives. *Alakhov et al.*[1] have detected such a side-reaction, *i.e.* an electrophilic substitution at an indole ring, by mass spectroscopic investigations on mixtures of dipeptide derivatives. However, the nature and extent of this side reaction on the indole side chain in peptide synthesis have so far not been demonstrated.



(1)

In 1972 in the Munich laboratory, changes at tryptophan were established during the synthesis of Leu[15]-human gastrin I, which contains two tryptophan residues[2]. Later, in the "artificial" preparation of Leu[11]-human minigastrin I containing only one tryptophan residue a byproduct containing modified tryptophan could be isolated[3]. The product concerned was 10-(N_{in}-*tert*-butyltryptophan)-11-leucine-minigastrin I; after enzymatic digestion, N_{in}-*tert*-butyltryptophan [1′-*tert*-butyltryptophan; H-Trp(1′-*t*Bu)-OH] could by isolated and characterized. Other *tert*-butylated peptide derivatives were also detected.

In the Budapest laboratory similar substitution processes were presumed to take place in ACTH synthesis. In a simple model reaction tryptophan was subjected to relatively drastic *tert*-butylation conditions; *tert*-butyl groups were incorporated in the indole ring. In particular, crystalline 2′,5′,7′-tri-*tert*-butyltryptophan [H-Trp(2′,5′,7′-tri-*t*Bu)-OH] could be obtained.

Further collaborative work by the two groups led to the following findings:

1) When tryptophan derivatives are subjected to a *tert*-butylation reaction, *e.g.* etherification or esterification with isobutene/acid or "simulated" demasking reactions of *tert*-butyl esters and ethers with trifluoroacetic acid, the indole ring is singly or multiply alkylated depending on the conditions. The use of liquid HF leads to unusually high yields of alkylation products (up to 50%).

2) On the basis of model processes it has been established that N_{in}-*tert*-butyltryptophan *(1)* is formed as main product of the alkylation[4]. *(1)* was obtained in pure form independently in both laboratories; it proved to be identical with the tryptophan derivative isolated from the byproduct of synthetic Leu[11]-human-minigastrin I *(vide supra)*. H-Trp(1′-*t*Bu)-OH *(1)* (from methanol/ether): m.p. 177—178°C (dec.); $[\alpha]_D^{20} = -31.2 \pm 0.5°$ ($c = 1.7$; in 80% ethanol); $[\alpha]_{546}^{20} = -34.7 \pm 0.5°$; *(1)*·$H_2O$ (after lyophilization from dil. acetic acid): m.p. 170—172°C (dec.); $[\alpha]_D^{20} = -30.4 \pm 0.5°$ ($c = 1.7$; in 80% ethanol); $[\alpha]_{546}^{20} = -34.0 \pm 0.5°$; ^{1}H-NMR [$(CD_3)_2SO/CD_3COOD/D_2O$ (3:1:1), TMS = 0]: $\delta = 1.70$ ppm [s, 9H, $>NC(CH_3)_3$], no indole NH signal [in $(CD_3)_2SO$]; MS (70eV): $m/e = 260$ (4%; $M^{\oplus}$); 186 (30%; $M-74 \rightarrow C_9H_7N{-}C_4H_9$), 130 (100%; $186-56 \rightarrow C_9H_7N{-}H$; $m^* = 90.9$); IR (KBr): 1220 (ν_{C-C}, *t*Bu), 2970 cm^{-1} (ν_{C-H}, *t*Bu), ν_{N-H} (indole) absent; UV (H_2O): $\lambda_{max} = 286$ nm ($\varepsilon = 5640$).

3) Alkylation products other than N_{in}-*tert*-butyltryptophan *(1)* are formed. Besides 2′,5′,7′-tri-*tert*-butyltryptophan, the 2′-, 3′- *(vide infra)*, 5′- and 7′-*tert*-butyltryptophans as well as the 1′,5′-disubstitution product were detected. H-Trp(2′,5′,7′-tri-*t*Bu)-OH (from 50% ethanol): m.p. 229—230°C (dec); $[\alpha]_D^{26} = +38.8 \pm 0.4°$ ($c = 1$; in acetic acid); ^{1}H-NMR [$(CD_3)_2SO/CD_3COOD/D_2O$ (3:1:1), TMS = 0]: $\delta = 1.40$ (s, C-5′-*t*Bu), 1.51 (s, C-2′-*t*Bu), 1.53 ppm (s, C-7′-*t*Bu); MS (70eV): $m/e = 372$ (3%; $M^{\oplus}$); 328 (3%; M − 44), 298 (100%; $M-74 \rightarrow C_{21}H_{32}N$), 268 (15%; $298-2\times15$), 130 (only 1%!); IR (KBr): 2960 (ν_{C-H}, *t*Bu), 3520 (ν_{N-H}, indole), 1250 cm^{-1} (ν_{C-C}, *t*Bu); UV (0.01 N HCl in 50% ethanol): $\lambda_{max} = 274$ ($\varepsilon = 7880$), 281—284 sh, 293 nm sh.

4) Peptides have been synthesized with 1′-*tert*-butyl- *(1)* and 2′,5′,7′-tri-*tert*-butyl-tryptophan. The same compounds are formed as when the unsubstituted tryptophan peptides are treated by one of the above mentioned *tert*-butylation methods.

5) Characteristic of the mono-N_{in}-*tert*-butylation of tryptophan is a ^{1}H-NMR singlet at $\delta = 1.60$ to 1.72 ppm (substance- and solvent-dependent differences have been observed within this range). N_{in}-*tert*-butyltryptophan *(1)* can be identified by this signal in higher oligopeptides too. The same is true of the other *tert*-butylation products: in the case of 2′- and 7′-substitution the singlets lie between 1.40 and 1.55 ppm (usually separated if both substitutions are present at the same time), in 5′-substitution between 1.28 and 1.40 ppm, and in 3′-substitution (on a 3*H*-indole isomer) between 0.92 and 0.98 ppm.

6) All these findings have been confirmed by mass spectrometry and by IR and UV spectroscopy on both the model compounds and the derivatives of the free amino acids.

Received: January 18, 1977 [Z 680 IE]
revised: February 9, 1977
German version: Angew. Chem. *89*, 330 (1977)

CAS Registry numbers:
(1), 62029-62-3; H-Trp(2′,5′,7′-tri-*t*Bu)-OH, 62029-63-4; tryptophan, 6912-86-3

[1] *Y. B. Alakhov, A. A. Kiryushkin, V. Lipkin*, Chem. Commun. *1970*, 406.
[2] *E. Wünsch, E. Jaeger, M. Deffner, R. Scharf*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1716 (1972).
[3] *E. Jaeger, S. Knof, I. Schmidt, P. Thamm, E. Wünsch* in: Abstracts of the 1st USSR-FRG-Symposium on Peptide and Protein Chemistry, Dushanbe/Tadjikistan 1976. Moscow 1976, p. 4.
[4] In contrast to other 1′-alkyl- and 1′-aralkyltryptophans, H-Trp(1′-*t*Bu)-OH *(1)* was previously not accessible synthetically: *S. Yamada, T. Shioiri, T. Itaya, T. Hara, R. Matsueda*, Chem. Pharm. Bull. *13*, 88 (1965).

Selenol Esters—A Novel Class of Liquid-Crystal Compounds[**][1]

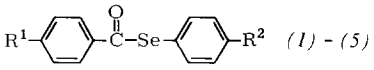
By *Gerd Heppke, Jürgen Martens, Klaus Praefcke*, and *Helmut Simon*[*]

Low-melting liquid crystals are of interest on account of their utility in electrooptic display systems[2]. Of the classes of compounds so far investigated, the esters of aromatic carboxylic acids with phenols have acquired importance because of their chemical and photochemical stability, low viscosity, and achromatism[3]. The corresponding thiol esters often show an extended mesophase region[4].

[*] Prof. Dr. K. Praefcke, Dr. J. Martens, Dr. H. Simon
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)
Priv.-Doz. Dr. G. Heppke
Institut für Anorganische und Analytische Chemie
der TU Berlin (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Gesellschaft von Freunden der Technischen Universität, Berlin. We thank Frau *U. Schulze* for experimental assistance. *K. P.* thanks Dr. *D. Erdmann*, E. Merck, Darmstadt, for helpful discussions and the supply of chemicals.

In continuation of our work on photo- and electron collision-induced reactions of thiol-[5] and selenol-esters[1,6] we have now synthesized the selenocarboxylic *Se*-aryl esters *(1)–(5)* as first examples exhibiting liquid crystal properties. The positions of their carbonyl absorptions are typical for this class of compounds[7].



(1) - (5)

	R^1	R^2	Yield [%] [a]	M.p. [°C]	Clear point [°C]	$\nu_{C=O}$ ($CHCl_3$) [cm^{-1}]
(1)	OCH_3	CH_3	28	60	58	1685
(2)	n-C_5H_{11}	CH_3	94	30	35	1690
(3)	n-C_7H_{15}	OCH_3	83	40	56	1685
(4)	OC_7H_{15}	CH_3	56	49	63	1675
(5)	p-$CH_3C_6H_4Se$—C(O)	CH_3	55	186	229	1680

[a] All compounds gave correct elemental analyses.

Under the polarizing microscope the new selenol esters *(1)—(5)* exhibit a nematic phase. Even these first examples show favorable transition temperatures, which should be further improved by variation of the substituents.

Experimental:

Finely powdered selenium (7.1 g, 0.09 g-atom), previously dried over conc. sulfuric acid in a dessicator, is added portionwise over 5 min to a solution of 4-methyl- or 4-methoxyphenylmagnesium bromide (0.1 mol) in boiling diethyl ether (100 ml) in the absence of moisture and air (purest argon) in accordance with a procedure[8] improved by us as regards protective gas, exclusion of light, amounts of reagents, reaction temperatures and times. The mixture is cooled, protected from light by wrapping the flask in Al foil, and treated dropwise at 0 to 5 °C (internal temperature of flask) with a solution of chloroformic acid (0.1 mol) [in the case of *(5)* 0.05 mol] in ether (100 ml). The mixture is stirred for 5 min and then extracted twice with a total of 400 ml saturated aqueous $NaHCO_3$ solution and then twice with water. The ethereal phase is dried with $MgSO_4$, evaporated down at a maximum temperature of 30 °C, and the resulting crude product purified by recrystallization: *(1)* from light petroleum (b.p. 30 to 70 °C)/ether, *(2)—(4)* from light petroleum (b.p. 30 to 70 °C), and *(5)* from ether.

Received: February 10, 1977 [Z 679a IE]
German version: Angew. Chem. *89*, 328 (1977)

CAS Registry numbers:
(1), 62029-99-6; *(2)*, 62067-42-9; *(3)*, 62030-00-6; *(4)*, 62030-01-7; *(5)*, 62030-02-8; 4-methoxyphenyl bromide, 104-92-7; 4-methylbenzeneselenol, 37773-23-2; 4-methoxybenzeneselenol, 37773-20-9; 4-methoxybenzoyl chloride, 100-07-2; 4-pentylbenzoyl chloride, 49763-65-7; 4-heptylbenzoyl chloride, 70-782-54-5; benzenedicarbonyl dichloride, 100-20-9

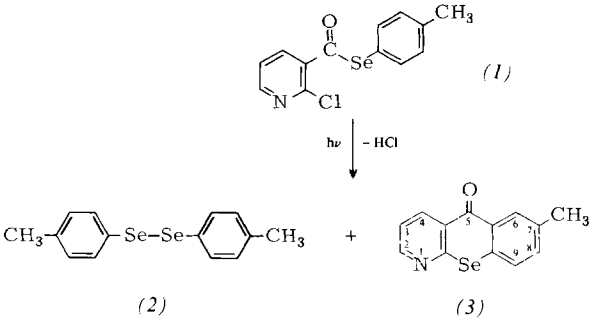
[1] Part 3 of Organic Selenium Compounds.—Part 2: *J. Martens, K. Praefcke, H. Simon*, Z. Naturforsch. *31b*, 1717 (1976).
[2] *G. W. Gray*, Mol. Cryst. Liq. Cryst. *21*, 161 (1973); *D. Demus*, Z. Chem. *15*, 1 (1975).
[3] *D. Demus* in *A. R. Kmetz, F. K. von Willisen:* Nonemissive Electrooptic Displays. Plenum Press, New York 1975, p. 83.
[4] *H. Reinboldt, F. Berti, G. Cilento*, Quimica 3, 140 (1951); Chem. Abstr. *46*, 7555d (1952); *M. J. S. Dewar, R. M. Riddle*, J. Am. Chem. Soc. *97*, 6658 (1975); *R. M. Reese, C. Maze, E. Oppenheim*, Mol. Cryst. Liq. Cryst. *36*, 41 (1976); *Y. B. Kim, M. Senō, ibid. 36*, 293 (1976); *J. Krause, L. Pohl*, 6th Int. Liq. Cryst. Conf., Kent, Ohio, August 1976.
[5] *K. Praefcke, H. Simon*, Chem. Ber. *109*, 3915 (1976) and earlier works cited therein, as well as unpublished results by *K. Praefcke et al.*
[6] *J. Martens, K. Praefcke, U. Schulze, H. Schwarz, H. Simon*, Tetrahedron *32*, 2467 (1976).
[7] *M. Renson, C. Draguet*, Bull. Soc. Chim. Belg. *71*, 260 (1962); Chem. Abstr. *58*, 3347g (1963).
[8] *F. Taboury*, Ann. Chim. (Paris) (8) *15*, 5 (1908); cf. also [7].

5*H*-[1]Benzoselenino[2,3-*b*]pyridine—A Novel Heterocyclic Ring System[**][1]

By *Behrouze Pakzad, Klaus Praefcke*, and *Helmut Simon*[*]

Azathioxanthones[2] are formed from thionicotinic *S*-aryl esters by photorearrangement. We have now found that UV irradiation[3] of the isoelectronic 2-(chloro)selenonicotinic acid *Se*-(*p*-tolyl) ester *(1)*[4] in benzene leads *via* loss of hydrogen chloride to a mixture of products, from which 57 % di-(*p*-tolyl) diselenide *(2)* and 25 % 7-methyl-5*H*-[1]benzoselenino[2,3-*b*]pyridin-5-one *(3)* can be isolated by column chromatography in the above order.

Compound *(3)* is yellow and melts at 128 to 130 °C. The quoted structure is consistent with spectroscopic data: IR ($CHCl_3$): $\nu_{C=O} = 1630\,cm^{-1}$; MS (vaporized at room temperature; exact mass determinations for the following signals): $m/e = 275$ (100 %, M^+, $C_{13}H_9NOSe$), 247 (22 %, $C_{12}H_9NSe$), 195 (16 %, $C_{13}H_9NO$), 167 (32 %, $C_{12}H_9N$); ^{1}H-NMR ($CDCl_3$): $\delta = 8.84$ (4-H, dd, $J_o \approx 8$, $J_m \approx 2$ Hz), 8.69 (2-H, dd, $J_o \approx 4.7$, $J_m \approx 2$ Hz), 8.48 (6-H, broad s, halfwidth 4 Hz), 7.21 to 7.63 (3-H, 8-H, 9-H, m), 2.46 ppm (CH_3, s).



(1)

(2) *(3)*

The heterocyclic ring system of ketone *(3)* was previously unknown.

Received: February 18, 1977 [Z 679b IE]
German version: Angew. Chem. *89*, 329 (1977)

CAS Registry numbers:
(1), 62029-64-5; *(2)*, 21856-94-0; *(3)*, 62029-65-6

[*] Prof. Dr. K. Praefcke, Dipl.-Ing. B. Pakzad, Dr. H. Simon
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[**] We thank the Technische Universität Berlin for support from the Forschungsprojektschwerpunkt „Präparative Organische Photochemie" (FPS 5/3).

[1] Part 4 of Organic Selenium Compounds [Part 16 of Organic Photochemistry].—Part 3: *G. Heppke, J. Martens, K. Praefcke, H. Simon*, Angew. Chem. *89*, 328 (1977); Angew. Chem. Int. Ed. Engl. *16*, 318 (1977) [Part 15: *C. Bak, K. Praefcke, K. A. Muszkat, M. Weinstein*, Z. Naturforsch. *32b* (1977), in press].
[2] *G. Buchholz, J. Martens, K. Praefcke*, Angew. Chem. *86*, 562 (1974); Angew. Chem. Int. Ed. Engl. *13*, 550 (1974).

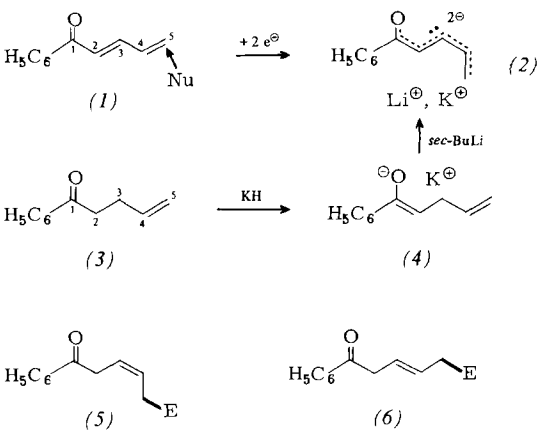
[3] *Ca.* 40 h (TLC check), in anhydrous benzene after rinsing with pure nitrogen, stationary N_2 atmosphere, Philips mercury high-pressure lamp HPK 125 W (quartz glass) at 20 °C, 0.005 mol in 1 liter. After concentration in a vacuum (Rotavapor) at 35 to 40 °C water-bath temperature the residue is chromatographed on 200 g silica gel (ϕ 0.15 to 0.30 mm): elution of *(2)* with 3 liters of light petroleum (b.p. 30 to 70 °C) and finally of *(3)* with 3 liters of light petroleum (b.p. 30 to 70 °C)/acetone (10:1).

[4] Prepared in 18 % yield according to [1]. Colorless crystals from light petroleum (b.p. 30 to 70 °C)/ether, m.p. 151 to 153 °C, IR ($CHCl_3$): $\nu_{C=O} = 1680\ cm^{-1}$; exact mass determination of MS molecular signal ($C_{13}H_{10}ClNOSe$, intensity: 3 %): calc. 310.9616, obs. 310.9652 amu, referred to the isotope ^{80}Se.

Doubly Deprotonated Allylacetophenone. First Example of a "Direct" E^5 Synthon[**]

By *Manat Pohmakotr* and *Dieter Seebach*[*]

Doubly unsaturated conjugated carbonyl compounds such as the ketone *(1)* react at the terminal C-5 atom with nucleophiles (N^5 attack)[1]. We have now found that this reactivity is reversed—as with N^1 and N^3 attack[2]—on use of the dianion derivative *(2)*. We obtained this derivative by double deprotonation of the allylacetophenone *(3)* containing two hydrogen atoms more. An α-carbonyl proton was first abstracted with potassium hydride (THF/45 min/0 °C) to give *(4)*[3], which was treated with *sec*-butyllithium (2 equiv. TMEDA/4 h/−78 to 0 °C)—a deep violet-red solution of *(2)* was obtained. Addition of an equimolar mixture of electrophile and hexamethylphosphoric triamide in a little THF (3 to 5 h/−78 °C to room temperature) permitted, after aqueous workup, isolation of product *(5)* or *(6)* (newly formed bonds appear bold in the formulas) which could be obtained pure in yields between 25 and 80 % by chromatography on silica gel (see Table 1). The configuration of these β,γ-unsaturated ketones is determined by the nature of the electrophile: pro-



(1) *(2)* *(3)* *(4)* *(5)* *(6)*

tonation, alkylation with halides and epoxide, and α-hydroxyalkylation with aliphatic aldehyde and ketone gave exclusively the *cis* compound *(5)*[4], whereas the reaction of *(2)* with aromatic carbonyl derivatives (benzaldehyde, allylacetophenone, benzophenone) furnished only *trans* adducts *(6)* (see Table 1, NMR coupling constants). In no case did we observe mixtures of configurational isomers *(5)*/*(6)*; structural isomers resulting from attack of the electrophile on an atom other than C-5 in *(2)* were not detected either on chromatographic analysis of the products. Apart from *(5)* or *(6)*, most of the product mixtures were also found to contain the dimer *(6j)* (5—10 %) of the starting ketone *(3)* and a mixture (15 to 45 %) of 1-phenyl-2-, -3-, and -4-penten-1-ones, *i.e.* of *(3)* and its isomers.

Treatment of the adducts of *(2)* to aldehydes and ketones or isobutylene oxide in 0.1 M solution [THF:CH_3OH (1:1)/6 h/room temperature] with 1 equivalent of sodium

Table 1. Products *(5)*, *(6)*, and *(7)* from the dianion *(2)* and electrophiles. All IR and ^{1}H-NMR spectral data are compatible with the structures given. The *cis* and *trans* coupling constants in *(5)* and *(6)* were determined in decoupling experiments. All compounds gave elemental analyses correct to within 0.3 %. *(7f)*, *(7g)*, *(7i)*, and *(7j)* are obtained as mixtures of two diastereoisomers (according to ^{13}C-NMR analysis).

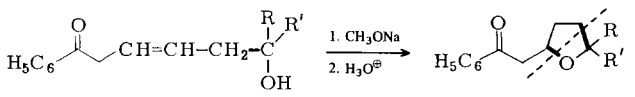
Electrophile treated with *(2)*	Products *(5)* and *(6)* No.	E	Yield [%]	Phys. data	J_{cis} *(5)* or J_{trans} *(6)* [Hz]	Product *(7)* No.	R	R′	Yield [%][a]	Phys. data n_D^{22}/m.p. [°C]
H_2O	*(5a)*	H	78	$n_D^{21} = 1.5392$	8					
D_2O	*(5b)*	D	76	$n_D^{21} = 1.5410$	7.5					
CH_3I	*(5c)*	CH_3	60—72	$n_D^{22} = 1.5362$	8					
n-C_4H_9Cl	*(5d)*	n-C_4H_9	59	$n_D^{21.5} = 1.5288$	8					
Isobutylene oxide	*(5e)*	$(CH_3)_2C(OH)CH_2$	32	$n_D^{22} = 1.5350$	8	*(7e)*			71	1.5196
Propanal	*(5f)*	$CH_3CH_2CH(OH)$	20—35	m.p. 36—37 °C	8.5	*(7f)*	H	C_2H_5	68	1.5206
2-Methylpropanal	*(5g)*	$(CH_3)_2CH—CH(OH)$	35	$n_D^{20.5} = 1.5312$	8	*(7g)*	H	$(CH_3)_2CH$	72	1.5168
Cyclohexanone	*(5h)*	$(CH_2)_5C(OH)$	25	m.p. 54—55 °C	9	*(7h)*		—$(CH_2)_5$—	85	1.5342
Benzaldehyde	*(6i)*	$C_6H_5CH(OH)$	38—53	m.p. 93—95 °C	16.5	*(7i)*	H	C_6H_5	94	49—53
Allylacetophenone	*(6j)*	$CH_2=CH—(CH_2)_2—C(C_6H_5)(OH)$	48	m.p. 64 °C	16.0	*(7j)*	$CH_2=CH—(CH_2)_2$	C_6H_5	65	1.5573
Benzophenone	*(6k)*	$(C_6H_5)_2C(OH)$	40—65	m.p. 111—112 °C	16.0	*(7k)*	C_6H_5	C_6H_5	86	84—85

[a] Based on *(5)* or *(6)*.

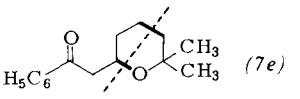
[*] M. Pohmakotr, M. Sc., Prof. Dr. D. Seebach [+]
Institut für Organische Chemie der Universität Giessen
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

[**] Part of the projected Doctoral Thesis by *M. P.*, Universität Giessen.—*M. P.* wishes to thank the DAAD for a stipend. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[+] To whom correspondence should be addressed.
Present address: Laboratorium für Organische Chemie der ETH
ETH-Zentrum, Universitätsstrasse 16, CH-8092 Zürich (Switzerland)



(5f)-(5h), (6i)-(6k) (7f)-(7k)



(7e)

methoxide followed by workup with aqueous acid gives the tetrahydrofurans or pyrans (7) in high yields (see Table 1). The double bond apparently shifts into conjugation with the carbonyl group, whereupon the HO group undergoes intramolecular addition.

Compound (2) is the first "direct" carbonyl derivative with reactivity umpolung at C-5. The only E^5 building blocks known hitherto have a protected carbonyl group[5] or their use depends upon a thio-Claisen rearrangement[6].

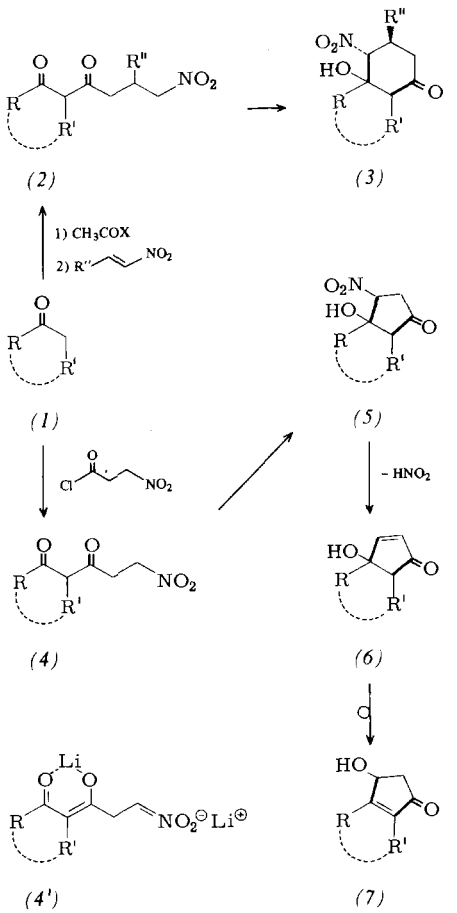
Received: January 25, 1977 [Z 656 IE]
German version: Angew. Chem. 89, 333 (1977)
Publication delayed at authors' request

CAS Registry numbers:
(1), 4734-99-0; (2), 61812-39-3; (3), 3240-29-7; (4), 61752-44-1; (5a), 61752-45-2; (5b), 61752-46-3; (5c), 61752-47-4; (5d), 61752-48-5; (5e), 61752-49-6; (5f), 61752-50-9; (5g), 61752-51-0; (5h), 61787-97-1; (6i), 61752-52-1; (6j), 61752-53-2; (6k), 61752-54-3; (7e), 10599-29-8; cis-(7f), 61752-55-4; trans-(7f), 61752-56-5; cis-(7g), 61752-57-6; trans-(7g), 61752-58-7; (7h), 61752-59-8; cis-(7i), 61752-60-1; trans-(7i), 61752-61-2; cis-(7j), 61752-62-3; trans-(7j), 61752-63-4; (7k), 61752-64-5; H_2O, 7732-18-5; D_2O, 7789-20-0; CH_3I, 74-88-4; n-C_4H_9I, 542-69-8; isobutylene oxide, 558-30-5; propanal, 123-38-6; 2-methylpropanal, 78-84-2; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; benzophenone, 119-61-9; potassium hydride, 7693-26-7; sec-butyllithium, 598-30-1; Z-1-phenyl-2-penten-1-one, 61752-65-6; E-1-phenyl-2-penten-1-one, 61752-66-7

[1] Examples: G. Köbrich, W. E. Breckoff, W. Drischel, Justus Liebigs Ann. Chem. 704, 51 (1967); E. J. Corey et al., J. Am. Chem. Soc. 94, 4395 (1972); Tetrahedron Lett. 1973, 1611; B. Ganem, ibid. 1974, 4467; F. Kido, T. Fujishita, K. Tsutsumi, A. Yoshikoshi, J. Chem. Soc. Chem. Commun. 1975, 337.
[2] D. Seebach, N. Meyer, Angew. Chem. 88, 484 (1976); Angew. Chem. Int. Ed. Engl. 15, 438 (1976); K. H. Geiss, D. Seebach, B. Seuring, Chem. Ber. 110 (1977), in press; and references cited therein.
[3] Hydrolysis at this point regenerates the starting ketone (3) with unshifted double bond.
[4] Cf. the dilithium derivative of 1,3,5-hexatriene: R. B. Bates et al., J. Am. Chem. Soc. 96, 5640 (1974); 97, 6271 (1975); J. Org. Chem. 41, 1620 (1976).
[5] I. Fleming, W. E. Long, Synth. Commun. 5, 177 (1975).
[6] H. Yamamoto et al., J. Am. Chem. Soc. 95, 2693, 4446, 5803 (1973).

merically pure form from carbonyl compounds (1) via 6-nitro-1,3-dicarbonyl compounds (2). Corresponding 5-nitro diketones (4) should cyclize to five-membered rings (5). We now describe an entry to the derivatives (4) and the first examples of their conversion into the products (5), (6), or (7), which are formed depending upon the structure of the precursors and upon the reaction conditions.

Slow addition of cooled amine-free solutions of the Li enolates of the ketones (1) to a stirred THF solution of an equimolar amount of β-nitropropionyl chloride[2] at −80 to −100°C furnishes the diketones (4) in 65 to 90% yield[3] (see Table 1, above). Cyclization was initially conducted under the conditions worked out for the reaction (2) → (3)[1] (variant A): Pouring of the dilithium salt (4'), dissolved in THF, into a large volume of water and slow neutralization with



(2) (3) (1) (5) (4) (6) (4') (7)

acetic acid. We have meanwhile discovered a simplified procedure (variant B), according to which a THF solution of the nitro diketone (4) is added to a buffer solution (pH = *ca.* 8.5). After a short reaction time, there result the hydroxycyclopentenones (6), which rearrange completely to the isomers (7) if the reaction is allowed to run over a prolonged period of time[4]. In only one case could we isolate the nitrocyclopentanone (5) (see Table 1), certainly formed as intermediate in all the reactions. The derivatives (5) and (6) are preferentially formed in one diastereomeric isomer; assignment has yet to be performed.

The IR, ^{1}H-, ^{13}C-NMR, and MS spectra, and elemental analyses of the new compounds (4) to (7) are in accord with the given structures. Thus the β-hydroxy ketone structure of these rearrangement products follows from the "coupled" ^{13}C-NMR signals of the carbonyl C atoms of (7) (splitting

4-Hydroxy-2-cyclopenten-1-ones from Ketones and 3-Nitropropionyl Chloride. A Facile Method for the Construction of Five-Membered Rings[**]

By *Dieter Seebach, Marvin S. Hoekstra,* and *Gerd Protschuk*[*]

We recently reported a cyclization[1] yielding highly functionalized and substituted six-membered rings (3) in diastereo-

[*] Prof. Dr. D. Seebach [+], Dr. M. S. Hoekstra, G. Protschuk
Institut für Organische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

[**] We acknowledge support of this work by the Deutsche Forschungsgemeinschaft (Project Se 158/11) and the Fonds der Chemischen Industrie.

[+] Present address: Laboratorium für Organische Chemie der ETH
ETH-Zentrum, Universitätsstrasse 16, CH-8092 Zürich (Switzerland)

Table 1. Yields and data of nitro diketones *(4)* and the five-membered ring derivatives *(5)* to *(7)*.

Product [Reaction variant]	Yield [a] [%]	Physical or spectroscopic data
(4a), R = C_2H_5, R′ = CH_3	80	b.p. 180°C/3 torr [b]
(4b), R—R′ = —$(CH_2)_4$—	65	m.p. 47—48°C
(4c), R—R′ = —$(CH_2)_5$—	73	m.p. 70—73°C
(4d), R—R′ = —$(CH_2)_6$—	69	m.p. 53—54°C
(4e), R—R′ = —$(CH_2)_{10}$—	75	m.p. 119°C
(4a) → *(7a)* [Var. B, 15 h]	35	^{1}H-NMR: α-hydroxy-CH, δ = 4.9 ppm (m)
(4b) → *(6b)* [Var. A]	42	^{1}H-NMR: vinyl-H, δ = 6.10 and 7.52 ppm
(4b) → *(7b)* [Var. B, 12.5 h]	31	^{1}H-NMR: OH, δ = 4.4 (br. s), α-hydroxy-CH, 4.8 ppm (m)
(4c) → *(6c)* [Var. A]	67	m.p. 68.8—70.2°C [c]
(4c) → *(6c)* [Var. B, 2.3 h] [d]	88	m.p. 68—70°C
(4c) → *(7c)* [Var. B, 18 h] [d]	60	b.p. 180°C/8 torr [b]
(4d) → *(6d)* [Var. A]	16	b.p. 160°C/0.01 torr [b]
(4e) → *(5e)* [Var. A]	38	m.p. 155—156°C

[a] Only acylation to give *(4c)* and its cyclization have so far been optimized.
[b] Bath temperature on molecular distillation.
[c] *Ca.* 90% diastereomer, separated by chromatography.
[d] See experimental.

by two geminal H atoms). As shown by the newly formed bonds emphasized by bold print in formula *(7)*, β-nitropropionyl chloride represents the synthetic building block

$$(HO)\overset{\ominus}{C}H—CH_2—\overset{\oplus}{C}O$$

None of the numerous other methods known for the construction of five-membered rings according to a (C_3+C_2) pattern gives derivatives having the same functionality as the above sequence of two readily executed steps. The cyclization step requires further optimization. Syntheses of jasmonoids, rethrolonoids, prostanoids, and other natural products containing five-membered rings are currently under investigation.

Procedure

3a-Hydroxy-4,5,6,7,8,8a-hexahydroazulen-1(3a*H*)-one *(6c)* and 3-hydroxy-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one *(7c)* from 2-(3-nitropropionyl)-1-cycloheptanone *(4c)*: A mixture of *(4c)* (2.13 g), diisopropylamine (3.1 ml), THF (80 ml), *n*-hexane (13 ml), and hydrochloric acid/borate buffer solution (200 ml, pH = 8) is vigorously stirred at room temperature for 2.3 h and then acidified with 10% aqueous acetic acid. The mixture is extracted three times with CH_2Cl_2, the organic phases are washed with 2.5% $NaHCO_3$ and H_2O, and dried over Na_2SO_4; 1.69 g of crude product is obtained on stripping off the solvent. Chromatography (SiO_2, ether/CCl_4 4:1) affords 1.46 g (88%) of *(6c)*, m.p. 68—70°C (from $CHCl_3/C_6H_{14}$). Reaction for 18 h under otherwise identical conditions (including work-up and purification) gives 0.99 g (60%) of *(7c)* as an oil, b.p. 180°C bath temperature/8 torr.

Received: March 9, 1977 [Z 694 IE]
German version: Angew. Chem. *89*, 334 (1977)

CAS Registry numbers:
(1a), 107-87-9; *(1b)*, 108-94-1; *(1c)*, 502-42-1; *(1d)*, 502-49-8; *(1e)*, 830-13-7; *(4a)*, 62250-63-9; *(4b)*, 62250-64-0; *(4c)*, 62250-65-1; *(4d)*, 62250-66-2; *(4e)*, 62250-67-3; *(5e)*, 62250-68-4; *(6b)*, 62250-69-5; *(6c)*, 62250-70-8; *(6d)*, 62250-71-9; *(7a)*, 62250-72-0; *(7b)*, 62250-73-1; *(7c)*, 62250-74-2; β-nitropropionyl chloride, 51834-15-2

[1] *D. Seebach, V. Ehrig*, Angew. Chem. *86*, 446 (1974); Angew. Chem. Int. Ed. Engl. *13*, 400 (1974); Chem. Ber. *108*, 1961 (1975).
[2] From commercially available (Aldrich) β-nitropropionic acid and thionyl chloride in the presence of a trace of DMF; 75% yield; b.p. 78°C/4 torr [*G. Barger, F. Tutin*, Biochem. J. *12*, 405 (1918)].
[3] For execution of this general 1:1 reaction of enolates with acyl chlorides, see: *A. K. Beck, M. S. Hoekstra, D. Seebach*, Tetrahedron Lett. *1977*, 1187.
[4] Cf. *G. Stork, C. Kowalski, G. Garcia*, J. Am. Chem. Soc. *97*, 3258 (1975); *T. Shono, Y. Matsumura, H. Hamaguchi, K. Nakamura*, Chem. Lett. *1976*, 1249; *G. Piancatelli, A. Scettri*, Synthesis *1977*, 116.

Trifluoromethanol, CF_3OH[**]

By *Konrad Seppelt*[*]

Very little is known about perfluorinated alcohols, except $(CF_3)_3COH$ and *c*-$(CF_2)_3CFOH$[1]. The reason for this is that primary and secondary perfluoroalcohols generally eliminate hydrogen fluoride with formation of carbonyl compounds. Methanol is stable towards hydrogen elimination, just as trifluoromethyl oxyfluoride is stable towards fluorine elimination[2]; but, as expected, the simplest perfluoroalcohol, CF_3OH, is unstable towards HF cleavage.

$$CH_3OH \longrightarrow \begin{matrix} H \\ \diagdown \\ C{=}O \\ \diagup \\ H \end{matrix} + H_2;\ \Delta H = +20.3\ \text{kcal/mol}$$

$$CF_3OF \longrightarrow \begin{matrix} F \\ \diagdown \\ C{=}O \\ \diagup \\ F \end{matrix} + F_2;\ \Delta H = +27.3\ \text{kcal/mol}$$

$$CF_3OH \longrightarrow \begin{matrix} F \\ \diagdown \\ C{=}O \\ \diagup \\ F \end{matrix} + HF;\ \Delta H \approx -20\ \text{kcal/mol}$$

It has now been possible, however, to isolate this compound as a product of the reaction of trifluoromethyl oxychloride with hydrogen chloride.

$$CF_3OCl + HCl \xrightarrow{-120\,^\circ C} Cl_2 + CF_3OH$$

The reaction principle is recombination of partially positively charged and partially negatively charged chlorine. The reaction temperature must be kept as low as possible, an inert solvent, *e.g.* CF_3Cl, being employed to take up the

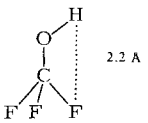
[*] Priv.-Doz. Dr. K. Seppelt
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1 (Germany)

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

heat of reaction. Excess HCl as well as CF_3Cl and Cl_2 can be pumped off completely at $-110°C$.

The colorless trifluoromethanol melts at $-82°C$ and has an extrapolated boiling point of $-20°C$. It was characterized by nuclear magnetic resonance spectra (^1H: singlet at $\delta = 8.65$ ppm *vs.* TMS; ^{19}F: singlet at $\delta = +54.5$ ppm *vs.* $CFCl_3$; ^{13}C: quartet at $\delta = +118$ ppm *vs.* TMS, $J_{CF} = 256$ Hz), mass spectrum ($m/e = 86$, CF_3OH^+), IR vapor phase spectrum 3675 (PQR, νOH), 1401, 1364, 1283, 1187, 1117 cm^{-1} and by controlled decomposition to CF_2O and HF at room temperature.

Although the decomposition of CF_3OH is thermodynamically much more strongly favored than that of the recently prepared $HOSF_5$[3], the alcohol is more stable; it decomposes slowly at $-20°C$, while $HOSF_5$ already starts to decompose at $-60°C$. This kinetic effect can be explained in terms of the larger intramolecular H···F distance, which has been estimated to be 2.2 Å in CF_3OH, and 1.9 Å in $HOSF_5$.



Because of this distance no intramolecular H···F bridge is observed in the IR vapor phase spectrum. Intermolecular bridges can be ruled out on the basis of the high vapor pressure of the alcohol: the boiling point of CF_3OH is about 85 °C lower than that of CH_3OH. A further explanation for the relative stability of CF_3OH can be that the HF elimination is not allowed as a synchronous reaction. In the case of $HOSF_5$ this can be cancelled on account of the d orbitals.

Received: February 7, 1977 [Z 671 IE]
German version: Angew. Chem. 89, 325 (1977)

CAS Registry numbers:
CF_3OH, 1493-11-4; trifluoromethyl oxychloride, 22082-78-6

[1] *S. Andreades, D. C. England*, J. Am. Chem. Soc. *83*, 4670 (1961).
[2] *R. S. Porter, G. H. Cady*, J. Am. Chem. Soc. *79*, 5628 (1957).
[3] *K. Seppelt*, Angew. Chem. *88*, 56 (1976); Angew. Chem. Int. Ed. Engl. *15*, 44 (1976); Z. Anorg. Allg. Chem. *428*, 35 (1977).

Cyclopropenes as Vinylcarbenoids: Intermolecular Carbene-Addition Reactions of Sulfinyl- and Sulfonylcyclopropenes at Room Temperature[**]

By *Michel Franck-Neumann* and *Jean-Jacques Lohmann*[*]

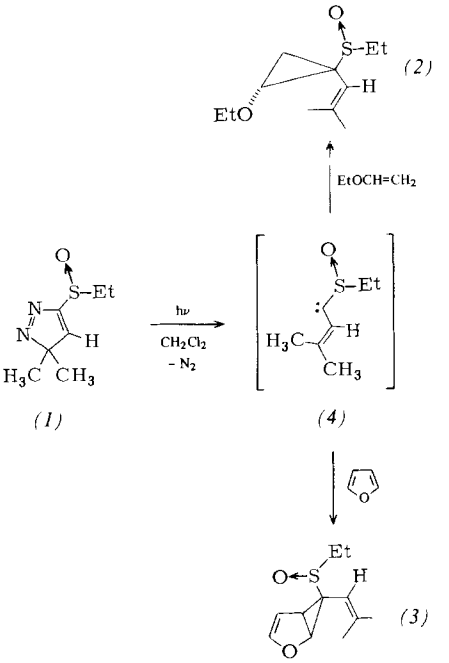
The interrelation between vinylethylene[1] and vinylcarbenes[2] on the one hand and cyclopropenes on the other has been the subject of numerous studies in recent years. In particular, the thermolytic (>150 °C) or photolytic ring-opening of cyclopropenes would appear to proceed *via* vinylcarbenes[3], which, however, are usually stabilized by intramolecular reactions.

We have now been able to demonstrate an isomerization of sulfinyl- and sulfonylcyclopropenes to the corresponding vinylcarbenes and found that the carbene forms react as intermolecular cycloaddition partners with nucleophilic olefins.

[*] Prof. Dr. M. Franck-Neumann, Dr. J.-J. Lohmann
Equipe de Recherche Associée au CNRS no 687
Institut de Chimie de l'Université Louis Pasteur
1, rue Blaise Pascal
F-67000 Strasbourg (France)

[**] We thank the Délégation Générale à la Recherche Scientifique et Technique (DGRST Grant. No. 74.7.1449) for support of this work.

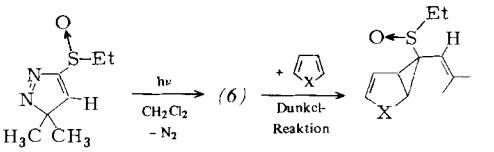
Irradiation[4] of the sulfinyl-3*H*-pyrazole *(1)*[5] in ether or methylene chloride leads to rapid and stoichiometric loss of one mol of nitrogen. After removal of the solvent at room temperature there remains a complex mixture of products. On irradiation in vinyl ether or furan, however, the products *(2)* and *(3)*, respectively, are formed smoothly and stereospecifically.



Compound *(2)* is isolated in the form of its *E*-*Z* isomers in 75 % yield[6]. IR and NMR spectra of the liquid product are consistent with the proposed structure[7]. The *trans*-divinylcyclopropane compound *(3)* (m.p. 76 °C, colorless) can be isolated in 95 % yield[6]. It remains unchanged an heating for two hours at 90 °C. Its IR and NMR spectra are in agreement with the given structure[7]. The NMR spectrum contains, in particular, the signals characteristic for similar dihydrofuran derivatives[8].

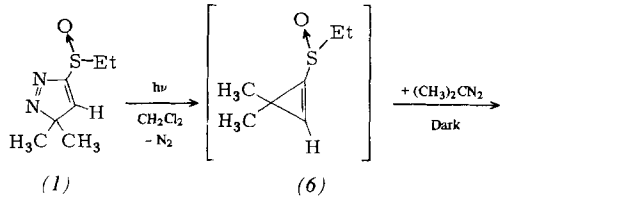
Apparently, photolysis of 3*H*-pyrazole *(1)* leads to formation of the carbene *(4)* which in the absence of reactive cycloaddition partners ought to cyclize to a cyclopropene.

In order to check this with the aid of a Diels-Alder trapping reaction the 3*H*-pyrazole *(1)* was irradiated in methylene chloride at $-25°C$ until complete extrusion of nitrogen, the UV irradiation switched off, and the irradiated solution immediately treated with cyclopentadiene. After several hours' standing at 5 °C and removal of solvent, however, no Diels-Alder adduct of a cyclopropene was detectable, but only polymers along with the carbene addition product *(5)* [*trans*-divinylcyclopropene structure, stability, compatible IR and NMR spectra], which could be isolated pure in *ca.* 30 % yield[6]. If the same experiment is carried out with furan instead of cyclopentadiene again only the carbene addition product *(3)* is formed, and in almost the same yield as in the irradiation in furan.

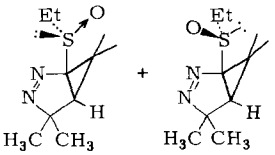


The "carbenoid" or its precursor involved thus has a relatively long lifetime in dilute solution in this temperature range which permits its direct identification: A solution of *(1)* in $CCl_4/DCCl_3$ solution was irradiated at −30°C and the 90-MHz Fourier NMR spectrum recorded immediately after complete extrusion of N_2. It shows the signals of the ethylsulfinyl group along with singlets at δ = 1.33 (3H), 1.36 (3H), and 8.07 ppm (1 H). This spectrum is compatible with the dimethyl-(ethylsulfinyl)cyclopropene structure *(6)*.

Subsequently we were also able to trap this intermediate chemically: Irradiation of *(1)* in methylene chloride, immediately followed by treatment of the solution with an excess of dimethyldiazomethane and then allowing the reaction mixture to stand for a few hours affords the diastereomeric products *(7a)* and *(7b)*, isolable in yields of 23% and 31%, respectively.



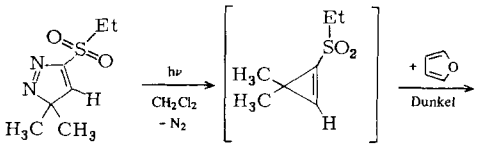
(1) *(6)*



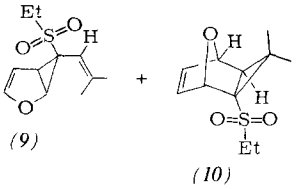
(7a) *(7b)*

Compounds *(7a)* and *(7b)* form colorless crystals (m.p. 35°C and 53°C resp.), are photolabile, and can be separated by thin-layer chromatography[6]. They have very similar IR, UV, and mass spectra [1520 cm^{-1} (azo group), 1060 cm^{-1} (sulfoxide group); $\lambda_{max} = 340$ nm, $\varepsilon = 145$ *(7a)* and 125 *(7b)*], but different NMR spectra [four CH_3 singlets and a 1-H singlet between δ = 0.9 and 2.0 ppm, Et—SO group in the case of *(7a)* as ABX_3 spectrum with $J_{AB} = 12.5$ Hz and an AB non-equivalence of 10 Hz, in the case of *(7b)* as AMX_3 spectrum with $J_{AM} = 12.5$ Hz and an AM non-equivalence of 60 Hz].

That the photolysis of *(1)* leads to a cyclopropene which can react further as vinylcarbene is also shown by the photolytic investigation of the sulfone *(8)*[9]: here the reactivity of the cyclopropene as dienophile is sufficiently great to compete with ring opening to the vinylcarbene and correspondingly the products *(9)* [m.p. 40°C, colorless] and *(10)* [exocyclopropane $J_{HH} < 0.4$ Hz] are isolated in the ration 1:5[10] in the irradiation in methylene chloride followed by addition of furan.



(8)



(9) *(10)*

Whether real equilibrium between cyclopropenes and vinylcarbenes is involved here is still an open question. The cyclopropenes do at least react with nucleophilic olefins similarly to carbenes, in the dark and even below room temperature. The cause for destabilization of the cyclopropene structure in favor of the vinylcarbene structure would appear to lie in the sulfur-oxygen grouping, for corresponding studies on a (ethylthio)-3*H*-pyrazole gave other results.

Received: February 9, 1977 [Z 682 IE]
revised: February 23, 1977
German version: Angew. Chem. 89, 331 (1977)

CAS Registry numbers:
(1), 62046-09-7; *E-(2)*, 61046-10-0; *Z-(2)*, 62075-56-3; *(3)*, 62046-11-1; *(4)*, 62046-12-2; *(5)*, 62046-13-3; *(6)*, 62046-14-4; *(7a)*, 62046-15-5; *(7b)*, 62075-57-4; *(8)*, 62046-16-6; *(9)*, 62046-17-7; *(10)*, 62046-18-8; furan, 110-00-9; cyclopentadiene, 542-92-7; dimethyl(ethylsulfonyl)cyclopropene, 62046-19-9

[1] *M. L. Manion, H. D. Roth*, J. Am. Chem. Soc. 97, 6919 (1975), and references cited therein.

[2] *J. H. Davis, W. A. Goddard III, R. G. Bergmann*, J. Am. Chem. Soc. 98, 4015 (1976).

[3] *R. D. Streeper, P. D. Gardner*, Tetrahedron Lett. *1973*, 767; *L. Schrader, W. Hartmann*, Tetrahedron Lett. *1973*, 3995; *A. Hartmann, W. Welter, M. Regitz, ibid. 1974*, 1825.

[4] In *ca.* 0.2% solutions; Pyrex apparatus ($\lambda > 290$ nm); mercury lamp Philips HPK 125; at 10 to 15°C under nitrogen.

[5] Obtained in quantitative yield from ethylsulfinylacetylene and dimethyldiazomethane: colorless crystals, m.p. 57°C.

[6] Compounds *(2)*, *(3)*, *(5)*, *(7a)*, and *(7b)* were obtained in pure form after chromatographic separation on silica gel (solvent: hexane with 50% ethyl acetate).

[7] The IR spectra in CCl_4 of compounds *(2)*, *(3)*, and *(5)* show characteristic bands for double bond, sulfoxide group, and three-membered ring at 1660, 1060, and 1020 cm^{-1}. The NMR spectra indicate the presence of an ethylsulfinyl- and an isobutenyl group: 1 vinyl-H as heptuplet at δ = 4.70 to 5.20 ppm; 6 methyl-H as very broad singlet at 1.70 to 1.85 ppm, which, in C_6D_6, splits into two fine CH_3 doublets ($J \approx 1.5$ Hz) between 1.50 and 1.60, and 1.60 and 1.80 ppm.

[8] *M. Franck-Neumann, C. Buchecker*, Angew. Chem. *82*, 549 (1970); Angew. Chem. Int. Ed. Engl. 9, 526 (1970); Tetrahedron Lett. *1973*, 2875.

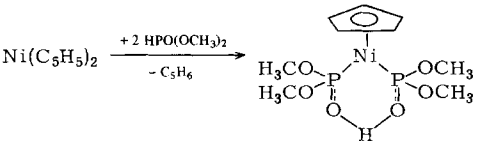
[9] From ethylsulfonylacetylene and dimethyldiazomethane: unstable crystals which polymerize before melting.

[10] Photolysis of *(8)* in furan leads to formation of compounds *(9)* and *(10)* in the ratio 1.3:1.

"Supersandwich"-Type Trinuclear Complexes with a Spiro Center[1]

By *Helmut Werner* and *Tri Ngo Khac*[*]

Bis(η-cyclopentadienyl)cobalt reacts with $HPO(OCH_3)_2$ *(1)* to form the trinuclear complex $(C_5H_5)_2Co_3[PO(OCH_3)_2]_6$ possessing a sandwich-type structure[2]. The reaction of bis(η-cyclopentadienyl)nickel with *(1)* gives the mononuclear compound *(2)*.



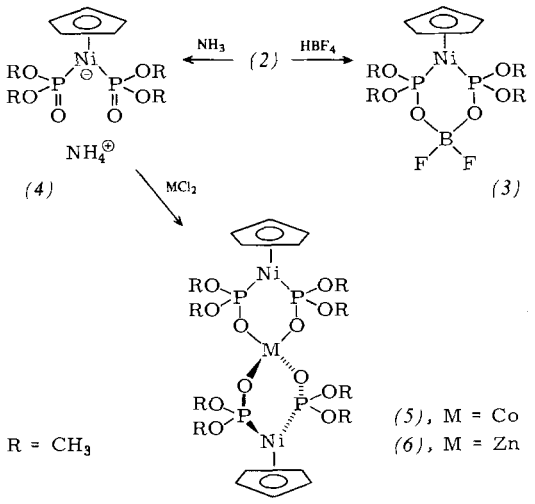
(2)

The equivalence of the CH_3 protons in the ^{1}H-NMR (pseudotriplet, sharp singlet after ^{31}P decoupling at 3.53 ppm[3]) and the phosphorus atoms in the ^{31}P-{^{1}H}-NMR spectrum (singlet at −147.0 ppm[4]) suggests that the bridging H atom

[*] Prof. Dr. H. Werner, Dipl.-Chem. Tri Ngo Khac
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

in *(2)* is probably bonded symmetrically to the two PO oxygen atoms as in the platinum complexes $Pt[(PR_2O)_2H]_2$ ($R = C_6H_5$[5], OCH_3[6]).

Reaction of *(2)* with HBF_4 leads to *(3)*, a complex containing the bis(dimethylphosphito)difluoroborate ion hitherto unknown in the free state. Compound *(2)* reacts with NH_3 to give the ammonium salt *(4)* shown by conductivity measurements and NMR data to coexist in equilibrium with *(2)* in dimethyl sulfoxide. Treatment of *(4)* in methanol with $CoCl_2$ and $ZnCl_2$ affords the trinuclear complexes *(5)* and *(6)*, respectively, having two different metals as coordination centers, which can be regarded as "supersandwich" complexes like $(C_5H_5)_2Co_2M[PO(OR)_2]_6$[7]. The spirocyclic structure around the central metal atoms is confirmed by the magnetic moments.



Preparation of the complex $(C_5H_5)_2Ni_3[PO(OCH_3)_2]_4$ analogous to *(5)* and *(6)* from *(4)* and NiX_2 (X = Cl, Br) could not be accomplished although the corresponding molecular ion was observed in the mass spectrum of *(2)*[7]. On reaction of *(2)* with $[Ni(NH_3)_6]Cl_2$ in ether the highly stable complex $[C_5H_5Ni\{P(OCH_3)_2O\}_2]_2Ni(NH_3)_2$ *(7)* is obtained, which does not loose ammonia on heating *in vacuo*. In the mass spectrum of *(7)* $[M-2NH_3]^+$ is observed as the fragment ion of highest *m/e* value.

Table 1. Data of the spirocyclic trinuclear complexes *(5)* and *(6)*.

(5): MS (70 eV): *m/e* (from 2% I_{rel}) 741 (3; M^+), 342 (3; $(2)^+$), 232 (2; $-HPO(OCH_3)_2$), 188 (100; $Ni(C_5H_5)_2^+$), 123 (92; $NiC_5H_5^+$). IR (KBr): $\nu(PO) = 1135\,cm^{-1}$. Magnetic moment (20 °C): $\mu_{eff} = 5.67\,\mu_B$ [8].
(6): MS (70 eV): *m/e* (from 3% I_{rel}) 746 (3; M^+), 342 (29), 232 (50), 188 (60), 123 (100). IR (KBr): $\nu(PO) = 1120\,cm^{-1}$. ^{1}H-NMR (δ-values, in C_6D_6 at room temp., 60 MHz): 5.12 (10H; s), 3.4 (24H; pseudotriplet).

Procedures

(2): $Ni(C_5H_5)_2$ (3.0 g, 15.9 mmol) and dimethyl phosphonate *(1)* (10 ml, 109.1 mmol) are heated under reflux for 30 min. After removal of the excess of *(1)* (10^{-3} torr) there remains an oily red substance which is dissolved in acetone. Filtration, removal of solvent, and crystallization from toluene/hexane (−30 °C) gives pale red crystals, m.p. 83 °C; yield 2.07 g (38%).

(3): HBF_4 (3 ml, 35%) is added dropwise to a stirred solution of *(2)* (1.0 g, 2.92 mmol) in propionic anhydride (5 ml). After addition of ether (10 ml) and cooling to −30 °C there appear red, air-stable crystals, m.p. 116 °C; yield 0.9 g (78%); M^+: *m/e* = 390 (83%).

(4): Dry NH_3 is passed into a stirred solution of *(2)* (353 mg, 1.03 mmol) in acetone (5 ml). The pale red precipitate is filtered off and washed with acetone; yield 340 mg (92%).

(5): A solution of *(4)* (435 mg, 1.21 mmol) in CH_3OH (10 ml) is added to a suspension of $CoCl_2$ (108 mg, 0.83 mmol) in CH_3OH (2 ml). After stirring for 2 h at room temperature, the solvent is removed, and the residue extracted with toluene. After filtration, evaporation, and cooling to −78 °C, bluish green crystals of *(5)* are obtained, m.p. 106 °C (dec.); yield 389 mg (82%).

(6): Preparation as for *(5)*. Pale red crystals, m.p. 115 °C; yield 89%.

Received: March 3, 1977 [Z 692 IE]
German version: Angew. Chem. 89, 332 (1977)

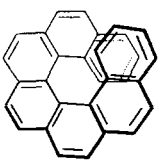
CAS Registry numbers:
(1), 868-85-9; *(2)*, 62125-99-9; *(3)*, 62126-00-5; *(4)*, 62126-01-6; *(5)*, 62154-29-4; *(6)*, 62154-30-7; $Ni(C_5H_5)_2$, 1271-28-9

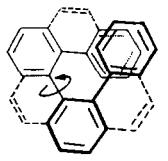
[1] Studies on the Reactivity of Metal π-Complexes, Part 24. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 23: *H. Werner, B. Juthani*, J. Organomet. Chem., in press.
[2] *V. Harder, E. Dubler, H. Werner*, J. Organomet. Chem. *71*, 427 (1974).
[3] In $[D_6]$-acetone, rel. to TMS int., 60 MHz.
[4] In $[D_6]$-acetone, rel. to H_3PO_4 ext., 100 MHz.
[5] *W. B. Beaulieu, T. B. Rauchfuss, D. M. Roundhill*, Inorg. Chem. *14*, 1732 (1975); *K. R. Dixon, A. D. Rattray*, Can. J. Chem. *49*, 3996 (1971).
[6] *A. Pidcock, C. R. Waterhouse*, J. Chem. Soc. *A 1970*, 2080.
[7] *H. Werner*, Angew. Chem. *89*, 1 (1977); Angew. Chem. Int. Ed. Engl. *16*, 1 (1977).
[8] Measured by Dr. *P. Köhler*, Universität Marburg.

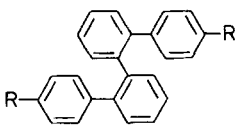
A New Type of Helical Hydrocarbon—Novel C—C Coupling by Sulfone Pyrolysis[**]

By *Fritz Vögtle, Manfred Atzmüller, Winfried Wehner*, and *Joachim Grütze*[*]

Apart from a series of [*n*]helicenes[1] very few molecules having helical structure have so far been reported[2]. In planning the synthesis of a new type helicoidal molecule we logically started from the heptahelicene skeleton *(1)*:


(1)


(2)



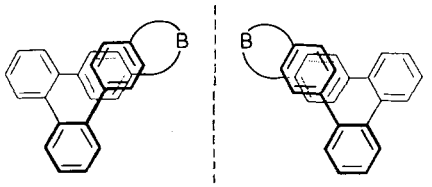
(3): R = H
(4): R = CH_3
(5): R = CH_2Br
(6): R = CH_2SH

Formal removal of the etheno bridges indicated by broken lines in *(2)* leads to the carbon skeleton of *o*-quaterphenyl *(3)*, whose conformational mobility can be prevented by a bridge between the terminal phenyl nuclei; this results in helix *(7)* fixed by clamping the ends[3], which should exhibit the com-

[*] Prof. Dr. F. Vögtle [+], Dipl.-Chem. M. Atzmüller, Dipl.-Chem. W. Wehner, Dr. J. Grütze
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Str. 1, D-5300 Bonn (Germany)
[+] To whom correspondence should be addressed.

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

bined properties of the helicenes (helicity[4]) and the cyclophanes (transannular steric and electronic interactions[5]).



(7) (7')

We were able to synthesize the first representatives of the new structural type (7) using the bis(bromomethyl) compound (5), obtained by bromination of 4,4'''-dimethyl-*o*-quaterphenyl (4), and the dithiol (6) as starting materials.

Since (7a) could not be isolated on reaction of (5) with Na_2S under dilution conditions (small amounts of the dimeric product are obtained[6]), longer bridges were chosen: (7b) to (7i), see Table 1. Double sulfur extrusion from (7d) and (7h) by the sulfone pyrolysis method[7] led *via* ring contraction to the desired hydrocarbons (7p) and (7q) with shorter bridges.

trum of the *o*-quaterphenylophane (7o) with the shortest bridge affords particularly impressive proof of fixation of the many-membered ring: at room temperature an AA'BB' system is observed for the CH_2 groups and, at remarkably high field, an AB system for the *p*-phenylene protons ($\delta_A = 5.84$, $\delta_B = 6.60$ ppm) lying in the anisotropic region of the oppositely placed benzene ring[9]. The sulfide (7b) having a longer bridge also provides some indication of a helical structure: the AA'BB' system of the $(CH_2)_2$ protons is retained at temperatures in excess of +200 °C; the free energy of activation $\Delta G_c^{\ddagger}$ for interconversion of the P and M helices is ≥ 104 kJ/mol (≥ 24.8 kcal/mol). Stiffening of the bridges by *meta*-phenylene units not only increases the "pitch" but also leads to conformational fixation of the helix: $\Delta G_c^{\ddagger}$ values of the same order of magnitude, which should suffice for resolution of enantiomers, are found for (7g) and (7h)[8].

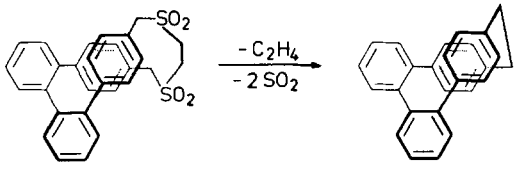
It is therefore all the more surprising that the representative with the shortest bridge, (7o), displays conformational mobility at considerably lower temperatures. At 50 °C both the CH_2 and *p*-phenylene protons exhibit broadening and coalesce at 115 °C to a sharp singlet and an AB system, respectively. The value of $\Delta G_c^{\ddagger}$, *i.e.* 79.3 kJ/mol (18.9 kcal/mol), is very

Table 1. Synthesized (4,4''')-*o*-quaterphenylophanes (7).

Cpd. [a]	Bridge B in (7)	m.p. [°C]	^{1}H-NMR [b]
(7a)	$-CH_2-S-CH_2-$	—	—
(7b)	$-CH_2-S-(CH_2)_2-S-CH_2-$	268—270	3.71 (s)
(7c)	$-CH_2-S-(CH_2)_3-S-CH_2-$	212—214	3.62 (s)
(7d)	$-CH_2-S-(CH_2)_4-S-CH_2-$	233—235	3.60 (s)
(7e)	$-CH_2-S-(CH_2)_5-S-CH_2-$	169—170	3.36 (s)
(7f)	$-CH_2-S-CH(C_6H_5)-S-CH_2-$	230—231	3.85 (d, J = 6 Hz) 3.19 (d, J = 4 Hz)
(7g)	$-CH_2-S-CH_2-(m\text{-}C_6H_4)-CH_2-S-CH_2-$	180—182	3.52; 3.80 (q, J = 15 Hz) 3.63; 4.03 (q, J = 16 Hz)
(7h)	$-CH_2-S-CH_2-[5\text{-}(H_3CO_2C)\text{-}1,3\text{-}C_6H_3]-CH_2-S-CH_2-$	184—185	3.33; 3.73 (q, J = 15 Hz) 3.95; 3.64 (q, J = 15 Hz)
(7i) [8]	$-CH_2-S-CH_2-[5\text{-}(HO_2C)\text{-}1,3\text{-}C_6H_3]-CH_2-S-CH_2-$	271—272	3.39; 3.80 (q, J = 15 Hz) 3.70; 3.95 (q, J = 14 Hz)
(7k)	$-CH_2-SO_2-(CH_2)_2-SO_2-CH_2-$	> 350 (dec.)	[c]
(7l)	$-CH_2-SO_2-(CH_2)_4-SO_2-CH_2-$	> 360	[c]
(7m)	$-CH_2-SO_2-CH_2-(m\text{-}C_6H_4)-CH_2-SO_2-CH_2-$	> 360	[c]
(7n)	$-CH_2-SO_2-CH_2-[5\text{-}(H_3CO_2C)\text{-}1,3\text{-}C_6H_3]-CH_2-SO_2-CH_2-$	> 195 (dec.)	3.80; 4.11 (q, J = 15 Hz) 4.07 (s)
(7o)	$-(CH_2)_2-$	185—186	3.22; 2.50 (AA'BB')
(7p)	$-(CH_2)_6-$	220—222	2.18—2.93 (m)
(7q)	$-CH_2-CH_2-[5\text{-}(H_3CO_2C)\text{-}1,3\text{-}C_6H_3]-CH_2-CH_2-$	223—225	2.47—3.29 (m)

[a] The structures of all compounds given have been confirmed by elemental analysis, mass spectra, and NMR spectra.
[b] Benzyl H, δ values [ppm], in $CDCl_3$.
[c] Sparingly soluble.

Although the pyrolysis of the ethano bridged disulfone (7k) also proceeds smoothly it does not conform to the pattern observed so far, which would predict formation of a cyclic system (7) having a $(CH_2)_4$ bridge: In contrast to the analogously bridged *ortho*-terphenyl system[7] the ethano bridge of (7k) is released together with SO_2 to form (7o) with a bridge shortened by four members.



(7k) (7o)

The conformational stability of the helix structure (7) depends upon the length of the bridge B. The ^{1}H-NMR spectrum of (7o) with the shortest bridge affords particularly impressive proof of fixation of the many-membered ring: at room temperature an AA'BB' system is observed for the CH_2 groups and, at remarkably high field, an AB system for the *p*-phenylene protons ($\delta_A = 5.84$, $\delta_B = 6.60$ ppm) lying in the anisotropic region of the oppositely placed benzene ring[9]. The sulfide (7b) having a longer bridge also provides some indication of a helical structure: the AA'BB' system of the $(CH_2)_2$ protons is retained at temperatures in excess of +200 °C; the free energy of activation $\Delta G_c^{\ddagger}$ for interconversion of the P and M helices is ≥ 104 kJ/mol (≥ 24.8 kcal/mol). Stiffening of the bridges by *meta*-phenylene units not only increases the "pitch" but also leads to conformational fixation of the helix: $\Delta G_c^{\ddagger}$ values of the same order of magnitude, which should suffice for resolution of enantiomers, are found for (7g) and (7h)[8].

It is therefore all the more surprising that the representative with the shortest bridge, (7o), displays conformational mobility at considerably lower temperatures. At 50 °C both the CH_2 and *p*-phenylene protons exhibit broadening and coalesce at 115 °C to a sharp singlet and an AB system, respectively. The value of $\Delta G_c^{\ddagger}$, *i.e.* 79.3 kJ/mol (18.9 kcal/mol), is very low, even in comparison with that of the stereotopically similar [4.3]paracyclophane ($\Delta G = 140.2$ kJ/mol; 33.5 kcal/mol)[10]. On the basis of model considerations and in accord with recent results obtained for the 1,8-diarylnaphthalene system[10], we interpret this value by assuming opening of the bond angles in the biphenyl system in (7o), owing to scissor-like diplacement and mutual repulsion of the *p*-phenylene rings pressed upon each other, which facilitates rotation about the central C—C bond of the 2,2'-substituted biphenyl system.

In the cyclic compounds having longer bridges the *p*-phenylene rings have more freedom to move; the bond angles of the biphenyl system should therefore not exhibit any opening in the ground state; the rotational barrier is then comparatively high.

As expected the bridging of the *o*-quaterphenyl system also has an observable effect on the UV spectrum: on going from the open-chain system (4) (shoulders at $\lambda = 233$ and 252 nm)

to the bracketed compound *(7o)* (λ_{max} = 255.5 nm) the longest wavelength absorption exhibits a 3.5 nm bathochromic shift.

Received: February 2, 1977 [Z 665 IE]
German version: Angew. Chem. *89*, 338 (1977)

CAS Registry numbers:
(4), 61846-70-6; *(5)*, 61846-71-7; *(6)*, 61846-72-8; *(7a)*, 61846-73-9; *(7b)*, 61846-74-0; *(7c)*, 61846-75-1; *(7d)*, 61846-76-2; *(7e)*, 61846-77-3; *(7f)*, 61846-78-4; *(7g)*, 61846-79-5; *(7h)*, 61846-80-8; *(7i)*, 61900-04-7; *(7k)*, 61846-81-9; *(7l)*, 61846-82-0; *(7m)*, 61846-83-1; *(7n)*, 61846-84-2; *(7o)*, 61846-85-3; *(7p)*, 61846-86-4; *(7q)*, 61846-87-5

[1] Reviews: *R. H. Martin*, Angew. Chem. *86*, 727 (1974); Angew. Chem. Int. Ed. Engl. *13*, 649 (1974); *H. Wynberg*, Acc. Chem. Res. *4*, 65 (1971).
[2] Review: *K. Mislow, D. Gust, P. Finocchiaro, R. J. Boettcher*, Top. Curr. Chem. *47*, 1 (1974); *F. Vögtle, G. Hohner*, Angew. Chem. *87*, 522 (1975); Angew. Chem. Int. Ed. Engl. *14*, 497 (1975); cf. also *H. A. Staab, E. Wehinger*, Angew. Chem. *80*, 240 (1968); Angew. Chem. Int. Ed. Engl. *7*, 225 (1968).
[3] In contrast, "head-to-tail" bridged helicenes are still unknown.
[4] For use of the helix model, cf. *R. S. Cahn, C. Ingold, V. Prelog*, Angew. Chem. *78*, 413 (1966); Angew. Chem. Int. Ed. Engl. *5*, 385 (1966).
[5] Reviews: *F. Vögtle, P. Neumann*, Angew. Chem. *84*, 75 (1972); Angew. Chem. Int. Ed. Engl. *11*, 73 (1972); Chimia *26*, 64 (1972); Top. Curr. Chem. *48*, 67 (1974).
[6] *(7a)* can be detected together with the dimer by mass spectrometry.
[7] *F. Vögtle, J. Grütze*, Angew. Chem. *87*, 543 (1975); Angew. Chem. Int. Ed. Engl. *14*, 559 (1975); *J. Grütze, F. Vögtle*, Chem. Ber. *110* (1977), in press.
[8] Attempts to resolve the racemate of the carboxylic acid *(7i)* synthesized for this express purpose with (−)-α-phenylethylamine and with brucine have not yet led to the desired result.
[9] The second AB system of the *p*-phenylene protons lies in the usual aromatic region.
[10] *R. L. Clough, J. D. Roberts*, J. Am. Chem. Soc. *99* (1977), in press. We are indebted to Prof. *Roberts* for communicating these results prior to their publication.

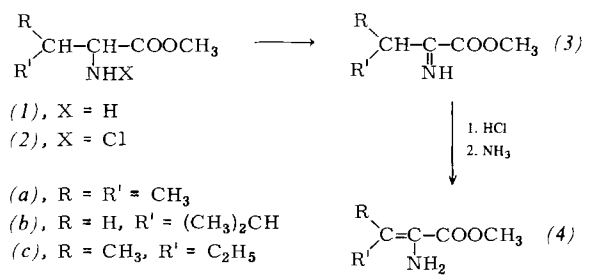
Facile Synthesis of α,β-Dehydro Amino Acid Esters[**]

By *Ulrich Schmidt* and *Elisabeth Öhler*[*]

Dedicated to Professor Hans Nowotny

α,β-Dehydro amino acid esters *(4)* serve as components of antibiotic peptides and as biosynthetic intermediates[2]. One method for the preparation of the esters *(4)* starts from *tert*-butoxycarbonyl amino acid esters[3, 4]. The α-imino acid esters *(3)* tautomeric with *(4)* are accessible by *N*-chlorination/dehydrochlorination of α-amino acid esters *(1)*[4, 5]. Rearrangement of the α-imino compounds into the esters *(4)* has not hitherto been observed. However, dehydrochlorination of *N*-(chloro)phenylalanine ester gives exclusively the thermodynamically more stable ester (α-aminocinnamic ester)[4].

We have now found that the α-imino acid esters *(3)* can be rearranged into the hydrochlorides of the α,β-dehydro amino acid esters by treatment with hydrogen chloride at low temperature. The esters *(4)* can be liberated from the hydrochlorides by ammonia. In the above reaction sequence it is unnecessary to isolate the α-imino acid esters *(3)*. After dehydrochlorination of the *N*-chloro compounds *(2)* they are rearranged directly in the reaction solution. α,β-Dehydrovaline methyl ester *(4a)*, -leucine methyl ester *(4b)*, and -isoleucine methyl ester *(4c)* are readily accessible by this method.



Procedure

α,β-Dehydro amino acid methyl esters (4): tert-Butyl hypochlorite[6] (1 equiv.) is added dropwise to an ice-cooled, stirred solution of amino acid methyl ester *(1)* (10 mmol) in anhydrous ether (20 ml) with exclusion of light. After 30 min the ether is removed *in vacuo*. A solution of the residue in chloroform (50 ml) is quickly treated with 0.5 N hydrochloric acid (10 ml), washed with water (10 ml), and briefly dried over Na_2SO_4 at 0 °C. After complete removal of solvent *in vacuo* the almost pure *N*-chloroamino acid methyl ester *(2)* is obtained.

A solution of diazabicyclo[5.4.0]undecene (DBU) (1.52 g, 10 mmol) in anhydrous ether (20 ml) is quickly added dropwise to a vigorously stirred solution of *(2)* (10 mmol) in anhydrous ether (80 ml) at room temperature. After 30 min the mixture is cooled to 0 °C and DBU·HCl filtered off under suction. The ethereal solution of the crude imino acid ester *(3)* is treated at −70 °C, with vigorous stirring, with a 1 N solution of hydrogen chloride in anhydrous ether (11 ml). After 15 min the solution is stirred for another 6 h at 0 °C, then allowed to stand for 15 h at −20 °C, and subsequently evaporated to dryness *in vacuo*. Residual *(4)*·HCl is repeatedly digested with anhydrous ether and rapidly filtered off under suction. In order to liberate *(4)* the crystalline *(4)*·HCl is dissolved in anhydrous chloroform and dry NH_3 is passed through the ice-cooled solution for 10 min; ammonium chloride is filtered off and the filtrate concentrated *in vacuo*. The oily residue is distilled in a bulb tube at 11 torr and an air-bath temperature of *ca.* 110 °C.—*(4a)*[3]: yield 80 % based on *(1a)*; *(4b)*[4]: yield 63 % based on *(1b)*. ^{1}H-NMR ($CDCl_3$): no evidence for the presence of *cis-trans* isomers; δ = 1.06 (d, 6H); 2.43 (m, 1H); 3.22 (br. s, 2H); 3.76 (s, 3H): 5.41 (d, 1H) (accompanied by signals of *ca.* 10 % of *(3b)*).—*(4c)*: yield 75 % based on *(1c)*. ^{1}H-NMR ($CDCl_3$): (shows the signals of *Z*- and *E* isomer in the ratio of about 1 : 1): δ = 1.02 and 1.04 (t, 3H); 1.74 and 2.02 (s, 3H); 2.12 and 2.46 (q, 2H); 3.40 (br. s, 2H); 3.76 (s, 3H).

Received: January 19, 1977 [Z 662a IE]
German version: Angew. Chem. *89*, 344 (1977)

CAS Registry numbers:
(1a), 4070-48-8; *(1b)*, 2666-93-5; *(1c)*, 2577-46-0; *(2a)*, 62125-88-6; *(2b)*, 55739-09-8; *(2c)*, 62125-89-7; *(4a)*, 10409-27-5; *(4a)*·HCl, 53267-36-0; *cis-(4b)*, 62125-90-0; *cis-(4b)*·HCl, 62125-91-1; *trans-(4b)*, 62125-92-2; *trans-(4b)*·HCl, 62125-93-3; *cis-(4c)*, 62125-94-4; *cis-(4c)*·HCl, 62125-95-5; *trans-(4c)*, 62125-96-6; *trans-(4c)*·HCl, 62125-97-7

[*] Prof. Dr. U. Schmidt, Dr. E. Öhler
Organisch-Chemisches Institut der Universität
Währinger Strasse 38, A-1090 Wien (Austria)

[**] Dehydro Amino Acids, Part 9. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich.—Part 8: ref. [1]. Also: Amino Acids and Peptides, Part 22.—Part 21: ref. [1].

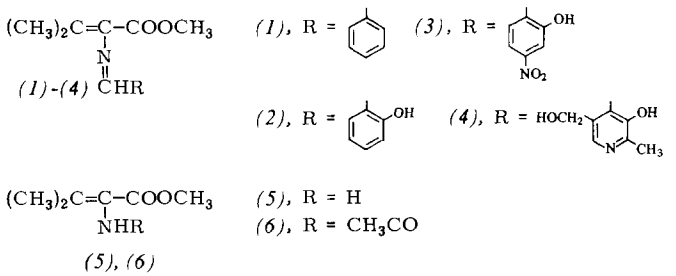
[1] *H. Poisel*, Chem. Ber. *110*, 948 (1977).
[2] Cf. *H. Poisel, U. Schmidt*, Chem. Ber. *108*, 2547 (1975); *B. W. Bycroft*, Nature *224*, 595 (1969), and references cited therein.
[3] *H. Poisel, U. Schmidt*, Angew. Chem. *88*, 295 (1976); Angew. Chem. Int. Ed. Engl. *15*, 294 (1976).
[4] *H. Poisel*, Chem. Ber. *110*, 942 (1977).—Earlier synthesis of dehydrovaline ester from the corresponding α-nitro α,β-dehydro carboxylic methyl ester: *C. Shin, M. Masaki, M. Ohta*, J. Org. Chem. *32*, 1860 (1967). In the analogous synthesis of the dehydroleucine ester [*C. Shin, M. Masaki, M. Ohta*, Bull. Chem. Soc. Jpn. *43*, 3219 (1970)] the nitro precursor was difficult to prepare and the product characterized inadequately.

[5] *H. Poisel, U. Schmidt*, Chem. Ber. *108*, 2547 (1975).—α-Iminoisovaleric ester from α-oxoisovaleric ester and phosphane imide: *C. Shin, M. Masaki, M. Ohta*, Bull. Chem. Soc. Jpn. *44*, 1657 (1971).
[6] An excess of *tert*-butyl hypochlorite is to be avoided, because the *N*-chloro compound *(2)* very easily reacts to give the *N,N*-dichloro compound which seriously interferes with the reaction.

Activation of Double Bonds in Dehydro Amino Acids: A Model for Pyridoxal-Containing Enzymes in Elimination-Addition Reactions[**]

By *Ulrich Schmidt* and *Erhard Prantz*[*]

N-Pyridoxylideneaminoacrylic acid is frequently assumed as an intermediate of elimination and exchange reactions on pyridoxal-containing enzymes[2, 3]. Short-lived intermediates in pyridoxal-containing enzymes with an absorption region at 455—470 nm were interpreted as *N*-pyridoxylideneaminoacrylic acid[3]. It was hitherto impossible to prepare derivatives of this acid for use in biomimetic studies. Nor could simpler models such as *N*-salicylideneaminoacrylic acid derivatives be obtained by β-elimination from substituted serines and cysteines[4].



In connection with our syntheses of dehydro amino acid derivatives with free amino groups[1, 5] we have now succeeded in the direct condensation of dehydrovaline ester with benzaldehyde, salicylaldehyde, 4-nitrosalicylaldehyde, and pyridoxal to give the Schiff bases *(1)* to *(4)*. These compounds are instructive models for the pronounced reactivity of *N*-pyridoxylideneaminoacrylic acid. The extreme ease of addition to the *o*-hydroxyl compounds *(2)* to *(4)* could be demonstrated with phenylmethanethiol:

Addition of phenylmethanethiol proceeds very reluctantly in the presence of 1 mol of diazabicyclo[5.4.0]undecene (DBU) as catalyst when attempted with 0.2 M ethanolic solutions of dehydrovaline methyl ester *(5)*[5], *N*-acetyldehydrovaline methyl ester *(6)*[6], and *N*-benzylidenedehydrovaline methyl ester *(1)*. Only 10—15% conversion takes place within 1 h. In contrast, addition to the *o*-hydroxyl Schiff bases *(2)* and *(3)* is 50% complete within 10 min, and 85—90% within 1 h.

The pyridoxylidene compound *(4)* cannot be included in this series owing to its sparing solubility. However, in 0.02 M solution the salicylidene compounds *(2)* and *(3)* have reacted to the extent of 30% within 20 min and the pyridoxylidene compound *(4)* to the extent of 50%.

These facts demonstrate that the introduction of electron acceptors (nitro group) and transition to the electron-poorer pyridine system (pyridoxylidene compound) fail to accelerate the reaction markedly. The significant enhancement of the ease of addition in the aminoacryloyl system is attributable to the *o*-hydroxyl group.

Procedure

N-Salicylidenedehydrovaline methyl ester (2): The water formed on reaction of a solution of dehydrovaline methyl ester (1.29 g, 0.01 mol) *(5)* and salicylaldehyde (1.22 g) in anhydrous benzene (50 ml) is removed by azeotropic distillation (progress of reaction checked by TLC; silica gel/chloroform; R_f of *(2)* = 0.7). When no starting material can be detected by TLC the residue left on distilling off the benzene is itself subjected to high-vacuum bulb-tube distillation at a bath temperature of 140°C. Yield 1.75 g (75%) of a yellow oil which crystallizes in a refrigerator (m.p. 20—25°C). ^{1}H-NMR ($CDCl_3$): δ = 2.00 (s with doublet character, 6H); 3.80 (s, 3H); 6.78—7.44 (m, 4H); 8.06 (s, 1H); 10.26 (br. s, 1H).

(1): pale yellow oil, yield 72%. ^{1}H-NMR ($CDCl_3$): δ = 1.98 (s, 3H); 2.08 (s, 3H); 3.80 (s, 3H); 7.20—7.90 (m, 5H); 8.12 (s, 1H).

(3): m.p. 156°C from benzene/light petroleum, yield 82%. ^{1}H-NMR ($CDCl_3$): δ = 2.08 (s, 6H); 3.88 (s, 3H); 7.20—7.76 (m, 3H); 8.36 (s, 1H); 11.06 (s, 1H).

N-Pyridoxylidenedehydrovaline methyl ester (4): A solution of dehydrovaline methyl ester *(5)* (1.29 g) and pyridoxal hydrochloride (2.04 g) in methanol (150 ml) is stirred at 50°C for 2 h. After approx. ½ h the hydrochloride of *(4)* starts to precipitate. The reaction mixture is evaporated down to 50 ml, filtered, washed with anhydrous ether, and dried in a vacuum (yield 1.0 g, 32%). The suspension of the hydrochloride in dichloromethane is treated twice with saturated $NaHCO_3$ solution and twice with water, dried, and evaporated. The residue is recrystallized from benzene to give 0.87 g of yellow crystals of m.p. 148°C (dec.). ^{1}H-NMR ($CDCl_3$): δ = 2.06 (s, 3H); 2.10 (s, 3H); 2.52 (s, 4H); 3.84 (s, 3H); 7.76 (s, 2H); 7.87 (s, 1H); 8.8 (s, 1H); 13.26 (br. s, 1H). UV (C_2H_5OH): λ_{max} = 218, 295 nm; on addition of aluminum nitrate a weak maximum appears at 485 nm whose extinction increases with time.

Received: January 19, 1977 [Z 662b IE]
German version: Angew. Chem. *89*, 345 (1977)

CAS Registry numbers:
(1), 62125-73-9; *(2)*, 62125-74-0; *(3)*, 62125-75-1; *(4)*, 62125-76-2; *(4)*·HCl, 62125-77-3; *(5)*, 10409-27-5; *(6)*, 39239-88-8; benzaldehyde, 100-52-7; salicylaldehyde, 90-02-8; 4-nitrosalicylaldehyde, 2460-58-4; pyridoxal, 66-72-8; phenylmethanethiol, 100-53-8

[1] *U. Schmidt, E. Öhler*, Angew. Chem. *89*, 344 (1977); Angew. Chem. Int. Ed. Engl. *16*, 327 (1977).
[2] For example, aspartate aminotransferase, cystathionine γ-synthetase, and tryptophanase.
[3] *Y. Karube, Y. Matsushima*, J. Am. Chem. Soc. *98*, 3725 (1976), references cited therein; cf. *A. E. Braunstein* et al., Eur. J. Biochem. *53*, 429 (1975).
[4] *K. Körte, U. Schmidt*, Monatsh. Chem. *102*, 207 (1971).
[5] *H. Poisel, U. Schmidt*, Angew. Chem. *88*, 295 (1976); Angew. Chem. Int. Ed. Engl. *15*, 294 (1976).
[6] *H. Poisel, U. Schmidt*, Chem. Ber. *108*, 2547 (1975).

[*] Prof. Dr. U. Schmidt, Mag. E. Prantz
Organisch-Chemisches Institut der Universität
Währinger Strasse 38, A-1090 Wien (Austria)

[**] Dehydro Amino Acids, Part 10. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich.—Part 9: ref. [1].—Also: Amino Acids and Peptides, Part 23.—Part 22: ref. [1].

Synthesis and Some Reactions of 1,1-Dimethyl-2,2-bis-(trimethylsilyl)-1-silaethene[1]

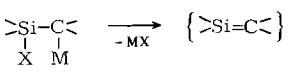
By *Nils Wiberg* and *Gerhard Preiner*[*]

The preparation of unsaturated compounds of type >Si=E (*e.g.* E = C<, N—, O) with silicon having coordination number

[*] Prof. Dr. N. Wiberg, Dipl.-Chem. G. Preiner
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

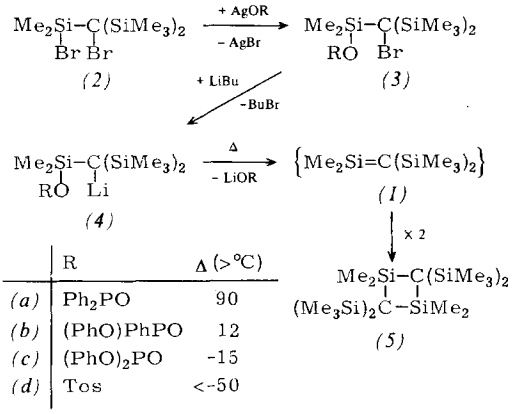
3 numbered for many years among the unsolved "classical problems" of silicon chemistry[2]. The transient existence of short-lived, rapidly dimerizing silaethenes containing the characteristic >Si=C< atomic grouping was first established as late as 1966, when they were detected as secondary products in the gas-phase pyrolysis of substituted silacyclobutanes at about 600 °C[3]. Since then it has been demonstrated that silaethenes can be generated by various other routes, both thermally as well as photochemically[4a, b]. The pyrolytically generated silaethenes (in particular $Me_2Si{=}CH_2$) can be trapped by certain reagents, particularly alcohols, ketones, and dienes[4a, c]. However, owing to the high temperatures necessary for the thermolytic generation of the silaethenes the choice of trapping reagent is severely limited, thus rendering the isolation of many preparatively interesting but thermolabile products impossible.

We have now found that elimination reactions according to the scheme:



(X = electronegative substituent, M = alkali metal) enable the synthesis of silaethenes under very mild conditions in organic solvents, and thus considerably extend their scope of application in synthetically useful reactions. As example we describe here the generation and a few reactions of 1,1-dimethyl-2,2-bis-(trimethylsilyl)-1-silaethenes *(1)*.

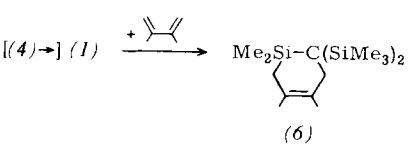
The unsaturated silicon compound *(1)*, which dimerizes to *(5)* in the absence of trapping reagents, is accessible *via* the following route using dimethylbis(trimethylsilyl)bromomethylbromosilane *(2)* as starting material:



	R	Δ (>°C)
(a)	Ph_2PO	90
(b)	(PhO)PhPO	12
(c)	$(PhO)_2PO$	−15
(d)	Tos	<−50

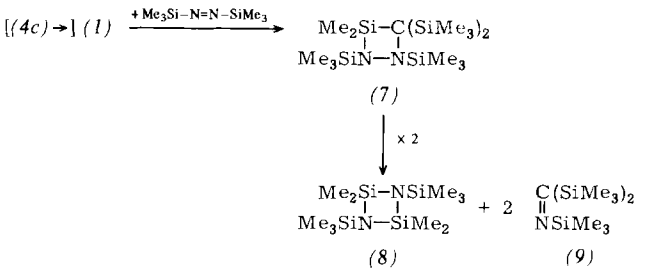
Thermolysis of the intermediate *(4)* in organic solvents proceeds more rapidly the more electronegative the substituent R (when R = Me, Ph, *(4)* does not decompose in the quoted way—at least up to 220 °C).

On heating *(4a—c)* in a high vacuum, the silaethene *(1)* is formed as gaseous product along with *(5)* and can be detected directly by mass spectrometry. On the other hand, product *(6)*, the formation of which by reaction of *(4)* with 2,3-dimethylbutadiene in organic media is explicable only as a Diels-Alder adduct of *(1)*, affords indirect evidence for the intermediary occurrence of *(1)* in the decomposition of *(4)*:

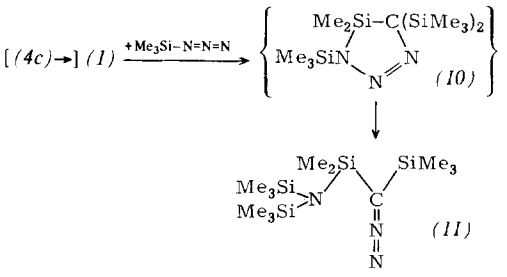


(6)

Apart from undergoing [2+4]cycloadditions, *(1)* obviously also undergoes other cycloadditions more rapidly than a dimerization to *(5)*. Thus *(1)*—generated from *(4c)*—reacts with blue bis(trimethylsilyl)diazene in a [2+2]cycloaddition with formation of the colorless four-membered ring compound *(7)*, which above 70 °C is converted into the colorless cyclosilazane *(8)* and the inky-blue ketimine *(9)*:



(Owing to the thermolability of the diazene[5] and *(7)* it is advantageous to use the precursor *(4c)*[9], which is reactive at low temperatures.) As a further example we might mention the reaction of *(1)* with trimethylsilylazide, which leads—most likely *via* a [2+3]cycloaddition product *(10)* containing a triazene grouping[6]—to the diazomethane derivative *(11)* in *ca.* 50 % yield[7] according to:



Experimental

To a solution of $(Me_3Si)_2CBr_2$[8] (32.46 g, 102.1 mmol) in 200 ml THF/100 ml Et_2O at −110 °C is added a solution of LiBu (103.9 mmol) in hexane (60 ml), and then 29 ml (203 mmol) $PhMe_2SiCl$. The reaction mixture is allowed to warm slowly to room temperature before removal of LiCl by filtration. Fractional distillation of the filtrate at 125 °C/high vacuum affords 36.15 g (96.9 mmol) colorless, crystalline $(Me_3Si)_2CBr{-}SiMe_2Ph$, which on treatment with 7 ml Br_2 (130 °C, 24 h) yields 34.66 g (92 mmol) *(2)* (subl. p. 100 °C/high vacuum; m.p. 152 °C) along with some PhBr.

For the synthesis of *(3)*, 10.5 mmol ROAg (prepared from $AgNO_3$ and RONa in water, dried in a high vacuum) is allowed to react with 10.0 mmol *(2)* in 10 ml THF for 6 h at room temperature. AgBr is filtered off, the filtrate evaporated down, and the remaining oily residue treated with 10 ml pentane and filtered free of insoluble material. The esters *(3)* crystallize from the pentane solution in 90 % yield; m.p. 63 °C *(3a)*, <0 °C *(3b)*, 29 °C *(3c)*, 89 °C *(3d)*.

For the synthesis of *(4)* a solution of LiBu (5 mmol) in hexane is added dropwise to a solution of *(3)* (5 mmol) in 30 ml pentane at −78 °C. Pure *(4a—c)* is recovered by filtration at −78 °C—if necessary after concentration of the solution. *(4d)* was not isolated.

Received: March 2, 1977 [Z 693 IE]
German version: Angew. Chem. 89, 343 (1976)

CAS Registry numbers:
(1), 62139-73-5; *(2)*, 62139-74-6; *(3a)*, 62139-75-7; *(3b)*, 62139-76-8; *(3c)*, 62139-77-9; *(3d)*, 62182-97-2; *(4a)*, 62139-78-0; *(4b)*, 62139-79-1; *(4c)*, 62139-80-4; *(4d)*, 62139-56-4; *(5)*, 54008-64-9; *(6)*, 62139-57-5; *(7)*, 62139-58-6; *(8)*, 2954-84-9; *(9)*, 62139-59-7; $(Me_3Si)_2CBr_2$, 29955-10-0; $PhMe_2SiCl$, 768-33-2; $Ph_2P(O)OAg$, 62139-60-0; $(PhO)PhP(O)OAg$, 62139-61-1; $(PhO)_2P(O)OAg$, 22350-95-4; Tos·OAg, 16836-95-6; 2,3-dimethylbutadiene, 513-81-5; $Me_3Si{-}N{=}N{-}SiMe_3$, 13436-03-8

[1] Unsaturated Silicon Compounds, Part 1. Also Part 40 of Compounds of Silicon and its Group Homologs.—Part 39: *N. Wiberg, G. Hübler*, Z. Naturforsch. *B31*, 1317 (1976).

[2] *W. Schlenk, J. Renning*, Justus Liebigs Ann. Chem. *394*, 221 (1912); cf. also: *F. S. Kipping*, J. Chem. Soc. *1927*, 104.

[3] *N. S. Nametkin, V. M. Vdovin, L. E. Gusel'nikov, V. I. Zav'yalov*, Izv. Akad. Nauk SSSR Ser. Khim. *1966*, 584; *L. E. Gusel'nikov, M. C. Flowers*, Chem. Commun. *1967*, 864.

[4] a) *L. E. Gusel'nikov, N. S. Nametkin, V. M. Vdovin*, Acc. Chem. Res. *8*, 18 (1975); and references cited therein; b) *A. G. Brook, J. W. Harris*, J. Am. Chem. Soc. *98*, 3381 (1976); *H. Sakurai et al., ibid. 98*, 7453 (1976); *O. L. Chapman et al., ibid. 98*, 7844 (1976); *M. Ishikawa, T. Fuchikami, M. Kumada*, J. Organomet. Chem. *118*, 139, 155 (1976); c) *C. M. Golini, R. D. Bush, L. H. Sommer*, J. Am. Chem. Soc. *97*, 7371 (1975); and references cited therein.

[5] *N. Wiberg*, Angew. Chem. *83*, 379 (1971); Angew. Chem. Int. Ed. Engl. *10*, 374 (1971).

[6] *N. Wiberg, H. J. Pracht*, J. Organomet. Chem. *40*, 289 (1972); and references cited therein.

[7] Apart from *(11)* the products include, *inter alia*, bis(trimethylsilyl)diazomethane $(Me_3Si)_2C{=}N{=}N$ which is also accessible *via* other routes; cf. *D. Seyferth, Th. C. Flood*, J. Organomet. Chem. *29*, C25 (1971).

[8] *D. Seyferth, R. L. Lamberth jr., E. M. Hanson*, J. Organomet. Chem. *24*, 647 (1970).

[9] *Note added in proof* (April 6, 1977): As an example of a carbonyl compound, benzophenone reacts with *(1)* to form a [2+2] cycloadduct decomposing above about 80°C.

Absolute Configuration of the Cancerostatic *S*(−)-Cyclophosphamide

By *Dorota A. Adamaik, Ryszard Kinas, Wolfram Saenger*, and *Wojciech J. Stec*[*]

Cyclophosphamide (Cytoxan, Endoxan, NSC 26271; *N,N*-bis(2-chloroethyl)tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-amine 2-oxide) *(1)* is a clinically tested cancerostatic[1]. The observation that patients treated with racemic (±)-*(1)* preferentially excreted (−)-*(1)*[2] led to synthesis of the two enantiomers[3]. Experiments on mice showed (−)-*(1)* to have a therapeutic index LD_{50}/ID_{90} towards ADJ/PC6 plasma cell tumor that is twice as high as that of the (+)-enantiomer[4]. These findings prompted us to carry out the present crystal structure analysis in order to elucidate structure-function relations.

(−)-*(1)* crystallizes from CCl_4 as irregular stout crystals of space group P1 with $a=10.500(4)$, $b=10.490(4)$, $c=10.761(4)$ Å, $\alpha=110.0(2)$, $\beta=110.0(2)$, $\gamma=108.9(2)°$; $Z=3$. 2635 X-ray reflections were recorded with a four-circle diffractometer (Cu-K_α radiation, $2\theta/\omega$ scan) and corrected for geometric factors. The structure could be solved by direct methods after determination of the normalized structure amplitudes E_{hkl} and refined in the usual way. The coordinates and temperature factors were varied both for the model (x,y,z) and for the enantiomorph $(\bar{x},\bar{y},\bar{z})$ taking account of the anomalous scattering of P and Cl. Final weighted discrepancy indices $(R_w=[\Sigma w(|F_{obs}|-|F_{calc}|)^2/\Sigma w|F_{obs}|^2]^{1/2}$ are 7.28% for (x,y,z) and 6.77% for $(\bar{x},\bar{y},\bar{z})$. On the basis of *Hamilton*'s *R* factor test[5], the model (x,y,z) could be ruled out with a reliability index of <0.005. Figure 1 shows the structure of (−)-*(1)*: The symmetrical phosphorus atom has the *S* configuration.

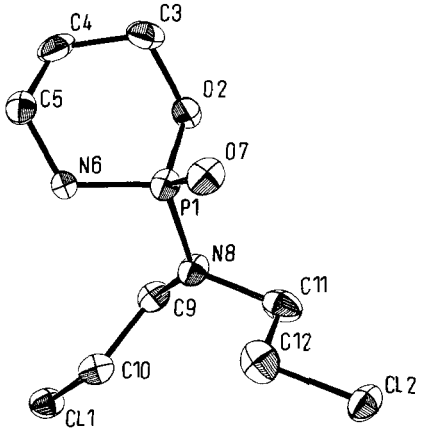


Fig. 1. Molecular structure of *S*(−)-cyclophosphamide. The thermal ellipsoids enclose the 20% probability distribution [7].

The conformation of *S*(−)-*(1)* is like that already described for the crystal structure of the racemate[6]. The oxazaphosphorin ring exists in the chair form, the substituent O(7) is axial, and the P—N bonds have partial double bond character. The C(9)—N(8)—C(11) plane is almost perpendicular to the O(2)—P(1)—N(6) plane, and the configuration of N(8) is planar (sp^2). Differences between the racemate and *S*(−)-*(1)* are seen only in orientations about the N—C bonds, thus indicating a certain degree of flexibility of the bis(2-chloroethyl)amino group while the rest of the molecule appears to be rigid.

Received: March 1, 1977 [Z 688 IE]
German version: Angew. Chem. *89*, 336 (1977)

CAS Registry number:
S-(−)-*(1)*, 60007-96-7

[1] Symposium on Cyclophosphamide in Pediatric Neoplasia, Cancer Chemother. Rep. *51*, No. 6 (1972).

[2] *P. J. Cox, P. B. Farmer, A. B. Foster, E. D. Gilby, M. Jarman*, Cancer Treatment Rep. *60*, 483 (1976).

[3] *R. Kinas, K. Pankiewicz, W. J. Stec*, Bull. Acad. Pol. Sci., Ser. Sci. Chim. *23*, 981 (1975).

[4] *P. J. Cox, P. B. Farmer, M. Jarman, M. Jones, W. J. Stec, R. Kinas*, Biochem. Pharmacol. *25*, 993 (1976).

[5] *W. C. Hamilton*, Acta Crystallogr. *18*, 502 (1965).

[6] *J. C. Clardy, J. A. Mosbo, J. G. Verkade*, Phosphorus *4*, 151 (1974).

[7] *C. K. Johnson*, ORTEP, Rep. ORNL-3894, Oak Ridge National Laboratory, Oak Ridge, Tenn. (1965).

A New *nido*-Carbaborane Type by $\eta^1-\eta^5$ Rearrangement of Pentamethylcyclopentadienylboranes[**]

By *Peter Jutzi* and *Arnulf Seufert*[*]

Formal replacement of BH^- units by isoelectronic CH moieties in the hypothetical hydroborate ions $B_nH_n^{4-}$ leads to corresponding *nido*-carbaborane systems[1]. We now report

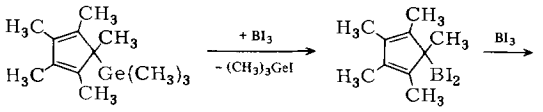
[*] Priv.-Doz. Dr. W. Saenger, Dr. D. A. Adamiak
Abteilung Chemie, Max-Planck-Institut für Experimentelle Medizin
Hermann-Rein-Strasse 3, D-3400 Göttingen (Germany)
Dr. R. Kinas, Doz. Dr. W. J. Stec
(Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences
Boczna 6, 90-362 Lodz (Poland)

[*] Doz. Dr. P. Jutzi, Dipl.-Chem. A. Seufert
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

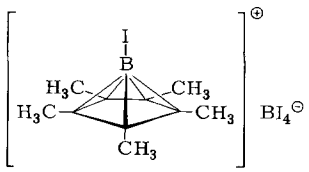
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

the first synthesis of derivatives of the $C_5BH_6^+$ ion with a pentagonal-pyramidal structure.

Reaction of pentamethylcyclopentadienyltrimethylgermane *(1)*[2] with two equivalents of boron triiodide proceeds *via* extrusion of trimethyliodogermane to form the salt *(3)* having a *nido*-carbaborane structure in the cation. Although the intermediate pentamethylcyclopentadienyldiiodoborane *(2)* cannot be isolated, it can be detected by NMR spectroscopy[3].



(1) *(2)*



(3)

Compound *(3)* proves to be fairly air-stable and is readily soluble in polar aprotic solvents such as methylene chloride and acetonitrile. Its constitution and structure are confirmed by analytical and spectroscopic data.

^{1}H-NMR (in CH_2Cl_2): $\delta CH_3 = 2.32$ ppm (quartet, $^3J_{HB} = 2.2$ Hz). ^{11}B-NMR (in CH_2Cl_2 *vs.* $BF_3 \cdot OEt_2$): $\delta(CH_3)_5C_5BI^+ = 50.8$ ppm (8 of 16 lines expected theoretically, $J = 2.2$ Hz); $\delta BI_4^- = 127.6$ ppm. ^{13}C-NMR (in $CH_2Cl_2/C_2D_2Br_4$; $\{^1H\}$): $\delta CH_3 = -10.11$, δC-ring = 115.2 ppm. Mass spectrum: $m/e = 273$ $C_{10}H_{15}BI^+$ (32% int.). Conductivity (in acetonitrile, 25 °C): 173.3 Ω^{-1} cm^2 mol^{-1} ($1.933 \cdot 10^{-3}$ M) [cf. $Et_4N^+BBr_4^-$: 176.9 Ω^{-1} cm^2 mol^{-1} ($1.753 \cdot 10^{-3}$ M)[4]].

Compared to cyclopentadienylboranes of type *(2)*, the ^{11}B resonance of the cluster *(3)* shows a drastic upfield shift ($\approx$80 ppm). Hence it is concluded that the positive charge in *(3)* is not localized on the boron atom but distributed over the entire cluster. Interestingly, coupling of the CH_3 protons with the ^{11}B isotope is observed with *(3)*, but not with *(2)*.

According to MO considerations and the resulting rules[1, 5] for orbital and electron requirements, the cluster *(3)* corresponds to a minimum on the energy surface. The bonding found in *(3)* should also apply to isoelectronic systems containing neighboring elements of boron[6]. Thus an alternative mode of bonding is available for η^5-cyclopentadienyl compounds of Main Group elements instead of the hitherto discussed "centrosymmetric π-bonding".

Procedure:

A solution of *(1)* (4.0 g, 16 mmol) in CH_2Cl_2 (10 ml) is added slowly to boron triiodide (12.5 g, 32 mmol) in CH_2Cl_2 (20 ml) at -20 °C. After stirring for 1 h, all volatile components are drawn off at 0 °C. Repeated recrystallization of the residue from CH_2Cl_2 affords the product *(3)* as colorless needles, m. p. 160 °C (dec.); yield 7.8 g (62 %).

Received: March 1, 1977 [Z 685 IE]
German version: Angew. Chem. 89, 339 (1977)

[1] *K. Wade*, Chem. Br. *11*, 177 (1975).
[2] *A. Davison, P. E. Rakita*, Inorg. Chem. *9*, 289 (1970).
[3] Compounds analogous to *(3)* with B—Br and B—Cl bonds in the cluster can be prepared from the corresponding cyclopentadienyldihaloboranes and the halides BX_3 or AlX_3: *W. Schmitt*, Diplomarbeit, Universität Würzburg 1977.
[4] *I. Y. Ahmed, C. D. Schmulbach*, Inorg. Chem. *8*, 1411 (1969).
[5] *R. W. Rudolph*, Acc. Chem. Res. *9*, 446 (1976); *R. E. Williams*, Inorg. Chem. *10*, 210 (1971).
[6] Compare the structures of $(C_5H_5)_2Be$ [*A. Haaland*, Acta Chem. Scand *23*, 2921 (1969)] and of $(CCH_3)_6^{2+}$ [*H. Hogeveen, P. W. Kwant*, J. Am. Chem. Soc. *96*, 2208 (1974)].

Determination of the Activation Volume $\Delta V^{\neq}$ of Simple Molecular Rearrangements by High-Resolution ^{1}H-NMR Spectroscopy at High Pressures[**]

By *Hans-Dietrich Lüdemann, Rudolf Rauchschwalbe*, and *Elmar Lang*[*]

High resolution NMR has become the most prominent method for the determination of the activation parameters $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ in simple intra- and intermolecular rearrangements. In modern monographs separate chapters are devoted to the calculation of these parameters from the temperature dependence of the proton signals[1]. An additional study of the pressure dependence of the spectra allows the determination of the activation volume from the relation:

$$\frac{d\ln k}{dp} = \frac{-\Delta V^{\neq}}{RT} \qquad (1)$$

In this communication we report the effect of pressure on two simple intramolecular rearrangements. The spectra were recorded in a recently developed high pressure NMR cell[3] fitting into the standard probe of a Varian XL 100 spectrometer. This cell can be operated at pressures up to 2000 bar and variable temperature with a resolution of 1 Hz.

1) Rotation of the dimethylamino group of N,N-dimethylacetamide around the C—N bond:

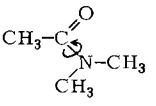


Figure 1 gives the signals of the two *N*-methyl groups in the vicinity of the coalescence temperature (T_c).

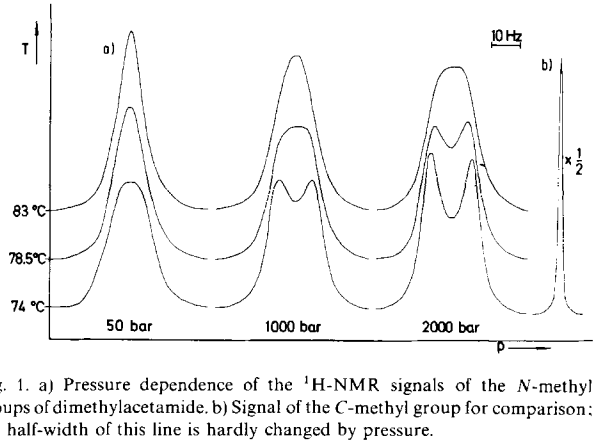


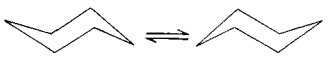
Fig. 1. a) Pressure dependence of the ^{1}H-NMR signals of the *N*-methyl groups of dimethylacetamide. b) Signal of the *C*-methyl group for comparison; the half-width of this line is hardly changed by pressure.

[*] Priv.-Doz. Dr. H.-D. Lüdemann, Dr. R. Rauchschwalbe, E. Lang
Institut für Biophysik und Physikalische Biochemie der Universität
Universitätsstrasse 31, D-8400 Regensburg (Germany)

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

Increasing pressure shifts the coalescence of the signals to higher temperatures with $\Delta T_c/\Delta p = 4.5\ \mathrm{K \cdot kbar^{-1}}$. $\Delta G^{\neq}$ and k_c were calculated at the various pressures by insertion of T_c, the low temperature values of the frequency difference, and the half-width of the signals into the standard equations[1, 2]. The inversion rates between 74 and 83 °C were calculated as a function of pressure assuming Arrhenius-type behavior. Insertion of these rates into eq. (1) yields $\Delta V^{\neq} = 10.3 \pm 1.0\ \mathrm{cm^3 \cdot mol^{-1}}$. The inversion of the dimethylamino group is thus connected with a considerable volume increase in the immediate vicinity of the molecule.

2) Ring inversion of cyclohexane:



An increase of pressure shifts T_c to lower temperatures ($\Delta T_c/\Delta p = -1.0\ \mathrm{K \cdot kbar^{-1}}$); within the limits of experimental error the difference $\Delta\nu$ between the chemical shifts is not affected by pressure. Also, the half-width b_E is only slightly changed. By application of the methods described in the first example, the inversion rates k were calculated as function of pressure. $\Delta V^{\neq}$ was found to be $-1.9 \pm 0.5\ \mathrm{cm^3 \cdot mol^{-1}}$. The data used are given in Table 1.

Table 1. Pressure dependence of the proton resonance spectra of cyclohexane in the coalescence region.

Pressure [bar]	50	1000	2000
Coalescence temperature [K]	217	216	215
Frequency difference [Hz]	48.5	48.5	48.5
Half-width [Hz]	15.5	16.5	17.0
Inversion rate (217 K) k_{217} [s^{-1}]	87	96	107

The unexpected result is that increasing pressure significantly accelerates the ring inversion. This can be qualitatively explained by assuming that the twist or boat conformations adopted by the molecule during ring inversion have slightly smaller molar volumes than the energetically more favorable chair forms. Further studies on substituted cyclohexanes and in other solvents will be necessary for a better description of this effect.

Experimental

Measuring frequency: 100.1 MHz, FT technique, 16k memory, spectral width: 1000 Hz.—*Example 1:* Solution (vol.-%) of dimethylacetamide (60), tetramethylsilane (20), and [D_6]-acetone (20).—*Example 2:* Solution (vol.-%) of cyclohexane (40), tetramethylsilane (30), [D_2]-dichloromethane (15), and [D_{14}]-methylcyclohexane (15).

Received: January 24, 1977 [Z 683 IE]
German version: Angew. Chem. *89*, 340 (1977)

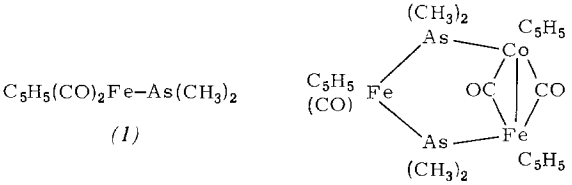
CAS Registry numbers:
Dimethylacetamide, 127-19-5; cyclohexane, 110-82-7; [D_{14}]-methylcyclohexane, 10120-28-2

[1] *H. Günther:* NMR-Spektroskopie. Georg Thieme Verlag, Stuttgart 1973, p. 239.
[2] *A. Jaeschke, H. Münsch, H. G. Schmid, H. Friebolin, A. Mannschreck,* J. Mol. Spectrosc. *31*, 14 (1969).
[3] *U. Gaarz, H.-D. Lüdemann,* Ber. Bunsenges. Phys. Chem. *80*, 607 (1976).

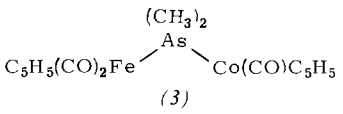
An Organometallic Five-Membered Ring with Hetero-Metal-Metal Bonding[**] [1]

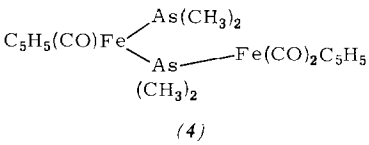
By *Erika Röttinger, Rainer Müller,* and *Heinrich Vahrenkamp*[*]

As Lewis bases, organometalloarsanes such as *(1)*[2] are capable of substituting CO ligands in metal complexes, and thus of forming As-bridged dinuclear complexes. Mild reaction conditions are necessary for the preparation of hetero dinuclear complexes, whereas at high temperatures reaction of the organometalloarsanes with themselves is predominant[1]. We have now observed the first combination of these two reaction possibilities with formation of the trinuclear metal-arsenic five-membered ring *(2)*.



Reaction of *(1)* with excess $C_5H_5Co(CO)_2$ at elevated temperature affords dark-green *(2)*. The expected simple As-bridged dinuclear complex *(3)* is not formed, even under milder conditions. It must be assumed, therefore, that *(1)* initially reacts with itself to give the non-isolable dinuclear organometalloarsane *(4)*, which then reacts with the cobalt complex $C_5H_5Co(CO)_2$. This assumption is supported by the fact that the dinuclear complex $[C_5H_5(CO)Fe{-}As(CH_3)_2]_2$, which can be formed *via (4)*, is obtained as main product of the reaction.





The heterocycle *(2)* manifests itself in the IR spectrum (cyclohexane, $\mathrm{cm^{-1}}$) by three CO stretching modes (1942 s, 1928 vs, 1758 vs) and in the ^{1}H-NMR spectrum (benzene, int. TMS, ppm) by three C_5H_5 signals (3.95, 4.35, 4.69) and four CH_3 signals (1.26, 1.34, 1.43, 1.50). Its structure was determined by X-ray crystallography[3]. Figure 1 shows the approximate planarity of the novel five-membered ring system and the CO-bridged hetero metal-metal bond. Since the IR spectrum of *(2)* in solution shows only one bridging CO group, while the solid state structure shows two such groups, *(2)* must be a fluxional molecule[4].

In the case of the two previously known five-membered heterocycles with carbonylmetal moieties[5] the synthetic route precluded formation of heterobimetallic species. Complexes

[*] Prof. Dr. H. Vahrenkamp, Dipl.-Chem. E. Röttinger, Dipl.-Chem. R. Müller
Chemisches Laboratorium der Universität
Albertstr. 21, D-7800 Freiburg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Rechenzentrum der Universität Freiburg.

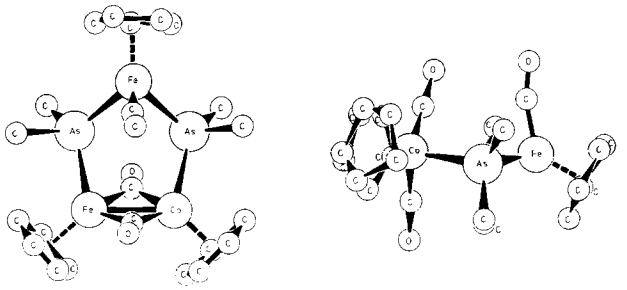


Fig. 1. Two views of the molecular structure of *(2)*. Averaged bond lengths (in clockwise direction) Co—Fe = 2.460, Fe—As = 2.363, As—Fe = 2.328, Fe—As = 2.340, As—Co = 2.348 Å.

such as *(2)*, however, appear to be accessible in a systematic way. Comparison of the stereochemistry of *(2)* with that of an open-chain M_3As_2 compound without metal-metal bonding[6] shows that the relief of steric strain is a driving force in the formation of *(2)*. Heterotrinuclear complexes with two dimethylarsenic bridges[7] should thus be capable of rearranging to metal-metal coupled heterocycles such as *(2)*, a prediction which is substantiated by preliminary findings[8].

Experimental:

Synthesis of *(2)*: A mixture of *(1)* (2.74 g, 9.7 mmol) and $C_5H_5Co(CO)_2$ (2.70 g, 15.0 mmol) in cyclohexane (50 ml) is stirred for 4 d at 85 °C. After removal of all volatile compounds *in vacuo* the reaction mixture is chromatographed on silica gel with benzene. The first, red (main) fraction contains $[C_5H_5(CO)Fe—As(CH_3)_2]_2$. The second, green fraction, after recrystallization from benzene/cyclohexane (4:1), affords 0.36 g (11 %) of *(2)*, m.p. 257 to 259 °C (dec).

Received: February 23, 1977 [Z 681 IE]
German version: Angew. Chem. 89, 341 (1977)

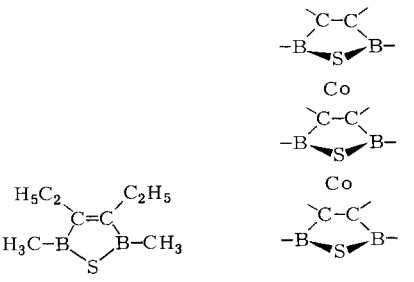
CAS Registry numbers:
(1), 52456-38-9; *(2)*, 62182-99-4; $C_5H_5Co(CO)_2$, 12078-25-0

[1] Part 33 of Organometallic Lewis Bases.—Part 32: *R. Müller, H. Vahrenkamp*, Chem. Ber., in press.
[2] *W. Malisch, M. Kuhn*, Angew. Chem. 86, 51 (1974); Angew. Chem. Int. Ed. Engl. 13, 84 (1974).
[3] Triclinic, P1, $Z = 2$, $a = 10.786(6)$, $b = 13.021(12)$, $c = 9.898(7)$ Å; $\alpha = 90.24(6)$, $\beta = 117.20(3)$, $\gamma = 105.87(5)°$. Nonius-CAD4 diffractometer, 3045 reflections corrected for absorption, $R = 0.076$.
[4] *F. A. Cotton*, J. Organomet. Chem. 100, 29 (1975).
[5] *M. Elder, W. L. Hutcheon*, J. Chem. Soc. Dalton 1972, 175; *K. M. Abraham, G. Urry*, Inorg. Chem. 12, 2850 (1973).
[6] *E. Röttinger, H. Vahrenkamp*, J. Chem. Res. 1977, (S) 76, (M) 0818.
[7] *M. Börner, H. Vahrenkamp*, J. Chem. Res. 1977, (S) 74, (M) 0801.
[8] *H. J. Langenbach, H. Vahrenkamp*, unpublished.

μ-Thiadiborolene-bis(η-thiadiborolenecobalt)—A "Homogeneous" Triple-Decker Sandwich with Three Heterocyclic Ligands[1]

By *Walter Siebert* and *Wilfried Rothermel*[*]

The triple-decker sandwich compounds previously reported in the literature are each made up of two cyclopentadienyl metal fragments bridged by homocyclic C_5H_5-[2] or heterocyclic C_2B_3-[3], C_2B_2S-[1], and C_4B-ligands[4]. We report here on the compound *(1)*·[Co*(1)*]$_2$ *(2)*, the first representative in which three thiadiborolene rings *(1)* are present as μ- and as η-ligands. *(2)* is formed from *(1)* and $Co_2(CO)_8$ *via* the isolable dinuclear complex *(1)*$_2$·$Co_2(CO)_4$[5].



(1)

(2)

The triple-decker structure follows from the analytical and spectroscopic data of the air-stable *(2)*. Besides the molecular ion $L_3Co_2^+$ [L = *(1)*] ($I_{rel} = 100$, referred to $^{11}B_5{}^{10}B$) the mass spectrum (70 eV) contains, *inter alia*, the fragments $L_2Co_2^+$ (73), L_2Co^+ (12), LCo^+ (7), L^+ (7), $\{L—CH_3\}^+$ (11), $(C_2H_5)_2C_2BCH_3^+$ (60) and $(C_2H_5)_2C_2B^+$ (25).—In the ^{1}H-NMR spectrum [δ = 2.80 (Q, 4; $J = 7.6$ Hz), 2.1 (M, 8), 1.50 (T, 6), 0.96 (T, 12), 0.78 (S, 6) and 0.73 (S, 12) ppm (in CS_2 rel. to TMS ext.)] the quartet proves the magnetic equivalence of the bridge-ligand methylene protons and thus also the triple-decker array. As in thiadiborolene mononuclear complexes[6], a multiplet (ABX_3 system) is observed for the CH_2 groups of the two terminal ligands. Two ^{11}B-NMR signals [δ = 14 (S, 2) and 30 (br. S, 4) ppm (in CS_2 rel. to BF_3·OEt_2 ext.)] are also compatible with *(2)*: as in *(1)*·$[Mn(CO)_3]_2$ (22.5 ppm)[7] and in *(1)*·$[Fe(C_2H_5)]_2$ (12.0 ppm)[1] the B atoms of the central ring experience strong electronic shielding.

In *(2)* the electron balance can be described in terms of the construction of the 30 valence-electron triple-decker[8] from three thiadiborolene dianions and two Co-d^6 cations. Consideration of *(2)* as a seven-atom cluster requires that the bonding molecular orbitals are occupied by 16 skeletal electrons [2 × 1 (Co), 2 × 3 (C), 2 × 2 (B), 4 (S)] according to the rule for *closo* compounds[9].

μ-(3,4-Diethyl-2,5-dimethyl-1,2,5-thiadiborolene)-bis(η-3,4-diethyl-2,5-dimethyl-1,2,5-thiadiborolenecobalt) (2)

$Co_2(CO)_8$ (1.30 mmol) reacts with *(1)* (2.77 mmol) in toluene (20 ml) under N_2 to give a deep-blue solution. After addition of further *(1)* (2.7 mmol) the mixture is heated under reflux for 1.5 h and the resulting red solution filtered. The filtrate is concentrated by evaporation and treated with petroleum ether. On cooling to −10 °C black shiny crystals are deposited; m.p. 172 to 175 °C (dec.) yield 0.57 g (71 %).

Received: February 25, 1977 [Z 684 IE]
German version: Angew. Chem. 89, 346 (1977)

CAS Registry numbers:
(1), 54677-51-9; *(2)*, 62166-62-5; $Co_2(CO)_8$, 10210-68-1

[*] Prof. Dr. W. Siebert, Dipl.-Chem. W. Rothermel
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

[1] Part 3 of Triple-Decker Compounds.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 2: *W. Siebert, T. Renk, K. Kinberger, M. Bochmann, C. Krüger*, Angew. Chem. 88, 850 (1976); Angew. Chem. Int. Ed. Engl. 15, 779 (1976).
[2] *H. Werner, A. Salzer*, Synth. Inorg. Met.-Org. Chem. 2, 239 (1972).
[3] *D. C. Beer, V. R. Miller, L. G. Sneddon, R. N. Grimes, M. Mathew, G. J. Palenik*, J. Am. Chem. Soc. 95, 3046 (1973).
[4] *G. E. Herberich*, lecture at the Int. Meet. Boron Chem., Ettal, July 1976.

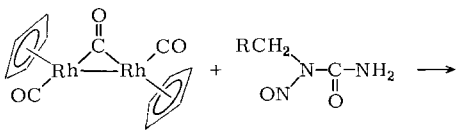
[5] *W. Rothermel*, Diplomarbeit, Universität Marburg 1976; *W. Siebert*, part of a lecture at the III. Int. Meet. Boron Chem., Ettal, July 1976.
[6] *W. Siebert, R. Full, J. Edwin, K. Kinberger, C. Krüger*, J. Organomet. Chem., in press.
[7] *W. Siebert, K. Kinberger*, Angew. Chem. *88*, 451 (1976); Angew. Chem. Int. Ed. Engl. *15*, 434 (1976).
[8] *J. W. Lauher, M. Elian, R. H. Summerville, R. Hoffmann*, J. Am. Chem. Soc. *98*, 3219 (1976).
[9] *K. Wade*, Chem. Brit. *11*, 177 (1975); literature cited therein.

Novel Synthesis of μ-Methylene Complexes[**]

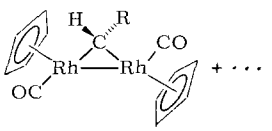
By *Wolfgang A. Herrmann, Carl Krüger, Richard Goddard,* and *Ivan Bernal*[*]

As recently reported[1], *N*-alkyl-*N*-nitrosourea derivatives are suitable for use as especially mild nitrosylation reagents in organometallic chemistry. We have now found that this class of compounds also provides a facile and productive entry to μ-methylene-transition metal complexes.

The rhodium complex *(1)* reacts with *N*-methyl-*N*-nitrosourea in boiling benzene to give a red coordination compound *(2a)* which is stable in the solid state and in solution. On the basis of total elemental analysis, osmometric molecular-weight determination, and ^{1}H-NMR, IR, and mass spectra the compound has been characterized as μ-methylenebis(carbonyl-η-cyclopentadienylrhodium) (*Rh—Rh*) (Table 1). The homologous μ-ethylidene derivative *(2b)* can be obtained in similar manner with *N*-ethyl-*N*-nitrosourea. Deuterium-labeling experiments confirm that the carbene bridge ligand originates from the alkyl groups of the organic reagent. The surprising formation of *(2a)* and *(2b)* requires ring opening of the metallacyclic system of *(1)*; mechanistic details are still unknown.



(1)



(2a), R = H
(2b), R = CH_3

The new procedure obviates use of diazoalkanes for methylene transfer[2]. A further advantage is the ready accessibility of numerous alkyl-substituted nitrosoureas.

We performed the first crystal structure determination[3] of an organometallic compound with bridging CH_2 by analyzing *(2a)* (Fig. 1): the carbene C atom, like the two Rh atoms, is located in a distorted tetrahedral environment. The *trans* orientation of the centrically bonded, almost parallel cyclopentadienyl rings leads to identical configurations at the chiral metal centers.

[*] Dr. W. A. Herrmann
Chemisches Institut der Universität
Universitätsstrasse 31, D-8400 Regensburg 1 (Germany)
Dr. C. Krüger, Dr. R. Goddard
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim-Ruhr 1 (Germany)
Prof. Dr. I. Bernal
Chemistry Department, University of Houston
Houston, Texas 77004 (USA)

[**] Transition Metal Methylene Complexes, Part 2.—Part 1: Ref. [3].—This work was supported by the Deutsche Forschungsgemeinschaft, the Alexander-von-Humboldt-Stiftung, and Degussa Hanau.

Table 1. Properties and spectroscopic data of *(2a)* and *(2b)*.

μ-CH_2[η-$C_5H_5Rh(CO)]_2$ *(2a)*: pale red needles, m.p. 94 °C.—^{1}H-NMR ([D_6]-acetone; τ [ppm], TMS int.): ^{3}4.50 (C_5H_5), ^{m}2.88 (CH_2); int. 5:1.—IR [cm^{-1}]: 1984 vs (νCO) [*n*-pentane]; 1950 vs (νCO), 2963 vw and 2903 w (νCH_2) [KBr].—MS (70 eV; T_I 50, T_S 80 °C): M^+ (*m/e* 406, rel. int. 34 %, isotopically corrected), $[M-CO]^+$ (378, 44), $(C_5H_5)_2Rh_2C^+$ (348, 59), $(C_5H_5)_2Rh^+$ (233, 100); ions <8 % not considered; m* 351.9 (406→378).
μ-CH_3CH[η-$C_5H_5Rh(CO)]_2$ *(2b)*: red-brown needles, dec. 111—112 °C.—^{1}H-NMR ([D_6]-acetone; τ [ppm], TMS int.): ^{3}4.57 (C_5H_5), ^{2}7.47 (CH_3), ^{m}1.32 (CH); int. 10:3:1.—IR [cm^{-1}]: 1970 vs (νCO) [*n*-pentane]; 1948 vs (νCO), 2965 vw, 2900 w, 2837 vw (νCH, νCH_3) [KBr].—MS (70 eV; T_I 100, T_S 60 °C): M^+ (420, 11), $(C_5H_5)_2Rh_2^+$ (336, 7), $(C_5H_5)_2Rh^+$ (233, 100); $C_9H_7Rh^+$ (218, 7), $C_5H_5Rh^+$ (168, 6); ions <3 % not considered.

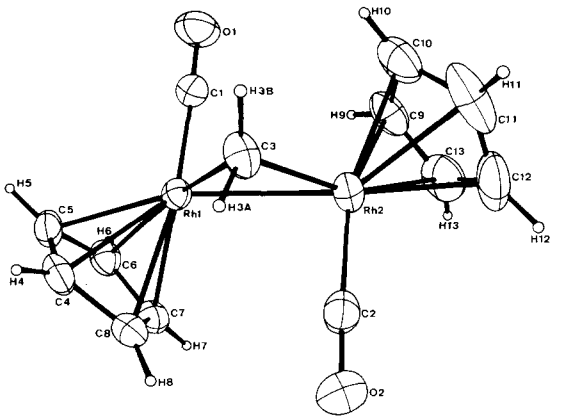


Fig. 1. ORTEP plot of μ-CH_2[η-$C_5H_5Rh(CO)]_2$.

Bond lengths [pm]		Angles [°]	
Rh1—Rh2	266.5(1)	Rh1—C3—Rh2	81.7(1)
Rh1—C1	183.1(4)	Rh1—C1—O1	178.2(4)
Rh2—C2	183.3(4)	Rh2—C2—O2	176.0(4)
Rh1—C3	202.9(4)		
Rh1—C_5H_5	225.9(30)	Torsional angle [°]	
Rh2—C_5H_5	225.6(22)	C1, Rh1, Rh2, C2	−176.90

Procedure[4]

μ-$CO[η-C_5H_5Rh(CO)]_2$[5] *(1)* (420 mg, 1.0 mmol) and *N*-methyl-*N*-nitrosourea (1.03 g, 10 mmol) are refluxed in benzene (50 ml) for 25 h. On column chromatography of the crude product on Kieselgel 60 (Merck 7734, Act. II—III; 20 × 3 cm; +15 °C) *(2a)* is eluted as an orange-yellow zone with *n*-pentane/benzene (2:1); it is recrystallized from *n*-pentane at −78 °C. Yield 349 mg (86 %). A small amount of *(1)* is developed as a deep red zone with benzene. Analogous reaction with *N*-ethyl-*N*-nitrosourea affords 240 mg (57 %) of *(2b)*.

Received: March 2, 1977 [Z 691 IE]
German version: Angew. Chem. *89*, 342 (1977)

[1] *W. A. Herrmann, I. Bernal*, Angew. Chem. *89*, 186 (1977); Angew. Chem. Chem. Int. Ed. Engl. *16*, 172 (1977).
[2] *W. A. Herrmann, B. Reiter, H. Biersack*, J. Organomet. Chem. *97*, 245 (1975).
[3] Crystal data: triclinic, space group P$\bar{1}$, a = 803.42(5), b = 909.98(6), c = 938.81(2) pm, α = 74.402(3), β = 81.923(3), γ = 82.685(6)°; 2718 observed reflections ($2\theta_{max}$ = 55°), $Mo_{K\alpha}$-radiation (0.71069 Å). Computer-controlled diffractometer Enraf-Nonius CAD-4. R = 0.0379 (R_w = 0.0546).
[4] All operations performed under N_2 and with use of dry solvents.
[5] We synthesized this compound, which was first prepared by *E. O. Fischer et al.* [Z. Naturforsch. *16B*, 835 (1961)] [6], by 80 hours' refluxing of η-$C_5H_5Rh(CO)_2$ (1.0 g) in benzene (40 ml)—yield 630 mg (67 %).—In place of *(1)* its precursor η-$C_5H_5Rh(CO)_2$ can also be used directly for preparation of *(2a)* and *(2b)* (yield <50 %).
[6] Structure: *O. S. Mills, J. P. Nice*, J. Organomet. Chem. *10*, 337 (1967); cf. *F. A. Cotton, D. L. Hunter*, Inorg. Chem. *13*, 2044 (1974).

Reviews

Abstracts of selected progress reports and review articles

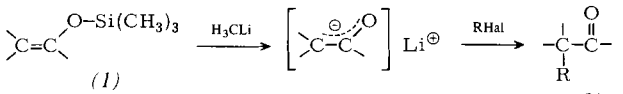
Applications of Mössbauer spectroscopy to the study of heterogeneous catalysis are considered by *J. A. Dumesic* and *H. Topsøe*. This technique largely satisfies the desire to study real catalysts (*i.e.* not only single crystals or films) *in situ* (*i.e.* not only in ultrahigh vacuum). Mössbauer spectroscopy is not restricted merely to catalytic systems containing iron or tin but can be applied to other systems containing "Mössbauer atoms" or "Mössbauer isotopes" such as antimony, europium, nickel, ruthenium, gold, and tungsten. The technique can also be modified so as to provide information about systems not containing any "Mössbauer atoms". [Mössbauer Spectroscopy Applications of Heterogeneous Catalysis. Adv. Catal. *26*, 121—246 (1977); 255 references]

[Rd 941 IE—F]

Soluble organic compounds present in drinking water are considered in a review by *J. S. Fritz*. These compounds are present in very low concentrations: humic material 1—5 mg/l, gas chromatographable organic compounds 0.5—3 µg/l, chloroform and chlorobromomethanes 1—300 µg/l. Concentration procedures suitable for the organic contaminants include resin sorption, solvent extraction, and water-gas distribution. Meanwhile, about 400 organic compounds have been detected in drinking water. [Concentration of Solutes from Aqueous Solution. Acc. Chem. Res. *10*, 67—72 (1977); 23 references]

[Rd 944 IE—L]

The chemistry of *O*-silyl enol ethers *(1)* and their manifold applications as highly reactive intermediates are summarized by *J. K. Rasmussen*. Compounds *(1)* can be obtained, for instance, from enolate ions and chlorosilanes and by hydrosilylation of α,β-unsaturated carbonyl compounds. Examples of the uses of *(1)* are the regiospecific synthesis of sterically



(1) *(2)*

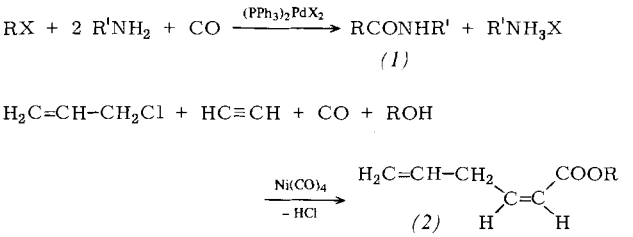
hindered ketones *(2)*, the synthesis of 1,3- and 1,4-diketones, α-halo carbonyl compounds, α-oximino aldehydes, and *trans*-1,2-diols [*O*-Silylated Enolates—Versatile Intermediates for Organic Synthesis. Synthesis *1977*, 91—110; 125 references]

[Rd 939 IE—M]

Surveys of work published in 1975 are compiled in a volume of the Journal of Organometallic Chemistry. *M. I. Bruce* reports about the structure of organo-transition metal complexes (pp. 1—149, 333 references), *L. S. Hegedus* is concerned with transition metal derivatives in organic synthesis (pp. 151—226, 337 references), *G. Marr* and *B. W. Rockett* discuss organic reactions of π complexes (pp. 227—359 references); papers about titanium, zirconium, and hafnium, about manganese, technetium, and rhenium, and about nickel, palladium, and platinum are reviewed by *P. C. Wailes* (pp. 361—382, 84 references), *P. M. Treichel* (pp. 383, 429, 198 references), and *D. M. Roundhill* (pp. 431—499, 298 references), respectively. [J. Organomet. Chem. *126* (1977)]

[Rd 940 IE—F]

Transition metal catalyzed reactions of organic halides with carbon monoxide, olefins, and acetylenes is the title of a review by *R. F. Heck*. On carbonylation, the halogen atom is specifically replaced by CO. Thus, in the presence of amines, amides *(1)* can be synthesized from the halides. Some of these metal-catalyzed carbonations are practicable alternatives to conven-

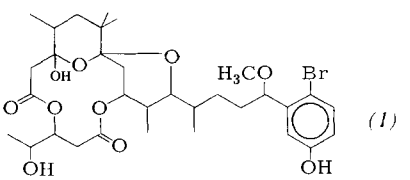


(1) *(2)*

tional organic syntheses. Furthermore, metal-catalyzed reactions of organic halides with olefins and acetylenes permit facile syntheses of, *e.g.*, esters *(2)*, amides, and aldehydes. [Transition Metal-Catalyzed Reactions of Organic Halides with CO, Olefins, and Acetylenes. Adv. Catal. *26*, 323—349 (1977); 44 references]

[Rd 942 IE—F]

Toxins from marine organisms are the topic of survey compiled by *P. J. Scheuer*. Tetrodotoxin, saxitoxin, and ciguatoxin have been studied because they can occur in edible marine organisms. The structure of ciguatoxin has not yet been elucidated; it is only known to be a hydroxylated lipid. Aplysiatoxin from the midgut of a species of sea hare proved to be the bromine compound *(1)*. The extremely potent palytoxin from



(1)

a coelenterate is a truly remarkable compound: its molecular weight is about 3000, and the molecule apparently does not contain any repeating units, any amino acids, or any of the common sugars. It is hardly attacked by enzymes. [Marine Toxins. Acc. Chem. Res. *10*, 33—39 (1977); 92 references]

[Rd 943 IE—L]

Trivialnamenkartei (Card File of Organic Trivial Names). 5. Ergänzungslieferung (5th Supplementary Batch). Issued by the Gesellschaft Deutscher Chemiker, Abteilung Chemie-Information und -Dokumentation Berlin. Verlag Chemie, GmbH, Weinheim 1976. 1st edit., 1024 cards, DM 208.—.

Every chemist knows that trivial names are both useful and infuriating. Useful because they are brief designations for compounds whose systematic names may be very cumbersome, and infuriating because they seldom give the least indication of the compound's structure. One is thus forced to fall back on memory when one wants to correlate the name with the structural formula, or one must turn to a good reference work. Such a reference work has been available for the last few years in the form of the Trivial Name Card File[*] which, if this new fifth batch is included, now contains more than 13000 entries. Like the previous cards, this fifth batch consists both of cards giving new names and of replacement cards that correct information given previously or bring it completely up to date. In the top left-hand corner each card bears the position number that applies on alphabetical arrangement of the cards according to the German spelling of the trivial names; in the top right-hand corner is the position number obtained by sorting arrangement according to American English spelling. Below these numbers are, respectively, the German and English trivial names. The center of the card is occupied by the structural formula with an indication of the stereochemistry, in the bottom left-hand corner is the molecular formula, and in the bottom right-hand corner are one or two references with the aid of which one can find the description of the compound in Chemischer Informationsdienst or Chemical Abstracts. The card file thus contains all that is needed for preliminary information about substances whose designations often sound truly exotic—no longer is one helpless in the face of pinseline, gentiakochianine, or colestipol; the contents do not become outdated and thus the investment is worthwhile. One might even take the presence of this card file as a criterion of the quality of a chemical library.

H. Neithard [NB 370 IE]

Strukturen der Materie und ihre Symmetrie, in Stereobildern (Structure of Matter and its Symmetry, in Stereoscopic Pictures). By *E. Egert* and *H. J. Lindner*. 3D Bildstudio R. Schmidt, 6101 Nieder-Ramstadt 1976. 1st edit., 30 pp., 42 figs. (stereoscopic pictures); in spiral binding; red-green spectacles and ruler/protractor included; DM 18.20 (from ten or more DM 16.00).

The structure of matter is three-dimensional and recognition of the spatial relationships is essential for its understanding. There are several possible ways of reproducing it. The widely used two-dimensional projection is convenient but not really satisfactory because "the ability to visualize three-dimensional structures from two-dimensional representations varies greatly between individuals". It is remarkable that a book containing structures of molecules and lattices in stereoscopic representation should appear at this time, when there are more than a dozen systems of molecular models that appear to satisfy the desire for three-dimensional viewing.

It is quite natural to see in three dimensions; why then should one not also see the larger molecules and lattices in that way, whose structures are too elaborate to be built with normal models? Although one can learn chemistry without stereoscopic pictures, it would be a pity to be denied this experience of space, which in view of the quality of the *Egert/Lindner* book becomes an esthetic pleasure.

Section a) deals with the crystal structures of metals and nonmetals, b) with ionic crystals, c) with the structures of inorganic molecules (boron and silicon compounds and metal complexes), d) with the structures of organic molecules, and e) with types of crystal lattice and symmetry elements.

The attempt to introduce stereoscopic pictures as teaching aids in the training of chemists is in itself nothing new: the materials supplied with the textbooks by *Klages*, *Holleman*, and *Wiberg*, and now by *Streitwieser* and *Heathcock*, and the book by *Bernal*, *Hamilton*, and *Ricci* use the method each within its own framework, as do Vol. A 1 of Molecular Structures and Dimensions and some Journals.

The new book attempts to show that this method of presentation has distinct advantages over models and, even if it does not replace them, it is undoubtedly a valuable extension thereof. The possibility of emphasizing the unit cell in an extended lattice is used with advantage. The transformation of the stereoformulas of D- and L-glyceraldehyde, placed in relation to one another by a mirror plane floating in space, into the Fischer projections becomes very clear. In the 14 Bravais lattices the angles drawn in can be viewed three-dimensionally. In the especially successful chapter on "Symmetry Elements" the symmetry axes and planes shown in space materially ease recognition of *e.g.* right- and left-handed screws and the understanding of symmetry operations (*e.g.* rotation-inversion). While spatial recognition requires some time and practice with the stereoscopic pictures of the older type, and even in *Bernal*'s book, it is evident as soon as one opens the present volume. The separations and angles between atoms in space can be obtained (measured off) by means of the ruler/protractor supplied; they are impressive in comparisons of enantiomers or diastereoisomers (the latter unfortunately not illustrated). The philosophy of the book—combination of stereoscopic pictures with brief but effective introductory text, is put expertly into practice. It is a pity that the diamond and graphite lattices were not arranged next to each other, that the adamantane structure was not emphasized in the diamond lattice, and that 5α-cholestane was not illustrated alongside the 5β-isomer.

An advantage of stereoscopic pictures over models is clearly that with the former numerous structures can be stored in a small space for examination and comparison. On the other hand, it can be interesting to model parts of the stereoscopic structures so as to view them from all sides.

The only "shortcoming" of the book is that it is limited largely to inorganic structures; the organic chemistry section is only three pages long and contains only two illustrative blocks, even if interesting ones. The chapter on natural products contains only 5β-cholestane; it is precisely complicated molecules that exceed the capacity of a model kit or cause much trouble, and here the advantage of stereoscopic pictures would be really evident. How impressive it would be to see in three dimensions (with symmetry relationships), for example staggered biphenyls, cumulenes and acetylenes of various lengths (with their π-electron distributions), spiro compounds, twistane enantiomers, asteranes, propellanes, triptycene, rotaxanes, catenanes, sterically strained and spatially hindered molecules, conformational changes on transition from ligands to complex, topomerization processes (inversion at nitrogen, bull-

[*] Cf. Angew. Chem. Int. Ed. Engl. 5, 326 (1966).

valene, hypostrophene, *etc.*), packing in organic crystal lattices, chiral natural products, carbohydrates, and the primary, secondary, and tertiary structures of peptides. The *meso/d,l-*, *erythro/threo-*, and *(R,S)*-notation also for chiral axes and planes could be ideally introduced. And it would be of great interest to have a section on biochemical structures, *e.g.* nucleic acid helices, hormones, and enzymes.

Since stereochemistry combines specialist areas from the whole of chemistry, there arises, on the basis of this book, a desire for a complete work with a similar title and in similar style which, based on the main types of bonding, should include both organic chemistry and biochemistry.

The book is reasonably priced and deserves wide distribution.

Fritz Vögtle [NB 367 IE]

The Hydrogen Bond. Recent Developments in Theory and Experiment. (3 volumes). Edited by *P. Schuster, G. Zundel* and *C. Sandorfy*. North-Holland Publishing Company, Amsterdam—New York 1976, 1st edit., *ca.* 1520 pp., bound, 3 vols. together $ 173.75.

The forty authors of this volume have attempted collectively to review our present state of knowledge of the hydrogen bond. After an introduction that touches on the field of H-bonding in excited molecules *(E. Lippert)*, the first volume (Theory) begins with a well-rounded treatise on energy hypersurfaces, in which the various approximation methods are carefully compared *(P. Schuster)*. Four articles are devoted to dynamics: these treat the one-dimensional motion of the proton in the double minimum potential *(J. Brockmann)*, coupling of several such tunnelling protons *(W. Weidemann)*, coupling of the proton motion to other nuclear vibrations in the strong-coupling approximation *(G. L. Hofacker et al.)*, and finally the direct solution of motions on two-dimensional energy surfaces *(P. Janoschek)*; here one misses a critical comparison of these various methods of consideration. The volume ends with treatment of the statistics of H-bonds in ice and water *(J. W. Perram)*.

Volume 2 (Structure and Spectroscopy) deals first with the geometry of the H-bond, as obtained from X-ray and neutron diffraction in solids *(I. Olovsson et al., Th. F. Kötzle* and *M. S. Lehmann)*, as well as with additional spectroscopic aspects concerning the angular dependence *(W. A. P. Luck)*. Recent information on the hydrogen stretching vibration is reviewed in detail *(D. Hadzi* and *S. Bratos)*, anharmonicity being treated separately *(C. Sandorfy)*. The peculiar continuum absorption in the infrared is discussed thoroughly *(G. Zundel)*, whereas little space is devoted to long-wave IR spectroscopy *(W. G. Rothschild)*. Two articles on nuclear resonance spectroscopy with reference to chemical shifts and quadrupole coupling complete the second volume *(E. E. Tucker* and *E. Lippert, R. Blinc)*.

The third volume (Dynamics, Thermodynamics and Special Systems) contains, in the section on dynamics, a pithy review of nuclear magnetic relaxation in liquid H-bonding systems *(H. G. Hertz* and *M. D. Zeidler)*. In addition, the less common incoherent neutron scattering is considered *(J. A. Jaik)*. The somewhat disconnected article on dielectric measurements does not contain any discussion of dielectric relaxation *(L. Sobzyk, H. Engelhardt* and *K. Bunzl)*. Treatment of matrix isolation spectroscopy *(H. E. Hallam)* and ferroelectrics *(V. H. Schmidt, H. Stiller)* is followed by a section on thermodynamics, containing a clear exposition of calorimetry and the connection between thermodynamic and spectroscopic measurements *(A. D. Sherry)* and a report on vapor pressure measurements *(H. Wolff)*. H-Bonding in adsorbates on silicon oxide and aluminum oxide is described at some length *(H. Knözinger)*. The third volume closes with a consideration of H-bonds in water *(W. A. P. Luck)* and a collection of data on the H-bonding in the various modifications of ice *(E. Whalley)*.

The individual articles vary greatly in type of presentation: some are pure literature reviews, some are detailed original work, and some are clear characterizations of a certain field. The review as a whole suffers greatly from the division into more than two dozen articles, although most of the articles are very satisfactory in their class. The work nevertheless adds up to an impressive collection of the literature up to about 1974, and one may await hopefully the planned continuation dealing with biological aspects; there, however, a better accord between fewer authors on content and presentation of both theory and experiment is desirable.

The three volumes must be commended to all who deal in any way with H-bonding, in particular to workers at Institutes where physicochemical research on hydrogen-bonding is in progress. They cannot, however, be regarded as a substitute for the 16-year old monograph by *Pimentel* and *McClellan*, and thus the reviewer hopes that one of the authors will find the courage and time to contract the contents of the collection in conherent form to a quarter of its length.

Peter Fromherz [NB 368 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Ammonia, Part III. Edited by *A. V. Slack* and *G. R. James*. Vol. 2 of "Fertilizer Science and Technology Series". Edited by *A. V. Slack*. Marcel Dekker, New York 1977. xv, 459 pp., bound, SFrs. 222.—.—ISBN 0-8247-6188-X

Topics in Phosphorus Chemistry, Vol. 8. Edited by *E. J. Griffith* and *M. Grayson*. John Wiley & Sons, New York 1976. viii, 664 pp., bound, $ 52.00.—ISBN 0-471-32789-1

Conservation of Resources. A Symposium Held at the University of Glasgow, 5th—9th April, 1976. Organised by The Royal Institute of Chemistry and The Industrial Division of the Chemical Society. The Chemical Society, London 1976, Special Publication No. 27. ix, 245 pp., paper, £ 6.00.—ISBN 0-85186-208-X

Versuchsauswertung. Presentation and evaluation of experimental results in science and technology. For students of all natural sciences and technical disciplines. By *R. H. Leaver* and *T. R. Thomas*. Friedr. Vieweg & Sohn, Wiesbaden 1977. v, 125 pp., paper, DM 17.80.—ISBN 3-528-03020-8

Analysis of Drugs of Abuse. By *E. Berman*. From the series "Heyden International Topics in Science". Edited by *L. C. Thomas*. Heyden, London 1977. x, 80 pp., bound, £ 5.50.—ISBN 0-85501-226-9

Zur Desaktivierung des katalytischen Einzelkorn- und Festbettreaktors. By *W. Klose*. From the series "reprotext". Verlag Chemie, Weinheim 1977. 169 pp., paper, DM 44.00.—ISBN 3-527-25715-2

Organic Reaction Mechanisms 1975. An Annual Survey Covering the Literature Dated December 1974 Through November 1975. Edited by *A. R. Butler* and *M. J. Perkins*. John Wiley & Sons, London 1977. 623 pp., bound, £ 27.50.—ISBN 0-471-01864-3

Liquid State Chemical Physics. By *R. O. Watts* and *I. J. McGee*. John Wiley & Sons, New York 1976. xiii, 334 pp., bound, $ 30.00.—ISBN 0-471-91240-9

Molecular Structure by Diffraction Methods, Vol. 4. Senior Reporters: *G. A. Sim* and *L. E. Sutton*. The Chemical Society, London 1976. xiv, 439 pp., bound, £ 28.50.—A volume in the series "Specialist Periodical Reports".—ISBN 0-85186-537-2

Fourier Transform NMR Techniques: A Practical Approach. By *K. Müllen* and *P. S. Pregosin*. Academic Press, London 1976. x, 149 pp., bound, £ 6.80.—ISBN 0-12-510450-2

Specialty Steels. Recent Developments. By *G. B. Rothenberg*. No. 83 of "Chemical Technology Reviews". Noyes Data Corporation, Park Ridge 1977. xi, 270 pp., bound, $ 39.00.—ISBN 0-8155-0649-X

Amino-acids, Peptides and Proteins, Vol. 8. Senior Reporter: *R. C. Sheppard*. The Chemical Society 1976. xvii, 504 pp., bound, £ 28.00.—A volume in the series "Specialist Periodical Reports".—ISBN 0-85186-074-5

Laser und ihre Anwendungen. Eine Einführung. By *Zs. Náray*. Volume 31 of "Technisch-physikalischen Monographien". Edited by *P. Görlich*. Akad. Verlagsgesellschaft Geest & Portig, Leipzig 1976. xi, 311 pp., bound, *ca.* DM 59.—.

Statistische Methoden. Ein Soforthelfer. By *L. Sachs*. Springer-Verlag, Berlin 1976. 3rd, revised edition, xiii, 105 pp., paper, DM 9.80.—ISBN 3-540-07824-X

Carbonium Ions, Vol. V: Miscellaneous Ions, Theory, and Structure. Edited by *G. A. Olah* and *P. von R. Schleyer*. From the series "Reactive Intermediates in Organic Chemistry". Edited by *G. A. Olah*. John Wiley & Sons, New York 1977. xii, 2491 pp., bound, $ 50.00.—ISBN 0-471-65342-X

Kristallographie. Eine Einführung für Naturwissenschaftler. By *W. Borchardt-Ott*. Vol. 180 of "Heidelberger Taschenbücher". Springer-Verlag, Berlin 1976. ix, 188 pp., paper, DM 19.80.—ISBN 3-540-07771-5

Reaction Mechanisms in Organic Chemistry. By *F. Badea*. Abacus Press, Tunbridge Wells 1977. 701 pp., bound, £ 18.85.—ISBN 0-85626-002-9

Gmelin Handbuch der Anorganischen Chemie. Springer-Verlag, Berlin 1977, 8th edition.
Main work, System No. 14: Kohlenstoff. Part D: Die Verbindungen. xxvi, 271 pp., bound, DM 595.00.—ISBN 3-540-93330-1
Supplement, Volume 32: Schwefel-Stickstoff-Verbindungen. Part 1: Verbindungen mit Schwefel der Oxidationszahl VI. xii, 268 pp., bound, DM 531.00.—ISBN 3.540-93328-X
Supplement, Volume 39: Transurane. Part B 3: Binäre Legierungssysteme 2. xxviii, 275 pp., bound, DM 617.00.—ISBN 3.540-93329-8
Index: Formula Index, Vol. 5: C_8—C_{12}. xv, 268 pp., bound, DM 601.00.—ISBN 3-540-93331-X

Römpps Chemie-Lexikon, Vol. 6: T—Z. By *O.-A. Neumüller*. Franckh'sche Verlagsbuchhandlung Stuttgart 1977. Seventh new and revised edition, pp. 3444—4088, bound, DM 160.00.—ISBN 3-440-03856-4

The Chemistry of Functional Groups. Edited by *S. Patai*. Supplement A: The Chemistry of Double-Bonded Functional Groups. Part 1 and 2. John Wiley & Sons, London 1977. Part 1: xv, 651 pp., bound, £ 29.00.—ISBN 0-471-99461-2; Part 2: xv, 1343 pp., bound, £ 29.50.—ISBN 0-471-99465-0—ISBN (Set) 0-471-66940-7

Struktur—Stoff—Reaktion. Organische Chemie. By *H. R. Christen*. Diesterweg Salle, Frankfurt/Verlag Sauerländer, Aarau 1976. vii, 266 pp., bound, DM 16.80.—ISBN 3-425-05402-6 (Diesterweg Salle); 3-7941-1374-1 (Sauerländer)

Pesticides in the Environment, Vol. 3. Edited by *R. White-Stevens*. Marcel Dekker, New York 1977. xiv, 366 pp., bound, SFrs. 125.00.—ISBN 0-8247-6192-8

Inorganic Chemistry of the Transition Elements, Vol. 5. Senior Reporter: *B. F. G. Johnson*. The Chemical Society, London 1977. xvi, 524 pp., bound, £ 29.00.—ISBN 0-85186-540-2—A volume in the series "Specialist Periodical Reports".

Stereoselective Reductions. Edited by *M. P. Doyle* and *Ch. T. West*. Vol. 6 of "Benchmark Papers in Organic Chemistry". Edited by *C. A. Vander Werf*. Dowden, Hutchinson & Ross, Stroudsburg 1977. xviii, 419 pp., bound, $ 38.00.—ISBN 0-87933-249-2

Elektrokinetische Grenzflächenvorgänge. By *J. Weigl*. A volume in the series "reprotext". Verlag Chemie, Weinheim 1977. 196 pp., paper, DM 36.00.—ISBN 3-527-25718-7

Vibrational Spectra of Organometallic Compounds. By *E. Maslowsky, Jr.* John Wiley & Sons, New York 1977. xii, 528 pp., bound, $ 31.70.—ISBN 0-471-58026-0

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3, P.O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 6
June 1977
Pages 339–422

Recent Applications of α-Metalated Isocyanides in Organic Synthesis

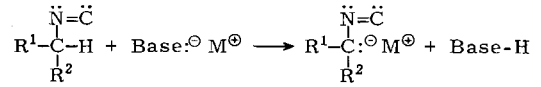
By Ulrich Schöllkopf[*]

Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

Being both nucleophilic and electrophilic, α-metalated isocyanides can add to polar double bonds, forming heterocycles. They are also synthons for α-metalated primary amines. This article describes recent or improved procedures for their use in organic synthesis: 1) In heterocyclic syntheses to give 2-oxazolines, 2-imidazolines, 2-thiazolines, oxazoles and oligooxazoles, thiazoles, triazoles, imidazolinones, pyrroles, 5,6-dihydro-1,3-oxazines and -thiazines, and (*via* cycloaddition with nitrones) 2-imidazolidinones. 2) In the field of formylaminomethylenation, for example transformation of estrone methyl ether and a keto sugar into the corresponding α-formylaminoacrylic esters, and the conversion of aldehydes and ketones by 3- and 4-pyridylmethyl isocyanides into *N*-(1-pyridyl-1-alkenyl)formamides and their hydrolysis to 3- and 4-acylpyridines. 3) In connection with the use of α-metalated isocyanides as synthons for α-metalated primary amines, the author demonstrates how they may be used for preparation of 1,2- and 1,3-amino alcohols, 1,2-diamines, 2,3-diaminoalkanoic acids and for synthesis of higher amino acids starting from simple amino acids.

1. Introduction

The activating effect of the cyano group on neighboring C—H bonds has been known for nearly a century[1]. However, it was only in 1968 that *Schöllkopf* and *Gerhart*[2] discovered that alkyl isocyanides *(1)* can be anionized (metalated) in the α-position, albeit not quite so readily as alkyl cyanides.

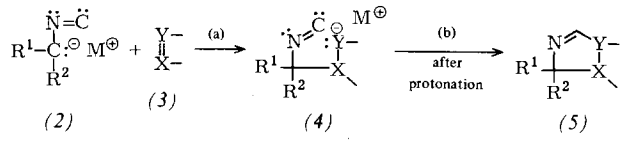


(1) *(2)*

Metalation (anionization) is accomplished with the usual bases employed in carbanion chemistry such as butyllithium (with and without complexing agent), potassium *tert*-butoxide, sodium methoxide, sodium hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or triethylamine; the precise choice depends upon the substituents R^1 and/or R^2. The α-metalated isocyanides *(2)* are not isolated but immediately subjected to further reaction in the same reaction vessel. Any alkyl isocyanide *(1)* can be metalated provided that its parent hydrocarbon is as acidic or more acidic than methane. *sec*-Alkyl isocyanides without activating substituents cannot be metalated; cyclopropyl and cyclobutyl isocyanide are exceptions to this rule.

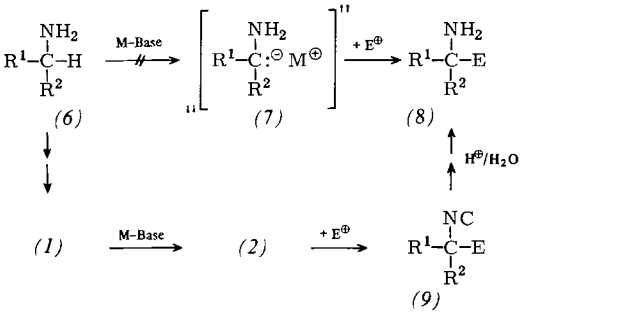
The significance of α-metalated isocyanides *(2)* in organic synthesis[3] is due, on the one hand, to the ambivalent nature of these reagents. They contain a nucleophilic center, the metalated (anionized) carbon atom, which can add to polar multiple bonds *(3)* [according to (a)], and an electrophilic center, the isocyanide carbon atom, which permits cyclization of the adducts *(4)* [according to (b)] to form heterocycles of type *(5)* (cf. Scheme 1).

[*] Prof. Dr. U. Schöllkopf
Organisch-chemisches Institut der Universität
Tammannstrasse 2, D-3400 Göttingen (Germany)



Scheme 1. Synthesis of heterocycles *(5)* from α-metalated isocyanides *(2)* and compounds with polar multiple bonds *(3)*.

On the other hand, the α-metalated isocyanides *(2)* are synthons for the (hypothetical) α-metalated primary amines "*(7)*" and permit chain extension of primary amines by electrophiles $E^{\oplus}$ [*(6)* → *(8)*]. Primary amines *(6)* have insufficient CH acidity for direct metalation and/or are preferentially metalated at the nitrogen. Thus synthetic equivalents (synthons) are required for "*(7)*", in which the amino group bears a mask which is readily introduced at the amine stage, is stable to bases, has an acidifying effect, and can be removed with ease after chain extension[4]. A mask largely fulfilling these requirements is the carbon atom of the isocyanide group. Amines *(6)* can be readily transformed into isocyanides *(1)*, either *via* the *N*-formyl derivatives[5] or directly by the Mąkosza variant of the long-known carbylamine reaction[6]. The isocyanide group is sufficiently stable towards bases and exerts an acidifying effect. After reaction of the metalated isocyanide *(2)* with $E^{\oplus}$, the adduct *(9)* can easily be converted into the amine *(8)* by acid hydrolysis (cf. Scheme 2).



Scheme 2. α-Metalated isocyanides *(2)* as synthons for α-metalated primary amines "*(7)*". Chain elongation of the amines *(6)* to *(8)*.

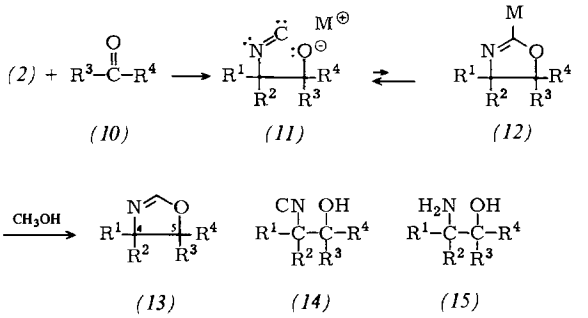
According to a toxicological study performed at Bayer AG[7], isocyanides appear to be practically non-toxic towards warm-blooded animals, with few exceptions. Nevertheless, all operations should be performed in a well-ventilated fume hood and all equipment washed with acids immediately after use. Both these measures are recommended if only because of the unpleasant odor of the lower alkyl isocyanides. Higher alkyl isocyanides, diisocyanides, or isocyanides containing a further functional group are largely or completely odorless.

Since the applications of α-metalated isocyanides *(2)* were summarized in 1974[3], the present article considers only selected examples and/or recent developments.

2. Syntheses of Heterocycles According to Scheme 1

2.1. 2-Oxazolines

On reaction with aldehydes and ketones *(10)*, α-metalated isocyanides *(2)* afford 2-oxazolines *(13)*[8]. Intermediates are known to be the carbonyl adducts *(11)* and the tautomeric 2-metalated 2-oxazolines *(12)* which are transformed into 2-oxazolines *(13)* on addition of water or (preferably) methanol, *i.e.* on alkaline workup. The mobile tautomeric equilibrium *(11)* ⇄ *(12)* lies almost entirely on the left-hand side. Addition of glacial acetic acid immediately after that of the carbonyl component leads to 2-isocyano alcohols *(14)*[9]. Protonation of *(11)* is reversible in alkaline medium, explaining why 2-oxazolines *(13)* are obtained under conditions of thermodynamic product control.

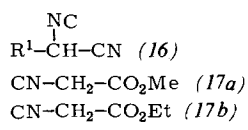


The advantage of this oxazoline synthesis consists in the linkage of the C-4—C-5 bond during the reaction. In contrast, conventional oxazoline syntheses start from 2-amino alcohols *(15)*, which are frequently difficult to obtain. Moreover, transformation of 2-amino alcohol into 2-unsubstituted 2-oxazoline is problematic[10]. Since 2-oxazolines *(13)*, as imino ethers, are easily hydrolyzed, our synthesis is recommended for the preparation of 2-amino alcohols *(15)*; this class of compounds commands interest owing to its documented or potential biological activity.

Hydrolysis of *(13)* generally proceeds readily with conc. HCl in methanol at room temperature[8]. However, some amino alcohols *(15)* eliminate water under these conditions or rearrange. In such cases it is recommended that the oxazolines *(13)* first be transformed in neutral or basic medium into the *N*-(β-hydroxyalkyl)formamides (heating in aqueous methanol, possibly in the presence of triethylamine) which are then deformylated. Warming with 2 mol of *p*-toluenesulfonic acid monohydrate in acetone or dichloromethane has proved convenient as a method for mild deformylation; *(15)* is precipitated as the ammonium toluenesulfonate—alternatively the compound may be warmed with 2 N caustic soda.

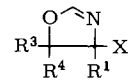
Mention should be made of some specific examples involving functionalized isocyanides. 1-Isocyanoalkyl cyanides *(16)* yield (in dichloromethane with triethylamine as base) 2-oxazoline-4-carbonitriles *(20a)*[11], and the isocyanoacetic esters *(17a)* and *(17b)* give (in ethanol with sodium cyanide as catalyst) the 2-oxazoline-4-carboxylic esters *(20b)* and *(20c)*, respectively, the precursors of serines *(15)*, $R^2 = CO_2H$[12], with diethyl isocyanomethanephosphonate *(18)* (under the same conditions) diethyl 2-oxazoline-4-phosphonate *(20d)*[13], and with *p*-toluenesulfonylmethyl isocyanide *(19)*[14] (according to the "cyanide method" or in methanol with potassium carbonate as base) 4-toluenesulfonyl-2-oxazolines *(20e)*[15,16], which can react further to give oxazoles by elimination of toluenesulfinate if $R^4 = H$[16]. Use of thallium ethoxide as base permits isolation of 4-ethoxy-2-oxazolines *(20f)*—formed by subsequent nucleophilic exchange of toluenesulfinate for ethoxide—which can be hydrolyzed to the otherwise somewhat inaccessible 2-hydroxyaldehydes

(21)[17]. The α-metalated *p*-toluenesulfonylmethyl isocyanide *(19)* is not only an ambivalent reagent but also contains a nucleofugal leaving group, thus considerably extending its scope (cf. also Sections 2.4 and 4.3).

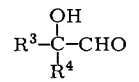


(16)

$CN-CH_2-CO_2Me$ *(17a)*
$CN-CH_2-CO_2Et$ *(17b)*
$CN-CH_2-PO(OEt)_2$ *(18)*
$CN-CH_2-SO_2-C_6H_4-CH_3(p)$ *(19)*



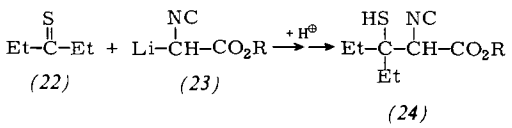
(20a), X = CN, R^1 = Alkyl
(20b), X = CO_2Me, R^1 = H
(20c), X = CO_2Et, R^1 = H
(20d), X = $PO(OEt)_2$, R^1 = H
(20e), X = $SO_2-C_6H_4-CH_3(p)$, R^1 = H
(20f), X = OEt, R^1 = H



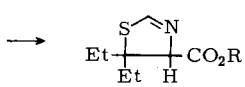
(21)

2.2. 2-Thiazolines

Diethyl thioketone *(22)* reacts with lithioisocyanoacetic esters *(23)* (in tetrahydrofuran at −60 °C) to form 3-ethyl-2-isocyano-3-mercaptopentanoic esters *(24)* which cyclize to give 5,5-diethyl-2-thiazoline-4-carboxylic esters *(25)*[18]. The synthesis should be applicable to other thioketones, the main difficulty probably lying in the preparation and manipulation of the (generally) unstable thioketones. 2-Thiazolinecarboxylic esters of type *(25)* command interest as starting compounds for the synthesis of structural variants of penicillin (cf. also Section 4.2).



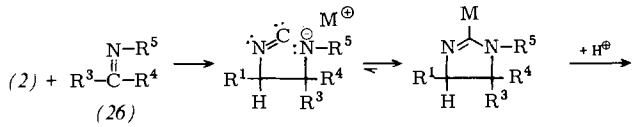
(22) *(23)* *(24)*



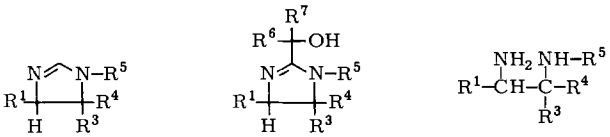
(25) *(a)*, R = Et
(b), R = $PhCH_2$

2.3. 2-Imidazolines

α-Metalated isocyanides *(2)* can also add to the carbonyl-analogous azomethine group. Thus lithiomethyl and lithiobenzyl isocyanide react with Schiff bases *(26)* (in tetrahydrofuran at −60 °C) to give 2-imidazolines *(29)*[19]. Methyl isocyanoacetate *(17a)* reacts (in methanol) at room temperature to form methyl 2-imidazoline-4-carboxylates *(29a)*, $R^1 = CO_2Me$, the amine present in trace amounts in azomethine presumably acting as anionizing base[19].—In contrast to the case of *(11)*, the analogous intermediate *(27)* cannot be detected in this reaction. The tautomeric equilibrium appears to lie predominantly on the side of the 2-metalated imidazoline *(28)*. This compound can be trapped—when working in aprotic media—with ketones, for example, to yield 2-hydroxymethyl derivatives *(30)*[19].



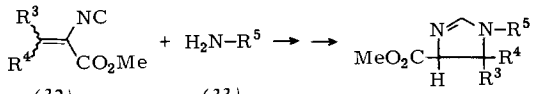
(2) + *(26)* → *(27)* ⇌ *(28)*



(29) *(30)* *(31)*

(29a), $R^1 = CO_2Me$

Alternatively, the methyl 2-imidazoline-4-carboxylates *(29a)* can be obtained from 2-isocyanoacrylic esters *(32)* (cf. Section 4.2) by addition of primary amines *(33)* or ammonia (in methanol at room temperature)[19]. The 1-unsubstituted 2-imidazole-4-carboxylic esters *(29b)* are readily accessible in this way.



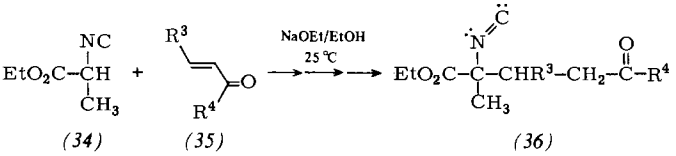
(32) *(33)*

(29a), R^5 = Alkyl
(29b), R^5 = H

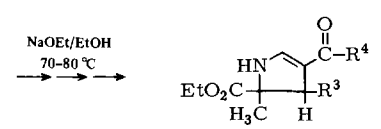
2-Imidazolines of type *(29)* warrant interest on account of their proven or potential pharmacological activity[20]. They are usually synthesized by ring closure from 1,2-diamines of type *(31)*; however, the latter are often difficult to prepare. Furthermore, ring closure to give 2-unsubstituted 2-imidazolines is problematical[20]. Since imidazolines are readily susceptible to acid hydrolysis, being cyclic amidines, this synthesis is also suitable for preparation of 1,2-diamines *(31)* or 2,3-diaminoalkanoic acids (α,β-diamino acids) *(31)*, $R^1 = CO_2H$[21], which are likewise biologically active or potentially so.

2.4. 2-Pyrrolines and Pyrroles

Reaction of, for example, ethyl isocyanopropionate *(34)* with α,β-unsaturated carbonyl compounds *(35)*, at room temperature under the conditions of the Michael addition, affords ethyl 2-isocyano-2-methyl-5-oxoalkanoates *(36)*[22], which cyclize to the pyrrolines *(37)* on heating to 70—80 °C, after abstraction of a proton from an α position to the carbonyl group[22]. Other Michael acceptors, such as acrylonitrile, react similarly[23].

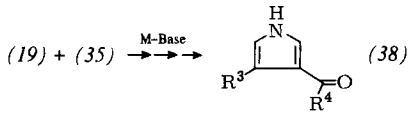


(34) *(35)* *(36)*

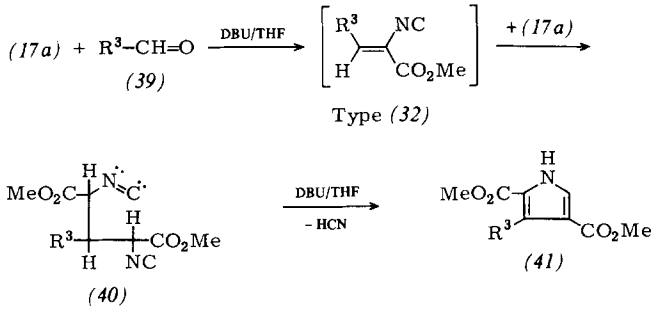


(37)

Particular preparative interest attaches to a synthesis developed by *van Leusen et al.*[24] for 3-acyl-substituted pyrroles of type *(38)* by reaction of *p*-toluenesulfonylmethyl isocyanide *(19)* with activated olefins *(35)* in glycol dimethyl ether/dimethyl sulfoxide with sodium hydride as base[24,25]. Michael addition and cyclization are followed by elimination of toluenesulfinate and tautomerization. 2-Unsubstituted 3-acylpyrroles are not readily accessible by conventional methods because Friedel-Crafts acylation occurs preferentially in position 2 of pyrroles.

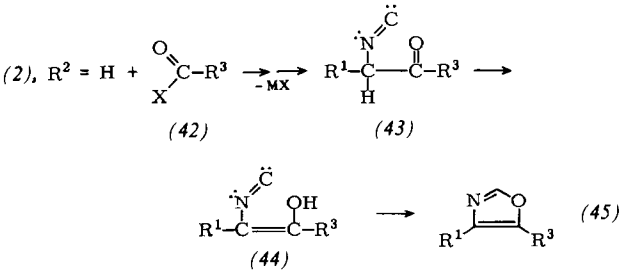


According to *Matsumoto et al.*[26], dimethyl 2,4-pyrroledicarboxylate *(41)* is formed on reaction of methyl isocyanoacetate *(17a)* (two equivalents) and an aldehyde *(39)* (one equivalent) in tetrahydrofuran in the presence of DBU. The course of this reaction, which was previously observed by *Schöllkopf* and *Schröder*[27] is still unclear in its details. Methyl α-isocyanoacrylate *(31)* is proposed as intermediate[26], and is assumed to give the pyrroledicarboxylate *(41)* *via* a Michael adduct *(40)*. The postulated methyl isocyanoacrylate *(32)* could neither be detected by spectroscopy nor trapped by addition of other nucleophiles; it would hardly be expected under these conditions (cf. Section 4.2), and yet control experiments showed that it does indeed give the esters *(41)* on reaction with methyl isocyanoacetate *(17a)* in the presence of DBU[26].



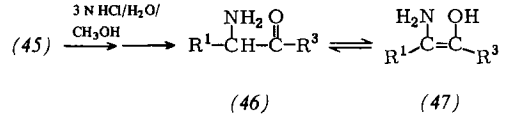
2.5. Oxazoles, Imidazoles, Thiazoles, and 2-Imidazolin-5-ones

Oxazoles *(45)* are formed on treatment of α-metalated isocyanides *(2)*, $R^2 = H$, with acylating agents *(42)* such as acyl chlorides, esters, *N*,*N*-dialkylamides, or imidazolides[28-30]. The intermediate α-isocyanoketones *(43)* are not isolable; they cyclize *via* the enols *(44)* to give oxazoles *(45)* on workup.

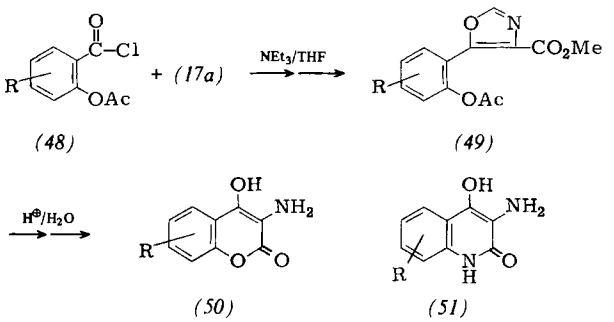


In some cases—especially with acyl chlorides—two equivalents of the metalated isocyanide *(2)* are required because the strongly acidic isocyano ketone *(43)* protonates unreacted *(2)*. However, an optimum choice of acylating agent, metalating agent, solvent, and reaction conditions also leads to good yields of oxazoles *(45)* when *(2)* and *(42)* are used in a ratio of 1 : 1[28-30].

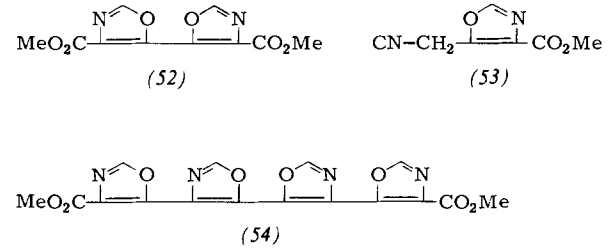
Oxazoles are valuable synthetic intermediates[31]. Their acid hydrolysis affords α-amino ketones *(46)* which are in equilibrium with α-amino enols *(47)*.



3-Amino-4-hydroxycoumarin derivatives *(50)*, which are key components for the preparation of bactericidal compounds, have been synthesized by *Matsumoto et al.*[32]. Their approach was to treat 2-chloroformylphenyl acetate *(48)* with methyl isocyanoacetate *(17a)* (in tetrahydrofuran with triethylamine as base) in order to obtain the oxazole derivatives *(49)* which yield the coumarin *(50)*[32] in a straightforward reaction on acid hydrolysis. 3-Amino-4-hydroxy-2(1*H*)-quinolinones *(51)* were synthesized in analogous fashion[33].

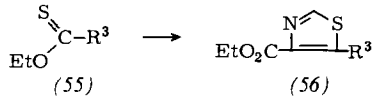


Not only monocyclic heterocycles can be synthesized with α-metalated isocyanides, but also sequences of heterocycles. Thus methyl isocyanoacetate *(17a)* and oxalyl diimidazolide—prepared *in situ* from oxalyl dichloride and imidazole[34]—react smoothly (in tetrahydrofuran with triethylamine as base) to give dimethyl 5,5′-bioxazole-4,4′-dicarboxylate *(52)*, while lithiated methyl 5-isocyanomethyl-4-oxazolecarboxylate *(53)*, the self-condensation product of methyl isocyanoacetate *(17a)*[30,35], yields dimethyl 5,4′:5′,5″:4″,5‴-quateroxazole-4,4‴-dicarboxylate *(54)* with oxalyl dichloride.

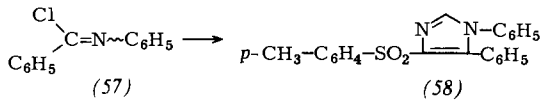


α-Metalated isocyanides *(2)* also react with hetero-analogous acylating agents. *Hartmann et al.*[36] obtained ethyl 4-thiazolecarboxylates *(56)* from thionic esters *(55)* and ethyl isocyanoacetate *(17b)* (in methanol with potassium cyanide as catalyst), and *van Leusen et al.*[37] prepared 1,5-diphenyl-4-(*p*-

toluenesulfonyl)imidazole *(58)* from α-metalated *p*-toluenesulfonylmethyl isocyanide *(19)* and the imidoyl chloride *(57)*.

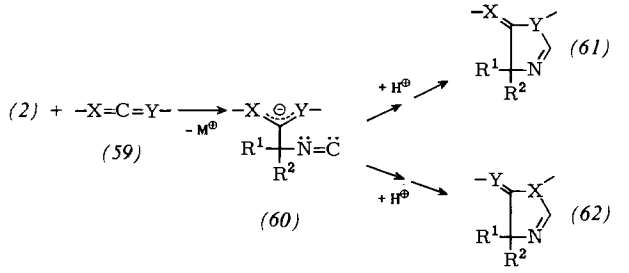


(55) *(56)*



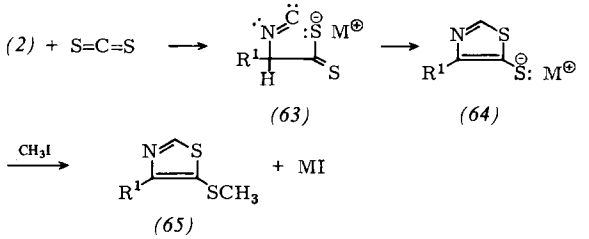
(57) *(58)*

Reactions of α-metalated isocyanides *(2)* with heteroallenes *(59)* have not yet been studied systematically. If $X \neq Y$, the intermediates *(60)* can cyclize to the heterocycles *(61)* or *(62)*.



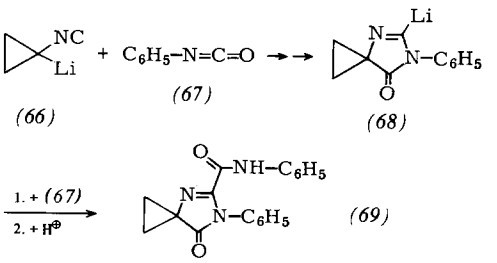
(59) *(60)* *(61)* *(62)*

α-Metalated isocyanides *(2)*, $R^2 = H$, react with carbon disulfide *via* the intermediates *(63)* to give thiazolethiolates *(64)*, which afford 5-(methylthio)thiazoles *(65)* with methyl iodide[38]. Other 5-(alkylthio)thiazoles should be accessible in analogous manner.



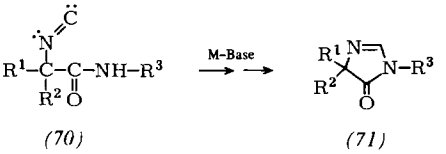
(63) *(64)* *(65)*

Reaction of 1-lithiocyclopropyl isocyanide *(66)* (in tetrahydrofuran at −65 °C) with phenyl isocyanate *(67)* gives mainly the bisadduct *(69)*[39] because the intermediate *(68)* quickly reacts with remaining isocyanate *(67)*.



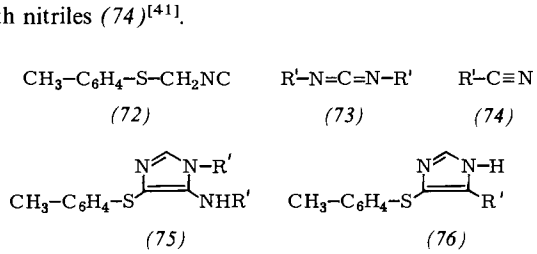
(66) *(67)* *(68)* *(69)*

2-Unsubstituted 5-imidazolinones of type *(71)* are formed, however, when 2-isocyanoalkanamides *(70)*—prepared from methyl 2-isocyanoalkanoates and amines with *p*-toluenesulfonic acid as catalyst[40]—are subjected to base-induced cyclization[40].



(70) *(71)*

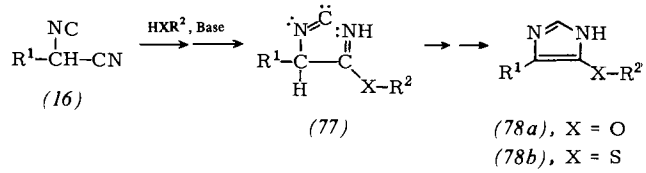
α-Metalated (4-methylphenylthio)methyl isocyanide *(72)* gives 5-amino-4-(4-methylphenylthio)imidazoles *(75)* with carbodiimides *(73)*; and 4(5)-(4-methylphenylthio)imidazoles *(76)* with nitriles *(74)*[41].



(72) *(73)* *(74)* *(75)* *(76)*

3. Other Heterocyclic Syntheses

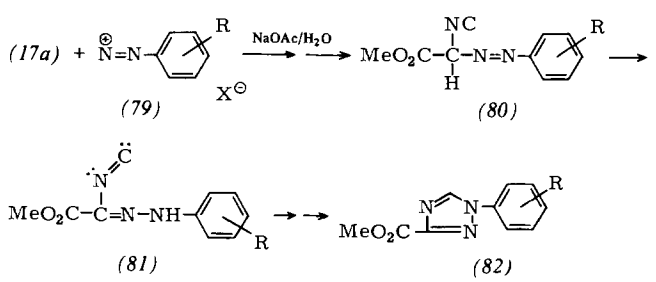
Alkyl isocyanides of type *(4)* containing a nucleophilic group Y which are able to undergo heterocyclization according to Scheme 1 (b), are not only accessible *via* Scheme 1 (a). It is self-evident that α-metalated isocyanides *(2)* are not essential for their preparation. Examples are provided by the synthesis of imidazolinones *(71)* by ring closure of the isocyano carboxamides *(70)* or cyclization of 2-iminoalkyl isocyanides *(77)*, formed by addition of alcohols or thiols (in the presence of basic catalysts) to isocyanonitriles *(16)*, to give the novel 5(4)-alkoxy- or 5(4)-(alkylthio)imidazoles *(78)*[42].



(16) *(77)* *(78a)*, X = O; *(78b)*, X = S

3.1. Triazoles

Like methyl cyanoacetate, methyl α-isocyanoacetate *(17a)* can also be coupled to arenediazonium ions *(79)* (in aqueous methanol with sodium acetate as base). The initially formed azo compounds *(80)* cyclize *via* the hydrazones *(81)* to give methyl 1-aryl-1*H*-1,2,4-triazole-3-carboxylates *(82)*[43].

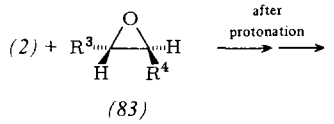


(17a) *(79)* *(80)* *(81)* *(82)*

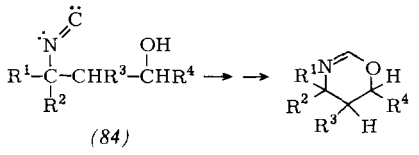
3.2. 5,6-Dihydro-4*H*-1,3-oxazines and -thiazines

Expectedly, α-metalated isocyanides *(2)* add to epoxides *(83)*, giving 3-hydroxy-alkyl isocyanides *(84)* which can be cyclized[44] to 5,6-dihydro-4*H*-1,3-oxazines *(85)*, *e.g.* by warming with cuprous oxide in benzene[44]. The additions *(2)* + *(83)* → *(84)* take place in accord with the pattern valid

for nucleophilic epoxide cleavage; *i.e.* the sterically less hindered carbon atom is substituted with inversion[44].



(83)

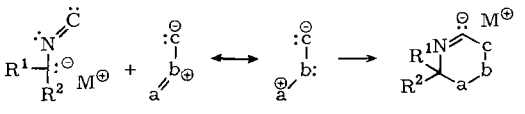


(84) *(85)*

Dihydrothiazines [S in place of O in *(85)*] are accessible analogously[45], although some episulfides [S in place of O in *(83)*] are attacked by α-metalated isocyanides *(2)* at sulfur in a reaction which is not entirely unexpected by the organometallic chemist[45].

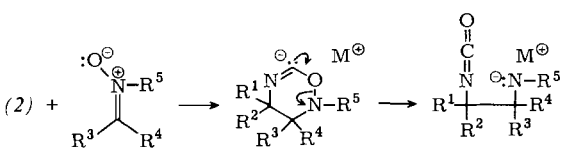
3.3. 2-Imidazolidinones

α-Metalated isocyanides *(2)* are ambivalent reagents. Consequently, they should react with the likewise ambivalent 1,3-dipoles *(86)*[46] to form metalated six-membered heterocycles of type *(87)*.

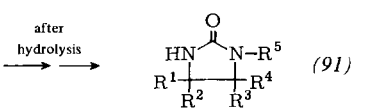


(2) *(86)* *(87)*

Among the numerous 1,3-dipoles[46] we have so far tried only nitrones *(88)*, which we found to give 1-substituted 2-imidazolidinones *(91)*[47]. This shows that cycloaddition to give *(89)* [according to *(2)* + *(86)* → *(87)*] is followed by ring opening to the metalated 2-isocyanato amines *(90)* which undergo straightforward further reaction to form the imidazolidinones *(91)*.



(88) *(89)* *(90)*

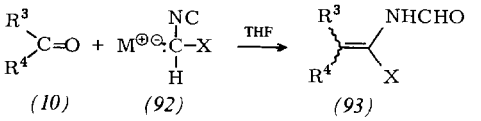


(91)

4. Formylaminomethylenation of Carbonyl Compounds

4.1. General

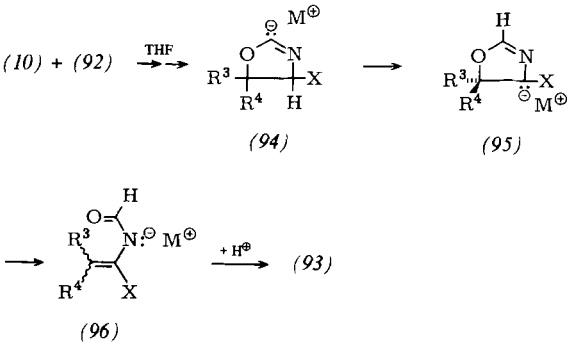
Reaction of α-metalated isocyanides of type *(92)* bearing a relatively strongly acidifying group X on the isocyano-substituted carbon atom with carbonyl compounds *(10)* in an aprotic medium gives *N*-(1-alkenyl)formamides of type *(93)* bearing the group X in the α position (Scheme 3). An oxo oxygen atom is formally replaced by the formylaminomethylene group in this reaction[27].



(10) *(92)* *(93)*

Scheme 3. Formylaminomethylenation of carbonyl compounds. X: substituent exerting a (−M) effect.

Formylaminomethylenation begins (cf. also Section 2.1) with nucleophilic carbonyl addition and formation of the 2-metalated oxazoline *(94)*. This product isomerizes by (probably intermolecular) proton shift from C-4 to C-2, to the oxazolinyl anion *(95)* in which the substituent X stabilizes the negative charge on C-4. Fast electrocyclic ring opening transforms *(95)*—at −70 to 0°C—into the "heteropentadienyl anion" *(96)* which can be isolated as the *N*-alkenylformamide *(93)* after protonation.

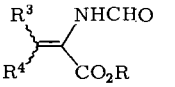


(94) *(95)* *(96)*

The following examples involving three types of α-metalated isocyanides *(92)*—*viz.* metalated isocyanoacetic esters [*(17)*, *i.e.* X = CO_2R], metalated *p*-toluenesulfonylmethyl isocyanide [*(19)*, *i.e.* X = SO_2—C_6H_4—CH_3], and metalated 3- and 4-pyridylmethyl isocyanides [X = 3- or 4-pyridyl]—should provide an indication of the scope of formylaminomethylenation.

4.2. α-Formylaminoacrylic Esters

α-Formylaminoacrylic esters *(97)* are obtained by formylaminomethylenation of aldehydes and ketones *(10)* with isocyanoacetate esters *(17)*. Two procedures have proved especially valuable. In the first one, the ester *(17)* is metalated with potassium *tert*-butoxide in tetrahydrofuran at −70°C; the carbonyl compound *(10)* is added and workup is as usual after warming to room temperature[27]. However, the sterically hindered carbonyl group in 3-methoxyestrone could be formylaminomethylenated in good yield only by refluxing in THF[48]. In the second procedure, sodioisocyanoacetic ester [type *(92)*, X = CO_2R] is generated *in situ* (in tetrahydrofuran) with sodium hydride as base. *(17)* and the carbonyl compound *(10)* are simultaneously added dropwise at 20°C[27,49].

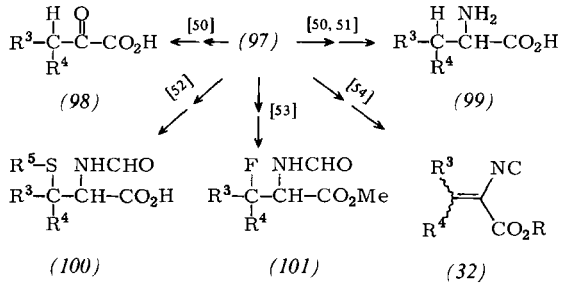


(97a), R = Me
(97b), R = Et

Formylaminomethylenation has several advantages over the classical azlactone procedure of *Erlenmeyer*[50] which gives

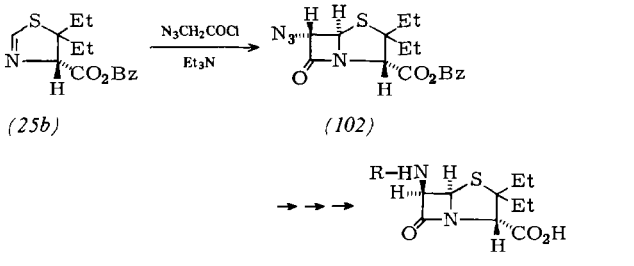
α-acylaminoacrylic acids. Less reactive carbonyl compounds can usually also be formylaminomethylenated under mild conditions and in good yields. Moreover, reaction gives not the acids but the esters which are more valuable for further reactions, and the formyl group can be removed easily and selectively.

Some of the many applications of formylaminoacrylic esters *(97)* are surveyed in Scheme 4.



Scheme 4. Some of the derivatives accessible from α-formylaminoacrylic esters *(97)*. R = Me or Et.

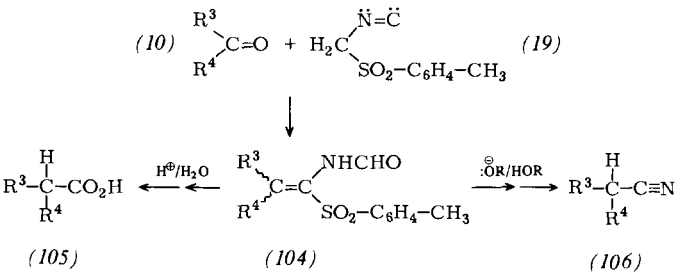
α-Isocyanoacrylic esters *(32)* add nucleophiles with great avidity at their double bond[54]. The addition products can be cyclized to heterocycles with ester groups. Thus, as already mentioned (cf. Section 2.3), reaction with ammonia gives 2-imidazoline-4-carboxylic esters of type *(29b)*[19], and that with hydrogen sulfide gives 5-substituted 2-thiazoline-4-carboxylic esters of type *(25)*[55a] (cf. also Section 2.2), which are of interest as starting compounds for synthesis of modified penicillins. For example, *Claes* and *Vanderhaeghe*[55b] synthesized (±)-2,2-diethyl-6β-phenoxyacetamidopenam-3α-carboxylic acid *(103)*, a structural variant of penicillin V, *via* the 6-azido-2,2-diethylpenamic ester *(102)* from benzyl 5,5-diethyl-2-thiazoline-4-carboxylate *(25b)*.



(103), R = $C_6H_5OCH_2CO$

4.3. *N*-(1-Toluenesulfonyl-1-alkenyl)formamides; Chain Elongation of Ketones

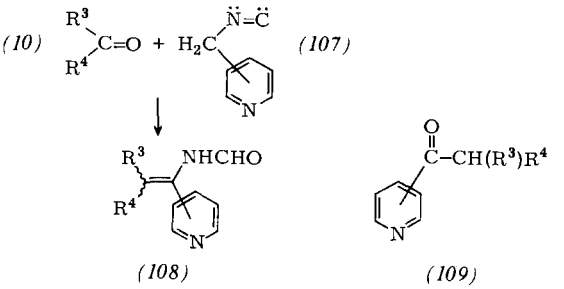
Formylaminomethylenation of ketones *(10)* with *p*-toluenesulfonylmethyl isocyanide *(19)* affords *N*-(1-toluenesulfonyl-1-alkenyl)formamides *(104)*[15]. These compounds can be transformed into the carboxylic acids *(105)*[15] with aqueous acids and into the nitriles *(106)* with alkoxide[56, 57]. This means that formylaminomethylenation with *(19)* solves an important problem of preparative organic chemistry, *i.e.* the straightforward and productive transformation of a ketone *(10)* into the next-higher carboxylic acid *(105)* or the next-higher nitrile *(106)*. Mention should be made of a particularly convenient single-pot process developed by *van Leusen et al.*[56] for the transformation *(10)* → *(106)*.



4.4. *N*-(1-Pyridyl-1-alkenyl)formamides

Since the pyridine ring exerts a comparatively strong electron-attracting effect—and can therefore function as X in *(92)*—aldehydes and ketones *(10)* can be formylaminomethylenated[58] with 3- or 4-pyridylmethyl isocyanides *(107)* to give *N*-(1-pyridyl-1-alkenyl)formamides of type *(108)*. Metalation is again best accomplished with (excess) potassium *tert*-butoxide (in THF as solvent). Reactions of *(107)* can also be conducted in such a way that 4-(3- and 4-(4-pyridyl)-2-oxazolines of type *(13)* are isolated[8]. On acid hydrolysis, the *N*-alkenylformamides *(108)* yield 3- and 4-acylpyridines *(109)*[58]. The procedure should also provide an entry to those pyridyl ketones which are accessible only with difficulty, if at all, by conventional methods.

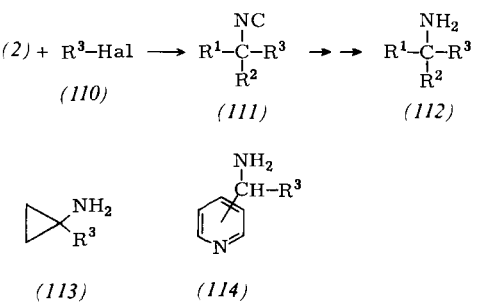
Heteroanalogs of benzyl isocyanide other than *(107)* should also react in the same way.



5. Chain Elongation of Primary Amines According to Scheme 2

5.1. Chain Elongation with Alkylating Agents; Amino Acid Synthesis

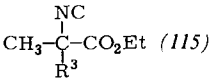
Chain elongation of common primary amines *(6)* with alkyl halides *(110)* as $E^{\oplus}$ to give higher amines *(112)*—as studied for a series of examples[59]—proceeds according to Scheme 2 *via* the metalated isocyanides *(2)*. In this way amines can also be prepared which cannot be obtained otherwise, or only with difficulty. For example, the tertiary cyclopropyl-



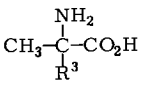
amines *(113)* are accessible *via* cyclopropyl isocyanide *(66)*, H in place of Li, or the 1-(pyridyl)alkylamines *(114)* *via* (pyridyl)methyl isocyanides *(107)*[59].

Reaction of α-metalated 2-isocyanopropionic ester, prepared from the ester *(34)* and potassium *tert*-butoxide or sodium hydride in THF or THF/DMSO[60, 61], with alkyl halides furnishes the higher 2-isocyano-2-methylalkanoic esters *(115)* and thence, by hydrolysis, amino acids[60, 61]. Examples are provided by the synthesis of α-methylphenylalanine *(116)*[60] or α-methylhistidine *(117)*[61b]. In attempts to synthesize optically active α-methyldopa *(118)*, alkylation of optically active menthyl and bornyl α-isocyanopropionate with 3,4-dimethoxybenzyl bromide was investigated. While the product yields were 80—85%, the enantiomeric purity was only 10%[61c].

Predictably, the reaction can also be applied to α-isocyano carboxamides. Thus benzyl 6-isocyanopenicillanate *(119a)* can be transformed, in dimethylformamide *via* the potassium derivative *(119b)* (readily obtained with potassium carbonate), into the compounds *(119c)* alkylated at C-6[62] whose isocyano group can then be converted into the amino group by *p*-toluenesulfonyl hydrate[62].



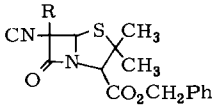
(115)



(116), $R^3 = CH_2-C_6H_5$

(117), R^3 = 4-Imidazolyl

(118), R^3 = 



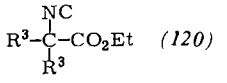
(119a), R = H

(119b), R = K

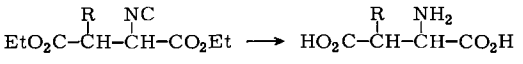
(119c), R = Alkyl

(119d), R = $CH_2-CH_2-CO_2Et$

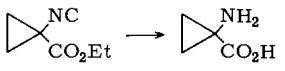
On alkylation of ethyl isocyanoacetate *(17b)* with "small" and/or particularly reactive alkyl halides *(110)*, bisalkylation to give *(120)* predominates[60]; nevertheless, α-halo carboxylic esters give satisfactory yields (in dimethyl sulfoxide with sodium hydride as base) of isocyanosuccinic esters of type *(121)*[63], which furnish aspartic acids *(122)* on hydrolysis[63]. The tendency to undergo double alkylation can be exploited in cycloalkylation, *e.g.* with 1,2-dibromomethane to prepare



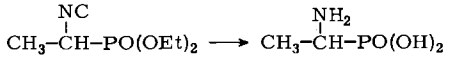
(120)



(121) *(122)*



(123) *(124)*



(125) *(126)*

ethyl 1-isocyano-1-cyclopropanecarboxylate *(123)*[60], the precursor of 1-amino-1-cyclopropanecarboxylic acid *(124)*.

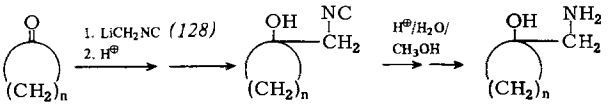
Amino acid synthesis by alkylation of 2-isocyanoalkanoic esters is comparable with the (acylamino)malonic ester method[64], and sometimes superior to it[63]. The isocyano ester procedure also permits synthesis of α-substituted amino acids.

Starting from the isocyanomethanephosphonic ester *(18)*[13], reaction of the lithium derivative with methyl iodide (in tetrahydrofuran at −70°C) gives the 1-isocyanoethanephosphonic ester *(125)*[65], whose hydrolysis should furnish 1-aminoethanephosphonic acid *(126)*. This suggests a facile synthesis of α-amino phosphonic acids—the phosphonic acid analogs of the amino acids[71].

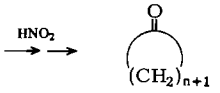
5.2. α- and β-Hydroxyalkylation of Primary Amines; Ring Expansion of Cyclic Ketones

One variant of α-hydroxyalkylation of primary amines *(6)* with carbonyl compounds *(10)* to form 2-amino alcohols *(15)* has already been mentioned in connection with 2-oxazoline syntheses (Section 2.1)[8]. Another variant consists in trapping of the adducts of type *(11)* obtained from *(2)* and *(10)* as isocyano alcohols *(14)* by addition of glacial acetic acid, and conversion of *(14)* into amino alcohols *(15)*, *e.g.* with hydrochloric acid in methanol. Which of the two methods is more favorable will have to be established from case to case.

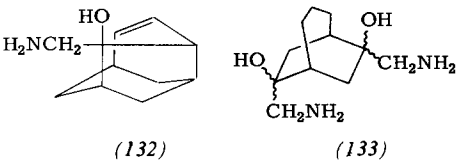
In the isocyanomethyllithium process for ring expansion of cyclic ketones, the cyclic ketone *(127)* is treated with isocyanomethyllithium *(128)* to give 1-(isocyanomethyl)-1-cycloalkanol *(129)*, which is hydrolyzed to the aminomethyl compound *(130)* before being subjected to a Tiffeneau-Demyanov rearrangement to yield the ring-enlarged ketone *(131)*[9b]. Recent applications of this procedure lie in the synthesis (and Tiffeneau-Demyanov rearrangement) of the tricyclic 2-amino alcohol *(132)*[66] and the bis(aminomethyl) compound *(133)*[67], which is not accessible by conventional methods from the diketone.



(127) *(129)* *(130)*

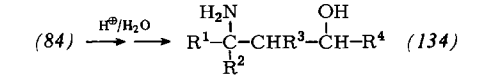


(131)



(132) *(133)*

In the β-hydroxyalkylation of primary amines *(6)* the α-metalated isocyanides *(2)* are allowed to react with epoxides

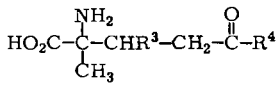


(84) *(134)*

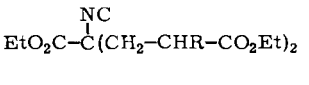
(83) (cf. Section 3.2) and the resulting 3-hydroxyalkyl isocyanides *(84)* are hydrolyzed to the 3-amino alcohols *(134)*[44].

5.3. Chain Elongation by Michael Addition or Cyanoethylation

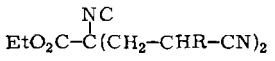
The Michael addition of 2-isocyanopropionic ester *(34)* to α,β-unsaturated carbonyl compounds *(35)*, giving the adducts *(36)*, has already been mentioned in Section 2.4. Hydrolysis of *(36)* should afford the amino acids *(135)*[22]. Ethyl isocyanoacetate *(17b)* reacts with sterically unhindered Michael acceptors to give bisadducts, such as *(136)* with ethyl acrylate, *(137)* with ethyl methacrylate[22], *(138)* with acrylonitrile, or *(139)* with methacrylonitrile[23]. Benzyl 6-isocyanopenicillanate *(119a)* gives the Michael adduct *(199d)* with ethyl acrylate[62].



(135)



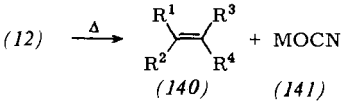
(136), R = H
(137), R = CH_3



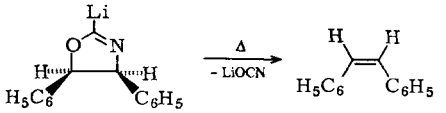
(138), R = H
(139), R = CH_3

6. Carbonyl-Olefination with α-Metalated Isocyanides

Some of the 2-metalated oxazolines *(12)* formed from α-metalated isocyanides *(2)* and carbonyl compounds *(10)* decompose to olefins *(140)* and metal cyanate *(141)* on warming (in tetrahydrofuran)[2].

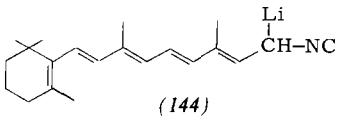


(140) *(141)*

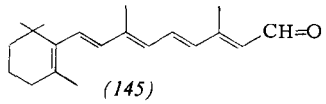


(142) *(143)*

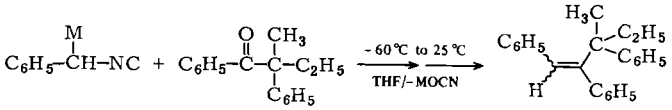
Since cyanate elimination is stereospecific—as illustrated by *(142)* → *(143)*[68]—we formulate the reaction as a 1,3-dipolar cycloreversion. Such a process is only rarely observed, in contrast to 1,3-dipolar cycloaddition[46]. Viewed preparatively, the reaction *(2)*+*(10)*→*(140)*+*(141)* amounts to a carbonyl-olefination. However, compared with the Wittig reaction it is of minimum significance because cyanate elimination can occur only if highly conjugated or phenyl-substituted olefins are formed. For example, all-*trans*-α-lithioretinyl isocyanide *(144)* and all-*trans*-retinal *(145)* give isomer-free (all-*trans*-)β-carotene[69], while lithio- or potassiobenzyl isocyanide *(146)* and highly sterically hindered (and hence inert) 2-methyl-1,2-diphenyl-1-butanone *(147)* cleanly afford 3-methyl-1,2,3-triphenyl-1-pentene *(148)*[70]. The olefination *(147)* → *(148)* should no longer occur with the relatively inert



(144)



(145)



(146), M = Li, K *(147)* *(148)*

compound benzylidenetriphenylphosphorane. In other words: carbonyl-olefination with metalated isocyanides *(2)* might occasionally be of use when the Wittig reaction is impeded by enhanced stability of the phosphonium ylide.

Thanks are due to F. Gerhart, D. Hoppe, R. Schröder, I. Hoppe, R. Harms, R. Meyer, D. Stafforst, R. Jentsch, K. Madawinata, H.-H. Hausberg, K.-W. Henneke, K.-H. Scheunemann, E. Eilers, K. Hantke, E. Blume, P.-H. Porsch, and P. Böhme for their dedicated assistance. Support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG, Ludwigshafen, is gratefully acknowledged.

Received: March 7, 1977 [A 162 IE]
German version: Angew. Chem. 89, 351 (1977)

[1] Cf. *P. Kurtz* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1952, 4th Edit., Vol. 8, p. 349.
[2] *U. Schöllkopf, F. Gerhart*, Angew. Chem. *80*, 842 (1968); Angew. Chem. Int. Ed. Engl. 7, 805 (1968).
[3] *D. Hoppe*, Angew. Chem. *86*, 878 (1974); Angew. Chem. Int. Ed. Engl. *13*, 789 (1974); previous surveys: *U. Schöllkopf*, Angew. Chem. *82*, 795 (1970); Angew. Chem. Int. Ed. Engl. *9*, 763 (1970); *U. Schöllkopf* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1970, 4th Edit., Vol. 13/1, p. 234.
[4] Concerning this problem and previous attempts to solve it, *D. Seebach, D. Enders*, Angew. Chem. *87*, 1 (1975); Angew. Chem. Int. Ed. Engl. *14*, 1 (1975).
[5] a) With phosgene: *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann*, Angew. Chem. 77, 492 (1965); Angew. Chem. Int. Ed. Engl. *4*, 472 (1965); b) with phosphorus oxide chloride: *H. Böhme, G. Fuchs*, Chem. Ber. *103*, 2775 (1970); *I. Ugi, R. Meyr*, Angew. Chem. *70*, 702 (1958); *I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, F. Rosendahl*, Org. Synth. *41*, 13 (1961); *F. Lautenschläger, G. F. Wright*, Can. J. Chem. *41*, 863 (1963); *K. Pilgram, F. Korte*, Tetrahedron Lett. *1966*, 881; c) with toluenesulfonyl chloride: *R. E. Schuster, J. E. Scott, J. Casanova, Jr.*, Org. Synth. *46*, 75 (1966); *I. Hagedorn, H. Tönjes*, Pharmazie *11*, 409 (1956); *12*, 567 (1957); *W. R. Hertler, E. J. Corey*, J. Org. Chem. *23*, 1221 (1958); *M. Lipp, F. Dallacker, T. Meier zu Köcker*, Monatsh. Chem. *90*, 41 (1959); *I. Hagedorn, U. Eholzer, A. Lüttringhaus*, Chem. Ber. *93*, 1584 (1960); d) with thionyl chloride/dimethylformamide: *H. M. Walborsky, G. E. Niznik*, J. Org. Chem. *37*, 187 (1972); *G. E. Niznik, W. H. Morrison III, H. M. Walborsky*, Org. Synth. *51*, 31 (1971); e) with triphenylphosphane/tetrachloromethane: *R. Appel, R. Kleinstück, K.-D. Ziehn*, Angew. Chem. *83*, 143 (1971); Angew. Chem. Int. Ed. Engl. *10*, 132 (1971); *N*-alkylformamides are obtained either by formylation of amines or (in the case of allyl compounds) from the halides by treatment with *N*-sodioformamide in acetonitrile; numerous applications are listed in [8, 59].
[6] *W. P. Weber, G. W. Gokel*, Tetrahedron Lett. *1972*, 1637; *W. P. Weber, G. W. Gokel, I. K. Ugi*, Angew. Chem. *84*, 587 (1972); Angew. Chem. Int. Ed. Engl. *11*, 530 (1972).
[7] Cf. [5a], footnote [67].
[8] *U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K.-H. Scheunemann, E. Eilers, E. Blume*, Justus Liebigs Ann. Chem. *1976*, 183.
[9] a) *W. A. Böll, F. Gerhart, A. Nürrenbach, U. Schöllkopf*, Angew. Chem. *82*, 482 (1970); Angew. Chem. Int. Ed. Engl. 9, 458 (1970); b) *U. Schöllkopf, P. Böhme*, Angew. Chem. *83*, 490 (1971); Angew. Chem. Int. Ed. Engl. *10*, 491 (1971).
[10] Cf. *Y. Ito, I. Ito, T. Hirao, T. Saegusa*, Synth. Comm. *4*, 97 (1974).

[11] *K. Hantke, U. Schöllkopf, H.-H. Hausberg*, Justus Liebigs Ann. Chem. *1975*, 1531.
[12] a) *D. Hoppe, U. Schöllkopf*, Justus Liebigs Ann. Chem. *763*, 1 (1972); b) with chloral to give trichlorothreonine; cf. *K. Matsumoto, Y. Urabe, Y. Ozaki, T. Iwasaki, M. Miyoshi*, Agric. Biol. Chem. *39*, 1869 (1975), and further references to work by this group given therein.
[13] *U. Schöllkopf, R. Schröder, D. Stafforst*, Justus Liebigs Ann. Chem. *1974*, 44.
[14] *van Leusen et al.* proposed the abbreviation "Tosmic" for *(19)*.
[15] *U. Schöllkopf, R. Schröder, E. Blume*, Justus Liebigs Ann. Chem. *766*, 130 (1972).
[16] *A. M. van Leusen, B. E. Hoogenboom, H. Siderius*, Tetrahedron Lett. *1972*, 2369.
[17] *O. H. Oldenziel, A. M. van Leusen*, Tetrahedron Lett. *1974*, 163.
[18] *K. Madawinata*, Dissertation, Universität Göttingen 1977.
[19] *U. Schöllkopf, R. Meyer, P. Böhme*, Justus Liebigs Ann. Chem. *1977*, in press.
[20] *R. J. Ferm, J. L. Riebsomer*, Chem. Rev. *54*, 593 (1954); *K. Hofmann* in *A. Weissberger:* The Chemistry of Heterocyclic Compounds. Imidazole and its Derivatives. Interscience, New York 1953, Vol. VI, 1, pp. 213ff.
[21] Cf. *J. P. Greenstein, M. Winitz:* Chemistry of the Amino Acids. Wiley, New York 1961, Vol. 3, p. 2463; *E. Atherton, J. Meienhofer*, J. Am. Chem. Soc. *94*, 4759 (1972).
[22] *U. Schöllkopf, K. Hantke*, Justus Liebigs Ann. Chem. *1973*, 1571.
[23] *U. Schöllkopf, P.-H. Porsch*, Chem. Ber. *106*, 3382 (1973).
[24] *A. M. van Leusen, H. Siderius, B. E. Hoogenboom, D. van Leusen*, Tetrahedron Lett. *1972*, 5337.
[25] For the synthesis of verrucarin E, see *A. Gossauer, K. Suhl*, Helv. Chim. Acta *59*, 1698 (1976).
[26] *M. Suzuki, M. Miyoshi, K. Matsumoto*, J. Org. Chem. *39*, 1980 (1974).
[27] *U. Schöllkopf, F. Gerhart, R. Schröder, D. Hoppe*, Justus Liebigs Ann. Chem. *766*, 116 (1972).
[28] *R. Schröder, U. Schöllkopf, E. Blume, I. Hoppe*, Justus Liebigs Ann. Chem. *1975*, 533.
[29] *M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okumura, K. Matsumoto*, J. Org. Chem. *38*, 3571 (1973); *M. Suzuki, T. Iwasaki, K. Matsumoto, K. Okumura*, Synth. Commun. *2*, 237 (1972).
[30] For the acylimidazoline method, see *K.-W. Henneke*, Dissertation, Universität Göttingen 1977.
[31] Reviews: *I. J. Turchi, M. J. S. Dewar*, Chem. Rev. *75*, 389 (1975); *R. Lakhan, B. Ternai*, Adv. Heterocycl. Chem. *17*, 99 (1974).
[32] *K. Matsumoto, M. Suzuki, M. Miyoshi, K. Okumura*, Synthesis *1974*, 500.
[33] *K. Matsumoto, M. Suzuki, N. Yoneda, M. Miyoshi*, Synthesis *1976*, 805.
[34] *H. A. Staab*, Angew. Chem. *74*, 407 (1962); Angew. Chem. Int. Ed. Engl. *1*, 351 (1962); *H. A. Staab, W. Rohr* in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim 1967, Vol. 5, pp. 53ff.
[35] Obtainable by reaction of *(17a)* in tetrahydrofuran at $-55\,^{\circ}C$ with 0.5 equiv. of butyllithium. Cf. *R. Jentsch*, Dissertation, Universität Göttingen 1973.
[36] *G. D. Hartman, L. M. Weinstock*, Synthesis *1976*, 681.
[37] *A. M. van Leusen, O. H. Oldenziel*, Tetrahedron Lett. *1972*, 2373.
[38] *U. Schöllkopf, P.-H. Porsch, E. Blume*, Justus Liebigs Ann. Chem. *1976*, 2122.
[39] *R. Harms*, Dissertation, Universität Göttingen 1975.
[40] *H.-H. Hausberg*, Dissertation, Universität Göttingen 1976; *U. Reiter*, Diplomarbeit, Universität Göttingen 1976, Dissertation, Universität Göttingen, planned for 1978.
[41] *A. M. van Leusen, J. Schut*, Tetrahedron Lett. *1976*, 285.
[42] Cf. [11]; *K. Hantke*, Dissertation, Universität Göttingen 1973.
[43] *K. Matsumoto, M. Suzuki, M. Tomie, N. Yoneda, M. Miyoshi*, Synthesis *1975*, 609.
[44] *U. Schöllkopf, R. Jentsch, K. Madawinata, R. Harms*, Justus Liebigs Ann. Chem. *1976*, 2105.
[45] *K. Madawinata*, Diplomarbeit, Universität Göttingen 1974.
[46] *R. Huisgen*, J. Org. Chem. *41*, 403 (1976); earlier references cited therein.
[47] *U. Schöllkopf, E. Blume*, unpublished; *H.-H. Lau*, Diplomarbeit, Universität Göttingen 1977.
[48] *U. Schöllkopf, K. Hantke*, Chem. Ber. *109*, 3964 (1976).
[49] *A. J. Brink, A. Jordaan*, Carbohydr. Res. *34*, 1 (1974).
[50] Review: *H. E. Carter*, Org. React. *3*, 198 (1946).
[51] *H.-J. Prätorius, J. Flossdorf, M.-R. Kula*, Chem. Ber. *108*, 3079 (1975).
[52] *U. Schöllkopf, D. Hoppe*, Justus Liebigs Ann. Chem. *1973*, 799.
[53] *K. Bischofberger, A. J. Brink, A. Jordaan*, J. Chem. Soc. Perkin Trans. I *1975*, 2457.
[54] a) *U. Schöllkopf, R. Harms, D. Hoppe*, Justus Liebigs Ann. Chem. *1973*, 611; b) *U. Schöllkopf, R. Meyer, ibid. 1977*, in press; that paper describes the addition of Grignard compounds *(32)* to *tert*-alkyl-substituted glycines.
[55] a) *U. Schöllkopf, D. Hoppe*, Angew. Chem. *85*, 1102 (1973); Angew. Chem. Int. Ed. Engl. *12*, 1006 (1973); b) *P. J. Claes, R. Vanderhaeghe*, Eur. J. Med. Chem. *11*, 359 (1976).
[56] *O. H. Oldenziel, A. M. van Leusen*, Synth. Commun, *2*, 281 (1972).
[57] *U. Schöllkopf, R. Schröder*, Angew. Chem. *85*, 402 (1973); Angew. Chem. Int. Ed. Engl. *12*, 407 (1973).
[58] *U. Schöllkopf, E. Eilers, K. Hantke*, Justus Liebigs Ann. Chem. *1976*, 969.
[59] *U. Schöllkopf, K.-W. Henneke, K. Madawinata, R. Harms*, Justus Liebigs Ann. Chem. *1977*, 40.
[60] *U. Schöllkopf, D. Hoppe, R. Jentsch*, Chem. Ber. *108*, 1580 (1975).
[61] a) *K. Matsumoto, T. Miyahara, M. Suzuki, M. Miyoshi*, Agric. Biol. Chem. *38*, 1097 (1974); b) *M. Suzuki, T. Miyahara, R. Yoshioka, M. Miyoshi, K. Matsumoto, ibid. 38*, 1709 (1974); c) *M. Suzuki, K. Matsumoto, T. Iwasaki, K. Okumura*, Chem. Ind. (London) *1972*, 687.
[62] *P. H. Bentley, J. P. Clayton*, J. Chem. Soc. Chem. Commun. *1974*, 278.
[63] *M. Bocheńska, J. F. Biernat*, Rocz. Chem. *50*, 1195 (1976).
[64] Cf. *A. C. Cope, H. L. Holmes, H. O. House*, Org. React. *9*, 107 (1957); *Th. Wieland, R. Müller, E. Niemann, L. Birkofer, A. Schöberl, A. Wagner, H. Söll* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1958, 4th Edit., Vol. 11/2, pp. 306ff.
[65] *U. Schöllkopf, I. Hoppe*, unpublished.
[66] *H. Tobler, R. O. Klaus, C. Ganter*, Helv. Chim. Acta *58*, 1455 (1975).
[67] *R. Greenhouse, T. Ravindranathan, W. T. Borden*, J. Am. Chem. Soc. *98*, 6738 (1976).
[68] *K.-H. Scheunemann*, Dissertation, Universität Göttingen 1977.
[69] *F. Kienzle*, Helv. Chim. Acta *56*, 1671 (1973).
[70] *K. Czempik*, Dissertation, Universität Göttingen 1976.
[71] α-Aminophosphonic acids: *W. F. Gilmore, H. A. McBride*, J. Am. Chem. Soc. *94*, 4361 (1972); *S. Asano, T. Kitahara, T. Ogawa, M. Matsui*, Agr. Biol. Chem. *37*, 1193 (1973); *K. Prajer, J. Rachoń*, Z. Chem. *15*, 209 (1975); *W. J. Stec, K. Lesiak*, J. Org. Chem. *41*, 3757 (1976).

Phosphacumulene Ylides and Phosphaallene Ylides[**]

By Hans Jürgen Bestmann[*]

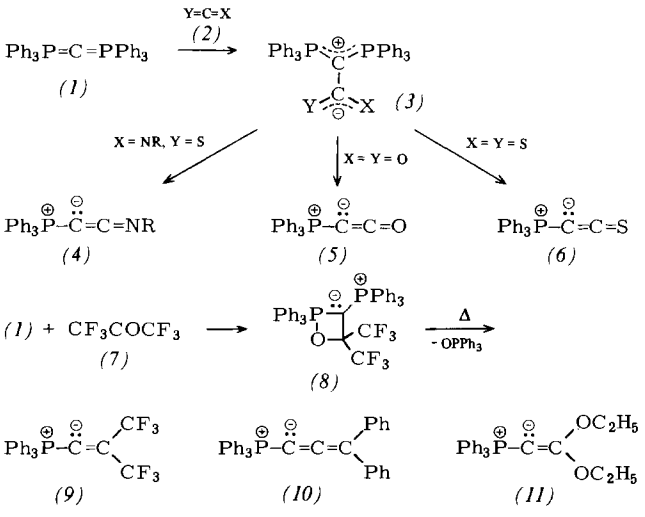
Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

Phosphacumulene ylides and phosphaallene ylides are nucleophilic compounds which can add reactants in a variety of ways. Cycloadditions can occur both at the polar C—P ylide bond and at the C=C double bond.

1. Introduction

In three reviews we reported[1-3] that the nucleophilic phosphorus ylides are comparable in their scope and versatility to Grignard reagents[4]. These investigations were initiated by the discovery of carbonyl olefination by *Wittig* and coworkers. The 80th birthday of the discoverer of this reaction, of such great importance in preparative chemistry, is a fitting occasion to report a further chapter of phosphorus ylide chemistry which has been studied in recent years by our research team, and is still advancing on a broad front.

In 1961, *Ramirez et al.* described the synthesis of hexaphenylcarbodiphosphorane *(1)*[5]. This compound was later reacted with *(2)*, by *Birum* and *Matthews*, to give the betaines *(3)*, whose thermolysis afforded ketenylidenetriphenylphosphorane *(5)*[6], the analogous thio compound *(6)*[6], and the imino derivatives *(4)*[7].

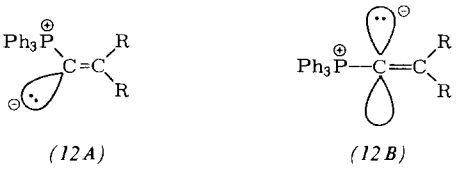


From *(1)* and hexafluoroacetone *(7)* the same authors obtained the 1,2-oxaphosphetane derivative *(8)* which decomposes on heating into triphenylphosphane oxide and *(9)*[8].

A comprehensive report of reactions employing the phosphaallene ylides *(1)* and *(9)* and the phosphacumulene ylides *(4)* to *(6)* was published in 1969[9]. Syntheses and some reactions of the subsequently prepared compounds *(10)*[10] and *(11)*[11] were considered in an earlier review[2]. Surprisingly, these compounds have since found little preparative use[12]. Having developed productive syntheses of *(4)*, *(5)*, *(6)*, and *(11)* and of other phosphacumulene and phosphaallene ylides, we have now studied the chemistry of these interesting molecules in detail.

2. Structure of Phosphacumulene Ylides and Phosphaallene Ylides

Two structures with different degrees of hybridization at the ylidic C atom are conceivable for phosphaallene ylides of the general type *(12)*. If this C atom is sp^2 hybridized, then structure *(12A)* having a P—C_α—C_β angle of *ca.* 120° is expected, whereas sp hybridization should lead to a linear molecule *(12B)*: Interaction of the lone pair on C with the d orbitals of phosphorus is expected in either case, although the exact nature of the interaction has yet to be established[13,14].



X-Ray structure analysis of diethoxyvinylidenetriphenylphosphorane *(11)* [= *(12)*, R = OC_2H_5][15] gave a nonlinear structure with a P—C_α—C_β angle of 125.6°. The C_α—C_β bond length of 1.314 Å is the same as an allenic double bond. An electron density maximum was observed at the position expected for the lone pair in the occupied sp^2 hybrid orbital; its intensity approaches that of the electrons belonging to a hydrogen atom attached to a benzene ring.

In the ^{1}H-NMR of *(11)* the two alkyl groups give rise to only one sharp triplet at $\tau = 8.96$ and a quartet at $\tau = 5.63$. No line broadening occurs on cooling to −70 °C. Hence we conclude that the triphenylphosphonio group of *(11)* is subject to fast inversion in solution, as is known for substituents at the N atom of C=N double bonds. Inversion barriers of 9.2 and 12.2 kcal/mol were measured for two ketenimines which are isoelectronic with the phosphaallene ylides *(12)*[16].

Phosphacumulene ylides of type *(13)* with X = NR, O, and S [= *(4)*, *(5)*, and *(6)*, respectively] can be described by the principal resonance structures *(13A)* and *(13B)* which differ in their geometry and electron distribution.

[*] Prof. Dr. H. J. Bestmann
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-8520 Erlangen (Germany)

[**] In line with IUPAC nomenclature, it is proposed that ylides of type $R_3P{=}C{=}C{=}X$ be designated as phosphacumulene ylides and those of type $R_3P{=}C{=}CR'_2$ as phosphaallene ylides.



(13A) (13B)

X = O, S, NR

Table 1. P—C_α—C_β angles and C_α—C_β bond lengths in phosphaallene ylides of type (12) and phosphacumulene ylides of type (13).

Type	Cpd.	Angle P—C_α—C_β [°]	Distance C_α—C_β [Å]
(12)	(11)	125.6	1.314
(13)	(4), X = NC_6H_5	134.0	1.248
(13)	(5), X = O	145.5	1.210
(13)	(6), X = S	168.0	1.204

As the electron acceptor character of X increases and its tendency to participate in double bonding decreases, the weight of structure (13B) in the resonance hybrid will increase. Thus the P—C_α—C_β angle should increase and the C_α—C_β bond length decrease in the order (4), (5), (6). These expectations are confirmed by the results of X-ray structure analysis of compounds (4), R = C_6H_5[17], (5)[18], and (6)[19], which are listed in Table 1 together with the corresponding data for (11).

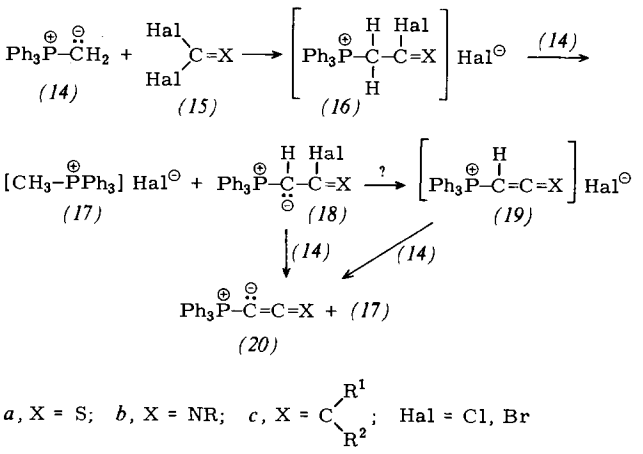
Along the series (11), (4), (5), (6), the PCCX grouping becomes progressively more linear, and the C_α—C_β distance shorter. Owing to the increasing contribution of structure (13B) to the resonance hybrid, and the greater delocalization of the carbanion lone pair the nucleophilic reactivity of the phosphacumulene ylides should decrease along the same series. Our studies, described below, confirm this.

3. Synthesis of Phosphacumulene Ylides and Phosphaallene Ylides

3.1. Phosphacumulene Ylides from Methylenetriphenylphosphorane and Geminal Dihalo Compounds

We have developed a synthesis for phosphacumulene ylides of the general type (20) from methylenetriphenylphosphorane (14) and geminal dihalo compounds (15)[20, 21]. Reaction of (14) with a geminal dihalo compound (15) in a molar ratio of 3 : 1 initially affords a phosphonium salt (16), primarily *via* nucleophilic substitution, which can be trans-ylidated with a further molecule of (14) to the phosphonium salt (17) and to the ylide (18). The third molecule of (14) removes hydrogen halide from (18). Additional salt (17) and the phosphacumulene ylide (20) are the final products. It has not yet been established whether (18) is initially transformed into the salt (19).

The overall reaction is: 3 (14) + 1 (15) → 1 (20) + 2 (17). The phosphonium salt precipitates during the reaction. After its separation, (20) is isolated by distillative removal of the solvent and recrystallization. Compound (14) and isocyanide dichlorides (15b), Hal = Cl, R = alkyl or aryl, give iminoketenylidenetriphenylphosphoranes (4), while the thioketenylidenetriphenylphosphorane (6) is obtained starting with thiophosgene (15a), Hal = Cl. Reaction is possible with



a, X = S; b, X = NR; c, X = $C(R^1)(R^2)$; Hal = Cl, Br

Table 2. Phosphacumulene ylides (20) from (14) and (15) (molar ratio 3 : 1).

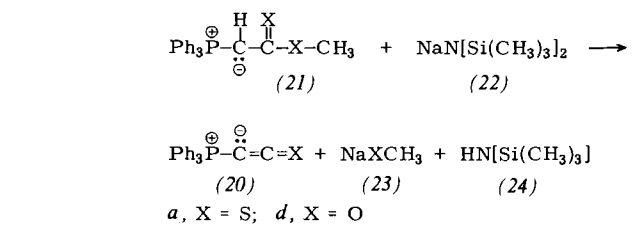
X	Hal in (15)	Yield [%]	M.p. [°C]	IR $\nu_{C=C=X}$ [cm^{-1}]
NC_6H_5	Cl	85	151—152	2000
NCH_3	Cl	70	157—158	1980
N-c-C_6H_{11}	Cl	68	137—139	2000
S	Cl	60	218—220	1950, 2110
$C_{13}H_8$ [a]	Br	80	188—189	1960
$C(CO_2CH_3)_2$	Cl	19	205	2100
$C(CN)CO_2CH_3$	Cl	51	220	2060

[a] $C_{13}H_8$ = 9-fluorenylidene.

compounds of type (15c) if R^1 and R^2 are substituents having electron-acceptor properties (Table 2).

3.2. Phosphacumulene Ylides by β-Elimination from Methoxycarbonylmethylenetriphenylphosphorane and Its Dithio Analog

Attempts to prepare ketenylidenetriphenylphosphorane (5) from (14) and phosgene (15), X = O, Hal = Cl, as described in the previous paragraph led only to impure products. A facile new synthesis of (5) and its thio analog (6) was discovered in the β-elimination of methanol and methanethiol, respectively, from methoxycarbonylmethylenetriphenylphosphorane (21d) and the corresponding dithio compound (21a)[22].



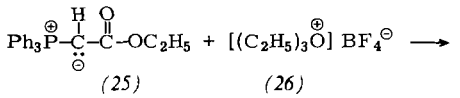
a, X = S; d, X = O

On reaction of (21d) with sodium bis(trimethylsilyl)-amide[23, 24] in benzene, the base eliminates methanol from (21d). The cumulene ylide (5) [= (20d)], hexamethyldisilazane (24), and sodium methoxide (23d) are formed. After (23d) has been filtered off, compound (5) is isolated by concentration of the solution and precipitation with ether (yield 80 %). In an analogous manner, reaction of (21a)[25] and (22) furnishes the phosphacumulene ylide (6) [= (20a)] (yield 76 %) alongside (24) and sodium methyl sulfide (23a).

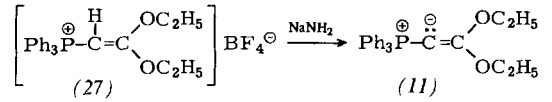
The mechanism of the elimination reaction has not yet been studied in detail[26].

3.3. Synthesis of Diethoxyvinylidenetriphenylphosphorane (11)

Synthesis of the acetal (11) from (5) starts from ethoxycarbonylmethylenetriphenylphosphorane (25), which is O-alkylated by triethyloxonium tetrafluoroborate (26) to give the vinylphosphonium salt (27). Deprotonation of (27) with sodium amide yields the corresponding ylide (11)[12].



(25) (26)

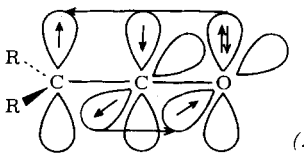


(27) (11)

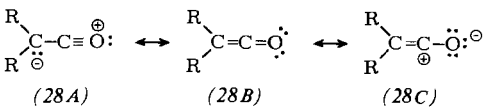
4. Nucleophilic Substitution of Phosphacumulene Ylides and Phosphaallene Ylides

4.1. General Reaction Scheme

In contrast to ketenes, the phosphacumulene ylides (4), (5), and (6) display no tendency to dimerize. Ketenes possess two orthogonal π-electron systems, one of which, being isoelectronic with that of the allyl anion, is occupied by four electrons, while the other is occupied by two electrons. The electron donor character of oxygen renders the π^4-electron system



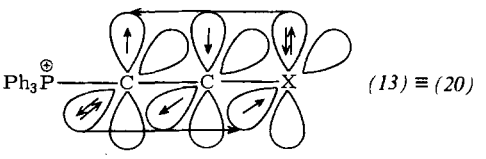
(28)



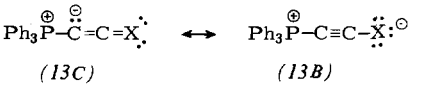
(28A) (28B) (28C)

nucleophilic with a partial negative charge on C_β. At the same time, the acceptor property of the oxygen atom in the π^2-system induces a partial positive dipolar character, being nucleophilic at C_β and electrophilic at C_α [(28A)↔(28B)↔(28C)]. This dipolarity is, no doubt, the driving force for dimerization and for numerous cycloaddition reactions of ketenes[27].

In the phosphacumulene ylides of type (13) [=(20)] both orthogonal π-electron systems are occupied by four electrons[28]. These compounds are isoelectronic with carbon dioxide, isocyanates, and carbodiimides. Unlike the ketenes (28) having a nucleophilic π^4 and an electrophilic π^2 system, both the π^4 systems of phosphacumulene ylides (13) are nucleophilic, *i.e.* these compounds have lost their electrophilic and thus their dipolar character compared to the ketenes (28). The notation (13C) ↔ (13B), which does not depict the true geometry of (13), expresses this situation. The driving force



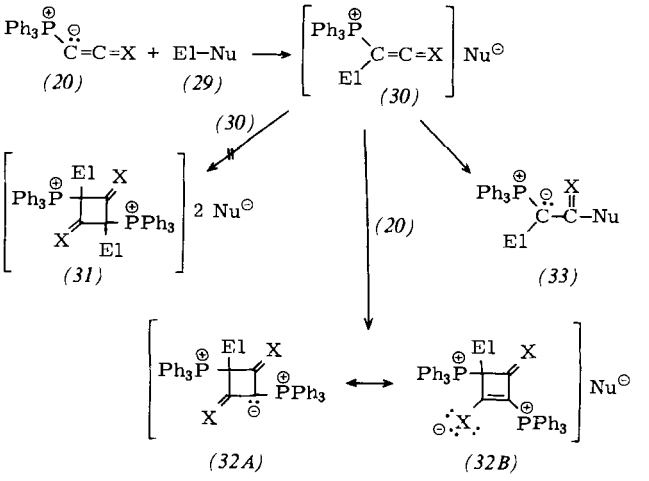
(13) ≡ (20)



(13C) (13B)

for dimerization is absent. Compounds (13) [=(20)] are monomeric.

If a nucleophilic substitution is performed with the phosphacumulene ylides (20) on a compound El-Nu (29), then the primary product is a phosphonium salt (30). Addition of the electrophile El to the lone pair of (20) transforms the nucleophilic $\pi^4 \perp \pi^4$ system into the dipolar $\pi^4 \perp \pi^2$ system of the ketenes (28), *i.e.* the phosphonium ion in (30) becomes a "true" dipolar ketene which, as such, reacts in known manner.



(20) (29) (30) (31) (33) (32A) (32B)

We have not yet detected dimerization of (30) to the bisphosphonium salt (31). Whenever (20) is a stronger nucleophile than $Nu^\ominus$, compound (30) always reacts with a second molecule of unreacted (20) in a [2+2]-cycloaddition to give the 1,3-cyclobutanedione derivatives (32) which, like all α-keto ylides, can be described by the resonance structures (32A) ↔ (32B)[29].

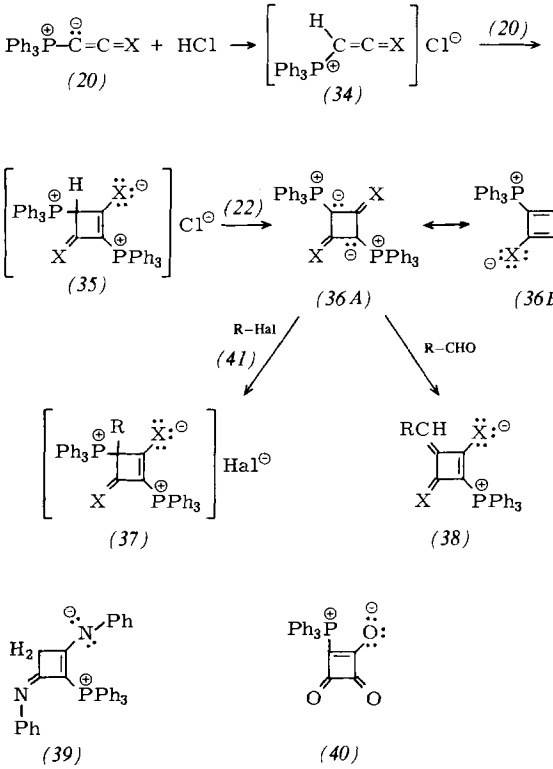
If the anion $Nu^\ominus$ is a stronger nucleophile than (20), then the ylide (33) will be formed.

Transformation of the $\pi^4 \perp \pi^4$ system of (20) into the dipolar $\pi^4 \perp \pi^2$ system of the ketenes (28) on nucleophilic reaction is the cause of the variety of reactions to be treated in this article. Particular preparative interest attaches to the cyclobutanedione derivatives (32), whose rings can readily be opened by nucleophilic reagents to form open-chain β-dicarbonyl compounds.

4.2. Dimers of Phosphacumulene Ylides

The dimers (36) of phosphacumulene ylides (20) are of particular interest because their resonance form (36B) represents a new kind of "push-pull" cyclobutadiene[30]. Synthesis of this dimer is accomplished by reaction of (20) with HCl in the molar ratio 2:1[31]. The initial step is addition of

a proton to the ylidic C atom to form *(34)*, which as a "true" ketene can undergo a [2+2]-cycloaddition with *(20)* to give the phosphonium salt *(35)* as described in the foregoing section. The salt *(35)* yields the stable dimer *(36)* on treatment with bases, especially *(22)*.



b, X = NPh ; *d*, X = O; Hal = Halogen

Evidence for participation of the cyclobutadiene structure *(36B)* is provided by the frequencies of the C=O bands in the IR spectrum of *(36d)* at 1650 and 1610 cm^{-1}, and of the C=N bands of *(36b)* at 1563 and 1527 cm^{-1}. Reaction of *(36)* with halogen compounds gives the phosphonium salts *(37)*[31,32] and treatment with aldehydes gives the monophosphoranes *(38)* (see Section 5.2.1).

Hydrolysis of *(36b)* gives compound *(39)*[33]. Oxidation of *(36d)* with the adduct of ozone to triphenyl phosphite[34] leads to the cyclobutanetrione derivative *(40)* whose structural relationship with squaric acid is clearly evident [IR: 1769, 1651, 1629 cm^{-1} (CO)].

4.3. Reaction with Halogen Compounds

4.3.1. General Reaction Course

Reaction of phosphacumulene ylides *(20)* with the halogen compounds *(41)* proceeds *via* nucleophilic substitution, giving initially the phosphonium salts *(42)*. Once more the nucleophilic $\pi^4 \perp \pi^4$ system has been transformed into a dipolar $\pi^4 \perp \pi^2$ system. Substitution is then followed immediately by a [2+2]-cycloaddition of *(27)* to *(42)*, yielding the four-membered ylide phosphonium salts *(37)*[35,36] which are also obtained from *(36)* and *(41)*.

The overall reaction is thus: 2 *(20)* + *(41)* → *(37)*. In all cases studied so far the second step was faster than the first one. Examples are presented in Table 3.

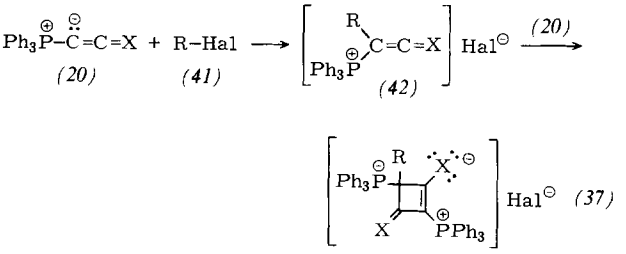


Table 3. Phosphonium salts *(37)* from phosphacumulene ylides *(20)* and halogen compounds *(41)* [35].

X	R	Hal	M.p. [°C] [a]	Yield [%]
O	CH_3	I	238—240	96
O	C_2H_5	I	226—227	85
O	C_3H_7	I	216—218	85
O	C_5H_{11}	I	212—214	87
O	C_6H_5—CH_2	Br	218—219	98
O	α-$C_{10}H_7$—CH_2	Br	213—215	95
O	Br	Br	204—206	96
NC_6H_5	CH_3	I	202—203	88

[a] All compounds listed decompose on melting.

In the ^{31}P-NMR spectrum of compounds *(37)*, the phosphonium P atom gives rise to a signal between −22 and −29 ppm and the ylidic P atom to one at −3 to +4 ppm (H_3PO_4 as external standard). Transannular coupling takes place between the two P atoms (J_{PP} = 5—7 Hz).

4.3.2. Possible Syntheses of β-Oxo Carboxylic Esters and Acetylenecarboxylic Esters

The 1,3-cyclobutanedione derivatives *(37)*, easily accessible from *(20)* and *(36)* by means of halogen compounds *(41)*, undergo ready ring opening. Treatment of compounds *(37)*, obtainable from *(5)* [= *(20)*, X = O] or *(36)* and *(41)*, with sodium methoxide gives the bis-ylides *(43)*[35]. Reaction of *(36d)* with methanol leads, *via* addition of a proton to the ylidic C atom and subsequent ring opening by the methoxide ion, directly to *(43)*, R = H[31].

The ylide function flanked by two carbonyl groups in the bisphosphoranes *(43)* is much more inert than that adjacent to only one CO group. Compounds *(43)* are hydrolyzed by water to the mono-ylides *(44)* and the Wittig reaction with aldehydes gives the phosphoranes *(45)*[35]. Examples of *(43)* and *(44)* are presented in Table 4.

Thermolysis of (1-acyl)methoxycarbonylmethylenetriphenylphosphoranes *(44)* affords acetylenecarboxylic esters *(46)*[37,38]. Compounds *(45)* likewise yield the alkenynecarboxylic esters *(47)*. Addition of piperidine to the triple bond of *(46)* leads to the enamines *(48)*, which can be hydrolyzed to the β-oxo carboxylic esters *(50)* with oxalic acid[38]. In the same reaction sequence, γ,δ-unsaturated β-oxo esters *(49)* are obtained from esters *(47)*.

Since *(5)*, and thus also *(37d)*, can easily be prepared starting from acetic esters (bromination, formation of phos-

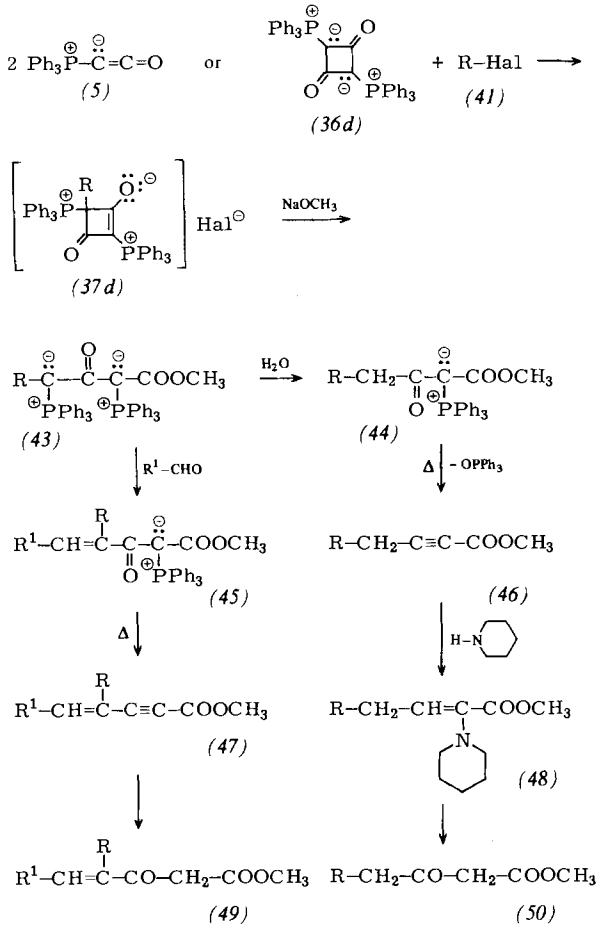
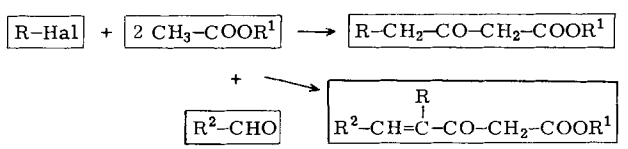


Table 4. Bis-ylides *(43)* from phosphonium salts *(37d)* and sodium methoxide; mono-ylides *(44)* by hydrolysis of *(43)*.

R	*(43)* M.p. [°C]	*(43)* Yield [%]	*(44)* M.p. [°C]	*(44)* Yield [%]
H	247 [a]	79	153—154	83
CH_3	212—215 [b]	85	112—114	71
C_2H_5	211—213 [b]	76	96—98	74
C_3H_7	200—202 [b]	80	126—128	69
C_5H_{11}	Oil	71	109—111	76

[a] From *(35d)* and methanol. [b] Melts with decomposition.

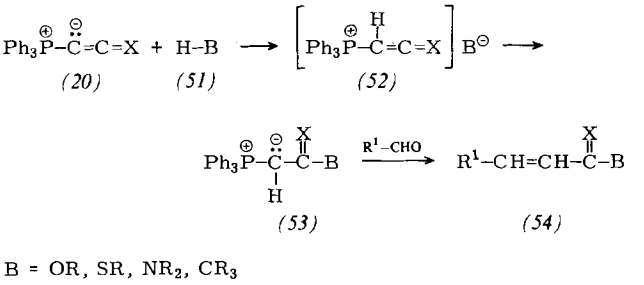
phonium salt and ylide) by the methods described, a highly versatile scheme is available for synthesis of β-oxo esters *(49)* and *(50)*:



4.4. Addition of Acidic Compounds

4.4.1. General Reaction Scheme

Matthews and *Birum*[39] reported that ketenylidenetriphenylphosphorane *(5)* adds ethanol, and mentioned that such additions also occur with imidazole, methanethiol, and malononitrile. However, no information was available about the nature of these addition products.



B = OR, SR, NR_2, CR_3

We have found that the phosphoranes *(20)* generally react with acidic compounds H—B *(51)*. In the initially formed ion pairs *(52)* the anion $B^{\ominus}$ is so nucleophilic that addition to give *(53)* is faster than cycloaddition of *(52)* to *(20)*.

The difference in the nucleophilic character of compounds *(20)* with X=NR [=*(4)*], X=O [=*(5)*], and X=S [=*(6)*] [*(4)* > *(5)* > *(6)*] is particularly evident in the reaction *(20)* + *(51)* → *(53)*. While *(4)* and *(5)* smoothly add alcohols, thiols, and acidic NH compounds, the thio compounds *(6)* react readily with thiols and phenols, less rapidly with aliphatic alcohols, and not with NH acids. Strongly activated CH_2 groups add readily to *(4)*, less rapidly to *(5)*, and not at all to *(6)*.

4.4.2. Possible Synthesis of Carboxylic Acid Derivatives

The addition of alcohols, thiols, and acidic amines to phosphacumulene ylides *(20)* is of particular preparative interest. Table 5 lists our studies.

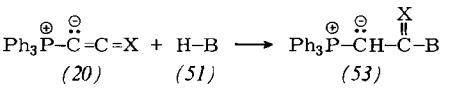
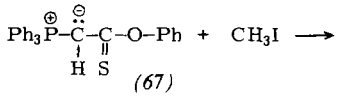


Table 5. Addition of alcohols, thiols, and NH acids H—B *(51)* to phosphacumulene ylides *(20)* to give products of type *(53)*.

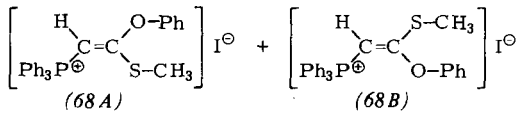
Product	X	B	M.p. [°C]	Yield [%]
(55)	NC_6H_5	OCH_3	179	72
(56)	NC_6H_5	OC_6H_4—OCH_3-*p*	159	68
(57)	NC_6H_5	SC_6H_5	151	59
(58)	NC_6H_5	SCH_2—C_6H_5	173	53
(59)	NC_6H_5		161	62
(60)	NC_6H_5		184	75
(61) [a]	NC_6H_5	H—B=*p*-CH_3—C_6H_4—SO_2NH_2	215	57
(62)	O	SCH_3	208	68
(63)	O	SC_6H_5	186	72
(64)	O		185	71
(65)	O		197	75
(66)	O	NH—SO_2—C_6H_5	195	83
(67)	S	OC_6H_5	109	69

[a] Product: $(C_6H_5)_3\overset{\oplus}{P}$—$\overset{\ominus}{C}$H—C(=N—$SO_2$—$C_6H_4$—$CH_3$-*p*)—NH—$C_6H_5$.

A wide variety of carboxylic acid derivatives, particularly those of α,β-unsaturated acids, can be prepared by Wittig reaction of the ylides *(55)*—*(67)*, listed in Table 5, according to the general scheme *(53)* + R^1—CHO → *(54)*. These products are often difficult to prepare by other methods. Thus *(55)* and *(56)* give imino ethers[40], *(57)* and *(58)* imino thioethers[41], and *(59)*—*(61)* amidines[41,42]. *(62)* and *(63)*



(67)



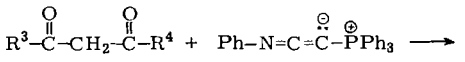
(68A) (68B)

yield *S*-methyl and *S*-phenyl esters, respectively, of thiocarboxylic acids[42,43], while *(64)* and *(65)* give acylimidazoles[44] and pyrazoles[41], respectively, and *(66)* affords acylsulfonamides[41].

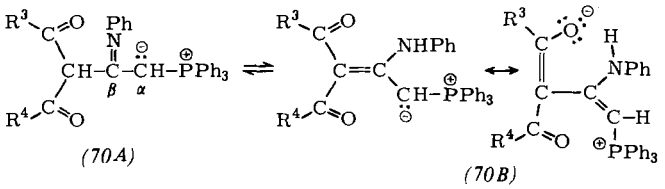
On reaction of *(67)* with methyl iodide, *S*-methylation takes place to give the two geometric isomers of the vinylphosphonium salt *(68)*[25,42,45].

4.4.3. Addition of CH Acids to *(20)*

Addition of CH acids of type $CH_2R^1R^2$ to *(4)* [=*(20)*, X=NR] and *(5)* [=*(20)*, X=O] requires compounds having two electron-attracting groups R^1 and R^2, *e.g.* 1,3-dicarbonyl compounds *(69)*, cyanoacetic esters, and malononitriles[46].



(69) (4)



(70A) (70B)

Table 6. Phosphoranes *(70)* from compounds of type *(20)*, X=NC_6H_5 [=*(4)*], or *(20)*, X=O [=*(5)*], and 1,3-dicarbonyl compounds *(69)*.

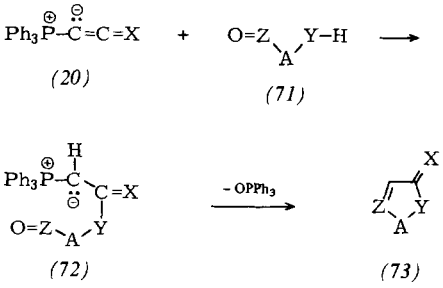
X in *(20)*	R^3	R^4	M.p. [°C]	Yield [%]
NC_6H_5	CH_3	CH_3	85	166
NC_6H_5	C_6H_5	CH_3	73	181
NC_6H_5	CH_3	NH—C_6H_5	75	188
O	C_6H_5	C_6H_5	78	147
O	C_6H_5	CH_3	71	151
O	CH_3	OCH_3	61	152

The adducts formed by *(69)* and *(4)*, R=NC_6H_5, can exist in the tautomeric forms *(70A)* and *(70B)*. The enol form is shown to predominate by the ^{1}H-NMR spectrum, which suggests partial double-bond character of the C_α—C_β bond in *(70)*[46,47].

Similar properties are observed for the adducts obtained from *(5)* and *(69)*, the enol form corresponding to *(70B)* being present. Owing to extensive delocalization of the lone pair in *(70)* and in analogous compounds obtained from *(5)*, these phosphoranes can no longer be subjected to Wittig reaction. Several adducts are shown in Table 6.

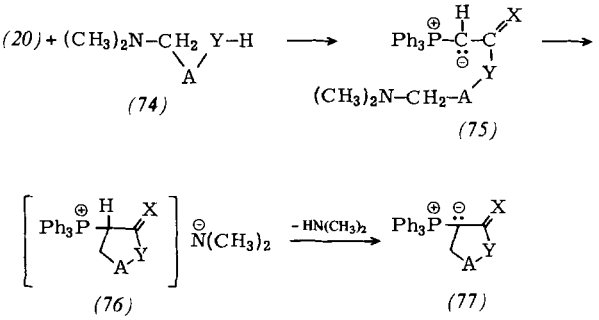
4.4.4. Addition of Acidic Compounds with Subsequent Cyclization

Phosphacumulene ylides *(20)* are interesting building blocks for the synthesis of heterocycles since they can react with molecules having an acid Y—H bond and a group capable of cyclization with the ylide function after addition[48]. Thus



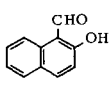
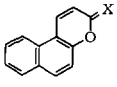
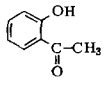
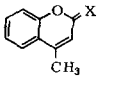
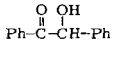
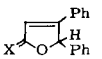
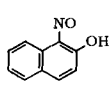
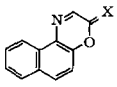
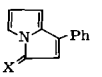
(20) (71) (72) (73)

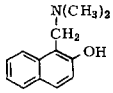
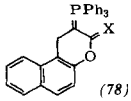
compounds of the general type *(71)* add to *(20)* to give first the ylides *(72)* which cyclize by intramolecular Wittig reaction with formation of a C=C double bond (Z=CH) or a C=N double bond (Z=N) (Table 7).



(74) (75) (76) (77)

Table 7. Heterocycles of types *(73)* and *(77)* from phosphacumulene ylides *(20)* and molecules having the general structure *(71)* and *(74)*, respectively.

(71)	*(73)*	X	M.p. [°C]	Yield [%]
		O	117	73
		NC_6H_5	137	68
		$C_{13}H_8$ [a]	197	41
		$C_{13}H_8$ [a]	162	78
		O	149	58
		NC_6H_5	209	29
		NC_6H_5	183	71
		O	81	86
		NC_6H_5	99	81

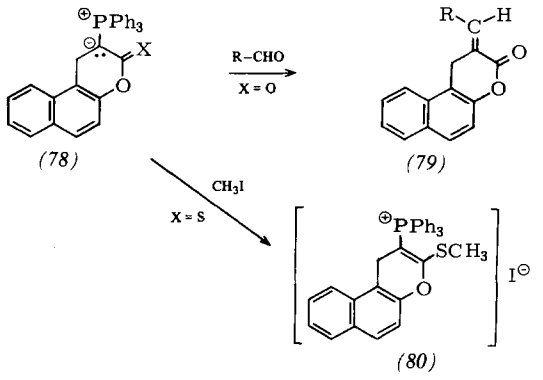
(74)	*(77)*	X	M.p. [°C]	Yield [%]
		O	217	69
		S	172 [b]	93

(78)

[a] $C_{13}H_8$=9-fluorenylidene.
[b] Softening without definite melting point.

Molecules of type *(74)* bearing a Mannich base group react with *(20)* initially giving ylides *(75)*, which are transformed into *(76)* by nucleophilic substitution of the dimethylamine anion. Elimination of dimethylamine from *(76)* affords the cyclic ylides *(77)* which can undergo most ylide reactions[1-3].

Table 7 lists heterocycles prepared by this general, highly versatile synthetic principle[48,49]. *(78)*, X=O, reacts with aldehydes to give the compounds *(79)*; and *(78)*, X=S, gives the phosphonium salt *(80)* with methyl iodide[41].



(78) *(79)* *(80)*

4.4.5. Addition of CH Acids to 2,2-Diethoxyvinylidenetriphenylphosphorane *(11)*

The enhanced reactivity of 2,2-diethoxyvinylidenetriphenylphosphorane *(11)* relative to phosphacumulene ylides *(20)* can be seen in the ability of *(11)* to add CH acids which do not react with *(20)*. Reactions of *(11)* with carbonyl compounds *(81)* bearing a CO—CH_2 group are of particular interest because of the opportunity to construct γ,δ-unsaturated β-dicarbonyl compounds and their enol ethers, as well as 2,3-dihydro-4-pyranones[50].

The reagent *(11)* and the carbonyl compounds *(81)* initially form the ion pair *(82)*, which is in equilibrium with the Michael adduct *(83)*. Irreversible loss of ethanol from *(83)* gives the phosphoranes *(84)* which are vinylogs of α-keto ylides; they are stable toward oxygen and are hydrolyzed only slowly by cold water. They can be described by the resonance structures *(84A)* and *(84B)*. Participation of *(84B)* is indicated by the appearance of the carbonyl band in the IR spectrum at 1587—1595 cm^{-1}. In the ^{1}H-NMR spectrum of *(84)*, $R^1=R^2=H$, the signal of this proton is split into a doublet by long-range coupling.

The phosphoranes *(84)* undergo Wittig reactions with aldehydes *(85)*. One obtains the enol ethers *(86)* of γ,δ-unsaturated β-dicarbonyl compounds. They can be cleaved by acids to the unsaturated β-dicarbonyl compounds *(87)* which exist almost entirely in one of their enolic forms *(87B)* or *(87C)* (Table 8). If R^1 in *(87)* is hydrogen, R^2 aliphatic, and R^3 aromatic then the compounds cyclize to give 2-alkyl-6-aryl-2,3-dihydro-4-pyrones *(88)*, which regenerate *(87)* on treatment with alcoholic potassium hydroxide solution.

Since *(11)* can easily be prepared starting from ethyl acetate, a versatile synthetic scheme can be drawn for γ,δ-unsaturated β-dicarbonyl compounds *(87)* and their enol ethers *(86)*.

Like the ketones *(81)*, many CH acids *(89)* which are not activated by CO groups also undergo Michael addition to *(11)*[51]. The phosphoranes *(90)* are obtained, some of which are listed in Table 9. While compounds *(90a)*—*(90d)* fail to react with carbonyl compounds, *(90e)*—*(90h)* and aromatic aldehydes, give the dienes *(91)*. The resulting fulvenes

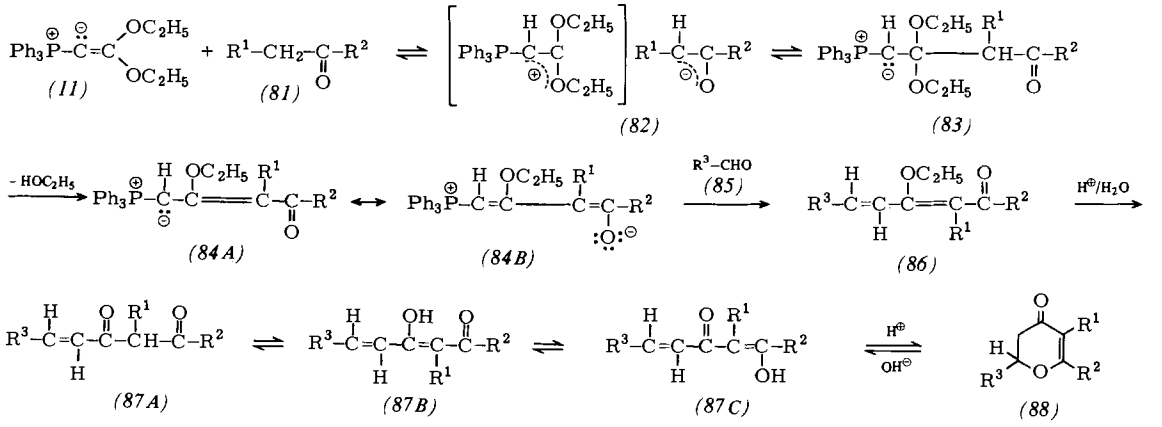


Table 8. Phosphoranes *(84)* from ketones *(81)* and the phosphaallene ylide *(11)*; enol ether *(86)* and 1,3-dicarbonyl compounds *(87)* from *(84)* and aldehydes *(85)*.

		(84)			*(86)*		*(87)*	
R^1	R^2	M.p. [°C]	Yield [%]	R^3	M.p. [°C]	Yield [%]	M.p. [°C]	Yield [%]
H	C_6H_5	174	65	C_6H_5	85	57	111	95
				CH_3	36	71 [a]	58	73
				n-C_8H_{17}	[b]	53 [a]	28	73
H	CH_3	146	55	C_6H_5	50	53	86	94
—$(CH_2)_4$—		177	69	C_6H_5	51	51	93	81
H	OC_2H_5	166	74	C_6H_5	55	66	44	61

[a] Hydrolysis initially gives the pyrones *(88)* (yield >90%). On treatment with alcoholic potassium hydroxide solution they are transformed into *(87)*.
[b] B.p. 134—136°C/0.2 torr.

(90e) polymerize very easily, whereas compounds *(90f)* to *(90h)* are stable.

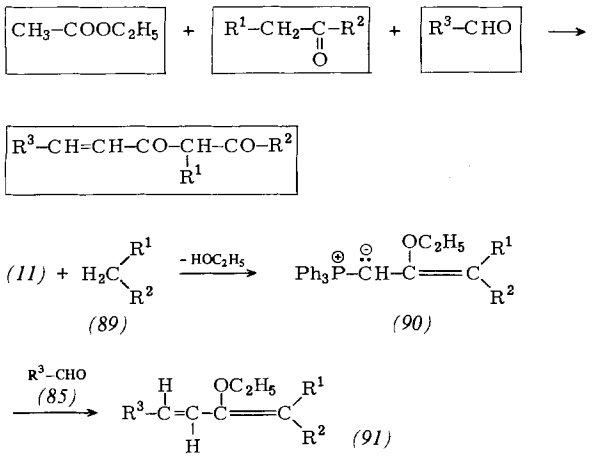


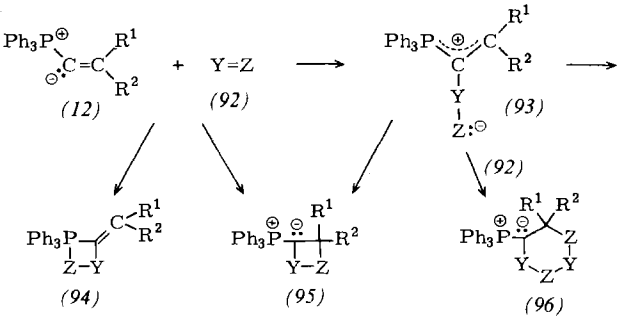
Table 9. Phosphoranes *(90)* from the phosphaallene ylide *(11)* and CH acids *(89)*.

	(89)	R^1	R^2	*(90)* M.p. [°C]	Yield [%]
a	Nitromethane	H	NO_2	211	49
b	Acetonitrile	H	CN	168	44
c	Benzyl cyanide	C_6H_5	CN	170	44
d	Dimethyl sulfone	H	SO_2—CH_3	163	61
e	Cyclopentadiene			117—120	39
f	Indene			160—163	50
g	Fluorene			192—194	54
h	Phthalide			208—212	55

5. [2+2]-Cycloaddition of Phosphacumulene Ylides and Phosphaallene Ylides

5.1. General Reaction Scheme

Phosphaallene ylides of the general formula *(12)* [example: *(11)*] can undergo [2+2]-cycloaddition at both the C=C and the ylidic C—P bond. Reaction of phosphaallene ylides with π^2 double bond systems *(92)* is expected to yield the cycloadducts *(94)*, *(95)*, and/or *(96)*[52].



Compounds *(12)* and *(92)* can give the dipolar intermediates *(93)*. 1,4-Cyclization to the phosphorus leads to the four-membered rings *(94)* with pentavalent phosphorus, which in most cases undergo secondary reactions. On 1,4-cyclization to the C_β atom, *(93)* can yield the four-membered ring *(95)* with an ylidic function at C_α. Formation of *(94)* and *(95)* is also possible by a concerted reaction without going through the dipolar bond *(93)*.

If the lifetime of *(93)* is sufficiently long, as a result of charge delocalization, then [4+2]-cycloaddition with a second molecule of *(92)*, giving the ylide *(95)* with a six-membered ring, may be expected to occur. Mechanistic studies on these cycloadditions have not yet been completed.

5.2. Reactions with Aldehydes and Ketones

5.2.1. Synthesis of 1,3-Cyclobutanedione Derivatives

Reaction of the phosphacumulene ylides *(20)* with aldehydes or ketones *(97)* gives the 1,3-cyclobutanedione derivatives *(100)* in the case of *(4)* [=*(20)*, X=NR][53] and *(5)* [=*(20)*, X=O][36]; the same products [*(100)*=*(38)*, R^1=H] are also obtained from the dimers *(36)* and aldehydes. Which of the two reaction routes shown actually leads to *(100)* cannot yet be decided.

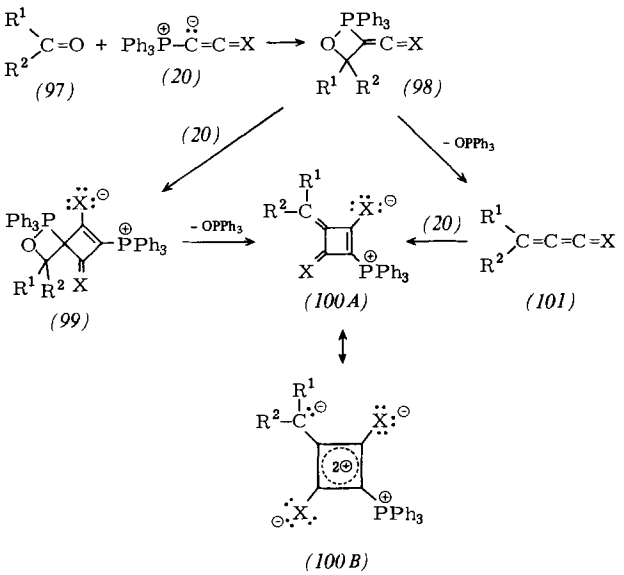
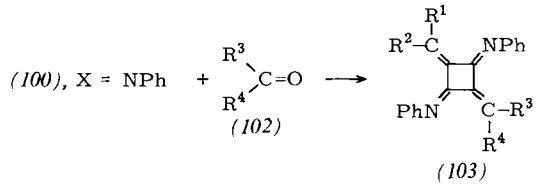


Table 10. Phosphoranes *(100)* from phosphacumulene ylides *(20)* and carbonyl compounds *(97)*.

	X	R^1	R^2	M.p. [°C]	Yield [%]
a	O	*p*-NC—C_6H_4	H	249	78
b	O	C_6H_5	CN	228	27
c	O	CF_3	*p*-Cl—C_6H_4	246	26
d	NC_6H_5	*p*-O_2N—C_6H_4	H	245	64
e	NC_6H_5	C_6H_5—CO	C_6H_5	232	58
f	NC_6H_5	$C_{13}H_8$ [a]		247	75

[a] $C_{13}H_8$ = 9-fluorenylidene.

A [2+2]-cycloaddition of the C=O bond of *(97)* to the ylidic C—P bond of *(20)* furnishes oxaphosphetane *(98)*[54], a dipolar ketene. It can react *via* [2+2]-cycloaddition to the C=C bond of *(20)*, giving spiro compounds *(99)* from which *(100)* arises on elimination of triphenylphosphane



(100), X = NPh + (102) → (103)

Table 11. Compounds (103) from phosphoranes (100), X = NC_6H_5. The relative orientation of R^1 and R^2 could not yet be determined. The geometrical isomerism indicated is arbitrary.

R^1	R^2	R^3	R^4	M.p. [°C]	Color	Yield [%]
p-NO_2—C_6H_4	H	p-NO_2—C_6H_4	H	245	black-red	65
p-CH_3—C_6H_4	H	p-CH_3—C_6H_4	H	239	red	36
p-CH_3—C_6H_4	H	p-NO_2—C_6H_4	H	221	red-violet	40
α-$C_{10}H_7$	H	α-$C_{10}H_7$	H	248	red	54
α-$C_{10}H_7$	H	p-NO_2—C_6H_4	H	218	red-violet	35

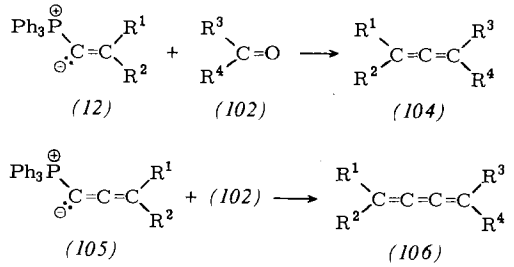
oxide. The second possible reaction route to (100) consists in elimination of triphenylphosphane oxide from (98) to form the alkylideneketene or -ketimine (101)[55], which in turn undergoes cycloaddition to (20) giving the four-membered ring (100). Some ylides of type (100) are shown in Table 10.

The cyclic ylides (100) with X = O cannot undergo further Wittig reaction. However, the *N*-phenylimino derivatives (100), X = NC_6H_5, react with carbonyl compounds (102) to form the deeply colored 1,3-bis(arylmethylene)-2,4-bis-(phenylimino)cyclobutanes (103) (Table 11), which also arise on reaction of (97) and (5) in the molar ratio 1:1[53]. The intermediate (100) then reacts with the second molecule of (97) to give (103), $R^1/R^2 = R^3/R^4$.

The reactivity of the ylides (100), X = NC_6H_5, crucially depends upon R^1 and R^2. Thus compounds (100e) and (100f) no longer react with carbonyl components. The diminished reactivity suggests increased delocalization of the negative charge, which can be explained in part by the contribution of a resonance structure (100B) with a cyclobutene dication. The negative charge on the exocyclic C atom of (100B) is further delocalized by ligands R^1 and R^2, *e.g.* by the benzoyl group in (100e) and by the fluorenylidene group in (100d).

5.2.2. Synthesis of Allenes and Butatrienes

Phosphaallene ylides of the general structure (22) undergo Wittig reaction ([2+2]-cycloaddition between carbonyl group and the ylide bond) with carbonyl compounds (102) to give allenes (104)[12,56]. With (11) [= (12), $R^1 = R^2 = OC_2H_5$], this reaction is possible only if there is no CH_2 group α to the carbonyl, since the Michael addition discussed in Section 4.4.5 will occur otherwise[50]. The allenes (104) obtained from (11) are particularly reactive. They dimerize in a known manner[12] or engage in secondary reactions[57]. Phosphacumulene ylides (105) and carbonyl compounds (102) react analogously to give butatrienes (106) (Table 12)[11,21].



(12) + (102) → (104)

(105) + (102) → (106)

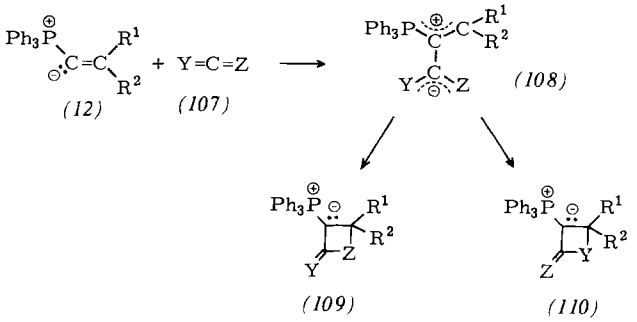
Table 12. Butatrienes (106) from phosphacumulene ylides (105) and carbonyl compounds (102).

R^1	R^2	R^3	R^4	M.p. [°C]	Yield [%]
C_6H_5	C_6H_5	p-NO_2—C_6H_4	H	136	69
C_6H_5	C_6H_5	3,4-$Cl_2C_6H_3$	H	113	80
$C_{12}H_8$ [a]		p-NO_2—C_6H_4	H	288	68
$C_{12}H_8$ [a]		$C_{12}H_8$ [a]		323	71

[a] $C_{12}H_8$ = biphenylylene.

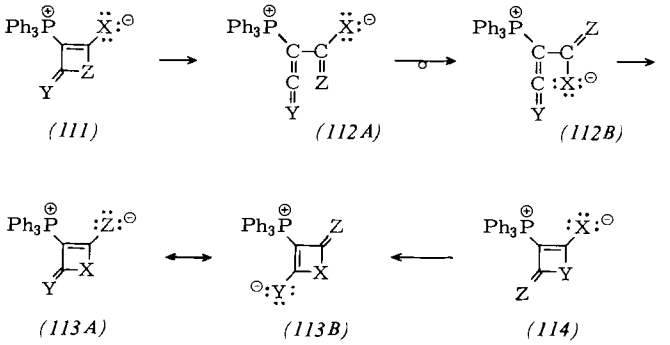
5.3. Reactions with Heteroallenes

Reaction of heteroallenes (107) and phosphaallene ylides (12) can form the polar intermediates (108) which are able to undergo 1,4 cycloaddition to give both (109) and (110). The direction of ring closure depends decisively upon the nucleophilic character of Z compared with that of Y. 1,4-Cyclizations involving phosphorus have not been observed in these reactions.



(12) + Y=C=Z (107) → (108) → (109), (110)

If the ylides (20) are reacted with (107), then formation of the four-membered rings (111) and (114) becomes possible (not all the resonance forms are shown).



(111) → (112A) → (112B)

(113A) ↔ (113B) ← (114)

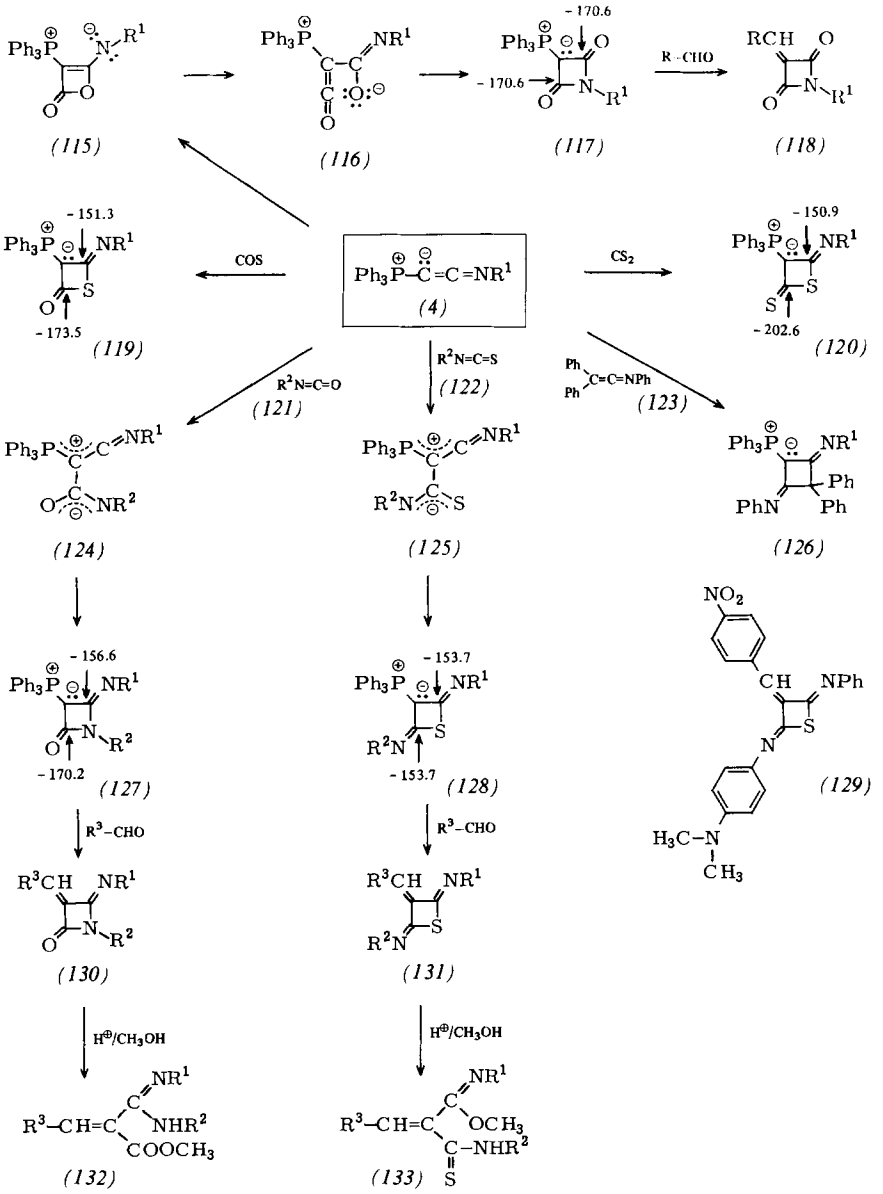
Compounds of type *(111)* can engage in electrocyclic ring cleavage to give *(112A)*. Ring closure, yielding the four-membered ring *(113)*, becomes feasible after prior rotation about the C—C bond, which gives the conformation *(112B)*. The overall reaction sequence amounts to exchange of the exocyclic substituent X with the ring member Z. *(114)* can rearrange analogously to *(113)*. Structural assignment of compounds *(111)*, *(113)*, and *(114)* is best accomplished by ^{13}C-NMR since the C atoms of the C=O, C=N—R, and C=S groups give rise to characteristic signals[58, 59] (see Scheme 1 for examples).

5.3.1. Cycloaddition of *N*-Substituted Keteniminylidenetriphenylphosphoranes

Reaction of *N*-phenylketeniminylidenetriphenylphosphorane *(4)*, $R^1 = C_6H_5$, with CO_2 affords the malonimidylide *(117)*[40] (see Scheme 1). We postulate initial formation of the cycloadduct *(115)* which rearranges to *(117)* according to the electrocyclic reaction sequence discussed in the preceding Section involving the open-chain intermediate *(116)*. Wittig reaction of *(117)* with aldehydes leads to the alkylidene- or arylmethylenemalonimides *(118)*. COS combines with *(4)* to give *(119)*, and CS_2 to form *(120)*[40].

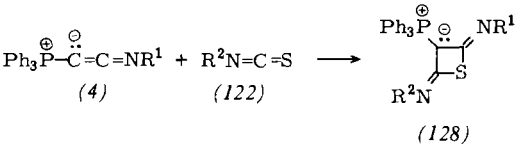
After reaction between *(4)* and isocyanates *(121)* the cycloadducts *(127)* can be isolated. Their ^{13}C-NMR spectra show that ring closure has taken place at the nitrogen. The mass spectrum of the crude product demonstrates formation of small amounts of a six-membered ring analogous to compound *(139)* discussed in Section 5.3.2. We therefore presume that *(127)* is formed in a multistep reaction *via* the polar intermediate *(124)*[40]. Wittig reaction of *(127)* with aldehydes furnishes the novel *N*-substituted arylmethylene- and alkylideneazetidinone derivatives *(130)*, whose acid methanolysis gives the amidines *(132)*.

On reaction of *(4)* with isothiocyanates *(122)*, 1,4-cyclization in the polar intermediate *(125)* occurs *via* the sulfur, which is more nucleophilic than the nitrogen. Thus are obtained the phosphoranes *(128)*[40], which are the first thietane-2,4-diimines (Table 13). Their structures follow from the



Scheme 1. Chemical shifts *vs.* TMS are given for the C atoms (arrow) of selected compounds ($R^1 = R^2 = C_6H_5$).

^{13}C-NMR spectra. Once again, the appearance of a peak due to a compound formed from *(122)* and *(4)* in the molar ratio of 2:1 in the mass spectrum of the crude product is indicative of a polar mechanism. Wittig reaction of *(128)* with aldehydes affords the thietane derivatives *(131)*; their acid methanolysis provides an entry to the amino ethers of arylmethylene- and alkylidene-monothioamides *(133)* of malonic acid which, like *(132)*, should be of interest as starting materials for syntheses of heterocycles.



(4) *(122)* *(128)*

Table 13. Thietane derivatives *(128)* from *(4)* and isothiocyanates *(122)*.

R^1	R^2	M.p. [°C]	Yield [%]
C_6H_5	C_6H_5	191	73
C_6H_5	CH_3	156	71
CH_3	CH_3	127	53
C_6H_5	*p*-$(CH_3)_2N-C_6H_4$	200	68

The thietane *(128)* obtained from *(4)*, $R^1=C_6H_5$, and *p*-dimethylaminophenyl isothiocyanate *(122)*, $R^2=(CH_3)_2N-C_6H_4$, can be transformed into *(129)* by treatment with *p*-nitrobenzaldehyde. Owing to the conjugation between donor and acceptor substituents on the phenyl groups, this compound is blackish-red in crystalline form and gives dark red solutions[40]. Further dyes of this kind can be prepared easily.

N-Phenyldiphenylketenimine *(123)* combines with *(4)* to give four-membered carbocyclic phosphoranes *(126)*[40].

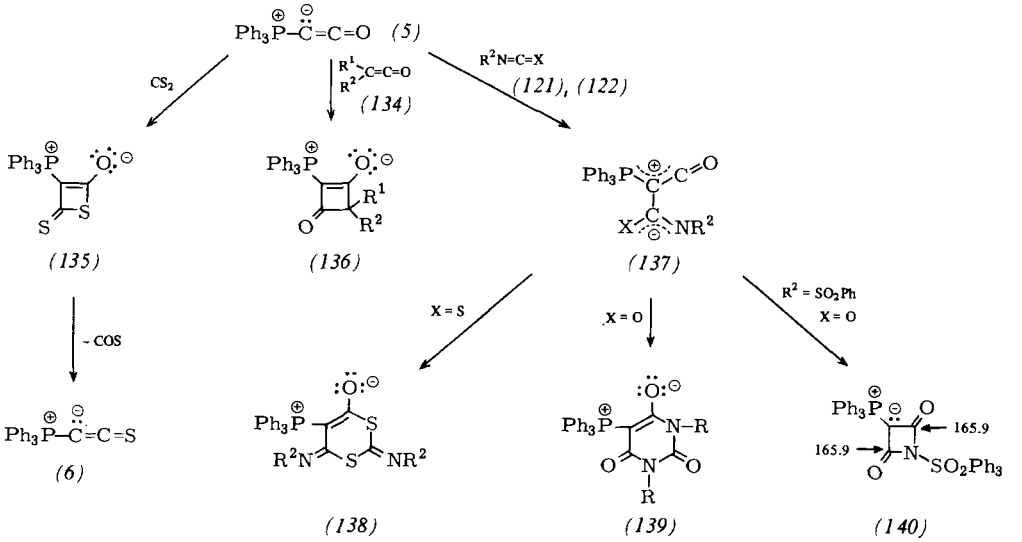
5.3.2. Cycloadditions of Ketenylidenetriphenylphosphorane *(5)*

Ketenes *(134)* undergo [2+2]-cycloaddition with ketenylidenetriphenylphosphorane *(5)* to give the 1,3-cyclobutadienones *(136)*[36]. *(5)* and CS_2 give thioketenylidenetriphenylphosphorane *(6)*. The four-membered ring *(135)* assumed as initial product decomposes by cycloreversion to COS and *(6)*[36].

Isocyanates *(121)* combine with *(5)* in the molar ratio 2:1 to form the pyrimidine derivatives *(139)*[36, 60]. If the reaction is performed with benzenesulfonyl isocyanate *(121)*, $R^2=SO_2C_6H_5$, then 1,4-cyclization proceeds faster than [4+2]-cycloaddition with a second molecule of isocyanate *(121)* in the dipolar intermediate *(137)*. The malonimide derivative *(140)*[41] is obtained.

Isothiocyanates *(122)* react with *(5)* once more in the molar ratio 2:1; however, the sulfur atom which is more nucleophilic than the nitrogen serves to close the ring. The products are the dithiane derivatives *(138)*, whose structure follows from the ^{13}C-NMR and mass spectra[60].

It remains to determine why iminoketenylidenetriphenylphosphorane *(4)* reacts with the heteroallenes *(121)* and *(122)* in the molar ratio 1:1 whereas ketenylidenetriphenylphosphorane reacts in the molar ratio 2:1. The assumption that stabilization of the positive charge in the polar intermediate *(137)* by the oxygen atom is greater than stabilization by the NR group in *(124)* and *(125)* would explain the difference in reaction stoichiometries. Such assumptions are in accord with calculations showing the $H-\overset{\oplus}{C}=O$ ion to be more stable than $H-\overset{\oplus}{C}=NH$[61], and the donor strength

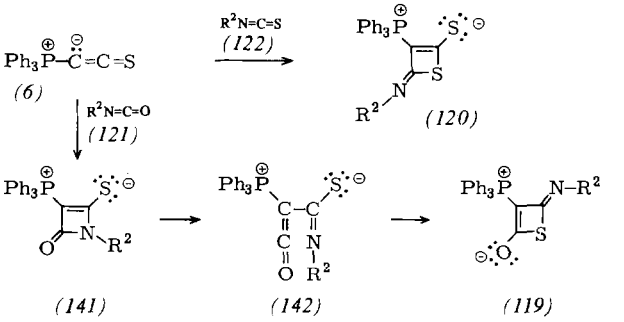


(135) *(136)* *(137)* *(6)* *(138)* *(139)* *(140)*

of an O atom in ketenes to be greater than that of the NR group in ketenimines[62]. The reason for benzenesulfonyl isocyanate *(121)*, $R^2=SO_2C_6H_5$, reacting with *(5)* in the molar ratio 1:1 is still unknown.

5.3.3. Cycloadditions of Thioketenylidenetriphenylphosphorane *(6)*

While compounds *(4)* and *(5)* react both with aromatic and with aliphatic compounds *(121)* and *(122)*, the more



(6) *(120)* *(141)* *(142)* *(119)*

inert thioketenylidenetriphenylphosphorane *(6)* reacts only with aromatic compounds and benzenesulfonylheteroallenes *(121)* and *(122)*.

Reaction of *(6)* and isocyanates *(121)* gives the same ylides *(119)* as are obtained from *(4)* and COS[41]. We assume electrocyclic ring opening of the primary cycloadduct *(141)* to give *(142)*, which undergoes retrocyclization at the sulfur to form *(119)*. Decomposition of *(141)* to *(5)* and an isothiocyanate *(122)* is also conceivable, *(122)* then undergoing [2+2]-cycloaddition to form *(119)*. However, since our studies show that *(5)* and *(122)* always combine in a [2+2+2]-cycloaddition to give a six-membered ring, we rule out the second route.

On reaction of *(6)* with isothiocyanates *(122)*, cycloaddition again takes place at the C=S bond; the resulting phosphorane *(120)* is also formed from *(4)* and CS_2[41].

The slight donor action of sulfur in the C=S bond as a contribution to stabilization of the positive charge in a polar intermediate analogous to *(138)* could swing the balance in favor of a 1:1 molar ratio in the reaction of *(6)* with *(121)* and with *(122)*.

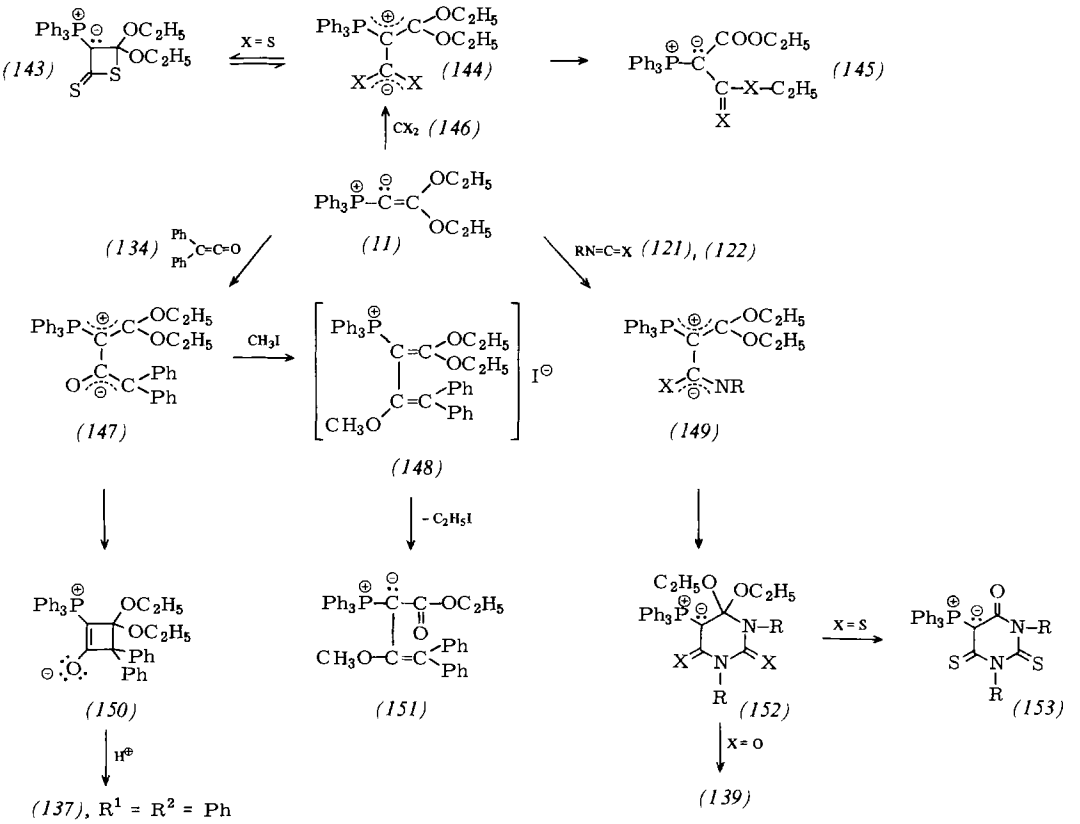
5.3.4. Cycloadditions of Diethoxyvinylidenetriphenylphosphorane *(11)*

In cycloaddition reactions of *(11)* with heteroallenes *(107)* the positive charge is particularly well delocalized in the polar intermediates of the general form *(108)* by the two ethoxy groups. Reaction of *(11)* and CO_2 *(146)*, X=O, gives the polar compound *(144)*, X=O, whose ^{1}H-NMR spectrum shows two triplets and two quartets with widely different chemical shifts for the two OC_2H_5 groups. On heating, *(144)*, X=O, rearranges by intramolecular nucleophilic substitution at one of the two polar CH_2—O bonds to give *(145)*, X=O[63].

On treatment of *(11)* with CS_2 *(146)*, X=S, the primary product *(144)*, X=S, undergoes 1,4-cyclization to *(143)*, owing to the pronounced nucleophilic character of the sulfur; the ^{1}H-NMR spectrum of *(143)* displays a triplet for the two C_2H_5 groups and two very close quartets owing to the diastereomerism of the H atoms belonging to the CH_2 groups. On heating, *(143)* is converted into the open-chain, polar species *(144)*, X=S, which then rearranges to *(145)*, X=S[63].

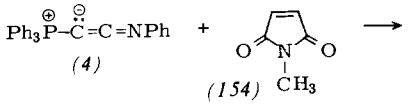
Compound *(11)* and diphenylketene *(134)*, $R^1=R^2=C_6H_5$, in the cold gives the dipole *(147)*, which is also recognized by two triplets and two quartets having very different chemical shifts in the ^{1}H-NMR spectrum. Methyl iodide attacks *(147)* at the oxygen to form the phosphonium iodide *(148)* which becomes *(151)* with loss of ethyl iodide on nucleophilic substitution. On warming to 30—40 °C, *(147)* undergoes irreversible 1,4-cyclization to *(150)*, which on acid treatment gives the cyclobutanedione derivative *(137)*, $R^1=R^2=C_6H_5$, also obtained from *(5)* and *(134)*, $R^1=R^2=C_6H_5$[63].

The lifetime of the polar compound *(149)* formed from *(11)* and isocyanates *(122)* is so long, owing to stabilization of the positive charge by the two ethoxy groups, that [4+2]-cycloaddition can compete with 1,4-cyclization: the six-membered rings *(152)* can be isolated. Acid cleavage of compounds *(152)*, X=O, gives the pyrimidinetrione derivatives *(139)*, which are also formed from *(5)* and *(121)*[63]. Analogous hydrolysis of the thio compounds *(152)*, X=S, gives the dithioxopyrimidinones *(153)* which are not otherwise accessible[60].

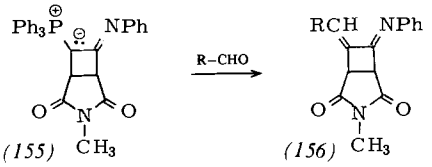


5.4. Cycloaddition to C=C Double Bonds

While ketenes add preferentially to electron-rich C=C double bonds[64], the nucleophilic compounds *(20)* will be expected to react with electron-poor double bonds. On reaction of *(4)*, R = C_6H_5, and *N*-methylmaleimide *(154)*, we obtained the *N*-phenyliminocyclobutane derivative *(155)*,



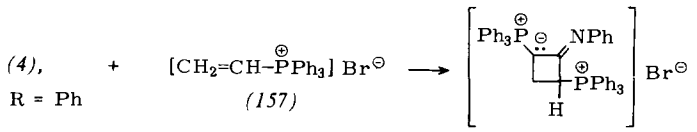
(4) *(154)*



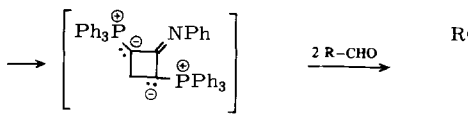
(155) *(156)*

which undergoes Wittig reactions giving *(156)*[65]. Compound *(4)*, R = C_6H_5, gives the same products in the molar ratio 2:1 with dimethyl maleate and dimethyl fumarate. Their structure has not yet been established unequivocally[40].

(4), R = C_6H_5, and triphenyl(vinyl)phosphonium bromide *(157)* add together to give the four-membered ring *(158)*. We have not yet succeeded in preparing the bis-ylide *(159)* in isolable form from *(158)*. However, it can be trapped with aldehydes to give the deeply colored cyclobutane derivatives *(160)*[65].



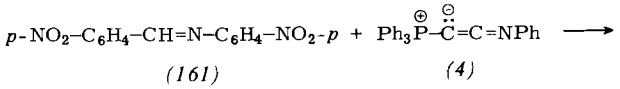
(4), R = Ph *(157)* *(158)*



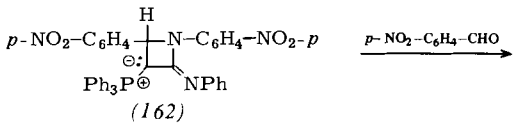
(159) *(160)*

5.5. Cycloaddition to C=N Double Bonds

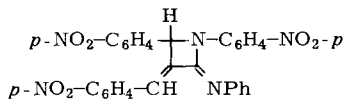
Schiff bases do not generally react with phosphacumulene ylides *(20)*. However, we were able to accomplish reaction of the activated species *N*-(*p*-nitrobenzylidene)-*p*-nitroaniline *(161)* with *(4)*, R = C_6H_5. The cycloadduct has the structure *(162)*. It reacts with *p*-nitrobenzaldehyde to give the 2-(phenylimino)azetidine derivative *(163)*.



(161) *(4)*



(162)

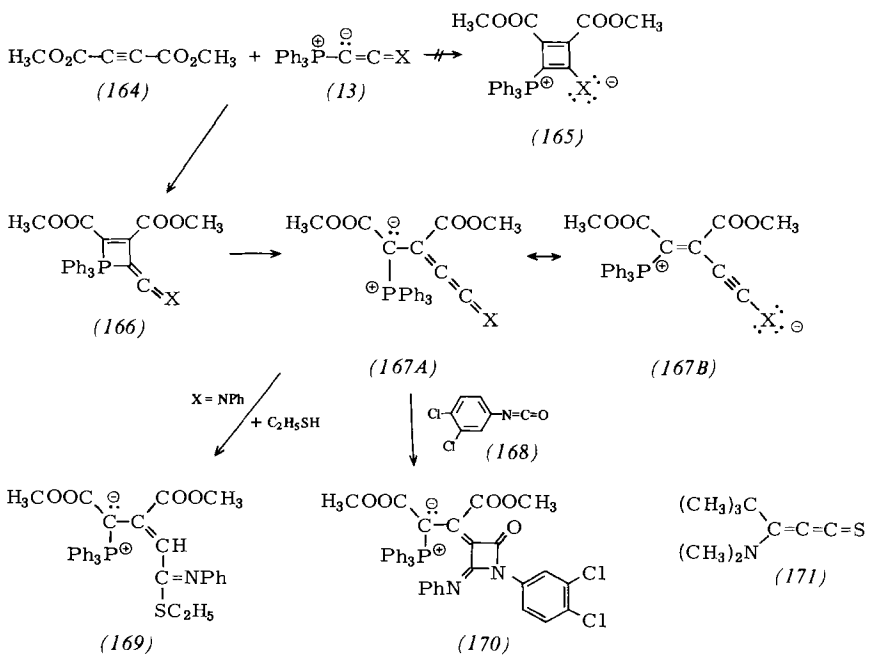


(163)

5.6. Cycloaddition to C≡C Triple Bonds

As may be seen from the results described so far, [2+2]-cycloadditions of *(20)* take place preferentially at the C=C double bond. The only exception is found in the C=O double bond of aldehydes and ketones, which adds to the ylidic bond.

Addition of dimethyl acetylenedicarboxylate *(164)* to the C=C double bond of *(20)* would, however, lead to a compound *(165)* shown in the cyclobutadiene-type resonance form. The reactants *(20)* and *(164)* combine to form the energetically more favorable phosphacyclobutene *(166)*[66] which undergoes electrocyclic ring opening to form *(167)*[67]. Together with compound *(171)*[68] discovered simultaneously,



(164) *(13)* *(165)* *(166)* *(167A)* *(167B)* *(168)* *(169)* *(170)* *(171)*

the ylides *(167)* are the first stable alkylidenethioketenes and alkylideneketenimines, respectively[55].

Owing to the reluctance of sulfur to form double bonds, we can expect a greater contribution of resonance structure *(167B)* to *(167)*, X=S. Accordingly, *(167)*, $X=NC_6H_5$, is more reactive than *(167)*, X=S. The analogy between the reactivity of *(20)* and *(167)* is self-evident.

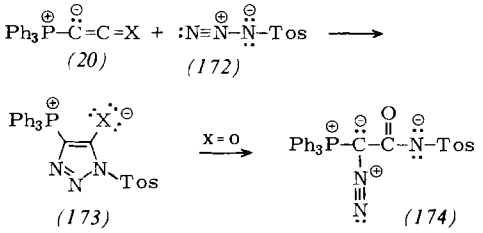
(167), $X=NC_6H_5$, adds ethanethiol to give *(169)*, and undergoes cycloaddition with 3,4-dichlorophenyl isocyanate to yield *(170)*.

6. 1,3-Dipolar Cycloaddition

The study of phosphacumulene ylides and phosphaallene ylides as 1,3-dipolarophiles is still in its infancy. The results we have obtained so far are surveyed in the following three sections.

6.1. Reaction of Phosphacumulene Ylides *(20)* with Toluenesulfonyl Azide

Compounds *(20)* add toluenesulfonyl azide *(172)* to give the triazole derivatives *(173)*[40,41].

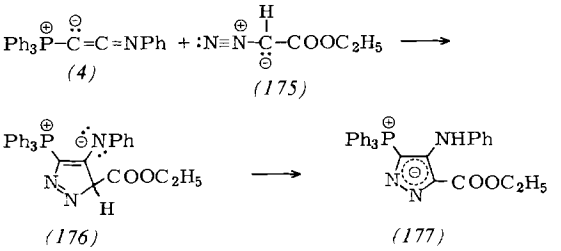


Tos = *p*-CH_3–C_6H_4–SO_2

When X=O, cycloaddition is followed by ring opening to give the final product *(174)*, whose aliphatic diazo character is seen from the band at 2150 cm^{-1} in the IR spectrum.

6.2. Reaction of *(4)* with Ethyl Diazoacetate

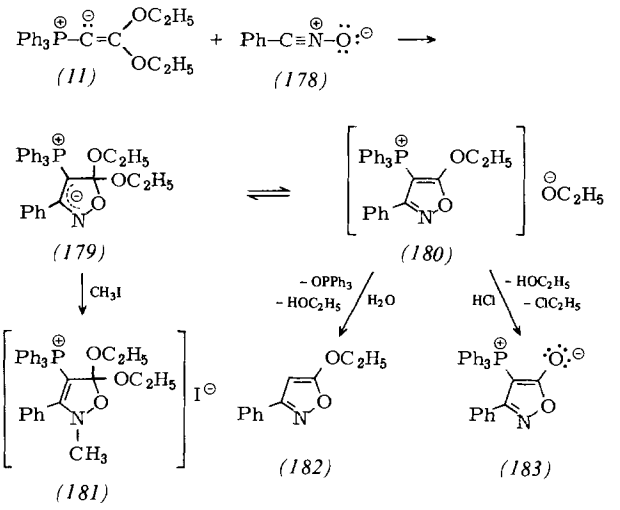
Ethyl diazoacetate reacts with *(4)*, $R=C_6H_5$, to give *(176)*. As shown by the ^{1}H-NMR and IR spectra, this compound rearranges to the tautomeric pyrazole derivative *(177)*[40].



On account of the delocalization of the ylidic electron pair in the aromatic heterocycle, compounds *(173)* and *(177)* are incapable of undergoing ylide reactions.

6.3. Reaction of *(11)* with Phenyl Nitrone

The acetal ylide *(11)* and phenyl nitrone afford the isoxazole derivative *(179)*, shown by its reactions and its ^{1}H-NMR spectrum to be in equilibrium with the phosphonium alkoxide *(180)*. On reaction of *(179)* ⇌ *(180)* with methyl iodide, *(179)* is removed from the equilibrium mixture by *N*-methylation. The phosphonium salt *(181)* is obtained.

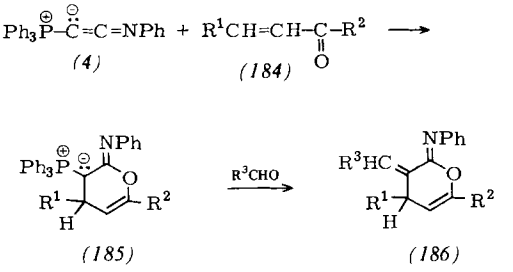


If the reaction product of *(11)* and *(178)* is treated with water, the corresponding phosphonium hydroxide is formed from *(180)*. It is hydrolyzed in known manner[1] to triphenylphosphane oxide and 5-ethoxy-3-phenylisoxazole *(182)*. Aqueous hydrochloric acid transforms *(180)* into the corresponding phosphonium chloride, which very readily loses ethyl chloride to give the phosphorane *(183)*[63].

7. [4+2]-Cycloaddition. Synthesis of Unsaturated Cyclic Imino Ethers

α,β-Unsaturated ketones *(184)*, such as vinyl methyl ketone *(184a)* and benzylideneacetophenone *(184b)* react with *(4)*, $R=C_6H_5$, by [4+2]-cycloaddition[69] to give the cyclic imino ether ylides *(185)*[65]. Their structure follows, *inter alia*, from the ^{13}C-NMR spectra which exhibit a signal at −155 to −157 ppm for the C atom of the C=N double bond, but no signal for a C atom in the carbonyl region, as would be expected for a [2+2]-cycloadduct.

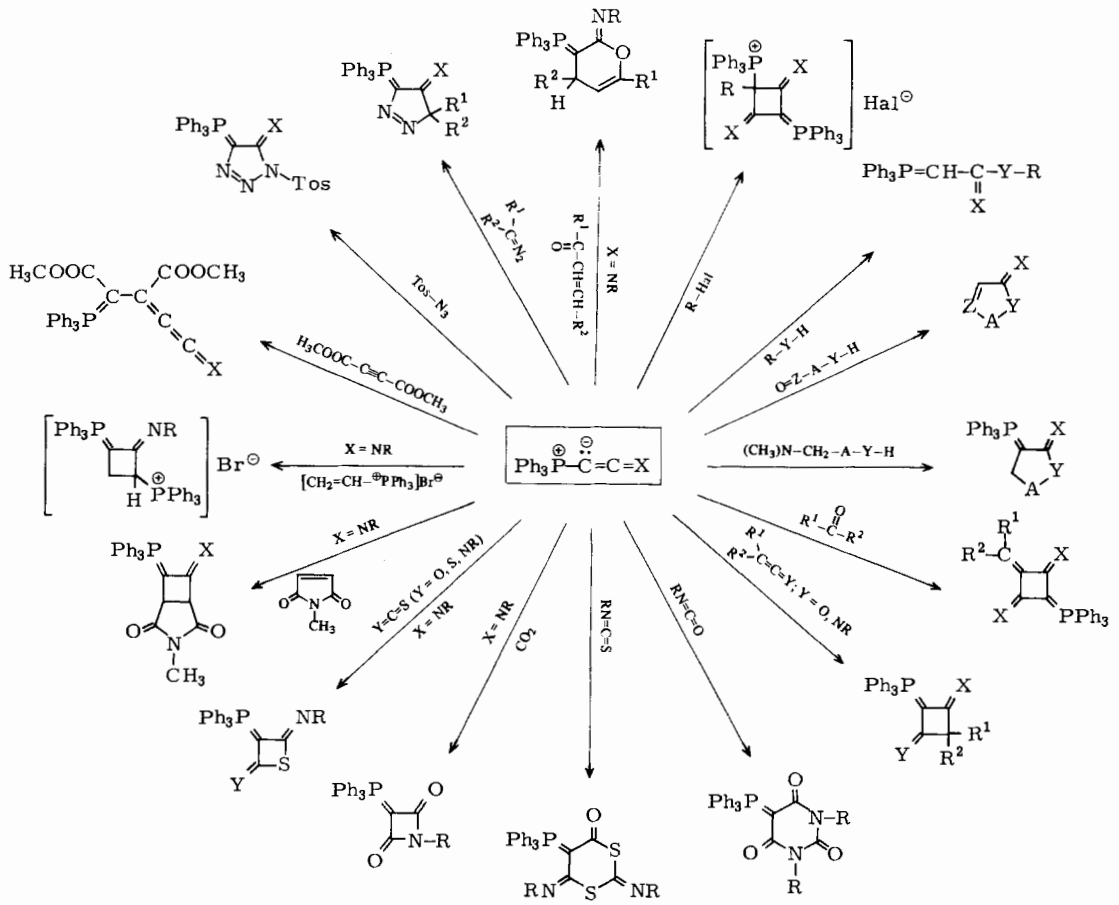
The phosphoranes *(185)* undergo Wittig reaction with aldehydes to form the α-arylmethylenimino or alkylidenimino lactones *(186)*[70].



a, R^1 = H, R^2 = CH_3; *b*, R^1 = R^2 = Ph

8. Conclusion

The orthogonal, strongly nucleophilic $\pi^4 \perp \pi^4$ electron system of the phosphacumulene ylides *(20)* [=*(13)*] and the ability to be transformed into the dipolar $\pi^4 \perp \pi^2$ system of ketenes by addition of an electrophile gives rise to a variety of addition reactions; those considered in the present article are summarized in Scheme 2.



Scheme 2. Addition reactions of phosphacumulene ylides. Most of the adducts are shown in the "phosphorane form" with a C=P double bond (cf. ref. [14]).

The adducts are ylides which can be used for numerous reactions[1-3]. [2+2]-Cycloadditions frequently lead to four-membered carbocyclic or heterocyclic carbonyl or imino compounds which can undergo ring cleavage, and are thus in turn also of interest as synthetic building blocks. Much scope for new experiments is available to the preparative chemist. The bonding in phosphacumulene ylides and their cycloadducts should be of particular interest to the theoretician[14].

This report was only made possible by the dedicated experimental work of Dr. G. Schmid, Dr. D. Sandmeier, Dr. R. W. Saalfrank, Dr. M. Ettlinger, Dipl.-Chem. Ch. Geismann, and Dipl.-Chem. L. Kisielowski, and by X-ray structure analyses performed by Prof. Dr. H. Burzlaff, Dr. U. Voll, and Dr. E. Wilhelm. I am grateful to all of them and my colleagues, especially Dr. P. Hofmann, for numerous stimulating discussions. We are all convinced that the above results represent but the beginning of an interesting new chapter of ylide chemistry.

Received: March 10, 1977 [A 165 IE]
German version: Angew. Chem. 89, 361 (1977)

[1] *H. J. Bestmann*, Angew. Chem. 77, 604, 651, 850 (1965); Angew. Chem. Int. Ed. Engl. 4, 583, 645, 830 (1965).
[2] *H. J. Bestmann, R. Zimmermann*, Fortschr. Chem. Forsch. (Top. Curr. Chem.) 20, 1 (1971).
[3] *H. J. Bestmann, R. Zimmermann*, Chem.-Ztg. 96, 649 (1972).
[4] Further reviews: *A. W. Johnson:* Ylid Chemistry. Academic Press, New York 1966: *H. J. Bestmann, R. Zimmermann* in *G. M. Kosolapoff, L. Maier:* Organophosphorus Compounds. Wiley, New York 1972, Vol. 3; *M. Schlosser* in *H. Zimmer, K. Niedenzu:* Methodicum Chimicum. Thieme, Stuttgart 1976, Vol. 7, p. 529; *S. Trippett:* Organophosphorus Chemistry. Specialist Periodical Reports, Chemical Society, London 1970–1975, Vol. 1–6.
[5] *F. Ramirez, N. B. Desai, B. Hansen, N. McKelvie*, J. Am. Chem. Soc. 83, 3539 (1961).
[6] *C. N. Matthews, G. H. Birum*, Tetrahedron Lett. *1966*, 5707; *C. N. Matthews, J. S. Driscoll, G. H. Birum*, Chem. Commun. *1966*, 736.
[7] *G. H. Birum, C. N. Matthews*, Chem. Ind. (London) *1968*, 653; X-ray structure analysis: *R. Chiocolla, J. J. Daly*, J. Chem. Soc. *A1968*, 568.
[8] *G. H. Birum, C. N. Matthews*, Chem. Commun. *1967*, 137.
[9] *C. N. Matthews, G. H. Birum*, Acc. Chem. Res. 2, 373 (1969).
[10] *K. W. Ratts, D. B. Partos*, J. Am. Chem. Soc. 91, 6112 (1969).
[11] *H. J. Bestmann, R. W. Saalfrank*, Angew. Chem. 82, 359 (1970); Angew. Chem. Int. Ed. Engl. 9, 367 (1970); *H. J. Bestmann, R. W. Saalfrank, J. P. Snyder*, Chem. Ber. 106, 2601 (1973).
[12] Use of *(1)* and *(5)* as complex ligands: *W. C. Kaska, D. K. Mitchell, R. F. Reichelderfer, W. D. Korte*, J. Am. Chem. Soc. 96, 2847 (1974);

H. Berke, E. Lindner, Angew. Chem. *85*, 668 (1973); Angew. Chem. Int. Ed. Engl. *12*, 667 (1973); *E. Lindner*, J. Organomet. Chem. *74*, 229 (1976).

[13] Cf. calculations on simple ylides without cumulated double bonds: *R. Hoffmann, D. B. Boyd, St. Z. Goldberg*, J. Am. Chem. Soc. *92*, 3929 (1970); *D. B. Boyd, R. Hoffmann, ibid. 93*, 1064 (1971); *I. Absar, J. R. Van Wazer, ibid. 94*, 2382 (1972); *K. A. Ostoja Starzewski, H. tom Diek, H. Bock*, J. Organomet. Chem. *65*, 311 (1974); *J. M. F. van Dijk, H. M. Buck*, Rec. Trav. Chim. Pays-Bas *93*, 155 (1974); *K. A. Ostoja Starzewski, H. Bock*, J. Am. Chem. Soc. *98*, 8486 (1976); *H. Lischka, ibid. 99*, 353 (1977).

[14] We prefer a polar formulation over one with a C=P double bond.

[15] *H. Burzlaff, U. Voll, H. J. Bestmann*, Chem. Ber. *107*, 1949 (1974).

[16] *J. C. Jochims, F. A. L. Anet*, J. Am. Chem. Soc. *92*, 5524 (1970).

[17] *H. Burzlaff, E. Wilhelm, H. J. Bestmann*, Chem. Ber., in press.

[18] *J. J. Daly, P. Wheatley*, J. Chem. Soc. *A 1966*, 1703.

[19] *J. J. Daly*, J. Chem. Soc. *A 1967*, 1913.

[20] *H. J. Bestmann, G. Schmid*, Angew. Chem. *86*, 274 (1974); Angew. Chem. Int. Ed. Engl. *13*, 273 (1974).

[21] *H. J. Bestmann, G. Schmid*, Tetrahedron Lett. *1975*, 4025.

[22] *H. J. Bestmann, D. Sandmeier*, Angew. Chem. *87*, 630 (1975); Angew. Chem. Int. Ed. Engl. *14*, 634 (1975).

[23] *U. Wannagat, H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

[24] For use of *(22)* in preparing ylides, cf. *H. J. Bestmann, W. Stransky, O. Vostrowsky*, Chem. Ber. *109*, 1694 (1976).

[25] *H. J. Bestmann, R. Engler, H. Hartung*, Angew. Chem. *78*, 1100 (1966); Angew. Chem. Int. Ed. Engl. *5*, 1040 (1966).

[26] For reaction of *(21d)* with organolithium compounds, cf. *H. J. Bestmann, R. Besold, D. Sandmeier*, Tetrahedron Lett. *1975*, 2293; *J. Buckle, P. G. Harrison*, J. Organomet. Chem. *77*, C22 (1974).

[27] An excellent treatment of this topic with exhaustive literature references is to be found in *L. Ghosez, M. J. O'Donnel* in *Marchand, Lehr:* Pericyclic Reactions. Academic Press, New York, Vol. 2, in press.

[28] The fact that the molecule has a $P—C_\alpha—C_\beta$ angle differing from 180° according to X-ray analysis can be neglected in these considerations. There is no interaction between the carbanion lone pair and the π-electrons of the C=O group in the same plane even when $P—C_\alpha—C_\beta$ is linear.

[29] Since IR spectroscopic data show the betaine form to make the greatest contribution, we generally employ the betaine form for the α-carbonylphosphoranes.

[30] *R. Gompper, G. Seybold*, Angew. Chem. *80*, 804 (1968); Angew. Chem. Int. Ed. Engl. *7*, 824 (1968); *ibid. 83*, 44 (1971) and *10*, 67 (1971); *R. Gompper, S. Mensch, G. Seybold, ibid. 87*, 711 (1975) and *14*, 704 (1975), resp.; *R. Gompper, J. Kroner, G. Seybold, H. U. Wagner*, Tetrahedron *32*, 629 (1976); *H. J. Lindner, B. v. Gross*, Chem. Ber. *107*, 598 (1974); *M. Neuenschwander, A. Niederhauser*, Chimia *22*, 491 (1968); Helv. Chim. Acta *53*, 519 (1970).

[31] *H. J. Bestmann, G. Schmid, D. Sandmeier, L. Kisielowski*, Angew. Chem. *87*, 275 (1977); Angew. Chem. Int. Ed. Engl. *16*, 268 (1977).

[32] *H. J. Bestmann, G. Schmid, D. Sandmeier, L. Kisielowski, Ch. Geismann*, unpublished.

[33] For hydrolysis of alkylidenephosphoranes, cf. ref. [1].

[34] *H. J. Bestmann, L. Kisielowski, W. Distler*, Angew. Chem. *88*, 297 (1976); Angew. Chem. Int. Ed. Engl. *15*, 298 (1976).

[35] *H. J. Bestmann, Ch. Geismann*, unpublished.

[36] *G. H. Birum, C. N. Matthews*, J. Am. Chem. Soc. *90*, 3842 (1968).

[37] *G. Märkl*, Chem. Ber. *94*, 3005 (1961); *S. T. D. Gough, S. Trippett*, J. Chem. Soc. *1962*, 2333; cf. also formation of *(46)* from *(44)* by reaction with PCl_5 and NaOH: *G. Märkl*, Angew. Chem. *74*, 217 (1962); Angew. Chem. Int. Ed. Engl. *1*, 160 (1962).

[38] *H. J. Bestmann, Ch. Geismann*, Justus Liebigs Ann. Chem. *1977*, 282, and further references cited therein.

[39] *C. N. Matthews, G. H. Birum*, Tetrahedron Lett. *1966*, 5707.

[40] *H. J. Bestmann, G. Schmid*, unpublished; *G. Schmid*, Dissertation, Universität Erlangen-Nürnberg 1974.

[41] *H. J. Bestmann, D. Sandmeier*, unpublished; *D. Sandmeier*, Dissertation, Universität Erlangen-Nürnberg 1977.

[42] *H. J. Bestmann, S. Pfohl*, Angew. Chem. *81*, 750 (1969); Angew. Chem. Int. Ed. Engl. *8*, 762 (1969).

[43] *H. J. Bestmann, H. Salbaum*, unpublished; cf. also ref. [2].

[44] *H. A. Staab, N. Sommer*, Angew. Chem. *74*, 294 (1962); Angew. Chem. Int. Ed. Engl. *1*, 270 (1962).

[45] Cf. also *H. Yoshida, M. Matsuura, T. Ogata, S. Inokawa*, Chem. Lett. *1974*, 1065 (1974); Bull. Chem. Soc. Jpn. *48*, 2907 (1975).

[46] *H. J. Bestmann, G. Schmid, D. Sandmeier*, unpublished.

[47] Cf. *H. J. Bestmann, G. Joachim, I. Lengyel, J. F. M. Oth, R. Merényi*, Tetrahedron Lett. *1966*, 3355; *H. I. Zeliger, J. P. Snyder, H. J. Bestmann, ibid. 1969*, 2199; *1970*, 3313; *J. P. Snyder, H. J. Bestmann, ibid. 1970*, 3317.

[48] *H. J. Bestmann, G. Schmid, D. Sandmeier*, Angew. Chem. *88*, 92 (1976); Angew. Chem. Int. Ed. Engl. *15*, 115 (1976).

[49] Concerning the method of cyclization with vinylphosphonium salts and carbonyl compounds with acidic H atoms developed by *E. E. Schweizer et al.*, see the literature surveys in refs. [2] and [3].

[50] *H. J. Bestmann, R. W. Saalfrank*, Angew. Chem. *82*, 359 (1970); Angew. Chem. Int. Ed. Engl. *9*, 367 (1970); Chem. Ber. *109*, 403 (1976).

[51] *H. J. Bestmann, M. Ettlinger, R. W. Saalfrank*, Justus Liebigs Ann. Chem. *1977*, 276.

[52] Concerning [2+2]-cycloaddition and its intermediates, ref. *R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. Int. Ed. Engl. *8*, 312 (1969).

[53] *H. J. Bestmann, G. Schmid*, Angew. Chem. *86*, 479 (1974); Angew. Chem. Int. Ed. Engl. *13*, 473 (1974).

[54] Concerning the detection of the oxaphosphetane intermediate in the Wittig reaction, cf. refs. [9, 27]; *E. Vedejs, K. A. J. Snoble*, J. Am. Chem. Soc. *95*, 5778 (1973); *H. J. Bestmann, W. Downey, K. Geibel*, unpublished; *W. Downey*, Diplomarbeit, Universität Erlangen-Nürnberg 1975; *M. Schlosser, A. Piskala, C. Tarchini, H. B. Tuong*, Chimia *29*, 341 (1975).

[55] Concerning the possible occurrence of alkylideneketenes as intermediates and their detection, cf. *G. A. Taylor*, Chem. Commun. *1968*, 1314; J. Chem. Soc. *C 1969*, 1755; *M. Rey, E. Dunkelblum, R. Allain, A. S. Dreiding*, Helv. Chim. Acta *53*, 2159 (1970); *R. F. C. Brown, F. W. Eastwood, K. J. Harrington*, Aust. J. Chem. *27*, 2373 (1974); *R. F. C. Brown, G. L. McMullen, ibid. 27*, 2385 (1974); *R. F. C. Brown, F. W. Eastwood, K. J. Harrington, G. L. McMullen, ibid. 27*, 2393 (1974); *R. F. C. Brown, F. W. Eastwood, S. Tinglim, G. L. McMullen, ibid. 29*, 1705 (1976); *G. J. Baxten, R. F. C. Brown, ibid. 28*, 1551 (1975); *H. Hart, D. L. Dean, D. N. Buchman*, J. Am. Chem. Soc. *95*, 6294 (1973); *O. L. Chapman, C. C. Chang, J. Kolc, N. R. Rosenquist, H. Tomioka, ibid. 97*, 6586 (1975).

[56] *H. Gilman, R. A. Tomasi*, J. Org. Chem. *27*, 3647 (1962).

[57] *R. W. Saalfrank*, Tetrahedron Lett. *1973*, 3985; *1974*, 4509; *1975*, 4405; Angew. Chem. *86*, 162 (1974); Angew. Chem. Int. Ed. Engl. *13*, 143 (1974).

[58] *E. Breitmaier, W. Voelter:* ^{13}C-NMR Spectroscopy. Verlag Chemie, Weinheim 1974.

[59] *G. L'abbé, S. Toppet, G. Verhelst, C. Martens*, J. Org. Chem. *39*, 3770 (1974); *G. L'abbé, E. van Loock, G. Verhelst, S. Toppet*, J. Heterocycl. Chem. *12*, 607 (1975); *G. L'abbé, G. Vermeulen, J. Flémal, S. Toppet*, J. Org. Chem. *41*, 1875 (1976); *G. L'abbé, G. Verhelst, S. Toppet, ibid.*, in press.

[60] *H. J. Bestmann, D. Sandmeier, R. W. Saalfrank*, unpublished.

[61] *W. A. Lathan, L. A. Curtiss, W. J. Hehre, J. B. Lisle, J. A. Pople.* J. Phys. Org. Chem. *11*, 175 (1974).

[62] *E. Sonveaux, L. Ghosez, J. M. André, A. Delhalle*, unpublished; cited in ref. [27].

[63] *H. J. Bestmann, R. W. Saalfrank*, unpublished; *R. W. Saalfrank*, Dissertation, Universität Erlangen-Nürnberg 1970.

[64] *R. Huisgen, L. A. Feiler*, Chem. Ber. *102*, 339 (1969); *R. Huisgen, L. A. Feiler, P. Otto, ibid. 102*, 3405 (1969); *L. A. Feiler, R. Huisgen, ibid. 102*, 3428 (1969).

[65] *H. J. Bestmann, G. Schmid*, unpublished.

[66] *H. J. Bestmann, O. Rothe*, Angew. Chem. *76*, 569 (1964); Angew. Chem. Int. Ed. Engl. *3*, 512 (1964).

[67] *H. J. Bestmann, G. Schmid, D. Sandmeier*, Angew. Chem. *87*, 34 (1975); Angew. Chem. Int. Ed. Engl. *14*, 53 (1975).

[68] *M. Parmentier, J. Galloy, M. van Meerssche, H. G. Viehe*, Angew. Chem. *87*, 33 (1975); Angew. Chem. Int. Ed. Engl. *14*, 53 (1975).

[69] Concerning [4+2]-cycloaddition between ketenes and vinyl ketones, cf. the survey in ref. [2].

[70] For methods of synthesizing α-methylene lactones, cf. *P. A. Grieco*, Synthesis *1975*, 67.

Flash Thermolysis of Organic Compounds

By Günther Seybold[*]

Flash thermolysis is a special form of gas-phase thermolysis that is particularly suitable for the production and isolation of thermolabile reaction products. The theoretical basis and the instrumental requirements of the method are first given, and the preparative importance of flash thermolysis for the synthesis of thioketenes, allenes, arynes, highly strained ring systems, quinodimethanes, and other reactive compounds is then demonstrated with the aid of examples.

1. Introduction

Thermolysis has long been of great preparative utility in organic chemistry. A special form of thermolysis, *i.e.* flash thermolysis, has recently found wide application in the synthesis of thermolabile compounds, in spectroscopic characterization of short-lived intermediates, and in the investigation of thermolytic reactions[1-4]. The principle of this technique has long been applied in isolated cases, but it is only recently that the great potential of the method has been recognized and utilized in systematic fashion.

Since the generation of radicals has been described in detail in earlier reviews[1,4], the present article will deal mainly with the application of flash thermolysis to the production of nonradical compounds.

2. The Principles of Flash Thermolysis

Flash thermolysis is a special form of gas-phase thermolysis characterized by three important features:

1) The substance to be pyrolyzed remains in the hot zone for only a very short time. The mean residence or contact times are between 1×10^{-3} and 1 s.

2) Flash thermolyses are carried out in such a way that the steady-state concentration of the substance to be pyrolyzed, and thus also the concentration of the products in the hot zone, is very low.

3) Immediately after passage through the hot zone the thermolyzate is cooled to very low temperatures (−196 °C) and thus protected from modification by subsequent reactions.

The short contact times and the low steady-state concentrations are achieved by arranging that the substance to be pyrolyzed flows through a heated tube (the reactor) and is condensed in a cold trap as soon as it leaves the hot zone.

The necessary flow can be produced in two ways.

a) A high vacuum is used, the substance being brought into the reactor by molecular distillation. In this case molecular beams are produced[5]. According to *Knudsen*'s work[5,6], when the pressure is $\leq 10^{-3}$ torr the contact time τ depends only on the molecular velocity V and the reactor geometry, but it is independent of the pressure and of the rate of addition of the substance. τ can be readily calculated. Thus, for a cylindrical tube of length L and diameter D:

$$\tau = 4 \cdot L/(V \cdot k) \text{ [s]}$$

where k is a correction factor taking account of the ratio L/D[6]. Thermal excitation of the molecules occurs mainly by molecule-wall collisions. This form of flash thermolysis is also called flash vacuum thermolysis (often abbreviated to FVT) or very low pressure pyrolysis (VLPP).

b) The compound to be pyrolyzed is carried into the reactor in a stream of inert gas, pressures of 10^{-1} to 10 torr generally being used. The contact times can be calculated from *Poiseuille*'s flow equation when the flow is nonturbulent[6]. For a cylindrical tube of length L and diameter D, with pressures P_1 and P_2 at the tube ends, we have

$$\tau = \frac{8 \eta L^2}{(D/2)^2 (P_1 - P_2)} \text{ [s]}$$

where η is the coefficient of friction of the inert gas. Thus, in this form of flash thermolysis τ depends on the geometry of the reactor, the pressure drop in the reactor, and the viscosity of the carrier gas. In contrast to the situation in vacuum flash thermolysis, thermal excitation occurs here mainly by molecule-molecule collisions.

If the pressures and the rate of substance injection E (mol/s) are constant, a steady state is established within the reactor. The steady-state concentration c depends on the contact time τ, the reactor volume R, and the injection rate E:

$$c = E\tau/R \text{ [mol/l]}$$

In very fast thermolytic reactions ($t_{1/2} \ll \tau$), c defines the product concentration in the reactor. The steady-state concentration in the reactor increases if the rate of injection E is increased (high throughput); this has the consequence that the occurrence of undesirable reactions is greatly enhanced, such as dimerization, polymerization, chain reactions, and generally speaking subsequent reactions with a bimolecular initiation step.

We shall now show, by an example, how the still just tolerable steady-state concentration and thus the optimal injection rate E can be calculated.

Let A be a reactive thermolysis product that can dimerize in the reactor in an undesirable side reaction:

$$2\,A \xrightarrow{k_2} A_2$$

[*] Dr. G. Seybold
Institut für Organische Chemie der Universität
Karlstrasse 23, D-8000 München 2 (Germany)
Present address: BASF AG, Farbenforschung, D-6700 Ludwigshafen (Germany)

(k_2 = rate constant). We then have:

$$-\frac{d[A]}{dt} = k_2 \cdot [A]^2$$

or, for small time intervals:

$$-\frac{\Delta[A]}{[A]} = \Delta t \cdot k_2 \cdot [A] = \tau \cdot k_2 \cdot [A]$$

where $\Delta t = \tau$, because the reaction takes place only in the reactor.

If the proportion of A that undergoes the undesirable side reaction is less than 1 %, we have

$$\Delta[A]/[A] \leq 0.01$$

The steady-state concentration of A can then have, at the most, the value:

$$[A] \leq 0.01/(k_2 \cdot \tau)$$

For $\tau = 10^{-3}$ s and $k_2 = 10^4$ to 10^8 l mol^{-1} s^{-1} (order of magnitude for fast molecule-molecule reactions), a steady-state concentration of 10^{-3} to 10^{-7} mol/l may not be exceeded. If A has radical character, then k_2 lies in the region 10^{10} to 10^{11} l mol^{-1} s^{-1} and the steady-state concentration must be kept extremely low, which in turn requires a very slow rate of injection and hence means low throughputs. Conversely, with stable products (stable with respect to bimolecular subsequent reactions) correspondingly high rates of injection can be used and high throughputs are achieved.

While subsequent reactions with a bimolecular primary step can in all cases be excluded by an appropriate choice of the experimental conditions, it is in principle impossible to avoid fast monomolecular subsequent reactions.

3. Apparatus for Flash Thermolysis

In correspondence with the three basic steps in the thermolysis method, namely injection of the substance, thermolysis in the hot zone, and quenching or condensation of the pyrolyzate, a flash pyrolysis apparatus must in principle consist of three components: an injection unit for the sample, pyrolysis tube, and lastly a cooling or condensation region. The apparatus requirements depend on the problem in question. If the end products are all relatively stable, it is usually sufficient to use one of the types of apparatus in which the heating jacket is outside the vacuum system (external heating). This type of flash thermolysis apparatus is derived from the apparatus often used for conventional gas-phase thermolysis, *e.g.* for the pyrolysis of esters[7], and is characterized by simple construction and easy cleaning; a simple type is illustrated in Figure 1. Many variants of this type are described in the literature[8–12, 102]. The contact times can be extended as desired by the introduction of quartz wool or other filling material into the pyrolysis tube.

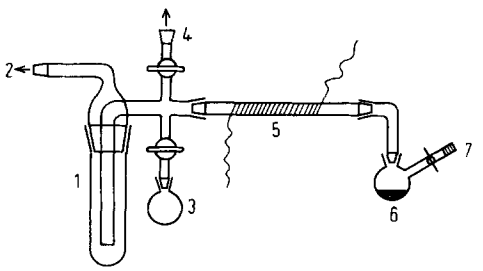


Fig. 1. Flash thermolysis apparatus with external heating. 1, cooling trap; 2, to pump; 3, solvent supply vessel; 4, to manometer; 5, electrically heated quartz tube; 6, substance supply vessel; 7, inert-gas inlet.

The disadvantage of this type of apparatus is the large distance between the hot zone and the cooling traps, and it is therefore unsuitable for the isolation of thermally very unstable products. For the latter purpose those types of apparatus are preferable in which the pyrolysis tube is heated inside the vacuum system[13–15]. This has the advantage that the distance between the surface of the cold traps and the hot zone can be kept very small, whereby even very short-lived molecules such as radicals can be investigated. The disadvantage here is the high cost of construction and operation of this type of apparatus, although this has been largely overcome in the apparatus developed by us[15] (Fig. 2). Our version is characterized especially by the facts that the contact times can be altered in a defined manner by changing the pyrolysis tube and that the capacity of the cold traps has been much increased by use of a rotatable cold finger. This apparatus has recently become commercially available[16]; it is suitable for preparative flash pyrolysis of amounts of up to 10 g. A modified injection system has been developed for substances of very low volatility[17].

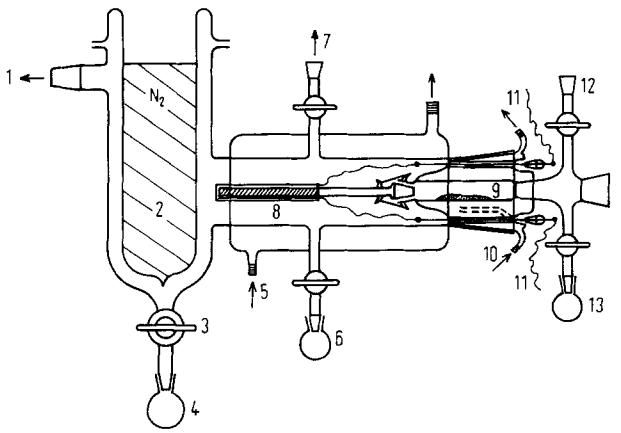


Fig. 2. Flash thermolysis apparatus with internal heating. 1, to pump; 2, rotatable cold finger; 3, coolable tap; 4, receiver; 5, cooling water inlet; 6, solvent supply vessel; 7, to manometer; 8, electrically heated quartz tube; 9, sublimation tube; 10, connection for thermostat; 11, electric leads; 12, inert-gas inlet; 13, storage vessel for volatile substances. The compounds to be pyrolyzed can optionally be introduced at 9 or 13.

The type of cold trap shown in Figure 2 has proved particularly valuable in flash thermolysis, since the labile pyrolyzate can be collected under very mild conditions as the trap thaws. In flash pyrolyses an inert low-boiling solvent is usually added, so that a solvent matrix is formed on the cold trap surface, in which the pyrolyzate exists in finely divided form. When the cold trap thaws out one then obtains a dilute solution of the pyrolyzate[15]. Moreover, a trapping agent may be used in place of the solvent.

One prerequisite for successful flash thermolysis in a molecular beam or in a stream of inert gas is an efficient pumping

system. High-vacuum pumps fitted with ionization gauges are generally used for this purpose[15].

If the cold trap is fitted with quartz or NaCl windows, the thermolyzate can be investigated directly by spectroscopic methods[1,2,18–20]. If the cold trap is replaced by the ion source of a mass spectrometer, the pyrolysis products can be investigated by mass spectroscopy[1,4,21,22]. The combination of pyrolysis with mass spectroscopy not only provides valuable information about short-lived molecules, *e.g.* the ionization potentials of radicals in the gas phase, but also permits the optimal thermolysis temperatures for preparative flash thermolysis to be determined.

4. Applications of Flash Thermolysis

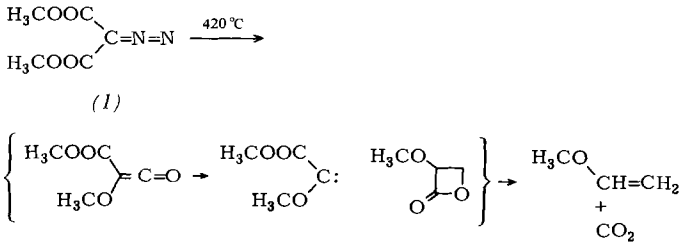
In the following sections the preparative uses of flash thermolysis will be demonstrated by selected examples, though the list of flash thermolyses given here is not claimed to be comprehensive.

Because of the short contact times, appreciably higher temperature are required in flash thermolyses than in thermolyses effected in solution or in the stationary gas phase. For example, whereas 1,2,3-benzothiadiazole in solution is completely cleaved at 200°C with evolution of N_2[23], in the gas phase with a contact time of 10^{-3} s a temperature of 850°C is required for quantitative fission[17]. Bond fissions leading to the formation of nonstabilized radicals generally require temperatures in excess of 1000°C. In the fission of methyl iodide into methyl and iodide radicals a conversion of 20% is achieved only above 1100°C[24]. The temperatures are lower when molecules with an even number of electrons are formed by the thermolysis, as is the case in retro-Diels-Alder reactions or when small stable molecules such as N_2, CO, CO_2, SO_2, or HX are expelled.

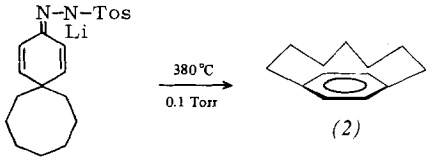
4.1. Flash Thermolysis with the Removal of Nitrogen

4.1.1. Flash Thermolysis of Diazoalkanes and Azides

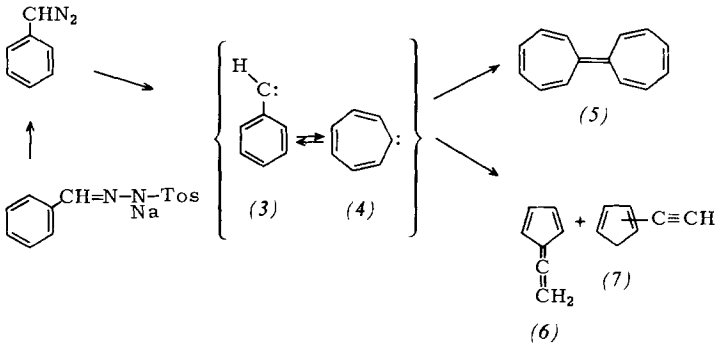
Because of their relatively long lives in the gas phase, the carbenes formed as the primary products in the flash thermolysis of diazoalkanes stabilize themselves by rearrangement[100]. For example, whereas the Wolff rearrangement does not occur on thermolysis of diazomalonic ester *(1)* in solution, it is observed on flash thermolysis[25].



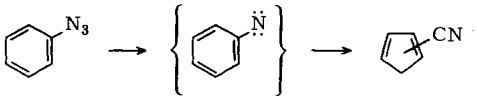
These considerations have found application in the preparation of [7]paracyclophane *(2)*[26]: the salt of the toluenesulfonylhydrazone affords first the diazo compound[27], which then decomposes in the gas phase with loss of nitrogen.



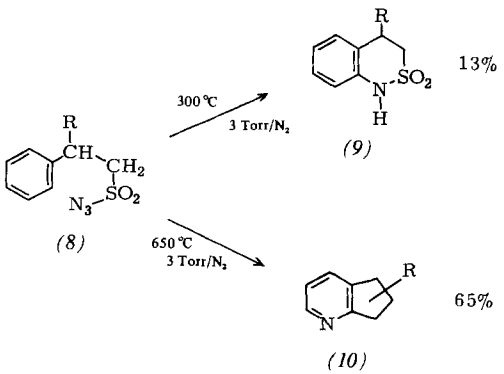
Flash thermolysis of phenyldiazomethane has been studied very thoroughly[28–32]. The phenylcarbene *(3)* first formed exists in equilibrium with cycloheptatrienylidene *(4)*, which at high steady-state concentrations dimerizes to heptafulvene *(5)*[28]; at low steady-state concentrations *(4)* stabilizes itself by ring contraction to give the products *(6)* and *(7)*[29]. If *p*-, *m*-, or *o*-tolyldiazomethane is used, dihydrocyclobutabenzene and styrene are formed as the end products in all cases[30,31]. The mechanism of these reactions has been elucidated by investigations with isotopically labeled compounds[32].



Phenylnitrene, formed as the primary product in the flash thermolysis of phenyl azide, stabilizes itself in a manner analogous to that observed with phenylcarbene: a cyclopentadienecarbonitrile is found as the main product[33–36,44]. *Wentrup et al.* also investigated the hetarylnitrenes formed in the flash thermolysis of annelated tetrazole derivatives[37,100].



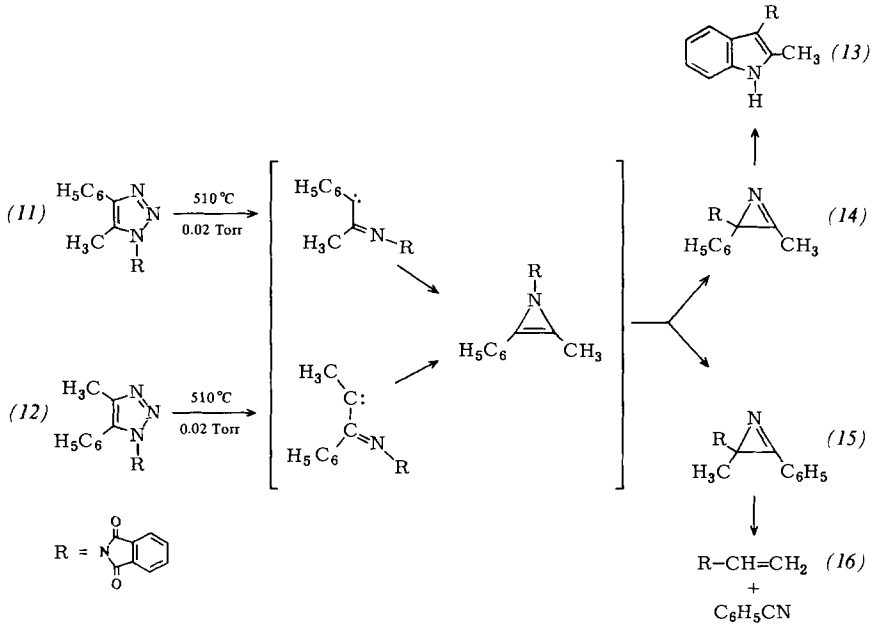
Flash thermolysis of the sulfonyl azide *(8)* gave surprising results: whereas at 300°C, as in thermolysis in solution, the formation of the thiazine derivative *(9)* predominated, at 650°C a 65% yield of the cyclopentapyridine derivative *(10)* was obtained[38]. Compound *(9)* is formed by an insertion



reaction of the nitrene formed as an intermediate. For the formation of *(10)* the authors assumed addition of the nitrene to the benzene ring with subsequent release of SO_2 and rearrangement.

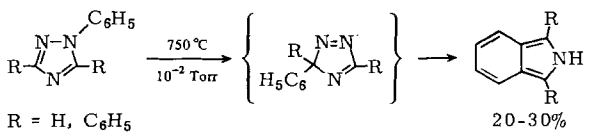
4.1.2. Flash Thermolysis of Triazoles and Thiadiazoles

Flash thermolysis of 1*H*-1,2,3-triazole derivatives has been thoroughly investigated by *Rees et al.*[39–41]. 2*H*-Azirines, indole derivatives, ketene imines, and nitriles could be isolated, depending on the nature of the substituent and the pyrolysis conditions. According to the experimental data available, flash thermolysis of 1,2,3-triazole very probably involves the antiaromatic 1*H*-azirine as an intermediate. Thus, flash pyrolysis of the isomeric triazoles *(11)* and *(12)* gives in each case the same mixture of products *(13)* to *(16)* together with benzonitrile[39].

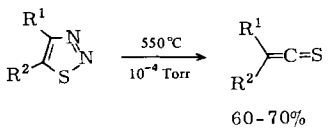


Similar results are obtained on using isotopically labeled compounds[41].

On flash thermolysis phenyl-substituted 1,2,4-triazoles yield, surprisingly, isoindoles, but the reaction becomes understandable if a primary 1,3-shift of the phenyl group is assumed[42].



Flash thermolysis of 1,2,3-thiadiazoles leads to good yields of thioketenes, a class of compounds that with a few exceptions was previously unknown[17,43]. Here the preparative advantage of flash thermolysis is particularly evident, since if the thermolysis of the thiadiazoles is carried out in a high-boiling solvent then only the secondary products derived from the thioketenes can be isolated[52].

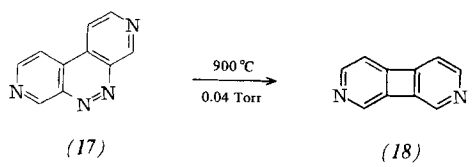


Flash thermolyses of benzotriazole[111] and benzothiadiazole[17] have also been investigated. In agreement with expectation, the ring-contraction products cyclopentadienecarbonitrile and fulvene-6-thione, respectively, are produced.

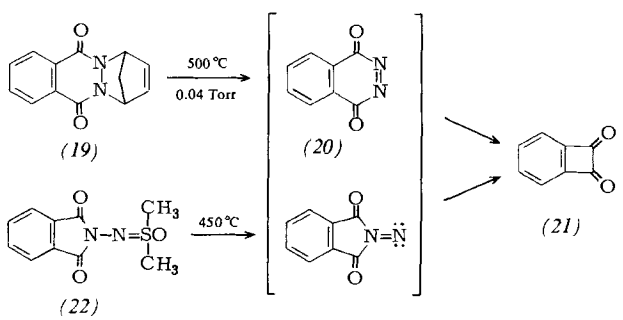
4.1.3. Flash Thermolysis of Pyridazine and Triazine Derivatives

The pyridazine derivative *(17)* loses nitrogen at 900 °C and the diazabiphenylene *(18)* is formed by ring contraction[45].

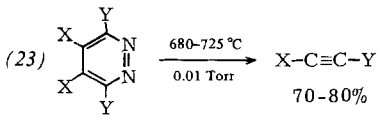
The diazanaphthoquinone *(20)* formed as an intermediate in the flash thermolysis of *(19)* behaves in the same way[46], the cyclobutabenzenedione *(21)* being isolated as the product



in 88 % yield. Compound *(21)* can also be prepared, but in a lower yield, by flash thermolysis of the sulfoximide *(22)*[8]. Nonannelated pyridazines such as *(23)* fragment into acetylene derivatives on flash thermolysis[107]; since no symmetri-



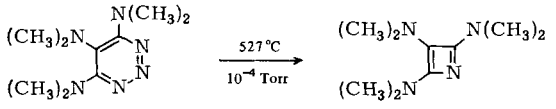
cally substituted acetylene is formed, it is impossible that the reaction should proceed through an intermediate cyclobutadiene or tetrahedrane[107].



(23)

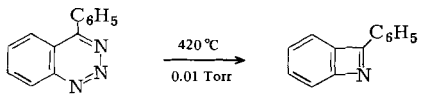
X = C_6F_5, C_2F_5, C_3F_7; Y = C_6F_5, 4-C_5F_4N

In contrast, on flash thermolysis of the triazine (24) an azacyclobutadiene could be isolated for the first time, namely tris(dimethylamino)azete (25)[47], in which the amino groups contribute in a special way to stabilization of the molecule[48].

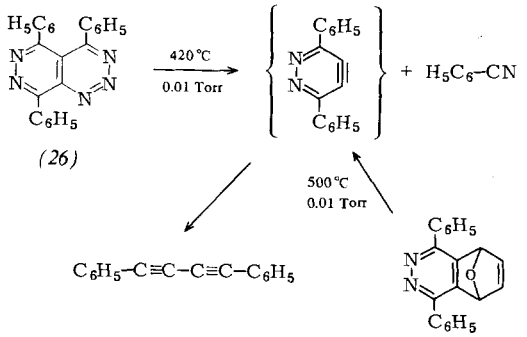


(24) (25)

Similarly, benzotriazines afford benzazete, which can also be isolated in substance[49] and whose structure had been proved by a series of interesting trapping reactions[50].

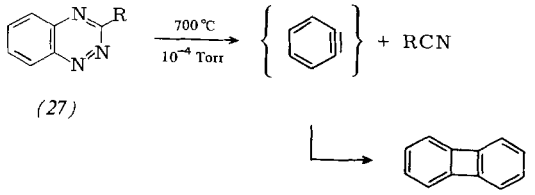


However, unlike benzotriazine, the pyridazinotriazine (26) on flash thermolysis affords benzonitrile and a diacetylene derivative. The authors postulate the formation of dehydropyridazine as an intermediate in this reaction[53].



(26)

The readily accessible 1,2,4-triazines (27) also decompose on flash thermolysis; they yield dehydrobenzene, nitrile, and nitrogen[51].

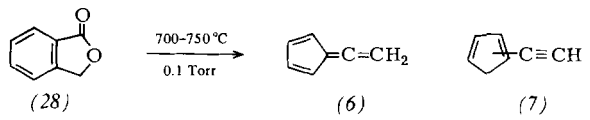


(27)

4.2. Flash Thermolysis with Removal of CO_2, CO, SO_2, or HX

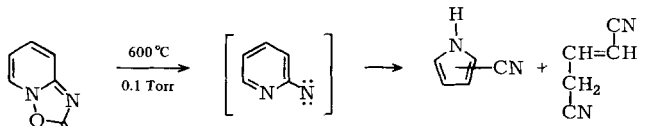
4.2.1. Flash Thermolysis of Lactones

The lactone (28) decomposes on flash thermolysis into carbon dioxide and the allenic derivative (6); a certain amount of the cyclopentadienylacetylene (7) is also produced as a secondary product from (6)[10, 54]. The reaction can be controlled in such a way that it serves as a preparative method for the allene (6)[10].



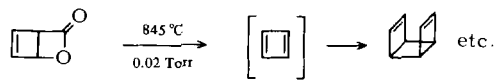
(28) (6) (7)

The pyridine nitrene (30) is similarly formed from the oxadiazolone derivative (29) and, as expected, stabilizes itself by the formation of mixed pyrrolecarbonitriles and by ring opening[55, 112].



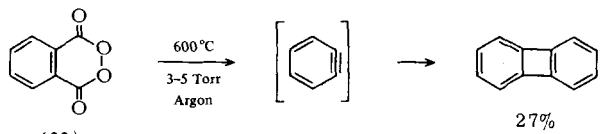
(29) (30)

Hedaya et al. studied the flash thermolysis of the lactone (31)[56]. At 845 °C this smoothly extrudes CO_2 with the formation of cyclobutadiene which on working-up dimerizes into *syn*-tricyclooctadiene (32).



(31) (32)

Attempts to prepare cyclobutadiene by flash thermolysis of the cyclobutadiene(tricarbonyl)iron complex have so far been unsuccessful[57, 58]. Ready and smooth loss of carbon dioxide was observed on flash thermolysis of the peroxide (33)[59].



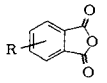
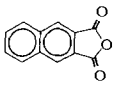
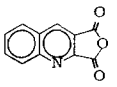
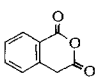
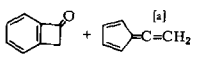
(33)

4.2.2. Flash Thermolysis of Acid Anhydrides

Cyclic acid anhydrides, *e.g.* succinic or maleic anhydride, split off carbon dioxide and carbon monoxide on flash thermolysis with the formation of olefins or acetylenes, respectively[101]. This reaction has been used especially for the preparation of arynes and hetarynes (Table 1), which are either trapped or are isolated as their dimers[60, 117]. Dehydropyridine stabilizes itself by ring opening to an acetylene derivative[62].

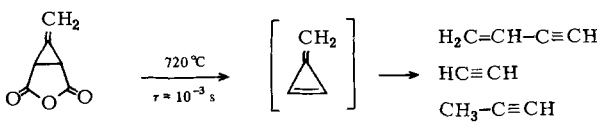
The reaction does not, however, always proceed so smoothly. In some cases only removal of carbon dioxide can be achieved[67, 68].

Table 1. Flash thermolysis of acid anhydrides.

Starting material	Intermediate	Ref.
		[60, 61, 63, 106]
		[103]
		[62]
		[103]
		[64]
		[65]
		[66]

[a] Products isolated.

Hedaya tried to prepare triafulvene *(34)* (unknown until recently) by this reaction, but was able to isolate only a mixture of acetylenes, whose composition could not be used

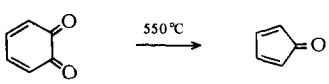


(34)

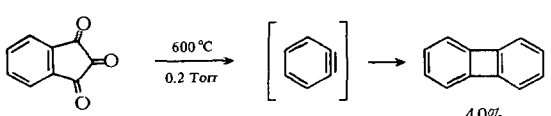
to establish with certainty the intermediate occurrence of *(34)*[69].

4.2.3. Flash Thermolysis of Quinones

On flash thermolysis, quinones lose one or two molecules of carbon monoxide[116]. The cyclopentadienone arising from the *o*-quinone at 550°C has been identified by *Chapman* by means of IR spectroscopy[19].



At higher temperatures two molecules of CO were removed, and it was concluded from the products that cyclobutadiene

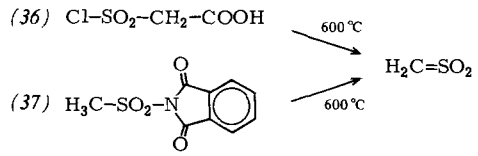


(35)

occurs as an intermediate[70–72]. However, direct proof is still lacking. Indantrione *(35)* splits off CO in a smooth reaction and gives biphenylene in a yield that amounts to 40% after working up[73, 117].

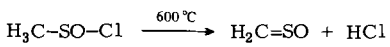
4.2.4. Flash Thermolysis of Carboxylic and Sulfonic Acid Derivatives

On flash thermolysis the methanesulfonic acid derivatives *(36)* and *(37)* give a highly reactive compound to which the structure of a sulfene could be assigned on the basis of trapping reactions and the IR spectrum[74, 75]. Sulfenes

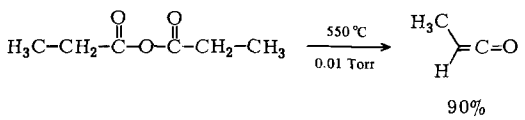


have in fact been postulated as intermediates in previous reactions, but so far their existence has not been demonstrated directly.

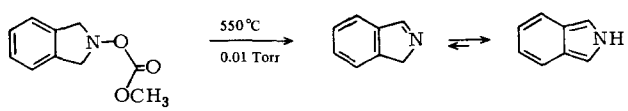
Sulfine could be obtained in the same way from methanesulfinyl chloride and other precursors[76].



A method similar in principle to the above has long served for making reactive ketenes on a preparative scale[77].

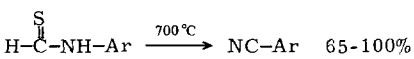


The fission of the ester *(38)* into isoindole, methanol, and carbon dioxide[78] is a related reaction. A further interesting

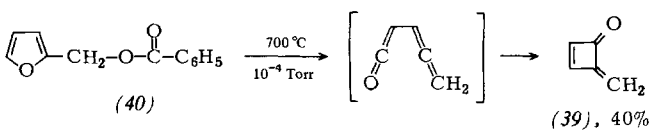


(38)

reaction of a carboxylic acid derivative is the formation of aromatic nitriles by flash thermolysis of thioformanilides[79].



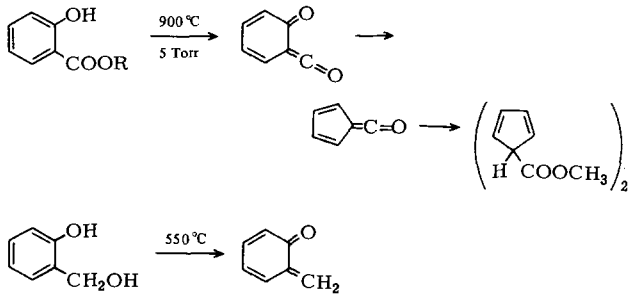
Trahanovsky obtained the very unstable methylenecyclobutenone *(39)* by flash thermolysis of the furan derivative *(40)*; he assumed that propadienylketene occurred as an intermediate[80].



(40) *(39)*, 40%

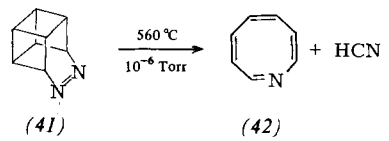
Fulven-6-one was demonstrated as an intermediate in the flash thermolysis of a salicylic ester[81, 82].

Quinone methides could be prepared in a related reaction and were then examined by IR spectroscopy[83].



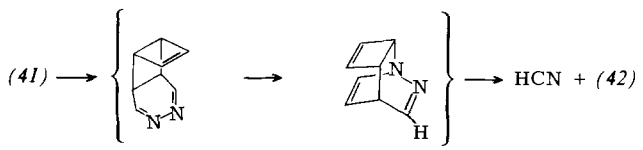
4.2.5. Flash Thermolysis of Diazabasketene

On conventional thermolysis in solution or in the gas phase, diazabasketene *(41)*, prepared as precursor of cubane in a multistep reaction, gave only an indefinite product mixture and not the expected cubane. Flash thermolysis of this compound *(41)* was investigated by *Hedaya*[84]. At 560°C the compound fragmented to hydrogen cyanide and a very labile compound to which the structure of azocine *(42)* could be assigned on the basis of spectroscopic findings and chemical reactions; this product *(42)* is stable only below −50°C.



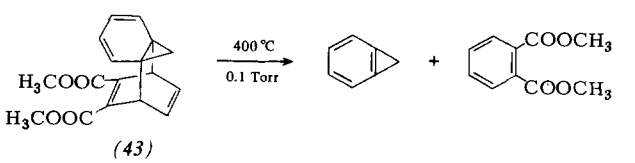
(41) *(42)*

For the interesting reaction *(41)* → *(42)* the course illustrated has been proposed[84]. Attempts to make *(42)* more easily accessible by flash thermolysis of tropyl azide were unsuccessful; the azide decomposes under these conditions into hydrogen cyanide, benzene, and nitrogen[51].



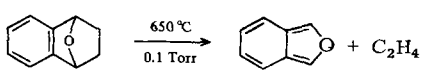
4.3. Retro-diene and -ene Reactions

The retro-Diels-Alder reaction is of preparative importance in organic chemistry[105]. If the conditions of flash thermolysis are chosen for this reaction, then thermally very sensitive products can be isolated. Thus, *Vogel* prepared cyclopropabenzene by flash thermolysis of the Diels-Alder adduct *(43)*[85].



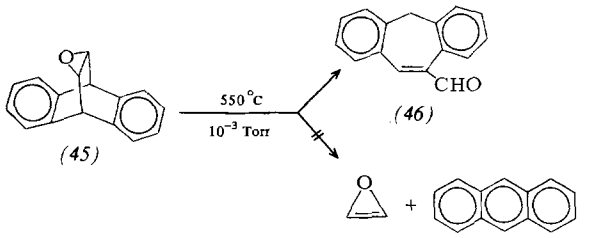
(43)

Another preparatively interesting reaction of this type is the fission of the epoxide *(44)* into isobenzofuran and ethylene[86].



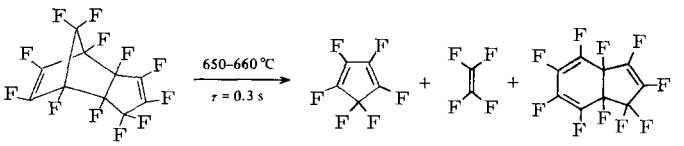
(44) 100%

Attempts to obtain oxirene by flash thermolysis of dibenzobarrelene oxide *(45)* ended in failure; the aldehyde *(46)* was the main product formed at 550°C[104]. However, pentatetraene and other sensitive olefins could be prepared smoothly by this reaction[115].



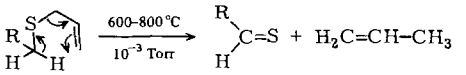
(45) *(46)*

Unusual products are often obtained in the pyrolysis of fluorinated organic compounds[109, 114]. For example, in flash thermolysis of the dimeric perfluorocyclopentadiene *(47)* the retro-Diels-Alder reaction competes with cycloelimination of difluorocarbene[110, 113].



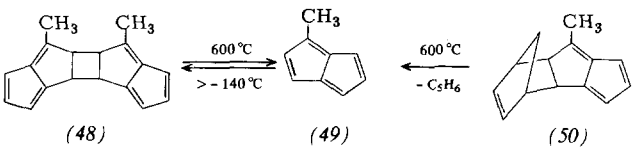
(47)

Flash thermolysis of allyl sulfides gives thiocarbonyl compounds in a reaction that is formally a retro-ene reaction[87, 88]. In this way thiocarbonyl compounds that were previously unobtainable, or obtainable only with difficulty, can be prepared by a relatively simple route: examples are thioacrolein, monothiobiacetyl, and thiobenzaldehyde.



4.4. Cleavage of "Dimeric" Molecules

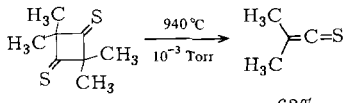
An interesting example of this type of reaction is the synthesis of the highly reactive methylpentalene *(49)* by flash thermolysis of the dimer *(48)*, which in turn is obtainable by a retro-Diels-Alder reaction of *(50)*. The latter reaction proceeds by way of methylpentalene *(49)*. This pentalene derivative *(49)* is stable essentially only below −140°C and at higher temperature dimerizes instantaneously into *(48)*. In spite of its instability, it was found possible to measure the IR and UV spectra of this compound, which is also of great theoretical interest[89].



(48) *(49)* *(50)*

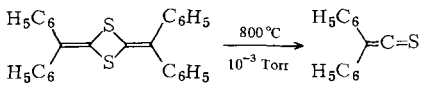
The cleavage of diketenes into the monomers, which must happen to thermally sensitive ketenes under the conditions of flash thermolysis, is a further example of this type of reaction[90]. The thermally very unstable dimethylthioketene was

first obtained by flash thermolysis of the cyclobutanethione *(51)* in 62% yield[91].

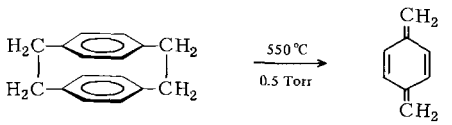


(51)

Bismethylene-1,3-dithietanes, *e.g.* the bisbenzhydrylidene compound, which are also formally thioketene dimers, can similarly be cleaved to monomers by flash thermolysis[17, 108].



A reaction that is of interest both industrially and theoretically is the fission of [2.2]paracyclophane into *p*-quinodimethane *(52)* whose IR and UV spectra were measured[18, 92]. The monomer *(52)* polymerizes at room temperature to a polymer which has found industrial use.

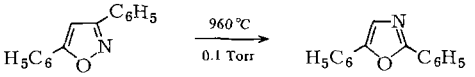


(52)

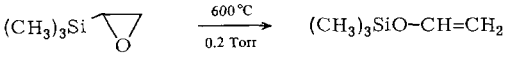
By suitable experimental arrangements it proved possible to deposit *(52)* on the surface of an article, so that the latter became covered by a film[93].

4.5. Rearrangements

Rearrangements have also been studied under the conditions of flash thermolysis, although in this type of reaction conventional thermolytic techniques are sufficient in many cases. Isoxazoles *(53)* rearrange at 960°C to oxazoles[94] and α,β-epoxy-silanes *(54)* are converted into enol ethers[95].

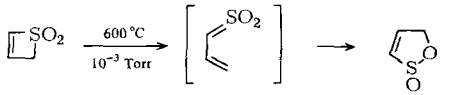


(53)



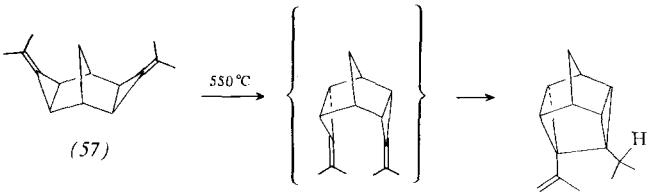
(54)

The sulfone *(55)* reacts on flash thermolysis by ring expansion, yielding *(56)*[96, 14].



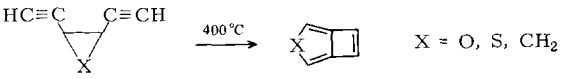
(55) *(56)*

By flash thermolysis at 550°C the cyclization product *(58)* is obtained from the tetracyclic starting material *(57)*[97].



(57) *(58)*

In an interesting reaction, bicyclic trienes *(60)*, *e.g.* cyclobutafuran, could be prepared from the three-membered ring compounds *(59)*[98, 99].



(59) *(60)*

5. Final Remarks

Thermolabile thermolysis products cannot in principle be isolated by conventional pyrolysis techniques, but they can be obtained, even on a preparative scale, with the aid of flash thermolysis. This has led to the first isolation of many compounds, some of which were also of theoretical interest.

Use of this technique is still relatively complicated, and the amount of reacting substance is generally limited. Each case should therefore be examined carefully to determine the reaction conditions and the requirements essential for the solution of the problem.

Apparatus for flash thermolysis is now available commercially, removing an important obstacle to the use of this method, and it can thus be expected that chemists will in future make increasing use of this technique for the preparation and study of reactive compounds.

Received: October 26, 1976 [A 170 IE]
German version: Angew. Chem. *89*, 377 (1977)
Translated by Express Translation Service, London

[1] *E. Hedaya*, Acc. Chem. Res. *2*, 367 (1969).
[2] *P. de Mayo*, Endeavour *31*, 135 (1972).
[3] *H. J. Hageman, E. Wiersum*, Chem. Br. *9*, 206 (1973).
[4] *D. M. Golden, G. N. Spokes, S. W. Benson*, Angew. Chem. *85*, 602 (1973); Angew. Chem. Int. Ed. Engl. *12*, 534 (1973).
[5] *M. Knudsen*, Ann. Phys. (Leipzig) *28*, 75, 999 (1909).
[6] *S. Dushman, J. M. Lafferty*: Scientific Foundations of Vacuum Technique. 2nd Edit., Wiley, New York 1962.
[7] *C. H. De Puy, R. W. King*, Chem. Rev. *60*, 431 (1960); *M. Hanack, W. Kraus* in Houben-Weyl-Müller: Methoden der Organischen Chemie. 4th Edit., Thieme, Stuttgart 1972, Vol. 5/1b, p. 105.
[8] *D. J. Anderson, D. C. Horwell, E. Stanton, T. L. Gilchrist, C. W. Rees*, J. Chem. Soc. Perkin I *1972*, 1317.
[9] *J. A. Oliver, P. A. Ongley*, Chem. Ind. (London) *1965*, 1024.
[10] *U. E. Wiersum, T. Nieuwenhuis*, Tetrahedron Lett. *1973*, 2581.
[11] *R. F. C. Brown, R. K. Solly*, Aust. J. Chem. *19*, 1045, 1052 (1966).
[12] *W. S. Trahanovsky, C. C. Ong, J. G. Pataky, F. L. Weitl, P. W. Mullen, J. C. Clardy, R. S. Hansen*, J. Org. Chem. *36*, 3575 (1971).
[13] *E. Hedaya, D. McNeil*, J. Am. Chem. Soc. *89*, 4213 (1967).
[14] *J. F. King, P. de Mayo, C. L. McIntosh, K. Piers, D. J. H. Smith*, Can. J. Chem. *48*, 3704 (1970).
[15] *G. Seybold, U. Jersak*, Chem. Ber. *110*, 1239 (1977).
[16] Manufacturer: Otto Fritz GmbH (Normag®), Feldstr. 1, D-6238 Hofheim.
[17] *G. Seybold, C. Heibl*, Chem. Ber. *110*, 1225 (1977).
[18] *J. M. Pearson, H. A. Six, D. J. Williams, M. Levy*, J. Am. Chem. Soc. *93*, 5034 (1971).
[19] *O. L. Chapman, C. L. McIntosh*, Chem. Commun. *1971*, 770.
[20] *J. S. Ogden, J. J. Turner*, Chem. Br. *7*, 186 (1971).
[21] *H. F. Grützmacher, J. Lohmann*, Justus Liebigs Ann. Chem. *705*, 81 (1967).

[22] *F. P. Lossing* in *C. A. McDowell:* Mass Spectrometry. McGraw-Hill, New York 1963, p. 442.
[23] *R. Huisgen, V. Weberndörfer*, Experientia *17*, 566 (1961).
[24] *S. W. Benson, G. N. Spokes*, J. Am. Chem. Soc. *89*, 2525 (1967).
[25] *M. Jones, D. C. Richardson, M. E. Hendrick*, J. Am. Chem. Soc. *93*, 3790 (1971).
[26] *A. D. Wolf, V. V. Kane, R. H. Levin, M. Jones*, J. Am. Chem. Soc. *95*, 1680 (1973).
[27] *G. M. Kaufman, J. A. Smith, G. G. VanderStouw, H. Shechter*, J. Am. Chem. Soc. *87*, 935 (1965).
[28] *R. C. Joines, A. B. Turner, W. M. Jones*, J. Am. Chem. Soc. *91*, 7754 (1969); *C. Wentrup, K. Wilczeck*, Helv. Chim. Acta *53*, 1459 (1970).
[29] *P. O. Schissel, M. E. Kent, D. J. McAdoo, E. Hedaya*, J. Am. Chem. Soc. *92*, 2147 (1970).
[30] *W. J. Baron, M. Jones, P. P. Gaspar*, J. Am. Chem. Soc. *92*, 4739 (1970).
[31] *R. Gleiter, W. Rettig, C. Wentrup*, Helv. Chim. Acta *57*, 2111 (1974).
[32] *E. Hedaya, M. E. Kent*, J. Am. Chem. Soc. *93*, 3283 (1971).
[33] *W. D. Crow, C. Wentrup*, Tetrahedron Lett. *1967*, 4379.
[34] *E. Hedaya, M. E. Kent, D. W. McNeil, F. P. Lossing, T. McAllister*, Tetrahedron Lett. *1968*, 3415.
[35] *W. D. Crow, C. Wentrup*, Chem. Commun. *1968*, 1026.
[36] *C. Thétaz, C. Wentrup*, J. Am. Chem. Soc. *98*, 1258 (1976).
[37] *R. Harder, C. Wentrup*, J. Am. Chem. Soc. *98*, 1259 (1976).
[38] *R. A. Abramovitch, W. D. Holcomb*, J. Am. Chem. Soc. *97*, 676 (1975).
[39] *D. J. Anderson, T. L. Gilchrist, G. E. Gymer, C. W. Rees*, Chem. Commun. *1971*, 1518; *T. L. Gilchrist, G. E. Gymer, C. W. Rees*, ibid. *1971*, 1519; J. Chem. Soc. Perkin I *1973*, 555.
[40] *T. L. Gilchrist, G. E. Gymer, C. W. Rees*, J. Chem. Soc. Perkin I *1975*, 1.
[41] *T. L. Gilchrist, C. W. Rees, C. Thomas*, J. Chem. Soc. Perkin I *1975*, 8.
[42] *T. L. Gilchrist, C. W. Rees, C. Thomas*, J. Chem. Soc. Perkin I *1975*, 12.
[43] *G. Seybold, C. Heibl*, Angew. Chem. *87*, 171 (1975); Angew. Chem. Int. Ed. Engl. *14*, 248 (1975).
[44] *W. D. Crow, M. N. Padden-Row*, Tetrahedron Lett. *1972*, 2231.
[45] *J. A. H. McBride*, J. Chem. Soc. Chem. Commun. *1974*, 359.
[46] *D. L. Forster, T. L. Gilchrist, C. W. Rees, E. Stanton*, Chem. Commun. *1971*, 695.
[47] *G. Seybold, U. Jersak, R. Gompper*, Angew. Chem. *85*, 918 (1973); Angew. Chem. Int. Ed. Engl. *12*, 847 (1973).
[48] *H. U. Wagner*, Angew. Chem. *85*, 920 (1973); Angew. Chem. Int. Ed. Engl. *12*, 848 (1973).
[49] *B. M. Adger, M. Keating, C. W. Rees, R. C. Storr*, J. Chem. Soc. Chem. Commun. *1973*, 19; *B. M. Adger, C. W. Rees, R. C. Storr*, J. Chem. Soc. Perkin I *1975*, 45.
[50] *C. W. Rees, R. Somanathan, R. C. Storr, A. D. Woolhouse*, J. Chem. Soc. Chem. Commun. *1975*, 740; *1976*, 125.
[51] *G. Seybold*, unpublished results, München 1973–1974.
[52] *H. Staudinger, J. Siegwart*, Ber. Dtsch. Chem. Ges. *49*, 1918 (1916).
[53] *T. L. Gilchrist, G. E. Gymer, C. W. Rees*, J. Chem. Soc. Chem. Commun. *1973*, 819; J. Chem. Soc. Perkin I *1975*, 1747.
[54] *C. Wentrup, P. Müller*, Tetrahedron Lett. *1973*, 2915.
[55] *R. F. C. Brown, R. J. Smith*, Aust. J. Chem. *25*, 607 (1972).
[56] *E. Hedaya, R. D. Müller, D. W. McNeil, P. F. D'Angelo, P. O. Schissel*, J. Am. Chem. Soc. *91*, 1875 (1969).
[57] *P. H. Li, H. A. McGee*, Chem. Commun. *1969*, 592.
[58] *E. Hedaya, I. S. Krull, R. D. Miller, M. E. Kent, P. F. D'Angelo, P. Schissel*, J. Am. Chem. Soc. *91*, 6880 (1969).
[59] *G. Wittig, H. F. Ebel*, Justus Liebigs Ann. Chem. *650*, 20 (1961).
[60] *E. K. Fields, S. Meyerson*, Adv. Phys. Org. Chem. *6*, 1 (1968).
[61] *E. K. Fields, S. Meyerson*, Chem. Commun. *1965*, 474.
[62] *M. P. Cava, M. J. Mitchell, D. C. DeJongh, R. Y. VanFossen*, Tetrahedron Lett. *1966*, 2947.
[63] *R. F. C. Brown, D. V. Gardner, J. F. W. McOmie, R. K. Solly*, Chem. Commun. *1966*, 407.
[64] *S. Meyerson, E. K. Fields*, Chem. Commun. *1966*, 275.
[65] *M. G. Reinecke, J. G. Newsom*, J. Am. Chem. Soc. *98*, 3021 (1976).
[66] *R. J. Spangler, J. H. Kim*, Tetrahedron Lett. *1972*, 1249.
[67] *M. P. Cava, L. Bravo*, Tetrahedron Lett. *1970*, 4631.
[68] *O. A. Mamer, F. P. Lossing, E. Hedaya, M. E. Kent*, Can. J. Chem. *48*, 3606 (1970).
[69] *I. S. Krull, P. F. D'Angelo, D. R. Arnold, E. Hedaya, P. Schissel*, Tetrahedron Lett. *1971*, 771.
[70] *H. J. Hageman, U. E. Wiersum*, Tetrahedron Lett. *1971*, 4329.
[71] *H. J. Hageman, U. E. Wiersum*, Chem. Commun. *1971*, 497; Angew. Chem. *84*, 314 (1972); Angew. Chem. Int. Ed. Engl. *11*, 333 (1972).
[72] *P. de Champlain, P. de Mayo*, Can. J. Chem. *50*, 270 (1972).
[73] *R. F. C. Brown, R. K. Solly*, Aust. J. Chem. *19*, 1045 (1966).
[74] *J. F. King, P. de Mayo, D. L. Verdun*, Can. J. Chem. *47*, 4509 (1969); *J. F. King, R. A. Marty, P. de Mayo, D. L. Verdun*, J. Am. Chem. Soc. *93*, 6304 (1971).
[75] *W. J. Mijs, J. B. Reesink, U. E. Wiersum*, J. Chem. Soc. Chem. Commun. *1972*, 412.
[76] *E. Block, R. E. Penn, R. J. Olsen, P. F. Sherwin*, J. Am. Chem. Soc. *98*, 1264 (1976).
[77] *A. D. Jenkins*, J. Chem. Soc. *1952*, 2563.
[78] *R. Bonnett, R. F. C. Brown*, J. Chem. Soc. Chem. Commun. *1972*, 393.
[79] *R. F. C. Brown, J. M. Coddington, I. D. Rae, G. J. Wright*, Aust. J. Chem. *29*, 931 (1976).
[80] *W. S. Trahanovsky, M. G. Park*, J. Am. Chem. Soc. *95*, 5412 (1973).
[81] *H. F. Grützmacher, J. Hübner*, Justus Liebigs Ann. Chem. *748*, 154 (1971).
[82] *H. F. Grützmacher, J. Hübner*, Justus Liebigs Ann. Chem. *1973*, 793.
[83] *C. L. McIntosh, O. L. Chapman*, Chem. Commun. *1971*, 771.
[84] *D. W. McNeil, M. E. Kent, E. Hedaya, P. F. D'Angelo, P. O. Schissel*, J. Am. Chem. Soc. *93*, 3817 (1971).
[85] *E. Vogel, W. Grimme, S. Korte*, Tetrahedron Lett. *1965*, 3625; *S. Tanimoto, R. Schäfer, J. Ippen, E. Vogel*, Angew. Chem. *88*, 643 (1976); Angew. Chem. Int. Ed. Engl. *15*, 613 (1976).
[86] *U. E. Wiersum, W. J. Mijs*, J. Chem. Soc. Chem. Commun. *1972*, 347.
[87] *H. G. Giles, R. A. Marty, P. de Mayo*, J. Chem. Soc. Chem. Commun. *1974*, 409.
[88] *H. G. Giles, R. A. Marty, P. de Mayo*, Can. J. Chem. *54*, 537 (1976).
[89] *R. Bloch, R. A. Marty, P. de Mayo*, J. Am. Chem. Soc. *93*, 3071 (1971); Bull. Soc. Chim. Fr. *1972*, 2031.
[90] Houben-Weyl-Müller: Methoden der Organischen Chemie. 4th Edit. Thieme, Stuttgart 1968, Vol. 7/4, p. 80.
[91] *G. Seybold*, Tetrahedron Lett. *1974*, 555.
[92] *W. F. Gorham*, DBP 1085673 (1960), Union Carbide.
[93] *W. F. Gorham*, J. Polym. Sci. A-1 *4*, 3207 (1966).
[94] *G. L. Aldous, J. H. Bowie, M. J. Thompson*, J. Chem. Soc. Perkin I *1976*, 16.
[95] *P. F. Hudrlik, C. N. Wan, G. P. Withers*, Tetrahedron Lett. *1976*, 1449.
[96] *J. F. King, K. Piers, D. J. H. Smith, C. L. McIntosh, P. de Mayo*, Chem. Commun. *1969*, 31.
[97] *R. Bloch, M. Bortolussi*, Tetrahedron Lett. *1976*, 309.
[98] *M. B. D'Amore, R. G. Bergman, M. Kent, E. Hedaya*, J. Chem. Soc. Chem. Commun. *1972*, 49; *K. P. C. Vollhardt, R. G. Bergman*, J. Am. Chem. Soc. *95*, 7538 (1973).
[99] *K. P. C. Vollhardt*, Top. Curr. Chem. *59*, 113 (1975).
[100] *C. Wentrup*, Top. Curr. Chem. *62*, 173 (1976).
[101] *F. O. Rice, M. T. Murphy*, J. Am. Chem. Soc. *64*, 896 (1942).
[102] *F. O. Rice, P. M. Ruoff, E. L. Rodowskas*, J. Am. Chem. Soc. *60*, 955 (1938).
[103] *E. K. Fields, S. Meyerson*, J. Org. Chem. *31*, 3307 (1966).
[104] *E. Lewars, G. Morrison, J. Fulford*, Chem. Ind. (London) *1976*, 488.
[105] *H. Kwart, K. King*, Chem. Rev. *68*, 415 (1968).
[106] *D. V. Gardner, J. F. W. McOmie, P. Albriktsen, R. K. Harris*, J. Chem. Soc. *C 1969*, 1994.
[107] *R. D. Chambers, M. Clark, J. A. H. McBride, W. Kenneth, R. Musgrave, K. C. Srivastava*, J. Chem. Soc. Perkin I *1974*, 125.
[108] *M. S. Raasch*, J. Org. Chem. *35*, 3470 (1970).
[109] *V. E. Platanov, G. G. Yakobson*, Synthesis *1976*, 374.
[110] *R. E. Banks, A. C. Harrison, R. N. Haszeldine*, J. Chem. Soc. *C 1966*, 2102.
[111] *C. Wentrup, W. D. Crow*, Tetrahedron *26*, 3965 (1970).
[112] The flash thermolysis of 4-phenyloxydiazolones leads to indazoles. *W. Reichen*, Helv. Chim. Acta *59*, 1636 (1976).
[113] *R. W. Hoffmann*, Angew. Chem. *83*, 595 (1971); Angew. Chem. Int. Ed. Engl. *10*, 529 (1971).
[114] *R. N. Warrener, E. E. Nunn, M. N. Paddon-Row*, Tetrahedron Lett. *1976*, 2639.
[115] *J. L. Ripoll*, J. Chem. Soc. Chem. Commun. *1976*, 235; Bull. Soc. Chim. Fr. *1974*, 2567.
[116] The flash thermolysis of some quinone-like compounds has recently been reported: *G. Schaden*, Angew. Chem. *89*, 50 (1977); Angew. Chem. Chem. Int. Ed. Engl. *16*, 50 (1977).
[117] *A. Martineau, D. DeJongh*, Can. J. Chem. *55*, 34 (1977).

Electrophotography

By John W. Weigl[*]

Electrophotographic images are formed by the displacement of matter in electric fields: the deposition of charged particles or the deformation of a plastic surface is controlled by a geometric field pattern, configured by the photo-response of a photoconductive insulating material. Image amplification up to 10^5 may be achieved by the application of external potentials and the judicious selection of imaging particles having a high ratio of absorbance per unit charge. These particles may be ions, colloids, photoresponsive pigments, or (most commonly) colored plastic "toner" composites. Of the many processes which have been invented to date, transfer xerography remains the most useful. This paper presents a concise review of electrophotographic imaging processes and materials, as well as of some of their applications.

1. Introduction

Photography requires a photoreceptor of sufficient sensitivity to capture the fleeting imprint of light arriving through a lens. Optical systems are inefficient, exposure times must be short, light sources are limited in intensity. The photon flux available at the image plane is far less than what would be required for each quantum to print out one molecule of photoproduct. Therefore, an amplification step must be provided: the primary ("latent") image must be intensified. This process step, called "development", may be chemical or electrical in nature. Free energy must be supplied during development to convert the latent image into a high-contrast visible record. It is highly desirable to introduce a threshold, below which exposure is ineffective. This minimizes the effects of inadvertent low-level photo or thermal pre-exposure and improves the shelf life of the materials.

Let us consider how much amplification is required. With practical light sources, projection optics can furnish at most about 10^{12} photons/cm^2 to the photoreceptor in exposure times of one second or less. About 10^{17} light absorbing molecules/cm^2 are required to form a dense black image[**]. Since primary photochemical or photophysical events can yield, at most, one molecule of photoproduct per absorbed photon, photography requires a 10^5-fold image intensification.

Many imaging processes are available which lack amplification: namely, those in which diazo compounds, photochromics, dye bleach materials, most photopolymers and photoresists, and certain high resolution "printout" emulsions based on inorganic salts are employed. These processes are useful for the photofabrication of integrated circuits and for contact duplication of transparencies, but they lack sufficient photographic sensitivity for employment in projection set-ups at reasonable exposures. Systems of this type have been amply discussed in the literature and fall outside the scope of this review[1].

In silver halide photography, the image is developed by the reductive precipitation of black silver filaments in those microcrystals of the salt which have received threshold exposure. Typically, absorption of a few dozen photons can nucleate the complete conversion of a 1 μm crystallite to a tangled mass of black atomic silver. The effective intensification is measured by the ratio of metal formed per grain to the minimum number of photons required to render the latter developable. Since each microcrystal is either fully developed or not at all, the emulsion chemist may trade off resolution *vs* developed image density (and hence photographic sensitivity) by adjusting mean grain size. The materials thus formed cover the gamut from colloidal ("Lippmann") emulsions, having gains of *ca.* 1000, to relatively coarse-grained layers offering 10^8 to 10^9-fold amplification, with corresponding reduction in image resolution[2].

Alternatively, the primary product of photolysis may be used to nucleate the reductive precipitation of silver or other metal ions from a developer solution. This process—called "physical development"—allows the external developer to supply the material which forms the final image. Silver halides, as well as PbI_2, TiO_2, and certain diazonium salts, may be exposed to furnish the development nuclei[3]. In all these systems, the free energy required for amplification derives from the chemical potential of the developer system. The literature on "chemical" photography is enormous; we refer to it only to provide a reference base for the subject of this review.

In electrophotography the primary quantum yield is generally much higher than the 1 % value reported for silver halides[2]. Under favorable conditions, absorption of a photon of actinic radiation has a 50—90 % chance of forming a mobile electronic charge carrier—the primary unit of image information in all electrophotographic processes. Displacement of such carriers in an electric field forms a "latent" image, which must be developed (at once, or subsequently) to become visible. The intensification required for projection speed is produced by some form of "physical" development; for example, by the motion of large colored particles in response to relatively few surface charges, by a change in electrostatic adhesion, by the electrostatic wrinkling of a smooth thermoplastic layer, or by the electroplating of metal ions. The free energy required for image gain is supplied in the form of an electrostatic potential, typically applied to a dielectric layer prior to exposure or to a bias electrode during development. For example, on typical xerographic photoreceptors a charge density of *ca.* 10^{12} electrons/cm^2 suffices to attract a dense black layer

[*] Dr. J. W. Weigl
Joseph C. Wilson Center for Technology, Xerox Corporation
Webster, New York 14580 (USA)

[**] For purposes of illustration, assume a black image consisting of a mixture of three dyes with peak (log 10) extinction coefficients of 3×10^4 l/mol·cm, having their absorption bands evenly spaced across the visible spectrum, and a molecular volume of (3.35 Å)^3. Such a layer would have an average linear (log 10) extinction coefficient of *ca.* 3×10^4 cm^{-1}. For an absorbance of 2.0 (99 % light absorption) the image must be 0.67 μm thick; therefore, 1.2×10^{17} dye molecules/cm^2 must be exposed. Hence, a dye-based "molecular" photochemical imaging system of quantum yield Φ would require at least $1.2 \times 10^{17}/\Phi$ photons/cm^2 (see Ref. [56]).

of 10 μm toner particles (absorbance ≥1.5). At a primary quantum yield of 0.5, full exposure requires *ca.* 2×10^{12} photons/cm^2—an effective gain of about 10^5 over the "molecular" system cited above[*].

Electrophotography is still a relatively young science. Although the first efforts to use photoconductography were made during the 1920's, the field became active only after 1950 when a growing need for inexpensive photocopies stimulated the development of a new technology based on electrostatic imaging[13]. This application did not require portability—a seemingly unattainable goal for electrophotographic cameras which generally require external electric connections as well as special illumination. Instead of competing with silver photography in compactness, photosensitivity, or pictorial rendition, electrophotography offered complementary advantages: instant delivery of inexpensive copies of text and graphics, high-contrast prints on plain (or nearly plain) paper, and a liberation from the need for dark storage of photosensitive materials prior to use.

The principles and applications of electrophotography have been described in several monographs[5–12] as well as in numerous journal articles (*e.g.*, [13–18])[**]. In the limited space allotted to the present review, we shall try only to provide an overview of the main electrophotographic imaging processes known to date, with emphasis on certain materials-related topics which may be of special interest to chemists and occasional digressions to describe interesting inventions.

Lack of space prohibits our discussion of the active new field of photoelectronic image processing and transmission, the capture, manipulation, and transmission of graphic information by electronic, rather than optical means[19].

1.1. Overview of Electrophotographic Processes

The photosensitive material is invariably a photoconductive insulator. Exposure is used to generate, in image configuration, a concentration of mobile electronic charge carriers, far in excess of their thermal population. Externally applied electrical free energy is used to convert the latent photoconductivity pattern into a visible image. Although processes and configurations vary widely, they may be conveniently classified, as follows:

Electrostatic Imaging Processes using External Development

Exposure of a charged photoconductive dielectric layer produces an electric field pattern which may be made visible by the motion and selective capture of small colored particles. Familiar examples include direct and transfer xerography, imaging by transfer of electrostatic charges, and "persistent internal polarization" processes. A related phenomenon is the formation of electrostatic images by the modulation of ion flow through photoconductor-coated screens.

Photoplastic Imaging

Exposure of an electric field-stressed thermoplastic produces a charge pattern which is developed by electrostatic surface deformation to produce a light-scattering image. Variants of this process include "Frost" and xerographic thermoplastic holography.

Photo-Active Pigment Electrography (PAPE)

Exposure of "electrically photosensitive" particles under high-field conditions alters their charge/mass ratio—and in many cases, their polarity—sufficiently to cause imagewise migration of exposed particles through a dielectric liquid or through a softened thermoplastic matrix. Examples include photoelectrophoresis and imagewise particle migration; photoelectrically controlled adhesion imaging ("Manifold") is closely related.

Photoconductography

Exposure of a coating exhibiting persistent photoconductivity generates an image pattern of conductive areas which can be used to direct the electrodeposition of ions, colloids, or conductive "toner" particles to form visible images.

2. Transfer Xerography

In 1938, *Carlson* demonstrated the basic principles of a new imaging process, designed to produce inexpensive copies of office documents[13, 20]. His basic concept was to use image illumination to form a charge pattern on a large-area photoconductor, to develop this by means of oppositely charged "toner" powder and to transfer, then fix the powder image onto a receiving sheet such as paper. This process and its variants were eventually named "xerography"[*]. In the nearly 40 years since *Carlson*'s first successful experiments, xerography has become a mature technology. Selenium alloys, inorganic photoconductors, and organic polymer coatings have replaced *Carlson*'s sulfur and anthracene layers, providing much higher photosensitivity, stability and spectral response range. Carbon-pigmented thermoplastic "toners" and sophisti-

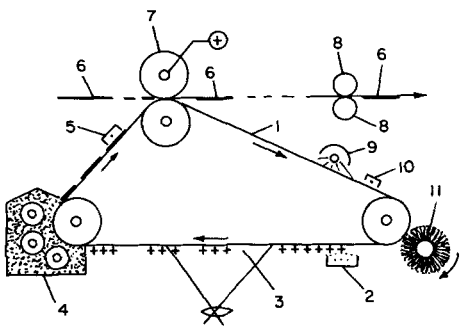


Fig. 1. Xerographic process steps—illustrated by a duplicator, based on a photoconductor-coated belt (1). Uniform charge, applied by scorotron (2) is converted into a latent image by flash exposure (3). Charged "toner" powder, applied by a brush mechanism (4), develops the image, is discharged by a corotron (5), then transferred to sheets of paper (6) by a pair of electrically biased rolls (7) and fused to the paper by heated pressure rollers (8). Charge remaining on the photoconductor is removed by uniform illumination (9) and AC corona (10); the remaining toner is brushed off (11). Within 3–5 seconds the same section of photoreceptor is ready to begin the cycle again. Duplicators such as this can turn out 1–2 copies per second.

[*] For independent estimates of electrophotographic gain and discussions of the implications of fluctuations in sensitivity, granularity, and other sources of "noise" upon image quality, see references [4, 179].

[**] The author has despaired of an attempt to provide adequate references to original work. In the limited space available it is quite impossible to cite any but the most pertinent publications: *Schaffert*'s monumental book [6] cites over 4000 patents and 1000 journal articles, and even it is far from complete! For a comprehensive background the reader is referred to the monographs cited and to recent publications—particularly in Photogr. Sci. Eng. and Japn. J. Electrophotogr.

[*] Greek: "dry writing" [20].

cated developer mixtures are used instead of lycopodium pollen. Several liquid development processes have been introduced. Elaborate automatic copiers, duplicators, and printers have been developed; yet, the basic process principles have endured with remarkably little change[5, 6].

The steps used in conventional ("transfer") xerography are outlined in Figure 1. A light image-modulated charge pattern on the surface of a photoconductive insulating layer is developed by the attraction or repulsion of charged thermoplastic "toner" powder; thus, positive or negative images may be produced. The toner image is transferred and fixed to paper or film; the photoreceptor is illuminated and reverse charged to remove residual charge, then cleaned and recycled.

2.1. Formation of Electrostatic Latent Image

Corona discharge devices—high-voltage "corotron" wires with stabilizing shields, optionally with "scorotron" control grids—have proven to be the most reliable means of applying a stable, uniform layer of charge to large-area photoconductors (Fig. 2)[21]. Gaseous ions, such as hydrated protons and CO_3^-, are transported to the surface of the dielectric[22] where they form a relatively stable blocking contact; *i.e.*, they are not readily injected into the bulk and thus discharged[23]. In the case of ZnO-binder layers, the charge layer is believed to comprise adsorbed O_2^- ions[24]; in other cases, the nature of the charge layer is less well identified.

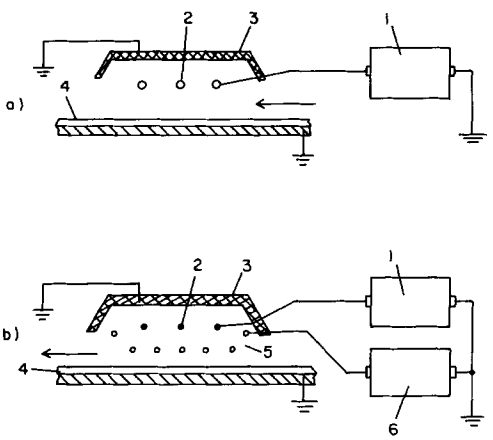


Fig. 2. Two common corona charging devices.—a) Three-wire corotron connected to high voltage power supply—typically 6–7 kV (1), and consisting of three 75 µm diameter tungsten wires (2) and a grounded shield (3). The photoconductor (4) passes under the corotron.—b) Scorotron, using three emitting wires set at 6–7 kV (2) and a seven-wire control grid (5) connected to a lower-voltage power supply (6), set at the potential to be applied to the photoconductor surface (4). After Ref. [6], p. 234.

Contact electrification of large areas has proven difficult to carry out reliably—partly because of asperities and chemical irregularities in the surface layers and partly because this process involves air breakdown and is therefore quite sensitive to fluctuations in ambient humidity. A somewhat more successful alternative is induction charging; this involves field-induced injection of carriers from the conductive base through the photoconductor, followed by surface trapping (Fig. 3)[25].

A dielectric overcoating may be used to protect the photoconductor surface and to act as a separate charge storage layer. Figure 4 shows one of several closely related photodielectric processes, whereby imagewise photodischarge of the photoconductor may be caused to impress a developable latent image across an overcoating of this type. The sequence of charging and illumination steps is readily altered to produce either positive or negative images of the original. Transfer, fixing, and cleaning steps are similar to those for other forms of xerography[26–31].

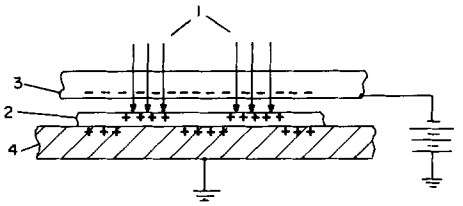


Fig. 3. Imagewise induction charging. Image illumination (1) of a photoconductor (2) in an external field applied by a closely spaced transparent electrode (3) may be used to form a latent image in a single step. Mobile charge is injected from the base electrode (4). Rear illumination may be used instead. After Ref. [21c].

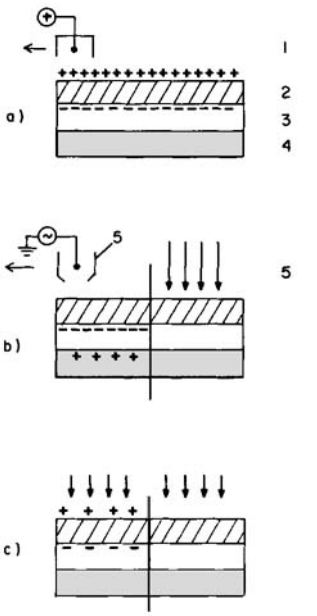


Fig. 4. A typical "photodielectric" process.—a) Charge is deposited by a conventional corotron (1) on dielectric (2), while countercharge is injected into the photoconductor (3) from base (4).—b) Image illumination (arrows) is applied through a transparent grounded AC corotron (5), to produce an equipotential surface whose charge density varies imagewise.—c) Uniform illumination produces a stable developable variable-potential image. After Ref. [29] (cf. also Ref. [27]).

In both plain and overcoated photoconductors, exposure produces a latent image consisting of a surface charge pattern. Field lines run from this surface to the counter-charge, induced in the base electrode or, in overcoated photoconductors, trapped at the interface between the dielectric and photoconductive layers. As Figure 5a shows, in charged areas the field lines run exclusively through the bulk of the dielectric. External fields appear only in the form of fringes around the charged areas; as *Schaffert*[32] and *Neugebauer*[33] observed, such fringes extend outward for a distance comparable to the thickness of the uppermost dielectric layer, be it the photoconductor itself or its overcoating. Close approach of a grounded counter-electrode draws the field lines outward in proportion to the ratio of capacitances of the dielectric and air gap (Fig. 5b). Charged particles introduced into this

space can now be drawn toward the interior, as well as toward the edges of the image, thus providing "solid area" development.

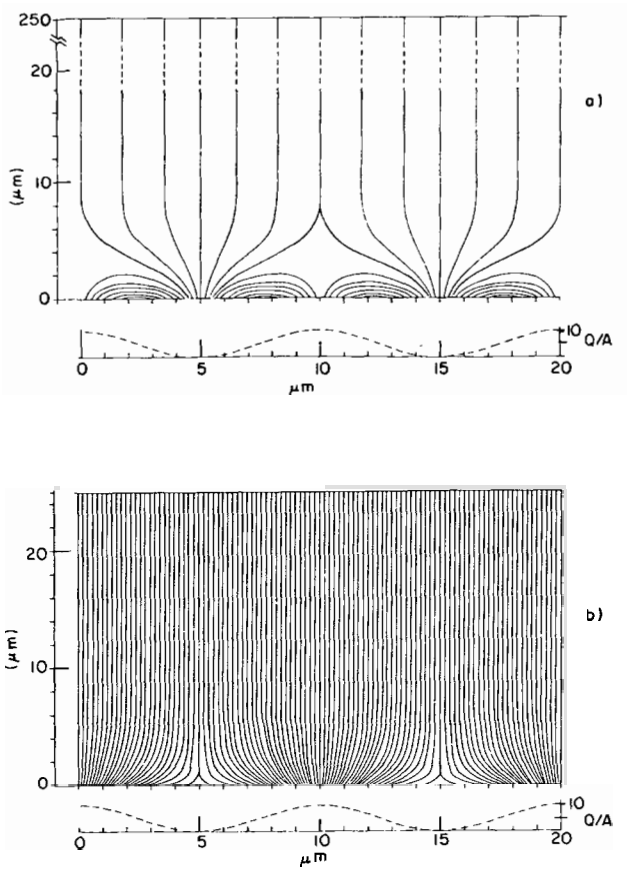


Fig. 5. Effect of electrode spacing on the electric field above a 25 μm selenium plate with sinusoidal charge pattern (Q/A in units of 10^{-4} C/m^2, $V_{max} = 500$ V). With the electrode relatively remote, at 250 μm (a), fringing fields predominate; as the electrode approaches close to 25 μm (b), the field lines are virtually straight and uniformly spaced. Adapted from Ref. [32].

2.2. Xerographic Development

In xerography the latent image is developed by the attraction of oppositely charged toner particles along electric field lines. A development system must provide:

Means for handling and introducing particles into the development space.

Reproducible means for charging the toner particles.

Control of the development field configuration[34, 35].

Contact electrification is generally used to apply the desired charge to dielectric toner powder. One way to do this is to pass the particles through a set of high-voltage-biased metal nozzles to form a charged aerosol. Ample space is required to insert the powder cloud between photoconductor and development electrode. Since individual toner particles approaching the latent image do not have sufficient capacitance to distort the field, they simply follow the existing field lines, depositing at the inner or outer edges of charged areas, according to their polarity. Central portions of the image lack external field and remain undeveloped (Fig. 6). The resultant edge enhancement is particularly useful for sharpening the perception of minor density differentials in soft-tissue xeroradiography[36, 37].

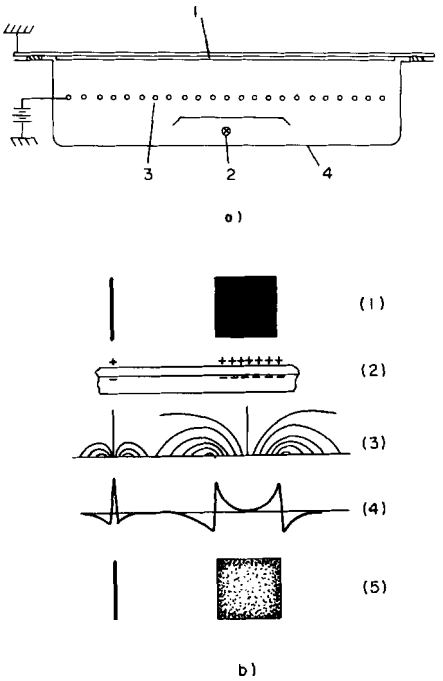


Fig. 6. "Edge development" of solid areas.—a) Schematic of powder cloud development with xeroradiographic plate in place: (1) selenium plate, face down; (2) powder cloud generator; (3) open wire control grid set at 1500 V; (4) container, typically 10 cm deep. After Ref. [37].—b) (1) Original to be reproduced, including black line and solid black square; (2) charge pattern on photoconductor resulting from exposure; (3) electrostatic field configuration—note strong lateral fringes; (4) normal field strength—note edge components; (5) developed image—note edge enhancement. After Ref. [35].

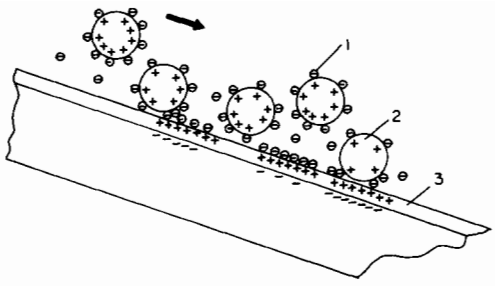


Fig. 7. Schematic of cascade development process: (1) 10 μm toner particles; (2) 500 μm carrier beads; (3) 50 μm thick photoconductor on conductive base. After Ref. [35].

Powder clouds proved unwieldy for use in photocopying applications. About 1945, *Wise*[38] devised "cascade development"—a method of delivering triboelectrically charged toner close to the photoreceptor surface (Fig. 7). The toner powder is mixed with 50—100 times its weight of relatively massive "carrier" particles having the desired triboelectric properties and the mixture is poured over the latent image. As such a developer mass slides and bounces over the photoreceptor, toner is knocked loose and redistributes itself between carrier beads and charged areas of the photoreceptor. In the usual case of insulating carriers, edge development is prominent and solid areas are largely suppressed. This is satisfactory for copying text and line drawings, but distorts the tone rendition of pictorial input. The size of carrier beads, typically 100–500 μm, makes it impractical to bring development electrodes close enough to straighten the field lines (cf. Fig. 5). Cascade development of solid areas may be improved somewhat by screening the latent image, albeit at the cost of maximum density[35, 39, 40].

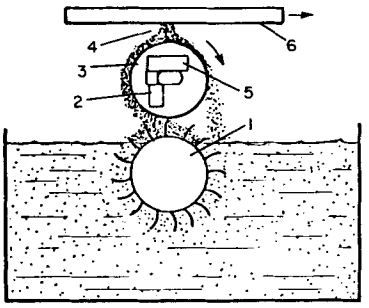


Fig. 8. Schematic of magnetic brush development: Feed roll (1) carries developer to pickup magnet (2). Development roll (3) forwards blanket of developer mixture into development zone (4), where development magnet (5) forms a raised "brush" structure, touching the photoconductor surface (6). After Ref. [42a].

A more rigorous solution is to raise the effective dielectric constant of the developer mixture sufficiently for it to act as its own "development electrode"; this may be accomplished by the use of conductive carrier beads. An elegant solution to the problem of handling such a developer mass was *Young* and *Giaimo*'s[41] invention of the "magnetic brush"—basically a magnet carrying a mixture of fine toner with coarse magnetized carrier beads in the form of a soft brush-like structure (Fig. 8). The latter are generally overcoated with a thin polymer layer which serves to provide the desired frictional charge on the toner as well as to prevent direct short circuits between developer mass and photoreceptor surface. The brush electrode may be biased to compensate for incomplete photoreceptor discharge or to alter contrast. When the proper choice of triboelectric properties is met and the mixture is well agitated, such a "brush" is capable of releasing toner in proportion to surface potential when drawn over an electrostatic latent image. By proper adjustment of the conductivity of the developer mixture, it can be made to favor either edge-contrast or solid-area development[41, 42].

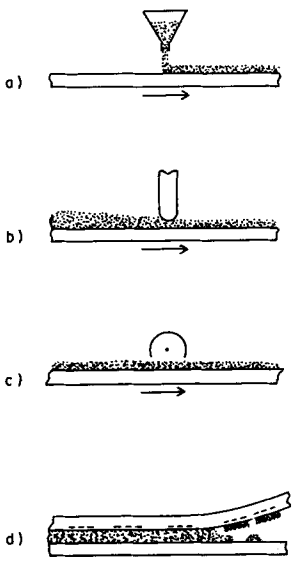


Fig. 9. Impression development.—a) Toner is applied to donor surface, b) leveled by means of a doctor blade, c) charged, and d) gently pressed against a photoconductor without shearing motion. Toner is deposited on the electrostatic image. After Ref. [43].

"Touchdown" (or "impression") development differs from the methods cited above in that the toner layer on a soft donor surface is gently pressed against the charge-bearing photoreceptor surface without shearing motion[34a, 43]. The "donor" may be a conductive brush fabric or an elastomer layer; the toner layer is generally precharged so as to keep the powder in place until it reaches the development zone (Fig. 9c). Close spacing between donor and photoreceptor may be used to provide solid-area coverage for pictorial xerography. Contrast can be controlled by biasing the development electrode. Since the toner now responds to absolute surface potentials—rather than to potential differences between adjacent areas, as with powder cloud and cascade—this method requires exceptionally close control of photoreceptor charging level and photodischarge, and special care must be taken to avoid background development. In an interesting variant of "touchdown" (originally proposed by *Wilson*) conductive toner is charged by induction from the development electrode and requires only a single-component magnetic brush[44, 45].

2.3. Other Process Steps in Transfer Xerography

The toner pattern is transferred to paper—generally with the assistance of an externally applied bias field (Fig. 10)[55]. Background in the final image may be reduced significantly by "selective transfer"—the use of corona charge to suppress transfer of the last layer of toner on the photoreceptor. An undesirable side effect of electrostatically assisted transfer is a slight lateral displacement of the pigment in the fringing fields as the paper is separated from the receptor; this effect has been shown[55, 107] to limit resolution in the final image to about 40—100 lp/mm, depending on toner particle size. Adhesive transfer, initially used by *Carlson*, is inherently capable of much higher resolution, but has the disadvantage of requiring specially coated sheets.

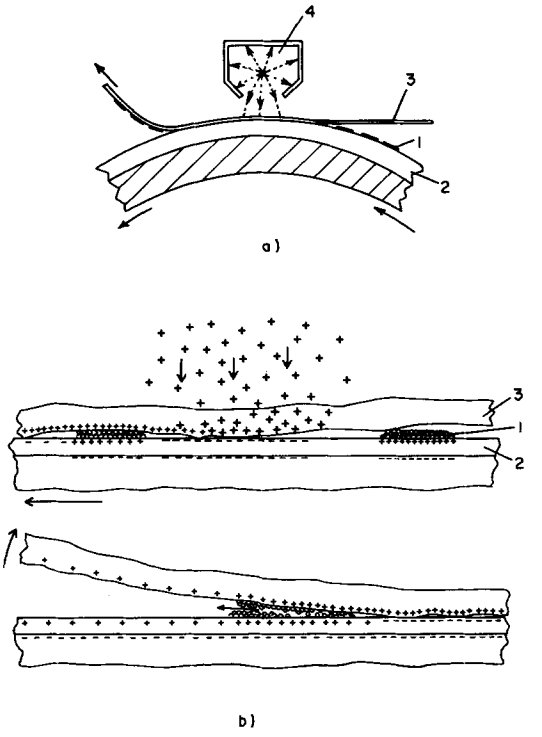


Fig. 10. a) Electrostatic transfer of negatively charged toner (1) from photoconductor (2) to paper (3), using a corotron (4) to apply reverse charge.—b) Detailed view at 50× magnification. After Ref. [55].

The thermoplastic toner may be fixed to the paper by radiant heat, or by contact with a heated roll having a fluorocarbon or silicone elastomer release surface[57]. Solvent vapor fixing is an alternative which has been used for special low-volume applications, particularly xeroradiography and color reproduction[58]. Residual charge on the photoreceptor is removed by uniform illumination; the last residues of toner are neutralized by AC corona and removed by mechanical means such as brushes, webs, wiper blades or vacuum nozzles[59].

2.4. Liquid Development

Three liquid development processes are known. The most important of these is an electrophoretic particle migration process which was invented independently by *Metcalfe* and *Wright* in Australia and by *Mayer* in the U.S. Micron-sized pigment particles are dispersed in a dielectric liquid, such as purified kerosene, and charged by selective adsorption of ionic species and polymers which are added as "charge control agents"; tacky fixatives may be included, as well. The dispersion is applied to the exposed photoreceptor, and pigment particles are electrophoretically deposited on the latent image (Fig. 11). Development rollers and other electrodes—or conductive additives—may be used to provide solid-area coverage. Because this method uses very fine particles which can approach the latent image very closely, electrophoretic development offers extraordinarily high image resolution; 800 lp/mm has been reported. Relatively simple apparatus may be used, and heat fixing may be avoided. Disadvantages include limited developer stability and objectionable carryout of suspending liquid on photoreceptor and copy sheets[46–48].

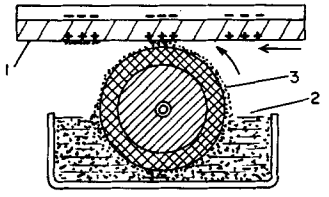


Fig. 11. Development of a latent image on a photoconductor (1) by means of electrophoretic liquid developer (2) and an applicator roll (3). After Ref. [6], p. 134.

A liquid version of induction-touchdown development, which avoids the liquid carryout problem, has been described by *Gundlach*[49]. Conductive ink is drawn out of the recesses of a finely patterned conductive applicator (*e.g.*, a gravure roll) onto the photoreceptor in response to the external field of the latent image pattern. Resolution is limited by the applicator pattern. In a third approach, *Gesierich*, *Cassiers*, and *Marx et al.* have described "selective wetting" development: aqueous developer is applied uniformly to a low-surface-energy photoreceptor, but retained selectivity only in charged areas. The effect may be understood in terms of an electrostatic enhancement of effective photoreceptor surface energy[50–53]. In this process, as in other liquid development schemes, incomplete transfer and cleaning are serious problems. For these reasons liquid development has, with rare exceptions[54], found its prime use in direct electrophotography.

2.5. Photoreceptors for Transfer Xerography

A typical photoreceptor comprises three layers (Fig. 12): a base electrode, a thin dielectric barrier layer, and the photoconductor itself.

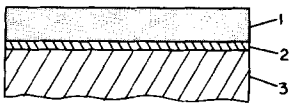


Fig. 12. Cross-section through typical xerographic photoreceptor: (1) photoconductive layer, (2) injection barrier, (3) base electrode.

The dark relaxation time of the photoreceptor must be long compared to the time between charging and development—usually 0.3 to 10 s, depending on the application. Mobile carriers must be absent initially, or swept out during the charging step. A thin barrier layer is used to minimize injection from the base electrode; metal oxides, sulfides, and organic polymers are commonly used[60]. The surface charge—believed to be generally in the form of adsorbed corona ions—may be stabilized by a surface layer of electron donors or acceptors for positive and negative charge, respectively, which appear to act as deep traps[*]. A series of investigations of ZnO surfaces has provided considerable insight into the energy levels involved[24, 63]; additional research in this area would be most desirable.

The optimal thickness of the photoconductor layer is determined by the potential required for development—typically, 300 to 800 volts. Since xerographic photoconductors are basically capacitive devices, and since each absorbed photon can generate, at most, one conduction electron, the voltage contrast produced by illumination is, in principle, proportional to the dielectric thickness. However, the transport of carriers becomes inefficient as the thickness increases past the mean trapping range of the carriers. In practice, the best compromise appears to be between 15 and 25 μm for organic and binder layers (dielectric constant 3 to 5) and between 30 and 100 μm for selenium and its alloys (dielectric constant from 6 to 9.5)[61].

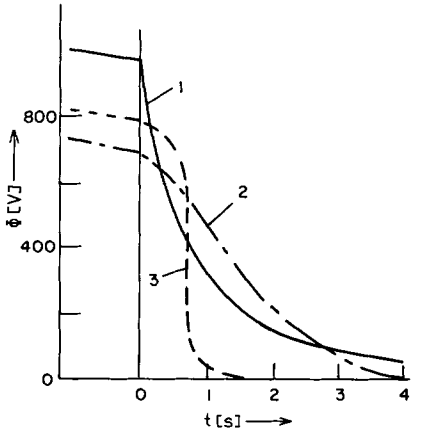


Fig. 13. Photoinduced discharge characteristics of typical photoconductors (steady illumination begins at time $t = 0$). (1) Typical homogeneous photoconductors such as selenium [62a] or PVK : THF charge transfer complex [73c]; (2) negatively charged ZnO-binder Electrofax layer [62b]; (3) phthalocyanine-binder plate exhibiting induction period followed by sharp discharge [66a].

[*] One of *Carlson*'s key contributions was his discovery that corona charge is not readily injected into xerographic photoconductors; hence they are stable against premature dark discharge [21a].

Dark and photo-induced discharge characteristics ("PIDC's") of typical xerographic photoconductors are shown in Figure 13. For high photosensitivity, the photoconductor must provide for effective light absorption in the desired spectral region, efficient separation of photoexcited electron/hole pairs in the applied field, and complete transport of the mobile charge carriers across the layer. Most photoconductor materials exhibit efficient transport either for electrons *or* for holes; it follows that the radiation should be absorbed strongly (extinction coefficient 10^4 to 10^5/cm), and for front illumination, electron-transport photoconductors should be charged negatively and hole transport layers positively. Since the required response times are of the order of 0.1 to 10 s, xerographic photoconductors are essentially "DC" devices, and drift mobilities of the order of 10^{-6} to 10^{-2} $cm^2/V \cdot s$ suffice[*].

Cycling stability requires that the photoreceptor be completely restored to its original state shortly after use; this is generally accomplished by optical untrapping and AC-corona neutralization of trapped carriers. In addition, the surface must be cleaned free of electrically active impurities, and surface abrasion, filming and mechanical failure must be minimized. Since transfer-xerographic photoreceptors must be reused, typically, between 10^4 and 10^6 times, this requirement places considerable stress on the reproducibility of materials and on the various erasure and cleaning steps.

Vitreous selenium, an amorphous mixture of eight-membered rings and linear Se-polymers produced by vacuum evaporation, has long been the basis of the most commonly used photoreceptors. Tellurium may be added to extend red response, and arsenic alloys have been found to enhance photosensitivity as well as stability against crystallization[64].

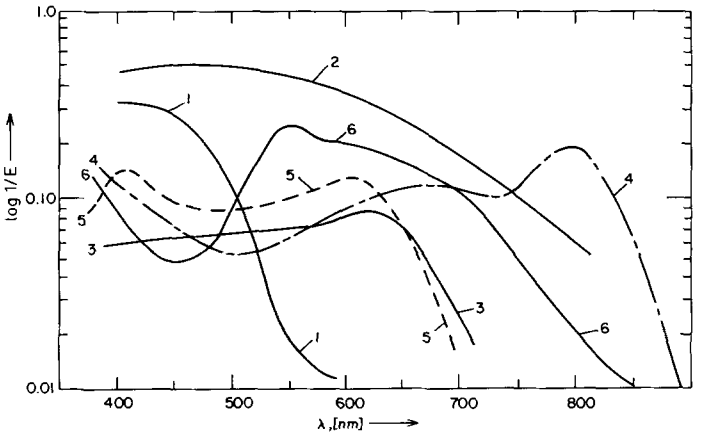


Fig. 14. Relative spectral response curves of typical xerographic photoreceptors. Data adapted from several sources. Photosensitivity ($1/E$) is measured, approximately, in cm^2/erg. (1) Selenium (after Ref. [64e]); (2) As_2Se_3 (after Ref. [62c]); (3) PVK:TNF, 1:1 molar complex of polyvinyl carbazole and trinitrofluorenone (after Ref. [73c]); (4) Phthalocyanine-binder photoreceptor (after Ref. [66a]); (5) ZnO-binder coating, dye-sensitized with Bromphenol Blue (after Ref. [62d]); (6) CdS-binder coating (after Ref. [65a]).

Dispersions of photoconductive pigments such as cadmium sulfide, zinc oxide and phthalocyanine in dielectric binders may be used, provided that the volume loading of pigment is sufficient to assure charge transport across the thin dielectric barrier to layers between adjacent particles[65, 66]. The particle-binder interface may be "doped" with sensitizing dyes, electron acceptors, or "supersensitizers" to enhance photoresponse, charge acceptance, and other desirable characteristics[67, 68].

Organic photoconductors are of special interest to chemists because their behavior bridges the gap between photochemistry and solid state physics. *Carlson*[69] used anthracene for some of his earliest experiments. Since then, many types of polynuclear aromatic and heterocyclic compounds have been shown to be useful, both in binder dispersion and as homogeneous polymers like polyvinylcarbazole[70, 71]. Although the inherent sensitivity of most of these materials lies in the ultraviolet, their response range may be extended into the visible by the addition of sensitizing dyes[67d, 72] and pigments[66c], or by the formation of donor-acceptor complexes having photoactive charge-transfer absorption bands in the visible range[71, 73]. Carrier generation in these materials is strongly field dependent: typically, the quantum yield is proportional to the square of the field intensity[74, 75]. Photogeneration of carriers appears to be analogous to the oxidation/reduction chemistry of photoexcited states of the same organic molecules in other media: singlet-singlet excitation is followed by electron transfer to a nearby site in the matrix—*i.e.*, a "redox" reaction takes place between neighboring molecules. Charge transfer complexing has been shown to enhance the quantum yield, as well as to extend spectral range—presumably by facilitating the initial separation of photogenerated electron-hole pairs, so that prompt ("geminate") recombination is suppressed by localization of carriers at adjacent D^+ and A^- sites[73]. Here, the slightly separated carriers may reside as an excited state, somewhat analogous to Pope's trapped "charge transfer exciton", until thermally activated diffusion, assisted by the strong externally applied field used in xerography, can remove the more mobile carrier from the generation site[76].

The slow, field-assisted drift of electronic charge carriers which follows their separation[82] may be represented, in molecular terms, as the migration of ion radical *states* through the matrix[*]. Only local orbital overlap between near neighbors is required for such a process; long range crystalline order is not necessary. Carrier transport may thus be considered analogous to the concentration-dependent spin migration between, *e.g.*, anthracenide ions through neutral anthracene in benzene solution[77]. From this perspective, charge transport is a purely molecular process—one which requires neither long-range structure nor cooperative effects, such as are invoked for band-model photoconductors. The effects of crystallinity and polymer tacticity are limited to the improvement of orbital overlap. Several investigators have found that electron donors such as aromatic amines, carbazoles and hydrocarbons transport holes but not (generally) electrons; conversely, efficient electron transport is observed in strong electron acceptors such as trinitrofluorenone[78–83].

Since the mechanism of dye sensitization, particularly in silver halides, has for decades been a controversial problem[2, 84], this subject has also been investigated in the context of electrophotography. The key question is whether the photoexcited dye sensitizes the UV-sensitive photoconductor by the transfer of neutral excitation energy or of charge carriers. Here electrophotography offers a convenient methodology:

[*] Most xerographic photoconductors exhibit transport characteristics with nonlinear field dependence; therefore, the term "mobility" must be used cautiously, with reference to the prevailing field intensity [61, 74, 75, 83].

[*] *Mulder et al.* were able to correlate the appearance of radical cations with photoconductivity in anthracene [82d].

one may construct a double layer photoreceptor, comprising a thin "sensitizing" layer in which visible light is strongly absorbed, coated over a relatively thick layer of UV-sensitive photoconductor (Fig. 15a). Since both layers may be made insulating, one may study the effects of both polarity and intensity of externally applied fields upon the photoresponse of the composite. Typical materials have included amorphous selenium and various organic pigments as "sensitizers", and layers of polyvinyl carbazole or trinitrofluorenone as photoconductors. The results have shown that—at least under high field conditions—the mechanism involves the photogeneration of charge carriers in the sensitizing layer and their injection and transport across the underlying photoconductor. Similar results have been obtained for the sensitization of amorphous selenium transport layers by the red-sensitive pigment, phthalocyanine. Spectroscopic measurements of the energy levels of the materials involved can be used to predict their ability to interact in this manner[74, 78, 80, 85]. Experiments of this type have led to a new family of double layer photoreceptors (Fig. 15a and b) in which a relatively thin "carrier generator" film sensitive to visible light is laminated to a much thicker, transparent, polymeric "active transport" layer. The former supplies photosensitivity, the latter dielectric strength and voltage contrast. Photoreceptors having desirable mechanical properties as well as high photosensitivity can be fabricated in this manner[79, 86].

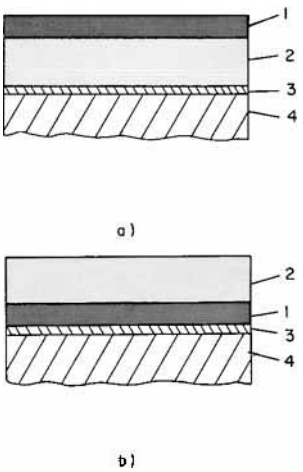


Fig. 15. Double layer photoreceptor with generator layer (a) at top, (b) at interface. (1) Generator (sensitizing) layer; (2) transport layer; (3) blocking interface; (4) base electrode.

Finally, the reader is reminded of the photoreceptor structure already shown in Figure 4, in which an *inert*, protective dielectric overlies a photoconductor layer. In some of the modes of use (*e.g.*[29]), the electrostatic latent image is formed exclusively across the dielectric layer so that the photoconductor is not subjected to prolonged high field stress. This allows the use of some highly sensitive photoconductor materials, such as sintered cadmium sulfide, whose excessive dark carrier concentration would prohibit their use in conventional single-layer photoreceptors. Since the imaging step requires simultaneous exposure and recharging, this process is most suitable for use with "slit scanning" optics. As mentioned previously, these photoreceptors have the advantage that the photoactive material is protected against corona ions, abrasion and other deleterious interactions with developer materials, paper, and cleaning devices used in the xerographic process.

2.6. Developer Materials

The "toner" particles used for developing xerographic images generally consist of 8—15 μm spheres of thermoplastic, colored by a dispersion of 5—10 % of submicron-sized carbon particles. Cyan, magenta, or yellow colorants may be substituted for use in color xerography[87, 88]. Pigment concentration and dispersion must be adjusted to impart a conductivity to the toner mass which is appropriate to the development process. For efficient *induction* development[44, 89], a conductivity greater than $10^{-4}\,\Omega^{-1}\,cm^{-1}$ is found to be desirable[90], whereas most other development processes require the toner to retain charge applied by contact electrification. The toner plastic is generally selected on the basis of its fusing characteristics: it must melt sharply at the lowest temperature consistent with stability in storage and under the vigorous agitation conditions which exist in xerographic development chambers[91, 92].

For cascade or magnetic brush development, typically, a 1—2 weight percent concentration of toner is dispersed in a freely mobile mass of glass, steel, or ferrite beads, each 100 to 500 μm in diameter[34, 42]. The beads are generally overcoated with an impact-resistant polymer, designed to transfer a controlled amount of positive or negative charge to the toner by contact electrification. The physicochemical effects responsible for charge transfer between insulators are as yet poorly understood[93]. The literature suggests that the process involves, in part, electron exchange, determined by the relative electrochemical potentials of the materials. However, charge exchange in dielectrics is a slow process, not likely to reach equilibrium[94]. In a churning developer mass, the situation is greatly complicated by abrasion and impact transfer of ions, polymer and adsorbates, and by the oxidation of polymer, as well as by localized electrical breakdown across the gaps between moving toner and carrier particles[95]. Humidity generally has profound effects on triboelectric behavior[39, 96]. In addition, the dielectric relaxation time of the developer mass must be kept below the development time if effective solid-area coverage is to be achieved; therefore, careful control of conductivity and dielectric constant are essential.

In a cycling process, additional long-term interactions of the developer with other system components must be taken into account. The toner particles must be readily transferable and fusible to the receiving sheet, but without being so soft as to coat the carrier beads. The developer mass must not abrade, poison or smudge the photoconductor surface; it must be readily removable by a simple cleaning system; it should not be excessively degraded by impaction, heat or corona oxidation. Finally, some blade cleaning systems require the addition of lubricants to minimize van der Waals forces between the photoconductor surface and toner residues[97]. Considering these complications, it will not surprise the reader that "practical" developer materials still tend to be selected by empirical choice, and that the patent literature abounds in mysterious recipes[98].

3. Direct Electrophotography: "Electrofax" and Related Processes

A chance observation is reported[99] to have led to the invention of "coated-paper xerography." It appears that *C. J. Young*[100] was experimenting with transfer xerography, using simple laboratory equipment: selenium "flat plates," a corona wand, a projector, and a rather dusty development box. To his astonishment, he discovered that a faint toner image had settled on a piece of "plain" paper, which had itself been accidentally charged, exposed, and sprinkled with toner residue—but never contacted to a selenium plate. Evidently, the paper itself was photosensitive! The experiment was quickly repeated with every type of paper available around the laboratory. The best results were obtained with a blank portion of glossy "LIFE" magazine cover stock. In due course, it turned out that those papers which were photosensitive had a surface sizing of zinc oxide. There followed the thought that xerographic images could be formed directly on white zinc oxide binder-coated paper and fused permanently to its surface—a process which became known under the trade name "Electrofax"[100]. Image transfer, and photoreceptor cleaning and recycling were avoided, albeit at the cost of requiring the use of a paper coating.

The commercial Electrofax base is generally treated with polymeric antistatics[101] to render it reliably conductive, and the zinc oxide is dye-sensitized[67] to extend its photosensitivity across the visible region. A uniform mixture of blue-, green-, and red-sensitive dyes may be used to keep the coating color a neutral light gray[102] while conferring panchromatic sensitivity. They key innovation in Electrofax was to produce images directly on the final sheet. (*Schaffert* has pointed out[103] that binder layers of zinc oxide, cadmium sulfide and other inorganic "phosphor" pigments had previously been shown to be useful for transfer xerography and persistent internal polarization[104, 105].)

Multiple filter exposures, alternating with dry[88a] or liquid[46c] development with "process" color toners may be used to produce full color prints. Electrofax has found wide use for low-volume black-and-white copying; in addition, at least one color copier has been marketed.

Metcalfe and *Wright* have described[108] an interesting form of "chargeless electrophotography", which owes its discovery to an amusing accident[109]. For some time after his invention of electrophoretic development, *Metcalfe* used to startle visitors to his laboratory by casually pulling a sheet of zinc oxide-coated paper out of his darkroom cabinet drawer, exposing it, and dipping it into a pan of his fine-particle liquid developer. As though by magic, a beautiful image appeared on the apparently *uncharged* sheet. This legerdemain was accomplished by means of a corotron, hidden within the drawer by the playful inventor[110]. But once the corotron accidentally failed to operate—and *Metcalfe* himself was astonished to find a negative image on his zinc oxide paper! Upon careful investigation, the latent image turned out to be an imagewise distribution of a 0.3 to 0.4 V positive Dember potential, created in the zinc oxide by the selective inward diffusion of photoelectrons, holes remaining trapped at the generation site close to the exposed surface[111]. The ultrafine liquid dispersion was able to develop these small potentials, offering extraordinarily high resolution, unaffected by the mottling due to corotron discharge streamers. Unfortunately, development times of the order of 30 seconds are required and the effect is strongly temperature-sensitive; therefore, the process has not been adaptable to automatic photocopiers.

Direct electrophotography on transparent organic photoconductor films has found use for the production of transparencies. Since the transfer step is omitted, images resolving 200 lp/mm and better can readily be produced, particularly with electrophoretic liquid developers[106]. "Strip-out" of additional pigment from a secondary donor film to a tackified primary image pattern provides a useful way to enhance image density[107].

4. Persistent Internal Polarization and Photoelectrets

We now turn to electrophotographic processes which are related to xerography, but differ in some essential respects. The first of these is "persistent internal polarization" ("PIP"), invented by *Kallmann et al.* in the USA[112] and, independently,—as "photoelectret imaging"—by *Fridkin et al.* in the USSR[113]. This process differs from xerography in the method used for establishing the electrostatic latent image. For xerography, as we have seen (Figs. 2 and 3), the *external* charge is applied to the photoconductor in the *dark*. In PIP, a polarizing field is applied to the photoconductor while the latter is *illuminated* to generate mobile charge carriers, which are separated and trapped within the layer. Blocking contacts serve to prevent degradation of contrast by corona deposition or electrode injection.

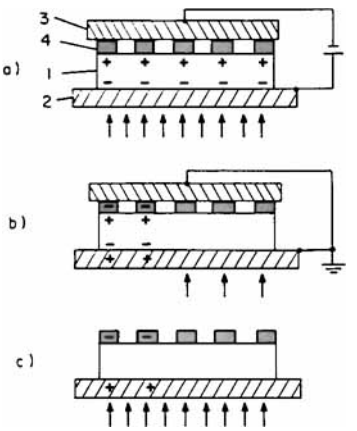


Fig. 16. Persistent Internal Polarization. In this form of PIP the polarizing field is applied to the photoconductor (1) on its base (2) by contact between an external electrode (3) and conductive dots (4) coated on the photoconductor surface. Illumination is shown by arrows.—(a) Plate is uniformly polarized, charge is trapped in the photoconductor layer.—(b) External electrode is grounded during image exposure.—(c) Electrode is lifted off, leaving developable latent image. After Ref. [112a].

The optical image may be projected onto the photoreceptor either *during* induction charging or *subsequently*; a developable surface pattern appears in illuminating areas in the first case, in dark areas in the second. In its polarized state, the photoconductor layer resembles an "electret"[114]. Special photoconductors having deep trapping levels—such as sulfur and ZnS : CdS phosphors—must be used if the photoinduced polarization state is to persist long enough to allow development of the field pattern. The presence of such traps in the bulk inherently

limits carrier transport; hence, the photosensitivity of PIP is very much lower than that of conventional xerography[115]. Although several uses for this process have been proposed, including portable cameras and displays, PIP appears to have found no commercial application.

5. Persistent Photoconductivity Imaging[*]

A number of attempts have been made to reverse the usual xerographic sequence: *i.e.*, to expose the photoconductor in a neutral state and then to charge it to form a latent image. This requires a photoconductor in which the photoexcited charge carriers retain their mobility sufficiently long to form a developable latent image. Materials suggested for this purpose include doped zinc oxide, acid-treated organic charge-transfer complexes, and photolyzable organic compounds[116-121]. None of these systems appear to have found practical use—at least in part because the photosensitivity of most photoconductive dielectrics is low in the absence of an external field capable of separating the newly formed carriers at the generation site.

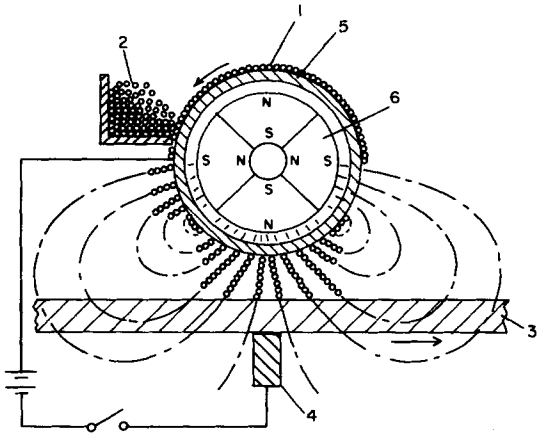


Fig. 17. Single-component magnetic brush. Magnetic toner (1) moves from a supply bin (2) to the imaging zone, where soft "bristles" make contact with the photoconductor (3), which is backed by a bias electrode (4). Either conductive shell (5) or sectored magnet (6) or both may be rotated to transport the toner. After Ref. [45a].

Shely's "Magnedynamic" process is a more sophisticated approach to "chargeless" electrophotography. An uncharged TiO_2-binder layer, coated on a metal-backed *dielectric* base, is exposed to an image pattern, then quickly developed with a positively biased "brush" of conductive magnetic toner loosely attached to a magnetized roller (Fig. 17). Illumination not only renders the photoconductor temporarily conductive, but also converts the contact between its surface and the subsequently applied toner mass from a blocking to an injecting state. In illuminated areas, positive charge is injected and toner is repelled, while in dark areas, toner is deposited by electrostatic attraction to the base. The positive toner image is thus developed; this may be transferred to paper, as in xerography, and the latent image redeveloped and reused a number of times without additional exposure. The photoreceptor may then be erased by ultraviolet exposure, cleaned, then rolled up, "rested" for several hours and reused at a later time[45, 89, 122].

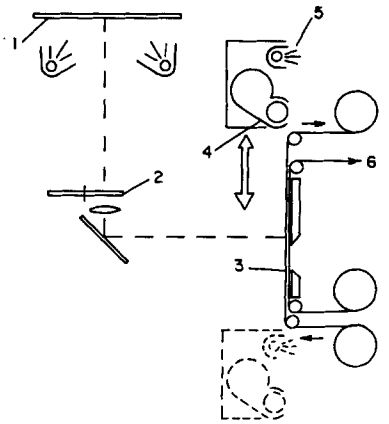


Fig. 18. Schematic of the Color-in-Color process. Original (1) is exposed through color filters (2) onto photoconductor (3). Magnetic toner development roll (4) and heat lamp (5) move up and down, parallel to face of fixed photoconductor sheet (3). Behind heat-absorbent toner pattern, dye is thermographically transferred to receiving paper (6). After Ref. [123a].

An ingenious extension of this process has been used for "Color-in-Color" imaging (Fig. 18). A special photoreceptor having a back coating of thermally vaporizable dye is prepared. After exposure through an appropriately matched color filter, a toner image is developed directly on the TiO_2 surface. The back of the photoreceptor is now pressed against the receiving sheet, while the front is uniformly irradiated. Toned areas absorb this radiation selectively and allow heat to be conducted to the back of the sheet, from which a corresponding dye pattern transfers to the receiving paper. The photoreceptor web is advanced to an adjacent section whose back side has been coated with a vaporizable dye of another color, and the process is repeated. Three photoreceptor sections having cyan, magenta and yellow back coatings, respectively, may thus be exposed through appropriate color filters to a stationary color original to cause a multicolor dye image to be deposited in registration on the receiving sheet[123].

6. Transfer of Electrostatic Images ("TESI")

In conventional xerography, as we have seen, the *developed (toner) image is transferred* to the receiving sheet, after which the photoreceptor must be erased and cleaned prior to reuse. An alternative, which obviates the toner transfer and cleaning steps, is to *transfer the electrostatic latent image itself* to a suitable receiving sheet prior to development. Transfer of an electrostatic charge pattern may be accomplished either *during* photoreceptor exposure (*i.e.*, while the latent image is being formed) (Fig. 19) or *after* a stable charge pattern is formed on the photoreceptor by conventional charging and exposure (Fig. 20). The names applied to these two process variants are "simultaneous TESI" and "sequential TESI," respectively[124, 125]. In either case, a dielectric-coated paper or film is pressed in intimate contact to the photoreceptor, generally in a suitable bias field. *Schaffert* and *Brodie et al.* have defined the conditions required for efficient charge transfer across the small air gap between dielectric surfaces[126, 127]. A third alternative, sequential TESI from a "persistently con-

[*] See also: Section 10, "Photoconductography".

ductive" latent image, has been described by *Sporer*[120] and by *Melz* and *Vahtra*[120, 172b].

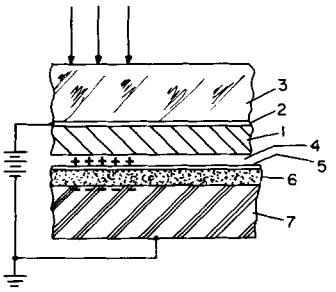


Fig. 19. Simultaneous TESI. Image radiation (arrows) enters the photoconductor (1) through a conductive-coated (2) glass backing (3). Positive charge is transferred across air gap (4) to a dielectric receiving layer (5) on a resilient conductive backing pad (6) and support (7). Threshold field across air gap is not exceeded in dark areas, therefore no charge is transferred there. After Ref. [128b].

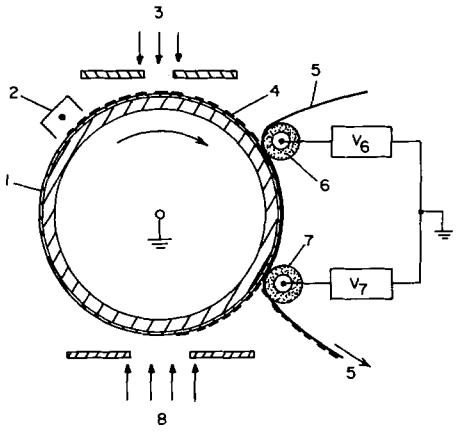


Fig. 20. Sequential TESI. Photoconductor drum (1) is charged (2) and slit-exposed (3). Latent image (4) is transferred to dielectric receiving sheet (5) with separately biased rolls (6, 7) at entrance and exist of transfer region. Sheet (5) is developed, photoconductor (1) is erased (8) and re-used. After Ref. [128b].

Although these processes were invented more than two decades ago, their commercial use has been delayed, in part by the need for specially coated paper and in part by the relatively severe effects of contact geometry and ambient humidity upon the efficiency of charge transfer. "Simultaneous TESI" has recently been applied to a CRT display terminal printer[128], and a compact copier has been introduced which uses the sequential process[129].

7. Photoplastic Imaging

In all the processes described so far, an electrostatic latent image is developed by the attraction of externally supplied charged particles. We now consider some alternatives in which the image-forming material is part of the photoreceptor.

The first of these is photoplastic imaging. The concept derives from the observation of *Thiemann*[130a] that the surface of a dielectric oil film could be deformed by writing on it by means of an electron beam; the surface deformations may be read out by means of schlieren optics[*]. This principle was later applied by *Glenn et al.*[131] for electron beam recording on softened thermoplastics, and eventually by *Mehl, Greig* and *Wolff, Gaynor et al.*, and others to direct optical relief recording on thermoplastic organic photoconductor layers (Fig. 21)[132, 133, 134].

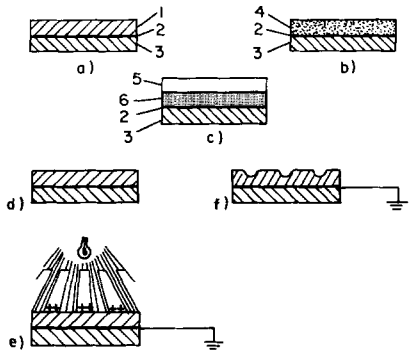


Fig. 21. Photoplastic imaging members (a—c) and process (d—f).—a) Transparent photoconductive thermoplastic film (1) on transparently metallized (2) film base (3). b) Photoconductive pigment dispersion in thermoplastic (4) replaces transparent layer (1). c) Frost configuration, in which transparent thermoplastic layer (5) overlies transparent photoconductive control layer (6).—d) Film (a) prior to imaging. e) Film has been charged and exposed, and... f) Heated to produce surface deformation.—After Ref. [133d].

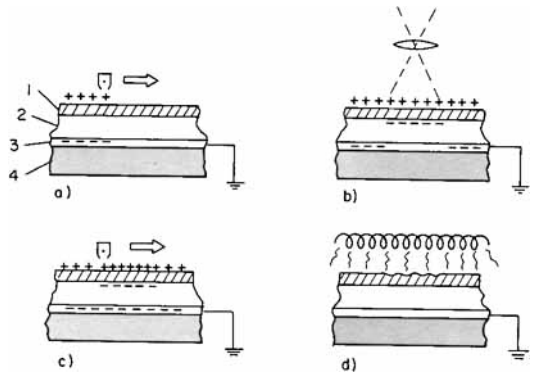


Fig. 22. Frost imaging process. Thermoplastic layer (1) on transparent photoconductor (2) over transparent metallized (3) film base (4) is a) charged, b) exposed, c) re-charged to constant surface potential, and d) heated to produce a light-scattering surface deformation in illuminated areas. After Ref. [139].

Meanwhile, *Gundlach* and *Claus*[135] devised an interesting two-layer variant of this process, called "Frost" imaging, which permits direct viewing of the deformation pattern without a schlieren screen (Fig. 22). The basic observation was that if a critical electrical stress is applied imagewise to a thin thermoplastic coating backed by a photoconductor layer, and the thermoplastic is then softened, the surface of the film will be deformed into a random wrinkle pattern. Since such a pattern scatters transmitted light, it may be used to display a latent electrostatic image. As *Cressman*[136] has shown, Frost deformation is due to a combination of two factors:

Mutual repulsion of trapped surface charges; this tends to increase the total surface area and produce a wrinkle pattern over the entire charged area.

Mutual attraction of trapped surface charge and counter charge induced in the photoconductor backing; this produces line deformation and enhances edge contrast.

The characteristic spatial frequency has been related to hydrodynamic instabilities[137]. The scattering image consists of random deformations having a preferred "cell spacing"

[*] This process is the basis of the "Eidophor" projection television system [130b].

of about twice the coating thickness. *Urbach et al.*[138] improved high frequency contrast by introducing a screen having the optimal spacing as "carrier" for the optical signals. High-resolution-screen thermoplastic holograms could be developed at the exposure site by means of a warm air stream so that the resultant holographic image could be viewed immediately. Resolution was sufficiently high that screen frequencies of 200 to 1000 cycles/mm could be used. *Sullivan et al.*[139] have described the effects of optical systems on the tone reproduction of Frost images.

Various photoconductors have been used for photoplastic recording, including selenium, dye- or charge transfer-sensitized organics, and phthalocyanine dispersions[133c, 135, 138]. Images may be erased by softening the film and discharging the field across it; the photoreceptor may then be used to form a new image. Since the photosensitivity depends upon light absorption in the layer, response has to be traded off against transparency, scattering efficiency against resolution, and image stability against ease of recycling. Although optical contact copying (*e.g.*, to diazo film) is not practical, photoplastic images may be replicated by surface casting[140]. Despite optimistic proposals to use photoplastic recording films for cyclic displays, "add-on-image" microfiche, and "instant" microfilm cameras, no commercial application has emerged[*].

8. Photoactive Pigment Electrography ("PAPE")

The first practical process which used the movement of electrically photosensitive particles to form images was invented by *R. W. Gundlach*[143]. He deposited a uniform layer of loose photoconductive toner on a flat electrode, charged the deposit, exposed it to a projected image and removed the loosely adherent powder from illuminated areas. The remaining toner pattern could be fused onto the plate. This imaging method has found extensive application in lofting—*e.g.*, the marking of ships' plates (particularly in Japan[144], Fig. 23). Attempts to adapt this process to photocopying did not meet with success[145]. However, more recently, photoconductive pigments have been used to form images in thermoplastic and liquid dispersions, which are easier to control than loose dry toner. These will be discussed in the next three sections.

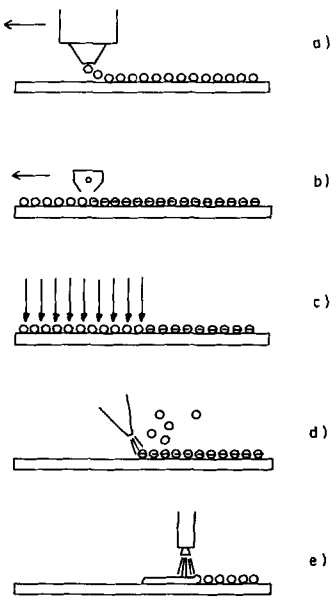


Fig. 23. Photoconductive toner imaging. Toner is a) deposited on base plate, b) charged, and c) exposed. The photodischarged powder is blown away (d), leaving toner electrostatically adhered in dark areas, to which it may be fused (e). After Ref. [144].

[*] Two related photoconductor-controlled elastomeric projection display devices, called "Elmikon" [141] and "Ruticon" [142], have been described in the literature.

8.1. Particle Migration Imaging

In the course of experiments on the photosensitization of charged Frost photoplastic layers by means of a thin overcoating of evaporated selenium, *W. L. Goffe* had occasion to use solvent vapor to soften the underlying thermoplastic layer. He made the startling observation that charged and exposed regions of the selenium layer did not merely deform, as expected, but literally tore themselves loose from the surface and raced through the thermoplastic layer to the transparent base electrode to which they then adhered tenaciously (Fig. 24). Detailed investigation of this phenomenon led him to the invention of a totally new form of electrophotography based upon the imagewise migration of charged photosensitive particles through a thin, temporarily softened thermoplastic[146]. Films capable of being imaged in this fashion are deliberately coated to produce a densely packed layer of microscopic selenium balls[148]. When these are charged, then illuminated, net negative charge is found to be firmly trapped on the illuminated selenium particles, forming a highly stable latent image[147]. The matrix is now softened by heat or solvent vapor, freeing the negatively charged selenium microspheres in illuminated areas to be attracted to the base by their counter-charge. This movement forms a "primary" image: in *exposed* regions, fully migrated particles pack closely at the base electrode, forming a dark red *negative* image, while unexposed particles spread out through the layer, allowing light

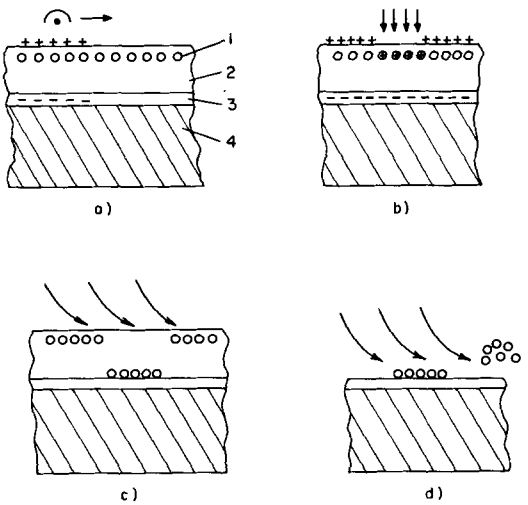


Fig. 24. Particle migrating imaging. Selenium particles (1) are imbedded just below the surface of 10 μm thermoplastic film on transparent metallized (3) film base (4). The film is a) charged, b) exposed, c) washed with hexane to leave (d) a dark, firmly adhered image of Se particles in illuminated areas of the film. After Ref. [148].

to be scattered forward and causing background areas to appear light blue. Full contrast may be developed in seconds by a quick solvent wash, which removes the thermoplastic and its residue of incompletely migrated pigment, leaving a fully developed deep red image on a clear background (Fig. 24).

The process is suitable for "instant" (and optionally "dry") high-resolution microimaging; negative images are formed (*i.e.*, dark selenium deposits correspond to illuminated areas). The sensitometric properties are well accounted for by particle size, extinction coefficients, and spectral response[148]. The process is strongly materials and configuration dependent: when dispersions of other photoconductive pigments, such as ZnO or phthalocyanine, are used, the image sense becomes positive, *i.e.*, particles migrate preferentially in dark areas[149]. The mechanism for this variant has not been explored in detail; a plausible hypothesis suggests that simultaneous ejection of electrons and holes from illuminated pigment particles into the surrounding thermoplastic discharges exposed areas, leaving the particles without external field to drive them to the base. Evidently, in these materials not much charge can be stably trapped on the particles themselves.

8.2. Photoelectrophoresis ("PEP")

In 1963, *V. Tulagin* invented an elegant solution to the intellectual challenge posed by single-step full-color electrophotography[150]. It was already known that the charge/mass ratio—and hence electrophoretic motion—of charged particles through a dielectric field could be influenced by their absorption of light. What *Tulagin* recognized was the power of using spectrally selective pigments: cyan pigment would respond only to red radiation, magenta particles to green, and yellow ones to blue light. The selective spectral response of individual electrically photosensitive particles in a mixture could therefore be used to devise an "instant" full-color reproduction process.

The inventor relates[151] that four quite separate concepts converged in his mind to enable this invention. Three were available to him when he started:

1. *Kaprelian*[152] had already shown that the electromigration of zinc oxide particles suspended in dielectric fluids could be influenced by illumination and had proposed that this effect could be used in an imaging system. *Yeh*[153] had extended this work to the cyan pigment, phthalocyanine, and experiments on the mechanism of charge exchange were already underway when *Tulagin* took over the project.
2. An experimental roller imaging device having just the right configuration was available in his laboratory. Originally designed for xerographic liquid development[154], its photoconductive plate was readily replaced by a transparent tin oxide-coated glass electrode through which a colored image could be projected into the imaging zone.
3. Brightly colored organic photoconductor pigments were under active investigation in an adjacent laboratory[106b]: in the eyes of the color photographer, the cyan phthalocyanines, the magenta quinacridones, and the yellow azo pigments were promptly perceived as potential red-, green-, and blue-selective sensors for a polychrome imaging system—and much simpler than the multi-layers prepared previously[152].
4. To these resources the inventor added an essentially aesthetic concept which he had harbored for years: "to pull a color image out of a black coating, instead of painting color on a white base."

Once outlined on paper, the new idea was swiftly demonstrated to be feasible. Within a year suitable materials were selected. *Tulagin* and his co-workers formulated an oil suspension of roughly equal parts of electrically photosensitive cyan, magenta, and yellow particles and pushed the brownish-black "ink" through a small gap between a transparent electrode and an electrically biased backing roller covered with a thin dielectric coating[150]. A full-color positive copy of an original image projected into the imaging zone through the transparent electrode was instantly reproduced on the latter as it emerged; a negative image comprising exposed pigment appeared on the dielectric coating of the roller (Fig. 25). To those who saw it at its inception, the speed, simplicity, and color rendition of the process were truly impressive.

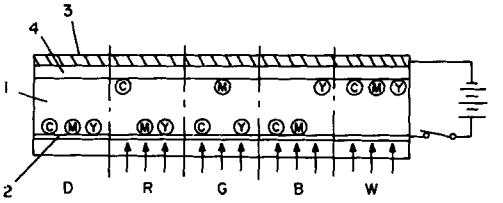


Fig. 25. Polychrome PEP. A dispersion of cyan Ⓒ, magenta Ⓜ, and yellow Ⓨ pigment particles in dielectric oil (1) is contained between a transparent "injecting electrode" (2) and a counterelectrode (3) coated with a blocking layer (4) to prevent particle oscillation. Exposure to light absorbed by each type of particle causes it to be detached and move to the marking electrode, leaving a subtractive color behind on electrode (2). Exposure to white light removes all particles, while in dark areas a black mixture remains. The positive color image formed on the lower electrode may be transferred and fixed to paper, whereupon this electrode is re-inked for the next use. Color of light (*R*ed, *G*reen, *B*lue, *W*hite) corresponds to color of particle mixtures left on electrode (2). In *D*ark area, the black particle mixture remains. After Refs. [6, 150].

Further study of PEP has revealed that complicated things happen in the narrow imaging zone between transparent electrode and imaging roller. The very compactness of polychrome PEP places a heavy burden upon the stability of process and materials. *Tulagin*'s original paper[150a] and subsequent publications and patents[155, 156] point out some significant problems:

Adventitious charge exchange between neighboring illuminated and dark particles must be minimized.

Maximum density is a sensitive function of ink film thickness and of the electric field within the imaging zone.

Unless special measures are taken, some particles tend to remain on the transparent electrode, forming background.

Most available pigments—particularly magenta—tend to have excessively broad absorption bands. Selectively filtered light sources can be used effectively to sharpen color response[156]. However, their properties as colorants remain imperfect. The color reproduction of the final prints is comparable to that obtainable by other non-masked color reproduction systems.

As expected, these problems have proven formidable and their solution has taken considerable time. No commercial use for the process has as yet been announced.

Snelling et al.[157] have demonstrated that monochrome PEP can be used to print very clean positive output from negative input directly on paper interposed between the imaging electrodes. Background may be suppressed by electrophoretic pre-deposition of the pigment on the imaging electrode. While working on this process, *Wells*[158] made the astonishing discovery that photosensitive pigments mixed in an ink with inert particles can be used to drive the two colorants in opposite directions to form complementary positive and negative images of *contrasting* colors! The process is called PEP-Stimulated Imaging ("PEPSI"); the phenomenon responsible is a photosensitized charge exchange between illuminated and inert particles. It permits the use of particularly sensitive pigments, such as phthalocyanine, to produce images of arbitrary color (Fig. 26). A photoconductor *layer* may be used instead of suspended phthalocyanine pigment to image inert colorant particles[159] (Fig. 27). Superposition of three filter-separated process color images on the same sheet of paper has been used experimentally to produce full-color positive prints[160].

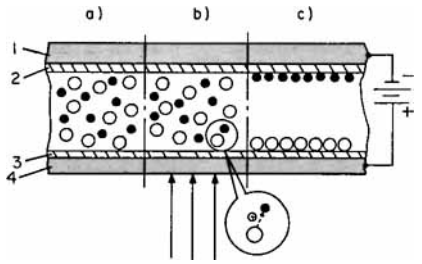


Fig. 26. PEP stimulated imaging (PEPSI). a) Mixture of photosensitive (○) and inert (●) pigments in a dielectric liquid is suspended in an electric field between electrodes (1, 4) with blocking layers (2, 3). b) In illuminated areas the pigments exchange charge and migrate c) to opposite sides of the liquid spacer. After Ref. [158].

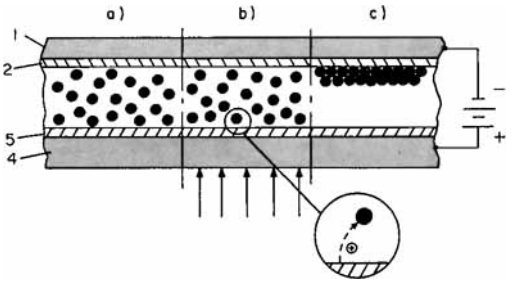


Fig. 27. "Layer PEPSI". a) Inert imaging particles (●) suspended in dielectric fluid are placed between photoconductor layer (5) on transparent base electrode (4) and a dielectric-coated (2) counter-electrode (1). b) Upon illumination in an external field, the photoconductor injects charge into nearby particles, causing them to move away. c) A high-contrast negative image is formed on electrode (1). After Ref. [159].

8.3. Manifold Imaging

The PAPE processes described so far share the concept that each pigment particle moves on its own. What happens if one sinters the particles together in 5–10 μm chunks of thermoplastic binder to force them to image as aggregates? As might be expected, the effective photographic speed rises—albeit at a sacrifice of resolution—and contrast is sharply enhanced.

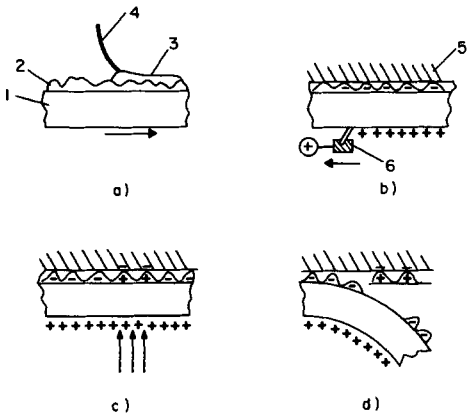


Fig. 28. Manifold imaging process. a) A sheet of plastic film (1), coated with a thermoplastic/wax dispersion of photoconductive pigment (2) is "activated" with hydrocarbon liquid (3), applied by a coating blade (4), and b) sandwiched to a metal foil (5) while another blade (6) applies contact charge. c) The softened manifold is exposed and d) separated into complementary images. After Ref. [161a].

VanDorn, Luebbe, et al. have described such a process (Fig. 28)[161a]. It is based on a coating of electrically photosensitive particles (such as the versatile phthalocyanine) in a wax-bonded thermoplastic binder. Prior to use, the dry layer is "activated" by a hydrocarbon liquid to loosen the weak adhesion between individual aggregates. The layer is then sandwiched between its metal foil backing and a plastic film backed by a transparent electrode to form an imaging "manifold". An image is projected through the film while a strong electric field is applied. When the layers are separated, exposed portions of the coating are completely transferred to the receiving sheet, while unexposed parts of the image remain completely on the donor. A pair of complementary high contrast images is thus formed. Either image may be electrostatically transferred to other receiving sheets, such as paper or cloth. Image-sense reversal may be accomplished by appropriate manipulation of the applied field. Various organic photoconductive pigments have been included in manifold coatings to produce black or single-color images. The size of the aggregates limits resolution to about 15 lp/mm. The authors have suggested a plausible mechanism based on electrostatic adhesion between the imagewise polarized thermoplastic layer and the counter-charge induced in the metal foil. Details of the separation and transfer process have recently been discussed by *Yang et al.*[161].

9. Photocontrolled Ion Flow Electrophotography ("PHIFE")

In conventional xerography, the dielectric imaging member is charged uniformly, then exposed to form an electrostatic latent image. Why not apply the charge imagewise to begin with? Several suggestions along these lines were made about 1960. For example, *Macgriff* and *McNaney* proposed switching individual members of a row of photoconductor-tipped corona electrodes by means of projected illumination. Unfortunately, the inventors did not succeed in fabricating arrays of photoconductive styli with sufficiently fast cycling response to enable a practical printer to be constructed[162, 163].

The first practical solution to the problem was devised by *Snelling*[164], who projected an image onto a Se-coated

metal screen interposed between an active corona source and a dielectric-coated paper. Illuminated areas of the screen freely passed corona ions to the dielectric, while the rims of the holes in dark areas quickly became charged and blocked additional corona ions from reaching the dielectric sheet. Development of the paper revealed a well defined negative image of the input. This was a "simultaneous PHIFE" process (analogous, in a sense, to *Walkup*'s "simultaneous TESI"[124]).

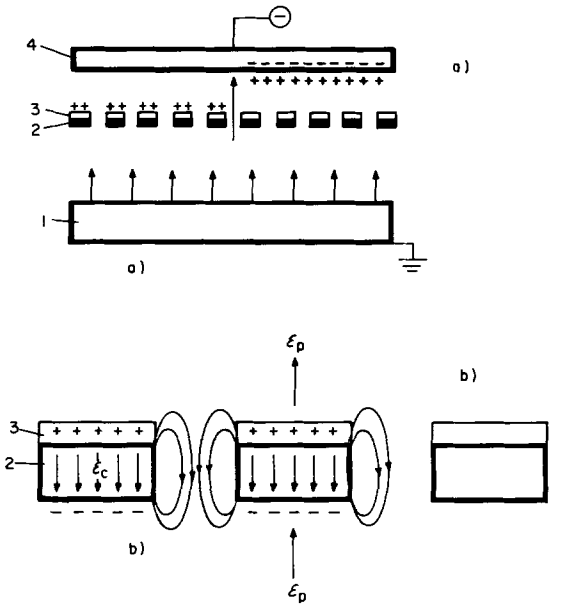


Fig. 29. Sequential PHIFE process. a) Corona ions are emitted from source (1) through a control screen (2) coated with photoconductor (3) towards dielectric-coated record sheet (4). Charged areas of the previously imaged screen block the passage of positive ions.—b) Enlarged section through screen shows full blockage of aperture at left, partial blockage of the one at right.

"Sequential PHIFE" processes were subsequently investigated in other laboratories[165] (Fig. 29). A latent electrostatic image is first produced on the screen by conventional charging and exposure, and the screen is then interposed between a corona source and a dielectric. Excellent positive images can be produced from both positive and negative input. *Pressman* has calculated the electrostatic fringing field patterns around small photoconductor-coated apertures and studied their use to control the passage of corona ions. His results show that excellent halftone reproduction is possible with 8 dot/mm screens. Multiple images can be printed from a single latent-image exposure[165a].

This process shares the important advantage of TESI that the photoconductor is never contaminated by developer or abraded by paper and feeding devices. Therefore, it appears peculiarly suitable for low-volume copying applications where more conventional apparatus is too complex. On the other hand, the screens may be a little fragile for use in fast duplicators. Rather than competing for the same applications, PHIFE and xerography promise to become nicely complementary[*].

[*] Another option—to use photoconductor-coated screens to control the flow of charged *toner* particles [166] (a photocontrolled version of electrostatic screen printing [167])—seems to have been abandoned as impractical. The toner evidently clogged the holes, and the cleaning brushes quickly abraded the photoconductor coating.

10. Photoconductography

Electrolytic imaging is the only form of electrophotography in which chemical change plays a significant role. A latent conductivity pattern is formed in a photoconductive insulator, then developed by electrochemical deposition. Photographic gain is achieved by drawing multiple charges through the photoconductor-electrolyte series circuit, by secondary chemical amplification, or both.

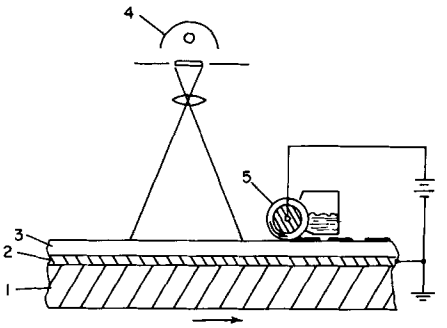


Fig. 30. Photo-electrolytic imaging process. The imaging sheet, consisting of a paper base (1), laminated to aluminum foil (2) and coated with a zinc oxide-binder mixture (3), is exposed from a microfilm projector (4), then developed by a biased sponge roll (5) wetted with silver salt solution.

Beginning about 1920, *Wilcke, Berchtold* and others[168] attempted to use image-illumination of various photoconductors to control the electrolytic coloration of contiguous layers such as paper and gelatin. Their work foundered for lack of photoconductor materials capable of adequate gain. A practical system[169] (Fig. 30) became possible when *Johnson* and *Neher*[119] found a way to dope zinc oxide in highly pigmented binder systems so as to enable the injection of multiple electrons per absorbed photon across the photoconductor layer[*]. In use, the dye-sensitized light-gray ZnO binder coating is imaged, then developed by passing it under a sponge wetted by an aqueous electrolyte containing reducible silver ions and biased about +100 V relative to the aluminum coating base. A dark-gray silver image forms where the photoconductor has been illuminated. Exposures of about 8×10^{16} photons/cm^2 are required, implying a system gain of only 2.0[**]. The intense exposure required limits this process to the projection printing of transparencies; it is not useful for "true" photography, such as the reproduction of opaque documents.

Generally, only a single image is formed on such a photoconductor, and the "fatigue" introduced by the long trapping life of the minority carriers has no adverse consequences. However, prompt re-exposure *is* needed for color printing. In the "Electro-color" version of this process, *Tulagin et al.*[173] substituted electrolytically reducible ionic dye precursors for the previously used metallic cations. Cyan, magenta, and yellow dye images were electroplated imagewise, in succession,

[*] The general conditions for such photoconductor gain have been defined by *Rose, Redington*, and others [170—172]. Injection contacts must be provided at both sides of the layer, and the minority carriers—holes, in the case of ZnO and CdS—must be trapped sufficiently long to permit passage of n majority carriers across the layer, n being a measure of the photoconductor gain. In a photoelectrolytic system, therefore, n ions may be deposited or removed for each photon absorbed, with corresponding photographic gain.

[**] *Johnson* and *Neher* [169b] cite an exposure of 25 mW s of visible radiation. Assuming an effective atomic volume of (4.1 Å)^3 for Ag, and an extinction coefficient of 10^5/cm, about 2×10^{17} silver atoms/cm^2 must be deposited to deposit an image of density *ca.* 1.0, the best available from the system.

each following an appropriately filtered exposure from a masked color negative which served as input. The fatigue problem alluded to above was solved by an engineering trick: a hot water wash between dye development and re-exposure, which served to free trapped holes while washing residues of the preceding developer from the surface[173b]. Although beautiful color prints were produced in experimental equipment, the process proved to be too slow, too difficult to automate, and ultimately too expensive to find significant commercial application[173b, 174].

An alternative approach to providing photoconductor gain was suggested by *Nail et al.*[175]: to use imagewise electrolysis to deposit a colloid whose ink receptivity differs from that of the surrounding photoconductor. The extra density of adhered ink provides, in effect, a 10—20-fold image intensification over the absorption of a monolayer of dye. Finally, it has been shown that one may achieve substantial chemical gain by using photoelectrolysis merely to deposit a pattern of development *nuclei*, which then serve as latent image for subsequent amplification, either by physical development[176] or by the local catalysis of photopolymerization[177]. ASA speeds of 100—150, comparable to those of fast silver halide emulsions, have been claimed in the literature. Despite the early apparent promise of such systems, they appear to have been abandoned. We conjecture that they failed because they required wet processing with unstable reagents.

11. Conclusion

What of the future? Pictorial electrophotography remains a tempting challenge. Figure 31 summarizes typical sensitometric properties of a few of the systems we have discussed. All of them (except for photoconductography) have image gain of about 10^4 to $10^5\times$, hence a photographic speed roughly equivalent to ASA 0.1 to 3. It is obvious that image reproduction may be altered by changes in materials and processing conditions. Nonetheless, a few interesting generalizations emerge.

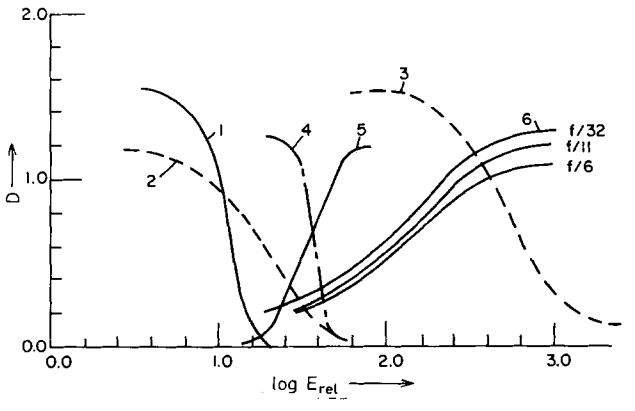


Fig. 31. Representative tone reproduction curves for electrophotographic processes. Horizontal coordinate: arbitrary ($\log_{10}$) exposure. Vertical coordinate: reflection density. (1) Xerography with magnetic brush development [180]; (2) xerography with optimal document screen [180]; (3) polychrome PEP [150a]; (4) manifold imaging [161]; (5) particle migration imaging [148]; (6) Frost: scattering image contrast depends on aperture of projection lens [139].

Photoelectrophoresis, particle migration imaging, and Frost are well suited to pictorial reproduction; they have the requisite fine grain, the "soft" tone-reproduction curves, and adequate exposure latitude. While fine-grain liquid development offers some promise for continuous-tone reproduction, dry xerography and manifold have problems: contrast is high, edges are sharp. These are accentuated in color xerography, where multiple images must be carefully registered with minimum moiré patterns. *Goren* and *Bestenreiner et al.* have given careful consideration to the improvements which might be achievable by optical screening and by modern electronic scanning methods—both familiar from other high-contrast processes used in the graphic arts[4b, 178, 180]. PHIFE, as *Pressman* has pointed out, is inherently screened and provides good tonal rendition[165a]. Optical buffering has been proposed as a means of controlling contrast as well as for color correction[4, 142]. Rapid advances in electronic image processing are likely to be of special benefit to electrophotography, where the pictorial elements are already represented in electronic form.

Schmidlin and *Shaw* have explored the limits of electrophotographic sensitivity in terms of the "detectivity" criterion, which quantifies the effect of the imaging system upon the signal/noise ratio of the incoming image. In xerography, it turns out that photoreceptor noise contributes relatively little to image noise, compared to fluctuations in developer spacing, toner particle size, and erratic adhesion in transfer. In PEP, on the other hand, *Schmidlin* suggests that fluctuations in particle size and adhesion could (in principle) be reduced sufficiently to improve the effective sensitivity by a factor of 100. Other systems have not yet been analyzed from this viewpoint[4a, 179].

What are some of the most interesting problems for the future—particularly for the chemist? A few have already been identified:

the nature of frictional electrification—a puzzle first encountered by the ancient Greeks—and more generally, the details of charge transfer across dielectric interfaces;

the roles of electrostatic and van der Waals forces in the adhesion and release of small particles;

the nature of ion adsorption and desorption on dielectrics, both in air and in dielectric liquid suspension;

an understanding of charge carrier generation and transport on a molecular level, particularly in disordered organic solids—a problem with spectroscopic, photochemical, as well as structural implications;

the rheology of thermoplastic composites;

the effects of materials composition and structure upon the ultimate limits of electrophotographic detectivity.

The field of electrophotography is still young, varied, and vital enough to admit significant advance by invention, as well as by scientific analysis. It cuts across many disciplines—from optics and photographic science to electronics and information theory; from mechanical engineering to the chemistry and physics of complex materials. The author hopes that this admittedly incomplete review will serve to stimulate new interest, and to keep the subject alive and open—rather than to close it by means of a deceptively tidy summary.

Received: September 20, 1976 [A 161 IE]
German version: Angew. Chem. 89, 386 (1977)

[1] *J. Kosar:* Light Sensitive Systems: Chemistry and Application of Non-Silver Halide Photographic Processes. Wiley, New York 1965; *P. P. Hanson,* "Unconventional Photographic Systems – a Bibliography of Reviews", Photogr. Sci. Eng. *14*, 438 (1970); *R. J. Cox:* Non-Silver Photographic Processes. Acad. Press, New York 1975.

[2] *C. E. K. Mees:* The Theory of Photographic Process. Macmillan, New York 1954.

[3] *M. R. Tubbs et al.*, J. Photogr. Sci. *17*, 162 (1969); *22*, 8, 61 (1974); *E. Berman*, Photogr. Sci. Eng. *13*, 50 (1969); *G. L. McLeod et al.*, *ibid. 13*, 93 (1969); *H. Jonkers et al.*, *ibid. 13*, 1 (1969); *V. M. Fridkin et al.:* Sensitized Photolysis on Semiconductors. Ref. [8], p. 347.

[4] a) *R. Shaw*, J. Appl. Photogr. Eng. *1*, 1 (1975); b) *R. Goren*, *ibid. 2*, 17 (1976).

[5] *J. H. Dessauer, H. E. Clark:* Xerography and Related Processes. Focal Press, London 1965.

[6] *R. M. Schuffert:* Electrophotography, 2nd Edit. Focal Press, London 1975.

[7] *E. M. Pell, K. J. Teegarden*, "Electrophotography", Appl. Opt. Suppl. *3* (1969).

[8] *W. F. Berg, K. Hauffe:* Current Problems in Electrophotography. de Gruyter, Berlin 1972.

[9] "Non-Silver and Unconventional Photographic Processes", Prepr. Int. Congr. Photogr. Sci., Moscow 1970, Sect. E.

[10] *P. Rice, R. M. Schaffert*, "Electrographic Processes", IEEE Trans. Electron Devices *19*, No. 4 (1972).

[11] *V. M. Fridkin:* Physical Principles of Electrophotography. Focal Press, London 1973.

[12] *D. R. White, J. W. Weigl:* Electrophotography: Second International Conference. Soc. Photogr. Sci. Eng., Washington, D.C., 1974.

[13] *C. F. Carlson*, "Xerography", in *P. A. Spencer:* Progress in Photography: 1955–1958. Focal Press, London 1958.

[14] *P. M. Cassiers*, Ind. Chem. Belge *25*, 773 (1960).

[15] *K. Hauffe*, Angew. Chem. *72*, 730 (1960).

[16] *J. H. Dessauer, G. R. Mott, H. Bogdonoff*, Photogr. Eng. *6*, 250 (1955); *J. H. Dessauer* in *W. F. Berg:* Photographic Science, Sect. IV. Focal Press, London 1963.

[17] *C. J. Claus*, Photogr. Sci. Eng. *7*, 13 (1963).

[18] *R. B. Comizzoli, G. S. Moser, D. A. Ross*, Proc. IEEE *60*, 348 (1972).

[19] *F. Stöckmann*, Appl. Phys. *7*, 1 (1975); *A. Rose*, J. Appl. Photogr. Eng. *2*, 70 (1976).

[20] *C. F. Carlson*, "History of Electrostatic Recording", in [5], Chapter I; *J. H. Dessauer:* My Years with Xerox: The Billions Nobody Wanted. Doubleday, Garden City, N.Y., 1971.

[21] a) *C. F. Carlson*, US-Pat. 2588699 (1952); b) *R. G. Vyverberg*, "Charging Photoconductive Surfaces", in [5], Chapter VII; c) *M. Levy, L. E. Walkup*, "Introduction to the Xerographic Process", *ibid.* Chapter II.

[22] *M. M. Shahin*, J. Chem. Phys. *45*, 26 (1966); Photogr. Sci. Eng. *15*, 22 (1971); in [7], p. 106.

[23] *R. M. Schaffert* in [6], pp. 31, 397, 441 ff.

[24] *W. Maenhout-Van der Vorst, F. Craenest*, Phys. Status Solidi *5*, 357 (1964); *K. Hauffe, R. Stechemesser*, Photogr. Sci. Eng. *11*, 145 (1967); *A. Kondo, T. Kitamura* in [10], p. 462; *F. Schelfaut, W. Maenhout-Van der Vorst* in [7], p. 96.

[25] *R. G. Vyverberg* in [21b], p. 201; *F. A. Schwertz*, US-Pat. 3254998 (1966).

[26] *L. Butterfield*, US-Pat. 2693416 (1954).

[27] *R. H. Hall*, US-Pat. 3084061 (1963); 3234019 (1966).

[28] *T. H. Moore*, US-Pat. 3124456 (1964).

[29] *M. J. Mitsui*, "Canography, Canon NP Process in Electrophotography", in [10], p. 396.

[30] *K. Nakamura* in [10], p. 405.

[31] *P. Mark*, Photogr. Sci. Eng. *18*, 254 (1974).

[32] *R. M. Schaffert*, Photogr. Sci. Eng. *6*, 197 (1962); in [6], pp. 467ff.

[33] *H. E. J. Neugebauer*, J. Appl. Opt. *3*, 385 (1964); in [5], pp. 217ff.

[34] a) *R. W. Gundlach*, "Development of Electrostatic Images", in [5], Chapter IX; b) *P. M. Cassiers, J. van Engeland*, Photogr. Sci. Eng. *9*, 273 (1965).

[35] *T. L. Thourson*, "Xerographic Development Processes: A Review", in [10], p. 495.

[36] *J. T. Bickmore*, "Aerosol Development", in [5], Chapter XI.

[37] *R. B. Lewis, H. M. Stark*, "High Sensitivity Electrophotographic Development", in [8], p. 322.

[38] *E. N. Wise*, US-Pat. 2618552 (1947).

[39] *E. H. Lehmann, G. R. Mott*, "Characteristics of Cascade Development", in [5], Chapter X.

[40] *W. A. Sullivan, T. L. Thourson*, Photogr. Sci. Eng. *11*, 115 (1967).

[41] *C. J. Young*, US-Pat. 2786439, 2786441 (1957); *E. C. Giaimo*, US-Pat. 2786440 (1957).

[42] a) *L. B. Schein*, in [12], p. 65; b) Photogr. Sci. Eng. *19*, 255 (1975).

[43] *S. L. Chang, C. V. Wilbur*, "Impression Development", in [12], p. 74.

[44] *J. C. Wilson*, US-Pat. 2846333 (1958).

[45] a) *A. R. Kotz*, US-Pat. 3816840 (1974); b) *G. R. Anderson*, US-Pat. 3455276 (1969).

[46] a) *K. A. Metcalfe*, J. Sci. Instrum. *32*, 74 (1955); b) *K. A. Metcalfe, R. J. Wright*, *ibid. 33*, 194 (1956); c) US-Pat. 2907674 (1959).

[47] *E. F. Mayer*, US-Pat. 2877133 (1959); 3672884 (1972); *V. E. Straughan, E. F. Mayer*, Proc. Nat. Electron. Conf. *13*, 959 (1957).

[48] *C. J. Claus, E. F. Mayer*, "Liquid Development", in [5], Chapter XII; *J. A. Dahlquist, I. Brodie*, J. Appl. Phys. *40*, 3020 (1969); *H. M. Stark, R. Menchel*, *ibid. 41*, 2905 (1970); *J. Van Engeland, W. Verlinden, J. Mariën*, "Continuous Tone Electrophotography using Electrophoretic Development", in [12], p. 80.

[49] *R. W. Gundlach*, US-Pat. 3084043 (1963).

[50] *W. Gesierich, E. Weyde, H. Haydn*, US-Pat. 3285741 (1966).

[51] *P. M. Cassiers et al.*, US-Pat. 3486922 (1969).

[52] *D. Marx, D. Winkelmann*, US-Pat. 3276424 (1966).

[53] *W. Gesierich*, Abstr. Int. Congr. Sci. Photogr., Paris 1965; *P. M. Cassiers*, Abstr. Int. Congr. Photogr. Sci., Tokyo 1967.

[54] *H. Tanaka, T. Saito, Y. Ando, K. Tanaka*, "Liquid Transfer System", in [12], p. 86.

[55] *P. G. Andrus, F. W. Hudson*, "Principles of Image Transfer and Fixation", in [5], Chapter XIV.

[56] *J. W. Weigl*, J. Chem. Phys. *24*, 370 (1956).

[57] *F. W. Hudson*, US-Pat. 3256002 (1966); *W. G. VanDorn*, US-Pat. 3268351 (1966); *R. Moser*, US-Pat. 3498596 (1970); *J. F. Byrne*, US-Pat. 3539161 (1970); and other patents.

[58] *C. R. Mayo*, US-Pat. 2684301 (1954); *C. F. Carlson*, US-Pat. 2776907 (1956); *R. W. Gundlach*, US-Pat. 2995464 (1961); and other patents.

[59] For a summary, see: *R. M. Schaffert* in [6], pp. 57–59, 166, 615.

[60] *J. H. Dessauer, H. E. Clark*, US-Pat. 2901348 (1959).

[61] *W. E. Spear* in [7], p. 8; *P. J. Warter*, *ibid.*, p. 65; *H. Seki* in [10], p. 421; *D. M. Pai, S. W. Ing*, Phys. Rev. *173*, 729 (1968); *J. G. Edmund*, J. non-cryst. Solids *1*, 39 (1968).

[62] a) *I. Chen, J. Mort*, J. Appl. Phys. *45*, 1164 (1974); b) *R. Comizzoli, H. Kiess* in [8], S. 102; c) *E. Montrimas, S. Tauraitiene, A. Tauraitis*, *ibid.*, p. 139; d) *W. Eckenbach*, *ibid.*, p. 133.

[63] *G. Heiland*, "Surface Properties of Zinc Oxide", in [12], p. 117.

[64] a) *W. Bixby, O. A. Ullrich*, US-Pat. 2753278 (1956); b) *R. A. Fotland*, J. Appl. Phys. *31*, 1558 (1960); c) *W. Bixby*, US-Pat. 2970906 (1961); d) *M. D. Tabak, P. J. Warter*, Phys. Rev. *173*, 899 (1968); e) *W. D. Hope, M. Levy*, "Xerographic Photoreceptors Employing Selenium", in [5], Chapter IV; to *J. S. Berkes* in [12], p. 137; g) *M. Scharfe*, *ibid.*, p. 142.

[65] a) *C. Wood*, "Xerographic Properties of Photoconductor/Binder Layers", in [5], Chapter V; b) *R. M. Schaffert* in [6], pp. 318 ff.

[66] a) *J. W. Weigl, J. Mammino, G. L. Whittaker, R. W. Radler, F. J. Byrne*, in [8], p. 287; b) *K. Hauffe, N. I. Ionescu, A. Meyer-Laack, K. Peetrikat*, *ibid.*, p. 271; c) *C. F. Hackett*, J. Chem. Phys. *55*, 3178 (1971).

[67] a) *E. K. Putzeiko, A. Terenin*, Zh. Fiz. Khim. *23*, 676 (1949); b) *C. J. Young, H. G. Greig*, RCA Rev. *15*, 471 (1954); c) *E. C. Giaimo*, *ibid. 23*, 96 (1962); d) *J. W. Weigl* in *W. F. Berg:* Photographic Science, Sect. IV. Focal Press, London 1963; e) *K. Hauffe et al.* in [7], p. 34; f) *E. Inoue, H. Kokado, T. Nakayama* in [10], p. 471; g) *G. Heiland, W. Bauer, N. Neuhaus*, Photochem. Photobiol. *16*, 315 (1972); h) *K. Hauffe*, Photogr. Sci. Eng. *20*, 124 (1976).

[68] *E. Inoue, T. Yamaguchi*, Bull. Chem. Soc. Jpn. *36*, 1573 (1963); *R. L. Clausen, D. K. Meyer*, US-Pat. 3271144 (1966).

[69] *C. F. Carlson* in [5], p. 36.

[70] For a summary, see: *M. Smith, J. W. Weigl*, "Organic Photoconductors", in [5], Chapter IV; *J. H. Sharp, M. Smith* in *P. J. Holmes:* Electrochemistry of Semiconductors, Chapter 8. Academic Press, New York 1970; *D. L. Stockman*, "The Present Status of Organic Photoconductors in Electrophotography", in [8], p. 194.

[71] *H. Hoegl*, J. Phys. Chem. *69*, 755 (1965); US-Pat. 3037861 (1962); 3232755 (1966); 3287120 (1966).

[72] *H. Meier, W. Albrecht, V. Tschirwitz* in [8], p. 163; *K. Morimoto, Y. Murakami* in [7], p. 50; *M. Ikeda et al.*, Photogr. Sci. Eng. *19*, 60 (1975).

[73] a) *M. Hayashi, M. Kuroda, A. Inami*, Bull. Chem. Soc. Jpn. *39*, 1660 (1966); b) *M. Lardon, E. Lell-Döller, J. W. Weigl*, Mol. Cryst. *2*, 241 (1967); c) *R. M. Schaffert*, IBM J. Res. Dev. *15*, 75 (1971); d) *W. D. Gill*, J. Appl. Phys. *43*, 5033 (1972); e) *B. Löhr, R. Arneth, D. Winkelmann* in [8], p. 219.

[74] *P. J. Regensburger*, Photochem. Photobiol. *8*, 429 (1968).

[75] *D. M. Pai*, J. Chem. Phys. *52*, 2285 (1970); *S. Fox* in [12], p. 170.

[76] *M. Pope*, J. Polym. Sci. *C17*, 233 (1967); *H. Seki*, Phys. Rev. *B2*, 4877 (1970); *W. R. Salaneck*, Appl. Phys. Lett. *22*, 11 (1973).

[77] *D. Lipkin, D. E. Paul, J. Townsend, S. I. Weissman*, Science *117*, 534 (1953).

[78] *J. W. Weigl*, Photochem. Photobiol. *16*, 291 (1972).

[79] *M. Smith, R. W. Radler, C. F. Hackett*, Can. Pat. 960073 (1974); *P. J. Regensburger*, US-Pat. 3894868, 3928034 (1975).

[80] *J. Rochlitz*, Chem. Ztg. *96*, 561 (1972).

[81] *W. Wiedemann*, "New Organic Photoconductive Layers", in [12], p. 224.

[82] a) *J. Mort, P. Nielsen*, Phys. Rev. *B5*, 3336 (1972); b) *J. Mort, ibid. B5*, 3329 (1972); c) *J. Mort* in *K. Masuda, M. Silver:* Energy and Charge Transport in Organic Semiconductors. Plenum Press, New York 1974; d) *B. J. Mulder, J. de Jonge*, Solid State Commun. *5*, 203 (1967).

[83] *W. D. Gill*, J. Appl. Phys. *43*, 5033 (1972); in *J. Stuke, W. Brenig:* Amorphous and Liquid Semiconductors, Vol. 2. Halsted Press, New York 1974, p. 901; *J. Mort, D. Pai:* "Photoconductivity and Related Phenomena", Elsevier, New York 1976.

[84] *H. Meier:* Spectral Sensitization. Focal Press, London 1968.

[85] *P. J. Regensburger, N. L. Petruzzella*, J. Non-Cryst. Solids *6*, 13 (1971); *R. J. Komp, T. J. Fitzsimmons*, Photochem. Photobiol. *8*, 419 (1968); *P. Nielsen*, Photogr. Sci. Eng. *18*, 186 (1974); *S. Kikuchi, Y. Takahashi, T. Sakata* in [7], p. 42.

[86] *Y. Hayashi, M. Hasegawa*, US-Pat. 3725058 (1973); *A. J. Cherry et al.*, US-Pat. 3791825 (1974); *M. D. Shattuck, W. J. Weiche*, US-Pat. 3837851 (1974); *P. J. Regensburger, J. J. Jakubowski*, US-Pat. 3850630 (1974); 3877935, 3879200, 3904407 (1975); *W. Wiedemann*, US-Pat. 3839034 (1974); *W. L. Goffe*, US-Pat. 3573906 (1971).

[87] For a review, see: *R. M. Schaffert* in [6], p. 69.

[88] a) *J. S. Rydz, S. W. Johnson*, RCA Rev. *19*, 465 (1958); b) *J. Ewing, J. Mammino, J. W. Weigl*, "Color Toners for Xerography", Abstr. Symp. Color Photogr. Systems. Soc. Photogr. Sci. Eng., Washington, D.C. 1963; c) *H. Bogdonoff*, "Rapid Access Color Hard Copy – an Overview" in *R. A. Eynard:* Color Theory and Imaging Systems. Soc. Photogr. Sci. Eng., Washington, D. C., 1973, p. 362; d) *W. L. Rhodes*, "Color-Xerography", *ibid.*, p. 383.

[89] *B. L. Shely*, US-Pat. 3563734 (1971); 3764313 (1973).

[90] *R. B. Nelson*, US-Pat. 3629245 (1972).

[91] *J. M. O'Reilly, P. F. Erhardt*, "Physical Properties of Toner Polymers", in [12], p. 95.

[92] *L. H. Lee*, "Thermal Fixing of Electrophotographic Images", in *L. H. Lee:* Adhesion Science and Technology, 9B. Plenum Press, New York 1975.

[93] *S. Kittaka*, J. Phys. Soc. Jpn. *14*, 523 (1959); *H. W. Gibson*, J. Am. Chem. Soc. *97*, 3832 (1975); *M. W. Williams*, J. Macromol. Sci. (Rev. Macromol. Chem.) *C14* (2), 251 (1976).

[94] *W. R. Harper*, Proc. Roy. Soc. London *A218*, 111 (1953); *H. Bauser, W. Klöpffer, H. Rabenhorst*, Proc. 1st Int. Conf. Static Electricity, Vienna 1970. Auxilia, S.A., 1970, Vol. 1, p. 2.

[95] *D. A. Hays, P. K. Watson*, "Contact Charging of Polymers", in [12], p. 108; *M. W. Williams*, IEEE Trans. Indust. Appl. *IA-12*, No. 2, 213 (1976).

[96] *C. R. Raschke*, "Triboelectric Studies of Dry Toners", in [12], p. 104.

[97] *R. M. Schaffert* in [6], p. 69.

[98] A list of 150 patents on this subject is tabulated by *R. M. Schaffert* in [6], pp. 764ff.; cf. also *M. W. Williams*, J. Macromol. Sci. Rev. Macromol. Chem. *C14*, 251 (1976).

[99] *E. E. Minett*, personal communication.

[100] *C. J. Young, H. G. Greig*, RCA Rev. *15*, 469 (1954); *J. A. Amick, ibid. 20*, 753 (1959).

[101] *F. M. K. Werduschegg, H. E. Carr*, Tappi *50*, 26 (1967).

[102] *H. R. Carrington, F. Gaesser*, US-Pat. 3403023 (1968).

[103] *R. M. Schaffert* in [6], p. 318.

[104] *A. E. Middleton, D. Reynolds*, US-Pat. 3121006, 3121007 (1964).

[105] *H. P. Kallmann, B. Rosenberg*, Phys. Rev. 97, 1596 (1955).

[106] a) *D. P. Habib, J. D. Plumadore*, J. Microgr. *7*, 249 (1974); b) *J. Mammino*, unpublished.

[107] *E. F. Mayer*, "STOP – A New Contrast-Amplifying Xerographic Process", Abstr. 1st Int. Congr. Reprogr., Cologne 1964; US-Pat. 3275436 (1966).

[108] *K. A. Metcalfe, R. J. Wright*, Austral. Pat. 243184 (1963); Can. Pat. 692101 (1964).

[109] *R. J. Wright*, personal communication.

[110] *J. W. Weigl*, digital investigation.

[111] *A. B. Amidon*, unpublished; *I. Tashiro, T. Kimura, K. Endo* in [7], p. 180; *R. M. Schaffert* in [6], p. 142.

[112] a) *H. P. Kallmann, J. Rennert, M. Sidran*, Photogr. Sci. Eng. *4*, 345 (1960); b) *H. P. Kallmann, J. R. Freeman*, Phys. Rev. *109*, 1506 (1958); c) *J. R. Freeman, H. P. Kallmann, M. Silver*, Rev. Mod. Phys. *33*, 553 (1961); d) *H. P. Kallmann, J. Rennert, J. Burgos*, Photogr. Sci. Eng. *6*, 65 (1962).

[113] *V. M. Fridkin, I. S. Zheludev:* Photoelectrets and the Electrophotographic Process. Consultants Bureau, New York 1961; *V. M. Fridkin*, J. Opt. Soc. Am. *50*, 545 (1960).

[114] *F. Gutmann*, Rev. Mod. Phys. *20*, 457 (1948).

[115] *R. M. Schaffert* in [6], p. 102.

[116] *H. P. Kallmann*, US-Pat. 2845348 (1952).

[117] *A. Rose*, US-Pat. 2976144 (1961); *J. A. Amick*, RCA Rev. *20*, 765 (1959).

[118] *P. M. Cassiers*, J. Photogr. Sci. *10*, 57 (1962).

[119] *E. G. Johnson, B. W. Neher*, US-Pat. 3010883, 3010884 (1961); 3257304, 3285837 (1966).

[120] *A. H. Sporer*, Photogr. Sci. Eng. *12*, 213 (1968).

[121] *J. P. Ebert*, US-Pat. 3081165 (1957).

[122] "Magne-Dynamic Process Theory", Instruct. Bull. 3M Corp., VHS-235 Duplicator.

[123] a) *D. H. Dybvig, T. J. Evensen, J. W. Ulseth, J. A. Wiese*, "Color-in-Color", in *R. A. Eynard:* Color: Theory and Imaging Systems. Soc. Photogr. Sci. Eng., Washington, D.C., 1973, p. 403; b) *D. H. Dybvig, J. W. Ulseth, J. A. Wiese*, US-Pat. 3601484 (1971).

[124] *L. E. Walkup*, US-Pat. 2825814 (1958).

[125] *C. F. Carlson, H. Bogdonoff*, US-Pat. 2982647 (1961); *L. E. Walkup*, US-Pat. 2833648 (1958); 2937943 (1960).

[126] *R. M. Schaffert*, IBM J. Res. Dev. *6*, 192 (1962); in [6], p. 550.

[127] *I. Brodie, J. A. Dahlquist*, J. Appl. Phys. *39*, 1618 (1968).

[128] a) *G. Day* et al., Abstr. 20th Nat. Conf. Nat. Microfilm Assoc., Washington, D.C., 1971; b) *R. L. Jepson, G. F. Day* in [12], p. 28; c) *I. Brodie*, Tappi *55*, 1389 (1972).

[129] *S. Tanaka et al.*, US-Pat. 3827801 (1974).

[130] a) *H. Thiemann*, Dissertation, ETH Zürich 1947; b) *H. Jensen*, Br. Kinematogr. *37*, 44 (1960).

[131] *W. E. Glenn*, J. Opt. Soc. Am. *48*, 841 (1958); J. Appl. Phys. *30*, 1870 (1959); J. SMPTE *69*, 577 (1960).

[132] *W. Mehl, H. G. Greig, N. E. Wolff*, Abstr. Org. Cryst. Symp., Ottawa 1962; *H. G. Greig*, RCA Rev. *23*, 413 (1962); *N. E. Wolff, ibid. 25*, 200 (1964).

[133] a) *J. Gaynor, S. Aftergut*, Photogr. Sci. Eng. *7*, 210 (1963); b) *S. Aftergut, J. Gaynor, B. C. Wagner, ibid. 9*, 30, 80 (1965); c) *J. J. Bartfai, E. Ozarow, J. Gaynor, ibid. 10*, 60 (1966); d) *J. Gaynor*, "Photosensitive Deformable Films", in [7], p. 512; e) *J. Gaynor, S. Aftergut*, J. Appl. Phys. *34*, 2102 (1963).

[134] *F. H. Nicholl*, RCA Rev. *25*, 209 (1964).

[135] *R. W. Gundlach, C. J. Claus*, Photogr. Sci. Eng. *7*, 14 (1963); *C. J. Claus, R. W. Gundlach*, "Imaging by Plastic Deformation", in [5], Chapter XIII.

[136] *P. Cressman*, J. Appl. Phys. *34*, 2327 (1963).

[137] *H. J. Budd*, J. Appl. Phys. *36*, 1613 (1965).

[138] *J. C. Urbach*, Photogr. Sci. Eng. *10*, 287 (1966); *J. C. Urbach, R. Meier*, Appl. Opt. *5*, 666 (1966); *T. L. Credelle, F. W. Spong*, RCA Rev. *33*, 206 (1972).

[139] *W. A. Sullivan, J. J. Kneiser*, Photogr. Sci. Eng. *8*, 206 (1964).

[140] *W. E. Glenn, C. S. Ih, D. Lamberty*, "A Focused-Image-Hologram Microfiche", in [12], p. 215.

[141] *W. Baumgärtner*, Z. Angew. Math. Phys. *18*, 31 (1967); *F. Mast et al.*, US-Pat. 2896507 (1959).

[142] *N. K. Sheridon*, IEEE Trans. Electron Devices *ED-20*, 1003 (1972); US-Pat. 3716359 (1973).

[143] *R. W. Gundlach*, Jap. Pat. 43-2242 (1967).

[144] *H. Goto* et al., "The Image Forming Process of Photoconductive Toner", in [7], p. 124.

[145] *M. L. Sugarman*, US-Pat. 2758939 (1956).

[146] *W. L. Goffe*, Photogr. Sci. Eng. *15*, 304 (1971).

[147] *S. Tutihasi*, Photogr. Sci. Eng. *18*, 394 (1974).

[148] *A. L. Pundsack*, Photogr. Sci. Eng. *18*, 642 (1974).

[149] *W. L. Goffe*, "Advances in Photographic Migration Imaging", Lecture, Soc. Photogr. Sci. Eng., April 1974.

[150] a) *V. Tulagin*, J. Opt. Soc. Am. *59*, 328 (1969); b) *L. Carreira, V. Tulagin*, US-Pat. 3477934 (1969); c) *V. Tulagin*, US-Pat. 3535221 (1970).

[151] *V. Tulagin*, personal communication.

[152] *E. K. Kaprelian*, US-Pat. 2940847 (1960); 3100426 (1963).

[153] *S. Yeh*, US-Pat. 3383993 (1968); unpublished results.

[154] *V. S. Mihajlov*, US-Pat. 3251688 (1966).

[155] *P. Cressman, G. C. Hartmann*, J. Chem. Phys. *61*, 2740 (1974); *G. Hartmann, F. Schmidlin*, J. Appl. Phys. *46*, 266 (1975); *F. W. Schmidlin* in [10], p. 448.

[156] *V. Tulagin, L. Carreira*, US-Pat. 3881920 (1975), and other patents; *J. Schneider, G. Squassoni, W. Schwarz, E. Forest et al.*, unpublished results.

[157] *C. Snelling*, US-Pat. 3741760 (1973); *W. L. Little Jr., R. H. Townsend*, US-Pat. 3703459 (1972); 3952700 (1976); *J. B. Wells*, US-Pat. 3645874 (1972); 3784294 (1974); *V. M. Marquart, R. H. Townsend*, US-Pat. 3427242 (1969).

[158] *J. B. Wells*, US-Pat. 3772013 (1973).

[159] *J. B. Wells, P. C. Swanton, J. W. Weigl, E. Forest*, US-Pat. 3850627 (1974); 3920330 (1975); 3954465 (1976).

[160] *A. B. Amidon*, unpublished results.

[161] a) *R. H. Luebbe, M. S. Maltz, G. Reinis, W. G. VanDorn*, "Manifold Imaging: A Versatile Projection-Speed Process", in [12], p. 48; b) *C. C. Yang, G. C. Hartmann*, IEEE Trans. Electron Devices *23*, 308 (1976); c) *V. Tulagin*, US-Pat. 3512968 (1970).

[162] *J. E. Macgriff*, US-Pat. 3056136 (1962); 3323131 (1967).

[163] *J. T. McNaney*, US-Pat. 3047867 (1962); 3126548 (1964).

[164] *C. Snelling*, US-Pat. 3220324 (1965).
[165] a) *G. Pressman*, "Photocontrolled Ion Flow Electrophotography", in [12], p. 37; b) *G. Pressman et al.*, US-Pat. 3713734 (1973); 3809556, 3809557 (1974); 3867673 (1975); c) *W. Ohta, K. Sakai*, DOS 2138561 (1972); d) *R. A. Fotland et al.*, US-Pat. 3761173, 3797926 (1973); 3879195 (1975); e) *L. F. Frank*, US-Pat. 3881921 (1975); f) *H. Tanaka et al.*, US-Pat. 3964827 (1976).
[166] *S. B. McFarlane*, US-Pat. 3339469 (1967); 3532422 (1970); *G. L. Pressman et al.*, US-Pat. 3647291, 3697164 (1972); 3839027 (1974).
[167] *D. Smith*, "Electrostatic Printing", Penrose Annual *59*, 143 (1966); *C. Childress*, "A True Electrostatic Printing Process", *ibid. 59*, 151 (1966).
[168] *K. Wilcke*, Photogr. Korresp. *57*, 173 (1920); *J. Berchtold*, Sci. Ind. Photogr. *26*, 465 (1955); *P. S. Hana*, Neth. Pat. 5142 (1920); *O. VonBronk*, U. K. Pat. 188030 (1922); *F. Goldmann*, U. K. Pat. 464112 (1937); *U. Schmieschek, F. Kluetke*, DBP 684619 (1939); *J. Jacobs, R. Frerichs*, US-Pat. 2764693 (1956); *J. J. Robillard*, Photogr. Sci. Eng. *8*, 18 (1964).
[169] a) *B. L. Shely, B. L. Clark*, US-Pat. 3072541 (1963); b) *E. G. Johnson, B. W. Neher*, US-Pat. 3011963 (1961).
[170] *A. Rose:* Concepts in Photoconductivity and Allied Problems. Wiley-Interscience, New York 1963.
[171] *R. W. Redington*, J. Appl. Phys. *29*, 189 (1958); US-Pat. 3322538, 3322539 (1967).
[172] a) *P. J. Melz* in [10], p. 433; b) *P. J. Melz, U. Vahtra, ibid.*, p. 437; c) *F. W. Schmidlin, S. Tutihasi* in *J. Stuke, W. Brenig:* Amorphous and Liquid Semiconductors. Taylor and Francis, London 1974, p. 381.
[173] a) *V. Tulagin, R. F. Coles, R. A. Miller*, US-Pat. 3172827 (1964); b) *D. K. Meyer et al.*, US-Pat. 3130655 (1964).
[174] *V. Tulagin, G. H. Kolb, D. K. Meyer*, US-Pat. 3154414 (1964).
[175] *N. R. Nail*, US-Pat. 3096260 (1963); *D. R. Eastman*, US-Pat. 3095808 (1963).
[176] *S. Tokumoto* et al., Photogr. Sci. Eng. *7*, 218 (1963).
[177] *E. Cerwonka, A. S. Deutsch, S. Levinos*, Report to U.S. Army Electronics Command, March 1966; *M. C. Zerner, J. F. Sobieski, H. A. Hodes*, Photogr. Sci. Eng. *13*, 184 (1969).
[178] *F. Bestenreiner et al.*, "Studies on Special Problems of Color Electrophotography", in [12], p. 9.
[179] *F. Schmidlin*, "Physical Theory of Charge Pigment Electrophotography", in [10], p. 418; "On the Ultimate Sensitivity of Xerography", Soc. Photogr. Sci. Eng. Symp. on Advances in Applied Photographic Processing, Washington, D.C., 1974.
[180] *R. Goren, L. M. Marks*, Photogr. Sci. Eng. *18*, 605 (1974).

COMMUNICATIONS

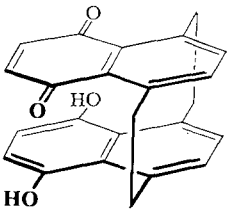
Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying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

Stereoisomeric Quinhydrones of the [2.2](1,4)Naphthalenophane Series[1]

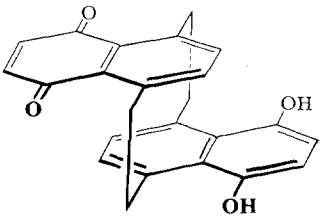
By *Heinz A. Staab* and *Claus P. Herz*[*]

Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

Strong orientation dependence of charge-transfer interactions was experimentally proved by the investigation of the diastereomeric quinhydrones of the [2.2]paracyclophane series[2] and similar donor-acceptor paracyclophanes[3]. In this connection the two intramolecular quinhydrones *(1)* and *(2)* of the [2.2](1,4)naphthalenophane series were of interest: donor and acceptor regions of the molecule are closely superposed in the *syn* isomer *(1)* whereas in the *anti* isomer *(2)* they are separated so far that direct through-space interaction between them is impossible.

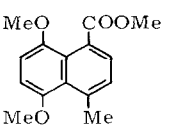


(1)

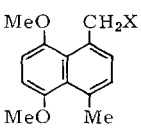


(2)

The synthesis of *(1)* and *(2)* started from methyl 1,4,4a,5,8,8a-hexahydro-4-methyl-5,8-dioxo-1-naphthoate[4] which, in the presence of tin(II) chloride, in acetic acid/hydrochloric acid (15 min, 80 °C, according to [5]) yielded methyl 1,4-dihydro-5,8-dihydroxy-4-methyl-1-naphthoate (m.p. 174—176 °C, dec.; yield 87 %). After etherification with dimethyl sulfate/sodium hydroxide to methyl 1,4-dihydro-5,8-dimethoxy-4-methyl-1-naphthoate (m.p. 85—86 °C; yield 76 %) aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 2 h, boiling benzene) led to methyl 5,8-dimethoxy-4-methyl-1-naphthoate *(3)* (m.p. 99—100 °C; yield 95 %). *(3)* was reduced by lithium tetrahydridoaluminate (2 h, boiling tetrahydrofuran) to the hydroxymethyl compound *(4)* (m.p. 78—79 °C; yield 94 %) which, *via* the bromomethyl derivative *(5)* (with phosphorus tribromide/benzene, 30 min, 5 °C) with dry trimethylamine, yielded the ammonium bromide *(6)*[6]. After conversion into the hydroxide *(7)* (silver oxide/



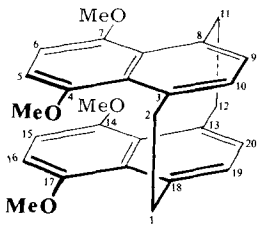
(3)



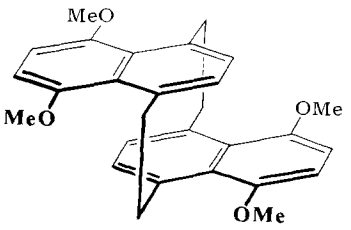
(4), X = OH
(5), X = Br
(6), X = $\overset{\oplus}{N}(CH_3)_3$ $Br^{\ominus}$
(7), X = $\overset{\oplus}{N}(CH_3)_3$ $OH^{\ominus}$

[*] Prof. Dr. H. A. Staab, Dipl.-Chem. C. P. Herz
Max-Planck-Institut für medizinische Forschung, Abteilung Organische Chemie
Jahnstrasse 29, D-6900 Heidelberg (Germany)

water, 20 h), refluxing in xylene with a water separator gave a mixture of *syn*- and *anti*-4,7,14,17-tetramethoxy[2.2]naphthalenophanes *(8)* and *(9)* which were separated by chromatography (silica gel/benzene). The assignment of *(8)*[6] (smaller R_F; m.p. 250—251 °C; yield 3 %) and *(9)*[6] (m.p. 280—281 °C; yield 23 %) was based on ^{1}H-NMR: in the *anti* isomer *(9)* protons on C-9,10,19,20 are more strongly shielded by the neighboring naphthalene unit than in the *syn* isomer *(8)* where all aromatic protons are on the periphery of the naphthalenophane system [*(8)*: δ = 2.9—3.3 (A part of AA'BB', 4H, methylene-H), 3.82 (s, 12H, CH_3O—), 4.1—4.5 (B part of AA'BB', 4H, methylene-H), 6.26 (s, 4H, aromatic H), 6.75 (s, 4H, aromatic H); *(9)*: δ = 2.5—3.1 (A part of AA'BB', 4H, methylene-H), 3.93 (s, 12H, CH_3O—), 3.8—5.4 (B part of AA'BB', 4H, methylene-H), 5.95 (s, 4H, aromatic H), 6.77 (s, 4H, aromatic H), in $CDCl_3$].

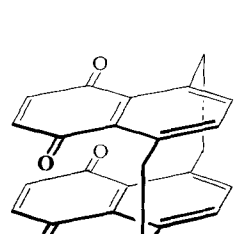


(8)

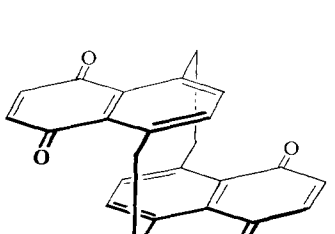


(9)

Demethylation of *(8)* with methylmagnesium iodide (60 min, 200 °C, under argon)[2] and subsequent oxidation with silver oxide (acetone, 60 min, 20 °C) of the intermediate tetrahydroxy[2.2](1,4)naphthalenophane resulted in the formation of *syn*-[2.2](1,4)-5,8-naphthoquinonophane *(10)*[6] (gold-yellow plates, dec. > 250 °C; yield 58 %). In the same way, the *anti* isomer *(11)*[6] (yellow crystals, dec. > 250 °C; yield 70 %) was obtained from *(9)*. Compounds *(10)* and *(11)*, the mass spectrometric fragmentations of which are practically the same and in agreement with the proposed structure, differ significantly in their ^{1}H-NMR spectra for the reasons mentioned for the pair of stereoisomers *(8)*/*(9)* [*(10)*: δ = 3.0—3.4 (A part of AA'BB', 4H, methylene-H), 4.0—4.4 (B part of AA'BB', 4H, methylene-H), 6.70 (s, 4H, quinonoid H), 7.13 (s, 4H, aromatic H); *(11)*: δ = 2.6—3.2 (A part of AA'BB', 4H, methylene-H), 3.8—4.4 (B part of AA'BB', 4H, methylene-H), 6.70 (s, 4H, quinonoid H), 6.92 (s, 4H, aromatic H), in [D_6]-dimethyl sulfoxide]. Under conditions comparable with those of the demethylation reaction (1 h, 200 °C, under argon) no *syn-anti* isomerization was observed whereas after 1 h at 230 °C *(10)* was converted into a *(10)*/*(11)* mixture (about 1 : 1 according to preliminary results).



(10)



(11)

On partial hydrogenation of *(10)* (1 equiv. H_2, palladium/charcoal, dioxane, 20 °C) the quinhydrone *(1)*[6] was formed as an almost black substance (dec. > 250 °C; yield 72 %). Correspondingly, the *anti*-isomer *(2)*[6] was obtained (dark brown microcrystals, dec. > 250 °C; yield 65 %) from *(11)*. ^{1}H-NMR absorptions are in agreement with the assignments to the *syn*- and *anti*-constitution [*(1)*: δ = 2.7—3.2 (m, 4H), 4.0—4.5 (m, 4H), 6.40 (s, 2H), 6.45 (s, 2H), 6.80 (br. s, 4H), 9.08 (s, 2H); *(2)*: δ = 2.3—3.1 (m, 4H), 3.7—4.5 (m, 4H), 6.11 (s, 2H), 6.27 (s, 2H), 6.73 (s, 2H), 6.90 (s, 2H), 9.12 (s, 2H), in [D_6]-dimethyl sulfoxide]. Mass spectra of *(1)* and *(2)* are, in analogy to the pairs of diastereoisomers *(8)*/*(9)* and *(10)*/*(11)*, almost undistinguishable; they agree with the structures suggested.

For further characterization the naphthoquinhydrones were reacted with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (tetrahydrofuran, 20 °C; yield 75—85 %): the bis(trimethylsilyl) ether of *(1)* forms garnet-red needles of m.p. 299—300 °C[6], that of *(2)* brick-red crystals of m.p. 211—212 °C[6].

The electronic spectra of the *syn*- and *anti*-quinhydrones *(1)* and *(2)* are surprisingly similar in their absorption curves. Whereas the bis-quinones *(10)* and *(11)* [λ_{max} = 390 nm (ε = 5305) and 390 (4260), resp.] do not show absorptions above 500 nm, *(1)* as well as *(2)* exhibit broad charge-transfer (CT) bands between 500 and 700 nm [*(1)*: λ_{max} = 540 nm (ε = 1233); *(2)*: 550 (731), in methanol]; they are not concentration-dependent and, thus, must be due to an intramolecular charge-transfer even in the case of the *anti*-quinhydrone. The bis(trimethylsilyl) derivatives of *(1)* and *(2)* have similar absorption spectra, too, the broad CT bands of the *anti* isomer [λ (sh) = 525 nm (ε = 900)] and the *syn* isomer [λ(sh) = 510 nm (ε = 1500), in chloroform] showing only relatively small differences considering the very different donor-acceptor orientation.

In view of our earlier results on the orientation dependence of CT absorptions[2, 3], the similarity of CT absorptions of *syn*- and *anti*-quinhydrones of the [2.2](1,4)naphthalenophane type is rather unexpected. The only explanation we can offer at present is the assumption that the direct donor-acceptor interaction through space in these systems is less important than the interaction transmitted through the annelated [2.2]paracyclophane system the strong transanular interaction of which is well-known.

Received: April 12, 1977 [Z 714a IE]
German version: Angew. Chem. *89*, 406 (1977)

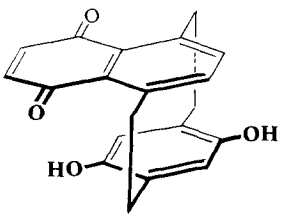
CAS Registry numbers:
(1), 62532-83-6; *(1)* bis(trimethylsilyl) ether, 62571-47-5; *(2)*, 62561-85-7; *(2)* bis(trimethylsilyl) ether, 62624-74-2; *(3)*, 62532-84-7; *(4)*, 62532-85-8; *(5)*, 62532-86-9; *(6)*, 62532-87-0; *(7)*, 62532-88-1; *(8)*, 62532-89-2; *(9)*, 62600-50-4; *(10)*, 62473-47-6; *(11)*, 62624-02-6; methyl 1,4,4a,5,8,8a-hexahydro-4-methyl-5,8-dioxo-1-naphthoate, 62532-90-5; methyl 1,4-dihydro-5,8-dihydroxy-4-methyl-1-naphthoate, 62532-91-6; methyl 1,4-dihydro-5,8-dimethoxy-4-methyl-1-naphthoate, 62532-92-7; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 84-58-2; *N*-methyl-*N*-trimethylsilyltrifluoroacetamide, 24589-78-4

[1] Orientation effects on charge-transfer interactions, Part 11.—Part 10: *M. W. Haenel, A. Flatow, V. Taglieber, H. A. Staab*, Tetrahedron Lett. *1977*, 1733.
[2] *W. Rebafka, H. A. Staab*, Angew. Chem. *85*, 831 (1973); *86*, 234 (1974); Angew. Chem. Int. Ed. Engl. *12*, 776 (1973); *13*, 203 (1974); Chem. Ber., in press; *H. A. Staab, C. P. Herz, H.-E. Henke*, Tetrahedron Lett. *1974*, 4393; Chem. Ber., in press; cf. MO calculation of *H. Vogler, G. Ege, H. A. Staab*, Tetrahedron *31*, 2441 (1975).
[3] *H. A. Staab, H. Haffner*, Tetrahedron Lett. *1974*, 4397; Chem. Ber., in press; *H. A. Staab, V. Taglieber, ibid.*, in press; *D. Schweitzer, K. H. Hausser, V. Taglieber, H. A. Staab*, Chem. Phys. *14*, 183 (1976).
[4] *J. Weichet, B. Kakáč, L. Bláha*, Collect. Czech. Chem. Commun. *27*, 843 (1962).
[5] *L. F. Fieser*, J. Am. Chem. Soc. *70*, 3165 (1948).
[6] Elemental analyses, molecular weights (mass spectrometric), and spectroscopic data are in agreement with the proposed structures.

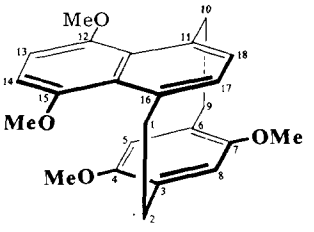
An Intramolecular Quinhydrone of the [2](1,4)Naphthaleno[2]paracyclophane Series[1]

By *Claus P. Herz* and *Heinz A. Staab*[*]

In connection with the problem of the transmission of donor-acceptor interactions in the stereoisomeric [2.2](1,4)naphthalenophane quinhydrones[1] we were interested in the quinhydrone *(1)* where 1,4-naphthoquinone as acceptor and hydroquinone as donor are linked together in a [2](1,4)naphthaleno[2]paracyclophane system.



(1)

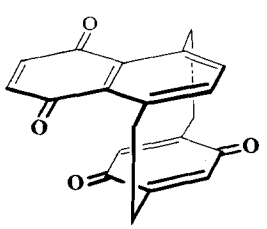


(2)

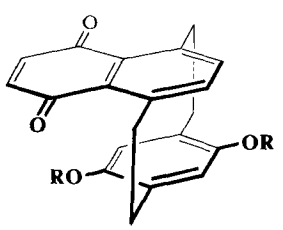
Joint 1,6-Hofmann elimination of (2,5-dimethoxy-4-methylbenzyl)trimethylammonium hydroxide[2] and (5,8-dimethoxy-4-methyl-1-naphthylmethyl)trimethylammonium hydroxide[1] in boiling toluene (12 h, water separator) yielded, in addition to the stereoisomer pairs of 4,7,12,15-tetramethoxy[2.2]paracyclophane[2] and of 4,7,14,17-tetramethoxy[2.2](1,4)naphthalenophane[1], the crossed product 4,7,12,15-tetramethoxy-[2](1,4)naphthaleno[2]paracyclophane *(2)*[3] [colorless cubes, m.p. 183.5—184 °C; yield 5—10 %; ^{1}H-NMR ($CDCl_3$): δ = 2.2—4.6 (m, 8H), 3.03 (s, 3H), 3.72 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 5.18 (s, 1H), 5.80 (s, 1H), 6.70 (s, 2H), 6.62 and 6.88 (AB, 2H, J_{AB} = 7 Hz)].

By demethylation with methylmagnesium iodide (30 min, 170 °C, under argon) and oxidation of the intermediate tetrahydroxy compound with silver oxide (1 h, 20 °C, acetone) [2]-(1,4)-*p*-benzoquinono[2](1,4)-5,8-naphthoquinonophane *(3)*[3] was obtained after chromatography (silica gel/chloroform) in 35 % yield [yellow needles, m.p. 190—191 °C; ^{1}H-NMR ($CDCl_3$): δ = 2.1—3.6 (m, 6H), 4.2—4.9 (m, 2H), 5.70 (s, 1H), 5.91 (s, 1H), 6.87 (s, 2H), 6.99 and 7.19 (AB, 2H, J_{AB} = 8 Hz)]. Due to incomplete demethylation, the dimethyl ether *(4)* of the quinhydrone *(1)* was formed as a by-product in this reaction sequence [red needles, m.p. 134—135 °C; yield 1—2 %; ^{1}H-NMR ($CDCl_3$): δ = 2.4—4.8 (m, 8H), 3.47 (s, 3H), 3.73 (s, 3H), 5.75 (s, 1H), 5.79 (s, 1H), 6.79 (s, 2H), 6.72 and 7.09 (AB, 2H, J_{AB} = 8 Hz)].

Partial hydrogenation of *(3)* (1 equiv. H_2, palladium/charcoal, dioxane, 20 °C) led to the quinhydrone *(1)*[3] [m.p. 193—195 °C (dec.); yield 74 %; M^+ (high-resolution) calc. 320.1046, obs. 320.1032; ^{1}H-NMR ([D_6]-dimethyl sulfoxide): δ = 2.2—3.4 (m, 6H), 3.8—4.6 (m, 2H), 5.45 (s, 1H), 5.65 (s, 1H), 6.84 (s, 2H), 6.83 and 7.26 (AB, 2H, J_{AB} = 8 Hz)].—With *N*-methyl-*N*-trimethylsilylacetamide (tetrahydrofuran, 20 °C) *(1)* was converted into the bis(trimethylsilyl) ether *(5)*[3] [brick-red crystals, m.p. 97—98 °C; yield 85 %; ^{1}H-NMR ($CDCl_3$): δ = 0.09 (s, 9H), 0.22 (s, 9H), 2.1—3.5 (m, 6H), 4.0—4.8 (m, 2H), 5.54 (s, 1H), 5.68 (s, 1H), 6.74 (s, 2H), 6.67 and 7.16 (AB, 2H, J_{AB} = 8 Hz)].



(3)



(4), R = Me; *(5)*, R = $SiMe_3$

The electronic spectra of the donor-acceptor [2.2]phanes *(1)*, *(4)*, and *(5)* are dominated by a broad structureless absorption around 400 nm [*(1)*: λ_{max} = 400 nm (ε = 1897), in dioxane; *(4)*: 402 (1870); *(5)*: 408 (1895), in chloroform]. This band is obviously due to the 1,4-naphthoquinone chromophore of the [2](1,4)-naphthalenophane system: this absorption is found with almost double the intensity for the bis-naphthoquinones of the [2.2](1,4)naphthalenophane series[1], and also *(3)* shows a similar broad absorption [λ_{max} = 375 nm (ε = 2050), in chloroform]. Whereas, however, for *(3)* this absorption ends at about 500 nm, for the donor-acceptor phanes *(1)*, *(4)*, and *(5)* absorption shoulders extend up to 570—600 nm. Thus, these compounds do not display such distinct charge-transfer absorptions as the quinhydrones of the [2.2](1,4)naphthalenophane[1] series. This result is especially surprising in comparison to the *anti*-[2.2](1,4)naphthalenophane quinhydrone showing that the discussion of indirect transmission of donor-acceptor interactions *via* the [2.2]paracyclophane system[1] calls for more experimental investigations.

Received: April 12, 1977 [Z 714b IE]
German version: Angew. Chem. *89*, 407 (1977)

CAS Registry numbers:
(1), 62532-93-8; *(2)*, 62532-94-9; *(3)*, 62562-60-1; *(4)*, 62532-95-0; *(5)*, 62532-96-1; (2,5-dimethoxy-4-methylbenzyl)trimethylammonium hydroxide, 52928-00-4; (5,8-dimethoxy-4-methyl-1-naphthylmethyl)trimethylammonium hydroxide, 62532-88-1; *N*-methyl-*N*-trimethylsilyltrifluoroacetamide, 24589-78-4

[1] Orientation effects on charge-transfer interactions, Part 12.—Part 11: *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 406 (1977); Angew. Chem. Int. Ed. Engl. *16*, 392 (1977).
[2] *H. A. Staab, C. P. Herz, H.-E. Henke*, Chem. Ber., in press.
[3] Elemental analyses, molecular weights (mass spectrometric), and spectroscopic data are in agreement with the proposed structures.

C—C Linkage of Carboxylic Acids with Allyl Alcohols Using 2-Phenylglycine as Vehicle[**]

By *Norbert Engel, Börries Kübel*, and *Wolfgang Steglich*[*]

Dedicated to Professor Burckhardt Helferich on the occasion of his 90th birthday

Claisen and Cope rearrangements are steadily gaining in importance for synthetic purposes[1]. We now wish to report an application to chain elongation of carboxylic acids which is based on dehydration of the esters *(5)* to form oxazolinones *(7)*[2].

The carboxylic acid *(2)* is coupled with 2-phenylglycine methyl ester *(1)* to yield the *N*-acyl-2-phenylglycine methyl ester *(3)*, which then undergoes base-catalyzed trans-esterification with the allyl alcohol in the presence of a 4-Å molecular sieve[3] to form *N*-acyl-2-phenylglycine allyl ester *(5)* (Table 1). Treatment of *(5)* with phosgene[4a] or

[*] Dipl.-Chem. C. P. Herz, Prof. Dr. H. A. Staab
Max-Planck-Institut für medizinische Forschung, Abteilung Organische Chemie
Jahnstrasse 29, D-6900 Heidelberg (Germany)

[*] Dipl.-Chem. N. Engel, Dr. B. Kübel, Prof. Dr. W. Steglich
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

[**] We are grateful to BASF, Ludwigshafen, for gifts of chemicals.

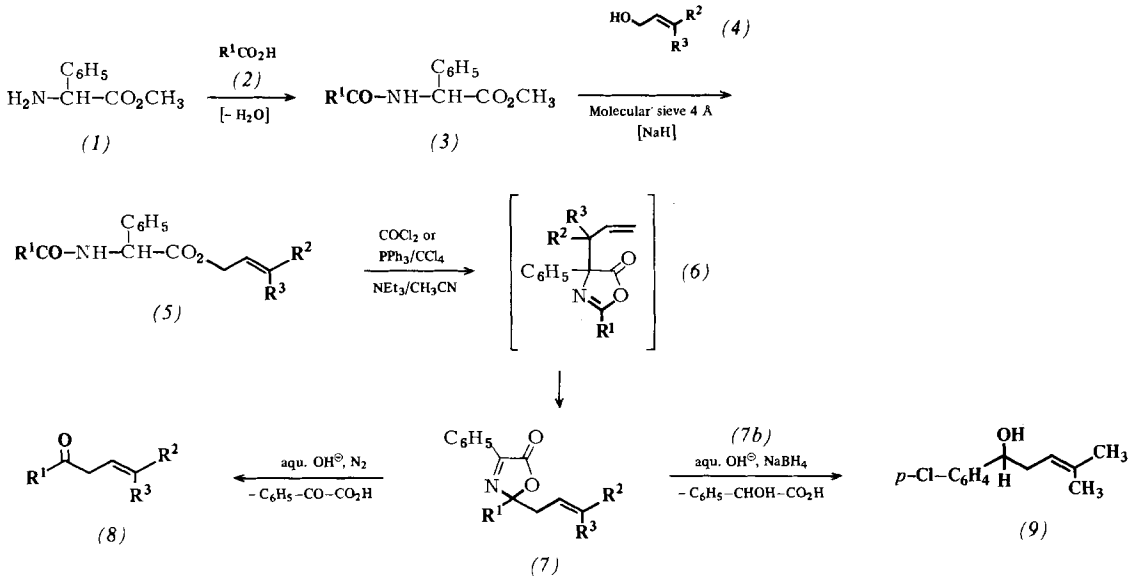


Table 1. *N*-Acyl-2-phenylglycine esters *(5)*, 3-oxazolin-5-ones *(7)*, and ketones *(8)* [a] prepared.

	Carboxylic acid *(2)*	Alcohol *(4)*		*(5)*		*(7)*		*(8)*	
	R^1CO_2H	R^2	R^3	Yield [%]	M.p. [°C]	Yield [%] [b]	M.p. [°C]	Yield [%]	M.p. [°C] (b.p. [°C/0.05 torr])
(2a)	$C_6H_5CO_2H$	CH_3	CH_3	*(5a)* 88 [c]	85 (MeOH/H_2O)	*(7a)* 93 B 90 C	Oil	*(8a)* 77	(110)
(2b)	*p*-Cl—$C_6H_4CO_2H$	CH_3	CH_3	*(5b)* 80 [c], 90	108 (MeOH/H_2O)	*(7b)* 86 A 95 B, 92 C	89 (MeOH)	*(8b)* 88	39—41 (130)
(2c)	*o*-Allyloxy-benzoic acid	CH_3	CH_3			*(7c)* 91 C	77 (cyclohexane)		
(2d)	*p*-$C_6H_4(CO_2H)_2$	CH_3	CH_3			*(7d)* [d] 86 C	140 (dec., EtOH)		
(2e)	3,4,5-$(MeO)_3C_6H_2CO_2H$	CH_3	CH_3			*(7e)* 90 C	Oil		
(2f)	Cinnamic acid	CH_3	CH_3	*(5f)* 82 [e]	163 (benzene)	*(7f)* 73	Oil		
(2g)	Nicotinic acid	CH_3	CH_3			*(7g)* 92 C	72 (petroleum ether)	*(8g)* 23	<30 (140)
(2h)	1-Methyl-3-indole-carboxylic acid	CH_3	CH_3			*(7h)* 70 C	120 (dec., cyclohexane)		
(2i)	(*RS*)-2,2-Dimethyl-1,3-dioxolane-4-carboxylic acid	CH_3	CH_3	*(5i)* 94 [e]	Oil	*(7i)* 77 B	Oil	*(8i)* 60	Oil
(2b)	*p*-Cl—$C_6H_4CO_2H$	Geraniol		*(5j)* 95	98 (T/P) [k]	*(7j)* 93 B	Oil		
(2j)	Cyclopropanecarboxylic acid	Farnesol		*(5k)* 83	Oil	*(7k)* 63 B	Oil	*(8k)* 88	(137—145)
(2k)	Geranic acid (*cis*/*trans*-mixture)	Farnesol		*(5l)* 74	Oil	*(7l)* 85 B	Oil		
(2b)	*p*-Cl—$C_6H_4CO_2H$	C_6H_5	H	*(5m)* 87	144 (MeOH)	*(7m)* 87 A 89 B	101 (petroleum ether)		
(2b)	*p*-Cl—$C_6H_4CO_2H$	Cl	CH_3 [f]	*(5n)* 82 [g]		*(7n)* 89 B	Oil [h]		
(2b)	*p*-Cl—$C_6H_4CO_2H$	$H_2C{=}CH$	H	*(5o)* 87	133 (T/P) [k]	*(7o)* 89 A	Oil		
(2b)	*p*-Cl—$C_6H_4CO_2H$	CH_3	HC≡C [i]	*(5p)* 80	112 (T/P) [k]	*(7p)* 86 A	Oil		
(2b)	*p*-Cl—$C_6H_4CO_2H$	Furfuryl alcohol		*(5q)* 83	144 (dec., T/P) [k]	*(7q)* 87 A 88 B	112 (MeOH)	*(8q)* 56	90 (140)
(2b)	*p*-Cl—$C_6H_4CO_2H$	CH_3	H	*(5r)* 87	130 (T/P) [k]	*(7r)* 92 A [j]	Oil		

[a] The crystalline compounds gave correct elemental analyses and the oils are spectroscopically pure. [b] For methods A, B, C, see procedure. [c] Prepared from the dicyclohexylammonium salt of *N*-acyl-2-phenylglycine instead of *(3)* and 3,3-dimethylallyl bromide instead of *(4)* in THF (6 h reflux). [d] Bisoxazolinone. [e] Prepared from the acyl chloride instead of *(2)* and 2-phenylglycine dimethylallyl ester instead of *(3)* and *(4)*. [f] Mixture with the (*Z*)-alcohol. [g] Crude product subjected directly to further reaction. [h] Contains *ca.* 50% of the (*Z*)-compound according to the ^{1}H-NMR spectrum. [i] (*Z*)-compound. [j] After 7 hours' refluxing in CCl_4 or several days' standing there is a mixture containing *ca.* 50% of *(6r)*; m.p. 107 °C (from methanol). [k] T/P = toluene/petroleum ether.

triphenylphosphane/CCl_4[4b] in triethylamine/acetonitrile affords 2-allyl-3-oxazolin-5-one *(7)*[2] in yields of up to 95%. Mild alkaline hydrolysis with aqueous barium or calcium hydroxide gives β,γ-unsaturated ketones *(8)* without shifting the isolated double bond (Table 1). If $NaBH_4$ is added during the cleavage of *(7b)* then the alcohol *(9)* is obtained directly (yield 81%, b.p. 120 °C/0.05 torr). Phenylglyoxylic acid or mandelic acid remains in the aqueous phase after hydrolysis. Examples of the new reaction sequence are given in Table 1.

Aromatic and heteroaromatic carboxylic acids can be transformed in a single move into *(7)* by treatment with 2-phenylglycine dimethylallyl or geranyl ester[5] and $PPh_3/CCl_4/NEt_3$[6].

With esters of allyl alcohols rearrangement stops at the stage of 4-allyl-2-oxazolin-5-one *(6)*[2,7], and with 2-butenyl

esters equilibration between *(6)* and *(7)* occurs on warming or prolonged standing.

Formation of the 3-oxazolin-5-ones *(7)* can be recognized from the C=O and C=N bands at *ca.* 1770 and 1610 cm^{-1}, resp., in the IR spectrum ($CHCl_3$). The 2-oxazolin-5-ones display these bands at 1810 and 1650 cm^{-1}, respectively. Characteristic differences also occur in the ^1H-NMR spectrum. Thus the signal of the phenyl protons appears at $\delta = 7.8$ in the case of *(6)*, and in a 3:2 distribution at $\delta = 7.5$ and 8.4 ppm in the case of *(7)*.

The novel method for chain elongation proceeds under very mild reaction conditions and affords high yields. Since organometallic intermediates are avoided, even sensitive functional groups remain intact. The amino acid serves merely as a vehicle and does not appear in the final product[8].

Procedure

Synthesis of *(5)*: Compound *(3)* (30 mmol), a molecular sieve (60 g; Merck, 4 Å, bead form, 2 mm), and compound *(4)* (45 mmol) in THF or toluene (80 ml) are shaken with an 80% NaH suspension in paraffin oil (50 mg) for 1—3 days. After filtration and washing, the Celite-clarified filtrate is evaporated down in a rotary evaporator. The residue is recrystallized.

Synthesis of *(7)*: Method A: An ice-cooled mixture of compound *(5)* (20 mmol), triethylamine (60 ml), and acetonitrile is treated within 30 to 45 min with phosgene (40 to 45 mmol, as a 5% solution in acetonitrile). When addition is complete the solution is stirred for 30 min and evaporated down in a rotary evaporator. The residue is partitioned between CH_2Cl_2 (150 ml) and water (100 ml). The organic phase is washed with 2% hydrochloric acid (100 ml) and vigorously stirred overnight with saturated $NaHCO_3$ solution (200 ml). Evaporation of the dried organic phase yields the NMR-pure product.

Method B: Triethylamine (27 mmol; 2.5 M in CH_3CN), CCl_4 or C_2Cl_6[9] (22.5 mmol; 2.5 M in CH_3CN), and triphenylphosphane (20 mmol) are added successively to compound *(5)* (10 mmol) and the mixture stirred overnight at room temperature. After evaporation in a rotary evaporator the triphenylphosphane oxide is removed by passage through a silica gel column with CCl_4/ethyl acetate.

Method C: Triethylamine (55 mmol), CCl_4 or C_2Cl_6[9] (45 mmol), and triphenylphosphane (40 mmol) are added successively, as described in method B, to *(2)* (10 mmol) and 2-phenylglycine dimethylallyl ester hydrochloride, the reaction mixture stirred overnight and then worked up.

Synthesis of *(8b)*: Compound *(7b)* (1 g) is stirred overnight in a suspension of calcium hydroxide (2 g) in water (40 ml) and THF (20 ml) under N_2 at room temperature. After removal of the THF in a rotary evaporator, the mixture is extracted with ether, the dried solution evaporated, and the residue distilled in a bulb tube; semicarbazone: m.p. 135 °C.

Received: February 11, 1977 [Z 675 IE]
German version: Angew. Chem. 89, 408 (1977)
Publication delayed at authors' request

CAS Registry numbers:
(1), 26682-99-5; *(2a)*, 65-85-0; *(2b)*, 74-11-3; *(2c)*, 59086-52-1; *(2d)*, 100-21-0; *(2e)*, 118-41-2; *(2f)*, 621-82-9; *(2g)*, 59-67-6; *(2h)*, 32387-21-6; *(2i)*, 62075-55-2; *(2j)*, 1759-53-1; *cis-(2k)*, 4613-38-1; *trans-(2k)*, 4698-08-2; *(3a)*, 62045-88-9; *(3b)*, 62045-89-0; *(3c)*, 62045-90-3; *(3d)*, 62045-91-4; *(3e)*, 62045-92-5; *(3f)*, 62045-93-6; *(3g)*, 62045-94-7; *(3h)*, 62045-95-8; *(3i)*, 62045-97-0; *(3j)*, 62045-98-1; *cis-(3k)*, 62045-96-9; *trans-(3k)*, 62045-99-2; *(4)*, $R^2 = R^3 = CH_3$, 556-82-1; *(4)*, $R^2 = C_6H_5$, $R^3 = H$, 4407-36-7; *E-(4)*, $R^2 = Cl$, $R^3 = CH_3$, 37428-53-8; *Z-(4)*, $R^2 = Cl$, $R^3 = CH_3$, 37428-46-9; *(4)*, $R^2 = H_2C{=}CH$, $R^3 = H$, 51042-92-3; *(4)*, $R^2 = CH_3$, $R^3 = HC{\equiv}C$, 6153-05-5; *(4)*, $R^2 = CH_3$, $R^3 = H$, 504-61-0; *(5a)*, 62046-00-8; *(5b)*, 62046-01-9; *(5f)*, 62046-02-0; *(5i)*, 62046-03-1; *(5j)*, 62046-04-2; *(5k)*, 62046-05-3; *(5l)*, 62046-06-4; *(5m)*, 62030-06-2; *Z-(5n)*, 62030-07-3; *E-(5n)*, 62030-08-4; *(5o)*, 62030-10-8; *(5p)*, 62030-09-5; *(5q)*, 62030-11-9; *(5r)*, 62030-12-0; *(6a)*, 62030-13-1; *(6b)*, 62030-14-2; *(6c)*, 62030-15-3; *(6d)*, 62030-17-5; *(6e)*, 62030-16-4; *(6f)*, 62030-18-6; *(6g)*, 62030-19-7; *(6h)*, 62030-20-0; *(6i)*, 62030-21-1; *(6j)*, 62030-30-2; *(6k)*, 62030-22-2; *(6l)*, 62030-23-3; *(6m)*, 62030-24-4; *(6n)*, 62030-25-5; *(6o)*, 62030-26-6; *(6p)*, 62030-27-7; *(6q)*, 62030-28-8; *(6r)*, 62030-29-9; *(7a)*, 62045-64-1; *(7b)*, 62045-65-2; *(7c)*, 62045-66-3; *(7d)*, 62045-67-4; *(7e)*, 62045-68-5; *(7f)*, 62045-69-6; *(7g)*, 62045-70-9; *(7h)*, 62045-71-0; *(7i)*, 62045-72-1; *(7j)*, 62045-73-2; *(7k)*, 62045-74-3; *(7l)*, 62045-75-4; *(7m)*, 62045-76-5; *E-(7n)*, 62045-77-6; *Z-(7n)*, 62045-78-7; *(7o)*, 62045-79-8; *(7p)*, 62045-80-1; *(7q)*, 62045-81-2; *(7r)*, 62045-82-3; *(8a)*, 36597-09-8; *(8b)*, 62045-83-4; *(8g)*, 62045-84-5; *(8i)*, 62045-85-6; *(8k)*, 62045-86-7; *(8q)*, 62045-87-8; *(9)*, 62030-03-9; geraniol, 106-24-1; farnesol, 4602-84-0; furfuryl alcohol, 98-00-0; *N*-benzoyl-2-phenylglycine dicyclohexylammonium salt, 62030-04-0; 3,3-dimethylallyl bromide, 870-63-3; 2-phenylglycine dimethylallyl ester·HCl, 62030-05-1

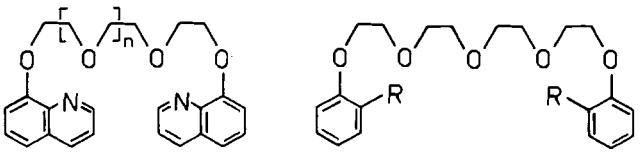
[1] *S. J. Rhoads, N. R. Raulins*, Org. React. *22*, 1 (1975).
[2] *B. Kübel, G. Höfle, W. Steglich*, Angew. Chem. *87*, 64 (1975); Angew. Chem. Int. Ed. Engl. *14*, 58 (1975).
[3] *D. P. Roelofsen, J. A. Hagendoorn, H. van Bekkum*, Chem. Ind. (London) *1966*, 1622.
[4] a) *I. Maeda, M. Takehara, K. Togo, S. Asai, R. Yoshida*, Bull. Chem. Soc. Jpn. *42*, 1435 (1969). Use of acetonitrile instead of chloroform leads to considerably better yields. *N,N*-Diethylcarbamoyl chloride can be removed by stirring with saturated $NaHCO_3$ solution. b) *R. Appel*, Angew. Chem. *87*, 863 (1975); Angew. Chem. Int. Ed. Engl. *14*, 801 (1975), and references cited therein. Polymer-bound phosphanes can be used in place of triphenylphosphane (*N. Engel*, unpublished).
[5] Prepared according to *J. Goerdeler, A. Holst*, Angew. Chem. *71*, 775 (1959), by alkylation of the dicyclohexylammonium salt of *N*-(*o*-nitrophenylsulfenyl)-2-phenylglycine with 3,3-dimethylallyl bromide or geranyl bromide in THF and subsequent removal of the *N*-protecting group with etheral HCl.
[6] *R. Appel, G. Bäumer, W. Strüver*, Chem. Ber. *108*, 2680 (1975).
[7] *S. Götze, B. Kübel, W. Steglich*, Chem. Ber. *109*, 2331 (1976).
[8] *W. Steglich, P. Gruber*, Angew. Chem. *83*, 727 (1971); Angew. Chem. Int. Ed. Engl. *10*, 655 (1971).
[9] *R. Appel, H. Schöler*, Chem. Ber., in press.

"Noncyclic Crown Ethers": The Terminal Group Concept[1]

By *Fritz Vögtle* and *Heinz Sieger*[*]

Dedicated to Professor Burckhardt Helferich on the occasion of his 90th birthday

The unusual complexing properties of the heptadentate species 1,11-bis(8-quinolyloxy)-3,6,9-trioxaundecane *(3)*[2] and the helical conformation of this open-chain neutral ligand in the crystalline RbI complex[3] raise a number of questions: is the arrangement of seven donor atoms particularly favorable, or are shorter chains having fewer donor atoms, as in *(1)* and *(2)*, also suitable as ligands? Are all the donor sites used for complexing in longer-chain "noncyclic crown ethers" such as *(4)*, as they are in *(3)*, leading to helices with more than one turn? What other "end groups" apart from quinolyl stabilize alkali metal ion complexes?



(1) – *(4)* *(5)* – *(13)*

n = 0, 1, 2, 4

[*] Prof. Dr. F. Vögtle, Dipl.-Chem. H. Sieger
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

Table 1. Noncyclic crown ethers synthesized.

Ligand	R	Symbol	Yield [%]	M.p. [°C]
(1)		$O_3(Quin)_2$	50	27
(2)		$O_4(Quin)_2$	43	103
(4)		$O_7(Quin)_2$	52	Oil
(5)	OCH_3	$O_5(OCH_3)_2$	88	Oil
(6)	NO_2	$O_5(NO_2)_2$	46	Oil
(7)	NH_2	$O_5(NH_2)_2$	74	Oil
(8)	$NHCOCH_3$	$O_5(NHCOCH_3)_2$	87	76—78
(9)	$N{=}CHC_6H_4$-2-OH	$O_5(Imine)_2$	88	Oil
(10)	$CO_2C_2H_5$	$O_5(CO_2R)_2$	47	Oil
(11)	CO_2H	$O_5(CO_2H)_2$	89	Oil
(12)	CHO	$O_5(CHO)_2$	48	Oil
(13)	H	$O_5(Ph)_2$	59	Oil
(14)		$O_5(Quinaldine)_2$	49	40
(15)		$O_3(Ph)_2$	75	65
(17)		$O_2(NO_2)_3$	56	198
(18)		$O_2(NO_2)(Quin)_2$	48	208
(19)		$O_2Ph(NO_2)_2$	54	135
(20)	OCH_3	$O_4(OCH_3)(Quin)$	70	Oil
(21)	C≡N	$O_3(CN)(Quin)$	78	Oil

In order to answer important questions relating to our understanding of noncyclic ionophores[4] we have synthesized the open-chain crown ethers *(1)*, *(2)*, and *(4)*, as well as *(5)* to *(13)* (Table 1). Alkali metal ion complexes could be obtained with almost all the ligands having polar end groups (Table 2). X-Ray structure analysis of its RbI complex[5] shows *(1)* to be a pentadentate neutral ligand; all the donor atoms are arranged at distances between 2.98 (N) and 3.07 or 3.18 Å (O) in almost planar fashion around the central ion; however, the Rb—O distance of 2.87 Å in the RbSCN complex of dibenzo[18]crown-6 is much shorter.

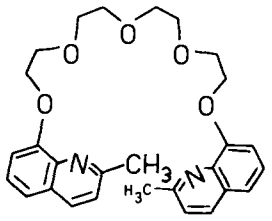
Thus it has been shown for the first time that hetero atoms located in terminally fixed groups can serve as donors in neutral ligands.

Table 2. Alkali and alkaline earth metal ion complexes of the new crown ethers. The crystals are colorless or yellow.

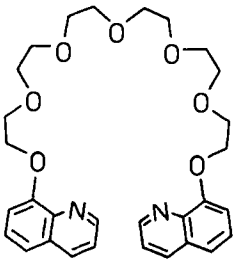
Reactants			Products		
Ligand	Salt	Stoichiometry	Yield [%]	M.p. [°C]	
(1)	KSCN	1:1	68	195—196	(needles)
	RbI	1:1	65	225	(platelets) [a]
(2)	KSCN	1:1	71	160—161	(platelets) [a]
	RbI	1:1	66	175	(needles)
(4)	KSCN	1:1	65	130—132	(microcrystals)
(6)	KSCN	1:1	75	95	(needles) [a]
(7)	KSCN	1:1 ($\frac{1}{2}$ H_2O)	58	83	(needles)
(8)	KSCN	1:1	61	111	(platelets)
(10)	$Ca(SCN)_2 \cdot 4H_2O$	1:1	72	166	(needles
(11)	KSCN	2:1 ($2H_2O$)	65	130—135	(microcrystals)
	$Ca(SCN)_2 \cdot 4H_2O$	1:1	54	120 (dec.)	(platelets)
(14)	KSCN	1:1	86	170—174	(needles)
	RbI	1:1	80	194—196	(microcrystals)
(20)	KSCN	1:1	54	99	(microcrystals)
(21)	NaSCN	1:1	36	140	(needles)

[a] Yellow crystals.

No steric hindrance of complexation by methyl groups was observed in the quinaldine compound *(14)*: it forms crystalline complexes with KSCN and RbI (Table 2), whose ^{1}H-NMR spectra—and especially the large upfield shift of the pyridine and methyl protons—reveal the presence of a helical structure even in solution.

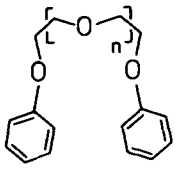


(14)

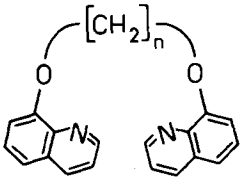


(4)

We were unable to obtain crystalline complexes of the reference compounds *(13)* and *(15)* having phenyl as a terminal group incapable of donating. Nor do two 8-quinolyloxy groups linked by an alkane chain as in *(16)* suffice for formation of crystalline complexes.



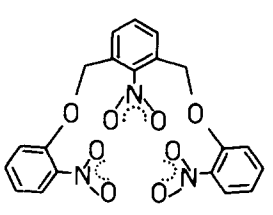
(15), n = 3
(13), n = 1



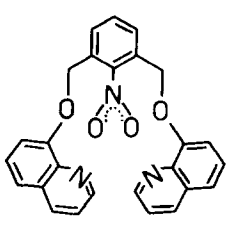
(16a), n = 8
(16b), n = 10

On the other hand, according to ^{1}H-NMR results (δCH_2O) only the seven ether oxygens appear to be involved in complexation of the formally nonadentate ligand *(4)*[6] with KSCN in $CDCl_3$; the upfield shift of the pyridine protons observed for *(3)* and *(14)* does not occur. Measurements of the complexation constant (K_S) and the kinetics of complexation and decomplexation of *(3)* show[4a] that the formation of crystalline alkali metal ion complexes does not parallel the stability of the complex or the selectivity[4c] of complexation in solution[7]. This can also be deduced from the finding that *(4)* does not form a crystalline RbI complex yet gives a KSCN complex, whereas *(1)* forms isolable complexes with RbI and KSCN.

It is highly remarkable that not only values for a 1:1 stoichiometry were found on determination of K_S by UV spectroscopy but also values for other ligand: cation ratios: *e.g.*, *(3)* forms 1:2 complexes with K^+ ions. This can be interpreted by assuming several metal cations to be accommodated at hitherto undefined sites. Formation of such loose addition complexes which, for *(3)* and Mg^{2+}, can even exist with the ratios 1:1, 1:2, 1:3, 1:4, and thus contrasts with the concept of complete enclosure of the cation as in the case of the cyclic crown ethers, hinders measurement of the complex constants by potential measurements with the usual ion-sensitive electrodes.



(17)

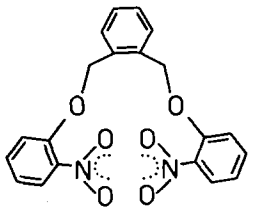


(18)

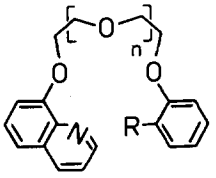
Apart from the end group donor effect geometrical factors also play a role: compounds *(17)* and *(18)* furnished with an adequate number of proven donor atoms neither form

crystalline complexes with alkali metal salts nor transfer alkali metal permanganates into organic phases.

The inferiority of the 2-nitrophenyl end group as against the 8-quinolyl group with regard to complexation follows qualitatively from the somewhat more pronounced phase transfer $NaMnO_4/CHCl_3$ on going from *(6)* to *(3)* as well as from *(19)* to the corresponding 8-quinolyl compound; in contrast to *(19)* the latter forms a crystalline KSCN complex.

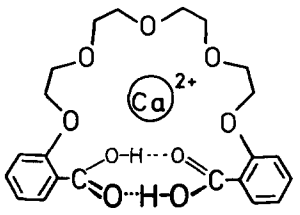


(19)



(20), R = OCH_3, n = 2
(21), R = C≡N, n = 1

Crystalline alkali metal ion complexes were also obtained with the asymmetrical open-chain ligands *(20)* and *(21)* which we synthesized for the first time (Table 2)[6].



(22)

The dicarboxylic acid *(11)* differs from the neutral ligands in several of its properties: in spite of the relatively high acidity ($pK_1 \approx 3.8$, $pK_2 \approx 4.75$; cf. benzoic acid: $pK = 4.4$; 2-methoxybenzoic acid: $pK = 4.1$) the carboxyl protons are not dissociated in the crystalline KSCN and $Ca(SCN)_2$ complexes (Table 2), as is also substantiated by IR spectroscopy; we interpret this phenomenon in terms of an attractive intramolecular terminal group interaction as shown in *(22)*. In this respect *(11)* represents a model for biotic noncyclic carboxylic ionophores[8]. In contrast to *(11)*, the diester *(10)* complexes $Ca(SCN)_2$, but not KSCN and RbI.

Received: March 1, 1977 [Z 689 IE]
German version: Angew. Chem. 89, 410 (1977)
Publication delayed at authors' request

CAS Registry numbers:
(1), 62107-72-6; *(1)*, KSCN complex, 62126-43-6; *(1)*, RbI complex, 62126-44-7; *(2)*, 62107-73-7; *(2)*, KSCN complex, 62126-40-3; *(2)*, RbI complex, 62126-41-4; *(4)*, 62107-74-8; *(4)*, KSCN complex, 62126-38-9; *(5)*, 62107-75-9; *(6)*, 62107-76-0; *(6)*, KSCN complex, 62126-36-7; *(7)*, 62107-77-1; *(7)*, KSCN complex, 62126-34-5; *(8)*, 62107-78-2; *(8)*, KSCN complex, 62126-32-3; *(9)*, 62107-79-3; *(10)*, 62107-80-6; *(10)*, $Ca(SCN)_2$ complex, 62126-63-0; *(11)*, 62107-81-7; *(11)*, KSCN complex, 62154-32-9; *(11)*, $Ca(SCN)_2$ complex, 62154-34-1; *(12)*, 62107-82-8; *(13)*, 20768-77-8; *(14)*, 62107-83-9; *(14)*, KSCN complex, 62154-22-7; *(14)*, RbI complex, 62126-61-8; *(15)*, 622-87-7; *(17)*, 62107-84-0; *(18)*, 62107-85-1; *(19)*, 62107-86-2; *(20)*, 62107-87-3; *(20)*, KSCN complex, 62126-60-7; *(21)*, 62107-88-4; *(21)*, NaSCN complex, 62154-24-9; KSCN, 333-20-0; RbI, 7790-29-6; NaSCN, 540-72-7

[1] Ligand Structure and Complexation, Part 12. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are indebted to Dr. *E. Weber*, *U. Heimann*, and *W. Rasshofer* for their various experimental contributions.—Part 11: *W. Rasshofer*, *F. Vögtle*, Justus Liebigs Ann. Chem. *1977*, in press.
[2] *E. Weber*, *F. Vögtle*, Tetrahedron Lett. *1975*, 2415.
[3] *W. Saenger*, *H. Brand*, *F. Vögtle*, *E. Weber* in *B. Pullman*: Proceedings of the 9. Jerusalem Symposium on Quantum Chemistry and Biochemistry. D. Reidel, Dorderecht 1977.
[4] a) *B. Tümmler*, *G. Maass*, *E. Weber*, *W. Wehner*, *F. Vögtle*, J. Am. Chem. Soc. *99* (1977), in press; b) Review: *B. C. Pressmann*, Annu. Rev. Biochem. *45*, 501 (1976); c) *M. Güggi*, *M. Oehme*, *E. Pretsch*, *W. Simon*, Helv. Chim. Acta *59*, 2417 (1976); and references to earlier publications.
[5] We thank Doz. Dr. *W. Saenger*, Max-Planck-Institut, Göttingen, for performing these studies and communicating the results.
[6] An X-ray structure analysis is in progress.
[7] $\lg K_S$ is 3.22 (2.49) ± 0.01 for the 1:1 (1:2) sodium complex with *(3)*, and 3.51 (2.14) ± 0.02 for the potassium complex. Values in the order of 10^6 (10^4) are calculated for the rate constants of complexation (decomplexation).
[8] Concerning the special role of carboxylic ionophores, cf. ref. [4b].

Isolation of Isomeric Iodohydroborates of Type $[B_{10}H_{10-n}I_n]^{2-}$

By *Klaus-Georg Bührens* and *Wilhelm Preetz*[*]

A sharp increase in the number of geometrical isomers with increasing value of n (up to 5) might be expected[2] for the halohydroborate ions $B_{10}H_{10-n}X_n^{2-}$ (X = Cl, Br, I; $n = 1-10$)[1], which we recently isolated by high voltage electrophoresis. The question arising is whether electrophilic substitution gives all isomers in the expected statistical distribution or whether some are formed preferentially, as suggested by LCAO/MO calculations[3].

In the case of the lower iodohydroborates electrophoretic separation over a prolonged period (3 h) leads to separate zones (Fig. 1a). Subsidiary zones are also observed to a lesser extent with the brominated species but are not isolable. No separation at all is seen with the chlorinated species.

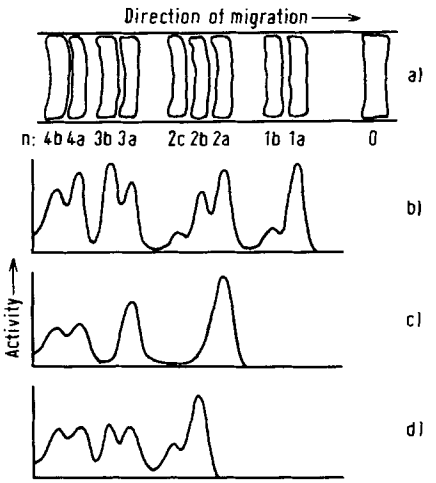


Fig. 1. a) Pherogram. b) Activity profile of the compounds $B_{10}H_{10-n}I_n^{2-}$ ($n = 1$—4) labeled with ^{131}I; c) secondary products of 2-$B_{10}H_9I^{2-}$ *(1a)* with $^{131}I_2$; d) secondary products of 1-$B_{10}H_9I^{2-}$ *(1b)* with $^{131}I_2$.

Analysis of the substances isolated from the various subzones shows them to be isomeric iodohydroborates. The reaction scheme for the formation of the species detected by electrophoresis could be established; the isolated compounds and their characteristic IR frequencies are listed in Table 1.

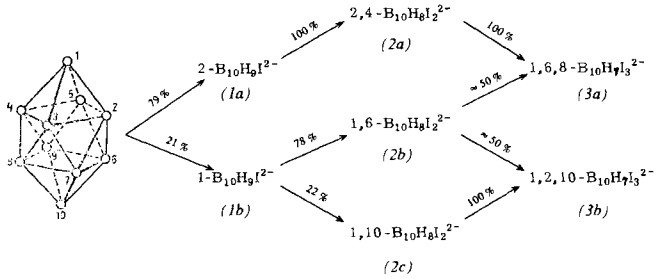
Separation of the isomers is feasible because of differences in molecular shape, since the ion mobility depends upon the shape of the ion[4]. Spherical particles are subject to less drag and will therefore migrate faster than extended ellipsoidal particles. In *(1b)* the molecular axis is lengthened by *ca.* 20% relative to that of $B_{10}H_{10}^{2-}$. In contrast, *(1a)* is more compact and migrates somewhat faster. The assignment could be confirmed because this isomer pair is accessible by an

[*] Prof. Dr. W. Preetz, Dr. K.-G. Bührens
Institut für Anorganische Chemie der Universität
Olshausenstrasse 40-60, D-2300 Kiel (Germany)

Table 1. Characteristic IR frequencies [cm^{-1}] of the isomeric iodohydroborates.

2-$[(CH_3)_4N]_2B_{10}H_9I$	*(1a)*	2510 s, 2480 vs, 2475 sh, 1070 vw, 1005 w, 815 m, 785 m, 770 m, 720 m
1-$[(CH_3)_4N]_2B_{10}H_9I$	*(1b)*	2485 s, 1100 w, 1010 m, 870 w, 840 m, 810 m, 735 m
2,4-$[(CH_3)_4N]_2B_{10}H_8I_2$	*(2a)*	2510 sh, 2495 s, 1100 s, 1070 m, 1005 w, 830 w, 780 s, 760 sh
1,6-$[(CH_3)_4N]_2B_{10}H_8I_2$	*(2b)*	2510 sh, 2490 s, 2470 sh, 1120 sh, 1100 s, 1020 w, 1000 w, 875 m, 790 s, 770 sh, 720 m
1,6,8-$[(CH_3)_4N]_2B_{10}H_7I_3$	*(3a)*	2510 sh, 2495 s, 1170 w, 1100 s, 870 w, 785 s, 770 s
1,2,10-$[(CH_3)_4N]_2B_{10}H_7I_3$	*(3b)*	2545 sh, 2530 s, 1130 m, br, 1120 sh, 1020 sh, 860 m, 800 m

alternative route[5]. Although the influence of substituents on the molecular geometry becomes slighter with increasing degree of iodination, the experimentally observed separation effects can likewise be interpreted in terms of ionic shape.



The reaction course for the initial substitution steps follows from a study of the individual steps of the reaction chains with the aid of radioactive iodine (Fig. 1). Since *(1a)* gives a homogeneous compound *(2a)*, the secondary product of which *(3b)* is also formed from *(1b)* *via* *(2b)*, the two I atoms must be in the 2,4 position in *(2a)*. Assignment of the isomers *(2b)* and *(2c)* resulting from *(1b)* is based upon the shape of the molecule. Only *(2b)* gives two secondary products, of which *(3a)* is also formed from *(2a)*, and *(3b)* also from *(2c)*. Further iodination leads to a complicated situation since six of the twenty possible isomers of $B_{10}H_6I_4^{2-}$ can be derived from *(3a)* and *(3b)*. In fact only two zones are observed which could represent mixtures.

Initial attack of I_2 on $B_{10}H_{10}^{2-}$ gives an almost statistical distribution, *i.e.* corresponding to the ratio of equatorial and axial positions (4 : 1). Formation of *(1b)* is only slightly favored (21 %). Further substitution proceeds under the directing influence of the iodine atoms already present, avoiding substitution at adjacent sites. It has also been observed in intramolecular rearrangements of $B_{10}H_8[N(CH_3)_3]_2$ that isomers with neighboring groups are less stable[6].

Received: March 1, 1977 [Z 686 IE]
German version: Angew. Chem. 89, 412 (1977)

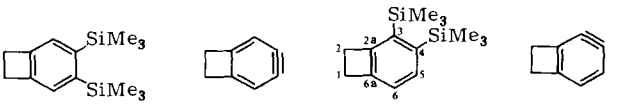
CAS Registry numbers:
(1a), 62228-02-8; *(1b)*, 61491-42-7; *(2a)*, 62228-04-0; *(2b)*, 62228-07-3; *(2c)*, 62228-06-2; *(3a)*, 62228-05-1; *(3b)*, 62228-03-9

[1] *K.-G. Bührens, W. Preetz*, Angew. Chem. *89*, 195 (1977); Angew. Chem. Int. Ed. Engl. *16*, 173 (1977).
[2] *T. E. Haas*, Inorg. Chem. *3*, 1053 (1964); *W. N. Lipscomb*: Boron Hydrides. Benjamin, New York 1963.
[3] *W. N. Lipscomb, R. Hoffmann*, J. Chem. Phys. *37*, 520 (1962).
[4] *J. T. Edward, D. Waldron-Edward*, J. Chromatogr. *20*, 563 (1965).
[5] *A. P. Schmitt, R. L. Middaugh*, Inorg. Chem. *13*, 163 (1974).
[6] *W. R. Hertler, W. H. Knoth, E. L. Muetterties*. J. Am. Chem. Soc. *86*, 5434 (1964).

3,4-Bis(trimethylsilyl)benzocyclobutene—Synthesis by Acetylene Cotrimerization and Conversion into 1,2-Dihydrocyclobuta[*c*]benzyne[**]

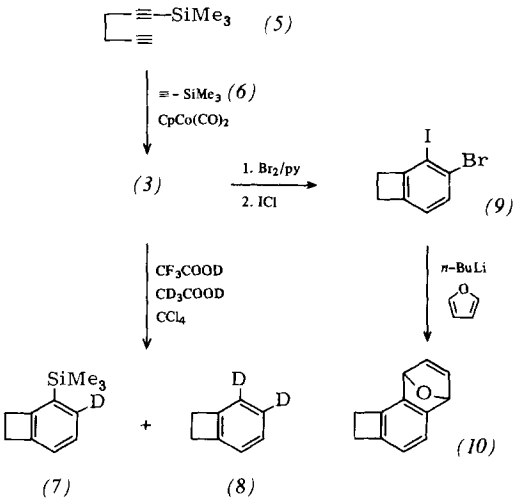
By *Russel L. Hillard III* and *K. Peter C. Vollhardt*[*]

We recently reported the synthesis of 4,5-bis(trimethylsilyl)-benzocyclobutene *(1)*, a versatile synthetic intermediate *en route* to a variety of substituted benzocyclobutenes[1] and strained ring systems derived from 1,2-dihydrocyclobuta[*d*]-benzyne *(2)*[2]. We have now accomplished the synthesis of the isomeric 3,4-bis(trimethylsilyl)benzocyclobutene *(3)* and its conversion into 1,2-dihydrocyclobuta[*c*]benzyne *(4)*.



(1) *(2)* *(3)* *(4)*

Addition of a solution of 1-trimethylsilyl-1,5-hexadiyne *(5)*[3] (5 mmol), trimethylsilylacetylene *(6)*[4] (15 mmol), and dicarbonyl(cyclopentadienyl)cobalt [$CpCo(CO)_2$] (5 mol-%) in *n*-octane (10 ml) to refluxing *n*-octane (20 ml) under N_2 over a period of 5 d, followed by column chromatography with pentane on silica gave as a cocyclized product *exclusively* isomer *(3)* as a colorless oil[5] in 22 % yield [MS: *m/e* 248.1409 (calc. 248.1416, M^+, 21 %), 233 (79 %), 73 (100 %); ^{1}H-NMR (CCl_4): τ 2.60 (d, J = 8 Hz, 1 H), 3.11 (d, J = 8 Hz, 1 H), 6.87 (m, 4 H), 9.67 (s, 18 H); ^{13}C-NMR ($CDCl_3$): δ = 153.5 ppm (C-2a), 146.0 (C-6a), 134.1 (C-5), 122.1 (C-6), 34.1 (C-1 or C-2), 28.7 (C-1 or C-2), 2.6 ($Si(CH_3)_3$); UV (95 % ethanol): λ_{max} = 276 ($\lg\varepsilon$ = 3.52), 285 sh (3.46)].



Treatment with trifluoroacetic acid gave benzocyclobutene[1]. Deuteriodesilylation of *(3)* to *(7)* and *(8)* in $CD_3COOD/CF_3COOD/CCl_4$ (*ca.* 1 : 1 : 5 g/g) follows pseudo-first order kinetics and indicates that the $Si(CH_3)_3$ group at the 4-position is 500 times more susceptible to hydrolysis than that at the 3-position. This value appears to be a composite of a steric (and possibly electronic) factor of the *ortho*-

[*] R. L. Hillard and Professor Dr. K. Peter C. Vollhardt
Department of Chemistry, University of California, and
the Materials and Molecular Research Division,
Lawrence Berkeley Laboratory, Berkeley, California 94720 (USA)

[**] This work was supported by the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, the National Institute of Health, and the American Cancer Society (Special Grant No. 795).

$Si(CH_3)_3$ substituent (*ca.* 40)[1] and a strain factor due to the four membered ring (*ca.* 10)[6].

The high selectivity observed in electrophilic substitutions lends itself to synthetic exploitation. Thus bromination of *(3)* with bromine/pyridine (mol. ratio 2:1) leads quantitatively to 4-bromo-3-(trimethylsilyl)benzocyclobutene[5], which on reaction with iodine monochloride affords the compound *(9)*[5]. Cyclobuta[1,2-*c*]benzyne *(4)* can be generated from *(9)* with *n*-butyl lithium and trapped with furan in 59% yield as the colorless adduct *(10)*[5] (m.p. 80—81 °C). So far we have not been able to detect dimers derived from *(4)*.

Received: February 1, 1977 [Z 690 IE]
German version: Angew. Chem. 89, 413 (1977)

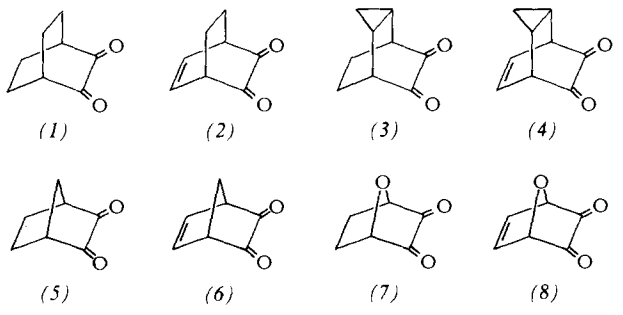
CAS Registry numbers:
(3), 62107-89-5; *(4)*, 62107-90-8; *(5)*, 1578-34-3; *(6)*, 1066-54-2; *(9)*, 62107-91-9; *(10)*, 62107-92-0; furan, 110-00-9

[1] *W. G. L. Aalbersberg, A. J. Barkovich, R. L. Funk, R. L. Hillard III, K. P. C. Vollhardt*, J. Am. Chem. Soc. 97, 5600 (1975); *R. L. Hillard III, K. P. C. Vollhardt*, in press.
[2] *R. L. Hillard III, K. P. C. Vollhardt*, J. Am. Chem. Soc. *98*, 3579 (1976); *R. L. Funk, K. P. C. Vollhardt*, Angew. Chem. *88*, 63 (1976); Angew. Chem. Int. Ed. Engl. *15*, 53 (1976).
[3] Prepared from the reaction of 1,5-hexadiynylmagnesium bromide with trimethylsilyl chloride (29%; b.p. 38—42 °C/0.5 torr).
[4] *L. Brandsma*: Preparative Acetylene Chemistry, Elsevier, New York 1971.
[5] All new compounds gave satisfactory analytical and/or spectral data.
[6] *A. R. Bassindale, C. Eaborn, D. R. M. Walton*, J. Chem. Soc. *B 1969*, 12; *C. Eaborn, D. R. M. Walton, D. J. Young, ibid. B 1969*, 15.

Interaction between the Nonbonding Orbitals of α-Dicarbonyl Systems and π or Walsh Orbitals[**]

By *Rolf Gleiter, Richard Bartetzko, Peter Hofmann*, and *Hans-Dieter Scharf*[*]

The interaction between the nonbonding orbitals n_1 and n_2 in 1,2-dicarbonyl systems is explained by a through-bond mechanism[1]. On the basis of the photoelectron spectra (PE) of glyoxal, biacetyl, and camphor quinone it could be shown that the energy difference $\Delta(n)=|\varepsilon(n_+)-\varepsilon(n_-)|$ between the linear combinations $n_+=(n_1+n_2)/\sqrt{2}$ and $n_-=(n_1-n_2)/\sqrt{2}$ is almost independent of the alkyl substituents and of the dihedral angle between the carbonyl groups; values of Δ(n) are found between 1.6 and 2.0 eV.



(1) *(2)* *(3)* *(4)*

(5) *(6)* *(7)* *(8)*

[*] Prof. Dr. R. Gleiter, Dipl.-Ing. R. Bartetzko
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)
Dr. P. Hofmann
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-8520 Erlangen (Germany)
Prof. Dr. H.-D. Scharf
Institut für Organische Chemie der Technischen Hochschule
Prof.-Pirlet-Strasse 1, D-5100 Aachen (Germany)

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

It is surprising, however, that the energy difference Δ(n) is strongly influenced by double bonds or three-membered rings separated by two σ bonds from the C_2O_2 fragment. This is shown by the PE spectra of the bicyclic α-diketones *(1)*—*(8)*[3].

The experimental first PE bands of the compounds *(1)*—*(8)* are compiled in Table 1. A common feature is the almost constant first ionization potential (8.7—9.2 eV) and a large energy difference between the first and the second band. The assignment is based on the validity of Koopmans' theorem ($-\varepsilon_J=I_{v,J}$)[4]. Both methods of calculation used predict the same orbital sequence (MINDO/3[5] and EH[6]).

Table 1. Comparison of measured vertical ionization potentials ($I_{v,J}$) and orbital energies (ε_J) of *(1)* to *(8)*; all values in eV.

Cpd.	Band	$I_{v,J}$	Δn	Assignment	MINDO/3	Δn
(1)	1	9.0	1.5	$a_1(n_+)$	− 9.12 (a_1)	1.3
	2	10.5		$b_1(n_-)$	−10.40 (b_1)	
	3	11.2		$a_2(\sigma)$	−10.84 (a_2)	
(2)	1	8.9		a′(n_+)	− 8.82 (a′)	
	2	10.5	1.9	a′(π)	−10.12 (a′)	1.6
	3	10.8		a″(n_-)	−10.48 (a″)	
	4	11.55		a″(σ)	−11.00 (a″)	
(3)	1	8.9		a′(n_+)	− 8.82 (a′)	
	2	10.3	2.6	a″(Walsh)	−10.06 (a″)	2.93
	3	10.7		a′(Walsh)	−10.22 (a′)	
	4	11.5		a″(n_-)	−11.75 (a″)	
(4)	1	8.7		a′(n_+)	− 8.69 (a′)	
	2	10.3		a′(π)	− 9.82 (a′)	
	3	10.5	3.1	a″(Walsh)	−10.12 (a″)	3.07
	4	10.9		a′(Walsh)	−10.68 (a′)	
	5	11.8		a″(n_-)	−11.76 (a″)	
(5)	1	9.0	1.5	a′(n_+)	− 8.99 (a′)	1.5
	2	10.5		a″(n_-)	−10.55 (a″)	
	3	11.2		a″(σ)	−11.29 (a″)	
(6)	1	8.7		a′(n_+)	− 8.67 (a′)	
	2	10.6	2.4	a′(π)	−10.28 (a′)	2.1
	3	11.1		a″(n_-)	−10.78 (a″)	
	4	12.1		a″(σ)	−11.52 (a″)	
(7)	1	9.2	2.3	a′(n_+)	− 9.57 (a′)	1.1
	2	11.5		a″(n_-)	−10.73 (a″)	
	3	11.7		a′(2p)	−11.29 (a′)	
(8)	1	8.9		a′(n_+)	− 8.69 (a′)	
	2	10.8	2.8	a′(π)	−10.65 (a′)	2.2
	3	11.7		a″(n_-)	−10.95 (a″)	
	4	12.0		a′(2p)	−11.57 (a′)	

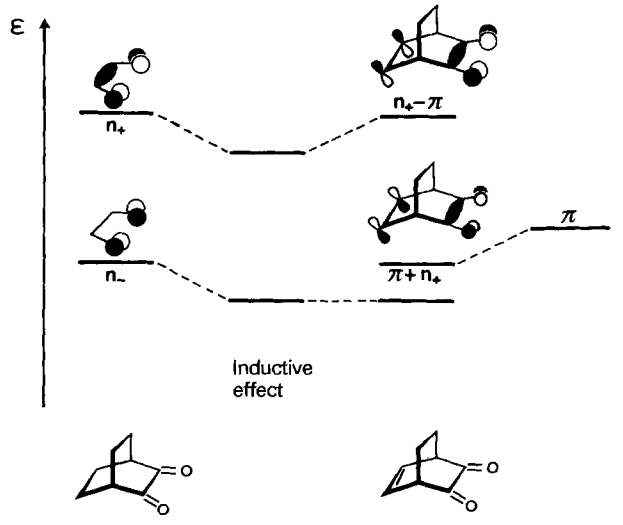


Fig. 1. Qualitative interaction diagram for the n_+ and n_- orbitals of the C_2O_2 group and the π orbital in *(2)*.

These results can readily be interpreted by assuming n_+ to be above n_- for the orbital sequence in the C_2O_2 moiety and a strong interaction between π- or Walsh orbitals and n_+ and/or n_-. In Figure 1 the orbital sequence in *(2)* is explained as the result of an inductive effect of the double bond on n_+ and n_- and a homoconjugative interaction between the π and the C_2O_2 part.

Received: March 1, 1977 [Z 687 IE]
German version: Angew. Chem. *89*, 414 (1977)

CAS Registry numbers:
(1), 4216-89-1; *(2)*, 1754-68-1; *(3)*, 59952-76-8; *(4)*, 59896-73-0; *(5)*, 6236-71-1; *(6)*, 17994-26-2; *(7)*, 59896-74-1; *(8)*, 55058-68-9

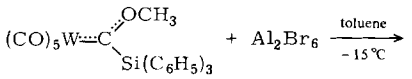
[1] *J. R. Swenson, R. Hoffmann*, Helv. Chim. Acta *53*, 2331 (1970); *R. Hoffmann*, Acc. Chem. Res. *4*, 1 (1971); *R. Gleiter*, Angew. Chem. *86*, 770 (1974); Angew. Chem. Int. Ed. Engl. *13*, 696 (1974).
[2] *D. O. Cowan, R. Gleiter, J. A. Hashmall, E. Heilbronner, V. Hornung*, Angew. Chem. *83*, 405 (1971); Angew. Chem. Int. Ed. Engl. *10*, 401 (1971).
[3] *H. D. Scharf, P. Friedrich, A. Linckens*, Synthesis *1976*, 256.
[4] *T. Koopmans*, Physica (Utrecht) *1*, 104 (1934).
[5] *R. Bingham, M. J. S. Dewar, D. H. Lo*, J. Am. Chem. Soc. *97*, 1285 (1975).
[6] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *R. Hoffmann, W. N. Lipscomb, ibid. 36*, 2179 (1962); *37*, 2872 (1962).

Triphenylsilylcarbyne Complexes of Tungsten[1]

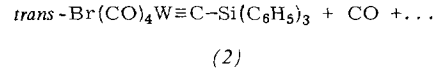
By *Ernst Otto Fischer, Helmut Hollfelder, Peter Friedrich, Fritz Roland Kreissl*, and *Gottfried Huttner*[*]

Having already prepared *trans*-bromotetracarbonyldiethylaminocarbynetungsten[2] with an electron-repelling substituent on the carbyne C atom, we now describe the synthesis of *trans*-bromotetracarbonyltriphenylsilylcarbynetungsten *(2)* and dicarbonylcyclopentadienyltriphenylsilylcarbynetungsten *(3)* as the first carbyne complexes containing an electron-withdrawing hetero atom[3].

Reaction of pentacarbonylmethoxy(triphenylsilyl)carbenetungsten *(1)*[4] with aluminum bromide under mild conditions affords *(2)* as ivory-colored diamagnetic crystals which dissolve readily in dichloromethane but only moderately well in *n*-pentane.



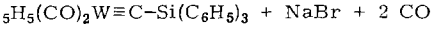
(1)



(2)

The complex *(2)* reacts with sodium cyclopentadienide in tetrahydrofuran (evolution of CO, deepening of color) to give *(3)* as orange diamagnetic crystals which are readily soluble in ether and dichloromethane.





(3)

The IR spectra of *(2)* and *(3)* (CH_2Cl_2; cm^{-1}) show the expected vibrations in the νCO region (2132 w, 2052 vs and 2003 s, 1926 vs, respectively).—The ^{1}H-NMR spectrum ([D_6]-acetone, −30 °C) diplays a multiplet for *(2)* at δ = 7.55 ppm which is assigned to the triphenylsilyl group; the corresponding signal of *(3)* appears at δ = 7.53 ppm and is accompanied by a singlet due to the cyclopentadienyl protons at δ = 5.89 ppm (intensity ratio 15:5).—The ^{13}C-NMR spectrum of the two complexes (Table 1) evidences the relatively strong deshielding of the carbyne carbon atom, whose signal exhibits a considerable paramagnetic shift relative to arylcarbyne and alkylcarbyne complexes of tungsten[5].

Table 1. $^{13}C\{^1H\}$-NMR spectra of the carbyne complexes *(2)* and *(3)* in CD_2Cl_2; δ values in ppm, *vs.* CD_2Cl_2 = 54.16 ppm.

	W≡C	CO	C_6H_5		C_5H_5	Measuring temp. [°C]
(2)	337.14	192.57	135.72	131.73		−40
	(146.5) [a]	(131.8) [a]	130.75	128.60		
(3)	354.29	222.24	135.93	134.32	92.56	−20
	(178.2) [a]	(202.6) [a]	130.00	128.27		

[a] $^1J(^{183}W-^{13}C)$ in Hz for satellites.

Although the spectroscopic data prove that *(3)* has basically the same structure as already confirmed by X-ray studies for other cyclopentadienyldicarbonyltungsten-carbyne complexes[6], X-ray analysis[7] of *(3)* was undertaken in order to establish whether the triphenylsilyl substituent has a recognizable influence on the W—$C_{carbyne}$ bond length (Fig. 1).

The pseudooctahedral structure expected for *(3)* was confirmed. The W—$C_{carbyne}$ distance of 181(2) pm is just as long as that in $C_5H_5(CO)_2WC-C_6H_4CH_3$ *(4)* (182(2) pm[6a]); exchange of the *p*-tolyl group in *(4)* for the triphenylsilyl group in *(3)* apparently causes no change in the W—$C_{carbyne}$ bond length. As in *(4)*, the central group W≡C—R is almost linear (176(1)°). Within the limits of experimental accuracy all the SiC bonds in *(3)* are of equal length. Compared with a C_{sp}—Si single bond (181 pm[8]) the $C_{carbyne}$—Si bond length of 187(2) pm appears somewhat elongated; however, the effect is by no means so pronounced as in $(CO)_5Cr-[C(OEt)(SiPh_3)]$[4], for which a C_{sp^2}—Si distance of 200(2) pm was found.

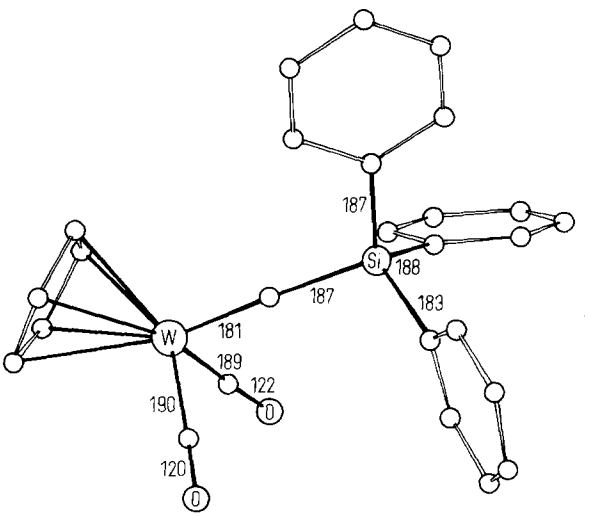


Fig. 1. Molecular structure of π-$C_5H_5(CO)_2W\equiv C-Si(C_6H_5)_3$ *(3)*.

Procedure

All operations should be performed under N_2 and with dried (Na, P_4O_{10}) and N_2-saturated solvents.

(2): An excess of Al_2Br_6 is added to a stirred solution of *(1)* (1.57 g, 2.5 mmol) in toluene (30 ml) at −78 °C. On

[*] Prof. Dr. E. O. Fischer, Dipl.-Chem. H. Hollfelder, Dipl.-Chem. P. Friedrich, Dr. F. R. Kreissl, Doz. Dr. G. Huttner
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

warming to −15 °C the reaction mixture evolves CO and slowly changes color from dark red to yellow. After 30 min methanol is added (5 ml) at −100 °C. The orange reaction mixture is then evaporated to dryness at −30 °C; the residue is taken up in the minimum amount of CH_2Cl_2 necessary (−50 °C) and chromatographed on silica gel (column: $l=15$, $d=2.5$ cm). After concentration of the yellow zone to 2 ml, addition of pentane (50 ml) at −78 °C leads to deposition of a finely crystalline precipitate. The mother liquor is decanted off and the precipitate recrystallized five times at −78 °C from CH_2Cl_2/pentane (1:40) and dried for 2 d at −30 °C *in vacuo*. Ivory crystals, dec. >*ca.* 65 °C; yield 1.5 g (93 %).

(3): An excess of NaC_5H_5[9] is added to a stirred solution of *(2)* (2.25 g, 3.5 mmol) in tetrahydrofuran (30 ml) at −78 °C, the reaction mixture evolving CO and turning orange-brown. Removal of solvent and chromatography of the residue at −30 °C on silica gel (column: $l=25$, $d=2.5$ cm) in pentane/CH_2Cl_2 (1:1) gives an orange zone which is evaporated to 2 ml at −30 °C. After addition of pentane (50 ml) at −78 °C fine crystals of *(3)* precipitate. They are recrystallized three times at −78 °C from ether/pentane and dried for 2 d at −20 °C *in vacuo*. Orange crystals, m.p. 103—104 °C; yield 1.1 g (55 %).

Received: March 8, 1977 [Z 695 IE]
German version: Angew. Chem. *89*, 416 (1977)

CAS Registry numbers:
(1), 62319-83-9; *(2)*, 62319-82-8; *(3)*, 62319-81-7; Al_2Br_6, 18898-34-5; ^{13}C, 14762-74-4

[1] Transition Metal-Carbyne Complexes, Part 30. This work was supported by the Deutsche Forschungsgemeinschaft and BASF AG, Ludwigshafen.—Part 29: ref. [6b].

[2] *E. O. Fischer, G. Kreis, F. R. Kreissl, W. Kalbfus, E. Winkler*, J. Organomet. Chem. *65*, C 53 (1974).

[3] Cf. *R. A. Andersen, A. L. Galyer, G. Wilkinson*, Angew. Chem. *88*, 692 (1976); Angew. Chem. Int. Ed. Engl. *15*, 609 (1976). The complex described does not contain a terminal, sp-hybridized carbyne ligand.

[4] *E. O. Fischer, H. Hollfelder, P. Friedrich, F. R. Kreissl, G. Huttner*, Chem. Ber., in press.

[5] *E. O. Fischer, U. Schubert*, J. Organomet. Chem. *100*, 59 (1976).

[6] a) *E. O. Fischer, T. L. Lindner, G. Huttner, P. Friedrich, F. R. Kreissl*, Chem. Ber., in press; b) *G. Huttner, A. Frank, E. O. Fischer*, J. Isr. Chem., in press.

[7] Crystal data: monoclinic, space group C2/c; $a=2709.5$, $b=1011.5$, $c=1941.9$ pm, $\beta=120.09°$; $Z=8$; 1350 independent diffraction data: Syntex $P2_1$ four-circle diffractometer, $Mo_{K\alpha}$ ($\lambda=71.069$ pm), graphite monochromator. Solution: Syntex XTL, conventional, $R_1=0.049$.

[8] *L. Pauling*: The Nature of the Chemical Bond. Cornell University Press, Ithaca, N. Y.

[9] *R. B. King*, Organometallic Syntheses, Vol. 1, p. 64. Academic Press, New York 1965.

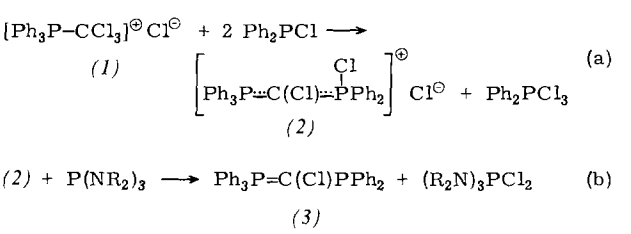
Synthesis of a Stabilized $1\lambda^5,3\lambda^5$-Diphosphacyclobutadiene[1]

By *Rolf Appel, Fritz Knoll*, and *Horst-Dieter Wihler*[*]

Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

(Trichloromethyl)triphenylphosphonium chloride *(1)* is not only the first isolable intermediate in the reaction of triphenylphosphane with tetrachloromethane[2], but also a now readily accessible starting compound for the synthesis of phosphorus carbon ylides whose existence was hitherto only suspected or whose preparation is difficult[3]. From *(1)* and chlorodiphenylphosphane we have now obtained chloro(triphenylphosphoranediyl)methylchlorodiphenylphosphonium chloride *(2)*, which can be dechlorinated to the yellow ylide *(3)* by trimorpholinophosphane or tris(dimethylamino)-phosphane.

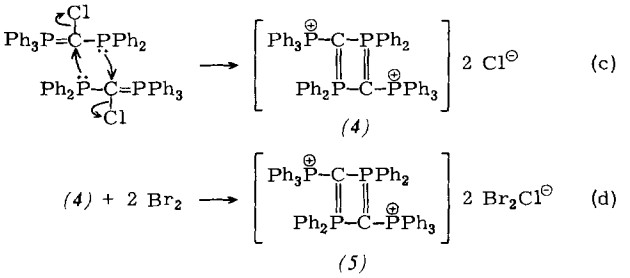
[*] Prof. Dr. R. Appel, Dr. F. Knoll, Dipl.-Chem. H.-D. Wihler
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)



(a)

(b)

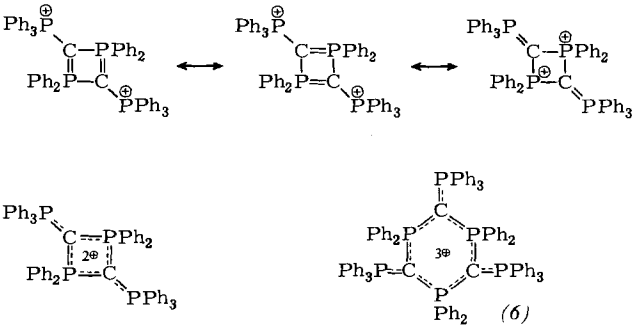
The ylide *(3)* is thermally unstable. On heating, or even on conducting reaction (b) without cooling, 1,3-cyclosubstitution occurs with dimerization to give 1,1,3,3-tetraphenyl-2,4-bis(triphenylphosphonio)-$1\lambda^5,3\lambda^5$-diphosphacyclobutadiene dichloride *(4)*, which melts at 385 °C, dissolves without decomposition in water, and does not display any ylide reaction. Compound *(4)* reacts with bromine to give a bright yellow solid, m.p. 365 °C, identified as the polyhalide *(5)* by the ^{31}P-NMR spectrum of the cation and its reaction with cyclohexene to regenerate *(4)*.



(c)

(d)

The unusual stability of the cation and its almost undetectable polarizing effect upon the counterion Br_2Cl^-[4] in spite of the double charge suggest extensive delocalization of the positive charge with participation of the exocyclic P atoms.



To our knowledge *(4)* and *(5)* contain the first four-membered PC ring system having partly endocyclic double bonds. In the uncharged ring systems of the cyclophosphazenes the four-membered ring is still unknown. We assume a stabilizing contribution of the positive charge in the case of *(4)* by partial withdrawal of π-electron density from the ring into the external P—C bonds.

Two triplets are observed in the ^{31}P-NMR spectrum of *(4)* at $\delta=14.4$ and 33.64 ppm [$J(P_aP_b)=7.35$ Hz], indicating a symmetrical structure in which each P atom must be surrounded by two identical P atoms having a different environment from the first one. However, a decision between the proposed structure *(4)* and the six-membered ring structure *(6)*, which could not be ruled out *a priori*, only became possible on considering the ^{13}C-NMR and the field desorption mass spectrum. In the ^{13}C-NMR spectrum (CD_3OD, TMS internal) the signal of the ring C atom ($\delta=18.29$ ppm) is split into 12 lines ($^1J_{CP}=111.69$, $^1J_{CP_2}=76.17$, $^3J_{CP}=15.4$ Hz), which is compatible with a four-membered ring but not with

a six-membered ring; a 36-line spectrum would be expected for *(6)*. The FD mass spectrum[5] also provides important evidence in favor of the four-membered ring. The peak at $m/e=459$ corresponds to the dication of *(4)*, but could also be assigned to the trebly charged cation *(6)*. The latter possibility is discounted by the appearance of the highest mass peak at $m/e=917$, *i. e.* for $[K^{2+}-H^+]^+$ and by the absence of ions in the range $m/e=1000$—1500. Another line at $m/e=841$ arises from a cation containing one less phenyl group $[K^{2+}-Ph^+]^+$.

Procedure

(2): To an ice-cooled, stirred solution of *(1)*[2] (17.4 g, 41.8 mmol) in a minimal amount of CH_2Cl_2 is slowly added dropwise Ph_2PCl (18.4 g, 83.6 mmol) diluted with the same amount of CH_2Cl_2. After 2 h the precipitated trichlorodiphenylphosphorane is filtered off (10 g = 34 mmol = 82 %) and that remaining in solution decomposed with 1,2-epoxybutane. The solvent is distilled off *in vacuo* and the dry residue dissolved in CH_3CN. Ether is added to the gently stirred solution until it becomes slightly turbid; precipitation is complete within 30 min. The product is filtered off, washed with ether, and dried *in vacuo* at 40 °C. Yield: 16.8 g (71 %) of *(2)*, m.p. 192 °C (dec.). ^{1}H-NMR: multiplet at $\delta=7.4$ to 8.0 ppm. ^{31}P-NMR: two doublets at $\delta=-23.63$ and $+62.63$ ppm; $J(P,P)=42.5$ Hz.

(4): To a solution of *(2)* (8.5 g, 15 mmol) in CH_2Cl_2 is added solid trimorpholinophosphane (4.3 g, 15 mmol) in a single batch and the mixture is stirred at room temperature for 10 to 20 min. After evaporation to dryness at 40 °C the residue is taken up in benzene and the mixture filtered. The filter cake is stirred with CH_2Cl_2, whereupon $(OC_4H_8N)_3PCl_2$ dissolves. The white residual solid is recrystallized from methanol. After washing with CH_2Cl_2 it is dried at 80 °C. Yield: 5.8 g (79 %) of *(4)*, m.p. 385 °C.—The action of bromine on the solution of *(4)* in CH_2Cl_2 gives *(5)*, dec. 365 °C, in quantitative yield. ^{31}P-NMR: two triplets at $\delta=14.44$ and 33.64 ppm; $J(P,P)=7.35$ Hz.

Received: March 14, 1977 [Z 696 IE]
German version: Angew. Chem. *89*, 415 (1977)

CAS Registry numbers:
(1), 57557-88-7; *(2)*, ionic form, 62414-93-1; *(2)*, bonded form, 62337-52-4; *(3)*, 62337-54-6; *(4)*, 62337-53-5; *(5)*, 62414-92-0; Ph_2PCl, 1079-66-9; ^{13}C, 14762-74-4

[1] Part 7 of Phosphorus-Carbon-Halogen Compounds.—Part 6: *R. Appel, W. Morbach*, Angew. Chem. *89*, 203 (1977); Angew. Chem. Int. Ed. Engl. *16*, 180 (1977).
[2] *R. Appel, F. Knoll, W. Michel, W. Morbach, H.-D. Wihler, H. Veltmann*, Chem. Ber. *109*, 58 (1976).
[3] *R. Appel, H. Veltmann*, Tetrahedron Lett. *1976*, 399; *R. Appel, F. Knoll, H. Veltmann*, Angew. Chem. *88*, 340 (1976); Angew. Chem. Int. Ed. Engl. *15*, 315 (1976); *R. Appel, G. Erbelding*, to be published.
[4] *A. P. Mironenko, S. B. Stepina, V. E. Plyushchev, L. A. Zotova*, Zh. Neorg. Khim. *1968*, 2838; *A. P. Mironenko, L. H. Kulikova, J. J. Alekseeva, S. B. Stepina, V. E. Plyushchev, L. J. Pokroskaya, ibid. 1974*, 3272.
[5] We are indebted to Prof. Dr. *H. D. Beckey* and Dr. *H. R. Schulten*, Bonn, for recording the spectrum.

Preparation of Cyclohexasilane, Si_6H_{12}

By *Edwin Hengge* and *Dieter Kovar*[*]

Following the discovery of the first cyclic hydrosilicon Si_5H_{10}[1], we have now succeeded in preparing and characterizing the next homolog Si_6H_{12}. Starting from dodecaphenylcyclohexasilane, first obtained by *Kipping et al.*[2] from Ph_2SiCl_2 by reaction with alkali metal, we were able to remove all the phenyl groups with the aid of $AlCl_3$/HCl and to isolate Si_6Cl_{12}[3]. $AlCl_3$ had already been used on former occasions for cleaving Si-phenyl bonds in simple silanes[4]. The cleavage reaction, shown by our investigations to be electrophilic, also proceeds without ring cleavage with phenylcyclosilanes, whereas hydrogen chloride under pressure in the absence of $AlCl_3$ effects only partial removal of the phenyl groups[5]. Use of $AlCl_3$ has the considerable practical advantage that the reaction occurs with gaseous HCl and use of liquified HCl (bomb tube) can be avoided.

Si_6Cl_{12} can be smoothly hydrogenated to unsubstituted cyclohexasilane with pure $LiAlH_4$ in benzene/ether. Si_6H_{12} is a colorless liquid which ignites spontaneously on exposure to air. Owing to its low vapor pressure the new compound is easier to handle than Si_5H_{10}. Its ^{1}H-NMR, IR, Raman, and mass spectra were recorded for purposes of characterization.

^{1}H-NMR (60 MHz; in benzene TMS int.): singlet at $\tau=6.50$, $J_{SiH}=195$ Hz
IR [cm^{-1}]: 330 w, 384 m (br), 519 w, 625 vs, 720 vs (br), 865 m, 892 vs, 904 vs, 2120 vs
Raman [cm^{-1}]: 114 s (p), 350 vs (p), 379 w (p), 455 m, 476 vs (sh), 517 vw (p), 625 w, 655 m, 736 vw (?), 893 m, 2128 vs (br, p)
MS: Molecular ion at m/e 180, usual isotopic distribution due to ^{29}Si; fragmentation pattern results from successive loss of H and SiH_4

Assuming a chair conformation similar to that of cyclohexane, the Raman spectrum should display 14 lines ($6A_{1g}+8E_g$), which are indeed observed (νSiH must be counted fourfold). In the IR spectrum 13 vibrations are expected ($5A_{2u}+8E_u$) of which 9 are observable, the SiH stretching vibration being multiply degenerate; the ring deformation vibrations lie outside the range of measurement. These results and the polarization measurements strongly suggest the assumed conformation of cyclohexasilane.

Procedure

Benzene (200 ml) and $AlCl_3$ (1 g, 7.5 mmol) are added to Si_6Ph_{12} (4 g, 3.6 mmol). HCl is passed into this stirred suspension until a clear solution is obtained. $AlCl_3$ is filtered off, and a freshly prepared 0.5 M ethereal solution of $LiAlH_4$ (100 ml) is added to the vigorously stirred filtrate with ice-cooling (1 h). Stirring is continued at room temperature, the ether removed, and the precipitate filtered off; residual benzene is drawn off at 1 torr. At 0.01 torr and 80 °C Si_6H_{12} condenses over as a colorless liquid, yield 0.39 g (60 %).

Received: March 17, 1977 [Z 698 IE]
German version: Angew. Chem. *89*, 417 (1977)

CAS Registry numbers:
Si_6H_{12}, 291-59-8; Si_6Ph_{12}, 1591-06-6

[1] *E. Hengge, G. Bauer*, Angew. Chem. *85*, 304 (1973); Angew. Chem. Int. Ed. Engl. *12*, 316 (1973).
[2] *F. S. Kipping, J. E. Sands*, J. Chem. Soc. Trans. *119*, 830 (1921).
[3] *E. Hengge, D. Kovar*, J. Organomet. Chem. *125*, C29 (1977).
[4] *J. D. Austin, C. Eaborn, J. D. Smith*, J. Chem. Soc. *1963*, 4744.
[5] *E. Hengge, F. Lunzer*, Monatsh. Chem. *107*, 371 (1976).

[*] Prof. Dr. E. Hengge, Dipl.-Ing. D. Kovar
Institut für Anorganische Chemie der Technischen Universität
Stremayrgasse 16, A-8010 Graz (Austria)

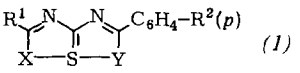
New Synthetic Methods for 6aλ^4-Thiapentalenes

By *Gerrit L'abbé, Gabriël Verhelst*, and *Guido Vermeulen*[*]

1,6,6aλ^4-Thiapentalenes and analogous compounds have recently acquired considerable interest owing to their ability

[*] Prof. Dr. G. L'abbé, G. Verhelst, G. Vermeulen
Department of Chemistry, University of Leuven
Celestijnenlaan 200 F, B-3030 Heverlee (Belgium)

to engage in no-bond resonance[1]. We have now found that a series of 6aλ⁴-thia-1,6-heteropentalenes of general structure *(1)* can be prepared from the readily available 5-amino-1,2,3,4-thiatriazole *(2)*[2]. Thus, when *(2)* is reacted with two equivalents of benzoyl chloride and triethylamine, a thermostable compound *(1a)* is obtained which exhibits spectral data (strong $M^{\bullet+}$, no ν(C=O) above 1600 cm^{-1}, symmetrical according to ^{13}C-NMR) consistent with its formulation as 2,5-diphenyl-3,4-dioxa-3aλ⁴-thia-1,6-diazapentalene (compounds *(1)* have to be designated as 3aλ⁴-thia-1,6-diaza-3,4-diheteropentalenes owing to the two nitrogen atoms). Furthermore, compound *(1a)* was converted by P_4S_{10} into a mixture of oxadithiadiazapentalene *(1e)* and the known[3] orange trithiadiazapentalene *(1f)*. Substituted benzoyl chlorides furnished compounds *(1b)* to *(1d)*.



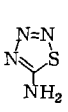
(1)

Table 1. Compounds of type *(1)* prepared.

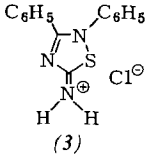
Cpd.	X	Y	R^1	R^2	M.p. [°C]	Yield [%] [a]
(1a)	O	O	Ph	H	195—197	36
(1b)	O	O	*p*-MeO—C_6H_4	MeO	241—242	23
(1c)	O	O	*p*-Me—C_6H_4	Me	242—244	43
(1d)	O	O	*p*-NO_2—C_6H_4	NO_2	270—275	80
(1e)	O	S	Ph	H	152—153	11 [b]
(1f) [3]	S	S	Ph	H	208—209	55 [b]
(1g)	NPh	NPh	Ph	H	278—282	86
(1h)	O	NPh	Ph	H	204—205	84
(1i)	S	NPh	NHMe	H	284—285	66
(1j)	S	NPh	NHPh	H	244—245	68

[a] Yield based on *(2)*.
[b] Yield based on *(1a)*; mixture of *(1e)* and *(1f)*.

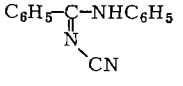
Compound *(2)* was similarly treated with two equivalents of *N*-phenylbenzimidoyl chloride in the presence of triethylamine, but the unknown salt *(3)* (m.p. 227—227.5 °C) and *(4)* (m.p. 231—233 °C) were obtained instead of the anticipated



(2)

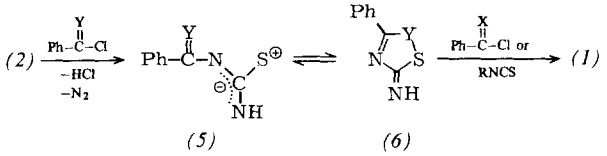


(3)



(4)

(1g). Compound *(3)* was the sole product formed when equimolar quantities of *(2)* and the imidoyl chloride were reacted in the absence of base. The salt *(3)* decomposes quantitatively to *(4)* and sulfur in the presence of bases. In order to avoid this base-induced decomposition in our attempted synthesis of thiatetraazapentalenes, pyridine was added to a mixture of *(3)* and *N*-phenylbenzimidoyl chloride: *(1g)* was obtained in 86 % yield. Similar treatment of *(3)* with benzoyl chloride furnished *(1h)* (84 %), and methyl and phenyl isothiocyanate yielded *(1i)* and *(1j)*, respectively, in addition to *(4)*.



(5) *(6)*

We believe, the inner salts of type *(5)* to be the key intermediates in our reactions.

Procedures

Synthesis of *(1a)*: To an ice-cooled solution of benzoyl chloride (0.02 mol) and triethylamine (0.02 mol) in dry tetrahydrofuran (10 ml) is added dropwise with stirring a tetrahydrofuran solution of *(2)* (0.01 mol in 15 ml). The reaction mixture is allowed to warm to room temperature and stirred for another two hours until nitrogen evolution has ceased. The solvent is removed and the residue is washed with water, dried, and crystallized from chloroform.

Synthesis of *(1g)*: Equimolar amounts (0.01 mol) of *(2)* and *N*-phenylbenzimidoyl chloride are allowed to react in dry acetonitrile (20 ml) until nitrogen evolution has ceased (2 hours). The precipitate *(3)* is collected, dried, and crystallized from methanol (yield 87 %).—To an ice-cooled mixture of *(3)* and *N*-phenylbenzimidoyl chloride (2.5 mmol of each) is added dropwise with stirring pyridine (10 ml). The reaction mixture is stirred for one hour at 0 °C, and then heated at reflux temperature for another hour. The mixture is poured onto ice and *(1g)* is filtered off, dried, and crystallized from CCl_4/hexane. Compounds *(1h)* to *(1j)* are prepared in a similar manner.

Received: March 4, 1977 [Z 700 IE]
German version: Angew. Chem. *89*, 420 (1977)

CAS Registry numbers:
(1a), 62302-08-3; *(1b)*, 62302-09-4; *(1c)*, 62302-10-7; *(1d)*, 62302-11-8; *(1e)*, 62337-60-4; *(1f)*, 17280-68-1; *(1g)*, 62302-12-9; *(1h)*, 62302-13-0; *(1i)*, 62302-14-1; *(1j)*, 62302-15-2; *(2)*, 6630-99-5; *(3)*, 62302-16-3; *(4)*, 55434-77-0; benzoyl chloride, 98-88-4; *N*-phenylbenzimidoyl chloride, 4903-36-0; methyl isothiocyanate, 556-61-6; phenyl isothiocyanate, 103-72-0

[1] Reviews: *N. Lozac'h*, Adv. Heterocycl. Chem. *13*, 161 (1971); *E. Klingsberg*, Lect. Heterocycl. Chem. *1*, 19 (1972); *L. K. Hansen, A. Hordvik, L. J. Saethre* in *C. J. M. Stirling*: Organic Sulphur Chemistry. Butterworths, London 1975, pp. 1—17; *R. Gleiter* and *R. Gygax*, Fortschr. Chem. Forsch. *63*, 49 (1976).
[2] Review: *K. A. Jensen, C. Pedersen*, Adv. Heterocycl. Chem. *3*, 263 (1964).
[3] *J-L. Derocque, J. Vialle*, Bull. Soc. Chim. Fr. *1967*, 3079; *J-L. Derocque, M. Perrier, J. Vialle, ibid. 1968*, 2062.

Preparation of a β-Phosphatrimethinecyanine Dye[**]

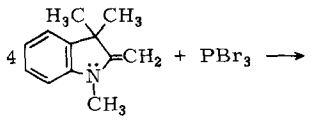
By *Norbert Gamon* and *Christian Reichardt*[*]

We wish to report the first synthesis of a β-phosphatrimethinecyanine dye. Hitherto, only phosphamonomethinecyanines[1,3] but no phosphapolymethinecyanines containing the structural unit —P= were known (cf. [1-4]).

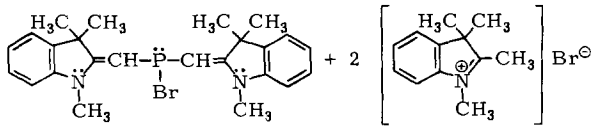
Reaction of the enamine *(1)* with phosphorus tribromide in boiling dichloromethane affords bromobis(1,3,3-trimethylindolin-2-ylidenemethyl)phosphane *(2)* as a yellow powder, which is extremely sensitive to hydrolysis[5,6]. The preparation of *(4)* from *(2)*, whose UV/Vis spectrum in chloroform shows it to be slightly dissociated, can be accomplished by alkylation of the bromide ion with trimethyloxonium tetrafluoroborate. β-Phosphabis(1,3,3-trimethylindolin-2-yl)trimethinium tetrafluoroborate *(4)* forms dark blue, very fine crystals with a

[*] Prof. Dr. C. Reichardt, Dipl.-Chem. N. Gamon
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

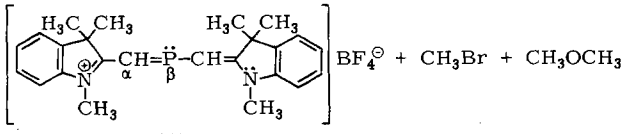
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The results are taken from the Diplomarbeit of *N. Gamon*, Universität Marburg 1977.—Presented at the 6th International Color Symposium in Freudenstadt on September 30, 1976.



(1)



(2) (3)



(4)

metallic sheen, which dissolve in chloroform to give a dark blue solution ($\lambda_{max}=586$ nm)[5, 6].

The ^{1}H-NMR spectrum of *(4)* ($CDCl_3$) contains, *inter alia*, a doublet at 8.01 ppm ($J_{^{31}P,^1H}=15$ Hz) for the two α-methine protons, and the ^{31}P-NMR spectrum ($CDCl_3$) consists of just one downfield signal with a suggestion of triplet structure at +355.8 ppm (H_3PO_4 as external standard)[7]. The ^{13}C-NMR signal ($CDCl_3$) of the α-methine C atoms at +122.0 ppm is split into a doublet by the neighboring P atom ($J_{^{13}C,^{31}P}=39.7$ Hz).

Table 1. Longest wavelength UV/Vis absorption maxima of *(4)* and the analogous CH and N compounds in chloroform.

	$\tilde{\nu}_{max}$ [cm^{-1}]	$\varepsilon\times10^{-5}$ [1/mol·cm]	$\lvert\Delta\tilde{\nu}\rvert$ [cm^{-1}]
β-CH-cyanine	18080	1.39	0
β-P-cyanine *(4)*	17060	≥0.64	1020
β-N-cyanine	16610	1.14	1470

Table 1 compares the UV/Vis absorption maximum of *(4)* with the maxima of two analogous trimethinecyanines. The bathochromic shift of 1020 cm^{-1} (33 nm) relative to β-CH-cyanine can be understood as the resultant of two opposing effects: replacement of the β-CH group by the more electropositive P atom should lead to a hypsochromic shift[8], which, however, is overcompensated by elongation of the polymethine chromophore owing to the greater covalent radius of phosphorus and the consequent bathochromic shift. The absorption maximum of $\lambda_{max}=17210$ cm^{-1} (581 nm) calculated for *(4)*, paying due attention to *both* chromophore length *and* electronegativity, agrees well with the experimental value of 17060 cm^{-1}.

Procedure[6]

(2): *(1)* (13.9 g, 80 mmol) in CH_2Cl_2 (90 ml) is added dropwise at 25 °C to a vigorously stirred solution of PBr_3 (5.4 g, 20 mmol) in CH_2Cl_2 (100 ml) and the mixture is heated under reflux for 2 h. After cooling, precipitated *(3)* is filtered off, the filtrate evaporated to dryness, and the residue extracted on a glass frit with hot diethyl ether (3 × 50 ml). Product *(2)* crystallizing from the extract is dried at 90 °C/10^{-4} torr for 3 h; yield 6.6 g (72%); m.p. 163–166 °C (dec.).

(4): Compound *(2)* (0.84 g, 1.8 mmol) and trimethyloxonium tetrafluoroborate (0.27 g, 1.8 mmol) are stirred vigorously in chloroform (25 ml) at 25 °C for 1 h. The filtered dark blue solution is covered with a layer of petroleum ether (80 ml). After two days precipitated *(4)* is filtered off and dried at 70 °C/10^{-4} torr for 30 min; yield 98%; m.p. 220 °C (decomposition with evolution of gas).

Received: March 15, 1977 [Z 697 IE]
German version: Angew. Chem. *89*, 418 (1977)

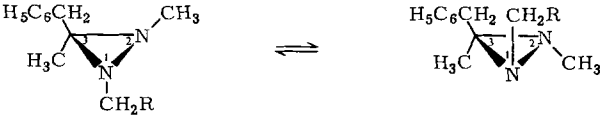
CAS Registry numbers:
(1), 118-12-7; *(2)*, 62302-17-4; *(3)*, 21635-75-6; *(4)*, 62302-19-6; *(4)*, β-CH-cyanine analog, 61575-72-2; *(4)*, β-N-cyanine analog, 62302-20-9; PBr_3, 7789-60-8; trimethyloxonium tetrafluoroborate, 420-37-1

[1] *K. Dimroth, P. Hoffmann*, Angew. Chem. *76*, 433, 512 (1964); Angew. Chem. Int. Ed. Engl. *3*, 384 (1964); Chem. Ber. *99*, 1325 (1966).
[2] *A. J. Ashe III*, J. Am. Chem. Soc. *93*, 3293 (1971).
[3] Review: *K. Dimroth*, Fortschr. Chem. Forsch. *38*, 1 (1973).
[4] *G. Märkl*, Angew. Chem. *78*, 907 (1966); Angew. Chem. Int. Ed. Engl. *5*, 846 (1966).
[5] All new compounds gave correct elemental analyses and spectral data compatible with their structure and composition.
[6] Because of the extreme sensitivity of *(2)* and *(4)* to hydrolysis all experiments were performed in absolutely anhydrous solvents under dry nitrogen.
[7] The ^{31}P chemical shift of *(4)* most closely resembles that of λ^3-phosphazenes: *E. Niecke, R. Kröher*, Angew. Chem. *88*, 758 (1976); Angew. Chem. Int. Ed. Engl. *15*, 692 (1976).
[8] *H. Kuhn*, Angew. Chem. *71*, 93 (1959); we are grateful to Prof. *Kuhn*, Göttingen, for helpful discussions.

Column Chromatography on Triacetylcellulose. Preparative Separation of Enantiomeric Diaziridines[**]

By *Harri Häkli* and *Albrecht Mannschreck*[*]

According to *Hesse* and *Hagel*[2] microcrystalline, swollen triacetylcellulose represents a versatile sorbent for the separation of enantiomers by column chromatography. We have tested triacetylcellulose as a stationary phase for low-pressure chromatography of enantiomeric diaziridines. The separation of invertomers within this class of compounds had been predicted[3a] and was accomplished for diastereoisomers, *e.g.* (1*R*, 2*R*, 3*S*)- and (1*S*, 2*S*, 3*S*)-*(1)*[3b]. However, the enrichment of enantiomers *via* diastereomeric salts with optically active acids has failed as yet[4]. In two cases[5] a slight kinetic enrichment was achieved; in a further case[5b] a purity of 63.5% was attained (after additional separation *via* a derivative of chloral). This procedure presumes a non-substituted nitrogen atom and in principle can only yield one of the enantiomers. Enantiomers like (1*R*,2*R*)- and (1*S*,2*S*)-*(2)* are of interest



(1*R*,2*R*,3*S*)-*(1)* R = C_6H_5 (1*S*,2*S*,3*S*)-*(1)*
(1*R*,2*R*)-*(2)* R = H (1*S*,2*S*)-*(2)*

[*] Prof. Dr. A. Mannschreck, FK H. Häkli [+]
Institut für Chemie der Universität
Universitätsstrasse 31, D-8400 Regensburg 1 (Germany)

[+] Present address: Department of Chemistry, University of Jyväskylä, SF-40100 Jyväskylä 10 (Finland)

[**] Protonenresonanz-Untersuchungen zur Inversion am dreibindigen Stickstoffatom, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. Professor Dr. *G. Hesse*, Erlangen, Germany, informed us about the details of his method of separation. We are grateful to Dr. *G. Becher*, Dipl.-Chem. *T. Burgemeister*, and Dr. *R. Rauchschwalbe*, Regensburg, Germany, for helpful suggestions.—Part 4: [1].

because of their chiroptical properties and since their racemization by consecutive nitrogen inversions[1] must proceed *via* two enantiomeric transition states, whereas the equilibration kinetics[1] for the diastereoisomers of *(1)* are more complicated.

3-Benzyl-1,2,3-trimethyldiaziridine[3b], (±)-*(2)*, in ethanol/H_2O (96:4) was passed through a column of triacetylcellulose[2] (85 g, particle size 0.056 to 0.071 mm, column length 30 cm, internal diameter 2.5 cm, 22 °C). A membrane pump generated a flow of ≈135 ml/h. Figure 1 shows an analytical chromatogram. Preparative separations were performed with 100 mg of (±)-*(2)* which were conducted through two columns in such a way that a total of seven passages took place ("recycling"). This was achieved with a manual gauge[6] which, in addition, separated the first 10% of eluate containing predominantly (+)-*(2)*. Thus, the remaining eluate resulted in practically pure (−)-*(2)* when divided by a fraction collector: 26 mg, $[\alpha]_{436}^{22} = -141 \pm 4°$ (0.05 g/100 ml CCl_4), enantiomeric purity[7] $P = 97 \pm 3$ %. Together the seperated frontier eluates contained 46 mg of (+)-*(2)*, $[\alpha]_{436}^{22} = +85 \pm 5°$ (0.35 g/100 ml CCl_4), $P = 59 \pm 3$ %. The ^{1}H-NMR spectra were in agreement with those of (±)-*(2)*[1,3b] although they showed ≈2% (by weight) of *n*-hexane originating from the eluent. The intensities of ^{1}H-NMR signals in the presence of an optically active auxiliary compound served for the measurement of P[1,4,8]. (±)-*(2)* in [D_8]-toluene at 34 °C exhibits *two* C—CH_3 singlets at δ = 2.87 and 2.93 (line widths 1.5 Hz) in the presence of 0.27 equivalents of (+)-tris[3-heptafluorobutyryl)-D-camphorato]europium(III). In the samples with enriched (+)-*(2)* the signal intensity at 2.87 prevailed; the (−)-*(2)* fractions showed practically only the signal at 2.93. The P values were determined by repeated cutting out of diagrams, dividing into the components, and weighing of the pieces. The CD spectrum of (−)-*(2)* in *n*-hexane at 25 °C, calculated for $P = 100$ %, exhibited maxima at 268 nm ($\Delta\varepsilon = -0.12$ l cm^{-1} mol^{-1}), 262 (−0.12), 256 (−0.08), 219 (≈ +1.6), and 214 (≈ +1.7).

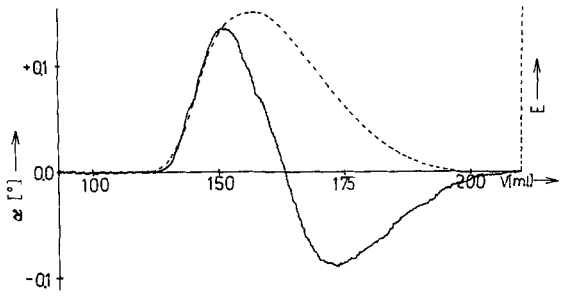


Fig. 1. Analytical chromatogram of 50 mg of (±)-*(2)* in ethanol/H_2O (96:4) after passage through a triacetylcellulose column (cf. text): α: Rotation angle (——) at 365 nm, measured by flow through a polarimeter. *E*: Extinction (– – – – –) at 254 nm, measured by flow through a photometer. *V*: Volume of the eluate (injection at $V = 0$).

The thermal racemization of (+)-*(2)*, obtained by chromatography, in toluene at 89.9 °C was monitored by polarimetry at 436 nm. This process was of first order with a half-life of 56.9 min and $\Delta G^{\neq} = 27.57 \pm 0.02$ kcal/mol for a *trans*→*cis* nitrogen inversion[1,3b]. This is in satisfactory agreement with the value 27.2 ± 0.1 kcal/mol[1] (C_2Cl_4, 89.9 °C) for an inversion in the diastereoisomers of *(1)* mentioned above.

Received: March 17, 1977 [Z 699 IE]
German version: Angew. Chem. 89, 419 (1977)

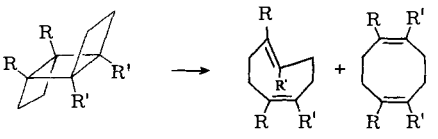
CAS Registry numbers:
(±)-*(2)*, 23191-19-7; (+)-*(2)*, 62413-55-2; (−)-*(2)*, 62413-56-3; triacetylcellulose, 9012-09-3; (+)-tris[3-(heptafluorobutyryl)-D-camphorato]europium(III), 34788-82-4

[1] *A. Mannschreck, W. Seitz* in IUPAC: XXIIrd Int. Congr. Pure Appl. Chem., Vol. 2. Butterworths, London 1971, p. 309.
[2] *G. Hesse, R. Hagel*, Justus Liebigs Ann. Chem. *1976*, 996, and earlier papers.
[3] a) *A. Mannschreck, R. Radeglia, E. Gründemann, R. Ohme*, Chem. Ber. *100*, 1778 (1967); b) we refer to *these* two stereoisomers because of the formulae given; in fact, however, the *racemates* of the two diastereoisomers were separated: *A. Mannschreck, W. Seitz*, Angew. Chem. *81*, 224 (1969); Angew. Chem. Int. Ed. Engl. *8*, 212 (1969).
[4] *H. Häkli, A. Mannschreck*, unpublished results.
[5] a) *R. G. Kostyanovskii, A. E. Polyakov, V. I. Markov*, Bull. Acad. Sci. USSR, Div. Chem. Sci. *1975*, 191; Chem. Abstr. *82*, 170758 (1975); b) *R. G. Kostyanovskii, A. E. Polyakov, G. V. Shustov*, Tetrahedron Lett. *1976*, 2059.
[6] Dreh-Probenaufgabe-Ventil, Latek GmbH, Heidelberg, Germany.
[7] *M. Raban, K. Mislow*, Top. Stereochem. *2*, 199 (1967).
[8] *A. Mannschreck*, Nachr. Chem. Tech. *23*, 295 (1975).

cis,trans-1,5-Cyclooctadienes[**]

By *Hans-Dieter Martin, Mirko Hekman, Günther Rist, Hans-peter Sauter*, and *Daniel Bellus*[*]

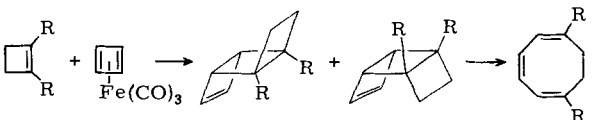
In some cases, eight-membered rings having *trans*-configurated double bonds differ considerably in their ground state energy[1], their reactivity[2], and their spectroscopic properties[3] from the *cis*-configurated stereoisomers. This confers interest upon methods for the preparation of such strained cycloolefins[4]. We here report thermal valence isomerizations permitting productive syntheses of *cis,trans*-1,5-cyclooctadienes *(2)*, which are either isolated or, if isolation is precluded by excessive reactivity, can be trapped by dienes.



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

(a), R = $COOCH_3$, R' = H;
(b), R = CN, R' = H;
(c), R = R' = $COOCH_3$

The inversion of a C atom known to occur on thermal cleavage of bicyclo[2.2.0]hexanes to form 1,5-hexadienes is also applicable to tricyclo[4.2.0.0^{2,5}]octanes[5,6]. The valence isomerization *(1)* → *(2)* can therefore be regarded as providing a synthetic entry to strained *trans*-cycloalkanes.



(4) *(5)* *(6)* *(7)* *(8)*

(a), R = $COOCH_3$
(b), R = CN

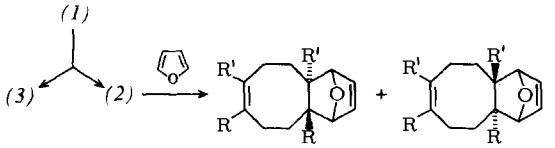
[*] Prof. Dr. H.-D. Martin, Dipl.-Ing. M. Hekman
Institut für organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)
Dr. G. Rist, Dr. H. Sauter, Dr. D. Bellus
Zentrale Forschung, Ciba-Geigy AG
CH-4002 Basel (Switzerland)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG.—Part 23 of the series "Small Rings".—Part 22: *H.-D. Martin, H.-J. Schiwek, J. Spanget-Larsen, R. Gleiter*, Tetrahedron Lett., in press.—Also Part 7 of the series "Synthesis and Reactivity of Four-Membered Ring Compounds".—Part 6: *D. Bellus*, Helv. Chim. Acta *58*, 2509 (1975).

Reaction of dimethyl cyclobutenedicarboxylate *(4a)* with the cyclobutadienecarbonyliron complex *(5)* at 0°C furnishes the two stereoisomers *(6a)* (m.p. 47—48°C) and *(7a)* in the ratio of 10:1.

Both isomers undergo thermal cleavage to give the cyclooctatriene derivative *(8)*[7] (m.p. 68—69°C), *(7a)* somewhat faster than *(6a)*. Hydrogenation of *(6a)* (Pd/C, CH_3OH) affords *(1a)* (m.p. 42—44°C). Heating of *(1a)* to 75°C in inert solvents gives *(3a)* as the only isolable monomer (m.p. 77—78°C). However, if a mixture of $CHCl_3$ and furan is used as reaction medium, not only *(3a)* but also an adduct *(9a)* or *(10a)* (m.p. 78—80°C) of *(2a)* to furan is obtained on chromatographic separation. Compound *(3a)* does not undergo cycloaddition under these conditions.

The dinitrile *(4b)* likewise adds to the cyclobutadiene complex *(5)* to form the relatively labile tricyclics *(6b)* and *(7b)* in the ratio of 4:1. Detectable isomerization to *(8b)* (m.p. 140—142°C) occurs already at 25°C. Hydrogenation of *(6b)* (Pd/C, CH_3OH, 0°C) leads to *(1b)*, which on account of the high reactivity and lability of *(2b)* is reacted directly with furan (50°C, 1 h). Unlike *(1a)*, *(1b)* yields *(3b)* (m.p. 125—126°C) and, *via* the intermediate *(2b)*, a pair of stereoisomers *(9b)* and *(10b)* (m.p. 166—168°C and 154—156°C, respectively).



(a), R = $COOCH_3$, R' = H; *(9)* *(10)*
(b), R = CN, R' = H

The instability of the disubstituted *cis,trans*-cyclooctadienes *(2a)* and *(2b)* results from the joint action of ring or torsional strain and the electron-withdrawing substituents, both of which increase the molecules' reactivity. However, it may be expected that, as the number and size of the substituents increase, the reactivity in cycloadditions will decrease and the configurative stability increase. This is indeed observed in the comparatively stable tetracarboxylic ester *(2c)*.

At 105°C *(1c)*[7] isomerizes to a 2:1 mixture of *(2c)* and *(3c)* which can be separated by chromatography over silica gel. The ^{13}C-NMR spectrum of *(2c)* recorded between −20°C and +90°C displays a clear temperature dependence owing to conformational mobility, which however is frozen at −20°C [^{13}C-NMR of *(2c)* (TMS, CD_3NO_2): (+90°C) 31.2, 36.1 (CH_2), 52.5, 52.6 (OCH_3), 140.4, 149.5 (C=C), 169.7, 170.2 (C=O); (−20°C) 25.3, 35.8, 35.9, 36.9 (CH_2), 52.9, 53.0, 53.1, 53.3 (OCH_3), 134.5, 145.5, 149.1, 150.8 (C=C), 168.0, 169.7, 170.1, 172.7 (C=O)].

Compound *(2c)* fails to give a Diels-Alder adduct on heating to 105°C in furan, presumably because of excessive steric hindrance. As in tetracyclo[4.4.0.0^{2,5}.0^{7,10}]decanes[8], the rate-determining step in the thermolysis of *(1)* and *(6)* is probably cleavage of the internal substituted bond of the four-membered ring. This is evidenced by the kinetic parameters compared with those of the reference compound dimethyl bicyclo[2.2.0]-hexane-1,4-dicarboxylate *(11)* [E_a (kcal/mol), log A, solvent: *(1a)* 25.5, 12.6, $CDCl_3$; *(1c)*, 26.5, 12.2, C_6D_5Cl; *(6a)*, 24.1, 11.5, CCl_4; *(11)*, 25.5, 12.1, C_4Cl_6; 24.6, 11.7, $C_6D_5CD_3$; 24.6, 11.7, $C_6D_5NO_2$].

Received: March 21, 1977 [Z 701 IE]
German version: Angew. Chem. 89, 420 (1977)

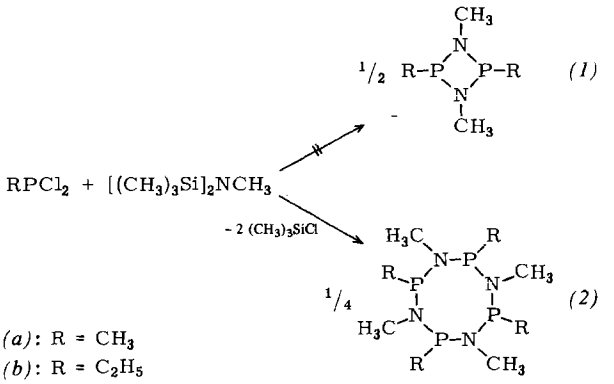
CAS Registry numbers:
(1a), 62301-96-6; *(1b)*, 62301-97-7; *(1c)*, 62357-28-2; *(2a)*, 62301-98-8; *(2b)*, 62301-99-9; *(2c)*, 62302-00-5; *(3a)*, 62301-98-8; *(3b)*, 62302-01-6; *(3c)*, 34271-69-7; *(4a)*, 1128-10-5; *(4b)*, 3716-97-0; *(5)*, 12078-17-0; *(6a)*, 62302-02-7; *(6b)*, 62302-03-8; *(7a)*, 62357-29-3; *(7b)*, 62357-30-6; *(8a)*, 62302-04-9; *(8b)*, 62302-05-0; *(9a)*, 62302-06-1; *(9b)*, 62302-07-2; *(10a)*, 62357-31-7; *(10b)*, 62357-32-8; furan, 110-00-9

[1] *R. B. Turner, W. R. Meador*, J. Am. Chem. Soc. *79*, 4133 (1957).
[2] *K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kühlhorn, J. Schneider*, Justus Liebigs Ann. Chem. *589*, 122 (1954); *K. T. Burgoine, S. G. Davies, M. J. Peagram, G. H. Whitham*, J. Chem. Soc. Perkin I, *1974*, 2629.
[3] *C. Batich, O. Ermer, E. Heilbronner, J. R. Wisemann*, Angew. Chem. *85*, 302 (1973); Angew. Chem. Int. Ed. Engl. *12*, 302 (1973); *A. C. Cope, C. F. Howell, J. Bowers, R. C. Lord, G. M. Whitesides*, J. Am. Chem. Soc. *89*, 4024 (1967).
[4] See *e.g., M. Jones, P. Temple, E. J. Thomas, G. Whitham*, J. Chem. Soc. Perkin I, *1974*, 433.
[5] *D. Belluš, H.-C. Mez, G. Rihs, H. Sauter*, J. Am. Chem. Soc. *96*, 5007 (1974).
[6] *H.-D. Martin, E. Eisenmann*, Tetrahedron Lett. *1975*, 661.
[7] *E. Vogel, O. Roos, K. H. Disch*, Justus Liebigs Ann. Chem. *653*, 55 (1962).
[8] *H.-D. Martin, M. Hekman*, Angew. Chem. *88*, 447 (1976); Angew. Chem. Int. Ed. Engl. *15*, 431 (1976).

$(RPNCH_3)_4$, Cyclotetra(λ^3-phosphazanes) Synthesis and Crystal Structure Analysis

By *Werner Zeiss, Wolfgang Schwarz*, and *Heinz Hess*[*]

While attempting to prepare the hitherto unknown permethylated 1,3,2λ^3,4λ^3-diazadiphosphetidine *(1a)* from methyldichlorophosphane and heptamethyldisilazane we obtained a compound which had the correct composition but twice the desired molecular mass *(2a)* in good yield:



(a): R = CH_3
(b): R = C_2H_5

The reaction with ethyldichlorophosphane took place in precisely the same way to give *(2b)*.

In the $^{31}P\{^1H\}$-NMR spectrum, *(2a)* shows a signal at −91.7 ppm, and *(2b)* one at −100 ppm[1], which both lie in the usual range for alkyldiaminophosphanes[2]. In contrast, 1,3,2λ^3,4λ^3-diazadiphosphetidines having methyl groups attached to the phosphorus and *tert*-butyl groups attached to the nitrogen, or *vice versa*, give ^{31}P shifts of −171.4 ppm or −201.7 and −281.7 ppm[3], respectively.—The ^1H-NMR spectra[1] of compounds *(2)* are complex owing to virtual H—P coupling. Compound *(2a)* exhibits approximately two quintets in the ratio 1:1; while deviation from the signal shape and intensity distribution of a quintet is only slight for the NCH_3 protons (δ = 2.95), *i.e. ca.* 1:3:4:3:1, it leads to a broad accumulation of signals in the case of the PCH_3 protons (δ = 1.41). The spectrum of *(2b)* also shows a "quintet"

[*] Dr. W. Zeiss
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)
Dr. W. Schwarz, Prof. Dr. H. Hess
Institut für Anorganische Chemie der Universität
Pfaffenwaldring 55, D-7000 Stuttgart 80 (Germany)

($\delta = 2.87$) for the NCH_3 protons and two complex groups of signals for the PC_2H_5 protons in the ratio 3:3:2. $\{^{31}P\}$-decoupling[4] gives two singlets for *(2a)*, and one singlet for the the NCH_3 protons, a quartet for the PCH_2 protons ($\delta = 1.78$), and a triplet for the CH_3 protons ($\delta = 0.97$) in the case of *(2b)*. No change is observed in the ^1H-NMR spectrum of *(2a)* in 1,2-dichlorobenzene up to 170°C.

In the mass spectra (70 eV, 25°C) a molecular peak is observed only for *(2a)*, but an intense $(M-R)^+$ peak is seen in both cases. Further degradation leads *via* loss of $(RPNCH_3)$ units to the $(PNCH_3)^+$ ion (base peak).

On the basis of these findings the eight-membered ring structure which is unusual in cyclo(λ^3-phosphazanes) appears likely for *(2a)* and *(2b)*. It was proved by X-ray structure analysis of *(2a)*. The compound crystallizes in the tetragonal space group P4nc with $a = b = 8.775(2)$, $c = 9.920(2)$ Å; $Z = 2$. The structure was solved from 598 independent diffractometer data (512 observed) by Patterson and Fourier syntheses and refined to $R = 0.026$ (for observed reflections).

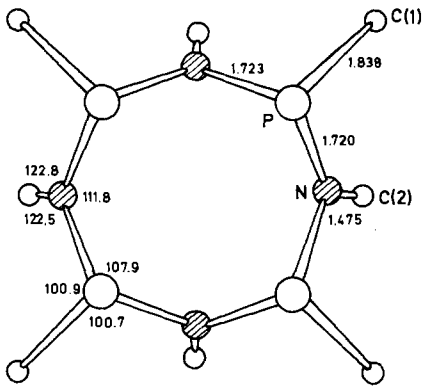


Fig. 1. Molecular structure of octamethylcyclotetra(λ^3-phosphazane) *(2a)*; bond lengths [Å] and bond angles [°].

The molecule has 4 mm (C_{4v}) symmetry to within the standard deviation; the eight-membered ring thus has the ideal crown configuration. The *P*-methyl group occupies the equatorial position, and the phosphorus lone pair the axial position. In contrast, the nitrogen lone pair is stereochemically almost inactive; the nitrogen has almost planar coordination. The structure is analogous to that of $(SNCH_3)_4$[5] except for the missing *S*-methyl groups. The P—N bond length is in good agreement with values determined for other cyclo(λ^3-phosphazanes)[6].

The eight-membered ring structure has therefore been confirmed for the first time in the cyclophosphazane *(2a)*, and it is the first P—N eight-membered ring to have the ideal crown shape. Only a strongly distorted crown has hitherto been found in *cis*-$[Cl(C_6H_5)PN]_4$[7]. All the other cyclotetra(phosphazenes) assume the boat, chair, or saddle form.

Formation of *(2a)* was recently reported during the reaction of $CH_3N(PCH_3Cl)_2$ with $(CH_3NH)_2Si(CH_3)_2$[8]; the melting point (75°C) and extreme sensitivity to hydrolysis of this product, which was isolated in only 2% yield, differ from the properties we have observed for *(2a)*.

Procedure

$RPCl_2$ (0.06 mol) and anhydrous acetonitrile (10 ml) are added to heptamethyldisilazane (0.06 mol) with stirring, water-cooling, and passage of a countercurrent of N_2. After removal of the water-bath an exothermic reaction ensues; when it has subsided the reaction mixture is heated under reflux for 15 min. At room temperature or −30°C *(2a)* or *(2b)* slowly precipitates as analytically pure colorless shiny crystals which are dried at 0.1 torr and room temperature. Yield *ca.* 50%. Relative molecular mass (osmometrically in $CHCl_3$): *(2a)* 273, *(2b)* 342. Neither compound has a sharp melting point; they both soften at *ca.* 120°C and 115°C, respectively, and finally melt at 180—185°C *(2c)* and 150—155°C *(2b)*.

Received: March 7, 1977;
supplemented: March 21, 1977 [Z 703 IE]
German version: Angew. Chem. *89*, 423 (1977)

CAS Registry numbers:
(2a), 58962-63-3; *(2b)*, 62302-21-0; heptamethyldisilazane, 920-68-3; CH_3PCl_2, 676-83-5: $C_2H_5PCl_2$, 1498-40-4

[1] All NMR spectra recorded in $CDCl_3$ as solvent *vs.* 85% H_3PO_4 (external) or TMS (internal): ^{31}P upfield shifts and ^1H downfield shifts given as positive.
[2] *W. A. Frank* in *G. M. Kosolapoff, L. Maier:* Organic Phosphorus Compounds, Vol. 4. Wiley, New York 1972, p. 315.
[3] *O. J. Scherer, G. Schnabl*, Chem. Ber. *109*, 2996 (1976); Angew. Chem. *88*, 845 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976).
[4] Measurements by: *H. Huber*, Institut für Organische Chemie der Universität München.
[5] *A. L. Macdonald, J. Trotter*, Can. J. Chem. *51*, 2504 (1973).
[6] *W. Schwarz, H. Hess, W. Zeiss*, unpublished $[(CH_3OPNC_6H_5)_2]$; *E. Niecke, W. Flick, S. Pohl*, Angew. Chem. *88*, 305 (1976); Angew. Chem. Int. Ed. Engl. *15*, 309 (1976); *K. W. Muir*, J. Chem. Soc. Dalton Trans. *1975*, 259.
[7] *G. J. Bullen, P. A. Tucker*, J. Chem. Soc. Dalton Trans. *1972*, 1651.
[8] *U. Wannagat, H. Autzen*, Z. Anorg. Allg. Chem. *420*, 119 (1976).

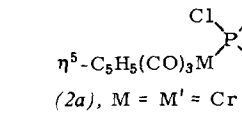
Synthesis of Dinuclear Complexes Containing PCl_2 and PF_2 Bridges[1]

By *Wolfgang Malisch* and *Peter Panster*[*]

We recently synthesized transition metal-dichlorophosphanes of *(1)* and deduced a high charge density at the trivalent phosphorus from the ready oxidation of the species[1]. A further consequence of this electronic situation (transition metal substituent as donor) has now been observed in the extreme ease of addition to 6A metal-pentacarbonyl units. Reaction with tetrahydrofuran-solvated species of this kind at room temperature yields what we believe to be the first homo- or hetero-dinuclear complexes containing chlorine-substituted phosphorus bridges.

$$\eta^5\text{-}C_5H_5(CO)_3M\text{–}PCl_2 + THF \cdot M'(CO)_5 \longrightarrow$$

(1a), M = Cr
(1b), M = W

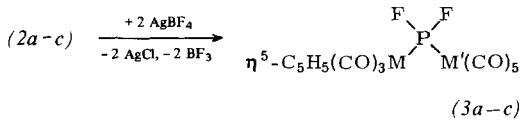


$\eta^5\text{-}C_5H_5(CO)_3M$ + THF

(2a), M = M' = Cr
(2b), M = W, M' = Cr
(2c), M = M' = W

[*] Priv.-Doz. Dr. W. Malisch, Dr. P. Panster
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

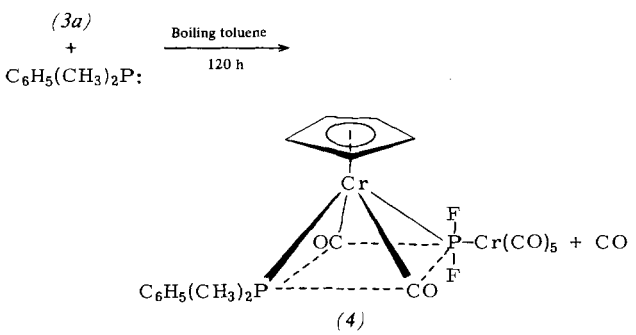
The colored compounds *(2a—c)* can be stored indefinitely in solution under N_2, are stable for a brief period when exposed as solids to the air, and decompose with evolution of $M(CO)_6$ only upon being heated to their melting point. Thus on coordinative participation of their P lone pair, the functional metallophosphanes experience a considerable inductive, and possibly also mesomeric ($d_M \rightarrow d_P$)π strengthening of the central bond system[2], with the result that the elimination of metal halide characteristic for the compounds in the free state is completely suppressed[1]. A further effect, the enhanced electrophilic character of the 5B element atom, follows from the proclivity of the fixed phosphanes to replacement in nucleophilic substitution reactions. It satisfies the requirements for controlled chlorine/fluorine replacement which always succeeds with $AgBF_4$ irrespective of the nature of the metallic center[3].



(3a—c)

Thus a clear-cut and generalizable entry is now available to PF_2-bridged complexes formerly known only in isolated cases[4].

The readily crystallizing dinuclear compounds *(3a—c)* differ from their chlorine homologs in their lower solubility. Their $Cp(CO)_3M—PF_2$ ligand can be liberated neither by thermal treatment[5] nor by the action of strongly basic phosphanes, which attack the $Cp(CO)_3M$ unit with exclusive *trans* substitution.



(4)

The constitution of *(4)* and the other bridged complexes follows from spectroscopic data (cf. Table 1). In the case of *(3c)* in particular, ^{19}F- and ^{31}P-NMR analysis of the heterospin system $^{183}W^1—^{31}P^{19}F_2—^{183}W^2$ permits characterization of the entire central bond system, all the theoretically expected couplings being detected. Without exception, positive coordination shifts $\Delta(\delta P_{complex} - \delta P_{ligand}$[1]) are calculated for the novel η^5-$C_5H_5(CO)_3M—PCl_2$ ligand system from the ^{31}P signals, the values obtained being 33 ppm (Cr), and 75 and 163 ppm, respectively, (W); owing to the *abnormal* downfield shift of *(3a)* and *(4)*, negative values of Δδ will probably have to be assigned to the still unknown fluorine analogs in the free state[6]. Cl/F exchange has only a slight effect on the frequencies of the $M(CO)_5$ stretching vibrations, suggesting a practically identical σ-donor/π-acceptor behavior of the two metallodihalophosphanes[7]. Like the magnitude of $^1J[^{31}P^{183}W(CO)_5]$[8], the frequencies also indicate strongly electropositive character of the transition metal grouping, which can also be detected by chemical means.

Table 1. Characteristic data of μ-phosphido complexes *(2)*, *(3)*, and *(4)* [a].

	M.p. [°C] [b] Color	δC_5H_5 (d) $^3J(^1H^{31}P)$	NMR [c] $\delta^{31}P$ $^1J(^{31}P^{19}F)$ $^1J(^{31}P^{183}W)$	$\delta^{19}F$ $^2J(^{19}F^{183}W)$
(2a)	147—149	4.13	388.0	
	golden yellow	1.1		
(2b)	>163	4.68	287.2	
	yellow	0.5	108	
(2c) [d]	176—178	4.65	198.6	
	ocher yellow	<0.5	J_1: 111; J_2: 264	
(3a)	123—124	4.05	461.4 (t)	8.8 (d)
	green	0.7	1121	
(3b)	138—139	4.51	403.3 (t)	15.9 (d)
	golden yellow	0.5	1069	14.0
			105	
(3c) [d]	143—144	4.58	342.7 (t)	21.2 (d)
	yellow	0.6	1050	
			J_1: 110; J_2: 296	J_1: 14.8; J_2: 13.2
(4) [e]	156—158	4.22 (m)	484.4 (dt)	11.4 (dd)
	yellow-green	<0.5	1090	

[a] Analytical data in agreement with given formulae.
[b] Sealed capillary, Cu block.
[c] Chemical shifts [ppm] downfield (^1H, ^{31}P) and upfield (^{19}F) rs. TMS int. H_3PO_4 ext., and $CFCl_3$ ext.; coupling constants in Hz. Solvent: C_6D_6 (^1H), THF (^{19}F, ^{31}P).
[d] η-$C_5H_5(CO)_3W^1—PX_2—W^2(CO)_5$.
[e] NMR parameters for $C_6H_5(CH_3)_2P$ in *(4)*: δ^1H: C_6H_5 −7.07 (m), CH_3 −1.27 (d), $^2J(^1H^{31}P)$ 9 Hz; $\delta^{31}P$: −50.7, $^3J(^{31}P^{19}F)$ 6 Hz, $^2J(^{31}P^{31}P)$ 42 Hz.

Procedure

(2c): A solution of $C_5H_5(CO)_3WPCl_2$[1] (1.13 g, 2.60 mmol) in THF (20 ml) is added to the THF·$W(CO)_5$ complex generated photochemically from $W(CO)_6$ (0.93 g, 2.64 mmol) in THF (70 ml). After stirring for 2 d the filtrate of the reaction mixture is evaporated *in vacuo*, unreacted $W(CO)_6$ is sublimed off, and the dark residue extracted with hot cyclohexane. Compound *(2c)* (0.94 g, 48 %) crystallizes on cooling.

(3c): $AgBF_4$ (0.83 g, 4.26 mmol) is added portionwise to a stirred solution of *(2c)* (1.58 g, 2.08 mmol) in benzene (60 ml) over 1 h at 50 °C. After completion of BF_3 and AgCl formation the mixture is filtered hot, the solvent distilled off from the filtrate *in vacuo*, and the crude product recrystallized from cyclohexane. Yield 0.91 g (60.2 %) of *(3c)*.

Received: March 21, 1977 [Z 702 IE]
German version: Angew. Chem. *89*, 421 (1977)

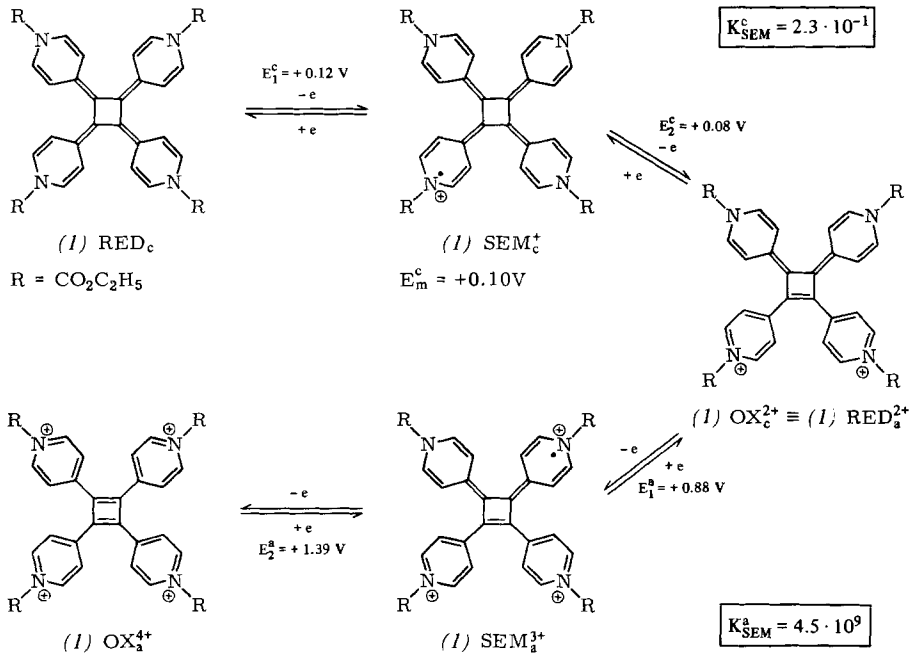
CAS Registry numbers:
(1a), 60803-47-6; *(1b)*, 60803-49-8; *(2a)*, 62319-80-6; *(2b)*, 62319-79-3; *(2c)*, 62319-78-2; *(3a)*, 62319-77-1; *(3b)*, 62319-76-0; *(3c)*, 62319-75-9; *(4)*, 62319-74-8; THF·$Cr(CO)_5$, 105038-41-2; THF·$W(CO)_5$, 36477-75-5; $W(CO)_6$, 14040-11-0

[1] Transition metal-substituted 5B element systems, Part 17.—This work was supported by the Deutsche Forschungsgemeinschaft.—Part 16: *W. Malisch, R. Alsmann*, Angew. Chem. *88*, 809 (1976); Angew. Chem. Int. Ed. Engl. *15*, 769 (1976).
[2] *M. J. Barrow, G. A. Sim*, J. Chem. Soc. Dalton Trans. *1975*, 291.
[3] $AgBF_4$ only reacts with the free phosphanes at elevated temperatures. Only decomposition products can then be isolated.
[4] *C. S. Kraihanzel*, J. Organomet. Chem. *73*, 137 (1974).
[5] The mass-spectrometric degradation behavior of *(3a—c)* likewise fails to provide any evidence for the existence of these phosphanes.
[6] The same situation is encountered in the metal-free ligands PCl_3 and PF_3, cf. *E. Moser, E. O. Fischer, W. Bathelt, W. Gretner, L. Knauss, E. Louis*, J. Organomet. Chem. *19*, 377 (1969).
[7] νCO [cm^{-1}] measured in C_6H_{12}: *(2a)* 2074, 2037*, 1987*, 1970*, 1956, 1949, 1935; *(3a)* 2074, 2033*, 2000, 1981*, 1974*, 1954, 1940 [*absorptions of $Cp(CO)_3M—PX_2$ ligands].
[8] *E. O. Fischer, L. Knauss, R. L. Keiter, J. G. Verkade*, J. Organomet. Chem. *37*, C8 (1972).

Reversible Transition between a [4]Radialene and a Cyclobutadiene by Electron Transfer[**]

By *Michael Horner* and *Siegfried Hünig*[*]

There are only few π-systems that can exist in five oxidation states which are connected by four reversible one-electron transfers[1]. In the present communication we describe the first example of such a system, in which a [4]radialene and a cyclobutadiene occur[2]. The reversible electron transfer is made possible by four *N*-substituted pyridyl moieties. The deep-red, sparingly soluble radialene *(1)* RED_c[3], which shows a typical radialene spectrum[4], serves as educt.



Voltammetric oxidation in methylene chloride/nitromethane[5] with DC, AC, and cyclic voltammetry affords similar potentials of which the CV data in particular fulfil the criteria for reversibility[6]. At +0.10 V (E_M^c) two electrons are transferred, as indicated by the doubly large current function $i_p^a/v^{1/2}$[7], compared to E_1^a and E_2^a. From the difference in the peak potentials $i_p^a - i_p^c = 30$ to 40 mV it follows that a two-stage redox system

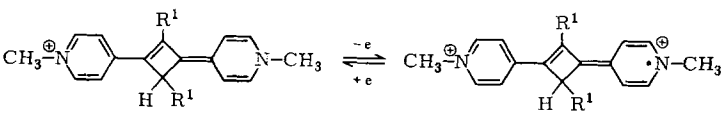
$$(1)\,RED_c + (1)\,OX_c^{2+} \rightleftharpoons 2(1)\,SEM_c^+$$

is present with $K_{SEM}^c = 2.3 \times 10^{-1}$. Thus 19% of the radical cation *(1)* SEM_c^+ is present in the equilibrium. This small proportion of *(1)* SEM_c^+ is obviously determined by the greater thermodynamic stability of *(1)* OX_c^{2+}, which functions as *(1)* RED_a^{2+} for the following oxidation step. Despite the high sensitivity of the R = $CO_2C_2H_5$ groups on pyridinium nitrogen towards solvolysis, treatment of *(1)* RED_c in chloroform/acetonitrile with excess silver fluoroborate as oxidizing agent affords deep-blue solutions of *(1)* $OX_c^{2+} \equiv$ *(1)* RED_a^{2+}, which show a spectrum typical for cyanins with λ_{max} = 676 nm ($\log\varepsilon > 5.03$), and gradually decompose. The chromophore consists of two crossed pyridinetrimethinecyanins. In the equilibrium

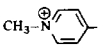
$$(1)\,SEM_c^+ + (1)\,SEM_a^{3+} \rightleftharpoons 2(1)\,OX_c^{2+}/RED_a^{2+}$$

> 99.9% of the latter is present because $E_1^a - E_2^c = 0.80$ V.

The following oxidation steps are sharply separated from one another. The radical cation *(1)* SEM_a^{3+} is reached with $E_1^a = +0.88$ V. For *(1)* SEM_c^+, *(1)* OX_c^{2+}/RED_a^{2+}, and *(1)* SEM_a^{3+} the selected resonance formulae reveal that the four pyridine moieties are equivalent. A bond fixation in the sense of polyolefins and heteropolyolefins, which according to *Dewar*[8] contain practically no delocalization energy, occurs only in the case of the radialene *(1)* RED_c and the cyclobutadiene *(1)* OX_a^{4+}. For radialenes absence of delocalization has been demonstrated[9]; for cyclobutadiene a negative delocalization energy is expected because of its antiaromaticity[10]. This energy difference must be provided in the transition from *(1)* SEM_a^{3+} to *(1)* OX_a^{4+} (lifetime > 20 s). From this it follows that K_{SEM}^a is 4.5×10^9 [> 99.9% *(1)* SEM_a^{3+}]. Calculations using the potential difference $E_2^a - E_1^a = 0.51$ V and neglecting electrostatic effects yield an energy contribution of 11.8 kcal/mol as the highest value for the formation of the cyclobutadiene structure in *(1)* OX_a^{4+}. *Breslow*[11] obtained a value between 12 and 16 kcal/mol using, in part irreversible, potentials of asymmetrically substituted cyclobutadiene precursors.



(2a) RED^+ $E_a = 0.49$V R^1 =  *(2a)* SEM^{2+}

(2b) RED^{3+} $E_b = 0.69$V R^1 =  *(2b)* SEM^{4+}

That electrostatic effects play only a subordinate role is shown by a comparison of the potentials E_2^c and E_2^a of *(1)*

[*] Dr. M. Horner, Prof. Dr. S. Hünig [+]
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[+] Author to whom correspondence should be addressed.

[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Gesellschaft für Chemisches Apparatewesen (DECHEMA).

with the potentials E_a and E_b of equally charged cyanines *(2a)* and *(2b)*: the oxidation of the monocation *(1)*SEM_c^+ takes place at a potential about 0.41 V more negative than that of *(2a)*RED^+, that is "easier". In contrast the trication *(1)*SEM_a^{3+} is oxidized at a potential about 0.70 V more positive that *(2b)*RED^{3+}, that is essentially "more difficultly".

The precursor for the system *(1)* is *r*-1, *c*-2, *t*-3, *t*-4-tetra-4-pyridylcyclobutane *(3)*[12], which is formed in 70% yield by photodimerization of 4,4'-dipyridylethylene[13] in aqueous methanol, the solvent differing from that used in the literature procedure[14]. Quaternization of *(3)* with ethyl chloroformate and simultaneous deprotonation furnishes *(1)*RED_c in 55% yield[3].

Received: March 28, 1977 [Z 707 IE]
German version: Angew. Chem. *89*, 424 (1977)

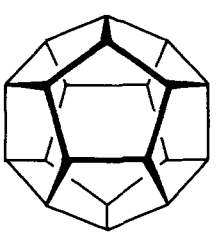
CAS Registry numbers:
(1)RED_c, 62415-93-4; *(1)*SEM_c^+, 62415-86-5; *(1)*$RED_a^{2+} \equiv$ *(1)*OX_c^{2+}, 62415-94-5; *(1)*SEM_a^{3+}, 62415-87-6; *(1)*OX_a^{4+}, 62415-95-6; *(2a)*RED^+, 62415-96-7; *(2a)*SEM^{2+}, 62415-88-7; *(2b)*RED^{3+}, 62415-97-8; *(2b)*SEM^{4+}, 62415-89-8; tetra-4-pyridylcyclobutane, 62415-98-9; 4,4'-dipyridylethylene, 1135-32-6; ethyl chloroformate, 541-41-3

[1] *S. Hünig, M. Horner, P. Schilling*, Angew. Chem. *87*, 548 (1975); Angew. Chem. Int. Ed. Engl. *14*, 556 (1975).
[2] From the dissertation by *M. Horner*, Universität Würzburg 1977.
[3] Elemental analysis and IR and NMR spectra of the isolated substances are fully consistent with the quoted structures.
[4] UV ($CHCl_3$) λ_{max} (log ε): 557 (4.35), 515 (4.27), 478 (4.57), 413 (sh), 385 (4.74), 374 (4.75), 320 (4.39), 309 (sh). Other [4]radialenes: *G. W. Griffin, L. I. Peterson*, J. Am. Chem. Soc. *85*, 2268 (1963); *B. Heinrich, A. Roedig*, Angew. Chem. *80*, 367 (1968); Angew. Chem. Int. Ed. Engl. *7*, 375 (1968); *S. K. Koster, R. West*, Chem. Commun. *1971*, 1380; J. Org. Chem. *40*, 2300 (1975).
[5] Ag/AgCl sat. KCl in acetonitrile as reference electrode, $N(C_4H_9)_4BF_4$ as supporting electrolyte, CV: 20 mV/s.
[6] *E. R. Brown, R. F. Large:* Cyclic Voltammetry, AC-Polarography and Related Techniques, in *A. Weissberger:* Physical Methods of Chemistry. Interscience, New York 1971. Vol. 1, Part 11a, p. 423.
[7] *D. S. Polcyn, I. Shain*, Anal. Chem. *38*, 370 (1966).
[8] *M. J. S. Dewar, C. Dellano*, J. Am. Chem. Soc. *91*, 789 (1969); *M. J. S. Dewar, A. J. Harget, N. Trinajstic, ibid. 91*, 6321 (1969).
[9] *S. K. Koster, R. West*, J. Org. Chem. *40*, 2300 (1975).
[10] *R. Breslow*, Pure Appl. Chem. *28*, 111 (1971).
[11] *R. Breslow, D. R. Murayama, S. I. Murahashi, R. Grubbs*, J. Am. Chem. Soc. *95*, 6688 (1973).
[12] *G. Kassebeer*, Dissertation, Universität Braunschweig 1966.
[13] Improved preparation by *H. Berneth*, Universität Würzburg, unpublished.
[14] *S. E. Burkle*, PhD Thesis, University of New Hampshire 1973; Chem. Abstr. *80*, 81877t (1974).

Symmetry and Vibrational Frequencies of Dodecahedrane[**]

By *Otto Ermer*[*]

The as yet unknown dodecahedrane molecule *(1)*[11] with I_h symmetry (icosahedral group) is characterized by a very high torsional strain and a very small angle strain.



(1)

The partial conformations around all 30 symmetry-equivalent C—C bonds are exactly eclipsed, while the equivalent C—C—C and H—C—C angles (60 each) are close to the tetrahedral value. In the case of I_h symmetry all bond angles and torsion angles in the dodecahedrane molecule are fixed; they are: C—C—C 108°, H—C—C 110.9052°, C—C—C—C 0° and ±116.5651°[2], H—C—C—C ±121.7175°, H—C—C—H 0°.

The question arises, whether the minimum energy structure of dodecahedrane does in fact have I_h symmetry, or whether a deformation to lower symmetry exists leading to energetically more favorable torsion angles. Such a distortion would inevitably result in increased angle strain, since five-membered rings become non-planar, so that the average C—C—C angle is smaller than 108° and the average H—C—C angle larger than 110.9052°. Non-bonded repulsions between H atoms do not play an important role in this context at a calculated shortest H...H distance of 2.328 Å. (The calculated C—C and C—H bond lengths are 1.538 and 1.107 Å, respectively.)

We report here on force field calculations which show that the minimum energy structure of dodecahedrane indeed most likely has I_h symmetry. The decrease in torsional energy when distorting dodecahedrane away from I_h symmetry cannot compensate for the simultaneous increase in angle strain.

The problem under discussion is equivalent to the question of whether the optimum dodecahedrane geometry with I_h symmetry corresponds to a true minimum or to a partial maximum of the potential energy[2]. This may be analyzed in a straightforward manner if one applies symmetry-conserving energy optimization methods, and if one calculates the matrix **F** of the second derivatives of the potential energy with respect to the Cartesian atomic coordinates at the minimum and partial maximum, respectively. Both requirements are satisfied by the Newton-Raphson procedure. Diagonalization of the mass-weighted **F** matrix affords the vibrational frequencies and normal coordinates. If one or more imaginary frequencies result—corresponding to one or more negative eigenvalues of **F**—we are dealing with a partial maximum, otherwise with a true energy minimum.

The vibrational frequencies of dodecahedrane of I_h symmetry calculate with the aid of our previously described force field[4] are listed in Table 1. As angle deformation constants and reference angles for the methine group the values for the methylene group were used. All frequencies are real, and the dodecahedrane geometry of highest symmetry accordingly corresponds, within our force field, to a true energy minimum. Moreover, the I_h structure is fairly rigid, as expressed

Table 1. Calculated vibrational frequencies of dodecahedrane (in cm^{-1}; IR active T_{1u}; Raman active, A_g and H_g).

A_g	2899	T_{1u}	2898
	732		1310
			760
T_{1g}	1275		
		T_{2u}	2892
T_{2g}	1239		1242
	500		1107
			770
G_g	2892		
	1200	G_u	2893
	1052		1249
	733		913
			512
H_g	2895		
	1300	H_u	1249
	1166		1147
	1101		1089
	846		414
	395		

[*] Dr. O. Ermer
Abteilung für Chemie der Universität
Universitätsstrasse 150, D-4630 Bochum (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

by the relatively high value (395 cm^{-1}) for the lowest vibration frequency.

To establish what changes in the force field would be necessary for I_h symmetrical dodecahedrane to correspond to a partial energy maximum, *i.e.* to make less symmetrical structures energetically more favorable, we have performed a number of calculations with modified potential constants. A decrease in the C—C—C reference angle and an increase in the H—C—C reference angle has little influence, since not all angles become smaller and larger, respectively, on distortion but only the respective average values. A decrease in the angle deformation constants or an increase in the torsional constant effects the transition from the minimum to a maximum. As the relatively high value for the lowest vibrational frequency suggests, the changes in these constants necessary for the transition are absurdly large: For example, when reducing the deformation constant of the C—C—C and H—C—C angles by the same factor a decrease to about one fifth of the original values is required, when raising the torsional barrier around the C—C bonds an increase by a factor of about eight; when simultaneously reducing the angle deformation constants and raising the torsional barrier (equal changing factors) a change by a factor of about three effects the conversion from minimum to maximum. Hence we conclude that the dodecahedrane molecule has I_h symmetry.

Received: March 25, 1977 [Z 705 IE]
German version: Angew. Chem. 89, 431 (1977)

CAS Registry number:
Dodecahedrane, 4493-23-6

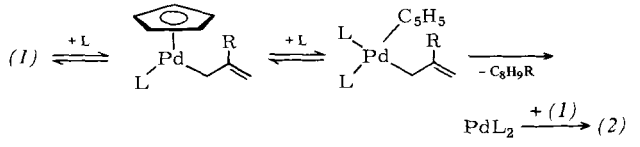
[1] *L. A. Paquette, M. J. Wyvratt, O. Schallner, D. F. Schneider, W. J. Begley, R. M. Blankenship*, J. Am. Chem. Soc. *98*, 6744 (1976); *P. E. Eaton, R. H. Mueller, J. R. Carlson, D. A. Cullison, G. F. Cooper, T. C. Chou, E. P. Krebs*, J. Am. Chem. Soc. *99*, 2751 (1977); *J. M. Schulman, T. Venanzi, R. L. Disch, ibid.* 97, 5335 (1975).
[2] The cosine of this angle is $-\sqrt{5}/5$.
[3] *O. Ermer*, Struct. Bonding 27, 161 (1976).
[4] *O. Ermer, S. Lifson*, J. Am. Chem. Soc. *95*, 4121 (1973).

A General Method for the Synthesis of Sandwich-Type Complexes with a Pd—Pd or Pt—Pt Bond[1]

By *Helmut Werner* and *Alfred Kühn*[*]

Methods for the synthesis of metal complexes containing metal-metal bonds are still being sought after. We recently found[2] that reaction of the η^3-allyl-η^5-cyclopentadienylpalladium complexes *(1a—c)* with tertiary phosphanes or phosphites in the molar ratio 1:1 leads to dinuclear complexes having the composition $(\mu\text{-}C_5H_5)(\mu\text{-}C_3H_4R)Pd_2L_2$ *(2)*. Crystal structure analyses prove both the sandwich-like structure as well as the presence of a direct Pd—Pd single bond[2,3].

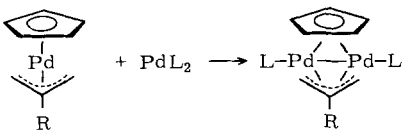
On the basis of NMR studies we had discussed the following suggested mechanism for the formation of *(2)*[4]:



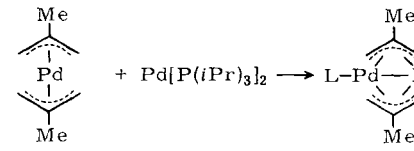
The decisive step should be a nucleophilic attack of the very short-lived species PdL_2 (with $L=PPh_3$, $P(OMe)_3$ or $P(OPh)_3$) on *(1)*, leading, after reorientation of the ligand sphere, to formation of the characteristic structural element L—Pd—Pd—L.

[*] Prof. Dr. H. Werner, Dipl.-Chem. A. Kühn
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

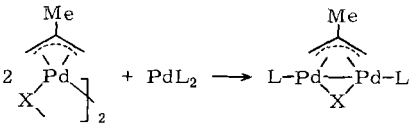
We have now confirmed this assumption [see eq. (A)] and shown, moreover, [eqs. (B) and (C)] that dinuclear complexes with two η^3-bonded, bridge-forming allyl ligands and with one allyl ligand and one halide ion are also accessible *via* an analogous route. As reaction partner PdL_2, we used the compounds with $L=P(iPr)_3$[5], $P(tBu)_3$, and $P(C_6H_{11})_3$[6].



(1a), R = H — *(2a)*, R = H, L = $P(iPr)_3$
(1b), R = Me — *(2b)*, R = Me, L = $P(iPr)_3$
(1c), R = tBu — *(2c)*, R = tBu, L = $P(iPr)_3$
(1d), R = Cl — *(2d)*, R = Cl, L = $P(iPr)_3$
(2e), R = Me, L = $P(C_6H_{11})_3$



(3) — *(4)*, L = $P(iPr)_3$



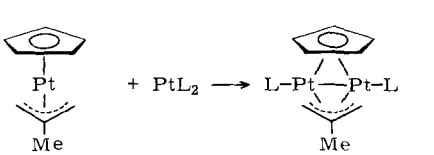
(5a), X = Cl — *(6a)*, X = Cl, L = $P(iPr)_3$
(5b), X = I — *(6b)*, X = I, L = $P(iPr)_3$
(6c), X = Cl, L = $P(tBu)_3$

It must be mentioned that reaction of *(1d)* with PR_3 or $P(OR)_3$ in the molar ratio 1:1 does not lead to the corresponding dinuclear complexes *(2)* but to the η^1-allyl compounds $C_5H_5Pd(C_3H_4Cl)L$, which in some cases are isolable and eliminate allene with formation of $C_5H_5Pd(L)Cl$ on warming[7]. Such a C_3H_4-elimination is probably also the reason for the formation of $(\mu\text{-}C_5H_5)(\mu\text{-}Cl)Pd_2[P(iPr)_3]_2$—previously prepared by *Felkin et al.*[8] by reaction of $C_5H_5Pd[P(iPr)_3]Cl$ with Mg in THF—as a side-product in the reaction of *(1d)* with $Pd[P(iPr)_3]_2$.

Attempts to synthesize a compound of type *(2)* with $L=P(tBu)_3$ have so far proved unsuccessful. Reaction of *(1b)* or *(1c)* with $P(tBu)_3$ in the molar ratio 1:1 affords $Pd[P(tBu)_3]_2$ in 50% yield[6], which is inert toward *(1b)* or *(1c)* even at elevated temperatures.

(4) is the first example of an allyl complex in which not just a single metal atom M but an M_2 fragment is coordinated sandwich-like by two symmetrically π-bonded allyl groups. A compound of type *(6)*, $(\mu\text{-}C_3H_5)(\mu\text{-}I)Pd_2(PPh_3)_2$, has been described by *Kobayashi et al.*[9]; it was prepared from $(C_3H_5PdI)_2$ and PPh_3.

Systematic application of our knowledge about the mechanism of formation of *(2)* has also enabled the first synthesis of an analogous dinuclear complex containing a Pt—Pt bond.



(7) — *(8)*, L = $P(iPr)_3$

The rate of the reaction of *(7)* with $Pt[P(iPr)_3]_2$[6] is markedly lower than that of the reaction of *(1b)* with

$Pd[P(iPr)_3]_2$—probably because *(7)* is considerably less reactive than *(1b)*, and because the palladium complexes PdL_2 have a stronger nucleophilic character than their PtL_2 analogs.

Procedure

(2a): A solution of $Pd[P(iPr)_3]_2$ (114.4 mg, 0.77 mmol) in toluene (2.5 ml) is added dropwise with stirring to a solution of *(1a)* (56.9 mg, 0.77 mmol). The reaction mixture changes color from deep-red to orange. On cooling the solution to −30 °C orange-yellow crystals are formed. These are recovered by filtration on a G3 frit, washed with pentane, and dried in a high vacuum. M.p. 64 °C, yield 116.5 mg (68 %).—Preparation of *(2b—e)* and *(4)* analogous to that of *(2a)*; for better crystallization, however, it is recommended that some pentane be added to the toluene solution.

(6a—c): Starting materials analogous to those for *(2a)*. For isolation of the product the solvent is removed, the residue treated with pentane, and the resulting solution filtered. On cooling to −30 °C yellow crystals are obtained; these are washed with pentane and dried in a high vacuum. Yield 70—90 %.

Received: March 31, 1977 [Z 710 IE]
German version: Angew. Chem. *89*, 427 (1977)

CAS Registry numbers:
(1a), 1271-03-0; *(1b)*, 33593-95-2; *(1c)*, 58496-57-4; *(1d)*, 58376-35-5; *(2a)*, 62586-44-1; *(2b)*, 62586-43-0; *(2c)*, 62586-42-9; *(2d)*, 62586-41-8; *(2e)*, 62586-40-7; *(3)*, 41348-25-8; *(4)*, 62586-39-4; *(5a)*, 12081-18-4; *(5b)*, 12281-94-6; *(6a)*, 62586-38-3; *(6b)*, 62586-37-2; *(6c)*, 62586-36-1; *(7)*, 35770-30-0; *(8)*, 62586-35-0; $Pd[P(iPr)_3]_2$, 52359-16-7; $Pd[P(C_6H_{11})_3]_2$, 33309-88-5; $Pd[P(tBu)_3]_2$, 53199-31-8

[1] Studies on the Reactivity of Metal π-Complexes, Part 25. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 24: *H. Werner, Tri Ngo Khac*, Angew. Chem. *89*, 332 (1977); Angew. Chem. Int. Ed. Engl. *16*, 324 (1977).
[2] *H. Werner, D. Tune, G. Parker, C. Krüger, D. J. Brauer*, Angew. Chem. *87*, 205 (1975); Angew. Chem. Int. Ed. Engl. *14*, 185 (1975).
[3] *H. Werner, A. Kühn, D. J. Tune, C. Krüger, D. J. Brauer, J. C. Sekutowski, Yi-Hung Tsay*, Chem. Ber. *110*, 1763 (1977).
[4] *H. Werner*, Angew. Chem. *89*, 1 (1977); Angew. Chem. Int. Ed. Engl. *16*, 1 (1977).
[5] *W. Kuran, A. Musco*, Inorg. Chim. Acta *12*, 187 (1975).
[6] *S. Otsuka, T. Yoshida, M. Matsumoto, K. Nakatsu*, J. Am. Chem. Soc. *98*, 5850 (1976).
[7] *D. J. Tune, H. Werner*, Helv. Chim. Acta *58*, 2240 (1975).
[8] *A. Ducruix, H. Felkin, C. Pascard, G. K. Turner*, J. Chem. Soc. Chem. Commun. *1975*, 615.
[9] *Y. Kobayashi, Y. Iitaka, H. Yamazaki*, Acta Crystallogr. *B28*, 899 (1972).

Imidazolidin-2-ones by Anodic Oxidation of Conjugated Dienes in the Presence of Dimethylurea[1][**]

By *Herbert Baltes, Ludwig Stork*, and *Hans J. Schäfer*[*]

Conjugated dienes *(1)* can be anodically dimerized and dimethoxylated in methanol[2]. On electrolysis in acetonitrile/water, 1-acetylpyrrolines and oxazolines are formed[3]. In less nucleophilic electrolytes, dienes ought to react oxidatively with urea derivatives to give heterocyclic compounds containing two heteroatoms.

We have now found that the preparative electrolysis of *(1)* at a graphite anode in acetonitrile/sodium perchlorate in the presence of 1,3-dimethylurea *(3)* affords the 4,5-disubstituted 1,3-dimethylimidazolidin-2-ones *(4)* and *(5)* (see Table 1), presumably *via* the intermediate radical cation *(2)*.

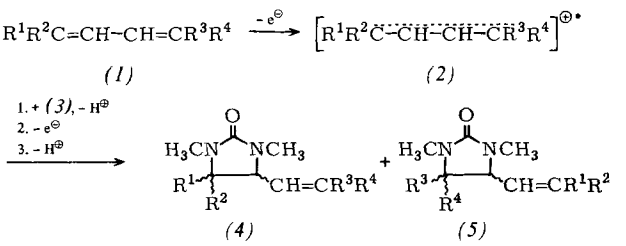


Table 1. Yields and oxidation potentials in the anodic preparation of imidazolidin-2-ones *(4)* and *(5)*.

	(1)				Anode potential E_p [a] [V]	*(4)* + *(5)* Yield [%] [b]
	R^1	R^2	R^3	R^4		
(a)	CH_3	CH_3	CH_3	CH_3	0.8—0.9	44 (50)
(b)	CH_3	CH_3	CH_3	H	1.0	39 (40 [c, d])
(c)	CH_3	H	CH_3	H	1.1—1.2	38 (40 [d])
(d)	H	$-(CH_2)_2-$		H	1.2—1.4	(15)
(e)	H	H	H	H	1.5	— [e]

[a] Against Ag/0.1 M $AgNO_3$ in acetonitrile.
[b] Isolated yields referred to current consumption; values quoted in brackets are chromatographic yields (3 % OV 225 on Chromosorb W).
[c] 15 % *(4b)* and 25 % *(5b)*, gas-chromatographically separated (15 % SE 30 on Chromosorb W).
[d] *Cis/trans* mixture (1 : 1).
[e] *(3)* (E_p = 1.68 V [a]) is oxidized more readily than *(1e)* (E_p = 2.0 V).

Procedure

(1) (0.1 mol) in an electrolyte consisting of acetonitrile (100 ml), sodium perchlorate (6.1 g) and *(3)* (0.1 mol) is electrolyzed at a graphite anode (P 127, Sigri, Meitingen) at 0 °C, a current density of 30 mA/cm², and at controlled potential until consumption of 0.1 F. Acetonitrile and unreacted *(1)* and *(3)* are distilled off. After hydrolysis with saturated sodium chloride solution the reaction mixture is extracted with ether and distilled over a short Vigreux column.

Received: March 30, 1977 [Z 708 IE]
German version: Angew. Chem. *89*, 425 (1977)

CAS Registry numbers:
(1a), 764-13-6; *(1b)*, 28823-41-8; *(1c)*, 592-46-1; *(1d)*, 542-92-7; *(1e)*, 106-99-0; *(3)*, 96-31-1; *(4a)*, 62609-55-6; *(4b)*, 62609-56-7; *cis-(4c)*, 62609-57-8; *trans-(4c)*, 62609-58-9; *(4d)*, 62609-59-0; *cis-(5b)*, 62609-60-3; *trans-(5b)*, 62609-61-4

[1] Anodic Oxidation of Organic Compounds, Part 20.—Part 19: *J. Knolle, H. Schäfer*, Electrochim. Acta, in press.
[2] *H. Schäfer, E. Steckhan*, Chem. Ing. Tech. *44*, 186 (1972); Angew. Chem. *81*, 532 (1969); Angew. Chem. Int. Ed. Engl. *8*, 518 (1969); *T. Shono, A. Ikeda*, Chem. Lett. *1976*, 311.
[3] *H. Baltes*, Dissertation, Universität Münster 1978.

Synthesis of α,β-Unsaturated Cyclic Ketones by Sensitized Photooxidation of Silyl Enol Ethers[**]

By *Edgar Friedrich* and *Werner Lutz*[*]

Chiral ketones are acquiring increasing importance in preparative organic chemistry, particularly in the synthesis of

[*] Dipl.-Chem. H. Baltes, L. Stork, Prof. Dr. H. J. Schäfer
Organisch-Chemisches Institut der Universität
Orléansring 23, D-4400 Münster (Germany)

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

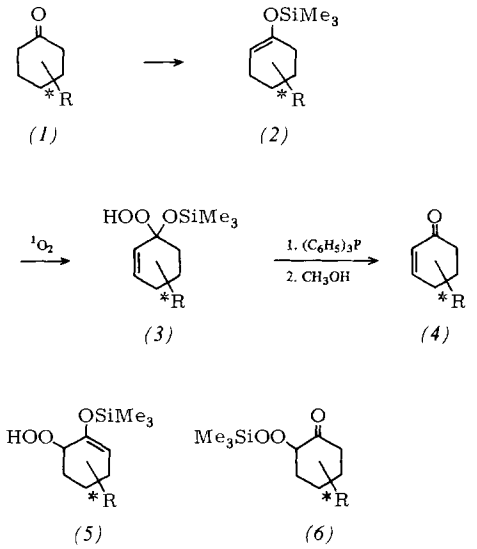
[*] Dipl.-Chem. E. Friedrich, Dr. W. Lutz
Institut für Organische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Giessen (Germany)

[**] Part of planned Dissertion by *E. Friedrich*, Universität Giessen.—We thank Professor *D. Seebach* and the Fonds der Chemischen Industrie for support of this work.

natural products. α,β-Unsaturated cyclohexenones chirally substituted at C-6 have hitherto not been synthesized. We have now found simple access to compounds *(4)*, which can be obtained in good yields under mild conditions and with only little loss of optical purity.

Achiral or chiral ketones *(1)*[1] react regioselectively with lithium diisopropylamide (LDA)[2] to give lithium enolates[3], which on reaction with trimethylchlorosilane afford the silyl enol ethers *(2)*. Sensitized photooxidation[4] of *(2)* followed by reduction of the hydroperoxides *(3)* with triphenylphosphane and subsequent methanolysis leads to formation of the ketones *(4)* (see experimental procedure and Table 1).

Formation of products *(3)* in a prototropic ene-reaction competes with two other ene-reactions, which lead to *(5)* (likewise prototropically) and *(6)* (silatropically). In the reduction step these side products are transformed into α-hydroxyketones that can readily be separated by distillation or by chromatography on silica gel (see Table 1).



Procedure:

(*R*)-6-Methyl-2-cyclohexen-1-one *(4a)* from (*R*)-2-methylcyclohexanone *(1a)*[1]: Reaction of (*R*)-2-methylcyclohexanone (3.26 g, 29.1 mmol), LDA, and trimethylchlorosilane according to Ref.[3] affords 3.58 g (19.4 mmol = 66.7%) silylenol ether [b.p. 64 to 66 °C/12 torr, $\alpha_D^{20} = +9.2°$ (1 dm, neat)]. This is dissolved in anhydrous tetrahydrofuran (140 ml) (10 mg Rose Bengal as sensitizer) in a glass Dewar flask and irradiated externally at −78 °C with two 450-W Hanovia medium pressure lamps using a 2% solution of $K_2Cr_2O_7$ as filter. Dry oxygen is passed through the enol ether solution during the reaction. On completion of reaction (established by thin-layer chromatography) triphenylphosphane (20 mmol) is added to the solution, the mixture stirred for 2 h at room temperature, and then treated with 50 ml anhydrous methanol (reaction time 14 h at room temperature). After concentration by evaporation the residue is digested with pentane, the resulting solution dried over $MgSO_4$, filtered, and the solvent removed. Distillation over quartz wool affords 6-methyl-2-cyclohexen-1-one[5] (1.49 g = 69.7%), b.p. 58 to 62 °C/12 torr.

Received: March 24, 1977 [Z 704 IE]
German version: Angew. Chem. 89, 426 (1977)

CAS Registry numbers:
(1a), 22554-29-6; *(1b)*, 22617-19-2; *(1c)*, 13368-65-5; *(1d)*, 14013-97-3; *(1f)*, 5432-85-9; *(1g)*, 108-94-1; *(4a)*, 62392-84-1; *(4b)*, 62392-85-2; 5-methyl-2-cyclohexenone, 54307-74-3; 3-methyl-2-cyclohexenone, 1193-18-6; *(4d)*, 6091-50-5; *(4e)*, 1753-40-8; *(4f)*, 500-02-7; *(4g)*, 930-68-7; α-hydroxy-3-methylcyclohexanone, 62392-78-3; α-hydroxymenthone, 62392-79-4; α-hydroxy-4-isopropylcyclohexanone, 62392-86-3; α-hydroxycyclohexanone, 533-60-8; trimethylchlorosilane, 75-77-4

[1] *D. Enders, H. Eichenauer*, Angew. Chem. *88*, 579 (1976); Angew. Chem. Int. Ed. Engl. *15*, 549 (1976).
[2] *M. Schlosser, G. Heinz*, Chem. Ber. *102*, 1944 (1969); *H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead*, J. Org. Chem. *34*, 2324 (1969); *G. Stork, P. F. Hudrlik*, J. Am. Chem. Soc. *90*, 4462 (1968); *D. Seebach, M. Teschner*, Chem. Ber. *109*, 1601 (1976).
[3] Generation of chiral lithium enolates of (+)-(*S*)-3-methyl-2-pentanone: *D. Seebach, V. Ehrig, M. Teschner*, Justus Liebigs Ann. Chem. *1976*, 1357.

Table 1. Products of the photooxidation of silyl enol ethers *(2)* from ketones *(1)*. Purification: (A) extraction (*n*-pentane) and distillation, (B) column chromatography on silica gel with $CHCl_3/Et_2O$ (10:1).

	Starting ketone *(1)* Rotation/opt. purity [%]	Purification	Products: Ketones *(4)* [e] Rotation/opt. purity [%]	Yield [%]	α-Hydroxyketones from *(5)* Yield [%]	α-Hydroxyketones from *(6)* Yield [%]
a	(*R*)-2-Methylcyclohexanone [1] $[\alpha]_D^{20} = -11.3°/74.2$	A	6-Methyl-2-cyclohexenone $\alpha_D^{20} = +39.0° > 54.5$ [a]	69.7	—	—
b	(*R*)-2-Ethylcyclohexanone [1] $\alpha_D^{20} = -26.2°$	A	6-Ethyl-2-cyclohexenone $\alpha_D^{20} = +27.8°$	82.8	—	—
c	(*R*)-3-Methylcyclohexanone [6] $\alpha_D^{20} = +12.5°$/opt. pure	B	5-Methyl-2-cyclohexenone [6] $[\alpha]_D^{20} = -91.0°$ ($c = 0.81$, $CHCl_3$)/opt. pure 3-Methyl-2-cyclohexenone	42.5 [b] 22.3 [b]	17.8	—
d	(−)-Menthone [7] $[\alpha]_D^{20} = -28.9°$/opt. pure	A	6-Isopropyl-3-methyl-2-cyclohexenone $[\alpha]_D^{20} = +40.3°/82.0$	48.8 [c]	5.8	22.3
e	(−)-Menthone	B	2-Isopropyl-5-methyl-2-cyclohexenone [8] $[\alpha]_D^{20} = -77.9°$ ($c = 0.565$, $CHCl_3$)	23.7 [d]	39.2	30.6
f	4-Isopropylcyclohexanone	B	4-Isopropyl-2-cyclohexenone	53.1	11.5	6.7
g	Cyclohexanone	B	2-Cyclohexenone	67.6	1.4	10.8

[a] Hydrogenation with Pd/C affords 2-methylcyclohexane with 54.5% optical purity.
[b] A mixture of 3- and 5-methylsilyl enol ethers is obtained which was photooxidized.
[c] Synthesis of the silyl enol ether from the Li enolate.
[d] Synthesis of the silyl enol ether from menthone/$ClSiMe_3/Et_3N$ [2] and separation of the pure product by preparative gas chromatography. Rotation: $[\alpha]_D^{25} = -78.36°$ [8].
[e] The chiral ketones were stored in quartz vessels.

[4] The sensitized photooxidation of silyl enol ethers has previously only been investigated on an acyclic derivative: *M. Rubottom, M. L. Lopez Nieves*, Tetrahedron Lett. *1972*, 2423.
[5] (±)-Compound: *G. Stork, W. N. White*, J. Am. Chem. Soc. *78*, 4604 (1956).
[6] *N. M. Allinger, C. K. Riew*, J. Org. Chem. *40*, 1316 (1975).
[7] *A. S. Hussey, R. H. Baker*, J. Org. Chem. *25*, 1434 (1960).
[8] *J. Read, G. J. Robertson*, J. Chem. Soc. *1926*, 2209.

Hydrogenation of Cubane[1][**]

By *Reinhard Stober* and *Hans Musso*[*]

The high strain energy in the cubane skeleton *(4)*[2] would suggest that three C—C bonds could be hydrogenolytically cleaved under relatively mild conditions.

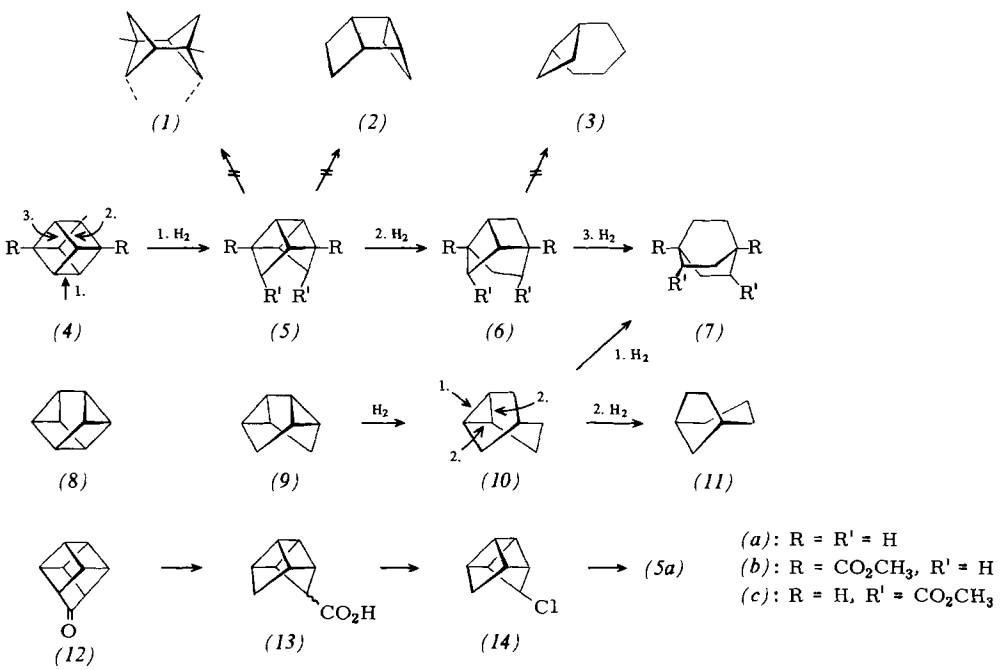
It has now been found that on hydrogenation of cubane *(4a)* in methanol over palladium/carbon at 20 °C and normal pressure, one mol of hydrogen is taken up in *ca.* 2 h with formation of secocubane *(5a)*, which on further uptake of hydrogen is slowly converted *via* tricyclo[4.2.0.0^{4,7}]octane *(6a)* into bicyclo[2.2.2]octane *(7a)*. Besides *(7a)* *ca.* 12% bicyclo[3.2.1]octane *(11)* is obtained, whose formation can be explained in terms of a rearrangement of *(4a)* to the cuneane *(8)* and of *(5a)* to the secocuneane *(9)* and their hydrogenation[3]. The separate hydrogenation of *(5a)* leads, *via* at least three gas-chromatographically recognizable intermediates, likewise to *(7a)* and *(11)* in the ratio 4:3. Dimethyl cubane-1,4-dicarboxylate yields, *via* only one dihydro- and one tetrahydro intermediate [*(5b)* and *(6b)*, respectively] pure bicyclo[2.2.2]octane-1,4-dicarboxylic ester *(7b)*[4], while the *endo,endo,endo*-secocubane ester *(5c)* affords the 2,5-dicarboxylic ester *(7c)* *via* *(6c)*. With Pd/C, *(4b)* does not yield *(7c)*, whereas with Pt in glacial acetic acid *(7b)* together with small amounts of *(7c)* are observed. Tricyclo[3.1.1.1^{2,4}]octane *(1)*, tricyclo[4.2.0.0^{2,5}]octane *(2)*, and bicyclo[4.2.0]octane *(3)* and corresponding dicarboxylic esters could not be detected in any of the reactions.

From these findings it can be concluded that the diester *(4b)* is attacked by hydrogen specifically at a non-substituted C—C bond on Pd/C, and that in the secocubane derivatives *(5a)* to *(5c)* the C—C bonds 2 and 3 inclined opposite to the already open bond 1 and common to two four-membered tings are cleaved. Thus the cubane skeleton also follows the empirical rules found for the hydrogenolysis of other cage compounds with small rings[5] and based on calculated enthalpies of formation ΔH_f^0 and strain energies SE (in kcal/mol)[6]:

	ΔH_f^0	SE
(1)	64.5	93.7
(2)	50.3	79.5
(3)	−4.4	30.7
(4)	148.6	165.9
(5)	88.9	112.0
(6)	32.9	62.1
(7)	−22.2	13.0
(11)	−23.0	12.1

Specifically those bonds are opened which afford the greatest relief of strain.

Secocubane *(2a)* was prepared by cleavage of homocubanone *(12)* with potassium *tert*-butoxide in THF/H_2O to the *exo-endo*-mixture of the carboxylic acids *(13)*[7], Grob degradation[8] to the *exo*-chloride *(14)* and dehalogenation[9]; m.p. 101—103 °C; ^{1}H-NMR ($CDCl_3$): qi 3.29 (2H, J = 3 Hz), m 3.04 (4H), d 2.43 (*endo* 4-H, 7-H, J = 10 Hz), m 2.15 (*exo* 4-H, 7-H); ^{13}C-NMR ($CDCl_3$): 25.9, 40.1 and 47.2 ppm. The hydrogenation products were identified by gas-chromatographic and spectroscopic comparison with authentic samples: *(6a)*[10], *(6c)*[11], *(7b)*[12], *(7c)*[13].



[*] Dipl.-Chem. R. Stober, Prof. Dr. H. Musso
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee, D-7500 Karlsruhe (Germany)

[**] We thank Prof. *J. D. Dunitz*, Zürich, Dr. *M. Tichý*, Prague, and Prof. *R. Askani*, Giessen for providing comparison samples, the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support, and BASF AG for supplying cyclooctatetraene.

Received: April 4, 1977 [Z 711 IE]
German version: Angew. Chem. *89*, 430 (1977)

CAS Registry numbers:
(2), 28636-10-4; *(4a)*, 277-10-1; *(4b)*, 29412-62-2; *(5a)*, 3104-90-3; *(5b)*,

62476-37-3; (5c), 13366-97-7; (6a), 3104-91-4; (6b), 62476-38-4; (6c), 62504-65-8; (7a), 280-33-1; (7b), 1459-96-7; (7c), 25225-85-8; (11), 6221-55-2; (12), 15291-18-6; (14), 62476-39-5

[1] Part 6 of The Hydrogenolysis of Small Hydrocarbon Rings.—Part 5: *U. Biethan, U. Cuntze, H. Musso*, Chem. Ber. *110* (1977), in press.

[2] *B. D. Kybett, S. Carroll, P. Natalis, D. W. Bonnell, J. L. Margrave, J. L. Franklin*, J. Am. Chem. Soc. *88*, 626 (1966).

[3] The hydrogenation of *(9)* via *(10)* to give *(7a)* and *(11)* is well known: *N. A. Le Bel, R. N. Liesemer*, J. Am. Chem. Soc. *87*, 4301 (1965); *I. C. Kochenko, E. M. Milvitskaja, A. F. Platé*, J. Org. Chem. USSR *8*, 560 (1972); Zh. Org. Khim. *8*, 555 (1972).

[4] The same observation was made independently by *K. J. Toyne*, University of Hull, private communication.

[5] *H. Musso*, Chem. Ber. *108*, 337 (1975); *E. Ōsawa, P. v. R. Schleyer, L. W. K. Chang, V. V. Kane*, Tetrahedron Lett. *1974*, 4189; *B. Deppisch, H. Guth, H. Musso, E. Ōsawa*, Chem. Ber. *109*, 2956 (1976).

[6] *E. M. Engler, J. D. Andose, P. v. R. Schleyer*, J. Am. Chem. Soc. *95*, 8005 (1973). The calculations for some intermediates were carried out by *E. Ōsawa*, Sapporo, Japan.

[7] *W. G. Dauben, L. N. Reitman*, J. Org. Chem. *40*, 835 (1975).

[8] *K. B. Becker, M. Geisel, C. A. Grob, F. Kuhnen*, Synthesis *1973*, 493.

[9] All new compounds gave correct analyses and spectra; *R. Stober*, Dissertation, Universität Karlsruhe 1977.

[10] *R. Askani*, Chem. Ber. *110* (1977), in press.

[11] *N. A. Sasaki, R. Zunker, H. Musso*, Chem. Ber. *106*, 2992 (1973).

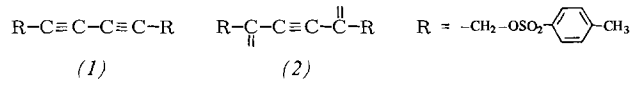
[12] *J. C. Kauer, R. E. Benson, G. W. Parshall*, J. Org. Chem. *30*, 1431 (1965); *O. Ermer, J. D. Dunitz*, Helv. Chim. Acta *52*, 1861 (1969).

[13] *M. Tichý, J. Sicher*, Collect. Czech. Chem. Commun. *37*, 3106 (1972).

Crystallographic Analysis of a Topochemical Polymerization

By *V. Enkelmann* and *G. Wegner*[*]

Macroscopic single crystals[1] of polymer are formed from suitably substituted diacetylenes by topochemical polymerization. The polymerization is initiated thermally or by irradiation. Since polymerizable diacetylenes polymerize extremely rapidly on irradiation with X-rays, only structural data for the polymers[2] or for the inactive monomers[3] have thus far been available.



(1) *(2)*

We have now succeeded in elucidating the structure of a polymerizable diacetylene, hexa-2,4-diyne-1,6-diyl-bis-*p*-toluenesulfonate *(1)*, by recording X-ray data at 120 K. Since the structure of the corresponding polymer *(2)* at 120 K was also solved recently, the coordinates of each of the individual atoms before and after the reaction are now known.

For the three-dimensional X-ray structure analysis we used crystals of *(1)* which had been crystallized from acetone. The intensity data were collected by equi-inclination Weissenberg photographs (multifilm technique) at 120 K and the intensities determined by visual estimation. During the time necessary for recording a photograph the conversion never exceeded 5 %. A new monomer crystal was employed for each photograph. 1450 independent reflections were evaluated. Crystallographic data of the monomer at 120 K: $a = 1490(1)$, $b = 511.0(5)$, $c = 2602(4)$ pm, $\beta = 92(1)°$; space group $P2_1/c$. As in the case of the low-temperature form of the polymer *(2)*[4] the asymmetric unit consists of two independent molecules. The structure was solved by direct methods[5] and refined by the method of least squares (full matrix). The isotropic refinement was terminated at an R factor of 10 %.

[*] Dr. V. Enkelmann, Prof. Dr. G. Wegner
Institut für Makromolekulare Chemie der Universität
Stefan-Meier-Strasse 31, D-7800 Freiburg (Germany)

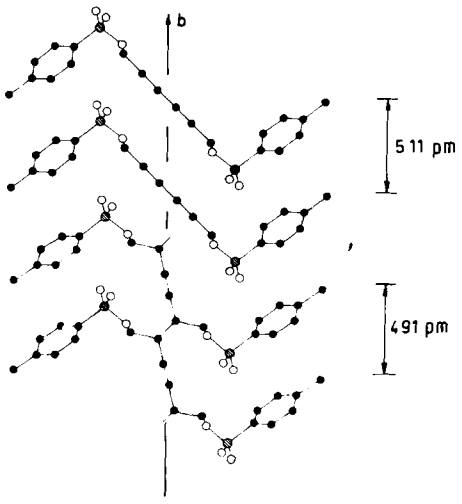


Fig. 1. Projection of neighboring molecules of *(1)* (above) and *(2)* (below) onto the plane of the main chain.

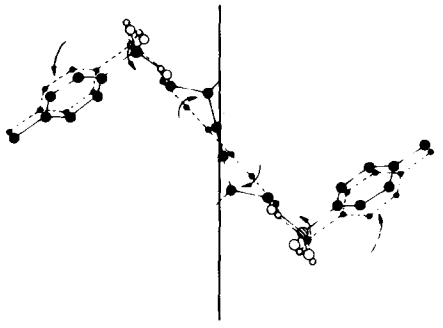


Fig. 2. Change of position of atoms on polymerization (projection of the monomer structure—dotted—onto that of the polymer).

Figure 1 shows a projection of neighboring molecules of the monomer and of the polymer in the low-temperature form on the plane of the main chain. During polymerization the length of the stacking axis b falls from 511 to 491 pm. The difference of 20 pm per addition must be accommodated by the monomer lattice, since no phase separation is observed. Projection of the monomer structure onto that of the polymer is illustrated in Figure 2. Besides the expected shifts of the coordinates of the atoms forming the main chain, shifts and rotations of the side groups are also observed whose contribution to the total mechanism of the polymerization was previously not taken into consideration[6].

Received: March 30, 1977 [Z 709 IE]
German version: Angew. Chem. *89*, 432 (1977)

CAS Registry numbers:
(1), 32527-15-4; *(2)*, 32535-60-7

[1] *G. Wegner*, Makromol. Chem. *154*, 35 (1972).

[2] *E. Hädicke, E. C. Mez, C. H. Krauch, G. Wegner, J. Kaiser*, Angew. Chem. *83*, 253 (1971); Angew. Chem. Int. Ed. Engl. *10*, 266 (1971); *D. Kobelt, E. F. Paulus*, Acta Crystallogr. *B30*, 232 (1974).

[3] *A. W. Hanson*, Acta Crystallogr. *B31*, 831 (1975); *E. Hädicke, K. Penzien, H. W. Schnell*, Angew. Chem. *83*, 1024 (1971); Angew. Chem. Int. Ed. Engl. *10*, 940 (1971); *E. H. Wibenga*, Z. Kristallogr. *102*, 193 (1940).

[4] *V. Enkelmann, G. Wegner*, Makromol. Chem. *178*, 635 (1977); *V. Enkelmann*, Acta Crystallogr., in press.

[5] *J. P. Declercq, G. Germain, P. Main, M. M. Woolfson*, Acta Crystallogr. *A29*, 231 (1973).

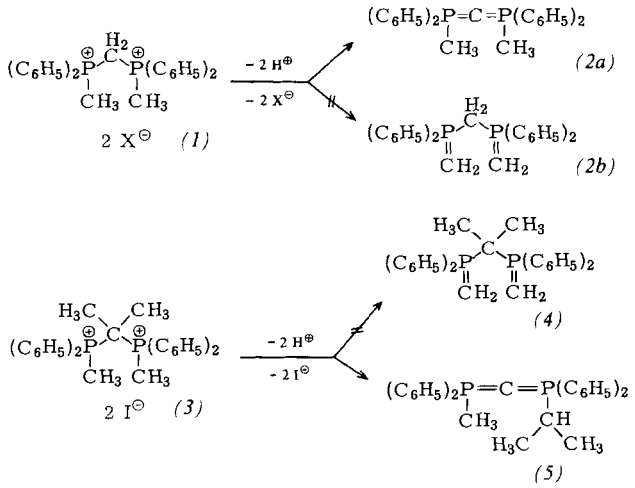
[6] *R. H. Baughman*, J. Polymer Sci. Phys. Ed. *12*, 1511 (1974).

"Carbodiphosphoranes" by a New Rearrangement of Phosphorus Ylides

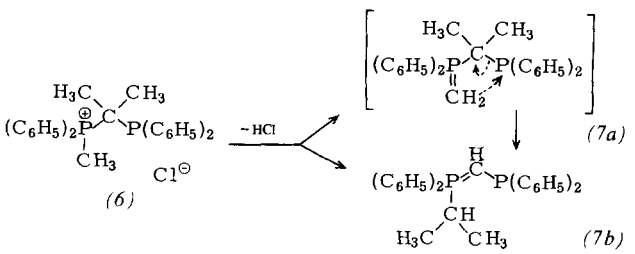
By *Anette Wohlleben* and *Hubert Schmidbaur*[*]

On account of their synthetic potential in organic chemistry[1], their particular ligand properties in metal complexes[2], and their unusual physicochemical properties (triboluminescence, crystal structure)[3], "carbodiphosphoranes" $R_3P{=}C{=}PR_3$ attract current interest[4].

The aryl-substituted compounds, which are usually bright yellow (*e.g. (2a)*), are formed with surprising ease on deprotonation of the conjugated phosphonium salts *(1)*; thus it is impossible to obtain the isomeric methylenebisphosphoranes (*e.g. (2b)*) in this way. In order to force deprotonation in the peripheral alkyl groups we have prepared a phosphonium salt *(3)* which is completely alkylated at the central $^{\oplus}P{-}C{-}P^{\oplus}$ bridge; this would be expected to rule out formation of a carbodiphosphorane.



However, in this case too we did not obtain the bisphosphorane *(4)* which appeared promising as a double ylide ligand; instead the carbodiphosphorane *(5)* was unexpectedly formed. In order to gain a clearer view of the reaction course, which seems to be complicated by extensive rearrangement, the monophosphonium salt *(6)* was also synthesized and subjected to the action of strong bases. A deep yellow ylide is formed which again does not have the structure *(7a)* but *(7b)* instead:



The structures of *(5)* and *(7b)* have been confirmed by elemental analysis and ^1H-, ^{13}C-, and ^{31}P-NMR spectra. As suggested in the formula [*(7a)*→*(7b)*], the mechanism of the hitherto unobserved rearrangement is to be interpreted in terms of nucleophilic attack by the ylidic carbanion in *(7a)* on the second P atom, whereupon the PCP bridge weakened by steric interaction opens at this P atom. A proton shift from the new PCH_2P bridge to the α-C atom of the concomitantly formed isopropylidene group completes the process, which can be formulated appropriately for the formation of *(5)* from *(3)*. Such prototropic processes in ylides are known and have already been carefully studied[5]; not so the ready P—C—P cleavage. The results imply that rearrangements can also be expected in the case of analogously configurated phosphorus compounds in other systems[6].

Procedure:

(3)→*(5)*: Reaction of methylenebis(diphenylphosphane) (1.75 g, 4.25 mmol) and methyl iodide (excess, 5 ml) in a sealed tube (2 d at 40 °C) affords compound *(3)*, yield 2.0 g (68 %), m.p. 283 °C.—^1H-NMR (CD_3OD; δ [ppm], J [Hz]): δCH_3P 2.8, d, 6H, *J*(HCP) 12.5; δCH_3C 2.0, t, 6H, *J*(HCCP) 16.0; δC_6H_5 7.9, m, 20H.

Methylenetrimethylphosphorane (1.44 g, 1.60 mmol) is added to *(3)* (0.56 g, 0.80 mmol) in ether (10 ml) and the yellow mixture stirred for two hours. After tetramethylphosphonium salt has been filtered off, the solution is concentrated, extracted with *n*-hexane, and crystallized. Yield 0.23 g (65 %) of *(5)*, m.p. 103 °C.—^1H-NMR (C_6D_6): δCH_3P 1.0, d, 3H, *J*(HCP) 12.0; δCH_3C 0.6, dd, 6H, *J*(HCCH) 7.0, *J*(HCCP) 16.0; δCH 2.0, m, 1H; δC_6H_5 8.0, m, 20H. ^{13}C-NMR (C_6D_6): δCH_3P 20.85, d, *J*(PC) 57.4; δCH_3C 17.9, s; δCH 28.45, d, *J*(PC) 66.2; δC 1.04, dd, *J*(PC) 122 and 128. ^{31}P-NMR (C_6D_6): δP 5.03 and −17.8, AB, *J*(PCP) 88.

(6)→*(7b)*: CH_3Cl (10 ml) is condensed onto $[(C_6H_5)_2P]_2CH_2$ (4.1 g, 10 mmol) dissolved in THF (20 ml) in a sealed tube. Heating (50 °C, 2 d) gives rise to *(6)* (3.8 g, 82 %), m.p. 185 °C.—^1H-NMR ($CDCl_3$): δCH_3P 2.8, d, 3H, *J*(HCP) 12.5; δCH_3C 1.70, dd, 6H, *J*(HCCP) 18.5 and 7.5; δC_6H_5 8.1, m, 20H. ^{31}P-NMR (CD_3OD): δP 3.7 and 31.8, AB, *J*(PCP) 73.

Finely powdered NaH (0.24 g) is added portionwise to a suspension of *(6)* (1.93 g, 4.2 mmol) in THF (30 ml). After 4 d at 20 °C the mixture is filtered, concentrated, extracted with *n*-hexane, and crystallized. Yield 0.93 g (52 %) of *(7b)*, m.p. 83 °C.—^1H-NMR (C_6D_6): δCH_3 1.10, dd, 6H, *J*(HCCH) 7.0, *J*(HCCP) 16.3; δCHC_2 2.60, m, 1H; δCH=P 1.60, dd, *J*(HCP) 1.5 and 10.4; δC_6H_5 7.9, m, 20H. ^{13}C-NMR (C_6D_6): δCH_3 16.7, s; δCHC_2 26.3, d, *J*(PC) 61.0; δCP_2 2.5, dd, *J*(PC) 9.8 and 114.7; δC_6H_5 131.7, m. ^{31}P-NMR (C_6D_6): δP 20.0 and 29.5, AB, *J*(PCP) 136.

Received: December 14, 1976 [Z 626 IE]
German version: Angew. Chem. 89, 428 (1977)
Publication delayed at authors' request

CAS Registry numbers:
$(C_6H_5)_2(CH_3)P^+CH_2P^+(CH_3)(C_6H_5)_2$, 61484-29-5; *(2a)*, 60798-30-3; *(3)*, 61484-30-8; *(5)*, 61484-31-9; *(6)*, 61505-87-1; *(7b)*, 61484-32-0; methylene-(bisdiphenylphosphane), 2071-20-7; ^{13}C, 14762-74-4; ^{31}P, 7723-14-0

[*] Prof. Dr. H. Schmidbaur, Dipl.-Chem. A. Wohlleben
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

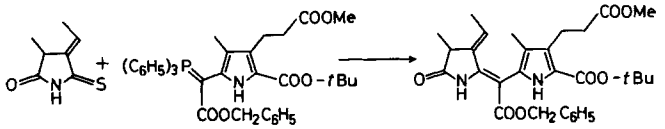
[1] *F. Ramirez, N. B. Desai, B. Hansen, N. McKelvie*, J. Am. Chem. Soc. *83*, 3539 (1961); *G. H. Birum, C. N. Matthews, ibid. 90*, 3842 (1968); and references cited therein.
[2] *W. C. Kaska, D. K. Mitchell, R. F. Reichelderfer, W. D. Korte*, J. Am. Chem. Soc. *96*, 2847 (1974); *W. C. Kaska, R. F. Reichelderfer*, J. Organomet. Chem. *78*, C47 (1974); *H. Schmidbaur, O. Gasser*, Angew. Chem. *88*, 542 (1976); Angew. Chem. Int. Ed. Engl. *15*, 502 (1976); and references cited therein.
[3] *J. I. Zink, W. C. Kaska*, J. Am. Chem. Soc. *95*, 7510 (1973); *A. T. Vincent, P. J. Wheatley*, J. Chem. Soc. Dalton *1972*, 617.
[4] *H. Schmidbaur, O. Gasser*, J. Am. Chem. Soc. *97*, 6281 (1975); *M. S. Hussain, H. Schmidbaur*, Z. Naturforsch. *31b*, 721 (1976); *R. Appel, F. Knoll, H. Schöler, H.-D. Wihler*, Angew. Chem. *88*, 769 (1976); Angew. Chem. Int. Ed. Engl. *15*, 701 (1976).

[5] *H. Schmidbaur, W. Buchner, D. Scheutzow*, Chem. Ber. *106*, 1251 (1973); *H. Dreeskamp, R. Bausch*, unpublished; *R. Bausch*, Dissertation, Universität Bochum 1975; *H. J. Bestmann, H. G. Liberda, J. P. Snyder*, J. Am. Chem. Soc. *90*, 2963 (1968); and references cited therein.
[6] Cf. *R. Appel, F. Knoll, W. Michel, W. Morbach, H.-D. Wihler, H. Voltmann*, Chem. Ber. *109*, 58 (1976).

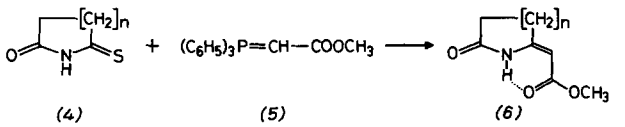
Reaction of Monothiodicarboximides with Phosphorous Ylides: A New Synthesis of ω-Alkylidenelactams[**]

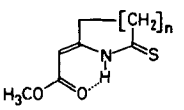
By *Albert Gossauer, Ralf-Peter Hinze*, and *Harald Zilch*[*]

In the course of our work on the synthesis of bile pigments we found that the substituted monothiosuccinimide *(1)* reacts regioselectively with the phosphorane *(2)* in boiling toluene, yielding the 5-alkylidene-2-pyrrolidinone *(3)* in 79 % yield[1].



On the basis of this result, we have examined the reactivity of some cyclic monothiodicarboximides towards the phosphorous ylide *(5)* as a typical resonance-stabilized Wittig reagent. The five- to seven-membered monothiocarboximides *(4)*, $n = 1$—3, were found to give the corresponding alkylidenelactams *(6)*[2] (cf. Table 1)[3]. As their N—H stretching frequencies are independent of concentration, and hence characteristic for intramolecular bonding, the *Z*-configuration has been assigned to the products *(6)*.





In addition to *(6)* the corresponding alkylidenethiolactams *(7)*[2] are obtained as by-products in yields between 4 and 14 %, the reaction of monothioglutarimide being less regioselective than those of the corresponding five- and seven-membered homologs.

Most likely, formation of the alkylidenelactams *(6)* takes place by a reaction analogous to the Wittig olefin synthesis involving the C=S bond (cf. [4]).

Table 1. Alkylidenelactams *(6)* [2] from monothioimides *(4)*.

	Reactant *(4)*		Products *(6)* [a]		
n	M.p. [°C]	Yield [b] [%]	Yield [c] [%]	M.p. [°C]	$\tilde{\nu}_{N-H}$ [d] [cm^{-1}]
1	111—113 [e]	66	58	57—58	3355
2	118—119 [f]	45	43	48—49	3275
3	43—44	51	39	—	3230

[a] Purified by preparative TLC on silica gel with ether/*n*-hexane as eluent and subsequent crystallization from ether/*n*-hexane. [b] In boiling toluene for 20 h. [c] In boiling xylene for 4 h. [d] 6.0, 3.0, 1.2, and 0.6×10^{-2} M in CCl_4. [e] Lit. value [5]: 112—114 °C. [f] Lit. value [5]: 118—119 °C.

Preparation of the monothioimides (4):

The cyclic dicarboximide[6] (0.04 mol) is dissolved in ethanol (40 ml) and silver carbonate (prepared from 10 g $AgNO_3$ and 4 g anhydrous Na_2CO_3) is added. The mixture is heated under reflux until the formation of carbon dioxide is complete. The resulting silver salt of the imide is separated by filtration, dried, and suspended in ethyl iodide (30 ml). After the mixture has been heated for 2 h under reflux, the silver iodide which separates is filtered off, and the filtrate concentrated to dryness by evaporation of the solvent. The remaining readily hydrolyzable lactim ether is dissolved without purification in dry pyridine (20 ml), and hydrogen sulfide (dried over Al_2S_3) is introduced into the solution for 1 h. The product obtained after removal of the solvent is purified by chromatography on silica gel with CH_2Cl_2 as eluent.

Received: March 24, 1977 [Z 717 IE]
German version: Angew. Chem. *89*, 429 (1977)

CAS Registry numbers:
(4), $n=1$, 4166-00-1; *(4)*, $n=2$, 5693-95-8; *(4)*, $n=3$, 62609-10-3; *(5)*, 2605-67-6; *(6)*, $n=1$, 62609-11-4; *(6)*, $n=2$, 62609-12-5; *(6)*, $n=3$, 62609-13-6; *(7)*, $n=1$, 62609-14-7; *(7)*, $n=2$, 62609-15-8; *(7)*, $n=3$, 62609-16-9; 2,5-pyrrolidinedione, 123-56-8; 2,6-piperidinedione, 1121-89-7; tetrahydro-1*H*-azepine-2,7-dione, 4726-93-6

[*] Doz. Dr. A. Gossauer, Dr. R.-P. Hinze, H. Zilch
Institut für Organische Chemie der Technischen Universität
Schleinitzstrasse, D-3300 Braunschweig (Germany)

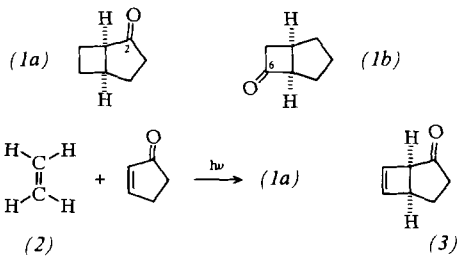
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *A. Gossauer, R. P. Hinze*, unpublished results.
[2] UV, IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometric data, as well as the results of elemental analysis are in agreement with the given formulae.
[3] An analogous reaction of cyclic dicarboximides has been observed only in the case of succinimides: *W. Flitsch, R. Schindler*, Synthesis *1975*, 686.
[4] *U. Schöllkopf*, Angew. Chem. *71*, 260 (1959).
[5] *U. Berg, J. Sandström*, Acta Chem. Scand. *20*, 689 (1966).
[6] For a synthesis of adipimide *(4)*, $n=3$ see *A. R. Doumaux, D. J. Trecker*, J. Org. Chem. *35*, 2121 (1970).

Reviews

Abstracts of selected progress reports and review articles

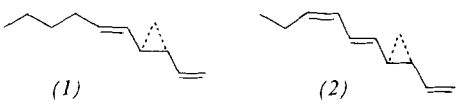
The uses of bicyclo[3.2.0]heptanones *(1)* **in organic syntheses** are surveyed by *S. M. Ali, T. V. Lee,* and *S. M. Roberts. cis*-Condensed bicyclics *(1)*, especially the readily accessible bicyclo[3.2.0]heptan-2-ones *(1a)* and -6-ones *(1b)* react differently, depending upon the nature and position of the substituents. The most appropriate synthesis of *(1a)* is by photoannelation of 2-cyclocyclopentenone and alkenes, *e.g. (2)*, and that of *(1b)* consists in the regiospecific cycloaddition of ketenes (subject to extensive variation) to cyclopentenes, *e.g.* cyclopentadienes. Fragmentation reactions of *(1)* and simple unsaturated derivatives in many cases require modifica-



tions of the molecule which can frequently be accomplished stereoselectively (*e.g.* reduction of bicyclo[3.2.0]hept-6-en-2-one *(3)* with $LiAlH_4$ to give the *endo* alcohol; bromination of *(3)* to give 2-*exo*,3-*endo*-dibromobicyclo[3.2.0]heptan-6-one). Cleavage of the C^1—C^5 bond of *(1)* by heating or by acid treatment leads to seven-membered ring systems (synthesis of tropolone and β-thujaplicin). Opening of the four-membered ring of *(1)* gives cyclopentane derivatives, including precursors of prostaglandins; opening of the five-membered ring gives cyclobutane derivatives. Other bicyclic ring systems are obtained by rearrangements. [The Use of Bicyclo[3.2.0]-heptanones as Versatile Synthons in Organic Chemistry. Synthesis *1977*, 155—166; 70 references]

[Rd 945 IE—M]

Volatile compounds from seaweeds are surveyed by *R. E. Moore.* The odor of brown seaweed *(Dictyopteris divaricata)* is due to non-isoprenoid C_{11} hydrocarbons; apart from the principal components *(1)* and *(2)*, undecatrienes and -tetraenes and



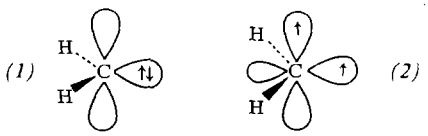
substituted cycloheptadienes also occur. The edible red seaweed *Asparagopsis taxiformis* contains chlorinated, brominated, and iodinated hydrocarbons, ketones, alcohols, and carboxylic acids, among other compounds. It may well be that the chloroform and carbon tetrachloride present in traces in the upper atmosphere and in drinking water arise from such algae. [Volatile Compounds from Marine Algae. Acc. Chem. Res. *10*, 40—47 (1977); 58 references]

[Rd 947 IE—L]

Analysis of the soil atmosphere by gas chromatography is considered by *K. A. Smith.* Apart from the usual components of air, various other compounds were detected, including NH_3, NO, NO_2, H_2S, CS_2, organosulfur compounds, H_2, hydrocarbons (C_2 to C_4), and other organic compounds such as volatile fatty acids, aldehydes, alcohols, and ketones. These substances are produced by roots or soil bacteria. Changes in the concentration of biologically active gases such as O_2 and CO_2 can affect plant growth and biological processes in the soil.—In addition the fate of gases such as brominated hydrocarbons in the soil is also examined. [Gas-Chromatographic Analysis of the Soil Atmosphere. Adv. Chromatogr. *15*, 197—231 (1977); 112 references]

[Rd 946 IE—F]

CIDNP studies on carbene reactions are reviewed by *H. D. Roth.* It could be shown by this method, for example, that singlet carbenes [type *(1)*], which only react *via* insertion with C—H bonds, can also undergo abstraction reactions, abstracting preferentially chlorine from chlorohydrocarbons, whereas triplet carbenes [type *(2)*] preferentially abstract



hydrogen. It was also established that the photosensitized decomposition of some diazo compounds which proceeds *via* carbenes is accompanied by energy transfer. [Chemically Induced Nuclear Spin Polarization in the Study of Carbene Reaction Mechanisms. Acc. Chem. Res. *10*, 85—91 (1977); 45 references]

[Rd 948 IE—L]

The proteinase inhibitors of plants and microorganisms is the title of a survey by *M. Richardson.* The article deals with the specificity, distribution, and occurrence of these proteins, and with modern procedures for their isolation. Homologies in the amino acid sequences and details of the reactive sites are compiled. There follow an account of experiments for intracellular localization of protein inhibitors and a description of the physiology and biological function of these substances. Their role in nutrition, in therapy, and in the laboratory are considered in conclusion. [The Proteinase Inhibitors of Plants and Microorganisms. Phytochemistry *16*, 159—169 (1977); 159 references]

[Rd 949 IE—R]

Phenomena of oscillation in biological systems are the subject of a symposium reported by *A. Boiteux, B. Hess, Th. Plesser,* and *J. D. Murray.* Although there are numerous periodic processes in living systems, only few of them can be attributed to the function of only one or just a few enzymes. Theoretical and experimental analysis show that a temporal and spatial organization rests on the following prerequisites: autocatalysis, network feedback of the enzymatic reactions, and a pronounced distance from equilibrium. [Oscillatory Phenomena in Biological Systems. A Meeting Report. FEBS Lett. *75*, 1—4 (1977)]

[Rd 950 IE—R]

Propellanes. Structure and Reactions. By *D. Ginsburg*. Monographs in Modern Chemistry, Vol. 7. Edited by *H. F. Ebel*. Verlag Chemie, GmbH, Weinheim 1975. 1st Edit., viii, 272 pp., *ca.* 600 formulas, bound DM 138.—.

Ten years of propellane chemistry—is that a reason for writing a book about it? The author himself gives the best reply: the monograph is written so well that the question never even occurs to the reader.

A pioneer in this field of research, *Ginsburg* reports on the worthwhile results of 365 publications that appeared up to 1974. In this he covers a wide field and makes it convincingly clear why propellanes are the ideal molecules for studying many types of problems (bond fluctuation, aromaticity, homoconjugation, stereoelectronics, ring strain, dualism of photoinduction and thermal excitation, conservation of orbital symmetry, *etc.*). The reader finds all that is worth knowing about the synthesis, structure, and reactions of this fascinating class of substances. The book offers at the same time a glimpse into the preparative organic laboratory, for experimental details are discussed in detail when they are necessary for an understanding of the problem.

The particular attraction that endows this book with exceptional status is the courage repeatedly to leave pure chemistry aside. The marginal comments scattered here and there display a personal style and provide intellectual satisfaction.

The book contains an unusually large number of structural formulas; reading at a glance is thus made much easier. (That a few printing errors have crept in can be forgiven in a first printing.)

The book has given the reviewer valuable pointers for his own research. For those interested in alicyclic chemistry it is a true mine of information. Anyone new to the subject itself but finding pleasure in an elegantly formulated and highly stimulating text will also find his money well spent.

Günther Maier [NB 376 IE]

Isoelectric Focusing. Edited by *N. Catsimpoolas*. Academic Press, New York—London 1976. 1st Edit., xii, 265 pp., bound, $ 23.50.

The intention behind this work has been to validate the vigorous development of the isoelectric focusing(IF) method and to report new variants and the present state of knowledge. The book is aimed at users of the method who require an introduction and/or more information about it.

A defined individual theme is treated in each of the nine chapters. The authors are experts in their field who can provide valuable indications for the uses of IF from their own experience.

After a highly interesting review of the history and the future prospects of IF, with a brief description of the physical principles (*A. Kolin*), detailed theoretical-mathematical considerations of the method are given in Chapter 2 (37 pp., *H. Rilbe*). There follows a section on carrier ampholytes (*O. Vesterberg*), which outlines *inter alia* their synthesis and physicochemical properties and contains indications of the biological and biochemical aspects (*e.g.* interaction with proteins). In three further chapters the application of IF to gel-stabilized carrier systems is described. There is a general presentation of the technique (*A. Chrambach* and *G. Baumann*), and special mention must be made of the description of two-dimensional working (combination of gel electrophoresis with IF) in Chapter 5 (*C. W. Wrigley*) and of the comprehensive treatment of the preparative application of IF in granulated gels (Chapter 6, 48 pp., *B. J. Radola*). In these last two contributions precise experimental details are given together with numerous examples of separations. A section on its own (*J. Bours*) is devoted to IF in free solution, and there critical indications can be found about evaluating separation results (artefacts). Specialized applications are continuous working (Chapter 7, *J. S. Fawcett*) and "Trans-IF" (Chapter 9, *N. Catsimpoolas*); both these make great demands on apparatus.

The book makes no claim to comprehensive treatment of its theme and the numerous techniques, yet it provides much useful information.

Kurt Hannig [NB 374 IE]

Mikrobiologie (Microbiology). Vol. 13 of the further education series "Medizin und Werbung". By *H. Nolte*. Karl Demeter Verlag, Gräfeling 1976. 1st Edit., 78 pp., DM 11.80.

According to the publishers, this further education series is intended to provide essential basic information. This must be taken with a pinch of salt, for one cannot expect miracles in a booklet of 41 pages of text. On delving into the work, however, one cannot fail to wonder at the way in which the "basic information" has been presented. In the clumsily and unscientifically written and arbitrarily assembled sections on general and medical microbiology factual errors and unnecessary verbiage just about balance each other. A section "Metabolism of Bacteria" that is devoted exclusively to an extremely vague description of alcoholic fermentation in yeasts (!) and the statement that metabolites are the substances (enzymes, hormones, vitamins!) responsible for trouble-free occurrence and control of metabolism speak for themselves. Technical terms, if used at all, are not explained. In four pages of suspect hand-drawings the bacterial cell enjoys a representation in which an enzyme is sketched in (!)—it is presumably a mesosome, for the indicating arrow for "nuclear substance" points to an empty space. Five pages of terminology include, *inter alia*, DNA = complex, high-molecular protein, RNA = ribose = pentavalent sugar, cytoplasm = living substance of the cell = semifluid fine-grained mass. Finally in 26 pages of "programmed learning" one is invited to check what beauties one has retained from the text. For example, one must fill in that plants form carbohydrates from CO_2 by photosynthesis (= formation of chlorophyll with the aid of light energy).

The reviewer cannot recommend this pamphlet (indeed, must advise against reading it), and must contradict the author in at least the one point where he states that everything in nature has its sense.

Hans Bender [NB 373 IE]

Anorganisches Grundpraktikum (Basic Practical Course in Inorganic Chemistry). By *C. Mahr* and *E. Fluck*. Verlag Chemie, GmbH, weinheim 1976. 5th completely new, revised edition, XI, 460 pp., 84 figs., 6 tables, paperback, DM 39.80.

This book is divided into three parts. The first of these introduces experimental methods and apparatus by means of experiments and explanations, and the fundamental laws of chemistry in aqueous solutions are treated: 1. Conductivity of electrolyte solutions, indicators, neutralization, *etc.*; 2. Chemistry of complexes; 3. Solubility product; 4. Redox potentials, galvanic cells, electrolysis, *etc.*; 5. Reaction rate, catalysis.

In the second part the authors turn to the preparation, reactions, and detection of nonmetals and their compounds and ions, and then to the properties and reactions of the

most important oxidation states of metal cations. The nonmetals are arranged according to their position in the periodic system and the metals according to the methods of separation used in classical qualitative analysis. The separation of cationic groups is described in detail. In addition, this part of the book contains prescriptions for the preparation of nonmetals, their compounds, and complexes and further theoretical chapters (chemical bonding, paper chromatography, ion exchangers, adsorption, acid-base theory, spectroscopic analysis, and chemistry of complexes).

The third part covers the most important analytical reactions with organic reagents. Procedures differing from the classical methods for the separation of cations on semimicroscale are then proposed, in which reactions and crystallization are studied in drops under a microscope. In addition, a paper-chromatographic separation of the classical cationic groups is described. The anions are detected in mixtures by special reactions.

The Brønsted acid-base definition is used for reactions in aqueous systems and the Lewis acid-base system for reactions in molten salts. The many well-chosen experiments are described in detail and their theory is thoroughly explained; some of them are explained with the aid of illustrations, so that the student can carry out the work on his own. The general chapters with carefully selected experiments give a good review of the theoretical principles and the most important procedures. The well subdivided, clearly written book therefore can be recommended as an introductory practical chemistry text suitable for chemists and students of natural sciences.

Claus Hadenfeldt [NB 371 IE]

Applications of Mössbauer Spectroscopy. Vol. I. Edited by *R. L. Cohen*. Academic Press, Inc., New York 1976. 1st Edit., xi, 349 pp., illustrated, bound $ 2450.

Although it is only just over 15 years ago that *Rudolf Mössbauer* discovered the recoilless emission and absorption of gamma quanta by atomic nuclei, Mössbauer spectroscopy has become an important tool for investigations in a wide range of fields. The present first volume in a series devoted to its applications deals primarily with the results in metallurgy, solid-state chemistry, and the chemistry and biochemistry of colloids and surface boundaries. Following a brief introduction by the editor to the underlying physical principles, *L. H. Schwartz* looks critically at the extensive literature on Mössbauer-spectroscopic investigation of the phase changes in iron alloys. The method's application to the study of corrosion phenomena is dealt with by *G. W. Simmons* and *H. Leidheiser, Jr.* The special experimental technique required for biochemical research is given an illuminating description by *G. Lang* in a section leading into the chapter on biological studies. Two further sections provide information about experiments on the biological transport of iron, on structural questions concerning iron-containing storage compounds (*W. T. Oosterhuis* and *K. Spartalian*), and on measurements in enzyme systems (*P. G. Debrunner*). The final chapter is divided into four sections dealing with reactions in the solid state (*P. K. Gallagher*), analysis of archaeological artefacts (*A. Kostikas, A. Simopoulos*, and *N. H. Gangas*), examination of works of art (*B. Keisch*), and some applications in the field of polymer science (*V. I. Goldanskii* and *L. A. Korytko*). All the contributions are characterized by their critical treatment of the material. Admittedly much of the material has already been covered in earlier review articles, but with the ever-increasing difficulty in following the wealth of literature this volume will prove a valuable aid to all who wish to become familiar with Mössbauer spectroscopy.

Ekkehard Fluck [NB 375 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Workshop Computer Applications in Fermentation Technology 1976. Volume 3 of the GBF Monograph Series (Gesellschaft für Biotechnologische Forschung mbH, Braunschweig-Stöckheim). Edited by *R. P. Jefferis III*. Verlag Chemie, Weinheim 1977. 152 pp., paper, DM 65.00.—ISBN 3-527-25719-5

Homo investigans. Der soziale Wissenschaftler. By *W. A. P. Luck*. Volume 8 of "steinkopff taschenbücher". Dr. Dietrich Steinkopff Verlag, Darmstadt 1976. xiv, 317 pp., paper, DM 24.80.—ISBN 3-7985-0458-X

Statistical Mechanics. By *J. E. Mayer* and *M. Goeppert Mayer* (deceased). John Wiley & Sons, New York 1977. xiv, 491 pp., bound, $ 29.00.—ISBN 0-471-57985-8

Iminium Salts in Organic Chemistry. Edited by *H. Böhme* and *H. G. Viehe*. Vol. 9, Part 1 of the series "Advances in Organic Chemistry". Edited by *E. C. Taylor*. John Wiley & Sons, New York 1977. xi, 631 pp., bound, $ 54.00.—ISBN 0-471-90692-1

Organic Chemistry of Drug Synthesis. By *D. Lednicer* and *L. A. Mitscher*. John Wiley & Sons, New York 1977. xvii, 471 pp., bound, $ 27.75.—ISBN 0-471-52141-8

Gmelin Handbuch der Anorganischen Chemie. Main work, System-Nr. 31: Radium. Springer-Verlag, Berlin 1977. 8th edition, xiv, 131 pp., bound, DM 298.00.—ISBN 3.540-93333-6

Chronologie Chemie 1800—1970. By *S. Neufeldt*. Verlag Chemie, Weinheim 1977. vii, 359 pp., bound, DM 78.—.—ISBN 3-527-25676-8

Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry. By *A. P. G. Kieboom* and *F. van Rantwijk*. Delft University Press 1977. xi, 157 pp., paper, Dfl. 45.00.—ISBN 90-298-0101-8

Molecular Symmetry and Group Theory. By *A. Vincent*. John Wiley & Sons, London 1977. ix, 156 pp., bound, £ 5.90.—ISBN 0-471-01867-8

Lehrprogramm Biochemie II.: Dynamische Biochemie. By *H. Schmidkunz* and *A. Neufahrt*. Verlag Chemie, Weinheim 1977. 3rd revised edition 1977. xi, 356 pp., paper, DM 26.—.—ISBN 3-527-25705-5

Radiochemistry, Vol. 3. Senior Reporter: *G. W. A. Newton*. The Chemical Society, London 1977. viii, 141 pp., bound, £ 11.50.—ISBN 0-85186-274-8—A volume in the series "Specialist Periodical Reports".

Programmierte Prüfung Fachrechnen. Chemie—Physik—Physikalische Chemie. By *W. Klein, H. Mayer*, and *G. Reif*. From the series "Ausbildung". Verlag Chemie, Weinheim 1977. 377 pp., bound, DM 22.80.—ISBN 3-527-25692-X

Organolithic Macromolecular Materials. By *A. D. Wilson* and *S. Crisp*. Applied Science Publishers Ltd., London 1977. ix, 298 pp., bound, $ 32.00.—ISBN 0-85334-699-2

Verordnung über gefährliche Arbeitsstoffe. Band 2: Technische Regeln (TRgA). By *E. Quellmalz*. WEKA-Verlag Fachverlag für Verwaltung und Industrie, Kissing 1977. 309 pp., paper, DM 36.00.—ISBN 3-8111-4907-5

Electrochemistry of Biological Molecules. By *G. Dryhurst*. Academic Press, New York 1977. xii, 601 pp., bound, $ 47.00.—ISBN 0-12-222650-X

Metal Ions in Biological Systems, Vol. 6: Biological Action of Metal Ions. Edited by *H. Sigel*. Marcel Dekker, New York 1977. xiii, 453 pp., bound, SFrs. 130.—.—ISBN 0-8247-6403-X

Analytical Chemistry. By *G. D. Christian*. John Wiley & Sons, New York 1977. 2nd edit., xvi, 648 pp., bound, £ 11.35.—ISBN 0-471-15617-5

Immunologie. By *G. Bundschuh* and *B. Schneeweiss*. Gustav Fischer Verlag, Stuttgart 1976. xxvi, 451 pp., bound, DM 42.00.—ISBN 3-437-10451-9

Pericyclic Reactions, Vol. I. Edited by *A. P. Marchand* and *R. E. Lehr*. Vol. 35 of the series "Organic Chemistry". Edited by *A. T. Blomquist* and *H. H. Wasserman*. Academic Press, New York 1977. xi, 286 pp., bound, $ 28.00.—ISBN 0-12-470501-4

Thermochemical Kinetics. Methods for the Estimation of Thermochemical Data and Rate Parameters. By *S. W. Benson*. John Wiley & Sons, New York 1977. 2nd edit., xi, 320 pp., bound, $ 27.00.—ISBN 0-471-06781-4

Foams. Proceedings of a Symposium Organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and Held at Brunel University, September 8—10, 1975. Edited by *R. J. Akers*. Academic Press, London 1976. x, 301 pp., bound, $ 23.50.—ISBN 0-12-047350-X

Spectres D'Absorption Ultraviolets de Composés Organiques Azotés et Corrélations Spectrochimiques, Fascicule 1. By *P. Grammaticakis*. Librairie Lavoisier—Technique et Documentation, Paris 1977. 107 pp., paper, 120 F.—ISBN 2-85206-009-4

Annual Reports in Medicinal Chemistry, Vol. 11. Edited by *F. H. Clarke*. Academic Press, New York 1976. ix, 330 pp., paper, $ 16.50.—ISBN 0-12-040511-3

Quantitative Analytical Chemistry. By *J. S. Fritz* and *G. H. Schenk*. Allyn and Bacon, Boston 1977. 3rd edit., xiv, 689 pp., bound, $ 15.95.—ISBN 0-205-04203-1

Reviews in Macromolecular Chemistry. Edited by *G. B. Butler, K. F. O'Driscoll*, and *M. Shen*. Marcel Dekker, New York 1976. Vol. 14A: xiii, 344 pp., bound, $ 32.50 (ISSN 0557-6458); Vol. 14B: xvi, 315 pp., bound, $ 32.50 (ISSN 0557-6458)

Seminaranleitungen zum Lehrbuch Modellvorstellungen in der Chemie. By *R. L. Keiter*. Walter de Gruyter, Berlin 1977. x, 233 pp., paper, DM 28.00.—ISBN 3-11-004589-3

Elementary Modern Physics. By *R. T. Weidner* and *R. L. Sells*. Allyn and Bacon, Boston 1977. x, 515 pp., bound, $ 15.95.

Essentials of Cell Biology. By *R. D. Dyson*. Allyn and Bacon, Boston 1977. x, 467 pp., bound, $ 15.95.—ISBN 0-205-04649-5

Gas Kinetics and Energy Transfer, Vol. 2. Senior Reporters: *P. G. Ashmore* and *R. J. Donovan*. The Chemical Society, London 1977. xiii, 392 pp., bound, £ 24.00.—A volume of the series "Specialist Periodical Reports"—ISBN 0-85186-766-9

Photobiologie, Band 2: Die biologischen Funktionen des Lichts. By *R. K. Clayton*. Band 34 of the series "taschentext". Verlag Chemie/Physik-Verlag, Weinheim 1977. xi, 223 pp., paper, DM 22.—.—ISBN 3-527-21037-7 (Verlag Chemie); 3-87664-537-9 (Physik-Verlag)

Index of Reviews in Organic Chemistry—2nd Cumulative Edition 1976. Compiled by *D. A. Lewis* and *P. Charnock*. The Chemical Society, London 1977. 308 pp., paper, £ 6.50.—ISBN 0-85186-539-9

Dynamics of Molecular Collisions, Part B. Edited by *W. H. Miller*. Vol. 2 of the series "Modern Theoretical Chemistry". Edited by *W. H. Miller, H. F. Schaefer III, B. J. Berne*, and *G. A. Segal*. Plenum Press, New York 1977. xv, 380 pp., bound, $ 47.40.—ISBN 0-306-33502-6

Topics in Phosphorus Chemistry, Vol. 9. Edited by *E. J. Griffith* and *M. Grayson*. John Wiley & Sons, New York 1977. v, 516 pp., bound, $ 32.65.—ISBN 0-471-32782-4

Alicyclic Chemistry, Vol. 5. Senior Reporter: *W. Parker*. The Chemical Society, London 1977. ix, 439 pp., bound, £ 28.00.—A volume of the series "Specialist Periodical Reports"—ISBN 0-85186-612-3

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE

International Edition in English

Volume 16 · Number 7
July 1977
Pages 423 – 492

The Wittig Reaction in Industrial Practice[**]

By Horst Pommer[*]

Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

The effects of a scientific discovery on industrial practice are illustrated with reference to the Wittig reaction. The aim of utilizing the Wittig reaction for linking terpenoid building blocks to give vitamin A and carotenoids on an industrial scale prompted extensive research and development work of a synthetic and chemical engineering nature. The importance of the Wittig reaction and its variants in the synthesis of active compounds and fine chemicals in industrial research is demonstrated in the present article.

1. Discovery of the Wittig Reaction

Shortly after World War II, *Wittig* directed his attention to the question of the existence of pentavalent nitrogen compounds and discovered, in the course of these studies, the nitrogen ylides of type *(1)*[1].

Formation of the nitrogen ylides *(1)* was proved by addition to benzophenone *(2)* to give the (2-hydroxy-2,2-diphenylethyl)trimethylammonium salt *(3)*.

$$(CH_3)_4\overset{\oplus}{N}Hal^{\ominus} + C_6H_5Li \longrightarrow C_6H_6 + \underset{(1)}{(CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{C}H_2} + LiHal$$

$$\underset{(1)}{} + \underset{(2)}{(C_6H_5)_2C{=}O} \xrightarrow{HX} \underset{(3)}{(C_6H_5)_2C(OH)-CH_2-\overset{\oplus}{N}(CH_3)_3X^{\ominus}}$$

Wittig's studies were always highly systematic, and it was therefore only a matter of course that the investigations carried out on nitrogen would be repeated with the next higher element of Group V, phosphorus. The declared aim of this work was stated, in a 1953 publication with *Geissler*[2], to be the preparation of stereoisomers of pentaphenylphosphorus as

48 *Wittig und Geissler*

Überraschend war das Verhalten von V gegenüber Benzophenon. Bei dieser Umsetzung wurden Triphenyl-phosphinoxyd (etwa 80%) und 1,1-Diphenyl-äthylen (84%) vom Schmp. 5—6° (Mischprobe) gewonnen. Danach hat sich die Methylengruppe gegen den Sauerstoff des Ketons vielleicht über den Vierring VI:

$$(C_6H_5)_3P{=}CH_2 + O{=}C(C_6H_5)_2 \longrightarrow \underset{VI}{(C_6H_5)_3P(-CH_2)-O-C(C_6H_5)_2} \longrightarrow (C_6H_5)_3\overset{(+)}{P}-\underset{(-)}{O} + CH_2{=}C(C_6H_5)_2$$

ausgetauscht;

Fig. 1. The Wittig reaction; facsimile of the first publication [2].

[*] Prof. Dr. H. Pommer
BASF Aktiengesellschaft
D-6700 Ludwigshafen/Rh. (Germany)

[**] Based on an address delivered on the occasion of Prof. *Wittig*'s 80th birthday.

representatives of a new class of compounds. This work led to the first synthesis of crystalline methylenetriphenylphosphorane. When it was attempted to add this product to benzophenone (by analogy with *(1)*) a surprising new reaction was observed. In a total of six lines of text, *Wittig* and *Geissler* described the almost quantitative conversion of methylenetriphenylphosphorane with benzophenone to give triphenylphosphane oxide and 1,1-diphenylethylene (Fig. 1).

This reaction has since become general chemical knowledge as the Wittig reaction, or Wittig olefination, and it influenced the development of synthetic organic chemistry in the following years to an almost unparalleled degree. It initiated creative activity in laboratories throughout the world as the challenge was taken up to establish the preparative potential of the reaction, to study its mechanistic aspects, *e.g.* its stereochemistry, or to investigate its effects on neighboring disciplines.

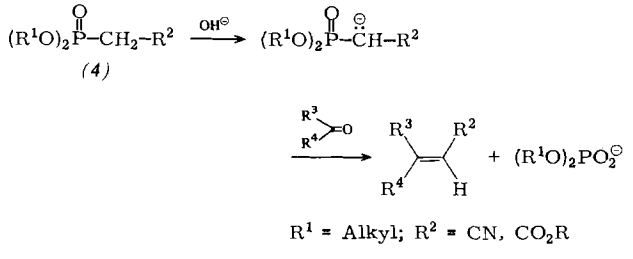
2. The Wittig Reaction and Its Variants in Industrial Practice

2.1. Process Simplification

The traditionally close contacts between the chemistry departments of German universities and the chemical industry led to the very early use of the Wittig reaction in industrial practice. At the beginning of the 1950's, when research at BASF was directed toward the development of syntheses for vitamin A and β-carotene, *Wittig* revealed the new reaction he had discovered in discussions with *Reppe* and *Pommer*. Its significance for the synthesis of compounds of the aforementioned kind was quickly recognized. Studies were immediately undertaken with the aim of utilizing the new reaction for an industrial-scale synthesis of unsaturated compounds, specifically vitamin A and carotenoids.

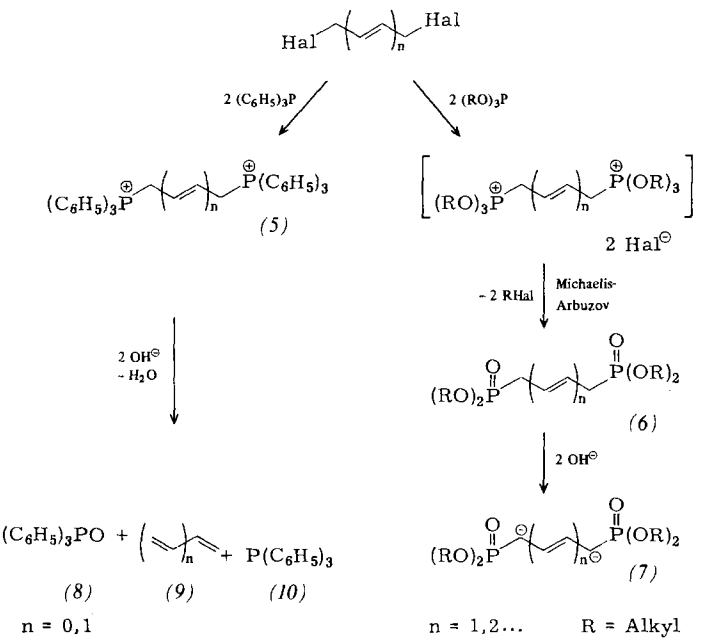
Simple though the reaction is in the laboratory, its translation to an industrial scale was fraught with difficulties, especially when the stringent criteria of safety and economics were taken into account. Other proton acceptors had to be found instead of the originally used organolithium compounds which are consumed in a molar ratio of 1:1; industrially acceptable solvents also had to be found. A further task was to develop an industrial synthesis of triphenylphosphane, which is also consumed in a molar ratio of 1:1 and leaves the reaction as triphenylphosphane oxide[4].

The question arose whether the Wittig reaction is limited to the use of triphenylphosphane. Other phosphorus derivatives were investigated at an early stage with the aim of simplifying the practical application of the Wittig reaction. *Wittig*'s co-workers[5] examined aryl phosphites, while at BASF *Pommer* and *Stilz* concentrated on alkyl phosphites, whose adducts with alkyl halides rearrange to phosphonates



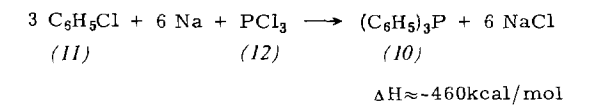
in a Michaelis-Arbuzov reaction[6]. The latter authors found that phosphonates *(4)*, like alkylidenephosphoranes, can be subjected to olefination, and set down the results of this work in a number of patent applications[7].

Working independently, *Horner et al.*[8] found this reaction to proceed with phosphane oxides and were the first to publish a report. Today this reaction is known as PO-activated olefination or the Wittig-Horner reaction. It is particularly useful as a variant of the Wittig reaction when the carbanion generated from the phosphonate *(4)* is resonance-stabilized by neighboring electron-withdrawing groups such as carbonyl, carboxylate, nitrile, or phenyl groups[9]. The activated phosphonic esters *(4)* can be deprotonated under mild conditions; thus aqueous alkali suffices to transform the alkoxycarbonyl or cyanomethylenephosphonates into the carbanions required for olefination[7]. Behavior deviating from that of triphenylphosphoranes is observed with the dianions *(7)* of vinylogous α,β-bisphosphonates, which can easily be prepared and subjected to double olefination; in contrast, the bis(triphenylphosphonium) salts *(5)* decompose to triphenylphosphane oxide *(8)*, olefin *(9)*, and triphenylphosphane *(10)* with alkali[10].



2.2. Production and Regeneration of Triphenylphosphane

The Wittig reaction of triphenylphosphorus ylides proves superior to PO-activated olefination when applied to compounds with alkyl groups or containing terpenoid hydrocarbon moieties. Hence the Wittig reaction became the preferred method for the production of vitamin A. For this reason,



the long-known synthesis of triphenylphosphane *(10)* from chlorobenzene *(11)*, sodium, and phosphorus trichloride *(12)* had to be developed into a safe industrial process. The problem

was eventually solved by a continuous process with a small controllable reaction volume (Fig. 2).

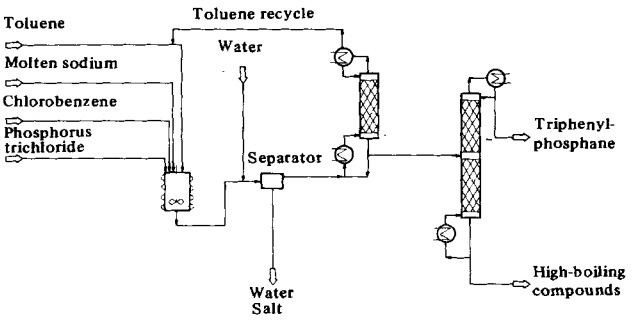
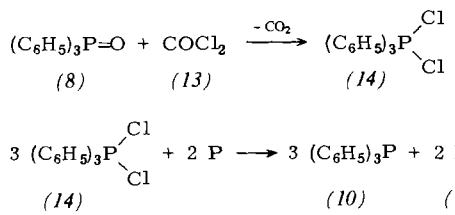


Fig. 2. Flowsheet of the industrial production of triphenylphosphane.

Since the expensive triphenylphosphane is irreversibly transformed into triphenylphosphane oxide during the Wittig reaction it was necessary either to utilize this unavoidable product in some other way or to find a way of re-using it. A new economical process was developed for recycling the triphenylphosphane oxide[11]. Triphenylphosphane oxide *(8)* is converted with phosgene into the dichloride *(14)* which gives triphenylphosphane *(10)* and phosphorus trichloride with elemental phosphorus.



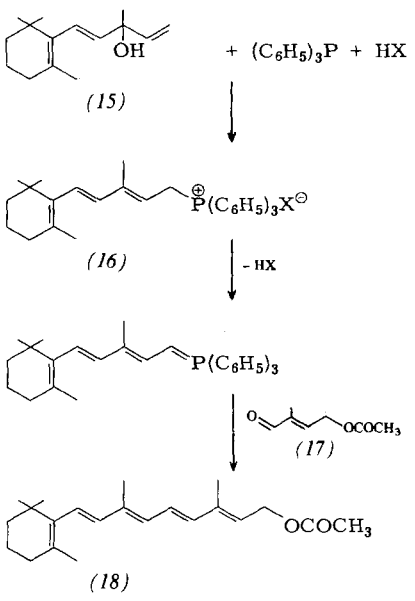
It was possible to adapt the Wittig reaction to industrial practice in various other respects. Metal alkoxides were found to be inexpensive and easily handled proton acceptors as replacement for the originally employed organolithium compounds, and it was found that industrial solvents such as methanol and dimethylformamide could be used as reaction medium.

The decision to employ the Wittig reaction in an industrial synthesis thus prompted a series of studies which were essential for making it an economic proposition.

2.3. The BASF Vitamin A Process

A vitamin A production plant came on stream at BASF in 1971[25]. The key step of the BASF vitamin A synthesis employs Wittig olefination to link a C_{15} unit, *viz.* vinyl-β-ionol *(15)*, with a C_5 unit, *viz.* γ-formylcrotyl acetate *(17)*, as shown in the now well-known reaction scheme[4]. Vitamin A is obtained in the form of its acetate *(18)*.

Control of the exceptionally large amounts of heat involved, 60±2 kcal/mol in the reaction described above, proved fairly difficult. Even with sophisticated safety arrangements, execution of a Wittig reaction in a reaction vessel of several cubic meters in capacity still remained problematic. An industrial solution was found in the choice of a continuous adiabatic process with a small reaction volume.



A flowsheet of the industrial process used for the production of vitamin A and carotenoids is shown in Figure 3[25].

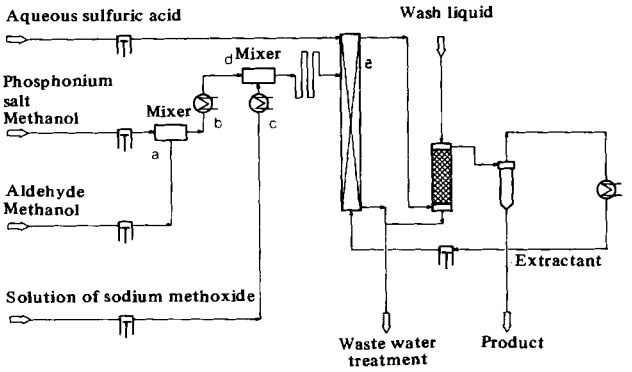


Fig. 3. Flowsheet of the continuous industrial Wittig synthesis. See text for details.

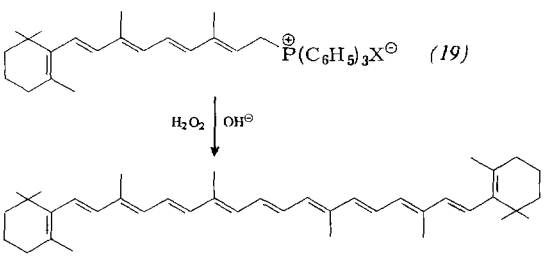
A solution of the triphenylphosphonium salt in methanol is mixed continuously with a methanolic solution of the carbonyl compound in a mixing reactor a) and cooled down to −30°C in a precooler b). A solution of sodium methoxide is simultaneously cooled to −25°C in another precooler c). Both solutions are then passed *via* cooled metering pumps into the mixing reactor d) and reacted therein. Reaction ensues immediately and is complete after a short residence time. The temperature rises and is maintained below the decomposition threshold of the phosphorane by running the reaction under adiabatic conditions. The mixture of reaction products and triphenylphosphane oxide, which is gelatinous owing to the formation of sodium chloride, is then passed to an extraction column in which the desired reaction product is extracted, after acidification with sulfuric acid, by a countercurrent of hydrocarbons. The hydrocarbon extract is washed, again continuously, with aqueous alcohol in a second column in order to remove final traces of triphenylphosphane oxide. The desired product is obtained by gentle evaporation of the extract in a thin-film evaporator. The distillate re-enters the extraction cycle. Figure 4 gives an impression of the dimensions of the plant.



Fig. 4. Part of the distillation equipment in the BASF vitamin A plant.

2.4. Production of β-Carotene and Citranaxanthin

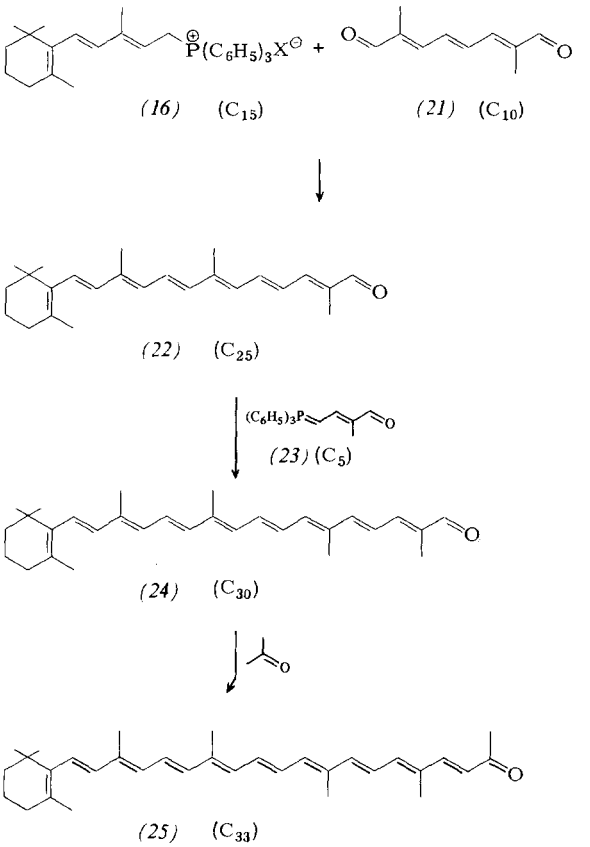
While the production of vitamin A doubtless represents the most important industrial application of the Wittig reaction to date, the process of linking isoprenoid units by the Wittig reaction has provided convenient access to other products of economic significance. These include β-carotene *(20)* and citranaxanthin *(25)*, which occurs in citrus fruit. Both compounds are used as food dyes. β-Carotene and other symmetrical carotenoids can be obtained, *e.g.* by oxidative coupling of resonance-stabilized alkylidenetriphenylphosphoranes *(19)*, two alkylidene moieties combining with elimination of triphenylphosphane oxide to give the symmetrical olefin. This reaction was discovered in 1963 by *Bestmann*[12] in the autoxidation of alkylidenephosphoranes and studied in detail. The specific use of hydrogen peroxide brought about a substantial improvement in yield[13]. The preferred mode of operation consists in the reaction of aqueous solutions of the respective phosphonium salts with hydrogen peroxide in the presence of weak bases.



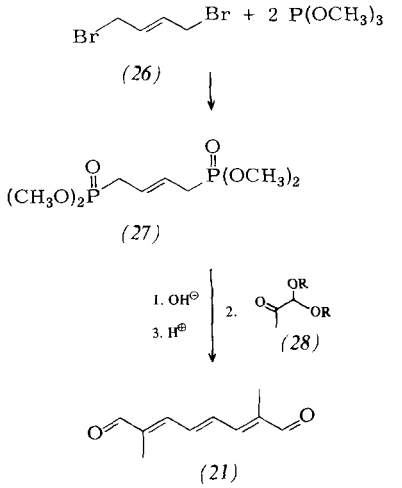
(20)

Production of citranaxanthin *(25)* can start from the same C_{15} unit *(16)* as in vitamin A synthesis, which is linked to one side of the C_{10}-dialdehyde *(21)* to form the aldehyde *(22)*. Subsequent Wittig reaction with the C_5-phosphorane *(23)* and aldol condensation with acetone[26] furnishes citranaxanthin *(25)*[4, 27].

The ability of the vinylogous bisphosphonates to undergo double olefination is exploited in the synthesis of the C_{10}-dialdehyde *(21)*[10], which is not possible, as already mentioned, with the corresponding bis-ylides. Reaction of 1,4-dibromo-2-butene *(26)* and trimethyl phosphite gives the 2-butene-1,4-bis(dimethyl phosphonate) *(27)*, which is converted with



alkoxide into the double anion and by addition of methylglyoxal diethyl acetal *(28)* into the bis(diethyl acetal) of the C_{10}-dialdehyde *(21)*.

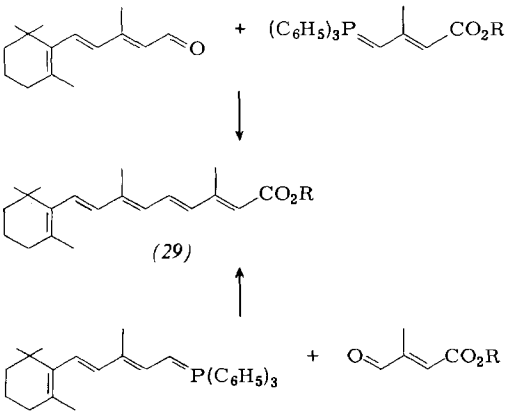


R = C_2H_5

The phosphonate and triphenylphosphane methods are mutually complementary; this is particularly apparent in the synthesis of citranaxanthin *(25)*.

2.5. Production of Vitamin A Acid

One of the first compounds to be synthesized by the Wittig reaction in an industrial laboratory was vitamin A acid *(29)*. The synthetic building blocks just happened to be available in the main laboratory of BASF when the first details of the new reaction became known[4].

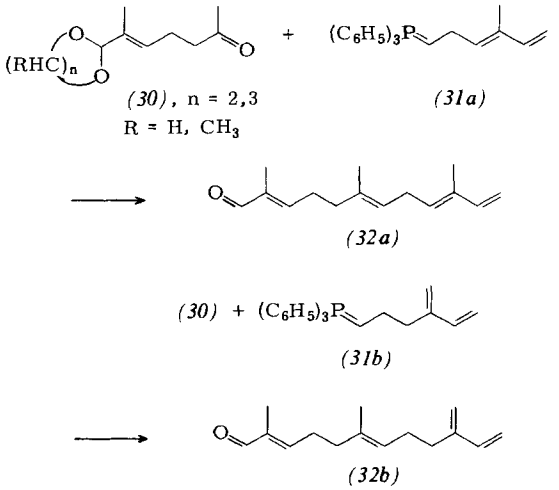


R = H, CH_3

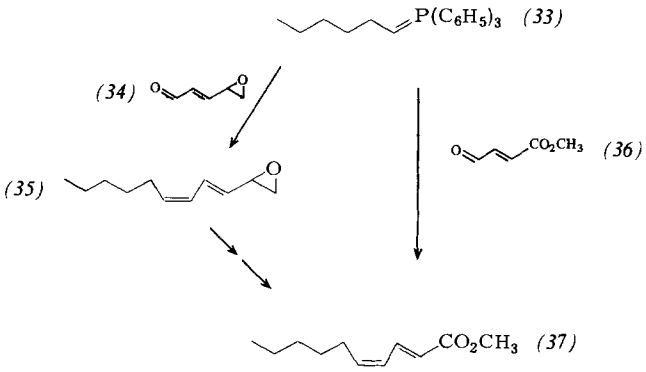
Vitamin A acid was investigated in the 1950's by *Kimmig* in connection with its efficacy in the therapy of various skin diseases. It has been used for several years in medical practice for the treatment of acne[30].

2.6. Production of Aromas and Flavors

Since antiquity, terpenoid aromas and flavors have been among the most valuable objects of commerce. They are today being used in increasing amounts and the only way of satisfying demand would seem to be to synthesize them on an industrial scale. Introduction of the Wittig reaction into industrial practice opened a route to economic synthesis. The sesquiterpenes α- and β-sinensal [*(32)* and *(33)*, respectively], which determine the aroma of natural orange oils, may be cited as examples. They can be synthesized by linkage of a C_8- and a C_7 unit [*(30)* and *(31)*, respectively] with the aid of a Wittig reaction[14].



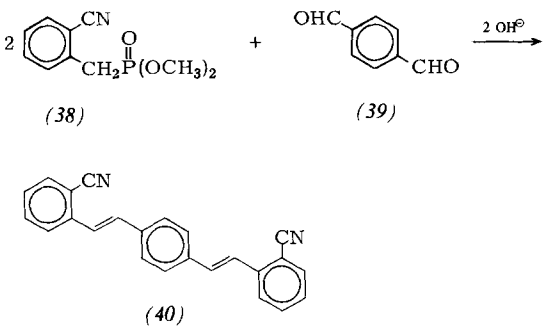
The quality of many perfumes and flavors depends very much upon their purity, and especially their stereochemical purity. The synthesis of "pear ester" *(37)* published by *Ohloff et al.*[15], in which hexylidenetriphenylphosphorane *(33)* reacts with 4,5-epoxy-2-*trans*-pentenal *(34)* under the usual conditions of the Wittig reaction, gives the desired *cis* double bond to the extent of 87%. Subsequent oxidative degradation of the epoxide *(35)* to "pear ester" reduces the *cis-trans* ratio to 75:25. Starting likewise from hexylidenetriphenylphosphorane *(33)*, the synthesis developed at BASF[16] employs fumaric ester hemialdehyde *(36)* and gives "pear ester" *(37)* directly. Linkage of *(33)* and *(36)* to give the *cis* double bond with



a selectivity of 85% is accomplished with the aid of the salt-free variant of the Wittig reaction originally introduced by *Schlosser*[17].

2.7. Production of the Optical Brightener ®PALANIL Brilliant White R

Industrial applications of the Wittig reaction or its variants are not limited to terpenoid compounds. Thus, BASF produces 2,2'-(*p*-phenylenedivinylene)dibenzonitrile *(40)* as an optical brightener for cotton and polyester fibers which is commercially available under the trade name ®PALANIL Brilliant

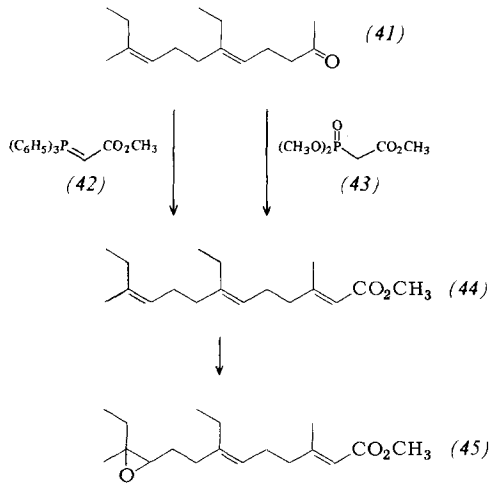


White R. Smooth double reaction affords the desired compound *(40)* from the *o*-cyanobenzylphosphonate *(38)* and terephthalyl aldehyde *(39)*[18].

3. The Wittig Reaction in Industrial Research and Development

3.1. Synthesis of Juvenile Hormone and Juvenile Hormone Mimics

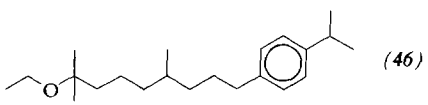
The Wittig reaction has proved particularly useful in the research and development of active compounds for the synthesis of compounds having specific effects in crop protection, animal nutrition, and medicine. It is one of the standard synthetic reactions suitable for preparing complex unsaturated compounds efficiently and in adequate amounts for detailed studies of the quality of active compounds. A few selected examples from the wealth of available material will now be presented.



A new era in the control of insect pests began with the structural elucidation of the C_{18}-Cecropia juvenile hormone *(45)*[18] by *Röller et al.* in 1967[19]. There are good reasons for hoping that selective destruction of pests can be achieved with juvenile hormones or structurally related compounds (juvenile hormone mimics) by using the species-specific hormonal activity to halt insect development in the larval stage. The very first juvenile hormone synthesis by *Röller et al.*[20] in 1967 made use of PO-activated olefination in two synthesis steps. In 1969 two published syntheses of the juvenile hormone *(45)* originating from industrial research laboratories also utilized the Wittig reaction and PO-activated olefination, respectively[28].

The two syntheses differ in the preparation of the unsaturated ketone *(41)*, which is also obtained *via* two Wittig olefinations in one case[21], and in the use of methoxycarbonylmethylenetriphenylphosphorane *(42)*[21] or dimethyl methoxycarbonylmethylphosphonate *(43)*[22] for synthesis of the unsaturated ester *(44)*.

The hopes pinned on juvenile hormones have not yet been fulfilled. Greater promise is now seen in juvenile hormone mimics, also synthesized with the aid of the Wittig reaction and its variants. Among the many compounds synthesized,

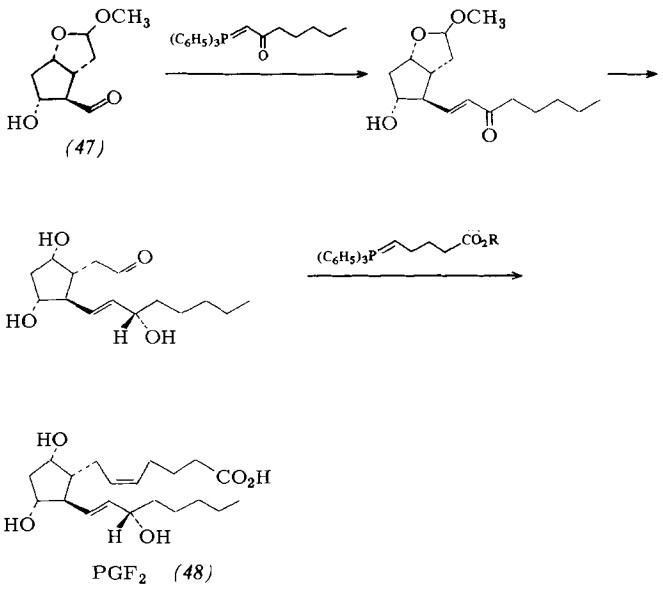


2-ethoxy-9-(*p*-isopropylphenyl)-2,6-dimethylnonane *(46)* is understood to have an extremely effective action on stable flies and houseflies[23].

3.2. Synthesis of Prostaglandins

In recent years the development of prostaglandins has played a prominent role in medical research. Chemists in industry and at universities have paved the way for detailed pharmacological studies on these compounds, occurring in only minute amounts in nature, by synthesizing prostaglandins and their derivatives.

A common feature of these compounds, which display such pronounced and varied activity and structural complexity, is a polysubstituted cyclopentane ring. In nearly all prostaglandin syntheses, the side chains on the cyclopentane ring *(47)* have been introduced by a Wittig reaction. The synthesis of prostaglandin PGF_2 *(48)* developed by *Woodward* and co-workers[24] at the Woodward Research Institute at Basel serves as an illustrative example.



(47)

PGF_2 *(48)*

4. Conclusion

The applications of the Wittig reaction presented above are but a small portion of the available material. New syntheses are currently being developed in numerous laboratories, and some of them will doubtless acquire industrial significance. Through his work, undertaken with the sole aim of expanding man's knowledge, *Wittig* has confirmed that pure science is also the motor of economic progress—a fact that is all too frequently overlooked in present-day discussions.

Received: March 23, 1977 [A 166 IE]
German version: Angew. Chem. *89*, 437 (1977)

[1] *G. Wittig, M. Wetterling*, Justus Liebigs Ann. Chem. *557*, 193 (1947).
[2] *G. Wittig, G. Geissler*, Justus Liebigs Ann. Chem. *580*, 44 (1953).
[3] Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1972. Volumes V/1b to V/1d; *A. W. Johnson*: Ylid Chemistry. Academic Press, New York 1966; *A. Maercker*, Org. React. *14*, 270 (1965).
[4] *H. Pommer*, Angew. Chem. *72*, 811, 911 (1960); *H. Pommer, A. Nürrenbach*, Pure Appl. Chem. 43, 527 (1975).
[5] *G. Wittig*, personal communication.
[6] *A. E. Arbusów, A. A. Dunin*, Ber. Dtsch. Chem. Ges. *60*, 291 (1927).
[7] *W. Stilz, H. Pommer*, DBP 1 109672 (1958); DBP 1 108208 (1959), both BASF.
[8] *L. Horner, H. Hoffmann, H. G. Wippel*, Chem. Ber. *91*, 61 (1958); *L. Horner, H. Hoffmann, H. G. Wippel, G. Klahre, ibid. 92*, 2499 (1959).
[9] *J. Boutagy, R. Thomas*, Chem. Rev. *74*, 87 (1974); *L. Horner*, Fortschr. Chem. Forsch. 7, 1 (1966); *G. Wittig*, Accad. Naz. Lincei *1968*, 341.
[10] *W. Stilz, H. Pommer*, DBP 1 092472 (1958), BASF; *W. Stilz*, Diplomarbeit, Universität Tübingen 1954.
[11] *G. Wunsch, G. Wintersberger, G. Geierhass*, DBP 1 247310 (1966), BASF; *R. Appel, W. Heinzelmann*, DBP 1 192205 (1962), BASF.
[12] *H. J. Bestmann, O. Kratzer*, Chem. Ber. *96*, 1899 (1963); *H. J. Bestmann, L. Kiesilowski, W. Distler*, Angew. Chem. *88*, 297 (1976); Angew. Chem. Int. Ed. Engl. *15*, 298 (1976).
[13] *B. Schulz, J. Paust, J. Schneider*, DOS 2505869 (1976); BASF; *A. Nürrenbach, J. Paust, H. Pommer, J. Schneider, B. Schulz*, Justus Liebigs Ann. Chem., in press.
[14] *M. Baumann, W. Hoffmann, H. Pommer*, Justus Liebigs Ann. Chem. *1976*, 1626.

[15] G. Ohloff, M. Pawlak, Helv. Chim. Acta 56, 1176 (1973).
[16] M. Baumann, W. Hoffmann, DOS 2534859 (1975), BASF; Synthesis, in press.
[17] M. Schlosser, Top. Stereochem. 5, 1 (1970).
[18] W. Stilz, H. Pommer, DBP 1108219 (1959); W. Stilz, H. Pommer, K.-H. König, DBP 1112072 (1959), both BASF.
[19] H. Röller, K. H. Dahm, C. C. Sweeley, B. M. Trost, Angew. Chem. 79, 190 (1967); Angew. Chem. Int. Ed. Engl. 6, 179 (1967).
[20] K. H. Dahm, B. M. Trost, H. Röller, J. Am. Chem. Soc. 89, 5292 (1967).
[21] H. Schulz, I. Sprung, Angew. Chem. 81, 258 (1969); Angew. Chem. Int. Ed. Engl. 8, 271 (1969).
[22] W. Hoffmann, H. Pasedach, H. Pommer, Justus Liebigs Ann. Chem. 729, 52 (1969).
[23] M. Schwarz, R. W. Miller, J. E. Wright, W. F. Chamberlain, D. E. Hopkins, J. Econ. Entomol. 67, 598 (1974).
[24] J. Ernest, Angew. Chem. 88, 244 (1976); Angew. Chem. Int. Ed. Engl. 15, 207 (1976); W. Bartmann, Angew. Chem. 87, 143 (1975); Angew. Chem. Int. Ed. Engl. 14, 337 (1975).
[25] W. Reif, H. Grassner, Chem.-Ing. Tech. 45, 646 (1973).
[26] H. Yokoyama, M. J. White, J. Org. Chem. 30, 2481 (1965).
[27] H. Freyschlag, W. Reif, A. Nürrenbach, H. Pommer, DBP 1210780 (1963); Brit. Pat. 1137429 (1966); Swiss Pat. 506513 (1967); all BASF.
[28] W. S. Bowers, Science 164, 323 (1969); C. A. Henrick, J. B. Siddall, DBP 2202021 (1972), Zoecon; A. Franke, G. Mattern, W. Traber, Helv. Chim. Acta 58, 268 (1975).
[29] J. Kimmig, personal communication.
[30] H. König, K. Lämmerhirt, J. Paust, C. H. Pich, H. Schumacher, Arzneim.-Forsch. 24, 1184 (1974), and subsequent publications.

Steric Interactions in Organic Chemistry: Spatial Requirements of Substituents

By Hans Förster and Fritz Vögtle[*]

Dedicated to Professor Georg Wittig on the occasion of his 80th birthday

From the very extensive factual material available on steric interactions in organic chemistry, the present paper reviews the investigations that provide information about the "size" ("spatial requirement") of the substituents. After an introductory section on the results obtained with the aid of spectroscopic data and by analysis of chemical reactions, attention is turned to conformational processes, including hindered rotation in ethanes, in the biphenyl system, in butadienes, multiply substituted arenes, molecular propellers, and triptycenes. The main emphasis is placed on the explanation of sterically hindered ring inversions in bridged arenes, a class of compounds particularly suitable for the study of steric interactions. The results obtained by variation of the parameters in this system are also discussed with respect to the spatial requirements of organic substituents.

1. Introduction

While steric effects are encountered throughout organic chemistry and in many guises, they are difficult to quantify. As early as 1941[1] the situation was described in the following words: "Steric hindrance ... has become the last refuge of the puzzled organic chemist." Indeed, the influence of steric interactions on reaction rates and on the position of equilibrium in chemical reactions has long been called upon, with greater or lesser justification, to account for experimental findings.

Kehrmann[2] was probably the first to recognize the influence of space filling by substituents on chemical reactions. *Viktor Meyer*[3], *Wegscheider*[4], and *Goldschmitt*[5] in particular studied sterically hindered reactions[6]. The steric origin of the observed effects was successfully demonstrated, but the first correlations with "radical weights" or atomic volumes of the substituents were unsatisfactory and contradictory. The amount of information on sterically influenced reactions subsequently increased very quickly[7]. The terminology[8] was modified in line with the various manifestations of the steric effects, but attempts at empirical quantitative description were seldom made. In the present review we shall try to present a critical collection of data on the quantification of steric effects insofar as they permit a differentiation beyond a general "large or small" classification.

2. The "Size" of Substituents

Since "size" is a geometric concept, the size of substituents should be expressed in geometric units. Van der Waals radii or volumes can be determined by several methods[9], whose results, however, differ considerably. In particular, in the case of atoms containing few electrons (elements of the second row) the values obtained will depend largely on the surroundings of the atom in question, *i.e.* on the type of the bonding, the state of aggregation, and the temperature[9, 10]. The measured size parameters are compromises between several effects and can thus have different values under different conditions. The problem becomes even greater in the case of polyatomic substituents, and it will come as

[*] Dr. H. Förster, Prof. Dr. F. Vögtle
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

no surprise that compromise solutions had to be found for the construction of space-filling molecular models[11].

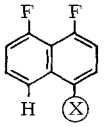
Geometric data do not provide the experimental chemist with an immediate insight into the energetic significance of steric interactions between the groups in a given molecular system, and it is therefore desirable to represent the size of a substituent by an energy contribution to the steric interaction in various systems. Empirical calculations can then be used to determine geometrical quantities; such procedures have recently been perfected[12]. If steric interaction contributes to ΔG or ΔG^{+} values ($\Delta\Delta G$ or $\Delta\Delta G^{+}$), then $\Delta\Delta H$ or $\Delta\Delta H^{+}$ should contain the component of the potential energy that arises from the deformation due to the steric interaction, while $\Delta\Delta S$ and $\Delta\Delta S^{+}$ are a measure of the decrease in translational, vibrational, and rotational motions due to the steric interaction; this interpretation is particularly valid when solvent influences are small[13]. Space filling by a substituent should thus be measurable as an enthalpy component of its steric influence in a suitable reaction. The advantage of this procedure is that the measurements are carried out under the "normal conditions" of chemical reactions and therefore isolate the steric components under these conditions. Nevertheless, the results obtained from a few experiments cannot be generalized: according to the geometry of the transition state (or the reactants) various steric restrictions arise in different systems, and the number of these restrictions increases as the symmetry of the energy-determining geometry decreases.

If it is to lead to reliable conclusions, the information must therefore be obtained by the analysis of model systems embodying as many different structures as possible. Analysis of thermodynamic data for their steric content is simple where the nonsteric effects can be readily calculated from other investigations and/or when steric factors predominate.

In what follows we review the work that enables the substituents to be arranged according to their size.

3. Determination of the Relative Spatial Requirements by Analysis of Spectroscopic Data

Distortion of a molecular skeleton due to steric causes can be detected by spectroscopic methods. Examples of this are the UV investigations into "steric hindrance of resonance"[14], in which for example the distortions of the resonating groups in *o*-halogenated acetanilides or nitrobenzenes are found to increase with increasing size of the halogen[15]. Remarkably, the "through space" F-F coupling in 4-substituted 1,8-difluoronaphthalenes *(1)* has been correlated with the size of the substituent in position 4[16].



(1)

X = H, Br, CN, CH_3, NO_2, NH_2, NHAc, Cl

4. Determination of the Relative Spatial Requirements by Analysis of Chemical Reactions

Taft[17] investigated the rate of base and acid hydrolysis of substituted aliphatic carboxylic esters and *o*-substituted benzoic esters[18]. Because of the low sensitivity of the acid hydrolysis of esters to polar influences, it is possible to obtain steric substituent constants E_s[17] analogously to the substituent constants for the description of polar effects or resonance effects[19]:

$$E_s = \log(k/k_0)_A$$

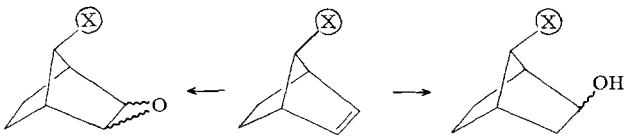
Charton showed later in a statistical analysis[20a] that the E_s values from the aliphatic series can be correlated with van der Waals radii, but that this was not the case for the E_s values from the series of *o*-substituted benzoic acids (E_s^o). It was concluded that the E_s constants describe steric and the E_s^o constants electronic factors. From the rates of esterification and hydrolysis[20b, 20c] of acids XCO_2H and esters XCO_2R, by using the relationship:

$$\log k = \psi v + h$$

Charton was also able to obtain new steric substituent constants for substituents for which, because of their unsymmetrical structure, v cannot be obtained directly from:

$$v_X = r_X - r_H,$$

where r_X and r_H are the van der Waals radii of X and H. Since steric parameters of this type are energy parameters ($\Delta G^{+} = -2.303\,RT\,E_s$), a linear dependence on the van der Waals radii is not *a priori* comprehensible[20d], especially as the ΔH^{+} and ΔS^{+} values do not always vary in the same way as r_X.



(2c) *(2a)* *(2b)*

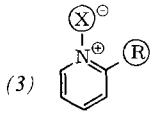
The *exo/endo* ratio in the hydroboration and epoxidation of *(2a)* to *(2b)* and *(2c)*, respectively, depends on the space filling by the substituent X[21]; conclusions about the size of X appear possible. Insertion of the $Sn(CH_3)_3$ group between Br and Cl:

$$C(CH_3)_3 > CH_3 > Br > Sn(CH_3)_3 > Cl > H$$

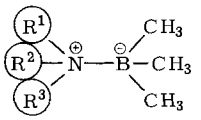
permits the conclusion that the increase in bond length on passing from C—C to C—Sn plays an important role. The order $CH_3 > Br$ is remarkable for the same reason, since it contradicts the results obtained by most other authors.

In a comparison of the base strength of substituted pyridines *(3)* towards Lewis acids of various sizes, *H. C. Brown*[22, 23b] found a strong dependence on space filling by the substituents;

the same was true for the rates of the reactions of these bases with methyl iodide.



(3)



(4)

X = $H^{\oplus}$, BH_3, BF_3, $B(CH_3)_3$

R = H, CH_3, C_2H_5, i-C_3H_7, t-C_4H_9

The dissociation energies of trialkylamine-trimethylborane adducts *(4)* similarly depend on steric factors[23]. However, only alkyl substituents can be compared in the investigation of such systems.

5. Determination of Relative Spatial Requirements by the Analysis of Conformational Processes

The requirement for a large contribution from the steric ("non-bonded" electronic) effect and a small one from other ("through-bond" electronic) influences is best met in conformational processes, since in these no bond is broken and none formed. Conformational processes are especially suitable when the following conditions are fulfilled:

a) If rotations around single bonds without a double bond component are being observed and/or the substituents are far away from the pivot bond, so that the transmission of electronic effects is prevented, the non-steric influences within the conformational process and within the substitulogous series[24] of compounds remain constant. Since no ionic species appear, solvent effects need be expected only when dipole forces make an appreciable contribution.

b) Since in conformational processes the "space filling" parameter is measured as the difference between the energy contents of different geometries of the same molecule, the requirements are that this difference should be as clearly expressed as possible and that the energy content of only *one* geometry should be determined by the substituent whose size is to be defined. This means that either the ground state *or* the transition state of a dynamic process or *one* ground state of an equilibrium is energetically determined by the size of the substituents, and not both to different extents. The requirement for a markedly different steric strain between structures favors measurements in dynamic processes over equilibrium determinations, since narrower limits are set on obtaining the populations of energy-richer equilibrium conformations.

c) The information value of stereochemical investigations increases if exact conclusions can be drawn about the structure with the greatest steric strain. This is most so when the number of possible molecular motions is smallest, *i.e.* when most rigid parts are contained in the molecular skeleton. At the same time, the entropy contribution in ΔG decreases with increasing rigidity. The assignment of relative substituent size and activation enthalpy thereby becomes more precise.

d) The conformational process or the equilibrium should be studied on compounds with the widest possible selection of substituents. However, this requirement is in contradiction to requirements b and c, since the range of processes that can be followed experimentally is strictly limited for rigid systems with strong steric interactions. Compromise solutions must therefore be found if, after variation of the parameters, it still proves impossible to use a sufficient variety of substituents.

e) Optional requirements are ease of synthesis of the variously substituted (substitulogous) compounds and ready monitoring of the stereochemical process [*e.g.* by dynamic NMR (DNMR) measurements[25]].

These requirements have been met in various ways by the conformationally mobile systems described below.

5.1. Hindered Rotation

5.1.1. Ethanes

Ever since *Pitzer*[26] postulated hindrance to free rotation around the C—C single bond in ethanes, the cause of the potential threshold has been the subject of many studies[27]. Steric factors alone cannot explain the findings[28], even in ethanes with large substituents. Since the substituents are oriented away from one another, bond lengths increasing with size can partially compensate the effect of steric interaction through space[29, 30]. The rotation threshold is more obviously connected with space filling by the substituents in the case of groups extending sideways, such as the methyl group[30]. Nevertheless, the lateral interaction remains slight, as is shown in *Anderson*'s P values $(\Delta G_X - \Delta G_H)$[30a] (Table 1). *Anderson* calls this the anisotropy of the van der Waals radius. The unfavorable orientation of the substituents and the effect of dipole forces (in the presence of strongly polar substituents) make ethane derivatives seem unfavorable for investigations of space requirements.

Similar reservations apply to the A values[31] as measures of size. The A values defined by *Winstein*[32] as the logarithm of the ax/eq equilibrium constant in the cyclohexane system[33] presumably contain other components besides the steric contribution of the *cis*-diaxial 1,3-interaction[34]. Furthermore, the steric component of the A values does not correspond to the expectations for larger atoms, since the longer bond lengths decrease the interaction with the small hydrogen atoms at C-3 and C-5[35]. This can be seen, for example, by comparing the A values for Cl, Br, and I (Table 1). If the two hydrogens on C-3 in cyclohexane derivatives are replaced by two methyl groups[36], the expected sequence of steric interactions is obtained. The values for Cl, Br, and I (Table 1) are calculated, since the axial isomers of these derivatives could no longer be detected[36]. Thus, the hindered rotation in ethanes and also the position of equilibrium in cyclohexanes are not very suitable for comparisons of spatial requirements:

a) The unfavorable orientation of the substituents leads on lateral contact only to relatively weak steric interactions, and therefore

b) it is impossible to exclude considerable participation of nonsteric interactions in the small effects that are measured.

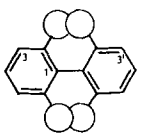
Table 1. Quantitative estimation of the spatial requirements of organic substituents (values in kcal/mol (kJ/mol)), arranged in order of increasing n values [see (34)]. The n values are taken as a measure of the substituent size; see Section 5.2, especially Fig. 1.

X \ System (experimental quantity												
	$\Delta\Delta G_c^{\ddagger}$ [30] P values	ΔG_{ac}^{0} [31] A values	ΔG_{ac}^{0} [36] A values	(6) $\Delta G^{\ddagger}$ [44]	(8) E_A [46]	(12) $\Delta G_c^{\ddagger}$ [48]	(15) $\Delta G^{\ddagger}$ [51]	(17) $\Delta G_c^{\ddagger}$ [58]	(23) ΔG_{298}^{0} [68]	(34) n values [82][e]	(10) $\Delta G_c^{\ddagger}$ [47]	van der Waals radii [9] [pm]
	—	—	—	—	—	—	—	15.8 (66.2) [f]	—	—	—	—
—H	0	0	—	12.8 (53.6)	—	—	5.4 (22.6) [a]	17.1 (71.6)	0	—	—	120
—F	1.1 (4.6)	0.15 (0.6)	0.34 (1.42)	16.0 (67.0)	—	—	9.0 [b] (37.7)	18.6 (77.9)	0.35 (1.5)	5.1	—	147
>N→O	—	—	—	—	—	—	—	—	—	5.2 [g]	—	152
—OH	—	0.52 (2.2)	—	—	—	9.5 (39.8)	—	—	—	6.3	—	152; O
—NH_2	—	1.20 (5.0)	—	—	—	—	—	—	—	7.2	—	155; N
—NO_2	—	1.10 (4.6)	—	—	—	—	14.5 [c] (60.7)	—	—	7.9	—	—
—Cl	3.5 (14.7)	0.43 (1.8)	7.34 (30.7)	16.4 (68.7)	11.3 (47.3)	11.4 (47.7)	14.7 [b] (61.6)	21.9 (91.7)	—	8.1	9.5 (39.8)	175
—CH_3	—	1.70 (7.1)	—	—	—	11.2 (46.9)	15.4 [a] (64.5)	20.9 (87.5)	0.70 (2.9)	8.5	—	—
—CN	—	0.17 (0.7)	—	—	—	10.4 (43.6)	—	—	—	8.9	—	—
—Br	3.8 (15.9)	0.38 (1.6)	15.07 (63.1)	16.6 (69.5)	12.5 (52.3)	12.7 (53.2)	16.6 [a] (69.5)	21.0 (88.0)	1.10 (4.6)	9.2	11.1 (46.5)	185
—OCH_3	—	0.60 (2.5)	—	—	—	9.2 (38.5)	—	23.4 (98.0)	—	9.5	—	—
—I	4.2 (17.6)	0.43 (1.8)	28.37 (118.8)	16.6 (69.5)	15.9 (66.6)	—	18.8 [d] (78.7)	—	—	9.9	12.4 (51.9)	198
—SCH_3	—	0.70 (2.9)	—	—	—	—	—	—	—	10.3	—	—
—CO_2CH_3	—	1.20 (5.0)	—	14.7 (61.6)	—	—	—	—	—	12.1	—	—

[a] Y = Br, Z = H; [b] Y = Cl, Z = H; [c] Y = Z = Br; [d] Y = I, Z = H; [e] n see Table 3; [f] value for the analogous quinoline derivative (17a); [g] value for the analogous pyridine derivative (34a).

5.1.2. The Biphenyl System

In the biphenyl system (5)[37] the orientation of the colliding groups is more favorable than in the ethanes. By suitable



(5)

substitution of biphenyl various groups can thus for the first time be reliably arranged in the order of "size"[38]:

$$Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F > H$$

The "interference values" calculated from X-ray data show the same sequence[39]. The results are not quite conclusive, since the series was obtained by combining the findings for many derivatives carrying various substituents in the *ortho*-positions.

The position of several identical *o*-substituents relative to one another is not without influence on the sequence obtained[37]; this could be an expression of a slight through-bond or through-space electronic influence. The effects of substituents in positions 4 and 4′ are probably electronic in nature[37], showing that requirement a) (see Section 5) is not completely satisfied in the biphenyl system.

Comparison of the "sizes" of OCH_3, CH_3, and F makes it clear that the interaction of the methoxy group occurs *via* the oxygen. On the other hand, the size of group R in OR-substituted biphenyl derivatives cannot be neglected[40]. In this connection it is interesting to note the sequence of the "buttressing" effect[37a, 41] of substituents in position 3 and 3′:

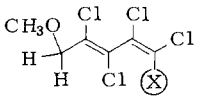
$$NO_2 > Br > Cl > CH_3 > OCH_3$$

Here the methyl group appears to be smaller than Cl and the nitro group larger than Br. The lateral interaction of methyl groups due to their conical form[9a, 20a] is weaker than that of the more extensive spherical substituents such as Cl, which is in agreement with the P values in the ethane system[30]. The strong buttressing effect of aromatically bonded nitro groups indicates that the nitro-oxygen atoms extend in the plane of the benzene ring[42]; on the other hand, the steric interaction of the nitro group in *o*-nitrobiphenyl derivatives is weakened by the twisted orientation of the nitro groups. These examples show the importance of the *interaction geometry* with respect to the evasive behavior of substituents of lower symmetry (anisotropic space require-

ment). In spite of the relative rigidity of the biphenyl system, considerable differences are found between the activation entropies[43]; comparison of activation enthalpies would therefore be preferable.

5.1.3. Butadienes

Numerical values of the steric buttressing effects in chiral penta- and hexasubstituted butadienes *(6)* were determined by *Mannschreck, Köbrich et al.*[44] for some substituents by means of DNMR spectroscopy (Table 1). The sequence of the $\Delta G_c^{\neq}$ values shows a slight buttressing effect for "flat" substituents such as methoxycarbonyl and dichlorovinyl;



(6)

X = H, CO_2CH_3,  , $Sn(CH_3)_3$, F, $Si(CH_3)_3$, Cl, CH_2OH, Br, I, CH_2OCH_3, $SiPh(CH_3)_2$, $C(CH_3)_2OH$

apparently these groups are twisted out of the plane of the double bond even in the ground state. Comparison of Cl, Br, and I with one another and of $C(CH_3)_2OH$ with $Si(CH_3)_3$ and $Sn(CH_3)_3$ shows again an inverse effect between size and increasing bond length:

$$Cl \approx Br \approx I \text{ and } C(CH_3)_2OH > Si(CH_3)_3 > Sn(CH_3)_3$$

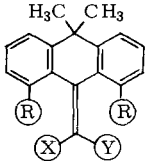
The strong effect of fluorine substituents [$\Delta\Delta G_c^{\neq} = 3.2$ kcal/mol (13.4 kJ/mol)] can, however, hardly be explained on steric grounds.

5.1.4. Methylenedihydroanthracenes

The rate of the ring inversion in substituted methylenedihydroanthracenes *(7)* is controlled to a considerable extent by steric interactions between the groups X, Y, and R[45]. The sequence

$$Br > Cl > CH_3 > C_6H_5 > CO_2CH_3 \gg H$$

again demonstrates the weak steric interaction of flat substit-



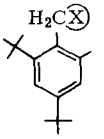
(7)

uents (C_6H_5, CO_2CH_3), while the position of CH_3 is explained by a "cogwheel effect".

5.1.5. Multiply Substituted Arenes

Many authors chose arenes carrying several substituents as model systems for the study of steric interactions. For the series of compounds *(8)* *Cupas*[46] found the sequence

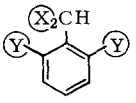
$$I > Br > Cl$$



(8)

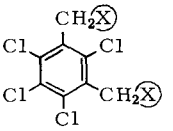
X = Cl, Br, I

with considerable differences between the rotation barriers (Table 1). *Schaefer*'s results for *(9)*, *(10)* (Table 1)[47a], and *(11)*[47b] confirm this sequence.



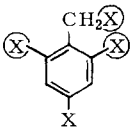
(9)

X = F, Cl, Br, I
Y = H, Cl, Br



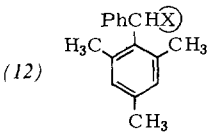
(10)

X = Cl, Br, I

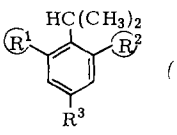


(11)

X = Cl, Br



(12)



(13)

R^1, R^2 = CH_3, Cl, Br
R^3 = CH_3, NO_2

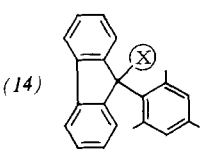
The magnitude of the $\Delta G^{\neq}$ values (Table 1) for the rotation barriers in *(12)* gives the sequence[48]:

$$Br > SH \approx Cl \approx CH_3 > CN > OH > OCH_3$$

while the equilibrium positions found for *(13)*[48,49] lead to:

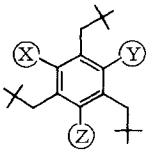
$$Br \approx CH_3 > Cl$$

In *(14)* an increasing rotation barrier of the mesityl group is observed as the size of the substituent X decreases—here the steric interaction influences preferentially the ground state[50].



(14)

X = H, OH, Cl



(15)

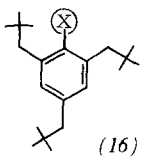
X, Y, Z = H, F, Cl, Br, I, CH_3, NO_2

Rotational hindrance of the neopentyl groups in multiply ring-substituted 1,3,5-trineopentylbenzenes *(15)* was investigated by *Carter*[51] for several combinations of X, Y, and Z. Since the rotation barriers measured were determined

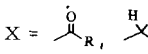
mainly by the smaller substituents (X, Y, or Z), it was possible to determine relative "sizes". This gives the sequence:

$$I > Br > CH_3 > Cl > F > H$$

The nitro group (in a twisted orientation) can be assigned the position $Cl > NO_2$[52], similar to its position in the biphenyl sequence. Linear free-energy relationships can be derived from data reported by *Anderson* (ethane derivatives)[30] and by *Cupas* (arenes)[46]; as expected, the arenes *(8)* more similar to *(15)* correlate with a gradient nearer to unity. The sp^2-sp^3 rotation barriers of many alkyl and acyl substituents X were also compared in the analogous system *(16)*[53].



(16)

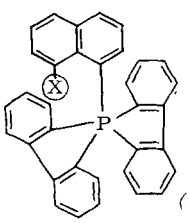
X = 

R = CH_3, C_2H_5, i-C_3H_7, t-C_4H_9, C_6H_5

Rotation barriers increase with increased branching. Acyl substituents hinder rotation more strongly than the corresponding alkyl substituents. This is to be expected from the larger spread of the acyl groups and the fact that the range of action of O is greater than that of H[54]. In *(15)*, X = Y = Z = Br, and *(15)*, X = Y = Br, Z = NO_2, large contributions from the "all-*cis*-conformers" could be demonstrated[55], in which all three neopentyl groups are directed to the same side of the benzene ring—an indication that steric effects cannot be regarded merely from the standpoint of destabilizing interactions but that attractive steric interactions must also be reckoned with[55, 56].

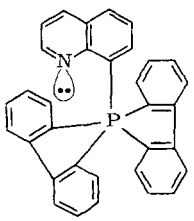
5.1.6. Molecular Propellers

Propeller molecules[57] offer a wide field for the study of steric phenomena. *Hellwinkel*[58] investigated the combined rotation/pseudorotation of the naphthyl and spiran units in

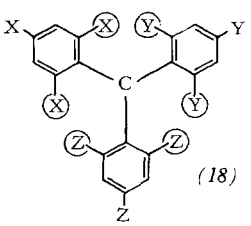


(17)

X = H, F, Cl, Br, CH_3, OCH_3, $N(CH_3)_2$



(17a)



(18)

X = Y = CH_3

Z = OCH_3

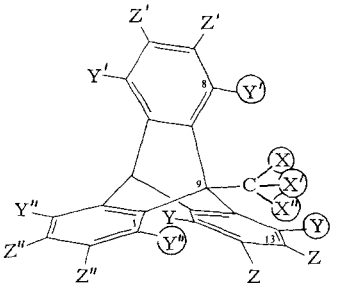
spirophosphoranes *(17)* and *(17a)*. A marked dependence on the space filling of the substituent on C-8 of the naphthyl group (Table 1) was observed. The sequence found in *(17)* was:

$$N(CH_3)_2 > OCH_3 > CH_3 \approx Br \approx Cl > F > H$$

and on the extreme right of this sequence should be placed the electron pair on the nitrogen atom in *(17a)*. Unlike what happens in most other systems, the methyl group of the OCH_3 substituent in *(17)* is brought into the steric interaction[59]. In the triphenylmethanes *(18)*, however, the CH_3 group hinders "ring rotation" more than does the OCH_3 group[60].

5.1.7. Triptycenes

Interesting conclusions about the effect of the relative orientation of colliding groups on rotation thresholds and equilibrium positions can be expected from 9- (bridgehead) and 1,8- or 1,8,13-(*peri*-)substituted triptycenes *(19)*[61]. In this system both "end-on" interactions (variation of the substituents X) and "side-on" interactions (variation of the substituents Y) can be investigated. However, the available results do not permit any clear conclusions. Unexpectedly, when X = X′ = X″ = Y′ = Y″ = Z = Z′ = Z″ = H, but Y = OCH_3 a larger

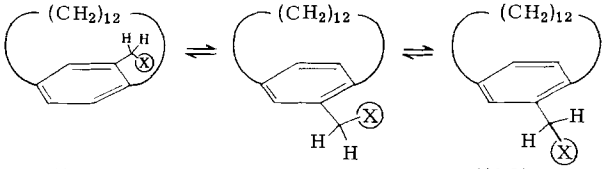


(19)

interaction is observed than for the analogous compound with Y = CH_3. The best explanation for this phenomenon seems to be cogwheel-like coupled rotation of the two methyl groups in positions 1 and 9[61] (the "gear-effect"[62]), these groups being arranged exactly like spur gears. The two spherical substituents Cl and Br, however, range themselves as expected in regard to size (Br > Cl). The position of the conformer equilibrium in 9-benzyl-substituted triptycenes indicates besides repulsive steric effects attractive interactions explicable by charge-transfer stabilization[63]. Non-steric effects here again appear important, particularly for equilibrium positions where the energy differences are relatively slight.

5.2. Steric Hindrance of Ring Inversion in Phanes

Investigations of bridged compounds[64] have recently contributed much to our understanding of steric (and electronic) effects[65], yielding a wealth of detailed information.



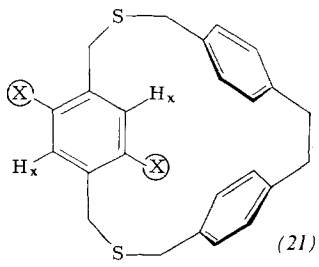
(20A) (20B) (20C)

In some cases comparative studies with varied substituents have been carried out:

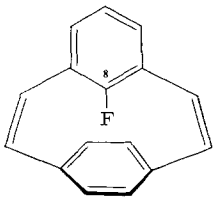
In the parabenzenophane system *(20)* the activation energies of the process (A)⇌(B)⇌(C) were found to be in the sequence[66]:

$$OH > Br > CO_2C_2H_5$$

which was ascribed to the extent of the steric hindrance of benzyl rotation. This surprising sequence, however, indicates rather a steric ground-state effect.



(21)



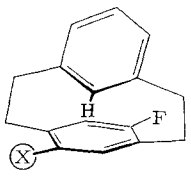
(22)

X = H, F, OCH_3, CH_3, Cl

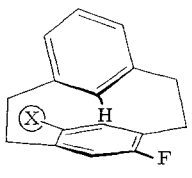
Tabushi et al.[67] compared the chemical shift of the H_X-proton in *(21)* with that of the H_X-proton in the dithiol starting material [the corresponding *p*-phenylenebis(methanethiol)]. As the steric repulsion between X and the unsubstituted benzene rings increases, the effect of the ring current on the H_X shrift decreases. The sequence:

$$Cl > CH_3 > OCH_3 > F > H$$

is the expected one except for $Cl > CH_3$; if the dithiol is a valid reference compound, this could be indicative of an

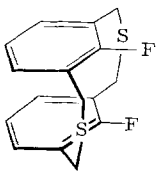


syn-(23)

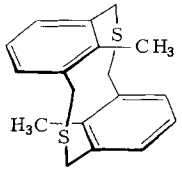


anti-(23)

X = H, CH_3, Br



syn-(24)



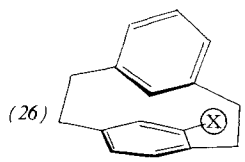
anti-(25)

increased repulsion (or diminished attraction) between the aromatic π-cloud and the electronegative substituent Cl as compared with the CH_3 group. A surprisingly strong destabilizing interaction between the substituent F and an aromatic π-system was also found by *Boekelheide*[68] in 8-fluoro[2.2]metaparabenzenophanediene *(22)*. Replacement of the H by F in position 8 decreases the rate of flip of the *meta*-ring by a factor of at least 10^{11}. Since an increase of only 50 pm (0.5 Å) is obtained from the bond lengths and van der Waals radii of H and F, the question arises whether the potential energy function of the repulsion really rises so steeply in this region, or whether an especially strong destabilizing interaction exists between F and the π-cloud. From the position of the *syn/anti*-equilibrium in the metaparaphanes *(23)*, however, the expected sequence has been derived (Table 1):

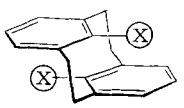
$$Br > CH_3 > F > H$$

Contrary to the situation with *(25)*, the *syn*-conformation of *(24)* predominates (*syn/anti* ratio 7:1), and that cannot be explained by an unusual repulsion between a π-cloud and a fluorine atom; accordingly, here attractive forces must be in operation[68]. The proportion of the *syn*-conformations in the metaparaphane system *(26)* decreases in the sequence

$$H > CHO > CH_2OH > CH_3 > COCH_3 > CO_2CH_3$$



(26)

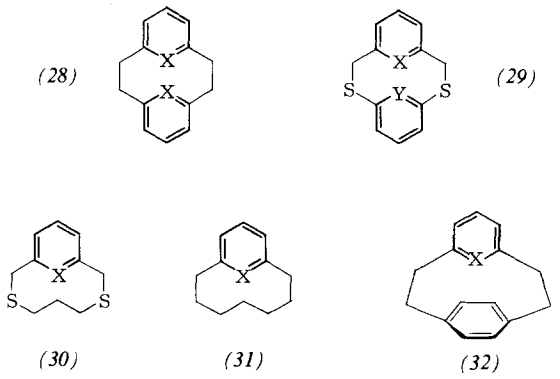


(27)

and this is attributed mainly to steric repulsion[69, 70]. The [2.2]metaphane system *(27)* might appear suitable for studying special interactions between substituents X and aromatic π-systems, for its conformation can be determined very exactly by means of the $^3J_{HH}$ coupling constants (H atoms of the ethylene bridges)[71].

Steric effects are especially marked when colliding parts of molecules are forced into close neighborhood by rigid groups and the possibilities of evasion are reduced to a minimum. This is largely the case with intra-annular interactions. Since extension or compression of bonds never contributes to any considerable extent to the total strain[12, 72], the often substantial van der Waals interaction energy is partly converted into angle deformation and torsion also affecting rigid groups[72]; in suitable structures one thus obtains a particularly large proportion of non-bonded interactions. Admittedly, the energetic results of such increased steric interactions can only be specified in the activation parameters of dynamic processes, and here too there are usually few possibilities of varying the colliding groups, unless it is possible to adjust the system to the steric requirements without a decisive change in the structure. Many of the conformational processes studied on phane systems with intra-annular steric interactions thus permit the size of substituents to be obtained only as a two-

sided comparison in the sense of a rigid/not rigid decision. Nevertheless, some important details could be studied on such systems, as for example the question of the "size" of the free electron pair on the nitrogen, which had arisen from conformational investigations of piperidines[73].

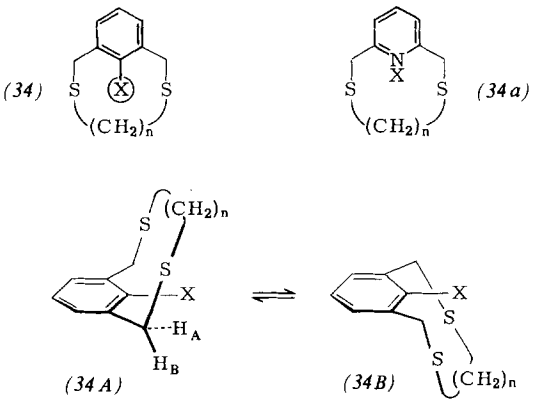


(28) (29) (30) (31) (32)

Phanes of the types (28)—(32), X=N, show in all cases lower flip thresholds than their carbocyclic analogs (X=C—H) (Table 2):

C—H > N⊖

(34A) ⇌ (34B) the intra-annular substituent X can still just pass through the interior of the ring[82]. The range of the



(34) (34a) (34A) (34B)

measurements can therefore be suited to the substituents. The following advantages are thus obtained:

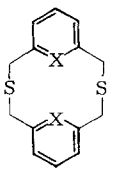
a) Each substituent meets the same interaction partner; effects due to different polarizability can therefore be ascribed to the substituent alone.

b) Owing to the flexibility of the chain, no distinct steric destabilization of the ground state is present[83].

Table 2. Quantitative estimation of the "spatial requirements" of electron pairs. $G_c^{\ddagger}$ values in kcal/mol (kJ/mol).

X	Y	(28)	(29)	(30)	(31)	(32)
N	N	14.8 (62.0) [74]	<13.6 (<57.0)	<10.2 (<42.7) [76]	9.0 (37.7) [76]	10.7 (44.8) [79]
C—H	C—H	> 27 (>113) [75]	>23 (>96) [75]	10.2 (42.7) [77]	11.5 (48.2) [78]	20.6 (86.3) [65b, 68]
C—H	N		20.5 (85.9)			

If the size of the intra-annular substituent in such systems is increased, the barriers to the flip become much greater; in [3.3]dithiametabenzophane (33), X=C—H, and in the



(33)

X = N⊖, C-H, C-F, C-Cl, C-Br

pyridine analog (33), X=N, inversion of the mediocycle (*i. e.* the central large ring) is too fast for the DNMR method; when X=C—F it is observable, and if X=C—Cl or C—Br it lies above the accessible temperature range[80].

In the phane system (34), however, by choosing an aliphatic chain of suitable length, the diameter of the large ring can be adjusted so that in the topomerization process[81]

c) The chain contains only nonpolar bonds. Specific interactions between the substituent and the chain are thus unlikely.

d) The collision does not occur quasi-"one-dimensionally", but in a "two-dimensional" girdle, as the oligomethylene bridge "embraces" the intra-annular substituent in the transition state.

e) The benzyl protons absorbing as an AB system appear only slightly in long-range coupling. DNMR analysis is thereby simplified.

As a result of the synthetic variability it has already been possible to measure the free activation enthalpy of the diastereotopomerization for a large number of substituents X (Table 3); the series could be extended without difficulty to other substituents. The steric interaction of most of the substituents was measured for two or three bridge lengths $n+4$.

In Figure 1 the $\Delta G_c^{\ddagger}$ values for (34) and (34a) are plotted against n. It may be seen that $\Delta G_c^{\ddagger} = f(n)$ leads to similar slopes in all cases, even though a few lines do intersect. The lines for substituents whose DNMR investigation was possible at only one bridge length have been interpolated.

Table 3. Free activation enthalpies at the coalescence temperature ($\Delta G_c^{\ddagger}$) for the topomerization process *(34A)* ⇌ *(34B)* [82] of metaphanes *(34)*, arranged in order of increasing n values of the substituents (values in kcal/mol (kJ/mol)).

X \ n	3	4	5	6	7	8	9	10	12
(34a).	$T_c < -60°C$								
—H	10.2 (42.7)								
—F		23.5 (98.4)	15.3 (64.1)	10.5 (44.0)					
(34a) →O		21.3 (89.2)	15.8 (66.2)	12.7 (53.2)					
—OH				16.3 (68.3)					
—NH_2				24.0 (100.5)					
—NO_2						15.2 (63.7)			
—Cl					23.5 (98.4)	15.4 (64.5)	11.6 (48.6)		
—CH_3					25.8 (108.1)	16.6 (69.5)	12.0 (50.3)		
—CN						23.6 (98.8)	14.5 (60.7)		
—Br						22.5 (94.2)	15.4 (64.5)	9.5 (39.8)	
—OCH_3						23.2 (97.3)	17.9 (75.0)	10.5 (44.0)	
—I								14.6 (61.2)	
—SCH_3								17.4 (72.9)	
—CO_2CH_3								23.6 (98.8)	
—SO_2CH_3									16.9 (70.8)

The value of n at $\Delta G_c^{\ddagger} = 15$ kcal/mol (62.8 kJ/mol) could be taken as a measure of the size of a substituent ("n values", Table 1).

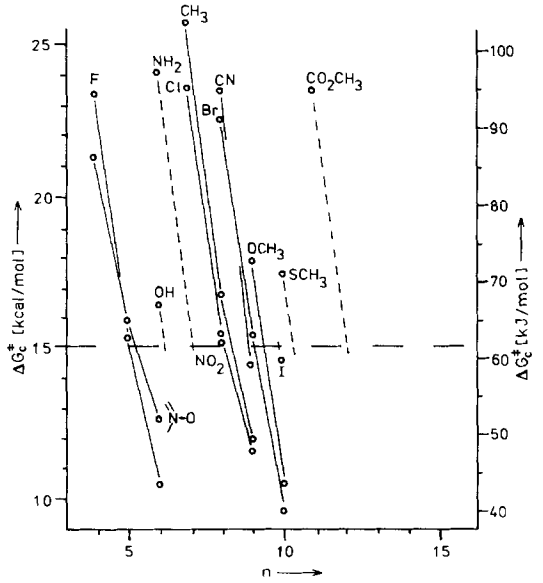


Fig. 1. Dependence of the free activation enthalpies $\Delta G_c^{\ddagger}$ for the topomerization process *(34A)* ⇌ *(34B)* on the bridge length $n+4$ in metaphanes *(34)*. n-Values: points of intersection of the straight lines with $\Delta G_c^{\ddagger} = 15$ kcal/mol (62.8 kJ/mol).

This $\Delta G_c^{\ddagger}$ value corresponds to coalescence at approximately 30 °C. It would, however, be desirable to have an exact $\Delta H^{\ddagger} = f(n)$ relationship. Different $\Delta H^{\ddagger}/n$ values could then be considered as related to different polarizability/bond-deformability of these substituents. $\Delta G^{\ddagger}$ values could replace the only imprecisely measurable $\Delta H^{\ddagger}$ values when $\Delta S^{\ddagger}$ is the same for one chain length (independently of the substituent).

Complete line-shape analyses[84] for some suitable cycles *(34)*, X = CH_3, $n = 7$ or 8, and *(34)*, X = OCH_3, $n = 9$, gave the following results: $\Delta S^{\ddagger}$ becomes more strongly negative with increasing activation enthalpy and increasing bridge length; substituents of lower symmetry also lead to a lowering of $\Delta S^{\ddagger}$. This agrees with the expectation that in the transition state of the process *(34A)* ⇌ *(34B)* the possibilities of rotation of chain members and substituents X are limited. Comparison of $\Delta G_c^{\ddagger}$ values is thus not without its problems[25, 81]. Differentiation between substituents with the same n value should, however, be reliable, even though the jump from one n value to another is difficult to quantify.

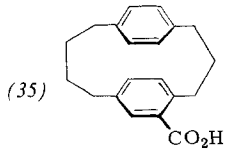
The method presented above arranges substituents according to their extension; the mobile $(CH_2)_n$ chains adapt themselves to substituents of different shape[83]; the results found for this system are thus not in any case applicable to other systems without any modifications. According to the method of measurement, the order of arrangement of in particular the unsymmetrical substituents often varies, showing how strongly a result may depend on special structural features. The aim of such conformational investigations must therefore be to isolate the individual effects involved in the broad concept of "steric interactions" by using many methods of measurement, and to characterize these effects. For this purpose not only is a large selection of systems necessary but also, within each system, there must be a graded variation of the structural characteristics. The effect of changing a single parameter within

groups of similar compounds will now be illustrated by some examples.

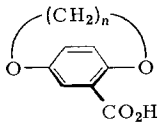
5.3. Variation of a Single Parameter

5.3.1. Size of the Mediocycle

A change in the width of the mediocycle has a very strong effect on the inversion barriers: in the phanes *(34)* shortening of the bridge by one methylene group in the sterically critical region leads to an increase in $\Delta G_c^{\ddagger}$ of *ca.* 7 kcal/mol (29.3 kJ/mol). The [4.3]parabenzenophane *(35)*[85] racemizes at a measurable rate; the corresponding [4.4]phane is no longer separable into the enantiomers. The paraphane *(36)*, $n=9$, can be racemized above 70°C, but *(36)*, $n=8$, is stable, and *(36)*, $n=10$, is no longer separable into enantiomers[86, 87].

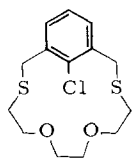


(35)

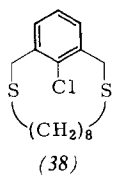


(36)

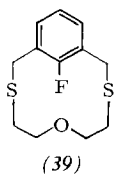
If methylene groups are replaced by heteroatoms the change in the bond lengths is generally as expected. Thus, replacement of $-CH_2-$ by —S— always facilitates inversion of the mediocycle, as is clearly shown by comparing phanes *(28)* with *(29)*, and *(31)* with *(30)*. If in the phanes *(33)* or *(34)* the —S— is replaced by —N(Tos)—[88], the inversion barriers increase by *ca.* 5 kcal/mol (20.9 kJ/mol). However, contrary to expectation, the topomerization threshold for the dioxaphane *(37)* is lower than that for *(38)* by *ca.* 1 kcal/mol (4.2 kJ/mol)[89], which is a sign that shortening the chain by four times 11 pm (0.11 Å) can be compensated by the greater flexibility of the C—O—C bonding and the suppression of



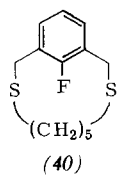
(37)



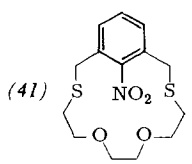
(38)



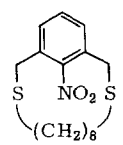
(39)



(40)



(41)

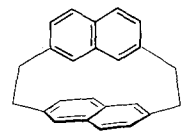


(42)

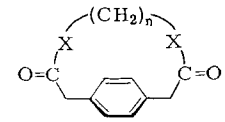
some *gauche*-H—H interactions. In *(39)* and *(41)* the $\Delta G_c^{\ddagger}$ values are again higher than those in the corresponding dithia compounds *(40)* and *(42)*. The nature of the atoms concerned in the steric interaction is thus also important[89, 90].

5.3.2. Flexibility

The change in molecular flexibility also has marked effects in other systems: Although there are two intra-annular H-π-interactions in the [2.2]naphthalenophane *(43)*, the ring-flip process is not more strongly hindered than in the [2.2]metaparaphane *(32)*, X=C—H[91]. This can be explained as a consequence of the greater flexibility of naphthalene compared with benzene[91–94]. If rigid ester or amide groups are introduced into the methylene bridge of [*n*]parabenzenophanes



(43)



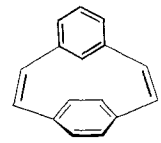
(44)

X = NH, O
R = H, CH_3

such as *(44)*, then the hindrance to *p*-phenylene ring-rotation is greater than would be expected from the bond lengths alone[95].

5.3.3. Changes in the Basic Skeleton

Even relatively slight changes in the basic molecular skeleton can have very drastic effects. Comparison of the coalescence temperatures of the flip processes in metaparabenzenophane *(32)*, X=C—H ($T_c=157$ °C) with that in the diene *(45)* ($T_c=-96$ °C)[65b, 68] shows clearly the decreased steric interaction

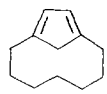


(45)

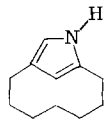
due to broadening of the angle in the bridge[96]. In the series *(46)*—*(49)* the free activation enthalpy for ring inversion increases rapidly with increasing angle α[97, 98]; $\Delta G_c^{\ddagger}$ amounts to 11.5 kcal/mol (48.2 kJ/mol) for *(46)*, to 18.2 (76.2) for *(47)*, and to >23 (>96) for *(48)* and *(49)*.



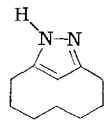
(46)



(47)

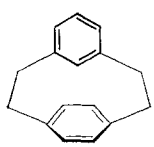


(48)

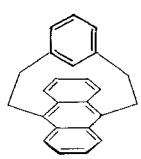


(49)

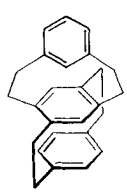
From a comparison of the coalescence temperatures[99] or the $\Delta G^{\ddagger}$ values for *(50)*[68], *(51)* and *(52)*[100] with those of the parent substance *(32)*, X=C—H, one may deduce the influences on the ground and the transition states. In *(50)* the ground state is destabilized by π-π interaction between the *m*-phenylene nucleus and the anthracene skeleton, but the transition state is stabilized relative to [2.2]metaparaphane



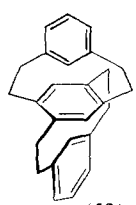
(32)



(50)



(51)



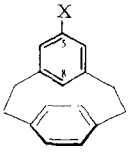
(52)

	(32)	*(50)*	*(51)*	*(52)*
$\Delta G_c^{\ddagger}$ [kcal/mol]	20.6	17.5	17.8	18.1
[kJ/mol]	86.3	73.3	74.6	75.8
T_c [°C]	156	82	100	116

owing to the smaller loss of resonance energy. In *(51)* and *(52)* the flip is clearly facilitated by the prescribed boat-like deformation[101] of the central benzene ring.

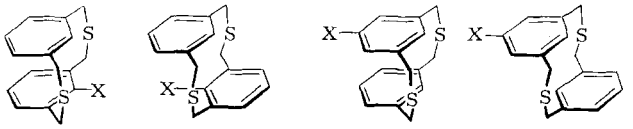
5.3.4. Influence of Substituents

Strong steric compression of atoms and bonds must affect the electron distribution in the molecule. Since substituents also change the electron distribution, it should be possible to establish an influence of substituents on sterically hindered processes. *Boekelheide* found in the [2.2]metaparabenzenophane *(53)* a considerable influence of substituents at C-5 on the topomerization threshold[68, 102]. The relationship found between $\log(k_x/k_H)$ and Hammett's σ-parameters can be explained by assuming two opposing effects: stabilization of the ground state by electron-attracting substituents through the charge-transfer interaction of *m*- and *p*-rings, and destabilization of the transition state by electron-donor substituents, counteracting the charge displacement of H-8 and C-8 in the transition state.



(53)

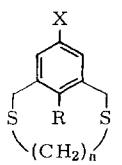
X = H, F, Br, NO_2, $COCH_3$, NH_2, OCH_3



syn-(54) *anti-(54)* *syn-(55)* *anti-(55)*

In compounds *(54)* and *(55)* the phanes with $X=NO_2$ exist preferentially in the *syn*-conformation, while those with $X=NH_2$ tend to adopt the *anti*-conformation[103]; this supports the assumption of charge-transfer interactions in *(53)*[104].

Such opposing effects are not to be expected in the metabenzenophane system *(56)*. However, here too the extra-annular substituents display a remarkable influence on the topomerization barriers[84]. A reasonably good correlation ($r=0.9$, 0.94, and 0.98) exists here with σ_R^0 parameters[105]; Hammett's parameters with an inductive component gave no correlation. The influence of substituents increases with increasing steric strain in the transition state and increasing polarizing effect of the substituent R. Hence it can be concluded that in the transition state of the topomerization *(34A)*⇌*(34B)* the intra-annular substituent is bent strongly out of plane and thus influences mainly the π-system[106].



(56)

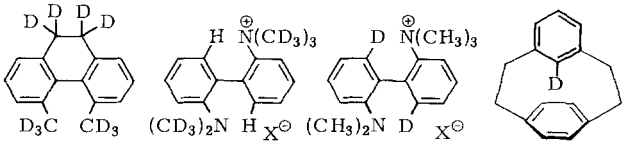
X = H, F, Cl, Br, I, NO_2, NH_2, NHAc, t-C_4H_9, CH_3, $CO_2C_2H_5$, CN

R = CH_3, OCH_3; n = 7, 8, 9

5.3.5. Deuterium Isotope Effects

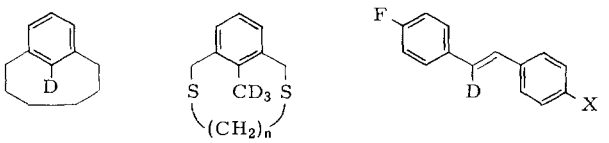
Bartell[107] was the first to indicate that the smaller vibration amplitude of the C—D bond compared with the C—H bond was important for an explanation of the secondary deuterium isotope effect[108]. The fact that deuterium requires less space than hydrogen has been proved in numerous cases. The effect is so small that its detection can be taken as an indicator for the sensitivity of steric interactions in the process under study:

H. C. Brown[109] found the heat of reaction to be increased by up to 0.23 kcal/mol (0.96 kJ/mol) on the formation of the BF_3 adduct when 2,6-dimethylpyridine is replaced by 2,6-bis(trideuteriomethyl)pyridine. The influence of isotopes on the rate of racemization was investigated in the biphenyl system[110–112]; this again made clear the importance of the geometry of the energy-determining structure. In distinction from *(57)* ($k_D/k_H=1.18$)[110] and *(59)* ($k_D/k_H=1.18$)[111], no isotope effect was found for *(58)* in spite of the presence of 15 D atoms[112]. In *(58)* the D atoms clearly do not participate in an end-on interaction in the planar transition state, so that the shorter bond lengths do not come into play. Metaparabenzenophane *(60)*[68, 113] forces such interaction in an extreme measure, and accordingly, with $k_D/k_H=1.20$, exerts a very strong isotope effect on the flip rate.



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

Similar relationships occur in the metaphane *(61)*[78]. The coalescence temperature of the deuterated derivative is *ca.* 3.5 °C lower than that of the deuterium-free compound ($k_D/k_H=1.07$). No isotope effect could, however, be established for the metaphanes *(62)* in spite of the three D atoms—here the orientation is clearly less favorable[84].



(61) *(62)*, n = 7,8 *(63)*

In *(63)* the substituent effect is clearly better transferred to the ^{19}F chemical shift than in the deuterium-free compound[114]—an example of a steric isotope effect in a compound that is itself only slightly sterically hindered.

Received: October 1, 1976 [A 167 IE]
German version: Angew. Chem. *89*, 443 (1977)
Translated by Express Translation Service, London

[1] *F. E. Ray*: Organic Chemistry. Lippincott, Chicago 1941.
[2] *F. Kehrmann*, Ber. Dtsch. Chem. Ges. *41*, 4357 (1908).
[3] *V. Meyer*, Ber. Dtsch. Chem. Ges. *27*, 510 (1894).
[4] *R. Wegscheider*, Ber. Dtsch. Chem. Ges. *28*, 1471 (1895).
[5] *S. Goldschmitt* in *K. Freudenberg*: Stereochemie. Deuticke, Leipzig 1933, p. 451.

[6] *L. Anschütz*, Angew. Chem. *41*, 691 (1928).

[7] Earlier reviews: a) *E. D. Hughes*, Quart. Rev. *2*, 107 (1948); b) *M. S. Newman:* Steric Effects in Organic Chemistry. Wiley, New York 1956.

[8] For an explanation of the nomenclature of steric effects see: a) *W. J. le Noble:* Highlights of Organic Chemistry. Dekker, New York 1974, pp. 201 ff.; b) see [14c], pp. 215, 284; c) *J. March:* Advanced Organic Chemistry: Reactions, Mechanisms and Structure. McGraw-Hill, New York 1968, pp. 116, 233; d) see [37a]; e) see [7b]; f) for steric strain, see also *J. F. Liebman, A. Greenberg*, Chem. Rev. *76*, 311 (1976); g) for the reflex effect, see *H. Dürr, G. Ourisson, B. Waegell*, Chem. Ber. *98*, 1859 (1965).

[9] a) *H. A. Stuart:* Molekülstruktur. Springer, Berlin 1967, p. 81; b) *A. Bondi*, J. Phys. Chem. *68*, 441 (1964).

[10] *S. C. Nyburg, J. T. Szymański*, J. Chem. Soc. Chem. Commun. *1968*, 669.

[11] a) See [9a], p. 97; b) *G. Briegleb*, Fortschr. Chem. Forsch. *1*, 642 (1950); c) *W. Koltun*, Biopolymers *3*, 665 (1965); d) cf. also *F. Vögtle*, Chem. Ztg. *96*, 692 (1972).

[12] a) *T. L. Hill*, J. Chem. Phys. *14*, 465 (1946); b) *F. Westheimer* in [7b], p. 523; reviews: c) *J. E. Williams, P. J. Stang, P. v. R. Schleyer*, Annu. Rev. Phys. Chem. *19*, 531 (1968); d) *H. A. Scheraga*, Adv. Phys. Org. Chem. *6*, 103 (1968). Examples of recent force-field calculations: e) *N. L. Allinger, J. F. Viskocil, U. Burkert, Y. Yuh*, Tetrahedron *32*, 33 (1976); f) *N. L. Allinger, M. J. Hickey, J. Kao*, J. Am. Chem. Soc. *98*, 2741 (1976); g) *J. Andose, K. Mislow, ibid. 96*, 2168 (1974).

[13] For a detailed account see: a) *R. W. Taft jr.* in [7b], pp. 561, 660; b) see [19b], p. 20.

[14] a) *J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Vissier, B. M. Wepster*, Rec. Trav. Chim. Pays-Bas *77*, 491 (1958); b) *W. F. Forbes, W. A. Mueller*, Can. J. Chem. *33*, 1145 (1955); c) cf. also *L. N. Ferguson:* The Modern Structural Theory of Organic Chemistry. Prentice Hall, Englewood Cliffs 1963, pp. 345, 510; d) *B. M. Wepster*, Progr. Stereochem. *2*, 99 (1958); e) *G. H. Beaven, E. A. Johnson* in *G. W. Gray:* Steric Effects in Conjugated Systems. Butterworths, London 1958.

[15] *J. E. Ungnade*, J. Am. Chem. Soc. *76*, 5133, 1601 (1954).

[16] *F. B. Mallory, C. W. Mallory, M.-C. Fedarko*, J. Am. Chem. Soc. *96*, 3536 (1974).

[17] Cf. [13a], p. 556.

[18] Cf. also [5—7].

[19] a) *L. P. Hammett:* Physical Organic Chemistry. McGraw-Hill, New York 1970; b) *J. Hine:* Structural Effects on Equilibria in Organic Chemistry. Wiley, New York 1975, p. 65); c) *H. H. Jaffé*, Chem. Rev. *53*, 191 (1953); d) *D. H. McDaniel, H. C. Brown*, J. Org. Chem. *23*, 420 (1958); e) cf. also [13a]; f) *N. B. Chapman, J. Shorter:* Advances in Linear Free Energy Relationships. Plenum Press, London 1972.

[20] a) *M. Charton*, J. Am. Chem. Soc. *91*, 615 (1969); b) *97*, 1552 (1975); c) J. Org. Chem. *41*, 2217 (1976); d) cf. also *D. F. DeTar, C. J. Tenpas*, J. Am. Chem. Soc. *98*, 4567 (1976).

[21] *D. D. Davis, A. J. Surmatis, G. C. Robertson*, J. Organomet. Chem. *46*, C9 (1972).

[22] *H. C. Brown, D. Gintis, L. Domash*, J. Am. Chem. Soc. *78*, 5387 (1956).

[23] a) cf. also [13a], p. 633; b) see [19b], p. 229.

[24] "Substitulogous" compounds differ only by exchange of one (or more) substituents in one (or more) distinct positions. For the first definition of "substitulogous, cf. [64b].

[25] a) *G. Binsch*, Top. Stereochem. *3*, 97 (1966); b) *I. O. Sutherland*, Annu. Rep. NMR Spectrosc. *4*, 71 (1971); c) *L. M. Jackman, F. A. Cotton:* Dynamic Nuclear Magnetic Resonance Spectroscopy. Academic Press, New York 1975.

[26] *J. D. Kemp, K. S. Pitzer*, J. Chem. Phys. *4*, 749 (1936).

[27] a) *E. B. Wilson*, Adv. Chem. Phys. *2*, 367 (1959); b) *D. J. Millen*, Prog. Stereochem. *3*, Vol. 4 (1962); c) *J. P. Lowe*, Prog. Phys. Org. Chem. *6*, 1 (1968); d) Science *179*, 527 (1973); e) *G. Karabatsos, D. J. Fenoglio*, Top. Stereochem. *5*, 167 (1970); f) *S. Sternhell* in [25c], p. 163; g) *E. B. Wilson*, Chem. Soc. Rev. *1*, 293 (1972).

[28] a) *G. J. Szasz*, J. Chem. Phys. *23*, 2449 (1955); b) *I. R. Epstein, W. N. Lipscomb*, J. Am. Chem. Soc. *92*, 6094 (1970); c) cf. also [27, 30].

[29] a) *F. J. Weigert, M. B. Winstead, J. I. Garrels, J. D. Roberts*, J. Am. Chem. Soc. *92*, 7359 (1970); b) *B. L. Hawkins, W. Bremser, S. Borcic, J. D. Roberts, ibid. 93*, 4472 (1971).

[30] a) *J. E. Anderson, H. Pearson*, J. Chem. Soc. Chem. Commun. *1971*, 871; b) Tetrahedron Lett. *1972*, 2779; c) *J. E. Anderson, C. W. Doecke, H. Pearson*, J. Chem. Soc. Perkin II *1976*, 336.

[31] a) *J. Hirsch*, Top. Stereochem. *1*, 199 (1967); b) For the "*A* value" of an exocyclic double bond see *J. B. Lambert, R. R. Clikeman*, J. Am. Chem. Soc. *98*, 4203 (1976).

[32] *S. Winstein, N. J. Holness*, J. Am. Chem. Soc. *77*, 5562 (1955).

[33] a) *E. L. Eliel*, Angew. Chem. *77*, 784 (1965); Angew. Chem. Int. Ed. Engl. *4*, 761 (1965); b) *E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morrison:* Conformational Analysis. Wiley, New York 1965; c) *E. L. Eliel*, J. Chem. Educ. *37*, 126 (1960).

[34] Cf. a) *S. Wolfe*, Acc. Chem. Res. *5*, 102 (1972); b) *E. L. Eliel, ibid. 3*, 1 (1970); c) *N. S. Zefirov, L. G. Gurvich, A. S. Shashkov, M. Z. Krimer, E. A. Vorab'eva*, Tetrahedron *32*, 1211 (1976).

[35] a) *F. R. Jensen, C. H. Bushweller, B. H. Beck*, J. Am. Chem. Soc. *91*, 344 (1969); b) *A. J. Berlin, F. R. Jensen*, Chem. Ind. (London) *1960*, 998.

[36] *D. S. Bailey, J. A. Walder, J. B. Lambert*, J. Am. Chem. Soc. *94*, 177 (1972).

[37] Reviews of the biphenyl system: a) *E. L. Eliel:* Stereochemistry of Carbon Compounds. McGraw-Hill, New York 1962, pp. 156 ff.; b) *R. Adams, H. C. Yuan*, Chem. Rev. *12*, 261 (1933); c) *H. Gilman:* Organic Chemistry. Wiley, New York 1938.

[38] *R. W. Stoughton, R. Adams*, J. Am. Chem. Soc. *54*, 4426 (1932).

[39] *W. M. Stanley, R. Adams*, J. Am. Chem. Soc. *52*, 1200 (1930).

[40] Cf. [37c], p. 285.

[41] a) Cf. also [48]; b) *W. Theilacker, R. Hopp*, Chem. Ber. *92*, 2293 (1959); c) *A. G. Pinkus, H. C. Custard*, Can. J. Chem. *53*, 2024 (1974).

[42] Cf. [16].

[43] a) *D. M. Hall, M. M. Harris*, J. Chem. Soc. *1960*, 490; b) *F. W. Cagle jr., H. Eyring*, J. Am. Chem. Soc. *73*, 5628 (1951).

[44] *H. O. Bödecker, V. Jonas, B. Kolb, A. Mannschreck, G. Köbrich*, Chem. Ber. *108*, 3497 (1975).

[45] a) *P. T. Leung, D. Y. Curtin*, J. Am. Chem. Soc. *97*, 6790 (1975); b) cf. also *H. Cho, R. G. Harvey, P. W. Rabideau, ibid. 97*, 1140 (1975).

[46] *C. A. Cupas, J. M. Bollinger, M. Haslanger*, J. Am. Chem. Soc. *90*, 5502 (1968).

[47] a) *J. Peeling, J. B. Rowbotham, L. Ernst, T. Schaefer*, Can. J. Chem. *52*, 2414 (1974); b) *J. Peeling, L. Ernst, T. Schaefer, ibid. 52*, 849 (1974).

[48] *A. Mannschreck, L. Ernst*, Chem. Ber. *104*, 228 (1971).

[49] However, $CH_3 > Br$ was found in an investigation of 1,3,5-trisubstituted anilinium ions: *A. Mannschreck, H. Muensch*, Tetrahedron Lett. *1968*, 3227.

[50] a) *A. Rieker, H. Kessler*, Tetrahedron Lett. *1969*, 1227; b) *W. T. Ford, T. B. Thompson, K. A. J. Snoble, J. M. Timko*, J. Am. Chem. Soc. *97*, 95 (1975); c) cf. also [61].

[51] *B. Nilsson, P. Martinson, K. Olsson, R. E. Carter*, J. Am. Chem. Soc. *96*, 3190 (1974).

[52] *B. Nilsson, P. Martinson, K. Olsson, R. E. Carter*, J. Am. Chem. Soc. *95*, 5615 (1973).

[53] *E. Dahlberg, B. Nilsson, K. Olsson, P. Martinson*, Acta Chem. Scand. Ser. B *29*, 300 (1975).

[54] The authors of [53] started from the opposite expectation.

[55] *R. E. Carter, B. Nilsson, K. Olsson*, J. Am. Chem. Soc. *97*, 6155 (1975).

[56] a) *F. Bernardi, N. D. Epiotis, R. C. Yates, H. B. Schlegel*, J. Am. Chem. Soc. *98*, 2385 (1976); b) cf. also [63].

[57] *K. Mislow*, Acc. Chem. Res. *9*, 26 (1976).

[58] *D. Hellwinkel, W. Lindner, H. J. Wilfinger*, Chem. Ber. *107*, 1428 (1974).

[59] *K. Sakamoto, M. Oki*, Tetrahedron Lett. *1973*, 3989.

[60] *M. J. Sabacky, S. M. Johnson, J. C. Martin, I. C. Paul*, J. Am. Chem. Soc. *91*, 7542 (1969).

[61] *M. Oki*, Angew. Chem. *88*, 67 (1976); Angew. Chem. Int. Ed. Engl. *15*, 87 (1976).

[62] *C. Roussel, A. Lidén, M. Chanon, J. Metzger, J. Sandström*, J. Am. Chem. Soc. *98*, 2847 (1976), and references cited therein.

[63] *F. Suzuki, M. Oki*, Bull. Chem. Soc. Jpn. *48*, 596 (1975).

[64] a) *B. H. Smith:* Bridged Aromatic Compounds. Academic Press, New York 1964; b) For nomenclature, see *F. Vögtle, P. Neumann*, Tetrahedron Lett. *1969*, 5329; Tetrahedron *26*, 5847 (1970).

[65] Reviews: a) *F. Vögtle, P. Neumann*, Angew. Chem. *84*, 75 (1972); Angew. Chem. Int. Ed. Engl. *11*, 73 (1972); b) Chimia *26*, 64 (1972); c) Top. Curr. Chem. *48*, 67 (1974); d) Synthesis *1973*, 85; cf. also [70].

[66] *M. Nakazaki, K. Yamamoto, S. Okamoto*, Tetrahedron Lett. *1969*, 4597.

[67] *F. Imashiro, M. Oda, T. Iida, Z. Yoshida, I. Tabushi*, Tetrahedron Lett. *1976*, 371.

[68] *S. A. Sherrod, R. L. da Costa, R. A. Barnes, V. Boekelheide*, J. Am. Chem. Soc. *96*, 1565 (1974).

[69] *D. T. Hefelfinger, D. J. Cram*, J. Am. Chem. Soc. *92*, 1073 (1970).

[70] *D. J. Cram, J. Cram*, Acc. Chem. Res. *4*, 204 (1971).

[71] *C. Krieger, E. Langer, H. Lehner*, Monatsh. Chem. *107*, 19 (1976).

[72] a) *N. L. Allinger, J. T. Sprague, T. Liljefors*, J. Am. Chem. Soc. *96*, 5100 (1974); b) *R. H. Boyd*, J. Chem. Phys. *49*, 2574 (1968).

[73] a) *M. Aroney, R. J. W. Le Fèvre*, J. Chem. Soc. *1958*, 3002; b) *J. B. Lambert, R. G. Keske*, J. Am. Chem. Soc. *88*, 620 (1966); c) *N. L. Allinger, A. Hirsch, M. A. Miller*, Tetrahedron Lett. *1967*, 3729; d) *H.-J. Schneider, C. Sturm*, Angew. Chem. *88*, 574 (1976); Angew. Chem. Int. Ed. Engl. *15*, 545 (1976); e) *M. A. Robb, W. J. Haines, I. G. Csizmadia*, J. Am. Chem. Soc. *95*, 42 (1973).

[74] a) *I. Gault, B. J. Price, I. O. Sutherland*, J. Chem. Soc. Chem. Commun. *1967*, 540; b) *J. R. Fletcher, I. O. Sutherland, ibid. 1969*, 1504.

[75] F. Vögtle, A. Effler, Chem. Ber. 102, 3071 (1969).
[76] a) S. Fujita, H. Nozaki, Bull. Chem. Soc. Jpn. 44, 2827 (1971); b) S. Fujita, S. Hirano, H. Nozaki, Tetrahedron Lett. 1972, 403.
[77] R. H. Mitchell, V. Boekelheide, Tetrahedron Lett. 1969, 2013.
[78] S. Hirano, H. Hara, T. Hiyama, S. Fujita, H. Nozaki, Tetrahedron 31, 2219 (1975).
[79] V. Boekelheide, K. Galuszko, K. S. Szeto, J. Am. Chem. Soc. 96, 1578 (1974).
[80] F. Vögtle, L. Schunder, Chem. Ber. 102, 2677 (1969).
[81] H. Kessler, Angew. Chem. 82, 237 (1970); Angew. Chem. Int. Ed. Engl. 9, 219 (1970).
[82] F. Vögtle, J. Grütze, R. Nätscher, W. Wieder, E. Weber, R. Grün, Chem. Ber. 108, 1694 (1975) and references cited therein.
[83] On the problem of favorable arrangement in larger ring systems see: a) J. Dale, Angew. Chem. 78, 1070 (1966); Angew. Chem. Int. Ed. Engl. 5, 1000 (1966); b) J. Sicher, Progr. Stereochem. 3, 202 (1962): c) for conformational calculations on cycloalkanes see: J. B. Hendrickson, J. Am. Chem. Soc. 89, 7036, 7043, 7047 (1969).
[84] H. Förster, F. Vögtle, J. Chem. Research (S) 1977, 30.
[85] D. J. Cram, W. J. Wechter, R. W. Kierstead, J. Am. Chem. Soc. 80, 3126 (1958).
[86] A. Lüttringhaus, G. Eyring, Justus Liebigs Ann. Chem. 604, 111 (1957).
[87] It is, to say the least, surprising that the substituted [10]paracyclophane corresponding to (36) should racemize even at room temperature — A. T. Blomquist, R. E. Stahl, Y. C. Meinwald, B. H. Smith, J. Org. Chem. 26, 1687 (1961).
[88] a) F. Vögtle, P. Neumann, Tetrahedron Lett. 1970, 115, and unpublished work; b) P. Neumann, Dissertation, Universität Heidelberg 1973.
[89] E. Weber, W. Wieder, F. Vögtle, Chem. Ber. 109, 1002 (1976).
[90] A similar problem arises in the "tailoring" of cavities for cations in crown ethers.
[91] V. Boekelheide, C. H. Tsai, Tetrahedron 32, 423 (1976).
[92] H. J. Lindner, Tetrahedron 32, 753 (1976).
[93] a) H. Wynberg, W. C. Nieuwpoort, H. T. Jonkman, Tetrahedron Lett. 1973, 4623; b) cf. B. R. Gelin, M. Karplus, J. Am. Chem. Soc. 97, 6996 (1975).
[94] In this connection cf. the flexibility of helicene skeletons: R. H. Martin, Angew. Chem. 86, 727 (1974); Angew. Chem. Int. Ed. Engl. 13, 649 (1974).
[95] a) K. Sakamoto, M. Oki, Bull. Soc. Chem. Jpn. 46, 270 (1973); b) K. Sakamoto, M. Oki, ibid. 47, 2739 (1974).
[96] Similarly [2.2]parabenzenophanediene is less strained than [2.2]paracyclophane; cf. [65].
[97] S. Hirano, T. Hiyama, S. Fujita, T. Kawaguti, Y. Hagashi, H. Nozaki, Tetrahedron 30, 2633 (1974).
[98] For the same reason the differences between the flip thresholds for [2.2]furanophane and thiophenophane cannot be ascribed solely to the larger action radius of S compared with O; cf. a) H. Nozaki, T. Koyama, T. Mori, Tetrahedron 25, 5357 (1969); b) F. Vögtle, R. Lichtenthaler, Chem.-Ztg. 94, 727 (1970); c) cf. [74b].
[99] The $\Delta G_c^{\neq}$ values given were evaluated from data in [100].
[100] N. Kannen, T. Umemoto, T. Otsubo, S. Misumi, Tetrahedron Lett. 1973, 4537. A similar effect can be seen in the triple-layered [2.2]parabenzeno[2.2](2,5)furanophane: S. Mizogami, T. Otsubo, Y. Sakata, S. Misumi, ibid. 1971, 2791.
[101] H. Lehner, Monatsh. Chem. 107, 565 (1976).
[102] S. A. Sherrod, R. L. de Costa, Tetrahedron Lett. 1973, 2083.
[103] a) F. Vögtle, W. Wieder, H. Förster, Tetrahedron Lett. 1974, 4361; b) W. Wieder, R. Nätscher, F. Vögtle, Justus Liebigs Ann. Chem. 1976, 924.
[104] cf. also [63].
[105] a) R. W. Taft, J. Phys. Chem. 64, 1805 (1960); b) R. W. Taft, E. Price, I. R. Fox, E. C. Lewis, K. K. Andersen, G. T. Davis, J. Am. Chem. Soc. 85, 3146 (1963); c) A. R. Katritzky, R. D. Topsom, Angew. Chem. 82, 106 (1970); Angew. Chem. Int. Ed. Engl. 9, 87 (1970); d) T. B. Grindley, A. R. Katritzky, R. D. Topsom, J. Chem. Soc. Perkin II 1975, 443; e) cf. also [19b], p. 55.
[106] The changes in bond lengths and bond angles in the benzene skeleton due to the substituents are probably too small to be responsible for such effects: a) J. Trotter, Tetrahedron 8, 13 (1960); b) A. Domenicano, P. Mazzeo, A. Vaciago, Tetrahedron Lett. 1976, 1029.
[107] a) L. S. Bartell, Tetrahedron Lett. 1960, 13; b) J. Am. Chem. Soc. 83, 3567 (1961).
[108] R. E. Carter, L. Melander, Adv. Phys. Org. Chem. 10, 1 (1973).
[109] H. C. Brown, M. E. Azzaro, J. G. Koelling, G. J. McDonald, J. Am. Chem. Soc. 88, 2520 (1966).
[110] K. Mislow, R. Graeve, A. J. Gordon, G. H. Wahl, J. Am. Chem. Soc. 86, 1733 (1964).
[111] R. E. Carter, L. Dahlgren, Acta Chem. Scand. 24, 633 (1970).
[112] C. Heitner, K. T. Leffek, Can. J. Chem. 44, 2567 (1966).
[113] S. A. Sherrod, V. Boekelheide, J. Am. Chem. Soc. 94, 5513 (1972).
[114] P. J. Mitchell, L. Phillips, J. Chem. Soc. Chem. Commun. 1975, 908.

Photodielectric Polymers for Holographic Use

By Shimon Reich[*]

The use of polymeric materials as "thick" recording media for holographic applications is discussed. These materials offer some interesting applications owing to their high diffraction efficiency, high storage density, excellent angular and spectral discrimination, as well as *in situ* real-time recording. The present state of art is outlined, as are prospects for the future.

1. Introduction

As often happens in science, *Gabor*'s idea[1, 2] of holography originated before the relevant technology for hologram recording was available. To appreciate this point we must briefly refresh our memory as to what holography really is; an interference method of recording light waves scattered by an object which is illuminated with coherent light. The scattered waves are caused to interfere with a phase-related reference wave, the reference beam, and thus produce an interference pattern. A record of this pattern contains all the information necessary to reconstruct the original wave scattered from the object. It accordingly contains the whole information about both the phase and the amplitude of this wave and is therefore called a hologram, being derived from the Greek "ὅλος", or whole. Recording and viewing configurations for a hologram are shown in Figure 1.

From the point of view of technology therefore we need a source of coherent light and a medium on which the interference pattern constituting the holographic information is efficiently recorded.

A practical coherent light source was realized only in 1960 with the advent of lasers, changing the fate of the idea of a holographic record from an interesting exercise in optics

[*] Dr. S. Reich
Polymer Department, Weizmann Institute of Science
Rehovot (Israel)

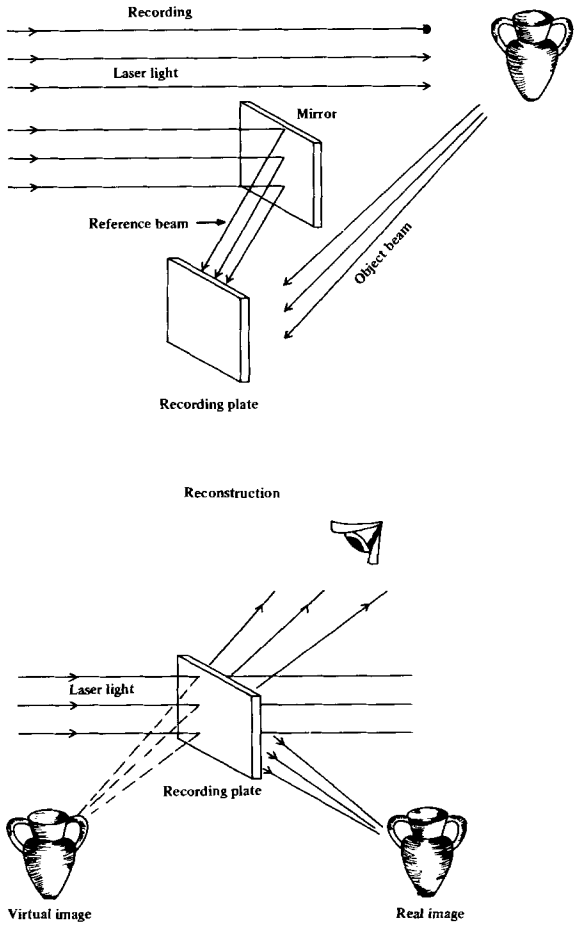


Fig. 1. Hologram recording and reconstruction configurations.

to a flourishing new branch of science and technology. As far as the recording medium was concerned the photographic plate was sufficiently advanced for holographic use. However, as we shall see it is not the ideal medium for many applications of the holographic method. To understand this we must look into the parameters that make the holographic record efficient. We know already that the hologram is just an interference pattern recorded on a piece of film; to see the object we must reconstruct the original wavefront diffracted by it. This is performed by illuminating the record with the readout beam.

The efficiency of this process is measured by so-called diffraction efficiency which is the ratio of the power in the diffracted image to the incident power of the reconstructing beam. This ratio does not exceed the theoretical value of 6.25 %[3] for an absorption light sensitive material—such as the photographic plate. However, the theory tells us that this limit is exceeded when instead of the "absorption material" we use a "phase material". The diffraction efficiency for a phase material may in some cases reach the ultimate limit of 100%.

In contrast to a photographic plate where the information is recorded by the magnitude of light absorption, in pure phase material this is done by photoinducing local changes in refractive index in the recording plate. By passing light through a "phase record" transparency we change the phase of the wavefront due to modulation of the refractive index; in conventional transparency we change the amplitude due to absorption. We see, therefore, that a good phase material would be a transparent photosensitive plate in which we can modulate the amplitude of the refractive index by light. To make this process efficient we wish to achieve the maximum amplitude of this modulation by investing minimum energy per unit area of the plate. It appears already at this stage of definition that polymers may indeed perform well as phase material. They are good film formers, they can be transparent and of good optical quality, they can serve as a solid solvent for various photosensitizers and also be photochemically activated by proper chemical substitution both in the UV or visible spectrum range. Polymers also exhibit a very wide rheological flexibility and can be formed as hard blocks or elastic sheets, viscoelastic films, adhesives between transparent glass plates, or coating on suitable substrates.

This physicochemical versatility together with the advanced technology of polymer chemistry, make them an attractive proposition as phase materials. For the last six years there have been serious attempts to produce polymeric phase material for holographic use. We shall try to follow one line in this attempt, namely the thick photodielectric polymers, and appreciate its achievements and prospects for the future.

2. Relevant Parameters in Thick Photodielectric Polymers

2.1. What are Photodielectric Materials?

We know already that, depending upon the type of recording materials, the storage mechanism for holographic information produces absorption or phase changes. These are best described in terms of a complex dielectric constant ε^*

$$\varepsilon^* \text{ (exposure)} = \varepsilon' + i\varepsilon'' \tag{1}$$

when $\varepsilon' = \text{const}$ and ε'' is the exposure dependent part of ε^*, then the recording material is an absorption medium, sometimes called an amplitude medium; when $\varepsilon'' = 0$ and ε' is primarily exposure dependent, this is a pure phase material which we shall call here a photodielectric.

2.2. What Are Thick Photodielectric Holograms?

Thick holograms have thicknesses hundreds of times greater than the wavelength of light[*]. To understand the basic difference between thick and thin holograms let us inspect Figure 2. We see recording and reconstruction geometries for thick and thin simple holographic gratings. When two monochromatic plane waves are overlapped on a thin photodielectric material, a record of sinusoidal variation in index of refraction (fringes of varying optical path) will result. The spacing d of these fringes is (Fig. 2a):

$$d = \lambda_0 / 2 \sin \theta_0 \tag{2}$$

where λ_0 = wavelength of recording laser; $2\theta_0$ = angle between object and reference beams.

[*] A more accurate definition [4] is: thick hologram $\equiv Q \geq 10$ where $Q = 2\pi\lambda D / n d^2$; D = hologram thickness; n = index of refraction; d see text.

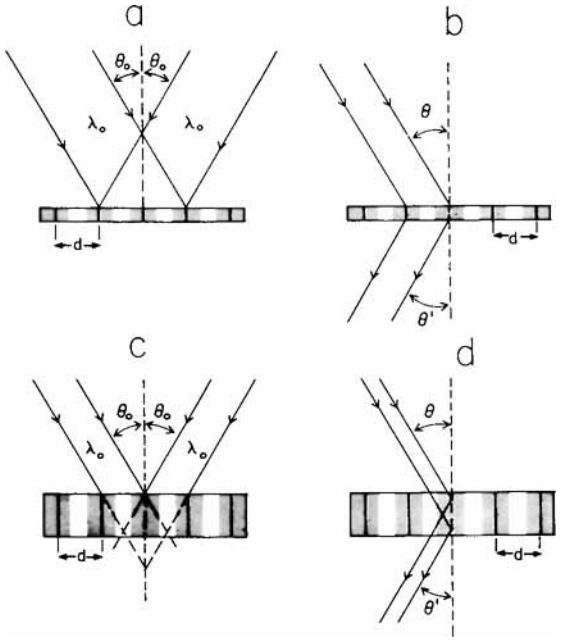


Fig. 2. Thin and thick photodielectrics, recording (left) and reconstruction (right) configurations: a, b, c, d—see text.

When reconstructing this hologram (Fig. 2b) with wavelength λ and incident angle θ the reconstruction will obey the thin gratings formula:

$$k\lambda = d(\sin\theta + \sin\theta') \qquad (3)$$
$$k = 0, 1, 2, 3, \ldots$$

where θ' is the angle for reconstruction. The angular discrimination for reconstruction is poor, since equation (3) is fulfilled for many θ' whatever the values of λ and θ in the incident wave may be. This is not the case in a thick photodielectric hologram. Upon recording, we produce in the plate a set of planes of varying index of refraction (Fig. 2c). Now the condition for reconstruction is obviously the Bragg condition (Fig. 2d).

$$2d\sin\theta = k\lambda \qquad (4)$$

The angular characteristics for reconstruction for such a grating will vary when we change λ, or both λ and θ. For large values of D the angular discrimination at fixed λ becomes critical—a small fraction of a degree. The diffraction efficiency (X) for such a thick hologram, which is sometimes also called a volume hologram, is given by the "coupled wave" theory[5–7] as

$$X \approx \sin^2(\pi D \Delta n/\lambda \cos\theta_B) \qquad (5)$$

where D = thickness of material; Δn = change in the refractive index; θ_B = Bragg angle (*i.e.* the half-angle between recording beams for the symmetrical case). Whenever the argument of the sine function approaches a multiple of $\pi/2$, the diffraction efficiency approaches 100%. In practice the limit of 100% can be reached to within a few percent only due to absorption and other unavoidable losses.

2.3. Some Other Important Parameters

Exposure sensitivity: The exposure required to produce a prescribed change in refractive index, and hence phase, for a given set of experimental conditions. Usually measured in joule/cm^2.

Spectral response: A measure of the exposure as a function of wavelength to produce a given phase change. Usually specified by means of a plot of sensitivity *vs.* λ.

Resolving power: A measure of the finest detail that a photodielectric can unambiguously record as a spatial variation of the refractive index.

Storage density: The maximum density of elementary units of information that the photodielectric can store; bits per unit volume.

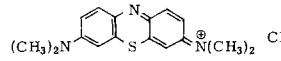
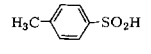
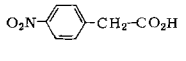
Signal to noise ratio (SNR): SNR can be measured by recording Fresnel holograms[8] of a diffusely illuminated data mask consisting of a square with an opaque center. The recording geometry is arranged so as to have a known number of bits per unit area of the hologram. The average signal is determined from a scan across the bright area of the reconstructed image, and the average noise is determined from a scan across the dark area. The ratio of the average signal power to the average noise power is the SNR. Usually measured in dB.

In addition to the above well defined parameters, there is a class of experimental parameters which are much harder to standardize, but are of great practical importance. Those are temporal stability, temperature and humidity sensitivity and stability, mechanical integrity, and solvent stability.

3. Photopolymers

In recent years a number of photopolymers have been proposed for recording phase holograms[9–16]. These are mixtures of one or more monomers with a dye-sensitized catalyst that initiates polymerization when activated by light. Typical formulations[9, 17] involve the photopolymerization of acrylates of barium, calcium, and lead, or acrylamide with methylenebis-(acrylamide) into polyamides. Table 1 shows an example[9].

Table 1. Starting material for a photopolymer [9]. The monomers were dissolved in water (pH = 6.3), and the photocatalysts in glycerol.

Monomers		Conc.
Barium acrylate	$(H_2C{=}CH{-}CO_2)_2Ba$	3.6 mol/l
Lead acrylate	$(H_2C{=}CH{-}CO_2)_2Pb$	0.9 mol/l
Acrylamide	$H_2C{=}CH{-}CONH_2$	30 g/100 ml solution
Photocatalysts		**Conc.**
Methylene blue		0.0022 mol/l
p-Toluenesulfinic acid		0.1 mol/l
4-Nitrophenylacetic acid		0.1 mol/l

Consider an example with methylene blue, which provides sensitization for He—Ne laser wavelength. In the excited state

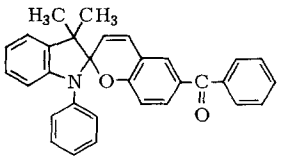
it reacts with the *p*-toluenesulfinic acid to produce free radicals. Thus a free radical photopolymerization is initiated. A photopolymer of this kind is therefore a self-developing real time material. Fixing is achieved by uniform illumination so as to complete the polymerization process or by UV illumination that deactivates the methylene blue dye to a colorless product. The deactivation is effected by the UV photolysis products of the 4-nitrophenylacetic acid. The sensitivity of the material is about 0.5 mJ/cm^2 when presynthesized with 2 mJ/cm^2 of 632.8-nm light. This is considerably lower than that of a typical absorption material used in holography such as Agfa 8E75 Scientia ($\approx$0.0075 mJ/cm^2).

A system of acrylamide and methylenebis(acrylamide) is even less sensitive than the acrylate system ($\approx$5 mJ/cm^2 in the red spectral region[17]). The maximal amplitude of modulation of the refractive index (Δn) is high ($\approx$ 2.7%). The materials are capable of recording about 2000 lines per mm. This resolving power is apparently limited by formation of polymer clusters. Both volume and surface gratings are produced during the recording process. High diffraction efficiencies of approximately 50% are easily obtained. Plates of a few 100 µm in thickness can be prepared. Some of the photopolymer systems suffer a pronounced reciprocity failure *i.e.* they do not obey the Bunsen-Roscoe law which postulates that the sensitivity is independent of irradiation[17].

The time and light stability is not very good. The handling of the materials which have to be mixed just before use is inconvenient.

The mechanism of hologram formation in photopolymers was explained by *Colburn* and *Haines*[18]. A quite general characteristic of the polymerization process is that the resulting polymer exhibits higher density than the monomer. Thus, upon polymerization, an increase of index of refraction is observed. This is a pure density effect since the molecular polarizability per repeat unit of a polymer, for example, a vinyl polymer, is lower than the corresponding monomer[19]. According to *Colburn* and *Haines* when the photopolymer is illuminated by the interference pattern "fringes" of polymer exposed to higher light intensity will polymerize to a greater extent than other areas. This will create a gradient of monomer concentration driving a diffusion of the monomer from low irradiance areas (high concentration) to high irradiance areas (low concentration). This process will result in modulation of density and therefore index of refraction in the photopolymer plate that follows the interference pattern—*i.e.* the hologram.

An ingenious new photopolymer system was recently proposed by *Tomlinson*, *Chandross*, *Weber*, and *Aumiller*[19]. They call it a multicomponent photopolymer. They chose a liquid mixture of two monomers having very different rates of photopolymerization and molecular polarizabilities. During exposure, a preferential polymerization of the more sensitive monomer will result, creating gradients of this species. Diffusion depletes the areas of lower exposure. Thus the less exposed areas will be enriched in the second component which is chosen to produce a polymer of different index of refraction. Thus a selection process in chemical composition is established which will follow the intensity distribution in the holographic interference pattern. The refractive index modulation resulting from the above process is larger than the density effect described earlier.



(1)

Another ingenious photopolymer system was presented by *Jeudy* and *Robillard* in 1975[20]. They used a reversal photosensitization process in an *in situ* real time holographic recording. The reversed sensitization is accomplished by the use of a photochromic sensitizer, which reversibly changes color upon irradiation. They introduced indolinospiropyran *(1)* into acrylamide dissolved in poly(vinyl alcohol) with triethanolamine serving as promoter. When irradiated with UV light (λ = 300—400 nm) compound *(1)* goes into an excited state with an absorption band peaking near 600 nm. The colored excited species acts as a sensitizer for photopolymerization in the red region of the spectrum. The recording takes place only when the plate is subjected to UV irradiation. When the UV light is turned off, the sensitizer is deactivated from the colored excited state to a colorless ground state and the plate becomes transparent. This scheme possesses several advantages:

a) There is no need for fixation since the material is sensitive to red light only when irradiated with UV.

b) This scheme overcomes the classical dilemma in phase material; they should be as transparent as possible to exhibit high diffraction efficiency in the image reconstruction process; on the other hand, they must interact through absorption with the laser light in the recording stage. The reversal photosensitization solves this problem in an elegant way—the hologram is perfectly transparent on reconstruction.

4. Polymeric "Solid Network" Photodielectrics

In 1970 *Tomlinson*, *Kaminow*, *Chandross*, *Fork*, and *Silvast* reported a new photodielectric medium sensitive in the UV range[21]. They found that suitably prepared poly(methyl methacrylate) (PMMA), when irradiated with actinic radiation (325 nm, He—Cd$^+$ laser), will change its refractive index by 8‰. This self-developing photodielectric is a pure phase material capable of very high resolution ($\approx$ 5000 lines/mm) and high diffraction efficiency ($\approx$ 70%). Though it is much less sensitive than dichromate-gelatin[21] it offered the great advantage of no wet processing. The authors realized the potential applications for this system for thick holograms[21, 22] as well as for induction of optical waveguides[23] into slabs of transparent PMMA.

The mechanism responsible for the observed modulation of the refractive index was attributed to photochemical cross-linking[21] or to photopolymerization of residual monomer[24]. The above system suffers mainly from two disadvantages; its exposure sensitivity is about 10^4 times lower than that of the photopolymer family, and its response is limited to the UV spectral range. To overcome these limitations *Laming*[25], *Zech*[26], and others[27, 28] introduced sensitizers active in the blue-green range of the spectrum into PMMA and other polymers. The materials obtained are pure phase materials a hundred times more sensitive than unsensitized PMMA and are capable of high resolution ($\approx$3000 lines/mm) with

diffraction efficiencies exceeding 90 %. Typical sensitizers are quinones such as *p*-benzoquinone, 2,5-dichloro-*p*-benzoquinone, 2,5-dimethyl-*p*-benzoquinone, chloranil, duroquinone[16], and α-diketones such as camphorquinone have also been used[27, 28].

Apart from PMMA a broad family of polymers was tried as host materials, such as poly(vinyl acetate)[26], cellulose acetate butyrate, ethyl methacrylate[26], as well as acrylic polyesters and epoxies[27, 28].

In all these systems, the sensitizers are introduced into the polymer *via* a solvent, this procedure is dictated by the stabilizing nature of most of the sensitizers. For example, introduction of *p*-benzoquinone into methylmethacrylate monomer will hinder the radical polymerization process.

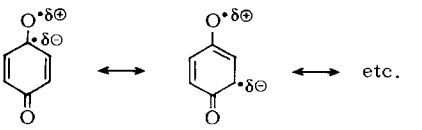
Recently[29] poly(α-cyanoacrylates) were tested as a polymeric host for sensitizers. Quinone sensitizers are introduced into the monomer. The methyl α-cyanoacrylate monomer for example, is highly reactive and it polymerizes both by free radical and by anionic initiation. When performed on a large scale bulk polymerization is inhibited by the introduction of quinone sensitizers. However, for large ratios of surface area to volume, anionic initiation is dominant and the polymerization occurs rapidly. When polymerization occurs, the excellent bonding and filling properties of the cyanoacrylates allow for the formation of an exact replica of a substrate of high optical quality to be achieved—such as optically polished glass—so that a recording plate of high optical quality is obtained. Furthermore, the volume of the polymer remains practically constant during the polymerization process[30], which is rather an exception. This allows the material to be used as a filling between glass optical elements and subsequently holographic optical elements (see Section 6) are recorded on it.

An important advantage in the preparation of these materials is that no solvent is needed to introduce the sensitizers into the polymer. Thus, the slow evaporation usually necessary in preparing other quinone-sensitized photodielectric media is avoided, resulting in excellent optical quality. The plasticizing action of the solvent on a polymer tends to degenerate its dimensional stability; also when it reacts with the sensitizer, the solvent degrades the sensitivity of the recording plate. Eliminating the solvent, thus makes it possible to obtain improved dimensional and chemical properties.

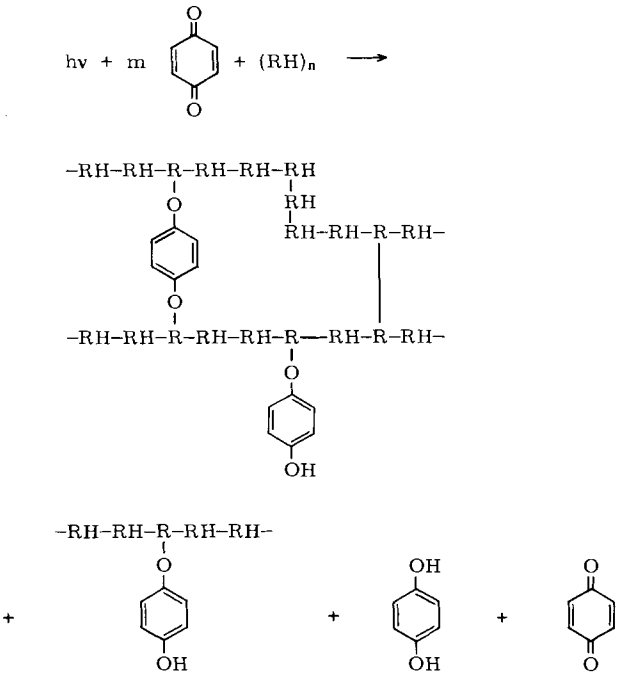
The fixation of the holographic record in solid network photodielectrics is generally performed by flooding the hologram with long-wave UV light. This procedure is believed to convert unreacted *p*-benzoquinone into quinhydrone complexes. The low sensitivity of this family of materials combined with a reciprocity failure effect observed in many of them permits hologram recording under conditions of high ambient illumination.

5. Recording Mechanism of Quinone-Sensitized Photodielectrics

It is known that a quinone sensitizer such as *p*-benzoquinone is a good hydrogen abstractor[31]. When irradiated with blue light, it is excited to the (n, π^*) triplet state which is responsible for the hydrogen abstraction.



Upon introducing this sensitizer into PMMA, for example the following photochemical reaction shown in Scheme 1 is expected[32].



Scheme 1. RH = methyl methacrylate unit with an abstractable hydrogen atom.

We see that *p*-benzoquinone may act as a hydrogen abstractor resulting in hydroquinone by a double abstraction and R—R crosslinkages.

Thus the *p*-benzoquinone effects photochemical branching and crosslinking in the PMMA. This scheme is well supported by a recent study[32]. When plotting the change in index of refraction Δn for various exposures *versus* the intrinsic viscosity of the post-exposure dissolved photodielectric, a monotonically increasing curve is obtained (see Fig. 3). This crosslinking mechanism is also supported by the observa-

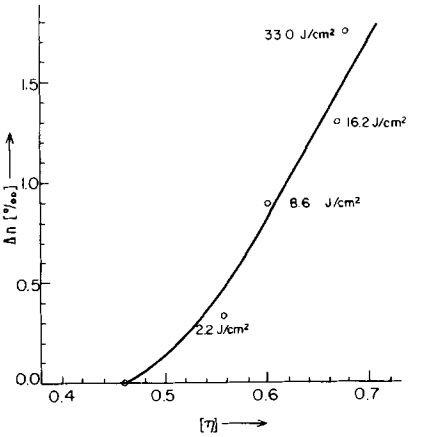


Fig. 3. Refractive index modulation Δn at various exposures for PMMA *versus* the intrinsic viscosity $[\eta]$ of the post-exposure dissolved photodielectric in chloroform. Dimensions of $[\eta]$: dl/g.

tion[29] that the main contribution to the index variation Δn is due to density increment.

Holograms are recorded, as we already know, by means of a small spatial modulation of the permittivity, $\Delta\varepsilon$, in the recording plate. This modulation is induced by variation of the molecular polarizability Δp or by a change in the number of molecules per unit volume ΔN which is a change in the density $\Delta\rho$. The Lorenz-Lorentz relation states that:

$$\varepsilon = \left(1 + \frac{2}{3\varepsilon_0} Np\right) \Big/ \left(1 - \frac{1}{3\varepsilon_0} Np\right) = \phi(p, N) \tag{6}$$

so that

$$\Delta\varepsilon = \frac{\partial\phi}{\partial p}\Delta p + \frac{\partial\phi}{\partial N}\Delta N \tag{7}$$

It was recently shown[29] that for certain families of quinone-sensitized polymers, the main photochemical effect is an increase in the density of the photodielectric material. The modulation of molecular polarizability is a secondary effect.

The above mechanism would suggest certain properties, some of them characteristic of macromolecular media. It would suggest that the holographic record in quinone-sensitized photodielectrics is a pure volume phenomenon and therefore obeys a master curve for different thicknesses of the recording plate. This is shown in Figure 4 where the refractive index modulation Δn is plotted *versus* exposure for various thicknesses of the recording plates.

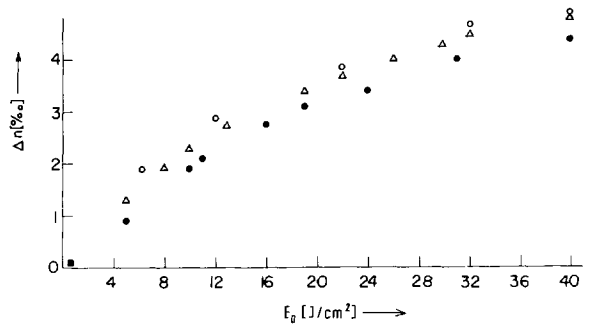


Fig. 4. Refractive index modulation Δn *versus* exposure (E_0) for PMCA plates of various thicknesses. △, 20 μm thick plate; ●, 30 μm; ○, 130 μm; ■, 1300 μm.

An extensive crosslinking of a solid polymer network also leads to a cooperative noise generation process. When the crosslinkage density is high enough, a local mechanical stress in the vicinity of one cluster of crosslinks will affect another adjacent cluster creating a small, relative displacement—this process will have a two-fold result. It interferes with the initial distribution of the crosslinks in the photodielectric—the record of the holographic signal—creating noise. A long term effect of creep of adjacent planes of high density towards each other will alter the spacing of the holographic volume grating in a thick record[33]. The last effect is particularly serious in reflection holograms in which the spacing of the adjacent grating planes is small $\lambda/2$ (the reflection holograms are recorded by impinging the signal and the reference beams one against the other in a frontal configuration with the recording plate in between, so that planes of high and low density are recorded parallel to the surface of the plate with a spacing of 244 nm for an argon blue laser (light). This effect is characteristic of viscoelastic polymeric medium[33].

6. Potential Uses of Polymeric Photodielectric Materials

Thick photodielectric polymers have not yet emerged from the laboratory to the market so that many of the applications are potential rather than actual. In 1963 *van Heerden*[34] already realized that thick holograms are capable of storing many holographic records at one time. This is due to their excellent angular and spectral discrimination, each hologram being recorded by using a different signal and reference beam direction. Thus in the volume of a small cube very many holograms are recorded.

In Figure 5 the excellent angular discrimination capabilities of a thick photodielectric are presented. The figure shows the reconstruction of 4 out of 20 superimposed but independent holograms that were recorded in a 1 mm thick plate. To separate the component holograms, the angular orientation between the reference beam and the sample was changed by 15 minutes of arc after each recording. Figure 5 depicts (a) the reconstructed image from the first recording, (b and c) those from the tenth and eleventh, and (d) that from the twentieth. The signal to noise ratio remains fairly constant for all reconstructed images, and there is little, if any, interaction between the reconstructed images.

In principle a 1 cm^3 cube of a high resolution material is capable of storing over 10^{12} bits of information. This figure, however, must be reduced by $\left(\frac{1}{\mathrm{SNR}}\right)^2$; taking SNR = 100:1 we obtain 10^8 bits[4]. Since an average book of 200 pages contains around 10^6 bits of information, one hundred such books may be stored in this cube. A large library of 100000 books may be therefore stored in a plate 1 cm thick, 25 cm wide and 40 cm high. This tremendous storage capacity may be used for archival purposes, for computer optical memories and even for storing cinematographic information. The stored information will be retrieved by slowly revolving the photodielectric in front of a powerful laser beam.

Another important use which is of immediate realizability is the production of holographic optical elements, such as lenses[35], spectral filters[4, 36], and diffraction gratings. Use of thick photodielectrics permits construction of holographic lenses with diffraction efficiencies of over 90 %[37]. It should be quite feasible to produce holographic gratings in thicknesses 10 mm or greater, with diffraction efficiencies of about 100 %, a spectral resolution of 0.1 nm, and an angular resolution of a few seconds of arc[4]. The use of such elements may be particularly desirable in very compact optical instruments and in integrated optics.

Another promising use is for display purposes, both for advertising use as well as for the display of rare artifacts. This may be particularly attractive when the three-dimensional holographic images are displayed in color[38]. By using thick,

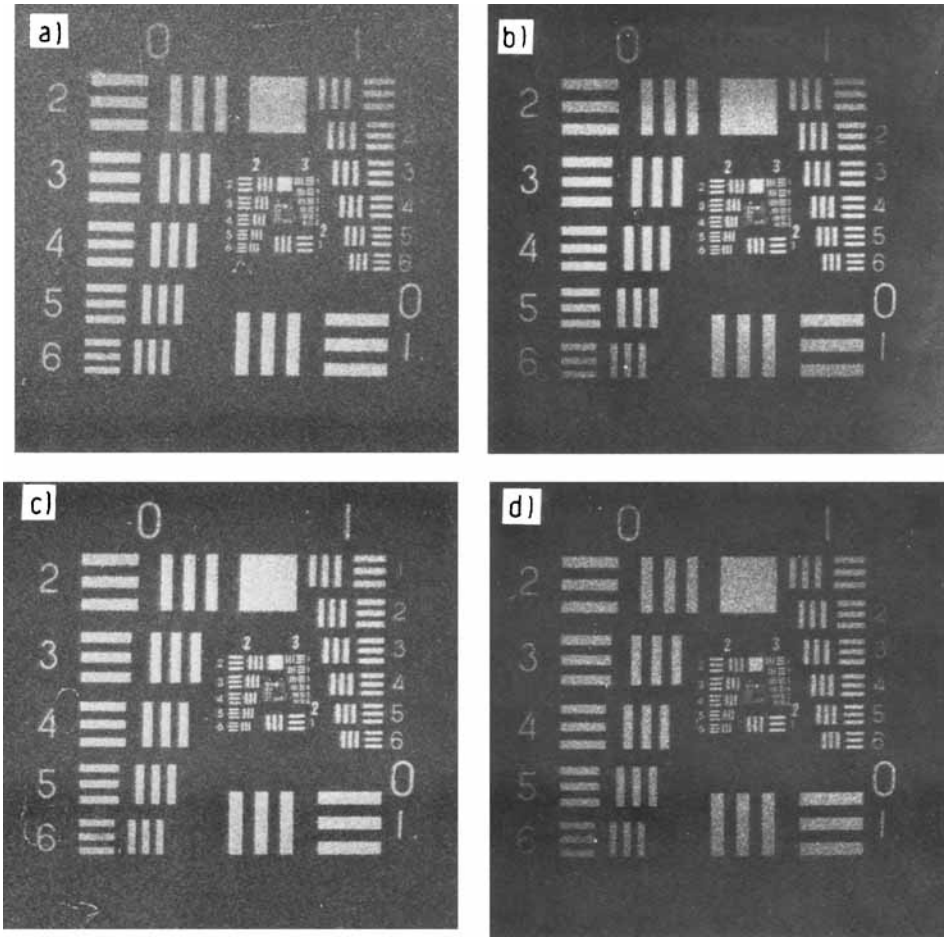


Fig. 5. Reconstructed images from multiple exposure hologram of twenty records; 1-mm thick PMCA plate. a) first recording; b) tenth recording; c) eleventh recording; d) twentieth recording.

reflection holograms, it is possible to record a scene illuminated with red, green and blue laser light. Read-out is performed by illuminating the holograms with a well collimated white light source. Such a technique may ultimately provide 3d pictures in color for illustration in books.

Finally, since many photodielectrics are *in situ* real time materials which do not require any wet process, they may be very successfully used for nondestructive testing applications[39]. This employs a holographic interferometric technique. The underlying principle is that the reconstructed image duplicates the original object in phase and amplitude. The reconstructed image may be substituted for the actual object in an interferometric application. This image may be used as a "standard" to test other similar objects. Likewise, the reconstructed image and the actual object can be compared by interferometry, which reveals the slightest differences in optical path. This technique may be used to measure vibrations, stress and strain patterns in three-dimensional objects. For instance, flaws may be easily detected by superimposing the hologram of an object before and after mechanical stressing. Figure 6 shows a real time differential hologram used to detect disbonds in a bonded honeycomb structure. A differential pressure of 20 torr was applied between two exposures, thus producing the interferometric effect. The holograms were recorded on a photoconductor-thermoplastic device[40]. This device records thin phase holograms by photoinducing a surface relief on a charged thermoplastic layer[41]. The use of thermoplastic polymers in these devices will not be reviewed in this article.

The main handicap of photodielectric materials is their low sensitivity and a narrow spectral response. The various materials are best compared with the aid of their "holographic sensitivity"[4, 42]. The so-called figure of merit S is given for thick holographic materials by

$$S=(X)^{1/2}/E_0 D \tag{8}$$

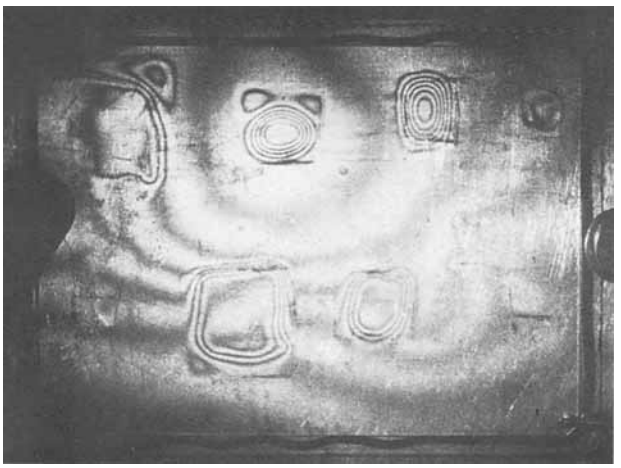


Fig. 6. Real time differential hologram of a stressed honeycomb structure recorded on photoconductor-thermoplastic device (recorded by Prof. *A. A. Friesem*).

where X = diffraction efficiency; E_0 = exposure; D = thickness of photodielectric. It is evident from Table 2, that the photodielectrics are many orders of magnitude behind the conventional photographic materials. Improving the sensitivity may bring the use of photodielectrics into the realms of both display and non-destructive testing. Another important development would be the introduction of panchromatic photodielectrics which will make color holography of high diffraction efficiency realistic. This would revive the old idea of *Lippman*[43, 44] of producing color photographs by an interference method and combine it with the 3d effect of holography.

Table 2. Figure of merit S for some recording materials used in holography [4]. PMMA, poly(methyl methacrylate); PBQ, *p*-benzoquinone; CAB, cellulose acetate butyrate; PMCA, poly(methyl α-cyanoacrylate).

Material	PMMA	PMMA +PBQ	CAB +PBQ	PMCA +PBQ	Dupont Photopolymer	
log$S$	−3	0	+1	+1	+2	
Material	NRC Photopolymer		Dichromate-gelatin		Kodak 649F bleached	Agfa 8E75
log$S$	+2		+4		+6	+8

An interesting and promising system could be created by using light-induced *cis-trans* transformations of small molecules embedded in a transparent polymeric host or bound chemically to the macromolecules. When accompanied by a change in the refractive index of the material, such *cis-trans* transformations may provide a thick photodielectric material with read/write/erase capability, that would be very attractive for optical computer memories.

Received: September 28, 1976 [A 168 IE]
German version: Angew. Chem. *89*, 467 (1977)

[1] *D. Gabor*, Proc. R. Soc. *A 197*, 459 (1949).
[2] *D. Gabor*, Proc. R. Soc. *B 64*, 449 (1951).
[3] *R. J. Collier, C. B. Burckhardt, L. H. Lin:* Optical Holography. Academic Press, New York 1975, Chap. 9.
[4] *M. R. B. Forshaw*, Opt. Laser Technol. Feb. 1974, p. 28.
[5] *H. Kogelnik*, Bell Syst. Tech. J. *48*, 2909 (1969).
[6] *D. Kermisch*, J. Opt. Soc. Am. *59*, 1409 (1969).
[7] *W. J. Tomlinson*, Appl. Opt. *14*, 2456 (1975).
[8] *W. H. Lee, M. O. Green*, J. Opt. Soc. Am. *61*, 402 (1971).
[9] *J. A. Jenney*, J. Opt. Soc. Am. *60*, 1155 (1970); *61*, 281 E (1971).
[10] *J. A. Jenney*, J. Opt. Soc. Am. *61*, 1116 (1971).
[11] *B. L. Booth*, Appl. Opt. *11*, 2994 (1972).
[12] *B. L. Booth*, Appl. Opt. *14*, 593 (1975).
[13] *E. T. Kurtzner, K. A. Haines*, Appl. Opt. *10*, 2194 (1971).
[14] *R. H. Wopschall, T. R. Pampalone*, Appl. Opt. *11*, 2096 (1972).
[15] *E. F. Haugh*, US-Pat. 3658526.
[16] *V. C. Chambers, Jr.*, US-Pat. 3479185.
[17] *R. L. Van Renesse*, Opt. Laser Technol., Feb. *1972*, p. 24.
[18] *W. S. Collburn, K. A. Haines*, Appl. Opt. *10*, 1636 (1971).
[19] *W. J. Tomlinson, E. A. Chandross, H. P. Weber, G. D. Aumiller*, Appl. Opt. *15*, 539 (1976).
[20] *M. J. Jeudy, J. J. Robillard*, Opt. Commun. *13*, 25 (1975).
[21] *W. J. Tomlinson, I. P. Kaminow, E. A. Chandross, R. L. Fork, W. T. Silfvast*, Appl. Phys. Lett. *16*, 486 (1970).
[22] *J. M. Moran, I. P. Kaminow*, Appl. Opt. *12*, 1964 (1973).
[23] *S. E. Miller*, Bell Syst. Tech. J. *48*, 2059 (1969).
[24] *M. J. Bowden, E. A. Chandress, I. P. Kaminow*, Appl. Opt. *13*, 112 (1974).
[25] *F. P. Laming* in Society of Plastics Engineers Technical Meeting (Oct. 1970); Polym. Eng. Sci. *11*, 421 (1972).
[26] *R. G. Zech*, J. Opt. Soc. Am. *62*, 1396A (1972).
[27] *A. Bloom, R. A. Bartolini, D. L. Ross*, Appl. Phys. Lett. *24*, 612 (1974).
[28] *R. A. Bartolini, A. Bloom, H. A. Weakliem*, Appl. Opt. *15*, 1261 (1976).
[29] *A. A. Friesem, Z. Rov-Noy, S. Reich*, J. Appl. *16*, 427 (1977).
[30] *H. W. Coover, Jr., F. B. Joynes, N. H. Shearer, Jr., T. H. Wicker, Jr.*, SPE (Soc. Plast. Eng.) J. *15*, 413 (1959).
[31] *J. Malcolm Bruce* in *S. Patai*: The Chemistry of Quinoid Compounds. Wiley, New York 1974, Part 1, Chap. 9.
[32] *Y. L. Freilich, M. Levy, S. Reich*, J. Polym. Sci. (Chem.), in press.
[33] *S. Reich, A. A. Friesem, Z. Rav-Noy*, International Conference on Application of Holography and Optical Data Processing, Jerusalem 1976.
[34] *P. J. van Heerden*, Appl. Opt. *2*, 393 (1963).
[35] *J. N. Latta, R. C. Fairchild*, J. Opt. Soc. Am. *63*, 486 (1973).
[36] *B. H. Crawford*, J. Sci. Instrum. *31*, 333 (1954).
[37] *J. N. Latta*, Appl. Opt. *10*, 2698 (1971).
[38] *A. A. Friesem* in *W. Low, M. Schieber:* Applied Solid State Physics. Plenum Press, New York 1970, p. 29.
[39] *K. Erf:* Holographic Nondestructive Testing. Academic Press, New York 1974.
[40] *A. A. Friesem, Z. Rav-Noy, K. Stadler*, C. R. Journées D'Electronique, P. D. 2-1, Lausanne 1975.
[41] *J. C. Urbach, R. W. Meier*, Appl. Opt. *5*, 666 (1969).
[42] *R. J. Collier, C. B. Burckhardt, L. H. Lin:* Optical Holography. Academic Press, New York 1971, p. 276.
[43] *G. Lippmann*, C. R. Acad. Sci. *112*, 274 (1891).
[44] *G. Lippman*, J. Phys. (Paris) *3*, 97 (1891).

Entropy, Binding Energy, and Enzymic Catalysis[**]

By M. I. Page[*]

Why are enzyme-catalyzed reactions so much faster than uncatalyzed reactions, and why are enzymes so specific? What is the effect of mere approximation of enzyme and substrate, and what is the influence of the strain energy? Attempts to answer these questions have led to comparisons between entropy changes in intermolecular and intramolecular reactions, and to determinations of the intrinsic energy of the bond arising by non-covalent interaction between enzyme and substrate.

1. Introduction

All of biology and chemistry is the result of intramolecular and intermolecular forces. The intermolecular non-covalent forces that hold two molecules together are responsible for such diverse phenomena as the existence of inert gas dimers to the formation of antibody-antigen complexes. The formation of enzyme-substrate complexes is also the result of these forces and the intrinsic binding energy resulting from the non-covalent interaction of a substrate with an enzyme appears to be responsible for a large fraction of the difference in the rates of enzyme and non-enzyme catalyzed reactions[1].

There appears to be nothing unusual in the pathways by which covalent bonds are formed and broken in enzyme-catalyzed reactions; the mechanisms used to account for ordinary chemical reactions are also applicable to nature's reactions. In fact, the rate enhancement of *some* enzyme-catalyzed reactions may be accounted for directly in terms of normal chemical mechanisms, such as covalent catalysis in which a covalent bond is formed between the enzyme and the substrate[2]. However, the actual mechanism does not always explain the enormous rate enhancements observed in enzyme-catalyzed reactions. This is especially true when the mechanism involves general acid or general base catalysis since these pathways are not particularly efficient as judged by the relatively small rate enhancements brought about by converting an intermolecular general acid- or general base-catalyzed reaction into an intramolecular one[3,4].

In the subsequent discussion we will address ourselves to the following questions:

1) Why are enzyme-catalyzed reactions so fast?

2) Why do some small non-specific substrates that bind to the active site of the enzyme react so slowly?

3) Why is the binding energy resulting from the non-covalent interaction of enzyme and substrate so large?

We believe that a large fraction of the rate enhancement brought about by enzymes is due to the high intrinsic binding energy between the substrate and the closely-packed covalently linked atoms in the protein. These substrate-enzyme interactions are greater than substrate-solvent or substrate-solid interactions because the number and, possibly, the magnitude of the dispersion forces are greater within the enzyme-substrate complex. However, we also believe that the separation of the substrate binding process from the chemical mechanisms of catalysis to explain specificity and the rate enhancement, respectively, does not give a comprehensive understanding of enzyme catalysis.

An upper limit to the rate enhancement that may be brought about by binding the reactants to the active site of an enzyme, or by covalently binding them together as in an intramolecular reaction, may be obtained, in the absence of strain effects, from the different entropy changes that occur in bimolecular and unimolecular reactions. It will be shown that theoretical and experimental studies of intramolecular reactions indicate that this maximum is about 10^8 mol l^{-1}.

It will also be shown that there is no justification for using the relative rates of a series of intramolecular reactions to substantiate novel theories of enzyme action. The variation may be adequately rationalized by the difference in entropy changes and strain-energy changes in the systems studied.

2. Some Selected Problems

2.1. Rate Enhancement

The rate of an enzyme-catalyzed reaction is very much higher than that of the uncatalyzed reaction. For example, liver esterase-catalyzed hydrolysis of esters proceeds very much faster than the non-enzyme catalyzed reaction[5]. However, several problems arise on putting even this simple statement on a more quantitative basis. Should one compare the rate of an enzyme-catalyzed hydrolysis reaction with the rate of the water-, the acid-, or the base-catalyzed hydrolysis of the same substrate? It appears that whatever the actual comparison made, the rate of the enzyme-catalyzed reaction is often about 10 orders of magnitude faster than that of the non-enzymic reaction. For example, the turnover number for the liver esterase-catalzyed hydrolysis of ethyl acetate is about 10^{13} times greater than the rate of the pH-independent water-catalyzed hydrolysis and about 10^{10} times greater than the hydroxide ion-catalyzed hydrolysis at $pH \approx 7$[5]. Another example is the increase of more than 10^9 brought about by triosephosphate isomerase in the rate of enolization of dihydroxyacetone phosphate compared with the uncatalyzed reaction[6]. This is a lower limit since for this reaction the rate-limiting step is diffusion apart of the enzyme and the product, D-glyceraldehyde 3-phosphate, rather than any bond making or breaking processes[6]. It is worth recalling that such large numbers as these mean that, for example, a rate enhancement of 10^{10}

[*] Dr. M. I. Page
Department of Chemical Sciences
The Polytechnic
Huddersfield HD1 3DH (England)

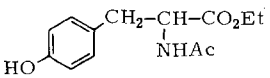
[**] Based on a lecture presented at the symposium on "Drug-Receptor and Drug-Enzyme Interactions" at Namur (Belgium) in May 1976.

would alter the half-life of a reaction from, say, 300 years to one second.

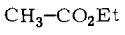
Another difficulty with evaluating the rate enhancement brought about by the enzyme is that it sometimes involves a comparison of the rates of reactions of different kinetic order which gives a number having the units of concentration (see Section 3).

2.2. Specificity

The situation where a large substrate binds poorly to an enzyme may be rationalized in terms of steric effects: the substrate is simply too large to fit into the active site. However, it is more difficult to explain why some small nonspecific substrates that can bind to the active site of enzyme react very slowly. For example, the rate of acylation of chymotrypsin by the specific substrate *N*-acetyl-L-tyrosine ethyl ester *(1)* is more than 4×10^7 times greater than that by the small nonspecific substrate ethyl acetate *(2)*[7, 8]. The reactivities of the ester group in these two molecules are probably similar and ethyl acetate should be able to fit into the active site and yet its free energy of activation is at least 43 kJ mol^{-1} higher than that of the larger substrate.



(1)



(2)

It is these two problems, the rate enhancement and the specificity of enzyme-catalyzed reactions, that we would like to understand.

3. Approximation and Intramolecular Reactions

The factors responsible for the efficiency of enzymic catalysis are usually interpreted in terms of the following contributions:

1) covalent catalysis;
2) general acid-base catalysis;
3) approximation;
4) strain or distortion.

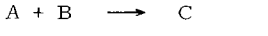
Covalent catalysis occurs where an electrophilic or nucleophilic group on the peptide chain of the enzyme forms a bond with the substrate. Acidic and basic groups may act as general acids or general bases by, respectively, adding protons to or removing protons from the substrate. These mechanisms of catalysis have been well described[2] and we shall not consider them further. Enzymes are also thought to be effective by bringing the reactants together which is referred to as approximation or proximity, the effect of having the reactants near each other. Enzymes may also facilitate the reaction by inducing some sort of strain or distortion in the substrate. This may be manifested by geometric, desolvation, or electrostatic destabilization but this phenomenon is basically dependent upon the binding energy between the enzyme and the substrate since such destabilization induced in the substrate will only result in a rate enhancement if it is "paid for" by the binding energy[7, 9].

Attention here will be focused on approximation and the use of intramolecular reactions as models for enzyme-catalyzed reactions.

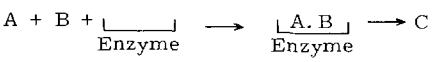
It has long been known that intramolecular reactions (a), in which the reactants are covalently bonded to one another, often proceed very much faster than the analogous intermolecular reaction (b). These intramolecular reactions are frequently taken as models for enzyme-catalyzed reactions where the reactants are held close together in the enzyme-substrate complex *(3)*. It is therefore suggested that the enzyme also facilitates the reaction by this approximation of reactants.



(a)

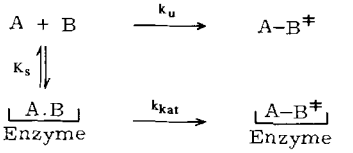


(b)



(3)

The problem, then, is to estimate the maximum rate difference between k_{cat} (for the enzyme-catalyzed reaction) and k_u (for the uncatalyzed reaction) [equation (c)] simply on the basis of approximation and in the absence of strain or solvation effects and without involving chemical catalysis by the enzyme.



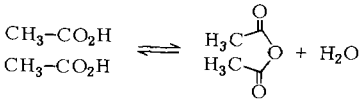
(c)

An understanding of intramolecular reactions is therefore of relevance to this problem of enzymic catalysis and we shall now attempt to rationalize the rate enhancements found in these systems.

Typical rate enhancements and favorable equilibria of intramolecular reactions are illustrated by some reactions of succinic acid and its derivatives. The equilibrium constant for

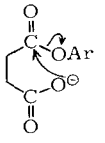


(d)

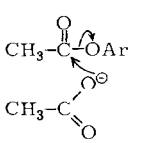


(e)

succinic anhydride formation from succinic acid [equation (d)] is 3×10^5 mol l^{-1} more favorable than that for acetic anhydride formation from acetic acid [equation (e)][10], an analogous intermolecular reaction. A similar situation exists



(4)

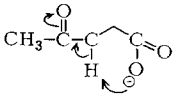


(5)

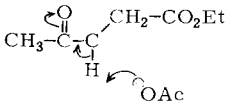
for the rates of reactions. For example, the rate of succinic anhydride formation from the succinate monoester, by intramolecular nucleophilic attack of the carboxylate group on the ester group *(4)*, is also about 10^5 mol l^{-1} greater than that of the analogous intermolecular formation of acetic anhydride *(5)*[11]. A special explanation for the rate differences which is peculiar to the activated complex is not required since the favorable reactions of intramolecular systems over their intermolecular counterparts are manifested in both rates and equilibria[4].

The rate enhancements and favorable equilibria have units of concentration because a unimolecular reaction is being compared with a bimolecular one. For this reason the rate enhancement is sometimes called the "effective concentration" or "effective molarity", which is the hypothetical concentration of one of the reactants in the intermolecular reaction required to make the intermolecular reaction proceed at the same rate as that of the intramolecular one.

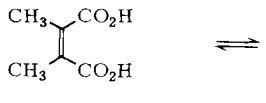
In general, however, the effective concentrations or rate enhancements of intramolecular reactions do not show a constant value but cover a very wide range from about 1 to 10^{15} mol l^{-1}[4]. For example, the intramolecular general base catalyzed enolization reaction of 4-oxopentanoate *(6)*, in which the neighboring carboxylate group removes a proton in a five-membered ring transition state, shows an effective concentration of 0.5 mol l^{-1} compared with the analogous intermolecular reaction of *(7)*[12]. However, the equilibrium constant for the dehydration of dimethylmaleic acid *(8)* to give the five-membered ring acid anhydride *(9)* is about 10^{12} mol l^{-1} times more favorable than that for acetic anhydride formation from acetic acid[10, 13].



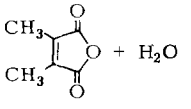
(6)



(7)



(8)



(9)

We believe that it is this wide variation in rate enhancements which has caused so much confusion in the literature and retarded a rational explanation of intramolecular catalysis.

Given this large range of rate enhancements one is again led to ask the question: "What is the maximum rate increase expected from approximation by simply bringing the reactants together without invoking strain or solvation effects"? Until recently[14], it had been generally accepted that the small rate enhancements are normal with the value 55 mol l^{-1} being commonly used. Thus the observation of a larger value was thought to require a special interpretation, such as rotamer distribution[15], orbital steering[16], stereopopulation control[17], vibrational activation[18], or freezing at the reactive centers of enzymes (FARCE)[19].

We believe that the large effective concentrations or rate enhancements are to be expected from known chemical principles[4, 14]. It is the observation of a low effective concentration, if anything, which requires a special explanation.

Actually it is quite easy to set an *upper* limit to the rate enhancement that may be brought about by covalently binding the reactants together, as in an intramolecular reaction, or by binding them to the active site of an enzyme. This may be done by considering the different entropy changes that occur in bimolecular and unimolecular reactions[4, 14].

There are different degrees of freedom lost in intramolecular and analogous intermolecular reactions which gives rise to large differences in the entropy change between the two systems. For a non-linear molecule containing n atoms there are three degrees of translational freedom, *i.e.* its freedom to move along the three axes in space; there are also three degrees of rotational freedom representing the freedom of the whole molecule to rotate about its center of gravity. This leaves $3n-6$ degrees of freedom associated with internal motions in the molecule, *i.e.* vibrations and internal rotations. On forming the product of a bimolecular association reaction [equation (f)] there is a loss of three degrees of translational

	A + B	⇌	A–B
Translation	3 + 3		3
Rotation	3 + 3		3
Vibration	3n − 6 + 3n′ − 6		3n + 3n′ − 6

(f)

freedom and a loss of three degrees of rotational freedom. There is a gain of six new vibrational modes in the product. However, in the uni- and intra-molecular reaction [equation (g)] there is *no* net change in the number of degrees of freedom

	A B	⇌	A–B
Translation	3		3
Rotation	3		3
Vibration	3n − 6		3n − 6

(g)

of translation, rotation, and vibration upon forming the product. The entropy associated with these motions may easily be calculated from the partition functions[4], which are simply an indication of the number of quantum states that the molecule may occupy for each type of movement.

The translational entropy of a molecule is proportional to its mass, the temperature, and the volume of space available to it. For a standard state of 1 mol l^{-1} and at 298 K physical constants make up the bulk of the contribution to translational entropy which for most molecules, therefore, has only a small dependence upon mass. A molecule rotates about its center of gravity and the rotational entropy of a molecule is proportional to the moment of inertia, the temperature, and the symmetry of the molecule. However, again physical constants make up the major contribution and so for average size molecules there is only a small dependence of rotational entropy upon the actual size and structure of the molecule. The entropy accociated with internal rotation, that is the rotation about a single bond of one group against another, depends upon the moment of inertia and the symmetry of the rotating group, the temperature, and the energy barrier to rotation. Finally, the vibrational entropy of a molecule depends upon the frequency of vibration and the temperature.

In Table 1 are shown some typical values of these entropy terms. For a standard state of 1 mol l^{-1} the translational entropy is normally about 120 to 150 J K^{-1} mol^{-1}, and, as previously mentioned, this value is not very dependent upon the molecular weight. For the majority of medium-sized molecules the entropy of rotation is about 85 to 115 JK^{-1} mol^{-1} and not normally very dependent upon the size and structure of the molecule. The exceptionally small value for water, 44 JK^{-1} mol^{-1}, results because in this molecule nearly all the mass is concentrated at the center of gravity and hence the moment of inertia, and thus the entropy, is small. The entropy of internal rotation makes a comparatively small contribution to the total entropy of the molecule and the vibrational contribution is even smaller except for the very low vibrational frequencies.

Table 1. Typical entropy contributions from translational, rotational, and vibrational motions at 298 K [14].

Motion	S^0 [JK^{-1} mol^{-1}]
Three degrees of translational freedom molecular weights 20 to 200 standard state 1 mol l^{-1}	120—148
Three degrees of rotational freedom	
water	44
n-propane	90
endo-dicyclopentadiene $C_{10}H_{12}$	114
Internal rotation	13—21
Vibrations $\omega = 1000$ [cm^{-1}]	0.4
800	0.8
400	4.2
200	9.2
100	14.2

These calculations apply to the gas phase and it is not possible, at present, to perform similar entropy calculations in the liquid phase. However, the entropy of a molecule in solution may be obtained from observed or empirically estimated entropies of vaporisation, the change in entropy for the transfer of a molecule from the liquid to the gas phase[4, 14]. The entropy change for a bimolecular reaction may thus be estimated in the gas phase and in solution (Table 2). In the gas phase, for a standard state of 1 mol l^{-1} and at 298 K the total loss of translational and rotational entropy for a bimolecular association reaction is about -220 JK^{-1} mol^{-1} and this value has only a small dependence upon the masses, sizes, and structures of the molecules involved. However, this loss is often compensated to varying extents by low frequency vibrations in the product or transition state. For several reactions having "tight" transition states or covalently bonded products the change in internal entropy is about $+50$ JK^{-1} mol^{-1}[4, 14] so the total entropy change is predicted to be about -170 JK^{-1} mol^{-1}, which is the value observed experimentally for many bimolecular gas phase reactions[4, 14]. In solution, the entropy change for a bimolecular reaction is estimated to be only about 20 JK^{-1} mol^{-1} less than that in the gas phase, at the same standard state of 1 mol l^{-1}. This is because the product or transition state usually has a higher boiling point than the reactants and consequently has a more negative entropy of transfer from the gas phase to solution (Table 2)[14].

Table 2. Entropy changes for a bimolecular reaction [4, 14] at a standard state of 1 mol l^{-1} and at 298 K in JK^{-1} mol^{-1}.

Gas	A	+	B	⇌	Product or transition state	ΔS
S_{trans}	135		135		140	−130
S_{rot}	100		100		110	− 90
S_{int}	12		12		74	+ 50
S_{tot}	247		247		324	−170
$-\Delta S_{vap}$	−40		−40		−60	
Solution	A	+	B	⇌	Product or transition state	−150

These suggestions are in accord with the well known experimental fact that equilibrium and activation entropies for Diels-Alder reactions of -125 to -170 JK^{-1} mol^{-1} are very similar in the gas and liquid phases. Many other bimolecular association reactions, which are apparently free of solvation effects, also have similarly large negative entropy changes in solution[4, 7, 14].

Since this large loss of entropy for a bimolecular reaction is avoided if the reactants are bound to an enzyme active site (equation (c)) or converted in an intramolecular reaction [equation (a)], the maximum entropic advantage from approximation may now be estimated [equation (h)].

$$A + B \rightleftharpoons A\cdots\cdots B \rightleftharpoons A - B \qquad (h)$$

	"Loose" transition state or product	"Tight" transition state or product	Maximum
ΔS [JK^{-1} mol^{-1}]	−40	−150	−210
Effective concentration [mol l^{-1}]	10^2	10^8	10^{11}

The theoretical most negative entropy change for a bimolecular reaction is about -210 JK^{-1} mol^{-1} which is equivalent to 63 kJ mol^{-1} at 298 K and makes such a reaction unfavorable by a factor of 10^{11} mol l^{-1}. However, this is very rare and a more general situation is that this large loss of translational and rotational entropy is compensated for by an entropy change of about $+60$ JK^{-1} mol^{-1}, resulting from changes in internal motions on going from the reactants to the product or transition state and from differences in entropies of vaporization of reactants and products giving bimolecular reactions a total entropy change of about -150 JK^{-1} mol^{-1}. Since this loss of entropy does not take place for a reaction in which the reactants are bound to the active site of an enzyme [equation (c)] or for an intramolecular reaction [equation (a)] the approximate *maximum* effective concentration or rate enhancement for these reactions from entropic factors alone is about 10^8 mol l^{-1}. In the comparatively rare situation of a bimolecular reaction having a very "loose" transition-state or product then association will be even less entropically unfavorable since the entropy of the low frequency vibrations in the "loose" complex will counterbalance the large loss of translational and rotational entropy[4, 14]. The rate enhancement for the analogous intramolecular reaction will, therefore, be smaller, perhaps in the range of 100 mol l^{-1} or less.

It is important to emphasize that these entropy differences will not necessarily be reflected in the observed entropy changes of a reaction since these are dominated by solvent effects and are difficult to interpret[7].

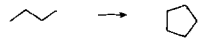
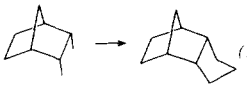
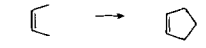
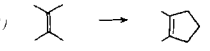
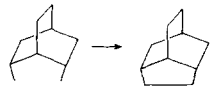
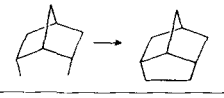
In summary, rate enhancements of about 10^8 mol l^{-1} are expected for intramolecular and enzymic reactions simply on the basis of the difference in entropy changes between bimolecular and unimolecular reactions. Reactions which show rate enhancements greater than this are probably the result of additional contributions from potential energy differences. Smaller rate enhancements may result either from a "loose" transition state or product or from unfavorable entropy changes, such as the loss of internal rotations, and/or potential energy changes in the intramolecular reaction[4].

It is instructive to examine how these factors may account for the large variation in rate enhancements found in intramolecular reactions because these differences have often been used to justify new concepts and theories related to enzyme catalysis. We believe that the variation in the rates of reaction observed in the systems used by the proponents of these theories may be satisfactorily explained using the existing concepts of entropy and strain-energy effects[4].

4. Strain-Energy Effects

The intramolecular reaction, which invariably proceeds *via* a cyclization step, is often accompanied by the introduction and sometimes the relief of strain in the molecule; these changes may therefore either decrease or increase the effective concentration. As a model for the changes in strain energy that occur when a molecule undergoes cyclization one may examine an analogous hydrocarbon system[4]. The strain energy of a hydrocarbon may be evaluated either from a "molecular mechanics" procedure[20] or from a group additivity scheme[21]. Table 3 shows examples of the changes in strain energy that occur upon cyclization of some hydrocarbons[20–22]. Also shown are the estimated changes in entropy due to the loss of internal rotation upon cyclization[4].

Table 3. Estimated relative energy changes of ring closure reactions of hydrocarbons at 298 K in kJ mol^{-1} (see also Section 1).

System		ΔH Strain	$-T\Delta S$ Int. Rot.	$\log K_{rel}$ $\log k_{rel}$
	*(10)*	33.5	16.3	0.0
	*(11)*	26.8	10.9	2.1
	*(12)*	23.8	10.9	2.6
(13) 	*(14)*	14.0	10.9	4.3
	*(15)*	18.8	5.4	4.5
	*(16)*	−4.2	5.4	8.5

The combination of these data gives the predicted relative rates or equilibrium constants for a series of intramolecular reactions of similar structure to these hydrocarbons. For example, Fig. 1 shows a plot of the observed relative equilibrium constants for anhydride formation from a series of dicarboxylic acids[13] against the predicted values calculated as just described. This comparison means that, for example, the change in strain energy in the cyclization of 2,3-dimethyl-2-butene *(13)* to 1,2-dimethylcyclopentene *(14)* is used as a model for the cyclization of dimethylmaleic acid *(8)* to dimethylmaleic anhydride *(9)*. The justification for this procedure is that the strain energy is, to a crude approximation, characteristic of the ring size of a molecule and not of its constituent atoms[4]. In Figure 2 are shown the data for the hydrocarbons

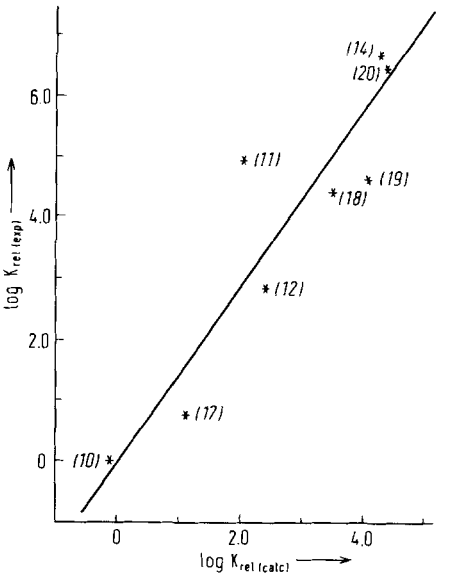


Fig. 1. Relative equilibrium constants $K_{rel(exp)}$ for anhydride formation from dicarboxylic acids plotted *vs.* $K_{rel(calc)}$ for cyclization of the corresponding hydrocarbons [products *(10)*, *(11)*, *(12)*, *(14)*, see Table 3; *(17)* to *(20)*, see below].

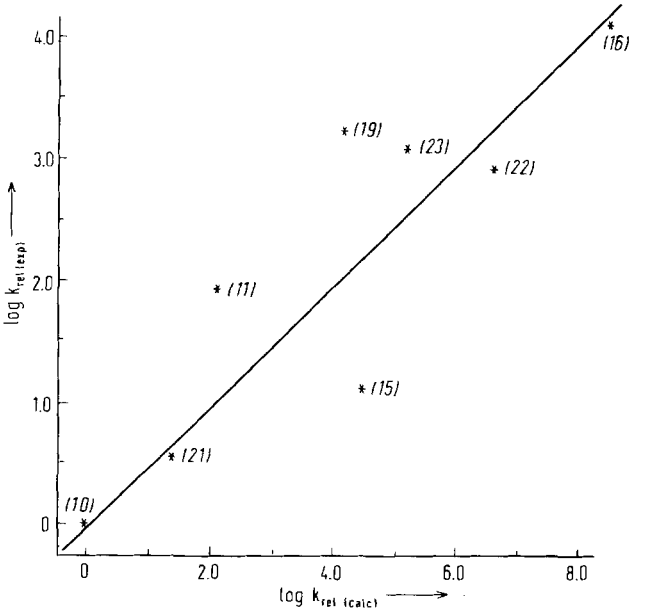
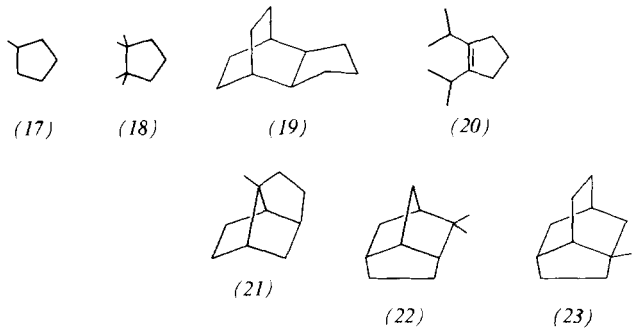


Fig. 2. Relative rate constants $k_{rel(exp)}$ for acid-catalyzed lactonization of hydroxy acids, plotted *vs.* $k_{rel(calc)}$ for cyclization of the corresponding hydrocarbons [products *(10)*, *(11)*, *(15)*, *(16)*, see Table 3; *(19)*, *(21)* to *(23)*, see above].



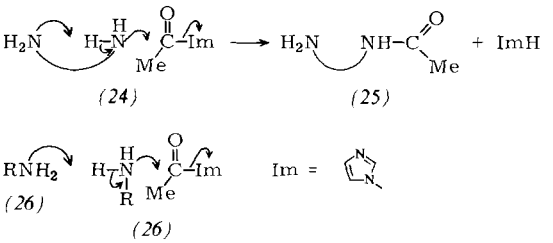
(17) (18) (19) (20) (21) (22) (23)

which correspond to the hydroxy acids and lactones used to justify the concept of "orbital steering"[16]. Despite the obvious limitations to the use of such models, the results do serve to show that the variation in the rates and equilibria of a series of intramolecular reactions may be accounted for simply by the differences in the strain energies of the reactants and products, or transition states, and by the differences in the entropy changes due to the loss of internal rotations[4]. Several other series of intramolecular reactions have been treated in this way and show similarly good correlations[23].

5. Reactions with "Loose" Transition States

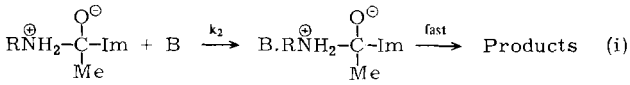
Bimolecular reactions which proceed through "loose" transition states are entropically less unfavorable than those involving "tight" transition states[4, 14]. This is because the entropy of low frequency motions in the transition state compensates for the large loss of translational and rotational entropy. Consequently, an analogous intramolecular reaction should show a smaller rate enhancement or effective concentration. Such a situation exists in proton transfer reactions and, to date, all reactions involving intramolecular general acid or general base catalysis have low effective concentrations. This appears to be true for proton transfer to or from both electronegative atoms and carbon atoms[4]. Presumably this is because such reactions either have a transition state which is a very loose hydrogen-bonded complex or have a rate-limiting step which is diffusion controlled[24]. Thus there does not seem to be much of an advantage upon changing an intermolecular general acid or general base catalyzed reaction to an intramolecular one.

A system which exemplifies this situation is the intramolecular general base-catalyzed aminolysis of acetylimidazole by several diamines *(24)* to give the corresponding amides *(25)* and imidazole. The effective concentration of the catalyzing amino group compared with the analogous intermolecular



(24) (25) (26)

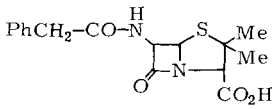
reaction of the amines *(26)* is only about 1 mol l^{-1}[3]. Potential energy effects are not predominant in this reaction since there is only a small sensitivity to the structure of the diamine[3]. General base catalysis in the intermolecular reaction of the amines *(26)* probably involves rate-limiting diffusion-controlled encounter of the tetrahedral intermediate with the base[25], k_2 in equation (i). The transition state is thus very



(i)

loose and the bimolecular step (k_2) will be associated with a small entropy change giving rise to the low effective concentration of the intramolecular reaction.

A similar situation exists for the aminolysis of benzylpenicillin *(27)*. The rate constant for the uncatalyzed reaction of ethylenediamine with benzylpenicillin is at least 25 times greater than that of a monoamine of the same basicity, which is indicative of intramolecular general base catalysis. However, the effect of intramolecularity itself is small and the effective concentration compared with the intermolecular general base-



(27)

catalyzed reaction is only about 1 mol l^{-1}, which is also suggestive of a "loose" transition state[26].

In summary, there is little or no advantage of having the catalyst covalently bonded to one of the reactants if the transition state is a very "loose" one.

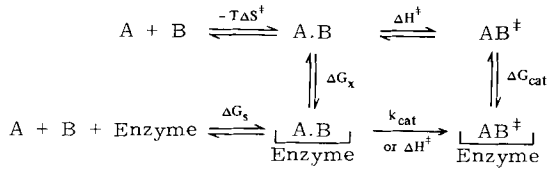
6. Binding Energy and Enzymic Catalysis

Bringing two molecules together is entropically unfavorable and although the situation for an enzyme-bound substrate [equation (c)] is similar to an intramolecular reaction [equation (a)] where this large loss of entropy is avoided, there will, of course, be an unfavorable entropy change for initially binding the substrate to the enzyme. If catalysis is to be efficient then this large loss of entropy must be compensated by the binding energy resulting from the favorable noncovalent interaction between the substrate and the enzyme.

The importance of binding is evident when the substrate concentration is below K_M, the Michaelis constant, and the rate of reaction is given by v_{max}/K_M so that an increase in binding, that is a smaller value of K_s, results in an increased rate of reaction. We will consider two examples where the binding energy compensates for the loss of entropy occurring in the uncatalyzed reaction; these are for the situation where there is no chemical catalysis by the enzyme and for the case of the substrate reacting with a catalytic group on the enzyme[1, 7].

6.1. Reaction without Chemical Catalysis by the Enzyme

Suppose two compounds A and B react to form a transition state AB^+ in an uncatalyzed reaction. The free energy of activation may be arbitrarily separated into the entropy and enthalpy of activation [equation (k)]. This *same* transition



(k)

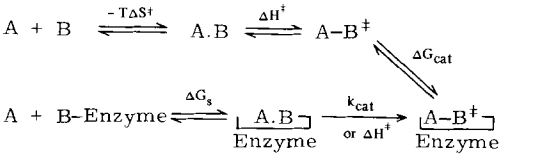
state may be reached with the reactants bound to the active site of an enzyme, *i.e.* we are considering a process in which there is no chemical catalysis by the enzyme, the function of which is simply to bring the reactants together. Any increase in the rate of reaction brought about by the enzyme is given by the enthalpy of binding the enzyme and substrates minus the entropy of association of the transition state and the enzyme[1] [equation (l)]. The term $T\Delta S_x$ in equation (l)

$$\Delta G_{cat} = \Delta H_s - T\Delta S_x \quad (l)$$

represents the unfavorable loss of entropy in having the enzyme act as a catalyst. Any excess of the intrinsic binding energy between the enzyme and substrates over this entropy loss will thus appear as catalysis of the reaction. Pictorially, the entropy effect may be regarded as "entropic strain" that is compensated by the binding energy[1].

6.2. Reaction with a Group in the Enzyme[7]

Suppose, as previously, two molecules A and B react to form a transition state $AB^{\ddagger}$, but this is now compared with the situation where B is covalently bonded to the enzyme [equation (m)]. Any free-energy advantage of the enzymic



(m)

reaction is then given by equation (n) which may be simplified to equation (o), if it is assumed that the entropy of activation $T\Delta S^{\ddagger}$ is equal to the entropy change of binding the substrate A to the enzyme, $T\Delta S_s$, which will be, as we have already seen, approximately true.

$$\Delta G_{cat} = \Delta H_s + T\Delta S^{\ddagger} - T\Delta S_s \quad (n)$$
$$\Delta G_{cat} = \Delta H_s \quad (o)$$

In this case the amount of catalysis is given directly by the binding energy between the enzyme and substrate and shows the advantage of covalent catalysis in enzymic reactions.

It should be emphasized, again, that the quantities referred to here will not be reflected in measured enthalpies and entropies of reaction which are dominated by solvent effects.

Before going on to consider the magnitude of the enzyme-substrate binding energy it is worth pointing out that the classical separation of specificity and catalysis may not be valid[1]. Often the specificity of the substrate binding process, which may be described by some sort of "lock and key" model, is treated as a separate process from the catalytic rate acceleration which is explained in chemical terms. In fact, many enzymes exhibit their specificity in their maximal rates of catalysis rather than in substrate binding.

In the derivation of equation (o) it was assumed that $T\Delta S^{\ddagger} = T\Delta S_s$, which will be true for good substrates that bind tightly. However, poor substrates, which will often have a smaller enthalpy of binding, will bind more loosely and the loss of entropy will be smaller so that $T\Delta S_s$ may be less than $T\Delta S^{\ddagger}$. Since enough entropy will then not have been lost to reach the transition state k_{cat} would be smaller but the apparent free energy of binding would be unchanged for the poorer substrate, if changes in $T\Delta S_s$ are exactly compensated by changes in ΔH_s. Much or all of the more favorable intrinsic binding energy of good substrates may therefore appear as a rate acceleration rather than as an increase in the binding constant. Only when $T\Delta S_s = T\Delta S^{\ddagger}$ will the increased interaction energy of good substrates be reflected in better binding.

7. The Magnitude of the Binding Energy

Observed free energies of binding substrates to enzymes are often less than the enthalpic intrinsic binding energy because much of the binding energy is "used up" in bringing about the required loss of entropy and in inducing any destabilization of the reactants[1]. However, there are a few examples of free energies of binding that indicate that the interaction energy between proteins and other molecules is very much greater than is generally believed. For example, in Table 4 are given the binding constants of several associations showing large free energies of binding[7]. In addition to these examples there are other instances involving the favorable association

Table 4. Some examples of large binding energies [7].

System	Binding constant [mol l^{-1}]	$-\Delta G$ [kJ mol^{-1}]	Ref.
1) Camphor/Fe^{II} cytochrome P 450	2.2×10^8	46	[30]
2) Amethopterin/dihydrofolate reductase	10^{10}	57	[31]
3) Amethopterin/reductase-NADPH complex	10^{11}	63	[32]
4) Biotin/avidin	10^{15}	85	[33]
5) Glucose-1-phosphate/phosphoglucomutase	10^{15}	85	[34, 7]

of large molecules such as the inhibition of proteolytic enzymes by protein inhibitors to form complexes with dissociation constants as low as 10^{-13} mol l^{-1}[27], the high affinity of the *lac* repressor for its specific locus in *E. coli* DNA shown by half-maximal binding of repressor to operator occurring at a repressor concentration of 10^{-13} mol l^{-1}[28] and the low dissociation constants of antibody-antigen complexes like the value of 6×10^{-12} mol l^{-1} for the shark IgM antibody-dinitrophenylated ΦX-174 virus complex[29a]. The formation of stable complexes between the serine proteinases and protein inhibitors is not the result of covalent bond formation between the two proteins but is simply a consequence of the summation of a large number of non-covalent interactions[29b]. In all of these complexes there are, of course, a very large number of interactions and it is difficult to appreciate the magnitude

of the individual forces involved. A better estimate of the magnitude of the intrinsic binding energy between a molecule and a protein may be obtained from the increased binding energy that is observed when the "molecule" is added as a substituent to a larger molecule. This aspect of the binding energy has been given the trivial name of the anchor principle[11].

8. The Anchor Principle[11]

The intrinsic binding energy of a small group or "molecule" A may be obtained from a comparison of the free energies of binding the larger molecule B and the molecule A—B, where A is a covalently bonded substituent. The tight binding of the small molecule A to an enzyme requires the loss of its translational and rotational entropy which makes an unfavorable contribution to the overall free-energy change. However, when A is a substituent in the molecule A—B most of this entropy loss is accounted for in the binding of B since the loss of entropy upon binding A—B will be much the same as that upon binding B, $T\Delta S_{AB} \approx T\Delta S_B$. The difference in the free energies of binding A—B and B therefore approximates the true binding energy of A [equation (p)].

$$\Delta G_{AB} - \Delta G_B = \Delta H_{AB} - T\Delta S_{AB} - \Delta H_B + T\Delta S_B \approx \Delta H_{AB} - \Delta H_B \quad \text{(p)}$$
$$\Delta G_{AB} - \Delta G_B \approx \Delta H_A$$

Consequently, this difference, $\Delta G_{AB} - \Delta G_B$, is very much greater than the observed free energy of binding of A, ΔG_A, since it is free of the unfavorable entropy term.

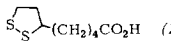
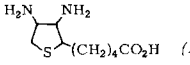
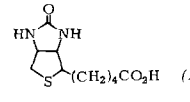
Incidentally, a comparison of ΔG_A with $\Delta G_{AB} - \Delta G_B$, provides a lower limit to the intrinsic loss of entropy upon the binding of A [equation (q)].

$$\Delta G_{AB} - \Delta G_B - \Delta G_A = \Delta H_{AB} - \Delta H_B - \Delta H_A + T\Delta S_A \quad \text{(q)}$$
$$\Delta G_{AB} - \Delta G_B - \Delta G_A \approx T\Delta S_A$$

In Table 5 are shown some data for the binding of various molecules to the protein avidin[33]. Urea *(28)* binds weakly to avidin but the difference between the free-energies of binding

Table 5. Dissociation constants K for various avidin complexes at $T = 298$ K [33]. *(28)*: typical component A; *(29)*, *(30)*: typical component B; *(31)*: typical species A—B.

Avidin·S $\overset{K}{\rightleftharpoons}$ Avidin + S

S		K	$-\Delta G$ [kJ mol^{-1}]
H_2N–CO–NH_2	*(28)*	3.6×10^{-2}	8
	*(29)*	7×10^{-7}	≈35
	*(30)*	3×10^{-7}	≈37
	*(31)*	10^{-15}	≈85

biotin *(31)* and some analogous molecules lacking the ureido group [*(29)* and *(30)*] is very much greater than the free-energy of binding urea. Of course, the ureido group in biotin is not an ideal model for urea, but this example does serve to show that if the required loss of translational and rotational entropy is brought about by the binding of one molecule, the anchor molecule B which, in this case, is the biotin analog *(29)* or *(30)*, then a large favorable decrease in the free energy of binding is made possible by the addition of the ureido group. This change, about 50 kJ mol^{-1} (Table 5), is an indication of the intrinsic binding energy of urea to avidin.

This model for evaluating intrinsic binding energies depends on the assumption that the loss of entropy for binding A—B is similar to that for B [equation (p)]. If the anchor molecule B is only loosely bound then the intrinsic binding energy of A in A—B may cause a greater restriction of motion in A—B so that $T\Delta S_{AB} > T\Delta S_B$ and consequently there will be no change, or even a decrease, in the observed binding constant. Intrinsic binding energies estimated in this way are, therefore, likely to be lower limits.

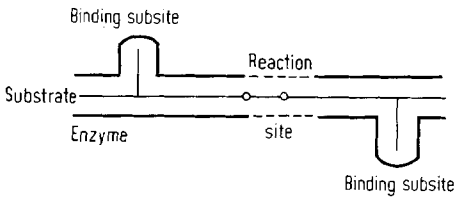
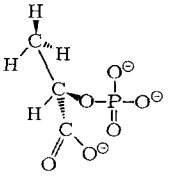


Fig. 3. Reaction site and binding subsites of an enzyme, schematic. o—o, substrate bond to be broken.

The importance of subsites for various parts of the substrate at some distance from the bond breaking site (Fig. 3) may be accounted for by the anchor principle. For example, the catalytic efficiency of pepsin in cleaving polypeptides is sensitive to changes in substrate structure some distance from the peptide bond which is cleaved[35a]. The binding of the peptide chain to the subsites provides the required binding energy to compensate for the loss of translational and rotational entropy and any destabilization of the substrate required to reach the transition state. If this anchoring is incomplete then the required loss of entropy to reach the transition state will not occur upon binding and a slower rate of catalysis will be observed [cf. equation (p)]. This provides one explanation for the variation in k_{cat} of up to 7×10^3 with K_M remaining approximately constant for substrates of pepsin with different amino acids that bind at subsites removed from the place of bond fission[35a].

Evidence for this restriction of motion of the molecule upon binding to the protein comes from NMR and ESR spectroscopy. For example, ESR spectra indicate that the nitroxide groups in some acyl chymotrypsins are not free to rotate with respect to the enzyme[35b]. NMR studies show that even the internal rotation of the methyl group of L-phospholactate *(32)*, an inhibitor of pyruvate kinase, is restricted upon binding to the enzyme[19].

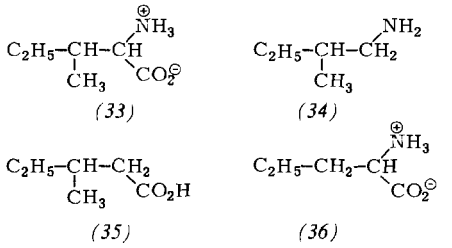


(32)

One of the most interesting problems concerned with enzyme-substrate interactions is the magnitude of the binding energy between small substituents and proteins. We believe that the usual method of evaluating these interactions from the energy of transfer of the substituent from one liquid to another underestimates the binding energy.

For example, the binding energies of isoleucine *(33)* and the related compounds *(34)* to *(36)* to isoleucyl-tRNA synthetase are given in Table 6[36]. Isoleucine has a free-energy of binding of -29.7 kJ mol^{-1} and replacing the carboxylate

Table 6. Contribution of small groups to the binding energy, illustrated for isoleucine *(33)* and the related compounds *(34)* to *(36)* in the system *(33)* to *(36)*/Ile-tRNA synthetase.



(33)

(34)

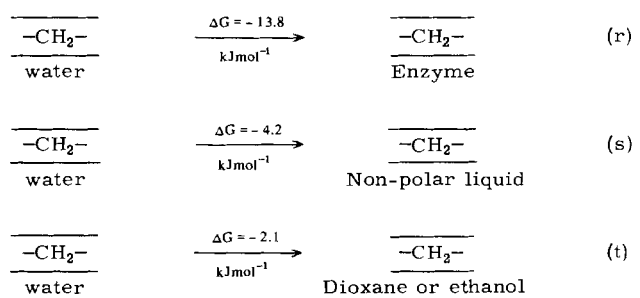
(35)

(36)

Cpd.	Group removed	$-\Delta G$ [kJ mol^{-1}]	$-\Delta\Delta G$ [kJ mol^{-1}]
(33)	—	29.7	—
(34)	CO_2^-	11.7	18.0
(35)	NH_3^+	<1.7	>28.0
(37)	β-CH_3	15.9	13.8

group of this molecule with hydrogen [giving *(34)*] lowers the binding energy to -11.7 kJ mol^{-1}, which indicates that the carboxylate group has an intrinsic binding energy of -18 kJ mol^{-1} with the enzyme. Similarly, the protonated amino group has an estimated binding energy of at least -28 kJ mol^{-1}. These are intrinsic binding energies and are presumably so favorable because the required loss of entropy upon binding is already compensated by the binding energy of the remainder, or the "anchor" part, of the amino acid molecule.

The intrinsic binding energy of a methylene group estimated in this way is -13.8 kJ mol^{-1} (Table 6) and a similar value is obtained from data for valyl-tRNA[37a]. The addition of a methylene group to substituted phenyl *N*-methylcarbamates increases the free energy of binding these compounds to acetylcholinesterase by as much as 12.1 kJ mol^{-1}[37b]. Why are these numbers so large? It is often assumed that the interior



of a protein is analogous to an organic liquid[38] and that the transfer of a group from water to a non-polar liquid may be taken as a model for the transfer of the same group from water to the enzyme [equations (r) to (t)]. However, the change in interaction energy estimated in this way for a methylene group, about -4.2 kJ mol^{-1} for transfer to a non-polar liquid[39] and about -2.1 kJ mol^{-1} for transfer to dioxane or ethanol[40], is at least three times *less* favorable than the change upon transfer to an enzyme. There are many other examples which show that these estimations of the interaction between a substituent and a non-polar liquid underestimate the forces between the same substituent and an enzyme[7].

The comparison between the two "enzymic" process [equation (r)] and the analogous "non-polar" process [equation (s)] involves an examination of the following changes in interaction energies[41]. Firstly, since the initial state is the same in the two systems, changes in energy when the solute is removed from water will be the same in each case. When a solute is transferred to a non-polar liquid [equation (s)] there is a gain of solute-solvent interactions and a loss of solvent-solvent interactions, which is equivalent to the free energy of formation of a cavity in the solvent of a suitable size to accommodate the solute molecule[42].

When a solute is transferred to an enzyme [equation (r)] there is a gain of solute-enzyme interactions if water is initially absent from the binding site. If water is initially bound to the site of binding and is then displaced by the substituent there is also a gain of water-water interactions and a loss of water-enzyme interactions. However, the sum of the free energy changes of these two interactions would be thermodynamically unfavorable, otherwise water would not initially be bound to the enzyme, and hence, in this situation, the observed free energy of transfer of a substituent from water to an enzyme provides a *lower* limit to the magnitude of enzyme-substrate interactions.

Approximately 16 localized water molecules have been detected within the chymotrypsin molecule[43] but much larger numbers in general for proteins are probably unlikely[44]. If water is *not* initially bound to the enzyme then the transfer in equation (r) could be thermodynamically more favorable than that in equation (s) because the latter process involves a loss of solvent-solvent interactions, *i.e.* the free energy of cavity formation, and thus the free-energy change for equation (s) provides an underestimation of solute-solvent interactions. According to the scaled particle theory[45], and other calculations[46], the free energy of cavity formation in non-polar liquids is of similar magnitude, but, of course, of opposite sign, to the free energy of interaction of the solute with the solvent. This, therefore, may explain, in some cases, part of the discrepancy between equations (r) and (s) since the enzyme may have a ready-made "cavity" and the binding of a substituent to this site would not result in the unfavorable changes which accompany cavity formation in liquids. However, it is difficult to see how water could be prevented from binding to a site that may be occupied by a methylene group, and another important factor is that the *number* of the favorable dispersion or van der Waals interactions of the substituent with the enzyme are probably greater than with a liquid solvent.

The atoms in an enzyme molecule are very closely packed since they are linked together by covalent bonds and, in

some cases, the polypeptide chains are cross-linked by covalent disulfide bonds. The fraction of space occupied by the atoms in a molecule of protein is 0.75[47] which may be compared with 0.74, the value for the most efficient known way of packing spheres, cubic close-packing or hexagonal close-packing. In a liquid the fraction of space occupied is very much less, for example upper limits for water, cyclohexane and carbon tetrachloride are 0.36, 0.44, and 0.44, respectively[47]. The inside of a protein thus contains little space and is more analogous to a solid than to a liquid. It may be more appropriate, therefore, to compare equation (r) with the free-energy of transfer of a substituent from water to a solid [equation (u)]. An indication of this energy change may be estimated from the fusion of hydrocarbons[41]. The enthalpy of melting

$$\underset{\text{water}}{\overline{\underline{-CH_2-}}} \longrightarrow \underset{\text{Pure liquid}}{\overline{\underline{-CH_2-}}} \longrightarrow \underset{\text{Solid}}{\overline{\underline{-CH_2-}}} \qquad \text{(u)}$$

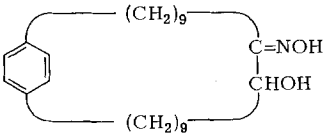
per additional methylene group in *n*-alkanes, up to $C_{20}H_{42}$, containing an even number of carbon atoms is 4.1 ± 0.1 kJ mol^{-1}[48]. The heat capacity changes per additional methylene group are also approximately constant, about 26 and 15 JK^{-1} mol^{-1} for the liquid and solid respectively[48]. The hypothetical enthalpy of melting per additional methylene group at, say, 25 °C will therefore not deviate much from the above values. There will, of course, be an unfavorable entropy change on transfer from the liquid to the solid but it can now be estimated from equations (s) and (u) that the maximum favorable free-energy of transfer of a methylene group from water to a non-polar solid is about -8.3 kJ mol^{-1}[41].

The atoms in an enzyme surrounding the substrate are very compact and most are separated only by their covalent radii. In a liquid, a solute is surrounded by molecules separated by their van der Waals radii. Hence the effective coordination number is much greater in the enzyme than it is in a liquid. For example, the van der Waals radii for carbon, nitrogen, and oxygen are about 2.2 times greater than their respective covalent radii and a very simple treatment of the packing of spheres shows that the coordination number of a sphere is about 2.5 times greater when surrounded by other spheres separated by such covalent radii than when they are separated by van der Waals radii. In a liquid a large fraction of the surface of a solute molecule is surrounded by empty space between the solvent molecules[49]. Even in a non-polar solid the closest approach of neighboring molecules is governed by their van der Waals radii; therefore the energy of transfer of a group from water to a solid may underestimate the interaction energy between the same group and an enzyme. Such a comparison indicates that as far as interaction energy is concerned enzymes may be more solid-like than solids!

Not only will there be a greater surface area of contact between a bound molecule and a protein, compared with the situation in a liquid, giving rise to a greater number of interaction energies but also the dispersion forces themselves may be greater. It has been suggested that dispersion interactions between a molecule and surrounding atoms is greater if the atoms are covalently bonded to each other[49].

Physical adsorption of molecules on to solid surfaces possesses certain similarities to enzyme-substrate binding. The atoms in a solid present a closely-packed surface and in some cases, for example graphite, the interatomic distance is similar to that found in covalently bonded molecules. Instead of the normal r^{-6} dependence of the London attractive potential between a pair of molecules there is a r^{-3} dependence for the interaction between a molecule and a solid[50]. This longer range interaction is the basic reason why gases are adsorbed at pressures lower than those at which they condense to liquids or solids. The differential heat of adsorption is often of the order of twice the heat of condensation of the adsorbed vapour[51].

The formation of clathrates and cage-type compounds also shows similarities to the enzyme-substrate binding process. The acylation of the oxime *(37)* with 4-nitrophenylalkanecarboxylates shows saturation type kinetics consistent with the pre-equilibrium formation of an inclusion complex between



(37)

the oxime and the substrate[52]. The binding constants are about 10^5—10^6 mol l^{-1} which are larger than the values of 10^2—10^3 mol l^{-1} usually observed with cycloamyloses[53]. Interestingly, the oxime *(37)* is not acylated by smaller chain esters such as 4-nitrophenyl acetate[52]; this is presumably because there is not enough binding energy with this smaller molecule to compensate for the loss of entropy upon binding.

It has recently been concluded that the contribution of non-covalent interactions to the stability of the cofactor-protein complex formed from D-serinedehydratase and pyridoxamine phosphate is at least 20—30 times greater than the contribution of the covalent >C=N— bond[54].

A large fraction of the rate acceleration of chemical reactions brought about by enzymes thus appears to be due to the high intrinsic binding energy between the substrate and the closely-packed covalently linked atoms in the enzyme.

I thank Professor W. P. Jencks for many stimulating discussions and his continual encouragement. I thank Professor P. von R. Schleyer for some of the molecular-mechanics calculations.

Received: September 30, 1976 [A 171 IE]
German version: Angew. Chem. 78, 456 (1977)

[1] *W. P. Jencks, M. I. Page*, Proc. Eighth FEBS Meeting, Amsterdam, *29*, 45 (1972).
[2] *W. P. Jencks:* Catalysis in Chemistry and Enzymology. McGraw-Hill, New York 1969; *M. L. Bender:* Mechanisms of Homogeneous Catalysis from Protons to Proteins. Wiley, New York 1970; *T. C. Bruice, S. J. Benkovic:* Bioorganic Mechanisms. Vol. 1. Benjamin, New York 1966.
[3] *M. I. Page, W. P. Jencks*, J. Am. Chem. Soc. *94*, 8818 (1972).
[4] *M. I. Page*, Chem. Soc. Rev. *2*, 295 (1973).
[5] *P. Greenzaid, W. P. Jencks*, Biochemistry *110*, 1210 (1971).
[6] *A. Hall, J. R. Knowles*, Biochemistry *14*, 4348 (1975).
[7] *W. P. Jencks*, Adv. Enzymol. Relat. Areas Mol. Biol. *43*, 219 (1975).
[8] *J. McConn, E. Ku, A. Himoe, K. G. Brandt, G. P. Hess*, J. Biol. Chem. *246*, 2918 (1971).

[9] *W. P. Jencks* in *N. O. Kaplan, E. P. Kennedy:* Current Aspects of Biochemical Energetics. Academic Press, New York 1966, p. 273.
[10] *W. P. Jencks, F. Barley, R. Barnett, M. Gilchrist*, J. Am. Chem. Soc. *88*, 4464 (1966); *T. Higuchi, L. Eberson, J. D. McRae, ibid. 89*, 3001 (1967).
[11] *T. C. Bruice, U. K. Pandit*, J. Am. Chem. Soc. *82*, 5858 (1960); *V. Gold, D. G. Oakenfall, T. Riley*, J. Chem. Soc. *B1968*, 515.
[12] *R. P. Bell, M. A. D. Fluendy*, Trans. Faraday Soc. *59*, 1623 (1963).
[13] *L. Eberson, H. Welinder*, J. Am. Chem. Soc. *93*, 5821 (1971).
[14] *M. I. Page, W. P. Jencks*, Proc. Natl. Acad. Sci. USA *68*, 1678 (1971).
[15] *T. C. Bruice* in *P. D. Boyer:* The Enzymes. 3rd Edit., Vol. 2. Academic Press, New York 1970, p. 217.
[16] *D. R. Storm, D. E. Koshland Jr.*, Proc. Natl. Acad. Sci. USA *66*, 445 (1970); *A. Dafforn, D. E. Koshland Jr., ibid. 68*, 2463 (1971); *D. R. Storm, D. E. Koshland Jr.*, J. Am. Chem. Soc. *94*, 5805, 5815 (1972).
[17] *S. Milstein, L. A. Cohen*, Proc. Natl. Acad. Sci. USA *67*, 1143 (1970).
[18] *R. A. Firestone, B. G. Christensen*, Tetrahedron Lett. *1973*, 389.
[19] *T. Nowak, A. S. Mildvan*, Biochemistry *11*, 2813 (1972).
[20] *E. M. Engler, J. D. Andose, P. von R. Schleyer*, J. Am. Chem. Soc. *95*, 8005 (1973); *N. L. Allinger, J. T. Sprague, ibid. 94*, 5734 (1972); *N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, ibid. 90*, 5773 (1968).
[21] *S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, R. Walsh*, Chem. Rev. *69*, 279 (1969).
[22] *P. von R. Schleyer*, personal communication; the strain energies of the alkenes are calculated using *Allinger*'s force field [20].
[23] *M. I. Page*, unpublished observations.
[24] *W. P. Jencks*, Chem. Rev. *72*, 705 (1972).
[25] *M. I. Page, W. P. Jencks*, J. Am. Chem. Soc. *94*, 8828 (1972).
[26] *A. R. Martin, J. J. Morris, M. I. Page*, J. Chem. Soc. Chem. Commun. *1976*, 495, and unpublished observations.
[27] *J.-P. Vincent, M. Lazdunski*, Biochemistry *11*, 2967 (1972); *R. J. Baugh, C. G. Trowbridge*, J. Biol. Chem. *247*, 7498 (1972).
[28] *A. D. Riggs, R. F. Newby, S. Bourgeois*, J. Mol. Biol. *51*, 303 (1971).
[29a] *C. L. Hornick, F. Karush*, Immunochemistry *9*, 325 (1972).
[29b] *D. S. Ryan, R. E. Feeney*, J. Biol. Chem. *250*, 843 (1975); *H. Ako, R. J. Foster, C. A. Ryan*, Biochemistry *13*, 132 (1974); *R. Huber, D. Kukla, W. Bode, P. Schwager, K. Bartels, J. Deisenhofer, W. Steigemann*, J. Mol. Biol. *89*, 73 (1974).
[30] *B. W. Griffin, J. A. Peterson*, Biochemistry *11*, 4740 (1972).
[31] *W. C. Werkheiser*, J. Biol. Chem. *236*, 888 (1961).
[32] *M. N. Williams, M. Poe, N. J. Greenfield, J. M. Hirshfield, K. Hodgsteen*, J. Biol. Chem. *248*, 6375 (1973).
[33] *N. M. Green*, Biochem. J. *89*, 599 (1963); Adv. Protein Chem. *29*, 85 (1975).
[34] *J. W. Long, W. J. Ray, Jr.*, Fed. Proc. *31*, 419 (1972).
[35a] *G. P. Sachdev, J. S. Fruton*, Biochemistry *9*, 4465 (1970).
[35b] *K. Flohr, R. M. Paton, E. T. Kaiser*, J. Am. Chem. Soc. *97*, 1209 (1975).
[36] *E. Holler, P. Rainey, A. Orme, E. L. Bennett, M. Calvin*, Biochemistry *12*, 1150 (1973).
[37a] *R. B. Loftfield, E. A. Eigner*, Biochim. Biophys. Acta *130*, 426 (1966); *S. L. Owen, F. E. Bell*, J. Biol. Chem. *245*, 5515 (1970).
[37b] *B. Hetnarski, R. D. O'Brien*, J. Agric. Food Chem. *23*, 709 (1975); *R. L. Metcalf, T. E. Fukoto, ibid. 13*, 220 (1965).
[38] *W. Kauzmann*, Adv. Protein Chem. *14*, 1 (1959).
[39] *H. D. Nelson, C. L. DeLigny*, Rec. Trav. Chim. Pays-Bas *87*, 623 (1968).
[40] *Y. Nozaki, C. Tanford*, J. Biol. Chem. *246*, 2211 (1971).
[41] *M. I. Page*, Biochem. Biophys. Res. Commun., *72*, 456 (1976).
[42] *D. D. Eley*, Trans. Faraday Soc. *35*, 1281, 1421 (1939).
[43] *J. Birktoft, D. W. Blow*, J. Mol. Biol. *68*, 187 (1971).
[44] *W. Kauzmann, K. Moore, D. Schultz*, Nature *248*, 447 (1974); *M. Pincus, L. L. Thi, R. P. Carty*, Biochemistry *14*, 3653 (1975).
[45] *R. A. Pierroti*, J. Phys. Chem. *67*, 1840 (1963); *69*, 281 (1965); *H. Reiss*, Adv. Chem. Phys. *9*, 1 (1965).
[46] *H. H. Uhlig*, J. Phys. Chem. *41*, 1215 (1937); see also *O. Sinanoğlu* in *B. Pullman:* Proc. Internat. Conf. Mol. Assoc. Biol. Academic Press, New York 1968.
[47] *M. H. Klapper*, Biochim. Biophys. Acta *229*, 557 (1971); *F. M. Richards*, J. Mol. Biol. *82*, 1 (1974).
[48] *J. Timmermans:* Physico-Chemical Constants of Pure Organic Compounds. Vol. 2. Elsevier, New York 1965.
[49] *E. Grunwald, E. Price*, J. Am. Chem. Soc. *86*, 4517 (1964).
[50] *J. M. Honig*, Ann. N. Y. Acad. Sci. *58*, 741 (1954); *M. Polanyi, F. London*, Naturwissenschaften *18*, 1099 (1930); *J. H. de Boer*, Trans. Faraday Soc. *32*, 10 (1936).
[51] *S. J. Gregg:* The Surface Chemistry of Solids. Chapman and Hall, London 1965.
[52] *Y. Murakami, J. Sunamoto, H. Okamoto, K. Kawanami*, Bull. Chem. Soc. Jpn. *48*, 1537 (1975).
[53] *D. L. Vander Jagt, F. L. Killian, M. L. Bender*, J. Am. Chem. Soc. *92*, 1016 (1970).
[54] *N. D. Schonbeck, M. Skalski, J. A. Sahfer*, J. Biol. Chem. *250*, 5359 (1975).

COMMUNICATIONS

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

(A→D)-Cyclization of a Nickel(II) Δ^{18}-Dehydro-1-methylidene-1,19-secocorrinate[**]

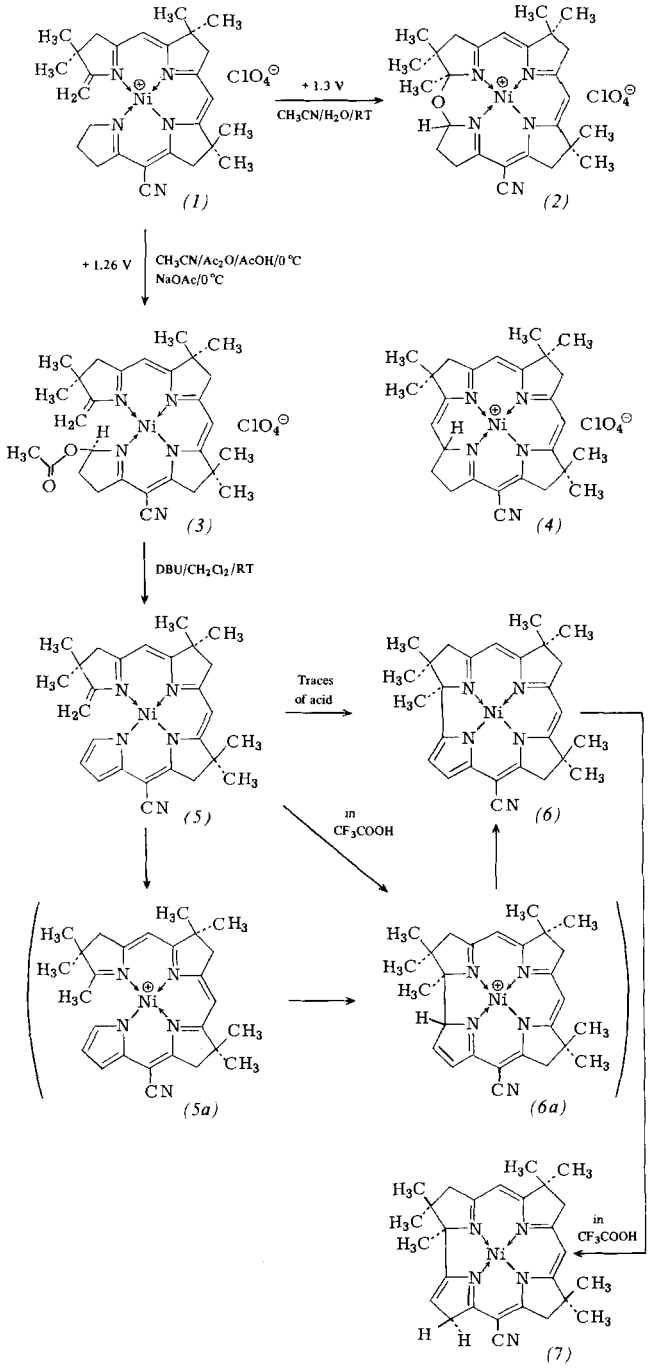
By *Vittorio Rasetti, Bernhard Kräutler, Andreas Pfaltz*, and *Albert Eschenmoser*[*]

Direct coupling of rings A and D in the formation of the corrinoids has proved not to be the bottleneck that had been envisaged at the start of synthetic work on corrins[1]. On the contrary, the simplest synthetic routes presently available for corrinoids and corrins use (A→D)-cyclizations in chromophore construction[2]. Here we report, as a further example,

[*] Dipl. sc. nat. V. Rasetti, Dr. B. Kräutler, dipl.-sc. nat. A. Pfaltz, Prof. Dr. A. Eschenmoser
Organisch-Chemisches Laboratorium der ETH Zürich
Universitätsstrasse 16, CH-8006 Zürich (Switzerland)

[**] This work was supported by the Swiss National Science Foundation. The German-English translation is by *C. Wintner*.

a facile (A→D)-closure in the Δ^{18}-dehydro-1-methylidene-1,19-secocorrin series, induced by traces of acid at room temperature [see *(5)*→*(6)* in the reaction scheme]. This is the type of ring closure considered by *A. I. Scott* in his discussions of the biosynthesis of vitamin B_{12}[3].



We have previously reported[4] the electrochemical oxidation of nickel(II) 1-methylidene-1,19-secocorrinate perchlorate *(1)* in moist acetonitrile to yield almost quantitatively the 1,19-oxido derivative *(2)* *via* a sigmatropic 1,16-hydrogen shift and incorporation of oxygen from water. If this electrochemical oxidation is conducted in anhydrous acetonitrile/acetic anhydride/acetic acid (30:3:1) at 0 °C[5] and the mixture is immediately quenched with 2 mol. equiv. of sodium acetate when the current falls (at *ca.* 1.2 F), then crystalline nickel(II) 19-acetoxy-1-methylidene-1,19-secocorrinate perchlorate *(3)* can be isolated in up to 40% yield, in addition to starting material (*ca.* 35%) and side-product *(4)*[6] (*ca.* 5%). Treatment of *(3)* with 8 mol. equiv. of DBU[7] in methylene chloride at room temperature, carefully excluding oxygen, at once gives the nickel(II) secocorrinate *(5)*. The cyclization of *(5)* to the nickel(II) dehydrocorrinate *(6)* occurs with such ease that it is difficult to prevent. Crystallization of spectroscopically and analytically pure samples of *(5)* can be achieved in up to 50 to 65% yield by working with alkali-washed glassware and by rapid chromatography of the crude product at 0 °C, with exclusion of oxygen, on kieselgel[8] that has been pretreated with triethylamine dissolved in the eluent mixture benzene/methyl acetate/methylene chloride (1:1:1). Normal chromatography leads to mixtures of *(5)* and *(6)*, as does use of solvents such as chloroform, methylene chloride, or carbon tetrachloride of usual reagent purity. A ^{1}H-NMR spectrum of pure *(5)* is obtained only in deuteriochloroform that has been treated with basic alumina immediately prior to use; even in this solvent the ^{13}C-NMR spectrum (recorded over a period of *ca.* 65 hours) was that of *(6)*. Preparatively the cyclization *(5)*→*(6)* is carried out at room temperature in methyl acetate/methylene chloride (1:1) on alumina[9] pre-

Table 1. Spectroscopic properties of *(3)* and *(5)* [13].

(3): Mp 185 °C (dec.); λ_{max} (ethanol) = 267 (log ε = 4.24), 286 (shoulder/4.20), 321 (shoulder/4.28), 331 (4.33), 393 (shoulder/3.66), 424 (shoulder/3.86), 470 (4.09) nm; λ_{min} = 258 (4.22), 298 (4.13), 368 (3.52) nm. IR ($CHCl_3$): 2200 (CN), 1740 (acetate), 1575/1507 (chromophore) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.23/1.32/1.43/1.45/1.46/1.51 (6s/6CH_3); 2.16 (s/CH_3COO), 1.9—2.6 (m/CH_2), 2.86/2.98 (AB-system/J = 19 Hz/CH_2), 3.17 (s/CH_2), 3.32 (s/CH_2), 3.0—3.5 (m/CH_2), 4.82/5.22 (AX-system/J = 2 Hz/=CH_2), 5.87 (m/CH), 6.02/6.40 (2s/—CH=) ppm. MS (130 °C): m/e = 483 (71 %/$M^+ - HClO_4 - CH_3COOH$), 481 (68 %/$M^+ - HClO_4 - CH_3COOH - H_2$), 468 (100 %/$M^+ - HClO_4 - CH_3COOH - CH_3$).

(5): Mp > 250 °C; λ_{max} (ethanol): 268 (shoulder/log ε = 4.19), 282 (4.23), 307 (flat/4.16), 320 (shoulder/4.15), 372 (4.17), 477 (3.68), 578 (3.74) nm; λ_{min} = 337 (4.06), 440 (3.62), 514 (3.62) nm. IR ($CHCl_3$): 2210 (CN), 1625, 1610, 1575, 1555 (strong), 1500 (strong) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.10/1.15/1.19/1.33/1.35/1.42 (6s/6CH_3), 2.56/2.78 (AB-system/J = 18 Hz/CH_2), 2.80 (s/CH_2), 3.14 (s/CH_2), 4.40/4.95 (AX-system/J = 2 Hz/=CH_2), 5.56 (s/2 —CH=), 6.05/6.26/6.38 (3 m/pyrrole-CH) ppm. MS (< 160 °C): m/e = 483 (45 %/M^+ with ^{58}Ni), 468 (100 %/$M^+ - CH_3$ with ^{58}Ni).

UV/VIS of *(5)* [or *(6a)*] in CF_3COOH: λ_{max} = 315 (4.26), 330 (4.26), 408 (shoulder/3.89), 438 (shoulder/4.06), 452 (4.19) nm; λ_{min} = 284 (3.95), 324 (4.25), 360 (3.47) nm. ^{1}H-NMR (CF_3COOH): δ = 1.05 (s/CH_3), 1.39 (s/CH_3), 1.44 (s/CH_3), 1.49 (s/3CH_3), 1.57 (s/CH_3), 3.02/3.40 (AB-system/J = 18 Hz/CH_2), 3.32 (s/CH_2), 3.46 (s/CH_2), 4.91 (s broad/H on C-19), 6.16/6.46 (2s/2—CH=), 7.25/7.61 (AB-system/J = 6 Hz/—CH= on C-17 and C-18) ppm.

treated with methyl acetate/acetic acid (100:1)[10]. The crystalline product is isolated in over 90% yield, and is identical in its spectroscopic properties with *(6)* as previously obtained[4a,11] by pyrolysis of the chloride salt of *(2)*[12].

The reaction *(5)*→*(6)* is doubtless initiated by protonation of the exocyclic methylidene group on ring A, after which the closure step *(5a)*→*(6a)* can take place. The ^{1}H-NMR spectrum of *(5)* dissolved in trifluoroacetic acid is that to be expected from the intermediate *(6a)*, and is clearly different from the ^{1}H-NMR spectrum of *(6)* dissolved in trifluoroacetic acid, corresponding to the constitution *(7)*[4]. We have here a case where two distinct protonated forms of a single pyrrole derivative are separately observable; of the four possible *C*-protonations of the pyrrole nucleus in *(6)*, that giving *(7)* is likely to be both kinetically and thermodynamically favored.

Received: March 28, 1977 [Z 706 IE]
German version: Angew. Chem. 89, 475 (1977)

CAS Registry numbers:
(1), 60502-84-3; *(2)*, 62447-47-6; *(3)*, 62415-59-2; *(4)*, 62448-23-1; *(5)*, 62415-57-0; *(6)*, 62415-27-4; *(6a)*, 62415-56-9; *(7)*, 62448-21-9

[1] *R. Bonnett, V. M. Clark, A. Giddey, A. R. Todd*, J. Chem. Soc. *1959*, 2087; *A. W. Johnson*, in Vitamin B_{12} and Intrinsic Factor; 2. Europäisches Symposium über Vitamin B_{12}. Enke-Verlag, Stuttgart 1962, p. 1; *A. Eschenmoser*, Pure Appl. Chem. *7*, 297 (1963); *R. B. Woodward*, Pure Appl. Chem. *17*, 519 (1968).

[2] *A. W. Johnson*, Chem. Br. *3*, 253 (1967); Pure Appl. Chem. *28*, 195 (1971); Chem. Soc. Rev. *4*, 1 (1975); Phil. Trans. Roy. Soc. *B 273*, 319 (1976); *A. Eschenmoser*, Pure Appl. Chem. *20*, 1 (1969); Q. Rev. Chem. Soc. *24*, 366 (1970); Pure Appl. Chem. Suppl. IUPAC Congress Boston *2*, 69 (1971); Naturwissenschaften *61*, 513 (1974); Chem. Soc. Rev. *5*, 377 (1976).

[3] a) *A. I. Scott*, Tetrahedron *31*, 2639 (1975); b) *A. I. Scott*, Heterocycles *2*, 125 (1974); Science *184*, 760 (1974).

[4] a) *B. Kräutler, A. Pfaltz, R. Nordmann, K. O. Hodgson, J. D. Dunitz, A. Eschenmoser*, Helv. Chim. Acta *59*, 924 (1976); b) *B. Kräutler*, Thesis ETH Zürich, 1977 ("Eine elektrochemische Redox-Simulation der lichtinduzierten A/D-Secocorrin → Corrin-Cycloisomerisierung". Juris-Verlag, Zürich 1977).

[5] 1.26 ± 0.2 V, Pt-electrode, 0.1 N calomel reference electrode, $LiClO_4$, in acetonitrile/acetic anhydride/acetic acid (30:3:1) under argon. For details, see [4b], p. 224.

[6] The dihydrocorphin complex *(4)* is the major product if the oxidation of *(1)* is carried out at room temperature instead of 0°C (see [4b], p. 230). UV/VIS of *(4)* in CH_3OH: $\lambda_{max} = 269$ ($\log\varepsilon = 4.27$), 333 (4.53), 395 (3.81), 421 (3.79), 506 (4.00) nm [4b].

[7] DBU = 1,8-diazabicyclo[5.4.0]-7-undecene (see *H. Oediger, F. Möller, K. Eiter*, Synthesis *1972*, 591). Treatment of *(3)* in pyridine at room temperature gave primarily the dihydrocorphin derivative *(4)*.

[8] Kieselgel 60, Merck.

[9] Woelm alumina for chromatography, acid, activity III.

[10] See *V. Rasetti*, Thesis ETH Zürich, in preparation.

[11] See *A. Pfaltz*, Thesis ETH Zürich, in preparation.

[12] The constitution of *(6)* has been verified by an X-ray structure analysis in the laboratory of Prof. *K. Hodgson* (Stanford University).

[13] The spectroscopic properties of *(6)* and *(7)* may be found in [4a], those of *(4)* in [4b]. Satisfactory elementary analyses have been obtained for compounds *(3)*, *(4)*, *(5)*, and *(6)*.

Difluorooxobromine(v) Ion, $BrOF_2^+$ [**]

By *Manfred Adelhelm* and *Eberhard Jacob*[*]

Synthesis of the cation $ClO_2F_2^+$ containing chlorine(VII) was first achieved by *Christe*[1] by reaction of chloryl fluoride ClO_2F with platinum hexafluoride. As the existence of the oxidation state +VII of bromine was also demonstrated[2], and it was later shown by one of us *(E.J.)* that the less stable bromyl fluoride BrO_2F yielded, by cocondensation with SbF_5, a fluoroantimonate of BrO_2^+[3], we have attempted to oxidize BrO_2F with PtF_6 to the unknown $BrO_2F_2^+$.

Bromyl fluoride and platinum hexafluoride were cocondensed *in vacuo* at −196°C in a low-temperature infrared cuvette. Reaction took place on warming up to −120°C. The red-brown film was stable at room temperature and showed four additional bands besides the absorptions of PtF_6^- and PtF_5[4]: 1052 (1002) vs, 930 (890) m, 365 (355) vs, 315 (304) m. On cautious heating to 110°C the color changed to mustard-yellow and the absorption at 930 (890) cm^{-1} disappeared. This band must be assigned to the strongest band of BrO_2^+[3].

The reaction could be carried out on a preparative scale using a Teflon PFA or stainless steel reaction vessel[5]. We obtained a brown to yellow-brown product, which proved to be relatively stable at room temperature in the absence of moisture. Its IR spectrum was identical with that of the thin films. Reaction of the finely powdered product with excess nitryl fluoride at −78°C furnishes the oxide fluorides $BrOF_3$ and BrO_2F, which can be identified by IR spectroscopy[6].

On cocondensation of the oxide fluorides with arsenic pentafluoride the cations are regenerated in the form of hexafluoroarsenates. The BrF stretching vibrations could then also be measured, which are masked by PtF absorptions in the PtF_6^-/PtF_5-containing products.

The following reactions appear to take place:

$$BrO_2F + 2.5\,PtF_6 \rightarrow BrOF_2^+PtF_6^- + {}^1/_2O_2^+PtF_6^- + PtF_5$$
$$BrO_2F + \quad PtF_6 \rightarrow BrO_2^+PtF_6^- + {}^1/_2F_2$$

The side reaction yielding BrO_2^+ can largely be suppressed by using an excess of platinum hexafluoride.

$$BrOF_2^+PtF_6^- + NO_2F \rightarrow BrOF_3 + NO_2^+PtF_6^-$$
$$BrO_2^+PtF_6^- + NO_2F \rightarrow BrO_2F + NO_2^+PtF_6^-$$
$$BrOF_3 + AsF_5 \rightarrow BrOF_2^+AsF_6^-$$
$$BrO_2F + AsF_5 \rightarrow BrO_2^+AsF_6^-$$

The main product of the reaction of BrO_2F with PtF_6 is therefore the new cation $BrOF_2^+$[7].

Table 1 lists the results of the IR measurements. The assignments suggested correspond to the fundamental vibrations of the isoelectronic $SeOF_2$[8].

Table 1. Fundamental vibrations of $BrOF_2^+$ and gaseous $SeOF_2$ in cm^{-1}.

	$SeOF_2$ [8]	$BrOF_2^+$ [a]	$Br^{18}OF_2^+$ [b]	Intensity
$\nu_1(A')$	1049	1062	1002	vs
$\nu_2(A')$	667	655		s
$\nu_3(A')$	362	365	355	vs
$\nu_4(A')$	253	290		w
$\nu_5(A'')$	637	630		s
$\nu_6(A'')$	282	315	304	m

[a] $BrOF_2^+AsF_6^-$, thin film at −78°C.
[b] $Br^{18}OF_2^+PtF_6^-$, powder, AgBr-disk.

Thus, whereas ClO_2F can be oxidized by PtF_6 to $ClO_2F_2^+$[1], the analogous reaction with BrO_2F does not lead to $BrO_2F_2^+$ but to $BrOF_2^+$ and O_2^+. So far, this appears to be the only case in which the oxygen is partially eliminated from an oxide fluoride by PtF_6. Complete elimination of the oxygen by PtF_6 has been observed in the case of $XeOF_4$[9].

Received: April 5, 1977 [Z 712 IE]
German version: Angew. Chem. *89*, 476 (1977)

CAS Registry numbers:
$BrOF_2^+$, 62521-26-0; $Br^{18}OF_2^+$, 62521-27-1; BrO_2F, 22585-64-4; PtF_6, 13693-05-5; NO_2F, 10022-50-1

[*] Dr. M. Adelhelm
Abteilung Chemie der Pädagogischen Hochschule
Reuteallee 46, D-7140 Ludwigsburg (Germany)
Dr. E. Jacob
M.A.N., Neue Technologie
Dachauer Strasse 667, D-8000 München (Germany)

[**] Low-temperature Co-condensation of Fluorine Compounds, Part 3.—Part 2: *E. Jacob, R. Opferkuch*, Angew. Chem. *88*, 190 (1976); Angew. Chem. Int. Ed. Engl. *15*, 158 (1976).

[1] *K. O. Christe*, Inorg. Nucl. Chem. Lett. *8*, 453 (1972); *K. O. Christe, R. D. Wilson, E. C. Curtis*, Inorg. Chem. *12*, 1358 (1973).

[2] *E. H. Appelman*, J. Am. Chem. Soc. *90*, 1900 (1968); *E. H. Appelman, M. H. Studier, ibid. 91*, 4561 (1969); *R. J. Gillespie, G. J. Schrobilgen*, Inorg. Chem. *13*, 1230 (1974).

[3] *E. Jacob*, Angew. Chem. *88*, 189 (1976); Angew. Chem. Int. Ed. Engl. *15*, 158 (1976).

[4] Values in cm^{-1}; in brackets, values of the product obtained from $Br^{18}O_2F$ (*ca.* 98 % ^{18}O).

[5] Procedure as in [3].

[6] $BrOF_3$: *R. Bougon, T. B. Huy*, C. R. Acad. Sci. Ser. C *283*, 461 (1976); BrO_2F: *E. Jacob*, Z. Anorg. Allg. Chem., in press.

[7] Independently of us, *R. J. Gillespie* and *P. Spekkens*, as well as *R. Bougon*, have obtained the $BrOF_2^+$ ion by reaction of $BrOF_3$ with Lewis acids: *R. J. Gillespie*, lecture, 6th Eur. Fluorine Symp. Dortmund, March 28—April 1, 1977; *R. Bougon*, 6th Eur. Fluorine Symp., private communication.

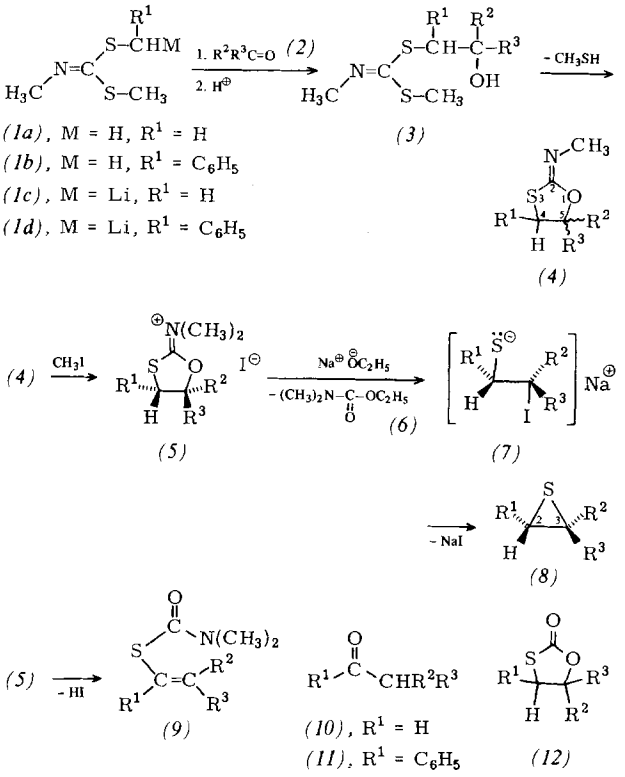
[8] *L. E. Alexander, I. R. Beattie*, J. Chem. Soc. *A 1972*, 1745.

[9] *K. O. Christe, R. D. Wilson*, J. Fluorine Chem. *7*, 356 (1976).

Homologization of Aldehydes and Ketones to Thiiranes or *S*-Vinyl Thiocarbamates *via* 2-Alkylimino-1,3-oxathiolanes[**]

By *Dieter Hoppe* and *Rainer Follmann*[*]

We have previously reported on the metalation of dialkyl *N*-alkyl- (or *N*-aryl)iminodithiocarboxylic esters of type *(1)* to give the lithium compounds and on their conversion with carbonyl compounds *(2)* to β-thioalkanols *(3)* or to 2-alkyl- (and 2-aryl)imino-1,3-oxathiolanes *(4)*[1]. In some cases we had observed formation of thiiranes *(8)*[1]. Since methods for the general syntheses of thiiranes[2] in which direct formation of the (C-2)—(C-3) bond occurs are rare[3], we have extended the scope of this secondary reaction.



To increase their reactivity the 2-methylimino-1,3-oxathiolanes *(4)* [obtained from *(1a)* or *(1b)* and the carbonyl compound *(2)*[1]] were alkylated with methyl iodide in nitromethane to the immonium iodides *(5)* and then cleaved with sodium ethoxide in ethanol to the thiiranes *(8)* (cf. Table 1) and ethyl *N*,*N*-dimethylcarbamate *(6)*.

Presumably the β-iodothiolate *(7)* is formed as intermediate. In favor of this (or a related) intermediate is the fact that the reaction of 5-(cyclo)alkyl-substituted imino-1,3-oxathiolanes[4] proceeds with extensive retention[5] of the configuration at C-2 and C-3 in *(8)*, relative to C-4 and C-5 in *(4)*. Thus *trans-(4i)* afforded the *trans*-thiirane *(8i)* (^{1}H-NMR, $CDCl_3$: τ = 6.37 and 7.08, ^2J = 5.2 Hz), while *cis-(4i)* yielded over 95 % *cis-(8i)* (τ = 5.89 and 7.04, ^2J = 7.0 Hz)[6]. In contrast *trans*-4,5-diphenyl-1,3-oxathiolane *(4k)* reacts less stereoselectively to give a 57:43 mixture of *cis*- and *trans*-stilbene sulfide *(8k)*.

In the reactions of the *cis*-immonium salts *(5h)* and *(5i)*, besides *(8)* we also isolated the 1,3-oxathiolane-2-ones *cis-(12h)* and *cis-(12i)*, formed by hydrolysis of *(5)*.

On heating, the salts *(5)* eliminate hydrogen iodide to give the *S*-vinyl *N*,*N*-dimethylthiocarbamates *(9)*, which as thioenol esters are hydrolyzable to the carbonyl compounds, *e.g.* with trifluoroacetic acid[7]. The reaction sequence thus permits homologization of aldehydes or ketones to the next-higher aldehyde *(10)* [with *(1a)*] or aryl ketone *(11)* [with *(1b)*].

Procedure

2-Methylimino-1,3-oxathiolanes *(4)*: 40 mmol of the *N*-alkyliminodithiocarboxylic ester *(1a)* or *(1b)* is added dropwise at −78 °C to a solution of lithium diisopropyl amide (44 mmol) in tetrahydrofuran/*n*-hexane (60 ml, *ca.* 2:1). After one hour's stirring compound *(2)* (40 mmol) is added and the reaction mixture is stirred for a further hour, then warmed to −30 °C and neutralized with 5.3 g acetic acid. The solvent is removed under a water-jet vacuum, the residue dissolved in ether (100 ml) and water (50 ml), and the organic phase washed with water and dried over sodium sulfate. The mixture of *(3)* and *(4)* remaining after removal of ether is heated for 2—6 h under reflux in benzene to ensure complete cyclization. Crystallization (ether/cyclohexane) and chromatography of the mother liquor over silica gel (neutral), *e.g.* with ether/*n*-pentane (2:1), R_F *ca.* 0.4, yielded *(4)* (IR: 1650—1670 cm^{-1}).

Thiiranes *(8)*: A mixture of *(4)* (10 mmol) and methyl iodide (20 mmol) in nitromethane is stirred in the dark for

Table 1. Prepared 2-methylimino-1,3-oxathiolanes *(4)*, thiiranes *(8)*, and *S*-vinyl *N*,*N*-dimethylthiocarbamates *(9)*.

(1)	R^1	*(2)*	R^2	R^3	*(4)* [a]	Yield [%] [*cis*:*trans*]	*(8)* [a]	Yield [%] [*cis*:*trans*]	*(9)* [a]	Yield [%]
(1a)	H	*(2a)*	H	*n*-C_6H_{13}	*(4a)*	59	*(8a)*	92		
(1a)	H	*(2b)*	H	cyclohex-3-enyl	*(4b)*	63	*(8b)*	82		
(1a)	H	*(2c)*	H	$-CH_2CH(CH_3)CH_2CH_2CH=C(CH_3)_2$	*(4c)*	59	*(8c)*	88		
(1a)	H	*(2d)*	CH_3	CH_3	*(4d)*	54			*(9d)*	64
(1a)	H	*(2e)*	CH_3	$C(CH_3)_3$	*(4e)*	51			*(9e)*	60
(1a)	H	*(2f)*	CH_3	C_6H_5	*(4f)*	67			*(9f)*	81
(1a)	H	*(2g)*	CH_3	β-naphthyl	*(4g)*	56	*(8g)*	45		
(1b)	C_6H_5	*(2h)*	H	$C(CH_3)_3$	*(4h)*	62 [50:50]	*(8h)*	50 [b] [5:95]		
(1b)	C_6H_5	*(2b)*	H	cyclohex-3-enyl	*(4i)*	82 [10:90] [c]	*(8i)*	91 [9:91]		
						from *cis-(4i)*:		71 [d] [95: <5]		
(1b)	C_6H_5	*(2i)*	H	C_6H_5	*(4k)*	74 [57:43]	*(8k)*			
						from *trans-(4k)*:		60 [57:43]		
(1b)	C_6H_5	*(2d)*	CH_3	CH_3	*(4l)*	84	*(8l)*	71	*(9l)*	78

[a] ^{1}H-NMR and IR spectra confirm the structures. New compounds *(4)*, *(8)*, *(9)*, and *(12)* gave correct analyses. [b] 24 % *cis-(12h)* also isolated. [c] Isomeric ratio of crystallized fraction; in crude product *cis*:*trans* = 35:65. [d] Together with 25 % *cis-(12i)*.

[*] Dr. D. Hoppe, Dipl.-Chem. R. Follmann
Organisch-chemisches Institut der Universität
Tammannstr. 2, D-3400 Göttingen (Germany)

[**] Metalated Nitrogen Derivatives of Carbonic Acid in Organic Synthesis, Part 11.—Part 10: *D. Hoppe*, Justus Liebigs Ann. Chem. *1976*, 1843.

12 h at 0—5 °C and then 2—6 h at 20 °C [TLC check for *(4)*]. The solvent is removed *in vacuo* (bath-temperature max. 40 °C), and to the *N,N*-dimethyl-*N*-(1,3-oxathiolan-2-ylidene)ammonium iodide *(5)* is added a solution of 1 M sodium ethoxide in ethanol (10 ml) and the mixture stirred for 8 h at 20 °C and for 30 min at 40 °C. Removal of solvent and filtration over 100 g silica gel with *n*-pentane/ether (10 : 1) yields *(8)*, R_F 0.8—0.9.

S-Vinyl *N,N*-dimethylthiocarbamates *(9)*: A solution of *(5)* in nitromethane is heated for 4 h at 80 °C, the solvent removed, and the residue chromatographed over silica gel with *n*-pentane/ether (1 : 5). R_F of *(9)* *ca.* 0.6; IR: 1655 (C=O) 1630—1640 cm^{-1} (C=C).

Received: April 7, 1977 [Z 713 IE]
German version: Angew. Chem. 89, 478 (1977)

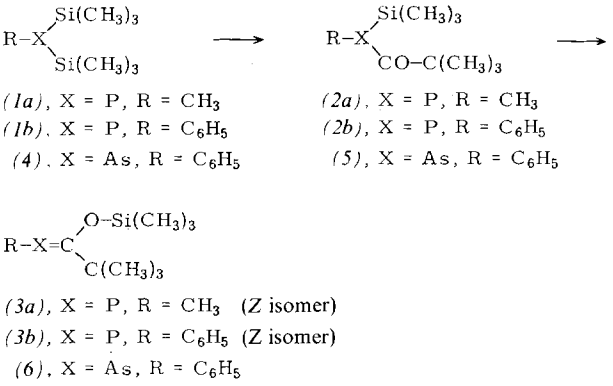
CAS Registry numbers:
(1a), 18805-25-9; *(1b)*, 56971-42-7; *(2a)*, 111-71-7; *(2b)*, 100-50-5; *(2c)*, 106-23-0; *(2d)*, 67-64-1; *(2e)*, 75-97-8; *(2f)*, 98-86-2; *(2g)*, 93-08-3; *(2h)*, 630-19-3; *(2i)*, 100-52-7; *(4a)*, 62533-81-7; *(4b)*, 62533-82-8; *(4c)*, 62533-83-9; *(4d)*, 62533-64-6; *(4e)*, 62533-65-7; *(4f)*, 62533-66-8; *(4g)*, 62533-67-9; *cis-(4h)*, 62533-68-0; *trans-(4h)*, 62533-69-1; *(4i)*, 62533-70-4; *cis-(4k)*, 62533-71-5; *trans-(4k)*, 62533-72-6; *(4l)*, 62533-73-7; *(5h)*, 62533-74-8; *(5i)*, 62533-75-9; *(6)*, 687-48-9; *(8a)*, 5633-78-3; *(8b)*, 62533-76-0; *(8c)*, 62533-77-1; *(8g)*, 62533-78-2; *cis-(8h)*, 62533-74-3; *trans-(8h)*, 62533-80-6; *(8i)*, 62533-54-4; *cis-(8k)*, 3372-81-4; *trans-(8k)*, 57694-36-7; *(8l)*, 62533-55-5; *(9d)*, 62533-56-6; *(9e)*, 62533-57-7; *(9f)*, 62533-58-8; *(9l)*, 62533-59-9; *cis-(12h)*, 62533-60-2; *(12i)*, 62533-61-3

[1] *D. Hoppe*, Angew. Chem. *87*, 449 (1975); Angew. Chem. Int. Ed. Engl. *14*, 424 (1975).
[2] Review: *M. Sander*, Chem. Rev. *66*, 297 (1966).
[3] In the course of our studies such methods became known: *A. I. Meyers, M. E. Ford*, Tetrahedron Lett. *1975*, 2861; J. Org. Chem. *41*, 1735 (1976); *C. R. Johnson, A. Nakanishi, N. Nakanishi, K. Tanaka*, Tetrahedron Lett. *1975*, 2865; cf. also: *K. Hirai, Y. Kishida*, Heterocycles *2*, 185 (1974).
[4] Synthesis and ^{1}H-NMR spectra of 2-(*N*-carbamoylimino)-1,3-oxathiolane-4-carboxylic acid esters see: *T. Hayashi, M. Akano, T. Yokono, J. Uzawa, S. Kambe, H. Midorikawa*, Bull. Chem. Soc. Jpn. *45*, 578 (1972), and earlier work by these authors.
[5] The observed retention should be regarded as the result of two inversion steps at C-5. In contrast alkali-metal *N*-(1,3-oxathiolan-2-ylidene)imides *(4)*, alkali metal instead of CH_3, which occur as intermediates in the sulfuration of oxiranes with alkali-metal thiocyanates, react with inversion at C-5; cf. *C. C. Price, P. F. Kirk*, J. Am. Chem. Soc. *75*, 2396 (1953).
[6] *E. Haloui, D. Canet*, J. Mol. Struct. *24*, 85 (1975).
[7] *P. Blatcher, J. I. Grayson, S. Warren*, J. Chem. Soc. Chem. Commun. *1976*, 547; references to other methods given therein.

Phenyl-[2,2-dimethyl-1-(trimethylsiloxy)propylidene]-arsane, an Arsane with an Isolated As=C Bond[**]

By *Gerd Becker* and *Gerhard Gutekunst*[*]

P-Alkyl- or -arylbis(trimethylsilyl)phosphanes *(1)* react with 2,2-dimethylpropionyl chloride (pivaloyl chloride) in cyclopentane with substitution of a trimethylsilyl group by the acyl moiety[1]. The products *(2)* are stable for some time only below 0 °C and rearrange, *via* a 1,3 shift of the trimethylsilyl group from the phosphorus to the oxygen atom, into the [2,2-dimethyl-1-(trimethylsiloxy)propylidene] phosphane *(3)*.



(1a), X = P, R = CH_3
(1b), X = P, R = C_6H_5
(4), X = As, R = C_6H_5

(2a), X = P, R = CH_3
(2b), X = P, R = C_6H_5
(5), X = As, R = C_6H_5

(3a), X = P, R = CH_3 (*Z* isomer)
(3b), X = P, R = C_6H_5 (*Z* isomer)
(6), X = As, R = C_6H_5

By application of these reactions to *As*-alkyl- or arylbis(trimethylsilyl)arsanes *(4)* we have been able to synthesize the first acyclic compounds containing an isolated As=C double bond[2]. The methyl, *tert*-butyl, and phenyl compounds were investigated, but only reaction of the phenyl compound was found to proceed without side-reactions. If substitution of both trimethylsilyl groups is avoided by suitable choice of conditions, almost pure phenyl-(2,2-dimethylpropionyl)trimethylsilylarsane *(5)* remains after condensing off all the volatile components. In contrast to the analogous phosphane this compound is stable at room temperature for a short time; we attribute this to less pronounced spatial interaction of the bulky substituents at the central atom, since the bonds from the arsenic atom are longer than those from phosphorus. Rearrangement to the phenyl-[2,2-dimethyl-1-(trimethylsiloxy)propylidene]arsane *(6)* can be followed ^{1}H- and ^{13}C-NMR spectroscopically. The resonances caused by the carbon atom of the C(O) group appear at very low field (Table 1). Noteworthy here is the small difference between *(5)* and *(6)*, even though the carbon atom is doubly linked to the oxygen atom in *(5)* and to the arsenic atom in *(6)*. Whether similar polarities of C=O and As=C double bonds are responsible for the almost equal chemical shifts cannot be decided on the grounds of NMR data alone. The analogous phosphanes absorb in the same region. Since phenyl-(2,2-dimethylpropionyl)-trimethylsilylphosphane *(2b)* could not be measured on account of thermal instability the values of the stable methyl compounds are listed in Table 1 for comparison[1].

Table 1. Characteristic ^{1}H- and ^{13}C-NMR data of *(5)* and *(6)* compared with the corresponding methyl- and phenylphosphanes. Chemical shifts in δ values [ppm] rel. TMS ext., downfield positive; limits of error: δ^1H: ±0.1 ppm, δ^{13}C: ±1.0 ppm (without solvent).

	C(O)	$C(CH_3)_3$	$C(CH_3)_3$		$Si(CH_3)_3$	
	^{13}C	^{13}C	^{13}C	^{1}H	^{13}C	^{1}H
(5)	228.5	51.0	26.5	1.12	1.5	0.18
(2a)	229.0	46.0	27.0		0.0	
(6)	239.0	47.0	30.0	1.26	2.0	−0.14
(3b)	216.0	43.0	30.0		1.0	
(3a)	215.5	42.0	29.0		1.0	

The IR spectra confirm the given structures of the compounds. The bands between 1650 and 1701 cm^{-1} are assigned to the carbonyl stretching vibrations of *(5)*, and the bands at 1043 and 762 cm^{-1}[1] to the stretching vibrations of the C—O and Si—O single bonds in *(6)*, respectively. As shown

[*] Doz. Dr. G. Becker, Dipl.-Chem. G. Gutekunst
Institut für Anorganische Chemie der Universität, Lehrstuhl Anorganische Chemie I
Engesserstrasse, Gebäude Nr. 30.45, D-7500 Karlsruhe 1 (Germany)

[**] Part 1 of The Formation and Properties of Acylarsanes. This work was supported by the Deutsche Forschungsgemeinschaft. The results were presented in a lecture delivered at the Chemiedozententagung in Marburg March 23, 1977.

by the molecular weight (determined cryoscopically in benzene) and the mass spectrum, *(6)* is monomeric.

The assignment of the substituents at the As=C double bond can be determined only by an X-ray structure analysis. Studies on models suggest the presence of *Z* isomers in which the aryl and the trimethylsiloxy group are situated at the same site.

Procedure

A solution of phenylbis(trimethylsilyl)arsane (22.4 g, 75.1 mmol) and 2,2-dimethylpropionyl chloride (9.1 g, 75.5 mmol) in cyclopentane (25 ml) is allowed to stand for 12 h at 4 °C. The reaction is followed ^{1}H-NMR spectroscopically. After condensing off all components that are volatile at −20 °C, there remains almost pure *(5)*. The rearrangement to *(6)* is complete after 12 h at 50 °C: reddish liquid, b.p. 82 to 86 °C/5×10^{-2} torr; quantitative yield.

Received: April 13, 1977 [Z 715 IE]
German version: Angew. Chem. *89*, 477 (1977)

CAS Registry numbers:
(2a), 60820-22-6; *(3a)*, 60820-26-0; *(3b)*, 60820-29-3; *(4)*, 38003-96-2; *(5)*, 62533-62-4; *(6)*, 62533-63-5; 2,2-dimethylpropionyl chloride, 3282-30-2

[1] *G. Becker*, Z. Anorg. Allg. Chem. *423*, 242 (1976).
[2] For a review of known As=C systems see: *P. Jutzi*, Angew. Chem. *87*, 269 (1975); Angew. Chem. Int. Ed. Engl. *14*, 232 (1975).

$[C_5H_5(CO)_2Mn—N_2H_2—Cr(CO)_5]$, a Complex with a Diazene Bridge and Two Different Coordination Centers[1]

By *Dieter Sellmann* and *Klaus Jödden*[*]

Three kinds of diazene (diimine) transition metal complexes have been proposed as intermediates of N_2 reduction in enzymatic nitrogen fixation, *viz.* mononuclear complexes *(1)*, homodinuclear complexes *(2)*, and heterodinuclear complexes *(3)*[2].

M–HN=NH *(1)* M–HN=NH–M *(2)* M–HN=NH–M′ *(3)*

Hitherto, however, the diazene structure of the N_2H_2 ligand could be demonstrated unequivocally only in complexes of type *(2)*[1,3].

We have now been able to synthesize the first complex of type *(3)* in which the HN=NH molecule bridges two different metal centers.

Reaction according to

$$\eta\text{-}C_5H_5(CO)_2Mn(N_2H_4) + (OC)_5Cr(THF) \xrightarrow[20\,^\circ C]{THF} \eta\text{-}C_5H_5(CO)_2Mn\text{–}N_2H_4\text{–}Cr(CO)_5 + THF$$

(4)

affords the heteronuclear hydrazine complex *(4)* which precipitates as orange-yellow crystals analytically pure from tetrahydrofuran at −78 °C [IR (KBr) in cm^{-1}: 3332 s, 3310 m, 3283 s (ν_{NH}), 1570 m (δ_{NH}); ν_{CO} (THF) 2068 w, 1935 s, 1898 s, 1849 s.—^{1}H-NMR (90 MHz, [D_6]-acetone, −30 °C, rel. to TMS in ppm): 4.56 (s, $\delta C_5H_5(5)$), 4.80 (br, $\delta NH_2(2)$), 5.50 (br, $\delta NH_2(2)$).—UV (THF, 20 °C): λ_{max} 410, 240 nm; ε_{max} 3700, 31 100 l/mol·cm.—Dec. p. 88 °C].

The hydrazine complex *(4)* can be oxidized in THF solution to the heteronuclear diazene complex *(5)* by atmospheric oxygen or preferably (60 % yield) by hydrogen peroxide:

$$(4) + H_2O_2 \xrightarrow[-25\,^\circ C]{THF} \eta\text{-}C_5H_5(CO)_2Mn\text{–}HN{=}NH\text{–}Cr(CO)_5 + 2\,H_2O$$

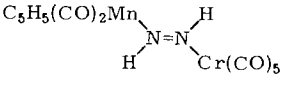
(5)

Compound *(5)* crystallizes as analytically pure, deep-violet needles from THF at −78 °C. It is stable in the solid state, decomposing only above 104 °C. In CH_3OD rapid exchange of the N_2H_2 protons occurs at room temperature to form η-$C_5H_5(CO)_2Mn$—DN=ND—$Cr(CO)_5$ (νND in KBr: 2428 m, 2382 m cm^{-1}). Even traces of bases, *e.g.* NaOH, effect fast decomposition in solution, yielding the hydrazine complex *(4)*, and simultaneously probably also the labile dinitrogen complex η-$C_5H_5(CO)_2Mn$—N≡N—$Cr(CO)_5$. The structure and composition of *(5)* follow from the method of preparation, elemental analysis, chemical reactions, and spectroscopic data (Table 1).

Table 1. Spectroscopic data of *(5)*.

IR (KBr) in cm^{-1}: 3250 m, 3215 m (ν_{NH}); ν_{CO} (THF) 2064 m, 1960 s, 1942 vs, 1908 s.—^{1}H-NMR (90 MHz, [D_6]-acetone, −30 °C, rel. to TMS in ppm): 15.64 (d, δNH(1)), 14.74 (d, δNH(1), $^3J_{HH}$ = 23.5 Hz), 5.10 (s, $\delta C_5H_5(5)$).—MS (70 eV, T_S 76 °C): M^+ at m/e = 398.—UV (THF, 20 °C): λ_{max} 528, 245 (sh), 237 nm; ε_{max} 14 800, 31 200, 33 700 l/mol·cm.

Apart from the molecular ion, the mass spectrum[4] displays, *inter alia*, successive loss of the seven CO ligands of *(5)*; the presence of a M—HN=NH—M′ group in *(5)* is evidenced by the intense absorption in the visible region of the electronic spectrum and the large chemical shift of the NH protons in the ^{1}H-NMR spectrum, which is typical for protons bound to sp^2-hybridized N atoms[1]. Moreover, the ^{1}H-NMR spectrum permits the first determination of the proton coupling constant of the HN=NH molecule: coordination to different metal centers leads to magnetic non-equivalence of the two diazene protons, thus affording an AX system with $^3J_{HH}$ = 23.5 Hz. By analogy with ethylene, which exhibits a coupling constant of 19.1 Hz[5] for the *trans* protons, this value suggests a *trans* configuration of the diazene ligand and a *trans* structure of complex *(5)*[6].



Thus the isoelectronic character of the HN=NH and H_2C=CH_2 molecules is manifested, not in their—completely different—chemical behavior, but rather in their similar proton coupling constants.

Received: April 19, 1977 [Z 718 IE]
German version: Angew. Chem. *89*, 480 (1977)

CAS Registry numbers:
(4), 62708-03-6; *(5)*, 62708-02-5; η-$C_5H_5(CO)_2Mn(N_2H_4)$, 31921-91-2; $(OC)_5Cr(THF)$, 15038-41-2

[*] Prof. Dr. D. Sellmann, Dr. K. Jödden
Laboratorium für Anorganische und Analytische Chemie der Gesamthochschule
Warburger Strasse 100, D-4790 Paderborn (Germany)

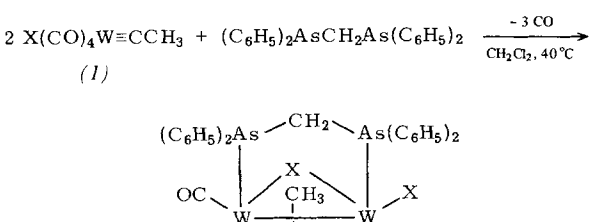
[1] Reactions of Complexed Ligands, Part 19. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 18: *D. Sellmann, A. Brandl, R. Endell*, J. Organomet. Chem. *111*, 303 (1976).

[2] Cf. *J. R. Postgate*: The Chemistry and Biochemistry of Nitrogen Fixation. Plenum Press, London 1971; *J. Chatt, G. A. Heath, R. L. Richards*, J. Chem. Soc. Dalton Trans. *1974*, 2074; *J. Chatt, A. J. Pearman, R. L. Richards, ibid. 1976*, 1520.
[3] *G. Huttner, W. Gartzke, K. Allinger*, J. Organomet. Chem. *91*, 47 (1975).
[4] We are grateful to Prof. Dr. *J. Müller*, Berlin, for recording the spectrum.
[5] *H. Günther*: NMR-Spektroskopie. Thieme, Stuttgart 1973, p. 372.
[6] While $^3J_{HH,trans}$ usually decreases for olefins on coordination to transition metals owing to the change in sp hybridization such an effect will only be slight for σ-bonded diazene since the sp^2 hybridization of the N atoms is retained on coordination.

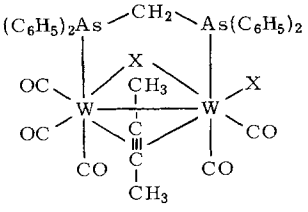
Synthesis of Alkyne-Bridged Dinuclear Complexes by Reaction of *trans*-Halotetracarbonyl(methylcarbyne)-tungsten with Methylenebis(diphenylarsane)[1]

By *Ernst Otto Fischer, Alexander Ruhs, Peter Friedrich*, and *Gottfried Huttner*[*]

trans-Bromotetracarbonyl(phenylcarbyne) complexes of chromium and tungsten[2] react with donor molecules such as triphenylarsane with the substitution of one or two carbonyl ligands[3]. In contrast, the reaction of *trans*-halotetracarbonyl-(methylcarbyne)tungsten[2] *(1)* with methylenebis(diphenylarsane) in the ratio 2:1 leads surprisingly to the synthesis of dinuclear compounds of type *(2)* with the release of three equivalents of carbon monoxide. The bridging ligand dimethylacetylene is probably formed from the carbyne ligands in the coordination region of the metal atoms.



(1)



(2)

(a): X = Cl
(b): X = Br

The diamagnetic, red-brown complexes *(2a)* and *(2b)* are readily soluble in acetone or methylene chloride but then slowly begin to decompose on exposure to air and at room temperature. Both compounds are insoluble in nonpolar solvents.

Since no definite conclusions about the structure of the new compounds could be drawn from their spectra, we established the structure of *(2b)* by X-ray structure analysis[4] (cf. Fig. 1).

The asymmetrical unit of the triclinic cell[4] contains, in addition to a molecule of *(2b)*, a molecule of acetone which is only held by van der Waal's forces. Crystals of *(2b)* become amorphous at temperatures above 273 K with loss of the solvent component; measurement was therefore carried out at 206 K.

[*] Prof. Dr. E. O. Fischer, Dipl.-Chem. A. Ruhs, Dipl.-Chem. P. Friedrich, Doz. Dr. G. Huttner
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

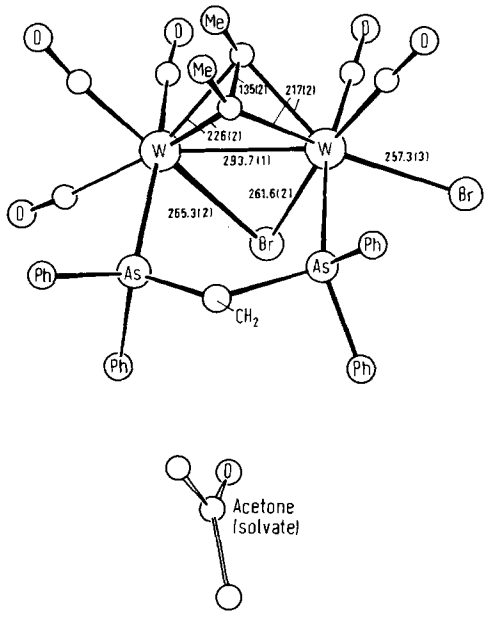


Fig. 1. Molecular structure of the dinuclear compound *(2b)* in crystalline form.

The basic structural units of *(2b)* are two pseudooctahedrally coordinated tungsten atoms which are linked by three different bridging ligands; according to the diamagnetism of the complex a metal-metal bond is also present (d_{W-W} 293.7 (1) pm; compare $[C_5H_5(CO)_3W]_2$: 322.2 (1) pm[5]). The substitution with different terminal ligands (three CO groups or two CO groups and one Br atom respectively) causes the bonding of the bridging ligands between the tungsten atoms to be unsymmetrical; this can be clearly recognized from the $W-C_{acetylene}$ distances (Fig. 1). As in other alkyne-bridged complexes[6], the triple bond is characteristically lengthened by the coordination to two metal centers; the acetylene ligand is also bent (Me—C—C 133 (2)°).

The following spectroscopic data of compound *(2b)* in solution are in agreement with the X-ray findings: The IR spectrum (CH_2Cl_2) shows five bands in the ν_{CO} region at 2023 s, 1978 vs, 1945 s, 1930 s and 1881 m cm^{-1}. In the ^1H-NMR spectrum (CD_2Cl_2, −20 °C, rel. to TMS int.) signals are found at δ = 7.40 (m, 20), 3.13 (s, 3), 2.60 (s, 3), and 2.13 (s, 2). The methylene protons appear at surprisingly high field when compared with other μ-methylenebis(diphenylarsane) complexes[7]; their differing magnetic environments result in a broadening of the signal. The CH_3 groups of the dimethylacetylene ligand are also not equivalent—their resonance lines appear at different field strengths.—In the ^{13}C-NMR spectrum (CD_2Cl_2, −20 °C, rel. to CD_2Cl_2 = 54.2 ppm) both the two carbon atoms of the acetylene (99.68 and 100.44) as well as those of the methyl groups (19.74 and 22.55) exhibit different chemical shifts. A signal at δ = 205.52 can be assigned to the carbonyl groups and that in the region from 128.71 to 135.18 to the phenyl groups. The signal of the methylene carbon atom is to be found at δ = 3.15.

Experimental

All work must be carried out under N_2 with anhydrous and oxygen-free solvents.

(1b)[2] (1.39 g, 3 mmol) and $[(C_6H_5)_2As]_2CH_2$ (0.76 g, 1.5 mmol) are dissolved in 40 ml CH_2Cl_2 at −20 °C. The solu-

tion is slowly warmed until it boils; the color changes from pale yellow to brown with evolution of gas. Reaction is complete after *ca.* 20 min. The product is cooled to −30 °C and purified by column chromatography on silica gel with CH_2Cl_2/pentane (2:1). When the red-brown band of the complex *(2b)* reaches the last third of the column, the uppermost layer of silica gel containing the decomposed products is removed. The column is then eluted with CH_2Cl_2/ether (1:1) and the solvent removed. The remaining residue is dissolved in acetone at −20 °C and after cooling slowly to −78 °C red-brown crystals of analytically pure *(2b)* are formed; yield 0.9 g (43 %).

The analogous reaction of *(1a)*[2] (1.26 g, 3 mmol) with $[(C_6H_5)_2As]_2CH_2$ (0.76 g) in CH_2Cl_2 (40 ml) affords 0.74 g (41 %) of *(2a)*.

Received: April 20, 1977 [Z 719 IE]
German version: Angew. Chem. 89, 481 (1977)

CAS Registry numbers:
(1a), 50726-30-2; *(1b)*, 50726-31-3; *(2a)*, 62708-05-8; *(2b)*, 62708-04-7; ^{13}C, 14762-74-4

[1] Transition Metal-Carbyne Complexes, Part 32.—Part 31: *E. O. Fischer, T. L. Lindner*, Z. Naturforsch. *32b*, 713 (1977).
[2] *E. O. Fischer, G. Kreis, C. G. Kreiter, J. Müller, G. Huttner, H. Lorenz*, Angew. Chem. *85*, 618 (1973); Angew. Chem. Int. Ed. Engl. *12*, 564 (1973).
[3] *E. O. Fischer, A. Ruhs, F. R. Kreissl*, Chem. Ber. *110*, 805 (1977).
[4] Crystal data: triclinic, space group $P\bar{1}$; $Z=2$; $a=1215.1$, $b=1552.2$, $c=1345.5$ pm, $\alpha=93.15$, $\beta=122.34$, $\gamma=100.17°$, $V=2076.1\times10^6$ pm^3; $d_{calc}=1.99$ g/cm^3; 3001 independent reflections: Syntex-P2$_1$ four-circle diffractometer. Solution: Syntex-XTL, conventional, $R_1=0.049$.
[5] *R. P. Adams, D. M. Collins, F. A. Cotton*, Inorg. Chem. *13*, 1086 (1974).
[6] *F. A. Cotton, J. D. Jamerson, B. R. Stults*, J. Am. Chem. Soc. *98*, 1174 (1976); *A. N. Nesmeyanov, A. J. Gusev, A. A. Pasynskii, K. N. Anisimov, N. E. Kolobova, Yu. T. Struchkov*, Chem. Commun. *1968*, 1365.
[7] *R. Colton, C. J. Commons*, Aust. J. Chem. *26*, 1493 (1973); *R. Colton, J. E. Garrard, ibid. 26*, 529 (1973).

Temperature Dependence of the Selectivity of the Halogen Donors $XCCl_3$[**]

By *Bernd Giese* and *Klaus Jay*[*]

Reaction of alkyl radicals *(1)* with the halogen donors $BrCCl_3$ and CCl_4 leads to the formation of alkyl bromides and alkyl chlorides, respectively[1]. Since the abstraction of bromine from $BrCCl_3$ requires a lower activation energy than that of chlorine from CCl_4, the radical selectivities of the competition system $BrCCl_3/CCl_4$ ($\lg k_{Br}-\lg k_{Cl}$) are temperature dependent[2a].

$$RBr \xleftarrow[k_{Br}]{BrCCl_3} \underset{(1)}{R\cdot} \xrightarrow[k_{Cl}]{CCl_4} RCl$$

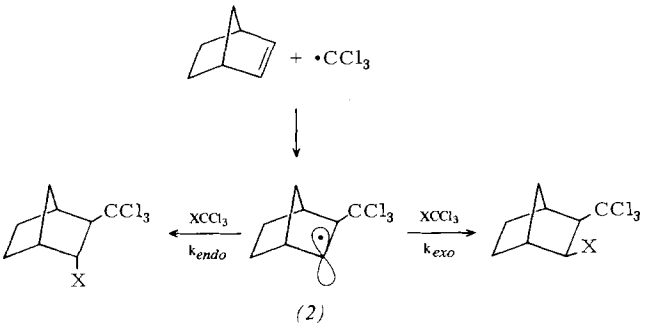
$$\lg\frac{k_{Br}}{k_{Cl}} = \frac{\Delta H^{\ddagger}_{Cl}-\Delta H^{\ddagger}_{Br}}{2.303RT} - \frac{\Delta S^{\ddagger}_{Cl}-\Delta S^{\ddagger}_{Br}}{2.303R}$$

Variation of the radical *(1)* is accompanied by such large changes in the activation entropy differences ($\Delta S^{\ddagger}_{Cl}-\Delta S^{\ddagger}_{Br}$) that the radical selectivities become equal within the temperature range 60±20 °C—the isoselective temperature T_{is}[2]. Below and above T_{is} the order of radical selectivity is exactly reversed.

[*] Priv.-Doz. Dr. B. Giese, Dipl.-Chem. K. Jay
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

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

On the basis of this observation it can be predicted that the selectivities of the halogen donors $XCCl_3$ (X = Br, Cl) in the radical competition systems also coincide at approximately 60±20 °C. This prediction can be tested by studying the radical addition of $XCCl_3$ to 2-norbornene in which the *exo*-trichloromethylnorbornyl radical *(2)* is formed during the primary attack[3].



(2)

The radical *(2)* is attacked from both the *endo* and the *exo* side. Halogen transfer from $XCCl_3$ (X = Br, Cl) is predominantly *endo* due to the shielding influence of the *exo*-trichloromethyl group. The temperature dependence of the stereoselectivity ($\lg k_{endo}-\lg k_{exo}$) of the abstraction of bromine from $BrCCl_3$[4] and of chlorine from CCl_4 was determined between 0 and 127 °C. The selectivity plots shown in Figure 1 demonstrate that below 90 °C the transfer of chlorine from the less reactive CCl_4[1, 2a] proceeds with greater selectivity than the transfer of bromine from the more reactive $BrCCl_3$. At 90 °C—the isoselective temperature T_{is}—the selectivities of the halogen donors $XCCl_3$ become equal; their order is reversed above 90 °C. Here, the more reactive $BrCCl_3$ is more selective than the less reactive CCl_4. The selectivity principle[5] is thus only valid below 90 °C. The isoselective temperature deviates but slightly from the expected value of 60±20 °C.

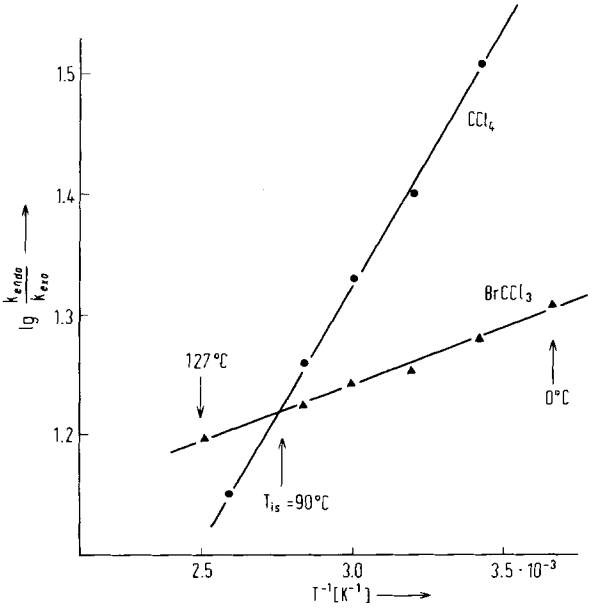


Fig. 1. Temperature dependence (0 to 127 °C) of the stereoselectivity ($\lg k_{endo}-\lg k_{exo}$) of halogen transfer from $XCCl_3$ (X = Br, Cl) to the norbornyl radical *(2)*.

The activation parameters can be calculated from the selectivity plots shown in Figure 1—correlation coefficient $r=0.993$

(X=Br); $r=0.999$ (X=Cl). The data in Table 1 show that the activation enthalpy of chlorine transfer from the Cl—CCl_3 bond, which is stronger by 18 kcal/mol[6], is influenced to a greater extent by the steric shielding of the radical than that of bromine transfer from Br—CCl_3. The activation entropy of chlorine abstraction, however, remains constant whereas that of bromine transfer to the *exo* position of the radical *(2)* is clearly not so favorable.

Table 1. Differences between the activation enthalpies [kcal mol^{-1}] (average error ±7%) and the activation entropies [cal K^{-1} mol^{-1}] (average error ±0.5 cal K^{-1} mol^{-1}) of halogen transfer from $XCCl_3$ to the norbornyl radical *(2)*.

$XCCl_3$	$\Delta H^{\neq}_{exo}-\Delta H^{\neq}_{endo}$	$\Delta S^{\neq}_{exo}-\Delta S^{\neq}_{endo}$
X=Br	0.5	−4.1
X=Cl	2.0	−0.1

Since perhalomethanes are used as halogenating agents in radical substitution reactions[1], the occurrence of the isoselective temperature at 90°C is also of preparative significance.

Received: April 20, 1977 [Z 720 IE]
German version: Angew. Chem. *89*, 482 (1977)

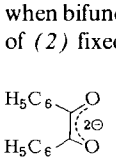
CAS Registry numbers:
(2), 62698-32-2; $BrCCl_3$, 75-62-7; CCl_4, 56-23-5; 2-norbornene, 498-66-8; norbornene adducts: X=*exo*-Br, 62742-49-8; *endo*-Br, 21087-26-3; *exo*-Cl, 19640-08-5; *endo*-Cl, 21087-25-2

[1] *W. C. Danen* in *E. S. Huyser*: Methods in Free-Radical Chemistry, Vol. 5. Marcel Dekker, New York 1974.
[2] a) *B. Giese*, Angew. Chem. *88*, 159 (1976); Angew. Chem. Int. Ed. Engl. *15*, 173 (1976); b) *ibid. 88*, 161 (1976) and *15*, 174 (1976), respectively.
[3] *D. I. Davies* in: Essays on Free-Radical Chemistry. Special Publication No. 24 of the Chemical Society, London 1970, p. 201.
[4] In the reaction with $BrCCl_3$ which proceeds with a bromine extraction of at least 99.5%, the hitherto unobserved *exo-cis* addition product is also formed. This compound was separated by preparative gas chromatography and identified by NMR spectroscopy.
[5] *B. Giese*, Angew. Chem. *89*, 162 (1977); Angew. Chem. Int. Ed. Engl. *16*, 125 (1977).
[6] *K. W. Egger, A. T. Cocks*, Helv. Chim. Acta *56*, 1516 (1973).

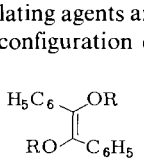
2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexaoxa-2,11-cyclooctadecadiene: A New Crown Ether from Benzoin[1][**]

By *Andreas Merz*[*]

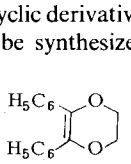
Recently, we found[2] that the stilbenediol dianion *(1)* is formed from benzoin *(4)* and aqueous sodium hydroxide under conditions of phase-transfer catalysis[3]. *(1)* is alkylated by dialkyl sulfates and alkyl tosylates to give predominantly the *E* isomers of the α,β-dialkoxystilbenes *(2)*[2,4]. However, when bifunctional alkylating agents are used, cyclic derivatives of *(2)* fixed in the *Z* configuration can also be synthesized,



(1)



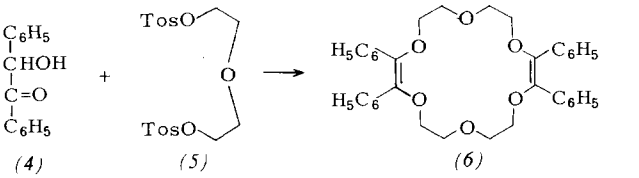
(2)



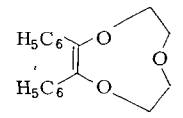
(3)

e.g. with ethylene glycol ditosylate the 2,3-dihydro-5,6-diphenyl-1,4-dioxine *(3)* is obtained.

From the structure of *(3)* it is evident that the stilbenediol unit is a potential building block for crown ether systems. Thus, the title compound *(6)* is indeed obtained with a yield of 20% by reacting *(4)* with diethylene glycol ditosylate *(5)* in boiling benzene with 50% aqueous sodium hydroxide as base and tetra-*n*-butylammonium bromide as phase-transfer catalyst[5].



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



(7)

The smaller crown ether 2,3-diphenyl-1,3,7-trioxa-2-cyclononene *(7)* is also produced in 14% yield.

Apart from the related compound dibenzo-[18]crown-6[6], in which the double bounds are integrated into benzene rings, *(6)* is the only macrocyclic polyether to have double bonds within its ring and thus fills a gap in the series of known [18]crown-6 systems.

In addition to their use as complexing agents[7] and phase-transfer catalysts[8], crown ethers have recently become especially important as basic structural units of receptor molecules for "host-guest-molecule" relationships and for the separation of enantiomers by "chiral recognition"[9]. On account of its ready accessibility and the many conceivable reactions which could take place at its double bonds with their prochiral centers, the new crown ether *(6)* could prove very valuable.

Experimental

A mixture of *(4)* (4.24 g, 0.02 mol), *(5)* (8.33 g, 0.02 mol), tetra-*n*-butylammonium bromide (100 mg, *ca.* 0.3 mmol), 50% aqueous NaOH (20 ml), and benzene (100 ml) is stirred at 80°C for 14 h. The product is then poured into water and the organic phase used for further purification. The partially solid residue is suspended in ethyl acetate and filtered under suction: 1.1 g crude *(6)*, m.p. 165—175°C (19.5%); purified by recrystallization from chloroform/ethyl acetate. Physical data of *(6)*: colorless needles, m.p. 173—175°C (slow heating); mass spectrum (70 eV), *m/e*: 564 ($M^{\cdot+}$, 100%), 238 ($C_{16}H_{14}O_5^{+}$, 70%), 105 ($C_6H_5CO^{+}$, 96%); ^{1}H-NMR ($CDCl_3$): δ=4.00 and 7.26, slightly broadened singlets, intensity ratio 4:5; IR (KBr): $\tilde{\nu}_{C=C}=1620$, $\tilde{\nu}_{C-O}=1255$, 1135, 1120, 1060 cm^{-1}; UV (CH_2Cl_2): λ_{max} [nm] (ε) = 300 (17200), 245 (9800), 228 (14000).

After filtration with dichloromethane through a short silica gel column 800 mg (14%) of *(7)*, m.p. 78°C, are obtained from the mother liquor. Physical data of *(7)*: mass spectrum (70 eV), *m/e*: 282 ($M^{\cdot+}$, 98%), 177 ($M^{\cdot+}-C_6H_5CO^{\cdot}$, 100%), 149 (85%), 133 (16%), 105 ($C_6H_5CO^{+}$, 97%); ^{1}H-NMR: δ=3.7—4.1 (m, 4H), 4.1—4.4 (m, 4H), 7.14 (narrow m, 10H); IR (KBr): $\tilde{\nu}_{C=C}=1625$, $\tilde{\nu}_{C-O}=1250$, 1145, 1070 cm^{-1}; UV (*n*-hexane): λ_{max} [nm] (ε) = 306 (9700), 245 (6800), 222 (12900).

Received: April 27, 1977 [Z 723 IE]
German version: Angew. Chem. *89*, 484 (1977)

[*] Dr. A. Merz
Institut für Chemie im Fachbereich Chemie und Pharmazie der Universität
Universitätsstrasse 31, D-8400 Regensburg (Germany)

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

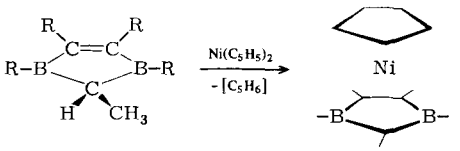
CAS Registry numbers:
(4), 119-53-9; *(5)*, 7460-82-4; *(6)*, 62726-46-9; *(7)*, 62698-60-6

[1] Phase-Transfer-Catalyzed Reactions, Part 6.—Part 5: *A. Merz, R. Tomahogh*, Chem. Ber. *101*, 96 (1977).
[2] *A. Merz, R. Tomahogh*, to be published.
[3] *E. V. Dehmlow*, Angew. Chem. *86*, 187 (1974); Angew. Chem. Int. Ed. Engl. *13*, 170 (1974); *M. Mąkosza*, Pure Appl. Chem. *43*, 439 (1975).
[4] *A. Merz*, Angew. Chem. *85*, 868 (1973); Angew. Chem. Int. Ed. Engl. *12*, 846 (1973).
[5] The reaction also proceeds—but more slowly—without the addition of tetra-*n*-butylammonium bromide; the "template effect" [8] postulated for the synthesis of crown ethers still has to be reconciled with the mechanistic concepts of phase-transfer catalysis [3]. In homogeneous solution (NaOH in dimethyl sulfoxide) the yield of *(6)* is much lower.
[6] *C. J. Pedersen*, J. Am. Chem. Soc. *89*, 7017 (1967).
[7] *C. J. Pedersen, H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. Int. Ed. Engl. *11*, 16 (1972).
[8] *G. W. Gokel, H. D. Durst*, Synthesis *1976*, 168.
[9] *D. J. Cram et al.*, Pure Appl. Chem. *43*, 327 (1975).

η-Cyclopentadienyl(η-diborolenyl)nickel—A Diamagnetic Nickelocene Analog[1]

By *Walter Siebert* and *Manfred Bochmann*[*]

1,2,5-Thiadiborolenes react as two-electron acceptors with metal carbonyls to form double-[2] and triple-decker[3] compounds. The structurally related 1,3-diborolenes[4] *(1)* should likewise form mono- and dinuclear complexes as three-electron acceptors after elimination of H. We now report the thermal reaction of *(1)* (R = C_2H_5) with nickelocene, which affords the diamagnetic species *(2)*.



(1) *(2)*

The spectroscopic and analytical data of the orange-red, in solution air-sensitive compound *(2)* are in accord with a sandwich structure. Apart from the molecular ion $C_5H_5NiL^+$ [L = {*(1)* – H}, R = C_2H_5] (I_{rel} = 100 % relative to $^{11}B_2{}^{58}Ni$), the mass spectrum (70 eV) displays *inter alia* the fragments $\{C_5H_5NiL-C_2H_5\}^+$ (14), $\{C_5H_5NiL-C_2H_5-C_2H_4\}^+$ (14), $\{LNi-H\}^+$ (25), $\{NiL-C_2H_5\}^+$ (16), and $C_5H_5Ni^+$ (13). In the ^{1}H-NMR spectrum [δ = 3.97 (S, 5), 1.3 (M, 4), 0.70 (S, 3), 0.66 (T, 6), 0.37 (T, 6); in C_6D_6 relative to external TMS] only one of the two ABX_3 multiplets for the magnetically nonequivalent methylene protons can be recognized since the CH_2 signals of the BC_2H_5 group are superposed by the two triplets and the singlet.—The ^{11}B-NMR signal exhibits a pronounced upfield shift (Δδ = 33.3) on going from free *(1)* [δ = 68.6; in hexane relative to external $BF_3 \cdot OEt_2$] to complex *(2)*, which can be explained only in terms of a *pentahapto* bonding of the C_3B_2 ring.

The electron balance in *(2)* can be described by assuming construction of the sandwich from two aromatic rings (C_5^-, $C_3B_2^{3-}$) and the Ni d^6 cation. On viewing *(2)* as nickelacarbaborane with a *nido*-C_3B_2Ni skeleton it follows that the bonding molecular orbitals are to be occupied by $2n+4 = 16$ skeletal electrons[5] [3 × 3 (C), 2 × 2 (B), 3 (Ni)]. Complex *(2)*, which is isoelectronic to the metallocenes $[Fe(C_5H_5)_2]$, $[Co(C_5H_5)_2]^{\oplus}$, and $[Ni(C_5H_5)_2]^{2\oplus}$[6], is derived from the paramagnetic, 20-electron sandwich compound nickelocene by replacement of two CH groups by BR groups and from the diamagnetic η-cyclopropenyl complex $[Ni(C_5H_5)(C_3Ph_3)]$[7] by insertion of two BR groups with ring expansion. The metal center in *(2)* is formally Ni^{IV} (for comparison, see $[Ni(\eta^5\text{-}C_2B_9H_{11})_2]$[6]).

[*] Prof. Dr. W. Siebert, M. Bochmann
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

(η-Cyclopentadienyl)(η-1,3,4,5-tetraethyl-2-methyl-1,3-diborolenyl)nickel (2)

Nickelocene (0.61 g, 3.23 mmol) and *(1)* (0.60 g, 3.16 mmol) are heated to 180 °C for 2.5 h under N_2. The brownish red product isolated at 120 °C/0.1 torr crystallizes from ether/methanol at −10 °C as orange-red, hexagonal platelets, m.p. 46 °C; yield: 0.26 g (26 %).

Received: April 27, 1977 [Z 722 IE]
German version: Angew. Chem. *89*, 483 (1977)

CAS Registry numbers:
(2), 62708-15-0; $Ni(C_5H_5)_2$, 1271-28-9

[1] Diborylethylene Compounds as Ligands in Metal Complexes, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: *W. Siebert, R. Full, J. Edwin, K. Kinberger, C. Krüger*, J. Organomet. Chem. *131*, 1 (1977).
[2] *W. Siebert, R. Full, C. Krüger, Y.-H. Tsay*, Z. Naturforsch. *B31*, 203 (1976); *R. Full*, Dissertation, Universität Würzburg 1976.
[3] *W. Siebert, K. Kinberger*, Angew. Chem. *88*, 451 (1976); Angew. Chem. Int. Ed. Engl. *15*, 434 (1976); *W. Siebert, T. Renk, K. Kinberger, M. Bochmann, C. Krüger, ibid. 88*, 850 (1976) and *15*, 779 (1976); *W. Siebert, W. Rothermel, ibid. 89*, 346 (1977) and *16*, 333 (1977), respectively.
[4] *P. Binger*, Angew. Chem. *80*, 288 (1968); Angew. Chem. Int. Ed. Engl. *7*, 286 (1968).
[5] *K. Wade*, Chem. Br. *11*, 177 (1975); references cited therein.
[6] *R. J. Wilson, L. F. Warren Jr., M. F. Hawthorne*, J. Am. Chem. Soc. *91*, 758 (1969).
[7] *M. D. Rausch, R. M. Tuggle, D. L. Weaver*, J. Am. Chem. Soc. *92*, 4981 (1970).

Halogenonitrosylmolybdates—Isolation of the First Classical Mo^I Complex

By *Sabyasachi Sarkar* and *Achim Müller*[*]

Little is known about classical complexes of the lower oxidation states of molybdenum (Mo^0, Mo^I, Mo^{II})[1], and although the oxidation of $[Mo(NO)(CN)_5]^{4-}$ has repeatedly been investigated no corresponding Mo^I complex could be isolated. We recently reported salts with the anions $[Mo(NO)X_4]^-$ *(1)* and $[Mo(NO)X_5]^{2-}$ *(2)* (X = Cl, Br)[2] as mononuclear coordination compounds with simple ligands where Mo can be regarded as being in the formal oxidation state II (nitrosyl group as NO^+[1], $\{MNO\}^4$ configuration[3]). We have therefore attempted the synthesis of the missing species between $K_4[Mo(NO)(CN)_5]$ (formally $Mo^{0[1]}$) containing the $[MoNO]^+$ group and *(1)* as well as *(2)* with the group $[MoNO]^{3+}$ in the series[4]

$[MoNO]^+$	$[MoNO]^{2+}$	$[MoNO]^{3+}$
$\{MoNO\}^6(\equiv e^4b_2^2)$	$\{MoNO\}^5(\equiv e^4b_2^1)$	$\{MoNO\}^4(\equiv e^4)$

in order to systematically study the electron distribution over the three centers M—N—O.

The Mo^I-compound[5] $Cs_2[Mo(NO)Cl_4H_2O]$ *(3)* containing the $[MoNO]^{2+}$ group is isolated as stable green crystals by a new method for the *reduction* of nitrosyl complexes[6]:

[*] Prof. Dr. A. Müller, Dr. S. Sarkar [**]
Institut für Chemie der Universität
Postfach 500500, D-4600 Dortmund 50 (Germany)

[**] Alexander-von-Humboldt-Foundation Fellow.

$$Cs_2[Mo(NO)Cl_5] \underset{\text{conc. HCl/Br}_2}{\overset{\text{dil. HCl/Mg}}{\rightleftharpoons}} Cs_2[Mo(NO)Cl_4H_2O]$$
(2) *(3)*

(Reduction and simultaneous substitution due to the strong *trans*-effect of NO). Compound *(3)* can be reconverted into *(2)* by "oxidation" and has been characterized by elemental analyses, thermogravimetry, magnetic measurements, as well as by photoelectron spectroscopy (XPS), ESR, VIS, and IR

Table 1. Characteristic data of the Mo^I complex *(3)*.

Magnetism	$\mu_{eff} = 1.77\,\mu_B$ (293 K)
Electronic transition [a]	$E(b_2 \rightarrow e(^*NO)) \approx 17000\ cm^{-1}$
ESR [d]	[b] $g_\perp = 1.99$ (2.02), $g_\parallel = 1.90$ (1.97) [c] $g_{sol.} = 1.95$ (2.00), $A(^{95/97}Mo) = 23$ G
TG	*(3)* $\xrightarrow[-H_2O]{135-150\,^\circ C/vac}$ $\{Cs_2[Mo(NO)Cl_4]\}$

[a] Reflectance spectrum of the solid. [b] Powder at room temperature. [c] Solution in hydrochloric acid at room temperature. (The possibility of a ligand exchange reaction is not excluded). [d] Values for the Mo^I species $[Mo(NO)(CN)_5]^{3-}$ which exists only in solution are given in brackets [7a]; $\Delta g_{sol} = g_e - g_{sol}$ (see text).

Table 2. IR spectra (solid state; nujol, KBr) of *(3)* [cm^{-1}].

(3)	*(3)* deuterated	*(2)*	Species $\{(ON)MoO/Cl_4\}$ skeleton C_{4v}	
3470 s 3385 s [a]	2591 s 2493 s [a]			ν(OH), ν(OD)
1624 vs	1624 vs	1676 vs	A_1	ν(NO)
1603 s (1573 sh)	1186 m			$\delta(H_2O)$, $\delta(D_2O)$
550 w [c]	550 w	579 w	A_1	ν(MoN)
625 w [c]	625 w	608.5 w	E	δ(MoNO)
381 vw	≈360 sh		A_1	ν(Mo—OH_2), ν(Mo—OD_2)
304 s, br	304 s, br	320 vs, br	E [b]	$\nu_{as}(MoCl_4)$

[a] Additional very weak bands appear at 3190 and 2364 cm^{-1}, respectively. [b] $\nu_s(MoCl_4)$ is overlapped by $\nu_{as}(MoCl_4)$. [c] In principle reverse assignments are possible.

spectral studies. The data presented in Tables 1 and 2 confirm that the new species has C_{4v} symmetry with the ground state configuration $e^4b_2^1$. The electron density in the group $[MoNO]^{n+}$ is expectedly larger in the reduced species *(3)* than in *(2)*. Comparison of the ESR data with those of the only known Mo^I-species in solution[7a] showed a greater difference $|g_\perp - g_\parallel|$ as well as a greater Δg_{av} value for *(3)* (see [7]).

A knowledge of the complexes of the series $[Mo(NO)]^{n+}$, $n = 1$—3 should improve our understanding of nitrosyl complexes and especially the coordination complexes of lower valent molybdenum. Redox and ligand exchange reactions permit development of a "classical" complex chemistry of Mo^0, Mo^I, and Mo^{II}, the various complexes being stabilized by the NO group.

Experimental

To a suspension of *(2)* (1 g) in dilute, oxygen-free hydrochloric acid (20 ml, 3 N) is added Mg powder (0.14 g) in the cold. On addition of methanol (10 ml) green crystals of *(3)* separate slowly. Yield *ca.* 50 %.

Received: March 24, 1977 [Z 716 IE]
German version: Angew. Chem. 89, 479 (1977)

CAS Registry numbers:
(2), 61505-69-9; *(3)*, 62669-50-5

[1] *A. G. Sharpe:* The Chemistry of Cyano Complexes of the Transition Metals. Academic Press, London 1976; *F. A. Cotton, G. Wilkinson:* Advanced Inorganic Chemistry. Wiley-Interscience, New York 1972; *D. L. Kepert:* The Early Transition Elements. Academic Press, London 1972.

[2] *S. Sarkar, A. Müller*, Angew. Chem. *89*, 198 (1977); Angew. Chem. Int. Ed. Engl. *16*, 183 (1977).

[3] This notation takes into consideration the strong metal-NO interaction in such complexes (less d-electron delocalization into the other Mo-ligand bonds): {MNO} in the perturbing field of the other ligands; see also *J. H. Enemark, R. D. Feltham*, Coord. Chem. Rev. *13*, 339 (1974).

[4] Equivalent formulations (for C_{4v} symmetry).

[5] Designation as Mo^I is justified if the d character dominates in e in the case of the configuration e $(xz,yz,\pi^*\text{-NO})^4b_2(xy)^1$.

[6] Hitherto the only reduction reactions (maintaining the structure of the complexes!) known entailed concomitant change of the NO group. Cf. *K. G. Caulton*, Cood. Chem. Rev. *14*, 317 (1975).

[7] a) *R. G. Hayes*, J. Chem. Phys. *47*, 1692 (1967); b) *B. A. Goodman, J. B. Raynor, M. C. R. Symons*, J. Chem. Soc. *A 1968*, 1973.

Formation of Benzocyclobutenone by Gas-Phase Pyrolysis[**]

By *Peter Schiess* and *Markus Heitzmann*[*]

We recently demonstrated the formation of alkenylketenes by elimination of hydrogen chloride from β,γ-unsaturated acyl chlorides at 400 to 600 °C in the gas phase. In turn, the alkenylketenes are transformed into α,β;γ,δ-unsaturated aldehydes by an intramolecular 1,5-hydrogen shift[1].

We have now found that thermal HCl elimination also occurs readily with *ortho*-alkyl-substituted aromatic acyl chlorides *(1)*[2]. The *ortho*-quinonoid ketene *(2)* formulated

[*] Prof. Dr. P. Schiess, Dipl.-Chem. M. Heitzmann
Institut für Organische Chemie der Universität
St. Johanns-Ring 19, CH-4056 Basel (Switzerland)

[**] This work was supported by the Schweizerischer Nationalfonds (Project No. 2480075) and by CIBA-GEIGY AG.

as intermediate is stabilized by 1,5-hydrogen shift to give the aldehyde, provided that the alkyl side chain bears β-protons[3]. Thus gas-phase pyrolysis (600 °C/0.3 s) of 2-propylbenzoyl chloride *(1)*, R^1 to R^4 = H, $R^5 = C_2H_5$, gives a mixture of the isomeric aldehydes *(3)*[4]. If the side chain is a methyl group, however, then benzocyclobutenone *(4)* is obtained (see Table 1).

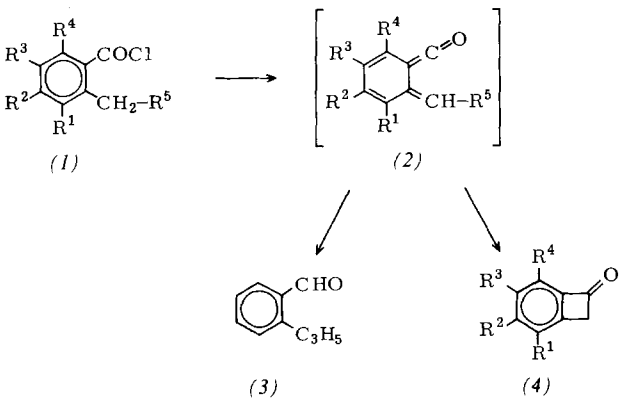


Table 1. Formation of benzocyclobutenones *(4)* by gas-phase pyrolysis [a] of *(1)*, $R^5 = H$.

	R^1	R^2	R^3	R^4	Pyrolysis temp. [°C]	Conversion [%]	Yield [b] [%]	M.p. [°C] b.p. [°C/torr]	
(a)	H	H	H	H	630	76	28 (37)	89—90/14	[6a]
(b)	H	H	CH_3	H	620	72	27 (37)	45—46 98—101/14	[7]
(c)	CH_3	H	H	H	600	77	61 (80)	53—54 98—100/14	[7]
(d)	H	CH_3	H	CH_3	560	95	72 (76)	47—48 111—113/12	[6b]
(e)	H	CH_3O	H	H	590	59	43 (72)	49—50 95—105/1.5	[6c]
(f)	H	H	—CH=CH—CH=CH—		550	89	73 (82)	96—97	[7]

[a] 14 torr, contact time *ca.* 0.3 s.
[b] Based on amount of acyl chloride weighed in (reacted).

In the case of compounds *(1a)* and *(1b)* the conditions necessary for HCl elimination are so drastic that benzyl chloride and other volatile decomposition products derived from *(4)* arise on complete reaction of the acyl chloride[5]. With compounds *(1c)* to *(1f)*, 1,4-elimination of HCl is facilitated by steric or electronic substituent effects and/or bond delocalization in the aromatic ring, and the benzocyclobutenones *(4)* can be isolated in excellent yields. The above method of preparing benzocyclobutenones[6] should compete successfully with other procedures on account of the ready accessibility of the reactants and experimental simplicity.

Procedure

o-Toluoyl chloride (30.0 g, 0.194 mol) is distilled at 12 torr through a quartz tube (30 × 1 cm) packed with quartz chips heated to 620 °C over a period of 2.5 h. The pyrolyzate condensed onto a cold finger (−78 °C) located at the end of the tube is dissolved in tetrahydrofuran (300 ml) and stirred for 1 h at 25 °C with saturated sodium hydrogen carbonate solution (400 ml). Extraction with pentane and fractional distillation (Vigreux column, 10 × 1 cm) affords benzocyclobutenone *(4a)* (6.5 g; b.p. 89 to 90 °C/14 torr[6a]). *o*-Toluic acid (6.4 g) can be recovered by acidification of the aqueous phase.

Received: April 28, 1977 [Z 724 IE]
German version: Angew. Chem. *89*, 485 (1977)

CAS Registry numbers:
(1a), 933-88-0; *(1b)*, 22328-43-4; *(1c)*, 21900-46-9; *(1d)*, 938-18-1; *(1e)*, 31310-08-4; *(1f)*, 10008-12-5; *(3)*, C_3H_5 = *E*-2-propenyl, 62708-40-1; *(3)*, C_3H_5 = *Z*-2-propenyl, 62708-41-2; *(3)*, C_3H_5 = allyl, 62708-42-3; *(4a)*, 3469-06-5; *(4b)*, 62708-43-4; *(4c)*, 62708-44-5; *(4d)*, 6670-28-6; *(4e)*, 22246-27-1; *(4f)*, 62708-45-6

[1] *P. Schiess, P. Radimerski*, Helv. Chim. Acta *57*, 2583 (1974); Chimia *26*, 652 (1972).
[2] Concerning pyrolytic 1,4-eliminations from *ortho*-substituted arenes, see *P. de Champlain, J. L. Lucke, R. A. Marty, P. de Mayo*, Can. J. Chem. *54*, 3749 (1976).
[3] *R. F. C. Brown, M. Butcher*, Aust. J. Chem. *22*, 1457 (1969).
[4] A 75% yield is formed of a mixture (b.p. 103 to 110 °C/12 torr) [7] of *E*-2-propenyl-, *Z*-2-propenyl-, and 2-allyl-benzaldehyde in a ratio of 71:20:9, which is transformed into 2-propylbenzaldehyde (dinitrophenylhydrazone [7] m.p. 155 to 156 °C) on catalytic reduction.
[5] *E. Hedaya, M. E. Kent*, J. Am. Chem. Soc. *92*, 2149 (1970).
[6] a) *M. P. Cava, K. Muth*, J. Am. Chem. Soc. *82*, 652 (1960); *R. J. Spangler, J. H. Kim*, Tetrahedron Lett. *1972*, 1249; b) *H. Hart, R. W. Fish*, J. Am. Chem. Soc. *82*, 749 (1960); *H. Hart, J. A. Hartlage, R. W. Fish, R. R. Rafos*, J. Org. Chem. *31*, 2244 (1966); c) *M. Tomita, S. Minami, S. Uyeo*, J. Chem. Soc. *C 1969*, 183.
[7] All new compounds gave correct elemental analyses and spectral data compatible with the proposed structure.

A Geometrically Isomeric Bilatriene-abc[**]

By *Heinz Falk* and *Karl Grubmayr*[*]

The synthesis and constitution of bile pigments have already been extensively investigated[1]. However, only very recently has any appreciable understanding of their structure (configuration, conformation, tautomerism) been achieved[2–4]. Geometrical isomers of a bile pigment were hitherto unknown; they are of interest, however, with regard to hypotheses on the function of the plant photoreceptor phytochrome[5].

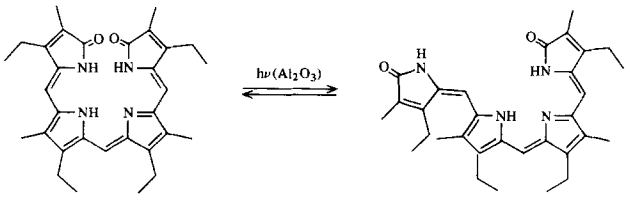
We have now been able to demonstrate a $Z \rightleftharpoons E$ isomerization in a bilatriene-abc, *viz.* etiobiliverdin-IV-γ *(1)*, and to isolate the new isomer.

After irradiation of *(1)*, which had been adsorbed on aluminum oxide, chromatographic separation afforded besides the educt a slowly migrating product which was characterized as an isomer by its mass spectrum [MS (70 eV, 140 °C); *m/e* (%): 498 (100, M^+), 483 (15), 469 (16), 249 (13, M^{2+})]. The reaction is photoreversible, *i.e.* on renewed irradiation of the

[*] Prof. Dr. H. Falk, Mag. rer. nat. K. Grubmayr
Organisch-Chemisches Institut der Universität
Währingerstrasse 38, A-1090 Wien (Austria)

[**] This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung (Project No. 2732).

product under the given conditions the mixture of both forms is regenerated, the more rapidly migrating component proving to be identical with the educt in all its properties[6]. The absorption spectrum of the isomer [UV-VIS ($CHCl_3$): 262 (18000), 323 (27000), 369 (41000), 598 (21000), nm (ε)] differs from that of the educt by a hypsochromic shift of the long-wave band of about 38 nm.



(Z,Z,Z)-(1) *(E,Z,Z)-(1)*

Owing to its structural analogy with the methyl ester of biliverdin[2] and in view of the characteristics of partial structures[4, 7], the educt is assigned the configuration *(Z,Z,Z)-(1)*. For the product, five geometric isomers are conceivable. Three of these, namely those having the configurations (*E,Z,E*), (*Z,E,Z*), and (*E,E,E*) are ruled out on the basis of the ^{1}H-NMR spectra, which should be analogous to that of the educt[6] (this is of course very much simplified by the formal C_{2v} symmetry). Only the configurations (*E,Z,Z*) and (*E,E,Z*) are consistent with the typical spectrum[8] for the isolated material, which shows four separate methyl signals, a methyl triplet of an ethyl group separated from the signal of the other three groups, and three methine signals. The positions of these methine signals compared with those in *(Z,Z,Z)-(1)*[6] and the finding that no isomerization is observed in the pyrromethene unit[9] afford evidence for the isomeric product having the configuration *(E,Z,Z)-(1)*.

Procedure

A solution of *(Z,Z,Z)-(1)*[6, 10] (249 mg, 0.5 mmol) in $CHCl_3$ (20 ml) is added to 5 g Al_2O_3 (after *Brockmann*, degassed, loaded with argon) and the solvent evaporated. After slurrying in *n*-hexane (200 ml) the vigorously stirred suspension is irradiated in an argon atmosphere for 2 h at 10 °C with a 200-W tungsten lamp. CH_3OH (25 ml) is then added to the suspension, the mixture filtered, and the residue washed with CH_3OH. After removal of solvent from the filtrate in a rotary evaporator the residue is chromatographed on 40 g Al_2O_3 (after *Brockmann*) with $CHCl_3$ in the absence of light. 180 mg *(Z,Z,Z)-(1)* is obtained as a rapidly migrating zone and (after addition of about 1 % CH_3OH) also 25 mg crude *(E,Z,Z)-(1)*. Re-chromatography of this fraction on silica gel thin-layer plates (0.5 mm, $CHCl_3/CH_3OH$ = 20/1) affords 20 mg (8 %) pure *(E,Z,Z)-(1)*, m.p. 260 °C.

Received: May 9, 1977 [Z 726 IE]
German version: Angew. Chem. *89*, 487 (1977)

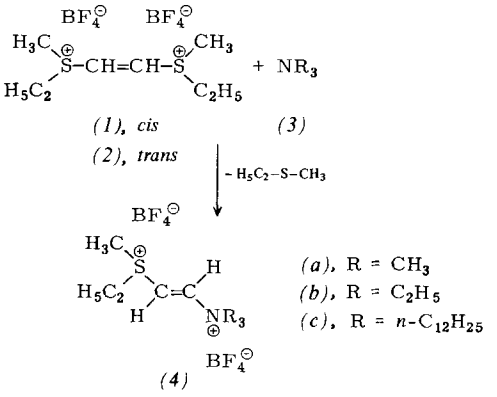
CAS Registry numbers:
(Z,Z,Z)-(1), 62796-03-6; *(E,Z,Z)-(1)*, 62796-04-7

[1] *W. Rüdiger*, Fortschr. Chem. Org. Naturst. *29*, 60 (1971); *F. Hudson, K. M. Smith*, Chem. Soc. Rev. *4*, 363 (1975).
[2] *W. S. Sheldrick*, J. Chem. Soc. Perkin Trans. 2, *1976*, 1457.
[3] *R. Bonnett, J. E. Davies, M. B. Hursthouse*, Nature *262*, 326 (1976).
[4] *H. Falk, S. Gergely, K. Grubmayr, O. Hofer*, Justus Liebigs Ann. Chem. *1977*, 565; Z. Naturforsch. *32b*, 299 (1977); *D. L. Cullen, P. S. Black, E. F. Meyer, D. A. Lightner, G. B. Quistad, C. S. Pak*, Tetrahedron *33*, 477 (1977).
[5] *R. K. Clayton*: Light and Living Matter. McGraw-Hill, New York 1971, Vol. 2.
[6] Spektroscopic properties: *K. M. Smith*, J. Chem. Soc. Perkin Trans. 1, *1972*, 1471.
[7] *H. Falk, K. Grubmayr, U. Herzig, O. Hofer*, Tetrahedron Lett. *1975*, 559.
[8] ^{1}H-NMR ($CDCl_3$, δ, 100 MHz): 9.09 (broad, 3H), 6.71 (s, 1H), 6.23 (s, 1H), 5.90 (s, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 2.51 (q, *J* = 7.5 Hz, 6H), 2.06 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H), 1.82 (s, 3H), 1.19 (t, *J* = 7.5 Hz, 9H), 0.78 (t, *J* = 7.5 Hz, 3H).
[9] *H. Falk, S. Gergely, O. Hofer*, Monatsh. Chem. *105*, 853, 1004 (1974); *H. Falk, O. Hofer, ibid. 105*, 995 (1974).
[10] *H. Falk, K. Grubmayr*, Synthesis, in press.

Vinylenedionium Salts Containing Different Onium Groups[**]

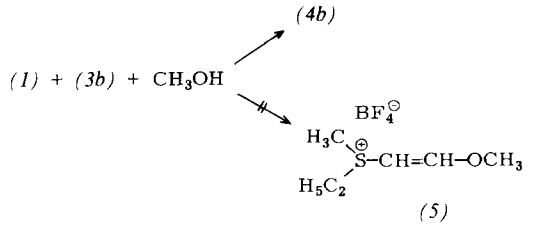
By *Heinz Braun, Anton Amann*, and *Manfred Richter*[*]

Vinylenediammonium[1], vinylenediphosphonium[2], and vinylenedisulfonium[3] salts are well known. In contrast, vinylenedionium salts containing dissimilar onium groups have to our knowledge so far not been described. We report here on the synthesis of S^+,N^+-substituted vinylenedionium salts.



On reaction with the *cis*-vinylenedisulfonium salt *(1)*[3a] in the molar ratio 1 : 1 the trialkylamines *(3a)* to *(3c)* afford the *trans*-salts *(4a)* to *(4c)*. Compound *(4a)* was also synthesized from the *trans*-salt *(2)*[3a] and *(3a)*. According to NMR spectral data the reaction of *(1)* with *(3b)* in acetone at room temperature is complete within a few minutes. To our knowledge the substitution of an sp^2-bonded sulfonium group by a tertiary amine has hitherto not been observed.

Compounds *(4)* are stable at room temperature, *(4a)* and *(4b)* are crystalline and water-soluble, *(4c)* (yield 80 %, picryl sulfonate dec. 124 to 127 °C) is obtained as a wax which is soluble in benzene.

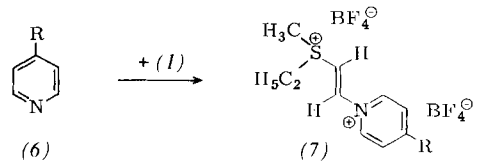


[*] Dr. H. Braun, A. Amann, M. Richter
Organisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

Reaction of *(1)* with *(3b)* and methanol in the molar ratio 1:1:1 in acetone affords *(4b)*. The methoxyvinylsulfonium salt *(5)*[3b] was not detectable by NMR spectroscopy.

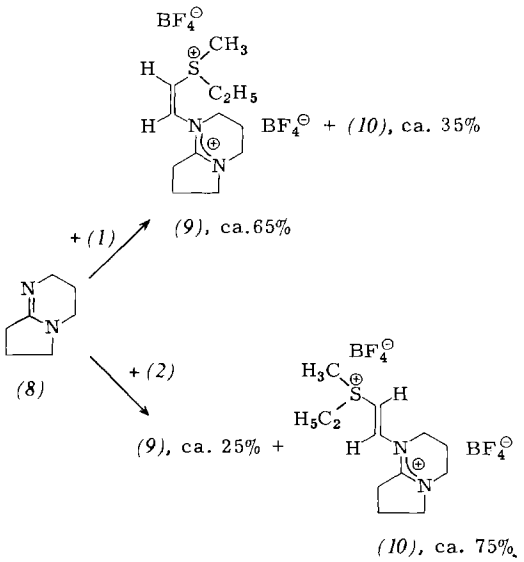
The hypernucleophilic pyridines *(6a)* and *(6b)*[4] react with *(1)* to give the crystalline salts *(7a)* and *(7b)*, respectively.



(6) *(7)*

(a), R = NH_2
(b), R = $N(CH_3)_2$

Reaction of *(1)* or *(2)* with the typical elimination reagent *(8)*[5] furnishes mixtures of the stereoisomeric amidinium salts *(9)* and *(10)*. The product patterns were determined NMR spectroscopically on the crude reaction mixtures. The reactions of *(8)* with *(1)* and *(2)* proceed stereoselectively with retention of configuration. This finding is not consistent with an initial elimination step *via* ethynylsulfonium salt[6].



(8)

(9) crystallizes in pure form from the reaction mixture formed on reaction of *(1)* with *(8)*. Compound *(10)* was isolated by fractional crystallization. *(9)* and *(10)* are the first *cis,trans*-isomer pair of a vinylenedionium salt containing dissimilar onium groups.

Supporting evidence for the constitutions of the compounds described here was provided by correct CHN analyses and by IR, ^{1}H-NMR, and ^{13}C-NMR data (Table 1). The configurations of *(4)* and *(7)* were determined by ^{1}H-NMR spectroscopy. Vinylammonium salts of known stereochemistry[7], and the compounds *(9)* and *(10)* in particular, were used for comparison.

Strong nucleophiles substitute the ammonium group in *(4)* chemospecifically[8]. The vinyl-group proton situated α to the sulfonium group can be replaced selectively by deuterium[8].

Procedure

Compound *(4b)*: A freshly prepared solution of *(3b)* (4.05 g, 0.04 mol) in anhydrous acetone (50 ml) is added dropwise within 5 min at room temperature to a stirred suspension of *(1)* (14.10 g, 0.04 mol) in acetone (250 ml). Solvent is removed from the resulting light-red solution by evaporation (bath-temperature 30 to 40 °C). The residue crystallizes on addition of a little ethanol. After washing with cold ethanol and drying (*ca.* 0.01 torr) there remains 13.10 g (87 %) of light-beige *(4b)*. Recrystallization from methanol/ethanol furnishes 12.05 g (80 %) colorless crystals.

Compound *(7b)*: A suspension of *(1)* (6.00 g, 17 mmol) and *(6b)* (2.08 g, 17 mmol) in anhydrous acetone (150 ml) is stirred for 30 min at room temperature. Work-up of reaction mixture as for *(4b)*. Recrystallization from methanol affords 6.49 g (95 %) *(7b)* as colorless crystals, m.p. 147 °C (dec).

Received: May 11, 1977 [Z 727a IE]
German version: Angew. Chem. *89*, 488 (1977)

CAS Registry numbers:
(1), 56533-77-6; *(2)*, 56553-75-4; *(3a)*, 75-50-3; *(3b)*, 121-44-8; *(3c)*, 102-87-4; *(4c)*, 62882-16-0; *(4b)*, 62882-18-2; *(4c)*, 62882-43-3; *(6a)*, 504-24-5; *(6b)*, 1122-58-3; *(7a)*, 62882-45-5; *(7b)*, 62882-47-7; *(8)*, 3001-72-7; *(9)*, 62882-49-9; *(10)*, 62882-51-3

[1] *A. Halleux, H. G. Viehe*, J. Chem. Soc. *C 1968*, 1726.
[2] a) *A. M. Aguiar, H. Aguiar*, J. Am. Chem. Soc. *88*, 4090 (1966); b) *H. Christol, H. J. Cristeau, M. Soleiman*, Bull. Soc. Chim. Fr. *1976*, 161, and references cited therein.
[3] a) *H. Braun, A. Amann*, Angew. Chem. *87*, 773 (1975); Angew. Chem. Int. Ed. Engl. *14*, 755 (1975); b) *H. Braun, A. Amann*, Angew. Chem. *87*, 775 (1975); Angew. Chem. Int. Ed. Engl. *14*, 756 (1975).
[4] *W. Steglich, G. Höfle*, Angew. Chem. *81*, 1001 (1969); Angew. Chem. Int. Ed. Engl. *8*, 981 (1969).
[5] For a summary see: *H. Oediger, F. Möller, K. Eiter*, Synthesis *1972*, 591.
[6] Cf. in the case of vinylenediphosphonium salts: *H. C. Christol, H. J. Cristeau, J. P. Joubert, M. Soleiman*, C. R. Acad. Sci., Ser. *C 279*, 167 (1974).
[7] *F. E. Herkes, H. E. Simmons*, J. Org. Chem. *38*, 2845 (1973).
[8] *H. Braun, A. Amann*, Angew. Chem. *89*, 489 (1977); Angew. Chem. Int. Ed. Engl. *16*, 473 (1977).

Table 1. Yields and some physical data of the prepared compounds.

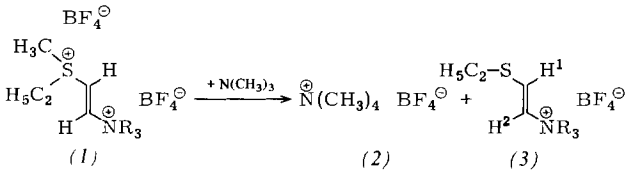
Cpd.	Yield [%]	Dec. [°C]	$^+SCH_3$	$^+SCH_2$—CH_3	^{1}H-NMR [a] $^+$S—CH=	=CH—N^+	^3J [Hz]
(4a)	50 [b] 80 [c]	215—216	6.84 s	6.38 q 8.52 t	2.57 d [d]	2.38 d	13.5
(4b)	80 [b]	111—113	6.83 s	6.38 q 8.51 t	2.68 s		—
(7a)	75 [b]	208—210	6.83 s	6.43 q 8.46 t	3.10 d [d]	1.98 d	13.5
(9)	42 [b]	158	6.94 s	6.52 q 8.53 t	4.27 d	2.40 d	8.5
(10)	33 [c]	161	6.98 s	6.58 q 8.58 t	3.88 d	2.20 d	13.5

[a] 60 MHz, τ values in D_2O with sodium (trimethylsilyl)propanesulfonate as internal standard; [b] from *(1)*; [c] from *(2)*; [d] assignment confirmed by selective deuteriation [8].

Reactions of (2-Dialkylsulfoniovinyl)trialkylammonium Salts[**]

By *Heinz Braun* and *Anton Amann*[*]

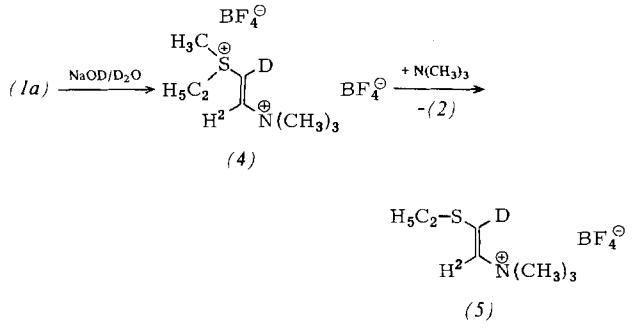
Trialkylamines undergo reaction with vinylenedisulfonium salts with substitution of a sulfonium group to give the salts *(1)*[1]. We have examined whether further exchange of an onium group can be achieved by reaction of *(1)* with a tertiary amine. Reaction of *(1a)* or *(1b)* with trimethylamine affords, however, an almost quantitative (NMR spectra) 1:1 mixture of *(2)* and *(3a)* or *(3b)*, respectively. Compound *(3a)* is crystalline, *(3b)* was obtained as a colorless oil which was analyzed as crystalline hexafluorophosphate.



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

(a), R = CH_3
(b), R = C_2H_5

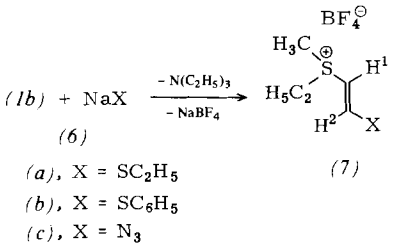
If the weakly acid solution of *(1a)* in deuterium oxide is adjusted to pH ≈ 7.5 with dilute sodium deuterium oxide solution H/D exchange of one of the two olefinic protons can be observed NMR spectroscopically.



(4)

(5)

The monodeuteriated compound *(4)* was isolated. It yields compound *(5)* on reaction with trimethylamine in dimethoxyethane. The structure of *(5)* was deduced NMR spectroscopically by comparison with *(3a)* and with β-substituted vinylammonium compounds[2] (Table 1). The structure of *(4)* was inferred from *(5)*. The reaction *(1a)* → *(4)* shows that sp^2 bonded protons are more strongly acidified by sulfonium groups in the α position than by ammonium groups. The selective deuteration of compounds having a structure analogous to *(1)*[1], moreover, enabled unequivocal assignment of the CH=CH signals in the ^1H- and ^{13}C-NMR spectra[3].



(6) *(7)*

(a), X = SC_2H_5
(b), X = SC_6H_5
(c), X = N_3

Strong nucleophiles substitute the ammonium group in *(1)* chemospecifically: reaction of *(1b)* with *(6a)* or *(6b)* in methanol at 0 °C yields the oily tetrafluoroborates *(7a)*[4] or *(7b)*, respectively. Reaction of *(6c)* with *(1b)* in water at room temperature yields *(7c)*. The crude solutions of compounds *(7)* still contain < 5 % of the corresponding *cis* isomer (NMR spectra). Compounds *(7b)* and *(7c)* were obtained in sterically pure form as the crystalline 2,4,6-trinitrobenzenesulfonate and hexafluorophosphate, respectively.

Vinylsulfonium salts are excellent Michael acceptors and productive building blocks in syntheses[5]. The reaction sequence *cis*-vinylenedisulfonium salt → *trans*-*(1)*[1] → *trans*-*(7)* constitutes a novel route to *trans*-substituted vinylsulfonium salts. The *cis* isomers of *(7)* are formed stereoselectively from *cis*-vinylenedisulfonium salts and *(6)*[3, 4b]. The method thus offers the possibility of synthesizing both isomeric vinylsulfonium salts from a readily accessible starting compound.

Compound *(7)* and its *cis* isomer[3] are to our knowledge the first azidovinylsulfonium salts reported in the literature. The compounds are interesting water-soluble "vinyl azides"[6].

Procedure

A solution of trimethylamine (126 mg, 2.13 mmol) in anhydrous acetone (1.3 ml) was added to a stirred solution of *(1b)* (400 mg, 1.06 mmol) in acetone at room temperature. After 1 h the reaction mixture was concentrated to 7 ml and filtered free from precipitated *(2)*. The filtrate after removal of solvent and drying (0.01 torr) afforded 285 mg (98 %) *(3b)* as a colorless oil.—Hexafluorophosphate: an aqueous solution of *(3b)* (285 mg) was treated with an excess of aqueous ammonium hexafluorophosphate solution. Recrystallization of the precipitate from ethanol yielded 230 mg (72 %) of colorless crystals, m.p. 78 to 79 °C.

Compound *(7c)*: A solution of *(1b)* (5.00 g, 0.13 mol) and *(6c)* (0.87 g, 0.13 mol) in water (50 ml) was stirred for 30 min at room temperature. After removal of water (rotary evaporator, bath temperature 40 °C) the residue was treated with 10 ml acetone and 15 ml dichloromethane and then filtered to remove sodium tetrafluoroborate. After removal of solvent and drying there remained 2.33 g (76 %) *(7c)* together with

Table 1. Yields and some physical data of the compounds prepared.

Cpd.	Yield [%]	M.p. (dec.) [°C]	^1H-NMR [a] SCH_3	SCH_2—CH_3	H^1	H^2	$^3J_{H^1,H^2}$ [Hz]
(3a)	74	175—176	—	7.12 q 8.70 t	2.75 d	3.62 d	13.8
(4) [b]	40	215—217	6.84 s	6.38 q 8.52 t	—	2.38 t	*ca.* 2 [c]
(5)	47	173—174	—	7.09 q 8.68 t	—	3.58 [d]	*ca.* 2 [c]
(7b) [e]	78	[f]	7.04 s	6.62 q 8.64 t	4.10 d	2.13 d	14.6
(7c)	76	[g]	6.97 s	6.54 q 8.59 t	4.00 d	2.40 d	12.8

[a] 60 MHz, in [D_6]acetone with TMS internal; [b] in D_2O with sodium (trimethylsilyl)propanesulfonate internal; [c] $^3J_{D,H^2}$; [d] signal not resolved; [e] in $CDCl_3$; [f] 2,4,6-trinitrobenzenesulfonate m.p. 166 to 168 °C (dec.); [g] hexafluorophosphate m.p. 79 to 80 °C (dec.).

[*] Dr. H. Braun, A. Amann
Organisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

$<5\,\%$ of its *cis* isomer (NMR spectrum) as a yellow oil which gradually solidified. The hexafluorophosphate (yield 86 %) forms colorless crystals (from acetone/ether) which decompose between 79 and 80 °C.

Received: May 11, 1977 [Z 727b IE]
German version: Angew. Chem. *89*, 489 (1977)

CAS Registry numbers:
(1a), 62882-16-0; *(1b)*, 62882-18-2; *(2)*, 661-36-9; *(3a)*, 62882-20-6; *(3b)*, 62882-22-8; *(3b)*, hexafluorophosphate, 62882-23-9; *(4)*, 62882-25-1; *(5)*, 62882-27-3; *(6a)*, 811-51-8; *(6b)*, 930-69-8; *(6c)*, 26628-22-8; *trans-(7a)*, 56554-09-7; *cis-(7a)*, 56554-01-9; *trans-(7b)*, 62882-29-5; *cis-(7b)*, 62882-31-9; *trans-(7b)*, 2,4,6-trinitrobenzenesulfonate, 62882-32-0; *cis-(7b)*, 2,4,6-trinitrobenzenesulfonate, 62882-33-1; *trans-(7c)*, 62882-35-3; *cis-(7c)*, 62882-37-5; *trans-(7c)*, hexafluorophosphate, 62882-38-6; *cis-(7c)*, hexafluorophosphate, 62882-39-7

[1] *H. Braun, A. Amann, M. Richter*, Angew. Chem. *89*, 488 (1977); Angew. Chem. Int. Ed. Engl. *16*, 471 (1977).
[2] *F. E. Herkes, H. E. Simmons*, J. Org. Chem. *38*, 2845 (1973).
[3] *H. Braun, A. Amann*, unpublished.
[4] a) *H. Braun, A. Amann*, Angew. Chem. *87*, 773 (1975); Angew. Chem. Int. Ed. Engl. *14*, 755 (1975); b) *H. Braun, A. Amann*, Angew. Chem. *87*, 775 (1975); Angew. Chem. Int. Ed. Engl. *14*, 756 (1975).
[5] For a summary see: a) *B. M. Trost, L. S. Melvin* in *A. T. Blomquist, H. H. Wasserman*: Sulfur Ylides. Academic Press, New York 1975; b) *J. P. Marino* in *A. Senning*: Topics in Sulfur Chemistry. Thieme, Stuttgart 1976.
[6] *G. L'abbé*, Angew. Chem. *87*, 831 (1975); Angew. Chem. Int. Ed. Engl. *14*, 775 (1975), and references cited therein.

Lithium 7b*H*-Indeno[1,2,3-*jk*]fluorenide, an Organolithium Compound Having a "Sandwich" Structure[**]

By *Dieter Bladauski, Hans Dietrich, Hans-Jürgen Hecht*, and *Dieter Rewicki*[*]

Crystal structure studies have shown that alkyllithium compounds[1] exist in systems associated *via* electron-deficient bonds and containing Li atoms of coordination number ≥ 4. Amine[2] or ether complexes[3] of organolithium derivatives with resonance-stabilized carbanions, on the other hand, are composed of typical intimate ion pairs with ionic and covalent bonding contributions, the lithium lying in a trigonal environment made up of the carbanion π-base and the N and O basic centers.

We have now accomplished the first isolation of the lithium salt of a hydrocarbon exhibiting extreme charge delocalization in crystalline form, without any need for hetero atom bases as crystallization-promoting or stabilizing ligands. The ruby-red compound lithium 7b*H*-indeno[1,2,3-*jk*]fluorenide *(1)* slowly crystallizes on interdiffusion of dilute benzene solutions of 7b*H*-indeno[1,2,3-*jk*]fluorene and butyllithium and contains one half molecule of benzene per formula unit. X-Ray structure analysis[4] performed at $-160\,^{\circ}C$ revealed the structure shown in Figure 1.

The crystal lattice consists of isolated units containing two carbanions and two lithium ions each. The essentially planar

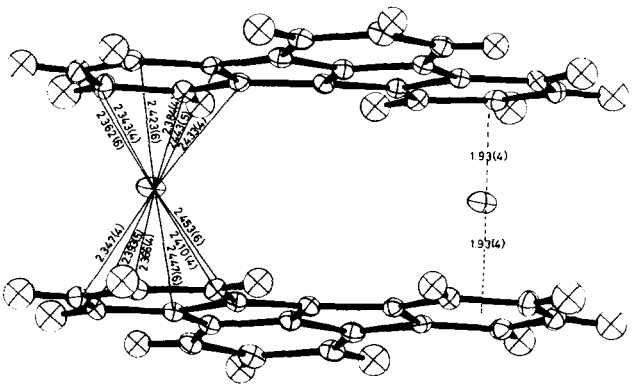


Fig. 1. Structure of the lithium salt *(1)*; *xy* projection of a section of the unit cell. The benzene molecules incorporated in the lattice are omitted for the sake of clarity.

carbanions[5] (mean deviation of the plane through the molecule: 0.04 Å) are mutually parallel and separated by 3.9 Å; the central six-membered rings are *anti* orientated. The lithium ions are coordinated in sandwich fashion with a pair of external six-membered rings. The distance between the lithium ion situated almost concentrically above the six-membered rings and the two rings is uniformly 1.93(4) Å, and the distance to the C atoms of the six-membered ring varies between 2.343(4) and 2.453(6) Å, having a mean value of 2.41(4) Å. The benzene incorporated into the lattice lies outside the coordination sphere of the lithium.

On comparison with the known structures of organolithium compounds, structure *(1)* is seen to have the following distinctive features: 1) This is the first case of lithium being present in *linear* coordination with two *hexahapto*-bonded six-membered ring ligands in the form of a bis(arene)metal type complex. The Li—C distances, which are only 0.25 Å longer on average than in alkyllithium compounds and correspond approximately to those in indenyllithium[2], as well as the short $Li^{\oplus}$—ring distance[6] show the "sandwich" structure to be a consequence of bonding interactions and not merely a packing phenomenon.—2) In contrast to the lithium compounds with resonance-stabilized carbanions examined so far[2] no preferred orientation of the lithium atoms on the C center of highest charge density can be detected in the case of *(1)*. On the basis of charge densities at the carbanion calculated by MO methods, the $Li^{\oplus}$ should be preferentially located over the five-membered rings. The observed position of the lithium can be interpreted by assuming that, given pronounced charge delocalization within the carbanions and in the absence of hetero atom bases, the structure of the lithium compound is largely determined by covalent interaction between the unoccupied atomic orbitals of lithium and the occupied molecular orbitals of the carbanion and to a lesser degree by electrostatic interactions.

Received: May 12, 1977 [Z 733 IE]
German version: Angew. Chem. *89*, 490 (1977)

CAS Registry numbers:
(1), 50888-67-0

[*] Dipl.-Chem. D. Bladauski, Dr. H.-J. Hecht, Prof. Dr. D. Rewicki [+]
Institut für Organische Chemie der Freien Universität
Thielallee 63—67, D-1000 Berlin 33 (Germany)
Prof. Dr. H. Dietrich
Fritz-Haber-Institut der Max-Planck-Gesellschaft
Faradayweg 4—6, D-1000 Berlin 33 (Germany)
[+] To whom correspondence should be addressed.

[**] Strained Alkyl-Aromatic Systems, Part 4. This work was supported by the Fonds der Chemischen Industrie.—Part 3: *P. Luger, Ch. Tuchscherer, M. Grosse, D. Rewicki*, Chem. Ber. *109*, 2596 (1976).

[1] *H. Dietrich*, Acta Crystallogr. *16*, 681 (1963); *E. Weiss, E. A. C. Lucken*, J. Organomet. Chem. *2*, 197 (1964); *R. Zerger, W. Rhine, G. Stucky*, J. Am. Chem. Soc. *96*, 6048 (1974).
[2] *W. E. Rhine, G. D. Stucky*, J. Am. Chem. Soc. 97, 737 (1975); and references cited therein.
[3] *D. Bladauski, D. Rewicki*, Chem. Ber., in press; *H. Dietrich, D. Rewicki*, unpublished work.
[4] Monoclinic space group $P2_1/a$; $a = 1114.2(7)$, $b = 1482.9(6)$, $c = 1008.1(4)$ pm, $\beta = 117.99(5)^{\circ}$; $Z = 4$. 8818 independent data recorded on an automatic single-crystal diffractometer (Siemens-AED) up to

$\theta = 40.0°$ with Zr-filtered $Mo_{K\gamma}$ radiation and corrected in the usual way. Refinemeut gave $R = 0.089$ after convergence of all parameters.

[5] Comparison of the ring strain of the carbanion with that of 7b*H*-indeno[1.2,3-*jk*]fluorene is considered elsewhere. See also *H. Dietrich, D. Bladauski, M. Grosse, K. Roth, D. Rewicki*, Chem. Ber. *108*, 1807 (1975).

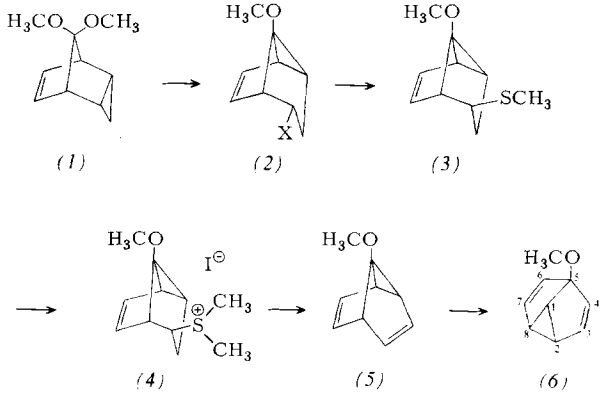
[6] Having a value of 1.93 Å this distance is considerably smaller than the sum of the van der Waals radius of an aromatic ring (*ca.* 1.7 Å) and the ionic radius of $Li^{\oplus}$ (0.68 Å). The shortening is comparable with that in bis(η-cyclopentadienyl)beryllium and -magnesium [*R. Schneider, E. O. Fischer*, Naturwissenschaften *50*, 349 (1963); *Ch. Wong, T. Lee, K. Chao, S. Lee*, Acta Crystallogr. *B28*, 1662 (1972)].

5-Methoxysemibullvalene

By *Reinhard W. Hoffmann, Norbert Hauel*, and *Fritz Frickel*[*]

Dedicated to Professor Burckhardt Helferich on the occasion of his 90th birthday

The equilibrium between the valence isomers of semibullvalene is influenced by substituents in the 1,5-positions[1]. In all the derivatives (alkyl, aryl, cyano) so far obtained, the 1-isomer predominates. However, a π-donor substituent is predicted to favor the 5-position[2]. We describe the synthesis of 5-methoxysemibullvalene *(6)*, the first donor-substituted semibullvalene.



(a), X = I; *(b)*, X = Br; *(c)*, X = Cl

Reaction of *(1)*[3] with an equimolar amount of AlX_3 (ether, 0 °C) led to *(2)* in 70 to 78 % yield[4]. $(C_2H_5)_2AlCl$ in refluxing ether gave 90 % of *(2c)*. The *endo*-position of the halogen in *(2)* follows from the coupling pattern of the CHX proton in the ^{1}H-NMR spectra. The absence of hydrogen *anti*-peri-planar to the halogen thwarted attempted E_2-eliminations (KOtBu, DMSO, 80 °C). Reaction of *(2a)* with an excess of sodium methanethiolate (DMF, 24 h, 25 °C) gave 80 % of crude *(3)*, which has been alkylated by an excess of methyl iodide to *(4)* (neat, 24 h, 25 °C, 71 %) (cf. Table 1).

Elimination of the axially positioned sulfonium group in *(4)* (KOtBu/DMSO, 1 h, 25 °C) proceeded smoothly to give > 70 % of a methoxysemibullvalene[5] (b.p. 19 °C/0.01 torr)[6]. The structure *(6)* rather than *(5)* is deduced from the ^{1}H-NMR-spectrum (CCl_4): $\tau = 4.5$ (d, $J = 4.6$ Hz, 4-H, 6-H); 5.0 (dd, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz, 3-H, 7-H); 6.7 (d, $J = 5$ Hz, 2-H, 8-H); 6.9 (s, OCH_3); 7.1 (t, $J = 5$ Hz, 1-H). ^{13}C-NMR ($CDCl_3$/TMS): δ = 51.43, d; 51.60, d; 52.41, q; 100.26, s; 120.26, d; 124.43, d. The ^{13}C-NMR spectrum (CF_2Cl_2) exhibited a broadening and a shift of the C-2, C-8 and the C-4, C-6 signals between −30 and −130 °C. This can be interpreted by assuming the presence of less than 10 % of *(5)* in the equilibrium. Hence the prediction[2] of *(6)* being favored in the equilibrium *(5)* ⇌ *(6)* is substantiated.

Table 1. Physical data of the new compounds.

(2a) [5], b.p. 44—46 °C/10^{-4} torr; ^{1}H-NMR (CCl_4): τ = 7.38—8.53 (m, 4H); 6.68 (s, 3H); 6.59 (broad d, $J = 5$ Hz, 1H); 5.58—5.95 (ddd, $J_1 = 11$ Hz, $J_2 = 7$ Hz, $J_3 = 5$ Hz, 1H); 4.29 (m, 2H).

(2b) [5], b.p. 28—31 °C/10^{-4} torr; ^{1}H-NMR (CCl_4): τ = 7.45—8.60 (m, 4H); 6.68 (s, 3H); 6.59 (broad d, $J = 5$ Hz, 1H); 5.50—5.81 (ddd, $J_1 = 10$ Hz, $J_2 = 7$ Hz, $J_3 = 5$ Hz, 1H); 4.26 (m, 2H).

(2c) [5], b.p. 86—89 °C/11 torr; ^{1}H-NMR ($CDCl_3$): τ = 7.46—8.58 (m, 4H); 6.66 (s, 3H); 6.54 (broad d, $J = 5$ Hz, 1H); 5.44—5.68 (ddd, $J_1 = 10$ Hz, $J_2 = 7.5$ Hz, $J_3 = 5.5$ Hz, 1H); 4.22 (m, 2H).

(3), ^{1}H-NMR (CCl_4): τ = 8.15 (m, 2H); 7.8—8.0 (m, 1H) with s (3H) at 7.96; 7.18 (m, 1H); 6.88 (m, 1H); 6.64 (s, 3H); 4.35—4.62 (m, 2H).

(4) [5], m.p. 136—137 °C (from ethanol/ether); ^{1}H-NMR (CCl_4): τ = 7.61—7.81 (m, 2H); 7.40—7.59 (m, 2H); 7.02 (s, 3H); 7.00 (s, 3H); 6.59 (s, 3H); 6.15—6.35 (m, 2H); 4.3 (dd, $J_1 = 5$ Hz, $J_2 = 3$ Hz, 1H); 4.08 (dd, $J_1 = 5$ Hz, $J_2 = 2$ Hz, 1H).

[*] Prof. Dr. R. W. Hoffmann, Dipl.-Chem. N. Hauel, Dr. F. Frickel
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

Received: May 2, 1977;
supplemented: May 16, 1977 [Z 735 IE]
German version: Angew. Chem. *89*, 491 (1977)

CAS Registry numbers:
(1), 14224-84-1; *(2a)*, 62962-12-3; *(2b)*, 62962-13-4; *(2c)*, 62962-14-5; *(3)*, 62962-15-6; *(4)*, 62962-16-7; *(5)*, 62962-17-8; *(6)*, 62962-18-9

[1] Cf. *D. R. James, G. H. Birnberg, L. A. Paquette*, J. Am. Chem. Soc. *96*, 7465 (1974); *L. A. Paquette, W. E. Volz, ibid. 98*, 2910 (1976).

[2] *M. J. S. Dewar, W. W. Schoeller*, J. Am. Chem. Soc. *93*, 1481 (1971); *R. Hoffmann, W. D. Stohrer*, J. Am. Chem. Soc. *93*, 6941 (1971); *M. J. S. Dewar, D. H. Lo*, J. Am. Chem. Soc. *93*, 7201 (1971).

[3] Cf. *R. Bicker, H. Kessler, A. Steigel*, Chem. Ber. *107*, 3053 (1974); and references quoted therein.

[4] This reaction has been independently discovered by *M. A. Battiste*, University of Florida, personal communication, July 1975.

[5] The substance yielded a correct CH-analysis.

[6] Reaction of *(2a)* with C_6H_5SeNa and *m*-chloroperbenzoic acid-induced oxidative elimination also led to the formation of *(6)*.

Synthesis and Chemistry of Alkylidenediaziridines

By *Gerrit L'abbé, Chih-Chou Yu*, and *Suzanne Toppet*[*]

Aziridinimines have been reported by *Quast*[1], but their valence isomers, alkylidenediaziridines, were hitherto unknown. We report here on their synthesis, thermal isomerization and behavior in cycloaddition reactions.

When ketenimines *(1a)* to *(1c)* are treated with methanesulfonyl azide at room temperature, evolution of nitrogen occurs and, as indicated by the ^{1}H-NMR spectra ($CDCl_3$) of the crude reaction mixtures, almost single products are obtained. These were isolated by careful crystallization from appropriate solvents (see Table 1) and identified as alkylidenediaziridines *(2a)* to *(2c)*[2] on the basis of:
molecular weight determination (osmometric);
^{1}H-NMR (non-equivalence of the alkylidene methyl groups with signals at δ = 1.7 and 1.8);
^{13}C-NMR spectra [olefinic carbon absorptions at δ = 98 (C-β) and 162 (C-α), Δδ = 64, which is characteristic for enediamines[3]].

The IR spectra (KBr) manifested absorptions at 1630 to 1650 cm^{-1}, which are unusually low for stretching vibrations of C=C bonds attached to three-membered rings[4a]; however, this is not without precedence[4b].

[*] Prof. Dr. G. L'abbé, Chih-Chou Yu, and Dr. Suzanne Toppet
Department of Chemistry, University of Leuven
Celestijnenlaan 200 F, B-3030 Heverlee (Belgium)

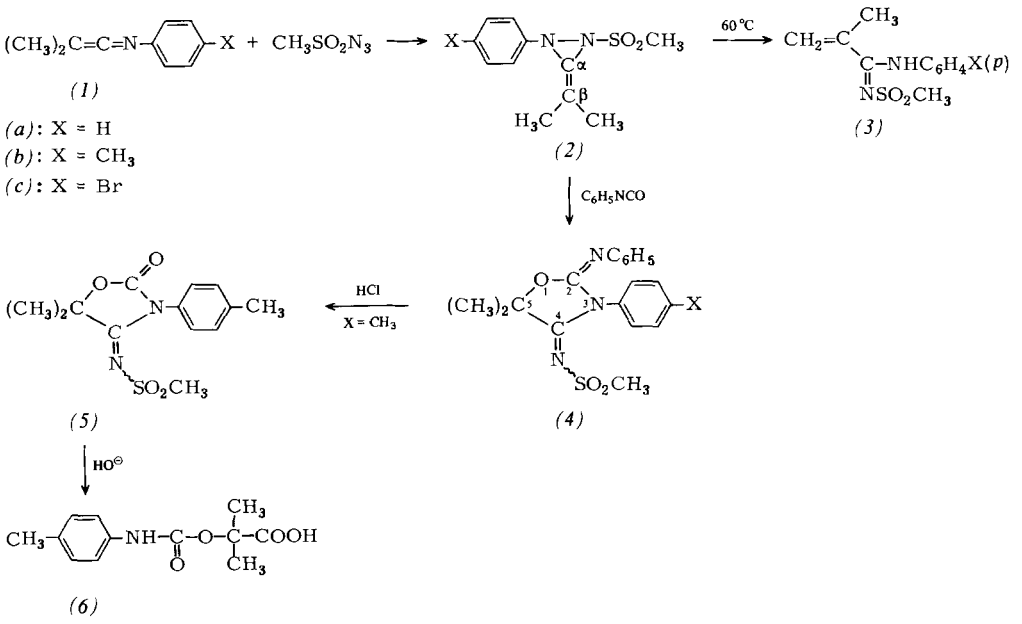


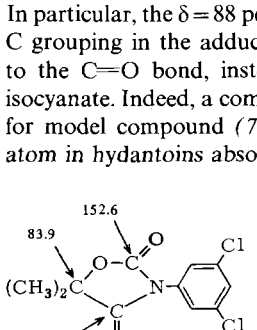
Table 1. Compounds synthesized.

	Yield [%]	Recrystallization solvent	M.p. [°C]	$M^{+\cdot}$ [calc/found]
(2a)	42	Carbon tetrachloride	82—83	238.0775/238.0781
(2b)	56	Carbon tetrachloride	93—94	252.0931/252.0904
(2c)	74	*n*-Hexane/chloroform	119—120	317.9859/317.9850
(3a)	78	Ether/chloroform	105—106	238.0774/238.0763
(3b)	84	Ether/petroleum ether	93—94	252.0931/252.0941
(3c)	≈100	Ether/chloroform	121—122	317.9859/317.9868
(4a)	64	Methanol	165—166	357.1145/357.1128
(4b)	70	*n*-Hexane/chloroform	192—193	371.1302/371.1322
(4c)	73	*n*-Hexane/chloroform	203—204	437.0228/437.0207
(5)	82	Methanol	190—191	296.0829/296.0807
(6)	24	Carbon tetrachloride	138—139	237.0999/237.0992

Compounds *(2a)* to *(2c)* underwent quantitative isomerization into methacrylic amidines *(3)* upon heating in chloroform for 2 to 3 days (see Table 1).

Whereas phenyl isothiocyanate, *tert*-butyl isothiocyanate, dicyclohexylcarbodiimide, acetonitrile, and benzonitrile were unreactive towards *(2)*, phenyl isocyanate reacted readily at room temperature to give the oxazolidinimines *(4a)* to *(4c)* in good yields (Table 1).

The IR spectra (KBr) of *(4)* showed characteristic imine bands at 1700 to 1710[5] and 1600 cm^{-1}, while the NMR spectra indicated the presence of two equivalent methyl groups (at $\delta = 1.95$ in the ^{1}H-NMR and at $\delta = 25$ in the ^{13}C-NMR). The ring carbon absorptions were found at $\delta = 147$ (C-2), 168 (C-4) and 88 (C-5) in the ^{13}C-NMR spectra ($CDCl_3$). In particular, the $\delta = 88$ peak reveals the presence of a O—C—C grouping in the adducts, meaning that addition occurred to the C=O bond, instead of the C=N bond, of phenyl isocyanate. Indeed, a comparable absorption value was found for model compound *(7)*[6], whereas the corresponding C-atom in hydantoins absorb at about $\delta = 60$ ppm[7].



(7) [6]

In further accord with its structure, *(4b)* underwent acid hydrolysis in ethanol at room temperature to yield *(5)* in 82% yield. Its identification was based on IR (1795, 1625 cm^{-1})[5], ^{13}C-NMR [$\delta = 153$ (C-2), 86.4 (C-5); comparable with those in model *(7)*], and also on its expected[8] conversion into the urethane *(6)* upon basic hydrolysis in 20% methanolic potassium hydroxide.

Experimental

Synthesis of *(2a)* to *(2c)*: The ketenimine *(1)* was treated with a five-fold excess of methanesulfonyl azide at room temperature until gas evolution ceased (1 to 2 days). The excess of azide was then distilled off under reduced pressure at room temperature and the crude products were crystallized from CCl_4 [*(2a)* and *(2b)*] or *n*-hexane/ether *(2c)*.

Cycloadditions: A mixture of *(2)* and a ten-fold excess of phenyl isocyanate was stirred at room temperature for 2 to 3 days. Then the excess of isocyanate was removed *in vacuo* and the residue crystallized from the appropriate solvent (see Table 1).

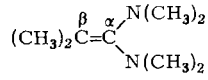
Received: May 9, 1977 [Z 738 IE]
German version: Angew. Chem. 89, 492 (1977)

CAS Registry numbers:
(1a), 14016-34-3; *(1b)*, 18779-86-7; *(1c)*, 62962-26-9; *(2a)*, 62962-27-0; *(2b)*, 62962-28-1; *(2c)*, 62962-29-2; *(3a)*, 62962-30-5; *(3b)*, 62962-31-6; *(3c)*, 62962-32-7; *(4a)*, 62962-33-8; *(4b)*, 62962-34-9; *(4c)*, 62962-35-0; *(5)*, 62962-36-1; *(6)*, 62962-37-2; methanesulfonyl azide, 1516-70-7; phenyl isocyanate, 103-71-9

[1] *H. Quast, E. Schmitt*, Angew. Chem. *82*, 395 (1970); Angew. Chem. Int. Ed. Engl. *9*, 381 (1970); *H. Quast, L. Bieber*, Angew. Chem. *87*, 422 (1975); Angew. Chem. Int. Ed. Engl. *14*, 428 (1975); *H. Quast, P. Schäfer*, Tetrahedron Lett. *1977*, 1057.

[2] The formation of *(2a)*—*(2c)* is rationalized by 1,3-dipolar cycloaddition of the azide to the C=C and/or C=N bond of the ketenimines to give sulfonyl-substituted adducts which are expected to be unstable and lose nitrogen, yielding *(2)*.

[3] Compound *(8)* exhibits ^{13}C-NMR absorptions ($CDCl_3$) at $\delta = 96$ (C-β) and 150 (C-α).



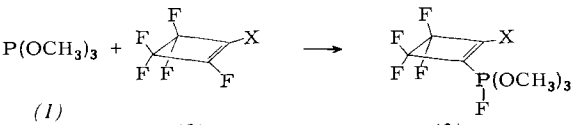
(8)

[4] a) Alkylideneaziridines, for instance, have been reported to absorb at 1770 to 1792 cm^{-1} in the IR spectra; see *M. G. Ettlinger, F. Kennedy*, Chem. Ind. (London) *1956*, 166; *A. T. Bottini, J. D. Roberts*, J. Am. Chem. Soc. *79*, 1462 (1957); *H. Quast, W. Risler*, Angew. Chem. *85*, 411 (1973); Angew. Chem. Int. Ed. Engl. *12*, 414 (1973).—b) No high C=C stretching absorptions have been reported for ring ethoxycarbonyl substituted alkylidenecyclopropanes and alkylideneaziridines; see *J. Meinwald, J. W. Wheeler, A. A. Nimetz, J. S. Liu*, J. Org. Chem. *30*, 1038 (1965); *J. K. Crandall, W. W. Conover, J. B. Komin*, J. Org. Chem. *40*, 2042 (1975); M. Vidal, A. Dussauge, M. Vincens, Tetrahedron Lett. *1977*, 313; *E. M. Bingham, J. C. Gilbert*, J. Org. Chem. *40*, 224 (1975).
[5] *C. J. Wilkerson, F. D. Greene*, J. Org. Chem. *40*, 3112 (1975).
[6] This compound is a commercial fungicide, see Chem. Abstr. *71*, 101838a (1969). —The numbers linked to the formula by arrows are the δ values of the ^{13}C-NMR signals recorded in [D_6]-dimethyl sulfoxide.
[7] *L. F. Johnson, W. C. Jankowski*: Carbon-13 NMR Spectra. A Collection of Assigned, Coded and Indexed Spectra. Wiley, New York 1972, spectrum number 178.
[8] *H. Rollema, A. Westerbrink*, Pharm. Weekbl. *107*, 652 (1972); Chem. Abstr. *78*, 7869j (1973).

Phosphoranes as Intermediates in the Michaelis-Arbusov Reaction[**]

By *Gert Bauer* and *Gerhard Hägele*[*]

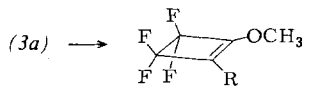
The Michaelis-Arbusov reaction is generally considered to proceed *via* an intermediary phosphonium ion[1]. There is only little evidence quoted in the literature which would indicate that phosphoranes are also possible intermediates[2]. We have now been able to prepare the first cyclobutenyl(fluoro)trimethoxyphosphoranes *(3)* in pure form and in almost quantitative yields from trimethyl phosphite and 1-halo(pentafluoro)-cyclobutenes.



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

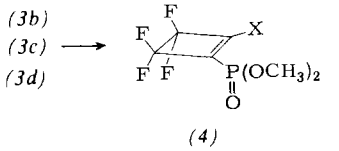
(a): X = F; *(b)*: X = Cl; *(c)*: X = Br; *(d)*: X = I

While the pure phosphoranes *(3)* are relatively stable at temperatures around 0 °C, heating or, surprisingly, dissolution in methylene chloride induces autogenic decomposition reactions: *(3a)* does not furnish the expected Michaelis-Arbusov product *(4a)*, but the compounds *(5a)* to *(5g)*.



(5e): R = P(O)$(OCH_3)_2$
(5f): R = P(O)(OCH_3)F
(5g): R = P(O)F_2

Compounds *(3b)* to *(3d)*, on the other hand, afford the desired dimethyl phosphonates *(4)*.



(4)

Secondary reactions[3] of the phosphonic acid esters of type *(4)* prepared here for the first time, show that the P(O)$(OCH_3)_2$ group activates the vinylically bonded halogen.

The structures and purity of compounds *(3)* to *(5)* have been confirmed by elemental analyses and NMR spectra (Table 1), and in the case of *(4)* and *(5)* also by chromatography and mass spectra.

Procedures

(2-Chloro-3,3,4,4-tetrafluorocyclobuten-1-yl)(trimethoxy)-fluorophosphorane *(3b)*:*(2b)* (8.9 g, 0.05 mol) is dissolved in ether under anhydrous nitrogen and treated dropwise with 6.2 g (0.05 mol) *(1)*. After the exothermic reaction has subsided the solution is heated under reflux for 1 h. After removal of volatile components by distillation at 30 °C/0.05 torr there remains 15 g (almost quantitative yield) of *(3b)* as a pure, colorless liquid.

Dimethyl 2-chloro-3,3,4,4-tetrafluorocyclobuten-1-ylphosphonate *(4b)*: 12.1 g (0.04 mol) of *(3b)* is dissolved in 200 ml CH_2Cl_2. After evolution of gas has subsided the solution is allowed to stand for 30 min at room temperature and then heated under reflux for 10 min. Subsequent fractional distillation affords 6.45 g (60%) of *(4b)* as a colorless liquid, b.p. 48 °C/0.02 torr, $n_D^{25} = 1.4022$.

Table 1. NMR data of compounds *(3b)* and *(4b)* [a].

Chemical shifts [b]	δ_P	$\delta_{F(1,2)}$	$\delta_{F(3,4)}$	$\delta_{F(PF)}$	δ_H					
(3b)	−72.82	49.736	45.539	87.50	3.730					
(4b)	0.11	50.810	45.918	—	3.875					
Coupling constants [c]	$^1J_{PF}$	$^3J_{PF}$	$^4J_{PF}$	$^2J_{FF}(1,2)$	$^2J_{FF}(3,4)$	$^2J_{FF}^{cis}$	$^3J_{FF}^{trans}$	$^4J_{FF}$	$^4J_{FH}$	$^3J_{PH}$
(3b)	−845	∓ 73.88	± 12.59	195.27	190.23	−14.59	25.96	0.7	1.81	15.13
(4b)	–	∓ 4.86	± 12.24	197.04	196.41	−12.57	27.28	–	—	11.67

[a] *(3b)* as saturated solution in ligroin (b.p. 40 to 60 °C); *(4b)*: 50 vol.-% in CCl_4. [b] δ_P against 85% H_3PO_4; δ_F against C_6F_6; δ_H against TMS. [c] *J* values in Hz.

[*] Prof. Dr. G. Hägele, Dr. G. Bauer
Institut für Anorganische Chemie und Strukturchemie der Universität Universitätsstrasse 1, D-4000 Düsseldorf (Germany)

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

Received: May 17, 1977 [Z 739 IE]
German version: Angew. Chem. *89*, 493 (1977)

CAS Registry numbers:
(1), 121-45-9; *(2a)*, 697-11-0; *(2b)*, 377-94-6; *(2c)*, 697-08-5; *(2d)*, 33021-45-3; *(3a)*, 62962-19-0; *(3b)*, 62962-20-3; *(3c)*, 62962-21-4; *(3d)*, 62962-22-5; *(4b)*, 62990-99-2; *(4c)*, 62962-08-7; *(4d)*, 62962-09-8; *(5e)*, 23466-21-9; *(5f)*, 62962-10-1; *(5g)*, 62962-11-2

[1] *Houben-Weyl:* Methoden der Organischen Chemie. Thieme, Stuttgart 1964, Vol. 12/1, p. 433; Vol. 12/2, p. 80; *Kosolapoff-Maier:* Organo-Phosphorus Compounds. Wiley, New York 1972, Vol. 7, p. 23, and references cited therein.

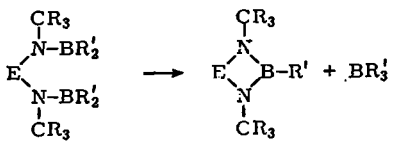
[2] *I. L. Knunyants, V. V. Tyuleva, E. Ya. Pervova, R. N. Sterlin*, Izv. Akad. Nauk SSSR, Ser. Khim. *1964*, 1797; Bull. Akad. Sci. USSR *1964*, 1705; Chem. Abstr. *62*, 2791 d (1965).

[3] *G. Bauer*, Dissertation, Universität Düsseldorf 1977.

New Pathways to Four-Membered Boron-Nitrogen Heterocycles

By *Wolfgang Storch, Wolfgang Jackstiess, Heinrich Nöth*, and *Gerhard Winter*[*]

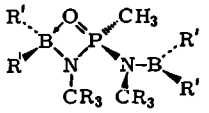
Condensation of boron-nitrogen compounds preferentially affords the borazine ring system[1], ring closure being preceded by linkage of B—N chains[2]. Similar observations are made on formation of heteroborazines[3]. Thermolysis of borylaminoelement compounds of type *(1)*[4] $E[NCH_3—B(CH_3)_2]_2$ *(1)*, with $E=CH_3P, C_6H_5P, CH_3(S)P, (CH_3)_2Si, CH_3B, C_6H_5B$, yields trimethylborane, oligomeric and/or polymeric iminoelement compounds $(ENCH_3)_n$, as well as derivatives of borazine and heteroborazines. In contrast, only the hydrolysis- and oxidation sensitive diazaboretidines *(2)*[5] are obtained if intermolecular condensation is hindered by introduction of the bulky *tert*-butyl group in place of the CH_3 group on the N atoms of *(1)*. Yields and characteristic data of selected compounds are listed in Table 1.



(3) *(2)* (a)

R = CH_3

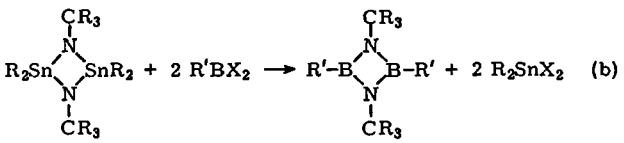
Starting compounds of type *(3)* are accessible by reaction of the corresponding *N*-lithio derivatives of the diamines $E(NHCR_3)_2$ with R'_2BX (X = Cl, Br, R' = CH_3, C_2H_5; X = R' = F). Their thermal stability is determined by the nature of the element E and the migrational tendency of the substituent R'. Thus compounds *(3)* having $E=(CH_3)_2Si$, CH_3P, or $CH_3(S)P$ and $R'=CH_3$ are unstable at room temperature. Accordingly, their attempted preparation merely affords *(2a)*, *(2b)*, or *(2c)*. When $R'=C_2H_5$, the threshold of BR'_3 elimination rises to 70 to 75 °C. Compound *(3)* with $E=CH_3(O)P$ and $R'=CH_3$ is particularly stable, owing to intramolecular B—O coordination as shown in *(4)*, which has been confirmed by NMR spectroscopy.



(4)

Unlike the reaction of $E[N(Li)C(CH_3)_3]_2$ with R_2BX, that with RBX_2 or BX_3 generally gives difficultly separable mixtures, even when performed at −70 °C. The reason lies in the cleavage of Si—N or P—N bonds by the boron halides, which competes with LiX formation.

Diazadiboretidines[6] cannot be obtained by reaction (a) since the corresponding bis(borylamino)boranes *(3)*, E = RB, have not yet been prepared. On the other hand, reaction of boron halides RBX_2 and BX_3 with the diazadistannetidines



(5) *(6)* (b)

R = CH_3

(5) according to (b) leads, even under mild conditions, to the diazadiboretidines *(6)*, which are extremely sensitive to hydrolysis and oxidation.

This reaction also permitted the first preparation of compounds functionalized at the boron atom (*e.g. (6b)* with R' = Cl). Difficulties encountered in the removal of tin halides also formed in the reaction preclude any increase in yield over 75 %, in spite of quantitative reaction. The reactant *(5)* is obtained by treatment of $(CH_3)_2SnBr_2$ with $LiHNC(CH_3)_3$ in the ratio of 1:2 and subsequent elimination of H_2NCR_3 from the resulting $R_2Sn(NHCR_3)_2$ at 100 °C[7].

Table 1. Physical properties of some compounds of types *(2)* and *(6)*.

	E	R'	Yield [%]	B.p. [°C/torr]	δ(¹¹B) [a]	δ(¹⁴N) [a]	δ(³¹P) [a]
(2a)	$(CH_3)_2Si$	CH_3	75	27/10^{-2}	36.4	−263	—
(2b)	CH_3P	CH_3	64	40–42/10^{-2}	33.7	−271	126.6
(2c)	$CH_3(S)P$	CH_3	86	78–80/10^{-2}	36.5	−267	87.1
(2d)	$CH_3(S)P$	F	93	55/10^{-2}	20.1	—	71.8
(2e)	$CH_3(S)P$	C_2H_5	83	72–75/10^{-2}	37.2	−269	87.3
(2f)	$CH_3(O)P$	CH_3	78	65/0.3	34.8	−240	34.5
(6a)	CH_3B	CH_3	58	80/10^{-2} [b]	38.5	−267	—
(6b)	Cl—B	Cl	75	85/10^{-2} [b]	31.5	—	—

[a] A positive sign denotes a downfield shift relative to the standard [$BF_3 \cdot O(C_2H_5)_2$; saturated aqueous $NaNO_3$ solution; 85 % H_3PO_4; all external]. [b] Sublimation.

[*] Prof. Dr. H. Nöth, Dr. W. Storch, W. Jackstiess, G. Winter
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

Experimental

1,3-Di-*tert*-butyl-2,4-dimethyl-1,3,2λ^5,4-diazaphosphaboretidine 4-oxide *(2f)*: *(3f)* (2.9 g, 10 mmol) is heated to 160 to 170 °C for 5 h in a slow current of N_2. $B(CH_3)_3$ (0.5 g, 90 %) ($\delta^{11}B$: −86.3; ref. [1]: −86.5) condenses in a cold trap at −78 °C. Only *(2f)* can be detected in the residue by NMR spectroscopy. Distillation at 65 °C/0.3 torr afforded *(2f)* (1.8 g, 78 %) as a colorless liquid which forms needle-like crystals (m.p. 53 to 55 °C).

1,3-Di-*tert*-butyl-2,4-dimethyl-1,3,2,4-diazadiboretidine *(6a)*: CH_3BBr_2 (4.1 ml, 43 mmol) in CH_2Cl_2 (10 ml) is slowly added dropwise to a stirred solution of *(5)* (9.5 g, 22 mmol) in CH_2Cl_2 (15 ml) at −65 °C. The reaction mixture is warmed up and heated under reflux for 2 h; all volatiles are then removed *in vacuo* and the residue fractionated by sublimation. $(CH_3)_2SnBr_2$ (12 g, 90 %) sublimed at 30 to 65 °C (oil-bath temperature)/10^{-2} torr, and *(6a)* (2.5 g, 67 %) between 80 and 100 °C/10^{-2} torr. The colorless crystals of *(6a)* are freed from traces of $(CH_3)_2SnBr_2$ by resubliming twice.

Received: May 4, 1977 [Z 729 IE]
German version: Angew. Chem. 89, 494 (1977)

CAS Registry numbers:
(2a), 62948-94-1; *(2b)*, 62948-93-0; *(2c)*, 62948-92-9; *(2d)*, 62948-91-8; *(2e)*, 62948-90-7; *(2f)*, 62948-89-4; *(3a)*, 62962-44-1; *(3b)*, 62948-88-3; *(3c)*, 62948-87-2; *(3d)*, 62948-86-1; *(3e)*, 62948-85-0; *(3f)*, 62948-84-9; *(5)*, 62948-83-8; *(6a)*, 62948-82-7; *(6b)*, 62948-81-6; CH_3BBr_2, 17933-16-3; $ClBBr_2$, 13709-71-2

[1] Gmelins Handbuch der Anorganischen Chemie, Supplement to 8th Edition, Vol. 22. Springer-Verlag, Heidelberg 1975.

[2] *K. Niedenzu, K. E. Blick, J. Boehnig*, Z. Anorg. Allg. Chem. *387*, 107 (1972); *P. Fritz, K. Niedenzu, W. Dawson*, Inorg. Chem. *4*, 886 (1965).

[3] *J. Geisler, H. Nöth*, Chem. Ber. *103*, 2234 (1970); *H. Nöth, M. J. Sprague*, J. Organomet. Chem. *23*, 323 (1970); *H. Nöth, W. Tinhof*, Chem. Ber. *108*, 3109 (1975).

[4] *W. Storch*, part of a lecture at the IIIrd International Meeting on Boron Chemistry, Ettal, July 1976.

[5] A siladiazaboretidine was first reported by *W. Fink*, Chem. Ber. *96*, 1071 (1963), and λ^3-phosphadiazaboretidines by *E. Niecke, W. Bitter*, Angew. Chem. *87*, 34 (1975); Angew. Chem. Int. Ed. Engl. *14*, 56 (1975).

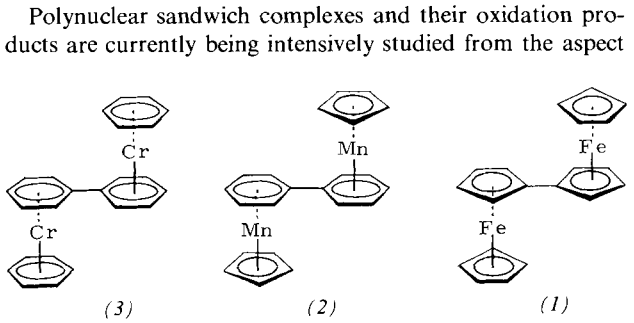
[6] *M. F. Lappert, M. K. Majumdar*, Adv. Chem. Ser. *42*, 208 (1964); *P. Geymayer, E. G. Rochow, U. Wannagat*, Angew. Chem. *76*, 499 (1964); Angew. Chem. Int. Ed. Engl. *3*, 633 (1964); *P. J. Paetzold, P. P. Habereder, G. Maier, M. Sandner*, Fortschr. Chem. Forsch. *8*, 437 (1967).

[7] Diazadistannetidines were first prepared in this way by *D. Hänssgen, J. Pohl*, Angew. Chem. *86*, 676 (1974); Angew. Chem. Int. Ed. Engl. *13*, 607 (1974).

μ-(η-Biphenyl)-bis[(η-benzene)chromium(0)], the Arenechromium Analog of Biferrocene[**]

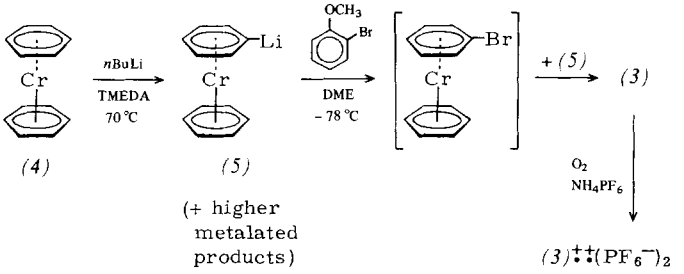
By *Christoph Elschenbroich* and *Jürgen Heck*[*]

Polynuclear sandwich complexes and their oxidation products are currently being intensively studied from the aspect of interactions in systems containing mixed oxidation states[1]. As opposed to such compounds in the bis(η-cyclopentadienyl)- and (η-cyclopentadienyl)(η-arene) series, *(1)*[2] and *(2)*[3], no corresponding representative of the bis(η-arene)metal type has so far been reported[4].



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

We have now synthesized μ-(η-biphenyl)-bis[(η-benzene)-chromium(0)] *(3)* by reaction of lithiated[5] bis(η-benzene)-chromium with *o*-bromoanisole.



Complex *(3)* [orange-brown, microcrystalline from toluene, m.p. 285—287 °C (dec.)], the composition of which was confirmed analytically as $C_{24}H_{22}Cr_2$, is moderately soluble in benzene and cyclohexane, sparingly soluble in ethers and is sublimable at 170 °C/10^{-4} torr.

Spectroscopic and physical data of *(3)* and *(3)*‡‡.
(3), MS (70 eV): m/e = 414 (4 %; M^+), 284 (21 %; $C_{12}H_{10}CrC_6H_6^+$), 206 (20 %; $C_{12}H_{10}Cr^+$), 154 (77 %; $C_{12}H_{10}^+$), 130 (3 %; $C_6H_5Cr^+$), 78 (100 %; $C_6H_6^+$), 52 (59 %; Cr^+).—Field ionization: 208 (14 %; $[M+2H]^{2+}$), 207 (100 %; M^{2+}), 205 (9 %; $[M-4H]^{2+}$).
(3), ^{1}H-NMR ([D$_8$]toluene): δ = 4.87, 4.32, 4.15 (η-$C_{12}H_{10}$); 4.10 (η-C_6H_6).
(3), Polarography (10^{-4} M in CH_3CN, 0.1 M Et_4NBF_4): $E_{1/2}$ = −0.82, −0.37 V (against Ag/AgCl electrode).
(3)‡‡, ESR (THF, +25 °C): $\langle g \rangle$ = 1.9872; a(11 ^{1}H) = 3.27 G.

Air oxidation of *(3)* leads to formation of the dication *(3)*‡‡, which can be isolated as the bis-hexafluorophosphate *(3)*‡‡$(PF_6^-)_2$. The ESR spectrum of *(3)*‡‡ in solution is characteristic for a diradical, since hyperfine splitting by eleven protons, equivalent within the resolution attained, is observed. An interaction between the two halves of the molecule, to which we assign a *trans* configuration in analogy to the structures of biferrocene[6] and μ-(η-biphenyl)-bis(tricarbonylchromium)[7], manifests itself in the polarogram:

$$(3) \xrightarrow[-e^-]{(E_{1/2})_1 = -0.82\ V} (3)^{\ddagger} \xrightarrow[-e^-]{(E_{1/2})_2 = -0.37\ V} (3)^{\ddagger\ddagger}$$

The separation $\Delta E_{1/2}$ = 0.45 V between the two oxidation waves is similar to that of the biferrocene system ($\Delta E_{1/2}$ = 0.33 V[8]). Consistent with the electron-donor character of the (η-C_6H_6)Cr(η-C_6H_5) moiety, mono-oxidation of *(3)* occurs at a potential more negative than that of (η-C_6H_6)$_2$Cr ($E_{1/2}$ = −0.76 V[9]). The second oxidation step, on the other hand, requires a substantially more positive potential, since the positive charge in *(3)*‡ renders the removal of a further electron more difficult.

Procedure

(4) (4.04 g, 19.4 mmol) is lithiated with *n*-butyllithium (40 mmol, 26.6 ml of a 1.55 M solution in hexane) in the presence of 6.15 ml (40 mmol) *N,N,N',N'*-tetramethylethylenediamine (TMEDA) over 24 h at 70 °C. The red solution of the metalation product obtained on addition of 250 ml dimethoxyethane (DME) is cooled to −78 °C and slowly (6h) treated with a solution of *o*-bromoanisole (2.2 ml, 17.5 mmol)

[*] Prof. Dr. Ch. Elschenbroich, J. Heck
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

[**] Metal π-Complexes of Benzene Derivatives, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 6: *Ch. Elschenbroich, F. Gerson*, J. Am. Chem. Soc. 97, 3556 (1975).

in DME (140 ml). After warming to 0°C and hydrolysis with 2 ml H_2O the solution is evaporated to dryness. The residue is taken up in a toluene/methanol/water mixture (1:1:1) and oxidized by passage of a stream of air. The orange-red aqueous solution is covered with a layer of benzene, treated with 25 g each of $Na_2S_2O_4$ and KOH, and stirred for 2 h. For separation of higher substitution products the brown benzene phase is concentrated to 100 ml and chromatographed on Al_2O_3/10 % H_2O (2.5 × 25 cm column) with toluene/THF (9:1). The solvent of the eluate is removed and the residue fractionally sublimed in a temperature gradient (Cu mantle 2 × 45 cm, bath temperature 180°C, 10^{-4} torr). Compound *(3)* is obtained as the lowermost red-brown zone and can be recrystallized from toluene. Yield *ca.* 200 mg (5 %).

Received: May 9, 1977 [Z 731 IE]
German version: Angew. Chem. *89*, 497 (1977)

CAS Registry numbers:
(3), 62962-47-4; $(3)^+$, 62990-76-5; $(3)^{++}$, 62962-46-3; *(4)*, 1271-54-1; *o*-bromoanisole, 578-57-4

[1] *C. LeVanda, K. Bechgaard, D. O. Cowan, U. T. Mueller-Westerhoff, P. Eilbracht, G. Candela, R. L. Collins*, J. Am. Chem. Soc. *98*, 3181 (1976); *W. H. Morrison, D. N. Hendrickson*, Inorg. Chem. *14*, 2331 (1975).
[2] *M. D. Rausch*, J. Org. Chem. *26*, 1802 (1961).
[3] *E. O. Fischer, S. Breitschaft*, Chem. Ber. *99*, 2213 (1966).
[4] Mass spectrometric findings suggest the presence of the complex

$(\eta\text{-}C_6F_6)Cr\text{-}\mu\text{-}(\eta\text{-}C_6H_5C_6F_5)Cr(\eta\text{-}C_6H_6)$

in the product of reaction of $(\eta\text{-}C_6F_6)(\eta\text{-}C_6H_6)Cr^0$ with tBuLi. (M^+ not observed however): *M. J. McGlinchey, T. S. Tan*, J. Am. Chem. Soc. *98*, 2271 (1976); *Zaitseva et al.* synthesized the dinuclear complex

$\mu\text{-}[\eta\text{-}C_6H_5(CH_2)_4\text{-}\eta\text{-}C_6H_5]\text{-}\{[C_6H_5(CH_2)_4\text{-}\eta\text{-}C_6H_5]Cr\}_2$

in which the two sandwich complex units are linked *via* tetramethylene bridges: *A. N. Nesmeyanov, N. N. Zaitseva, G. A. Domrachev, V. D. Zinov'ev, L. P. Yur'eva, I. I. Tverdokhlebova*, J. Organomet. Chem. *121*, C52 (1976).
[5] *Ch. Elschenbroich*, J. Organomet. Chem. *14*, 157 (1968).
[6] *A. C. MacDonald, J. Trotter*, Acta Crystallogr. *17*, 872 (1964).
[7] *P. Corradini, G. Allegra*, J. Am. Chem. Soc. *82*, 2075 (1960).
[8] *W. H. Morrison Jr., S. Krogsrud, D. N. Hendrickson*, Inorg. Chem. *12*, 1998 (1973).
[9] *A. A. Vlček*, Z. Anorg. Allg. Chem. *304*, 109 (1960).

Synthesis and Properties of Tris(trimethylsilyl)aluminum[**]

By *Lutz Rösch*[*]

Attempts to synthesize tris(trimethylsilyl)aluminum have so far merely led to isolation of cleavage products (polysilanes and methylaluminum compounds) from whose occurrence the intermediary formation of silylaluminum compounds was postulated[1].

We have now been able to synthesize tris(trimethylsilyl)aluminum *(1)* in *ca.* 90 % yield.

The crystalline product ignites spontaneously in air. Its NMR spectrum shows in addition to the signal of the coordinated tetrahydrofuran (THF) only one sharp signal in the neighborhood of the tetramethylsilane signal. On decomposition with H_2O or D_2O trimethylsilane or trimethyldeuteriosilane, respectively, are formed. The given composition was confirmed by elemental analysis and by the mass spectrum. The latter shows the signal for the molecular ion along with the expected isotopic splitting as well signals for the expected fragmentation products.

$$3\ Hg[Si(CH_3)_3]_2 + 2\ Al \xrightarrow{\text{Pentane/THF}} 2\ Al[Si(CH_3)_3]_3 \cdot THF + 3\ Hg$$

(1)

Compound *(1)* is not very stable thermally; it already begins to decompose at *ca.* 50°C with formation of polysilanes and methylaluminum compounds. Those products would indicate that dimethylsilanediyl is formed in the decomposition.

The vibrational spectra show two bands (both in the IR as well as in the Raman spectrum) in the region where AlSi stretching vibrations are expected to appear. From their intensities these are assigned to the symmetrical and the asymmetrical vibrations [$\nu_{as}AlSi_3$: IR 416 cm^{-1} (m), R 418 cm^{-1} (0); ν_sAlSi_3: IR 360 cm^{-1} (w), R 362 cm^{-1} *(2)*]. It follows that the $AlSi_3$ group has a trigonal pyramidal structure, as would be expected in view of the coordination with THF.

Attempts to prepare base-free tris(trimethylsilyl)aluminum have so far failed. On the other hand, it is possible to replace THF by other donors, *e.g.* phosphanes. Thus, the adduct *(2)* with tris(trimethylsilyl)phosphane can be obtained by suitable modification of the experimental conditions.

$$[(CH_3)_3Si]_3Al \cdot P[Si(CH_3)_3]_3 \quad (2)$$

This compound is also colorless and crystalline, and is formed in *ca.* 90 % yield. It formally possesses three positively polarized trimethylsilyl groups on the phosphorus and three negatively polarized such groups on the aluminum. The difference in character of the silyl groups is confirmed by the vibrational spectrum, which displays two pairs of SiC stretching vibrations. The ^{1}H-NMR spectrum shows a doublet for the trimethylsilyl groups bound to phosphorus $^3J_{HCSiP}$ 5.2 Hz and a singlet for those bound to aluminum in the correct ratio. We conclude from the above findings that no exchange takes place between the silyl groups on the phosphorus and those on the aluminum. Consistent with this conclusion, both trimethylsilane as well as hexamethyldisiloxane are formed on hydrolysis with water.

Procedure

All operations should be carried out under oxygen in the absence of air and moisture.

(1): A solution of sublimed $(Me_3Si)_2Hg$ *(5 g)* in pentane (50 ml) and THF (2 ml) is stirred together with aluminum powder *(5 g)* until disappearance of the yellow-green color can be observed (*ca.* 24 h). The solution is filtered through a glass frit and the readily volatile components removed by evaporation in an oil-pump vacuum at room temperature. The residue is recrystallized twice from a small amount of pentane at −78°C. 2.7 g (90 %) $Al[Si(CH_3)_3]_3 \cdot THF$ is obtained as a white crystalline powder.

(2): A mixture of 2.5 g $(Me_3Si)_2Hg$, 3 g aluminum powder and 1.3 g $(Me_3Si)_3P$ in 50 ml pentane is treated in the same way as described for *(1)*. After *ca.* 3 d, 2.1 g of the phosphane adduct (88 %) *(2)* is obtained as a white crystalline powder, m.p. ≈60°C (dec).

Received: May 10, 1977 [Z 732 IE]
German version: Angew. Chem. *89*, 497 (1977)

CAS Registry numbers:
(1), 62962-49-6; *(2)*, 62962-48-5; $(Me_3Si)_2Hg$, 4656-04-6

[*] Dr. L. Rösch
Institut für Anorganische und Analytische Chemie
der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. We thank Prof. *J. Müller* for recording the mass spectrum.

[1] *E. Wiberg, O. Stecher, H.-J. Andrascheck, L. Kreuzbichler, E. Staude*, Angew. Chem. *75*, 516 (1963); Angew. Chem. Int. Ed. Engl. *2*, 507 (1963).

Reaction of Dicyanocobyrinic Heptamethyl Ester with Ascorbic Acid[**]

By *Albert Gossauer, Burghard Grüning, Ludger Ernst, Wulf Becker*, and *William S. Sheldrick*[*]

Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday

Most reactions of cyanocobalamin (vitamin B_{12}) which proceed with alteration of the oxidation state of the complex-bonded cobalt ion are accompanied by the formation of by-products which are called stable yellow corrinoids[1]. Despite numerous attempts, it has not previously proved possible to elucidate the structure of these compounds. Owing to the biological (metabolism of the vitamin B_{12}-coenzyme in the living cell) and pharmacological interest (incompatibility of cyanocobalamin and vitamin C in mixtures of vitamins), we have investigated the formation of such pigments by treating dicyanocobyrinic heptamethyl ester *(1)*[2] with ascorbic acid. As the former is readily soluble in aprotic solvents, its use as substrate is more advantageous from the preparative and analytical point of view.

Thus, reaction of a solution of *(1)* in methanol-water with ascorbic acid in the presence of oxygen yields a yellow corrinoid *(4)*, whose physical data are summarized in Table 1, and whose structure was established by X-ray analysis[3] (Figure 1).

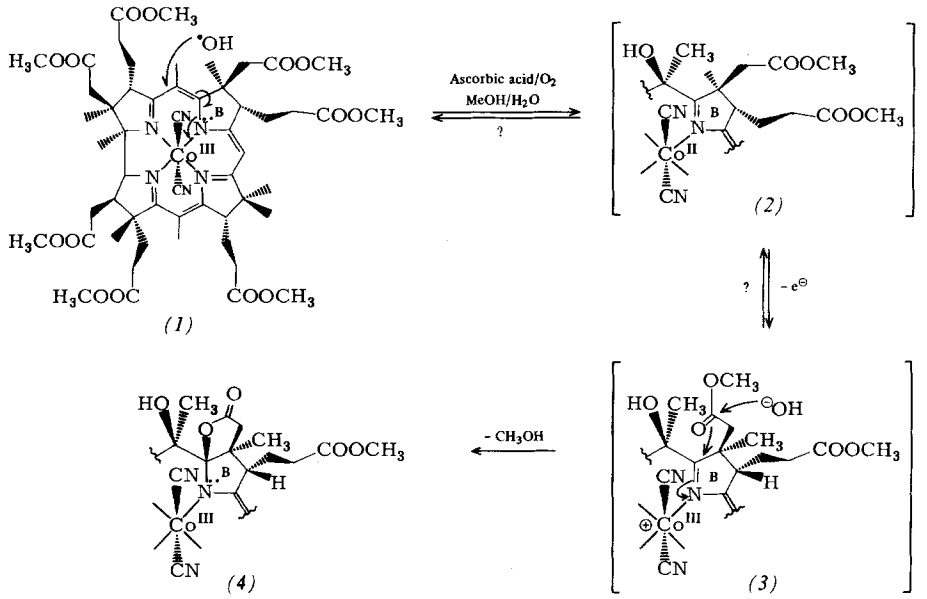


Table 1. Physical data of compound *(4)* [a].

M.p. [°C]	UV/VIS (CH_3OH) λ_{max} [nm] (log ε)	IR ($CHCl_3$)	^{1}H-NMR (100 MHz, $CDCl_3$, TMS internal) δ [ppm]	^{13}C-NMR (25.16 MHz, $CDCl_3$, TMS int.) δ [ppm]
196—197 [b] 177—178 [c]	488 (4.00) 469 (3.99) 321 (4.02) 269 (sh) 220 (4.73)	3410 (assoc. OH) 2990 (CH) 2960 (CH) 1785 (lactone-C=O) 1735 (ester-C=O) *etc.*	5.39 (OH exchangeable for D); 5.04 (10-H); 4.22 (H-19, d, J = 10 Hz); 3.75, 3.70, 3.67, 3.64 (each 1 OCH_3); 3.74 (2 × OCH_3); 2.17 (15-CH_3); 1.85 (5-CH_3); 1.44, 1.29 (each 2 × CH_3); 1.22, 1.13 (each 1 CH_3)	191.8 (C-4); 176.8, 175.6, 175.0, 174.4, 174.0, 172.9, 172.8 (2C), 172.2 and 172.0 (7 ester and lactone-CO as well as C-9, 11 and 16); 164.6 (C-14); 134.1 and 129.8 (each 1 C=N; 112.2 (C-6); 100.8 (C-15); 76.1 (C-19); 59.0, 56.0 and 53.7 (C-3, 8, 13); 58.7 (C-17); 52.4 (2 × CH_3O); 52.0 (CH_3O); 51.8 (2 × CH_3O); 51.7 (CH_3O); 50.8, 46.8 and 45.5 (C-2, 7 and 12); 45.4 and 40.7 (CH_2 at C-2 and C-7); 40.0 (C-18); 33.0, 32.5, 32.3, 31.7, 31.2, 30.0, 25.8 and 23.2 (other CH_2); 30.7 (pro-S CH_3 at C-12); 23.2 (CH_3 at C-5); 15.0 (CH_3 at C-15); 21.7, 20.1, 18.4, 17.3 and 16.1 (other CH_3)

[a] Best reaction conditions: *(1)* (100 mg), ascorbic acid (400 mg), and $NaHCO_3$ (210 mg) were dissolved in a mixture of phosphate buffer (pH = 7.2, 16 ml) and methanol (10 ml). An aqueous solution of EDTA (0.01 M, 2 ml) was added, and a stream of oxygen was passed into the mixture, kept at 65 °C, for 3 h. On preparative TLC on silica gel and eluting with methylene chloride/methanol (97:3) the product (30%) was isolated, and some starting material (48%) was recovered.
[b] From methanol/ether.
[c] From benzene/*n*-hexane.

[*] Doz. Dr. A. Gossauer, Dipl.-Chem. B. Grüning
Institut für Organische Chemie der Technischen Universität
Schleinitzstrasse, D-3300 Braunschweig (Germany)
Dr. L. Ernst, Dipl.-Chem. W. Becker, Doz. Dr. W. S. Sheldrick
Abteilung für Physikalische Messtechnik der Gesellschaft für Biotechnologische Forschung mbH
Mascheroder Weg 1, D-3300 Braunschweig-Stöckheim (Germany)

[**] Part 1 in the series on the structure of the stable yellow corrinoids.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

The hydroxy group at C-5 (O-5) is situated above the plane of the molecule. It may be inferred from the values of the bond lengths and angles in *(4)* that the atoms of the "inner" ring between N-22 and N-24 form a polyazamethine system with four conjugated double bonds. The (C-15)—(C-16) bond is, however, significantly longer than that in related corrins

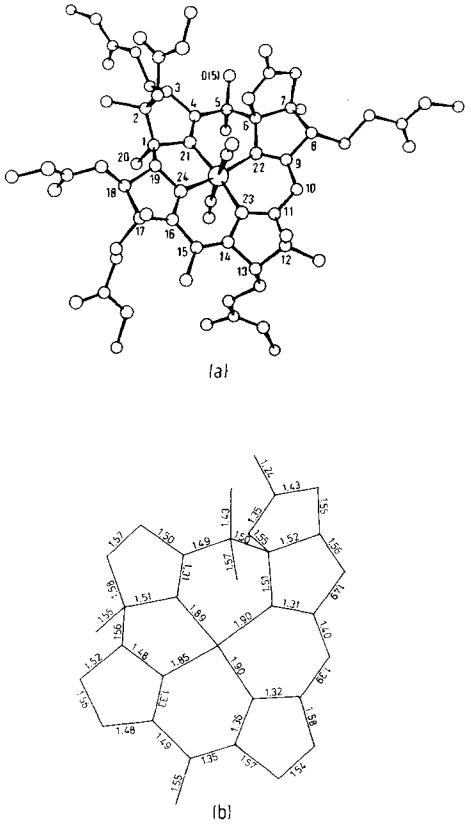


Fig. 1. a) Structure of *(4)* with numbering of the atoms; b) bond lengths (Å) in the chromophore of *(4)*. Standard deviations are: 0.01 Å for Co—N, and 0.02 Å for other bond lengths.

(*e.g.* 1.46 in cobyrinic acid[4]). On the other hand, the (N-21)—(C-4) bond remains as an isolated double bond. Compound *(4)* crystallizes together with one molecule of methanol, which is hydrogen-bonded to the CN ligand situated above the plane of the molecule (O—H···N = 2.67 Å) and with O-5 (O···H—O = 2.66 Å), as well as with one molecule of water which is linked by an O—H···N bridge of 2.82 Å to the CN ligand situated below the plane of the molecule.

In the ^{1}H-NMR spectrum, the transformation of *(1)* into *(4)* is demonstrated in particular by the shift of the (C-5)—CH_3 signal from $\delta = 2.13$ (or 2.08) to $\delta = 1.85$ and by the appearance of a singlet for the OH group. The ^{13}C-NMR spectra display the following characteristic differences[5]: (i) C-4 is deshielded both by interruption of the conjugation at C-5 and the presence of a OH group at this position. Thus, C-4 whose resonance frequency in *(1)* lies in the range $\delta = 171$—176, gives rise to an isolated peak at $\delta = 191.8$ in *(4)*; (ii) a diminution of the number of signals in the characteristic range for C-5 and C-15 ($\delta = 100$—105) from two to one; (iii) a displacement of the C-6 signal from $\delta = 164$ to $\delta = 112.2$ ppm. The lactone ring in *(4)* is readily recognizable in the ^{1}H- and ^{13}C-NMR spectra by the absence of one methoxy signal, as well as in the IR spectrum, by the presence of a characteristic absorption band at $\tilde{\nu}_{max} = 1785\ cm^{-1}$.

The transformation of *(1)* into *(4)* may be rationalized as follows: Addition of a hydroxy free radical at C-5 and concomitant reduction of the complex bonded cobalt ion lead to the formation of a cobalt(II) complex *(2)* which is readily re-oxidized to the corresponding cobalt(III) intermediate *(3)*. Stabilization of the latter takes place by intramolecular attack of the acetic ester residue at C-7 with closure of the lactone ring.

Hydroxylation reactions of organic substrates which are induced by ascorbic acid in aqueous media are well known. Most likely, they involve free radicals and formation of hydrogen peroxide as an intermediate[6]. In fact, *(1)* can be transformed into *(4)*, although in lower yield, by treatment with H_2O_2. The regioselective formation of *(4)* is interesting from a mechanistic point of view. Probably, the closure of a five-membered lactone ring from the acetic ester chain at C-7 is the rate-determining step of the reaction.

Received: April 27, 1977 [Z 725 IE]
German version: Angew. Chem. 89, 486 (1977)

CAS Registry numbers:
(1), 36522-80-2; *(4)*, 62905-92-4; ascorbic acid, 50-81-7

[1] *J. M. Pratt:* Inorganic Chemistry of Vitamin B_{12}. Academic Press, London 1972, chapter 15; *W. Friedrich:* Vitamin B_{12} und verwandte Corrinoide. Thieme, Stuttgart 1975, p. 87.

[2] Synthesized from cyanocobalamin (E. Merck, Darmstadt) according to the procedure given by *L. Werthemann*, Ph. D. Thesis, ETH Zürich 1968.

[3] From methanol/ether, *(4)* crystallizes orthorhombically (space group: $P2_12_12_1$), with $a = 19.054(2)$, $b = 31.416(2)$, $c = 9.540(1)$ Å; $Z = 4$, $d_{calc.} = 1.33\ g \cdot cm^{-3}$. The structure was solved by Patterson and difference syntheses and refined with the program SHELX-76 to the present values: $R = 0.098$ and $R_w = 0.103$ (Co anisotropic) for 4499 independent reflections ($F \geq 3.0\sigma$ (F), 2208 Friedel pairs). The absolute configuration assigned to cobyrinic acid [4] [see *(1)*] was thereby confirmed.

[4] *K. Venkatesan, D. Dale, D. Crowfoot Hodgkin, C. E. Nockolds, F. H. Moore, B. H. O'Connor*, Proc. Roy. Soc. London A *323*, 455 (1971).

[5] For assignments of the ^{13}C-NMR signals of *(1)* see: *A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, R. J. Cushley, P. J. Whitman*, J. Am. Chem. Soc. *96*, 8069 (1974); *A. R. Battersby, M. Ihara, E. McDonald, J. R. Redfern, B. T. Golding*, J. Chem. Soc. Perkin Trans. 1, *1977*, 158.

[6] *J. H. Green, B. J. Ralph, P. J. Schofield*, Nature *198*, 754 (1963).

Novel Monobridged Dinuclear Platinum Species

By *E. A. V. Ebsworth, Hugh M. Ferrier, Bernard J. L. Henner, David W. H. Rankin, Francis J. S. Reed, Heather E. Robertson*, and *John D. Whitelock*[*]

In most of the dinuclear platinum complexes known the platinum atoms are linked by *two* bridging ligands. Two ligands capable of forming *singly* linked complexes are dimethyl sulfide and dimethyl telluride[1]. Recently *Manzer* and *Parshall*[2] described the cyanide-linked dinuclear cation

trans-$[PtH(PEt_3)_2]_2CN^+$

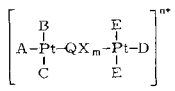
in which the lone pairs of electrons on carbon and nitrogen each act as nucleophiles. This is, however, an example of a different type of bridging in which three, rather than two, bonds separate the metal atoms. As far as we are aware no examples of monobridged bis-platinum(IV) species have been reported as yet.

We report here the formation of several monobridged bis-platinum(II) species and one monobridged bis-platinum(IV) cation; we have characterized them by NMR spectroscopy, and in one case, by IR spectroscopy and analysis (see Table 1).

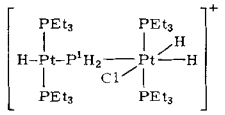
[*] Prof. E. A. V. Ebsworth [+], H. M. Ferrier, Dr. B. J. L. Henner, Dr. D. W. H. Rankin, Dr. F. J. S. Reed, Dr. H. E. Robertson, J. D. Whitelock
Department of Chemistry, Edinburgh University
West Mains Road, Edinburgh EH9 3JJ (Scotland)

[+] To whom correspondence should be addressed.

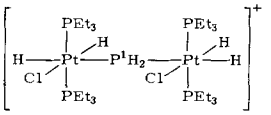
Table 1. Some NMR parameters of monobridged dinuclear platinum species.



Q	X	m	A	B	C	D	E	n	δ(Q)	^1J(PtQ) [Hz]
(1)=P	H	2	H	PEt_3	PEt_3	H	PEt_3	1	−169.7	1202
(4)=P	H	2	Cl	PEt_3	PEt_3	Cl	PEt_3	1	−152.0	2804
P	H	2	Br	PEt_3	PEt_3	Br	PEt_3	1	−147.8	2788
P	H	2	I	PEt_3	PEt_3	I	PEt_3	1	−148.7	2631
(5)=P	H	2	PEt_3	PEt_3	Cl	Cl	PEt_3	1	−117.1	3054, 1887
P	H	2	PEt_3	PEt_3	Br	Br	PEt_3	1	−121.8	3090, 1830
P	H	2	PEt_3	PEt_3	I	I	PEt_3	1	−136.6	3048, 1745
(6)=P	H	2	Cl	PEt_3	Cl	Cl	PEt_3	0	−120.9	2630, 1880
P	H	2	Br	PEt_3	Br	Br	PEt_3	0	−124.9	2680, 1850
P	H	2	I	PEt_3	I	I	PEt_3	0	−138.7	2630, 1758
(3)=P	H	1	H	PEt_3	PEt_3	H	PEt_3	0	−155.8	463
(7)=P	F	2	Cl	PEt_3	Cl	Cl	PEt_3	0	+211.0	4519, 4453
									δQH	^3J(PtP) [Hz]
(8)=S	H	1	H	PEt_3	PEt_3	H	PEt_3	1	−0.4	12.4
Se	H	1	H	PEt_3	PEt_3	H	PEt_3	1	−3.3	10.9



(A)



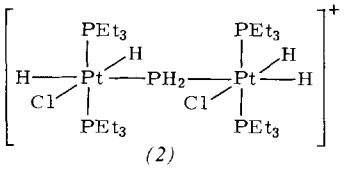
(B)

	δP^1	$^1J(Pt^{II}P^1)$ [Hz]	$^1J(Pt^{IV}P^1)$ [Hz]
(A)	−188.4	1275	830
(2)=(B)	−224.0	—	791

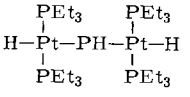
Treatment of two equivalents of *trans*-$[PtClH(PEt_3)_2]$ with one equivalent of trimethylsilylphosphane, Me_3SiPH_2, affords the compound (1)

trans-$[PtH(PEt_3)_2]_2PH_2^+Cl^-$ (1)

and Me_3SiCl. This follows the identification of the same cation as one of the products of the reaction between *trans*-$[PtClH(PEt_3)_2]$ and H_3SiPH_2[3]. Compound (1) has been isolated as yellow crystals which give a conducting solution in dichloromethane. Its NMR parameters, as well as its IR data and C,H elemental analyses, confirm its identity.



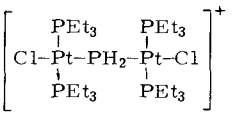
(2)



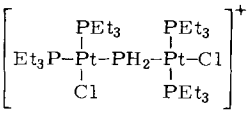
(3)

The PH_2 bridged cation (1) undergoes reactions typical of both a platinum(II) hydride and a phosphonium ion. Thus with HCl either the completely oxidized species (2) is obtained or the partially oxidized complex, containing one four-coordinate and one six-coordinate Pt atom (see (A) in Table 1), depending on the proportion of HCl used. Treatment with potassium *tert*-butoxide, on the other hand, brings about proton abstraction from the bridging group to give the neutral compound (3).

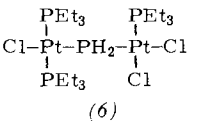
The reaction between $SiMe_3PH_2$ and $PtCl_2(PEt_3)_2$ also yields products containing PH_2 bridges. If *trans*-$[PtCl_2(PEt_3)_2]$ is used, cation (4) is identified as the initial product which then partly rearranges to give the *cis,trans* isomer (5). When *cis*-$[PtCl_2(PEt_3)_2]$ is used as the starting material again both isomers of the PH_2 bridged cation are observed. In addition, in each reaction mixture resonances are found which are assigned to the neutral complex (6).



(4)

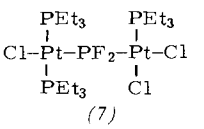


(5)



(6)

Analogous products are obtained using *trans*-$[PtBr_2(PEt_3)_2]$ and *trans*-$[PtI_2(PEt_3)_2]$; the symmetrical PH_2 bridged diodide is the least stable with regard to isomerization.



(7)

The monobridged dinuclear complex (7) with a PF_2 bridge was found to be a product of the reaction between PF_2Cl and either *trans*-$[PtClH(PEt_3)_2]$ or a mixture of *trans*-$[PtCl(Me_3Si)(PEt_3)_2]$ and *trans*-$[PtCl_2(PEt_3)_2]$.

An attempt to prepare a dinuclear species with an SH bridge by the action of $SiMe_3SH$ on *trans*-$[PtClH(PEt_3)_2]$ was unsuccessful but this complex was obtained by the treatment of a mixture of *trans*-$[PtClH(PEt_3)_2]$ and $AgBF_4$ with *trans*-$[PtH(SH)(PEt_3)_2]$[4]. This reaction, similar to that used[2] to synthesise *trans*-$[PtH(PEt_3)_2]_2CN^+$, yielded the complex *(8)* and AgCl. The selenium analog was prepared similarly.

trans-$[PtH(PEt_3)_2]_2SH^+BF_4^-$ *(8)*

Received: May 5, 1977 [Z 730 IE]
German version: Angew. Chem. *89*, 495 (1977)

CAS Registry numbers:
(1)-Cl, 62906-17-6; *(2)*, 62906-16-5; *(3)*, 62906-15-4; *(4)*, A=Cl, D=Cl, 62960-63-8; *(4)*, A=Br, D=Br, 62960-62-1; *(4)*, A=I, D=I, 62960-61-6; *(5)*, C=Cl, D=Cl, 62906-07-4; *(5)*, C=Br, D=Br, 62906-06-3; *(5)*, C=I, D=I, 62906-05-2; *(6)*, A=Cl, C=Cl, D=Cl, 62906-04-1; *(6)*, A=Br, C=Br, D=Br, 62906-03-0; *(6)*, A=I, C=I, D=I, 62906-02-9; *(7)*, 62906-01-8; *(8)*-BF_4, Q=S, 62906-00-7; *(8)*-BF_4, Q=Se, 62905-98-0; *(4)*, 62990-74-3; *trans*-$[PtClH(PEt_3)_2]$, 16842-17-4; *trans*-$[PtCl_2(PEt_3)_2]$, 13965-02-1; *cis*-$[PtCl_2(PEt_3)_2]$, 15692-07-6; *trans*-$[PtBr_2(PEt_3)_2]$, 13985-90-5; *trans*-$[PtI_2(PEt_3)_2]$, 15636-79-0; *trans*-$[PtCl(Me_3Si)(PEt_3)_2]$, 15559-62-3; Me_3SiPH_2, 17446-52-5; PF_2Cl, 14335-40-1; Me_3SiSH, 18338-27-7

[1] *P. L. Goggin, R. J. Goodfellow, F. J. S. Reed*, J. Chem. Soc. Dalton Trans. *1974*, 576; *P. L. Goggin, R. J. Goodfellow, S. R. Haddock*, Chem. Commun. *1975*, 176.
[2] *L. E. Manzer, G. W. Parshall*, Inorg. Chem. *15*, 3114 (1976).
[3] *J. M. Edward*, Ph. D. Thesis, Edinburgh (1975).
[4] *I. M. Blacklaws, E. A. V. Ebsworth, D. W. H. Rankin, H. E. Robertson*, unpublished work.

Coordination Number 3 in Oxozincates: $Rb_8[OZnO_2ZnO_2ZnO_2ZnO]$ and $K_2[Zn_6O_7]$[1]

By *Karl-Rainer Wambach* and *Rudolf Hoppe*[*]

Although the amphoteric nature of $Zn(OH)_2$ has long been known the only hydroxozincate to have been characterized in detail is $Na[Zn(OH)_3]$ having the coordinate number 5[2]. All the oxozincates studied so far exhibit the coordination number 4, whether they are *framework* ($BaZnO_2$[3], $Na_2Zn_2O_3$[4]), *layer* ($SrZnO_2$[5]), *chain* (K_2ZnO_2[6]), or "*soro*" zincates (Na_6ZnO_4[7]). We have now found a case of coordination number 3 while searching for anions of unusual structure[8].

Rb_2ZnO_2, obtained from intimate mixtures of $RbO_{0.48}$ and active ZnO [Rb:Zn = 2.3:1, closed Ni cylinders, 600 °C, 50d] as colorless, transparent, coarse single crystals of almost spherical habit, proves to be extremely sensitive to hydrolysis and, according to rotating crystal, Weissenberg, and precession photographs, is monoclinic with $a = 9.55_8$, $b = 6.33_5$, $c = 15.91$ Å, $\beta = 118.5_7$, $Z = 8$ in $P2_1/c$.

For purposes of structure elucidation 759 symmetry-independent reflections *h0l-h4l* were recorded [Mo-K_α, two-cycle diffractometer, Stoe Stadi 2]. The structure was solved by Patterson syntheses with least squares refinement (cf. Fig. 1); $R = 7.32\%$ for 759 of 759 possible reflections.

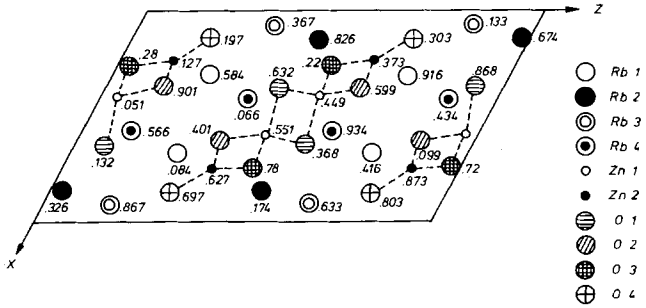


Fig. 1. Unit cell of Rb_2ZnO_2, projection along [010]; heights in fractions of *b*.

Primary structure: Half of the Zn atoms are in a tetrahedral environment of O and the other half in a trigonal-planar environment [interatomic distances: 2.01 Å (4×), and 1.84, 1.91, and 1.97 Å, respectively].

Secondary structure: Surprisingly, "isolated" tetranuclear chains are present $[OZnO_2ZnO_2ZnO_2ZnO]$ which are almost linear with respect to Zn. This is the first *oligooxozincate*.

Tertiary structure: The linear groups are oriented parallel to one another along (120), being slightly inclined (*ca.* 10°) towards (010).

Each $[Zn_4O_8]$ group is surrounded by a total of 14 Rb atoms which link them to 12 other such groups. The coordination number of Rb towards O^{2-} is 4 (Rb-1, Rb-2, Rb-3) or 4+1 (Rb-4).

$K_2Zn_6O_7$, which is likewise very sensitive to hydrolysis, was obtained in studies on the ZnO rich side of the K_2ZnO_2/ZnO phase diagram in the form of coarse, slightly yellow tinted single crystals [K:Zn = 2.2:3, closed Ni cylinders (under argon), 700 °C, 200d]; it forms tetragonal crystals with $a = 10.91_2$, $c = 3.32_5$ Å, $c/a = 0.305$, $Z = 2$ in $P4_2$ nm.

The I_0 data of 354 symmetry-independent reflections were recorded (four-cycle diffractometer, Philips PW 1100), and the structure solved by direct methods (cf. Fig. 2); at the present state of refinement $R = 8.52\%$ for 297 of 354 possible reflections.

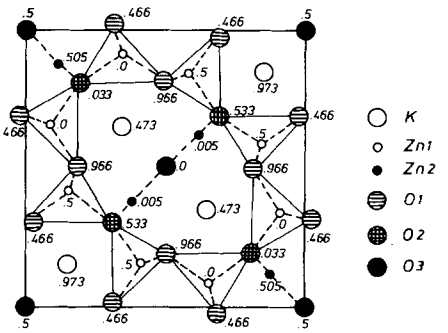


Fig. 2: Unit cell of $K_2Zn_6O_7$, projection along [001]; heights in fractions of *c*.

Primary structure: Two thirds of the Zn atoms are surrounded "tetrahedrally" by four O atoms, and the other third in "trigonal-planar" fashion by three O atoms [interatomic distances: 1.88, 1.96, 2.04, and 2.07 Å, and 1.85, 1.93, and 2.08 Å, respectively].

Secondary structure: The ZnO_4 tetrahedra (with Zn-1) form rings made up of tetrahedra parallel to (001) according to

$$[\{O_{1/2}(ZnO_{3/2})\}_2\{O_{2/2}(ZnO_{2/2})\}_2\{O_{1/2}(ZnO_{3/2})\}_2\{O_{2/2}(ZnO_{2/2})\}_2]$$

the atoms participating in ring formation being enclosed in parentheses when they belong to a tetrahedron; different tetrahedra are indicated by curly brackets. Each ring contains eight Zn atoms. Zn—O—Zn groups (with Zn-2) are incorporated between opposite $\{O_{1/2}(ZnO_{3/2})\}_2$ units of the rings in such a way that the rings are subdivided by two trigonal planar $ZnO_{3/2}$ units.

Tertiary structure: The O atoms not participating in ring formation are responsible for two-dimensional bridging parallel to (001), while along [001] the O atoms involved in ring formation supplement these linkages to form a three-dimensional skeleton.

[*] Prof. Dr. R. Hoppe, Dipl.-Chem. K.-R. Wambach
Institut für Anorganische und Analytische Chemie der Universität
Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

The arrangement and mutual linkage of the rings is of such a kind that each K atom is surrounded by eight O atoms roughly occupying the corners of a cube around K [interatomic distances: 2.79, 2.82, 2.87 (2×), 2.90 (2×), 2.95, 3.05 Å].

If the usual interpretation of the structure of ZnO and the oxozincates mentioned above is adopted, *i.e.* assuming a covalent Zn—O bond (sp^3 hybrid orbitals), it remains inexplicable why Rb_2ZnO_2 should not be isotypic with K_2ZnO_2, both containing $ZnO_{4/2}$ tetrahedral chains analogous to SiS_2. It is even more difficult to understand that a trigonal planar configuration should occur in $K_2Zn_6O_7$ whose composition shows it to be so close to ZnO. However, a plausible interpretation can be formulated if the predominant role is assigned not to the hybridization of the orbitals but to the influence of the counterions (Rb^+ in place of K^+) and account is taken of the composition of the Zn/O part of the zincate.

Received: May 16, 1977 [Z 736 IE]
German version: Angew. Chem. *89*, 498 (1977)

CAS Registry numbers:
Rb_2ZnO_2, 63018-05-3; $K_2Zn_6O_7$, 62990-75-4

[1] Part of the Thesis by *K.-R. Wambach*, Universität Giessen.
[2] *H. G. v. Schnering*, Naturwissenschaften *48*, 665 (1961).
[3] *H. G. v. Schnering, R. Hoppe, J. Zemann*, Z. Anorg. Allg. Chem. *305*, 241 (1960).
[4] *E. Vielhaber, R. Hoppe*, Z. Anorg. Allg. Chem. *338*, 209 (1965).
[5] *H. G. v. Schnering, R. Hoppe*, Z. Anorg. Allg. Chem. *312*, 87 (1961).
[6] *E. Vielhaber, R. Hoppe*, Z. Anorg. Allg. Chem. *360*, 7 (1968).
[7] *P. Kastner, R. Hoppe*, Z. Anorg. Allg. Chem. *409*, 69 (1974).
[8] *P. Kastner, R. Hoppe*, Naturwissenschaften *61*, 79 (1974); *G. Brachtel, R. Hoppe, ibid. 63*, 339 (1976). *H. Rieck, R. Hoppe*, Naturwissenschaften *61*, 126 (1974); *H. Rieck, R. Hoppe*, Z. Anorg. Allg. Chem. *400*, 311 (1973).

Hexameric $KN_2Co[P(CH_3)_3]_3$—A Novel Potassium-Dinitrogen Cluster[**]

By *Reinhard Hammer, Hans-Friedrich Klein, Peter Friedrich*, and *Gottfried Huttner*[*]

In the few previously reported bimetal-dinitrogen complexes, in which the N_2-unit is bonded side-on or end-on to a transition metal and an electropositive main group element, ether- or alkoxide-donor ligands are essential components of the molecular structures[1]. We have now synthesized a potassium salt of the dinitrogentris(trimethylphosphane)cobalt anion[2], which crystallizes free of ether from ethereal solutions.

Surprisingly, the dark brown solutions of the olefintris(trimethylphosphane)cobaltates *(1)*[3] in tetrahydrofuran or diethyl ether react spontaneously under 1 bar N_2 in accordance with Eq. (a), whereupon the color changes to bright orange and the dinitrogencobaltate *(2)* is formed in almost quantitative yield.

$$K[(Me_3P)_3Co(olefin)] + N_2 \xrightarrow{20\,^\circ C} K[(Me_3P)_3CoN_2] + olefin \quad (a)$$

(1) *(2)*

olefin = propene, cyclopentene

(2) is also obtained from the magnesium complex *(3)*[1a] according to Eq. (b). On slow cooling of *(2)* in pentane/diethyl ether (4:1) orange-red crystals are formed which are

$$[(Me_3P)_3CoN_2]_2Mg(THF)_4 + 2\,K \xrightarrow{Et_2O} 2\,(2) + Mg + 4\,THF \quad (b)$$

(3)

stable up to 140 °C under 1 bar N_2 but immediately ignite on exposure to air. The structure of compound *(2)* was determined by X-ray crystallography. The monoclinic unit cell (space group C2/c)[4] contains four $[KN_2Co(PMe_3)_3]_6$ molecules. Their fundamental structural unit can be described in simple terms as a double cube made up of six K atoms and six N_2 groups (Fig. 1).

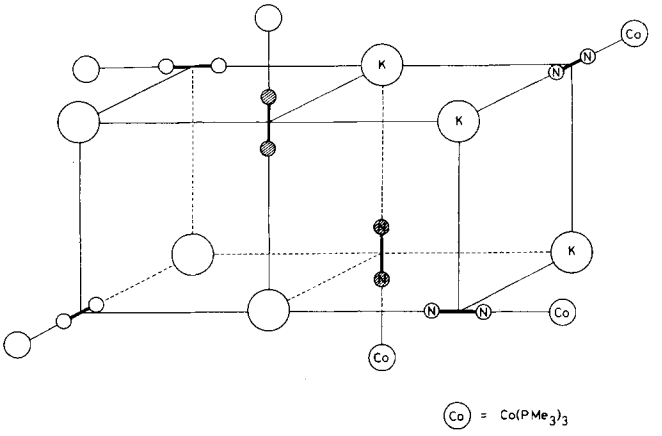


Fig. 1. Crystal structure of *(2)* [for bond lengths see text].

The N_2 dumbbells [*d*(NN): 116 to 118 pm] are orientated pairwise along the three axes of the inversion-symmetric skeleton. In the extension of these axes the N_2 units bear terminal $Co(PMe_3)_3$ groups, which shield the cluster externally [*d*(CoN): 170 to 171 pm]. Each dinitrogen unit is involved in bonding, both along the N—N axis as well as perpendicular to it: along the axis each unit is bonded to a cobalt atom outside the cluster, and to a potassium atom inside the cluster [*d*(KN): 276 to 293 pm]. Perpendicular to the N—N axis, two and three K—N_2 interactions, respectively, are observed: The N_2 groups bound to the corners of the double cube are thus each in contact with two K atoms; the two N_2 groups at the center of the edges (hatched groups in Fig. 1), on the other hand, have three nearest K neighbors in the plane perpendicular to the N—N axis.

It would appear that the observed structure of the complex cluster has no parallel in the structural chemistry of molecules; however, there are striking similarities when compared with solid-state structures (ThC_2, ...)[5]. Accordingly the usual electron counting rules of molecular chemistry cannot be applied in a simple manner. Since there are more bonds than electron pairs in the cluster, the bonding might be best described with models having multicenter electron-deficient bonds.

Procedure

A solution of chlorotris(trimethylphosphane)cobalt[6] (485 mg, 1.50 mmol) in tetrahydrofuran (50 ml) saturated with propene is stirred together with 500 mg clean pieces of potassium for 24 h at 20 °C under argon. The volatile components are removed *in vacuo*, and the ocher-colored residue taken

[*] Dr. R. Hammer, Doz. Dr. H.-F. Klein [+], Dipl.-Chem. P. Friedrich, Prof. Dr. G. Huttner [++]
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

[+] Author to whom correspondence should be addressed.

[++] Lehrstuhl für Synthetische Anorganische Chemie, Fachbereich Chemie der Universität, D-7750 Konstanz (Germany)

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

up in 20 ml ether. The filtered red-brown solution is stirred under 1 bar N_2, whereupon its color changes within a few minutes to orange-red. After 2 h the reaction mixture is filtered and slowly cooled to −78 °C. The solution is decanted off and the orange-red crystals dried at 20 °C/0.1 torr. Yield of *(2)*: 450 mg (85 %).—IR: ν(NN): 1795 vs (br) and 1758 m (br) cm^{-1} (Nujol mull); ν(NN): 1868 vs (br) and 1843 m (br) cm^{-1} (THF). Conductivity of *(2)* (0.25 M in THF, 20 °C, 1 bar N_2): $\kappa < 10^{-6}\ \Omega^{-1}\ cm^{-1}$.

Received: May 20, 1977 [Z 745 IE]
German version: Angew. Chem. 89, 499 (1977)

CAS Registry numbers:
$K[(Me_3P)_3Co(propene)]$, 63181-07-7; $K[(Me_3P)_3Co(cyclopentene)]$, 63181-08-8; *(2)*, 63181-09-9; *(3)*, 63181-11-3; $(Me_3P)_3CoCl$, 53432-06-7

[1] a) *R. Hammer, H.-F. Klein, U. Schubert, A. Frank, G. Huttner*, Angew. Chem. *88*, 648 (1976); Angew. Chem. Int. Ed. Engl. *15*, 612 (1976); b) *K. Jonas, ibid. 85*, 1050 (1973) and *12*, 997 (1973); *C. Krüger, Y.-H. Tsay, ibid. 85*, 1051 (1973) and *12*, 998 (1973); *K. Jonas, D. J. Brauer, C. Krüger, P. J. Roberts, Y.-H. Tsay*, J. Am. Chem. Soc. *98*, 74 (1976); c) *M. Mercer, R. H. Crabtree, R. L. Richards*, J. Chem. Soc. Chem. Commun. *1973*, 808.

[2] Dinitrogencobaltates $NaN_2Co(PR_3)_3$ were first described by *M. Aresta, C. F. Nobile, M. Rossi, A. Sacco*, Chem. Commun. *1971*, 781.

[3] *R. Hammer, H.-F. Klein*, unpublished.

[4] $a = 2767.3$, $b = 1627.4$, $c = 2802.5$ pm, $\beta = 115.94°$; $d_{calc} = 1.25\ g/cm^3$. Data collection with a Syntex-$P2_1$ diffractometer; solution of structure (2639 independent reflections, $R_1 = 0.085$) with Syntex-XTL.

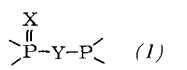
[5] *A. F. Wells*: Structural Inorganic Chemistry, 3rd Ed. Clarendon Press, Oxford 1962, pp. 761 ff.

[6] *H.-F. Klein, H. H. Karsch*, Inorg. Chem. *14*, 473 (1975).

cis-2-Telluro-1,3,2λ⁵,4λ³-diazadiphosphetidine—A Fluxional Redox System

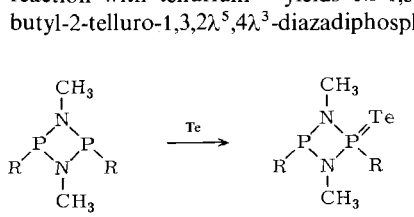
By *Otto J. Scherer* and *Günter Schnabl*[*]

Judicious choice of X and Y and of the other ligands attached to the two P atoms in the phosphorus-chalcogen compounds *(1)* [*e.g.* X=O, S; Y=O, S, $(CH_2)_n$, NR] known in such great variety should permit preparation of a fluxional redox system in which X undergoes reversible intramolecular shift.



(1)

Conditions for the study of such a process are ideally fulfilled by *cis*-1,3,2λ³,4λ³-diazadiphosphetidine *(2)*[1], whose 1:1 reaction with tellurium[2] yields *cis*-1,3-dimethyl-2,4-di-*tert*-butyl-2-telluro-1,3,2λ⁵,4λ³-diazadiphosphetidine *(3)*.

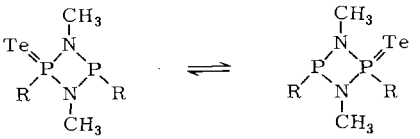


(2) R = $C(CH_3)_3$ *(3)*

Unlike the few known phosphorus-tellurium compounds of similar kind[3], compound *(3)* is exceptionally stable[4]. Temperature dependent ^{1}H- and ^{31}P-NMR studies[5] show *(3)* to have dynamic behavior.

[*] Prof. Dr. O. J. Scherer, Dr. G. Schnabl
Fachbereich Chemie der Universität
Pfaffenbergstrasse 95, D-6750 Kaiserslautern (Germany)

The site-exchange of the tellurium is fast on the NMR time scale[6] but can be perceptibly slowed down by lowering the temperature. Compound *(3)* forms pale yellow crystals (softening 77—83 °C, melting range 83—90 °C) which dissolve very well in ether and methylene chloride, readily in benzene



R = $C(CH_3)_3$

or toluene, and modestly in pentane. Elemental analysis, mass spectrum [16 eV: *m/e* = 362 (50 % M^+), 178 (100)], molecular weight determination (378, cryoscopic in benzene), and a crystal structure analysis[7] confirm the composition and structure of the molecule, which is monomeric both in solution and in the solid state.

Procedure

Tellurium (0.67 g, 5.25 mmol) is added to an ice-cooled (*ca.* 6 °C) stirred solution of *(2)*[1] (1.2 g, 5.12 mmol) in benzene (16 ml). After 3 h at room temperature, excess tellurium is filtered off (G4 frit), the solvent is drawn off and the product *(3)* dried under oil-pump vacuum; yield quantitative.

Received: May 24, 1977 [Z 747 IE]
German version: Angew. Chem. 89, 500 (1977)

CAS Registry numbers:
(2), 63104-58-5; *(3)*, 63104-59-6

[1] *O. J. Scherer, G. Schnabl*, Angew. Chem. *88*, 845 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976).

[2] *cis*-$[RP(Te)NCH_3]_2$ can also be synthesized.

[3] Examples: a) *K. J. Irgolic*: The Organic Chemistry of Tellurium. Gordon and Breach, New York 1974, p. 256; b) *O. J. Scherer, G. Schnabl*, Chem. Ber. *109*, 2996 (1976); c) *W.-W. Du Mont, H.-J. Kroth*, J. Organomet. Chem. *113*, C 35 (1976); d) *D. H. Brown, R. J. Cross, D. Millington, ibid. 125*, 219 (1977); the following fast equilibria $R_3PTe + R'_3P \rightleftarrows R'_3PTe + R_3P$ and $R_3PTe \rightleftarrows R_3P + Te$ were first mentioned in [3c] and [3d] (tellurium shift probably bimolecular).

[4] Compound *(3)* can be stored at room temperature for several weeks, *e.g.* in benzene solution, and for several months in crystalline form (sealed flask, daylight).

[5] ^{1}H-NMR spectrum (*ca.* 15 % in CH_2Cl_2, TMS int., 35 °C): $\delta CH_3C = 1.12$ (d), $^3J_{PH} = 16.9$ Hz; $\delta CH_3N = 2.56$ (t), $^3J_{PH} = 13.7$ Hz. −50 °C: δCH_3C (λ^3P) = 1.13 (d), $^3J_{PH} = 13.7$ Hz; δCH_3C (λ^5P) = 1.12 (d), $^3J_{PH} = 19.9$ Hz; $\delta CH_3N = 2.49$ (dd), $^3J_{\lambda^3PH} = 10.7$, $^3J_{\lambda^5PH} = 16.5$ Hz. $^{31}P\{^1H\}$-NMR spectrum (*ca.* 15 % in CH_2Cl_2, 85 % H_3PO_4 ext., −60 °C): $\delta(\lambda^3P) = 200.4$ (d), $\delta(\lambda^5P) = 119.5$ (d), $^2J_{PP} = 18.0$ Hz.

[6] The concentration dependence of the coalescence temperature ($T_c \approx -30$ °C for a 35 % solution and ≈ -10 °C for a 3.5 % solution) measurable at higher dilutions show that both an intramolecular and an intermolecular exchange can occur. Formation of a mixture of *(2)* and *cis*-$[RP(Te)NCH_3]_2$ conceivable in the latter case can be detected neither in the ^{1}H- nor in the ^{31}P low-temperature NMR spectrum.

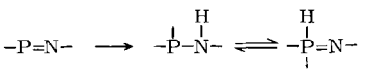
[7] Dr. *S. Pohl*, Bielefeld, personal communication.

Synthesis of a Secondary Aminophosphane[1]

By *Edgar Niecke* and *Gerhard Ringel*[*]

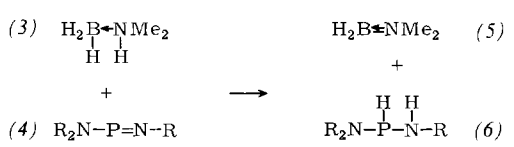
Aminoiminophosphanes, phosphorus-nitrogen compounds containing a strongly polar $3p_\pi(P)—2p_\pi(N)$ bond *(1)*, undergo addition with proton donors to give aminophosphanes *(2a)* and the tautomeric iminophosphoranes *(2b)*[2].

[*] Priv.-Doz. Dr. E. Niecke, Dipl.-Chem. G. Ringel
Anorganisch-chemisches Institut der Universität
Tammannstrasse 4, D-3400 Göttingen (Germany)



(1) *(2a)* *(2b)*

By using dimethylaminoborane *(3)*, which is also an efficient proton- and hydride-transfer agent, we have now been able to synthesize a secondary aminophosphane *(6)*. Compounds of this type were previously considered incapable of existing in the free state[3].



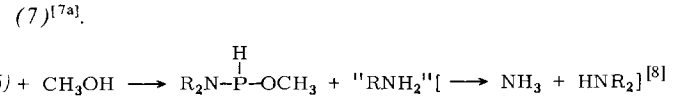
(3) *(4)* *(5)* *(6)*

R = $SiMe_3$

Even at 0°C the reaction of *(3)* with bis(trimethylsilyl)-amino(trimethylsilylimino)phosphane *(4)* leads quantitatively to (dimethylamino)borane *(5)* and *N,N,N'*-tris(trimethylsilyl)-diaminophosphane *(6)*, which can be separated by distillation.

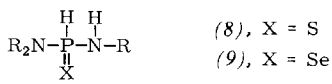
Composition and constitution of *(6)* are confirmed by elemental analysis and by IR, NMR and mass[4] spectra. The IR spectrum (capillary film) shows characteristic absorptions at 3400 m, 3180 m, br[5] (νNH), and 2265 s (νPH) cm^{-1}. The ^{31}P-NMR spectrum (30% in CH_2Cl_2, 85% H_3PO_4 ext.) proves the presence of a secondary phosphane: δ = 33.8 (d), $^1J_{HP}$ = 220 Hz. Finally, the ^1H-NMR spectrum (30% in CH_2Cl_2, TMS int.) exhibits all the four groups of signals expected for *(6)*: 0.12 $^4J_{HP}$ = 0.75 Hz [$N(SiMe_3)_1$]; 0.21, $^4J_{HP}$ = 1.18 Hz [$N(SiMe_3)_2$]; 1.22 [NH]; 6.93 [PH] ($^1J_{HP}$ = 220.2 Hz, $^3J_{HH}$ = 6.65 Hz).

The colorless diaminophosphane is remarkably thermally stable towards α-elimination at the central atom. This surprising observation for secondary phosphanes containing the —PH—X (X = electronegative ligand) skeletal unit can possibly be explained by the steric and electronic stabilizing effect of the trimethylsilyl group in the molecule. *(6)* is practically inert towards hydrolysis[6]; however, in the presence of methanol the RHN—P bond is smoothly cleaved, resulting in formation of the bis(trimethylsilyl)aminomethoxyphosphane *(7)*[7a].



(6) *(7)*

The high reactivity of *(6)* on oxidative attack at the phosphorus atom [in the finely divided state *(6)* is pyrophoric] manifests itself *e.g.* by the addition of sulfur or selenium at room temperature to give the phosphoranes *(8)*[7b] and *(9)*[7c].



(8), X = S
(9), X = Se

The chemical behavior of the secondary aminophosphane is, in addition, determined by the presence of a labile P—H bond in the molecule[9].

Procedure

A solution of *(3)* (5.9 g, 0.1 mol) in ether (50 ml) is added dropwise to an ice-cold solution of *(4)* (30.6 g, 0.11 mol) in ether (100 ml). The stirred reaction mixture is warmed to room temperature and the solvent, together with most of the aminoborane *(5)* that is formed, is removed in an oil-pump vacuum at 30°C. Double fractional distillation of the residue at 60°C/0.5 torr yields 23 g (82%) pure aminophosphane *(6)*.

Received: May 24, 1977 [Z 748 IE]
German version: Angew. Chem. *89*, 501 (1977)

CAS Registry numbers:
(3), 74-94-2; *(4)*, 50732-21-3; *(5)*, 15973-91-8; *(6)*, 63104-54-1; *(7)*, 63104-55-2; *(8)*, 63104-56-3; *(9)*, 63104-57-4

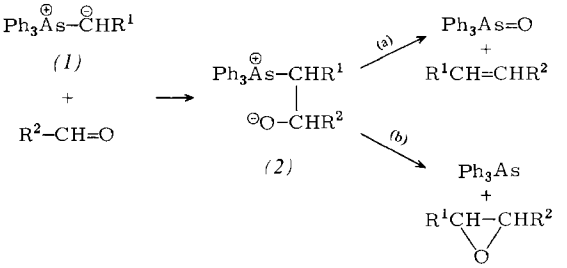
[1] Part 12 of Investigations on Phosphazenes having Coordination Numbers 2 and 3.—Part 11: *E. Niecke, G. Ringel, S. Pohl*, J. Am. Chem. Soc., in press.
[2] Review: *E. Niecke, O. J. Scherer*, Nachr. Chem. Tech. *23*, 395 (1975).
[3] Secondary aminophosphanes stabilized as complex ligands are already known: *G. Huttner, H. D. Müller*, Angew. Chem. *87*, 596 (1975); Angew. Chem. Int. Ed. Engl. *14*, 571 (1975).
[4] Mass spectrum (70 eV): molecular ion at *m/e* 280 (73%), characteristic fragments {M − H} 279 (100), {M − CH_3} 265 (40), {M − $H_2NSi(CH_3)_3$} 191 (52).
[5] Both the position and broad contour of these bands are consistent with the presence of a hydrogen bond.
[6] Even a mixture of water and *(6)* can be separated by distillation.
[7] a) *(7)*: b.p. 32°C/0.1 torr; νPH = 2275 cm^{-1}; $\delta^{31}P$ = 121.9, $^1J_{PH}$ = 216.6 Hz.—b) *(8)*: m.p. 21°C; νNH = 3470, 3220 [5] cm^{-1}, νPH = 2250 cm^{-1}; $\delta^{31}P$ = 35.8, $^1J_{PH}$ = 539.6 Hz.—c) *(9)*: m.p. 24°C; νNH = 3470, 3210 [5] cm^{-1}, νPH = 2245 cm^{-1}; ^{31}P = 9.5, $^1J_{PH}$ = 525.9 Hz.
[8] Owing to the thermolability of trimethylsilylamine only the decomposition products could be identified; cf. also: *N. Wiberg, W. Uhlenbrock*, Chem. Ber. *104*, 2643 (1971).
[9] *N. Niecke, C. Ellinghausen, G. Ringel*, unpublished.

Reaction of Arsonium Ylides with Carbonyl Compounds—Effect of Substituents at Arsenic[1]

By *Ian Gosney, Terence J. Lillie*, and *Douglas Lloyd*[*]

While phosphonium ylides form alkenes and sulphonium ylides form epoxides as the products of Wittig reactions, arsonium ylides *(1)* can give rise to either alkene or epoxide, or a mixture of both[2] (see Scheme 1).

The product distribution depends upon the nature of R^1 in *(1)*: more stabilized arsonium ylides [R^1 = —C(O)R] always afford alkenes[3], whereas less stabilized ylides [R' = H, CH_3, C_6H_5] produce epoxides almost exclusively[4].



Scheme 1. Reaction of arsonium ylides with carbonyl compounds.

In this communication we show for the first time that the nature of the arsonium group also influences the course of the reaction, but not in a manner that can be correlated with the relative stabilities of the arsonium ylides.

[*] Dr. I. Gosney, Dr. T. J. Lillie
Department of Chemistry, University of Edinburgh
West Mains Road, Edinburgh EH9 3JJ (Scotland)
Dr. D. Lloyd
Department of Chemistry, University of St. Andrews
Purdie Building, St. Andrews, Fife KY16 9ST (Scotland)

We have studied the reaction between arsonium salts of type *(3)* and benzaldehyde in tetrahydrofuran solution, using *n*-butyllithium to generate the ylide. The results are summarized in Table 1 and clearly show that electron-donating substituents at the arsenic atom promote the formation of alkene [path (a) in Scheme 1]. At one extreme, reaction of *(3j)* gives a notable yield of stilbene almost to the exclusion of stilbene oxide; at the other, reaction of *(3a)* yields predominantly stilbene oxide.

Table 1. Reaction products of compounds *(3a)* to *(3j)* with benzaldehyde and *n*-butyllithium in tetrahydrofuran.

	$X_2YAs^{\oplus}-CH_2Ph\ \ Br^{\ominus}$ [a] *(3)*		Yields [b]	
	X	Y	*cis*+*trans*-Stilbene oxide [c] [%]	*cis*+*trans*-Stilbene [c] [%]
(a)	C_6H_5	C_6H_5	79	7
(b)	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	66	10
(c)	C_6H_5	p-$(CH_3)_2NC_6H_4$	65	11
(d)	p-$(CH_3)_2NC_6H_4$	C_6H_5	57	15
(e)	p-$(CH_3)_2NC_6H_4$	p-$CH_3OC_6H_4$	33	12
(f)	p-$(CH_3)_2NC_6H_4$	p-$(CH_3)_2NC_6H_4$	24	25
(g)	C_6H_5	C_2H_5	47	27
(h)	C_2H_5	C_6H_5	13	62
(i)	n-C_3H_7	C_6H_5	18	70
(j)	C_2H_5	C_2H_5	1	87

[a] All new compounds gave correct elemental analyses and spectral data.
[b] Determined by gas chromatography.
[c] Samples were almost entirely *trans*; only small amounts ($\approx 1\,\%$) of the *cis*-isomer were detected.

From these data it follows that the course of the reaction for arsonium ylides is related not solely to the nature of the carbanion moiety, as hitherto assumed, but also to the electronic character of the substituents at arsenic, although at present the relative importance of the two effects is not assessable.

We assume that heterolytic cleavage of the As—C bond in *(2)* occurs in an opposite sense depending upon whether an alkene or an epoxide is formed; in the former case the electrons are displaced towards carbon and in the latter case towards the arsenic atom. Thus electron-donating substituents at arsenic should increase the ratio of alkene to epoxide. The results compiled in Table 1 support this view.

General procedure

To a slurry of *(3)* (1.0 mmol) in anhydrous tetrahydrofuran (20 ml) is added 0.70 ml of a 1.6 M solution of *n*-butyllithium in *n*-hexane. The mixture is stirred at room temperature (N_2 atmosphere) and the resulting deeply colored solution is treated with benzaldehyde (1.0 mmol); a rapid decolorization takes place[5]. After 24 h the mixture is diluted to 50 ml with chloroform and the solution is analyzed by GC (2 % 20 M carbowax column; 180 °C) using α-methylstilbene as reference standard. The products are isolated by concentration *in vacuo* and chromatography over silica.

Received: May 4, 1977 [Z 728 IE]
German version: Angew. Chem. *89*, 502 (1977)

CAS Registry numbers:
(3a), 7516-59-8; *(3b)*, 36260-75-0; *(3c)*, 62882-52-4; *(3d)*, 62882-53-5; *(3e)*, 62882-54-6; *(3f)*, 62882-55-7; *(3g)*, 62882-56-8; *(3h)*, 2629-42-7; *(3i)*, 62882-57-9; *(3j)*, 62882-58-0; *cis*-stilbene oxide, 1689-71-0; *trans*-stilbene oxide, 1439-07-2; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0; benzaldehyde, 100-52-7

[1] This work was supported by the Science Research Council.
[2] *A. W. Johnson*: Ylid Chemistry. Academic Press, New York 1966.
[3] *A. W. Johnson, H. Schubert*, J. Org. Chem. *35*, 2678 (1970); *N. A. Nesmeyanov, V. V. Prardina, O. A. Reutov*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1965*, 1474.
[4] *S. Trippett, M. A. Walker*, J. Chem. Soc. *C 1971*, 1114; *I. Gosney, D. Lloyd*, Tetrahedron *29*, 1697 (1973).
[5] Compounds *(3g)* to *(3j)* were heated under reflux for 3 h.

Regiospecific Synthesis of Mono- and Polyiodo Derivatives of Benzene

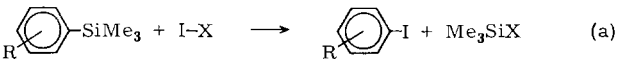
By *Guy Félix, Jacques Dunoguès, Françoise Pisciotti*, and *Raymond Calas*[*]

The method most commonly employed for the synthesis of aromatic iodo compounds consists in the substitution of a nitro group by an iodine atom *via* amino and diazo compounds as intermediates. This method is not always convenient, even for monoiodination; on polyiodination, problems arise because many steps are involved starting from materials which are often difficult to prepare. On the other hand, it is known that the Me_3Si group in aryl(trimethyl)silanes can be replaced by iodine on reaction with iodine[1] or iodine chloride[2], and we have recently reported on the synthesis of polysilylated aromatic compounds[3].

We describe here the regiospecific formation of mono- and polyiodo derivatives of benzene from the corresponding commercially available chloro compounds *via* the trimethylsilyl derivatives as intermediates. These syntheses proceed rapidly, afford high yields of desired product, and are easy to carry out.

Three reagents were employed:
I_2 (procedure A)
ICl (procedure B)
IBr (procedure C)

The reactions proceed according to equations (a) and (b). Results are summarized in Table 1.



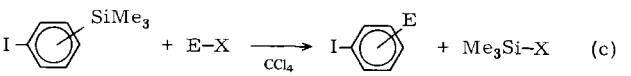
(a)

$$C_6H_{6-n}(SiMe_3)_n + n\ I{-}X \longrightarrow C_6H_{6-n}I_n + n\ Me_3SiX \qquad (b)$$

The yields are 80 % or more, regardless of whether the trimethylsilyl groups are partially or totally replaced by iodine. Procedure B affords almost quantitative yields. The substituents have little if any effect on the orientation of the reaction. For example, *o*-, *m*-, and *p*-iodotoluene are obtained in comparable yields, and the yields of *o*- and *p*-iodobenzenesulfonic acids are only slightly lower than the yield of the *meta* derivative.

Mixed dihalobenzenes can also be easily synthesized, even if the halogen atom is in the *meta* position.

The last two examples in Table 1 show that the Me_3Si group in iodo(trimethylsilyl)benzenes can also be replaced by electrophiles in accordance with equation (c).

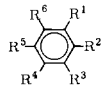


(c)

E–X = Me_3SiO_3S–Cl, Br–Br

[*] Dr. G. Félix, Dr. J. Dunoguès, Dr. F. Pisciotti, Prof. R. Calas [+]
Laboratoire de Chimie Organique, Université de Bordeaux I
351 Cours de la Libération, F-33405 Talence (France)
[+] Author to whom correspondence should be addressed.

Table 1. Compounds synthesized.



Starting compound						Product [a]	Yield [%] (Procedure)	B.p. [°C/torr] (M.p. [°C])
R^1	R^2	R^3	R^4	R^5	R^6			
CH_3	Me_3Si	H	H	H	H	$R^2=I$	87 (A), 96 (B)	97—100/25
CH_3	H	Me_3Si	H	H	H	$R^3=I$	90 (A), 96 (B)	95—97/25
CH_3	H	H	Me_3Si	H	H	$R^4=I$	93 (A), 97 (B)	98—100/25 (35.5)
Me_3Si	Me_3Si	H	H	H	H	$R^1=R^2=I$	87 (A), 96 (B)	A: 158—160/25, B: 171—176/30
Me_3Si	H	Me_3Si	H	H	H	$R^1=R^3=I$	85 (A), 95 (B)	A: 155/25 (39) B: 170—172/30 (39.5)
Me_3Si	H	H	Me_3Si	H	H	$R^1=R^4=I$	90 (A), 97 (B)	A: 155/25 (130) B: 170—172/30 (129)
Me_3Si	Me_3Si	H	Me_3Si	H	H	$R^1=R^2=R^4=I$	95 (B)	(91.5)
Me_3Si	Me_3Si	H	Me_3Si	Me_3Si	H	$R^1=R^2=R^4=R^5=I$	95 (B)	(253)
Me_3Si	Cl	H	H	H	H	$R^1=I$	92 (B)	130/30
Me_3Si	H	Cl	H	H	H	$R^1=I$	90 (B)	125—127/30
Me_3Si	H	H	Cl	H	H	$R^1=I$	94 (B)	125/30
Me_3Si	Me_3Si	H	H	H	H	$R^1=I$	81 (C)	154—158/30
Me_3Si	H	Me_3Si	H	H	H	$R^1=I$	85 (C)	146—150/30
Me_3Si	H	H	Me_3Si	H	H	$R^1=I$	82 (C)	146—150/30 (112—115)
Me_3SiO_3S	Me_3Si	H	H	H	H	$R^1=SO_3Na$, $R^2=I$	85 (B)	
Me_3SiO_3S	H	Me_3Si	H	H	H	$R^1=SO_3Na$, $R^3=I$	93 (B)	
Me_3SiO_3S	H	H	Me_3Si	H	H	$R^1=SO_3Na$, $R^4=I$	89 (B)	
Reaction (c), E—X = Me_3SiO_3S—Cl							80	
E—X = Br—Br							80	*o*: 104—105/30 *m*,*p*: 96—97/30

[a] Only the substituents for which the product differs from the starting material are given.

Experimental

Arylsilanes are obtained in high yields from chloroarenes by means of a Grignard reaction in tetrahydrofuran as solvent (all the monosilyl compounds were obtained in this way). Polysilyl derivatives are obtained from chloroarenes using $Me_3SiCl/Mg/HMPT$[3] as silylating agent. 1,4-Bis(trimethylsilyl)benzene can be prepared directly from benzene[4]. In reaction (c) we used $ClSO_3SiMe_3$[5] as sulfonating agent under the conditions previously described in the literature[3a, b]. For the bromination reaction according to equation (c) we also employed a procedure already described in the literature[6].

Synthesis of *m*-iodotoluene (Procedure A): A mixture of trimethyl-(*m*-tolyl)silane (16.4 g, 0.1 mol), iodine (25.4 g, 0.1 mol), and aluminum (100 mg) is heated under reflux for 4 hours. After cooling, the reaction mixture is taken up in 100 ml ether and washed, firstly with 50 ml of a 0.3 M aqueous solution of sodium thiosulfate and then with distilled water. After drying over Na_2SO_4 the *m*-iodotoluene is isolated by distillation. Yield: 19.6 g (90 %), b.p. 95 to 97 °C/25 torr.

Synthesis of 1,2,4,5-tetraiodobenzene (Procedure B): ICl (3.25 g, 2×10^{-2} mol) is added slowly to a solution of 1,2,4,5-tetrakis(trimethylsilyl)benzene[3b] (1.85 g, 0.5×10^{-2} mol) in CCl_4 (50 ml). The mixture is allowed to stand at room temperature for ½ h and then heated under reflux for 1 h. After cooling, 1,2,4,5-tetraiodobenzene is separated by filtration and recrystallized from benzene as white needles. Yield: 2.7 g (95 %), m.p. 253 °C.

Synthesis of *m*-iodophenyl(trimethyl)silane: A solution of IBr (11.4 g, 0.055 mol) in CCl_4 (30 ml) is added dropwise at 0 °C to a solution of *m*-bis(trimethylsilyl)benzene (11.1 g, 0.05 mol) in CCl_4 (80 ml) and the mixture allowed to stand for 1 to 2 h without cooling. After removal of $BrSiMe_3$ and CCl_4 by distillation the residue is taken up in ether and treated as in Procedure A. Yield: 11.5 g (85 %).

Received: May 9, 1977 [Z 737 IE]
German version: Angew. Chem. 89, 502 (1977)

CAS Registry numbers:
trimethyl(*o*-tolyl)silane, 7450-03-5; trimethyl(*m*-tolyl)silane, 3728-44-7; trimethyl(*p*-tolyl)silane, 3728-43-6; 1,2-bis(trimethylsilyl)benzene, 17151-09-6; 1,3-bis(trimethylsilyl)benzene, 2060-89-1; 1,4-bis(trimethylsilyl)benzene, 13183-70-5; 1,2,4-tris(trimethylsilyl)benzene, 17864-15-2; 1,2,4,5-tetrakis(trimethylsilyl)benzene, 17156-61-5; *o*-chlorophenyl(trimethyl)silane, 15842-76-9; *m*-chlorophenyl(trimethyl)silane, 4405-42-9; *p*-chlorophenyl(trimethyl)silane, 10557-71-8; trimethylsilyl *o*-trimethylsilylbenzenesulfonate, 55562-92-0; trimethylsilyl *m*-trimethylsilylbenzenesulfonate, 55562-93-1; trimethylsilyl *p*-trimethylsilylbenzenesulfonate, 1899-77-0; Table 1, Products from top to bottom: 614-37-2; 625-95-6; 624-31-7; 615-42-9; 626-00-6; 624-38-4; 615-68-9; 636-31-7; 615-41-8; 625-99-0; 637-87-6; Na 2-iodobenzenesulfonate, 62973-69-7; Na 3-iodobenzenesulfonate, 51119-76-7; Na 4-iodobenzenesulfonate, 22067-89-6; I_2, 7553-56-2; ICl, 7790-99-0; IBr, 7789-33-5; Me_3SiO_3S—Cl, 4353-77-9; Br_2, 7726-95-6

[1] *B. O. Pray, L. H. Sommer, G. M. Goldberg, G. T. Kerr, P. A. Di Giorgio, F. C. Whitmore*, J. Am. Chem. Soc. *70*, 433 (1948); *C. Eaborn*, J. Chem. Soc. *1949*, 2755; *1959*, 3077; *C. Eaborn, D. R. M. Walton, D. J. Young*, J. Chem. Soc. *B 1969*, 15.

[2] *L. M. Stock, A. R. Spector*, J. Org. Chem. *28*, 3272 (1963); *W. G. L. Aalbersberg, A. J. Borkovich, R. L. Funk, R. L. Hillard III, K. P. C. Vollhardt*, J. Am. Chem. Soc. *97*, 5600 (1975); *R. L. Funk, K. P. C. Vollhardt*, J. Chem. Soc. Chem. Commun. *1976*, 833.

[3] a) *P. Bourgeois*, Thèse d'Etat, Bordeaux 1970; b) *P. Bourgeois, R. Calas*, J. Organomet. Chem. *84*, 16 (1975); c) *R. Calas, J. Dunoguès*, J. Organomet. Chem. Library *2*, 277 (1976).

[4] *J. Dunoguès, R. Calas, N. Ardoin*, J. Organomet. Chem. *43*, 127 (1972); *M. Laguerre, J. Dunoguès, R. Calas, N. Duffaut, ibid. 112*, 49 (1976).

[5] *N. Duffaut, R. Calas, J. Dunoguès*, Bull. Soc. Chim. Fr. *1963*, 512.

[6] *R. A. Benkeser, A. Torkelson*, J. Am. Chem. Soc. *76*, 1252 (1954).

This column contains abstracts of selected progress reports and review articles. Orders for photocopies of publications reviewed should be directed to specialist libraries offering such services, *e.g.* British Library Lending Division, Boston Spa, Wetherby, Yorkshire LS23 7BQ, England. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Phenethylamines and tryptamines as well as related compounds of plant origin are reviewed by *T. A. Smith*. These compounds can be used in chemotaxonomic studies, and also command practical interest since many of them exert far-reaching physiological effects on higher animals. [Phenethylamine and Related Compounds in Plants. Phytochemistry *16*, 9—18 (1977); 183 references. Tryptamine and Related Compounds in Plants. *Ibid. 16*, 171—175 (1977); 119 references]

[Rd 951 IE—R]

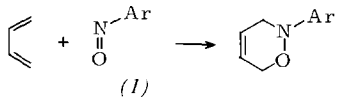
Phosphates in ceramics form the subject of a comprehensive survey by *A. E. R. Westman*. Following a general description of the structure of phosphates and phosphorus acids and oxides, the author discusses the four most important two-component and three-component systems, namely Na_2O—P_2O_5, CaO—P_2O_5, K_2O—Na_2O—P_2O_5, and CaO—Al_2O_3—P_2O_5, including notably the composition of the liquid phases. Technical glasses and their applications are discussed extensively. Further sections deal with refractories, porcelain, ceramic-metal systems, cements, and similar substances. [Phosphate Ceramics. Top. Phosphorus Chem. *9*, 231—405 (1977); 963 references]

[Rd 952—L IE]

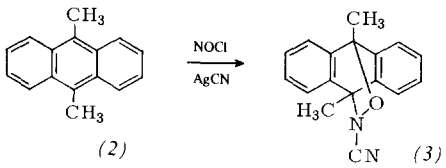
Micelles of ionic detergents in aqueous solutions are reviewed in a paper by *L. R. Fisher* and *D. G. Oakenfull*. In fairly concentrated solutions, 10—100 detergent molecules aggregate into micelles, shaped like oblate spheres, with the nonpolar hydrocarbon chains pointing inward and the polar groups outward. The "bound" gegenions also lie in this layer, while the "nonbound" ones are further off. The detergent molecules and their gegenions are in dynamic equilibrium with their environment; the mean residence time of a molecule in a micelle is 10^{-5} s. [Micelles in Aqueous Solution. Chem. Soc. Rev. *1*, 25—42 (1977); 89 references]

[Rd 954—F IE]

Electrophilic *C*-nitroso compounds *(1)* are the subject of a survey (Tilden lecture) by *G. W. Kirby*. NO compounds are more reactive than the corresponding NO_2 compounds. Their dimerization, rearrangement to oximes, and Diels-Alder reaction with dienes have long been known. Nitrosyl cyanide, a particularly strongly electrophilic compound, can be captured with *(2)* relatively safely and then liberated from the



(1)



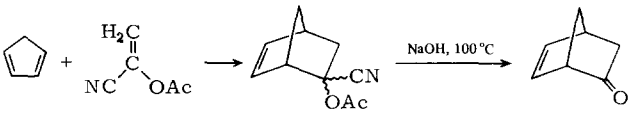
(2) *(3)*

(3) ⇌ *(2)* + NC–N=O

adduct *(3)*. *C*-Nitrosocarbonyl compounds can be prepared from hydroxamic acids by oxidation, captured with *(2)*, and liberated from *(3)*, where —CN is replaced by —COR. [Electrophilic *C*-Nitroso-compounds. Chem. Soc. Rev. *6*, 1—24 (1977); 45 references]

[Rd 953—F IE]

Reactions with ketene synthons are surveyed by *S. Ranganathan*, *D. Ranganathan*, and *A. K. Mehrotra*. Ketene synthons permit reactions which are not feasible with ketene itself. For instance, while norbornenones are not accessible by [4+2]-addition of ketene to cyclopentadienes, use of the ketene synthons of type $H_2C{=}CX^1X^2$ permits the synthesis of intermediates $>CX^1X^2$, *e.g. (2)*, which can be transformed into carbonyl compounds such as *(3)*. Suitable compounds are the esters



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

(1) and α-chloroacrylonitrile whose [1+4]-adducts can be converted into ketones under mild conditions. α-Chloroacryloyl chloride likewise affords norbornenone-like ring systems (chloride → azide → isocyanate → amine → imine → ketone). This reaction sequence is particularly suitable for dealing with 5-substituted cyclopentadienes in prostaglandin syntheses. Nitroethane is an interesting ketene synthon which can be used above all for the reaction of highly sensitive cyclopentadienes to give norbornenones (reaction at −100°C; cleavage of the nitronate with $TiCl_3$ at pH 5—6 to form the ketones). Adducts of acrylic acid can also be transformed *via* several steps into the ketones. The ideal ketene synthon—very easy addition to dienes and extremely facile transformation of the adducts into the final products—has yet to be discovered. [Ketene Equivalents. Synthesis *1977*, 289—296; 28 references]

[Rd 955—M IE]

Methods of Seawater Analysis. By *K. Grasshoff*. With Contributions by *T. Almgreen, R. Dawson, M. Ehrhardt, S. H. Fonselius, B. Josefsson, F. Koroleff*, and *K. Kremling*. Verlag Chemie, Weinheim—New York 1976. 1st edit., xv, 324 pp., 58 figs., 29 tables, bound, DM 98.—.

Methods for the determination of elements and chemical compounds in seawater have developed very rapidly in recent years. Thus, routine procedures can now be used for quantitative analysis of trace metals and many organic compounds for which not a single reliable value was available ten years ago. The analytical methods for "classical" components of marine chemistry (*e.g.* for silicate, nitrate, and ammonia) have meanwhile also been improved. A powerful impetus toward this development came from the need to monitor changes in the environment—and thus also in the sea—including those due to human activity.

In view of this development, the books hitherto available on analysis of seawater are in part outdated. The best of them, "A Practical Handbook of Seawater Analysis" by *J. D. H. Strickland* and *T. R. Parsons*, is after all nearly ten years old. It is therefore very welcome that *Grasshoff* and his colleagues have taken the trouble to provide a largely new volume.

In this book methods are described for the determination of "dissolved" materials (particle size $<0.45\,\mu m$) as well as of particulate carbon and nitrogen. The authors do not restrict themselves to giving precise analytical directions, but also tell the reader about the occurrence and concentration range of the materials in seawater and about the physical and chemical background of the analytical process. After two general sections on the collection, filtration, and storage of seawater samples, methods are described for the determination of the following substances and parameters: the salinity, calcium, strontium, magnesium, chloride, sulfate, bromide, fluoride, boric acid, oxygen, hydrogen sulfide, thiosulfate, pH, alkalinity, total carbon dioxide, phosphate, ammonia, nitrite, urea, silicate, arsenate, and organically bound nitrogen. Only slight changes in these procedures are likely to be made in the near future, but the situation is different for the other materials and groups treated in the book, namely the trace metals zinc and cadmium, particulate organic carbon and nitrogen, polyphenolic compounds, aromatic and chlorinated hydrocarbons, and carbohydrates. In the case of these materials the development of analytical methods is at present so rapid that the procedures described do not all represent current practice. For example, there is no mention of atomic absorption spectrophotometry, by which many heavy metals can be very elegantly determined; similarly, the methods published recently for the analysis of chlorinated hydrocarbons in seawater are not yet taken into account.

The nutrient salts dissolved in seawater are now determined automatically in many seaborne and land laboratories, and in view of their importance these methods are described in a special section.

"Methods of Seawater Analysis" will be of great value to marine chemists, practising analysts, and many marine biologists. However, since it does not include all the substances and groups occurring in seawater, *Strickland* and *Parson*'s "Handbook" is still essential. To keep up to date with the analytical procedures the *Grasshoff* book should be revised and supplemented a few years hence.

Günter Weichart [NB 377 IE]

Principles of Pyrometallurgy. By *C. B. Alcock*. Academic Press, London—New York 1976. 1st edit., xiii, 348 pp., various figs. and tables, bound, 8.50.

This monograph is an excellent presentation of the physicochemical principles of high-temperature isolation of metals.

The book is divided into three chapters describing very clearly the experimental data, theoretical principles, and models, which can be read independently of one another.

The thermodynamics and kinetics of roasting and sintering reactions as preliminaries to isolation of the metals are treated in the first chapter. The second chapter contains the most important principles of extractive metallurgy and isolation of the metals from sulfides, oxides, and halides. Reduction of iron ores is briefly described, but not the direct reduction process. Refining processes are given in the third chapter, namely zone melting, high-temperature distillation, remelting of metals in slags (including the electro-slag-remelting process), vacuum degassing, chemical transport, and electrolytic methods.

Owing to the number and variety of the processes described it cannot be expected that the reader will receive a complete picture in the mere 340 pages of this book. An extensive bibliography (including monographs) is therefore given at the end of each section; the original literature cited extends up to 1972.

In many respects this book and *F. D. Richardson*'s two-volume "Physical Chemistry of Melts in Metallurgy", a work published in 1974 by Academic Press, complement each other. Unlike *Richardson*, however, *Alcock* cites also the most important German publications. The book is addressed to advanced students in the fields of inorganic (industrial) chemistry, applied physical chemistry, and metallurgy. In addition, it provides a good review for engineers and chemists working in industry. As there are few modern books dealing with the economically important field of raw-material treatment, *Alcock*'s work can be recommended.

Norbert Nowack [NB 378 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

New Applications of Organometallic Reagents in Organic Syntheses. Edited by *D. Seyferth*. Journal of Organometallic Chemistry Library 1. Elsevier Scientific Publishing Co., Amsterdam 1976. x, 488 pp., bound, $ 44.75.—Proceedings of a Symposium at the American Chemical Society National Meeting held in New York City, April 6—9, 1975.—ISBN 0-444-41473-8

Organometallic Chemistry Reviews: Organosilicon Reviews. Edited by *D. Seyferth, A. G. Davies, E. O. Fischer, J. F. Normant*, and *O. A. Reutov*. Journal of Organometallic Chemistry Library 2. Elsevier Scientific Publishing Co., Amsterdam 1976. viii, 404 pp., bound, $ 39.75.—ISBN 0-444-41488-6

Organometallic Chemistry Reviews. Edited by *D. Seyferth, A. G. Davies, E. O. Fischer, J. F. Normant,* and *O. A. Reutov.* Journal of Organometallic Chemistry Library 3. Elsevier Scientific Publishing Co., Amsterdam 1977. vi, 342 pp., bound, Dfl. 103.—ISBN 0-444-41538-6

Industrial Waste Water and Wastes—2 (Stockholm, 1975). Edited by *B. Göransson.* IUPAC Applied Chemistry Division. Pergamon Press, Oxford 1977. pp. 135—209, bound, $ 35.00.—ISBN 0-08-020954-8 (Y)/0-08-021057-0 (R)

25th International Congress of Pure and Applied Chemistry (Jerusalem, 1975). Edited by *Y. Marcus* and *L. Ben-Dor.* Pergamon Press, Oxford 1977. 73 pp., bound, $ 18.75.—ISBN 0-08-020952-1

Colloquium Spectroscopicum Internationale—XVIII (Grenoble, 1975). Edited by *J. P. Robin.* IUPAC Physical Chemistry Division. Pergamon Press, Oxford 1976. pp. 45—126, bound, $ 8.00.—ISBN 0-08-021569-6

Marine Natural Products (Aberdeen, 1975). Edited by *R. J. Thomson.* IUPAC Organic Chemistry Division. Pergamon Press, Oxford 1976. 44 pp., bound, $ 8.00.—ISBN 0-08-021242-5

Macromolecular Chemistry—11 (Jerusalem, 1975). Edited by *H. Eisenberg.* IUPAC Macromolecular Division. Pergamon Press, Oxford 1977. pp. 91—253, bound, $ 35.00.—ISBN 0-08-020975-0

Weinbau. Ein Lehr- und Handbuch für Praxis und Schule. Edited by *B. Götz.* Verlag Eugen Ulmer, Stuttgart 1977. 452 pp., bound, DM 54.—.—ISBN 3-8001-1205-1

Modified Polymers, Their Preparation and Properties (Bratislava, 1975). Edited by *A. Romanov.* IUPAC Macromolecular Division. Pergamon Press, Oxford 1977. 70 pp., bound, $ 15.00.—ISBN 0-08-020953-X

Anatomie und Physiologie des Menschen, Band 1: Die Zelle. 15 Lehrprogramme. By *D. F. Culclasure.* Verlag Chemie, Weinheim 1977. 2nd revised Edit., xxi, 131 pp., paper, DM 15.50 (single volume); DM 12.10 per volume when ordering the complete series (15 volumes).—ISBN 3-527-25711-X

Temperature, Part I: Arts and Concepts. Edited by *Th. H. Benzinger.* Vol. 9 of the series "Benchmark Papers in Human Physiology. Edited by *L. L. Langley.* Dowden, Hutchinson & Ross, Stroudsburg 1977. xiii, 353 pp., bound, $ 37.50.—ISBN 0-470-99067-8

Three-Dimensional Nets and Polyhedra. By *A. F. Wells.* A volume of the series "Wiley Monographs in Crystallography". John Wiley & Sons, New York 1977. xii, 268 pp., bound, $ 36.00.—ISBN 0-471-02151-2

Organic Chemistry. By *D. C. Neckers* and *M. P. Doyle.* John Wiley & Sons, New York 1977. xxxvi, 1147 pp., bound, $ 27.90.—ISBN 0-471-63091-8

The Uncertainty Principle and Foundations of Quantum Mechanics. Edited by *W. C. Price* and *S. S. Chissick.* John Wiley & Sons, London 1977. xvii, 572 pp., bound, £ 19.50.—ISBN 0-471-99414-6

IIC Studies. Studies in Industrial Property and Copyright Law. Vol. 1: Standards of Patentability for European Inventions. By *H. Ullrich.* Published by the Max-Planck Institute for foreign and international Patent, Copyright, and Competition Law, München. Verlag Chemie, Weinheim 1977. xxi, 116 pp., paper, DM 58.—.—ISBN 3-527-25695-4

Semimetals & Narrow-Bandgap Semiconductors. By *D. R. Lovett.* Vol. 10 of the series "Applied Physics Series". Edited by *H. J. Goldsmith* and *D. W. G. Ballentyne.* Pion Ltd., London 1977. viii, 256 pp., bound, £ 8.50.—ISBN 0-85086-060-1

Gmelin Handbuch der Anorganischen Chemie. Titan-Organische Verbindungen. Teil 1: Einkernige Verbindungen 1. Springer-Verlag, Berlin 1977. 8th Edit., xiv, 212 pp., bound, DM 481.—ISBN 3-540-93334-4

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone (06201) 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*) Pappelallee 3, P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE

International Edition in English

Volume 16 · Number 8
August 1977
Pages 493–558

Advances in Phase-Transfer Catalysis[1]

New synthetic methods (20)

By Eckehard V. Dehmlow[*]

Phase-transfer catalysis (PTC) has grown into a versatile preparative method in the last few years. The most notable new developments include the use of crown ethers as phase-transfer catalysts and the introduction of solid-liquid PTC. Some representative examples have been selected from the large number of new PTC reactions and some of them are summarized in tables.

1. Introduction

Three years ago we published in Angewandte Chemie an initial survey of a new method in preparative organic chemistry, in which substances located partly in an aqueous and partly in an organic medium are made to react in the presence of onium salt catalysts[2]. This phase-transfer catalysis (PTC) often has considerable advantages over conventional methods, namely:

saving on expensive anhydrous aprotic solvents,
shorter reaction time and/or lower reaction temperature,
use of aqueous sodium hydroxide instead of alkali metal alkoxides,
simpler workup.

The PTC method sometimes offers further advantages, such as:

the discovery of reactions that do not proceed otherwise,
modification of the selectivity and the product ratio (*e.g.* *O*-/*C*-alkylation), *i.e.* increased yields by suppression of side reactions.

The field has been developing very fast, as can be seen from the fact that some 400 new publications have appeared since 1974, and this circumstance, combined with the good response to our previous review[2], motivated the publication of the present article. The aim has been not to give a complete literature survey, but to describe new research on the mechanisms and to discuss the practical applications of PTC, with special reference to:

assessment of the practicability of the reactions on the basis of tabulated literature data on the extraction of anions and cations,
use of crown ethers as catalysts instead of onium salts,
the extension of PTC to solid-liquid reactions,
reaction mechanism in the presence of concentrated sodium hydroxide solution,
development of PTC versions of new types of reactions.

The concept of phase-transfer catalysis has meanwhile gained ground in the literature: three PTC-based preparations have been included in "Organic Syntheses", namely the alkylation of phenylacetonitriles[3], a PTC version of the carbylamine reaction[4], and the addition of alkylphenylacetonitriles to alkynes[5], so that PTC can now be regarded as an established method. The various fields have been surveyed not only in ref. [2], but also by *Mąkosza*[6] and in a brochure by *Brändström*[7a], which gives a thorough physical and mathematical derivation of the theory of ion-pair extraction together with a description of some preparative applications.

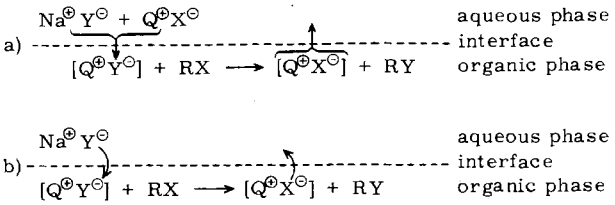
2. Fundamentals and Mechanisms

2.1. Mechanism of the Displacement Reactions

The assumed mechanism of PTC in the case of nucleophilic substitutions in particular[8] is shown in Scheme 1a, in which $Q^{\oplus}$ is an onium salt cation and $Y^{\ominus}$ is assumed to be more

[*] Prof. Dr. E. V. Dehmlow
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

lipophilic than $X^{\ominus}$. The catalyst cation $Q^{\oplus}$ migrates with the anion $Y^{\ominus}$ from the aqueous phase into the organic phase, where the weakly solvated ion pair formed undergoes very fast further reaction, after which $Q^{\oplus}$ returns to the aqueous phase with the anion $X^{\ominus}$. (The ion pairs are shown in square brackets throughout.)

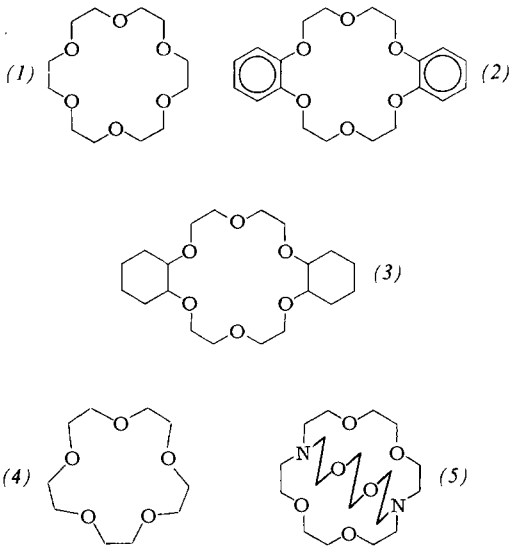


Scheme 1. PTC in nucleophilic substitutions (ion pairs in square brackets).

However, highly lipophilic catalyst cations are generally used, so that $Q^{\oplus}$ does not exist in the aqueous phase in any appreciable concentration. *Brändström*[7b] and more recently *Landini et al.*[174] have shown that $Q^{\oplus}$ stays in the organic phase and only the anions are exchanged across the interface, so that the simpler mechanism shown in Scheme 1 b applies. Apart from this slight variation, the mechanism of the displacement reactions discussed in ref. [2] is supported by subsequent investigations[9, 10]. In particular, there is a certain correlation between the rate constant of the PTC reaction and the ability of the catalyst to extract the anion into the organic phase[9]. However "correlation" here does not mean "proportionality", since other factors, such as anion solvation and anion-cation interactions in the ion pair dissolved in the organic phase, are also involved. Thus, it can be shown that a specific amount of water of solvation migrates into the organic medium with the anion and there influences the relative reaction rates (*e.g.* Cl:Br:I) and the absolute reaction rate[10]. For example, 3.4, 2.1, and 1.1 molecules of water are extracted per $Cl^{\ominus}$, $Br^{\ominus}$, and $I^{\ominus}$ ion respectively in the case of a water-chlorobenzene system with $Q^{\oplus} = C_{16}H_{33}P^{\oplus}(C_4H_9)_3$[10]. The question may arise whether the ion pair $[Q^{\oplus}Y^{\ominus}]$ or only the "free" anion $Y^{\ominus}$ is involved in the nucleophilic substitution (or both). The concentration of $Y^{\ominus}$ in the organic phase is determined by the dissociation equilibrium $[Q^{\oplus}Y^{\ominus}] \rightleftarrows Q^{\oplus} + Y^{\ominus}$. Kinetic measurements carried out by *Brändström* on several examples have shown that, in solvents of relatively low polarity (such as CH_2Cl_2, $CHCl_3$, and benzene), the ion pair is the dominant nucleophilic species[11, 12]. In solvents of higher dielectric constant, such as acetone, the dissociated anion presumably also plays a part.

2.2. Crown Ether PTC

Crown ethers can solubilize organic and inorganic alkali metal salts even in nonpolar organic solvents by providing the cation with an "organic mask" by complex-formation[13]. It follows logically from the mechanism of PTC shown above that $Q^{\oplus}$ need not necessarily be an onium salt but can also be an alkali metal ion complexed with a crown ether. Crown ethers were introduced into PTC by several teams in the years 1972—1974[14–19], and since then they have often been recommended, particularly for solid-liquid PTC reactions (see Section 2.3). However, their use outside the laboratory is not very attractive, since they are 50—100 times as expensive as the most inexpensive commercial quaternary ammonium salt Aliquat 336® = Adogen 464®.



So far nearly always only [18]crown-6 *(1)*, dibenzo[18]-crown-6 *(2)* and dicyclohexyl[18]crown-6 *(3)* have been used, irrespective of whether the other component is a potassium or a sodium salt. However, compounds *(1)*—*(3)* are known to bind potassium better than sodium, and stable sodium complexes are formed instead by the smaller crown ether [15]crown-5 *(4)*, which has so far been neglected. Detailed descriptions are now available for the laboratory preparation of these four crown ethers [cf. [20, 21] for *(1)*, [22] for *(2)* and *(3)*, and [20] for *(4)*], and an even simpler method has recently been reported for the direct preparation of *(1)* and *(4)* from ethylene oxide[68]. Other compounds sometimes suggested for use as ligands include differently substituted crown ethers[23], *Lehn*'s cryptates[24] [particularly [2.2.2], with the trade-name Kryptofix 222® (Merck) and with the formula *(5)*], and the so-called "polypodes"[25] and "octopus molecules"[26]. However, these have not gained wider application, since they are relatively difficult to prepare and are commercially unavailable or have only recently become available.

2.3. Solid-Liquid PTC

The high rate of PTC reactions in comparison with conventional reactions in hydroxylic solvents is due to the presence of weakly solvated and therefore highly reactive ion pairs in organic media. As mentioned in Section 2.1, a certain amount of water of hydration is co-extracted with the ion pair migrating from the aqueous to the organic phase. This can sometimes interfere, and sometimes it can fully suppress a reaction or direct it to a different path. It was therefore reasonable to suggest that the use of troublesome water should be abandoned, and that PTC should be carried out with solid salts. However, this raised new problems: dissolution on the crystal surface and deposition of a new salt, stirring speed, particle size of the salt, and possibly also deposition of the new salt on the salt to be dissolved acquire major importance. A further difficulty occurs when crown ether com-

plexes can be prepared only in homogeneous solutions in hydroxylic solvents, from which the undesirable solvent must then be displaced with the aid of a nonpolar one. This undoubtedly leaves a more or less substantial solvation envelope on the ion pair. In spite of these apprehensions, however, in many cases solid-liquid PTC is free from complications. Crown ethers are often used as catalysts, but quaternary ammonium salts generally also seem suitable. Recently it has been found that open-chain polyethers, diamines, and polyamines can also be used to catalyze the reaction of solid alkali metal salts with alkylating agents[32, 33].

The changed character of some well-known anions under these conditions is particularly remarkable. Thus, fluoride[18] and acetate[27] ions become strong nucleophiles and bases, and a slow substitution sometimes occurs even at room temperature (for the experimental data see Table 6). We have investigated a case in which liquid-liquid PTC fails while solid-liquid PTC is successful[28, 29]: sodium trichloro- or tribromoacetate is quite stable when dissolved in water and boiled with the phase-transfer catalyst, chloroform, and an olefin although $Q^{\oplus}{}^{\ominus}O_2CCX_3$ is extracted into the chloroform. With finely powdered solid sodium trihaloacetate decomposition and dihalocarbene addition occur slowly at room temperature and fast at 50—80°C in the presence of a phase-transfer catalyst.

$$[Q^{\oplus}{}^{\ominus}O_2CCX_3]_{org} \rightarrow [Q^{\oplus}X^{\ominus}] + CO_2 + :CX_2 \rightarrow \text{addition products}$$

In the conventional version of this reaction expensive anhydrous dimethoxyethane is used as the solvent. The sodium trihaloacetate does not react in this medium at room temperature, only at about 80°C and above. Solid-liquid PTC thus enables us to achieve something here that otherwise could not be done so simply, namely to obtain dihalocarbenes in a neutral solution at relatively low temperatures.

The changed reactivity observed in solid-liquid PTC has made some authors call these processes "reactions of naked anions", a striking though inaccurate phrase. It is true that in polar solvents, such as acetonitrile and acetone, partial dissociations of ion pairs does occur, particularly when the cation is a crown ether complex. On the other hand, however, as was tested in the reaction between *e.g.* benzyl chloride and solid potassium acetate in acetonitrile, the "anion activation" (relative reaction rate) depends to a large extent on the nature of the complexing agent used. Furthermore, the anion activation is not connected in a simple way with the extent to which the crown ether solubilizes potassium acetate[32]. The conclusion is that anion-cation interactions must play a part. In substitution reactions of benzyl tosylate with [18]crown-6 complexes in homogeneous acetonitrile solution, *Liotta et al.* observed extensive leveling out of nucleophilicity: $I^{\ominus}$, $Br^{\ominus}$, $Cl^{\ominus}$, and $F^{\ominus}$ ions gave practically the same reaction rate, while acetate and azide ions remarkably gave a reaction 7—10 times as fast[34]. Whereas the sequence of nucleophilicities in acetonitrile was similar to that found in the gaseous phase, the absolute reaction rates in acetonitrile were about 10^{11} times lower[34]. It must therefore be assumed that solvation persists in non-polar solvent solution, but is less pronounced and is very similar for different anions or ion pairs (cf. [30, 31]).

2.4. Mechanism of PTC in the Presence of Aqueous Alkali

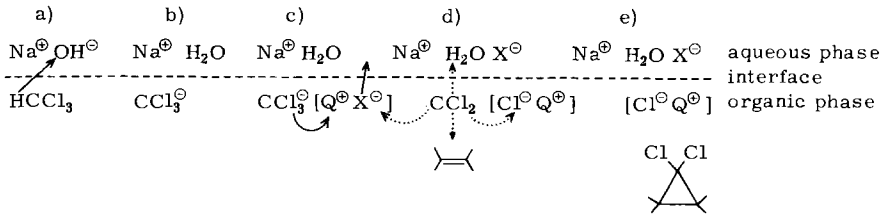
Some of the PTC reactions of the greatest interest for preparative purposes are carried out in the presence of concentrated aqueous alkalis—reactions such as the alkylation of C—H acidic compounds with a pK_a value down to 22—24, carbene synthesis, hydrolysis, H/D exchange and isomerizations, eliminations, and Wittig and Horner reactions.

At first sight, the mechanisms of these reactions have little in common. The C—H acidic compounds exhibit a gradual transition: relatively strong acids of the type of acetylacetone dissolve in sodium hydroxide and can be extracted into the organic medium by the catalyst as ion pairs, while weaker C—H acids are present in the organic medium partly as ion pairs and partly as the unchanged neutral molecules, and very weak acids such as fluorene are presumably almost entirely un-ionized.

Yet all three types can be alkylated by PTC. In the first two cases the mechanism is as shown in Scheme 1b, with the rider that $Y^{\ominus}$ is the conjugated base of the substrate; in the case of the alkylation of very weak C—H acids (and in the other reactions mentioned above) it was assumed before that the quaternary ammonium hydroxide is extracted and then reacts further in the organic medium[2]. These quaternary ammonium hydroxides are known to be soluble to some extent in nonpolar media. For example, Triton B (benzyltrimethylammonium hydroxide) is marketed as a methanolic solution. Displacement by a solvent like toluene is in principle possible, but only a slight solubility remains after the thorough removal of methanol. The solubility can be increased by using more lipophilic cations (see Section 3.2). However, further investigations have now shown that the phase transfer of $OH^{\ominus}$ ions frequently does not explain the catalytic reaction, for as soon as a more lipophilic anion is present—and it is formed necessarily from the alkylating agent—it is extracted preferentially into the organic medium (cf. Table 5). In fact, when tetrabutylammonium chloride in benzene is shaken with concentrated caustic soda, titration shows that only 0.5—2% of it is in the OH form and about 50% of it remains in the chloride form in the organic phase; the rest is in the aqueous phase[*]. The situation is of course different when the organic medium is partially miscible with water or rather aqueous caustic soda (*e.g.* THF or higher alcohols), for then a large amount of the $OH^{\ominus}$ form is titratable in the organic layer.

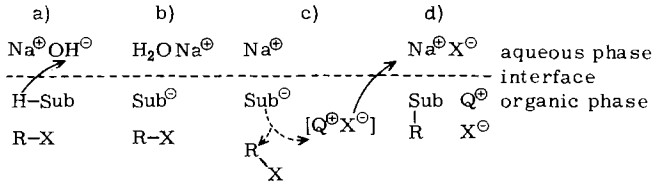
Catalysis by micellar[35] or reverse micellar systems[35, 36] similarly cannot be decisive for the course of the reaction in the presence of concentrated alkalis. Typical micelle-forming compounds (surfactants) have rod-shaped molecules with a polar head and a long lipophilic tail, whereas typical PTC compounds have a symmetrical structure. Besides, the fact that the ammonium salt is present in the organic phase and the latter contains practically no titratable alkalinity indicates that the onium salt does not bring about either partial dissolution of the organic substances in water (micellar phase) or partial dissolution of NaOH in the organic medium (reverse micelles).

[*] In the conc. $NaOH/CH_2Cl_2$ system, more than 97% of the ammonium salt is in the organic phase, while when dilute NaOH is used, this salt is distributed between the two phases according to the lipophilicity. CH_2Cl_2 reacts with $NR_4^{\oplus}OH^{\ominus}$ slowly forming $NR_4^{\oplus}Cl^{\ominus}$ [44].



Scheme 3. Stages in the preparation of dichlorocarbene by the PTC method.

After the exclusion of all other possibilities only the interfacial area remains as a site for the PTC reaction in the alkylation of very weak C—H acids (H-Sub) and the preparation of carbenes. According to the mechanism proposed by *Makosza*[6], a double layer of deprotonated substrate molecules and alkali metal gegenions is formed at the interface (Scheme 2). The cations and anions are present in different phases, neither can exist in the other phase, and both are extensively immobilized by Coulombic forces, so that only H/D exchange and isomerization are possible as fast reactions at this stage (a, b). The catalyst ion pair $[Q^{\oplus}X^{\ominus}]$ acts partly by facilitating the deprotonation but mainly by detaching the substrate anions anchored at the phase boundary, with the release of the original gegenion of the catalyst into the water and fast subsequent reaction with the alkylating agent (c, d). This assumption is supported by the finding that a number of PTC reactions proceed without a catalyst but are accelerated by one[6]. Furthermore, we have been able to show that the alkylation of benzyl cyanide[67] proceeds equally fast with the catalysts tetrabutylammonium chloride and tetrabutylammonium picrate. These two catalysts also have the same activities in the preparation of dichlorocarbene[37]. However, their extraction constants differ by a factor of no less than 10^6 (Table 5). If the small amount of extracted $OH^{\ominus}$ were significant, the competition with the picrate would show a very pronounced effect. Further indications of reactions at the interface have been published very recently[176].



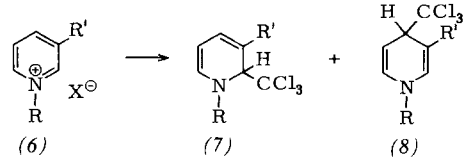
Scheme 2. Stages in the PTC alkylation of very weak C—H acids (H-Sub).

The analogous sequence shown in Scheme 3 is followed in the preparation of dihalocarbenes: first an $Na^{\oplus}/CCl_3^{\ominus}$ double layer is formed (a, b) and then the "anchored" $CCl_3^{\ominus}$ at the interface is detached by the catalyst cation (c). However, it is very important to note that no *stable, long-lived* $[Q^{\oplus}CCl_3^{\ominus}]$ exists in the organic medium; instead, the free carbene (d) coming from (c) is in equilibrium with the "anchored" trichloromethylide (b) *via* (c), and thus remains reactive for days when the subsequent sequence of steps is slow. In contrast, conventional dihalocarbene reactions come to an end the moment contact is established with the base. For example, $LiCCl_3$ decomposes above $-73\,^{\circ}C$[175]. The following species compete for the free carbene (d): the leaving group $Cl^{\ominus}$ (reverse reaction), any free halide $X^{\ominus}$ that may be present (the mixed carbenes: CClX can be captured as adducts), water or $OH^{\ominus}$ (hydrolysis), and finally the olefin (e). Since H_2O is present in the other phase, CCl_2 hydrolyzes very slowly. The proportion of hydrolysis of the chloroform varies between 4 and 58 %, depending on the nucleophilicity of the olefin used. In addition, the reaction rate depends on the nucleophilicity of the olefin[38] (cf. Table 1).

Table 1. Reaction of 0.4 mol of chloroform with 0.2 mol of 50 % NaOH and 0.1 mol of olefin in the presence of 1 mmol of TEBA (triethylbenzylammonium chloride) for 4 h at 23 °C [38].

Olefin	Amount of $HCCl_3$ consumed [mmol]	of this, amount hydrolyzed [mmol]	[%]	As CCl_2 adduct [mmol]
Without TEBA (cyclohexene)	3.4	3.4	100	0.0
With TEBA, without olefin	20.8	20.8		—
3,3-Dimethylbut-1-ene	25.0	14.5	58	12.0
n-Hexene	53.6	8.4	15.7	45.2
Cyclohexene	67.3	11.85	17.6	55.45
2-Methylbut-2-ene	80.4	3.3	4.1	77.1

Another indication of the importance of the phase boundary is that, in the presence of concentrated caustic soda, the kinetics becomes independent of the stirring speed only at over 750 rpm, whereas in "normal" PTC reactions this already happens at speeds between 80[39] and 200[9a] rpm. On shaking pyridinium salts *(6)* in chloroform with aqueous alkali, only the adducts *(7)* and *(8)* are formed in a clean reaction, but not pyridylmethanols, which tend to undergo resinification[40,41,6]. This again indicates that $OH^{\ominus}$ is not extracted into organic media.



(6) *(7)* *(8)*

It still remains to be established whether the mechanism shown in Schemes 2 and 3 applies not only to the alkylation of weak C—H acids and the formation of carbenes but also to all other reactions with aqueous caustic soda. In the hydrolysis of esters with concentrated NaOH, we have found that besides tetrabutylammonium hydrogen sulfate (best catalyst) anionic and non-ionic micelle-forming agents were effective catalysts[42].

2.5. Polymer-Bound Catalysts

Several authors have recently used polymer-bound catalysts. This "three-phase catalysis" method[43] simplifies the removal

of the catalyst after the reaction, but presents problems connected with swelling, mixing, and diffusion during the reaction. These problems are often not easy to solve. The reaction of course again takes place at the interface. In the case of dichlorocarbene additions carried out in a system of aqueous NaOH, chloroform, and olefin at room temperature in the presence of weakly or strongly basic commercial ion exchangers, we obtained very low yields[44] in preliminary experiments, although examples from the literature indicate that these reactions are in principle possible. A survey is shown in Table 2.

Table 2. Reactions of polymer-bound catalysts.

Reaction	Catalyst	Max. yield [%]	Ref.
$CN^{\ominus}$ + R Br(Cl)	Crosslinked polystyrene with $-CH_2-N^{\oplus}(CH_3)_2(n\text{-}C_4H_9)Cl^{\ominus}$	92 (50)	[43]
Dichlorocarbene addition	Crosslinked polystyrene with $-CH_2-N^{\oplus}(CH_3)_2(n\text{-}C_4H_9)Cl^{\ominus}$	99	[43]
$CN^{\ominus}$ + R Br	Crosslinked polystyrene with $-CH_2-CO-(CH_2)_n-N^{\oplus}(CH_3)_3Cl^{\ominus}$	100	[45]
O/*C*-Alkylation of β-Naphthol	Crosslinked polystyrene with $-CH_2-CO(CH_2)_n-N^{\oplus}(CH_3)_3Cl^{\ominus}$	60—95 % (*O*-Alkylation)	[45]
Dichlorocarbene Addition	Amberlite IRA-400	66	[46]
$I^{\ominus}$, $CN^{\ominus}$ + R Br	Crosslinked polystyrene with onium salts, crown ethers, and other ligands	95	[47]

The kinetics of this three-phase catalysis have been settled recently. The activity of the resin is directly proportional to the number of $NR_4^{\oplus}$ groups, though only at a relatively low substitution density. Normal ion-exchange resins, in which a higher proportion of the phenyl rings carry $NR_3^{\oplus}$ groups, have been found to be much less suitable[173].

3. Choice of Solvent and Catalyst

3.1. Extraction Constants with Water/Organic Solvent Systems

The distribution of onium salts between water and an organic medium depends to a large extent on the latter's nature. Table 3 shows some of the values obtained by *Brändström* for tetrabutylammonium bromide[48].

Table 3. Apparent extraction constants calculated from the distribution of 0.1 M $N(C_4H_9)_4^{\oplus}Br^{\ominus}$ between water and the solvent (after *Brändström* [48]).

CH_2Cl_2	35	$ClCH_2-CH_2-CH_2Cl$	2.9	*n*-$C_3H_7-CO-CH_3$	1.7
$CHCl_3$	47	C_6H_5Cl	< 0.1	$C_2H_5-CO-CH_3$	14
$CDCl_3$	41	*o*-$Cl_2C_6H_4$	< 0.1	*n*-C_4H_9OH	69
CCl_4	< 0.1	$CH_2=CCl_2$	< 0.1	$C_2H_5-CHOH-CH_3$	23
CH_3-CHCl_2	0.5	*trans*-CHCl=CHCl	< 0.1	*n*-C_3H_7-CN	13.7
$ClCH_2-CH_2Cl$	6.1	*cis*-CHCl=CHCl	33	CH_3NO_2	168
$ClCH_2-CHCl_2$	8.6	$CHCl=CCl_2$	0.2	$ClCH_2-CN$	170000
$Cl_2CH-CHCl_2$	145	$CH_3COOC_2H_5$	0.2	Cl_3C-CN	2.3
$Cl_2CH-CCl_3$	< 0.1	$C_2H_5OC_2H_5$	< 0.1		
n-C_3H_7Cl	< 0.1	$C_2H_5-CO-C_2H_5$	1.1		

The solvents in the right-hand column can hardly be used, because of their partial solubility in water and the risk of side reactions. It can be seen from these data that, of the aprotic solvents that are virtually immiscible with water, chloroform and dichloromethane show by far the most favorable extraction behavior. They are therefore nearly always preferable to other solvents occasionally used in PTC reactions, such as benzene, ether, chlorobenzene, and *o*-dichlorobenzene, when the reaction cannot be carried out without any solvent at all. When good nucleophiles are reacted with unreactive alkylating agents in dichloromethane, the difficulty is that reaction with this solvent gives rise to compounds of the type of *(9)* as by-products[49, 50]. By changing the conditions one can prepare these compounds *(9)* in a satisfactory manner[51–53].

$$CH_2Cl_2 + 2\,[Q^{\oplus}X^{\ominus}] \longrightarrow CH_2(X)_2 + 2\,[Q^{\oplus}Cl^{\ominus}]$$

(9)

X = *O*-Aryl, *O*-Alkyl, S-R, OCR, $CH(Z)(Y)$ (O)

When chloroform is used in the presence of strong bases, the danger is that a possibly undesirable dichlorocarbene reaction occurs and that orthoformic esters may be formed[54].

3.2. Extraction Constants for Cations and Anions

The extraction behavior of the quaternary ammonium salts with a great variety of anions has been elucidated in a series of fundamental studies by *Schill*, *Modin*, *et al.* A detailed theoretical discussion of the distribution of a salt $Q^{\oplus}X^{\ominus}$ between water and an organic phase has been presented by *Brändström*[7a] on the basis of this series of studies. The distribution D_Q of Q between the two phases is given by:

$$D_Q = \frac{[QX]_{org}}{[Q^{\oplus}]_{water}} = E_{QX}[X^{\ominus}]_{water} \qquad (a)$$

where $[QX]_{org}$ is the concentration or the activity of the ion pair in the organic phase, $[Q^{\oplus}]_{water}$ and $[X^{\ominus}]_{water}$ are the concentrations (activities) in water, and E_{QX} is the extraction constant. It is important to bear in mind that the distribution D_Q is governed not only by the distribution coefficient but also by $[X^{\ominus}]_{water}$, which is in turn influenced by the pH of the aqueous layer and the association and dissociation of the ion pair in the organic phase.

In the case of competition between two anions $X^{\ominus}$ and $Y^{\ominus}$ for $Q^{\oplus}$, we have:

$$\frac{[QX]_{org}}{[QY]_{org}} = \frac{E_{QX}[X^{\ominus}]_{water}}{E_{QY}[Y^{\ominus}]_{water}} \quad (b)$$

The extraction constants of *e.g.* symmetrical quaternary ammonium picrates have been listed in the literature[55] (Table 4).

Table 4. Extraction constants E_{QX} of picrates between water and an organic medium [55, 7a].

Solvent	Cation $N(CH_3)_4$	$N(C_2H_5)_4$	$N(n\text{-}C_3H_7)_4$	$N(n\text{-}C_4H_9)_4$	$N(n\text{-}C_5H_{11})_4$
CH_2Cl_2	1.5	219	2.9×10^4	4.8×10^6	2.5×10^8
$CHCl_3$	0.22	21	4365	8.1×10^5	
Benzene		0.22	35	3890	7.9×10^5
CCl_4				87	2.9×10^4

Comparison of the logarithms of these values (*i.e.* $\log E_{QX}$) shows that they increase by about 0.54 per carbon atom in the cation. In a first but relatively good approximation, this also applies to the quaternary ammonium salts of other anions. Less symmetrical ammonium ions have deviating absolute values but show a similar increase in the E_{QX} values within the homologous series[56, 57].

What is important is that the lipophilicity of a benzyl group is comparable not to that of an *n*-heptyl residue but to that of an *n*-propyl or *n*-butyl group.

For normal anions less lipophilic than picrate, a useful PTC catalyst should contain 15 or more carbon atoms, for otherwise the extraction of the salt is insufficient. Thus, TEBA is in many cases too hydrophilic. On the other hand, the salts of even lower ammonium cations are only sparingly soluble in concentrated solutions of alkali metal hydroxides, and TEBA is suitable in these cases.

For multiply charged anions the extraction rule is that a singly charged anion (*e.g.* $H_2PO_4^{\ominus}$) is extracted more easily than a doubly charged one (*e.g.* $HPO_4^{2\ominus}$), which in turn is extracted more easily than a triply charged one (*e.g.* $PO_4^{3\ominus}$). Therefore, tetrabutylammonium hydrogen sulfate can be used with advantage for the preparation of tetrabutylammonium salts of variously lipophilic anions according to *Brändström*, since, unlike the $HSO_4^{\ominus}$ ion, the sulfate formed in the neutralization remains quantitatively in the water.

Table 5 shows the extraction constants of some simple anions. It can be seen that the lipophilic groups have a strong influence on these values. If we ignore the concentration-dependent complicating factors (like ion-pair association and dissociation and the influence of the pH), we can attempt to predict whether a certain PTC reaction will proceed or not. For example, consider the reaction:

RX (0.05 mol, without solvent, ≈10 ml) + KOAc (0.1 mol in 20 ml of water) $\xrightarrow[0.5\ \text{mmol}]{Bu_4NX}$ ROAc

The relative reaction rates for X = Cl, Br, I will be affected by: a) the reaction itself (for which, I > Br ≫ Cl) and b) the relative degree of the extraction of $OAc^{\ominus}$ in comparison with $X^{\ominus}$. We assume that practically all $Q^{\oplus}$ is present in the organic phase and that the ratio of the extraction constants is independent of the medium. We now calculate the fraction x of $Q^{\oplus}$ that is paired with $OAc^{\ominus}$; substitution into Eq. (b) gives for iodide:

$$\frac{x}{0.05-x} = \frac{7.6\times10^{-3}}{1023} \times \frac{10}{x}$$

Solution of the quadratic equation gives $x = 0.0019$. This means that 3.8% of the tetrabutylammonium ions exist in the form of Bu_4NOAc and the rest (96.2%) in the form of Bu_4NI, this portion thus being inactive for the reaction. A similar calculation shows that, after a 50% conversion, only 0.002% of the catalyst exists in the $OAc^{\ominus}$ form. For chloride and bromide we obtain the more favorable values of respectively 72.8 and 23.7% for the $Q^{\oplus}OAc^{\ominus}$ form at the beginning of the reaction. The favorable acetate/bromide extraction relationship combined with the still fast reaction seems the best combination for the planned experiment. In the case of the iodide, the question is whether enough acetate is extracted to maintain the reaction. These obviously rough calculations were confirmed in principle by experiments in which the reactants were heated for 2 h at 100°C, and where the conversion was 100% for the bromide, 22% for the chloride, and 37% for the iodide[71].

Table 5. Anion extraction constants E_{QX} of tetra-*n*-butylammonium ion pairs between water and chloroform and—in square brackets—between water and dichloromethane [7a].

Anion	E_{QX}		Ref.	Anion	E_{QX}	Ref.
$Cl^{\ominus}$	0.78	(0.35)	[58, 59]	$CH_3COO^{\ominus}$	7.6×10^{-3}	[60]
$Br^{\ominus}$	19.5	(17)	[58, 59]	$C_6H_5\text{—}CH_2\text{—}COO^{\ominus}$	1.86	[60]
$I^{\ominus}$	1023	(2188)	[58, 59]	$C_6H_5\text{—}COO^{\ominus}$	2.45	[60]
$ClO_4^{\ominus}$	3020	(4.37×10^4)	[58, 59]	Salicylate	263	[60]
$NO_3^{\ominus}$	24.5	(79)	[58, 59]	3-Hydroxybenzoate	0.03	[60]
				Phenoxide	0.93	[60]
				Picrate	8.1×10^5	[60]
				p-Toluenesulfonate	214	[61]
				Naphthalene-2-sulfonate	2818	[61]
				Anthracene-2-sulfonate	1.3×10^5	[62]
				Trinitrobenzenesulfonate	2.9×10^4	[61]

Similar but somewhat more complicated calculations can be used to predict the ease of alkylation of weak C—H acids[7a].

The literature values for the extraction constants of quaternary ammonium hydroxides show scatter and are conflicting, unreliable, and several orders of magnitude too high. Firstly, they have sometimes been determined in the presence of water and organic solvents partially miscible with water (THF, alcohols). Secondly, the co-titration of tertiary amines in the organic medium easily leads to anomalies, these amines being formed in the reaction $R_4N^{\oplus}OH^{\ominus} \rightarrow R_3N + ROH$ or introduced as $R_3NH^{\oplus}X^{\ominus}$ impurities in $R_4N^{\oplus}X^{\ominus}$. A rough estimate of the extraction constant of tetra-*n*-heptylammonium hydroxide between water and benzene is 1.2, from which extrapolation gives $E_{Bu_4NOH} \approx 10^{-6}$[44]. This means that the extraction constant of hydroxyl ion is about 10^4 times smaller than that of chloride. This result should be valid, to a first approximation, for all water-immiscible solvents[44].

3.3. Empirical Comparison of Catalysts

3.3.1. Reactions without Concentrated Alkalis

Herriott and *Picker* compared the activities of 23 catalysts in the reaction of alkyl bromide with the thiophenoxide ion in a water/benzene system[9a]. It has been pointed out in Section 3.1 that benzene is not an ideal organic medium for such reactions. Accordingly, these authors found that the catalysts differed less in more strongly polar organic solvents. As shown in Section 3.2, the very hydrophilic catalysts such as the lower alkyl compounds up to tetra-*n*-propylammonium halide and TEBA fail almost completely. The same applies to alkylpyridinium salts. Surfactants of the type $(n\text{-}C_{6-16}H_{13-33})N^{\oplus}(C_2H_5)_3X^{\ominus}$ show somewhat better but still low activity. It has been found that symmetrical ions are more active than ions with only one long chain. In the case of the same substituents, phosphonium ions are somewhat better than ammonium ions, and alkyl groups are more suitable than phenyl groups in the onium salt. The highest activity is shown by methyltrioctylammonium chloride (tradenames of technical-grade, not entirely uniform product Aliquat 336® and Adogen 464®; cf. [69]), tetra-*n*-butylphosphonium chloride, ethyltrioctylphosphonium bromide, and dicyclohexyl[18]-crown-6, together with tetra-*n*-butylammonium salts, but the activity of this last group is reduced in benzene. Numerous examples from the literature, where no rigorous comparison of several catalysts was made, confirm that these ammonium and phosphonium salts with 15—25 carbon atoms can be used with advantage. Mention should be made here again of the possible undesirable effect of the gegenion (see Section 3.2).

3.3.2. Reactions in the Presence of Concentrated Alkalis

The situation is different here, because the solubilities are different, and even lower alkyl groups can often be used in the onium salt. Numerous catalysts have been compared in the case of dihalocarbene reactions[37, 46, 63]. There are only small differences between most tetraalkylammonium and tetraalkylphosphonium catalysts, and it is interesting to note that these differences do not run parallel for dichlorocarbene and dibromocarbene[37, 63]. Phosphonium salts with three or four aryl groups are inactive, and so are tetramethylammonium iodide and alkylpyridinium salts. On the other hand, tertiary amines are active in this case[64], since under the reaction conditions they are converted into catalysts of the type $R_3N^{\oplus}—CX_2H\ X^{\ominus}$[65]. The anion introduced with the catalyst also affects the catalytic activity; hydrogen sulfate and chloride are the best in this respect. The following catalysts can be particularly recommended for CCl_2 reactions: tripropylamine, tetrabutylammonium hydrogen sulfate or chloride, TEBA, Aliquat 336, trialkylsulfonium salts, and tetraalkylphosphonium salts, while symmetrical tetraalkylammonium bromides, Aliquat 336, and TEBA can be recommended for CBr_2 reactions. [18]Crown-6 and tetraphenylarsonium chloride were also found to be highly suitable in both cases.

We have compared some catalysts for the alkylation of benzyl cyanide[67] (cf. also [66]), and found that tetrabutylammonium hydrogen sulfate and chloride, tetraethylammonium bromide, and [18]crown-6 are the best, while TEBA and Aliquat 336 are somewhat less good. As regards the effect of the anions, iodide interferes, and perchlorate does so even more. We have found that ammonium salts have a low thermal stability at elevated temperatures. Thus, TEBA is converted into benzyldiethylamine to an extent of 72% after 20 h at 110°C in conc. NaOH and to one of 11.5% after 20 h at 60°C in conc. NaOH/CH_2Cl_2; phosphonium salts are somewhat more stable.

3.4. Amount of Catalyst

In substitution reactions the reaction rate is proportional to the amount of catalyst and can therefore vary within relatively wide limits. One generally uses between about 0.5 and 10 mol-% catalyst. When a lipophilic anion such as $I^{\ominus}$ threatens to bind the catalyst, or when a more selective reaction is attempted one can use molar quantities of the catalyst, which can often be easily recovered. Unlike most reaction products, many ammonium salts are insoluble in ether.

4. Preparative Applications

The most important recent preparative applications are listed in the following tables without any claim to comprehensiveness.

4.1. Simple Substitutions

Table 6 shows examples of simple substitutions and the preparation of esters, dithioesters, mixed phosphoric acid esters, aminophosphoric acid esters and phenyl aminosulfonates.

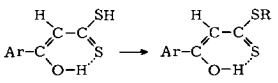
4.2. Alkylation of O—H, S—H, and N—H Bonds

While the preparation of ethers and thioethers is straightforward, *N*-alkylation generally requires an acidifying neighboring group (Table 7).

4.3. Alkylation of Activated C—H Bonds

The site of attack in the alkylation of ambidentate anions is influenced by the reactivity of the alkylating agent (dimethyl

Table 6. Recent examples of phase-transfer-catalyzed simple substitution reactions.

Reaction	Solvent	Catalyst	Yield [%]	Remarks	Ref.
$RBr \rightarrow ROAc$	CCl_4/H_2O	$(C_8H_{17})_3N^{\oplus}—C_3H_7Cl^{\ominus}$	68—75		[70]
$RBr \rightarrow ROAc$	Substrate/H_2O	NBu_4Br	100	2 h, 100 °C, 2 mol KOAc with RCl 22 %, with RI 37 %	[71]
$RX \rightarrow ROAc$ (X = Br, OTos, Cl)	CH_3CN or C_6H_6	[18]Crown-6	≈ 90	With sec. cpds, 10 % elimination	[27]
$RX \rightarrow RNO_2$ (much) + RONO (little)	CH_3CN	[18]Crown-6	32—70	With prim. alkyl	[72]
$ArCH_2X \rightarrow ArCH_2CN$	CH_3CN	[18]Crown-6	90—100		[72]
$ROMes \rightarrow RCN$	C_6H_6/H_2O	Aliquat 336	≈ 70		[73]
$RX \rightarrow RCN$ (X = Cl, Br)	C_6H_6 or CH_3CN	[18]Crown-6	≈ 100	With benzyl or prim. alkyl; with sec. cpds some elimination; with cyclohexyl only elimination	[74]
$RBr \rightarrow RCN$	Substrate/H_2O	Amines	Highly variable up to ≈ 100	Catalyst *in situ* from amines	[75]
$RX \rightarrow RCN$	Substrate/H_2O	Crown ethers	≈ 80		[16, 76]
$ArCOCl \rightarrow ArCOCN$	CH_2Cl_2/H_2O	NBu_4Br	≈ 60		[77]
$RX \rightarrow RF$ (X = OMes, Cl, Br)	Substrate/H_2O	$C_{16}H_{33}P^{\oplus}Bu_3Br^{\ominus}$	60—90	With benzyl and prim. cpds.	[78]
	CH_3CN or C_6H_6	[18]Crown-6	20—54	With sec. cpds; otherwise elimination	[18]
$RCH(CH_3)—OMes \rightarrow RCH(CH_3)—X$ opt. act opt. act (X = F, Cl, Br, I)	Substrate/H_2O	Aliquat 336	57—83	Opt. purity up to 89 % (for RCl)	[79]
$RX \rightarrow RY$ (X = OMes, Br, I) (Y = F, Cl, Br, I, SCN, ArS, $S^{2\ominus}$)	Substrate/H_2O	Crown ethers			[76]
$CH_2Cl_2 \rightarrow CH_2ClI + CH_2I_2$	Substrate/H_2O	$C_{16}H_{33}P^{\oplus}Bu_3Br^{\ominus}$			[80]
$p\text{-}Br—C_6H_4—CO—CH_2Br \rightarrow p\text{-}Br—C_6H_4—CO—CH_2O—CO—R$	CH_3CN or C_6H_6	Dicyclohexyl-[18]crown-6	92—98		[15]
$CH_2Cl_2 \rightarrow (RCOO)_2CH_2$	CH_2Cl_2	NBu_4HSO_4	60—87	Reaction with isolated Bu_4N salt	[53]
$R^1OPO_3H_2 \rightarrow R^1O—PO_2(OR^2)H$	CH_3CN	NMe_4OH	up to 87	Reaction with isolated Me_4N salt	[81]
	$CHCl_3$	NBu_4HSO_4		Reaction with isolated Bu_4N salt	[82]
$Ar—OH + R_2NSO_2Cl \rightarrow Ar—OSO_2NR_2$	C_6H_6/H_2O	TEBA	up to 97		[83]
$(R^1O)_2POH + CX_4 + R^2R^3NH \rightarrow (R^1O)_2PONR^2R^3$	CH_2Cl_2/H_2O	TEBA	up to 92		[84]

sulfate gives more *O*-alkylation than does methyl iodide[112, 113]). A number of studies have been published on the direction and stereochemistry of these reactions, both with intermediate isolation of the salts and also for the catalytic process[112–114] (see Table 8).

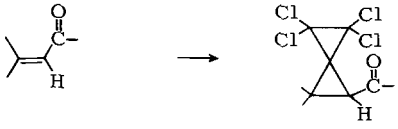
4.4. α-Elimination to Form Carbenes

Since the very large number of papers published on the PTC addition of dihalocarbenes to C=C bonds can hardly be surveyed here, only a few important results will be mentioned. Thus, α,β,γ,δ-unsaturated esters take up only one CX_2, and that across the γ,δ double bond[115, 116]. Reactions have also been carried out with imines[117] and enamines[87, 118]. In an NaOH/$CHCl_3$/TEBA system, naphthalene and anthracene give complex mixtures of ring-expansion products and their dimers[119]. The formation of the unusual reaction products *(10)*[120], *(11)*[115, 121], and *(12)*[122] has been elucidated.

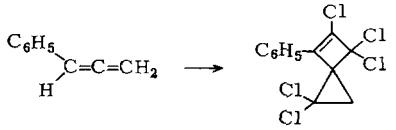
On the basis of our extensive optimizing experiments, the procedures described below can be recommended for dihalocarbene reactions. Contrary to earlier hypotheses[2], these give the same or sometimes even better yields with dibromocarbene than with dichlorocarbene. Furthermore, the previously used very large excess of bromoform can be dispensed with by the selection of dichloromethane as co-solvent.



(10)



(11)



(12)

Dichlorocarbene[37]: The substrate (0.1 mol) and TEBA (or tri-*n*-propylamine) (1 mmol) are dissolved in chloroform (0.4 mol) and ethanol (1 ml), and the solution is stirred vigorously with freshly prepared ice-cold 50 % NaOH (0.4 mol), first for 1 h at room temperature and then for 3—6 h at 50 °C, using a magnetic stirrer. The reaction mixture is then

Table 7. Recent examples of phase-transfer-catalyzed alkylation of O—H, S—H, and N—H bonds.

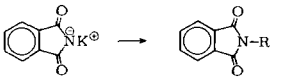
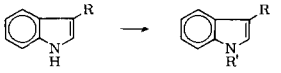
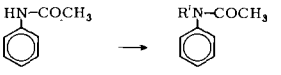
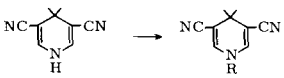
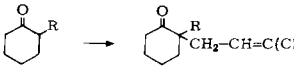
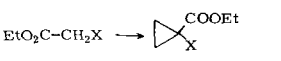
Reaction	Solvent	Catalyst	Yield [%]	Remarks	Ref.
$ArOH + RX + (RO)_2SO_2 \rightarrow ArOR$	CH_2Cl_2/H_2O	$Ph-CH_2N^{\oplus}Bu_3Cl^{\ominus}$	42—95		[85]
$ArOK + ClCH_2OCH_3 \rightarrow ArOCH_2OCH_3$	CH_3CN	[18]Crown-6	93—95		[86]
$ArOH + CH_2Cl_2 \rightarrow (ArO)_2CH_2$	CH_2Cl_2	Aliquat 336	80—97	Solid KOH	[51]
$ROH + CH_2Cl_2 \rightarrow (RO)_2CH_2$	CH_2Cl_2	Aliquat 336	65—79	Solid KOH	[51]
$ROH + HCCl_3 \rightarrow HC(OR)_3$	$CHCl_3/H_2O$	TEBA	33—36	conc. NaOH	[54]
$ROH + R'Cl \rightarrow ROR'$	Substrate/H_2O	NBu_4HSO_4	47—97	conc. NaOH	[39]
$R-\underset{OH}{\underset{|}{CH}}-CCl_3 + CH_3I \longrightarrow R\underset{OCH_3}{\underset{|}{CH}}-CCl_3$	C_6H_6/H_2O	NBu_4I	78—94	conc. NaOH	[88]
$RS^{\ominus}Na^{\oplus} + R'Br \rightarrow RSR'$	C_6H_6/H_2O	Aliquat 336	85—94		[52]
$RS^{\ominus}Na^{\oplus} + CH_2Cl_2 \rightarrow (RS)_2CH_2$	CH_2Cl_2/H_2O	Aliquat 336	90—96		[52]
$Na_2S + RX \rightarrow R_2S$	Substrate/H_2O	$C_{16}H_{33}P^{\oplus}Bu_3Br^{\ominus}$	90—100		[89]
	Toluene	$C_{16}H_{33}P^{\oplus}Bu_3Br^{\ominus}$	85—99		[90]
	C_6H_6/H_2O	$NBu_4^{\oplus}HSO_4^{\ominus}$	78—98	conc. NaOH	[91]
	Substrate/H_2O	TEBA	47—88	conc. NaOH	[92]
	Substrate/H_2O	TEBA	60	conc. NaOH	[92]
	CH_2Cl_2/H_2O	$NBu_4^{\oplus}HSO_4^{\ominus}$	93		[93]
	C_6H_6/H_2O	TEBA	82—95	conc. NaOH	[94]
	Toluene or C_6H_6 or CH_2Cl_2/H_2O	$PhCH_2N^{\oplus}Me_2C_{12}H_{25}Br^{\ominus}$	52—86	conc. NaOH	[95]
	Substrate/H_2O	TEBA	10—100	30% NaOH	[96]
	$CHCl_3/EtOH/H_2O$	$PhCH_2N^{\oplus}Me_3\ OMe^{\ominus}$	65—90		[97]

Table 8. Recent examples of phase-transfer-catalyzed alkylation of activated C—H bonds.

Reaction	Solvent	Catalyst	Yield [%]	Remarks	Ref.
$Ph-CHR-CN \rightarrow Ph-CRR'-CN$	Substrate/conc. NaOH	TEBA	54—94		[3, cf. also 98, 99]
$Me_2N-C(S)-CH_2-CN \rightarrow$	Substrate/conc. NaOH	Dibenzo-[18]crown-6	75—85		[17]
$Me_2N-C(S)-S-CHR-CN$	Substrate/conc. NaOH	NBu_4I	82—91		[100]
$(Me_2N)_2PO-CHR-CN \rightarrow$	Substrate/conc. NaOH	TEBA			
$(Me_2N)_2PO-CRR'-CN$	CH_2Cl_2/H_2O	NBu_4OH	71—100		[101]
$(EtO)_2PO-CH_2-CN \rightarrow (EtO)_2PO-CHR-CN$	CH_2Cl_2/H_2O	NBu_4Br	30—80		[102]
$ArSO_2-CH_2-X \rightarrow ArSO_2-CHRX$ (X = Cl, Br)	Substrate/conc. NaOH	TEBA	60—87		[103]
$CH_3SO_2-CH_2-COAr \rightarrow CH_3SO_2-\underset{ArCO-CH_2 \rightarrow}{\underset{|}{CH}}-COAr$	$CHCl_3$	NBu_4Br	63—81	NBu_4 salt isolated	[104]
$ArSO_2-CH_2-N=C \rightarrow ArSO_2-CHR-N=C$	CH_2Cl_2/conc. NaOH	NBu_4I	40—95		[105]
$Ar-CH_2-COCH_3 \rightarrow Ar-CHR-COCH_3$	Substrate/conc. NaOH	Dicyclohexyl-[18]crown-6	86		[76]
$Ar-CH_2-COAr \rightarrow Ar-CHR-COAr$	Substrate/conc. NaOH	TEBA	70—94		[106]
	Substrate/conc. NaOH	TEBA	34—89		[107]
$Ar-COCH_3 \rightarrow Ar-CO-(CH_2)_2CH=C(CH_3)_2$	Substrate/conc. NaOH	TEBA	10—40		[108]
	Substrate/conc. NaOH	TEBA	25—50		[108]
	Substrate/conc. NaOH	Dicyclohexyl-[18]crown-6	60		[76]
(X = CN, COOEt, $COCH_3$)	Substrate/conc. NaOH	TEBA	69—86		[109]
$C=N-CH_2-COOR \rightarrow C=N-CHR'-COOR$	CH_2Cl_2/conc. NaOH	TEBA	≈70	R' only alkyl or benzyl	[110]
$CH_3CO-CH^{\ominus}Na^{\oplus}-COOR \rightarrow$ $CH_3CO-CHR'-COOR$	C_6H_6	Aliquat 336	30—85	R' alkyl or benzyl	[111]

poured into a large volume of water. Without putting too much stress on complete phase separation, the bulk of the aqueous phase is discarded and the emulsion is broken by repeatedly pouring it into fresh water or possibly dilute hydrochloric acid. The liquid is dried and, if possible, processed further by distillation. Solid or high-boiling nonpolar products can be conveniently freed from dark by-products by eluting the solution in petroleum ether/ether or toluene down a short silica gel column.

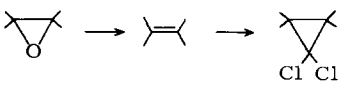
Dibromocarbene[63]: The substrate (0.1 mol) and Aliquat 336[*] (1 mmol) are dissolved in bromoform (0.2 mol), ethanol (1 ml), and dichloromethane (20 ml), and the solution is stirred vigorously with freshly prepared ice-cold 50 % NaOH (0.4 mol) for 1 h at room temperature and then for 3—6 h at 50 °C, using a magnetic stirrer. This is followed by processing as described above.

Other new preparative applications of CCl_2 obtained by PTC are shown in reactions (c)—(g):

$R_2NH \longrightarrow R_2N{-}CHO$ [123, 124] (c)

$N_2H_4 \longrightarrow CH_2N_2$ [19] (d)

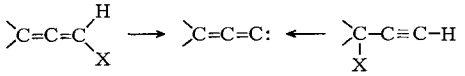
$R{-}\overset{\overset{NH}{\|}}{C}{-}NH_2 \longrightarrow R{-}C{\equiv}N$ [125] (e)


[126] (f)

$Ar{-}CHO \longrightarrow Ar{-}\underset{\underset{OH}{|}}{CH}{-}COOH$ [127] (g)

Japanese authors recommend the use of β-hydroxyethyltrialkylammonium salts as less active, selective catalysts, which attack *e.g.* only one out of a number of double bonds in the molecule[128, 129] (cf. also Section 4.8).

In the preparation of CX_2 by PTC, exchange with external halogens is possible. Both $HCBrCl_2$ and $HCBr_2Cl$ give adducts of all the combinations: CBr_2, CClBr, and CCl_2[38]. The use of dichloromethane as co-solvent seems to accelerate CX_2



[*] The thin commercial liquid product must be freed from high-boiling hydrocarbons, first by the application of aspirator vacuum and then oil-pump vacuum at 125 °C, which leaves behind a product with honey-like consistency.

reactions quite generally. Like dihalocarbenes, dialkylvinylidenecarbenes can be synthesized from haloallenes[130] or 3-halopropynes[131, 132].

4.5. Wittig and Horner Reactions

Wittig and Horner reactions that proceed with phase-transfer catalysis are shown in Table 9. The *E/Z* ratios have been found to depend on the solvent[133] and on the catalyst (extreme values 43:57 and 83:17)[137].

4.6. PTC Reactions with Oxidizing Agents

Table 10 gives a survey of the oxidizing agents used, together with the types of compounds to which they are applied.

Table 9. Recent examples of phase-transfer-catalyzed Wittig and Horner reactions.

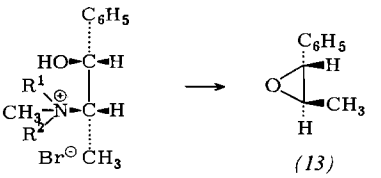
Reaction	Base	Solvent	Catalyst	Yield [%]	Ref.
$R{-}CHO + R'{-}CH_2PPh_3^{\oplus}X^{\ominus}$ (R, R' = alkyl, phenyl)	Solid KOtBu or K_2CO_3	THF or CH_2Cl_2	[18]Crown-6	82—97	[133]
	5 N NaOH	H_2O/C_6H_6	None	60—99	[134]
$Ar{-}CH_2PPh_3^{\oplus}X^{\ominus} + CH_2O$	Conc. NaOH	—	None	80—90	[135]
$2\,Ar{-}CH_2PPh_3^{\oplus}X^{\ominus} + OCH{-}CHO$	Conc. NaOH	H_2O/CH_2Cl_2	None	13—23	[136]
$Ar{-}CHO + (EtO)_2PO{-}CHR{-}X$ (R = CH_3, X = CN)	Dil. NaOH	H_2O/CH_2Cl_2	NBu_4Br	80	[102]
(R = H, X = CN, COOR, COPh, S—Ph, SO—R, SO_2R)	Conc. NaOH	H_2O/CH_2Cl_2	None	55—95	[137]
$Ar{-}CHO + (EtO)_2PO{-}CH_2{-}X$ (X = SR, SO_2R, SOR)	Conc. NaOH	H_2O/CH_2Cl_2	TEBA or crown ether	55—76	[138]
$Ar{-}CH{=}CH{-}CHO + (EtO)_2PO{-}CH_2Ar$	Conc. NaOH	H_2O/C_6H_6	NBu_4I	72—81	[139]
$Ar{-}CHO + (EtO)_2PO{-}CH_2{-}CH{=}CHAr$					
$RR'CO + (EtO)_2PO{-}CH_2X$ (R, R' = alkyl, aryl, X = CN, COOR, aryl)	Conc. NaOH	H_2O/CH_2Cl_2	NBu_4I	51—77	[140]

4.7. Miscellaneous PTC Reactions

A large number of other interesting reactions catalyzed in this way are shown in Table 11.

4.8. The Use of Optically Active Catalysts

Several teams have tried to accomplish kinetic racemate resolution and optical induction with optically active quaternary ammonium salts. The esterification of DL-acids in the presence of chiral catalysts derived from α-phenylethylamine led to products with disappointingly small or zero rotation[165]. Japanese authors have introduced catalysts derived from ephedrine, but, when reacted with strong bases under the conditions used, these are converted at least in part into the chiral epoxide *(13)*, which can simulate optical activity as an impurity in the reaction product. As a result, the previously asserted[166] formation of chiral epoxides, *e.g.* from benzaldehyde and trimethylsulfonium iodide in the presence of such catalysts has now been partially withdrawn[167]. We have, moreover, disproved[38] the formation of optically active dichlorocarbene adducts which had been asserted before[128], but which is *a priori* unlikely on the basis of the mechanism



(13)

Table 10. Recent examples of PTC reactions with oxidizing agents.

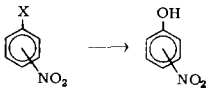
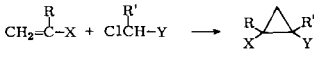
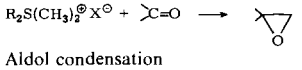
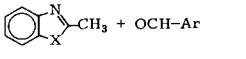
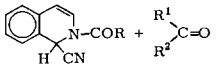
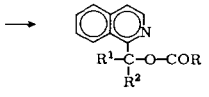
Oxidizing agent	Reaction	Solvent	Catalyst	Yield [%]	Remarks	Ref.
Peracetic acid	$Ar_2C{=}N{-}NH_2 \rightarrow Ar_2CN_2$	H_2O/CH_2Cl_2	$(C_8H_7)_3N^{\oplus}C_3H_7\ Cl^{\ominus}$	85	Cat. amounts of I_2 necessary	[141]
K_2CrO_4	$RCH_2X \rightarrow R{-}CHO$	HMPT	Dicyclohexyl- or dibenzo[18]crown-6	20—82		[142]
Air/KOH	Fluorene→fluorenone	C_6H_6	[18]Crown-6	100	Solid KOH	[143a]
	Aniline→azobenzene	C_6H_6	[18]Crown-6		Solid KOH	[143b]
NaOCl	$ArCH_2OH \rightarrow ArCHO$	H_2O/CH_2Cl_2	$NBu_4^{\oplus}HSO_4^{\ominus}$	47—92		[144]
	$R_2CHOH \rightarrow R_2CO$	H_2O/Ethyl acetate	$NBu_4^{\oplus}HSO_4^{\ominus}$	36—89		
	$RCH_2{-}NH_2 \rightarrow R{-}CN$	H_2O/Ethyl acetate	$NBu_4^{\oplus}HSO_4^{\ominus}$	60—76		
	$R_2CH{-}NH_2 \rightarrow R_2CO$	H_2O/Ethyl acetate	$NBu_4^{\oplus}HSO_4^{\ominus}$	84—98		
$K_3[Fe(CN)_6]$	Phenol oxidation	Homogeneous in $CHCl_3$	$NBu_4^{\oplus}HSO_4^{\ominus}$		$NBu_4^{\oplus}H_2Fe(CN)_6^{\ominus}$-solution prepared separately	[145]
$KMnO_4$	$RCH_2OH \rightarrow RCOOH$	H_2O/C_6H_6	NBu_4Br or	47—92		[146]
	$RCH{=}CHR \rightarrow R{-}COOH$		Aliquat 336	81—95		
	$RCH{=}CHR \rightarrow R{-}COOH$	C_6H_6	Dicyclohexyl[18]-crown-6	78—100	Solid $KMnO_4$	[14]
	$RCH{=}CHR \rightarrow R{-}COOH$	H_2O/C_6H_6	Dicyclohexyl-[18]crown-6	78	Sat. aq. soln.	[76]
	Subst. pyrocatechol→*o*-quinone		[18]Crown-6		Solid $KMnO_4$	[143c]
KO_2	$R{-}X \rightarrow R{-}OH$ (X = Halogen, OTos)	DMSO	[18]Crown-6	41—95	90% config. inversion	[147, 148]
		DMF, DME	[18]Crown-6	55—100		[149]
	$R{-}COOR' \rightarrow R{-}COOH + R'OH$	C_6H_6				
	$R{-}X \rightarrow R{-}O{-}O{-}R$	C_6H_6	Dicyclohexyl-[18]crown-6	42—77		[150]
	$R{-}COCl \rightarrow (R{-}COO)_2$	C_6H_6	None	53—74		[151]
		C_6H_6	Dicyclohexyl-[18]crown-6	55—95		[152]

Table 11. Recent examples of other phase-transfer-catalyzed reactions.

Reaction type	Solvent	Catalyst	Remarks	Ref.
Diazo transfer	C_6H_6 or CH_2Cl_2 or pentane/H_2O	Aliquat 336 or NBu_4X		[153]
Elimination				
$RCHBr{-}CHBrR' \rightarrow RCH{=}CHR'$	$Cl_2CHCHCl_2$ or toluene/H_2O	$C_{16}H_{33}\overset{\oplus}{N}Bu_3Br^{\ominus}$	NaI, $Na_2S_2O_3$ in H_2O	[154]
Curtius degradation	Toluene	NBu_4HSO_4	NBu_4N_3 first extracted, dried	[155]
Michael addition				
$R_2C{=}CRNO_2 + CH_2(COOR)_2$	C_6H_6/aq. NaOH	$C_{16}H_{33}\overset{\oplus}{P}Bu_3Br^{\ominus}$		[156]
$PhSO_2{-}CH{=}CH_2 + ClCH(CN)_2$	Substrate/aq. NaOH	TEBA		[159]
Benzoin condensation	Substrate/H_2O	[18]Crown-6		[157]
Darzens reaction	Substrate/aq. NaOH	TEBA		[103]
	CH_2Cl_2/aq. NaOH	NBu_4Br		[158]
	Substrate/aq. NaOH	TEBA		[159]
	C_6H_6/aq. NaOH	None		[160]
Aldol condensation				
$RR'C{=}O + CH_3CN$	CH_3CN	With or without [18]crown-6	Solid KOH	[161]
$R^3{-}CHO + R^1SO_2{-}CH_2{-}R^2$	CH_2Cl_2/aq. NaOH	TEBA		[162]
	Substrate/aq. NaOH	TEBA		[163]
	C_6H_6/aq. NaOH	With or without TEBA		[164]
				

(the intermediacy of free CCl_2 is well documented). Asymmetric inductions have been reported to occur in the phase-transfer-catalyzed reduction of ketones with hydridoborate in the presence of catalysts similarly derived from ephedrine. One team observed the formation of partially chiral products only from sterically rather hindered ketones[168], while another claimed an optical yield of up to 39 % even with acetophenone under similar conditions[169]. It is clearly necessary to check these results and also the reported maximum 6 % optical induction in an alkylation[170] with a catalyst of the same type.

The chiral catalysts discussed so far have their chirality center at a site removed from the positively charged nitrogen. However, a greater effect and a smaller tendency to disturbance by decomposition products can be expected when the nitrogen itself is chirally substituted, and we have tackled the preparation of such catalysts[165]. It is encouraging that *Wynberg et al.* have obtained optical inductions of up to 68 % in Michael additions in a homogeneous solution in the presence of quinine[171]. The same group has recently reported a true PTC reaction: the formation of optically active epoxides from chalcones with a benzylquinine salt and H_2O_2, with an optical yield of up to 25 %[172].

5. Future Prospects

Phase-transfer catalysis has reached a certain maturity in a few years, and we now know the important factors that govern the choice of the catalyst and the reaction conditions. It may be expected that remaining uncertainties about the course of the reactions in the presence of concentrated alkalis will soon be resolved. No doubt, PTC versions will in future be proposed for many more types of reactions. We can also expect innovations in the use of optically active catalysts with chirally substituted key atoms. In particular, however, preparative improvements should be possible in the field of reactions with bases stronger than aqueous sodium hydroxide. For reasons of stability, crown ethers and cryptates will be the main catalysts here.

The author wishes to thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Gesellschaft von Freunden der T.U. Berlin for supporting his work mentioned in this article. The author has also enjoyed the cooperation of colleagues named in the references, and would like to express his thanks to his wife, Dr. Sigrid Dehmlow, for critical discussions and her assistance with the preparation of the manuscript.

Received: November 2, 1976 [A 174 IE]
German version: Angew. Chem. *89*, 521 (1977)
Translated by Express Translation Service, London

[1] Phase-Transfer-Catalyzed Two-Phase Reactions in Preparative Chemistry, Part 2.—Part 1: [2].
[2] *E. V. Dehmlow*, Angew. Chem. *86*, 187 (1974); Angew. Chem. Int. Ed. Engl. *13*, 170 (1974); reprinted in: New Synthetic Methods. Vol. 1. Verlag Chemie, Weinheim 1975, p. 1; slightly altered reprint: Chem. Technol. *1975*, 210.
[3] *M. Mąkosza, A. Jończyk*, Org. Synth. *55*, 91 (1976).
[4] *G. W. Gokel, R. P. Widera, W. P. Weber*, Org. Synth. *55*, 96 (1976).
[5] *M. Mąkosza, J. Czyzewski, M. Jawdosiuk*, Org. Synth. *55*, 99 (1976).
[6] *M. Mąkosza*, Pure Appl. Chem. *43*, 439 (1975); Conference Paper, "Workshop" Interlaken, Sept. 23—24, 1976.
[7] a) *A. Brändström*: Preparative Ion Pair Extraction. An Introduction to Theory and Practice. Apotekarsocieteten/Hässle Läkemedel, Stockholm 1974; b) personal communication.
[8] *C. M. Starks*, J. Am. Chem. Soc. *93*, 195 (1971); *C. M. Starks, R. M. Owens, ibid. 95*, 3613 (1973)
[9] a) *A. W. Herriott, D. Picker*, J. Am. Chem. Soc. *97*, 2345 (1975); b) *D. H. Picker*, Dissertation, State University of New York at Albany, 1974 (Xerox University Microfilms 75-1652, Ann Arbor, Mich.).
[10] *D. Landini, A. M. Maia, F. Montanari, F. M. Pirisi*, J. Chem. Soc. Chem. Commun. *1975*, 950.
[11] *A. Brändström, H. Kolind-Andersen*, Acta Chem. Scand. *29B*, 201 (1975).
[12] Cf. [7a], pp. 101—104.
[13] Reviews: *J. J. Christensen, D. J. Eatough, R. M. Izatt*, Chem. Rev. *74*, 351 (1974); *C. J. Pedersen, H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. Int. Ed. Engl. *11*, 16 (1972).
[14] *D. J. Sam, H. E. Simmons*, J. Am. Chem. Soc. *94*, 4024 (1972).
[15] *H. D. Durst*, Tetrahedron Lett. *1974*, 2421.
[16] *D. Landini, F. Montanari, F. M. Pirisi*, J. Chem. Soc. Chem. Commun. *1974*, 879.
[17] *M. Mąkosza, M. Ludwikow*, Angew. Chem. *86*, 744 (1974); Angew. Chem. Int. Ed. Engl. *13*, 665 (1974).
[18] *C. L. Liotta, H. P. Harris*, J. Am. Chem. Soc. *96*, 2250 (1974).
[19] *D. T. Sepp, K. V. Scherer, W. P. Weber*, Tetrahedron Lett. *1974*, 2983.
[20] *G. Johns, C. J. Ransom, C. B. Reese*, Synthesis *1976*, 515.
[21] *G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, F. L. Cook*, J. Org. Chem. *39*, 2445 (1974).
[22] *C. J. Pedersen*, Org. Synth. *52*, 66 (1972).
[23] *M. Cinquini, P. Tundo*, Synthesis *1976*, 516; *M. Cinquini, F. Montanari, P. Tundo*, J. Chem. Soc. Chem. Commun. *1975*, 393.
[24] *B. Dietrich, J. M. Lehn*, Tetrahedron Lett. *1973*, 1225.
[25] *R. Fornasier, F. Montanari, G. Podda, P. Tundo*, Tetrahedron Lett. *1976*, 1381.
[26] *F. Vögtle, E. Weber*, Angew. Chem. *86*, 896 (1974); Angew. Chem. Int. Ed. Engl. *13*, 814 (1974).
[27] *C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, K. Smith*, Tetrahedron Lett. *1974*, 2417.
[28] *E. V. Dehmlow*, Tetrahedron Lett. *1976*, 91.
[29] *E. V. Dehmlow, T. Remmler*, J. Chem. Res. (S) *1977*, 72, (M) *1977*, 0766.
[30] *S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, J. S. Gall*, Tetrahedron Lett. *1960*, No. 9, 24.
[31] *D. J. Sam, H. E. Simmons*, J. Am. Chem. Soc. *96*, 2252 (1974).
[32] *A. Knöchel, J. Oehler, G. Rudolph*, Tetrahedron Lett. *1975*, 3167.
[33] *H. Normant, T. Cuvigny, P. Savignac*, Synthesis *1975*, 805.
[34] *C. L. Liotta, E. E. Grisdale, H. P. Hopkins, Jr.*, Tetrahedron Lett. *1975*, 4205.
[35] *J. H. Fendler, E. J. Fendler*: Catalysis in Micellar and Macromolecular Systems. Academic Press, New York 1975.
[36] *J. H. Fendler*, Acc. Chem. Res. *9*, 153 (1976).
[37] *E. V. Dehmlow, M. Lissel*, Tetrahedron Lett. *1976*, 1783.
[38] *E. V. Dehmlow, M. Lissel, J. Heider*, Tetrahedron *33*, 363 (1977).
[39] *H. H. Freedman, R. A. Dubois*, Tetrahedron Lett. *1975*, 3251.
[40] *V. Mann, G. Schneider, F. Kröhnke*, Tetrahedron Lett. *1973*, 683.
[41] *W.-H. Gündel*, Z. Naturforsch. *30b*, 616 (1975).
[42] *E. V. Dehmlow, S. Barahona*, unpublished.
[43] *S. L. Regen*, J. Am. Chem. Soc. *97*, 5956 (1975).
[44] *E. V. Dehmlow*, unpublished results; *E. V. Dehmlow, M. Slopianka, J. Heider*, Tetrahedron Lett. *1977*, 2361
[45] *J. M. Brown, J. A. Jenkins*, J. Chem. Soc. Chem. Commun. *1976*, 458.
[46] *P. A. Verbrugge, E. W. Uurbanus*, DOS 2324390 (1973); Chem. Abstr. *80*, 70420 (1974).
[47] *M. Cinquini, S. Colonna, H. Molinari, F. Montanari, P. Tundo*, J. Chem. Soc. Chem. Commun. *1976*, 394.
[48] *A. Brändström*, Lecture, Journees de Chimie Organique d'Orsay (17. Sep. 1975), and personal communication.
[49] *A. McKillop, J.-C. Fiaud, R. P. Hug*, Tetrahedron *30*, 1379 (1974).
[50] *L. Dalgaard, L. Jensen, S.-O. Lawesson*, Tetrahedron *30*, 93 (1974).
[51] *E. V. Dehmlow, J. Schmidt*, Tetrahedron Lett. *1976*, 95.
[52] *A. W. Herriott, D. Picker*, Synthesis *1975*, 447.
[53] *K. Holmberg, B. Hansen*, Tetrahedron Lett. *1975*, 2303.
[54] *M. Mąkosza, B. Jerzak, M. Fedoryński*, Rocz. Chem. *49*, 1783 (1975).
[55] *K. Gustavii*, Acta Pharm. Suec. *4*, 233 (1967).
[56] *B. Czapkiewicz-Tataj, J. Czapkiewicz*, Rocz. Chem. *49*, 1353 (1975).
[57] *R. Modin*, Acta Pharm. Suec. *9*, 157 (1972).
[58] *K. Gustavii*, Acta Pharm. Suec. *4*, 233 (1967).
[59] *K. Gustavii, G. Schill*, Acta Pharm. Suec. *3*, 241, 259 (1966).
[60] *R. Modin, A. Tilly*, Acta Pharm. Suec. *5*, 311 (1968).
[61] *R. Modin, G. Schill*, Acta Pharm. Suec. *4*, 301 (1967).
[62] *K. O. Borg, D. Westerlund*, Z. Anal. Chem. *252*, 275 (1970).
[63] *E. V. Dehmlow, J. Kranz*, unpublished.
[64] *K. Isagawa, Y. Kimura, S. Kwon*, J. Org. Chem. *39*, 3171 (1974).
[65] *M. Mąkosza, A. Kacprowicz, M. Fedoryński*, Tetrahedron Lett. *1975*, 2119.
[66] *M. Mąkosza, B. Serafinowa*, Rocz. Chem. *39*, 1223 (1965).

[67] *E. V. Dehmlow, E. Menzel*, unpublished.
[68] *J. Dale, K. Daasvatn*, J. Chem. Soc. Chem. Commun. *1976*, 295.
[69] *A. P. Bashall, J. F. Collins*, Tetrahedron Lett. *1975*, 3489.
[70] *T. Toru, S. Kurozumi, T. Tanaka, T. Miura, M. Kobayashi, S. Ishimoto*, Synthesis *1974*, 867.
[71] *E. V. Dehmlow, M. Slopianka*, unpublished.
[72] *J. W. Zubrick, B. I. Dunbar, H. D. Durst*, Tetrahedron Lett. *1975*, 71.
[73] *M. S. Newman, T. G. Barbee Jr., C. N. Blakesley, Z. ud Din, S. Gromelski Jr., V. K. Khanna, L.-F. Lee, J. Radhakrishnan, R. L. Robey, V. Sankaran, S. K. Sankarappa, J. M. Springer*, J. Org. Chem. *40*, 2863 (1975).
[74] *F. L. Cook, C. W. Bowers, C. L. Liotta*, J. Org. Chem. *39*, 3416 (1974).
[75] *W. P. Reeves, M. R. White*, Synth. Commun. *6*, 193 (1976).
[76] *D. Landini, A. M. Maia, F. Montanari, F. M. Pirisi*, Gazz. Chim. Ital. *105*, 863 (1975).
[77] *K. E. König, W. P. Weber*, Tetrahedron Lett. *1974*, 2275.
[78] *D. Landini, R. Montanari, F. Rolla*, Synthesis *1974*, 428.
[79] *D. Landini, S. Quici, F. Rolla*, Synthesis *1975*, 430.
[80] *D. Landini, F. Rolla*, Chem. Ind. (London) *1974*, 533.
[81] *R. A. Bauman*, Synthesis *1974*, 870.
[82] *F. C. V. Larsson, S.-O. Lawesson*, Tetrahedron *28*, 5341 (1972).
[83] *S. Schwarz, G. Weber*, Z. Chem. *15*, 270 (1975).
[84] *A. Zwierzak*, Synthesis *1975*, 507.
[85] *A. McKillop, J.-C. Fiaud, R. P. Hug*, Tetrahedron *30*, 1379 (1974).
[86] *G. J. H. Rall, M. E. Oberholzer, D. Ferreira, D. G. Roux*, Tetrahedron Lett. *1976*, 1033.
[87] *M. Mąkosza, A. Kacprowicz*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *22*, 467 (1974).
[88] *J. Villieras, C. Bacquet, J. F. Normant*, J. Organomet. Chem. *97*, 355 (1975).
[89] *D. Landini, F. Rolla*, Synthesis *1974*, 565.
[90] *D. Landini, F. Rolla*, Synthesis *1976*, 389.
[91] *A. Barco, S. Benetti, G. P. Pollini, P. G. Baradi*, Synthesis *1976*, 124.
[92] *A. Jonczyk, M. Mąkosza*, Rocz. Chem. *49*, 1203 (1975).
[93] Cf. [7a], p. 156.
[94] *R. Brehme*, Synthesis *1976*, 113.
[95] *J. Paleček, J. Kuthan*, Synthesis *1976*, 550.
[96] *M.-T. Maurette, A. Lopez, R. Martino, A. Lattes*, C. R. Acad. Sci. Ser. C *282*, 599 (1976).
[97] *R. Kreher, K. J. Herd*, Z. Naturforsch. *29b*, 683 (1974).
[98] *M. Mąkosza, R. Goetzen*, Rocz. Chem. *46*, 1239 (1972).
[99] *P. Vittorelli, J. Peter-Katalinić, G. Mukherjee-Müller, H.-J. Hansen, H. Schmid*, Helv. Chim. Acta *58*, 1379 (1975).
[100] *Y. Masuyama, Y. Ueno, M. Okawara*, Tetrahedron Lett. *1976*, 2967.
[101] *J. Blanchard, N. Collignon, P. Savignac, H. Normant*, Synthesis *1975*, 635; Tetrahedron *32*, 455 (1976).
[102] *E. D'Incan, J. Seyden-Penne*, Synthesis *1975*, 516.
[103] *A. Jończyk, K. Bańko, M. Mąkosza*, J. Org. Chem. *40*, 266 (1975).
[104] *B. Koutek, L. Pavlickova, M. Souček*, Collect. Czech. Chem. Commun. *39*, 192 (1974).
[105] *A. M. van Leusen, R. J. Bouma, O. Possel*, Tetrahedron Lett. *1975*, 3487.
[106] *M. Mąkosza, A. Jończyk, B. Serafinova, Z. Mroczek*, Rocz. Chem. *47*, 77 (1973).
[107] *A. Jończyk, T. Pytlewski*, Rocz. Chem. *49*, 1425 (1975).
[108] *V. M. Andreev, A. I. Bibicheva, M. I. Zhuravleva*, Zh. Org. Khim. *10*, 1470 (1974); J. Org. Chem. USSR *10*, 1479 (1974).
[109] *R. K. Singh, S. Danishefsky*, J. Org. Chem. *40*, 2969 (1975).
[110] *U. Schöllkopf, D. Hoppe, R. Jentsch*, Chem. Ber. *108*, 1580 (1975).
[111] *H. D. Durst, L. Liebeskind*, J. Org. Chem. *39*, 3271 (1974).
[112] *B. Cederlund, A.-B. Hörnfeldt*, Chem. Scr. *8*, 140 (1975); Acta Chem. Scand. *30B*, 101 (1976).
[113] *E. V. Dehmlow, E. Timm*, unpublished.
[114] *E. D'Incan, P. Viout*, Tetrahedron *31*, 159 (1975); *A. Jonczyk, M. Fedoryński, M. Mąkosza*, Rocz. Chem. *48*, 1713 (1974); *H. Kolind-Andersen, R. Dyrnesli, S.-O. Lawesson*, Bull. Soc. Chim. Belg. *84*, 341 (1975); *H. Kolind-Anderson, S.-O. Lawesson*, Acta Chem. Scand. *29B*, 430 (1975); *L. Dalgaard, L. Jensen, S.-O. Lawesson*, Tetrahedron *30*, 93 (1974); *L. Jensen, L. Dalgaard, S.-O. Lawesson, ibid. 30*, 2413 (1974).
[115] *E. V. Dehmlow, G. Höfle*, Chem. Ber. *107*, 2760 (1974).
[116] *G. V. Kryshtal, V. F. Kucherov, L. A. Yanovskaya*, Izv. Akad. Nauk SSSR, Ser. Khim. *1976*, 929.
[117] *M. Mąkosza, A. Kacprowicz*, Rocz. Chem. *48*, 2129 (1974); *J. Graefe*, Z. Chem. *14*, 469 (1974); *D. J. Sikkema, E. Molenaar, D. B. Van Guldener*, Rec. Trav. Chim. Pays-Bas *95*, 154 (1976).
[118] *J. Graefe, M. Adler, M. Mühlstädt*, Z. Chem. *15*, 14 (1975); *S. A. G. De Graaf, U. K. Pandit*, Tetrahedron *29*, 4263 (1973).
[119] *G. Blume, T. Neumann, P. Weyerstahl*, Justus Liebigs Ann. Chem. *1975*, 201.
[120] *C. W. Jefford, W. D. Graham, U. Burger*, Tetrahedron Lett. *1975*, 4717; *C. W. Jefford, V. de los Heros, U. Burger, ibid. 1976*, 703; *P. M. Kwantes, G. W. Klumpp, ibid. 1976*, 707.
[121] *E. V. Dehmlow, G. C. Ezimora*, Z. Naturforsch. *30b*, 825 (1975).
[122] *E. V. Dehmlow*, Tetrahedron Lett. *1975*, 203.
[123] *J. Graefe, I. Fröhlich, M. Mühlstädt*, Z. Chem. *1974*, 434.
[124] *M. Mąkosza, A. Kacprowicz*, Rocz. Chem. *49*, 1627 (1975).
[125] *J. Graefe*, Z. Chem. *15*, 301 (1975).
[126] *I. Tabushi, Y. Kuroda, Z. Yoshida*, Tetrahedron *32*, 997 (1976).
[127] *A. Merz*, Synthesis *1974*, 724.
[128] *T. Hiyama, H. Sawada, M. Tsukanaka, H. Nozaki*, Tetrahedron Lett. *1975*, 3013.
[129] *T. Hiyama, M. Tsukanaka, H. Nozaki*, J. Am. Chem. Soc. *96*, 3713 (1974).
[130] *T. B. Patrick*, Tetrahedron Lett. *1974*, 1407.
[131] *S. Julia, D. Michelot, G. Linstrumentale*, C. R. Acad. Sci. Ser. C *278*, 1523 (1974).
[132] *T. Sasaki, S. Eguchi, M. Ohno, F. Nakato*, J. Org. Chem. *41*, 2408 (1976); *T. Sasaki, S. Eguchi, T. Ogawa*, ibid. *39*, 1927 (1974); Heterocycles *3*, 193 (1975).
[133] *R. M. Boden*, Synthesis *1975*, 784.
[134] *W. Tagaki, I. Inoue, Y. Yano, T. Okonogi*, Tetrahedron Lett. *1974*, 2587.
[135] *R. Broos, M. Anteunis*, Synth. Commun. *6*, 53 (1976).
[136] *S. Hünig, I. Stemmler*, Tetrahedron Lett. *1974*, 3151.
[137] *M. Mikolajczyk, S. Grzejszczak, W. Midura, A. Zatorski*, Synthesis *1976*, 396.
[138] *M. Mikolajczyk, S. Grzejszczak, W. Midura, A. Zatorski*, Synthesis *1975*, 278.
[139] *C. Piechucki*, Synthesis *1976*, 187.
[140] *C. Piechucki*, Synthesis *1974*, 869.
[141] *J. R. Adamson, R. Bywood, D. T. Eastlick, G. Gallagher, D. Walker, E. M. Wilson*, J. Chem. Soc. Perkin Trans. I *1975*, 2030.
[142] *G. Cardillo, M. Orena, S. Sandri*, J. Chem. Soc. Chem. Commun. *1976*, 190.
[143] a) for procedure, see [143c], p. 182; b) unpublished, cited in [143c]; c) *G. W. Gokel, H. D. Durst*, Synthesis *1976*, 168.
[144] *G. A. Lee, H. H. Freedman*, Tetrahedron Lett. *1976*, 1641.
[145] *G. Brunow, S. Sumelius*, Acta Chem. Scand. *29B*, 499 (1975).
[146] *A. W. Herriott, D. Picker*, Tetrahedron Lett. *1974*, 1511.
[147] *J. San Filippo Jr., C.-I. Chern, J. S. Valentine*, J. Org. Chem. *40*, 1678 (1975).
[148] *E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, C. Shiner*, Tetrahedron Lett. *1975*, 3183.
[149] *J. San Filippo Jr., L. J. Romano, C.-I. Chern, J. S. Valentine*, J. Org. Chem. *41*, 586 (1976).
[150] *R. A. Johnson, E. G. Nidy*, J. Org. Chem. *40*, 1680 (1975).
[151] *R. A. Johnson*, Tetrahedron Lett. *1976*, 331.
[152] *A. Frimer, I. Rosenthal*, Tetrahedron Lett. *1976*, 2809.
[153] *H. Ledon*, Synthesis *1974*, 347.
[154] *D. Landini, S. Quici, F. Rolla*, Synthesis *1975*, 397.
[155] *A. Brändström, B. Lamm, I. Palmertz*, Acta Chem. Scand. *28B*, 699 (1974).
[156] *T. Sakakibara, R. Sudoh*, J. Org. Chem. *40*, 2823 (1975); *T. Sakakibara, M. Yamada, R. Sudoh, ibid. 41*, 736 (1976).
[157] *S. Akabori, M. Ohtomi, K. Arai*, Bull. Chem. Soc. Jpn. *49*, 746 (1976).
[158] *E. d'Incan, J. Seyden-Penne*, C. R. Acad. Sci. Ser. C *281*, 1031 (1975).
[159] *A. Jończyk, M. Mąkosza*, Synthesis *1976*, 387.
[160] *Y. Yano, T. Okonogi, M. Sunaga, W. Tagaki*, J. Chem. Soc. Chem. Commun. *1973*, 527.
[161] *G. W. Gokel, S. A. DiBiase, B. A. Lipisko*, Tetrahedron Lett. *1976*, 3495.
[162] *G. Cardillo, D. Savoia, A. Umani-Ronchi*, Synthesis *1975*, 453.
[163] *V. Dryanska, C. Ivanov*, Tetrahedron Lett. *1975*, 3519.
[164] *A. Jończyk*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *22*, 849 (1974).
[165] *E. V. Dehmlow, J. Heider*, unpublished.
[166] *T. Hiyama, T. Mishima, H. Sawada, H. Nozaki*, J. Am. Chem. Soc. *97*, 1626 (1975).
[167] *T. Hiyama, T. Mishima, H. Sawada, H. Nozaki*, J. Am. Chem. Soc. *98*, 641 (1976).
[168] *S. Colonna, R. Fornasier*, Synthesis *1975*, 531; *J. Balcells, S. Colonna, R. Fornasier, ibid. 1976*, 266.
[169] *J. P. Massé, E. R. Parayre*, J. Chem. Soc. Chem. Commun. *1976*, 438.
[170] *J.-C. Fiaud*, Tetrahedron Lett. *1975*, 3495.
[171] *H. Wynberg, R. Helder*, Tetrahedron Lett. *1975*, 4057.
[172] *R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg*, Tetrahedron Lett. *1976*, 1831.
[173] *S. L. Regen*, J. Am. Chem. Soc. *98*, 6270 (1976).
[174] *D. Landini, A. Maia, F. Montanari*, J. Chem. Soc. Chem. Commun. *1977*, 112.
[175] *G. Köbrich, H. Büttner, E. Wagner*, Angew. Chem. *82*, 177 (1970); Angew. Chem. Int. Ed. Engl. *9*, 169 (1970).
[176] *M. Mąkosza, E. Bialecka*, Tetrahedron Lett. *1977*, 183.

The Role of Birth Control in the Survival of the Human Race

By Rudolf Wiechert[*]

Analysis of the growth of the world's population shows that if no trenchant measures are taken, the number of the earth's inhabitants is likely to double to 8 billion people within as few as 35 years. Hormonal contraception is presently the best method available which would be capable of counteracting this trend. 6.5 tons of estrogen and 32 tons of progestogen would in theory be sufficient to protect the 500 million women of child-bearing age from unwanted pregnancies for one year.—In addition, the history, industrial methods of synthesis, mode of action and side effects of steroid contraceptives as well as the possible future developments are briefly mentioned.

1. Introduction

Politicians and scientists now agree that the survival of the human race is threatened by the consequences resulting from destruction of living space, the arms race, and the excessive growth of the world's population. In view of this, surprisingly few people are engaged in the task of dealing with the problems of environmental pollution and the population explosion.

In 1974 these two topics were the subject of a conference held in Bucharest that was attended by 5000 delegates from 138 countries. A world population plan of action aimed at reducing the birth rate was agreed upon. The efforts of the individual countries were to be coordinated and exchange of information was to take place.

The outcome of this conference and the hope that the governments concerned will put the recommendations into practice should enable one to view the future with a measure of optimism. However, if one considers the present rate of growth of the world population one cannot help seriously doubting whether we have the ability to master the problem.

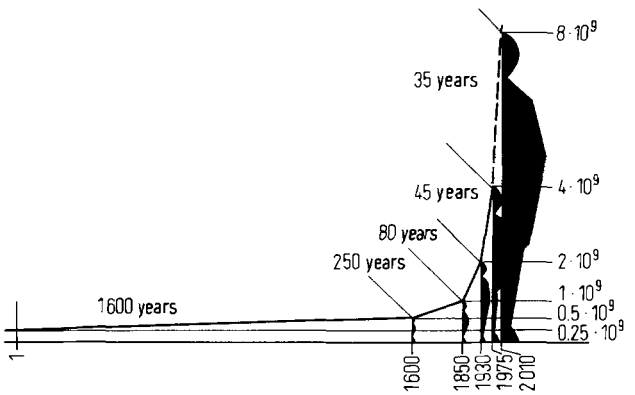


Fig. 1. World population and the times taken for it to double (based on data supplied by the United Nations).

The world population at present numbers approximately 4 billion. Figure 1 shows the growth of the world population and the periods of time required for it to double: in year 1 there were some 250 million people and it took 1600 years for that figure to double to 500 million. The present figure of 4 billion will have doubled to 8 billion in the next 35 years[1]. 220000 babies are born every day, *i.e.* another 6900 children every 45 minutes. To put it yet another way, over a period of 250 days 55 million people are born into the world, that figure being the same as the total number killed in the second world war.

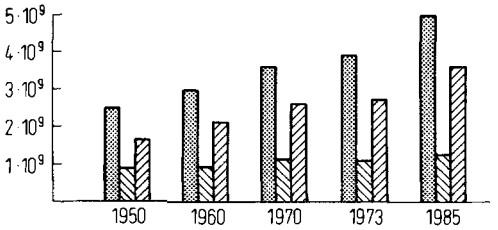


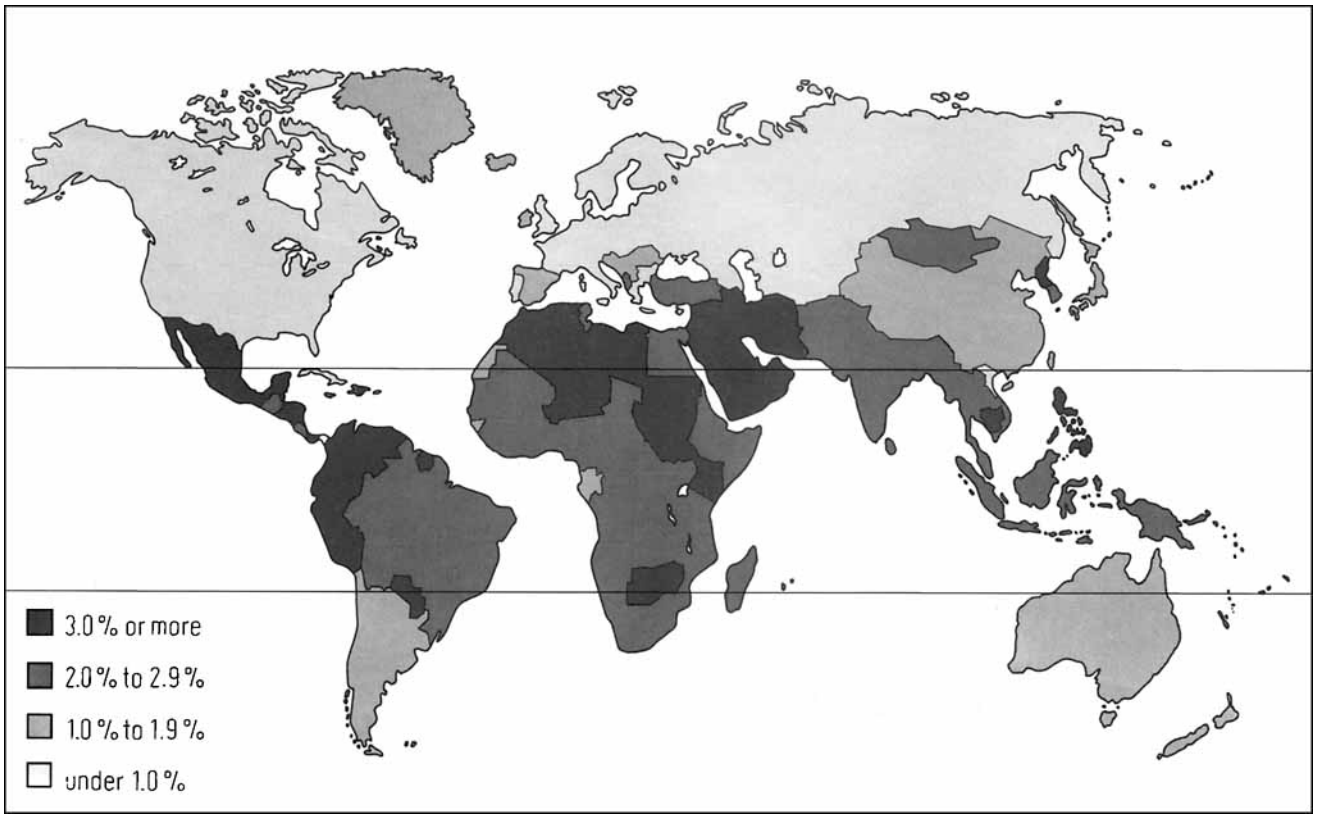
Fig. 2. Population growth in industrialized and developing countries: total population. population in the industrialized nations. population in the developing countries. Values for 1973 estimated, those for 1985 projected.

It is clear from the different population growth rates in the industrialized nations and the developing countries since 1950 that the general trend is determined almost exclusively by the latter (Fig. 2). It is striking to note that Pakistan's population is likely to double in only 21 years and that of India in 28. In contrast, the number of inhabitants of the German Federal Republic has in fact fallen slightly over the last decade. The world map (Fig. 3) shows the geographic distribution of population growth, the dark areas indicating the regions with the highest growth rates.

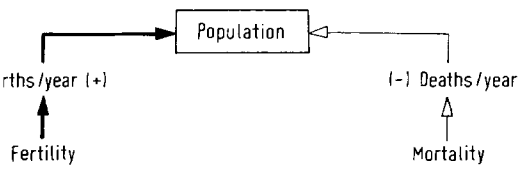
The population figures are determined by two regulating factors, which are represented in simplified form in Fig. 4. The first of these represents the growth rate and is dependent upon fertility and the number of years between generations. The second reflects the death rate in the population which is, to a great extent dependent upon the health of the people involved[2].

The population explosion that has taken place over the course of the last century has not been brought about by any rise in the birth rate but is due exclusively to a fall in the death rate. The industrialized nations have made considerable progress in medicine and have exported their knowledge to the developing countries, with the result that the death rates in those countries have fallen considerably.

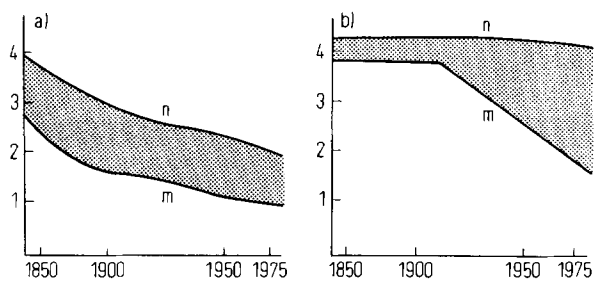
[*] Prof. Dr. R. Wiechert
Schering AG, Hauptdepartment Steroidchemie
Postfach 650311, D-1000 Berlin 65 (Germany)



g. 3. Geographic distribution of population growth in 1972 (after FSP Center U.S. April 1974).



g. 4. The change in population figures brought about by two regulating ;tors.



g. 5. Birth rates n and death rates m in a) industrialized nations and developing countries.

Fig. 5 shows the birth and death rates for the industrialized ıtions and the developing countries from 1850 to 1975. In e industrialized countries the fall in the death rate has ;en accompanied by a decline in the birth rate. However, the developing countries since approximately the beginning this century it has been possible to achieve only a decline the death rate.

Looking back at the figure showing the regulating factors ig. 4), it is clear that it is really only possible to reduce ›pulation growth *via* the left-hand factor, *i.e.* by reducing the birth rate, and the only way to do this is through birth control.

We saw on the world map (Fig. 3) the areas of our planet with the highest population growth rates and where birth control is most urgently required. Consequently, faced with the population explosion and all its inherent dangers, what can *Homo sapiens* do?

Table 1. Methods of birth control practised (estimates). There are approximately 500 million fertile and sexually active women of childbearing age (after [4, 11, 14]).

Pill	55×10^6
Condom	25×10^5
Intrauterine device	15×10^6
Spermicides	12×10^6
Sterilization (male and female)	10×10^6
Diaphragm	3×10^6
Injection	1×10^6
	121×10^6
Knaus-Ogino rhythm method Coitus interruptus Vaginal douches	40×10^6
Abortions (legal and illegal)	30×10^6
	70×10^6

There are now some 500 million women of child-bearing age[3]. The Medical Center of the George Washington University has published figures, based on estimates and sales figures, showing the methods of birth control practised (Table 1). It is interesting to note that almost 40 % of the women do not use any form of contraception. 55 million women use the ovulation-inhibiting steroid hormones known as "the pill"[4].

The development of hormonal contraceptives is one of the greatest scientific achievements of our century. It is a classic example of international cooperation between scientists of a wide variety of disciplines.

2. The Biology and Chemistry of Contraceptive Steroids

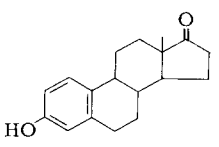
The possibility of hormonal contraception was first proposed by the Innsbruck physiologist *Haberlandt* in 1919[5]. Although a number of observations, papers, and hypotheses had already been published at that time concerning the corpus luteum and the ovarian tissue, none of the authors had seen any connection between his work and the possibility of hormonal contraception. Over the next few years *Haberlandt* was able to provide experimental evidence to support his hypothesis. He succeeded in making rabbits infertile by transplanting ovaries from other pregnant animals under their skin. He published his findings in the Münchner Medizinische Wochenschrift in 1921 under the title: "Hormonal sterilization of the female animal organism".

With considerable far-sightedness, *Haberlandt* writes in this very first paper of the possibility of clinical administration of extracts by injection or even by mouth. Over the course of the next ten years he carried out successful experiments with extracts of corpus luteum, ovary, and placenta. He explained the resulting sterility as brought about by inhibition of ovulation.

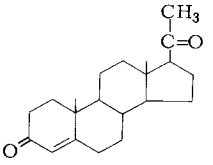
The space here is insufficient to mention every contribution that eventually led to the development of oral contraceptives, but the milestones along that road must be mentioned[6–8].

In 1923 *Aschheim* and *Zondeck* found a relatively abundant source of follicle hormone in the urine of pregnant women and pregnant mares. *Allan* and *Doisy* developed a test to determine its biological activity. The prerequisites for the isolation of the pure hormone were thus provided. In 1927, at *Schöller*'s suggestion, *Butenandt* began isolating the hormone from crude extracts. Two years later he, and also, independently, *Doisy* in the United States and *Laquer* in the Netherlands, succeeded in isolating estrone *(1)*. Clarification and confirmation of its structure followed shortly afterwards.

The second female sex hormone, namely the corpus luteum hormone progesterone *(2)*, was isolated from pig ovaries almost simultaneously by four research groups working independently. The test necessary for its isolation had already been developed in 1929 by *Allan*, *Corner* and *Hohlweg*.



(1)

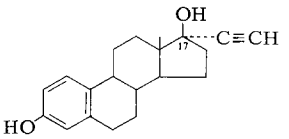


(2)

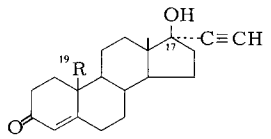
Soon after the two hormones, estrone and progesterone, had been isolated it was demonstrated in animal experiments that they inhibit ovulation and can be used to create a state of pseudo-pregnancy.

Since the pure hormones were available, it should have been possible to apply *Haberlandt*'s ideas about contraception. However, when orally administered, these two pure hormones were found to be rapidly metabolized and therefore exhibited a very weak effect. In 1938 *Inhoffen* and *Hohlweg* reported from Berlin the synthesis of 17α-ethynylestradiol *(3)*, an estrogen that is highly effective when administered by the oral route. Today, nearly 40 years later, this estrogen is still used in the majority of hormonal contraceptives.

In the same year *Inhoffen* and *Hohlweg* were also responsible for producing the first orally-active synthetic progesterone, 17α-ethynyltestosterone *(4)*, although they were in fact looking for an orally-active androgen. *Schöller* recommended that they test the substance for progestational activity, after, he writes, "they (meaning *Hohlweg* and *Inhoffen*) had informed [him] with great disappointment that it did not have the masculinizing effect they had hoped for".



(3)



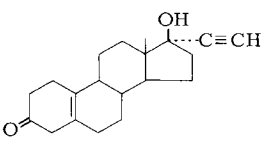
(4), R = CH_3
(5), R = H

In the United States *Djerassi* and *Colton* later synthesized 19-nor-compounds of 17α-ethynyltestosterone, *e.g. (5)*, the constituents of the first hormonal contraceptives used clinically.

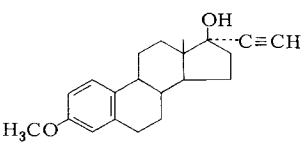
In 1951 in the United States, *Gregory Pincus* together with *Chang*, *Rock*, *Garcia* and others began working on the development of an oral hormonal contraceptive. Two women who were active in the American Family Planning Association, namely *Margaret Sanger* and the wealthy *Katherine Dexter*, had offered *Pincus* financial backing. When, in 1963, the above-mentioned orally-active 17α-ethynyl-19-nor-compounds became available, *Pincus*' team concentrated their studies on these steroids. Two years later the first effective method of hormonal birth control was available in the form of a daily dose of 10 mg of norethynodrel (17α-ethynyl-17β-hydroxy-19-nor-5(10)-androsten-3-one) *(6)* for 20 days.

It was a chance observation that eventually led to a small amount of estrogen being added to the progestogen: it was found that groups of women who received different batches of the progestogen exhibited different cycle patterns. With some batches a certain percentage of the women experienced intermediate bleeding, whereas this did not occur with other batches.

Closer examination of the progestogen *(6)* revealed that, because of the method of synthesis used, it occasionally contained small quantities of etherified 17α-ethynylestradiol *(7)*. The cycles of the women who had received these batches were by far the better controlled. This was the manner whereby the first oral contraceptive was discovered that contained both a progestogen and an estrogen and acted by inhibiting ovulation but at the same time enabling monthly menstruation to take place. Combination pills of this type are the ones used most commonly nowadays.



(6)



(7)

The mode of action is simple to explain: roughly half-way through a normal menstrual cycle an ovum capable of being fertilized is released by the ovary and passes along the fallopian tube to the uterus. In the lower section of the fallopian tube, before it reaches the uterus, it may be fertilized. If this is the case, hormones send messages *via* the brain and the pituitary gland to ensure that for the time being no more ova mature in the ovary.

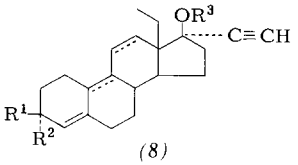
The pill supplies a woman with the hormones that bring about this state resembling pregnancy. The first combination method developed involved the administration of mixtures of a progestogen and an estrogen, *e.g. (6)* and *(7)*, from the 5th to the 24th day of each cycle.

The sequential method that came later mimics the natural sequence of hormone production: only the estrogen is given from the 5th to the 19th day of the cycle and the combination of estrogen and progestogen is then given from the 19th to the 24th day[9, 10].

Longer-acting hormonal contraceptives in the form of injections, implants, or tablets have not yet been developed to the same stage as the two methods described above and still have major disadvantages.

For a long time it was believed that the contraceptive effect of the steroid hormones was due solely to the inhibition of ovulation outlined above. We now know that this effect is the sum of several partial effects; in addition to inhibition of ovulation, changes have been observed in the cervical mucus, the endometrium, and the motility of the fallopian tubes. This raised the question whether contraception can be achieved without inhibiting ovulation. The answer came with the development of the famous "minipill". This supplies continuous small doses of only the progestogen. However, the minipill has not fulfilled expectations, and is now used only on a limited basis as an alternative in special cases[11].

Today's contraceptives still contain the estrogen used by *Pincus*, ethynylestradiol *(3)*, or its 3-methyl ether *(7)*. However, several improved variants of 17α-ethynyl-19-nortestosterone (norethisterone) have since been synthesized, which have proved clinically reliable[12, 13]. Seven progestogens are in use at present in the Federal Republic of Germany. It has been possible to reduce the required daily dose to almost one-hundredth of that necessary in the case of the first preparations tested.



(8)

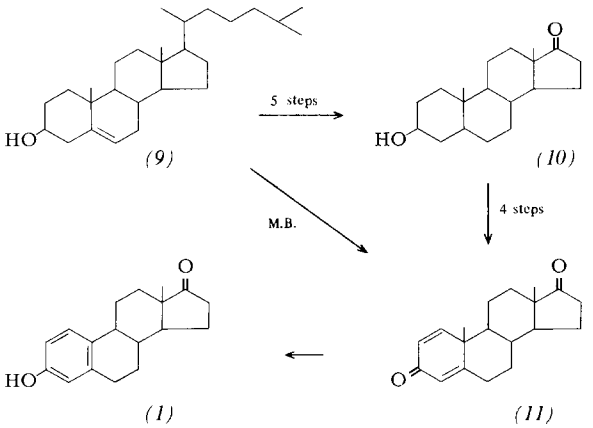
$R^1 = R^2 = H$
$R^1 = OAc$, $R^2 = H$
$R^3 = H$, OAc

A number of these structural changes can be seen in formula *(8)*. For example, the 3-keto group is removed or reduced and acetylated, or additional double bonds are introduced in positions 9 and 11. A quantitative and qualitative improvement in effect that is particularly worth mentioning was achieved by introducing a methyl group in position 18.

One feature that has remained common to all the compounds is that they belong to the 19-nor series and carry the ethynyl group in the 17α-position.

3. Syntheses of Contraceptive Steroids

The development of the methods of synthesizing estrone and the 19-nor steroids constitutes one of the most interesting chapters in the history of chemistry, providing an excellent illustration of the major advances made in theoretical and synthetic organic chemistry over the last 40 years[8, 12]. Following the first isolation of estrone from pregnant mare urine it was immediately clear that this would not be an adequate source of raw material for the large quantities of the hormone that it would soon be necessary to produce.



(9) *(10)* *(1)* *(11)*

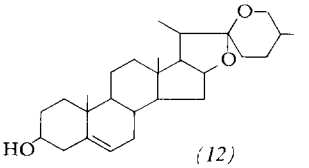
Cholesterol *(9)*, which is present in large quantities in such substances as wool fat, was the most obvious starting material. Two problems faced the chemists with regard to the synthesis of estrone from cholesterol: breakdown of the sterol side chain and elimination of the nonactivated 19-methyl group.

They succeeded in breaking down the side chain with chromic acid to give very moderate yields of the 17-ketone *(10)* after providing intermediate protection for the hydroxyl group and the double bond. In 1940, *Inhoffen* succeeded in aromatizing the diene-dione *(11)* to estrone *(1)* with elimination of the angular 19-methyl group. This reaction, which is carried out at approximately 600 °C in Tetralin, proceeds by a radical mechanism.

It was later found that ionic aromatization can be achieved by treating the dienone system with lithium and biphenyl, a reaction that can be carried out at the modest temperature of 66 °C.

17α-Ethynylestradiol *(3)* can be obtained from the estrone *(1)* with the aid of the appropriate Grignard reagent.

In the last few years, an interesting new development has taken place concerning the microbiological degradation of sterols. It is now possible to convert sterols, *e.g. (9)*, directly into the diene-dione *(11)*, with good yields by means of a microbiological process (M.B.). As a result of this process, sitosterol, which is present in large quantities in soya beans for example, has acquired major importance as a raw material.



(12)

For decades diosgenin *(12)* was undoubtedly the most widely used and most suitable raw material for the production of all steroids. Diosgenin is found in the roots of several varieties of *Dioscorea* which grow wild in such countries as Mexico, Guatemala, India, South Africa, and China (Fig. 6). This natural substance was discovered by *Russell E. Marker*.



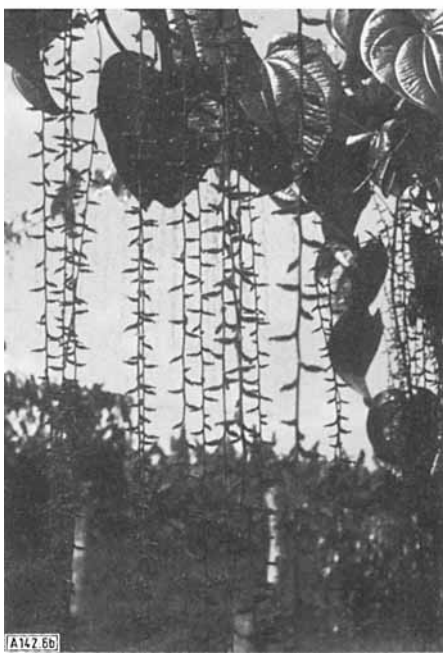
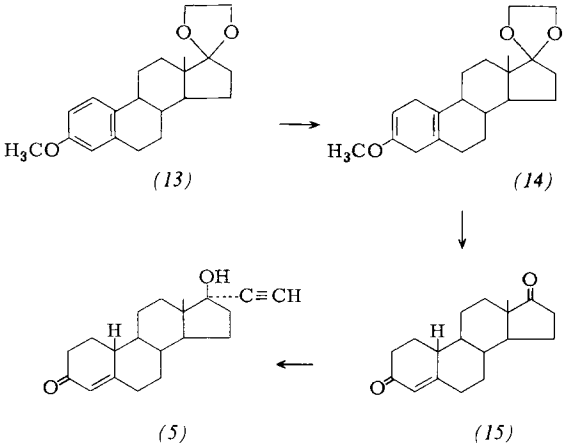


Fig. 6. a) The root and b) the foliage of *Dioscorea composita*.

Diosgenin can be converted into an androstene derivative in a number of stages which give excellent yields. The main country producing diosgenin is Mexico. In 1974 the State of Mexico began itself to undertake and monopolize gathering of the roots. For this reason, the sterols which are available throughout the world will certainly gain importance as a raw material.

Technically perfected and economic methods of producing completely synthetic estrogens and nor-steroids, whose capacity can be extended at will, have now been available for a number of years. The problems of producing completely synthetic steroids on an industrial scale are dealt with briefly in a later section.

Estrone is a suitable starting material for the production of the progestogen component 19-nortestosterone.



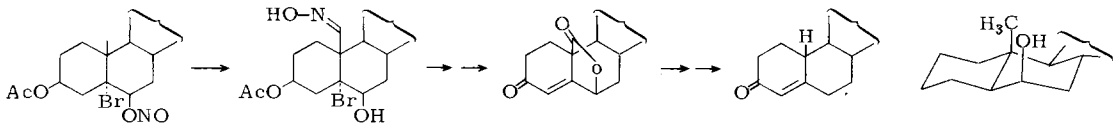
The key reaction is the reduction of phenols with lithium in liquid ammonia, developed by *Birch*. This converts the 17-ketal of the estrone methyl ether *(13)* into the enol ether *(14)*, which on acid hydrolysis gives 19-nor-4-androsten-3,17-dione *(15)*. The compound *(15)* can be converted stereoselectively into 17α-ethynyl-19-nor-testosterone *(5)*.

In 1960 *Barton* discovered a new possibility of synthesizing 19-nor steroids by intramolecular functionalization of the nonactivated 19-methyl group.

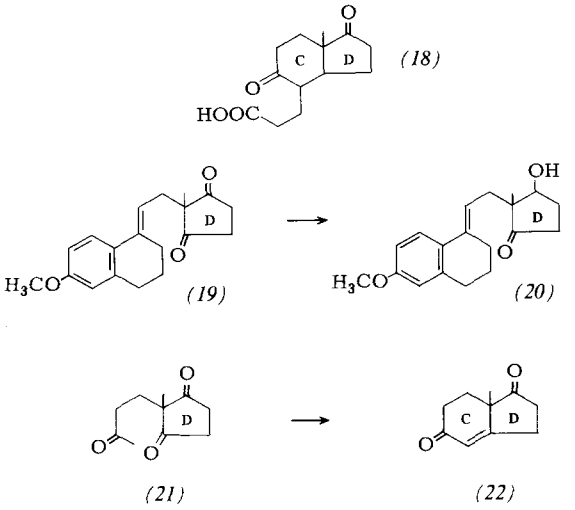
The action of light results in the transfer of the nitrite ester in *(16)* to the δ-carbon in the 19-methyl group to give *(17)*. For this to occur the nitrite residue and the methyl group must be axial. This radical reaction can also be achieved under modified conditions with hypoiodites or lead acetate and alkoxides. Compound *(17)* is then converted into a structure from which the C-19 can easily be eliminated in a number of stages.

All the methods of synthesizing steroids discussed so far start from natural substances that already contain the natural tetracyclic structure.

Producing totally synthetic steroids meant finally finding a solution to the difficult problem of synthesizing a substance with several asymmetric centers. In addition, it had to be possible to carry out the process economically on an industrial scale. Although methods of producing completely synthetic steroids had been worked out as early as 1939, with various and, in some cases, highly elegant solutions being published,



only three recently developed methods, in which all the requirements cited above are satisfied, are available for this purpose[12].



Chirality is introduced in each case at different stages in the synthesis. For example, the racemic building block *(18)*, which contains rings C and D, can be resolved into the enantiomers by classical methods. In another synthesis, the prochiral diketone *(19)* is reduced asymmetrically to the alcohol *(20)*, in high yields, by a microbial process. This gives rise to two chirality centers on the later C-atoms 17 and 18.

Finally, the optically active building block CD can be produced at a very early stage in the synthesis by an asymmetric ring closure reaction of the triketone *(21)*. This cyclization is carried out with catalytic quantities of L-proline, obtaining virtually optically pure *S*-configuration indene derivative *(22)* in yields of over 90 %.

To conclude this section on syntheses, it can be said that with the partially and totally synthetic methods of producing steroids we now have at our disposal a wide range of processes that make use of various sources of raw material.

There is not likely to be any shortage of supply of contraceptive steroids in the future.

It is worth mentioning at this point that the country with the largest population in the world, the People's Republic of China, has now built up its own steroid production and makes enough for its own requirements. The production is based on diosgenin obtained from the varieties of *Dioscorea* that grow in China and on fully synthetic production methods.

4. Experience with Contraceptive Steroids

Hormone contraception has been practised throughout the world since 1959 and we can now look back on a period of almost twenty years of use. In 1974, in the Federal Republic of Germany alone, some 34 % of the women of childbearing age were on the pill. Never before in the history of mankind have highly active drugs been used to such an extent for a nontherapeutic purpose, *i.e.* to influence a physiological process in healthy people. Scientists and governments were virtually unprepared to deal with this situation and with the multitude of problems created by it. We are now in the possession of extensive data enabling us to assess the advantages and the possible dangers involved.

There is no doubt that hormonal contraception is more reliable than any of the previously known methods of birth control. The failure rate is 0.2—0.6 per 100 women-years, and these figures even take account of errors in taking the pill and absorption anomalies caused *e.g.* by diarrhea.

The suppression of pituitary hormone stimulation over a prolonged period by ovulation inhibitors is no more unnatural than the situation that prevails during pregnancy and lactation.

Experts consider that the side effects[14] of ovulation inhibitors must be viewed in relation to the side effects and dangers of pregnancy, birth, or even abortion. To consider it in the right context, the method must be viewed as preventive medicine.

The most extensive prospective study of the side effects was published in Britain in 1974 by the Royal College of General Practitioners under the title "Oral Contraceptives and Health". At that time data had been assessed on 46000 women who had been taking oral contraceptives for more than 4 years. The report comes to the conclusion that the advantages of oral contraception outweigh the disadvantages.

In his detailed critical review of the available literature, *Döring*[15] differentiates between harmless, serious, and useful side effects. Here we shall cover just a few of the important points. Given the present state of knowledge, there is no evidence that women who use ovulation inhibitors are more likely to suffer from cancer. Indeed, there are even indications that progestogens give some protection against breast cancer.

The possibility that oral contraceptives promote thromboembolic diseases in predisposed women cannot be excluded on the basis of the data available at present. The risk, however, is much smaller than that associated with pregnancy. In statistical terms, it is equivalent to the risk of dying as a result of smoking $^1/_3$ of a cigarette per day.

Many women make use of oral contraceptives explicitly because of the useful side effects brought about by their application. During the years that the pill has been in use, good results have been obtained in the treatment of such conditions as dysmenorrhea, premenstrual tension, endometriosis, acne vulgaris, and intermediate bleeding. It is an interesting fact that the incidence of endogenous depression is lower among women taking the pill.

5. Other Methods of Birth Control

In addition to the most important method of birth control, namely oral contraceptives, the use of various intrauterine devices[9] has become more and more widespread over the last few years. A figure of as many as 20 million users has been quoted for 1975.

The mode of the action of these devices has not yet been fully clarified. It is thought that they may cause increased peristalsis of the fallopian tubes, with the result that the ovum arrives in the endometrium too early, before nidation is possible.

Copper-coated devices have a greater contraceptive effect, probably because they release minute quantities of the metal

and so cause biochemical changes in the reproductive organs and the sperm. Devices of this type remain effective for about two years.

The discovery of new methods of birth control more effective than those already available depends primarily on a better understanding of the physiological, biochemical, and immunological processes involved in reproduction. However, consideration must also be given to whether new methods are likely to be accepted by the majority of cultures.

The development of a new contraceptive is an extremely risky undertaking and involves a tremendous expenditure of time and money[16, 17]. Thus, if these imponderables are to be realistically assessed, one must be skeptical of those who quickly overestimate the value of every new possible method of birth control with optimism and lack of criticism.

The starting points for new methods of female contraception are offered by intervention in the physiological process of egg-cell development before and after fertilization. Increasing or reducing the rate at which the ovum is transported causes a fertilized egg cell to die. Transportation of the ovum can be influenced with the aid of hormones.

The environment in the fallopian tubes and the uterus is of decisive importance to the ability of the ovum to survive. Changes in the hormonal estrogen-progestogen balance also produce a change in the composition of the tubal and uterine secretions. The hormone-dependent process of implantation of the ovum in the endometrium can only take place if the structure of the uterine mucosa is right. Effective antiestrogens prevent implantation, for example.

The corpus luteum and the hormone it produces are of major importance to the normal course of a number of processes after fertilization. If no progesterone is available, a pregnancy cannot become established and one that has become established will be aborted.

There are a number of possible ways of intervening actively in these processes:

1. Degeneration of the corpus luteum, in which the progesterone is produced, *i.e.* luteolysis. It had been hoped that certain prostaglandins[19] of the $F_{2\alpha}$ series would cause abortion through luteolysis. This has been demonstrated in a number of animal species, *e.g.* in cattle, sheep, and guinea pigs. However, in women, prostaglandins cause abortion only by inducing labor. Their use involves a large number of unpleasant side effects since the action is not selective on the uterus but involves all other smooth-muscle organs to varying degrees. There are indications that these side effects can be averted by local administration.

2. Prevention of the establishment of pregnancy or production of an abortive effect requires true progesterone antagonists, *i.e.* antiprogestogens. Such substances are not yet available.

3. Another promising research direction is looking into compounds that intervene in the enzymatically-controlled biosynthesis of progesterone.

The use of immunological methods of contraception seems highly promising[18]. Some time ago prolonged sterility had been produced in a number of animal species by active immunization with sperm, seminal plasma and testicular and fetal extracts.

One method that might be feasible is active immunization with human chorionic gonadotropin or with the β-unit, a fragment of this peptide hormone. Such immunization has the great advantage of preventing only pregnancy, since the hormone concerned is formed only in the placenta.

New prospects for birth control are offered by the highly successful work done in recent years in the field of releaser hormones. These substances are produced in the hypothalamus and are responsible, since they cause the release of pituitary hormones, for the production of the steroid hormones. The releaser hormone of luteinizing hormone was isolated and synthesized a few years ago. It is a polypeptide comprising ten amino acids. This discovery has opened up the way for intensive biological research.

Another starting point is offered by one of the side effects of the pill which contribute to its contraceptive effect, namely the change produced in the cervical secretions. This important barrier to sperm penetration can be altered with the aid of progestogens so that it becomes impenetrable to sperm. Furthermore, sperm only becomes capable of fertilizing the ovum after it has been in the female genital tract for a certain time. This process, which is also dependent on hormones, is known as capacitation.

It will be clear from this brief review of possible future methods of birth control that there are numerous starting points for female contraception. It would be pointless, however, to speculate which of them can be developed to the point of being put into practice.

It is also too early to say whether one day a method of chemical birth control for men will be found[20]. We are still a long way from being able to suppress male fertility while maintaining potency and libido.

One of the reasons for this lies undoubtedly in the fact that insufficient research has so far been done on the reproductive process in men. A comparable male preparation to the female ovulation inhibitors would be one that inhibited spermatogenesis. However, ovulation takes place only once every four weeks, whereas spermatogenesis is a continuous process, millions of spermatozoa maturing every hour. It is easy to see that intervention here is far more complicated.

Although reversible inhibition of spermatogenesis can be achieved by administering large doses of progestogens, endogenous production of testosterone is brought to a standstill, resulting in loss of libido. This makes it necessary to administer an androgen in addition, again in large doses.

Apart from being badly tolerated, such a combination does not take effect until some weeks after the administration has been commenced. When the treatment is withdrawn, it again takes weeks or months for the fertility to be restored.

The results obtained with nonhormonal chemicals are even less favorable. It is to be hoped that the intensive research going on throughout the world in this very important field of reversible control of male fertility will in the end prove successful.

Finally, we must mention the growing importance of surgical sterilization of men in the developing countries, and also in the industrialized nations.

Female hormonal contraception could undoubtedly provide a reliable method of solving the problem of excessive growth of population. It would certainly not be too difficult to produce the quantities of hormones required to cover world requirements. Only about 6.5 tons of estrogen and 32 tons of progestogen per year would be needed to produce a modern, low-dose

contraceptive in sufficient quantities for the 500 million fertile women in the world.

The American anthropologist *Cora Du Bois* has a terse answer to the question of why this simple sum has not made any impact: in her view, every method of contraception that can be understood only in technical terms and every demographic improvement plan will prove unsuccessful until individuals are convinced of the importance of the problem.

6. Future Outlook

Throughout the millenia over many generations, man has observed that only fertility prevented his race from becoming extinct. The danger of extinction of the human race was only averted three or four generations ago, but this inherited drive has not been forgotten.

The difficulty of explaining the danger of overpopulation is clear when one considers that 900 million people are still illiterate, and the figure is rising despite the UNESCO literacy program.

In the developing countries imported family planning products are often regarded suspiciously as a new variant of colonial imperialism.

This means that the national and private organizations in the industrialized countries must take account of the cultural and social situation in the developing countries when offering assistance with population policy. Even in the industrialized countries family planning is more and more a part of development planning.

Birth control could provide one way for the human race to survive. However, the most important prerequisite is that every person is made aware of the urgent need to stem population growth. Achieving this state of awareness is one of the major tasks of our age.

Received: September 27, 1976 [A 142 IE]
German version: Angew. Chem. *89*. 513 (1977)
Translated by Express Translation Service, London

[1] *J. Linhard* in *R. Mackensen, H. Wewer:* Dynamik der Bevölkerungsentwicklung. Hanser, Munich 1973, p. 183ff.
[2] *D. Meadows:* Die Grenzen des Wachstums. Deutsche Verlagsanstalt, Stuttgart 1969.
[3] *J. Linhard*, unpublished report.
[4] Oral Contraceptives—50 Million Users. Population Rep. Ser. A, No. 1, April 1974. George Washington University Medical Center, Washington, D.C.
[5] *H. H. Simmer*, Geburtshilfe Frauenheilkd. *35*, 688 (1975).
[6] *J. W. Goldzieher, W. Rudel*, J. Am. Med. Assoc. *230*, 421 (1974).
[7] *R. Kaufmann:* Die Pille. Diderichs, Düsseldorf 1968.
[8] *L. F. Fieser, M. Fieser:* Steroide. Verlag Chemie, Weinheim 1961.
[9] *G. K. Döring:* Empfängnisverhütung. 6th Edit. Thieme, Stuttgart 1975.
[10] *J. Hammerstein*, Gynäkologe *5*, 120 (1972).
[11] Minipill—a Limited Alternative for Certain Women. Population Rep. Ser. A, No. 3. Sept. 1975. George Washington University Medical Center, Washington, D.C.
[12] *R. Wiechert*, Angew. Chem. *82*, 331 (1970); Angew. Chem. Int. Ed. Engl. *9*, 321 (1970).
[13] *F. Neumann, R. Wiechert*, Dtsch. Mus. Abrh. Ber. *42*, 1 (1974).
[14] Advantages of Orals Outweigh Disadvantages. Population Rep. Ser. A, No. 2, March 1975. George Washington University Medical Center, Washington, D.C.
[15] *G. K. Döring*, Fortschr. Med. *93*, 1345 (1975).
[16] *C. Djerassi*, Science *169*, 1941 (1970).
[17] *C. Djerassi*, Science *166*, 468 (1969).
[18] *H. G. Friesen*, Res. Reprod. *8*, 1 (1976).
[19] Prostaglandins. Population Rep. Ser. G, No. 6, Sept. 1975. George Washington University Medical Center, Washington, D.C.
[20] *B. Schenck, F. Neumann*, Sexualmedizin *4*, 248 (1975).

The Chlorofluorocarbon/Ozone Theory—A Scientific Status Report

By J. Peter Jesson[*]

In 1974 Professors *Rowland* and *Molina* of the University of California at Irvine developed a theory concerning the possible adverse impact of chlorofluorocarbons on the earth's ozone shield. These compounds are the working fluids responsible for the safety and efficiency of almost all air-conditioning and refrigeration equipment and are used as propellants in many types of aerosol products.—The present article is divided into five sections. The first is an historical perspective of the scientific situation up to the end of 1974. The second section examines the various findings and observations on which the theory is founded and outlines new knowledge gained in this sector since early 1975. The third section is devoted to the possible consequences of ozone depletion while the fourth and fifth sections consider the question of the risk taken in delaying a decision to stop production of certain halocarbons.

1. Introduction

1.1. State of Our Knowledge in June 1974

In their original paper[1] *Rowland* and *Molina* derived the ozone depletion theory from the following pieces of scientific information:

There are detectable concentrations of chlorofluorocarbons in the atmosphere [CCl_3F (FC-11) and CCl_2F_2 (FC-12)][2].

Gases rise in the atmosphere and, in the absence of rapid removal processes, are well mixed to altitudes above the ozone layer (most of the ozone is present at altitudes between 10 and 60 km)[3].

Ultraviolet light can break down chlorofluorocarbon molecules, releasing chlorine atoms[4].

[*] Dr. J. P. Jesson
Central Research and Development Department
E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898 (USA)

Computer models, which simulate both the "vertical diffusion" of molecules in the atmosphere and the gas phase chemical reactions (including photochemical processes), had already been developed[5].

A variety of gas phase reactions involving chlorine atoms, ozone, and other known atmospheric constituents had been identified in laboratory experiments and their rates established with varying degrees of certainty[6]. Some of the relevant reactions are:

$$Cl + O_3 \rightarrow ClO + O_2 \quad (1)$$
$$ClO + O \rightarrow Cl + O_2 \quad (2)$$
$$HCl + OH \rightarrow Cl + H_2O \quad (3)$$
$$Cl + CH_4 \rightarrow HCl + CH_3 \quad (4)$$
$$ClO + NO \rightarrow Cl + NO_2 \quad (5)$$

Reactions (1) and (2) describe the catalytic cycle for conversion of O_3 into O_2.

1.2. The Statement of the Theory

On the basis of this information *Rowland* and *Molina* put forward the important theory which suggests a possible impact of chlorofluorocarbon release on the steady state ozone concentration in the atmosphere. They presented new experimental information on ultraviolet absorption characteristics of chlorofluorocarbons and estimated the rate of destruction of CCl_3F and CCl_2F_2 by ultraviolet light at different altitudes.

1.3. The Initial Assessment

To assess the risks involved in a continued experimental program and to provide a baseline to determine whether new experimental information revises predicted ozone depletions up or down, it is necessary to carry out time dependent

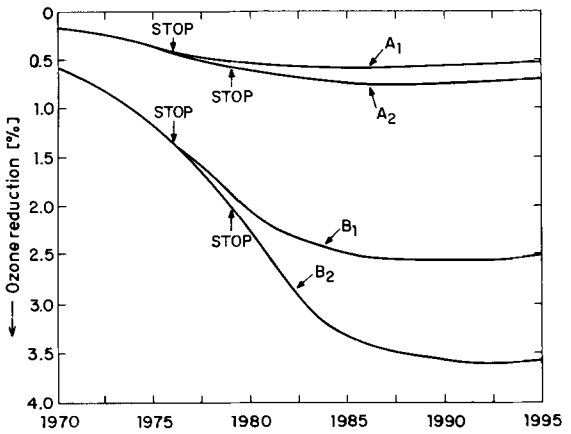


Fig. 1. A comparison of the effects on ozone depletion of stopping fluorocarbon production. Curves A_1B_1: production stop on January 1, 1976; curves A_2 and B_2: production stop on January 1, 1979. Calculations based on the original assumptions of *Wofsy et al.* [7] (B curves) and the best available data todate (A curves). In both cases ozone depletion would peak around 1990, but the estimates are now reduced by a factor of about 5 (the values in curves A are about a factor of 5 lower than the values in curves B).

ozone depletion calculations. This was first done by *Wofsy*, *McElroy*, and *Sze*[7]. The results of calculations based on their original assumptions are shown in Fig. 1 (B curves). These are compared with curves calculated using the same procedures but with the latest experimental input information (A curves). Two production scenarios were assumed in each case (curves A_1 and B_1 correspond to a production stop on January 1, 1976 curves A_2 and B_2 to a stop on January 1, 1979). It can be seen that the estimated short term risk (ozone depletion) is now about a factor of 5 less than the original estimate.

The second important step was to list critical experiments needed to validate or invalidate the theory. A broadly agreed upon experimental program[8] was rapidly set in motion and has now been in progress for about two years. Results have been obtained at an encouraging rate. The basic outline of the program remains the same although priorities change as new information is obtained. Thus it is now thought that chlorine nitrate ($ClONO_2$) is a molecule of considerable importance in the stratosphere, so that attempts to detect it would now rank high on most researchers' lists of experiments. As a secondary consequence simultaneous measurements of ClO and HCl as a function of altitude are urgently required in order to determine whether other molecules, analogous to $ClONO_2$, compete with HCl as a stratospheric chlorine reservoir.

2. The Elements of the Theory and New Experimental Results

We now examine the successive steps in the theory from production, and release of CCl_3F and CCl_2F_2 into the atmosphere, to the eventual removal of their decomposition products, and we consider the progress in defining each step experimentally.

2.1. Production and Release of Chlorofluorocarbons into the Atmosphere

Accurate data on the production and release of CCl_3F and CCl_2F_2 to the atmosphere have been obtained through a survey of the manufacturers carried out by independent examiners. The totals to the end of 1975 are now known. Release to the atmosphere is estimated as being close to 85 % of the amount produced at any given time; this value was obtained by breaking down sales in terms of end use (refrigeration, aerosols, closed cell foam *etc.*) and combining it with a release pattern for each application. For instance is takes roughly twenty years for all the CCl_3F in closed cell foam to be released, whereas aerosol propellants are released quickly.

Total world release to the atmosphere by the end of 1975 was 2.93×10^9 kilograms of CCl_3F and 4.4×10^9 kilograms of CCl_2F_2. Overall estimates of release to the atmosphere are probably accurate to $\pm 5\,\%$[9].

2.2. Tropospheric Lifetimes

It is still not known whether there are processes in the troposphere which destroy chlorofluorocarbons at a rate sufficiently fast to compete with photolysis in the stratosphere as a removal process. If there are such processes, they could lead to large downward revisions in ozone depletion calculations (it is presently assumed that chlorofluorocarbons have an infinite lifetime in the troposphere).

One way to check this point is to compare the amount of CCl_3F and CCl_2F_2 known to have been released to the atmosphere with the amount found to be present by atmospheric measurements. There have been extensive measurements of CCl_3F over a period of five years. Most of these measurements have been carried out at places with mid-latitudes in the Northern hemisphere. Whatever the latitude, any given set of measurements must be converted to a global average before it can be compared with calculated values. There is a higher concentration in the Northern hemisphere, where the halocarbons are released, than in the Southern hemisphere. Experimental latitude data were obtained by *Lovelock*[10] on a voyage of the Shackleton from the north to the south and back in 1971—2. We have used a least squares fit to these data to generate empirical latitude conversion factors[11].

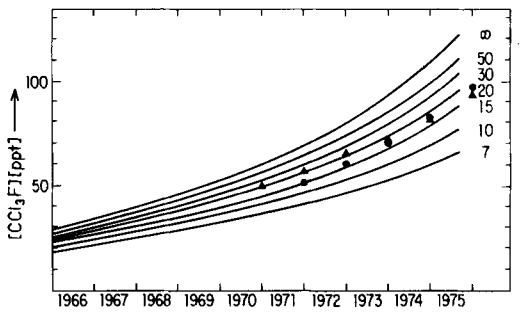


Fig. 2. A comparison of CCl_3F mixing ratios in the troposphere calculated for tropospheric lifetimes of ∞, 50, 30, 20, 15, 10, and 7 years (unbroken curves) with the measurements of *Lovelock*. ▲ Data from exponential least squares fit to all Bowerchalke (England) and Adrigole (Ireland) data (51 °N) adjusted for latitude. ● Southern Hemisphere data adjusted for latitude. ppt = parts per trillion.

A set of theoretical curves for CCl_3F concentrations, calculated as a function of tropospheric lifetime, is compared with the data of *Lovelock*[12] (corrected for latitude) in Figure 2. These data, which were collected in both the Northern and Southern hemispheres over a period of five years lie between the 15 and 20 year lifetime curves. The fact that the Northern and Southern data, after correction for latitude, lie close together is an indication of the internal consistency of the procedure. In all cases the relatively slow Hunten diffusion profile has been chosen. Faster diffusion will lead to longer estimated tropospheric lifetimes.

Recent data from *Rasmussen*[13] suggest a much smaller latitude gradient than found by *Lovelock*[10]. The data of *Rasmussen* could be interpreted in terms of less tropospheric removal than was previously assumed. Further work will be required to resolve this difference. The differences may be real and could be related to atmospheric circulation patterns giving bigger gradients over the Atlantic than over the Pacific. It should be noted, however, that the gradient measured by *Lovelock* has persisted almost unchanged to the present day (if this were not the case, the experimental lines in Fig. 2 would move apart as we approach the present day). A second important point is that if the Adrigole measurements of *Lovelock* are assumed to be high because of industrial release, the calculated global averages would be even lower than estimated in reference[11], indicating a still shorter lifetime. It would also mean a calibration discrepancy between the measurements of *Lovelock* and *Rasmussen*. (The data of *Lovelock* and *Rasmussen* should agree in the Southern hemisphere where there are no local sources of halocarbons, while *Lovelock*'s data in the Northern hemisphere should be higher then *Rasmussen*'s if there is an effect from proximity to centers of release. In fact the reverse is true, *Lovelock* and *Rasmussen* agree quite well in their Northern hemisphere measurements while *Lovelock*'s Southern hemisphere data are lower than those of *Rasmussen*.) Absolute calibrations and cross calibrations are urgently needed.

In recent months, the first direct evidence for possible tropospheric sinks has been obtained. Workers at the National Bureau of Standards have shown that chlorofluorocarbons can be broken down by ordinary sunlight in the presence of sand particles[14]. Large sections of the atmosphere contain sand or dust clouds. It has also been suggested[15] that the detection of $CHCl_2F$ in the troposphere is evidence of a sink for CCl_3F. However, in the meantime some of the measurements have been withdrawn, so that the situation with regard to $CHCl_2F$ is presently unclear. Tropospheric sinks are still an open question.

If the compounds have tropospheric lifetimes as short as ten years, up to 90% of the molecules could be destroyed in the troposphere, lowering depletion estimates by an order of magnitude.

2.3. Upward Mixing and Photolysis

After release halocarbons "diffuse" upwards in the atmosphere and a significant fraction of them reach the stratosphere.

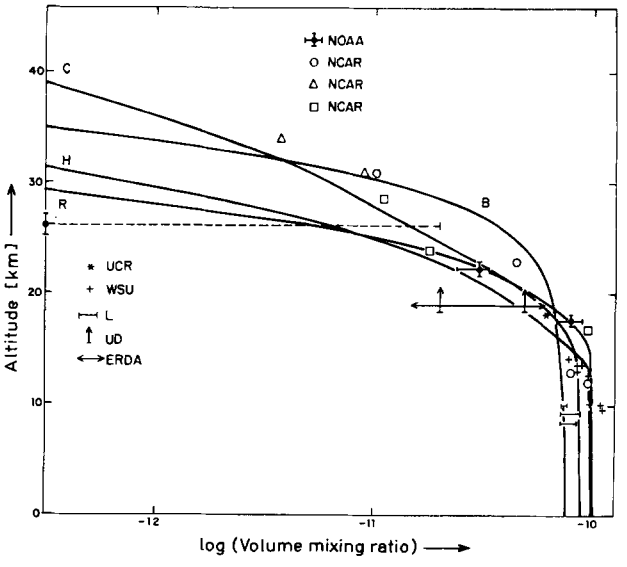


Fig. 3. Comparison of calculated and observed mixing ratios for CCl_3F in the stratosphere. Several eddy diffusion models were used in the calculation. The overall lifetime calculated for CCl_3F assuming an infinite tropospheric lifetime in *Crutzen*'s model II (C) is 34 years, in *Brasseur*'s "Maximum" model (B) 18 years, in *Hunten*'s model (H) 91 years, and in *Rowland*'s model A (R) 97 years. The measurements were carried out by the following groups: ERDA (Energy Research and Development Administration), October 25, 1974; L (*Lovelock*), June 1974; NCAR (National Center for Atmospheric Research), ○: September 9, 1973; △: May 7, 1974; □: June 2, 1975; all at 30° south; NOAA (National Oceanic and Atmospheric Administration), 41° north; UCR (University of California at Riverside), May 23, 1973; UD (University of Denver), August 12, 1968 and September 26, 1975; WSU (Washington State University), May 1975.—Concentrations (v/v).

Measurements have been made of CCl_3F concentrations from below the tropopause to high altitudes in the stratosphere. Figure 3 shows calculated and observed profiles of CCl_3F in the atmosphere for a variety of models. *Hunten*'s model is supported by ^{14}C measurements, but gives theoretical fluorocarbon concentrations (140 ppt at 16 km, 93 ppt at 21.5 km, and 40 ppt at 26 km) which are in poor agreement with the observed mixing ratios. The best fit to the observed data is obtained with the Crutzen II model (one of the faster diffusion schemes). The stratospheric chlorofluorocarbon profiles are largely indications of diffusion and photolysis. Since these steps in the theory have not been questioned, the measurements, although important, do not contribute greatly to the overall testing of the theory.

2.4. Chlorine Atoms by Photodissociation

At sufficiently high altitudes in the stratosphere, chlorofluorocarbon molecules are broken down by sunlight to release chlorine atoms.

2.5. Reactions of Chlorine in the Stratosphere

The fate of the liberated chlorine atoms in the stratosphere is by far the biggest gap in the theory. This concerns both the quantitative aspects of the known chemistry and, more importantly, the possibly existing but still unknown gas phase chemistry. The only way these questions can be answered is by direct measurement in the stratosphere.

The quantitative aspects of the known chemistry can be refined by laboratory measurements—primarily by measurement of reaction rate constants and photodissociation cross sections. This information is then used as input to computer models which attempt to simulate the atmosphere. The models predict concentrations of trace species (HCl, ClO, Cl, NO_2, NO, O_3 *etc.*) in the atmosphere as a function of altitude and these predictions are in turn tested by direct measurement, usually using balloons. Discrepancies are then discussed in terms of possible missing chemistry or inadequacies in the models or the available experimental data. It is believed that, over the next two years, this process will have progressed to the point where we have a good understanding of the effects of chlorine in the stratosphere.

We shall discuss the present situation using a unidimensional computer model of the atmosphere developed at Dupont, together with input information recommended to NASA for use in recent modelling comparisons. The test of the model is how well it can reproduce the concentrations of species already measured in the stratosphere. The modelling results described include multiple scattering of the sun's radiation but do not include diurnal effects.

The basic features of the model include a kinetic scheme covering in excess of 80 chemical and photolytic reactions for 30 atmospheric molecules, atoms, and radicals. Four of these species have fixed concentration profiles (O_2, N_2, H_2, and H_2O). The remaining 26 species (ranging from stable molecules like CH_4 and N_2O to highly reactive radicals and atoms such as HO_2 and $O(^1D)$) are floating, with concentration profiles determined by the kinetics and the boundary conditions. The atmosphere is divided vertically into a variable number of grid points (x) and the resulting array of $30 \times x$ coupled ordinary differential equations is solved using Gear integration techniques. Photodissociation rates are continuously updated. The model is fully time-dependent within the 24-hour average sun approximation and all depletion calculations are carried out using time-dependent fluorocarbon fluxes. Multiple scattering is incorporated using an isotropic scattering radiation model.

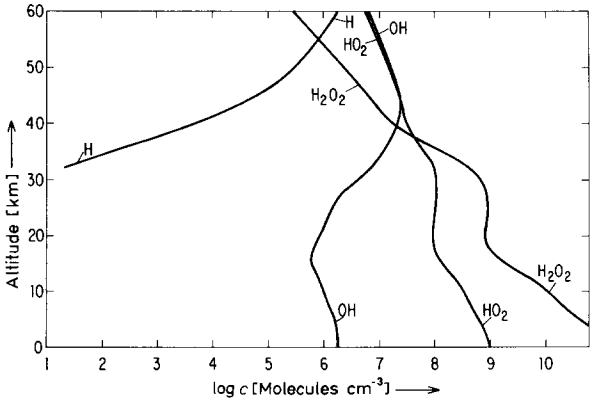


Fig. 4. Calculated concentration profiles for H, OH, HO_2, and H_2O_2 in the atmosphere under present day conditions.

Figure 4 shows calculated concentrations of hydrogen-containing species as a function of altitude. The content of OH radicals in the stratosphere has been measured by *Anderson*[16]. The calculated value of 2×10^7 radicals/cm^3 at 40 km is in good agreement with the measured value. Similar comparisons can be made with measurements on nitrogen-containing species such as NO, NO_2, and HNO_3. Again good agreement is obtained with experiment.

The molecules of greatest interest in the halocarbon problem are those containing chlorine. The detection of HCl in the stratosphere (the major postulated holding tank for chlorine) was recognized at an early date as the most important qualitative evidence supporting the Rowland-Molina theory. Most of the HCl arises from sources of atmospheric chlorine other than chlorofluorocarbons; CH_3Cl, CCl_4, and CH_3CCl_3 are major known contributors. The methyl chloride is of natural origin. The carbon tetrachloride could be either largely man-made or largely natural, depending on its somewhat uncertain atmospheric lifetime. The CH_3CCl_3 is probably man-made. In order to interpret the HCl measurements it is necessary to know the total amount of chlorine reaching the stratosphere—measurements of this type have not yet been made and we still do not know whether all sources of atmospheric chlorine have been identified.

The two other chlorine species, recognized as being important from the beginning, are Cl atoms and ClO radicals. These have recently been measured in spectacular experiments, once again carried out by *Anderson*[17]. The ratio of the concentrations [ClO]/[Cl] is in good agreement with theory but the absolute amounts are higher than predicted.

The chlorine problem has been complicated by the suggestion[18] that chlorine nitrate ($ClONO_2$), a molecule originally thought to be of no importance in stratospheric chemistry, may, in fact, play a major role. The calculated present day concentrations of the various chlorine species in the stratosphere arising from the known amounts of CH_3Cl, CCl_4,

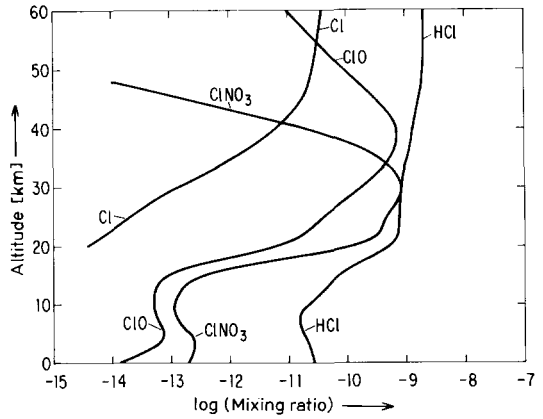


Fig. 5. Calculated concentration profiles for Cl, ClO, HCl and $ClNO_3$ in the stratosphere under present day conditions. Concentrations (v/v).

CH_3CCl_3, and fluorocarbons, are shown in Figure 5. As noted above, the calculations include multiple scattering, which reduces the calculated concentration of $ClONO_2$ (but does not materially effect ozone depletion estimates). The $ClONO_2$ concentrations calculated are, at all altitudes, below the upper experimental limit established by *Murcray*[19]. The inclusion of multiple scattering affects the concentration of all 26 floating species; sometimes, as in the case of $ClONO_2$, quite markedly. As an illustration of this type of effect, the percent change of concentration of $ClONO_2$ as a function of altitude, on including multiple scattering, is shown in Figure 6. Reductions in excess of 65% are calculated in the region just below 20 km.

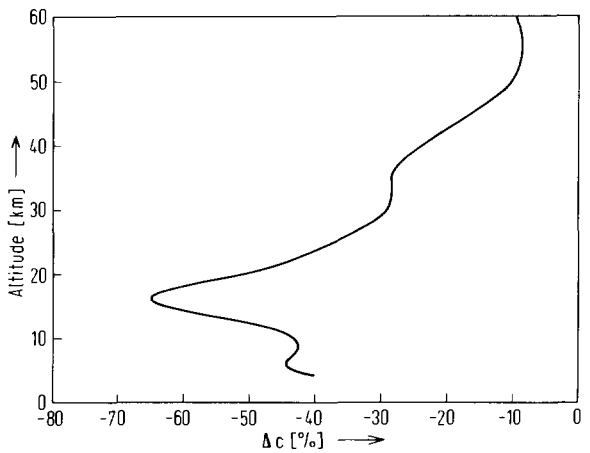


Fig. 6. Calculated effect of multiple scattering of sun's radiation on $ClONO_2$ concentration as a function of altitude. Change of concentration Δc is quoted. An albedo of 0.25 is assumed.

For meaningful comparison of theory and experiment in the case of chlorine species in the stratosphere most of the following steps are essential: a) construction of models which accurately account for diurnal variations, b) determination of the total amount of chlorine reaching the stratosphere, c) more extensive simultaneous measurements of Cl, ClO, and HCl, particularly determination of the [ClO]/[HCl] ratio, and d) measurement of $ClONO_2$ in the stratosphere. For the present, we briefly outline the current anomalies in the data on chlorine species in the stratosphere and indicate the types of explanations which may account for these anomalies.

HCl: hydrogen chloride has now been measured in the stratosphere at altitudes between 16 and 39 km using a balloon-borne, pressure-modulated radiometer[20]. A peak mixing ratio of about 2 ppb is observed at 32 km with a steady decrease above and below that altitude. From Figure 5 it can be seen that the calculated HCl mixing ratio at 32 km from the known sources of chlorine is *ca.* 0.8 ppb, a factor of about 2 too low. More importantly, the calculated HCl mixing ratio increases monotonically above 32 km, whereas the measured value goes through a maximum.

ClO and Cl: The measured ClO values peak between 30 and 35 km with peak values covering the range 2×10^8 to 8×10^8 radicals/cm^3. The calculated value in Figure 5 peaks at about 35 km with a value of 9×10^7 radicals/cm^3, *i.e.* between a factor of 2 and a factor of 9 less than the measured values.

As already mentioned above, the [Cl]/[ClO] ratio is in very good agreement with theory.

Variability of the overall data is expected (hence the importance of obtaining simultaneous measurements of ClO and HCl) so that from a theoretical point of view, the key feature to be explained is the decrease in HCl mixing ratio above 32 km. The following overall explanations are possible:

1. The ratio of ClO to HCl is higher than the models predict because of errors in the known chemical reaction rates. Under these circumstances more of the chlorine would be in the form of ClO and a decrease in concentration of HCl above 32 km would be calculated. This type of effect can be reproduced theoretically by arbitrarily adjusting reaction rates.

2. The ratio of ClO to HCl is similar to that calculated in the models. Under these circumstances the only likely explanation for the decrease in HCl mixing ratio would be the role of hitherto unknown chemical factors which have not been taken into consideration in the models (*e.g.*, another chlorine holding tank analogous to $ClONO_2$).

3. The decrease in HCl mixing ratio is an experimental artifact. This now seems unlikely since it has been observed on numerous occasions.

In all three cases it is possible that we are seriously underestimating the amount of chlorine reaching the stratosphere. It could be that the flux of CH_3Cl is much greater than currently assumed (the measured concentrations of CH_3Cl in the atmosphere are very variable, so that a serious underestimation of the flux is not unlikely) or there may be other unidentified sources of chlorine such as volcanic activity.

Alternatively, the current estimates of chlorine flux in the stratosphere may be quite accurate, in which case the high experimental values could arise from calibration errors.

2.6. Removal of Chlorine from the Stratosphere

This is the final step in the chain bringing the chlorine back to the earth's surface. At present this is assumed to occur by downward diffusion of HCl followed by rainout in the troposphere. If there are other stable chlorine compounds in the stratosphere, they could also contribute to this process.

From the above discussion it can be seen that the major uncertainties in the theory lie in the following areas:

The fate of the chlorine atoms in the stratosphere.
The tropospheric lifetimes.
The quantitative aspects of the known chemistry.
The problem of transport.

The uncertainties in these areas can be substantially narrowed within the two year period for research suggested by the National Academy of Sciences[21]; progress is already being made in that direction.

3. Current Estimates of the Effects of Fluorocarbons on Ozone

Although it is clear from Section 2 that much more research is required to settle the question whether chlorofluorocarbons have a significant effect on stratospheric ozone, it is important to make the best possible estimates of the effect on the basis of current knowledge, particularly to assess the potential risk of a continued experimental program.

Ozone depletion estimates can be made using the kind of computer models already described in Sections 1.3 and 2.3 of this article. The best starting point for the present discussion is an appraisal of the results published by the National Academy of Sciences (NAS) in September 1976[21]. The report concluded that continued release of fluorocarbons at 1973 levels would lead to an ultimate decrease in stratospheric ozone of about 7.5 % (a level which would be reached about 100 years from now). It was also concluded that the risks of delay are small (about 0.07 % incremental effect for each additional year of production).

Since the publication of the NAS report a number of rate constants have been refined (particularly those for the reactions HO_2+OH and $ClO+NO_2$). These result in a reduction of the 7.5 % figure to 3—5 % (5.1 % in the Dupont model, *ca.* 3 % in the NAS model), with a corresponding reduction in the incremental effect for continued production (*ca.* 0.05 % per year).

The NAS calculations did not include the effects of diurnal variations in the sun's radiation. Complete calculations of this type have not yet been carried out. Approximate treatments suggest that the effect will revise the depletion estimates upwards. Complete diurnal calculations should be available in the near future.

4. The Question of Delay

It is important to recognize that steady state depletion estimates, such as the 7.5 % NAS number, refer to conditions which would pertain about 100 years from now if chlorofluorocarbon production were maintained indefinitely at 1973 levels. These numbers are not directly relevant to the questions of immediate risk and of regulation. To address these questions we need estimates of the effects of allowing production to continue while research is being carried out, relative to stopping production immediately. The incremental effects for each additional year of production are *ca.* 1/100 of the steady state numbers (*i.e. ca.* 0.07 % for the NAS 7.5 % figure). In terms of the known latitudinal variation of ozone, a 0.07 % effect corresponds to the increased ultraviolet light experienced in moving 5 miles south of one's present location.

Considerations of this kind, combined with the uncertainties in the science, led the NAS to recommend that regulations restricting the production of chlorofluorocarbons not be enacted at this time and to allow up to two years delay for research to be carried out in order to establish the facts with regard to ozone depletion.

As an alternative approach to monitoring the risk of delay, it would be desirable, using measurements of trends in total ozone, to establish a sensitive early warning system for possible man-made effects on the ozone layer. An important first step has been taken in this direction by *Hill et al.* and by *Parzen* and *Pagano* using time-series analysis of ozone records from a number of specific ozone monitoring stations. *Hill et al.* reported at the Autumn 1976 meeting of the American Chemical Society that on the basis of a worldwide sample of nine stations, an abnormal global ozone change of 0.26 % per year persisting over 6 years would be judged statistically significant, if it were to occur and could not be explained by historical patterns. A resulting 1.56 % early warning can limit maximum reversible depletion to 2.3 % if the cause were due to the chlorofluoromethanes CCl_3F and CCl_2F_2. The analysis shows no abnormal global trend persisting in the 1970's. The potential exists for detecting even smaller changes by using data from all the current land based stations and satellites.

Thus, this approach already offers the possibility of an early warning system which could limit the maximum ozone depletion to a level close to that which many people would find acceptable, and that level would persist for a relatively short period of time.

This type of ozone-trend analysis should be given highest priority.

5. Tolerable Depletion

It is clear that many of man's activities such as the use of nitrogenous fertilizers, the flight of jet aircraft, and the production of halocarbons, will have some effect on the ozone layer. In each case an acceptable effect will have to be decided upon by governmental bodies. We do not live in a zero risk world. (*Conventional* subsonic aircraft are currently thought to have a 0.1—0.2 % impact on ozone.)

The NAS has suggested that a 2 % figure is one "which we think most informed people would judge to be tolerable". It is clear that new scientific knowledge could lead to ozone depletion estimates well below 2 %.

Received: April 25, 1977 [A 173 IE]
German version: Angew. Chem. *89*, 507 (1977)

[1] *M. J. Molina, F. S. Rowland*, Nature *249*, 810 (1974).
[2] *J. E. Lovelock et al.*, Nature *241*, 194 (1973).
[3] *E. A. Martell* in *B. M. McCormac*: Physics and Chemistry of Upper Atmosphere. Reidel, Dordrecht 1973, p. 24ff.
[4] *J. R. Majer, J. P. Simons*, Adv. Photochem. *2* (1964).
[5] *M. B. McElroy, J. C. McConnell*, J. Atmos. Sci. *30*, 1465 (1973).
[6] *R. Hampson et al.*: Chemical Kinetics Data Survey VI. National Bureau of Standards Interim Report 73—207 (1973).
[7] *S. C. Wofsy, M. B. McElroy, N. D. Sze*, Science *187*, 535 (1975).
[8] The Possible Impact of Fluorocarbons and Halocarbons on Ozone, May 1975. A Report of the Interdepartmental Committee for Atmospheric Sciences (ICAS 18a-FY 75), p. 64.
[9] *R. L. McCarthy, F. A. Bower, J. P. Jesson*, Atmos. Environ. *11*, 491 (1977).
[10] *J. E. Lovelock, R. J. Maggs, R. J. Wade*, Nature *241*, 194 (1973).
[11] *J. P. Jesson, P. Meakin, L. C. Glasgow*, Atmos. Environ. *11*, 499 (1977).

[12] D. H. Pack, J. E. Lovelock, G. Cotton, C. Curthoys, Atmos. Environ., in press.
[13] R. A. Rasmussen, private communication.
[14] P. Ausloos, R. E. Rebbert, L. C. Glasgow, J. Res. Nat. Bur. Stand., in press. American Chemical Society Meeting, New Orleans, March 1977.
[15] L. C. Glasgow, P. Meakin, J. P. Jesson, Winter Fluorine Conference, St. Petersburg, Florida, January 1977.
[16] J. G. Anderson, Geophys. Res. Lett. 3, 165 (1976).
[17] J. G. Anderson, American Geophysical Union Meeting, San Francisco, December 1976.
[18] F. S. Rowland, J. E. Spencer, M. J. Molina, Meeting of NASA Advisory Committee on Stratospheric Research, NASA, Jet Propulsion Laboratories, March 3, 1976.
[19] D. Murcray, private communication.
[20] J. R. Eyre, H. K. Roscoe, Nature 266, 243 (1977).
[21] Halocarbons: Effects on Stratospheric Ozone. The National Research Council, Washington, September 1976.

"Organic Metals"—The Intermolecular Migration of Aromaticity

By Jerome H. Perlstein[*]

The electrical conductivity of a wide variety of organic materials is reviewed and a comparison made between those materials which transport charge efficiently and those that do not. This comparison reveals that the most efficient conductors contain molecules a) whose radical ions form a new aromatic sextet upon one-electron oxidation or reduction and b) whose aromaticity can migrate by mixed-valence interaction. The electrical data are presented in light of the chemistry of these materials and the importance of chemical bonding interactions in the electron transport process. Several new examples are discussed and directions for further research explored.

("... an experimental and very real result of ours, points towards the reason why high-transition-temperature superconductors are so difficult to make ... We have realized that most high-transition-temperature superconductors are not very stable, they are metastable at best. Therefore, any search for high-transition-temperatures must concentrate on metallic phases that should never have been formed in the first place.")

Bernd T. Matthias[1]

1. Introduction

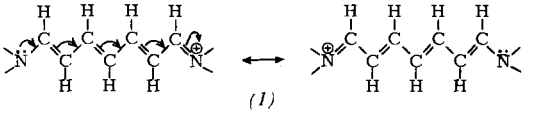
The concept that certain organic molecules in the solid state can have the electrical properties of a metal has received considerable attention among solid state chemists and physicists. No less than nine review articles[2–10] and the proceedings of three conferences[11–13] have been published on this subject in less than four years. One may well ask why write another review? A perusal of the literature on organic conductors indicates that the majority of papers have been directed toward solid state physics with little attention given to the needs of the synthetic organic and physical organic chemists who, after all is said and done, are the creators of those magnificent molecular structures which keep solid state research alive and well. This review then is written by a solid state chemist, for chemists and especially for those synthetic chemists I have had and still have the privilege to work with.

The majority of the theoretical models that have been developed to explain the creation and migration of electrons in organic conductors are highly physical in their origin as in fact they must be if the subject is to have a firm foundation. The chemist, however, in reading through the vast literature must be perplexed by an apparent lack of any chemical foundation for the subject; I say apparent, because either the foundation a) is obvious and therefore need not be stated or b) has been completely forgotten in what can only be described as a mad rush to synthesize and study anything that looks as if it might be potentially useful.

A close examination of what has been done chemically reveals that there are some unifying features of the chemistry which ought to have predictive consequences for what to look for in future materials; chemical features which the synthetic chemist can latch on to.

2. Some Solid State Fundamentals—Mixed Valence Interactions

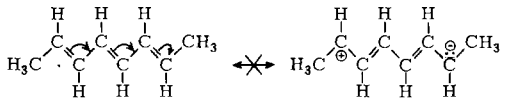
The most general feature of efficient charge transport in organic systems is the existence of equally spaced atoms or molecules not all in the same oxidation states. The simplest example[14] is a cyanine *(1)*, in which the resonance structures



(1)

indicate the migration of positive charge from one end of the molecule to the other. There are ten electrons distributed over nine atoms, *i. e. ca.* 1.1 electrons/atom. This incommensurate ratio arises from the formally different oxidation states of the two nitrogen atoms. Such a molecule would be "metallic" if it were infinitely long and one could attach electrical leads to it. Compare, however, *(1)* with *(2)*: the resonance structure for *(2)* is energetically unfavorable. Charge migration will thus not occur here. There are no mixed-valence interactions; all the π-electrons are on atoms in the same oxidation state

[*] Dr. J. H. Perlstein
Research Laboratories, Eastman Kodak Company
1669 Lake Avenue, Rochester, New York 14650 (USA)



(2)

and there is exactly one electron/atom. The bond lengths will thus alternate between pure single and pure double bond character. In *(1)* the π-electrons can delocalize over all sites, but in *(2)* they cannot.

There is a molecular orbital approach equivalent to the above resonance description which is instructive and can be applied to some practical examples from donor-acceptor chemistry. A linear array of iodine atoms each with one unpaired electron in a valence p orbital is shown in Figure 1.

In Figure 1a, two iodine atoms are brought together to form an I_2 molecule with two electrons in a bonding orbital. The separation between the filled bonding orbital and the empty antibonding orbital is four times the one-electron exchange integral t (also called the transfer integral).

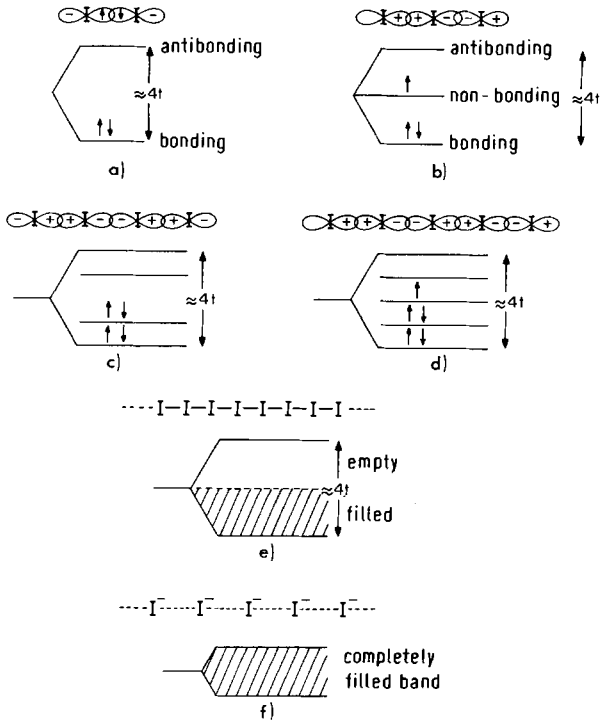


Fig. 1. LCAO-MO energy level scheme for: a) I_2 molecule; b) I_3; c) I_4; d) I_5; e) I_x; and f) $(I^-)_x$. Notice that separation between lowest filled and highest empty MO (*ca.* 4 *t*) is roughly independent of the number of atoms in the chain.

In Figure 1b, for a chain of three iodine atoms there are now three molecular orbitals and three valence electrons to fill them. The bonding-antibonding separation is still about 4 *t*. In Figures 1c and 1d, there are four and five iodine atoms bonded together with a concomitant increase in the number of energy levels. The total energy spanned by these states is still about 4 *t*. Finally in Figure 1e is shown a large number of iodine atoms bonded together. The number of energy levels has now increased enormously and the levels are still all crammed into a width of *ca.* 4 *t* wide. The resulting energy band (Fig. 1e) is only half-filled because in filling it we put *two* electrons into each state obeying the Pauli exclusion principle but there is only *one* valence p electron from each iodine atom. In this molecular orbital description, the electrons in Figure 1e can easily move into the nearby vacant adjacent levels and thus such a linear chain of iodine atoms would be metallic. It does not, however, exist. An iodine crystal is not metallic, it does not contain iodine atoms with equal bond lengths, and it is not mixed valence.

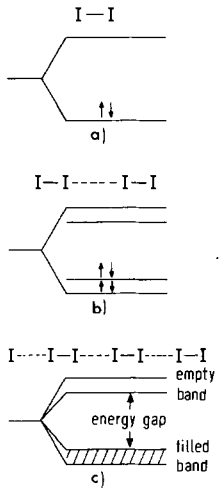


Fig. 2. LCAO-MO energy level scheme for a chain of I_2 molecules a) I_2; b) $(I_2)_2$; c) $(I_2)_x$. Dimerization produces an energy gap not present in Fig. 1e.

A chain of I_2 molecules is an insulator because it has a localized single bond between every two atoms. The equivalent MO picture is shown in Figure 2. In Figure 2a the I_2 energy level scheme is again shown; in Figure 2b two I_2 molecules are brought together. The bonding and antibonding orbitals of I_2 split into two states each, with the bonding orbitals filled. Finally in Figure 2c for the long linear array of I_2 molecules, the bonding orbitals of each I_2 molecule form a band which is completely filled and the antibonding orbitals also form a band which is completely empty. The linear I_2 chain is an insulator, the filled states are separated by a large energy gap from the empty states. Chemically this result comes as no surprise. Interestingly, however, Figure 2c is obtained from Figure 1e simply by moving every other

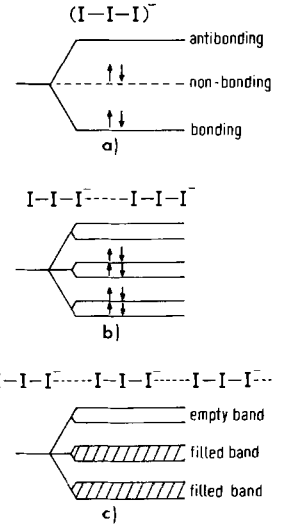


Fig. 3. LCAO-MO energy level scheme for a chain of I_3^- ions. a) I_3^-; b) $(I_3^-)_2$; and c) $(I_3^-)_x$.

iodine atom a little to the left. The one-dimensional iodine metal is thus transformed into the one-dimensional I_2 insulator by alternating the bond lengths (also called a Peierls' distortion or Peierls' instability in solid state physics). One can also see that a linear chain of I^- ions is an insulator as in Figure 1f, and that a linear chain of I_3^- ions is an insulator (Fig. 3a—c).

The instability of the metallic polyiodine chain with respect to a distortion into poly-I_2 insulator can be understood in still another way. The polyiodine chain has only one electron per bond or a bond order of $^1/_2$ while the poly I_2 chain has two electrons per bond or a bond order of unity. Thus as long as we insist on maintaining one electron per iodine atom, we cannot stabilize a metallic state.

3. Charge Transport in Donor-Acceptor Complexes: Aromatic Hydrocarbon-Halogen Interactions

Suppose we now do some chemistry. We take advantage of the known electron acceptor properties of iodine by placing it in the presence of a donor which transfers electrons to iodine. We thus start filling the empty antibonding band of Figure 2c. It is at this point where the chemist's perceptual knowledge of donor-acceptor interactions becomes crucial. If he uses a super-donor like an alkali atom, the empty antibonding band will be completely populated. As a consequence the I_2 bond order will drop precipitously towards zero causing the iodine atoms to separate into I^- ions and to become insulating (Fig. 1f). It would be preferable to transfer just a small electron density to I_2, and thus to maintain the bond order close to unity while at the same time putting electron density into the empty antibonding band (Fig. 2c). In effect the I_2 chain becomes mixed-valent by reducing some of the iodine molecules.

Table 1. Room temperature electrical conductivity of iodine complexes with aromatic hydrocarbons.

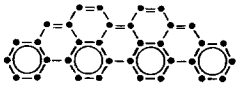
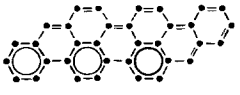
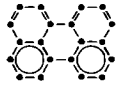
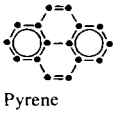
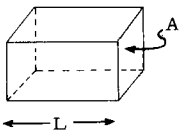
Donor (D)	Stoichiometry	σ [Ω^{-1} cm^{-1}]	Ref.
 Violanthrene	$DI_{4.0}$	0.022	[15]
 Isoviolanthrene	$DI_{1.52}$	0.0017	[16]
 Perylene	DI_3	0.1	[17—19]
 (3) Pyrene	$DI_{4.0}$	0.013	[19]
 (4) Pyridazine	$DI_{2-2.8}$	0.02—1	[20]
Uncomplexed aromatic hydrocarbons		$<10^{-14}$	
I_2		$\approx 10^{-11}$	[21, 24]

Table 1 presents a number of interesting complexes of iodine with aromatic hydrocarbons acting as weak donors. Structurally they are not well characterized but nevertheless represent the first examples of moderately high electrical conductivity in organic materials.

Electrical conductivity σ is experimentally determined from relation (a)

$$\sigma = \frac{L}{AR} \qquad \text{(a)}$$



where L and A are the specimen length and cross-sectional area in cm and cm^2, respectively, and R is the specimen resistance in ohms [Ω]. R is determined from Ohm's Law

$$R = \frac{V}{I} \qquad \text{(b)}$$

where V is the voltage measured along the length L when a current I in amperes is passed along L.

These iodine complexes have electrical conductivity 8—10 orders of magnitude larger than iodine itself and 12 orders of magnitude larger than the pure hydrocarbons. The unpaired spin concentration per iodine atom is small[22], about 0.016 electrons/I atom. The small free electron density is consistent with a weak donor-acceptor interaction

$$D + I_2 \rightleftarrows D^{\delta+}(I_2)^{\delta-} \qquad (5)$$

with $\delta \approx 0.032$ and with the fact that iodine readily sublimes out of the complexes in air.

The electrical conductivity measurements were unfortunately all performed on compressed powders. The polyiodine chain is broken up by such a procedure, lowering the σ values considerably. We can nevertheless get a good estimate of the true bulk values from the known spin density. σ depends on the product of two quantities[23], a) n the number of charge carriers/cm^3 in the band and b) μ, the velocity of charge carriers per unit of applied electric field (also called the mobility):

$$\sigma = ne\mu \qquad \text{(c)}$$

where e, the charge of an electron is in coulombs (1.6×10^{-19} C) and μ in cm^2/Vs. For I_2[24], μ is about 1[*]. For the perylene·I_3 complex of density[18] 2.94 g/cm^3:

$$n = \frac{(0.016/\text{I})(3 \times 6.02 \times 10^{23}\ \text{I/mol})(2.94\ \text{g/cm}^3)}{633\ \text{g/mol}} = 1.3 \times 10^{20}\ \text{electrons/cm}^3$$

$$\sigma = (1.3 \times 10^{20})(1.6 \times 10^{-19}\ \text{C})(1\ \text{cm}^2/\text{Vs}) = 20\ \Omega^{-1}\ \text{cm}^{-1}$$

This value for σ is about two orders of magnitude larger than the compressed powder measurements of Table 1 which

[*] This value is for holes. Electron mobility is probably somewhat larger.

is about right when a comparison between powder conductivities and single crystals is made on a large number of organic conductors.

In Table 2 the electron concentration n, the mobility μ, and the electrical conductivity σ of the perylene·I_3 complex are compared with the corresponding values for a variety of other well-known materials in order to put the conductivity data in better perspective.

Table 2. Electrical properties for a variety of well known materials.

Material	σ [Ω^{-1} cm^{-1}]	n [cm^{-3}]	μ [cm^2/Vs]
Ag	6.6×10^5	5.8×10^{22}	70
Cu	6.4×10^5	8.5×10^{22}	47
Hg	4.4×10^4	4.2×10^{22}	6.6
InSb	3.5×10^2		6.5×10^4
n-Type Si	4×10^1	1×10^{18}	240
TCNQ salts	$1-10^3$	$\approx10^{21}$	4 [25]
Perylene·I_3	2×10^1	1.3×10^{20}	$\approx$ 1
Anthracene	$\ll10^{-14}$	$\ll10^{+5}$	$\approx$ 1
Teflon	$\ll10^{-14}$		

Two comparisons can be made immediately. Organic crystalline materials generally have charge carrier mobilities of order unity comparable with that of mercury but considerably lower than that of the best semiconductors such as silicon or the good metals copper and silver. Secondly, where organic crystalline materials have high conductivity it is generally due to the presence of a high density of unpaired *electrons which are free to migrate* from molecule to molecule. Where the conductivities are low, however, it is not necessarily due to the absence of unpaired electrons (as shown by anthracene). The mere presence of radical ions is no guarantee that the unpaired spins will migrate, as will be shown by examples presented in Section 4.

Thus for the aromatic hydrocarbon-iodine complexes, I have assumed that the unpaired electrons associated with the hydrocarbon do not contribute to σ. The reasons for this will be outlined in Section 5.

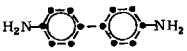
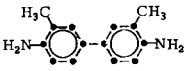
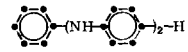
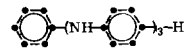
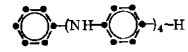
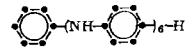
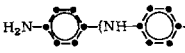
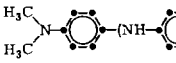
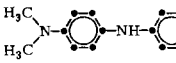
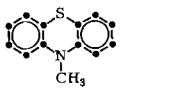
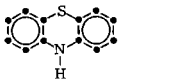
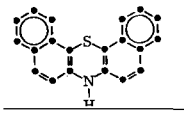
4. Aromatic Amine-Iodine Complexes

All else being equal, a decrease of the ionization potential of the donor will result in an increase in the amount of charge transferred from the donor to the I_2 antibonding band of Figure 2c. The bond order of I_2 will drop below unity and thus the iodine-iodine spacing will increase. Since the energy gap in Figure 2c is determined by the iodine-iodine spacing, this gap will also decrease. Will this gap go to zero? Probably not. At exactly $^1/_3$ electron/I atom transferred the polytriiodide state $(I_3^-)_x$ becomes stable (Fig. 3c). However, slightly more or slightly less than $^1/_3$ electron/I transferred should help to stabilize a metallic state.

Table 3 surveys some data on aromatic amines, oligoanilines, and phenothiazine complexes with iodine. Except for *N*-methylphenothiazine, all the data were determined by compressed powder measurements. The *N*-methylphenothiazine result is interesting. It shows the two order of magnitude increase in σ of single crystals over compressed powders.

The amine complexes as a group tend to be more air stable and somewhat more conductive than the aromatic hydrocarbon complexes.

Table 3. Room temperature electrical conductivity of iodine complexes of aromatic amines and phenothiazines.

Donor (D)	Stoichiometry	σ [Ω^{-1} cm^{-1}]	Ref.
 *(5)*	$DI_{2.5}$	0.45	[26]
 *(6)*	$DI_{2.5}$	0.034	[26]
 *(7)*	$DI_{2.4}$	0.34	[27]
	$DI_{1.7}$ $DI_{2.9}$ $DI_{3.4}$	3.9×10^{-4} 0.08 0.38	[27]
	$DI_{2.0-4.3}$	0.53—0.96	[27]
	$DI_{2.1-6.0}$	0.39—1.3	[27]
	$DI_{1.2-3.6}$	0.41—0.57	[27]
	$DI_{1.0}$	0.015	[27]
 *(8)*	$DI_{1.0}$	3.5×10^{-6}	[27]
	DI_3 [or $D_2(I_2)_3$]	0.71 (95)[a]	[28—31]
	DI_3	0.05	[28]
	DI_3	0.05	[28]

[a] Single crystal data in parenthesis.

Two crystal structures are known, that of *(7)*[32,33] and that of *(8)*[34]. In *(7)* the iodine atoms are indeed arranged in I_3^- columns with two short bonds of 2.99 Å and one longer bond of 3.44 Å. The interlayer amine spacing is large, about 3.77 Å. Little charge transport along the organic ions is expected for this large separation and the entire conductivity can be attributed to charge migration along an I_3^--like chain. In comparison, the crystal structure of *(8)* shows I^- ions and no polyiodine chain; the interlayer amine ring contacts are 3.42—3.48 Å.

The structure of *(7)* and its five order of magnitude higher conductivity than *(8)* strongly suggests that where high conductivity occurs in aromatic amine-halogen complexes it is due to charge migration along a polyhalogen chain.

5. Mixed-Valence Interaction and the Intermolecular Migration of Aromaticity

The picture that emerges from an examination of the data on iodine complexes is one in which there are separate chains

of donor molecules D and acceptors A with only partial charge transfer from D to A. D and A are then formally present in more than one oxidation state. We indicated earlier that such mixed-valence interaction is one condition necessary for stabilizing a metallic state against a distortion into an insulating state (the Peierls distortion)[*].

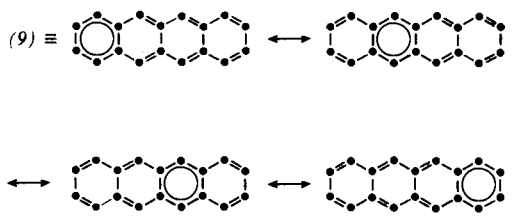
There is one serious dilemma, however. If there is partial charge transfer in the iodine complexes, then the mixed-valence donor stack should transport charge as well as the iodine acceptor chain. Nevertheless, although they form radical cations, the donors listed in Tables 1 and 3 do not seem to effectively transport charge. This observation is generally true for the large number of radical cations and radical anions that are known in organic chemistry, with a few exceptions.

An examination of efficient charge-transporting organic donors and organic acceptors shows one common chemical feature not possessed by other donors or acceptors—the donors upon forming a radical cation by loss of one electron also form a new aromatic sextet not present in the neutral donor. Similarly the acceptors upon gaining an electron form a new aromatic sextet not present in the neutral acceptor.



(9)

In a simple and convincing exposition, *Clar*[35] has shown that a molecule like naphthacene *(9)* has only one aromatic sextet. In *(9)* the Robinson-Clar[36] notation is used, where a circle symbolizes the aromatic sextet[36] and an arrow[35] indicates that the sextet can migrate intramolecularly from ring to ring as in *(10)*.



(10)

A structure such as *(11)* would be incorrect since it indicates that there are four aromatic sextets with a total of 24 π electrons.



(11)

Examination of the donors in Tables 1 and 3 shows that none of them forms a new aromatic sextet upon radical cation formation. Thus *(12)* has the same number of aromatic sextets as its radical cation *(13)*.



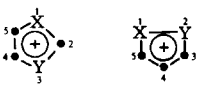
(12)



(13)

Examination of the donors and acceptors in Table 4 on the other hand indicates that at least one new aromatic sextet is formed upon radical ion formation. All of these donors form good electrical conductors when complexed with the acceptors 2,2′-(2,5-cyclohexadiene-1,4-diylidene)bispropanedinitrile (TCNQ) or 2,2′-(1,4,6,9-bicyclo[4.4.0]decatetraene-3,8-diylidene)bispropanedinitrile (TNAP), some of them having room temperature σ values within an order of magnitude of mercury metal. In those cases where crystal structures are known, there are separate stacks of donors and acceptors, so that charge migration can occur along each stack.

As a perusal of Table 4 indicates, the class of donor radical cations are all derivatives of either 1,3- or 1,2-dithiolium, -diselenolium, or -thiaselenolium cation *(30)*, the aromaticity of which has been reviewed in some detail in ref. [77].



X, Y = S, Se

(30)

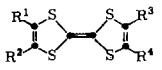
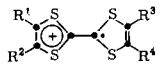
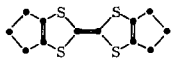
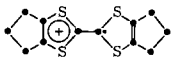
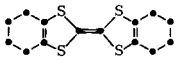
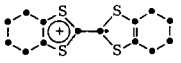
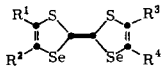
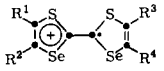
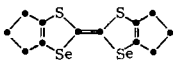
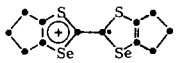
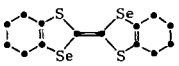
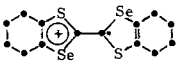
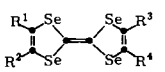
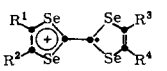
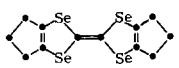
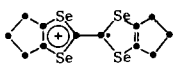
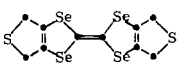
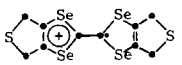
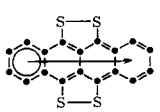
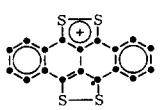
The aromaticity of the acceptor radical anions, particularly $TCNQ^{\cdot-}$, is consistent with a) the tendency toward ring bond length equalization in ring *(28)* on going from neutral TCNQ[78] to the anion radical[79], b) the small unpaired spin density per ring carbon atom (0.066) as determined by EPR[80,81], and c) *ab initio* calculations of the electron density[82] which indicate benzenoid character for the radical anion.

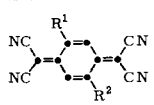
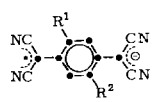
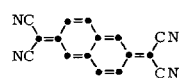
While the number of donors and acceptors which form a new aromatic sextet and have high electrical conductivity is presently limited in scope, there is considerable weight of other evidence which supports the conclusion that the presence of aromaticity plays an essential role in charge transport. Thus in Table 5 are listed a considerable number of donors and acceptors, none of which form a new aromatic sextet upon oxidation or reduction, respectively. Except for *(37)* and *(40)*, the σ values are considerably lower than those measurements in Table 4 which were done on compactions [*e.g.*, compare *(16)*, *(17)*, *(20)*, *(21)*, *(22)*, and *(27)*]. *(37)* is interesting in that the electrical conductivity of *ca.* $10^{-1}\,\Omega^{-1}\,cm^{-1}$ can only be due to the cation in the mixed-valence state. Compared to the fluoroborate of *(14)*[93] with $\sigma < 10^{-6}\,\Omega^{-1}\,cm^{-1}$, *(37)* is unusual and should be studied in more detail. *(40)* is also unusual. It is not formed cleanly by direct reaction of donor with acceptor in trichlorobenzene. An X-ray crystal structure would help to determine whether the donor contributes to the charge transport.

It would thus appear on the basis of what we have discussed so far that the ability for charge to efficiently migrate from one molecule to another is closely linked to the presence of an aromatic sextet which can also migrate from one molecule to another. Figure 4 qualitatively demonstrates for TCNQ how this charge migration might occur along with the aromaticity. A TCNQ stack will formally contain molecules with mixed valency; some neutral and some as radical anions but all equally spaced. In Figure 4a the radical anion is aromatic; the neutral molecule below it is not. Migration of the unpaired electron transfers the aromaticity to the neutral molecule as in Figure 4b and then again as in Figure 4c. The aromaticity in effect diffuses intermolecularly over the molecules in the chain. The idea here is similar to that expressed by *Clar*[35] for intramolecular migration of aromaticity as in *(10)*.

[*] There are other conditions necessary for stabilizing a "one-dimensional" metal. See Section 7.

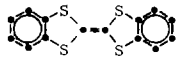
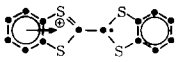
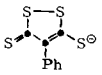
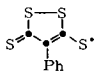
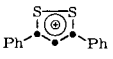
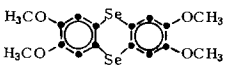
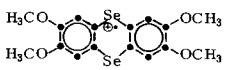
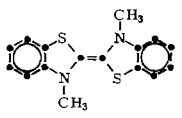
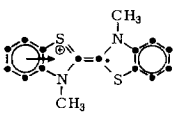
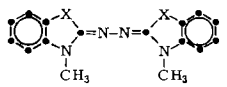
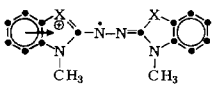
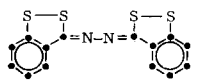
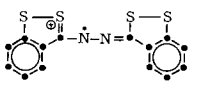
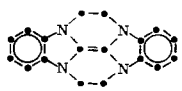
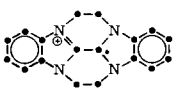
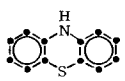
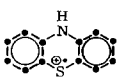
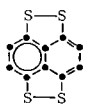
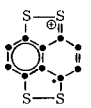
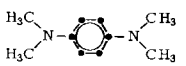
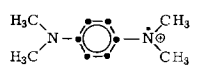
Table 4. Room temperature electrical conductivity of donor-acceptor salts containing new aromatic sextets.

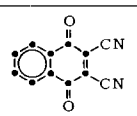
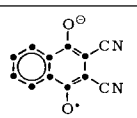
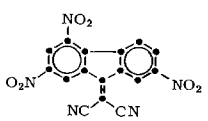
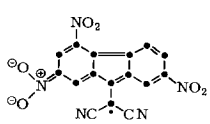
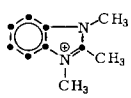
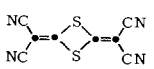
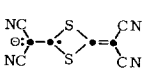
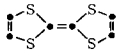
Neutral donor	Radical cation	New aromatic sextets	Complex with TCNQ (or TNAP)	σ [a] [Ω^{-1} cm^{-1}]	Ref. [e]
		1			
(14), R^{1-4} = H (TTF)			1:1 (1:1)	500 (40) [b]	[37—40; 41, 42]
$R^1 = R^4 =$ H, $R^2 = R^3 = CH_3$			1:1	50 [c]	[43, 44]
(15), $R^{1-4} = CH_3$			1:1	10^3 [c]	[45]
(16), $R^1 = R^3 = CH_3$, $R^2 = R^4 = C_2H_5$			1.3:2	10	[46]
			1:1	10 [d]	[47]
(17) 		1	1:1	(15) [d] 500	[47, 48, 49]
(18) 		1	1:1	(5×10^{-5}) [d]	[48]
		1			
(19), R^{1-4} = H			1:1	550	[50, 51; 52, 53]
(20), $R^1 = R^3$ = H, $R^2 = R^4 = CH_3$			1:1	10 [d]	[54]
(21) 		1	1:1	100 [d]	[55]
(22) 		1	1:1	2×10^{-6} [d]	[56]
			(3:2)	0.3 [b, d]	[56]
		1			
(23), R^{1-4} = H			1:1	800	[57, 58; 52]
(24), $R^{1-4} = CH_3$			1:1	800	[59, 60; 61]
(25)  (HMTSeF)		1	1:1	2×10^3	[62]
(26) 		1	1:1	6×10^2	[63]
(27) 		2	1:1	1	[64, 65, 66]
			1:2	100	[67, 68]
			(1:1)	2.5 [b, d]	[69]

Neutral acceptor	Radical anion	New aromatic sextets		Ref. [e]
(28)  TCNQ($R^1 = R^2$ = H)		1	$R^1 = R^2 = H$	[70, 71]
			$R^1, R^2 \neq H$	[72—74]
(29)  TNAP		1		[75, 76]

[a] All data taken on single crystals unless noted otherwise.
[b] Complex of donor with TNAP.
[c] Conductivity measurement at microwave frequencies.
[d] Conductivity measurement on compacted powders.
[e] References are to synthesis of molecules (first reference) and to conductivity data (second reference).

Table 5. Electrical conductivity of donor-acceptor salts which do not contain a new aromatic sextet.

Donor	Radical	Complex with acceptor [a]	σ [b] [Ω^{-1} cm^{-1}]	Ref.
(31) 		TCNQ (1:1) Br ($\approx$ 1:1.2)	$\approx 10^{-7}$ 3.4×10^{-1}	[83, 84] [85]
(32) 		no complex		[86]
(33) 		 (1:1)	10^{-7}—10^{-8}	[87]
(34) 		TCNQ (1:1)	5×10^{-10}	[73]
(35) 		TCNQ (1:3)	5×10^{-2}	[73]
(36) 		BF_4^- (2:1)	1.9×10^{-3}	[85]
		$TCNQI_2$ [d] (1:1)	6.7×10^{-2}	[73]
		BF_4^- (2:1)	3×10^{-4}	[85]
X = S		BF_4^- (2:1)	10^{-5}	[85]
X = O				
X = NCH_3				
(37) 		BF_4^- ($\approx$ 3:2)	3×10^{-1}	[85]
		Br ($\approx$ 5:2)	8×10^{-1}	[85]
(38) 		TCNQ (1:2)	1.6×10^{-3}	[73]
		(1:4—5)	1.6×10^{-2}	[73]
(39) 		TCNQ (1:1)	1.6×10^{-7}	[73]
(40) 		TCNQ (1:1)	40 [c]	[88]
(41) 		TCNQ (1:1)	$\approx 10^{-3}$	[89]
		(1:2)	$\approx 5 \times 10^{-2}$	[89]

Acceptor	Radical	Complex with donor	σ [b] [Ω^{-1} cm^{-1}]	Ref.
(42) 		 (1:2)	1.4×10^{-4}	[90]
(43) 		 (2:1)	2×10^{-2}	[91]
(44) 		 (1:1)	$< 10^{-6}$	[92]

[a] Numbers in parentheses represent donor/acceptor ratio in the complex.
[b] Compressed powder measurements unless otherwise indicated.
[c] Single crystal measurements.
[d] $TCNQI_2$: *(28)*, $R^1 = R^2 = I$.

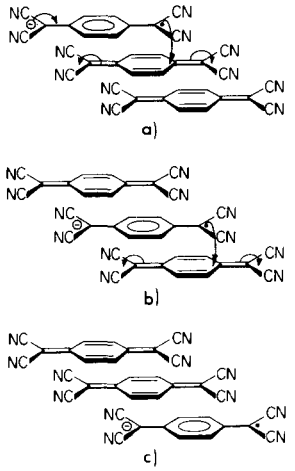
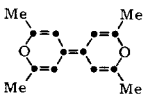
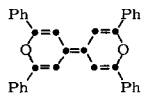
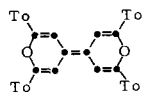
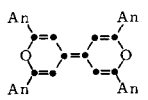
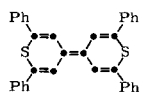
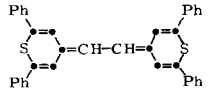


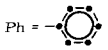
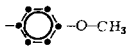
Fig. 4. Stacking arrangement for mixed-valence TCNQ ions: a) $TCNQ^{\bullet-}$ with aromatic sextet transfers charge to neutral TCNQ with no aromaticity resulting in b) and then again in c). Aromaticity migrates down the TCNQ stack along with the unpaired electron.

Perhaps the most important utility of the formation of a new aromatic sextet is its predictive capability. Thus *(45)*—*(47)* and the unannelated donors of *(31)* and *(35)*—*(38)* would be expected to form one aromatic sextet on one-electron oxidation. They belong to the more general class of Weitz radicals described by *Hünig*[95,96] in which there is an even number of carbon atoms between the heteroatoms. Any Weitz radical whose formation involves generation of a new aromatic sextet should transport charge more readily than any radical that does not have this capability. Table 6 lists some examples: if grown as single crystals the TCNQ salts *(52)* and *(53)* should be comparable to complexes listed in Table 4.

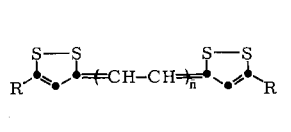
Table 6. Room temperature electrical conductivity of 1 : 1 salts of the acceptor TCNQ with Weitz type radical donors that form a new aromatic sextet.

Donor		σ [a] $[\Omega^{-1}\,cm^{-1}]$	Ref.
(48)		10^{-6}	[97]
(49)		1.7	[97]
(50)		10^{-1}	[97]
(51)		2.5×10^{-4}	[97]
(52)		38	[98]
(53)		27	[98]

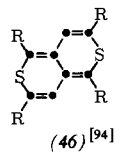
Me = $-CH_3$ To = 

Ph =  An = 

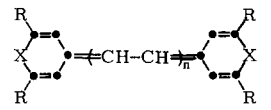
[a] Compressed powder measurements.



(45), n = 0,1,2,...



(46)[94]



(47), n = 0,1,2,...
X = NR, O, S, Se, Te

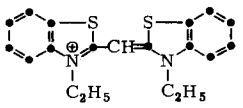
Table 6 also points out one of the dilemmas associated with choosing new donors. Substituting phenyl groups for methyl groups on the bispyranylidene rings enhances the conductivity by 10^6. Most of this difference is probably associated with the chemical reactivity of the methylated carbon in the cation radical state, but part of this difference is most likely related to the wrong stacking behavior of the radical ion, as in *(51)* where a bent CH_3—O bond sterically interferes with the overlap of neighboring donors and thereby severely reduces the transfer integral for charge migration.

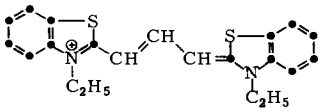
6. Tetracyanoquinodimethane Salts with Closed Shell Nonconducting Cations—General Structural Properties of $D_x^+\,TCNQ_y^-$

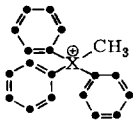
Tetracyanoquinodimethane *(28)* readily forms a radical anion reversibly, with a new aromatic sextet ($E_{PC}=+0.17$ V *vs.* SCE in CH_3CN[99]). Formation of the dianion is much more difficult ($E_{PC}=-0.36$ V *vs.* SCE in CH_3CN[99]) and only one isolable compound of the dianion has been reported[100]. The dianion has no additional aromatic stabilization.

Salts of the radical anion form a rich variety of stoichiometries[101] and crystal structures. In a number of instances a salt will form more than one phase depending on the rate and temperature of crystallization from solution (see Section 8).

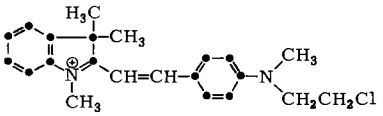
Crystal structures elucidated up to 1972 have been reviewed by *Shibaeva* and *Atovmyan*[102]. The general features of these structures indicate that the arrangement of the $TCNQ^-$ ions within a stack is a very strong function of the nature of the cation. Cations which are very much smaller than or very much larger than TCNQ do not form salts in which the TCNQ molecules are equally spaced and structurally equivalent. Thus the salts of small alkali metal cations[103], $Na^+TCNQ^{\bullet-}$ and $K^+TCNQ^{\bullet-}$, have $TCNQ^{\bullet-}$ dimer structures. $Rb^+(TCNQ)^{\bullet-}$ has two phases, one with dimers, the other with equally spaced but structurally non-equivalent ions[103]. Cs_2TCNQ_3 shows trimer formation[104]. Salts with large or bulky cations tend to show either TCNQ dimers


$(TCNQ)^{\bar{}}$ *(54)*


$(TCNQ)_2^{\bar{}}$ *(55)*


$(TCNQ)_2^{\bar{}}$ *(56)*

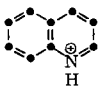
X = P, As

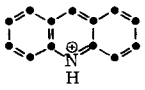

$(TCNQ)_2^{\bar{}}$ *(57)*

as in the examples *(54)*[102] and *(55)*[102], or tetramers as in *(56)*[102] and *(57)*[102].

The electrical conductivity of these salts is low ($\sigma < 10^{-2}$ Ω^{-1} cm^{-1}).

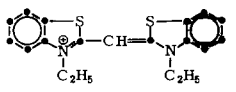
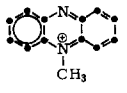
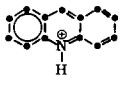
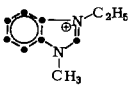
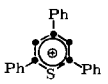
The best conductors ($\sigma > 10^{+2}$ Ω^{-1} cm^{-1}) in this group, *i.e. (58)*[105–107] and *(59)*[108], contain cations which are planar and approximately the same size as TCNQ.


$(TCNQ)_2^{\bar{}}$ *(58)*


$(TCNQ)_2^{\bar{}}$ *(59)*

Crystal structures of *(58)*[102] and *(59)*[109] show equally spaced and equivalent TCNQ molecules with an interplanar spacing of *ca.* 3.2 Å. The interplanar spacing of the cation is of the order of van der Waals spacing 3.5 Å for *(58)* and 3.4 Å for *(59)*, respectively. The mixed-valence TCNQ stack has a very low bond order ($^1/_4$) which could be increased to $^1/_2$ if dimers formed or to $^1/_3$ if tetramers formed.

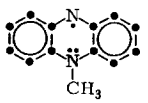
Table 7. Comparison [a] between electrical conductivity of closed shell cation TCNQ salts $D^+(TCNQ)^{\bar{}}$ and $D^+(TCNQ)_2^{\bar{}}$.

	1:1 Salts	TCNQ Structure	σ [b] [Ω^{-1} cm^{-1}]	Ref.
(60)	NaTCNQ ($T<80$ °C)	Dimerized-infinite stack	10^{-3}	[112, 113]
	($T>80$ °C)	Equally spaced equivalent ions	10^{-3}	[114, 113]
(61)	$K^+TCNQ^{\bar{}}$	Probably dimerized-infinite stack	2×10^{-4}	[103]
(62)	$Rb^+TCNQ^{\bar{}}$ (monoclinic)	Dimerized-infinite stack	3×10^{-6}	[79, 113]
(63)	$Rb^+TCNQ^{\bar{}}$ (triclinic)	Equally spaced ions	10^{-2}	[103]
(64)	 $TNCQ^{\bar{}}$	Isolated dimers	10^{-10}	[115]
(65)	 $TCNQ^{\bar{}}$ (NMP)	Equally spaced equivalent ions	143	[116—119]
1:2 Salts				
(66)	 $(TCNQ)_2^{\bar{}}$	As for *(65)*	100	[106, 120]
(67)	 $(TCNQ)_2^{\bar{}}$	As for *(65)*	70	[108, 109]
(68)	$(C_2H_5)_3\overset{\oplus}{N}H$ $(TCNQ)_2^{\bar{}}$	Tetramers-infinitely stacked	3.4	[121, 122]
(69)	 $(TCNQ)_2^{\bar{}}$	As for *(68)*	6.7	[123]
(70)	 $(TNCQ)_2^{\bar{}}$	unknown	8×10^{-1} [c]	[124]

[a] For a more extensive comparison, see Ref. [125].
[b] Single crystal measurements unless specified otherwise.
[c] Compressed powder measurements.

The TCNQ interplanar geometry, however, may be dominated by what appears to be a hydrogen bonded interaction[109] between the cyano group of TCNQ and the $HN^{\oplus}$ group of the cation in both *(58)* and *(59)* rather than the electron transfer energy between TCNQ sites. In addition the cations are also disordered (the $HN^{\oplus}$ group does not always point towards the same TCNQ stack) so that the transport properties may very well be dominated by this feature[110–111].

It is also generally found that regardless of cation size, the 1:2 salts $D^+(TCNQ)_2^{\bar{}}$ are orders of magnitude more conductive than their 1:1 counterparts $D^+TCNQ^{\bar{}}$. The 1:1 salts tend to form pairwise interacting $TCNQ^{\bar{}}$ ions either as isolated dimers such as in *(54)* with an interplanar separation of 3.2 Å or as stacked dimers as in the alkali TCNQ salts. In neither case does one have an infinite stack of equivalent equally spaced ions, which is one of the necessary conditions for high electrical conductivity. On the other hand, the 1:2 salts in almost all cases form a stacked arrangement of $(TCNQ)_2^{\bar{}}$ and even though in most cases the stack does not contain equivalent equally spaced molecules, the mixed-valence nature of the stack allows some charge migration to occur. Table 7 summarizes this result by comparing some 1:1 and 1:2 salts with different TCNQ stacking arrangements. Except for the *N*-methylphenazinium salt *(65)*, the best conductors are the 1:2 salts *(66)* and *(67)* with mixed-valence equally spaced TCNQ molecules. *(65)* is an unusual example. Available NMR evidence[126] indicates that there is incomplete charge transfer from the donor to the acceptor amounting to 6 mol %. Thus the TCNQ stack and the donor stack are formally mixed-valent with the presence of *N*-methylphenazinyl free-radical *(71)*.



(71)

Note too that *(71)* has a new aromatic sextet not present in *(65)*, so that charge transport along the donor stack may also occur. Further studies on molecules like *(71)*[127] would be highly desirable.

7. Does TCNQ· Form a Chemical Bond with Itself?

The separation between TCNQ molecular planes in the various structures in Tables 4 and 7 is large, about 3.2 Å. Nevertheless this is less than van der Waals spacing of 3.4—3.5 Å. Is there a chemical bond formed between these molecules? There is at present no satisfactory answer to this question. In discussing the properties of polyiodine chains, we assumed that one-electron molecular orbital theory would be adequate to understand the electrical properties where strong σ-bonded interactions occur. However, for aromatic hydrocarbons, this may not be a good starting point. The problem is illustrated in Figure 5. The lowest unoccupied orbital (LUMO) of TCNQ has b_{2g} symmetry in the D_{2h} point group[82, 128]. Reduction of TCNQ to $TCNQ^{\bar{}}$ places one unpaired electron in this orbital. If a bond is formed with another $TCNQ^{\bar{}}$, it is the b_{2g} orbitals which will overlap. The most favorable geometry is that which maximizes the overlap and minimizes the nuclear repulsion between the rings as shown in Figure 5a. This is the geometry which occurs in the highly conductive salts *(65)*, *(66)*, and *(67)* and is also the geometry which occurs in the nonconductive salt *(64)* which has isolated dimers.

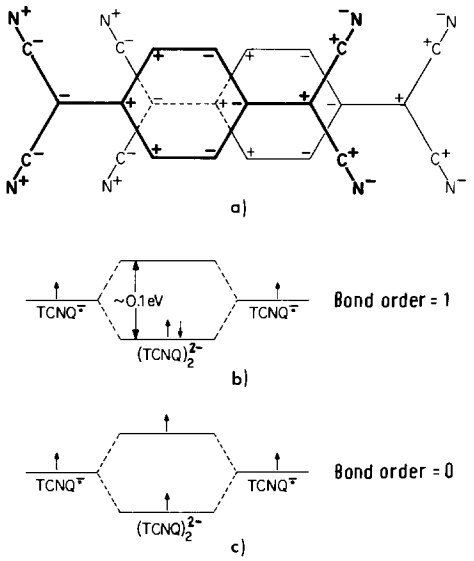
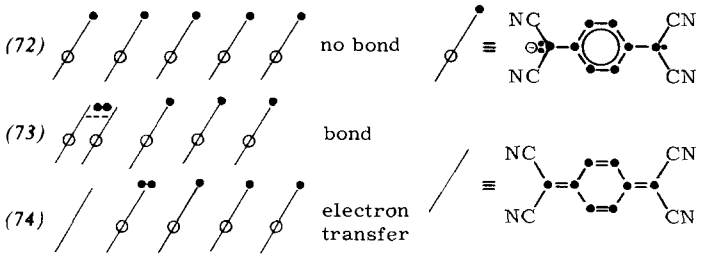


Fig. 5. a) Preferred stacking arrangement of TCNQ ions. Positive and negative signs of the b_{2g}-p_π orbitals above the plane of each molecule are indicated, b) LCAO-MO energy scheme for $(TCNQ^{\bar{}})_2$ assuming that Coulomb repulsion between electrons is small. c) Same as (b) but with large Coulomb repulsion.

If overlap occurs, there will be a bonding MO and an antibonding MO. The energy separation of these states is between 0.1 and 0.2 eV (2.3 to 4.6 kcal). If a σ bond is formed, the two electrons will occupy the bonding MO with bond order 1 (Fig. 5b). This is a very weak bond at best. If the Coulomb repulsion between the two electrons is large enough, then it may be more favorable to put one electron in the bonding MO and one in the antibonding MO as in Figure 5c. The bond order here is 0. The electrons are in effect localized on each TCNQ site and kept in this configuration because of their mutual Coulomb repulsion. The situation here is analogous to the low spin-high spin electron configurations occurring in the crystal field theory of transition metal ion complexes. At first sight, it would seem that a clear answer to the question might be had by measuring the magnetic susceptibility of the isolated dimer. The low spin state is a singlet, whereas the high spin state is a triplet. However, the problem is complicated by the fact that the singlet-triplet splitting here is not much larger than thermal energies and thus a bond-no bond dynamic equilibrium can exist whose equilibrium constant is a strong function of temperature. The theoretical aspects of this question have been reviewed by *Soos*[129, 130] and the experimental situation for the alkali $TCNQ^{\bar{}}$ salts has been discussed from different viewpoints by *Kommandeur*[131] and *Heeger*[132].

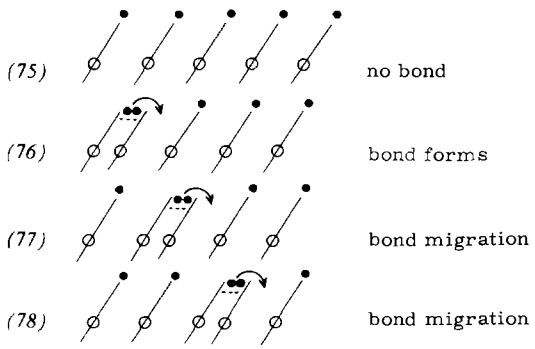
From a chemical point of view, the formation of a bond between two radical ions each with an aromatic sextet seems unlikely. The wave function for the bonding orbital with two electrons contains contributions in which both electrons reside on one TCNQ site. This contribution is in fact necessary if electron transport is to occur. But such a contribution destroys the aromatic sextet on one TCNQ without creating

a new aromatic sextet on the $TCNQ^{2-}$ dianion as in *(72)* to *(74)*:



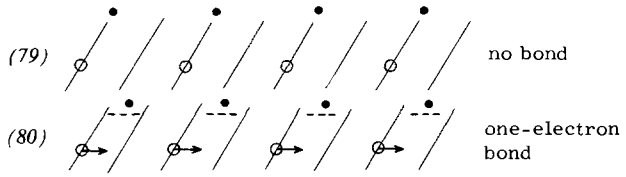
In *(72)* there are no bonds and no charge migration. In *(73)* two $TCNQ^{\cdot-}$ anions approach and form a bond. In *(74)* the bond breaks leaving two electrons on the second TCNQ site with aromaticity destroyed on the first site. Charge has migrated from the first site to the second but at the expense of destroying the aromaticity on the first site. *(74)* ought to be energetically unfavorable and lead to low conductivity with high activation energy.

What can occur instead of charge migration is bond energy migration as in *(75)*—*(78)*.

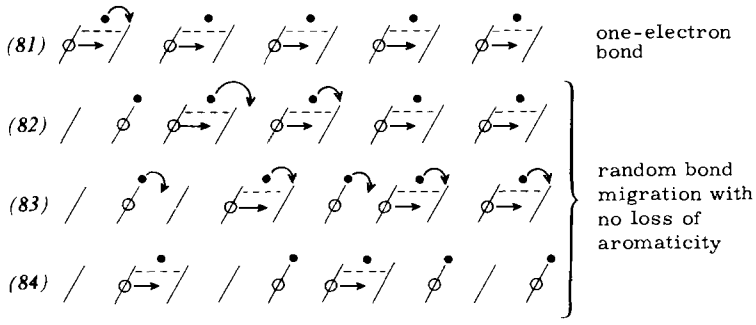


In *(75)* there is no bond. In *(76)* a bond forms between two ions. In *(77)* and *(78)* the bond migrates down the TCNQ chain. These bond migrations manifest themselves as excitons (singlet or triplet) or as charge density waves. As might be expected the charge density wave intensity is enhanced in the neighborhood of a phase transition. In the 1:1 salts, however, there is no charge migration associated with this charge density wave.

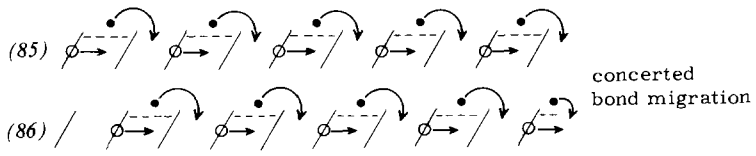
The mixed-valence 1:2 salts $D^{+}(TCNQ)_2^{-}$, on the other hand, formally have one neutral molecule and one radical anion between which a one-electron σ bond can form as in *(79)* and *(80)*.



In *(79)* there is no bond and the aromatic sextet is localized on every other site. In *(80)* a one-electron bond is formed and the aromatic sextet can migrate to the second site as indicated by the arrows. Considerable controversy surrounds the question whether the electron migration occurs more or less randomly as in *(81)*—*(84)*,



or concertedly as in *(85)*—*(86)*.



In *(81)*—*(84)* there will still be an activation energy for electrical conduction associated with the bond-breaking which occurs with increased temperature. The activation energy, however, will be much smaller than in *(72)*—*(74)* since the dianion contribution to the transport is virtually absent. In effect the mixed-valence state allows for the migration of charge without the formation of the highly energetic dianion.

The concerted migration of charge (the Peierls-Frölich superconductor)[133] in *(85)*—*(86)*, on the other hand, should occur with no activation energy since the σ bonds and the unpaired electrons migrate together. Further discussions of the experimental situation will be deferred to the next section.

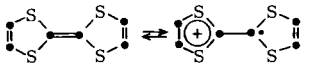
8. Tetracyanoquinodimethane Salts with Open Shell Conducting Cations, $D^{\frac{1}{2}+}TCNQ^{\cdot-}$

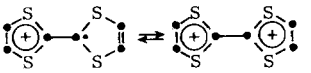
More has been said and written about the properties of this class since our discovery of its first member *(14)*[41] than about all the other organic conductive salts put together. The properties of *(14)* in particular have been studied in great detail. There presently exists a wealth of data on its electrical conductivity[134] and its pressure depen-

dence[135, 136], magnetoresistance[137], specific heat[138–140], Seebeck coefficient[141–143], EPR and magnetic susceptibility[66, 144–146], photoconductivity[147], visible and IR optical properties[148–152], thermal expansion[153], photoelectron spectra[154–158], X-ray structure[159], diffuse X-ray scattering[160–162], neutron scattering[163, 164], and chemical doping and impurity effects[165–167].

As has been pointed out, the donors of this class are all typified by the formation of an aromatic sextet upon one-electron oxidation to the cation radical. The cation radicals in Table 5, which do not have this property do not efficiently transport charge.

For many of the donors in Tables 4 and 6, the dication is also an isolable species[37, 95], the second oxidation potentials (*vs.* SCE in CH_3CN)[99] being unusually low for dication formation; *(87)* and *(88)* are examples.

(87)  $E_{pa} = +0.34$ V

(88)  $E_{pa} = +0.68$ V

Unlike the dianion $TCNQ^{2-}$, the dication TTF^{2+} may thus make significant contributions to the transport process along the donor stack since the dication contains a second aromatic sextet not present in the monocation.

That $TTF^{+\cdot}$ radical cation itself will efficiently transport charge has been well substantiated by a study of the mixed-valence halides, $(TTF)Br_{0.71}$ and $(TTF)I_{0.71}$. The halogen is present in the crystal structures as well-separated ions[168, 169] (*e.g.* I^- spacing in $(TTF)I_{0.71} \approx 5$ Å; compare with *(7)*)[169] and thus does not contribute to the electrical conductivity. Room temperature σ values for both these salts as single crystals lie in the range of 100 to $550\,\Omega^{-1}\,cm^{-1}$[170–171]. As with the TCNQ salts, a variety of stoichiometries and crystal structures can occur in these cation radical salts[93].

The electrical conductivity of salts formed between open shell cations and the open shell anions $TCNQ^{-\cdot}$ *(28)* and $TNAP^{-\cdot}$ *(29)* has been presented in Tables 4 and 6. Separate conducting donor and acceptor stacks exist in these salts as shown by X-ray structure investigations[159]. What is not known is the amount of charge transferred from the donor to the acceptor and whether or not this quantity is temperature dependent. Also not understood is how interstack interactions affect the conductivity along the stacks and perpendicular to them.

The temperature dependence of σ normalized to room temperature for six samples of *(14)* measured along the stacking axis is shown in Figure 6[172]. There are two distinct features:

a) a metallic region for $T > 60$ K in which the electrical conductivity *increases* with decreasing T and

b) a semiconducting or insulating region for $T < 60$ K in which the electrical conductivity *decreases* with decreasing T and approaches zero as $T \rightarrow 0$ K. Not shown is another weak inflection near 38 K[173].

TTF-TCNQ thus goes through an insulator-metal transition around 60 K. This is not an uncommon feature in the highly conducting organic salts and occurs in *(65)*, *(66)*, and *(67)*. Considerable controversy has ensued over what is the ratio

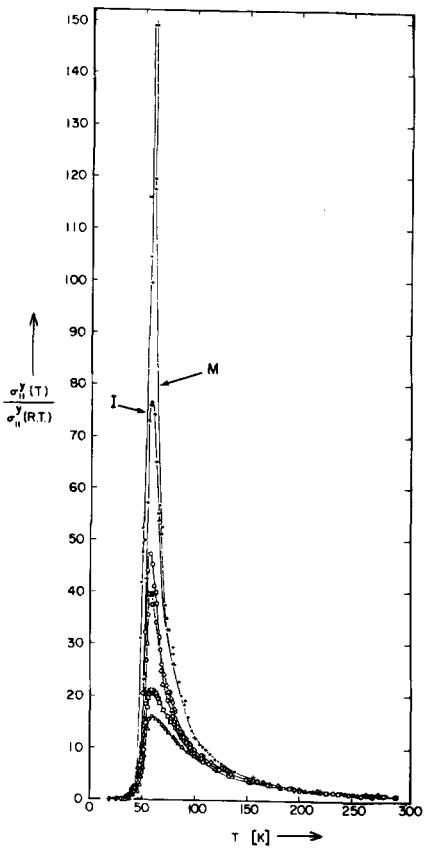


Fig. 6. Electrical conductivity along the stacking axis *vs.* temperature for six crystals of TTF-TCNQ *(14)*; data normalized to room temperature [172]. Notice that the peak conductivity varies from sample to sample. M: curve for metal; I: curve for insulator.

of the peak conductivity at $T = 60$ K to that at room temperature. For *(66)* the peak occurs at $T = 230$ K and the ratio to the room temperature value is only 1.10[106]. For TTF-TCNQ the ratio varies from 10 to 150 depending on the crystal sample as indicated in Figure 6. This is very much unlike the other high-conductivity salts *(66)* and *(67)* where the data appear more reproducible from sample to sample and the conductivity normalized to room temperature is sample independent.

If the true normalized conductivity of TTF-TCNQ is as high as 150, it could imply a mechanism such as in *(86)* in which there is concerted motion of the electrons with the chemical bonds. Such a mechanism is a superconducting-like state[*] in which the transporting charges are not scattered by the longitudinal vibrational motions of the molecules but travel with them.

On the other hand if the normalized conductivities are only 10 to 20 then a mechanism according to *(81)*—*(84)* is more reasonable, in which the transporting charges move randomly and are scattered randomly by the molecular vibrations.

No less than 17 laboratories have measured the normalized conductivity of TTF-TCNQ along the stacking axis[134]. Of these, 11 report normalized peak values of 26 or less, five report values ranging from 30 to 60, and one reports a value of 150.

[*] But not a true superconductor as in BCS theory.

The conduction mechanism is thus unresolved and will remain unresolved until more charge-transporting donors and acceptors unrelated to TTF or TCNQ are synthesized and examined. Compounds such as *(25)* which show no metal-insulator transition but remain metallic as T approaches 0 do not resolve the problem[62]. *(25)* is a two-dimensional conductor (there are "strong" exchange interactions both parallel and perpendicular to the stacking axis as shown by the structure in Figure 7).

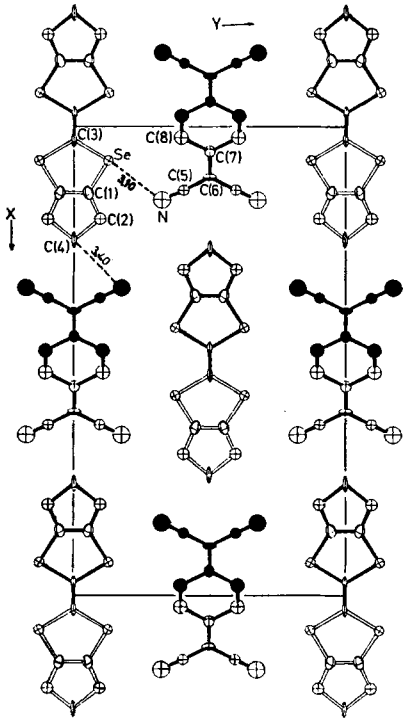


Fig. 7. Projection of crystal structure of HMTSeF-TCNQ *(25)* onto the stacking axis. Separate stacks of donor (D) and acceptor (A) occur along z with what appears to be a "strong" interaction between the Se atom of D and the nitrogen atom of A. [After *T. E. Phillips, T. J. Kistenmacher, A. N. Bloch, D. O. Cowan*, J. Chem. Soc. Chem. Commun. *1976*, 334.]

A concerted charge transport can only occur for a strictly one-dimensional stack. Any two- or three-dimensional coupling of the stacks destroys the one-dimensional concerted reaction. The transition to the insulating state in TTF-TCNQ at 60 K occurs either by (a) weak interstack interaction which destroys the concerted one-dimensional motion at 60 K, or (b) a simple metal-insulator transition due to a static lattice distortion at 60 K similar to that in Figure 2 which produces an insulating state.

The two transport mechanisms would seem to have vastly different consequences if an insulating layer could be placed between the chains and thus reduce two- or three-dimensional interactions. For the concerted charge-migration mechanism *(86)* the peak conductivities should get larger and shift to lower temperatures, whereas for a static Peierls' transition the peak should move out to higher temperature.

Neither of the above two mechanisms approaches the problem as to the nature of the charge transport perpendicular to the stacking axis. The structure of TTF-TCNQ shown in Figure 8[159] indicates that along the x-axis the molecular planes form a dihedral angle of 58.5° yet the electrical conductivity along x, although ≈ 100 times smaller than along y (the stacking axis), still has a metallic-like temperature dependence[66]. No concrete mechanism for the charge migration along the x-axis has been presented.

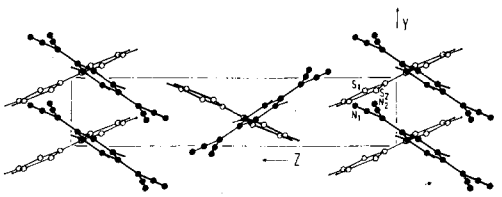
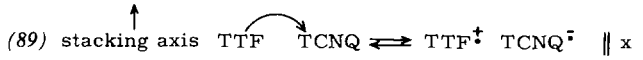


Fig. 8. Projection of crystal structure for TTF-TCNQ *(14)* along the x-axis [159]. Separate stacks of TTF and TCNQ occur along the y-axis but along x the donor and acceptor are at an angle of 58.5°.

Chemically, it seems reasonable to expect that as electrons migrate up and down the TCNQ stack and holes up and down the TTF stack, there will be many configurations in which a *neutral* TTF will be a neighbor to a *neutral* TCNQ. Interstack charge transfer might then occur at these points as shown in *(89)*. Interestingly enough, the equilibrium constant K_a for *(89)* will determine not only the conductivity



along the x-axis but also along the stacking axis, y. According to Reference [85], the conductivity along the stacking axis will depend on the product of neutral and ionic species concentrations and this will be determined by K_a which may be a strong function of temperature. Temperature-dependent X-ray data[174] from 45 K to room temperature show that below 60 K the bond lengths for TTF are like that of the neutral species but becoming more like the cation with increasing T suggesting that the equilibrium for *(89)* shifts from left to right with increasing T. Above the $T = 60$ K transition temperature experimental data from photoelectron spectroscopy, diffuse X-ray scattering and neutron scattering all indicate at least 0.5 electron transferred per TTF-TCNQ pair but definitely less than one electron transferred per pair.

9. Are Organic Conductors Thermodynamically Stable?

The binding energy for a number of salts has been calculated taking into account the ionization energy of the donor, electron affinity of the acceptor, the amount of charge transferred, and the Madelung energy[175–177].

For low-conductivity TCNQ salts with strong donors like the alkali metals, binding energies are typically -3.0 eV (*ca.* -70 kcal/mol). On the other hand, the mixed-valence high-conductivity salts like NMP-TCNQ *(65)*, TTF-TCNQ *(14)*, and (TTF)$Br_{0.7}$ either have a small binding energy [-0.6 eV for (TTF)$Br_{0.7}$[177]] or a positive binding energy [$+3.7$ eV for *(65)*, $+0.6$ eV for *(14)* assuming 0.5 electron transferred]. While polarization energy may also be important and was neglected in the above calculations, inclusion of polarization energies by estimation does not substantially change the conclusion that the conductive salts like *(65)* and *(14)* may not be thermodynamically stable (by instability here I do not mean that the ions do not exist as chemically stable species but rather the crystal structures which produce the

high conductivity may not be the most favored structures). Some observations bear on this point. Attempts to grow conducting crystals by slow crystallization of a saturated solution containing the salt invariably fails; rather the best conductive materials are obtained by rapid crystallization either by rapid cooling of a saturated solution or by interdiffusing of two solutions at room temperature, one of which contains the donor, and the other the acceptor. Thus, depending on the rate of crystallization from CH_3CN, NMP-TCNQ *(65)* exists either as the high-conductivity phase[178] with separate donor and acceptor stacks[116] or the low-conductivity phase $NMPH^{+}TCNQ^{\cdot}$ ($\sigma = 8 \times 10^{-5}\,\Omega^{-1}\,cm^{-1}$)[179] with alternating donor and acceptor[180]. Similar observations have been made on the crystallization of *(24)*[61] and *(55)*[181].

10. Where Do We Go From Here?

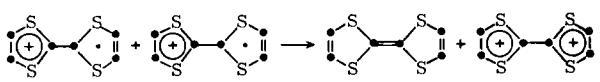
The synthetic organic chemist confronted by the multitude of confusing ideas in this area must wonder about what new contributions he can possibly make. There are a number of common chemical features of organic conductors, the implication of which needs to be explored much more thoroughly. These are as follows:

1) The creation and destruction of aromaticity in the charge generation and transport scheme. The best organic conductors consist of donors which generate a new aromatic sextet upon oxidation and of acceptors which do the same upon one-electron reduction. Extension of this observation to other $4n+2$ Hückel aromatic systems needs to be studied.

2) The presence of mixed valence states. This also is a necessary condition for charge transport and appears to be related to 1) in that aromaticity cannot migrate from molecule to molecule unless there are some neutral molecules in the stack which have no aromaticity. Thus the reaction

$$TCNQ^{-} + TCNQ^{-} \longrightarrow TCNQ + TCNQ^{2-}$$

is not favorable; aromaticity is not conserved. In comparison the reaction



may be energetically feasible since aromaticity is conserved. A comparison of other donor-acceptor combinations with and without this property would be worthwhile.

3) Finally, as pointed out in the last section, neither the phase diagram nor any experimental information on the thermodynamic stability of segregated stack complexes is known. A study of the thermochemistry of these systems would greatly facilitate our understanding of why these organic conductors form in the first place.

The author would like to acknowledge the many helpful discussions on organic molecular structure he has had with James Van Allan, Fred Chen, Neil Haley, and George Reynolds.

Received: September 17, 1976 [A 169 IE]
German version: Angew. Chem. *89*, 534 (1977)

[1] *B. T. Matthias*, Comments Solid State Phys. *3*, 93 (1970).
[2] *I. F. Shchegolev*, Phys. Stat. Solidi *A 12*, 9 (1972).
[3] *H. R. Zeller*, Festkörperprobleme *13*, 31 (1973).
[4] *W. Gläser*, Festkörperprobleme *14*, 205 (1974).
[5] *A. F. Garito, A. J. Heeger*, Acc. Chem. Res. *7*, 232 (1974).
[6] *L. N. Bulaevskii*, Sov. Phys. Usp. *18*, 131 (1975); Usp. Fiz. Nauk *115*, 263 (1975).
[7] *E. P. Goodings*, Endeavour *34*, 123 (1975).
[8] *E. M. Engler*, Chemtech. *6*, 274 (1976).
[9] *E. P. Goodings*, Chem. Soc. Rev. *5*, 95 (1976).
[10] *A. D. Yoffe*, Chem. Soc. Rev. *5*, 51 (1976).
[11] *K. Masuda, M. Silver:* Energy and Charge Transfer in Organic Semiconductors. Plenum, New York 1974.
[12] *H. G. Schuster:* Lecture Notes in Physics *34*, One-Dimensional Conductors. Springer-Verlag, Berlin 1975.
[13] *H. J. Keller:* Low-Dimensional Cooperative Phenomena. Plenum, New York 1975.
[14] *P. Day* in [13], p. 195.
[15] *H. Akamatu, H. Inokuchi, Y. Matsunaga*, Bull. Chem. Soc. Jpn. *29*, 213 (1956).
[16] *N. D. Parkyns, A. R. Ubbelohde*, J. Chem. Soc. *1961*, 2110.
[17] *M. M. Labes, R. Sehr, M. Bose*, J. Chem. Phys. *33*, 868 (1960).
[18] *T. Uchida, H. Akamatu*, Bull. Chem. Soc. Jpn. *34*, 1015 (1961).
[19] *J. Kommandeur, F. R. Hall*, J. Chem. Phys. *34*, 129 (1961).
[20] *R. J. Hoare, J. M. Pratt*, Chem. Commun. *1969*, 1320.
[21] *M. Rabinowitch*, Z. Phys. Chem. *119*, 82 (1926).
[22] *L. S. Singer, J. Kommandeur*, J. Chem. Phys. *34*, 133 (1961).
[23] *J. H. Perlstein* in *P. F. Weller:* Solid State Chemistry and Physics, Vol. 1. Marcel Dekker, New York 1973, p. 209.
[24] *A. Many, S. Z. Weisz, M. Simhony*, Phys. Rev. *126*, 1989 (1962).
[25] *M. M. Sayed, C. R. Westgate, J. H. Perlstein*, Electron. Lett. *9*, 529 (1973).
[26] *H. Kusakawa, S. Nishizaki*, Bull. Chem. Soc. Jpn. *38*, 313 (1965).
[27] *V. Hadek, P. Zach, K. Ulbert, J. Honzl*, Collect. Czech. Chem. Commun. *34*, 3139 (1969).
[28] *Y. Matsunaga*, Helv. Phys. Acta *36*, 800 (1963).
[29] *K. Kan, Y. Matsunaga*, Bull. Chem. Soc. Jpn. *45*, 2096 (1972).
[30] *Y. Matsunaga, Y. Suzuki*, Bull. Chem. Soc. Jpn. *45*, 3375 (1972).
[31] *G. Dix*, Phys. Stat. Solidi *A 24*, 139 (1974).
[32] *K. Huml*, Acta Crystallogr. *22*, 29 (1967).
[33] *V. Hadek*, J. Chem. Phys. *49*, 5202 (1968).
[34] *K. Toman, D. Ocenaskova*, Acta Crystallogr. *20*, 514 (1966).
[35] *E. Clar:* The Aromatic Sextet. Wiley, London 1972.
[36] *T. W. Armitt, R. Robinson*, J. Chem. Soc. *1925*, 1604.
[37] *F. Wudl, G. M. Smith, E. J. Hufnagel*, Chem. Commun. *1970*, 1453.
[38] *D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, N. D. Canfield*, J. Am. Chem. Soc. *93*, 2258 (1971).
[39] *L. R. Melby, H. D. Hartzler, W. A. Sheppard*, J. Org. Chem. *39*, 2456 (1974).
[40] *F. Wudl, M. L. Kaplan, E. J. Hufnagel, E. W. Southwick Jr.*, J. Org. Chem. *39*, 3608 (1974).
[41] *J. Ferraris, D. O. Cowan, V. Walatka Jr., J. H. Perlstein*, J. Am. Chem. Soc. *95*, 948 (1973).
[42] *P. A. Berger, D. J. Dahm, G. R. Johnson, M. G. Miles, J. D. Wilson*, Phys. Rev. *B 12*, 4085 (1975).
[43] *H. Prinzbach, H. Berger, A. Lüttringhaus*, Angew. Chem. *77*, 453 (1965); Angew. Chem. Int. Ed. Engl. *4*, 435 (1965).
[44] *D. O. Cowan, A. Bloch, T. Poehler, T. Kistenmacher, J. Ferraris, K. Bechgaard, R. Gemmer, C. Hu, P. Shu, W. Krug, R. Pyle, V. Walatka, T. Carruthers, T. Phillips, R. Banks*, Mol. Cryst. Liq. Cryst. *32*, 223 (1976).
[45] *J. P. Ferraris, T. O. Poehler, A. N. Bloch, D. O. Cowan*, Tetrahedron Lett. *1973*, 2553.
[46] *T. J. Kistenmacher, T. E. Phillips, D. O. Cowan, J. P. Ferraris, A. N. Bloch*, Acta Crystallogr. *B 32*, 539 (1976).
[47] *P. Calas, J. M. Fabre, M. K. El-Saleh, A. Mas, E. Torreilles, L. Giral*, C. R. Acad. Sci. *C 281*, 1037 (1975).
[48] *H. K. Spencer, M. P. Cava, F. G. Yamagishi, A. F. Garito*, J. Org. Chem. *41*, 730 (1976).
[49] *R. Schumaker, M. Ebenhahn, G. Castro, R. L. Greene*, Bull. Am. Phys. Soc. II *20*, 495 (1975).
[50] *E. M. Engler, V. V. Patel*, J. Chem. Soc. Chem. Commun. *1975*, 671.
[51] *M. V. Lakshmikantham, M. P. Cava, A. F. Garito*, J. Chem. Soc. Chem. Commun. *1975*, 383.
[52] *S. Etemad, T. Penney, E. M. Engler, B. A. Scott, P. E. Seiden*, Phys. Rev. Lett. *34*, 741 (1975).
[53] *S. K. Khanna, C. K. Chiang, A. F. Garito, A. J. Heeger*, Solid State Commun. *18*, 1405 (1976).
[54] *E. M. Engler, V. V. Patel*, Tetrahedron Lett. *1976*, 423.
[55] *H. K. Spencer, M. V. Lakshmikantham, M. P. Cava, A. F. Garito*, J. Chem. Soc. Chem. Commun. *1975*, 867.
[56] *R. C. Wheland, J. L. Gillson*, J. Am. Chem. Soc. *98*, 3916 (1976).
[57] *E. M. Engler, V. V. Patel*, J. Am. Chem. Soc. *96*, 7376 (1974).
[58] *M. V. Lakshmikantham, M. P. Cava*, J. Org. Chem. *41*, 882 (1976).
[59] *J. R. Andersen, K. Bechgaard*, J. Org. Chem. *40*, 2016 (1975).

[60] *K. Bechgaard, D. O. Cowan, A. N. Bloch*, J. Org. Chem. *40*, 746 (1975).
[61] *K. Bechgaard, D. O. Cowan, A. N. Bloch*, J. Chem. Soc. Chem. Commun. *1974*, 937.
[62] *A. N. Bloch, D. O. Cowan, K. Bechgaard, R. E. Pyle, R. H. Banks, T. O. Poehler*, Phys. Rev. Lett. *34*, 1561 (1975).
[63] *C. Berg, K. Bechgaard, J. R. Andersen, C. S. Jacobsen*, Tetrahedron Lett. *1976*, 1719.
[64] *C. Marschalk, C. Stumm*, Bull. Soc. Chim. Fr. *15*, 418 (1948).
[65] *C. Marschalk, P. Niederhauser*, Bull. Soc. Chim. Fr. *19*, 151 (1952).
[66] *J. H. Perlstein, J. P. Ferraris, V. V. Walatka, D. O. Cowan, G. A. Candela*, A. I. P. Conf. Proc. Magnetism Magnetic Materials *10*, 1494 (1972).
[67] *L. I. Buravov, O. N. Eremenko, R. B. Lyubovskii, L. P. Rozenberg, M. L. Khidekel, R. P. Shibaeva, I. F. Shchegolev, E. B. Yagubskii*, JETP Lett. *20*, 208 (1974).
[68] *R. P. Shibaeva, L. P. Rozenberg*, Sov. Phys. Crystallogr. *20*, 581 (1976).
[69] *G. R. Johnson, M. G. Miles, J. D. Wilson*, Mol. Cryst. Liq. Cryst. *33*, 67 (1976).
[70] *D. S. Acker, W. R. Hertler*, J. Am. Chem. Soc. *84*, 3370 (1962).
[71] *W. R. Hertler, H. D. Hartzler, D. S. Acker, R. E. Benson*, J. Am. Chem. Soc. *84*, 3387 (1962).
[72] *R. C. Wheland, E. L. Martin*, J. Org. Chem. *40*, 3101 (1975).
[73] *R. C. Wheland, J. L. Gillson*, J. Am. Chem. Soc. *98*, 3916 (1976).
[74] *R. C. Wheland*, J. Am. Chem. Soc. *98*, 3926 (1976).
[75] *J. Diekman, W. R. Hertler, R. E. Benson*, J. Org. Chem. *28*, 2719 (1963).
[76] *D. J. Sandman, A. F. Garito*, J. Org. Chem. *39*, 1165 (1974).
[77] *E. Campaigne, R. D. Hamilton*, Q. Rep. Sulfur Chem. *5*, 275 (1970).
[78] *R. E. Long, R. A. Sparks, K. N. Trueblood*, Acta Crystallogr. *18*, 932 (1965).
[79] *A. Hoekstra, T. Spoelder, A. Vos*, Acta Crystallogr. *B 28*, 14 (1972).
[80] *P. N. Reiger, G. K. Fraenkel*, J. Chem. Phys. *37*, 2795 (1962).
[81] *P. H. H. Fischer, C. A. McDowell*, J. Am. Chem. Soc. *85*, 2694 (1963).
[82] *H. Johansen*, Int. J. Quantum Chem. 9, 459 (1975).
[83] *R. N. Lyubovskaya, M. Z. Aldoshina, V. Ya. Rodionov, T. A. Chibisova, M. L. Khidekel*, Bull. Acad. Sci. USSR Div. Chem. Sci. *1974*, 168.
[84] *G. S. Bajwa, K. D. Berlin, H. A. Pohl*, J. Org. Chem. *41*, 145 (1976).
[85] *W. A. Barlow, G. R. Davies, E. P. Goodings, R. L. Hand, G. Owen, M. Rhodes*, Mol. Cryst. Liq. Cryst. *33*, 123 (1976).
[86] *M. Mizuno, M. P. Cava, A. F. Garito*, J. Org. Chem. *41*, 1484 (1976).
[87] *N. Loayza, C. Th. Pedersen*, J. Chem. Soc. Chem. Commun. *1975*, 496.
[88] *F. Wudl, D. E. Schafer, B. Miller*, J. Am. Chem. Soc. *98*, 252 (1976).
[89] *R. Somoano, V. Hadik, S. P. S. Yen, A. Rembaum, R. Derk*, J. Chem. Phys. *62*, 1061 (1975).
[90] *I. Maki, Y. Matsunaga, M. Nakakura, A. Nonaka*, Bull. Chem. Soc. Jpn. *48*, 1368 (1975).
[91] *P. Dupuis, J. Neel*, C. R. Acad. Sci. *C 268*, 653 (1969).
[92] *N. Haley, J. H. Perlstein*, unpublished results.
[93] *F. Wudl*, J. Am. Chem. Soc. 97, 1962 (1975).
[94] *B. A. Hess Jr., L. J. Schaad*, J. Am. Chem. Soc. *95*, 3907 (1973).
[95] *S. Hünig*, Pure Appl. Chem. *15*, 109 (1967).
[96] *S. Hünig, B. J. Garner, G. Ruider, W. Schenk*, Justus Liebigs Ann. Chem. *1973*, 1036.
[97] *J. Alizon, J. Gallice, H. Robert, G. Delplanque, C. Weyl, C. Fabre, H. Strzelecka*, Mol. Cryst. Liq. Cryst. *33*, 91 (1976).
[98] *J. VanAllan, G. A. Reynolds, J. H. Perlstein*, to be published.
[99] *M. R. Suchanski*, J. Electrochem. Soc. *123*, 181 c (1976).
[100] *S. G. Clarkson, B. C. Lane, F. Basolo*, Inorg. Chem. *11*, 662 (1972).
[101] *L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, W. E. Mochel*, J. Am. Chem. Soc. 84, 3374 (1962).
[102] *R. P. Shibaeva, L. O. Atovmyan*, J. Struct. Chem. USSR *13*, 514 (1972).
[103] *I. Shirotani, N. Sakai*, J. Solid State Chem. *18*, 17 (1976).
[104] *C. J. Fritchie Jr., P. Arthur Jr.*, Acta Crystallogr. *21*, 139 (1966).
[105] *R. G. Kepler, P. E. Bierstedt, R. E. Merrifield*, Phys. Rev. Lett. *5*, 503 (1960).
[106] *V. Walatka Jr., J. H. Perlstein*, Mol. Cryst. Liq. Cryst. *15*, 269 (1971).
[107] *K. Holczer, G. Mihály, A. Jánossy, G. Grüner*, Mol. Cryst. Liq. Cryst. *32*, 199 (1976).
[108] *L. I. Buravov, D. N. Fedutin, I. F. Shchegolev*, Sov. Phys. JETP *32*, 612 (1971).
[109] *H. Kobayashi*, Bull. Chem. Soc. Jpn. *47*, 1346 (1974).
[110] *J. H. Perlstein, M. J. Minot, V. Walatka*, Mater. Res. Bull. *7*, 309 (1972).
[111] *A. N. Bloch, R. B. Weisman, C. M. Varna*, Phys. Rev. Lett. *28*, 753 (1972).
[112] *M. Kono, Y. Saito*, Acta Crystallogr. *B 30*, 1294 (1974).
[113] *N. Sakai, I. Shirotani, S. Minomura*, Bull. Chem. Soc. Jpn. *45*, 3314 (1972).
[114] *M. Kono, Y. Saito*, Acta Crystallogr. *B 31*, 2007 (1975).
[115] *G. P. Saakyan, R. P. Shibaeva, L. O. Atovmyan*, Sov. Phys. Dokl. *17*, 1138 (1973).
[116] *C. J. Fritchie Jr.*, Acta Crystallogr. *20*, 892 (1966).
[117] *H. Kobayashi*, Bull. Chem. Soc. Jpn. *48*, 1373 (1975).
[118] *B. Morosin*, Phys. Lett. *A 53*, 455 (1975).
[119] *L. R. Melby*, Can. J. Chem. *43*, 1448 (1965).
[120] *H. Kobayashi, F. Marumo, Y. Saito*, Acta Crystallogr. *B 27*, 373 (1971).
[121] *H. Kobayashi, Y. Ohashi, F. Marumo, Y. Saito*, Acta Crystallogr. *B 26*, 459 (1970).
[122] *J. Jaud, D. Chasseau, J. Gaultier, C. Hauw*, C. R. Acad. Sci. *C 278*, 769 (1974).
[123] *D. Chasseau, J. Gaultier, C. Hauw, J. Jaud*, C. R. Acad. Sci. *C 276*, 661 (1973).
[124] *B. H. Klanderman, D. C. Hoesterey*, J. Chem. Phys. *51*, 377 (1969).
[125] *D. J. Dahm, P. Horn, G. R. Johnson, M. G. Miles, J. D. Wilson*, J. Cryst. Mol. Struct. *5*, 27 (1975).
[126] *M. A. Butler, F. Wudl, Z. G. Soos*, Phys. Rev. *B 12*, 4708 (1975).
[127] *W. C. Danen, F. A. Neugebauer*, Angew. Chem. *87*, 823 (1975); Angew. Chem. Int. Ed. Engl. *14*, 783 (1975).
[128] *F. Herman, A. R. Williams, K. Johnson*, J. Chem. Phys. *61*, 3508 (1974).
[129] *P. L. Nordio, Z. G. Soos, H. M. McConnell*, Annu. Rev. Phys. Chem. *17*, 237 (1966).
[130] *Z. G. Soos*, Annu. Rev. Phys. Chem. *25*, 121 (1974).
[131] *J. G. Vegter, J. Kommandeur*, Mol. Cryst. Liq. Cryst. *30*, 11 (1975).
[132] *S. K. Khanna, A. A. Bright, A. F. Garito, A. J. Heeger*, Phys. Rev. *B 10*, 81 (1974).
[133] *D. Allender, J. W. Bray, J. Bardeen*, Phys. Rev. *B 9*, 119 (1974).
[134] *G. A. Thomas, D. E. Schafer, F. Wudl, P. M. Horn, D. Rimac, J. W. Cook, D. A. Glocker, M. J. Skove, C. W. Chu, R. P. Groff, J. L. Gillson, R. C. Wheland, L. R. Melby, M. B. Salamon, R. A. Craven, G. DePasquali, A. N. Bloch, D. O. Cowan, V. V. Walatka, R. E. Pyle, R. Gemmer, T. O. Poehler, G. R. Johnson, M. G. Miles, J. D. Wilson, J. P. Ferraris, T. F. Finnegan, R. J. Warmack, V. F. Raaen, D. Jerome*, Phys. Rev. *B 13*, 5105 (1976).
[135] *C. W. Chu, J. M. E. Harper, T. H. Geballe, R. L. Greene*, Phys. Rev. Lett. *31*, 1491 (1973).
[136] *D. Jerome, W. Müller, M. Weger*, J. Phys. Lett. *35*, L-77 (1974).
[137] *T. Tiedje, J. F. Carolan, A. J. Berlinsky, L. Weiler*, Can. J. Phys. *53*, 1593 (1975).
[138] *T. Wei, S. Etemad, A. F. Garito, A. J. Heeger*, Phys. Lett. *45 A*, 269 (1973).
[139] *R. A. Craven, M. B. Salamon, G. DePasquali, R. M. Herman, G. Stucky, A. Schultz*, Phys. Rev. Lett. *32*, 769 (1974).
[140] *R. Viswanathan, D. C. Johnston*, J. Phys. Chem. Solids, *36*, 1093 (1975).
[141] *P. M. Chaikin, J. F. Kwak, T. E. Jones, A. F. Garito, A. J. Heeger*, Phys. Rev. Lett. *31*, 601 (1973).
[142] *J. F. Kwak, P. M. Chaikin, A. A. Russel, A. F. Garito, A. J. Heeger*, Solid State Commun. *16*, 729 (1975).
[143] *P. M. Chaikin, R. L. Greene, S. Etemad, E. Engler*, Phys. Rev. *B 13*, 1627 (1976).
[144] *Y. Tomkiewicz, B. A. Scott, L. J. Tao, R. S. Title*, Phys. Rev. Lett. *32*, 1363 (1974).
[145] *Y. Tomkiewicz, A. R. Taranko, J. B. Torrance*, Phys. Rev. Lett. *36*, 751 (1976).
[146] *R. M. Herman, M. B. Salamon, G. DePasquali, G. Stucky*, Solid State Commun. *19*, 137 (1976).
[147] *T. O. Poehler, A. N. Bloch, J. P. Ferraris, D. O. Cowan*, Solid State Commun. *15*, 337 (1974).
[148] *P. M. Grant, R. L. Greene, G. C. Wrighton, G. Castro*, Phys. Rev. Lett. *31*, 1311 (1973).
[149] *P. I. Perov, J. E. Fischer*, Phys. Rev. Lett. *33*, 521 (1974).
[150] *J. B. Torrance, B. A. Scott, F. B. Kaufman*, Solid State Commun. *17*, 1369 (1975).
[151] *W. T. Wozniak, G. DePasquali, M. V. Klein, R. L. Sweany, T. L. Brown*, Chem. Phys. Lett. *33*, 33 (1975).
[152] *D. B. Tanner, C. S. Jacobsen, A. F. Garito, A. J. Heeger*, Phys. Rev. *B 13*, 3381 (1976).
[153] *J. W. Cook Jr., D. A. Glocker, M. J. Skove*, J. Appl. Phys. *45*, 3679 (1974).
[154] *R. Gleiter, M. Kobayashi, J. Spanget-Larsen, J. P. Ferraris, A. N. Bloch, K. Bechgaard, D. O. Cowan*, Ber. Bunsenges. Phys. Chem. *79*, 1219 (1975).
[155] *P. Nielsen, A. J. Epstein, D. J. Sandman*, Solid State Commun. *15*, 53 (1974).
[156] *M. A. Butler, J. P. Ferraris, A. N. Bloch, D. O. Cowan*, Chem. Phys. Lett. *24*, 600 (1974).
[157] *R. S. Swingle, R. P. Groff, B. M. Monroe*, Phys. Rev. Lett. *35*, 452 (1975).
[158] *S. F. Lin, W. E. Spicer, B. H. Schechtman*, Phys. Rev. *B 12*, 4184 (1975).
[159] *T. J. Kistenmacher, T. E. Phillips, D. O. Cowan*, Acta Crystallogr. *B 30*, 763 (1974).
[160] *S. Kagoshima, H. Anzai, K. Kajimura, T. Ishiguro*, J. Phys. Soc. Jpn. *39*, 1143 (1975).

[161] F. Denoyer, F. Comès, A. F. Garito, A. J. Heeger, Phys. Rev. Lett. 35, 445 (1975).
[162] B. T. Matthias, Phys. Rev. Lett. 36, 343 (1976).
[163] R. Comès, S. M. Shapiro, G. Shirane, A. F. Garito, A. J. Heeger, Phys. Rev. Lett. 35, 1518 (1975).
[164] H. A. Mook, C. R. Watson Jr., Phys. Rev. Lett. 36, 801 (1976).
[165] R. V. Gemmer, D. O. Cowan, T. O. Poehler, A. N. Bloch, R. E. Pyle, R. H. Banks, J. Org. Chem. 40, 3544 (1975).
[166] T. D. Schultz, S. Etemad, Phys. Rev. B13, 4928 (1976).
[167] E. M. Engler, R. A. Craven, Y. Tomkiewicz, B. A. Scott, K. Bechgaard, J. R. Andersen, J. Chem. Soc. Chem. Commun. 1976, 337.
[168] S. J. LaPlaca, P. W. R. Corfield, R. Thomas, B. A. Scott, Solid State Commun. 17, 635 (1975).
[169] C. K. Johnson, C. R. Watson Jr., J. Chem. Phys. 64, 2271 (1976).
[170] R. J. Warmack, T. A. Callcott, C. R. Watson Jr., Phys. Rev. B12, 3336 (1975).
[171] R. B. Somoano, A. Gupta, V. Hadek, J. Chem. Phys. 63, 4970 (1975).
[172] A. J. Heeger, A. F. Garito in H. J. Keller: Low-Dimensional Cooperative Phenomena. Plenum, New York 1975.
[173] S. Etemad, Phys. Rev. B13, 2254 (1976).
[174] A. J. Schultz, G. D. Stucky, R. H. Blessing, P. Coppens, J. Am. Chem. Soc. 98, 3194 (1976).
[175] R. M. Metzger, J. Chem. Phys. 57, 2218 (1972).
[176] A. J. Epstein, N. O. Lipari, D. J. Sandman, P. Nielsen, Phys. Rev. B13, 1569 (1976).
[177] J. B. Torrance, B. D. Silverman, Phys. Rev. B15, 788 (1977).
[178] A. J. Epstein, S. Etemad, A. F. Garito, A. J. Heeger, Phys. Rev. B5, 952 (1972).
[179] L. B. Coleman, S. K. Khanna, A. F. Garito, A. J. Heeger, B. Morosin, Phys. Lett. A42, 15 (1972).
[180] B. Morosin, Acta Crystallogr. B32, 1176 (1976); personal communication.
[181] M. G. Kaplunov, D. N. Fedutin, M. L. Khidekel', I. F. Shchegolev, É. B. Yagubskii, R. B. Lyubovskii, J. Gen. Chem. USSR 42, 2292 (1972).

COMMUNICATIONS

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

Detection of an Orthonitrate by Vibrational Spectroscopy: Na_3NO_4[**]

By *Martin Jansen*[*]

It has recently been shown that Na_3NO_3 does not exist as orthonitrite (NO_3^{3-} anion) as formerly assumed, but instead has a structure derived from the perovskite type made up of $(NO_2^-)ONa_3$[1]. This suggests that Na_3NO_4[2] might also be an adduct, *viz.* $Na_2O \cdot NaNO_3$.

All attempts to prepare single crystals of Na_3NO_4 suitable for X-ray structure analysis have so far failed; however, vibrational spectroscopy should also provide unequivocal information as to whether nitrate ions are present in Na_3NO_4.

Na_3NO_4 was obtained as a microcrystalline colorless powder by heating of equimolar amounts of $NaNO_3$ (analytically pure, Merck) and Na_2O[3] in a sealed silver crucible (300 °C, 7 d). The product is extremely sensitive to moisture and CO_2, and decomposes within minutes to hydroxide and carbonate on exposure to air.

[*] Dr. M. Jansen
Institut für Anorganische und Analytische Chemie der Universität Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen (Germany)

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

The samples are sealed under argon in glass capillaries for recording the Raman spectrum (Coderg, LRDH 800, Ar laser, 514.5 nm)[4], which is reproduced in the form of a line diagram in Figure 1a.

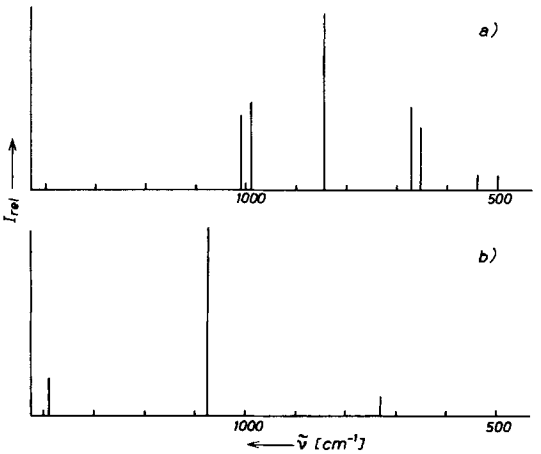


Fig. 1. Raman spectra of a) Na_3NO_4 and b) $NaNO_3$.

Comparison with the Raman spectrum of $NaNO_3$ (Fig. 1b) and other nitrates[5] shows that Na_3NO_4 does not contain NO_3^- ions; thermal degradation to nitrites can also be ruled out on the basis of the spectrum. Instead the Raman absorptions can be interpreted assuming an orthonitrate with tetrahedral NO_4^{3-} ions. A proposed assignment of the observed vibrational frequencies is shown in Table 1. The splitting of the vibrations ν_2, ν_3, ν_4, which should be degenerate in the case of strict T_d symmetry, is probably due to crystal field effects; it can be explained by assuming D_{2d} site symmetry. However, a final interpretation of the spectrum requires a knowledge of the space group of Na_3NO_4 and the site symmetry of NO_4^{3-}. The vibrational frequencies observed for NF_4^+[6] are given for comparison in Table 1; the similarity of the two spectra corresponds to expectations since NF_4^+ is isoelectronic with NO_4^{3-} and the atomic masses of O and F are comparable. The existence of NO_4^{3-} appears to apply only to the solid state: cold 1 N sodium hydroxide decomposes Na_3NO_4, regenerating NO_3^-.

Table 1. Raman spectrum of Na_3NO_4; comparison with NF_4^+ (in NF_4SbF_6).

Na_3NO_4	Assignment D_{2d}	T_d	NF_4^+
1012, 988	B_2, E	$F_2(\nu_3)$	1160, 1150
843	A_1	$A_1(\nu_1)$	843
669, 651	B_2, E	$F_2(\nu_4)$	604
540, 500	A_1, B_1	$E(\nu_2)$	437

Received: May 18, 1977 [Z 740 IE]
German version: Angew. Chem. 89, 567 (1977)

CAS Registry numbers:
Na_3NO_4, 62973-62-0; $NaNO_3$, 7631-99-4

[1] *M. Jansen*, Angew. Chem. *88*, 410 (1976); Angew. Chem. Int. Ed. Engl. *15*, 376 (1976); Z. Anorg. Allg. Chem., in press.
[2] *E. Zintl, W. Morawietz*, Z. Anorg. Allg. Chem. *236*, 372 (1938); *A. Klemenc, V. Gutmann*, Monatsh. Chem. *81*, 361 (1950); *R. Kohlmuller*, Ann. Chim. Paris [13] *4*, 1183 (1959).
[3] *A. Klemenc, G. Ofner, H. Wirth*, Z. Anorg. Allg. Chem. *265*, 221 (1951).
[4] Recorded by *D. Wald*.
[5] *S. D. Ross*: Inorganic Infrared and Raman Spectra. McGraw-Hill, London 1972.
[6] *K. O. Christe, R. D. Wilson, C. J. Schack*, Inorg. Chem. *16*, 937 (1977).

N,N-Bis(trimethylsilyl)enamines—Stereoselective Synthesis from *N,N*-Bis(trimethylsilyl)thioformamide[**]

By *Wolfgang Walter* and *Hans-Wolfgang Lüke*[*]

Monosilylated enamines have only recently been described[1]. In the course of our studies on silylated thioamides[2] we have now prepared the hitherto unknown *N,N*-bis(trimethylsilyl)enamines *(9)* and *(13)*, which are of preparative interest as masked *N*-unsubstituted enamines.

The starting material *(1)* was obtained as the first bis-silylated thioamide by metalation and silylation of *N*-trimethylsilylthioformamide *(2)*[2a] [eq. (a)] or alternatively by reaction of *O*-ethyl thioformate *(3)*[3] with lithium bis(trimethylsilyl)-amide *(4)* [eq. (b)].

$$\underset{(2)}{H\text{–}CS\text{–}NHSiMe_3} \xrightarrow[-\ LiCl]{1)\ n\text{BuLi},\ 2)\ Me_3SiCl} \underset{(1)}{H\text{–}CS\text{–}N(SiMe_3)_2} \qquad (a)$$

$$\underset{(3)}{H\text{–}CS\text{–}OEt} + \underset{(4)}{LiN(SiMe_3)_2} \xrightarrow[-\ LiCl]{Me_3SiCl} (1) + Me_3SiOEt \qquad (b)$$

The structure of *(1)*, which crystallizes as colorless needles that are very sensitive to hydrolysis, is confirmed by its IR and ^{13}C-NMR spectrum (Table 1).

In contrast to the thiophilic addition generally observed on attack of organolithium compounds *(5)* on thiocarbonyl groups[4], these compounds react with *(1)* by carbophilic addition to form the salts *(6)*. Carbophilic addition was also detected in the reaction of phenyllithium with *N,N*-dimethylthiobenzamide or -thioformamide[5]. Reaction of *(6)* with trimethylchlorosilane gives the 1-(trimethylsilylthio)-*N,N*-bis(trimethylsilyl)alkylamines *(7)*, which decompose spontaneously by elimination of trimethylsilanethiol *(8)* into the *N,N*-bis(trimethylsilyl)enamines *(9)*. Compound *(8)* condenses immediately with elimination of H_2S to give hexamethyldisilathiane *(10)*[6].

$$(1) + \underset{(5)}{RCH_2Li} \longrightarrow \underset{(6)}{H\text{–}C(SLi)(CH_2R)\text{–}N(SiMe_3)_2} \xrightarrow[-\ LiCl]{Me_3SiCl} \underset{(7)}{H\text{–}C(S\text{–}SiMe_3)(CH_2R)\text{–}N(SiMe_3)_2}$$

$$(7) \longrightarrow \underset{(9)}{H(R)C^2{=}C^1(H)N(SiMe_3)_2} + \underset{(8)}{[Me_3SiSH]} \xrightarrow{-\frac{1}{2}H_2S} \underset{(10)}{1/2\ (Me_3Si)_2S}$$

(a): R = H
(b): R = CH_3
(c): R = nC_3H_7

Table 1. Properties of the new compounds.

Compound	B.p. [°C/torr]	IR [a] [cm^{-1}]	^{1}H-NMR [b] δ rel. to TMS	^{13}C-NMR [c]
(1)	49—50/0.05	νNSi_2 882	9.90 (s) HCS, 0.40 (s) HCSi	205.9 CS, 1.5 CSi
(9a)	136/760	νC=C 1610 νNSi_2 935	6.13 (dd, $^3J_{tr}$ = 16 Hz, $^3J_{cis}$ = 8 Hz) 1-H, 4.27 (d, $^3J_{cis}$ = 8 Hz) H(R), 4.18 (d, $^3J_{tr}$ = 16 Hz) 2-H, 0.16 (s) HCSi	140.8 C-1, 97.9 C-2, 1.9 CSi
(9b)	52/10	νC=C 1645 νNSi_2 942	5.85 (dq, $^3J_{tr}$ = 13.5 Hz, ^4J = 1.6 Hz) 1-H, 4.94 (dq, $^3J_{tr}$ = 13.5 Hz, ^3J = 6.5 Hz) 2-H, 1.61 (dd, ^3J = 6.5 Hz, ^4J = 1.6 Hz) 2-CH_3, 0.14 (s) HCSi	134.2 C-1, 115.3 C-2, 14.9 C(R), 1.8 CSi
(9c)	71/4.2	νC=C 1640 νNSi_2 945	5.93 (dt, $^3J_{tr}$ = 13.6 Hz, ^4J = 1.1 Hz) 1-H, 5.07 (dt, $^3J_{tr}$ = 13.6 Hz, ^3J = 7 Hz) 2-H, 1.93 (qt, ^3J = 7 Hz, ^4J = 1.1 Hz) H^1(R), 1.35 (sexd, ^3J = 7 Hz, ^4J = 1.3 Hz) H^2(R), 0.90 (t, ^3J = 7 Hz) H^3(R), 0.17 (s) HCSi	133.7 C-1, 121.0 C-2, 32.4 C^1(R), 23.6 C^2(R), 13.6 C^3(R), 1.9 CSi
(11)	98/0.04	νNSi_2 945	7.2—7.7 (m) H(Ph), 5.83 (s) HC, 0.30 (s) MeSiS, 0.12 (s) MeSiN	64.2 C-1, 145.6 Ph^1, 128.4 $Ph^{2,3}$, 127.3 Ph^4, 4.0 MeSiS, 3.4 MeSiN
(13)	66/0.008	νC=C 1636 νNSi_2 930	6.36 (dt, $^3J_{tr}$ = 13.6 Hz, ^4J = 1.1 Hz) 1-H, 5.15 (dt, $^3J_{tr}$ = 13.6 Hz, ^3J = 7.3 Hz) 2-H, 3.26 (dd, ^3J = 7.3 Hz, ^4J = 1.1 Hz) CH_2, 0.33 (s) MeSiS, 0.19 (s) MeSiN	136.0 C-1, 114.5 C-2, 27.6 CH_2, 1.0 Me_3SiS, 2.0 Me_3SiN

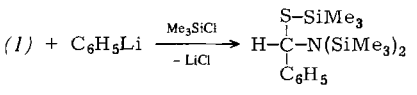
[a] Characteristic bands.
[b] *(1)*, *(9a)*, and *(11)* in CCl_4; *(9b)* and *(13)* in $CDCl_3$; *(9c)* in C_6D_6.
[c] All spectra in $CDCl_3$; assignments supported by off-resonance spectra.

Compound *(9)* exists exclusively in the *E* form. We were unable to detect an enamine-imine tautomerism due to metallotropism of the kind observed in stannyl-substituted enamines[7].

[*] Prof. Dr. W. Walter, Dipl.-Chem. H.-W. Lüke
Institut für Organische Chemie und Biochemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)

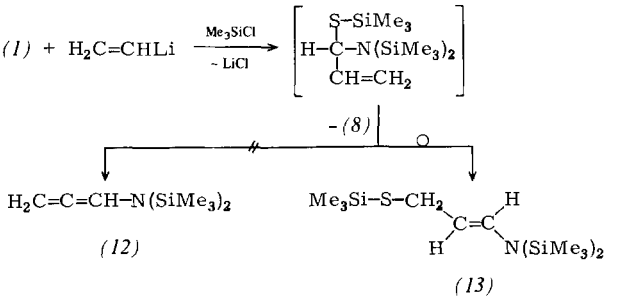
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

The proposed mechanism for the formation of *(9)* is supported by the isolation of *(11)* on reaction of *(1)* with phenyllithium.



(11)

Reaction of *(1)* with vinyllithium failed to give propadienylamine *(12)*, but instead afforded the enamine *(13)* (see Table 1) by allyl rearrangement.



(12) *(13)*

Procedure[8]

N,N-Bis(trimethylsilyl)thioformamide (1) according to eq. (a): Compound *(2)* (50 mmol) is suspended in pentane (50 ml). After dropwise addition of an equivalent amount of *n*-butyllithium in hexane (31 ml) the reaction mixture is stirred for 1 h before addition of trimethylchlorosilane (50 mmol). Stirring is continued for *ca.* 10 h, lithium chloride is filtered off, and the residue obtained on vacuum evaporation is recrystallized from pentane.—Synthesis of *(1)* according to eq. (b): A solution of *(4)* (0.1 mol) in hexane (120 ml) is added dropwise to compound *(3)* (0.1 mol). After three hours' stirring trimethylchlorosilane (0.1 mol) is added and the reaction mixture worked-up as described above.

Synthesis of *N,N-bis(trimethylsilyl)enamines (9)* and *(13)* and of the *silylthio compound (11)*: A solution of the organolithium compound (25 mmol) in a suitable solvent is added dropwise to a solution of *(1)* (25 mmol) in pentane (20 ml) at −45 °C. After brief stirring at room temperature, trimethylchlorosilane (25 mmol) is added. The resulting precipitate is filtered off and the product mixture is distilled[9].

Received: April 21, 1977 [Z 721 IE]
German version: Angew. Chem. 89, 550 (1977)

CAS Registry numbers:
(1), 63163-68-8; *(2)*, 58065-66-0; *(3)*, 29392-46-9; *(4)*, 4039-32-1; *(5a)*, 917-54-4; *(5b)*, 811-49-4; *(5c)*, 109-72-8; *(6a)*, 63163-69-9; *(6b)*, 63163-70-2; *(6c)*, 63163-71-3; *(7a)*, 63163-72-4; *(7b)*, 63163-73-5; *(7c)*, 63163-74-6; *(8)*, 18338-27-7; *(9a)*, 63163-75-7; *(9b)*, 63163-76-8; *(9c)*, 63163-77-9; *(10)*, 3385-94-2; *(11)*, 63163-78-0; *(13)*, 63163-79-1; Me_3SiCl, 75-77-4; C_6H_5Li, 591-51-5; ^{13}C, 14762-74-4; CH_2=CHLi, 917-57-7

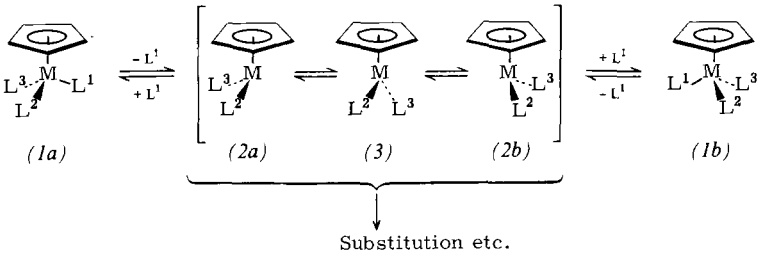
[1] *H. Ahlbrecht, D. Liesching*, Synthesis *1976*, 746.
[2] a) *W. Walter, H.-W. Lüke, J. Voss*, Justus Liebigs Ann. Chem. *1975*, 1808; b) W. Walter, H.-W. Lüke, Angew. Chem. *87*, 420 (1975); Angew. Chem. Int. Ed. Engl. *14*, 427 (1975).
[3] *R. Mayer, J. Orgis*, Z. Chem. *4*, 457 (1964).
[4] *E. Schaumann, W. Walter*, Chem. Ber. *107*, 3562 (1974); and references cited therein.
[5] *P. Beak, J. Yamamoto, C. J. Upton*, J. Org. Chem. *40*, 3052 (1975); *E. Schaumann, B. Kasper*, unpublished.
[6] ^{13}C-NMR ($CDCl_3$): $\delta = 4.0$.
[7] *B. de Jeso, J.-C. Pommier*, J. Organomet. Chem. *122*, C1 (1976).
[8] All operations performed under nitrogen. The solvents were dried by the usual methods.
[9] Compound *(9a)* cannot be separated from *(10)* by distillation.

Unsaturated Organometallic Intermediates: Electronic Structure and Structural Dynamics of $(\eta^5\text{-}C_5H_5)Mn(CO)_2$[**]

By *Peter Hofmann*[*]

Organometallic "half-sandwich" molecular fragments of the type $(C_nH_n)ML_2$ (n=4, 5, 6, 7) having only 16 electrons in their valence shell play an important role as intermediates in organometallic chemistry. This is especially true of the chemistry of optically active $CpML^1L^2L^3$ systems[1]. The electronic structure and the dynamic behavior (inversion) of such 16-electron species generated by thermal or photochemical dissociation are of crucial importance in the mechanism (Scheme 1) of S_N1 substitution of these molecules *(1a, b)* *via* chiral intermediates *(2a, b)* which in some cases proceeds with retention.

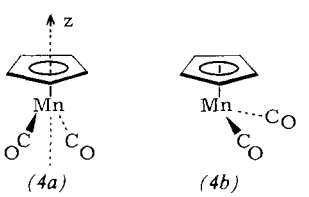
Schema 1



(1a) *(2a)* *(3)* *(2b)* *(1b)*

Substitution etc.

With the aid of the model system $CpMn(CO)_2$, whose formation has been demonstrated on photolysis of tricarbonyl(η^5-cyclopentadienyl)manganese ("cymantrene")[2], it proves possible to settle the questions of a "planar" *(4a)* or "pyramidal" *(4b)* ground state geometry and of possible energy barriers in Scheme 1 ($L^2=L^3=CO$, M = Mn) in terms of molecular orbital calculations and[3, 5] and perturbation theory.



(4a) *(4b)*

The most suitable starting point for constructing the valence MOs of a "planar" $CpMn(CO)_2$ *(4a)* is an analysis of the

[*] Dr. P. Hofmann
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-8520 Erlangen

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

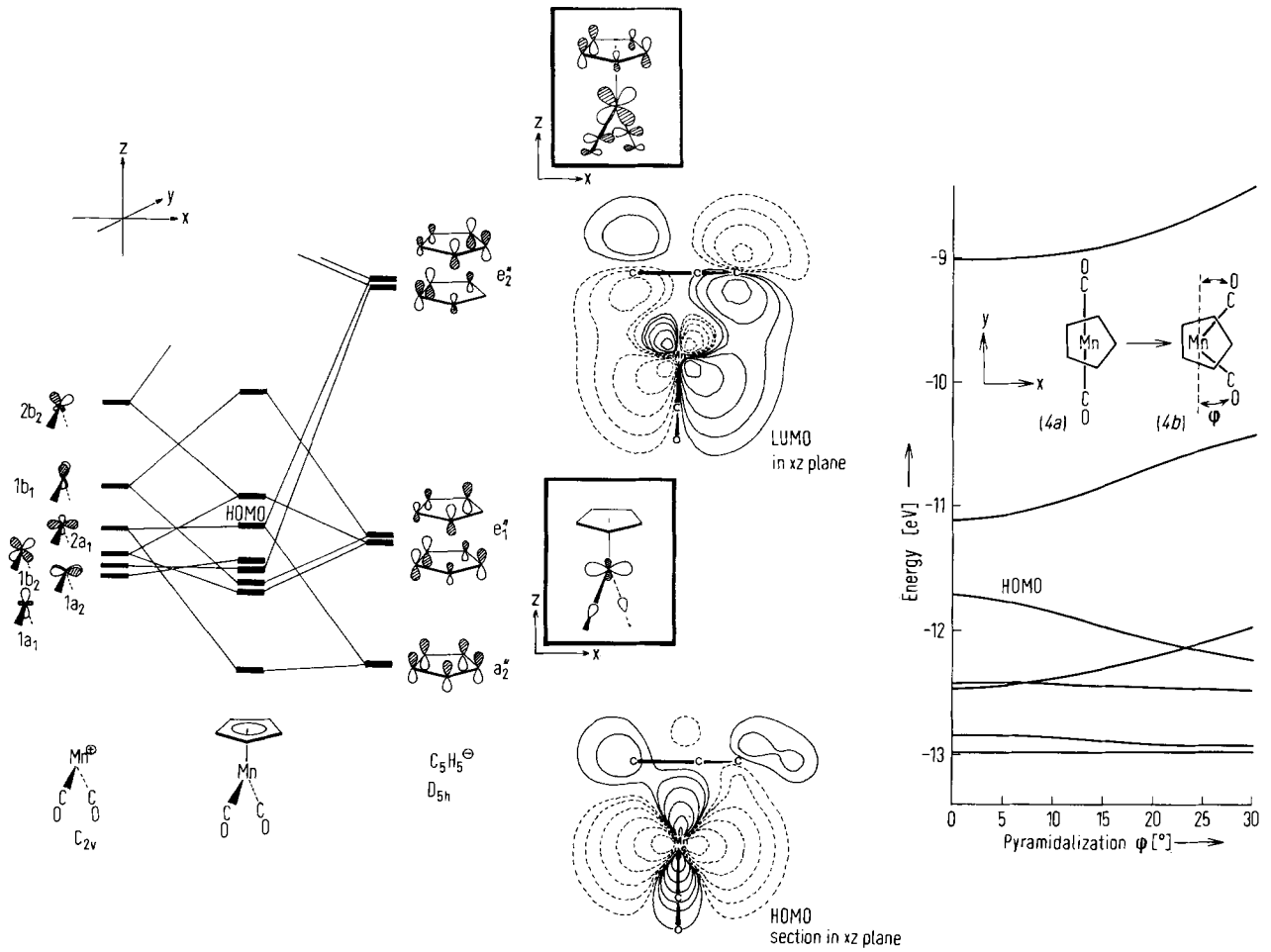


Fig. 1. Left: Interaction diagram for construction of the MOs of "planar" $CpMn(CO)_2$ *(4a)*.—Center: HOMO (below) and LUMO (above) for *(4a)*; contours at wavefunction values of 0.4, 0.2, 0.1, 0.05, 0.025, 0.0125.—Right: Calculated Walsh diagram for pyramidalization *(4a)* → *(4b)*.

interaction between the MOs of fragments constituting the complete molecule, for example between the orbitals of a $Mn(CO)_2^+$ moiety and the $C_5H_5^-$ ligand[6]. A corresponding diagram is shown in the left-hand third of Figure 1, the MOs of the metalcarbonyl fragment[7] are shown only qualitatively in their contribution at the metal center.

The small difference in energy between the HOMO and the LUMO is striking and relevant to our discussion. As shown by the calculated contour diagrams (Fig. 1, center) the HOMO is to be regarded as a nonbonding electron pair at the metal (*ca.* 90% Mn contribution), while the LUMO possesses mainly d_{xz} character at the manganese and has a large π^*_{CO} component. The model calculation of a Walsh diagram[8] for a transition to "pyramidal" geometry *(4b)* (Fig. 1, right-hand third) shows the pronounced increase in HOMO-LUMO separation expected from perturbation theory. The two frontier orbitals, of different pseudosymmetry in the "planar" system, start mixing on going from *(4a)* to *(4b)*. As a consequence the energy of the upper one increases and that of the lower one falls, and the overall stabilization leading to the "pyramidal" minimum is accompanied by rehybridization at the metal, charge shift into the CO groups, and strengthening of the Mn—C and weakening of the C—O bonds. The Walsh diagram reveals a planar structure for 18-electron systems such as $CpCo(CO)_2$, as is found experimentally for all molecules of that kind.

The energetically decisive lowering of the HOMO during the transition *(4a)* → *(4b)*, *i.e.* the barrier to inversion and hence the configurational stability of a $(C_nH_n)ML_2$ 16-electron system, therefore depends sensitively upon the distance to the LUMO in the planar geometry[9]. The metal and the ligands L as well as the C_nH_n ring accordingly exert a marked and predictable influence upon the ground state structure and inversion behavior of such molecular fragments.

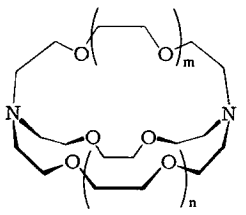
Received: April 20, 1977 [Z 741 IE]
German version: Angew. Chem. 89, 551 (1977)

[1] Review: *H. Brunner*, Fortschr. Chem. Forsch. 56, 67 (1975).
[2] *P. S. Braterman, J. D. Black*, J. Organomet. Chem. 39, C3 (1972).
[3] MO calculations of extended-Hückel type: *R. Hoffmann*, J. Chem. Phys. 39, 1397 (1963); *R. Hoffmann, W. N. Lipscomb, ibid.* 36, 2179, 3489 (1962); 37, 2872 (1962). Manganese parameters: 3d functions: *J. W. Richardson, W. C. Nieuwpoort, R. R. Powell, W. F. Edgell*, At. Data Nucl. Data Tables 36, 1057 (1962); 4s, 4p functions: *R. H. Summerville, R. Hoffmann*, J. Am. Chem. Soc. 98, 7240 (1976). The H_{ii} parameters are taken from a SCC calculation with quadratic charge dependence [4] on $CpMn(CO)_3$.
[4] *H. Basch, A. Viste, H. B. Gray*, Theor. Chim. Acta 3, 458 (1965).
[5] The MOs of the fragment *(4b)* are of significance in connection with the extensively utilized ability of the $CpMn(CO)_2$ group to stabilize unusual ligands.
[6] Concerning the fragment view of organometallic systems, cf. *M. Elian, R. Hoffmann*, Inorg. Chem. 14, 1058 (1975); *R. Hoffmann, P. Hofmann*, J. Am. Chem. Soc. 98, 598 (1976); *J. W. Lauher, R. Hoffmann, ibid.* 98, 1729 (1976).
[7] For a qualitative derivation of the MOs of a C_{2v}-$M(CO)_2$ fragment, cf. *J. K. Burdett*, J. Chem. Soc. Faraday Trans. 2 *1974*, 1599.
[8] The motion of the model corresponds to variable φ (cf. Fig. 1, right-hand third) and constant angle between the *z* axis and the Mn—C—O vectors.
[9] Cf. the MO analysis of inversion of XR_3: *C. C. Levin*, J. Am. Chem. Soc. 97, 5649 (1975).

Kinetics of Alkali Metal Complex Formation by Bicyclic Cryptates

By *Karsten Henco, Burkhard Tümmler*, and *Günter Maass*[*]

The diazapolyoxa macrobicyclics (cryptands) synthesized by *Lehn et al.* have stability constants up to 10^5 l mol^{-1} and are therefore the strongest complexing agents presently known for alkali metal ions in aqueous solution[1]. The kinetics of complex formation has so far only been examined for the [2.2.2] cryptand, the methods of potentiometry, ^{1}H-NMR and ^{23}Na-NMR spectroscopy merely yielding overall dissociation rate constants for the complexes of [2.2.2][2].



[2.1.1]: m = n = 0
[2.2.1]: m = 1, n = 0
[2.2.2]: m = n = 1

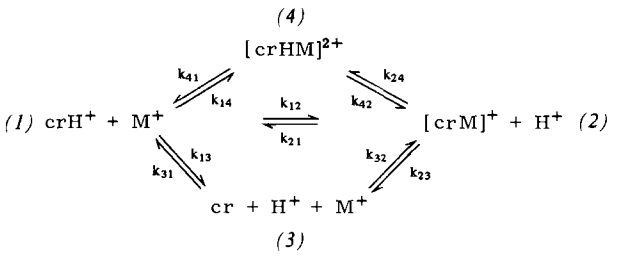
We here report studies on the kinetics of complexation of nonprotonated and singly protonated cryptands with sodium and potassium ions. For this purpose we employed the temperature jump relaxation procedure which permits determination of the rate constants of both association and dissociation[3]. The relaxation processes were registered as absorptions between 225 and 250 nm as functions of the cryptand concentration. In the chosen wavelength range the free nonprotonated ligand absorbs much more strongly than its mono- and di-protonated forms and than the complex formed by the ligand and the metal ion.

In the basic range (pH = 12.5) a concentration-dependent relaxation time was found for recombination of metal ion and unprotonated ligand, corresponding to the bimolecular mechanism[3].

$$M^+ + L \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} [LM]^+$$

Numerical evaluation yields the rate constants $k_{12} = 9 \times 10^4$ l mol^{-1} s^{-1} and $k_{21} = 1.4 \times 10^2$ s^{-1} for the Na^+/[2.1.1] system and $k_{12} = 3 \times 10^7$ l mol^{-1} s^{-1} and $k_{21} = 2 \times 10^3$ s^{-1} for the K^+/[2.2.1] system. We interpret the experimental finding by assuming that the diffusion-controlled encounter of metal ion and ligand is followed by stepwise replacement of the water molecules in the inner hydration shell of the metal ion by the coordination sites of the ligand. It should be emphasized that unimolecular conformational transitions such as the *exo/endo* conformational equilibria discussed by *Lehn et al.* do not represent the rate-determining step of complexation. Interestingly, K^+ recombines about one hundered times faster with [2.2.1] than does Na^+ with [2.1.1], although the ratios of the ionic to cavity radius are equal ($r_{Na^+}/r_{211} = r_{K^+}/r_{221} = 1.2$)[1]. The rate constant measured for the K^+/[2.2.1] system is comparable with the value found for binding of alkali metal ions to sterically unhindered polydentate ligands such as ethylenediaminetetraacetic acid (EDTA)[4]. On the other hand, the lower flexibility and the greater bond angle opening in the case of the smaller [2.1.1] cryptands render optimal adaptation of the metal ion to the cavity of the ligand so difficult that the rate of association is drastically reduced.

The two complexes having the greatest stability, the sodium complex of the [2.2.1] cryptand and the potassium complex of [2.2.2] (both with lg $K = 5.4$) were examined at pH = 6.3 in cacodylate buffer and at pH = 7.5 in Tris buffer. The ligands exist in the mono- and diprotonated form at the chosen pH values. In the temperature jump experiments two relaxation times were always observed: the fast relaxation (10 to 100 μs) is assigned to proton transfer in the acid-base system buffer-cryptand, and the slow relaxation (10 to 100 ms) to the binding of the metal ion to the monoprotonated ligand. Analysis of the concentration and pH dependence of the latter relaxation time shows that binding of the metal ion may precede or succeed protolysis, *i.e.* complex formation may proceed by the dissociative or the associative mechanism[3]:



cr = Cryptand

In the neutral pH region the intermediate state *(3)* of the free nonprotonated ligand is populated only very slightly. On the other hand, we could deduce from the saturation behavior of the slow relaxation at higher concentrations of salt and ligand that the intermediate state *(4)* is present in larger than negligible concentrations in solution. This complex $[crHM]^{2+}$ has not yet been detected by NMR spectroscopy[1]. The overall rate constants for the forward and reverse reaction $\vec{k}$ and $\overleftarrow{k}$ are listed in Table 1.

Table 1. Rate constants of alkali metal complex formation of bicyclic cryptates.

Ligand	Cation	Stability constant lg K	Rate constants $\vec{k}$ [l mol^{-1} s^{-1}]	$\overleftarrow{k}$ [s^{-1}]
[2.1.1]	Na^+	3.2	$(9 \pm 1)\ 10^4$	$(1.4 \pm 0.1)\ 10^2$
[2.2.1]	Na^+	5.40	$(6 \pm 2)\ 10^6$	18 ± 2
[2.2.1]	K^+	3.95	$(3 \pm 1)\ 10^7$	$(2 \pm 1)\ 10^3$
[2.2.2]	K^+	5.4	$(2 \pm 1)\ 10^6$	9 ± 3

The values measured for the [2.2.2] complex are of the same order of magnitude as the constants published by *Lehn et al.*[2].

Received: April 20, 1977 [Z 742 IE]
German version: Angew. Chem. *89*, 567 (1977)

CAS Registry numbers:
[2.1.1], 31250-06-3; [2.2.1], 31364-42-8; [2.2.2], 23978-09-8; Na^+, 17341-25-2; K^+, 24203-36-9

[*] Prof. Dr. G. Maass, Dipl.-Biochem. K. Henco, Dipl.-Biochem. B. Tümmler
Institut für Physiologische Chemie und Klinische Biochemie, Abt. Biophysikalische Chemie der Medizinischen Hochschule
Karl-Wiechert-Allee 9, D-3000 Hannover 61 (Germany)

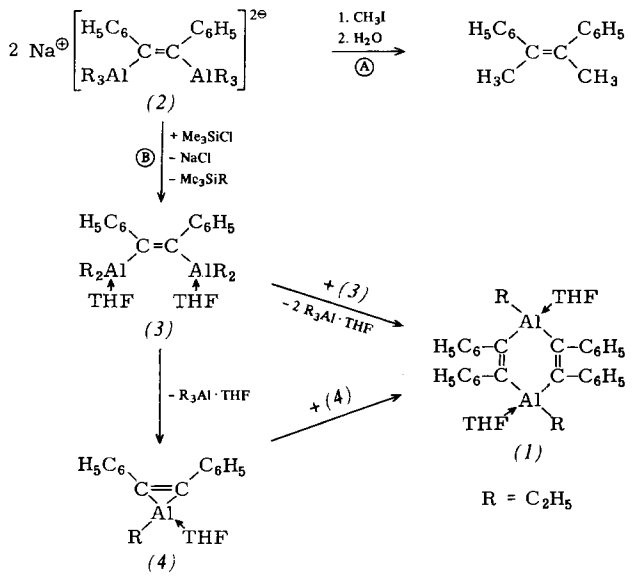
[1] *B. Dietrich, J. M. Lehn, J. P. Sauvage*, Tetrahedron Lett. *1969*, 2885; *J. M. Lehn, J. P. Sauvage*, J. Am. Chem. Soc. *97*, 6700 (1975).
[2] *J. M. Lehn*, Struct. Bonding *16*, 1 (1973); *J. M. Lehn, J. P. Sauvage, B. Dietrich*, J. Am. Chem. Soc. *92*, 2916 (1970); *J. M. Ceraso, J. L. Dye, ibid. 95*, 4432 (1973).
[3] *M. Eigen, L. De Maeyer* in *A. Weissberger*: Techniques of Chemistry, Vol. VI/2. Wiley, New York 1974, Chapter 3.
[4] *H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, R. Winkler*, Pure Appl. Chem. *20*, 93 (1969).

Synthesis and Structure Determination of a 1,4-Dialuminacyclohexadiene[**]

By *Heinz Hoberg, Vicente Gotor, Armin Milchereit, Carl Krüger*, and *Janine C. Sekutowski*[*]

Using (pentaphenyl)aluminacyclopentadiene[1], we have been able to investigate the influence of vinyl bound aluminum on the ligand properties of the C=C double bond towards transition metals[2]. We will now report on the synthesis, structure and some properties of a new type of model compound—1,4-diethyl-2,3,5,6-tetraphenyl-1,4-dialumina-2,5-cyclohexadiene *(1)*.

The reaction of the *cis*-dialuminum-ate complex *(2)*[3] with electrophiles should produce the intermediate *(3)* and, after the cleavage of R_3Al, either first *(4)* and then *(1)* or *(1)* directly. It was shown, however, that *(2)* can react with electrophiles in very different ways; reaction A occurs exclusively with alkyl halides (*e.g.* CH_3I) whereas reaction B is observed with $(CH_3)_3SiCl$ or $(C_2H_5)_2AlCl$ (molar ration 1:2) in polar solvents.



(2) *(3)* *(4)* *(1)*

In the second case a product is found in which Al:R = 1:1, this corresponds to *(4)* as well as to *(1)*. The molecular mass (560), which was determined vaporimetrically in benzene, decides in favor of *(1)*. Surprisingly, *(3)* cyclizes at as low a temperature as 20°C and not, as was at first expected, at a higher temperature. It still remains an open question as to whether the six-membered ring is formed according to the sequence *(3)* → *(4)* → *(1)* or to the sequence *(3)* → *(1)*.

The structure of the dialuminacyclohexadiene *(1)* was determined by an X-ray structural analysis from 3906 reflections (1644 unobserved). Cell data: $a = 10.0692(7)$, $b = 16.4599(9)$, $c = 12.0016(3)$ Å, $\beta = 68.708(3)°$. Since the space group is $P2_1/n$ where $Z = 2$, the molecule has a crystallographic inversion center. The Al_2C_4 ring (cf. Fig. 1) is planar, the Al atoms only deviate by 0.05 Å from the best plane and have a slightly deformed, tetrahedral coordination [CAlO 103.7(4), CAlC 114.5(8)°]. The Al—O [1.907(3) Å] as well as the Al—C [1.984(4) Å] bond lengths are similar to those found in (pentaphenyl)aluminacyclopentadiene[2b]. The C=C distance in *(1)* is 1.362(5) Å, the dihedral angle C10—C1C2′—C20′ is 7.52°, and the two phenyl rings are almost parallel with one another. The transannular distance Al1—Al1′ is 3.472(2) Å, *i.e.* there is no transannular bonding.

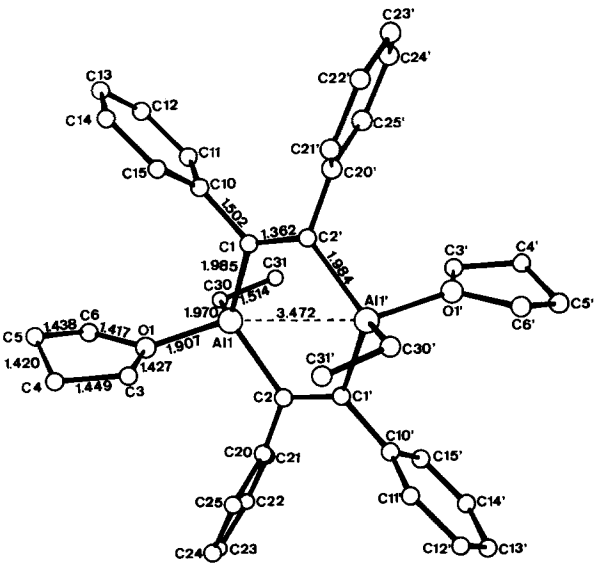


Fig. 1. Molecular structure of *(1)* and numbering of the atoms.

The organoaluminum compound *(1)* shows a striking behavior towards alkali metals in ether when *N,N,N′,N′*-tetramethylethylenediamine is added: *(1)* takes up four equivalents of lithium, during which neither elimination of Al[4] nor addition of Li to the C=C bonds[5] takes place but an *ortho*-metalation of the four phenyl groups occurs.

Experimental

A solution of trimethylchlorosilane (11.0 g, 101.8 mmol) in tetrahydrofuran (80 ml) is added drop by drop to *(2)* (23.0 g, 50.9 mmol)[3] in THF (250 ml) at 20°C over a period of 3 h. After approximately 15 h, the precipitated NaCl (5.8 g, 98 %) is filtered off; the solution is then concentrated under vacuum and the residue (17 g) is recrystallized from approximately 200 ml toluene. Yield: 13.7 g (88 %) *(1)*, m.p. 216 to 218°C.—^{1}H-NMR (C_4D_8O, 100 MHz, TMS int.): $\tau = 3.18$ (m; 20H, C_6H_5), 6.44 and 8.30 (m; 16H, $(CH_2)_4O$), 9.0 (t; 6H, CH_3—CAl).—MS: $m/e = 468$ [*(1)* − 2 THF].—Alcoholysis: after addition of 10 ml 2-ethylhexanol, 1.149 g (1.88 mmol) yield 80 Nml (3.57 mmol, 95 %) of ethane.—Hydrolysis: after addition of 20 ml 0.1 N H_2SO_4 and ether extraction, 0.68 g (3.78 mmol, 96%) *cis*-stilbene (GC) is formed from 1.2 g (1.96 mmol).

Received: May 12, 1977 [Z 734 IE]
German version: Angew. Chem. *89*, 563 (1977)

CAS Registry numbers:
(1), 63373-68-2; *(2)*, 43064-36-4

[*] Priv.-Doz. Dr. H. Hoberg, Dr. V. Gotor, A. Milchereit, Dr. C. Krüger [+], Dr. J. C. Sekutowski [+]
Max-Planck-Institut für Kohlenforschung
Postfach 011325, D-4330 Mülheim 1 (Germany)

[+] X-Ray structure analysis

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

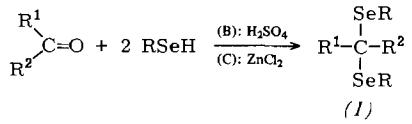
[1] *H. Hoberg, R. Krause-Göing*, J. Organomet. Chem. *127*, C29 (1977).
[2] a) *H. Hoberg, R. Krause-Göing, C. Krüger, J. C. Sekutowski*, Angew. Chem. *89*, 179 (1977); Angew. Chem. Int. Ed. Engl. *16*, 183 (1977); b) *C. Krüger, J. C. Sekutowski, H. Hoberg, R. Krause-Göing*, J. Organomet. Chem., in press.
[3] *H. Lehmkuhl, J. Culjković, H. Nehl*, Justus Liebigs Ann. Chem. *1973*, 666.
[4] *H. Lehmkuhl, K. Ziegler* in Houben-Weyl-Müller: Methoden der organischen Chemie, 4th Edit., Vol. XIII/4. Thieme, Stuttgart 1970, p. 125.
[5] 1 Mol of (pentaphenyl)aluminacyclopentadiene takes up 2 mol of lithium, which is added to a C=C bond, cf. [1].

Synthesis of Diselenoacetals and *O*-(Trimethylsilyl)-monoselenoacetals

By *Willy Dumont* and *Alain Krief*[*]

Methods for the synthesis of selenoacetals from carbonyl compounds have already been described[1, 2], but all demand drastic conditions [bubbling of HCl gas for 1 to 2 h (Method A)]. Moreover, the classical HCl method for the synthesis of phenylselenoacetals from aldehydes does not proceed as simply as described in the literature[1]. We have found that concentrated sulfuric acid (Method B) can be used with advantage for the synthesis of pure selenoacetals from aldehydes and selenophenol (see Table 1).

Zinc chloride[3] proved to be a very effective and mild reagent (Method C). It affords pure selenoacetals *(1)* in about 80 % yield from aldehydes or ketones and selenol (see Table 1).



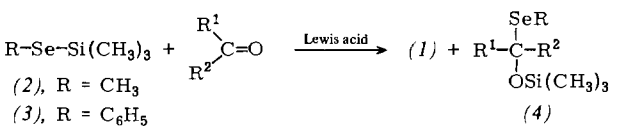
(1)

Table 1. Diselenoacetals *(1)* synthesized according to method B and method C.

R	R^1	R^2	Yield [%] [a]
C_6H_5	H	CH_3	70 (B), 89 (C)
C_6H_5	H	n-$C_{10}H_{21}$	75 (B)
C_6H_5	CH_3	CH_3	75 (B)
C_6H_5	$-CH_2(CH_2)_3CH_2-$		75 (B)
C_6H_5	H	n-C_6H_{13}	73 (B), 72 (C)
C_6H_5	CH_3	C_2H_5	85 (C)
p-ClC_6H_4	H	CH_3	82 (C)
p-ClC_6H_4	CH_3	CH_3	82 (C)
CH_3	H	n-C_6H_{13}	75 (C)
CH_3	CH_3	CH_3	90 (C)
n-C_4H_9	H	CH_3	60 (C)
n-$C_6H_{13}(CH_3)CH$	H	n-C_6H_{13}	60 (C)

[a] Yield of pure substance.

Methyl- and phenyl trimethylsilyl selenide [*(2)*[4] and *(3)*[5], resp.] do not react with carbonyl compounds at 25 °C or on heating (neither neat nor in solvents such as carbon tetrachloride, diethyl ether or acetonitrile). Selenoacetals are, however, obtained in high yield when half an equivalent of aluminum trichloride is added to a solution of two equivalents of *(2)* or *(3)* and one equivalent of the carbonyl compound in carbon tetrachloride. Interestingly, when magnesium bromide or, more so, when zinc chloride is used in place of $AlCl_3$, the *O*-(trimethylsilyl)monoselenoacetal *(4)* is also formed[6].



(2), R = CH_3
(3), R = C_6H_5

(4)

The hitherto unknown compounds of type *(4)* are also obtained on reacting carbonyl compounds and selenols in the presence of pyridine and chloro(trimethyl)silane[7] (see Table 2). These compounds can be used as starting material for the synthesis of α-halogenoalkyl selenides[8].

[*] Prof. Dr. A. Krief, Dr. W. Dumont
Département de Chimie, Facultés Universitaires
61, rue de Bruxelles, B-5000 Namur (Belgium)

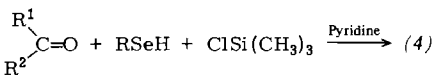


Table 2. Monoselenoacetals *(4)* synthesized from carbonyl compounds, selenol and chloro(trimethyl)silane in the presence of pyridine.

R	R^1	R^2	Yield [%] [a]
CH_3	n-C_6H_{13}	H	72
CH_3	n-C_4H_9	H	80
C_6H_5	CH_3	H	70
C_6H_5	n-C_3H_7	H	65
C_6H_5	n-C_6H_{13}	H	80
C_6H_5	CH_3	CH_3	50
CH_3	CH_3	CH_3	45

[a] Yield of pure substance.

Experimental

1,1-Bis(phenylseleno)heptane (method B): Concentrated sulfuric acid (6 ml) is added rapidly with stirring to a mixture of selenophenol (30 g, 0.19 mol) and heptanal (10.8 g, 0.094 mol) through which nitrogen is bubbled. The reaction is strongly exothermic and requires cooling with a water bath. After 30 min stirring, the mixture is diluted with ether (100 ml), washed with a dilute aqueous solution of sodium hydrogen carbonate, then with water, and finally dried over $MgSO_4$. To remove simultaneously formed diphenyl selenide an ethereal solution of the crude 1,1-bis(phenylseleno)heptane is slowly added under nitrogen and at 20 °C to a suspension of $LiAlH_4$ (1.5 g) in ether (150 ml). The mixture is refluxed for 30 min, cooled to 0 °C, and carefully treated with the minimum of an aqueous solution of KOH (50 %) until evolution of hydrogen has subsided. The mixture is rapidly filtered on celite and dried over $MgSO_4$. After purification (see below) and removal of ether there remains pure 1,1-bis(phenylseleno)-heptane in 73 % yield.

1,1-Bis(phenylseleno)heptane (method C): Heptanal (10.8 g, 0.094 mol) is slowly added under nitrogen to a solution of selenophenol (30 g, 0.19 mol) in CCl_4 (30 ml) in which is suspended anhydrous zinc chloride (6.8 g, 0.05 mol). After 3 hours' stirring at 20 °C the mixture is diluted with ether (100 ml), washed with an aqueous HCl solution (5 %) (2 times 50 ml), then with an aqueous solution of $NaHCO_3$, and finally with water. The organic phase is dried over $MgSO_4$, the solvent removed under vacuum and the crude product taken up in anhydrous ether. After treatment of the solution with $LiAlH_4$ as described above pure 1,1-bis(phenylseleno)heptane is obtained in 72 % yield.

1-Phenylseleno-1-(trimethylsiloxy)heptane: A solution of selenophenol (7.8 g, 0.05 mol) in pyridine (10 ml) is slowly added at 20 °C under nitrogen to a solution of anhydrous heptanal (5.7 g, 0.05 mol) and chloro(trimethyl)silane (7 g, 0.075 mol) in anhydrous pyridine (30 ml). After 12 hours' stirring at 20 °C, the mixture is diluted in carbon tetrachloride (100 ml), washed three times with 0.1 N NaOH, then with water, and finally dried over $MgSO_4$. Distillation of the filtrate affords 1-phenylseleno-1-(trimethylsiloxy)heptane in 80 % yield (b.p. 125–128 °C/0.1 torr).

Received: May 9, 1977 [Z 743a IE]
German version: Angew. Chem. *89*, 559 (1977)

CAS Registry numbers:
Table 1, compounds *(1)* from top to bottom: 26822-85-5; 53198-55-3; 35446-87-8; 53198-56-4; 60221-21-8; 56814-30-3; 62991-02-0; 62991-03-1; 56051-05-9; 56051-06-0; 26822-79-7; 62991-04-2; Table 2, compounds *(4)* from top to bottom: 62991-05-3; 62991-06-4; 62991-07-5; 62991-08-6; 62991-09-7; 62991-10-0; 62991-11-1; 34117-08-3; 33861-17-5; acetaldehyde, 75-07-0; undecanal, 112-44-7; 2-propanone, 67-64-1; cyclohexanone, 108-94-1; heptanal,

111-71-7; 2-butanone, 78-93-3; benzeneselenol, 645-96-5; *p*-chlorobenzeneselenol, 16645-10-6; methaneselenol, 6486-05-1; 1-butaneselenol, 16645-08-2; 2-octaneselenol, 62991-12-2; pentanal, 110-62-3; butanal, 123-72-8; chloro(trimethyl)silane, 75-77-4

[1] *D. Seebach, N. Peleties*, Chem. Ber. *105*, 511 (1972).—Under the experimental conditions described in this paper (starting from acetaldehyde, propanal or heptanal and selenophenol), we generally obtained after 2 hours' HCl bubbling a mixture of the desired selenoacetal, chloro(phenyl) selenide, an unknown compound and unreacted selenophenol, from which the selenoacetal can be isolated in less than 40% yield by thin-layer chromatography (SiO_2 Merck).

[2] *D. Van Ende, W. Dumont, A. Krief*, Angew. Chem. *87*, 709 (1975); Angew. Chem. Int. Ed. Engl. *14*, 700 (1975).

[3] $ZnCl_2$ seems to be consumed during the reaction. It has already been used successfully for the synthesis of thioacetals: *E. J. Corey, D. Seebach*, J. Org. Chem. *40*, 231 (1975).

[4] *J. W. Andersen, J. E. Drake*, Inorg. Nucl. Chem. Lett. *7*, 1007 (1971).

[5] *N. Ya. Derbach, N. A. Pasmusdeeva, E. S. Levchenko*, Zh. Org. Khim. *7* (7), 1543 (1971).

[6] The formation of *(1)* and/or *(4)* depends upon the reaction conditions (structure of the reactants, amount of Lewis acid, reaction times). We are currently investigating these features.

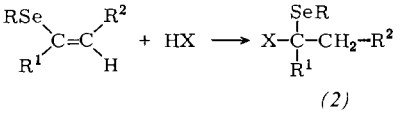
[7] *T. H. Chan, B. S. Ong*, Tetrahedron Lett. *1976*, 319, employed this method for the synthesis of the sulfur analogs. We thank Professor *Chan* for kindly providing the full experimental procedure.

[8] *A. Krief*, unpublished work.

α-Halogenoalkyl Selenides and α-(Phenylseleno)alkanide Anions

By *Willy Dumont, Mireille Sevrin*, and *Alain Krief*[*]

No general method for the synthesis of α-halogenoalkyl selenides *(2)*[1] has so far been described in the literature. We have found that these compounds can be obtained in quantitative yields by addition of gaseous HCl or HBr in benzene to vinyl selenides *(1)*[6]. (Method A, see Table 1) or by treatment of a mixture of an aldehyde and selenophenol with a saturated solution of gaseous HBr in benzene in the presence of anhydrous calcium chloride (Method B, see Table 2)[7].



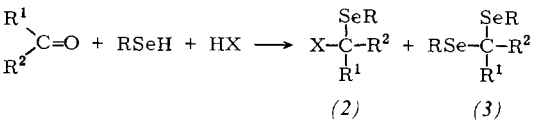
(A)

(2)

Table 1. α-Halogenoalkyl selenides *(2)* synthesized by Method A. In each case the yield is about 95%.

R	R^1	R^2	X
C_6H_5	H	H	Cl
C_6H_5	H	H	Br
C_6H_5	H	n-C_9H_{19}	Cl
C_6H_5	H	n-C_9H_{19}	Br
C_6H_5	H	n-C_5H_{11}	Cl
C_6H_5	H	n-C_5H_{11}	Br
C_6H_5	CH_3	H	Cl
C_6H_5	CH_3	H	Br
C_6H_5	CH_3	n-C_5H_{11}	Cl
C_6H_5	CH_3	n-C_5H_{11}	Br
CH_3	H	n-C_9H_{19}	Cl
CH_3	H	n-C_9H_{19}	Br
CH_3	H	n-C_5H_{11}	Cl
CH_3	H	n-C_5H_{11}	Br
CH_3	CH_3	n-C_5H_{11}	Br

[*] Prof. Dr. A. Krief, Dr. W. Dumont, Dipl.-Chem. M. Sevrin
Département de Chimie, Facultés Universitaires
61, rue de Bruxelles, B-5000 Namur (Belgium)



(B)

(2) *(3)*

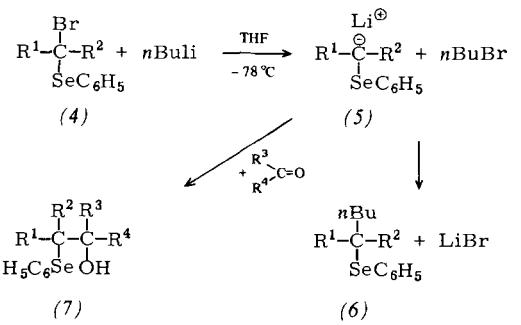
Table 2. Compounds synthesized by Method B.

R	R^1	R^2	X	Yield [%] [a] *(2)*	Yield [%] [a] *(3)*
C_6H_5	H	CH_3	Cl	40	23
C_6H_5	H	CH_3	Br	93	0
C_6H_5	H	n-C_5H_{11}	Br	90	0
C_6H_5	H	n-$C_{10}H_{21}$	Cl	40	15
C_6H_5	H	n-$C_{10}H_{21}$	Br	91	0
C_6H_5	CH_3	CH_3	Br	55	20
C_6H_5	CH_3	C_2H_5	Cl	0	40
CH_3	CH_3	CH_3	Cl	0	45
CH_3	CH_3	CH_3	Br	0	45
CH_3	H	n-$C_{10}H_{21}$	Cl	45	20
CH_3	H	n-$C_{10}H_{21}$	Br	54	17

[a] Determined by NMR analysis of the crude product mixture.

α-Bromoalkyl phenyl selenides *(4)* react rapidly (1 to 3 min) with n-butyllithium at −78 °C in tetrahydrofuran[3] with preferred cleavage of the Br—C bond and formation of the α-(phenylseleno)alkanide anions *(5)*[9]. On prolonged stirring of the reaction mixture at −78 °C these anions react with 1-bromobutane present in the medium to give *(6)*. The carbanion *(5)* in which R^1 and R^2 are both alkyl groups is much more reactive [90% yield of *(6)* after 1 h] than the parent compound *(5)* with $R^1 = R^2 = H$. Rapid hydrolysis of *(5)* or reaction with haloalkanes, which are more reactive than 1-bromo-n-butane, leads to variously substituted selenides.

Interestingly, aldehydes and ketones react much more rapidly with *(5)* than 1-bromo-n-butane. The β-(phenylseleno)-α-alkanols *(7)* are obtained in high yields (see Table 3). Olefins[10] and epoxides[11] are readily accessible from *(7)*. The advantages of this method starting from *(4)* are the ready accessibility of the starting material and the fact that the end product is not contaminated by undesirable butyl phenyl selenide (which is formed on reaction of selenoacetals with n-butyllithium).



(4) *(5)* *(7)* *(6)*

Table 3. Synthesized compounds of type *(7)*.

R^1	R^2	R^3	R^4	Yield [a] [%]
n-C_6H_{13}	H	H	n-C_6H_{13}	63
CH_3	H	H	n-C_6H_{13}	69
H	H	H	n-C_6H_{13}	70
CH_3	H	CH_3	CH_3	62
H	H	CH_3	CH_3	75
CH_3	CH_3	H	n-C_6H_{13}	62

[a] Yield of pure substance.

Other α-halogenoalkyl selenides, including the closely related α-bromoalkyl methyl selenides and α-chloroalkyl selenides, react differently under the same reaction conditions. First results show that *n*-butyllithium attacks at the selenium atom, and thus indicate that this reaction could open a new synthetic route to carbenes.

Experimental

1-Bromoethyl phenyl selenide by Method A: To 10 ml of benzene saturated with anhydrous HBr is added 1 mmol of phenyl vinyl selenide dissolved in 2 ml of benzene. The mixture is stirred at 20 °C for 2 h. Evaporation of benzene under vacuum leads to NMR-spectroscopically pure 1-bromoethyl phenyl selenide in 95% yield. Attempts to distill or chromatograph compounds *(2)* (with the exception of the bromo- and chloromethyl phenyl selenides) resulted in complete decomposition of the products. The chloro derivatives are stable at 0 °C for 1 month; the bromo analogs, especially those with R^1 and R^2 = alkyl, are less stable.

1-Bromoethyl phenyl selenide by Method B: To 10 ml of benzene saturated with anhydrous HBr and containing calcium chloride (1 g) is added a mixture of acetaldehyde (1 mmol) and selenophenol (1 mmol) in benzene (2 ml). After 2 h at 20 °C the mixture is filtered and the benzene removed by evaporation under vacuum. NMR spectroscopically pure 1-bromoethyl phenyl selenide is obtained in 93% yield.

2-(Phenylseleno)nonan-3-ol: *n*-Butyllithium (1 mmol) (2 N in hexane, Merck) is added at −78 °C under nitrogen to a solution of 1-bromoethyl phenyl selenide (1 mmol) in anhydrous tetrahydrofuran (10 ml). After 3 min (−78 °C), heptanal (1 mmol) in THF (2 ml) is added and the resulting solution is stirred for 2 h at −78 °C and 1 h at 25 °C. After hydrolysis and preparative thin-layer chromatography the alcohol *(7)* is obtained in 69% yield.

Received: May 9, 1977 [Z 743b IE]
German version: Angew. Chem. *89*, 561 (1977)

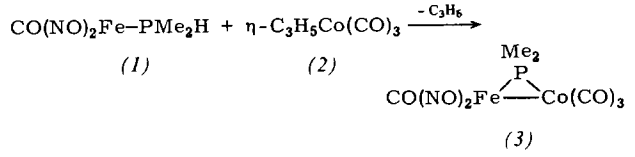
CAS Registry numbers:
(1), R = C_6H_5, R^1 = R^2 = H, 35167-28-3; *(1)*, R = C_6H_5, R^1 = H, R^2 = *n*-C_9H_{19}, 63017-55-0; *(1)*, R = C_6H_5, R^1 = H, R^2 = *n*-C_5H_{11}, 63017-56-1; *(1)*, R = C_6H_5, R^1 = CH_3, R^2 = H, 63017-57-2; *(1)*, R = C_6H_5, R^1 = CH_3, R^2 = *n*-C_5H_{11}, 63017-58-3; *(1)*, R = CH_3, R^1 = H; R^2 = *n*-C_9H_{19}, 63017-59-4; *(1)*, R = CH_3, R^1 = H, R^2 = *n*-C_5H_{11}, 63017-60-7; *(1)*, R = R^1 = CH_3, R^2 = *n*-C_5H_{11}, 63017-61-8; *(2)*, R = C_6H_5, R^1 = R^2 = H, X = Cl, 63017-68-5; *(2)*, R = C_6H_5, R^1 = H, R^2 = *n*-C_9H_{19}, X = Cl, 63017-69-6; *(2)*, R = C_6H_5, R^1 = H, R^2 = *n*-C_9H_{19}, X = Br, 63017-70-9; *(2)*, R = C_6H_5, R^1 = H, R^2 = *n*-C_5H_{11}, X = Cl, 63017-71-0; *(2)*, R = C_6H_5, R^1 = CH_3, R^2 = H, X = Cl, 63017-72-1; *(2)*, R = C_6H_5, R^1 = CH_3, R^2 = *n*-C_5H_{11}, X = Cl, 63017-73-2; *(2)*, R = C_6H_5, R^1 = CH_3, R^2 = *n*-C_5H_{11}, X = Br, 63017-74-3; *(2)*, R = CH_3, R^1 = H, R^2 = *n*-C_9H_{19}, X = Cl, 63017-75-4; *(2)*, R = CH_3, R^1 = H, R^2 = *n*-C_9H_{19}, X = Br, 63017-76-5; *(2)*, R = CH_3, R^1 = H, R^2 = *n*-C_5H_{11}, X = Cl, 63017-77-6; *(2)*, R = CH_3, R^1 = H, R^2 = *n*-C_5H_{11}, X = Br, 63017-78-7; *(2)*, R = R^1 = CH_3, R^2 = *n*-C_5H_{11}, X = Br, 63017-79-8; *(3)*, R = C_6H_5, R^1 = H, R^2 = CH_3, X = Cl, 26822-85-5; *(3)*, R = C_6H_5, R^1 = H, R^2 = *n*-$C_{10}H_{21}$, X = Cl, 53198-55-3; *(3)*, R = C_6H_5, R^1 = R^2 = CH_3, X = Br, 35446-87-8; *(3)*, R = C_6H_5, R^1 = CH_3, R^2 = C_2H_5, X = Cl, 56814-30-3; *(3)*, R = R^1 = R^2 = CH_3, X = Cl, 56051-06-0; *(3)*, R = CH_3, R^1 = H, R^2 = *n*-$C_{10}H_{21}$, X = Cl, 63017-80-1; *(4)*, R^1 = *n*-C_6H_{13}, R^2 = H, 63017-62-9; *(4)*, R^1 = CH_3, R^2 = H, 60466-51-5; *(4)*, R^1 = R^2 = H, 60466-50-4; *(4)*, R^1 = R^2 = CH_3, 63017-63-0; *(5)*, R^1 = *n*-C_6H_{13}, R^2 = H, 63017-64-1; *(5)*, R^1 = CH_3, R^2 = H, 53198-50-8; *(5)*, R^1 = R^2 = H, 22859-62-7; *(5)*, R^1 = R^2 = CH_3, 53230-01-6; *(6)*, R^1 = *n*-C_6H_{13}, R^2 = H, 63017-65-2; *(6)*, R^1 = CH_3, R^2 = H, 23170-96-9; *(6)*, R^1 = R^2 = H, 63017-66-3; *(6)*, R^1 = R^2 = CH_3, 63017-67-4; *(7)*, R^1 = R^4 = *n*-C_6H_{13}, R^2 = R^3 = H, 60245-62-7; *(7)*, R^1 = CH_3, R^2 = R^3 = H, R^4 = *n*-C_6H_{13}, 53188-74-2; *(7)*, R^1 = R^2 = R^3 = H, R^4 = *n*-C_6H_{13}, 52954-45-7; *(7)*, R^1 = R^3 = R^4 = CH_3, R^2 = H, 63017-81-2; *(7)*, R^1 = R^2 = H, R^3 = R^4 = CH_3, 28897-11-2; *(7)*, R^1 = R^2 = CH_3, R^3 = H, R^4 = *n*-C_6H_{13}, 53188-72-0; acetaldehyde, 75-07-0; heptanal, 66-25-1; undecanal, 112-44-7; 2-propanone, 67-64-1; 2-butanone, 78-93-3; benzeneselenol, 645-96-5; methaneselenol, 6486-05-1; 1-bromobutane, 109-65-9; heptanal, 111-71-7

[1] Previous syntheses: Chloromethyl phenyl selenide [2, 5], bromomethyl phenyl selenide [3—5], 1-bromomethyl phenyl selenide [4].
[2] *U. Schöllkopf, H. Küppers*, Tetrahedron Lett. *1963*, 105.
[3] *H. J. Reich, S. K. Shah*, J. Am. Chem. Soc. *97*, 3250 (1975), Ref. 13.
[4] From phenylselenium bromide and diazoalkane: *N. Petragnani, R. Rodriguez, J. V. Comasseto*, J. Organomet. Chem. *114*, 281 (1976).
[5] We found that bromo- and chloromethyl phenyl selenide can be obtained in 60% yield (together with *ca.* 18% selenoacetal) by reaction of dibromo- or dichloromethane with selenophenol under the conditions of phase transfer catalysis or with stoichiometric amounts of trimethylamine, the dihalomethane also being used as solvent in both cases.
[6] *H. J. Reich, F. Chow*, J. Chem. Soc. Chem. Commun. *1975*, 790; *A. Krief*, unpublished.
[7] α-Halogenoalkyl selenides were obtained in 60—90% yield by reaction of *O*-(trimethylsilyl)monoselenoacetals [8] with anhydrous HCl or HBr in dichloromethane at 20 or even −78 °C.
[8] *W. Dumont, A. Krief*, Angew. Chem. *89*, 559 (1977); Angew. Chem. Int. Ed. Engl. *16*, 540 (1977).
[9] Together with 10 to 15% butyl phenyl selenide formed by cleavage of the Se—C bond and, in some cases, also phenyl vinyl selenide (< 5%) arising from HBr elimination.
[10] *J. Remion, A. Krief*, Tetrahedron Lett. *1976*, 3843, and references cited therein.
[11] *W. Dumont, A. Krief*, Angew. Chem. *87*, 347 (1975); Angew. Chem. Int. Ed. Engl. *14*, 350 (1975).

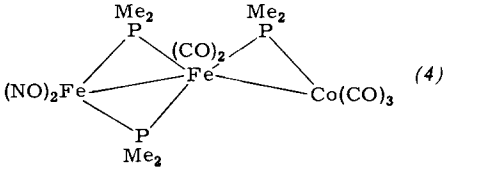
Phosphorus-Bridged Trinuclear Complexes Having Contiguous Metal-Metal Bonds[**]

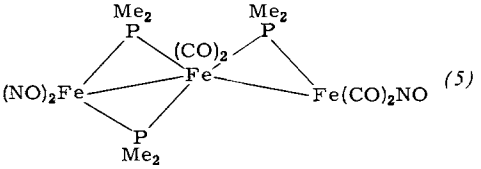
By *Egbert Keller* and *Heinrich Vahrenkamp*[*]

The metal-metal bond lengths in phosphorus- and arsenic-bridged dinuclear complexes can be modified by variation of the nature and number of the ligands, thus permitting some degree of control of the reactivity of such complexes[1]. We have now attempted to synthesize the hetero-dinuclear complex *(3)*, for which we expect a particularly short metal-metal bond, from *(1)* and *(2)* by the propene elimination method[2].



However, the reaction did not lead to *(3)*, but instead, as a result of rearrangements and exchange reactions, to several mononuclear complexes and the two new trinuclear complexes *(4)* and *(5)*.





[*] Prof. Dr. H. Vahrenkamp, Dipl.-Chem. E. Keller
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Computing Center of the University.

The crystallographic data[3] and the molecular dimensions of *(4)* and *(5)* are almost identical. We thus have one of those rare cases in which analyses and spectra[4] are more significant in identifying the compounds than structure determination. The most important structural characteristic of *(4)* and *(5)* is the contiguous metal-metal bonding (bond angle of 160° at the central iron atom) and the three bridging dimethylphosphido ligands (Fig. 1).

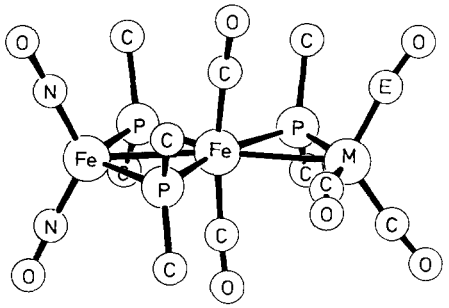


Fig. 1. Molecular structure of the trinuclear complexes *(4)* [M = Co, E = C; Fe—Fe = 2.67, Fe—M = 2.66 Å] and *(5)* [M = Fe, E = N; Fe—Fe = 2.66, Fe—M = 2.71 Å].

Neutral trinuclear complexes containing two consecutive base-bridged metal-metal bonds have not previously been reported. The stability of *(4)* and *(5)* seems to arise from the ability of the good π-acceptor ligands CO and NO to mop up the excess electron density caused by the bridging atoms which weakens the metal-metal bond[5]; other complexes of this kind[5, 6] require positive charges and 16-electron central metals for this purpose. The fact that all three metal atoms in *(4)* and *(5)* are coordinated differently is also unusual.

The failure of *(3)* to be formed is attributed, as in other cases[7], to the ligand sphere of this complex being too open, making it energetically less favorable than simpler complexes containing more ligands. On the other hand, a low number of ligands is an essential prerequisite for the aggregation observed in the formation of *(4)* and *(5)*. The formation of phosphorus-bridged clusters should therefore be feasible with *(1)* and *(2)* and reactants containing even fewer ligands.

Procedure

A mixture of *(1)* (2.5 g, 12 mmol) and *(2)* (2.0 g, 11 mmol) is stirred without a solvent for 2 d; 170 cm^3 of gas (propene, carbon monoxide) is evolved. After pumping off 1.3 g (70%) of $Co(NO)(CO)_3$ the reaction mixture is chromatographed on silica gel. Elution with cyclohexane successively gives $(CO)_4Fe(\mu\text{-}PMe_2)Co(CO)_3$, $[(CO)_3Fe\text{-}\mu\text{-}PMe_2]_2$, and $[(NO)_2Fe\text{-}\mu\text{-}PMe_2]_2$. The fourth, reddish-violet fraction eluted with benzene/cyclohexane (1 : 3) gives brown compound *(4)* (yield 420 mg, 13%; m.p. 182 °C) on recrystallization from benzene. The fifth, brown fraction gives the brown compound *(5)* (yield 15 mg, 0.7%; m.p. 162 °C) from hexane.

Received: May 20, 1977 [Z 744 IE]
German version: Angew. Chem. *89*, 568 (1977)

CAS Registry numbers:
(1), 63105-21-5; *(2)*, 12144-85-3; *(3)*, 63133-65-3; *(4)*, 63105-22-6; *(5)*, 63105-23-7; $(CO)_4Fe(\mu\text{-}PMe_2)Co(CO)_3$, 62589-30-4; $[(CO)_3Fe\text{-}\mu\text{-}PMe_2]_2$, 14811-43-3; $[(NO)_2Fe\text{-}\mu\text{-}PMe_2]_2$, 63105-24-8

[1] *E. Keller, H. Vahrenkamp*, Chem. Ber. *110*, 430 (1977); *H. J. Langenbach, H. Vahrenkamp, ibid. 110*, 1195, 1206 (1977); *H. J. Langenbach, E. Keller, H. Vahrenkamp*, Angew. Chem. *89*, 197 (1977); Angew. Chem. Int. Ed. Engl. *16*, 188 (1977).

[2] *B. C. Benson, R. Jackson, K. K. Joshi, D. T. Thompson*, Chem. Commun. *1968*, 1506.

[3] Both triclinic, Pī, $Z = 1$. *(4)*: $a = 8.479(9)$, $b = 9.482(13)$, $c = 8.482(6)$ Å, $\alpha = 95.85(9)$, $\beta = 112.00(7)$, $\gamma = 115.33(8)°$; 1212 reflections, $R = 0.085$. *(5)*: $a = 8.465(8)$, $b = 9.479(10)$, $c = 8.447(8)$ Å, $\alpha = 94.81(8)$, $\beta = 112.06(7)$, $\gamma = 116.36(8)°$; 1387 reflections, $R = 0.083$.

[4] The complexes were characterized by C, H, N, and metal analyses. ^1H- and ^{31}P-NMR, IR, and mass spectra are available. The ^{31}P-NMR spectra, displaying an ABX system, are particularly informative.

[5] *R. J. Haines, R. Mason, J. A. Zubieta, C. R. Nolte*, J. Chem. Soc. Chem. Commun. *1972*, 990.

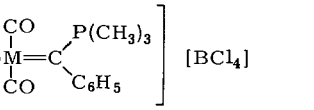
[6] *W. E. Douglas, M. L. H. Green*, J. Chem. Soc. Dalton Trans. *1972*, 1796.

[7] *W. Ehrl, H. Vahrenkamp*, J. Organomet. Chem. *63*, 389 (1973).

Molecular Structure of $[\eta\text{-}C_5H_5(CO)_2Re{=}C(C_6H_5)P(CH_3)_3][BCl_4]$ [**]

By *Fritz R. Kreissl* and *Peter Friedrich*[*]

Depending upon the ligand in the "*trans*-position" to the carbyne ligand, neutral or cationic carbonyl-carbyne complexes of chromium, molybdenum, tungsten, manganese, and rhenium[1] react with trimethylphosphane to give η^1- and η^2-ketenyl derivatives[2], dinuclear complexes with ylide bridges[3], or neutral or cationic, metal-substituted phosphorus ylides[4]. Spectroscopic data for the last-named organometallic compounds indicate predominance of structure *(1)* in the resonance hybrid[4].



(1a), M = Mn
(1b), M = Re

This kind of bonding has now been verified for *(1b)* by what we believe to be the first X-ray structure analysis[5] of a cationic transition-metal-substituted phosphorus ylide (cf. Fig. 1).

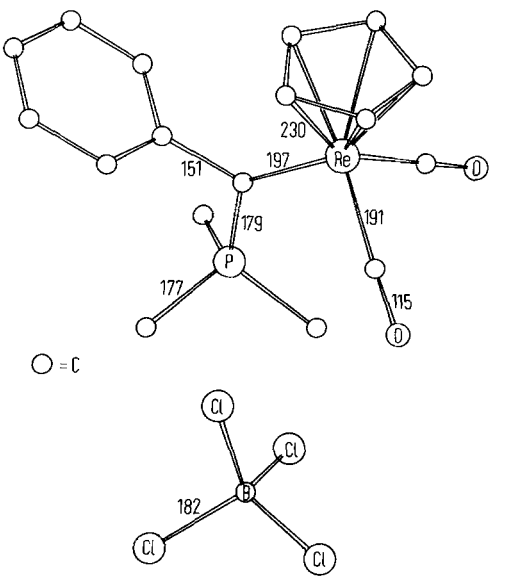


Fig. 1. Structure of the ylide complex *(1b)* (distances in pm).

[*] Dr. F. R. Kreissl, Dipl.-Chem. P. Friedrich
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

In *(1b)* the rhenium atom exhibits pseudooctahedral coordination, the bond angles and the distances to the carbonyl groups and to the cyclopentadienyl ring having the usual values[6].

The pronounced double bonding character of the M=C linkage suggested by the ^{13}C-NMR signal of the methylene carbon atom [$\delta = 262.2$ ppm, $^1J(^{31}P\text{-}^{13}C) = 14.7$ Hz] is confirmed by the rhenium-carbon distance of 197(1) pm. This bond is shorter than the tungsten-carbene carbon bond (213–215 pm[7]) found by *Casey et al.* for the isoelectronic complex $(CO)_5WC(C_6H_5)_2$, and can likewise be explained in terms of $d(M)_\pi$-$p(C)_\pi$ interaction. The sp^2-hybridized methylene carbon atom is almost coplanar with rhenium, phosphorus, and C-1 of the phenyl substituent. Opening of the Re—$C_{methylene}$—P bond to 128.2° is probably due to steric hindrance between the $C_5H_5(CO)_2Re$ unit and the $(CH_3)_3P$ group.

The phosphorus-methylene carbon bond length of 179(1) pm in *(1b)* is considerably greater than that of the corresponding bond in $(C_6H_5)_3P{=}CH_2$, *i.e.* 166.1 pm[8]; it is comparable with the three P—C_{methyl} bonds [176(2) to 180(2) pm] within the standard deviation and can be regarded as a single bond.

Received: May 27, 1977 [Z 749 IE]
German version: Angew. Chem. *89*, 553 (1977)

CAS Registry numbers:
(1a), 63181-55-5; *(1b)*, 63181-57-7; ^{13}C, 14762-74-4

[1] *E. O. Fischer, U. Schubert*, J. Organomet. Chem. *100*, 59 (1975); *E. O. Fischer, E. W. Meineke, F. R. Kreissl*, Chem. Ber. *110*, 1140 (1977); earlier references cited therein.

[2] *F. R. Kreissl, A. Frank, U. Schubert, T. L. Lindner, G. Huttner*, Angew. Chem. *88*, 649 (1976); Angew. Chem. Int. Ed. Engl. *15*, 632 (1976); *F. R. Kreissl, P. Friedrich, G. Huttner, ibid. 89*, 110 (1977) and *16*, 102 (1977); *F. R. Kreissl, K. Eberl, W. Uedelhoven*, Chem. Ber., in press.

[3] *F. R. Kreissl, P. Friedrich, T. L. Lindner, G. Huttner*, Angew. Chem. *89*, 325 (1977); Angew. Chem. Int. Ed. Engl. *16*, 314 (1977).

[4] *F. R. Kreissl, P. Stückler, E. W. Meineke*, Chem. Ber., in press; earlier references cited therein.

[5] 1834 diffraction data ($I \geq 3\sigma$, Syntex P21/XTL); monoclinic, space group $P2_1/c$, with $a = 1471.5$, $b = 1401.9$, $c = 1119.6$ pm, $\beta = 104.2°$, $V = 2239.6 \times 10^6$ pm^3; $R = 0.039$. The C_5H_5 ring is disordered.

[6] *E. O. Fischer, T. L. Lindner, G. Huttner, P. Friedrich, F. R. Kreissl*, Chem. Ber., in press.

[7] *C. P. Casey, T. J. Burkhardt, C. A. Bunnell, J. C. Calabrese*, J. Am. Chem. Soc. *99*, 2127 (1977).

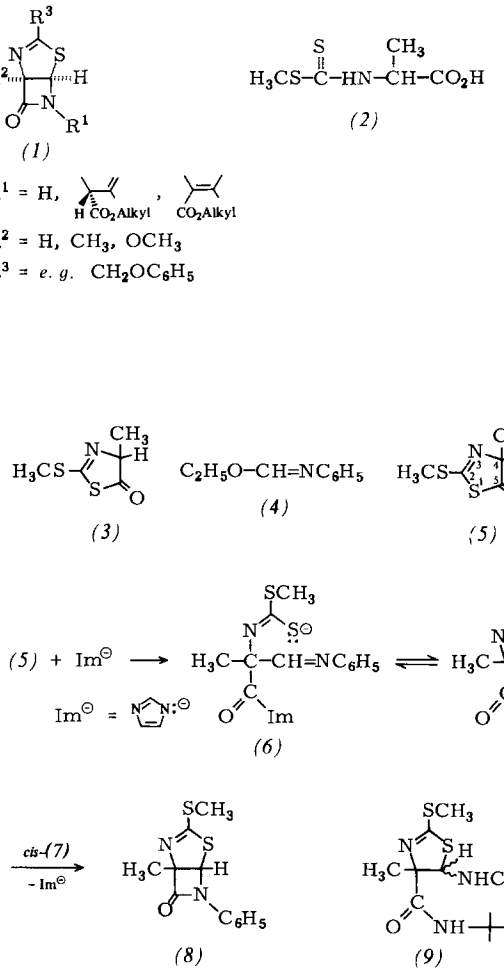
[8] *J. C. J. Bart*, Angew. Chem. *80*, 697 (1968); Angew. Chem. Int. Ed. Engl. *7*, 730 (1968).

A New *cis*-Stereospecific β-Lactam Ring Closure[**]

By *Edgar Raude* and *Dieter Hoppe*[*]

4-Thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones ("azetidinone-thiazolines") *(1)* are of utility in the synthesis of cephalosporins and penicillins[1], since the thiazoline ring protects acylamino and thio groups and, moreover, fixes them in a *cis*-orientation. We have now synthesized a compound of this type in only two steps from a Δ^2-thiazolin-5-one.

4-Methyl-2-methylthio-Δ^2-1,3-thiazolin-5-one *(3)*, obtained by cyclodehydration of 2-[(methylthio)thiocarbonylamino]-propionic acid[2] *(2)* with dicyclohexylcarbodiimide[3], was subjected to pyridine-catalyzed condensation with *O*-ethyl *N*-phenylformimidate[4] *(4)* to give the imine[5] *(5)* [67% yield; IR (film): 1725 (C=O), 1635 and 1550 cm^{-1} (both C=N); ^{1}H-NMR ($CDCl_3$): $\tau = 2.37$ (s, CH), 7.42 (s, SCH_3), 8.33 (s, CH_3)]. On heating with a suspension of sodium imidazolide (prepared *in situ* from imidazole and sodium hydride), *(5)* rearranges to the β-lactam[5] *(8)*, yield 88%. The IR data [(film): 1750 (C=O), 1540 (C=N)], the ^{1}H-NMR spectrum [($CDCl_3$): $\tau = 4.39$ (s, 5-H), 7.49 (s, SCH_3), 8.26 (s, CH_3)], as well as the loss of phenyl isocyanate in the mass spectrum[6], all evidence structure *(8)*.



Presumably, primary cleavage of the thiazolinone *(5)* gives the acylimidazolide *(6)*, which is in equilibrium with its (diastereomeric) cyclic tautomers *(7)*, of which only *cis*-*(7)* reacts further to give the bicyclic *(8)*. We interpret formation of the 5-amino-Δ^2-thiazoline-4-carboxamide[5, 7] *(9)* by irreversibly occurring addition of *tert*-butylamine and *(5)* (30 min at 25 °C, in dichloromethane) as indicating the above reaction course.

Experiments are in progress with the aim of extending this β-lactam synthesis to those formidic esters whose nitrogen atoms bear groups that are either suitable for cyclization or replacement by hydrogen.

4-Methyl-2-methylthio-4-(N-phenylimino)methyl-Δ^2-1,3-thiazolin-5-one: A solution of freshly distilled[8] *(3)*[3] (8.1 g, 0.05 mol), *(4)*[4] (7.5 g, 0.05 mol), and pyridine (0.8 g, 20 mol %) in anhydrous benzene (100 ml) is distilled over a packed column for 18 h, a benzene/ethanol mixture being drawn off at the head of the column (*ca.* 10 ml/min). The volume is maintained above 50 ml by addition of benzene. Rapid short-path distillation of the residue gives compound *(5)* (8.8 g, 67%), b.p. 145 to 148 °C/0.05 torr, as a viscous oil.

[*] Dr. D. Hoppe, Dipl.-Chem. E. Raude
Organisch-chemisches Institut der Universität
Tammannstrasse 2, D-3400 Göttingen (Germany)

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

1-Methyl-3-methylthio-6-phenyl-4-thia-2,6-diazabicyclo-[3.2.0]hept-2-en-7-one (8): A suspension of *(5)* (0.66 g, 2.5 mmol), imidazole (0.17 g, 2.5 mmol), and sodium hydride (0.060 g, 2.5 mmol) in anhydrous benzene (15 ml) and tetrahydrofuran (1 ml) is heated to boiling with vigorous stirring under N_2 for 5 h; the residue is extracted with hot benzene, and compound *(8)* (0.58 g, 88 %) is isolated from the filtrate; m.p. 126 to 127 °C (from methanol).

Received: May 4, 1977;
revised: May 27, 1977 [Z 750 IE]
German version: Angew. Chem. 89, 553 (1977)

CAS Registry numbers:
(3), 63148-45-8; *(4)*, 6780-49-0; *(5)*, 63148-46-9; *(8)*, 63148-47-0

[1] a) *R. D. G. Cooper, F. L. José*, J. Am. Chem. Soc. *92*, 2575 (1970); b) *J. E. Baldwin, F. J. Urban, R. D. G. Cooper, F. L. José, ibid. 95*, 2401 (1973); c) *S. Nakatsuka, H. Tanino, Y. Kishi, ibid. 97*, 5008, 5010 (1975); *H. Tanino, S. Nakatsuka, Y. Kishi*, Tetrahedron Lett. *1976*, 581; d) *G. Franceschi, M. Foglio, P. Masi, A. Suarato, G. Palmidessi, L. Bernardi, F. Arcamone, G. Cainelli*, J. Am. Chem. Soc. *99*, 248 (1977).
[2] Prepared from potassium alaninate, carbon disulfide, and methyl iodide in a procedure resembling that of *A. H. Cook, G. Harris, I. Heilbronn, G. Shaw*, J. Chem. Soc. *1948*, 1056.
[3] *J. H. Davies, R. H. Davis*, DOS 2205861 (1972), Shell Internationale Research Maatschappij, N. V.; Chem. Abstr. *77*, 140039 (1972).
[4] *L. Claisen*, Justus Liebigs Ann. Chem. *287*, 360 (1895).
[5] Correct C, H analyses were obtained.
[6] Concerning the mass spectra of *(1)*, cf. [1b].
[7] 4:3 mixture of diastereomers, yield 74 %. IR (film): 3360 and 3320 (NH), 1660 and 1460 (N—C=O), 1540 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): $\tau = 3.77$ and 5.86, as well as 4.43 and 4.93 (d, $J = 11$ Hz, 5-H and 5-NH).
[8] On storage, *(3)* dimerizes to 4-methyl-2-methylthio-1,3-thiazol-5-yl 2-[(methylthio)thiocarbonylamino]propionate but is regenerated quantitatively on distillation.

Dichloronitronium Hexachloroantimonate, $ONCl_2^{\oplus}SbCl_6^{\ominus}$

By *Kurt Dehnicke, Henning Aeissen, Marianne Kölmel*, and *Joachim Strähle*[*]

The dichloronitronium ion, which is isoelectronic with phosgene, was until now unknown. We have now synthesized this cation in the form of its hexachloroantimonate by reacting nitrogen trichloride with antimony pentachloride in the presence of sulfinyl chloride:

$$NCl_3 + SbCl_5 + SOCl_2 \xrightarrow{CCl_4} ONCl_2^{\oplus}SbCl_6^{\ominus} + SCl_2$$
(1)

The salt *(1)* forms shining, pale-yellow, hygroscopic crystals which are sparingly soluble in CCl_4 and stable up to 145 °C. Vacuum thermolysis yields nitrosyl hexachloroantimonate with the cleavage of chlorine:

$$ONCl_2^{\oplus}SbCl_6^{\ominus} \rightarrow NO^{\oplus}SbCl_6^{\ominus} + Cl_2$$

We have characterized *(1)* by elemental analysis, IR and Raman spectra as well as by a crystal structure analysis. It is the first NCl_2 compound with a pentavalent nitrogen atom.

The crystal structure (1817 symmetry-independent reflections, R = 4.26 %)[1] consists of almost undistorted $SbCl_6^{\ominus}$ octahedra and nearly completely planar $ONCl_2^{\oplus}$ ions (maximum deviation from the plane 0.038 Å). The unit cell contains two symmetry-independent sorts of cations, the differences between which lie within the range of their standard deviations (Table 1).

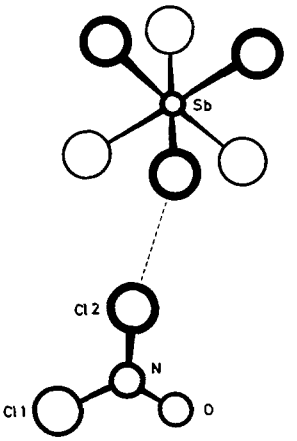


Fig. 1. Representation of an ion pair $NOCl_2^{\oplus}SbCl_6^{\ominus}$ in parallel projection [100]. The symmetry-independent ion pairs contained in the unit cell differ only very slightly from one another, therefore only the type II cation and the anion belonging to it are shown.

Table 1. Bond lengths [Å] and bond angles [°] of the $ONCl_2^{\oplus}$ ion.

Bond lengths, angles	Type I	Type II
N—O	1.30 (2)	1.32 (2)
N—Cl1	1.61 (2)	1.64 (2)
N—Cl2	1.72 (2)	1.69 (2)
Cl1—Cl2	2.857 (7)	2.851 (7)
O—Cl1	2.570 (15)	2.605 (16)
O—Cl2	2.599 (16)	2.590 (16)
Cl1—N—Cl2	118 (1)	118 (1)
O—N—Cl1	124 (2)	124 (1)
O—N—Cl2	118 (1)	119 (1)

The NO bond length in $ONCl_2^{\oplus}$ is 1.31 Å and lies between the length of a NO double bond (NO gas: 1.151 Å)[2] and that of a NO single bond (H_2N—OH: 1.47 Å)[3]; when compared with $OCCl_2$ (CO bond length = 1.166 Å)[4a], this represents a significant reduction in the π bond contribution. On the other hand the NCl bond lengths, with a mean value of 1.665 Å, are noticeably shorter than those in NCl_3 (1.75 Å)[5] and *N*-chlorosuccinimide (1.69 Å)[6], so that the NCl bond has a π bond contribution. The different sizes of the N—Cl1 and N—Cl2 bond lengths (1.63 and 1.71 Å respectively) are worthy of note, they produce the C_s-symmetry of the $ONCl_2^{\oplus}$ ion and are caused by a cation-anion interaction as indicated in Figure 1. The Cl atom of the long N—Cl bond is an average distance of 3.33 Å away from one of the Cl atoms of the $SbCl_6^{\ominus}$ ion—a distance which is smaller than the van der Waals bond length (3.5—3.6 Å) and corresponds to an ion pair. The effect is comparable with the intermolecular Cl...Cl interactions as observed in the crystal structures of Cl_2 (3.34 Å)[7], NCl_3 (3.37 and 3.42 Å)[5] and Cl_3VNCl (3.25 Å)[8].

The vibrational spectrum of *(1)* is in agreement with the crystallographic findings (Table 2). The bands expected for the O_h symmetry of the $SbCl_6^{\ominus}$ ion are observed [Raman: 330 (A_{1g}), 278 (E_g), 171 cm^{-1} (F_{2g}); IR: 347 cm^{-1} (F_{1u})].

In accordance with the reduced π bond contribution of the NO bond as compared to the CO bond in phosgene ($\nu CO = 1827\ cm^{-1}$)[4b], we observe the NO stretching vibration of the $ONCl_2^{\oplus}$ ion at 1650 cm^{-1} which resembles the situation

[*] Prof. Dr. K. Dehnicke [+], Dipl.-Chem. H. Aeissen
Fachbereich Chemie der Universität
Lahnberge, D-3350 Marburg (Germany)
Prof. Dr. J. Strähle, M. Kölmel
Institut für Anorganische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)
[+] Author to whom correspondence should be addressed.

Table 2. Raman spectrum of the $ONCl_2^{\oplus}$ ion.

$\tilde{\nu}$ [cm^{-1}]	Intensity	Assignment
1650 (IR)	m	νNO
747	m	$\nu_{as}NCl_2$
635	m	$\nu_s NCl_2$
420	w-m	δONCl
220	vw	δNCl_2

with the ONF_3 molecule (1690 cm^{-1})[9]. On account of the π bond contribution of the NCl bond, there should be a shift of the NCl stretching vibrations to shorter wavelengths as compared to the CCl vibrations of $OCCl_2$ (ν_{as} = 849, ν_s = 569 cm^{-1})[4b]; this shift is only observed in the symmetrical vibration, the asymmetrical vibration has bridging character as a result of the cation-anion interaction, and accordingly appears at a significantly longer wavelength (747 cm^{-1}) than in the phosgene molecule.

Received: May 27, 1977 [Z 751 IE]
German version: Angew. Chem. 89, 569 (1977)

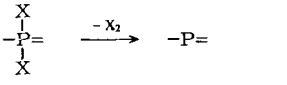
CAS Registry number:
(1), 63163-43-9

[1] Crystal data: monoclinic, space group $P2_1/c$, a = 9.870(2), b = 11.390(4), c = 21.783(6) Å, β = 102.14(2)°, Z = 8. Single crystal diffractometer CAD 4 (Enraf Nonius, Delft), Mo-K_α radiation, graphite monochromator.
[2] *N. L. Nichols, C. D. Hause, R. H. Noble*, J. Chem. Phys. *23*, 57 (1955).
[3] *E. A. Meyers, W. N. Lipscomb*, Acta Crystallogr. *8*, 853 (1955).
[4] a) *B. Zaslow, M. Atoji, W. N. Lipscomb*, Acta Crystallogr. *5*, 833 (1952); b) *J. Overend, J. C. Evans*, Trans. Faraday Soc. *55*, 1817 (1959).
[5] *H. Hartl, J. Schöner, J. Jander, H. Schulz*, Z. Anorg. Allg. Chem. *413*, 61 (1975).
[6] *R. N. Brown*, Acta Crystallogr. *14*, 711 (1961).
[7] *R. L. Collin*, Acta Crystallogr. *5*, 431 (1952).
[8] *J. Strähle, H. Bärnighausen*, Z. Anorg. Allg. Chem. *357*, 325 (1968).
[9] *N. Bartlett, J. Passmore, E. J. Wells*, Chem. Commun. *1966*, 213.

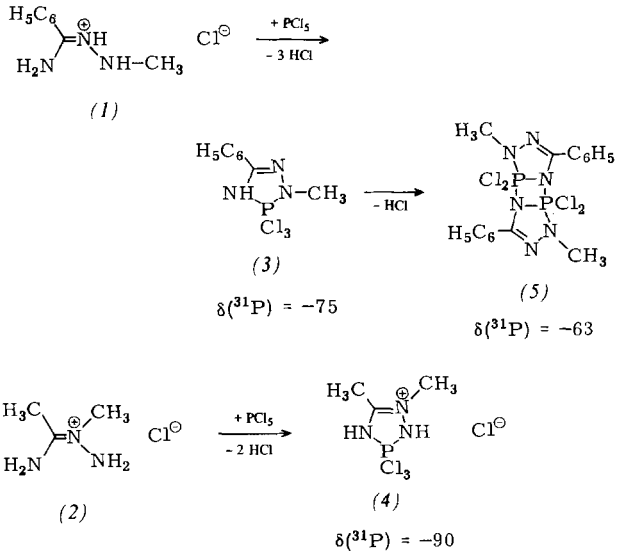
1,2,4,3λ^3-Triazaphospholes Synthesized by Reductive ($\sigma^4 \rightarrow \sigma^2$)-Elimination at Phosphorus[1]

By *Alfred Schmidpeter, Jörg Luber*, and *Helmut Tautz*[*]

Reductive eliminations which lead to the formation of dicoordinated phosphorus from tetra-coordinated phosphorus,



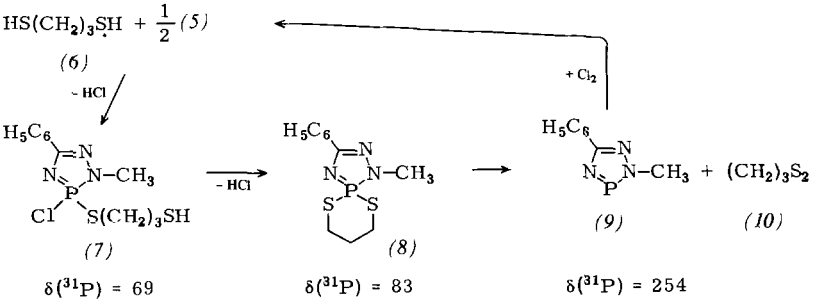
are unknown with acyclicly bound phosphorus and have only so far been found to occur, indeed in large numbers, with phosphabenzenes[2]. These reactions are apparently limited to phosphorus in a cyclic 6π system and provide evidence in favor of the σ^2 as opposed to the σ^4 phosphorin system. We have now observed the first other case of such an elimination with 1,2,4,3-triazaphospholes. It similarly shows that the aromaticity of the azoles is better preserved in the σ^2 phosphaderivatives than in the σ^4 derivatives. In the extension of earlier studies[3] on the reaction of acylhydrazines with phosphorus pentachloride, we have found that the N^1 or N^2 monosubstituted amidrazone hydrochlorides [*e.g. (1)* or *(2)*[4]] condense with PCl_5 already at 0°C to give 3,3,3-trichloro-1,2,4,3λ^5-triazaphospholines, such as *(3)*, or their hydrochlorides, such as *(4)*. At room temperature *(3)* loses a further molecule of HCl and is converted into the 1,2,4,3λ^5-triazaphosphole dimer *(5)* whereas *(4)* is still stable at 100°C.



In all products phosphorus is penta-coordinated on account of the fact that it is incorporated into a five-membered ring[5]; the ^{31}P-NMR shifts to higher fields (negative sign) confirm this. 1,2,4,3λ^5-Triazaphospholes having a tetra-coordinated phosphorus atom are only formed when Cl is substituted by *O*, *N* or *S* bonded groups[6].

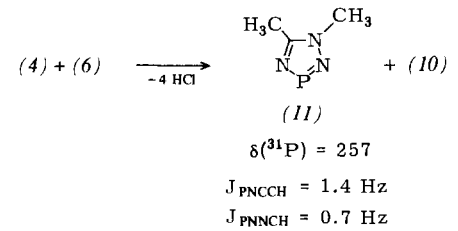
The reaction of *(5)* with 1,3-propanedithiol *(6)* (or 1,2-ethanedithiol) and triethylamine leads, *via* the spectroscopically identifiable substitution steps *(7)* and *(8)*, to a final, slightly slower, reductive elimination with the production of 1,2,4,3λ^3-triazaphosphole *(9)*[7]; typical product distribution after 3 h at 40°C in $CHCl_3$: 10% *(7)*, 40% *(8)*, 50% *(9)*.

1,2,4,3λ^3-Triazaphosphole *(11)* is formed in the same way from *(4)*. The products *(9)* and *(11)* were identified analytically and spectroscopically; the shift of the ^{31}P-NMR signal to very low field is especially characteristic.



(9) is chlorinated by PCl_5 or Cl_3CSCl and thus reconverted to *(5)*.

[*] Prof. Dr. A. Schmidpeter, Dr. J. Luber, Dipl.-Chem. H. Tautz
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)



2-Methyl-5-phenyl-1,2,4,3λ³-triazaphosphole (9)

45 g 1-methylbenzamidrazone hydrochloride *(1)* is added portionwise to 50 g PCl_5 in 500 ml CH_2Cl_2. After 12 h at room temperature with brief refluxing if necessary, and the evolution of HCl, the mixture yields an almost clear solution which is then evaporated. The residue is boiled with 300 ml acetonitrile and filtered under suction: 42 g (71 %) *(5)*, colorless crystals, m.p. = 200 to 202 °C.—10.6 g *(6)* and 19.8 g triethylamine in 40 ml benzene are added to 24.3 g *(5)* in 250 ml benzene with ice-cooling. After stirring for 12 h at room temperature, triethylammonium chloride is filtered off under suction, the filtrate evaporated, and the residue distilled: 15.3 g (86 %) *(9)*, b.p. = 108 to 110 °C/0.1 torr.

1,5-Dimethyl-1,2,4,3λ³-triazaphosphole (11)

20.6 g 2-Methylacetamidrazone hydrochloride *(2)* is stirred with 34.8 g PCl_5 in 500 ml CH_2Cl_2 at room temperature. After 24 h the *(4)* formed is filtered off under suction: 40 g (91 %).—25.9 g *(4)* is allowed to react with 10.1 g *(6)* and 40.4 g triethylamine as described for *(5)*: 3.4 g (29 %) *(11)*, b.p. = 91 to 92 °C/13 torr, m.p. = 39 to 41 °C.

Received: May 27, 1977 [Z 752 IE]
German version: Angew. Chem. *89*, 554 (1977)

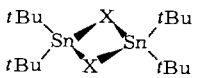
CAS Registry numbers:
(1), 28705-52-4; *(2)*, 63148-48-1; *(4)*, 63148-49-2; *(5)*, 63148-50-5; *(6)*, 109-80-8; *(9)*, 52713-97-0; *(11)*, 63148-51-6; PCl_5, 10026-13-8

[1] Part 21 of Four- and Five-Membered Phosphorus Heterocycles. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 20: *A. Schmidpeter, D. Schomburg, W. S. Sheldrick, J. H. Weinmaier*, Angew. Chem. *88*, 851 (1976); Angew. Chem. Int. Ed. Engl. *15*, 781 (1976).
[2] *K. Dimroth*, Fortschr. Chem. Forsch. *38*, 1 (1973); *H. Kanter, W. Molch, K. Dimroth*, Chem. Ber. *110*, 395 (1977).
[3] *A. Schmidpeter, J. Luber*, Chem. Ber. *108*, 820 (1975).
[4] To our knowledge *(2)* is the first N^2-monosubstituted amidrazone. It was synthesized from *O*-ethylacetimide hydrochloride and methylhydrazine in ethanol at −20 °C [analogously to the synthesis of unsubstituted amidrazones according to *W. Oberhummer*, Monatsh. Chem. *63*, 285 (1933)].
[5] *A. Schmidpeter, J. Luber*, Phosphorus *5*, 55 (1975).
[6] *A. Schmidpeter, H. Tautz, F. Schreiber*, unpublished.
[7] *Y. Charbonnel, J. Barrans*, Tetrahedron *32*, 2039 (1976).

Structure of the First Four-Membered Cyclic Diorganyltin Chalcogenides[**]

By *Heinrich Puff, Rudolf Gattermayer, Rudolf Hundt*, and *René Zimmer*[*]

In the diorganyltin chalcogenides Ph_2SnS[1] and Me_2SnS[2] so far examined by X-ray analysis, puckered six-membered rings have been found. We have now synthesized di-*tert*-butyltin chalcogenides



(1a), X = S
(1b), X = Se
(1c), X = Te

for the first time by the following routes:

$$2\,t\mathrm{Bu_2SnCl_2} + 2\,\mathrm{Na_2X} \rightarrow 4\,\mathrm{NaCl} + [t\mathrm{Bu_2SnX}]_2$$

and[3]

$$[t\mathrm{Bu_2Sn}]_4 + 4\,\mathrm{X} \rightarrow 2[t\mathrm{Bu_2SnX}]_2$$

The di-*tert*-butyltin chalcogenides occur as dimers in the solid state and also in solution, and form flat four-membered tin-chalcogen rings[4].

The new compounds *(1)* form monoclinic crystals having two molecules in the unit cell:

	Lattice constants				Cell vol.	Space group
	a [Å]	*b* [Å]	*c* [Å]	β [°]	[Å³]	
(1a) [5]	11.05_0	16.50_0	6.31_5	96.2_4	1144.7	$P2_1\text{-}C_2^2$
(1b) [6]	8.77_3	12.25_8	12.01_4	114.8_4	1172.5	$P2_1/c\text{-}C_{2h}^5$
(1c) [7]	8.74_0	12.50_9	12.14_5	114.0_0	1213.1	$P2_1/c\text{-}C_{2h}^5$

The X-ray structural analysis[8] showed that the four-membered, tin-chalcogen ring of the selenium derivative *(1b)* ($R = 0.064$) has a rhombic form whereas that of the sulfur derivative *(1a)* ($R = 0.051$) is slightly deformed—probably due to packing effects—but is still planar. The four tertiary carbon atoms lie almost in the same plane which is nearly perpendicular to the plane of the ring.

	Bond lengths [Å]				Angles [°]		
	Sn—X		Sn—C		XSnX	SnXSn	CSnC
(1a)	2.49	2.38	2.21	2.17	94.3	84.0	114.4
	2.47	2.42	2.23	2.26	94.0	87.6	117.3
(1b)	2.55		2.16	2.20	97.5	82.5	115.1

The vibrational spectra (IR and Raman), measured with powders, confirm the molecular symmetry as determined by X-ray analysis. Molecular weight measurements in chloroform show that the four-membered ring remains when the compounds are dissolved. The NMR spectra (^{1}H-, ^{13}C- and ^{119}Sn-NMR at room temperature, ^{1}H-NMR also at −100 °C) demonstrate that the molecular geometry in solution is the same as that in the solid state. In the mass spectra of the homologous compounds *(1)*, the molecular ion was observed in all cases; the distribution of the isotopes agrees with the calculated values.

Received: May 31, 1977 [Z 754 IE]
German version: Angew. Chem. *89*, 556 (1977)

CAS Registry numbers:
(1a), 52196-01-7; *(1b)*, 63163-40-6; *(1c)*, 63163-41-7

[1] *H. Schumann*, Z. Anorg. Allg. Chem. *354*, 192 (1967).
[2] *B. Menzebach, P. Bleckmann*, J. Organomet. Chem. *91*, 291 (1975); *R. Hundt*, Dissertation, Universität Bonn 1973.
[3] In this reaction intermediate products $t\mathrm{Bu_6Sn_3X_2}$ occur: *H. Puff, B. Gödert, W. Schuh, R. Zimmer*, unpublished.
[4] A similar molecular form has been found with $Na_4Sn_2S_6 \cdot 14\,H_2O$: *B. Krebs, S. Pohl, W. Schiwy*, Z. Anorg. Allg. Chem. *393*, 241 (1972).
[5] *R. Gattermayer*, Dissertation, Universität Bonn 1974; a second modification forms triclinic crystals.

[*] Prof. Dr. H. Puff, Dr. R. Gattermayer, Dr. R. Hundt, Dr. R. Zimmer
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

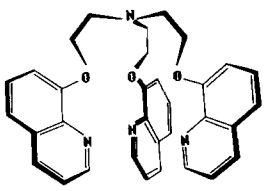
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[6] *B. Zschoche*, Staatsexamensarbeit, Bonn 1977.
[7] *W. Schuh*, Staatsexamensarbeit, Bonn 1977.
[8] The measurements were made using a four-circle diffractometer and the calculations were carried out using the X-ray program system of the IBM/370-168 computer at the regional university computer center at Bonn.

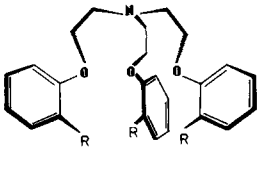
Noncyclic Cryptates[1]

By *Fritz Vögtle, Walter M. Müller, Winfried Wehner*, and *Egon Buhleier*[*]

Cryptates have been defined as complexes in which a bicyclic or larger neutral ligand of the crown ether type encloses a central ion in three dimensions[2]. We will now describe a new type *(1)* of neutral ligand for alkali metal ions which is not cyclic but still shows cryptand properties as regards the complete envelopment of the ion as well as the strength and selectivity of its complexation.

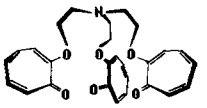


(1)

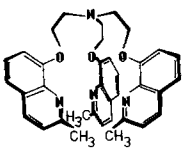


(2)

The topology of open chain cryptands is given by consequent combination of the polypode[2] ("octopus" molecule[3]) and terminal group concepts[4, 5].



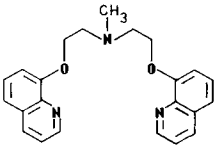
(3)



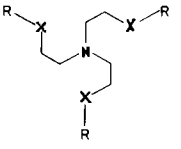
(4)

As is shown in Table 1, readily crystallizing complexes are formed with alkali, alkaline-earth, and heavy metal ions.

A first index of the cryptand-analogous complexation of *(1)* compared with that of the crown ether type dipode *(5)*, is provided by the clearly stronger phase transfer of solid $KMnO_4$ and (aqueous) Na and K picrates into organic phases; this phase transfer surpasses that of dibenzo[18]crown-6. The participation of the terminal quinolyl groups of *(1)* in cation complexation is supported by the similar ^{1}H-NMR spectra of all three quinolyl groups in the *(1)*·KSCN complex and of the OCH_3 protons in the *(2b)*·NaSCN complex; further support comes from the considerably lower phase transfer capacity of the comparable compound *(2a)* which has a phenyl group as donor atom free terminal group.



(5)



(6)

Potentiometric data confirm and specify these findings (Table 2).

Table 1. Noncyclic cryptands and their cryptates.

Ligand [a]	R [XR]	M.p. [°C]	Complex [a] with	LSW [c]	M.p. [d] [°C]
(1)		liq.	NaSCN	1:1:1	126—128
			KSCN	1:1	184—186
			RbI	1:1	115—118 (104—106)
			NH_4SCN	1:1	128—130 (118)
			$Ni(ClO_4)_2 \cdot 6H_2O$	1:1:1	234—237
			$H_2PtCl_6 \cdot 6H_2O$	1:1:4	195—200
(2a)	H	liq.	[b]	—	—
(2b)	OCH_3	63	NaSCN	1:1	78—80 (72)
(2c)	$NHCOCH_3$	167	[b]	—	—
(2d)	NO_2	liq.	[b]	—	—
(2e)	CH_3	liq.	[b]	—	—
(3)		liq.	BaI_2	1:1:1	170—174
(4)		liq.	KSCN	1:1	166—167
			RbI	1:1	177—179
			BaI_2	1:1:1	213—215 (165—168)
(5)		liq.	NaSCN	1:1	235—236
			RbI	1:1	250—254
(6a)	$[O\text{-}2,6\text{-}C_6H_3(OMe)_2]$	liq.	[b]	—	—
(6b)	$[O\text{-}2,6\text{-}C_6H_3Me_2]$	liq.	[b]	—	—
(6c)	$[O\text{-}2\text{-}C_5H_4N]$	liq.	$Th(NO_3)_4 \cdot 5H_2O$	1:1	125—129
(6d)	$[S—C(S)—NEt_2]$	78	$Cu(ClO_4)_2 \cdot 6H_2O$	1:1	111—114

[a] Correct analyses and/or high resolution mass spectra were obtained for all ligands and their complexes.
[b] No crystalline complexes could be produced from these ligands with the following salts: NaSCN, KSCN, RbI, $Co(ClO_4)_2$, $Ni(ClO_4)_2$, $Cu(ClO_4)_2$.
[c] Stoichiometry—ligand : salt : H_2O.
[d] Temperature at the beginning of sintering is given in brackets.

Of all the noncyclic ligands examined, *(1)* shows the highest complexation constants for alkali metal ions (in methanol/water); attention should be drawn to its preference for Na^+ over K^+ (and Li^+) and also to its high selectivity for divalent

[*] Prof. Dr. F. Vögtle, W. M. Müller, Dipl.-Chem. W. Wehner, Dipl.-Chem. E. Buhleier
Institut für Organische Chemie und Biochemie der Universität
Max-Planck-Strasse 1, D-5300 Bonn (Germany)

Table 2. Acidity and complex stability constants (log K) of selected ligands [potentiometric in methanol/H_2O (88:12); temperature 293 K; ionic strength: tetraethylammonium bromide; 10-fold salt excess of the ion to be measured].

Ligand	pK_a	Li^+	Na^+	K^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
(1)	7.02	<2	2.6	2.0	<2	2.06	2.14	2.7	3.2
(2a)	6.01	<2	<2	<2	<2	<2	<2	<2	<2
(2b)	6.40	<2	2.2	2.3	<2	<2	<2	2.0	2.1
(3)	5.92	<2	<2	<2	<2	<2	<2	3.3	3.6
(4)	7.09	<2	<2	<2	<2	<2	<2	<2	<2
(5)	7.78	<2	<2	<2	<2	<2	<2	<2	<2

ions, especially Ba^{2+} and Sr^{2+}. The even higher complexation constants of the pseudocryptand *(3)* for these divalent cations is especially striking; this compound has three terminal tropolone ether groups. In agreement with this, a BaI_2 complex of *(3)* could be isolated but a KSCN complex could not. In contrast, the complex stabilities for the smaller Li^+ and Ca^{2+} ions are clearly lower. We attribute this selectivity, on the basis of studies with space-filling models, to the fact that the pseudocavity cannot become sufficiently small to form a "skin-tight" wrapping around the small cations for steric reasons. Only *(1)* also has a log K value which is greater than 2 for Mg^{2+}.

In contrast with the favorable complexation by the terminal 8-quinaldyl group in spirally wound, open chain crown ethers[4], the OCH_3 groups of the three-armed compound *(2b)* seem rather to block the pseudocavity; here the $KMnO_4$ transfer and the complex stabilities for all cations are lower. In agreement with this concept of open chain cryptates, even lower complex stabilities are found with *(2a)* which has terminal phenyl groups.

In the ^{1}H-NMR spectra of the NaSCN and KSCN complexes of *(4)*, the methyl protons are shifted to higher fields ($\Delta\delta = 0.78$ and 0.88 respectively in $CDCl_3$) than those of the free ligand; on the basis of studies with models, this can be accounted for by a propeller-like twisting of the three quinaldyl groups. This interpretation is corroborated by the finding that the CH_3 shift of the K^+ complex to higher fields is larger than that of the Na^+ complex ($\Delta\Delta\delta = 0.1$): in the first case the CH_3 protons appear to lie further in the anisotropic region of the quinaldyl system than in the second, due to the larger volume of the metal ion.

The description and stereochemical formulation of *(1)* as an open chain cryptand also appears to be justified by the comparatively low complex stability of the analogous noncyclic crown ether *(5)* which also has terminal quinolyl groups: although *(5)* is capable of forming crystalline complexes (Table 1), its complexation constants are an order of magnitude smaller than those of *(1)* (Table 2); selectivity towards divalent ions is not observed.

Open chain cryptands such as *(1)* (whose topography is characterized by the tetrahedral arrangement of its four nitrogen atoms and which resembles that of *Lehn*'s "soccer ball" cryptands[6]), *(2b)* and *(4)* may collectively have the greatest complexation capacity of all neutral ligands so far investigated when the simplicity of their synthesis and the price of the starting materials are taken into account.

Received: May 27, 1977 [Z 753 IE]
German version: Angew. Chem. 89, 564 (1977)

CAS Registry numbers:
(1)/NaSCN, 63412-82-8; *(1)*/KSCN, 63412-84-0; *(1)*/RbI, 63448-75-9; *(1)*/$Ni(ClO_4)_2$, 63412-86-2; *(1)*/H_2PtCl_6, 63412-87-3; *(2b)*/NaSCN, 63412-89-5; *(3)*/BaI_2, 63412-90-8; *(4)*/KSCN, 63412-92-0; *(4)*/RbI, 63412-93-1; *(4)*/BaI_2, 63412-94-2; *(5)*/NaSCN, 63412-96-4; *(5)*/RbI, 63448-76-0; *(6c)*/$Th(NO_3)_4$, 63493-46-9; *(6d)*/$Cu(ClO_4)_2$, 63548-64-1; *(1)*, 63373-69-3; *(2a)*, 26253-40-7; *(2b)*, 63373-70-6; *(3)*, 63373-71-7; *(4)*, 63373-72-8; *(5)*, 63373-73-9

[1] Ligand Structure and Complexation, Part 20. This work was supported by the Fonds der Chemischen Industrie.—Part 19: *K. Frensch, F. Vögtle*, Tetrahedron Lett. *1977*, 2573.
[2] Review: *J.-M. Lehn*, Struct. Bonding *16*, 1 (1973); cf. also *J.-M. Lehn, J.-P. Sauvage*, J. Am. Chem. Soc. *97*, 6700 (1975).
[3] *F. Vögtle, E. Weber*, Angew. Chem. *86*, 896 (1974); Angew. Chem. Int. Ed. Engl. *13*, 814 (1974).
[4] *F. Vögtle, H. Sieger*, Angew. Chem. *89*, 410 (1977); Angew. Chem. Int. Ed. Engl. *16*, 396 (1977).
[5] *W. Raßhofer, G. Oepen, F. Vögtle*, Chem. Ber. *110* (1977), in press.
[6] *E. Graf, J.-M. Lehn*, J. Am. Chem. Soc. *97*, 5022 (1975); *B. Metz, J. M. Rosalky, R. Weiss*, J. C. S. Chem. Commun. *1976*, 533; in analogy, *(1)* also forms a stable crystalline ammonium complex (Table 1).

Double Ring-Closure Additions to *o*-(Methyleneamino)-phenyl Phosphites[1]

By *Alfred Schmidpeter, Josef Helmut Weinmaier*, and *Elmar Glaser*[*]

Methyleneaminophosphanes react with electron-deficient double- and triple-bond systems by [3+2]-cycloaddition[2] in which the induced charges are cancelled out by the formation of a λ^5-phosphazene:

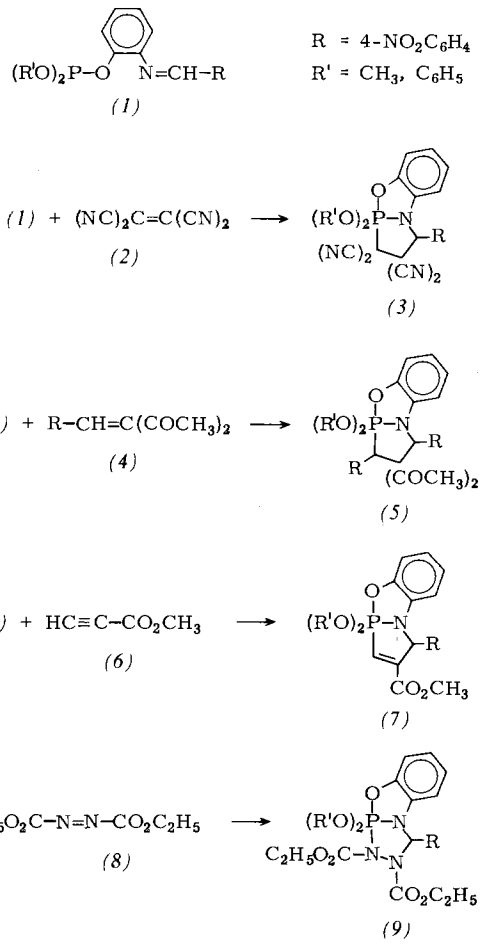


In the case of *o*-(methyleneamino)phenyl phosphites *(1)* however, the formal insertion of the three-membered *o*-oxyphenylene chain separates the two reaction centers—λ^3-phosphorus and the methylene carbon atom—into 1,6-positions from one another and makes a π bond-mediated compensation of charges impossible. In spite of this, these compounds again react with unsaturated systems in fundamentally the same way *i.e.* by 1,6-addition to P and C. Here, the charges equal out *via* a σ bond between P and N. Bicyclic σ^5-phosphoranes are the products.

2-(4-Nitrobenzylideneamino)phenyl dimethyl and -diphenyl phosphites *(1)* react with tetracyanoethylene *(2)* at 0°C and also (amongst other compounds) with 4-nitrobenzylideneacetylacetone *(4)*, methyl propiolate *(6)* or ethyl azodicarboxylate *(8)* after heating for several hours in benzene, to yield crystalline 1:1-adducts.

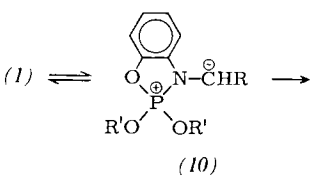
The ^{31}P-NMR shifts of *(3)*, *(5)* and *(7)* are found at $\delta = -35$ to -50 and those of *(9)* at $\delta = -50$ to -65 (to high field); they confirm the pentacoordination of the phosphorus. The ^{1}H-NMR spectra verify, on the basis of the diastereotopy of the *P*-methoxy groups, the addition to the benzylidene carbon atom of *(1)*; the values of the ^{31}P-^{1}H- and ^{1}H-^{1}H

[*] Prof. Dr. A. Schmidpeter, Dipl.-Chem. J. H. Weinmaier, E. Glaser
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

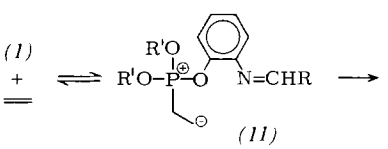


couplings also confirm the direction of addition in the formation of *(5)* and *(7)*.

It would seem obvious to interpret the reactions as [3+2]-cycloadditions to a 1,3-dipolar equilibrium form *(10)* of the phosphites *(1)*:



The direction found for the additions leading to *(5)* and *(7)* which, as far as can be discerned, is followed exclusively, speaks against this route and in favor of a preceding bimolecular equilibrium; in this equilibrium the reaction partner attacks the phosphorus electrophilically and thus forms the 1,3-dipolar intermediate *(11)* which can then react further in an intramolecular [3+2]-cycloaddition:



The reactions presented here profit from the fact that the intramolecular ring-closure is kinetically especially favorable[3] and that pentacoordination of phosphorus is especially easy to reach in the bridgehead position of the *bicyclo*octane framework[4]. However, double additions to phosphites which are bimolecular in both steps and which lead to *monocyclic* σ^5-phosphoranes, are apparently limited to carbonyl compounds[5].

Experimental Procedure

A solution of $(R'O)_2PCl$ (0.1 mol) in benzene (50 ml) is added to a solution of *p*-nitrobenzaldehyde *o*-hydroxyanil (0.1 mol) and triethylamine (0.1 mol) in benzene (100 ml). After 2 h at room temperature the triethylammonium chloride is filtered off, the filtrate evaporated and the residue recrystallized. Yellow crystals: *(1a)*, $R' = CH_3$, m.p. = 151 to 152 °C (from chloroform), 55 % yield; *(1b)*, $R' = C_6H_5$, M.p. = 94 to 96 °C (from benzene), 71 % yield.

Equivalent quantities of *(1a)* or *(1b)* and the reaction partner *(4)*, *(6)* or *(8)* are refluxed for 48 h in benzene. The oily residue remaining after evaporation is then purified by column chromatography and/or recrystallization from acetonitrile. Colorless to yellow crystals, 30—80 % yield.

Received: June 1, 1977 [Z 755 IE]
German version: Angew. Chem. *89*, 558 (1977)

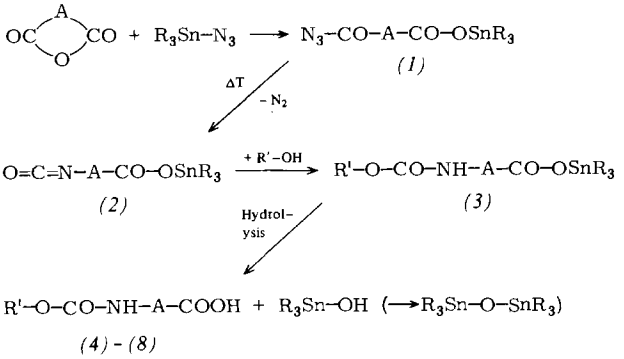
CAS Registry numbers:
(1a), 63181-20-4; *(1b)*, 63181-21-5; *(4)*, 29197-16-8; *(5a)*, 63181-22-6; *(5b)*, 63181-23-7; *(6)*, 922-67-8; *(7a)*, 63181-24-8; *(7b)*, 63181-25-9; *(8)*, 1972-28-7; *(9a)*, 63181-27-1; *(9b)*, 63181-26-0; $(R'O)_2PCl$ (R = Me), 3743-07-5; $(R'O)_2PCl$ (R = Ph), 5382-00-3; *p*-nitrobenzaldehyde *o*-hydroxyanil, 841-14-5

[1] Communication 23 on Four- and Five-Membered Phosphorus Heterocycles. This work was supported by the Fonds der Chemischen Industrie.—Communication 22: *A. Schmidpeter, M. Junius, J. H. Weinmaier, J. Barrans, Y. Charbonnel*, Z. Naturforsch. *B32* (1977), in press.
[2] *A. Schmidpeter, W. Zeiss*, Angew. Chem. *83*, 398 (1971); Angew. Chem. Int. Ed. Engl. *10*, 396 (1971).
[3] *W. Oppolzer*, Angew. Chem. *89*, 10 (1977); Angew. Chem. Int. Ed. Engl. *16*, 10 (1977).
[4] *A. Schmidpeter, J. H. Weinmaier*, Angew. Chem. *87*, 517 (1975); Angew. Chem. Int. Ed. Engl. *14*, 489 (1975).
[5] *F. Ramirez*, Synthesis *1974*, 90; *W. G. Bentrude, W. D. Johnson, W. A. Khan*, J. Am. Chem. Soc. *94*, 3058 (1972); *D. J. Scharf*, J. Org. Chem. *41*, 28 (1976).

Synthesis of *N*-Protected ω-Amino Acids with the Aid of Stannyl Azides[**]

By *Hans R. Kricheldorf, Gerd Schwarz*, and *Jürgen Kaschig*[*]

Acyl chlorides as well as carboxylic anhydrides and thioanhydrides can all be converted into isocyanates with stannyl azides. However, stannyl azides also add to isocyanates to form readily decomposable *N*-stannylcarbamoyl azides. This



[*] Dr. H.-R. Kricheldorf, Dipl.-Chem. G. Schwarz, Dipl.-Chem. J. Kaschig
Institut für makromolekulare Chemie der Universität
Stefan-Meier-Strasse 31, D-7800 Freiburg (Germany)

[**] We wish to thank the Schering A. G. (Bergkamen) and CIBA Geigy AG (Marienberg) for supplying us with chemicals used in this work.

side reaction can be avoided by first acylating the stannyl azides, *e.g.* with equimolar amounts of dicarboxylic anhydride, at 25—35 °C and subjecting the resulting acyl azides *(1)* to Curtius degradation. In this way the stannyl esters of ω-isocyanatocarboxylic acids are formed almost quantitatively. Since stannyl esters are resistant to alcoholysis, in contrast to silyl esters, alcohols can be added to the isocyanate group of *(2)* without side reactions. Hydrolysis of the resulting *N*-alkoxycarbonyl-ω-amino stannyl ester *(3)* gives the *N*-protected ω-amino acids, *e.g.* *(4)* to *(8)* (see Table 1), which usually crystallize well.

This method has the following advantages:

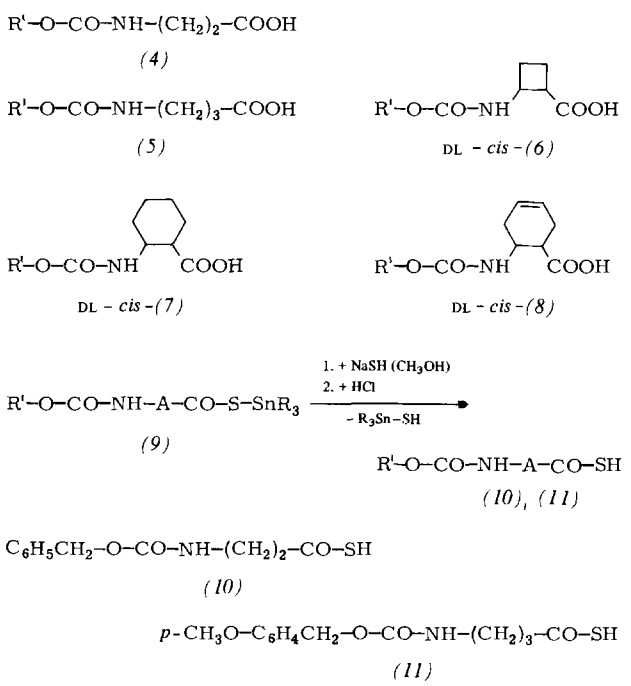
1) The synthesis can be carried out as a single-pot process.

2) ω-Amino acids are not required as starting materials.

3) The distannoxanes formed on hydrolysis of the stannyl esters *(3)* can easily be transformed by thionyl chloride into stannyl chlorides, which give stannyl azides with sodium azide[1, 2].

4) The preferred reagent tri-*n*-butylstannyl azide is not explosive, not sensitive to hydrolysis, not particularly toxic, stable on storage, and readily accessible in larger quantities[1, 2].

Succinic and glutaric thioanhydrides were reacted in the same way as the cyclic anhydrides[3]. The intermediate thioamino *S*-stannyl esters *(9)* were thiolyzed with sodium hydrogen sulfide solution in order to avoid hydrolysis of the CO—S bond. The yields of the thio amino acid derivatives thus obtained, *(10)* and *(11)* (see Table 1), were nevertheless lower than those of the analogous amino acid derivatives *(4a)* and *(5b)*, due primarily to the sensitivity of the sulfur compounds to oxidation and to their reluctance to crystallize.



Procedures

D,L-*cis*-6-(*tert*-Butyloxycarbonylamino)-3-cyclohexene-1-carboxylic acid *(8d)*, dicyclohexylammonium salt: Tri-*n*-butylstannyl azide (0.1 mol) and *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (0.1 mol) are stirred in anhydrous dioxane (50 ml) for 20 min at 30—35 °C. The IR spectrum then displays two azide bands of approximately equal intensity at 2090 and 2150 cm^{-1}. The reaction mixture is heated until vigorous evolution of N_2 starts and the exothermic reaction kept under control by cooling if required. After the reaction has subsided the mixture is heated for 40 min at 80—90 °C, *tert*-butanol (0.15 mol) and 1,4-diaminobicyclooctane (0.5 g) are added, and warming to 50—60 °C continued overnight. The isocyanate band at 2275 cm^{-1} provides a check on whether addition is complete. The reaction mixture is then stirred with 1 N sodium hydroxide solution (120 ml) for 30 min and diluted with dichloromethane (150 ml). The aqueous phase is separated off and re-extracted with dichloromethane (50 ml). After stirring of the aqueous phase with citric acid (20 g) and ethyl acetate (150 ml), the organic phase is separated off and treated with diethyl ether (200 ml) and dicyclohexylamine (0.1 mol). The pure product crystallizes overnight from the ethereal solution at 0 °C.

Table 1. Properties of *N*-protected ω-amino acids of types *(4)* to *(8)* and *(10)*, *(11)* prepared with the aid of tri-*n*-butylstannyl azide. *(a)*: $R' = C_6H_5CH_2$ (R'—O—CO=Z); *(b)*, $R' = p\text{-}CH_3—C_6H_4CH_2$ (R'—O—CO=Z(OMe)); *(c)*, $R' = p\text{-}NO_2—C_6H_4CH_2$ (R'—O—CO=Z(NO_2)); *(d)*, $R' = C(CH_3)_3$ (R'—O—CO=Boc); *(e)*, $R' = CCl_3CH_2$ (R'—O—CO=Troc).

Cpd.	Yield [a] [%]	M.p. [b] [°C]	Literature value for m.p. [°C]
(4a)	74	103—105	106 [4]
(4b)	76	90—92	—
(4c)	84	105—107	—
(4d)	80	71—73	73—74 [5]
(4e)	74	87—89	—
(5a)	86	64—66	66 [6]
(5b)	94	76—78	—
(5c)	88	144—146	—
(5d)	72	50—52	52—54 [7]
(5e)	65	46—48	—
(6b)	77	99—101	—
(6c)	67	135—137	—
(7a)	91	128—130	130—131 [8]
(7b)	83	132—134	—
(7c)	65	146—148	—
(7d)	65 [c]	176—179 [c]	—
(8b)	91	146—148	—
(8d)	76 [c]	166—168 [c]	
(10)	26	41—45	—
	37	oil	
(11)	50	oil	—

[a] Crystalline crude products.
[b] Recrystallized from ethyl acetate + petroleum ether; the results of C, H, N analyses agree with the calculated values (±0.3 %).
[c] Dicyclohexylammonium salt.

N-Benzyloxycarbonylthio-β-aniline *(10)*: Succinic thioanhydride[3] (0.1 mol) and tri-*n*-butylstannyl azide (0.1 mol) are dissolved in anhydrous dioxane (500 ml) and heated to 20—25 °C for 10 h, 40—45 °C for 20 h, and 80—90 °C for 40 min. 30 min after addition of benzyl alcohol (0.1 mol) the reaction mixture is concentrated in vacuum. The residue is dissolved in methanol (100 ml) and a small amount of phenolphthalein is added. An approximately 5 M solution of NaSH in methanol is then added under N_2 until a persistant red color appears. The solution is concentrated *in vacuo* and the residue dissolved in ethyl acetate (150 ml) and extracted twice under N_2 with water (2 × 80 ml). The aqueous extracts are acidified to pH = 1 with conc. hydrochloric acid. The precipitate is dissolved in ethyl acetate (200 ml) and partly induced to crystallize after concentration of the solution by addition of petroleum ether and cooling to −20 °C in the course of three days. The oily fraction obtained after concentration of the mother liquor at 10^{-3} torr shows the same IR and ^{1}H-NMR spectrum as the crystalline fraction.

Received: June 3, 1977 [Z 757 IE]
German version: Angew. Chem. 89, 570 (1977)

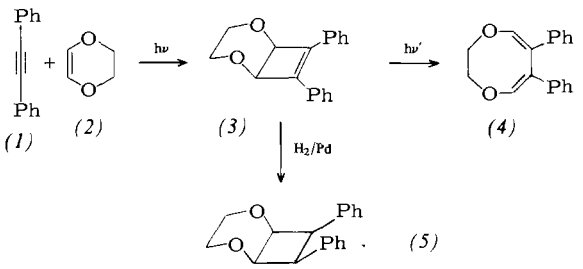
CAS Registry numbers:
(4a), 2304-94-1; *(4b)*, 63216-38-6; *(4c)*, 63216-39-7; *(4d)*, 3303-84-2; *(4e)*, 63216-40-0; *(5a)*, 5105-78-2; *(5b)*, 63216-41-1; *(5c)*, 63216-42-2; *(5d)*, 57294-38-9; *(5e)*, 63216-43-3; *(6b)*, 63216-44-4; *(6c)*, 63216-45-5; *(7a)*, 63216-46-6; *(7b)*, 63216-47-7; *(7c)*, 63216-48-8; *(7d)*, 63216-50-2; *(8b)*, 63216-51-3; *(8d)*, 63216-53-5; *(10)*, 63216-54-6; *(11)*, 63216-55-7; tributylstannyl azide, 17846-68-3; *cis*-4-cyclohexen-1,2-dicarboxylic anhydride, 935-79-5; succinic thioanhydride, 3194-60-3

[1] *H. R. Kricheldorf, E. Leppert*, Synthesis *1976*, 329.
[2] *J. Luijten, M. Janssen, G. J. M. van der Kerk*, Rec. Trav. Chim. Pays-Bas *81*, 202 (1962).
[3] *H. R. Kricheldorf, E. Leppert*, Makromol. Chem. *158*, 223 (1972).
[4] *R. H. Sifferd, V. du Vigneaud*, J. Biol. Chem. *108*, 753 (1935).
[5] *P. H. Bentley, H. Gregory, A. H. Laird, J. S. Morley*, J. Chem. Soc. *1964*, 6130.
[6] *M. Hont, V. du Vigneaud*, J. Biol. Chem. *127*, 43 (1939).
[7] *E. Schnabel*, Justus Liebigs Ann. Chem. *702*, 188 (1967).
[8] *W. L. F. Armarego, P. A. Reece*, J. Chem. Soc. Perkin Trans. I 2313 (1974).

6,7-Diphenyl-2,3-dihydro-1,4-dioxocin[**]

By *Gerd Kaupp* and *Michael Stark*[*]

Irradiation of 1,2-diphenylcyclobutene derivatives generally leads to elimination of diphenylacetylene (α-cleavage) or to oxidative formation of cyclobuta[*l*]phenanthrenes (dehydrocyclization)[1, 2]. The reaction course depends upon whether the phenyl groups can undergo free rotation after excitation of the *cis*-stilbene chromophore, or whether the partial rotations are sterically hindered[3]. We now report a β-cleavage, a rare event in photolyses of cyclobutenes[1, 4], which permits a ready synthesis of dihydrodioxocin *(4)* starting from the bicyclic *(3)*.



(1) *(2)* *(3)* *(4)* *(5)*

Photoaddition of diphenylacetylene *(1)* to *p*-dioxene *(2)*[5] affords *(3)* [^{1}H-NMR (CCl_4): δ = 7.75—7.15 (10H, m), 4.95 (2H, s), 4.0—3.5 (4H, sym. AA'BB')][6]. *cis*-Linkage of the rings in *(3)* is confirmed by catalytic hydrogenation to the symmetrical (^{1}H- and ^{13}C-NMR spectra) derivative *(5)* (m.p. 134—135 °C)[6]. Compound *(3)* displays a UV spectrum having pronounced fine structure [CH_3CN: $\lambda_{max}(\varepsilon)$ = 225 (22500), 229 (sh, 20500), 294 (16600), 298 (sh, 16500), 315 (sh, 10400), 319 nm (sh, 8500); EPA, 77 K: 228, 233, 236.5, 284 (sh), 296.5, 309, 322 nm] and an intense fluorescence spectrum showing only a hint of fine structure even at 77 K [cyclohexane: λ_{max}^{corr} = 383 nm, Φ_{fl} = 0.32; EPA, 77 K: *ca.* 355 (sh), 369, *ca.* 385 nm (sh)]. Disrotatory opening of the bicyclic *(3)* to the eight-membered ring *(4)* with a quantum yield Φ = 0.33 competes with fluorescence. The symmetrical structure of *(4)* is confirmed by the ^{1}H-NMR spectrum [CCl_4: δ = 7.2—6.9 (10H, m), 6.53 (2H, s), 4.08 (4H, br s, $\Delta\nu_{1/2}$ = 2 Hz)][6]. The UV spectrum [CH_3CN: $\lambda_{max}(\varepsilon)$ = 230 (sh, 16300), 244 (18400), 277 nm (sh, 5500)] also complies with expectations. Secondary photolysis of *(4)* to *(3)* and other products can largely be avoided. The complete absence of α-cleavage on photolysis of *(3)* is surprising.

1,6-cis-7,8-Diphenyl-2,5-dioxabicyclo[4.2.0]oct-7-ene (3)[6]:

Compound *(1)* (2.0 g, 11.2 mmol) is dissolved in *(2)* (90 g) and irradiated for 3 d with eight low-pressure mercury lamps (253.7 nm) in a Rayonet reactor at 30 to 35 °C. Excess *(2)* is distilled off, and compound *(3)* (1.05 g) crystallizes from the oily residue at −20 °C after addition of CH_3OH (50 ml). Chromatography of the mother liquor on SiO_2 (300 g) with benzene (5 l) yielded unreacted *(1)* (320 mg), *(4)* (100 mg), and *(3)* (860 mg; total yield 64%; m.p. 88 °C, CH_3OH).

6,7-Diphenyl-2,3-dihydro-1,4-dioxocin (4)[6]:

A solution of compound *(3)* (1.0 g, 3.8 mmol) in benzene (500 ml) is irradiated for 1 h with a high-pressure mercury lamp (Hanau TQ 150) through a Pyrex filter under N_2 at 25 °C. After concentration, compound *(4)* (850 mg) crystallizes from CH_3OH (15 ml) at −20 °C. The mother liquor still contains 30 mg of *(4)* (total yield 88%; m.p. 114 °C, CH_3OH) and 30 mg of *(3)*.

Received: June 8, 1977 [Z 756 IE]
German version: Angew. Chem. *89*, 555 (1977)

CAS Registry numbers:
(1), 501-65-5; *(2)*, 543-75-9; *(3)*, 63163-65-5; *(4)*, 63163-66-6; *(5)*, 63163-67-7

[1] *G. Kaupp*, Angew. Chem. and Angew. Chem. Int. Ed. Engl., in press.
[2] *G. Kaupp, M. Stark*, Chem. Ber., in press. *H. H. White, J. P. Anhalt*, Tetrahedron Lett. *1965*, 3937.
[3] *G. Kaupp, M. Stark, E. Teufel*, Lecture at Chemiedozententagung in Marburg (March 23, 1977).
[4] *J. M. Labrum, J. Kolc, J. Michl*, J. Am. Chem. Soc. *96*, 2636 (1974). Cyclobutenediones: *N. Obata, T. Takizawa*, J. Chem. Soc. Chem. Commun. *1971*, 587; *O. L. Chapman, C. L. McIntosh, L. L. Barber, ibid. 1971*, 1162.
[5] *R. I. Meltzer, A. D. Lewis, A. Fischman*, J. Org. Chem. *24*, 1763 (1959).
[6] All new compounds gave correct elemental analyses. *(3)* and *(5)* are stable up to at least 210 °C (> 6 h); *(4)* rapidly changes above 160 °C.

Hydrogenolysis of Trisubstituted Dichlorophosphoranes—A New Method for Deoxygenation of Oxophosphoranes

By *Mitsuo Masaki* and *Noboru Kakeya*[*]

Although tertiary phosphanes are versatile reducing agents, their use in industry is very limited, mainly owing to the lack of economical methods for regenerating the reagents from oxophosphoranes, *i.e.* from their oxidation products. We recently reported a convenient method for the reduction of the oxophosphoranes[1], involving their treatment with oxalyl chloride and reduction of the resulting dichlorophosphoranes with thiols in the presence of trimethylamine[2]. We have now found an even simpler method, which is illustrated by equations (a) and (b).

$$\underset{(1)}{R_3PO} + Cl_2 + CO \rightarrow \underset{(2)}{R_3PCl_2} + CO_2 \qquad (a)$$

$$\underset{(2)}{R_3PCl_2} + H_2 \rightarrow \underset{(3)}{R_3P} + 2HCl \qquad (b)$$

[*] Univ.-Doz. Dr. G. Kaupp, Dipl.-Chem. M. Stark
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

[*] Dr. M. Masaki, N. Kakeya
Polymer Research Laboratory, Ube Industries, Ltd.
Minami-kaigan, Goi, Ichihara, Chiba 290 (Japan)

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

Table 1. Reduction of oxophosphoranes *(1)* to phosphanes *(3)*.

	R_3PO *(1)*	Yield of *(3)* [%]	Recovery of *(1)* [%]
(a)	$(n\text{-}C_4H_9)_3PO$	90	10
(b)	$(n\text{-}C_8H_{17})_3PO$ [a]	92	8
(c)	$(C_6H_5)_3PO$ [b]	86	14

[a] Chlorination and hydrogenolysis were performed under conditions similar to the case of *(1a)* (see Experimental).
[b] Chlorination conditions: 1 h at 60 °C and then 1.5 h at 100 °C; hydrogenolysis conditions: 180 °C, 2 h.

When tri-*n*-butyl(oxo)phosphorane *(1a)* is treated with an equimolar amount of chlorine under carbon monoxide pressure in carbon tetrachloride at room temperature, an exothermic reaction occurs to give tri-*n*-butyl(dichloro)phosphorane *(2a)* and carbon dioxide. The formation of *(2a)* was confirmed by treatment of the reaction mixture with aniline and triethylamine to give tri-*n*-butyl(phenylimino)phosphorane [isolated in 94% yield based on *(1a)*].

The dichloro compound *(2a)* underwent hydrogenolysis at 160 °C and *ca.* 98 bar of hydrogen without any catalyst to give tri-*n*-butylphosphonium chloride, which was easily converted into the free base *(3a)* either by neutralization with sodium hydrogen carbonate or by thermal dissociation in refluxing toluene (further examples are shown in Table 1).

Oxo(triphenyl)phosphorane *(1c)* is known to be converted into the corresponding dichloro compound *(2c)* by phosgene[3]. The reaction of eq. (a) takes place with ease even under conditions where phosgene is scarcely formed from carbon monoxide and chlorine without catalyst. When a solution of chlorine in carbon tetrachloride is treated with *ca.* 59 bar of carbon monoxide at 60 °C for 1 h, neither phosgene nor oxalyl chloride was formed and the major amount of chlorine is recovered.

Experimental

A glass cylindrical vessel containing a solution of *(1a)* (2.18 g, 10 mmol) and chlorine (0.71 g, 10 mmol) in carbon tetrachloride (15 ml) was charged in an autoclave, which was then pressurized with CO to *ca.* 59 bar at 25 °C. The reaction mixture was shaken for 10 min, during which the temperature of the mixture rose to 60 °C at the highest by an exothermic reaction. The reaction mixture in the vessel was stripped of solvent and toluene (50 ml) was added. Some (*ca.* 35 ml) of the toluene was evaporated to remove the remaining carbon tetrachloride. The vessel containing the resultant toluene solution of *(2a)* was charged in an autoclave, which was pressurized with hydrogen to *ca.* 98 bar. The mixture was shaken at 160 °C for 1.5 h, and then neutralized with aqueous $NaHCO_3$. According to gas chromatography the reaction mixture contained 1.82 g of *(3a)* and 0.21 g of *(1a)*.

Received: May 23, 1977 [Z 761 IE]
German version: Angew. Chem. *89*, 558 (1977)

CAS Registry numbers:
(1a), 814-29-9; *(1b)*, 78-50-2; *(1c)*, 791-28-6; *(2a)*, 17417-07-1; *(2b)*, 22402-74-0; *(2c)*, 2526-64-9; *(3a)*, 998-40-3; *(3b)*, 4731-53-7; *(3c)*, 603-35-0

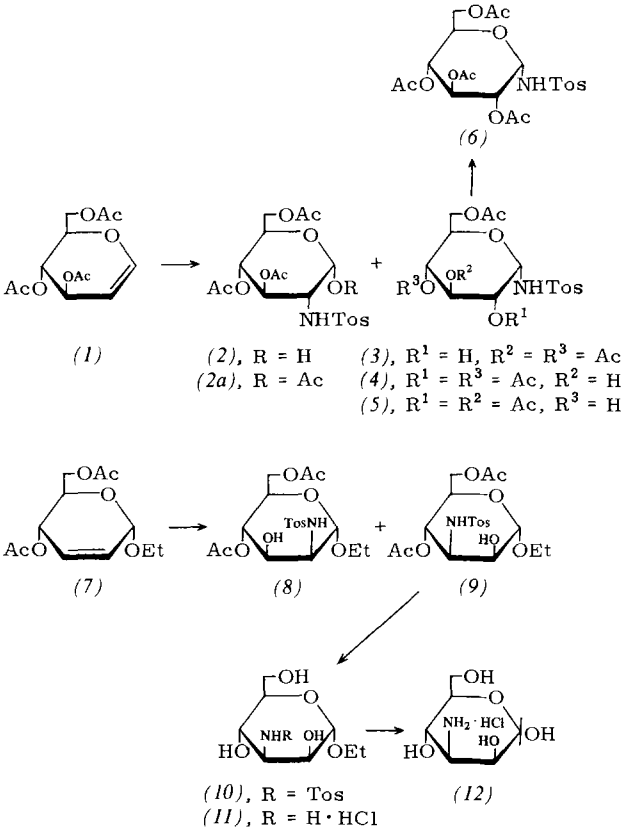
[1] *M. Masaki, K. Fukui*, Chem. Lett. *1977*, 151.
[2] Reduction of trisubstituted dichlorophosphoranes of type *(2)* with various reducing agents were previously known; reduction with molecular hydrogen is new (see references cited in Ref. [1]).
[3] *G. Wunsch, K. Winterberger, H. Geierhaas*, Z. Anorg. Allgem. Chem. *369*, 33 (1966).

Amino Sugars and *N*-Glycosides by Oxyamination of Unsaturated Carbohydrate Derivatives[**]

By *Ingolf Dyong, Quan Lam-Chi, Gerhard Schulte, Bert Fraser-Reid*, and *John L. Primeau*[*]

The synthesis of amino sugars has so far remained a difficult problem. Only 2-amino-2-deoxyaldoses have become more readily accessible through studies by *Lemieux et al.*[1], but in the case of all other amino sugars (*e.g.* 3-amino-3-deoxyaldoses) recourse is still being made to tedious multi-step syntheses. As has been found independently by each of our research groups, the single-step *cis*-oxyamination of olefins developed by *Sharpless et al.*[2] provides a particularly useful and widely applicable method in carbohydrate chemistry for the synthesis of nitrogen-containing sugar derivatives.

3,4,6-Tri-*O*-acetyl-D-glucal *(1)* reacts with chloramine-T, the sodium salt of *N*-chloro-*p*-toluenesulfonamide, in the presence of catalytic amounts of OsO_4[2] to give the four products *(2)*—*(5)*, which can easily be separated by chromatography on silica gel with toluene/diisopropyl ether/2-propanol (20:4:1) and are readily isolable in crystalline form. *(2)* [m.p. 159—160 °C, $[\alpha]_D^{21} = +70.9°$ ($CHCl_3$), yield 10.3%], after acetylation to *(2a)* [m.p. 125—126 °C, $[\alpha]_D^{24} = +74.4°$ ($CHCl_3$)], is identical with the known 1,3,4,6-tetra-*O*-acetyl-*N*-toluenesulfonyl-α-D-glucosamine[3]. Compounds *(3)*—*(5)* are tri-*O*-acetyl-*N*-tosyl-α-D-glucosylamines [total yield 30.6%]. Reac-



[*] Prof. Dr. I. Dyong, Q. Lam-Chi, G. Schulte
Organisch-Chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)
Prof. Dr. B. Fraser-Reid, J. L. Primeau
Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo
Waterloo, Ontario N2L 3G1 (Canada)

[**] Synthesis of Biologically Important Carbohydrates, Part 12. This work was supported by the Landesamt für Forschung des Landes Nordrhein-Westfalen, the Fonds der Chemischen Industrie, and the National Research Council of Canada.—Part 11: *I. Dyong, R. Knollmann, N. Jersch, H. Luftmann*, Chem. Ber., in press.

tions typical for sugars containing a free 1-OH (glycosidation, halogenation) do not occur, and on acetylation *(3)*, *(4)* and *(5)* each afford the same 2,3,4,6-tetra-*O*-acetyl-*N*-tosyl-α-D-glucosylamine *(6)* [m.p. 132—133 °C, $[\alpha]_D^{21} = +35.7°$ ($CHCl_3$)][4]. The oxyamination of *(1)* is thus strongly regioselective and most likely stereospecific, since no products having the *manno* configuration have so far been detected[5].

Earlier attempts to *cis*-hydroxylate ethyl 4,6-di-*O*-acetyl-α-D-hex-2-enopyranoside *(7)*[6] with OsO_4 led exclusively to the corresponding mannose derivative[7], and, as expected, *(7)* reacts within 40 h at 40 °C to give the amorphous ethyl 4,6-di-*O*-acetyl-*N*-tosyl-α-D-mannosaminide *(8)* [m.p. 48—54 °C, $[\alpha]_D^{25} = +14.5°$ ($CHCl_3$), yield 16%] and the ethyl 4,6-di-*O*-acetyl-3-deoxy-3-*N*-tosylamino-α-D-mannoside *(9)* [m.p. 146—148 °C, $[\alpha]_D^{25} = +43.7°$ ($CHCl_3$), yield 37 %]. *(8)*, *(9)* and unreacted *(7)* can be separated with chloroform/cyclohexane/2-propanol (6:10:1). The markedly different mass spectra of *(8)* and *(9)* are consistent with positional and not configurational isomers. Thus the mass numbers of the strong H_1^+ fragments[8] [*(8)*: $m/e = 241$ TosHNCH=CHOEt$^+$; *(9)*: $m/e = 88$ HOCH=CHOEt$^+$] appear with only low intensity in the spectrum of the other isomer. The main product *(9)* can be converted almost quantitatively into *(10)* [m.p. 168—170 °C, $[\alpha]_D^{25} = +61.9°$ (CH_3OH)] by the method of *Zemplen*, and into the hydrochloride *(11)* [m.p. 225–227 °C $[\alpha]_D^{25} = +59.7°$ (CH_3OH)] by reaction with sodium in liquid ammonia after treatment with acid. Cleavage of aglycon from *(11)* with 4 N HCl leads to a product that gives a negative Elson-Morgan test, *i.e.* a product which cannot be a 2-amino-2-deoxy sugar[9a]. The data of the crystalline hydrochloride are consistent with those of 3-amino-3-deoxy-D-mannopyranose hydrochloride *(12)* [decomp. pt. 165—167 °C, $[\alpha]_D^{25} = +15.2°$ (3 min) → $+5.8°$ (2 h; H_2O)], which hitherto was accessible only by multistep synthesis[9b].

Received: June 16, 1977 [Z 764 IE]
German version: Angew. Chem. *89*, 565 (1977)

CAS Registry numbers:
(1), 2873-29-2; *(2a)*, 63301-56-4; *(2b)*, 63301-57-5; *(3)*, 63301-58-6; *(4)*, 63301-59-7; *(5)*, 63301-60-0; *(6)*, 63301-61-1; *(7)*, 3323-72-6; *(8)*, 63301-62-2; *(9)*, 63301-63-3; *(10)*, 63301-64-4; *(11)*, 63301-65-5; *(12)*, 5505-63-5; sodium salt of *N*-chloro-*p*-toluenesulfonamide, 127-65-1

[1] *R. U. Lemieux, T. L. Nagabhushan*, Can. J. Chem. *45*, 401 (1967).
[2] *K. B. Sharpless, A. O. Chong, K. Oshima*, J. Org. Chem. *41*, 177 (1976); *A. O. Chong, K. Oshima, K. B. Sharpless*, J. Am. Chem. Soc. *99*, 3402 (1977).
[3] *F. Micheel, E. Michaelis*, Chem. Ber. *91*, 188 (1958): M.p. = 126—127 °C, $[\alpha]_D^{21} = +75 \pm 1°$ ($CHCl_3$).
[4] *(4)* and *(5)* are evidently formed from *(3)* by acyl migration. This rearrangement does not take place if treatment of the reaction solution with sodium hypochlorite is avoided by reconverting the *p*-toluenesulfonamide formed as byproduct into chloroamine-T [2]. Under such conditions only *(2)* [yield 10%] and *(3)* [m.p. 133—135 °C, $[\alpha]_D^{21} = +41.0°$ ($CHCl_3$), yield 30 %] are formed.—The data for *(6)* differ from those of the "tetraacetyl-*N*-*p*-tolylsulfonylglucosylamine" [m.p. 163 °C, $[\alpha]_D^{20} = +29.6°$ ($CHCl_3$)] obtained by *B. Helferich* and *A. Mitrowsky via* another route. However, after deacetylation with ammonia both compounds afford the same *gluco*-configurated product Chem. Ber. *85*, 1 (1952).
[5] Similar results were obtained with 3,4,6-tri-*O*-acetyl-D-galactal as with *(1)*. The products have *galacto* configuration. *Talo* isomers could not be detected.
[6] *R. J. Ferrier, N. Prasad*, J. Chem. Soc. *C 1969*, 570.
[7] *S. McNally, W. G. Overend*, J. Chem. Soc. *C 1966*, 1978; *C. L. Stevens, J. B. Fillipi, K. G. Taylor*, J. Org. Chem. *31*, 1292 (1966).—Accordingly, reaction of *cis*-2,5-dimethoxy-5,6-dihydro-2*H*-pyran with OsO_4 yields exclusively methyl-4-*O*-methyl-α-DL-lyxopyranoside [*R. M. Srivastava, R. K. Brown*, Can. J. Chem. *49*, 1339 (1971)].
[8] Nomenclature: *N. K. Kochetkov, O. S. Chizhov*, Adv. Carbohydr. Chem. Biochem. *21*, 39 (1966).
[9] a) *D. Horton* in *R. W. Jeanloz*: The Amino Sugars, Vol. IA. Academic Press, New York 1969, p. 7; b) *H. H. Baer, F. Kienzle*, Can. J. Chem. *41*, 1606 (1963); *H. H. Baer, H. O. L. Fischer*, J. Am. Chem. Soc. *82*, 3709 (1960): decomp. pt. = 165—167 °C, $[\alpha]_D^{26} = +17 \xrightarrow{4\,h} +6°$ (H_2O).

$K_6[Si_2Te_6]$—Synthesis and Structure of the First Tellurodisilicate

By *Günter Dittmar*[*]

While thio and seleno analogs of silicates have long been known[1], corresponding tellurium compounds have not yet been prepared.

It has now proved possible, by melting a stoichiometric mixture of the elements in an evacuated quartz tube, to obtain the compound $K_6[Si_2Te_6]$ as grayish black crystals having a metallic sheen, which are sensitive to air and moisture. Its structure was solved by complete X-ray analysis (space group C2/m, $Z = 2$; $a_0 = 965.2$, $b_0 = 1362.1$, $c_0 = 890.2$ pm, $\beta = 117.34°$; 1305 observed relexion data recorded with a four-circle diffractometer; unweighted R value for anisotropic temperature factors 6.1 %).

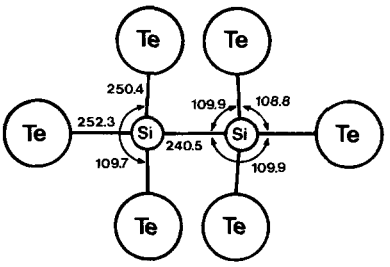


Fig. 1. Structure of hexatellurodisilicate(6−). Bond lengths [pm] and angles [°].

In contrast to Si_2Te_3[2], where the Si_2Te_6 units are linked two-dimensionally to form infinite double layers, the disilicate groups are isolated in $K_6[Si_2Te_6]$ (Fig. 1). The bond lengths have the values expected for covalent bonds. The Si_2Te_6 has 2/m symmetry but deviates only slightly from the ideal $\bar{3}$ 2/m symmetry. The bond angles at silicon indicate almost ideal tetrahedral coordination. The K atoms link the Si_2Te_6 groups in a deformed octahedral or trigonal-prismatic environment to form a three-dimensional network without any preferred planes of cleavage.

Procedure

Si (0.1680 g), K (0.7015 g), and Te (2.2892 g) are weighed into a quartz ampoule ($d = 20$ mm, $l = 50$ mm), which is then evacuated and sealed. The ampoule is heated in a corundum crucible to 630 °C (sillite furnace). After 1 h the temperature is slowly lowered to 280 °C over a period of 6 h, and cooling allowed to proceed further. Short grayish black prism isolated from the regulus can be stored under anhydrous liquid paraffin.

Received: June 1, 1977 [Z 767 IE]
German version: Angew. Chem. *89*, 566 (1977)

CAS Registry numbers:
$K_6[Si_2Te_6]$, 63393-80-6

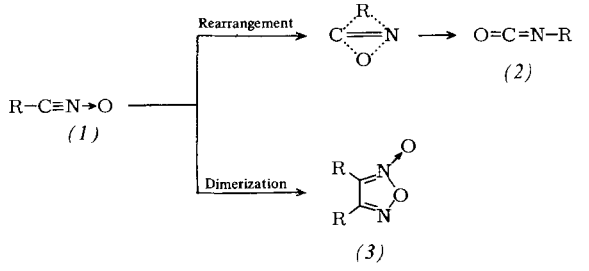
[*] Dr. G. Dittmar
Eduard-Zintl-Institut, Anorganische Chemie II, Technische Hochschule Hochschulstrasse 4, D-6100 Darmstadt (Germany)

[1] *A. Weiss, G. Rocktäschl*, Z. Anorg. Allg. Chem. *307*, 1 (1960); *G. Rocktäschl, W. Ritter, A. Weiss*, Z. Naturforsch. *19b*, 958 (1964); *H. Hahn, H. Schulze, L. Sechser*, Naturwissenschaften *52*, 451 (1965); *H. Hahn, W. Klingen, P. Ness, H. Schulze, ibid. 53*, 18 (1966); *B. Krebs, J. Mandt*, Z. Anorg. Allg. Chem. *388*, 193 (1972); *J. E. Iglesias, H. Steinfink*, J. Solid State Chem. *6*, 93 (1973); *J. T. Lemley*, Acta Crystallogr. *B 30*, 549 (1974).
[2] *G. Dittmar*, Dissertation, Technische Hochschule Darmstadt 1976; *K. Ploog, W. Stetter, A. Nowitzki, E. Schoenherr*, Mater. Res. Bull. *11* (9), 1147 (1976).

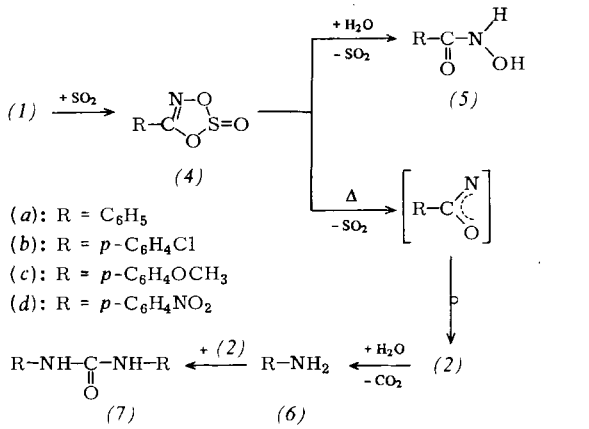
Catalyzed Rearrangement of Nitrile Oxides to Isocyanates[**]

By *Georg Trickes* and *Herbert Meier*[*]

The rearrangement of nitrile oxides *(1)* to isocyanates *(2)* is of particular interest because of the simultaneous shift of two ligands along a CN unit. This long-known reaction[1] has recently been studied in some detail by *Grundmann et al.*[2]. Use of the thermal rearrangement *(1)* → *(2)* is severely restricted by the competing dimerization of *(1)* to the furoxanes *(3)*.



While studying the photochemistry of 1,2,3-thiadiazole 1,1,2-trioxides[3] we discovered a catalytic process permitting the rearrangement *(1)* → *(2)* to be performed under such mild conditions that dimerization is avoided. A suitable catalyst is sulfur dioxide, which participates in the reaction as a dipolarophile.



(2) directly from *(1)* 70-95%
(7) directly from *(1)* 68-93% *(7)* from *(2)* 78-98%
(5) directly from *(1)* 81-94% *(5)* from *(2)* 98%

In this way the rearrangement of nitrile oxides *(1)* to the isocyanates *(2)* in excellent yields can be accomplished directly in boiling anhydrous benzene; however, 1,3,2,4-dioxathiazole 2-oxides *(4)* can also be isolated as intermediates[4]. Compounds *(4)* are extremely sensitive to moisture and quantitatively afford hydroxamic acids *(5)* on treatment with water at room temperature. The first published synthesis of *(4)*[5] utilized the reverse reaction of *(5)* with sulfinyl chloride.

If work-up is carried out in aqueous medium at 70—80 °C, compounds *(2)* yield the symmetrical urea derivatives *(7)* *via* the amines *(6)*.

[*] Prof. Dr. H. Meier, Dipl.-Chem. G. Trickes
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

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

Identification of *(2)*, *(4)*, *(5)*, and *(7)* utilized the usual analytical and spectroscopic methods (in some cases in comparison with authentic samples).

Received: June 21, 1977 [Z 766 IE]
German version: Angew. Chem. 89, 562 (1977)

CAS Registry numbers:
(1a), 873-67-6; *(1b)*, 15500-74-0; *(1c)*, 15500-73-9; *(1d)*, 2574-03-0; *(2a)*, 103-71-9; *(2b)*, 104-12-1; *(2c)*, 5416-93-3; *(2d)*, 100-28-7; *(4a)*, 19279-25-5; *(4b)*, 63324-79-8; *(4c)*, 19279-26-6; *(4d)*, 19279-27-7; *(5a)*, 495-18-1; *(5b)*, 1613-88-3; *(5c)*, 10507-69-4; *(5d)*, 1613-76-9; *(6a)*, 62-53-3; *(6b)*, 106-47-8; *(6c)*, 104-94-9; *(6d)*, 100-01-6; *(7a)*, 102-07-8; *(7b)*, 1219-99-4; *(7c)*, 1227-44-7; *(7d)*, 587-90-6

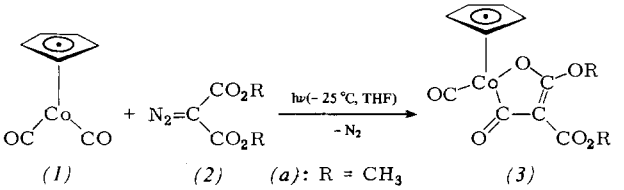
[1] *S. Gabriel, M. Hoppe*, Ber. Dtsch. Chem. Ges. *19*, 1145 (1886); *H. Wieland, ibid. 42*, 803, 4207 (1909).
[2] *C. Grundmann, J. M. Dean*, Angew. Chem. *76*, 682 (1964); Angew. Chem. Int. Ed. Engl. *3*, 585 (1964); *C. Grundmann, P. Kochs, ibid. 82*, 637 (1970) and *9*, 635 (1970), respectively; *C. Grundmann, P. Kochs, J. R. Boal*, Justus Liebigs Ann. Chem. *761*, 162 (1972).
[3] *H. Meier, G. Trickes, H.-P. Braun*, Tetrahedron Lett. *1976*, 171; *G. Trickes, H.-P. Braun, H. Meier*, Justus Liebigs Ann. Chem. *1977*, in press.
[4] Cf. *J. Sauer, K. K. Mayer*, Tetrahedron Lett. *1968*, 319; *E. Eibler, J. Sauer, ibid. 1974*, 2565.
[5] *I. L. Knunyants, E. G. Bykhovskaya, V. N. Frosin*, Dokl. Akad. Nauk SSSR *127*, 337 (1959); *H. Boeshagen*, DBP 1157231 (1963).

Carbene Addition to Dicarbonyl(η-cyclopentadienyl)cobalt[1]

By *Manfred L. Ziegler, Klaus Weidenhammer*, and *Wolfgang A. Herrmann*[*]

Oxidative addition with elimination of CO occupies a special place in the chemistry of dicarbonyl(η-cyclopentadienyl)cobalt *(1)*[2]. The reason for this is the low coordination number of the metal atom, which facilitates nucleophilic attack at the center of the molecule.

While aliphatic diazo compounds readily react with *(1)* on heating to give dinuclear μ-methylene cobalt complexes[3], we have now also been able to synthesize mononuclear derivatives—*via* a photochemical route starting from the dialkyl diazomalonates *(2a)* and *(2b)*. The green crystalline compounds *(3a)* and *(3b)*, obtained in *ca.* 60 % yield, are moderately air-stable, diamagnetic, and readily dissolve in strongly polar solvents. According to total elemental analysis and osmometric molecular weight determinations they have the empirical formulas $C_{12}H_{11}CoO_6$ and $C_{14}H_{15}CoO_6$, respectively. Since the mass spectra show no molecular ions, and the IR, ^{1}H-NMR and ^{13}C-NMR spectra (Table 1) provide only proof of the structure $(\eta^5\text{-}C_5H_5)Co(CO)L$ but no conclusive evidence about the constitution of the ligand L, we have carried out a crystal structure analysis on the ethyl derivative *(3b)*[4]. The presence of a five-membered metallacycle proves that the reaction



[*] Dr. W. A. Herrmann
Chemisches Institut der Universität
Universitätsstraße 31, D-8400 Regensburg 1 (Germany)
Prof. Dr. M. L. Ziegler, Dipl.-Chem. K. Weidenhammer
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1 (Germany)

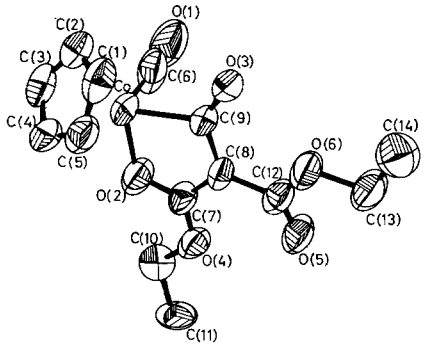


Fig. 1. ORTEP diagram of the carbene adduct *(3b)*.

Bond lengths [pm]		Angle [°]	
Co—C6	164.3(20)	O2—Co—C9	85.02(58)
Co—O2	192.2(12)	Co—O2—C7	112.64(85)
Co—C9	205.8(14)	O2—C7—C8	121.25(81)
O2—C7	129.1(19)	C7—C8—C9	115.3(1.3)
C7—C8	139.5(16)	C8—C9—Co	105.59(82)
C7—O4	131.6(21)		
C8—C9	144.7(26)		
C8—C12	146.0(20)		
C9—O3	116.3(18)		

Table 1. Spectroscopic data of the carbene addition products *(3a)* and *(3b)*.

(3a)	*(3b)*
IR [νCO in cm^{-1}]: 2052 vs; 1720 s, 1690 s-vs (sh, br) [CH_2Cl_2] 2032 vs; 1694 vs, 1683 vs (sh) [KBr]	2042 vs; 1720 s (sh), 1680 s (sh, br) [CH_2Cl_2] 2043 vs; 1712 vs (sh) [KBr]
^{1}H-NMR [a]: C_5H_5 ^{1}4.75 (5), CH_3 ^{1}6.25 (3) and ^{1}6.38 (3) [CD_2Cl_2]	C_5H_5 ^{1}4.83 (5), CH_2 ^{4}5.86 (4), CH_3 ^{3}8.76 and ^{3}8.78 (tot. int. 6) [$CDCl_3$]; 90-MHz FT spectrum C_5H_5 ^{1}5.50 (5), CH_2 ^{4}5.72 and ^{4}6.05 (tot. int. 4), CH_3 ^{3}8.80 and ^{3}9.01 (tot. int. 6) [C_6D_6]
^{13}C-NMR [b]: C_5H_5 92.61, CH_3 50.63, MCO *ca.* 200.0, remaining C: 161.50, 183.79, 205.63, 214.08	C_5H_5 92.61, CH_2 63.04 and 59.21, CH_3 14.69, MCO *ca.* 200.5, remaining C: 161.05, 183.60, 205.43

[a] τ values; TMS int.; +33 °C. [b] δ values; 22.63 MHz; TMS int.; +32 °C; *ca.* 1.5 M solution in CD_2Cl_2; "remaining C": assignments uncertain.

proceeds *via* the unusual 1,3-addition of bis(alkoxycarbonyl)-carbene : $C(CO_2R)_2$ to the substrate *(1)*. Linking of a carbene carbonyl oxygen atom to the metal atom and conversion of an M—CO— group into an M—Acyl function increases the coordination number of the central metal atom, which is finally located in a distorted tetrahedral environment. To our knowledge [2+3]-carbene additions of this type have hitherto not been observed in organometallic chemistry.

Experimental[5]:

A solution of *(1)* (3.60 g, 20 mmol) and *(2a)* (3.79 g, 24 mmol) or *(2b)* (4.50 g, 24 mmol) in tetrahydrofuran (200 ml) is irradiated (Hg high-pressure lamp TQ 150) for 10 h at −25 °C in a pyrex immersion-lamp apparatus furnished with internal and external cooling. The green reaction solution is concentrated by evaporation under high-vacuum at +20 °C and then purified by column chromatography (Kieselgel 60, Merck 7734; Act. II—III; 48 × 2 cm; 10 °C). The carbene adducts *(3a)* and *(3b)*, respectively, are eluted with acetone as rapidly migrating deep-green zones. The oily residue remaining after evaporation of the eluate is crystallized from ether/CH_2Cl_2 (10:1) at −35 °C. The dark green crystals have a metallic luster. After washing them with 3 × 10 ml ether they are recoverable in analytically pure form. *(3a)*: 3.60 g (58%); m.p. 145—149 °C. *(3b)*: 4.13 g (61%); m.p. 118 to 119 °C.

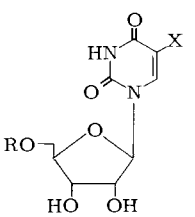
Received: June 10, 1977 [Z 758 IE]
German version: Angew. Chem. *89*, 557 (1977)

CAS Registry numbers:
(1), 12078-23-8; *(2a)*, 6773-29-1; *(2b)*, 5256-74-6; *(3a)*, 63301-85-9; *(3b)*, 63301-86-0.

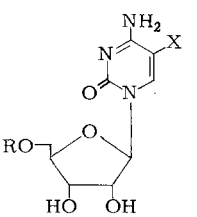
[1] Complex Chemistry of Reactive Organic Compounds, Part 19. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 18: *W. A. Herrmann, M. Huber*, J. Organomet. Chem., in press.
[2] *J. P. Collman, W. R. Rooper*, Adv. Organomet. Chem. 7, 53 (1968); *R. Kummer, W. A. G. Graham*, Inorg. Chem. 7, 523 (1968).
[3] *W. A. Herrmann*, Chem. Ber., in press.
[4] Crystal data: monoclinic, space group C_{2h}^5-$P2_1/c$; $a = 1124.6(4)$, $b = 799.7(5)$, $c = 1900.8(6)$ pm, $\beta = 119.50(2)°$; $Z = 4$. 1393 independent non-zero reflections were measured with an automatic Siemens single crystal diffractometer and corrected in the usual way ($R = 7.4$ %).
[5] All operations must be carried out in the absence of O_2 and H_2O.—Experimental and spectroscopic details: *W. A. Herrmann, M. L. Ziegler, K. Weidenhammer*, J. Organomet. Chem., in preparation.

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.



(1), X = R = H

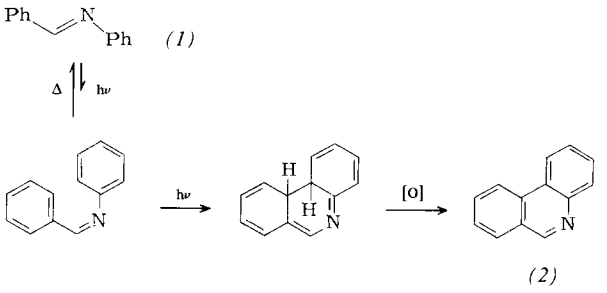


(2), X = R = H

Syntheses and rearrangements of 5-substituted pyrimidine nucleosides and nucleotides are reviewed in an article by *T. K. Bradshaw* and *D. W. Hutchinson* with particular emphasis on the derivatives of uridine *(1)* and cytidine *(2)*. X in *(1)* can, for example, be Cl, Br, NO_2 or CH_2OH, while with *(1)*, R = PO_3H or $(PO_3H)_2H$, 5-hydroxy derivatives are also obtained. Halogen derivatives of *(2)*, R = H, are also known; 5-hydroxymethyl compounds are not formed. In all syntheses the result strongly depends upon substitution pattern. Mechanisms are suggested for substitution at C-5 and for exchange reactions. Biochemically interesting in this connection is the mode of action of the thymidylate synthetase. [5-Substituted Pyrimidine Nucleosides and Nucleotides. Chem. Soc. Rev. *6*, 43—62 (1977); 110 references]

[Rd 956 IE—F]

The photochemistry of imines forms the theme of a review by *A. C. Pratt*. Especially dealt with are imines of the type $R^1R^2C{=}NR^3$, in which R^3 is alkyl, aryl or acyl. Typical reactions are, *inter alia*, geometrical isomerization, photoreduction to amines, photocyclizations of *N*-benzylideneanilines

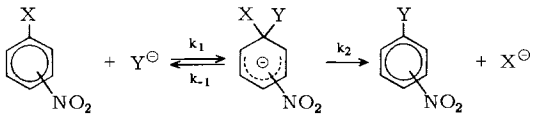


(2)

such as *(1)* to phenanthridine derivatives *(2)*, and the α-cleavage of *N*-acylimines. [The Photochemistry of Imines. Chem. Soc. Rev. *6*, 63—81 (1973); 59 references]

[Rd 957 IE—F]

Nucleophilic substitution—with emphasis on linear free energy relationships between reactivity and physical properties of leaving groups and substrates—is the subject of a review by *G. Bartoli* and *P. E. Todesco*. In a nucleophilic substitution, a nucleophile ($Y^{\ominus}$) replaces a nucleofugic (leaving) group X; an example is



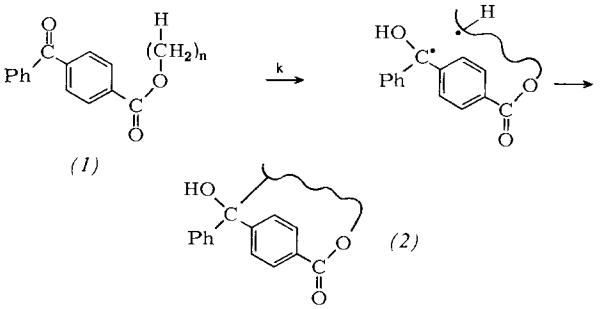
There is no order of precedence for $Y^{\ominus}$ and X that is valid under all conditions. Interactions between $Y^{\ominus}$, X and the rest of the substrate must be taken into consideration. In the case of halo-arenes and -heteroarenes it can be shown that the polarizability of the halogen and of the nucleophile (*e.g.* $C_6H_5S^{\ominus}$ and $CH_3O^{\ominus}$) play a decisive role. [Nucleophilic Substitution. Linear Free Energy Relationships between Reactivity and Physical Properties of Leaving Groups and Substrates. Acc. Chem. Res. *10*, 125—132 (1977); 48 references]

[Rd 958 IE—L]

Stereoselectivity in the binding of transition-metal chelates to nucleic acid constituents is reported on by *L. G. Marzilli* and *T. J. Kistenmacher*. It is known, for example, that ions such as Cu^{2+} destabilize the DNA double helix because they disrupt base-pairing through their binding to heterocyclic bases; in contrast, ions such as Mg^{2+} increase the stability of the double helix, since they minimize repulsion between negatively charged groups through their binding to phosphate chains. Which factors then determine the selectivity, *i.e.* determine which binding centers will be preferred by a given metal chelate? In this connection rules could be derived by systematically varying the geometry of the metal (particularly Cu(II) and Co(III)) and the size and hydrogen-bonding potential of chelate ligands (*e.g.* ethylenediamine, 2,4-pentanedionate, glycyl glycinate). Noteworthy are the strong hydrogen-bonding interactions involving exocyclic groups on the purine and the pyrimidine ring. These bonding interactions, coupled with repulsive nonbonded interactions, can influence the stability of the complex. [Stereoselectivity in the Binding of Transition-Metal Chelate Complexes to Nucleic Acid Constituents: Bonding and Nonbonding Effects. Acc. Chem. Res. *10*, 146—152 (1977); 29 references]

[Rd 959 IE—L]

Determination of the conformation of hydrocarbon chains in solution by photochemical probes is discussed in an article by *M. A. Winnik*. In such chains conformational equilibrium is reached in about 10 ns. The phosphorescence lifetimes of benzophenone derivatives such as *(1)* are of the order of 10—100 μs. Chemical reactions which quench the excited state, *e.g.* cyclization to *(2)*, shorten this time. The constant *k*



was measured in CCl_4, acetic acid, acetonitrile and other solvents; its value increases monotonically with the chain length. Compounds with $n<9$ do not cyclize. The basis of calculations was a diamond lattice model for the hydrocarbon chain. [Photochemical Probes of Hydrocarbon Chain Conformation in Solution. Acc. Chem. Res. *10*, 173—179 (1977); 35 references]

[Rd 960 IE—L]

The study of metal clusters can, according to *E. L. Muetterties*, provide a valuable insight into chemisorption and catalytic processes on surfaces. Metal clusters are discreet molecular species in which three or more atoms form a triangular or polyhedral array; the center position is almost always vacant and the periphery is usually enveloped by ligands. The range of examples extends from $Os_3(CO)_{12}$ and $Pd_3(CNR)_6$ through species having 4 to 10 or 12 metal atoms up to the ion $Pt_{15}(CO)_{30}^{2-}$. A cluster molecule may be regarded as a little piece of metal with chemisorbed species on the periphery. The chemistry of this molecule allows conclusions to be drawn about the processes taking place in heterogeneous catalysis. [Molecular Metal Clusters. Science *196*, 839–848 (1977); 75 references]

[Rd 961 IE—F]

Neutron Activation Tables. By *G. Erdtmann*. Vol. 6 of the series edited by *K. H. Lieser*. Verlag Chemie, Weinheim—New York 1976. 1st edit., 146 pp., 15 figs., bound, DM 78.—.

A brief introduction to the "Neutron Activation Tables" is followed by very clear definitions of the tabulated values.

The tables are set out clearly in the order of the mass numbers. Data are given for the following reactions of all stable elements and for a large number of synthetic elements: a) with slow reactor neutrons (mostly n, γ) reactions with thermal and epithermal neutrons, b) with fast reactor neutrons, and c) with 14.5 MeV neutrons. In each case the tables show the starting nuclide and its isotopic abundance, the reactions, the half-life of the product, the reaction cross section, the activities for all six irradiation times, and the strongest gamma lines and their intensities. The appendix provides information on the complex disintegration series of some radionuclides formed in neutron reactions.

Along with the very clear arrangement of the tables it should be particularly noted that the author has taken great care to collect and select the best-attested values from the most recent records of nuclear data. This is therefore a valuable reference work for daily use in the laboratory and will certainly be of use not only for the nuclear physicist, chemist, or physician but also for all those who are only occasionally concerned with neutron activation. Production and printing match the high quality of its contents.

R. Henkelmann [NB 372 IE]

An Introduction to the Chemistry of Heterocyclic Compounds. By *R. M. Acheson*. John Wiley & Sons Ltd., New York—London 1976. 3rd edit., xvii, 501 pp., bound, £ 17.75.

As the author states in the preface, the present book attempts to give the student a brief outline of the most important properties and chemical reactions of heterocyclic systems in about 500 pages. It is therefore intended as a bridge between the current original publications too specialized for the beginner and textbooks of organic chemistry in which, in the author's opinion, heterocyclic chemistry is frequently dealt with too summarily.

After a short introduction to the nomenclature, heterocycles, arranged predominantly in order of their ring size, are treated in ten main chapters. For all the more important representatives of the various classes exhaustive information is given on physical and chemical properties, reactivities, mechanisms, and approaches to syntheses. A pleasing feature is that almost every chapter section ends with interesting examples of substances, taken mostly from the chemistry of natural products. Each chapter contains an exhaustive bibliography, and at the end of the book there is a comprehensive subject and compound index.

The book represents the state of heterocyclic chemistry at the beginning of 1975. The wealth of results and new developments that have appeared since the last 1967 edition is suitably taken into account. Thus, classes or substances such as the benzotriazoles, relatively large ring systems (azonines, azocines, and diazepines) and the 1,2-dioxetanes (important in photochemical processes), new syntheses, spectroscopic results, and mechanistic ideas have now been included in the new edition. However, some interesting compounds, such as α-lactones, benzene trioxide, and benzene triimine, have been omitted. The use of the obsolete method using letters (instead of the clearer method of showing skeletons) and the unjustified rotation of formulas in synthetic schemes are a didactic weakness, but this does not diminish the scientific value of this work. The book does complete justice to the aim mentioned at the beginning, although it is rather expensive for the student.

Gerhard Bringmann [NB 381 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P.O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 9
September 1977
Pages 559–662

Heinrich Wieland Centennial: His Lifework and His Legacy Today[**]

By Bernhard Witkop[*]

Many of *Heinrich Wieland*'s friends and disciples remember all too well his sixtieth, sixty-fifth[1], seventieth, and eightieth birthdays; the last-named one was observed quietly on June 4, 1957[2]. He thanked us all with the Goethe quotation, behind which he tried to hide his emotion[3]. Of the two colleagues in Munich who were *Wieland*'s very close friends, *Hans Fischer*, in *Wieland*'s words, paraphrased from *Goethe*'s Faust, "could not be held back by the ringing of the Easter Bells from taking his own life, on Saturday, March 31, 1945"[4], but *Walter Gerlach* is with us today as a living link to a tradition so great and unique that the present student generation may have difficulties in grasping its true dimensions. It seems appropriate to let physics, as the more logical and mathematical science, lead us to an evaluation which would also facilitate a re-interpretation of the history of chemistry. In doing so, as a useful exercise in epistemology, let us look at the famous experiment of *Stern* and *Gerlach* (1920–1923) when the two scholars used a beam of silver atoms to prove the quantization of space and to measure the magneton[5–7]. These memorable experiments[8] were the turning point in the study of the mechanics of the atom, leading, eventually, to the electron spin, the development of molecular beam technique by *I. I. Rabi*, magnetic resonance, maser and laser and related work in pure physics[9]. In this presentation we are looking, as it were, at the "fine structure" of a small segment of the spectrum of physics. Will it be possible to transfer this kind of analysis to the historical development of modern organic chemistry and to the contributions of *Heinrich Wieland*, who always considered "biochemistry an area neglected by organic chemists"[10]?



Heinrich Wieland [photograph by *B. Witkop* at Starnberg in 1953].

Munich's tradition as the origin and nursery of great ideas and men of science began with *Liebig*, who passed the "olympic fire" on to *Adolf von Baeyer*, *Richard Willstätter*, *Heinrich Wieland*, and many others (Fig. 1)[11]. Just as our old master is very much present and with us at this moment, so are the disciples who, in the words of *A. W. von Hofmann* "have preceded us"[12]. *Liebig* continued his studies on silver fulminate, begun with *Kastner*, in Paris with *Vauquelin*: in 1832 *Gay-Lussac* presented the results to the Academy in the presence of *Alexander von Humboldt*. Thanks to *Humboldt* and *Gay-Lussac*'s sponsorship, *Liebig* was appointed

[*] B. Witkop
National Institutes of Health (4-330)
Bethesda, Maryland 20014 (USA)

[**] Commemorative lecture under the auspices of the Gesellschaft Deutscher Chemiker at the Fall Meeting in Munich, September 13, 1977.

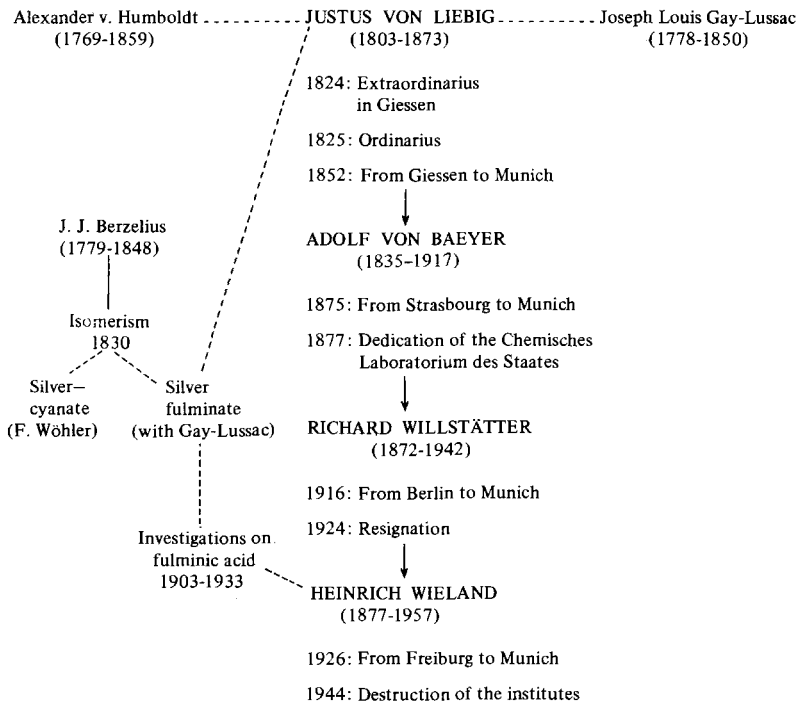


Fig. 1. The Munich Chair of Organic Chemistry in the course of history.

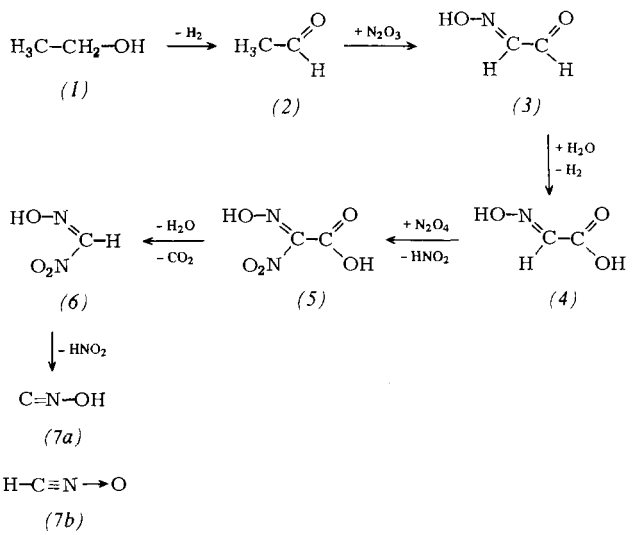


Fig. 2. Formation of fulminic acid *(7a)* or *(7b)* from alcohol, nitric acid, and mercury.

Extraordinarius for philosophy at Giessen in 1824[13]. *Liebig* performed an accurate analysis of silver fulminate. *Wieland*'s contribution to this highly traditional field came in 1903 when he elucidated the formation and polymerization of fulminic acid. He showed methylnitrolic acid *(6)* to be the key intermediate in the classical preparation of fulminic acid *(7)* from alcohol *(1)*, nitric acid, and mercury (Fig. 2).

Liebig's fulminic acid or 2-nitromalonamidonitrile *(11)* arises by dimerization of free fulminic acid through partial hydrolysis of the mercury salt. *Nef*'s formulation of fulminic acid as formoxime *(7a)* has recently been changed to that of formonitrile oxide *(7b)*[14]. Dimerization leads to (hydroxyimino)acetonitrile oxide *(8)* which adds more fulminic acid to yield furoxanaldoxime *(9)* that then rearranges to 4-nitro-Δ^4-isoxazolin-5-imine *(10)*, *Grundmann*'s prefulminuric acid *(10)*[15]. Ring opening of *(10)* leads to fulminuric acid *(11)*. Thus, *Wieland*'s essentially correct reaction mechanism of the oligomerism of fulminic acid was not revised until very recently. The identical composition of silver fulminate and silver cyanate was recognized by *Liebig* and prompted *Berzelius* to coin the term *isomerism* in 1830. *Wieland*'s extensive investigations on nitrogenous compounds have been reviewed by *Friederich Klages* and later by *Rolf Huisgen*[1] who by the use of modern methods and the entire armamentarium of electronic theory, quantum mechanics, and NMR spectroscopy expanded and completed his mentor's heritage in a manner hardly foreseeable.

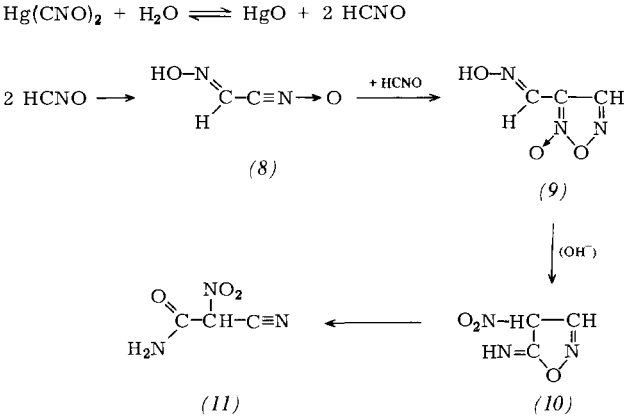


Fig. 3. Dimerization of fulminic acid *(7)* to fulminuric acid *(11)*.

Wieland himself enjoyed remembering his predecessor by telling the famous story of *Liebig*'s "Abendvorlesung" on February 12, 1853, when, in the presence of their majesties, King Maximilian II and the Queen of Bavaria, accompanied

by Princes and Princesses, a violent explosion injured not only *Liebig* but also members of the Royal Court[16]. According to *Wieland*, the beauteous Princess *Mary* saved the situation when she got up and returned, with a curtsy and a smile, a piece of equipment that had landed on her lap to the dumbfounded *Liebig*. *Frederick Schönbein*, a close friend of *Liebig*, characterized Munich in those days[17]: "Of all the cities in Europe, Munich probably has the largest number of eminent chemists. If I am not mistaken, there are no less than seven professors who teach their discipline and head their own laboratories".

In our historical analysis we now come to the dichotomy of style: classical *versus* romantic. Among *Liebig*'s scientific progeny we have proponents of both attitudes. We would certainly consider *Warburg* on the side of strict form, fact, reason, and rigid deduction. *Wieland*, on the other hand, shows in his work an artistic streak, is intuitive and guided more by emotion and imagination. During his student days he had trouble renting a room in Munich because he was an undaunted piano player to the extent that he enjoyed the reputation of a "forte-pianist" throughout the neighborhood. In the selection of his topics, especially among natural products (see Charts I and II), he was guided by his closeness to, and love of, nature. The details of this part of his research have been adequately described, but the latent underlying principles require some elaboration. Nowadays we face the question of classification of natural products: clearly *Wieland* was attracted by physiological activity rather than by taxonomy, but to some extent he had a sixth sense for the subtle aspects of biogenesis, as we know it today. From the tacky industrial yeast mother liquors of ergosterol production

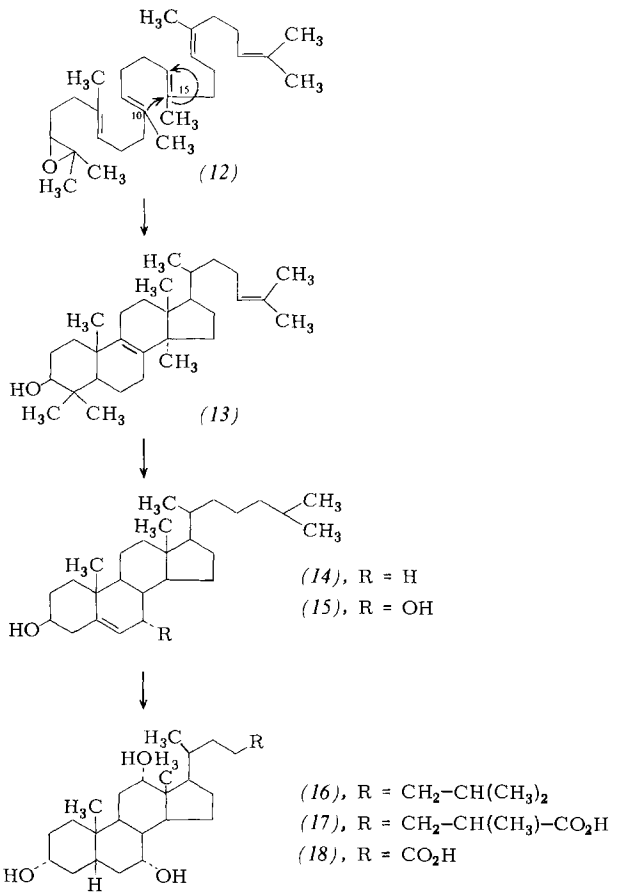


Fig. 4. Biosynthesis of cholic acid *(18)* by enzymatic stereoselective cyclization of squalene 2,3-epoxide *(12)* *via* lanosterol *(13)* and cholesterol *(14)* with intramolecular migration of the methyl groups at C-10 and C-15.

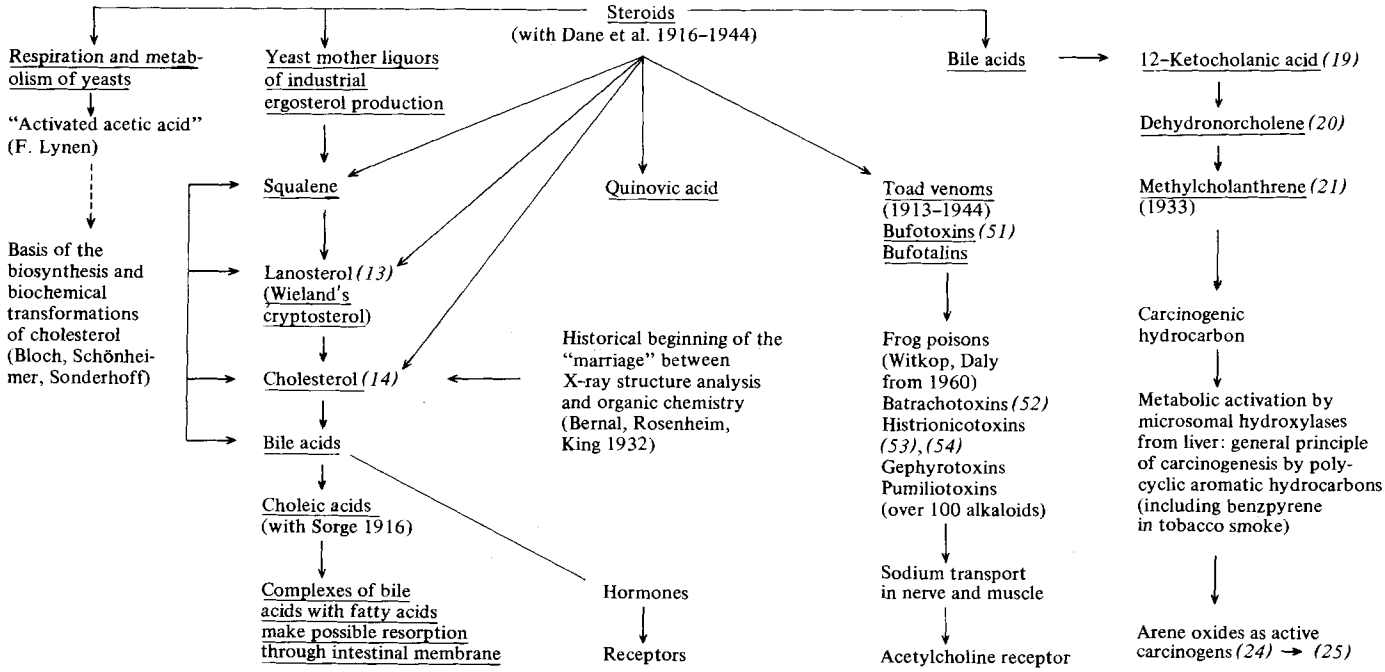


Chart I. *Wieland*'s work on natural products: juxtaposition of the static classical chemistry of natural products performed by *Wieland* and the dynamic biochemistry of metabolic processes that resulted therefrom. *Wieland*'s classical approach to natural products chemistry is apparent from the isolation and structural elicidation of key compounds, such as squalene, cryptosterol, and cholesterol from the yeast mother liquors of industrial ergosterol production. It was not until the 1940's that *Konrad Bloch*, *Rudolf Schönheimer*, and (in 1937) *Wieland*'s student *Robert Sonderhoff* introduced isotopic labeling, which permitted elucidation of the biosynthesis of cholesterol and the bile acids. Likewise, forty years elapsed between *Wieland*'s synthesis of the carcinogenic hydrocarbon methylcholanthrene and proof of the connection between formation of labile arene oxides in the liver or lung and carcinogenesis. The only compound that has not yet served as the basis for biochemical developments is quinovic acid, a pentacyclic triterpene from the mother liquors of quinine production. *Wieland*'s first foray into biochemical dynamics was his work on metabolism and respiration of yeast. These studies led to the concept of "activated acetic acid" and—through *F. Lynen*—to its structure.

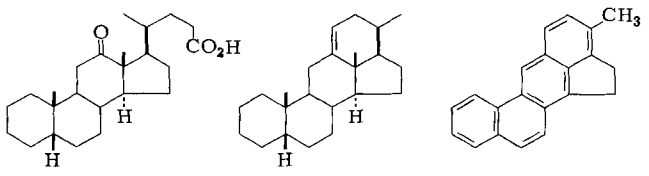
he hoped to isolate intermediates in steroidal biosynthesis. Indeed, he demonstrated the presence of squalene and "cryptosterol", *i.e.* lanosterol *(13)*; however, these precursors were not related with cholesterol *(14)* until *Konrad Bloch*[18] (Fig. 4) established a most fascinating concerted stereoselective intramolecular cyclization of squalene 2,3-oxide *(12)*, followed by oxidative rearrangement to cholesterol *(14)*.

The introduction of radioactive markers or deuterium goes back to *Rudolf Schönheimer*[19] who established the concept of the dynamic state of body constituents[20], and to *Wieland*'s laboratory, especially *Robert Sonderhoff*[21], the promising young biochemist who had such an early, tragic death. The new isotopic label technique showed clearly that *e.g.* cholic acid *(18)* arises from cholesterol *(14)* *via* intermediates *(15)*, *(16)*, and *(17)*. These transformations form the basis of concepts on the etiology of atherosclerosis as they were developed by *Ludwig Aschoff*, *Rudolf Schönheimer*, and others (Fig. 5).

L. Aschoff	1910	Cholesterol esters in atheromatous plaques
A. Windaus	1910	Morphological findings confirmed by chemical means, studies on the chemical constitution of cholesterol and related compounds
H. Wieland	1910	Studies on bile acids
G. Anitschkow	1913	Model of arteriomatosis in the rabbit
S. Thannhauser	1929	Cholesterol metabolic defects, origin of bile acids
R. Schönheimer	1925-1933	Proof of endogenous formation of cholesterol in the animal organism, arteriosclerosis research, metabolism of cholesterol

Fig. 5. Work on cholesterol metabolism and atherosclerosis [19].

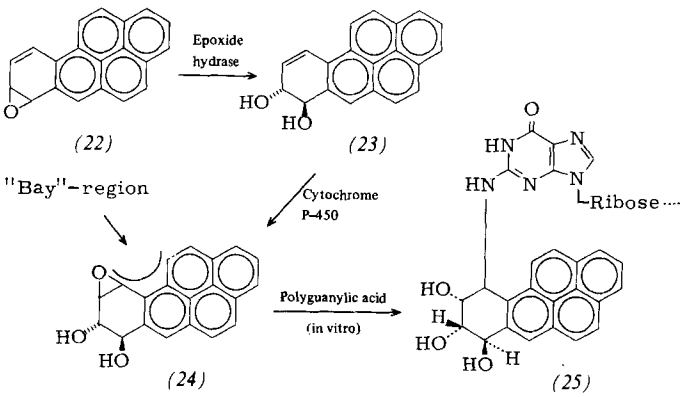
Wieland and *Dane* obtained methylcholanthrene *(21)* by distillation of 12-ketocholanic acid *(19)* and selenium dehydrogenation of dehydronorcholene *(20)* (Fig. 6). This hydrocarbon was soon found to be highly carcinogenic, and represents the starting point in a long search for a mechanism of carcinogenesis by polycyclic aromatic hydrocarbons. The mechanism would have delighted *Wieland*, because it shows how strongly reactions of an initially purely academic nature are involved in intermediate metabolism.



(19) *(20)* *(21)*

Fig. 6. Formation of methylcholanthrene *(21)* from 12-ketocholanic acid *(19)* *via* dehydronorcholene *(20)*.

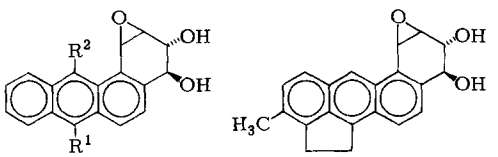
Metabolic activation starts with hepatic hydroxylase P-448 (P-450) to yield, by insertion of an oxygen atom, (autoxidizable) phenols[22] or, by addition of oxygen to a double bond, (labile) arene oxides[23] that open up to *trans*-dihydrodiols with the aid of epoxide-hydrase. Thus benzo[*a*]pyrene would initially form the epoxide *(22)*, easily opened to the (synthetically accessible) optically active highly mutagenic and carcinogenic *trans*-diol *(23)*, presumably the precursor of the "ultimate carcinogen" *(24)* by a second epoxidation at the so-called



(22) *(23)* *(24)* *(25)*

Fig. 7. Mechanism of carcinogenesis by a carcinogenic aromatic hydrocarbon.—An intermediate aliphatic epoxide is likewise postulated in the case of aflatoxin B_1 which causes liver cancer. However, it reacts with guanine units of DNA to form 2-(N^7-guanyl)-2,3-dihydro-3-hydroxyaflatoxin B_1 [26a].

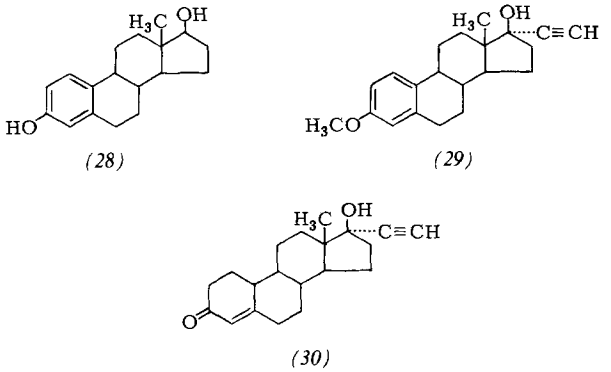
bay region (Fig. 7). Opening of this short-lived diol-epoxide *(24)* *in vitro* by the 2-amino group of polyguanylic acid or *in vivo* by similar electrophilic groups (or phosphate residues) of DNA[24] leads to adducts *(25)* which probably introduce errors in transcription, unless the faulty nucleic acid sequence is removed by excision with the help of special enzymes and repair mechanisms[25]. The active mutagens and probably carcinogenic metabolites of benzanthracene and of 3-methylcholanthrene are similarly formulated as *(26)* and *(27)* (Fig. 8)[26].



(26) *(27)*

Fig. 8. Presumably carcinogenic metabolites of benzanthracene *(26)* and methylcholanthrene *(27)*.

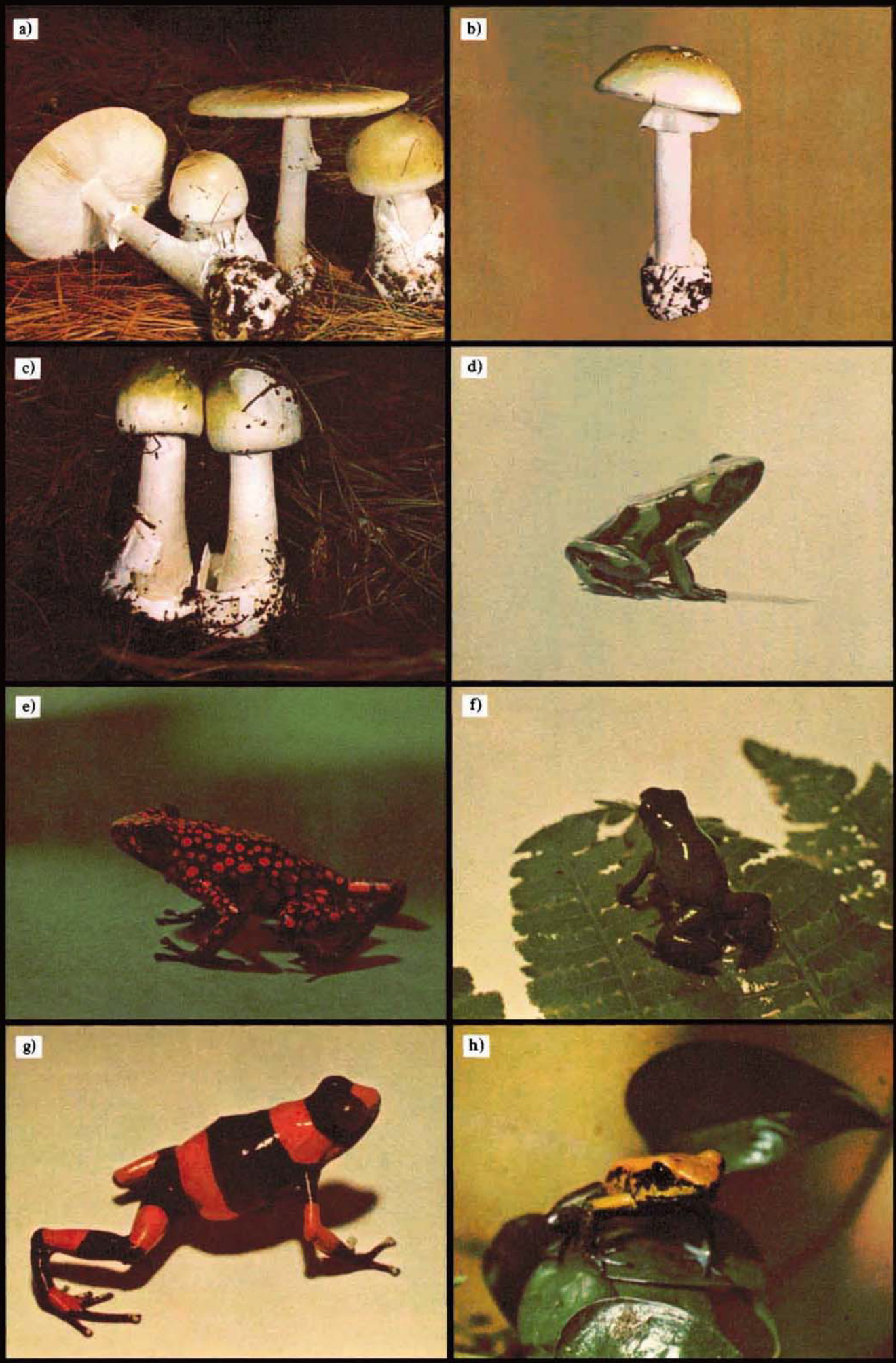
Through *Wieland* and *Windaus* we learned about steroids. Subsequently steroidal hormones such as estradiol *(28)* (Fig. 9) were systematically modified to give new estrogens (*e.g.* mestranol *(29)*) and developed from there into antifertility, agents (*e.g.* norethindrone *(31)*).



(28) *(29)* *(30)*

Fig. 9. Stepwise modification of the estrogenic properties of estradiol (*28*) *via* mestranol *(29)* to the contraceptive norethindrone *(30)*.

The introduction of contraceptive steroids has slowed down the population explosion and changed the culture and morals of the present generation. This provides a straightforward and impressive example for the interdependence of science


a)
b)
c)
d)
e)
f)
g)
h)

and culture. Immunosuppression through corticoids has made possible a new technology of organ transplantation. The intricate action of steroid hormones on their target cell nuclei has only recently been elucidated[27]. Accordingly, cell function is modified by hormonal action in six steps (Fig. 10).

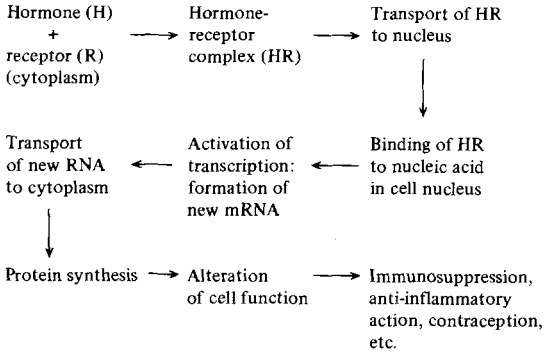


Fig. 10. Mechanism of action of steroidal hormones [27].

The first formulation *(31)* of the bile acids and cholesterol (Fig. 11) rested on an overuse of the so-called Blanc rule and led to an "intelligent error" (in ecclesiastical terms: *oh felix culpa*). The transition from the old *(31)* to the new formulation *(33)* is easier to follow by looking at the somewhat unusual presentation *(32)*.

A highly historical event occurring in the year 1932 was the fortunate consequence of this error, namely, the "marriage" of X-ray crystallographic analysis with "the ocean of organic chemistry" (Fig. 13), in a manner reminiscent of "*Lo Sposalizio Di Venezia Col Mare*" as the beginning of Venice as a great Mediterranean power[28]. This wedding

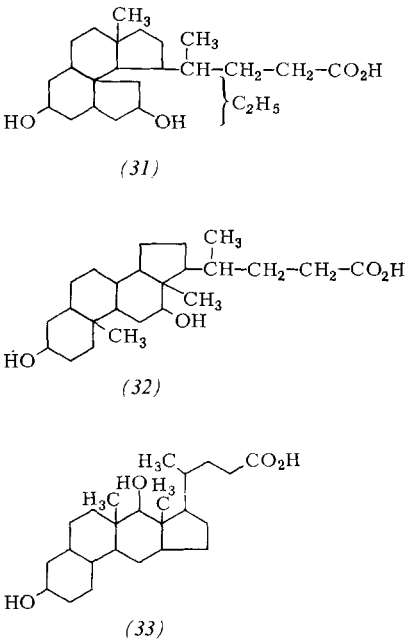


Fig. 11. Comparison of the old formula of deoxycholic acid *(31)* with the revised formula *(33)* via a helpful intermediate way of writing *(32)*.

opened a new era, initially recognized and accepted by classical organic chemists with considerable reluctance. To the crystallographer *Bernal*, and the interpreters *Rosenheim* and *King*, *Wieland*'s old structure *(31)* should be a "thick molecule". But the crystalline dimensions of deoxycholic acid called for a "thin, lath-like molecule" as represented by the flat tetracyclic structure *(33)* which *Wieland* and *Dane* by 1932 had independently deduced from new chemical evidence. Thereafter, important natural compounds, precious by virtue of

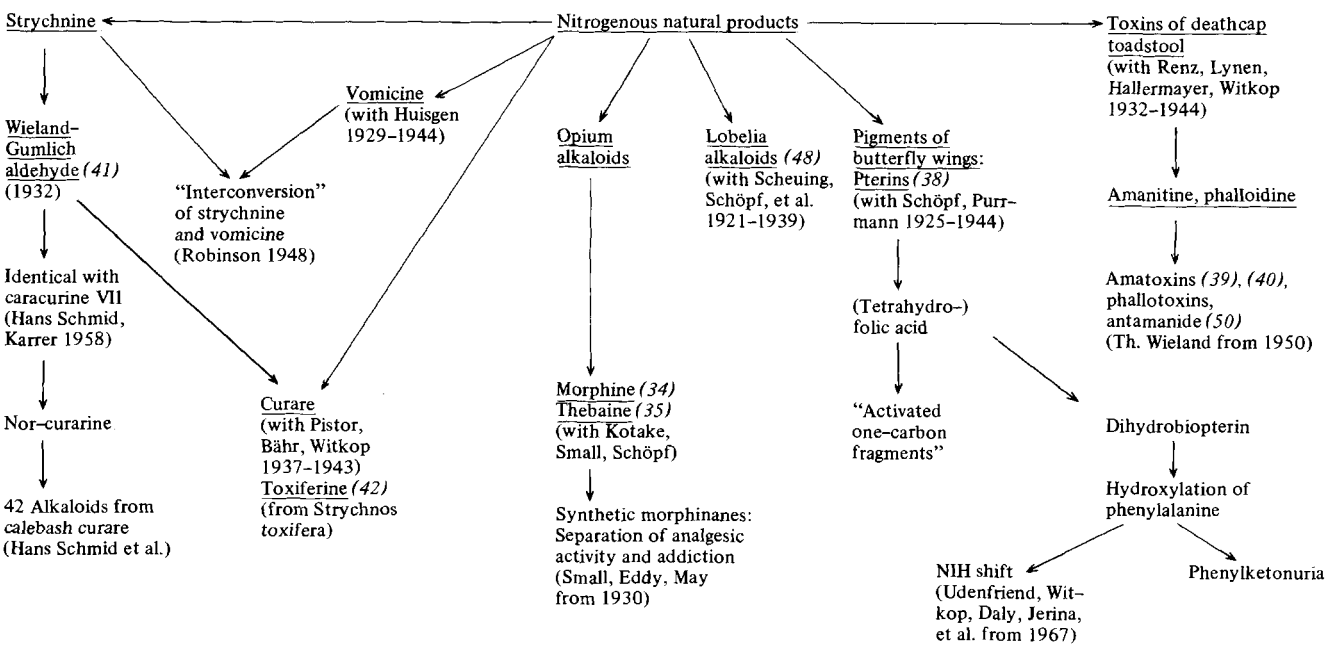
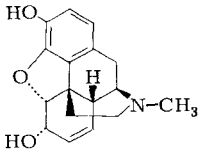


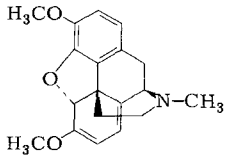
Chart II. *Wieland*'s studies on nitrogenous natural products have had a lasting effect on developments in biochemistry. For example, work on the pigments of butterfly wings with *Schöpf* and *Purrmann* provided the basis of the chemistry of pterins, from which the entire dynamics of the folic acid components of important enzymes can be derived, and also the mechanisms of enzymatic hydroxylation which led to the discovery of the NIH shift. The toxins of the deathcap toadstool have been further investigated by *Wieland*'s son *Theodor*, and utilized in various ways in molecular biology. The antamanides were used by *Isabella Karle* in X-ray studies on the folding and unfolding of cyclic peptides. Synthetic work on the opium alkaloids was continued in Bethesda by *Wieland*'s student *L. F. Small*, *E. Mosettig*, and *E. L. May*, and resolved into addictive and analgetic components. In *Paul Karrer*'s laboratory, *Hans Schmid* (1917—1976) demonstrated how the Wieland-Gumlich aldehyde obtained from strychnine by oxidation could be transformed into alkaloids from calebash curare also investigated by *Wieland*. (*Wieland*'s fields of study are underlined in Chart II.)

their paucity, became fully known up to the last conformational detail and their absolute stereochemistry. *Dorothy Hodgkin*'s very personal, charming, and lucid account of her brilliant X-ray analysis of vitamin B_{12}[29] is essential and pleasurable reading for every chemist[30]. Further examples are selected (Fig. 12) with a strong *pro domo* attitude and an explicable admiration for the pioneering work of *Isabella* and *Jerome Karle*, the inventors of the "symbolic addition procedure"[31].

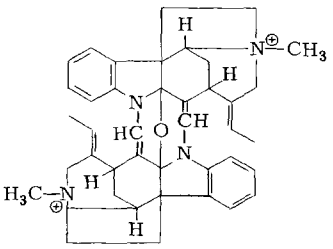
At this juncture, we should return first to *Wieland*'s work on "alkaloids" (Chart II) that covers a wide range from basic



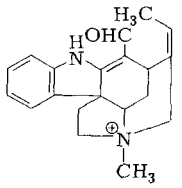
(34)



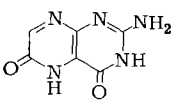
(35)



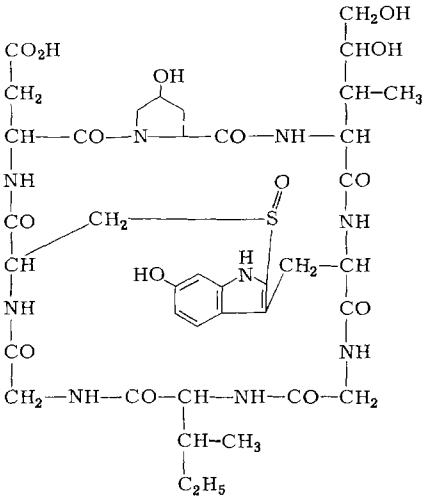
(36)



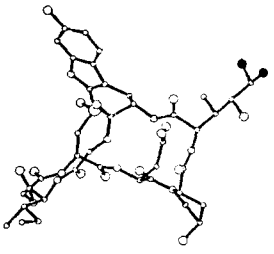
(37)



(38)



(39)



(40)

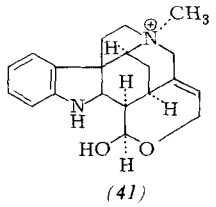
Fig. 12. Some nitrogenous natural products investigated by *Wieland*.

plant products—strychnine, vomicine, lobelines *(38)*, morphine *(34)*, thebaine *(35)*, calabash curare alkaloids *(36)*—to non-basic butterfly wing pigments *(38)* and cyclic peptides *(39)* and *(40)*[32] from *Amanita phalloides*, the most poisonous mushroom known (Figs. 12 and 16).

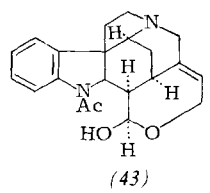
Wieland's intuition and "prepared mind"[33] in selecting topics for his research, recalls *Goethe*'s way of linking good fortune or serendipity to merit: "Wie sich Verdienst und Glück verketten, das geht den Toren niemals ein, wenn sie den Stein der Weisen hätten, der Weise mangelte dem Stein."[34] Historians and sociologists must examine "cases of serendipity gained and serendipity lost"[35]. In *Wieland*'s work, such gains and losses often merge, become latent or dormant and then surface again to produce spectacular results. The most striking example in this respect is a rather academic degradation product of strychnine (Fig. 13), the so-called Wieland-Gumlich aldehyde *(41)*[36]. It was probably standing on the shelf when *H.-J. Pistor*, *K. Bähr*, and I started postdoctoral work on calabash curare in *Wieland*'s private laboratory in 1950. We then isolated, from the bark of *Strychnos toxifera* toxiferine-I *(42)*, one of the most toxic alkaloids known[37]. It was not until 1958 that this alkaloid was recognized in *Paul Karrer*'s laboratory by *Hans Schmid* and his collaborators as the product of a condensation and dimerization of the Wieland-Gumlich aldehyde or its methobase[38–41]. The *N*-acetyl derivative of the Wieland-Gumlich aldehyde occurs as diabolin *(43)* in calabash curare as well as its methochloride. Over 40 tertiary and quaternary alkaloids [*e.g.* C-calebassin, *(44)*] were separated and isolated from calabash curare by *H. Schmid* and *P. Karrer* using cumbersome column chromatography. X-Ray analysis finally confirmed the complex structures based on chemical reactions[42].

The lobelia alkaloids *(48)* were introduced into pharmacology as respiratory stimulants by *Wieland*'s brother *Hermann*[43], into industrial production by an intriguingly simple synthesis[44] at C. H. Boehringer, Ingelheim, by *Georg Scheuing*[45]; they helped to start postpartum respiration for *Wieland*'s first grandchild.

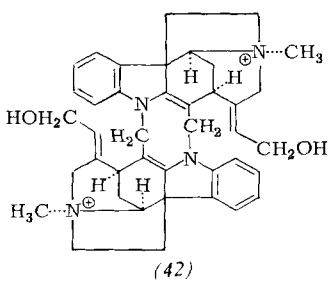
Racemic lobeline (Fig. 14) or *cis*-2,6-diphenacyl-*N*-methylpiperidine *(48)* is easily obtained by catalytic hydrogenation



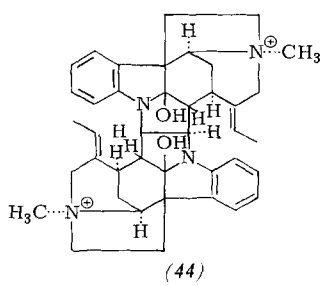
(41)



(43)



(42)



(44)

Fig. 13. Wieland-Gumlich aldehyde *(41)* is not only a natural product *(43)* but is also the parent substance for most of the alkaloids from *Strychnos toxifera* and calebash curare.

of the methosulfate of 2,6-diphenacylpyridine *(45)*, whereas its hydrochloride yields lobelanidine *(47)*, and its free base the pyridine-dicarbinol *(46)* on hydrogenation.

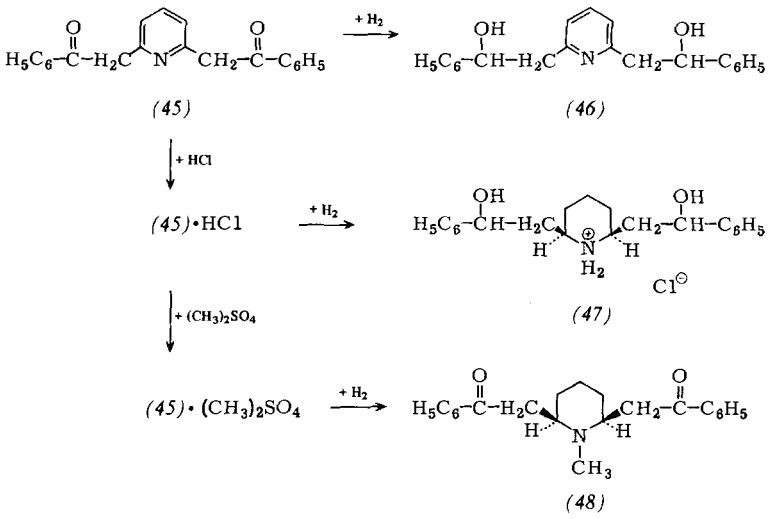


Fig. 14. *Scheuing*'s synthesis of norlobelanidine *(47)* and lobeline *(48)* by catalytic reduction of the hydrochloride and methosulfate of 2,6-diphenacylpyridine *(45)*.

Lyndon F. Small, from *Wieland*'s laboratory, brought back to the United States an interest in opium alkaloids and in their replacement by nonaddictive synthetic analgesics. More than 40 years later, thanks to the efforts of the late *Nathan B. Eddy* and *Everette May*, the search for a better analgesic[46] has come to a point at which separation of analgesic power from undesirable morphine-type drug dependence holds more than promise. On optical resolution of a 5,9-dialkylbenzomorphane a levorotatory antipode *(49)* was obtained (Fig. 15) which was a better analgesic than morphine, was not addicting in rhesus monkeys and, like desmethyl-*N*-allylmorphine (nalorphine), was an antagonist of morphine. The reversal of the two alkyl groups in 5-methyl-9α-propyl-6,7-benzomorphane also gave long-acting opiate antagonesis[47,48]. Further development of this principle of optical resolution has led in the case of *N*-tetrahydrofurfurylnoroxymorphones to compounds suitable for clinical testing[48a].

Here we enter the new area of opiate receptors in the brain[50] and of endogenous analgesic peptides, such as endorphin, derived from β-lipotropin[49].

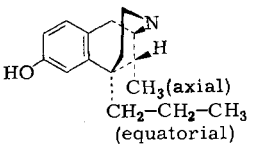


Fig. 15. Optical resolution of a benzomorphane into a levorotatory analgetically active, non-addicting antagonistic antipode *(49)* and a dextrorotatory, weakly analgetic, strongly addicting antipode.

Effects in rhesus monkeys

	Levorotatory antipode *(49)*	Dextrorotatory antipode
ED_{50}	0.8 mg/kg	12.3 mg/kg
Physical dependence capacity	0	strong
Antagonism (nalorphine = 1)	0.2	0

"The new truths of science begin as heresy, advance to orthodoxy, and end up as superstition"[51]. This description, by *T. H. Huxley*, not necessarily in the same sequence, may be applied to some of the stages in *Wieland*'s work on pterins. When *Wieland*, in 1925, followed a suggestion of his disciple *Clemens Schöpf* to resuscitate *F. G. Hopkins*' work (1889—91) on butterfly pigments, he had, as pointed out more than once in this paper, an intuitive preconception of some metabolic significance of the pterins, especially when his student *Koschara* found xanthopterin *(38)* as a regular urinary metabolite[52]. For a while, especially during the war, pterin research was salvaged by giving it the label of "studies on the antipernicious anemia factor". From the vantage point of hindsight we now recognize the importance of *Wieland*'s work on pterins, to which his student *Robert Purrmann* contributed some crucial ideas and experiments. In a similar way research on curare was salvaged during the war by giving it the label of "relevance to surgery", because the toxiferines are strong muscle relaxants. These memories have gained significance because "the relevance of scientific research" has again been questioned today. *Wieland*'s work is ample proof that highly qualified research is always "relevant"[52a].

We are fully aware of the importance of the activated one-carbon units[53] in metabolism and of tetrahydrofolic acid and dihydrobiopterin as prosthetic groups of essential enzymes whose absence in genetic defects creates grave metabolic problems, such as phenylketonuria[54]. The search for rapid assays of enzymes involved in the biosynthesis and metabolism of catecholamines[55] led to the discovery of the "NIH-shift", the existence of arene oxides as extremely labile intermediates in the hydroxylation of aromatic substrates[56,57], and an understanding of the carcinogenic action of aromatic polycyclic hydrocarbons, such as the above-mentioned methylcholanthrene.

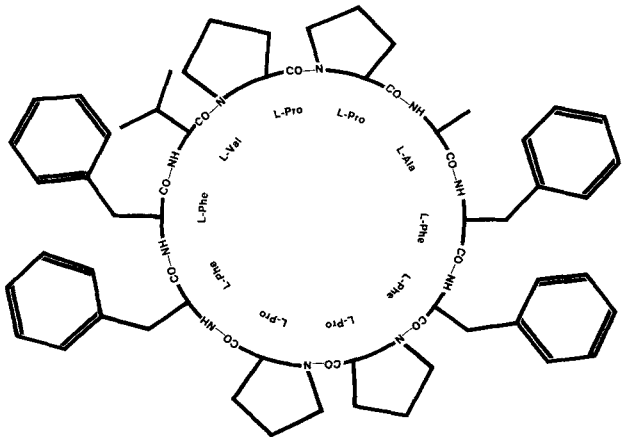
My entrance into *Wieland*'s private laboratory in 1938 required, as initiation fee, the work-up of half a ton of *Amanita phalloides* (Fig. 16), the deathcap, Europe's most poisonous and most fatal mushroom. The constant contact with these mushrooms, partly fresh, partly dried and powdered, led

Fig. 16. In the field of natural products, *Wieland's* legacy has proved extremely fruitful in two particular areas: *Theodor Wieland* has shown that constituents of the deathcap (toadstool) are important tools in molecular biology, and the first acetylene derivatives found in animals have been isolated from *Dendrobates histionicus.*—Most of the photographs of frogs were supplied by Dr. *C. W. Myers*, American Museum of Natural History, New York. (a) to (c): Deathcap toadstools *(Amanita phalloides)* at various stages of growth. They contain amatoxins [cf. *(39)*], phallotoxins and antamanide *(50)*. The photographs were provided by Dr. *D. M. Simons*, Wilmington, Delaware. (d): *Dendrobates histrionicus.* It contains the spirocyclic acetylene derivatives *(53)* and *(54)*. (e): *Dendrobates auratus.* It occurs in Panama, Costa Rica, Nicaragua, and Colombia and contains numerous pumiliotoxins which are all derivatives of *cis*-decahydroquinoline and in some cases bear acetylenic substituents. (f) *Dendrobates viridis.* Newly discovered species from western Colombia which mainly contains pumiliotoxin B. (g) *Dendrobates Lehmanii.* Newly disovered species [64a] containing about eight pumiliotoxins. (h): *Phyllobates aurotaenia*, a variant of the classical poison dart frog containing the extremely poisonous batrachotoxins *(52)*. (See p. 563.)

to unpleasant dermatitis and conjunctivitis, discomfitures which, in those days, were endured with a sense of pride to be in the vanguard of scientific battle. *Wieland* himself encouraged such an attitude. When *Rudolf Hallermayer*, shortly before the crystallization of amanitin, complained in 1941: "Herr Geheimrat, this morning it took about ten minutes until I was able to open my festering eyelids," the rejoinder came with ill-concealed satisfaction: "At long last we seem to be getting very good enrichment!"[58]

The crystallization of phalloidin by *F. Lynen* and *U. Wieland*, preliminary results on its hydrolysis, the crystallization of "amanitin"—these events are the beginning of a long natural product saga[59], an inheritance that took *H. Wieland's* second son *Theodor* a quarter of a century to explore completely and bring to full bloom[60]. In reprospect there is seen to be a continuity between work on phalloidin, its cleavage to secophalloidin by *Theodor Wieland*, and the general exploitation of such neighboring group effects for the extremely useful, selective nonenzymatic cleavage of peptides and proteins with cyanogen bromide—extending up to the sequence determination of immunoglobulin (molecular weight 148000 with more than 1200 amino acids)[60a].

The amatoxins *(39)* and *(40)*[32] are selective inhibitors of nucleotide polymerase B in the cell nucleus, while the related phallotoxins selectively bind to the actin of hepatocytes. The lipophilic cyclic decapeptide, antamanide, *(50)* has affinity to membranes which then are protected from the toxic effects of phalloidin. The natural and synthetic antamanides form complexes with lithium, sodium, and calcium ions. The alkali



(50)

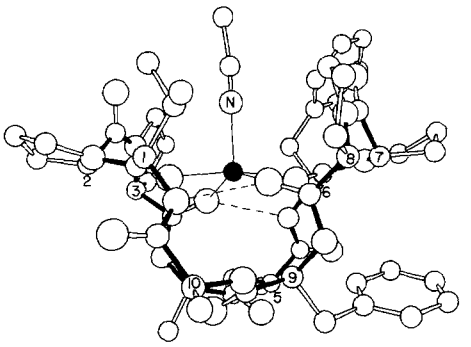


Fig. 17. In the lithium complex of natural antamanide the pentacovalent metal ion sits on the cyclic decapeptide folded to a saddle and bears a molecule of solvent as a "cap" (acetonitrile). In this structure the peptide carbonyls are directed towards the interior of the molecule, and the amide groups towards the exterior [61].

in the pentacovalent complexes sits in a saddle (Fig. 17) and has, as a cap, a molecule of solvent[61]. *Isabella Karle* extended this beautiful X-ray analysis to the uncomplexed antamanide in which the peptide backbone is turned inside out, more unfolded and held in place by a pair of intramolecular hydro-

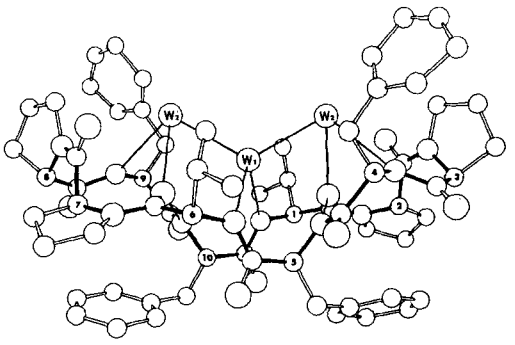


Fig. 18. In the uncomplexed trihydrate of synthetic [Phe^4,Val^6]antamanide the unfolded decapeptide is stabilized by three molecules of structural water (W). The amide groups are now directed to the interior of the molecule and the peptide groups to the exterior [63].

gen bonds of the (5→1) type[62] as well as by three[63] strategically placed molecules of structural water (Fig. 18). The uncomplexed synthetic [Phe^4, Val^6]antamanide exists, with little conformational change, also as a dodecahydrate (Fig. 19)[64].

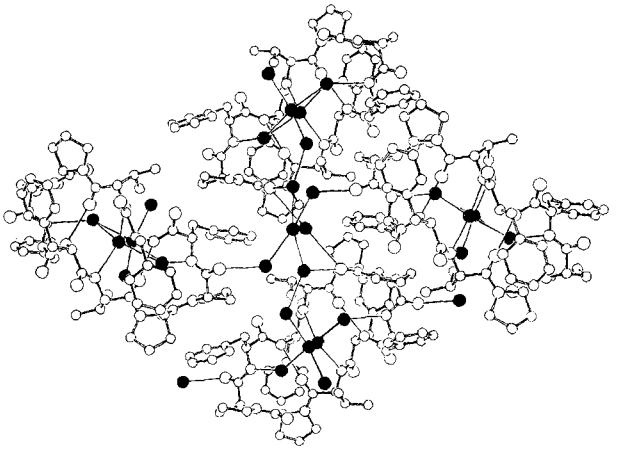
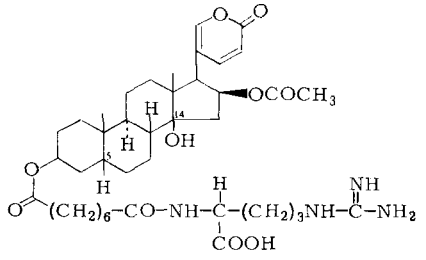


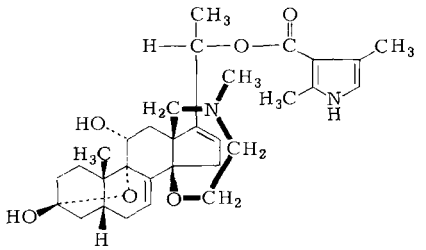
Fig. 19. In the uncomplexed dodecahydrate of synthetic [Phe^4,Val^6]antamanide the arrangement of the four antamanide molecules shown leaves channels in the crystal structure which are filled with structural water (solid circles) of varying degree of association. Such structures might possibly serve as models for explaining the unusual properties of water molecules in proteins and cell membranes [64].

The crystal lattice in this case contains cavities and channels that are filled with water molecules of various degrees of associative binding. Here one is reminded of the lipophilic peptide part of trans-membrane proteins, such as the surface glycoprotein of human erythrocytes, glycophorin, and in that respect the organization of water in the antamanide lattice gains in significance for membrane models and for understanding its protective action against phalloidin in the membranes of liver cells.

The digression from *Wieland*'s toad venoms [bufotoxin *(51)*] to frog toxins [batrachotoxin *(52)*] conceptually seems to be only a small step (Fig. 20): the disciple varies a theme given by the "*magister ludi*". When it comes to methodology and detail, the comparison shows up the great progress made since *Wieland*'s isolation of the cardiotonic bufotoxin in 1913. Just the initial phase, the process of collection, demonstrates this point: most of the toads *(Bufo vulgaris)*, about 27000, were "milked" and set free again by schoolchildren in the pleasant Black Forest area, and the result was 21 grams of crystalline bufotalin and bufotoxin *(51)*[65]. Bufotoxin *(51)* is a conjugate of an unusual steroid with suberylarginine linked at the 3-hydroxyl, originally formulated by *Wieland* as attached to the 14-hydroxyl. In addition, there is a β-acetoxy group at carbon 16, previously assigned to C(5). By contrast, the tiny poison dart frogs *(Phyllobates aurotaenia)* of Western Colombia, were collected in an impenetrable jungle with an annual rainfall of 12 meters. Transportation is only possible on the rivers by launch or balsa raft[66]. The frogs weigh only 1—2 grams and contain 50 micrograms of toxins, which the frog inactivates under stress or on death. One of the four components, batrachotoxinin A, the steroid moiety of batrachotoxin, was eventually crystallized and established a

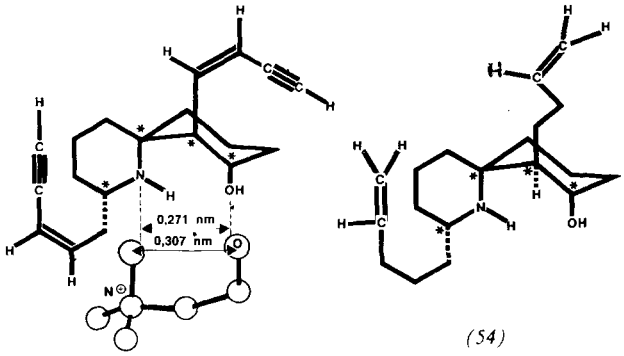


(51)

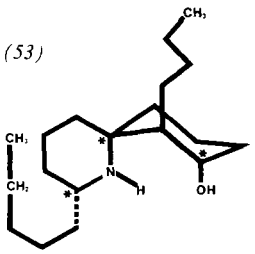


(52)

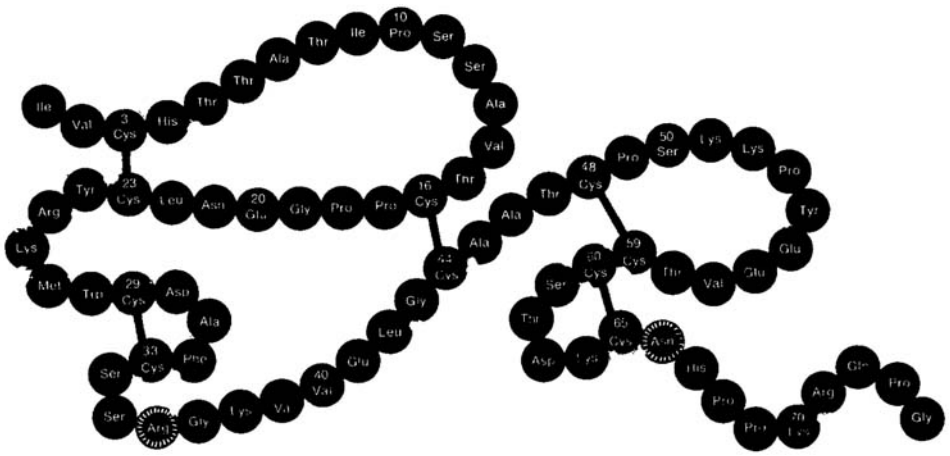
Fig. 20. The principal venom of the toad *Bufo vulgaris* is bufotoxin *(51)* which was formulated by *Wieland* as the conjugate with suberyl-arginine in position 14 and with an acetoxy group in position 5 instead of 16. The principal toxin of the frog *Phyllobates aurotaenia* is batrachotoxin *(52)* which shares the steroidal skeleton and some stereochemical features with bufotoxin.



(53) *(54)*



(55)



(56)

Fig. 21. The histrionicotoxins *(53)*, *(54)*, *(55)* show reversible binding to the ion conductance modulator of the acetylcholine receptor, while the snake venom, bungarotoxin *(56)* binds irreversibly to the recognition site of this receptor. A molecule of choline is shown under the formula of molecule *(53)* for comparison.

record for *Isabell Karle* as the smallest crystal, length 1/10 mm, which supplied all the X-ray data required for complete structure analysis[67]. In the ester, batrachotoxin *(52)*, we meet the familiar steroid skeleton with unprecedented new features, such as a new heterocyclic ring sharing a common axis with rings C and D in the manner of the propellanes. Ten years later batrachotoxin *(52)* has become one of the most useful tools in electrophysiology for the study of the properties of the sodium channel in axons, synapses, and muscle[68]. It opens up irreversibly and selectively the "gate" of sodium channels while its antagonist, the less toxic tetrodotoxin, the poisonous principle of the puffer fish, closes these sodium channels in a reversible manner.

Another frog, *Dendrobates histrionicus* (Fig. 16d), which occurs in many colorful varieties in Colombia, Ecuador, and Peru has given us the first acetylenic alkaloids [*(53)* and *(54)*] (Fig. 21) of animal origin[69]. They have proven their value in the study of receptor mechanisms: tritiated perhydrohistrionicotoxin *(55)* does not bind like bungarotoxin *(56)*, a powerful snake venom, to the recognition site of the acetylcholine receptor but to a special protein subunit, hopefully identifiable with the ion translocation site[70]. In all there are now known to be present more than 100 different novel alkaloids in the many *Phyllobates* and *Dendrobates* species of South America.

The contributions of the organic chemist, *John W. Daly*, and of the herpetologist-taxonomist, *Charles W. Myers*, have added up to more than the sum of their parts[71]. The significance of the frog toxins for the study of receptors, membranes, and ion transport may eclipse that of the toad and salamander *(Clemens Schöpf)* venoms, but the thematic origin clearly goes back to the old master, *Heinrich Wieland*.

When one mentions *Wieland*'s name to present-day biochemists, they remember him for his theories on the "activation of hydrogen" that brought him into—at times violent—opposition to *Warburg* (1883—1970), another founder of modern biochemistry[72]. *Wieland* "diminished" the role of oxygen to that of an acceptor for activated hydrogen by replacing O_2 by quinones, metals, or methylene blue[73]. *Warburg*'s feelings toward this hypothesis and its originator are best characterized by his reaction to reading his own obituary in the Times (of London) of January 12, 1938: "An error had occurred: he had been mistaken for a distant relation, the distinguished botanist and Zionist leader, also called *Otto Warburg* (1859—1938). The error was corrected on the following day with appropriate apologies. *Warburg* was mildly amused and mildly annoyed when, as a subscriber to the Times, he read the news of his demise; annoyed because he thought that deliberately no reference had been made to what he considered to be one of his most important discoveries, that of nicotinamide in the coenzymes of dehydrogenases and the chemical nature of its reversible reduction and oxidation. He commented: 'it looks as if the obituary was written jointly by poor old *Heinrich Wieland* and poor old *Torsten Thunberg*'. These two scientists had published much work on dehydrogenations without establishing the chemical mechanism and, quite wrongly, *Warburg* considered them his adversaries"[72]. Since the departure of *Wieland* and *Warburg*, we can now see the two scientists in the same historical perspective as *Isaac Newton* (1642—1727) and *Christian Huygens* (1629—1695): light, in its ambivalence, is understandable both in undular and corpuscular terms. Likewise the unity of biochemistry[73] now reigns in the close coupling of oxido-reduction mechanisms and of "anabolic *versus* catabolic, amphibolic and 'anaplerotic' processes"[74]. At the time of their controversy, their fascination by models, the surface of platinum[76] or of charcoal[77], served well as a formal basis for polemics, but action was not restored until *D. Keilin* turned to the living wax moth *(Galleria mellonella)* to establish the physiological role of cytochrome reactions[78].

There was then little reason to suspect that *Wieland*'s favorite two enzymes for—putatively metal-free—model dehydrogenations, *viz.* the "Schardinger enzyme", xanthine oxidase, and the "Thunberg enzyme", succinate dehydrogenase, would turn out to be multi-centered iron-sulfur-containing flavoprotein complexes[79]. In xanthine oxidase the iron-sulfur centers act as an electron reservoir serving to maintain molybdenum as Mo^{VI} (for efficient reduction) and flavin as $FADH_2$ (for efficient oxidation) as visualized by the plausible but unproven intermediates observable under anaerobic conditions[80]. The reaction of xanthine oxidase with oxygen involves both paired and unpaired electronic transition states between xanthine, oxygen, and reduced flavin adenine dinucleotide ($FADH_2$). A new form of active oxygen, the superoxide anion, $O_2^{\ominus}$, suspected by neither *Warburg* nor *Wieland*, enters the enzymatic arena[81].

The most recent investigations on the mechanism of biological oxidation, *Wieland*'s lifelong theme and quest, make use of the classical Schardinger enzyme, xanthine oxidase, in order to produce superoxide anion required for the activity of indoleamine 2,3-oxygenase, a novel catabolic enzyme discovered by *Hayaishi* (Fig. 22). In this system methylene blue, utilized

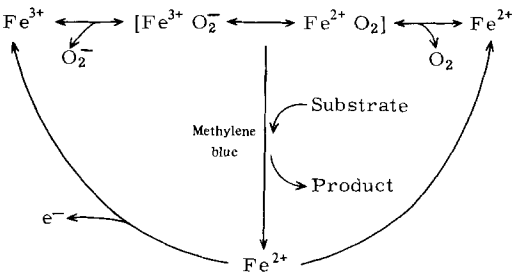


Fig. 22. The action of indoleamine 2,3-oxygenase involves a catalytically active ferric heme-superoxide complex that is in resonance equilibrium with the ferrous heme-dioxygen complex and, in the presence of substrate, is converted to product and ferrous heme-enzyme. Methylene blue, a cofactor, is required for maximum enzyme activity [82].

so often by *Wieland* as a substitute for oxygen in model reactions, surprisingly enough assumes the role of a new cofactor required for maximal enzymatic activity.

We approach the end of our excursion through the garden of *Wieland*'s natural products. We, the later generation, have accumulated enough knowledge through biosynthetic studies with labeled or radioactive precursors to recognize or predict the gross biogenetic origin of practically all natural products discussed so far[83]. Again, *Wieland* had anticipated much of this development. It was in his laboratory that studies on yeast, previously agitated under oxygen and, therefore, "verarmt"[84] (depleted) by combustion of intracellular ingredients, led to the discovery of an "induction time" until added acetic acid was further metabolized. This experiment furnished

information which did not become transformed into knowledge until *Feodor Lynen* provided the correct interpretation. "When does information become knowledge?" is a pertinent question[85] to ask especially in an age of the production of more data than the human brain is capable of grasping. *Lynen*'s postulate of an "activated acetic acid"[86] rested on a proper interpretation of the induction phenomenon and on the fact that on addition of an easily combustible substrate, such as a small amount of ethanol, the induction time became shorter. The further development has become history: *Lynen*'s discovery of the nature of active acetic acid as Acetyl-CoA, the biotin carboxylase ("aktivierte Kohlensäure"), the "doubly activated acetic acid" ("aktivierte aktivierte Essigsäure"), *viz.*, malonyl-CoA, the multienzyme complex of fatty acid synthesis, all these discoveries led directly to breath-taking new vistas impressively described in his Nobel lecture[87].

When we now compare the impact of *Wieland*'s example and discoveries on the growth and expansion of organic chemistry in its widest interpretation, *i.e.*, encompassing biochemistry and molecular biology, we could construct a tree somewhat comparable to the one based on the Gerlach-Stern experiment[9] with which we started this historical critical essay. "In a centenary celebration, the rich heir complacently goes over the treasure which past centuries have distilled"[88]; if we heed *Ortega*'s advice, expressed in 1932 as a reaction to what he then considered "the breakdown of the university in the face of men's present needs", we have to do more than worship the past or more than putting *Wieland* on a pedestal. "There is but one way left to save a classic: to give up revering him and use him for our own salvation... bring him close to us to make him contemporary, resurrect our classic by immersing him in life once more"[88].

There are types of excellence that involve doing something well and types that involve being a certain kind of person. *Wieland* excelled in both respects and both faculties grew commensurate with the risks and responsibilities. It is not everyone that finds the age he deserves. Perhaps he might have been worthy of a better century, but then we would not know how he met the challenges of his time.

We must not forget that at a time when, in the words of *Karl Jaspers*, the German universities had lost their dignity, students looked up for courage and help to their teachers. Barely a hundred years earlier another man had dishonored the constitution and broken the instruments of law, namely the narrow-minded and opinionated *Ernst August*, King of Hanover. Against his tyranny rose the "Seven Professors of Göttingen" as one man, among them the intrepid *Jacob Grimm* for whom "science meant the search for the metaphysical ethos in the physical world". To him doctrine and science were one, in the same way as thought and action formed an indissoluble unity. Thus, at the age of 52 years, he courageously faced an uncertain exile[89].

One hundred years later this bright example was followed by a great darkness fortunately illuminated by "professores" (confessors), such as *Kurt Huber* and *Heinrich Wieland*, who had the courage to stand up and be counted. *Wieland*'s student *Hans Carl Leipelt*, because of his allegiance to *Kurt* and *Clara Huber*, was arrested by the Gestapo on October 8, 1943, and hanged on January 29, 1945[90]. At the mock trial of *Leipelt*, *Wieland*, invited as a witness, defied the dreaded *Roland Freisler*, "President of the Folk Tribunal" by walking up to the helpless defendant and by exchanging a handclasp of deep sympathy and approval.

In today's agonizing world of constant redefinitions of old standards and values, he would not have seen a problem in reconciling excellence with democratic principles, *i.e.* equality with quality. He would have quoted *William Learned:* "The conception of a democratic education as one leveled to a colorless mediocrity is as grotesque an interpretation of democratic principles as (a conception) of health in which abounding vitality ... is deprecated on the ground that only average health is fair to the community. No one believes this."[91] "The right of competition may only be limited in order to preserve it. For excesses of competition lead to monopoly, as excesses of liberty lead to absolutism."[92]

We admire the scientist who uses his intellectual gifts in the service of one of the highest values of our civilization—the search for truth. At a time when many intellectuals place their gifts in the service of chicanery and lend themselves to the cause of tyranny and brutality, this requires great fortitude.

In Germany, more so than in the United States, the period of institutional crises, especially of the University, is not yet over. Many students in their radicalism laid claim to ownership of "their" university as an instrument for social change or experimentation. *Wieland*, as a protagonist of a correctly defined elitism[93], if called upon to express his opinion today, would have challenged such a claim: "Yes, the university is indeed owned. There are proprietors. They are not listed in your catalog. They are not students, faculty members, or alumni. Rather they are, especially for Munich, *Fraunhofer*, *Liebig*, *Baeyer*, *Willstätter*, *Thomas Mann*, *Max Weber*, *Karl Vossler*, *Kurt Huber*, and you may go back further to *Plato*, *Aristotle*, and *Confucius*. They are the proprietors. The rest of us hold the University in trust for them and for those whose names have yet to join this timeless throng."

Today we are happy in the knowledge that *Heinrich Wieland*, a faithful trustee during his lifetime, has entered the ranks of the scholarly proprietors.

Received: April 22, 1977 [A 175 IE]
German version: Angew. Chem. *89*, 575 (1977)

[1] Naturwissenschaften *30*, 333—373 (1942).
[2] *Rolf Huisgen*, Proc. Chem. Soc. *1958*, 210—219.
[3] *H. Wieland*, Starnberg, July 1957:
Meinen feyerlich Bewegten
Mache Dank und Freude kund:
Das Gefühl das Sie erregten
Schliesst dem Dichter selbst den Mund.
(Goethes Goldener Jubeltag 1825).
Cf. *R. Huisgen*, Naturwissenschaften *44*, 317—318 (1975); *C. Schöpf*, Angew. Chem. *71*, 1—5 (1959).
[4] *H. Wieland*, Angew. Chem. *62*, 1—4 (1950).—The passage from *Goethe*'s Faust, in the translation of *Philip Wayne*, is as follows:
"Of the depth of chanting, whence the blissful tone
That lames my lifting of the fatal glass?
Do bells already tell with vibrant drone
The solemn opening of the Easter Mass?"
[5] *O. Stern, W. Gerlach*, Z. Physik *8*, 110 (1921).
[6] *O. Stern, W. Gerlach*, Z. Physik *9*, 349 (1922).
[7] *O. Stern, W. Gerlach*, Phys. Z. *23*, 476 (1922).
[8] *E. Segrè*, Biogr. Mem. Nat. Acad. Sci *43*, 215—236 (1973).
[9] *G. Holton:* Thematic Origins of Scientific Thought: From Kepler to Einstein, Harvard University Press, Cambridge, Mass. 1973, p. 418. The author depicts a tree with extensive ramifications having its roots in the Stern-Gerlach experiment.
[10] "Natural organic chemistry is biochemistry, the chemistry of life processes": *F. Knoop*, Angew. Chem. *49*, 558 (1936).
[11] *F. Kröhnke*, Liebigs Ann. *1973*, 547—552; *H. A. Krebs*, Nature *215*, 1441—1445 (1967). Viewed historically both the autonomy and the

institutionalization of science began with *Liebig* as convincingly depicted by *Joseph Ben-David* in his study "The Scientist's Role in Society". Prentice-Hall, Englewood Cliffs, New Jersey 1971: "Toward the end of the century the laboratories of some of the professors became so famous that the ablest students from all over the world went there for varying periods of time. The list of students who worked in such places often included practically all the important scientists of the next generation. ... These unplanned and unexpected developments were an even more decisive step in the organization of science than the early nineteenth century reform. Research started to become a regular career, and scientists in a number of fields started to develop into much more closely knit networks than ever before. Their nuclei were now university laboratories training large numbers of advanced students, thus establishing between them personal relationships, highly effective means of personal communication, and the beginning of deliberately concentrated and coordinated research efforts in a selected problem area." (pp. 124—125.)

[12] *August Wilhelm von Hofmann*'s (1818—1892) three volumes of "Erinnerungen an vorangegangene Freunde" immortalize famous scholars, such as *Justus von Liebig, Friedrich Wöhler, Thomas Graham, Jean-Baptiste Dumas, Quintinio Sella, Peter Griess*, and many others. The endearing title probably has a Roman or Greek origin and is found engraved on the tombstone at Sérignan of *Jean-Henry Fabre*, the French entomologist: *Quos perisse putamus praemissi sunt* (whom we believe to have lost, preceded us).—Cf. *K. Guggenheim:* Sandkorn für Sandkorn, Die Begegnung mit J.-H. Fabre, Artemis Verlag, Zürich 1959.

[13] *H. Dechend:* Justus von Liebig. Verlag Chemie, Weinheim 1965.

[14] *W. Beck, E. Schuierer, K. Feldl*, Angew. Chem. *77*, 722 (1965); Angew. Chem. Int. Ed. Engl. *4*, 698 (1965).

[15] *C. Grundmann, R. K. Bansal, P. S. Osmanski*, Justus Liebigs Ann. Chem. *1973*, 898—909.

[16] *W. Prandtl:* Die Geschichte des Chemischen Laboratoriums der Bayerischen Akademie der Wissenschaften in München. Verlag Chemie, Weinheim 1952, p. 40.

[17] *F. Schönbein:* Menschen und Dinge. Mittheilungen aus dem Tagebuch eines Naturforschers. Anonym erschienen. Verlag von Rudolf Besser, Stuttgart und Hamburg 1855.

[18] *K. Bloch*, Science *150*, 19—28 (1965).

[19] *H.-J. Staudinger*, Freiburger Universitätsblätter. Verlag Rombach, Freiburg 1974, No. 44.

[20] *J. S. Fruton:* Molecules and Life, Historical Essays on the Interplay of Chemistry and Biology, Wiley-Interscience, New York 1972.

[21] *R. Sonderhoff, H. Thomas*, Justus Liebigs Ann. Chem. *530*, 195 (1937).

[22] *R. J. Lorentzen, W. J. Caspary, S. A. Lesko, P. O. P. Ts'o*, Biochemistry *14*, 3970—3977 (1975).

[23] *W. Levin, A. W. Wood, H. Yagi, D. M. Jerina, A. H. Conney*, Proc. Natl. Acad. Sci. (USA) *73*, 3867—3871 (1976); Nature *266*, 378 (1977).

[24] *M. Koreeda, P. D. Moore, H. Yagi, H. T. C. Yeh, D. M. Jerina*, J. Am. Chem. Soc. *98*, 6720—6722 (1976) and references cited therein.—Concerning the stereochemistry of opening of diol epoxides: *H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda, D. M. Jerina*, J. Am. Chem. Soc. *99*, 1604—1611 (1977).

[25] *K. Shinohara, P. A. Cerutti*, Proc. Natl. Acad. Sci. (USA) *74*, 979—983 (1977).

[26] *D. M. Jerina, J. W. Daly:* Oxidation at carbon, drug metabolism—from Microbe to Man. Taylor and Francis, London 1976, pp. 13—32.

[26a] *J. M. Essigmann, R. G. Croy, A. M. Nadzan, W. F. Busby, Jr., V. N. Reinhold, G. Büchi, G. N. Wogan*, Proc. Natl. Acad. Sci. (USA) *74*, 1870 (1977).

[27] *B. W. O'Malley, A. R. Means*, Science *183*, 610—620 (1974); *B. W. O'Malley, W. T. Schrader*, Sci. Am *234*, No. 2, 32—43 (1976); *B. S. McEwen*, Sci. Am. *235*, No. 1, 48—67 (1976).

[28] This event dates back to AD 1000 and was celebrated on August 15, La Sensa, *i.e.* L'Ascensione or L'Assunta, by the Doge sailing out into the Adriatic on his Maesta Nave (after 1311 *il Bucintoro*, probably from *Navilium Ducentorum Hominum*) to drop a golden ring, consecrated by the Pope, into the sea with the words: "*Desponsamus te, mare*" (we wed thee sea).—On his way from his home in Starnberg to the station, *Wieland* often passed a house with a big fresco of the "Buzentaur", a replica of the Bucintoro, used by *Ludwig* II of Bavaria for aquatic pageants on the lake with the inscription: "Schön war die Vergangenheit, schöner noch wird die Zukunft Starnbergs sein." At least for *Wieland*, Starnberg became his haven after the destruction of his house, Arcisstrasse 1, and his laboratory in 1944.

[29] *Dorothy Crowfoot-Hodgkin*, Prog. Chem. of Nat. Prod. *15*, 167—220 (1958).

[30] "The structure of vitamin B_{12}, as we think of it today, is based on a fascinating complex of evidence obtained by X-ray analysis and by more traditional chemical means. We have reached a position in which we can almost say we "see" the molecule—if not quite as clearly, perhaps, as we should like. We can assign positions in space to the atoms of this very large molecule within less than half an Ångstrom unit in two different crystal structures. We know its absolute configuration and the exact stereochemistry of all the different asymmetric centres present. Yet most of this knowledge rests on a way of using X-ray diffraction effects which is very far from rigid in its application. Part, at least, of our evidence that our method works at all is the character of the structure it has given us for B_{12}—a structure that fits in an extraordinarily reasonable way with such a variety of observations, chemical and stereochemical and biogenetic, that it is impossible not to believe it is essentially correct." Ref. [29], pp. 167—168.

[31] *J. Karle, I. L. Karle*, Acta Crystallogr. *21*, 849 (1966).

[32] *E. C. Kostansek, W. N. Lipscomb, R. R. Yocum, W. E. Theissen*, J. Am. Chem. Soc. *99*, 1273—1274 (1977).

[33] *H. A. Krebs, J. H. Shelley:* The creative process in science and medicine. Excerpta Medica, Amsterdam 1975.

[34] "How luck and merit are close-bound
Fools never see and never will;
And if the wise man's stone were found,
The stone would lack the wise man still."
The wise man's stone which conferred wealth, power, and long life, was the object of much alchemical research. Translation by *Charles E. Passage, J. W. Goethe:* Faust. The Library of Liberal Arts, Bobbs-Merril Co., Indianapolis, New York, Kansas City, 1965, p. 181.

[35] *B. Barber, R. C. Fox*, Am. Journal of Sociol. *64*, 128 (1958).

[36] *H. Wieland, W. Gumlich*, Justus Liebigs Ann. Chem. *494*, 191 (1932).

[37] *H. Wieland, K. Bähr, B. Witkop*, Justus Liebigs Ann. Chem. *547*, 156 (1941).

[38] *K. Bernauer, F. Berlage, W. v. Philipsborn, H. Schmid, P. Karrer*, Helv. Chim. Acta *41*, 2293 (1958).

[39] *K. Bernauer*, Progr. Chem. Nat. Prod. *17*, 183—247 (1959).

[40] *A. R. Battersby, H. F. Hodson*, Alkaloids *11*, 189—204 (1968).

[41] *M. Fehlmann, H. Koyama, A. Niggli*, Helv. Chim. Acta *48*, 303—304 (1964).

[42] *N. D. Jones, W. Novacki*, J. Chem. Soc. Chem. Commun. *1972*, 805.

[43] *Hermann Wieland*, Ber. Dtsch. Chem. Ges. *54*, 1784 (1921).

[44] *C. Schöpf, G. Lehmann*, Justus Liebigs Ann. Chem. *518*, 12 (1935).

[45] *G. Scheuing, R. Winterhalder*, Justus Liebigs Ann. Chem. *473*, 126 (1929).

[46] *N. B. Eddy, E. L. May*, Science *181*, 407—414 (1973).

[47] *K. C. Rice, A. E. Jacobson*, J. Med. Chem. *19*, 430 (1976).

[48] *K. C. Rice, W. A. Klee, M. D. Aceto, H. H. Swain, A. E. Jacobson*, J. Pharm. Sci. *66*, 193—197 (1977).

[48a] *H. Merz, K. Stockhaus, H. Wick*, J. Med. Chem. *20*, 844 (1977).

[49] *F. H. H. Loh, L. F. Tseng, E. Wei, C. H. Li*, Proc. Natl. Acad. Sci. (USA) *73*, 2895—2898 (1976).

[50] *S. H. Snyder*, Sci. Am. *236*, Nr. 3, 44—67 (1977).

[51] *Leonard Huxley:* Life and Letters of Thomas Henry Huxley. London, MacMillan 1900.

[52] *W. Koschara*, Hoppe-Seylers Z. physiol. Chem. *240*, 127 (1936).

[52a] Today's gigantic research effort is endangered precisely because of a too narrow interpretation of relevance; it can hardly be avoided that an increasingly centralistic bureaucracy will insist that research be directed towards the solution of certain national problems, or that certain areas, such as genetic engineering, be placed under state supervision. In his study "The Logic of Liberty" (London 1951), *Michael Polansky* pleads for freedom of research: "What technical inventions were the discoveries of the Nobel Laureates Planck, Einstein, Perrin, Millikan, Michaelson, Rutherford, Aston, Chadwick, Barkla, Heisenberg, Compton, Frank, G. Hertz, Rubens, Laue, Joliot, Fermi, Urey, Anderson, W. H. and W. L. Bragg, Schrödinger, Dirac, etc., unconsciously intended to produce? No one can tell—so the new theory of science must pass them over. One wonders how the great physicists in the list above would have fared if, before embarking on their investigation, they had to get a certificate of its social usefulness from a scientific directorate, as contemplated by Marxist scientists and their friends. To what conflicts may not have led their "arrogant pretence" to be the sole judges of their own preference!" (pp. 82—83).

[53] *M. Obermayer, F. Lynen*, Trends Biochem. Sci. *1*, 169—171 (1976).

[54] *G. A. Jervis*, Proc. Soc. Exp. Biol. Med. *82*, 514 (1953).

[55] *C. R. Creveling, J. W. Daly:* Methods of Biochem. Anal. *19*, 153—182 (1971).

[56] *J. W. Daly, D. M. Jerina, B. Witkop*, Experientia *28*, 1129 (1972).

[57] *D. M. Jerina, J. W. Daly*, Science *185*, 573—582 (1974).

[58] "If you want to become a chemist, so Liebig told me, when I worked in his laboratory, you have to ruin your health. Who does not ruin his health by his studies, nowadays will not get anywhere in Chemistry". *A. Kekulé*, Ber. Dtsch. Chem. Ges. *23*, 1308 (1890).

[59] *W. Litten*, Sci. Am. *232*, No. 3, 90—101 (1975).

[60] *Th. Wieland*, Science *159*, 946—952 (1968).

[60a] *B. Witkop*, Science *162*, 318—326 (1961); Adv. Protein Chem. *16*, 221 (1961).

[61] *I. L. Karle, J. Karle, Th. Wieland, W. Burgermeister, K. Faulstich, B. Witkop*, Proc. Natl. Acad. Sci. (USA) *70*, 1836—1840 (1973); *I. L. Karle*, J. Am. Chem. Soc. *99*, 4000 (1977).

[62] *I. L. Karle:* 4. American Peptide Symposium. Ann Arbor Science Publishers, Ann Arbor 1975, pp. 61—84.

[63] *I. L. Karle, J. Karle, Th. Wieland, W. Burgermeister, B. Witkop*, Proc. Nat. Acad. Sci. (USA) *73*, 1782—1785 (1976).
[64] *I. L. Karle, E. Duesler*, Proc. Nat. Acad. Sci. (USA) *73*, 2602 (1977). The dodecahydrate of antamanide was obtained in the presence of calcium ions. Concerning the possible presence of calcium ions in the crystal lattice, *Isabella Karle* expressed her views in a personal communication as follows: "The question arises as to the whereabouts of the Ca^{++} ions present in the crystallizing solution. Are they still in the mother liquor surrounding the crystal? Or is it possible that some of the sites in the inner core of the channel are partially occupied by Ca^{++} rather than by H_2O? The X-ray diffraction data cannot distinguish between the type of ion or atom occupying a site when dealing with partial occupancies, since the occupancy and the weight of an atom are not independent variables. The distances between the sites in the inner core and the H_2O in the bound layer are compatible with $Ca^{++}\cdots O$ ligands."
[64a] On booking at this frog, one is reminded of *Charles Darwin*'s description in The Voyage of the Beagle (1831), Chap. 5: "Amongst the Batrachian reptiles I found only one little toad *(Phryniscus nigricans)*, which was most singular from its color. If we imagine, first, that it had been steeped in the blackest ink and then, when dry, allowed to crawl over a board freshly painted with the brightest vermilion so as to color the soles of its feet and parts of its stomach, a good idea of its appearance will be gained. If it had been an unnamed species, surely it ought to have been called *Diabolicus*, for it is a fit toad to preach in the ear of Eve." Charles Darwin and the Voyage of the Beagle. Edited by *Nora Barlow*. (Rough notebooks kept during the voyage together with many previously unpublished letters written during the voyage.) Philosophical Library, New York 1946.
[65] *H. Wieland, W. Konz, H. Mittasch*, Justus Liebigs Ann. Chem. *513*, 1—25 (1934).
[66] *M. Latham*, Nat. Geogr. Magazine *129*, 683—693 (1966).
[67] *T. Tokuyama, J. W. Daly, B. Witkop, I. L. Karle, J. Karle*, J. Am. Chem. Soc. *90*, 1917 (1968).
[68] *E. X. Albuquerque, J. W. Daly, B. Witkop*, Science *172*, 995—1002 (1971); *E. X. Albuquerque, J. Daly* in *P. Cuatrecases:* Receptors and Recognition. Chapman and Hall, London 1977, Series B, Vol. 1, pp. 297—338.
[69] *J. W. Daly, I. L. Karle, C. W. Myers, T. Tokuyama, J. W. Waters, B. Witkop*, Proc. Natl. Acad. Sci. (USA) *68*, 1870—1875 (1971).
[70] *A. T. Eldefrawi, M. E. Eldefrawi, E. X. Albuquerque, A. C. Oliviera, N. Mansour, M. Adler, J. Daly, G. B. Brown, W. Burgermeister, B. Witkop*, Proc. Nat. Acad. Sci. (USA) *74*, 2172—2176 (1977).
[71] *C. W. Myers, J. W. Daly*, Bull. Am. Museum of Natl. History *157*, 177—262 (1976).
[72] *H. A. Krebs*, Biogr. Mem. Fellows R. Soc. *18*, 629—699 (1972).
[73] *W. Franke*, Naturwissenschaften *30*, 342—351 (1942).
[74] *W. D. McElroy*, Trends Biochem. Sci. *1*, 93 (1976).
[75] *J. S. Fruton:* Molecules and Life, Historical Essays on the Interplay of Chemistry and Biology. Wiley-Interscience, New York 1972.
[76] *H. Wieland:* On the Mechanism of Oxidation. Yale University Press, New Haven, Connecticut 1932; Naturwissenschaften *34*, 111 (1947).
[77] *O. Warburg:* Heavy Metal Prosthetic Groups and Enzyme Action. Oxford University Press, London, and New York 1949.
[78] *D. Keilin*, Proc. Roy. Soc. (London), Ser. B *98*, 312 (1925); *K. Okunuki* in *M. Florkin, E. H. Stotz:* Comprehensive Biochemistry. Elsevier, Amsterdam 1966, pp. 232—304.
[79] *H. Beinert, B. A. C. Ackrell, E. B. Kearney, Th. P. Singer*, Eur. J. Biochem. *54*, 185—194 (1975).
[80] *F. J. S. Olson, D. P. Ballou, G. Palmer, V. Massey*, J. Biol. Chem. *249*, 4363—4382 (1974).
[81] *F. J. S. Olson, D. P. Ballou, G. Palmer, V. Massey*, J. Biol. Chem. *249*, 4350—4362 (1974).
[82] *F. Hirata, T. Ohnishi, O. Hayaishi*, J. Biol. Chem. *252*, 4637, 4643 (1977).
[83] *K. Nakanishi*, Natural Products Chemistry. Academic Press, New York 1974.
[84] *H. Wieland, O. Probst, M. Crawford*, Justus Liebigs Ann. Chem. *536*, 51 (1938).
[85] *H. V. Wyatt*, Nature *235*, 86—89 (1972).
[86] *F. Lynen*, Justus Liebigs Ann. Chem. *552*, 270 (1942).
[87] *Feodor Lynen*, Angew. Chem. *77*, 929—944 (1965).
[88] *Ortega y Gasset:* In Search of Goethe from Within (Pidiendo un Goethe Desde Dentro), The Dehumanization of Art (and other writings on Art and Culture), Doubleday, Garden City, N. Y. 1956.
[89] *Jacob Grimm:* Über seine Entlassung. Schweighauserische Buchhandlung, Basel 1838.
[90] *Clara Huber:* Kurt Huber zum Gedächtnis, Bildnis eines Menschen, Denkers und Forschers, Dargestellt von seinen Freunden. Verlag Josef Habbel, Regensburg 1947, p. 39.
[91] *William S. Learned:* The Quality of the Educational Process in the United States and in Europe. Bulletin No. 20. The Carnegie Foundation for the Advancement of Teaching, New York 1927, p. 35.
[92] *Richard Hofstadter:* Social Darwinism in American Thought. The Beacon Press, 1955, p. 121.
[93] *Wieland*'s unconstrained elitist attitude in the area of science and research poses no problem even in today's more refined social philosophy and criticism; cf. the chapters on "Meritocracy and Equality" as well as "The Redefinition of Meritocracy" in *Daniel Bell:* The Coming of the Post-Industrial Society, a venture in social forecasting. Basic Books, Inc., New York 1973, pp. 408 and 446.

Electrocyclic Ring Opening Reactions of Ethylene Oxides[**]

By Rolf Huisgen[*]

Substituents capable of stabilizing negative charge endow ethylene oxides with the ability to undergo electrocyclic ring opening at the CC bond; heating or irradiation generates small equilibrium concentrations of carbonyl ylides which can engage in 1,3-dipolar cycloadditions. Apart from the normal conrotatory mode of ring opening, predicted by the Woodward-Hoffmann rules, the disrotatory process, forbidden by orbital symmetry, also appears to occur in the case of α-cyano-*cis*-stilbene oxide. Kinetic studies on α-cyano-*trans*- and -*cis*-stilbene oxide permit construction of the energy profile for electrocyclic ring opening to give the stereoisomeric carbonyl ylides and for their recyclization and rotation.

1. Ring Opening of the Cyclopropyl Anion

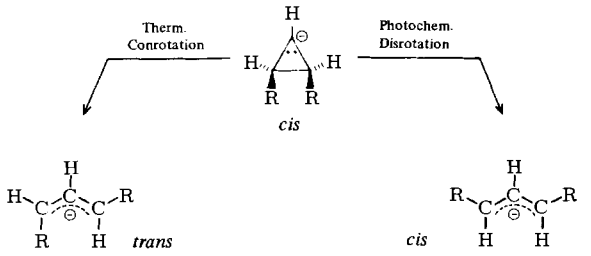
One of the most stimulating ideas to have permanently influenced our concept of the reaction event during the past decade is the principle of the conservation of orbital symmetry. The initial publication of the *Woodward-Hoffmann* rules in 1965 spurred an enormous number of experimental and quantum-chemical studies; the stream of relevant publications has not receded to this day.

Any formation or cleavage of a bond proceeds with conservation of orbital symmetry. This principle can be demonstrated for electrocyclic reactions, cycloadditions, and sigmatropic shifts. These processes involve the breaking or forming of several bonds coupled in a single step.

[*] Prof. R. Huisgen
Institut für Organische Chemie der Universität
Karlstrasse 23, D-8000 München 2 (Germany)

[**] Extended version of the Roger Adams Award Address, National Organic Symposium of the American Chemical Society, Fort Collins (Col.), June 24, 1975, and a plenary lecture delivered at the GDCh General Meeting at Cologne, Sept. 9, 1975.

Electrocyclic reactions are ring openings or closures in which a σ bond is transformed into a π bond, or *vice versa*. *Woodward* and *Hoffmann* advanced predictions about the steric course of such one-step processes[1]. The principle of conservation of orbital symmetry requires that ring opening of a cyclopropyl anion to an allyl anion occurs as a thermal conrotation or a photochemical disrotation.

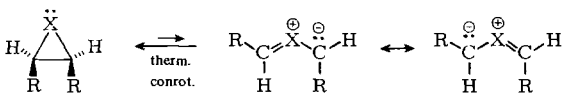


The substituents located in positions 2 and 3 of the cyclopropyl anion *in front of* or *behind* the plane of the ring rotate into the plane of the three C atoms on ring opening. The term "conrotation" refers to the steric course in which *cis* substituents move into the *endo* and *exo* positions of the allyl anion. On completion of "disrotation", on the other hand, the former *cis* substituents both appear in the *exo* position or—less likely—in the *endo* position of the allyl anion.

Numerous examples of electrocyclic ring opening reactions of cyclopropyl anions to form allyl anions have been reported; however, a clearcut, unequivocal experiment confirming the steric course has yet to be performed, twelve years after the original prediction.

2. Isoelectronic Analogs of the Cyclopropyl Anion

A remarkable new ring opening of substituted ethylenimines at the CC bond was observed independently by three research groups[2–4] in 1965/66. On heating, a small equilibrium concentration of a species arises which undergoes 1,3-dipolar cycloadditions *in situ* with suitable dipolarophiles.

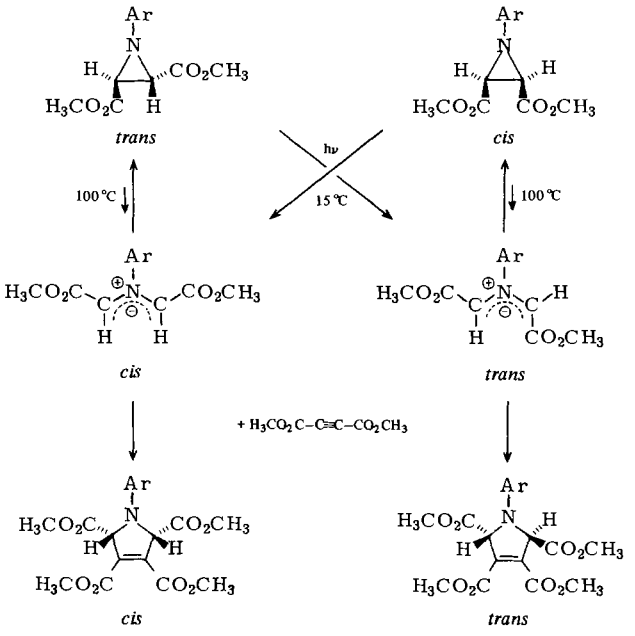


(1) *(2)*

X = NR, O

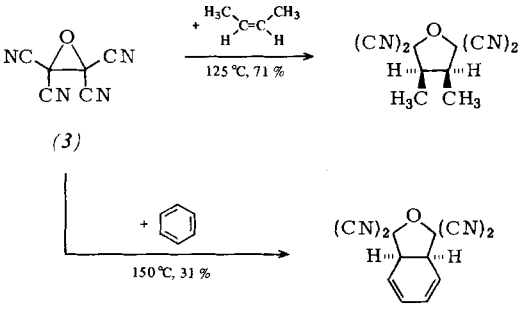
Ethylenimines (aziridines) *(1)*, X = NR, and ethylene oxides (oxiranes) *(1)*, X = O, possess a lone pair at the heteroatom and are isoelectronic with the cyclopropyl anion; in contrast to the last-named species, they have no net charge. Electrocyclic ring opening should lead to the hetero analogs *(2)* of the allyl anion in which the uncharged central carbon atom is replaced by an immonium or oxonium function. The negative charge is distributed over the terminal carbon atoms as in the allyl anion itself.

The hypothetical ring opening products *(2)* are 1,3-dipoles in the sense of the 1,3-dipolar cycloaddition concept[5]. 1,3-Dipoles are defined as "zwitterionic heteroallyl anions"; their 1,3-cycloadditions to dipolarophilic multiple bonds follow the ring-size classification 3+2→5, and they are symmetry-allowed concerted processes[6, 7]. The ring-opened valence tautomers *(2)* of aziridines and oxiranes should be *azomethine ylides* and *carbonyl ylides*, respectively[*]; these species are symbolized either as resonance structures as in *(2)* or with delocalized negative charge. Several entries into the class of azomethine ylides were developed previously[8, 9].



Scheme 1

The steric course of the novel aziridine ring opening precisely follows the pathway allowed by orbital symmetry. The reactions of Scheme 1, published in 1967[10], permitted the first verification of *Woodward* and *Hoffmann*'s prediction for the cyclopropyl anion. The aziridine-*trans*- and -*cis*-dicarboxylic esters undergo reversible conrotatory ring opening at 100 °C. In the process, the *trans*-diester yields the *exo,exo*-substituted *cis*-azomethine ylide; this product is trapped *in situ* by acetylenedicarboxylic ester as a dipolarophile to form the 3-pyrroline-*cis*-2,5-dicarboxylic ester. Conversely, the aziridine-*cis*-dicarboxylic ester gives an adduct having *trans* ester groups in positions 2 and 5. The reactions are highly stereospecific; no mutual contamination of the diastereomeric adducts could be detected. On irradiation a disrotatory ring opening of the aziridine was observed. In this case the relative configura-



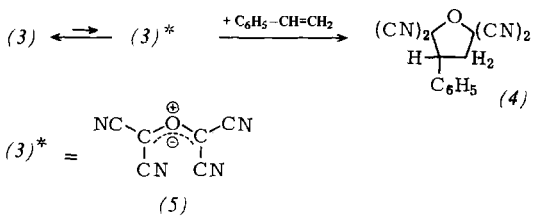
(3)

[*] These trivial names[5] have become accepted; see, *e.g.*, *R. M. Kellogg*, Tetrahedron *32*, 2165 (1976). Systematic names for these species are 2-azonia- and 2-oxoniaallyl anions.

tion of the ester groups is retained on going from the three- to the five-membered ring.

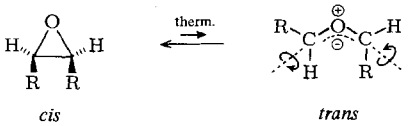
Whereas electrocyclic ring opening of aziridines meanwhile ranks among the thoroughly documented reactions, much less is known about the CC bond opening of ethylene oxides.

According to *Linn* and *Benson*[11], tetracyanoethylene oxide (oxiranetetracarbonitrile) *(3)* can add at elevated temperature to olefins, acetylenes, and even to benzene, forming 2,5-dihydro- and tetrahydrofuran derivatives. The configuration of the olefinic dipolarophile is retained.

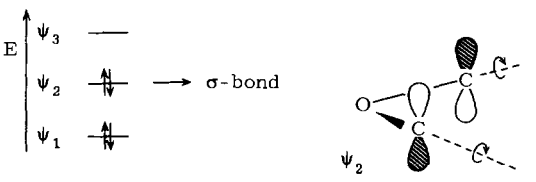


A kinetic study revealed that cycloaddition of tetracyanoethylene oxide *(3)* to styrene to give *(4)* is preceded by a first-order reaction[12]. Today there is no doubt that the "activated species" *(3)** is the carbonyl ylide *(5)*. In contrast to the irreversible electrocyclic ring opening of the cyclopropyl anion, aziridines and oxiranes are strongly favored at equilibrium with azomethine ylides and carbonyl ylides, respectively.

3. Orbital Control of Oxirane Ring Opening

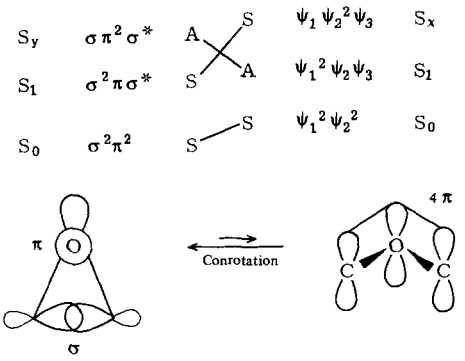


Electrocyclic ring opening at the CC bond entails 90° rotations about the two CO bond axes. In conrotation these motions occur in the same sense, both clockwise or both anticlockwise. A twofold symmetry axis passing through the O atom and the center of the oxirane CC bond is the molecular symmetry element dominating the conrotatory process. However, the symmetry concerned is only local; it applies to the bond system participating in the reaction and not to the substituents.



Scheme 2

The simplest application of the principle of conservation of orbital symmetry to the stereochemistry of electrocyclic ring closure consists in inspection of the symmetry properties of the HOMO, the highest occupied molecular orbital[1]. This is illustrated for the oxirane cyclization in Scheme 2. As in the allyl anion, the two lowest π molecular orbitals are occupied in the carbonyl ylide. The electron pair in ψ_2 is utilized to form the σ bond between the terminal carbon atoms. In order to achieve phase-consistent overlap, two 90° rotations in the same sense are required, *e.g.*, both clockwise, if the white half-orbitals are to undergo σ interaction.

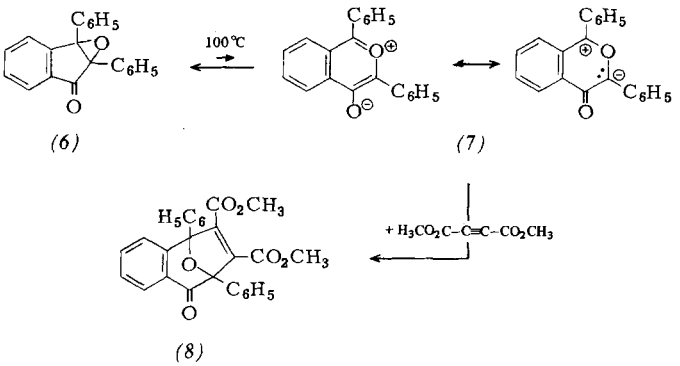


Scheme 3

A more sophisticated approach to orbital symmetry is provided by the correlation diagram of molecular states[13]. This leads to a correlation of the singlet ground states of oxirane and carbonyl ylide in the conrotatory process (Scheme 3). In an alternative model of orbital control due to *Evans*, *Zimmerman*[14], and *Dewar*[15], the 4π electron system of the allyl anion is characterized by a phase discontinuity in the transition state of the conrotatory process.

4. Cyclic Carbonyl Ylides

Since tetracyanoethylene oxide *(3)* contains four identical substituents, no experimental conclusions about the stereochemistry of ring opening can be drawn from the cycloadducts of *(5)*. The only examples providing information about the spatial course of the reaction concern cyclic carbonyl ylides.

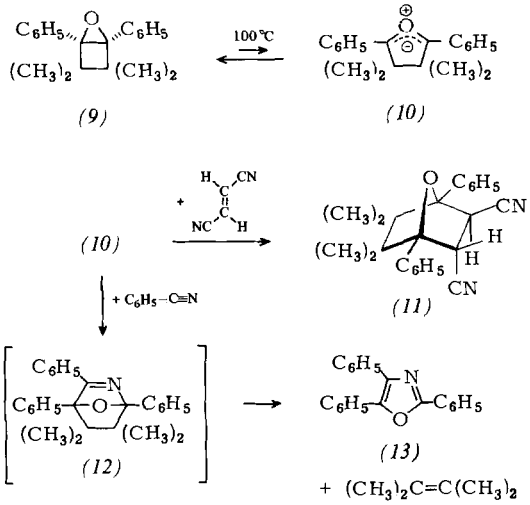


On heating 2,3-diphenylindenone 2,3-oxide *(6)* to 100°C, *Ullman* and *Milks*[16] observed reversible thermochromism; they attributed the red color to the benzopyrylium-olate *(7)* which can easily be recognized as a carbonyl ylide. Cycloadducts were obtained at 135—175°C with dimethyl acetylenedicarboxylate, norbornadiene, and cyclohexanone.

Thermal equilibrium according to *(6)*⇌*(7)* requires orbital symmetry-forbidden disrotatory processes. The ring skeleton exerts a geometrical constraint precluding conrotatory ring opening of *(6)*; the product would have to contain a phenyl group inside the hetero ring! The activation energy of ring opening is 29 kcal/mol[17].

UV irradiation leads to a photoequilibrium *(6)*⇌*(7)*. The first singlet excited states should be linked by symmetry-

allowed disrotatory processes. However, quenching and sensitization experiments, as well as quantum yields, suggested to *Ullman* and *Henderson*[17] that not the electronic excited states, but the vibrationally excited ground states were responsible for equilibration.



(9) *(10)* *(11)* *(12)* *(13)*

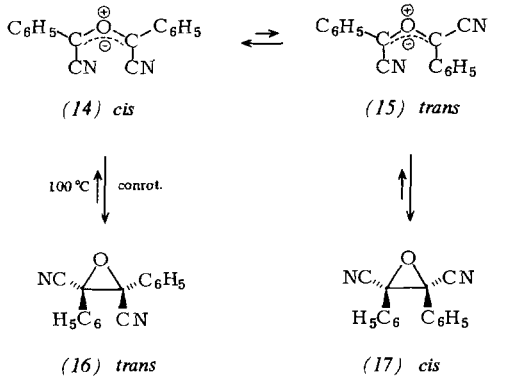
Arnold and *Karnischky*[18] attributed the purple-red color assumed by a solution of the bicyclic oxirane *(9)* at 100°C or on irradiation (253.7 nm) to the cyclic carbonyl ylide *(10)*; the color disappears at 22°C with a half-life of 8 min. Trapping with fumaronitrile affords the 1:1 adduct *(11)*, while the benzonitrile adduct *(12)* suffers spontaneous retro-Diels-Alder reaction to give triphenyloxazole *(13)*.

The feasibility of forbidden thermal disrotations in the cases *(6)*⇄*(7)* and *(9)*⇄*(10)* may be due, respectively, to the aromatic stabilization of *(7)* and to the enormous ring strain of *(9)* (57 kcal/mol for bicyclo[2.1.0]pentane).

5. Reactions of α,β-Dicyano-*trans*- and -*cis*-stilbene Oxides

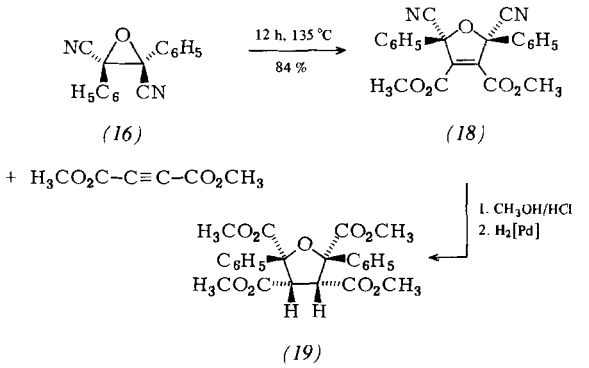
5.1. Cycloadditions and Stereochemistry of Ring Opening

The choice of an appropriate and representative model is of crucial importance in solving a problem. An example of an unfortunate choice of model may be quoted: The clarification of the *Walden* inversion was impeded for half a century by the use of α-halocarboxylic acids. This class of compounds abounds with complications which obscured conclusions on the mechanism of nucleophilic substitution[19].



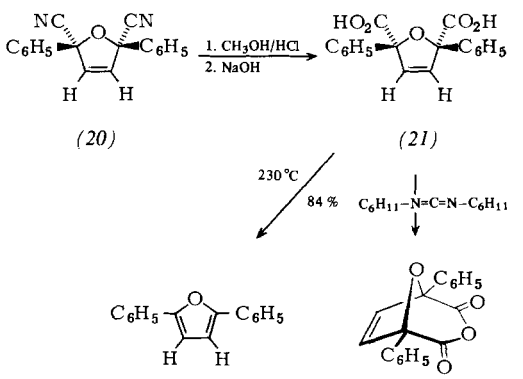
(14) cis *(15) trans* *(16) trans* *(17) cis*

Monocyclic oxiranes having two chiral centers are suitable objects for studying the steric course of the electrocyclic reaction. Our first models were α,β-dicyanostilbene oxides *(16)* and *(17)*[20], which equilibrate at as low a temperature as 100°C without acid or base catalysis to give a mixture of 85% *trans* and 15% *cis* form[21]. Dipole moments of 0.9 and 6.5 D confirm the *trans* and *cis* configurations of *(16)* and *(17)*, and correct an earlier structural assignment[22]. The two carbonyl ylides *(14)* and *(15)*, related by rotation about the CO axis, are plausible intermediates of isomerization; the overall activation energy for *(16)*→*(17)* is 27.2 kcal/mol[21].



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

As expected, the *trans*-oxirane *(16)* develops 1,3-dipolar activity above 100°C. *In situ* reaction with dimethyl acetylenedicarboxylate gives an 84% yield of the crystalline 2,5-dihydrofuran derivative *(18)*[21]. Conversion of the nitrile groups into ester groups and catalytic hydrogenation—known to involve *cis* addition of hydrogen—afford compound *(19)*, shown by its ^{1}H-NMR spectrum to possess a plane of symmetry. Hence the *cis*-carbonyl ylide *(14)* must have reacted, suggesting a conrotatory ring opening of the *trans*-oxirane *(16)*.

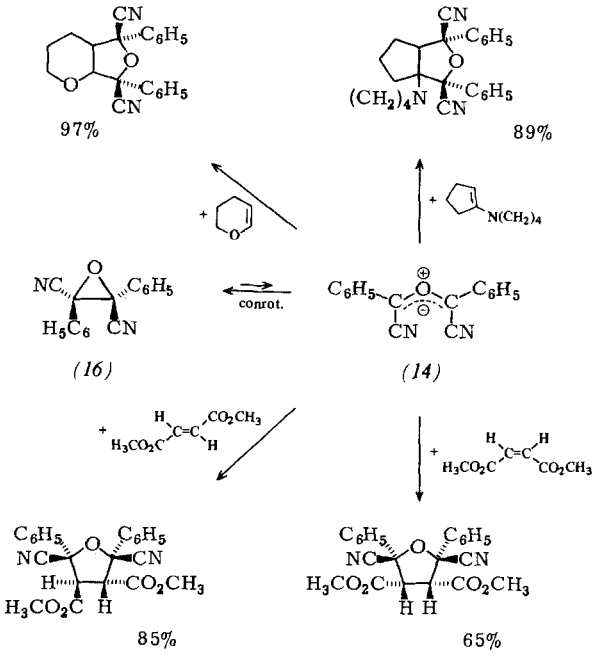


(20) *(21)*

Reaction of acetylene itself with *(16)* in cyclohexanone produces 91% of the adduct *(20)*[21]. The corresponding dicarboxylic acid *(21)* contains the functional groups in *cis* orientation, as demonstrated by anhydride formation on treatment with carbodiimide. Dehydrogenation with concomitant elimination of carbon dioxide occurs at 230°C. Formation of 2,5-diphenylfuran proves the CC ring cleavage of the oxirane *(16)* in contrast to the classical rupture at the CO bond.

The *trans*-oxirane *(16)* combines *via (14)* with various kinds of olefinic substrates to give tetrahydrofuran derivatives[21]. In Scheme 4, dihydropyran and *N*-(1-cyclopentenyl)-pyrrolidine serve as examples of electron-rich double bonds,

whereas dimethyl fumarate and maleate represent electron-poor olefins. Phenylated ethylenes and norbornene also give good yields of adducts. The nitrile groups display a *cis* orientation in all the adducts.



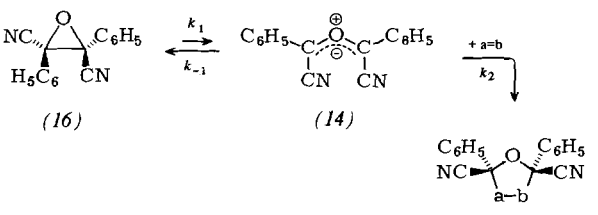
Scheme 4

Does this constitute proof of conrotatory ring opening? Alas, no: for the same cycloadducts are obtained starting from dicyano-*cis*-stilbene oxide *(17)* as from the *trans*-oxirane *(16)*[21]. An *ad hoc* hypothesis is readily conceived: the *trans*-carbonyl ylide *(15)* undergoes rotation to the *cis*-ylide *(14)* faster than cycloaddition. Comfort is even sought in the van der Waals interaction of *endo* substituents in the carbonyl ylide *(15)* being greater than in *(14)*, thus giving the latter an energetic advantage. However, this might all be a figment of the imagination, an attempt to save the conrotatory ring opening.

We clearly have to change our model. The first has failed to give the desired stereochemical information. Before going any further, however, we shall gather some kinetic information.

5.2. Rate Constants of Cycloadditions of α,β-Dicyano-*trans*-stilbene Oxide as Measured by Dilatometry

Adduct formation from the oxirane *(16)* involves a reversible system of first order, followed by a second order reaction; in the presence of a large excess of dipolarophile (designated as a=b) the cycloaddition becomes of pseudo-first order.



$$\frac{d[\text{Adduct}]}{dt} = k_1[\text{Oxirane}]\frac{k_2[a{=}b]}{k_{-1}+k_2[a{=}b]} = k_d[\text{Oxirane}] \quad (a)$$

$$k_d = \frac{k_1 k_2[a{=}b]}{k_{-1}+k_2[a{=}b]} \quad (b)$$

The value of k_d measured by dilatometry[23] is the first order overall rate constant for adduct formation. The material reaching the high-energy intermediate *(14)* at rate k_1 is rapidly channeled into recyclization (k_{-1}) and cycloaddition ($k_2[a{=}b]$). The fraction occurring in equation (a) is called the partition coefficient; it represents the mole fraction of carbonyl ylide *(14)* which leads directly to the cycloadduct. According to eq. (b), k_d is a function containing the dipolarophile concentration [a=b] in both the numerator and the denominator. k_d is a linear function of [a=b] only when $k_{-1} \gg k_2[a{=}b]$.

$$k_d = \frac{k_1}{k_{-1}} k_2[a{=}b] \quad (c)$$

These special conditions as defined by eq. (c) are fulfilled in the reaction of *(16)* with dimethyl fumarate (Table 1); the three values of k_d are proportional to the fumaric ester concentrations. Hence it is demonstrated that the electrocyclic ring opening equilibrium is completely established and that 1,3-dipolar cycloaddition is a slow subsequent reaction[24].

Table 1. Dilatometric rate constants of α,β-dicyano-*trans*-stilbene oxide *(16)* (40 mmol/l) to various dipolarophiles a=b in *o*-dichlorobenzene at 139 °C [24].

Dipolarophile a=b	[a=b] [mol/l]	$10^5 k_d$ [s^{-1}]	$10^5 k_d/[a{=}b]$ [$l \cdot mol^{-1} s^{-1}$]
Dimethyl fumarate	0.300	3.77	12.6
	0.522	6.51	12.5
	0.601	7.57	12.6
Diethyl maleate	0.501	0.50	0.99
N-Phenylmaleimide	0.527	4.86	9.2
Maleic anhydride	0.589	2.26	3.8
Cyclopentene	0.589	1.88	3.2
Norbornene	0.567	6.51	11.5
N-(1-Cyclopentenyl)-pyrrolidine	0.646	12.1	18.7

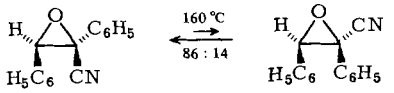
The k_d values of several dipolarophiles compiled in Table 1 are proportional to the cycloaddition rate constant k_2 after division by the dipolarophile concentration [a=b], and thus constitute a measure of the dipolarophilic activity for a given 1,3-dipole. Table 1 lists compounds with electron-poor double bonds, normal alkenes, and an enamine as an example of an electron-rich system. Dimethyl fumarate is 13 times more active than dimethyl maleate; *trans* disubstituted ethylenes are superior to the *cis* compounds in 1,3-dipolar cycloaddition[25] and Diels-Alder reaction[26] for obvious reasons. The angle-strained double bond of norbornene with its non-equivalent π-orbital lobes[27] reacts with *(14)* 3.6 times faster than cyclopentene.

On comparing dimethyl fumarate, cyclopentene, and *N*-(1-cyclopentenyl)pyrrolidine it is notable that both electron-withdrawing and electron-releasing substituents enhance dipolarophilic activity. A useful classification of 1,3-dipoles is based on the decisive HOMO-LUMO interaction according to *Sust-*

mann[28]. The above behavior classifies the carbonyl ylide *(14)* as a Sustmann type II species characterized by two HOMO-LUMO interactions of comparable strength. The narrow overall spread of the k_2 values corresponds to expectations for the bottom of a paraboloid function attained by plotting $\log k_2$ against the lowest ionization potential of the dipolarophiles[29].

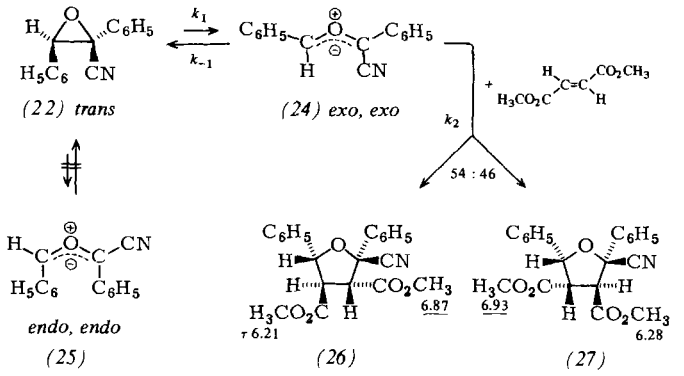
6. α-Cyano-*trans*-stilbene Oxide and Dimethyl Fumarate

6.1. Stereochemistry of Cycloaddition



(22) trans *(23) cis*

Monocyanostilbene oxides, prepared from benzaldehyde and α-chlorophenylacetonitrile and potassium *tert*-butoxide, turned out to be superior models for studying the stereochemistry of electrocyclic ring opening. In this case a temperature of 160 °C is necessary to establish the thermal *trans,cis* equilibrium [86% *(22)* and 14% *(23)*] with $t_{1/2} = 7.2$ h[30].



(22) trans *(24) exo, exo* *endo, endo* *(25)* *(26)* *(27)*

Scheme 5

Heating the *trans*-oxirane *(22)* in an excess of molten dimethyl fumarate to 130 °C produces the two cycloadducts *(26)* and *(27)*[30] in 99% yield. The NMR spectra—some of the τ values are entered in Scheme 5—permit assignment of configuration, the high τ value of the ester methyl located *cis-vicinal* to phenyl being an important criterion. Both adducts contain *cis* phenyl groups in positions 2 and 5, and *trans* ester groups in positions 3 and 4. The configurations of 1,3-dipole and dipolarophile are retained in the concerted cycloaddition. Thus, the carbonyl ylide involved must be the *exo,exo*-diphenyl isomer *(24)* expected as the product of conrotatory ring opening. The carbonyl ylide *(25)*, which would also account for the stereochemistry of the adducts, is energetically disqualified by the interaction of two large groups on the *endo* side.

6.2. Kinetics of Cycloaddition

The carbonyl ylide *(24)* fails to appear in spectroscopically detectable concentrations. It can be shown kinetically, however, that cycloaddition is preceded by reversible formation of a high energy intermediate. The aforementioned dilatometric study of cycloadduct formation with a variable excess of dimethyl fumarate affords the pseudo-first order k_d values defined in eq. (a) and (b). If these are plotted against the molar concentration of fumaric ester, then curves are obtained for various temperatures which approach plateau values (Fig. 1 A). This demonstrates that in eq. (b) the recyclization constant k_{-1} and the cycloaddition constant k_2[a=b] are of similar magnitude[31].

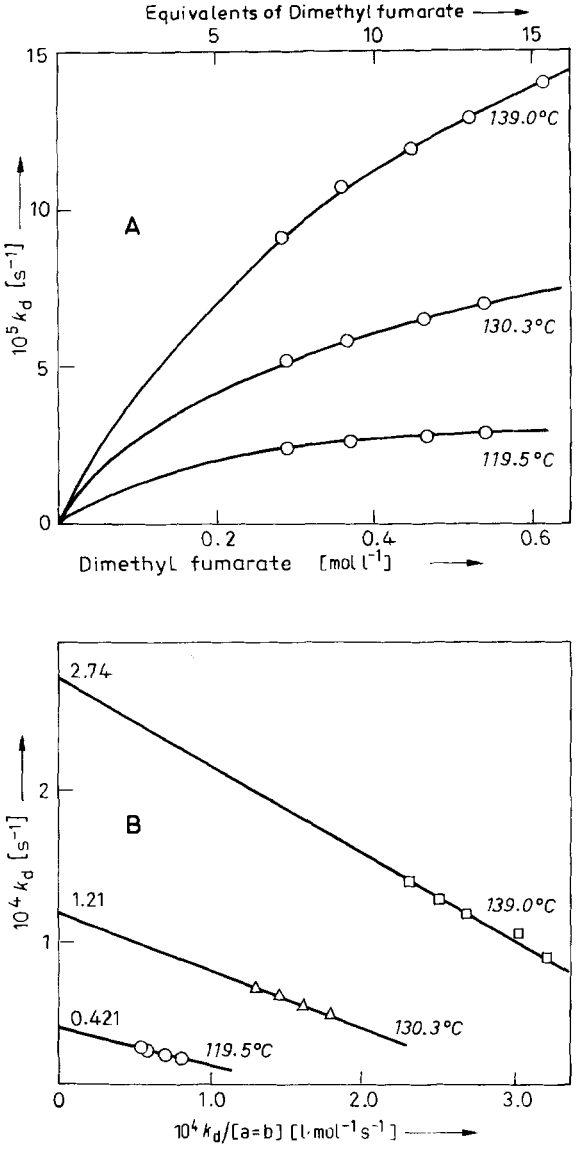


Fig. 1. Dilatometric rate measurements of the cycloaddition of α-cyano-*trans*-stilbene oxide *(22)* (40 mmol/l) with dimethyl fumarate in *o*-dichlorobenzene [30]. A) Plot of k_d *vs.* dimethyl fumarate concentration [a=b]. The curves were calculated with the values k_1 and k_{-1}/k_2 determined from Fig. 1 B. B) Plot of k_d *vs.* k_d/[a=b].

Equation (b) having the dipolarophile concentration [a=b] in the numerator and in the denominator can be transformed into the equation of a straight line by representing k_d as a function of k_d/[a=b]. When plotted according to eq. (d), the experimental values do indeed define straight lines (Fig. 1 B). The intercept is identical with the ring opening constant

$$k_d = k_1 - \frac{k_{-1} k_d}{k_2[\text{a=b}]} \qquad \text{(d)}$$

k_1. The Eyring activation parameters can be determined from the temperature dependence of this rate constant. The activation enthalpy amounts to 30.1 kcal/mol; the change in entropy, $\Delta S^{\neq} = 2$ cal K^{-1} mol^{-1}, is negligibly small, as expected for the conversion of the rigid oxirane *(22)* into the rigid carbonyl ylide *(24)*.

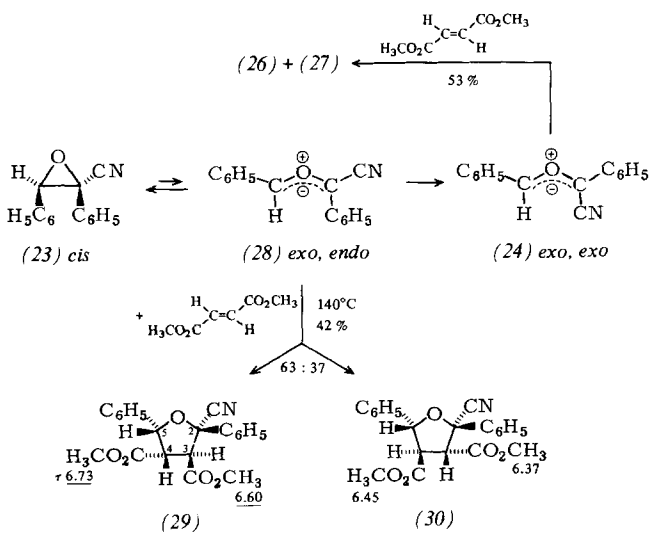
The slopes of the straight lines in Figure 1B correspond to the rate ratios of the reactions competing for the carbonyl ylide (k_{-1}/k_2). The increase in slope with temperature results from k_{-1} having a higher temperature coefficient than k_2. The intramolecular cyclization *(24)*→*(22)* should possess as small an activation entropy as the reversal *(22)*→*(24)*; hence $\Delta H^{\neq}$ accounts for virtually all the free energy of activation. In contrast, 1,3-dipolar cycloadditions display modest enthalpies of activation, but large negative entropies of activation[25]; k_2 consequently shows a much smaller dependence upon temperature than k_{-1}.

It should be mentioned in passing that *(22)* also undergoes cycloadditions with other olefinic and acetylenic dipolarophiles[24, 30].

7. α-Cyano-*cis*-stilbene Oxide and Dimethyl Fumarate

7.1. Stereochemistry of Addition

Reaction of the *cis*-oxirane *(23)*—*cis* and *trans* refer here to the orientation of the phenyl groups—in a dimethyl fumarate melt at 140°C furnishes 42% of two new adducts besides 53% of the cycloadducts *(26)* and *(27)* with *cis*-2,5-phenyl groups already discussed. All four diastereomeric tetrahydrofuran derivatives were separated by layer chromatography and characterized[30]. The ^{1}H-NMR spectra (some τ values shown in Scheme 6) leave no doubt that the phenyl groups in positions 2 and 5 of the new adducts *(29)* and *(30)* are *trans* located. The 63:37 ratio of *(29)* and *(30)* is remarkable in that the phenyl and the ester group twice appear in *cis-vicinal* positions, corresponding to a relatively high van der Waals strain. The reason lies in the more extensive π overlap of the reactants in the transition state leading to *(29)*.



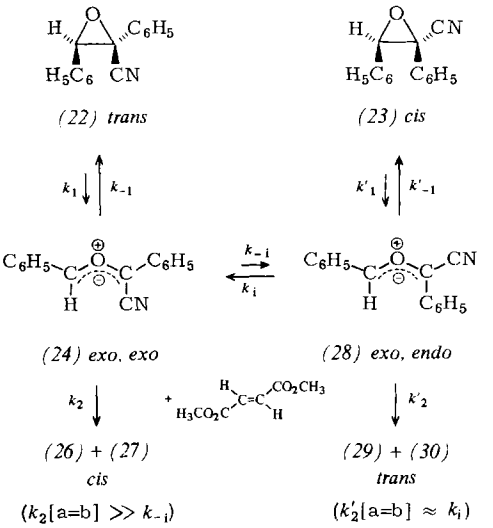
Scheme 6

The *trans*-2,5-diphenyl adducts *(29)* and *(30)* must originate from cycloaddition of the carbonyl ylide *(28)* which has an *exo*- and an *endo*-phenyl group.

7.2. Cycloaddition *versus* Rotation

A tentative interpretation: α-cyano-*cis*-stilbene oxide *(23)* opens conrotatorily to the *exo,endo*-diphenyl carbonyl ylide *(28)* which is only partly trapped by 1,3-dipolar cycloaddition to give *(29)* and *(30)*. Part of the carbonyl ylide *(28)* escapes by isomerization to the more stable *exo,exo*-diphenyl isomer *(24)*, which in turn is converted by fumaric ester into the *cis*-diphenyl adducts *(26)* and *(27)*.

Why is the *exo,exo* form *(24)* more stable than *(28)*? In the *exo,endo* isomer *(28)* the planar conformation is prohibited by the proximity of the *endo*-phenyl and the *endo*-hydrogen, whereas the conjugation is unimpaired in the *exo,exo*-isomer *(24)*.



Scheme 7

What support can we derive for the working hypothesis of partial trapping of *(28)*? In Scheme 7, α-cyano-*trans*- *(22)* and -*cis*-stilbene oxide *(23)* are interconnected by rotation *via* the stereoisomeric carbonyl ylides. Starting from the *trans*-oxirane *(22)*, reaction with dimethyl fumarate exclusively affords the *cis*-2,5-diphenyl adducts *(26)* and *(27)*. There is no concomitant rotation of the *exo,exo*-carbonyl ylide *(24)*, *i.e.* k_2[a=b], the rate of cycloaddition, is much greater than k_{-i}. In contrast, cycloaddition to give the *trans*-diphenyl adducts *(29)* and *(30)*, and rotation proceed at similar rates in the less favored *exo,endo*-carbonyl ylide *(28)*. Since the carbonyl ylide *(24)*, which arises by rotation with the rate constant k_i, does not return to *(28)* in the presence of dimethyl fumarate, k_i constitutes the product-determining step for the formation of the *cis*-diphenyl adducts *(26)* and *(27)* from the *cis*-oxirane *(23)*.

$$\frac{\textit{cis}\text{-Adducts } (26)+(27)}{\textit{trans}\text{-Adducts } (29)+(30)} = \frac{k_i}{k'_2[\text{a=b}]} \qquad \text{(e)}$$

The large negative entropy of activation of concerted cycloadditions and the only modest activation enthalpy has already been mentioned. In contrast, rotational barriers such

as those between the carbonyl ylides *(28)* and *(24)* are associated with activation entropies close to zero; a higher temperature coefficient should arise from the higher enthalpy of activation.

Table 2. Cycloadditions of α-cyano-*trans*- *(22)* and -*cis*-stilbene oxide *(23)* to dimethyl fumarate (excess, melt); temperature dependence of the ratio of *cis* and *trans*-2,5-diphenyl cycloadducts, *(26)*+*(27)* and *(29)*+*(30)* [30].

	Temp. [°C]	Conversion [%]	Reaction time	*cis* : *trans* *(26)*+*(27)* : *(29)*+*(30)*
trans *(22)*	130	99	45 h	100 : 0
cis *(23)*	100	26	30 d	31 : 69
cis *(23)*	120	87	14 d	44 : 56
cis *(23)*	130	80	130 h	49 : 51
cis *(23)*	140	95	120 h	57 : 43

The temperature dependence of the *cis*:*trans* cycloadduct ratio indeed fits eq. (e) (Table 2)[30]. In experiments with the *cis*-oxirane *(23)* in molten dimethyl fumarate at 100–140°C the proportion of stereospecifically formed *trans*-2,5-diphenyl adducts drops from 69 to 43%. Rotation gains ground, as confirmed by the increasing percentage of *cis* adducts, formed non-stereospecifically *via* rotation. The inadequate rate of ring opening precludes studies at lower temperatures; even at 100°C only 26% conversion takes place within 30 days.

Starting from the *cis*-oxirane *(23)*, competition between bimolecular cycloaddition (k'_2[a=b]) and unimolecular isomerization (k_i) for the carbonyl ylide *(28)* should depend upon the concentration [a=b] of the fumaric ester. If the ratio of *cis* to *trans* adducts is plotted against the reciprocal of the fumaric ester concentration, then eq. (e) predicts a straight line of slope k_i/k'_2.

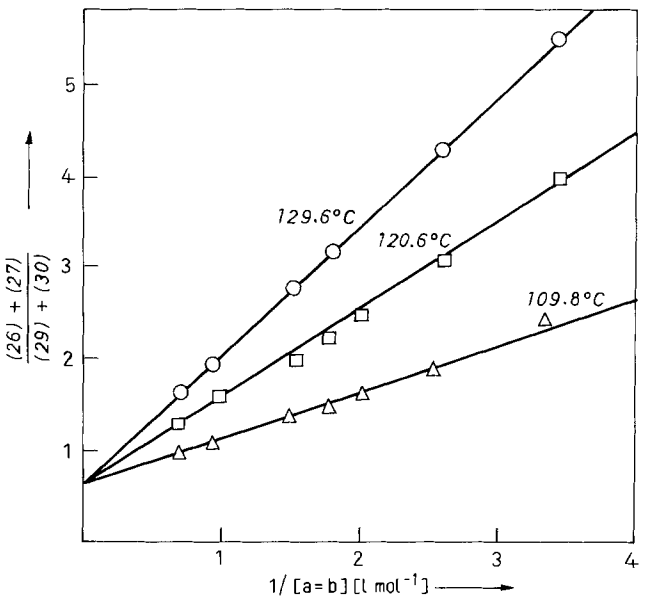


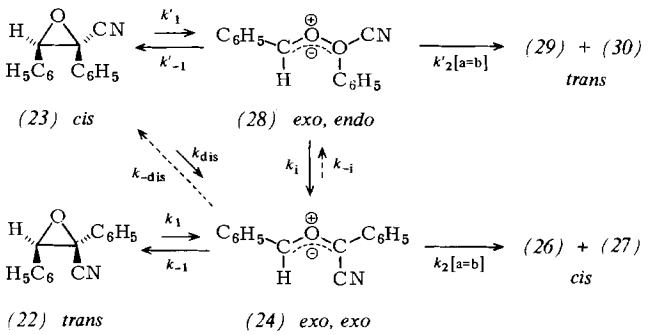
Fig. 2. Reaction of α-cyano-*cis*-stilbene oxide *(23)* with an excess of dimethyl fumarate in *o*-dichlorobenzene; dependence of the ratio of *cis*- and *trans*-2,5-diphenyl cycloadducts (*(26)*+*(27)*)/(*(29)*+*(30)*) upon the concentration [a=b] of fumaric ester [32].

The ratio of *cis*- to *trans* adducts was determined by NMR spectroscopy for several concentrations of fumaric ester in *o*-dichlorobenzene at various temperatures[32]. The experimental ratios define straight lines in Figure 2, thus indeed establishing the competition of first order isomerization with second order cycloaddition. For the reasons mentioned, the slope of the straight lines (k_i/k'_2) increases with temperature.

7.3. Two Pathways Leading to Nonstereospecific Cycloadducts

A blemish: the three straight lines of Figure 2 do not pass through the origin as required by eq. (e), but intersect the ordinate at the value 0.56. What does this mean? Even at an infinitely great concentration of fumaric ester (corresponding to 1/[a=b] = 0) 36% of *cis* adduct is formed alongside 64% of *trans* adduct; 36/64 is 0.56. The unavoidable conclusion: only 64% of the material is actually subjected to competition between unimolecular isomerization and bimolecular cycloaddition. How, then are the remaining 36% of *cis* adducts formed from the *cis*-oxirane *(23)* circumventing the *exo,endo*-carbonyl ylide *(28)*?

Only the most likely pathway from a total of four possibilities[32] will be considered, *viz.* the disrotatory pathway leading directly from the *cis*-oxirane *(23)* to the *exo,exo*-carbonyl ylide *(24)*. In trying to interpret this minor participation of symmetry-forbidden disrotation in ring opening, it should be borne in mind that disrotation already becomes effective at 100°C in the case of the bicyclic oxiranes *(6)* and *(9)*.



Scheme 8

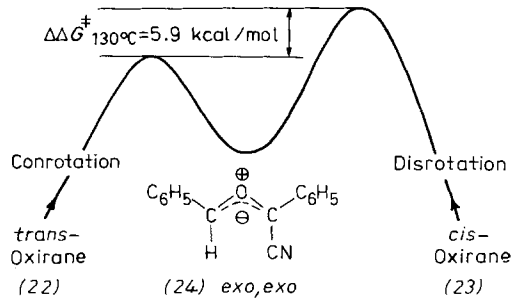
Thus Scheme 7 is replaced by Scheme 8 which includes disrotatory ring opening. Since the *cis*-2,5-diphenyl cycloadducts *(26)* and *(27)* are obtained exclusively from the *trans*-oxirane *(22)* (Scheme 6), k_{-i} and k_{-dis} must be negligibly small in the presence of fumaric ester. Treatment of the remaining complex reaction according to *Bodenstein*'s *quasi*-steady state principle affords eq. (f). Once again, the ratio of *cis*- to *trans*-2,5-diphenyl cycloadducts, *(26)*+*(27)* to *(29)*+*(30)*, is a linear function of 1/[a=b], the reciprocal of the fumaric ester concentration. The intercept, k_{dis}/k'_1, is the ratio of the rate constants of disrotatory and conrotatory ring opening of *(23)*. Its value of 0.56 means that the allowed conrotation is only about twice as fast as the forbidden disrotation.

$$\frac{\textit{cis}\text{-Adducts}}{\textit{trans}\text{-Adducts}} = \frac{k_{dis}}{k'_1} + \frac{k_i k'_1 + k_{dis} k'_{-1} + k_i k_{dis}}{k'_1 k'_2} \cdot \frac{1}{[a=b]} \qquad (f)$$

7.4. Orbital Symmetry-Allowed and -Forbidden Ring Opening

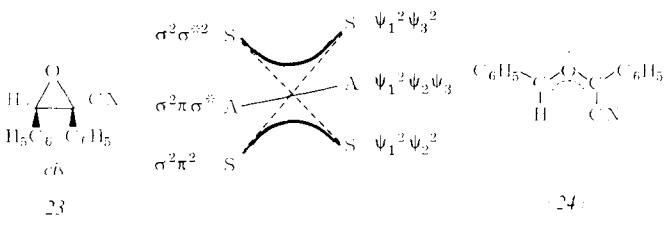
We should not forget that ring opening of the *trans*-oxirane *(22)* occurs by conrotation exclusively. The *cis* oxirane *(23)*

enters into the forbidden disrotation, because conrotation leads to the energetically less favorable of the two carbonyl ylides. A fairer comparison of symmetry-allowed and symmetry-forbidden is provided by the formation of one and the same *exo,exo*-carbonyl ylide *(24)* from the *trans*-oxirane *(22)* by conrotation and from the *cis*-oxirane *(23)* by disrotation (Scheme 8); the transition states of endothermic formation of the carbonyl ylides should structurally resemble the latter more closely than the oxiranes.



Scheme 9

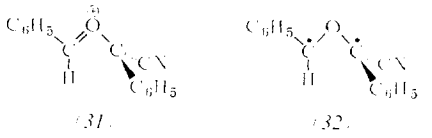
Let us compare orbital symmetry with laws in human society. Forbidden acts do occur, but they require a higher activation energy. As derived below, the transition states leading from *(22)* and *(23)* to the *exo,exo*-carbonyl ylide *(24)* differ in their free energy by 5.9 kcal/mol at 130°C (Scheme 9). Conrotatory ring opening should accordingly be 1600 times faster than the forbidden disrotation. $\Delta\Delta G^{\neq}$ of allowed and forbidden reactions is, however, smaller than in the few cases which have been successfully subjected to experimental measurement. In the electrocyclic ring closure of *trans,cis,cis,trans*-2,4,6,8-decatetraene to form 7,8-dimethyl-1,3,5-cyclooctatriene conrotation and disrotation differ by 12 kcal/mol in $\Delta G^{\neq}$ at 170°C[33]; in the case of 2,3,4,5-tetraphenyl-2,4-hexadiene, disrotatory ring closure to the cyclobutene derivative requires >7 kcal/mol more energy than the conrotatory mode[34].



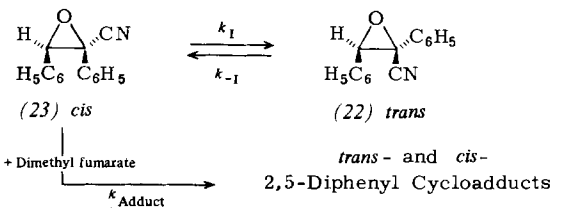
Scheme 10

The nature of "forbidden" processes is one of the toughest mechanistic problems of our time. The hard nut has not been cracked, neither here nor in any other case. One-step and two-step reactions have been considered.

The orbital symmetry correlation diagram of the molecular states for concerted disrotation is shown in Scheme 10. Formally, the ground state of the oxirane *(23)* should be correlated with the second excited singlet state of the carbonyl ylide *(24)*. However, configuration interaction prevents the crossing of correlation lines which connect states of the same symmetry. Correlation of the ground states, *(23)* → *(24)*, goes by way of an energy peak representing the forbiddenness of the process. It can be readily demonstrated that the energy gap between ψ_2 and ψ_3 should be smaller for the carbonyl ylide than for the azomethine ylide (Scheme 1) or the allyl anion, which could imply a reduced $\Delta\Delta G^{\neq}$ for conrotation and disrotation[24].



An attractive nonconcerted process is visualized in a ring opening which involves only one 90° rotation. Whether or not the oxonium ylide *(31)*—possessing no allyl anion orbital—and the diradical *(32)* are different species, is unsettled. *Dewar* and *Kirschner*[35] found in MINDO/3 calculations that the energy requirements of conrotatory and disrotatory ring opening of the cyclopropyl anion differ by a mere 9 kcal/mol, assuming the disrotation to involve two successive 90° rotations. The oxonium ylide *(31)* is an octet structure stabilized by substituents.



Temp [°C]	$10^6 k_I$ [s^{-1}]	$10^6 k_{Adduct}$ [s^{-1}]
130	1.17	1.15
170	5.32	5.39

Scheme 11

Determination of the energy difference of 5.9 kcal/mol in Scheme 9 is based on further kinetic information: The overall isomerization constant k_I of *cis*- to *trans*-oxirane, *(23)* → *(22)*, virtually equals the overall constant of cycloaddition in the presence of dimethyl fumarate[31] (Scheme 11). Hence it follows that the transition states of conrotatory and disrotatory ring opening of the *cis*-oxirane *(23)* represent the highest mountain passes in the entire energy panorama.

The free energy profile of Figure 3 is now accessible; the solid lines refer to experimental ΔG values at 130°C. The difference of 5.9 kcal/mol between the transition states of dis-

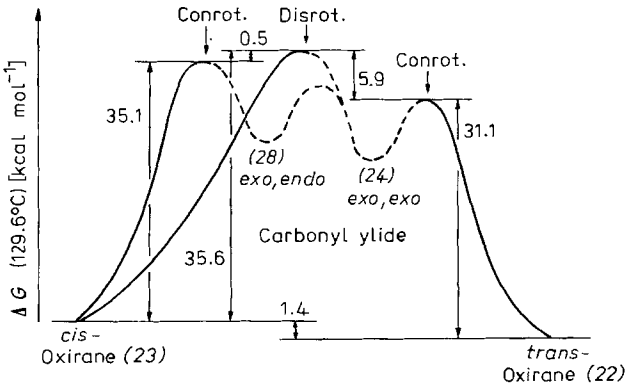
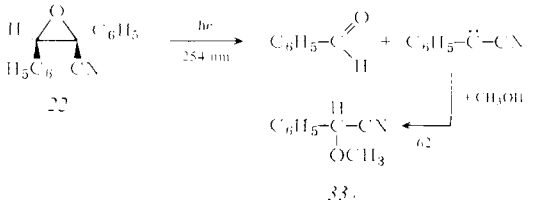


Fig. 3. Free energy profile for *cis,trans* isomerization of the α-cyanostilbene oxides *(23)* and *(22)* *via* the carbonyl ylides *(24)* and *(28)* [32].

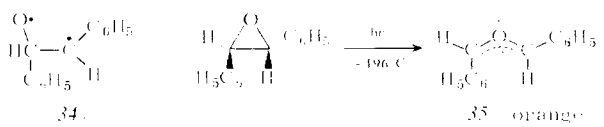
rotation and conrotation, both leading to carbonyl ylide *(24)*, is the result of a thermochemical cycle.

How deep are the energy valleys in which the carbonyl ylides hold their brief sojourn before reacting further? Solution of this problem requires an excursion into photochemistry.

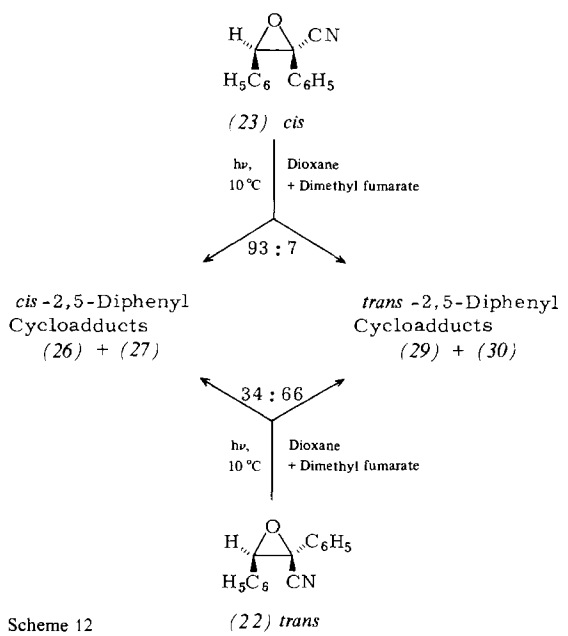
8. Photochemical Ring Opening of Oxiranes



Griffin et al.[36] observed an interesting photofragmentation of *vic*-diaryloxiranes into carbonyl compounds and carbenes; formation of *(33)* from *(22)* serves as an illustration[37]. Irradiation of *trans*- and *cis*-stilbene oxide in a matrix at −196 °C produces an orange and a deep-red color with absorption maxima at 490 and 510 nm, respectively. A diradical *(34)* arising from CO bond rupture was initially preferred for the colored species[38]; *Do-Minh*, *Trozzolo*, and *Griffin*[39]



later attributed the colors to the carbonyl ylides, *e.g. (35)*, which are formed by a disrotatory process. Carbene formation presumably results from photolysis of the carbonyl ylide[36] or from a second photoprocess starting from the oxirane.



Scheme 12

The experiments of Scheme 12, performed in 1972, offer a "missing link". On irradiation of α-cyano-*cis*- and -*trans*-stilbene oxides in dioxane with a mercury low-pressure lamp at 10 °C, the carbonyl ylides generated can be intercepted with dimethyl fumarate[40]. The principal products isolated are *cis*-2,5-diphenyl cycloadducts from the *cis*-oxirane *(23)* and *trans*-2,5-diphenyl adducts from the *trans*-oxirane *(22)*. The preferred ring-opening pathway, if not the only one operative, appears to be the disrotatory mode which is symmetry-allowed for the first singlet excited state. On the other hand, it is probably the singlet ground state of the carbonyl ylides which combines with dimethyl fumarate; the adduct ratios *(26)/(27)* and *(29)/(30)* match those from thermally generated carbonyl ylides (54:46 in Scheme 5, 63:37 in Scheme 6).

Why is the stereoselectivity in Scheme 12 not greater? The sequence of photochemical disrotatory ring opening and thermal conrotatory cyclization constitutes a *trans,cis* isomerization of the oxirane which precludes stereochemical purity. After irradiating the *trans*-oxirane *(22)* in the presence of fumaric ester, one isolates alongside 46% of cycloadducts some oxirane which contains *(22)*:*(23)* = 85:15[40]. Photoisomerization of the carbonyl ylides *(24)*⇌*(28)*, would provide a further source for stereochemical leakage.

Recently, also *Griffin et al.*[41] and *Lee*[42] described trapping reactions of photogenerated carbonyl ylides by [3+2→5] cycloadditions. The stereoselectivity observed by *Lee* on photoaddition of *cis*- and *trans*-stilbene oxide to methyl acrylate or maleic anhydride corresponds to that found by us. The complexity of oxirane photolysis is evidenced by the observation that triplet sensitizers enhance the yield of cycloadduct and produce identical adduct mixtures from *cis*- and *trans*-stilbene oxide; nevertheless, singlet carbonyl ylides appear to be the species entering into cycloaddition[41,42].

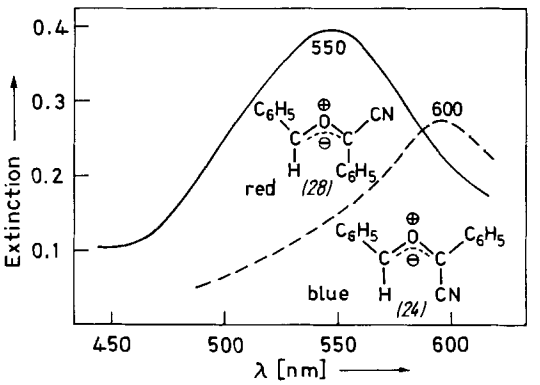


Fig. 4. Flash photolysis of α-cyano-*cis*- *(23)* and -*trans*-stilbene oxide (22). Matrix of isopentane/ether (6:1) at −196 °C, 25-joule argon flash, measurement with xenon lamp [43]. Extinction in arbitrary units.

In cooperation with the Max-Planck-Institut für Kohlenforschung we subjected the oxiranes *(22)* and *(23)* to flash photolysis in an isopentane/ether matrix at −196 °C. We attribute the colors observed (Fig. 4) to the carbonyl ylides *(28)* and *(24)*. The longer wavelength absorption measured in the experiment with the *cis*-oxirane *(23)* is attributable to the *exo,exo*-diphenyl isomer *(24)* with its unhindered carbonyl ylide conjugation[43].

The colors disappear with half-lives of 5 and 2.5 s, respectively, at −196 °C, corresponding to thermal recyclization of the carbonyl ylides. Flashing of oxirane solutions at room temperature does not lead to detectable colors; no absorption

was registered in the visible range even one microsecond after the flash. Thus, the carbonyl ylides must disappear with a half-life shorter than 0.5×10^{-6} s at 25 °C, indicating $\Delta G^{+} < 12.5$ kcal/mol for recyclization. A check on these results and supplementary measurements in the intermediate temperature range are required.

9. Energy Profile for the *cis,trans*-Isomerization of α-Cyanostilbene Oxide

Further kinetic data and relations—see ref. [24] for details—help to define reasonable maximum and minimum values for the rate constants of Scheme 8. These estimates provide the basis for the free energy profile of Figure 5 which offers upper and lower limits for the depth of the energy troughs corresponding to the carbonyl ylides *(28)* and *(24)*. The disrotatory ring opening of the *cis*-oxirane *(23)* has been omitted for the sake of clarity.

about the CO bond, the energy barrier is actually quite small. Indeed, significantly higher barriers to rotation, *viz.* 20—26 kcal/mol, were found for azomethine ylides having similar substitution patterns[44,45]. *Ab initio* calculations with the 4—31 G program[46] do in fact confirm that the resonance energy of the azomethine ylide is greater than that of the carbonyl ylide, both being considered as the unsubstituted parent compounds; *Hehre*[47] calculated the rotational barrier of the azomethine ylide as 29 kcal/mol and that of the carbonyl ylide as 14 kcal/mol.

In a different approach, *Hayes* and *Siu*[48] treated the structure of some 1,3-dipoles by a SCF configuration interaction technique in which the percentage of mixing of a doubly excited with a ground configuration was calculated. Twice that percentage is defined as "π diradical character" which in the case of azomethine ylides and carbonyl ylides amounts to 30 and 38 %, respectively. We suppose a decreasing rotational barrier with increasing "π diradical character".

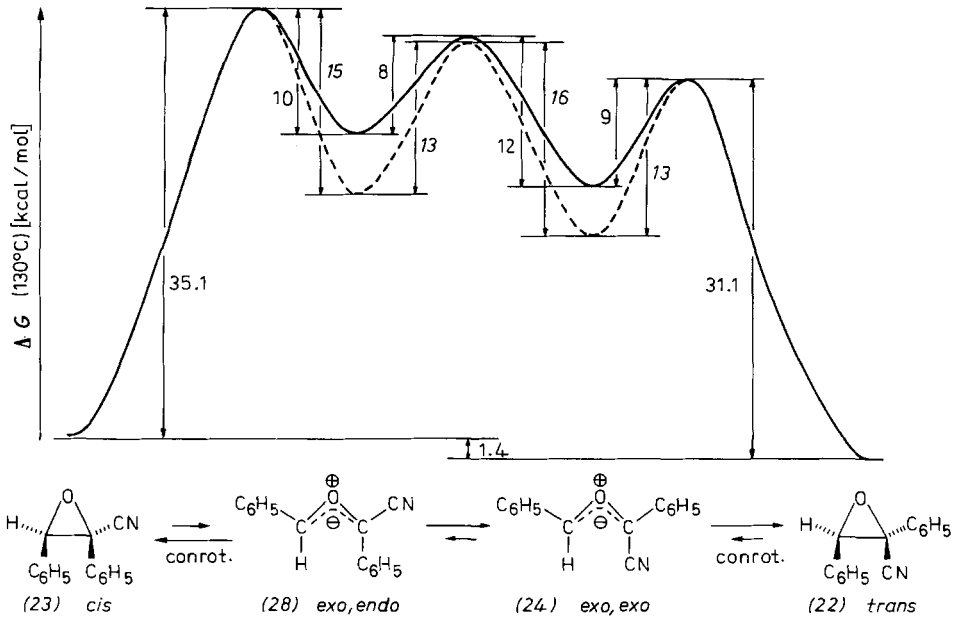


Fig. 5. Free energy profile (130 °C) for thermal *cis,trans*-isomerization of α-cyanostilbene oxides; maximum (in italics) and minimum ΔG^{+} values for the carbonyl ylides [43].

The energy profile clarifies why the carbonyl ylides are not visible in thermal equilibrium with the oxiranes. They lie roughly 20 kcal/mol above the energy level of the oxiranes. One should expect only one carbonyl ylide molecule per 10^{11} oxirane molecules at 130 °C. It is an enticing aspect of this study that indirect information on structure and reactivity of such high-energy intermediates can be acquired.

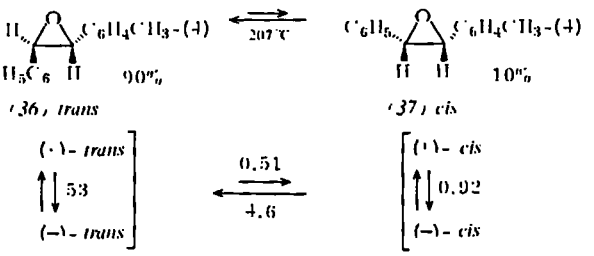
As the result of van der Waals pressure of the *endo*-phenyl and the *endo*-H, the energy level of the *exo,endo*-diphenyl-carbonyl ylide *(28)* is 3—4 kcal/mol above that of the *exo,exo*-isomer *(24)*. The recyclization barriers are 8—13 and 12—16 kcal/mol, respectively. The low rotational barrier for *(28)* → *(24)* is responsible for the lack of stereoselectivity observed in the 1,3-dipolar cycloadditions of *(28)* (Table 2, Fig. 2).

In view of the fact that the allyl anion resonance of the carbonyl ylide must be temporarily sacrificed on rotation

Is it permissible to use *free energy profiles* for picturing the reaction event, as done in Figures 3 and 5? Is not the standard enthalpy a better measure for the fictitious potential energy of the single molecule or collision complex? After critically examining the graphical representations of complex reactions, *Johnston*[49] concludes that the ordinate of the usual plots corresponds neither to the potential energy nor to the enthalpy, nor to the free energy in the strict sense. Nevertheless: "It cannot be said that these plots are meaningless. It can be said that they are an artificial, conventional, short-hand notation for complex reactions. Some people are able to communicate with each other using these symbols..."

Have we chosen a good model for the mechanistic study? It has provided the deepest insight so far into the stereochemistry and energetics of the electrocyclic oxirane ring opening including the energy requirements of the orbital symmetry-allowed and symmetry-forbidden courses. The limited 1,3-

dipolar activity of the *exo,endo*-carbonyl ylide *(28)* was disadvantageous; the cycloaddition could not suppress the rotation completely.



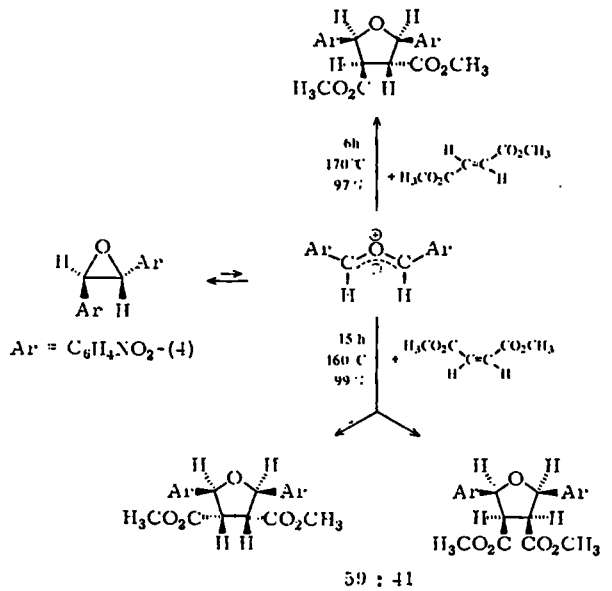
Scheme 13

A model used by *MacDonald* and *Crawford*[50] adds welcome evidence. The *trans* isomer *(36)* of the optically active 2-phenyl-3-*p*-tolyloxirane racemizes 60 times faster than the *cis* form *(37)*; the rate constants at 207 °C are given as $10^6 k$ $[s^{-1}]$ in Scheme 13. The intermediate carbonyl ylides possess a plane of symmetry. The preference of the *trans* isomer *(36)* in racemization rate is due to conrotatory ring opening to form the *exo,exo*-diaryl-carbonyl ylide, the energetically more favorable of the two open-chain species. The *trans,cis* isomerization proceeds *via* rotation of the carbonyl ylide. The *exo,endo*-carbonyl ylide arising from the *cis*-oxirane *(37)* displays the greater tendency to undergo rotation.

Comparison of the ring opening rates of *(36)* and *(37)* with those of α-cyano-*trans*- *(22)* and -*cis*-stilbene oxide *(23)* reveals that the additional nitrile group accelerates 540- and 1400-fold (extrapolation to 130 °C).

10. Synthesis of Heterocycles with Carbonyl Ylides

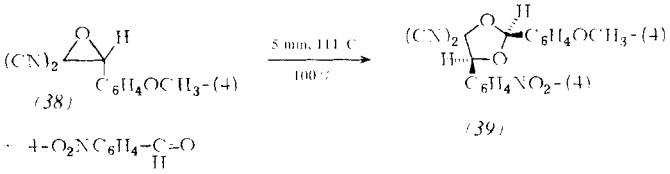
A brief outline of the preparative use and synthetic utility of carbonyl ylides may supplement the mechanistic study.



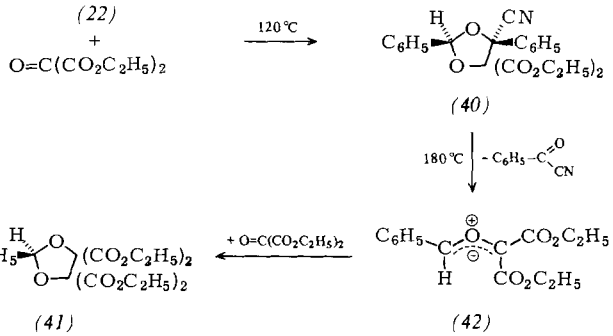
Scheme 14

How does the ability of oxirane to undergo thermal ring opening depend upon the number and nature of the substituents? The allyl anion character of the ring-opened species requires substituents capable of stabilizing negative charge. Tetra- and trisubstituted ethylene oxides have been examined so far. Just two substituents suffice in the case of *p,p'*-dinitro-*trans*-stilbene oxide, which reacts with dipolarophiles at 160—170 °C. Satisfactory yields of tetrasubstituted tetrahydrofurans are obtained with dimethyl fumarate and maleate (Scheme 14)[24].

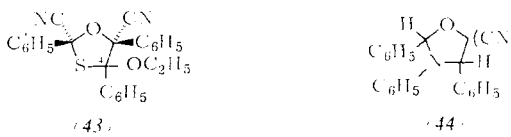
Photochemical oxirane ring opening also demands several activating substituents, of which at least one must be an aryl group, probably to ensure adequate long-wave absorption.



Apart from olefinic and acetylenic bonds, numerous hetero multiple bonds as dipolarophiles accept carbonyl ylides. *Robert et al.*[51] prepared 1,3-dioxolanes from 2-aryl-3,3-dicyanooxiranes and aromatic aldehydes, *e.g. (39)* from *(38)* and *p*-nitrobenzaldehyde in boiling toluene.

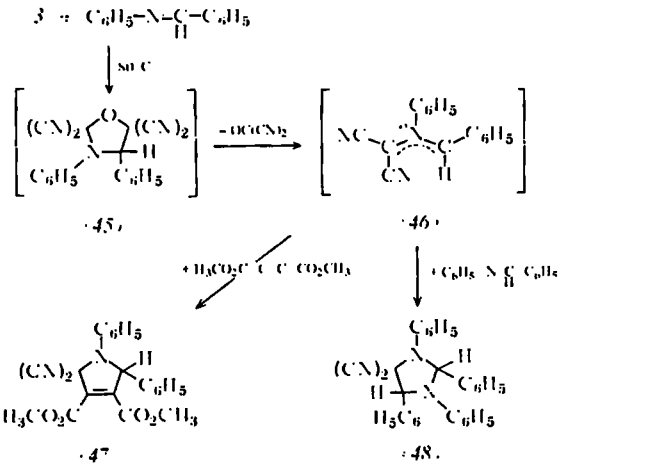


Addition of α-cyano-*trans*-stilbene oxide *(22)* to diethyl mesoxalate to form *(40)* is followed by a 1,3-dipolar cycloreversion; the new carbonyl ylide *(42)* adds afresh to the mesoxalic ester, yielding tetraethyl 1,3-dioxolanetetracarboxylate *(41)*[52].

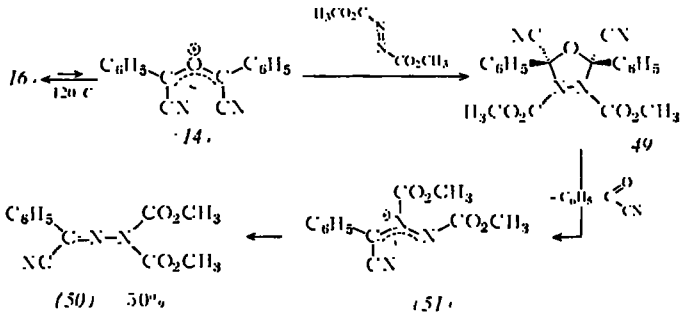


Addition of carbonyl ylides to the highly dipolarophilic CS double bond furnishes 1,3-oxathiolanes. Thus, α,β-dicyano-*trans*-stilbene oxide *(16)* combines with *O*-ethyl thiobenzoate at 120 °C to give 65 % of *(43)* (two diastereomers)[52]. Azomethines of the *N*-benzylideneaniline type add the carbonyl ylide from 1,1-dicyano-2-phenyloxirane at 111 °C to form 65 % of *(44)*[53].

In contrast, addition of tetracyanoethylene oxide *(3)* to *N*-benzylideneaniline is succeeded by elimination of mesoxalonitrile leading to the azomethine ylide *(46)*. The latter combines either with a second molecule of *N*-benzylideneaniline to give the imidazolidine *(48)* or with added dimethyl acetylenedicarboxylate, whereupon 62 % of the "mixed" product *(47)* is obtained. This observation reported by *Linn* and *Ciganek*[54] indicates interesting specificities. In a mixture of



benzylideneaniline and dimethyl acetylenedicarboxylate the tetracyanocarbonyl ylide *(5)* reacts preferentially with the first dipolarophile, but the intermediate azomethine ylide *(46)* faster with the second one. The role of dimethyl acetylenedicarboxylate as trapping reagent for *(46)* can also be played by fumaric ester, *N*-phenylmaleimide, and other electron-poor dipolarophiles[55].



A proclivity towards 1,3-dipolar cycloreversion is also found in the 1,3,4-oxadiazolidine *(49)*, which is formed from α,β-dicyano-*trans*-stilbene oxide and dimethyl azodicarboxylate at 120 °C. After elimination of benzoyl cyanide, the azomethine-imine *(51)*, a new 1,3-dipole, rearranges by an ester group shift to form the dimethyl hydrazonedicarboxylate *(50)*[56].

11. Conclusion

The chemistry of carbonyl ylides is still in its infancy. The electrocyclic ring opening of substituted ethylene oxides served so far as the main port of entry into this class of 1,3-dipoles. Reaction of carbonyl compounds with carbenes probably constitutes another general approach[57]; the intramolecular version was successfully applied by *Ibata et al.*[58] to make cyclic carbonyl ylides available. The synthetic potential of carbonyl ylides and their cycloadditions is far from being exhausted.

A sincere word of thanks goes to the author's young associates who dedicated their skill, enthusiasm and energy to the problem: they are Drs. Helmut Hamberger, Alexander Dahmen, and Volker Markowski. Dr. Horst Hermann of the Max-Planck-Institut für Kohlenforschung at Mülheim/Ruhr, Abt. Strahlenchemie, directed the flash spectroscopic studies.

Received: March 15, 1977 [A 176 IE]
German version: Angew. Chem. *89*, 589 (1977)

[1] *R. B. Woodward, R. Hoffmann*, J. Am. Chem. Soc. *87*, 395 (1965).
[2] *H. W. Heine, R. E. Peavy*, Tetrahedron Lett. *1965*, 3123; *H. W. Heine, R. Peavy, A. J. Durbetaki*, J. Org. Chem. *31*, 3924 (1966).
[3] *A. Padwa, L. Hamilton*, Tetrahedron Lett. *1965*, 4363; J. Heterocycl. Chem. *4*, 118 (1967).
[4] *R. Huisgen, W. Scheer, G. Szeimies, H. Huber*, Tetrahedron Lett. *1966*, 397.
[5] *R. Huisgen*, Proc. Chem. Soc. (London) *1961*, 357; Angew. Chem. *75*, 604 (1963); Angew. Chem. Int. Ed. Engl. *2*, 565 (1963).
[6] *A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, E. Spindler*, Chem. Ber. *100*, 2192, 2212 (1967).
[7] *R. B. Woodward, R. Hoffmann*, Angew. Chem. *81*, 797, 833 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781, 817 (1969).
[8] *R. Huisgen, R. Grashey, E. Steingruber*, Tetrahedron Lett. *1963*, 1441.
[9] *R. Huisgen, H. Gotthardt, H. O. Bayer, F. C. Schaefer*, Angew. Chem. *76*, 185 (1964); Angew. Chem. Int. Ed. Engl. *3*, 136 (1964); Review: *R. Huisgen*, J. Chem. Soc. Spec. Publ. *21*, 51 (1967).
[10] *R. Huisgen, W. Scheer, H. Huber*, J. Am. Chem. Soc. *89*, 1753 (1967).
[11] *W. J. Linn, R. E. Benson*, J. Am. Chem. Soc. *87*, 3657 (1965).
[12] *W. J. Linn*, J. Am. Chem. Soc. *87*, 3665 (1965).
[13] *H. C. Longuet-Higgins, E. W. Abrahamson*, J. Am. Chem. Soc. *87*, 2045 (1965).
[14] *H. E. Zimmerman*, Acc. Chem. Res. *4*, 272 (1971).
[15] *M. J. S. Dewar*, Angew. Chem. *83*, 859 (1971); Angew. Chem. Int. Ed. Engl. *10*, 761 (1971).
[16] *E. F. Ullman, J. E. Milks*, J. Am. Chem. Soc. *84*, 1315 (1962); *86*, 3814 (1964).
[17] *E. F. Ullman, W. A. Henderson jr.*, J. Am. Chem. Soc. *88*, 4942 (1966).
[18] *D. R. Arnold, L. A. Karnischky*, J. Am. Chem. Soc. *92*, 1404 (1970).
[19] *J. Steigman, L. P. Hammett*, J. Am. Chem. Soc. *59*, 2536 (1937), make the comment "mystification that has always surrounded the Walden inversion arises from the unlucky fact that the acid derivatives are the most easily accessible optically active substances".
[20] *T. Mukaiyama, J. Kuwajima, K. Ohno*, Bull. Chem. Soc. Jpn. *38*, 54 (1965).
[21] *H. Hamberger, R. Huisgen*, J. Chem. Soc. Chem. Commun. *1971*, 1190.
[22] *J. H. Boyer, R. Selvarajan*, J. Org. Chem. *35*, 1229 (1970).
[23] Dilatometric rate measurements of cycloaddition: *R. Huisgen, F. Mietzsch*, Angew. Chem. *76*, 36 (1964); Angew. Chem. Int. Ed. Engl. *3*, 83 (1964); *R. Huisgen, H. Seidl, I. Brüning*, Chem. Ber. *102*, 1102 (1969).
[24] *V. Markowski*, Dissertation, Universität München 1974.
[25] *R. Huisgen*, Angew. Chem. *75*, 742, 749 (1963); Angew. Chem. Int. Ed. Engl. *2*, 633, 640 (1963).
[26] *J. Sauer*, Angew. Chem. *79*, 76, 85 (1967); Angew. Chem. Int. Ed. Engl. *6*, 16, 25 (1976).
[27] *S. Inagaki, H. Fujimoto, K. Fukui*, J. Am. Chem. Soc. *98*, 4054 (1976).
[28] *R. Sustmann*, Tetrahedron Lett. *1971*, 2717; *R. Sustmann, H. Trill*, Angew. Chem. *84*, 887 (1972); Angew. Chem. Int. Ed. Engl. *11*, 838 (1972); *R. Sustmann*, Pure Appl. Chem. *40*, 569 (1974).
[29] For further literature and examples see *R. Huisgen*, J. Org. Chem. *41*, 403 (1976).
[30] *A. Dahmen, H. Hamberger, R. Huisgen, V. Markowski*, J. Chem. Soc. Chem. Commun. *1971*, 1192.
[31] *V. Markowski, R. Huisgen*, J. Chem. Soc. Chem. Commun. *1977*, 439.
[32] *R. Huisgen, V. Markowski*, J. Chem. Soc. Chem. Commun. *1977*, 440.
[33] *A. Dahmen, R. Huisgen*, Tetrahedron Lett. *1969*, 1465; *R. Huisgen*, Chim. Ind. (Milan) *51*, 963 (1969).
[34] *G. A. Doorakian, H. H. Freedman*, J. Am. Chem. Soc. *90*, 5310, 6896 (1968).
[35] *M. J. S. Dewar, S. Kirschner*, J. Am. Chem. Soc. *96*, 5244 (1974), and discussions with Professor *Dewar* in September 1974.
[36] Review: *G. W. Griffin*, Angew. Chem. *83*, 604 (1971); Angew. Chem. Int. Ed. Engl. *10*, 537 (1971).
[37] *P. C. Petrellis, H. Dietrich, E. Meyer, G. W. Griffin*, J. Am. Chem. Soc. *89*, 1967 (1967).
[38] *R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertoniere, R. L. Smith, G. W. Griffin*, J. Am. Chem. Soc. *92*, 1302 (1970).
[39] *T. Do-Minh, A. M. Trozzolo, G. W. Griffin*, J. Am. Chem. Soc. *92*, 1402 (1970).
[40] *V. Markowski, R. Huisgen*, Tetrahedron Lett. *1976*, 4643.
[41] *I. J. Lev, K. Ishikawa, N. S. Bhacca, G. W. Griffin*, J. Org. Chem. *41*, 2654 (1976).
[42] *G. A. Lee*, J. Org. Chem. *41*, 2656 (1976).
[43] *H. Hermann, R. Huisgen, V. Markowski*, Heterocycles (Sendai), in press.
[44] *H. Hermann, R. Huisgen, H. Mäder*, J. Am. Chem. Soc. *93*, 1779 (1971).
[45] *C. H. Ross*, Dissertation, Universität München 1975.
[46] *W. J. Hehre, R. Ditchfield, L. Radom, J. Pople*, J. Am. Chem. Soc. *92*, 4796 (1970).
[47] We express our gratitude to Professor *W. J. Hehre*, University of California at Irvine, for carrying out these calculations.
[48] *E. F. Hayes, A. K. Q. Siu*, J. Am. Chem. Soc. *93*, 2090 (1971).

[49] H. S. Johnston: Gas Phase Reaction Rate Theory. Ronald Press Comp., New York 1966, p. 317.
[50] H. H. J. MacDonald, R. J. Crawford, Can. J. Chem. 50, 428 (1972).
[51] A. Robert, J. J. Pommeret, J. Foucauld, Tetrahedron 28, 2085 (1972).
[52] R. Huisgen, S. Sustmann, Heterocycles (Sendai) 5, 141 (1976).
[53] A. Robert, J. J. Pommeret, E. Marchand, A. Foucauld, Tetrahedron 29, 463 (1973).
[54] W. J. Linn, E. Ciganek, J. Org. Chem. 34, 2146 (1969).
[55] J. W. Lown, K. Matsumoto, Can. J. Chem. 50, 534 (1972).
[56] H. Hamberger, R. Huisgen, V. Markowski, S. Sustmann, Heterocycles (Sendai) 5, 147 (1976).
[57] R. Bermes, Dissertation, Universität München 1963.
[58] K. Ueda, T. Ibata, M. Takebayashi, Bull. Chem. Soc. Jpn. 45, 2779 (1972); M. Hamaguchi, T. Ibata, Tetrahedron Lett., 4475 (1974); Chem. Letters, 499 (1974); 287 (1976); T. Ibata, ibid. 233 (1976); T. Ibata, T. Motoyama, M. Hamaguchi, Bull. Chem. Soc. Jpn. 49, 2298 (1976).

Macrolides. Recent Progress in Chemistry and Biochemistry

By Satoru Masamune, Gordon S. Bates, and (in part) John W. Corcoran[*]

Dedicated to Professor R. B. Woodward on the occasion of his 60th birthday

The progress of macrolide chemistry and biochemistry over the past several years has indeed been remarkable. This review attempts to cover the important contributions which have been made in the fields of structural and synthetic chemistry as well as in the biosynthesis and mode of antimicrobial activity of the "polyoxo" macrolide antibiotics. Emphasis has been placed on the recent synthetic achievements in this field.

1. Introduction

The chemistry of macrolide antibiotics originated with the isolation of pikromycin by *Brockmann* and *Henkel* in 1950[1]. Soon afterward *Streptomyces* organisms yielded several other antibiotics which appeared to be chemically and antimicrobially related to pikromycin. By the end of 1957 the elegant execution of classical chemical degradations of these antibiotics had led to the disclosure of the gross structures of methymycin[2], erythromycin A[3] and B[4], and carbomycin A (magnamycin)[5-8], demonstrating that each of them contains a lactone incorporated in a medium- or large-ring system. As the number of lactonic natural products has increased to well over one hundred, the word, "macrolide", originally[5] restricted to the above antibiotics *(vide infra)* has gradually been used in a broader sense and in some cases overextended to cover even a macrocyclic lac*tam* of plant origin[9,10]. Structural, stereochemical, and conformational studies of representative members of this steadily growing family have been actively pursued for the past two decades mainly by means of X-ray crystallographic, ^{1}H- and ^{13}C-NMR, and mass spectroscopic techniques[11], and our knowledge of the macrolides is quite rich in these respects. A few excellent reviews have already appeared[12-16]. Since it is not the purpose of this article to compile a complete documentation of the work, we intend to outline only the major course of development as far as the structure and stereochemistry are concerned. However, in order to provide interested readers with updated information a rather extensive list of macrolide compounds is included in Table 1, Section 7.

In contrast to a plethora of structural studies that have appeared in the past 25 years, it is only in recent years that we have witnessed major synthetic accomplishments in the field of macrolides, and efforts to further enrich our knowledge in this area are gaining momentum at an ever increasing rate. It is interesting to consider why we have had to wait so long for this development. In the last decade expertise in organic synthesis has already proved to be highly sophisticated, and general approaches, at least in principle, for syntheses of a vast number of important groups of compounds such as steroids, terpenes, and alkaloids, were available. In the field of antibiotics, total syntheses of penicillins and cephalosporins, and tetracyclins had already been completed by the end of the sixties. Thus, the macrolides were the only remaining major family of antibiotics which presented an academic challenge to synthetic organic chemists. We saw at least two major, general problems associated with the macrolide synthesis: one was the construction of a medium- or large-size lactone and the other involved the introduction of chiral centers into a straight chain aliphatic acid—say—through a *stereospecific* aldol condensation or acylation. There was a need to devise new synthetic methods for both problems. The first problem now has acceptable solutions, which have made possible the first total synthesis of methymycin[17], and of pyrenophorin[18], vermiculine[19], and nonactin[20,21]. The second problem presents much to be further investigated and still demands creativity and imagination for its satisfactory answer. In this article emphasis is placed on the synthesis

[*] Prof. Dr. S. Masamune [+] and Dr. G. S. Bates [**]
Department of Chemistry, University of Alberta
Edmonton, Alberta T6G 2G2 (Canada)
Prof. Dr. J. W. Corcoran
Department of Biochemistry, Northwestern University
Chicago, Illinois 60611 (USA)
[+] To whom correspondence should be addressed.
[**] Present address: Department of Chemistry, University of British Columbia, Vancouver, British Columbia V6T 1W5 (Canada)

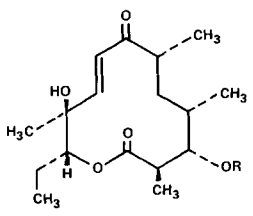
of macrolides in order to define the present and future problems in this area[22]. The macrolide antibiotics have also received due attention from the viewpoints of both their biosynthesis[23] and mode of antimicrobial activity[24, 25] and these subjects are updated in Section 6.

2. Structure and Classification

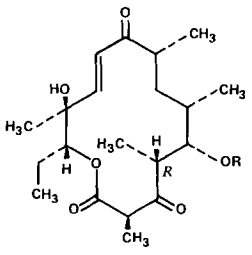
Because of the vast number of lactonic natural products commonly referred to as macrolides, a classification of these compounds into subgroups would now appear to be in order.

2.1. "Polyoxo" Macrolides

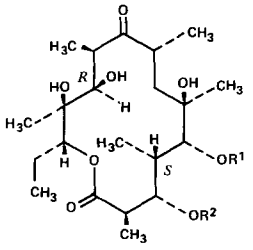
Categorized in this major subgroup are at least 50 antibiotics whose structures meet the criteria originally implied by *Woodward* in 1957 to include several antibiotics then available[5]. The lactones are normally 12-, 14-, or 16-membered. Other features are (1) an array of substituents uniquely and systematically (see Section 3) attached to the ring system and (2) the linkage of one or more sugars, very often one of them being nitrogen-containing. Methymycin *(1)* is the only member whose lactone is 12-membered. Typical "polyoxo" macrolides are pikromycin *(2)*, erythromycin A *(3)*, carbomycin A *(4)*, and tylosin *(5)*[26].



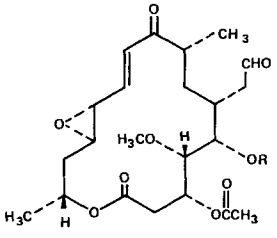
Methymycin *(1)*
R = Desosaminyl



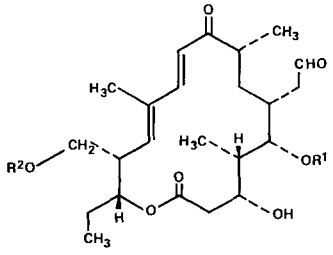
Pikromycin *(2)*
R = Desosaminyl



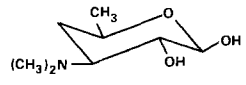
Erythromycin A *(3)*
R^1 = Desosaminyl
R^2 = Cladinosyl



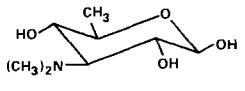
Carbomycin A *(4)*
R = (Isovaleryl)-mycarosyl-mycaminosyl



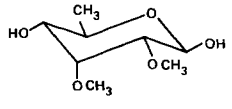
Tylosin *(5)*
R^1 = Mycarosyl - mycaminosyl
R^2 = Mycinosyl



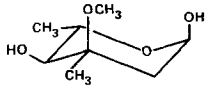
D-Desosamine



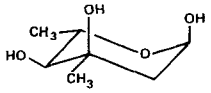
D-Mycaminose



D-Mycinose



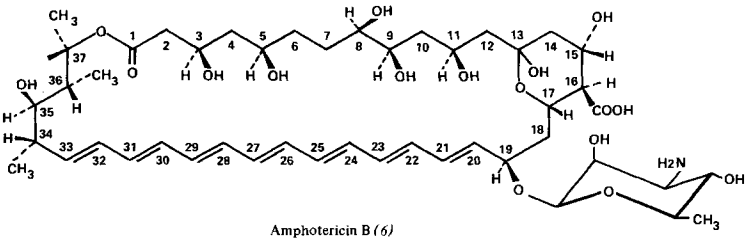
L-Cladinose



L-Mycarose

2.2. Polyene Macrolides[13]

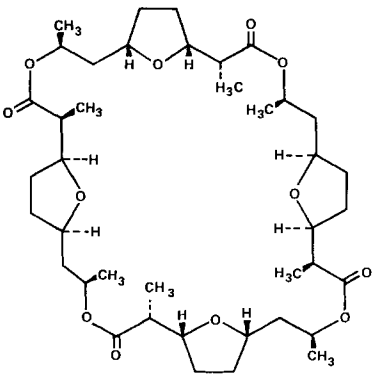
Characteristic of this group is the feature that the lactone ring carries few alkyl (mostly methyl) substituents and accommodates a conjugated polyene containing up to as many as seven *E* double bonds. Accordingly the size of the lactone enlarges to 38 members in some compounds. Most of these compounds are antifungal and not antibacterial agents. Amphotericin B *(6)* is a representative member and its structure has been fully elucidated[27].



Amphotericin B *(6)*

2.3. Ionophoric Macrolides

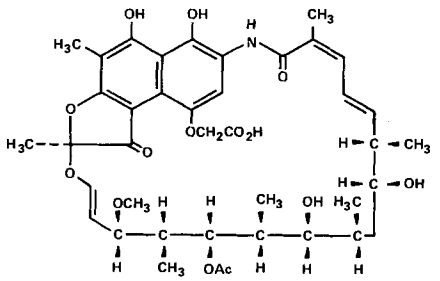
Macrolides of this group contain two or more lactone groups (oligonolide) in a very large ring system. An antibiotic of this group has a hydrophilic "hole" capable of binding an alkali metal cation and thus of transporting ions in biological systems. Nonactin *(7)*[15, 28] and boromycin[29] are included in this group. Several structurally similar antibiotics in an open (seco-acid) form have been isolated.



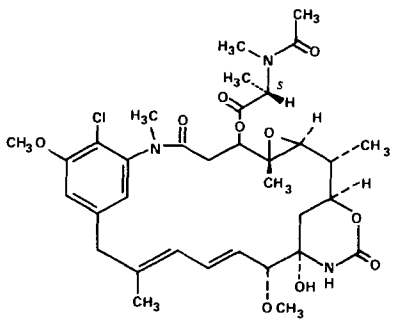
Nonactin *(7)*

2.4. Ansamycin[9, 10, 30, 31]

More than 10 antibiotics possess a unique structure in which two non-adjacent positions of an aromatic nucleus are connected by a long aliphatic bridge through an amide linkage (lactam). Therefore this group does not belong to the macrolides in the correct sense, but is included herein because of the close similarity of the aliphatic chain in structure and stereochemistry to that of the "polyoxo" macrolides (see Section 3). Rifamycins, *e.g.* rifamycin B *(8)*, and streptovaricins are typical representatives; most of the ansamycins are noted for their broad spectra of antibacterial activity and



Rifamycin B *(8)*



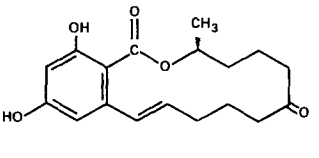
Maytansine *(9)*

are also interesting as potential antitumor agents. Also included in this class is maytansine *(9)*, which is unique in that it is *possibly* of plant origin[9, 32].

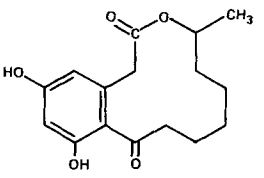
2.5. Other Macrolides

Under this heading are listed several lactonic compounds of medium-ring size which have not thus far grown into large families. Most of these lactones are of either mold or bacterial origin and exhibit varying biological activities. Examples are zearalenone *(10)*[33] (from *Gibberella zeae*), curvularin *(11)*[34] (from a species of *Curvularia*), pyrenophorin *(12)*[18, 35] (from *Pyrenophora avenae* and *Stemphylium radicinum*), vermiculine *(13)*[19, 36] (from *Penicillium vermiculatum*), and brefeldin A *(14)*[37] (from *Penicillium*, *Curvularia*, and *Ascochyla*).

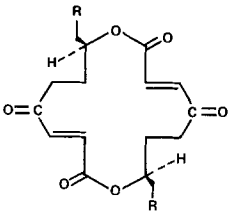
Some members of the cytochalasan family[38], cytostatically[39] active metabolites, possess 13- or 14-membered lactone rings, which are derived from the corresponding carbocyclic ketones through a Baeyer-Villiger type oxidation at a late stage of biosynthesis[40]. Because of this origin of the lactone and lack of similarity of these compounds to other macrolide antibiotics in structure and physiological activity, the cytochalasans are only briefly dealt with in this review (see Section 5.3).



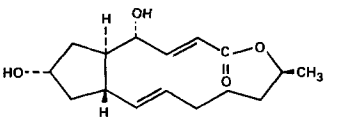
Zearalenone *(10)*



Curvularin *(11)*



Pyrenophorin *(12)*, R = H
Vermiculine *(13)*, R = $COCH_3$



Brefeldin A *(14)*

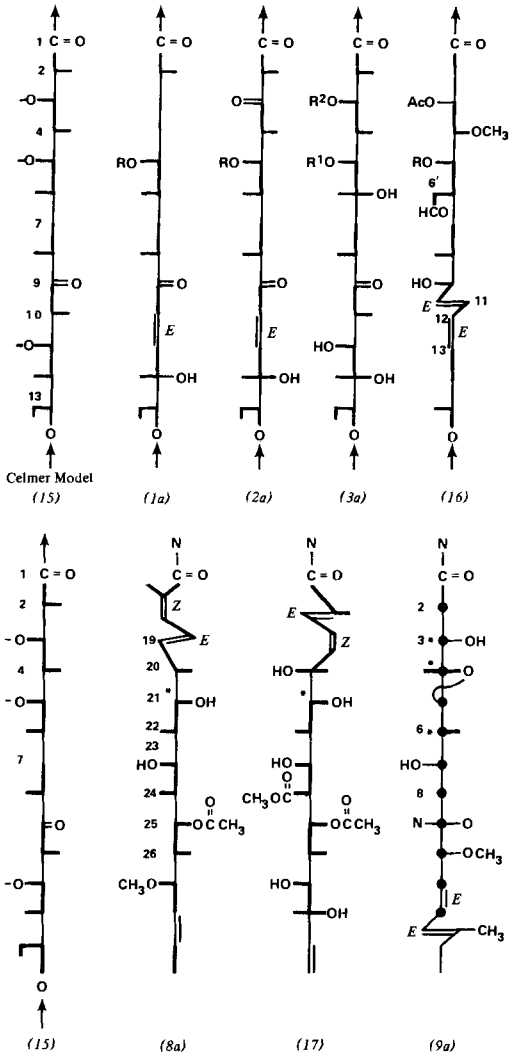
The above classification reflects our view and is not one that has already received general acceptance. There are certainly other ways to categorize the macrolide family. Some "polyoxo" macrolides are further subdivided according to their biological activities.

3. Stereochemistry

The stereochemistry of the "polyoxo" macrolide antibiotics is beautifully correlated in terms of what is commonly referred to as *Celmer*'s stereochemical model[14], expressed in the Fischer projection formula *(15)*. 12-Membered methymycin *(1a)* [missing C(2), C(3) or C(3), C(4)] and the 14-membered macrolides, whose stereochemistry has been elucidated, all pattern after the model *(15)*, and so-called "extra" hydroxy groups such as those at C(6) and C(12) of erythromycin A and C(8) of oleandomycin *(137)* (see Section 6.1) are apparently introduced at these carbon atoms at a late stage of biosynthesis with retention of the original stereochemistry (front side oxidation). The model has served to detect previously misassigned stereochemistry on several occasions, and, remarkably, thus far there have not been any observed irregularities.

Information is also available concerning the stereochemistry of leucomycin *(16)*, a 16-membered macrolide. X-ray analyses of desmycarosyl-"*iso*"-leucomycin A_3[41] and diacetyl-3,6'-bicycloleucomycin A_3[42] have shown beyond reasonable doubt that *(16)* has the stereochemistry shown above[43], and thus that model *(15)* is still valid. The extra 2 achiral carbon atoms [C(10) and C(11)] are inserted between C(9) and C(10) of the model. Carbomycin B has already been related to *(16)* chemically[14]. The stereochemistry of tylosin shown in structure *(5)* adopts the model for this compound and remains to be confirmed experimentally[44].

More interestingly, inspection of the stereochemistry of ansamycins[10, 30, 31] reveals that *Celmer*'s model applies even to these antibiotics, but with reversal of stereochemistry at C(21) (ansamycin numbering), which corresponds to C(5) in *(15)*, as shown in the formulas for rifamycin *(8a)* and streptovaricin *(17)*. An exception is maytansine *(9a)*[9, 45] where several chiral centers appear to possess the opposite absolute configuration compared to that in *(15)*. Of course this last comparison is subject very much to our arbitrary choice



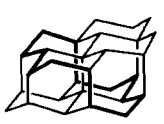
The center asterisked does not match with that of *(15)*.

of reference points. Some portions of acyclic compounds related to the ionophoric macrolides (cf. Section 2.3) may be stereochemically correlated with *(15)* as well.

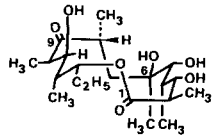
4. Conformation

Elaborate analyses of various spectroscopic data have been performed in order to define the conformation of 14-membered macrolide antibiotics in solution[46]. The conformational problems associated with molecules of this complexity arouse chemical interest and also undoubtedly have an important bearing on the structure-biological activity relationship of the antibiotics. We select herein only a few representative, most-studied molecules for discussion.

Basically patterning after the diamond lattice conformation *(18)* (bold line) proposed earlier for cyclotetradecane by *Dale*[47], *Celmer* advanced in 1965[48] a model

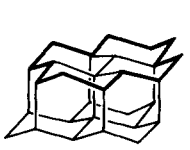


(18)

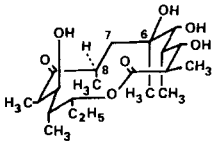


(19)

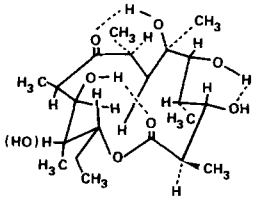
(19) for a preferred conformer of erythronolide B, the aglycone of erythromycin B [C(12)—OH missing in *(3)*]. Although the Celmer-Dale model *(19)* was in reasonable agreement with the ^{1}H-NMR data, mainly in terms of dihedral angles derived from the Karplus equation, it soon became apparent that further refinement was needed to remedy several major drawbacks. The earlier X-ray analysis of erythromycin A *(3)*[49] had demonstrated several important features: (1) The C(6)—OH, C(9)=O, and C(1)=O (lactone) groups are *syn*-oriented in space, and all the C—O axes of these groups are nearly parallel. In model *(19)*, the C(6)—OH and C(9)—C=O groups are *syn* to each other, but are *anti* to the lactonic C=O, and all to the C—O axes are oriented in different directions. (2) The crystal structure also shows, contrary to what is implied by model *(19)*, that the overall shape of the antibiotic is rather flat. Using the CPK molecular model we attempted unsuccessfully to close the lactone ring of the erythronolide B seco-acid constructed in the manner suggested in model *(19)*, mainly because of the non-bonded interaction of the three hydrogen atoms directed inside of the ring system and also because of the *syn*-periplanar oriented C(4)- and



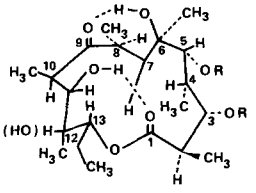
(20)



(19a)



(19b)



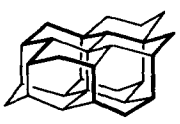
(19c)

C(6)-methyl groups. (Formula *(19)* is unrealistically stretched horizontally in comparison with the CPK model.) These arguments are subject to the usual criticism, such as more conformational freedom present in solution than in the lattice, and therefore by themselves do not invalidate *(19)*. However they deserve serious attention. Further studies demonstrated that with most of the macrolides or their derivatives, all of the vicinal proton-proton coupling constants fell in the range of either 10—12 Hz or 0—2 Hz and remained constant over a wide range of temperature and in a variety of solvents[50]. This implies that the ring system is rigid and its conformational freedom in solution is restricted *(vide infra)*. Therefore there were no strong reasons to believe that the preferred conformer differs greatly in geometry from the crystal structure. These considerations led to the proposal of a second diamond lattice model [as shown in *(20)* and *(19a)*], which removed most of the deficiencies of model *(19)*. Further modification involving a limited rotation along the C(7)—C(8) axis led to the *syn*-orientation of both C(9)=O and C(6)—OH and at the same time eliminated the disadvantageous 1,3-interaction between the C(4)- and C(6)-methyl groups. The resulting Perun model *(19b)* appears to accommodate quite well the ^{1}H-NMR

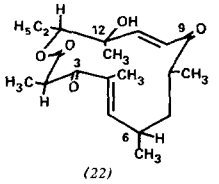
and CD data for erythronolide B, as well as the possible hydrogen bondings between C(6)—OH and C(9)=O, and between C(11)—OH and C(1)=O as suggested by its ^{13}C-NMR spectral parameters[51-53]. For the derivatives of both the C(3)—OH and C(5)—OH groups, such as erythromycin A *(3)* or B *(134)*, or the 3,5-diacetate of erythronolide B, the *syn*-periplanar disposition of the groups attached at the 3 and 5 positions (which is favored through hydrogen bonding is the case, as judged from the spectral data [cf. *(19c)*][52,54]. from model *(19b)* to avoid the non-bonded repulsion, if the ring system is still flexible enough to afford limited rotations about the C(4)—C(5) and C(5)—C(6) axes. Apparently this is the case, as judged from the spectral data [cf. *(19c)*][52,54]. After all this, model *(19c)* is now essentially the same as that demonstrated by the X-ray analysis of *(3)*[49]. Macrolides have only little, if any, conformational freedom in solution except in very few cases.

Extremely useful and somewhat surprising to us at the outset of our involvement in this project was the fact that the above conformational conclusion, reached after the above rather lengthy discussion, was revealed by relatively simple inspection of the CPK models built for these antibiotics. Thus, almost invariably when one succeeds in lactonizing the model of a seco-acid, the conformation of the resulting macrolide corresponds roughly to *(19b)* or *(19c)*. Moreover, the model exhibits some flexibility around the bonds discussed above. Of course if one chooses a differently substituted macrolide, the preferred geometry accordingly deviates from *(19b)* or *(19c)*.

Ogura et al.[55] have recently proposed another diamond model [*(21)* and *(22)*] for kromycin, a dehydrated aglycone of pikromycin *(2)*, more or less implying that the molecule is L-shaped [cf. *(22)*]. Both its X-ray analysis[56] and CPK-model studies indicate that two fragments including C(3)



(21)



(22)

through C(6) and C(9) through C(12) are nearly coplanar, with a very shallow dihedral angle between the planes, and that the ring system as a whole is flat (flatter than erythronolide) as a consequence of trying to link together the two coplanar segments. It has been already noted that the Perun model *(19b)* itself does not exactly follow a diamond framework, but deviates from it with varying substituents. For kromycin, the concept of the diamond lattice almost loses its meaning because of the relatively highly unsaturated lactonic system. Since some of the carbon atoms do not even lie close to the points of the lattice of *(21)*, it would appear to us that there is no *pressing* need to adhere to the diamond lattice concept in this case.

In summary, we have now reached the general agreement that a ("polyoxo") macrolide molecule is rigid and its most preferred conformation in solution is essentially the same or nearly the same as its crystal structure. The X-ray result in effect constitutes an important "backbone" for conformational arguments. It should also be pointed out that CPK models are very instrumental and vividly demonstrate the interesting structural feature that virtually all the O-containing substituents (OH and sugar) are located on one side of the aglycone and all alkyl groups on the other side (*e.g.*, erythronolide A and B).

Although spectral data of several 16-membered macrolide antibiotics[57] have been recorded, there are very few convincing arguments about their conformations. Thus far, no X-ray analysis of any *intact* antibiotics or aglycones has been recorded.

5. Synthesis

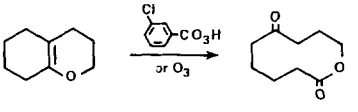
5.1. General Strategy

A macrolide synthesis unavoidably meets with two major problems—(1) the construction of a medium- or large-sized lactone and (2) the stereochemical control of numerous chiral centers embedded in the ring system of an aglycone—in addition to that of attachment of a sugar or sugars to the aglycone. In order to evaluate the overall synthetic scheme of each reported approach it appears logical to first examine the method of ring construction, very often illustrated by model studies, and then to consider its applicability to more stereochemically complex systems such as the naturally occurring macrolides.

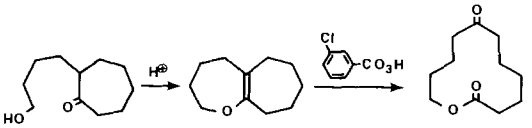
5.1.1. Rupture of the Fused Bond in a Bicyclo[*m.n.*0] system

Grob-type fragmentation of the single bond between the ring junctures [C(1) and C(m+2)] of a bicyclo[*m.n.*0] system or oxidative cleavage of the fused double bond leads to a monocyclic ($m+n+2$) membered ring. If the bicyclic precursor contains a lactone group as such or in a latent form, the above operation results in the formation of a macrocyclic lactone.

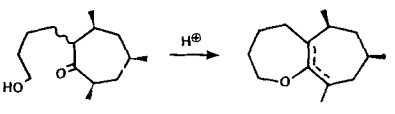
The method developed by *Borowitz et al.* involves oxidative cleavage of the vinyl ether *(23)*[58]. The reaction proceeded satisfactorily to yield *(24)*, and the method appeared encouraging. In principle it creates two crucial functional groups of methynolide, C(7)-ketone and C(1)-lactone, simultaneously with the ring opening, if applied to an appropriate precursor. Acid-catalyzed dehydration of *(25)* afforded *(26)* in good yields with subsequent cleavage (72%) to *(27)*[59]. However,



(23) *(24)*

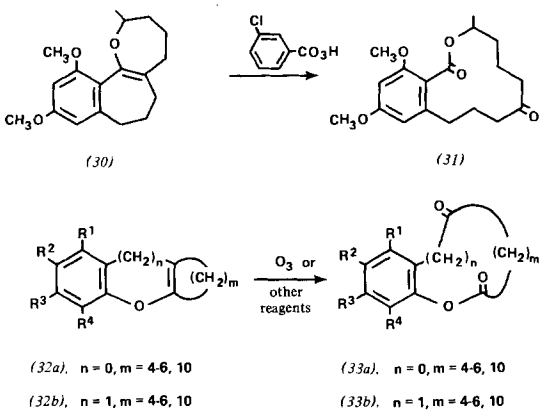


(25) *(26)* *(27)*

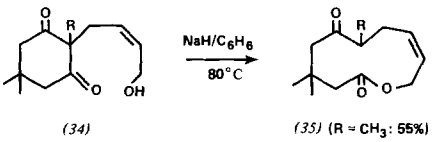


(28) *(29)*

with substituted ketones only poor yields of product were obtained. Thus, in the case of *(28)* cyclization "occurred to a minor extent" affording small amounts of a mixture of isomeric enol ethers *(29)*[60]. The behavior of the seven-membered ring system is unique and very often unpredictable because of our limited knowledge of this system. Obviously, modifications of *Borowitz*'s original procedure are required for the construction of structurally complex macrolides. However, in the original form it has found uses in several cases. Thus oxidative cleavage of vinyl ether *(30)* led to a compound *(31)*, which turned out to be isomeric to the dimethyl ether of curvularin *(11)*[61]. The benzofurans *(32a)* and benzopyrans *(32b)* were analogously converted into the corresponding oxolactones, *(33a)* and *(33b)*, respectively[62].



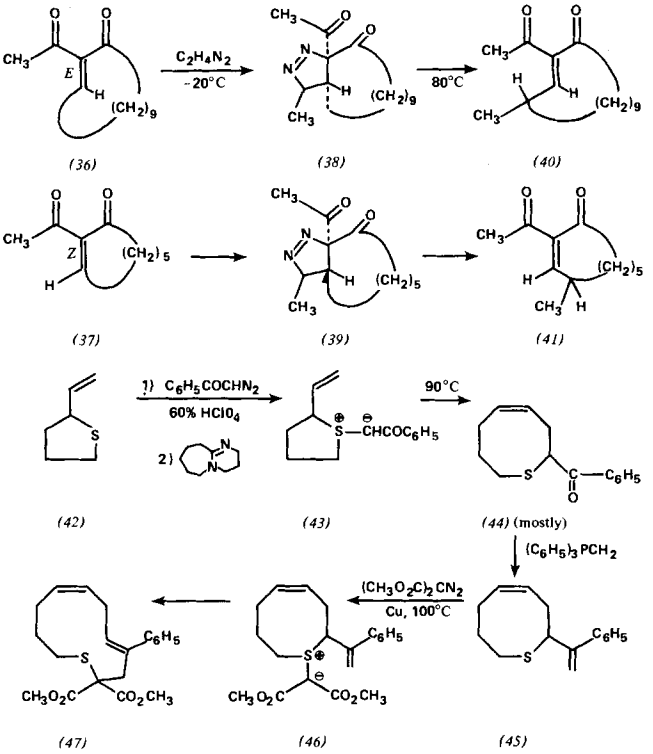
A novel example of the cleavage of a fused-bond involves an intramolecular retro-Dieckmann reaction as exemplified in the conversion of *(34)* to *(35)*[63], but obviously the application of this method to the synthesis of a particular compound of this type is limited.



The scope of the concept discussed in this section has by no means been fully explored and a clever use of *Grob*-type fragmentation on a properly functionalized system may possibly provide an ingenious solution to a specific synthetic problem. However, this approach very likely involves several complicated problems associated with the seven-membered or larger ring systems, and it is rather doubtful that it will become generally applicable to the synthesis of a large number of macrolides.

5.1.2. "Ring Growing" Reactions[64]

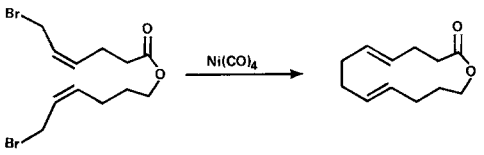
A "ring growing" process normally consists of two or three consecutive steps. A small carbon unit is formally inserted into a functionalized starting ring system, and this process can be repeated several times. The ring enlargement of a cyclic ketone using diazomethane is one of the most common examples. As a model experiment for macrolide syntheses, at least two such reactions have recently been reported. Addition of diazoethane to the *E*- and *Z*-enediones *(36)* and *(37)* affords the corresponding pyrazolines *(38)* and *(39)*, both of which undergo thermal elimination of N_2 to yield products *(40)* and *(41)*, respectively[65]. Repetition of the sequence creates stereochemical complications at both the pyrazoline and final stages, but apparently the stereochemistry of starting material and/or product determines the course of reactions to provide a single isomer at each step. Hence, this ring growing reaction shows high (and possibly predictable) stereoselectivity, which can be cleverly utilized, *if* the reaction happens to provide a product with the proper stereochemistry.



Another ring growing method is more efficient in the sense that it inserts a three-carbon unit in one sequence, uniquely employing a [2,3] sigmatropic rearrangement. Examples are the rearrangements of *(43)* to *(44)*, and *(46)* to *(47)*[64]. Thus by suitable choice of five-, six-, or seven-membered starting materials, syntheses of any desired medium- or large-size carbo- and heterocyclic systems can, in principle, be achieved. If they are to be utilized in the macrolide synthesis, these two methods, like the one discussed in Section 5.1.1, would create additional major stereochemical problems associated with medium-size ring systems during the course of each ring growth. Precise control of reaction courses would indeed be a challenging task.

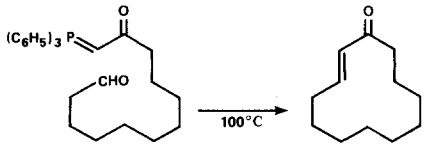
5.1.3. Cyclization of an Acyclic Precursor

Probably the first example of this type of approach reportedly aimed at the synthesis of a natural macrolide molecule utilized tetracarbonylnickel(0) to close the diallylic bromide termini of an ester-containing acyclic precursor[66], a reaction which has been successfully employed in the preparation of the 11- and 14-membered terpenes, humulene[67] and cembrene[68]. A model reaction is the cyclization of *(48)* to *(49)*. Proper modifications on *(48)* and further conversion of *(49)* (in particular, creation of chiral centers at the double bonds which is very likely to be necessitated) do not appear to



(48) (49)

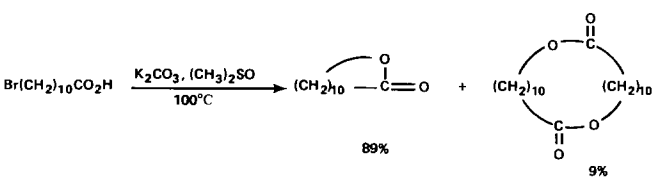
be readily executable operations. Use of a stabilized Wittig reagent effects carbon-carbon bond formation under near-neutral conditions and has been used with success in many cases for construction of medium- and large-size rings. In fact conversion of *(50)* into *(51)* proceeded in acceptable yields[69].



(50) (51) (20-30%)

At this stage one must consider whether it is possible to effect direct lactonization of the seco-acid corresponding to a natural macrolide. In this respect *Stoll*'s classical work concerning intra- *versus* intermolecular formation of esters from straight chain aliphatic ω-hydroxyacids[70] is truly discouraging. Indeed it is for this reason that the other methodologies for the ring construction discussed above have been sought, despite the fact that inclusion of lactone formation at a late stage of the synthesis would seem a more obvious approach than to resort to a scheme involving carbon-carbon bond formation or rupture for construction of the ring. The biosynthesis of a macrolide antibiotic also very likely proceeds through a final lactonization stage before the formation of the aglycone is completed (if the introduction of "extra" hydroxy groups is not involved). In addition, this lactonization approach offers an undisputable advantage: the already discussed stereochemical problems associated with medium- and large-ring systems no longer confront us and the entire synthesis is largely simplified.

Let us review two aspects of lactonization reactions. A well-known general problem associated with intra- *versus* intermolecular cyclization of a bifunctional acyclic compound obviously concerns the competition between reactions of the first and second order, *providing* the chain is long and *conformationally flexible*. The most common way in which to promote the intramolecular reaction is by the high dilution technique. In cases where a desired reaction proceeds with high efficiency, one can effectively realize the condition of high dilution by subjecting a reactant slowly to a reaction condition (for instance, by slow addition), so that reaction of the first portion is essentially complete before a second portion is introduced. Thus, controlled (one-hour) addition of 11-bromoundecanoic acid *(52)* (0.08 mol) to hot dimethyl sulfoxide (1 l) containing

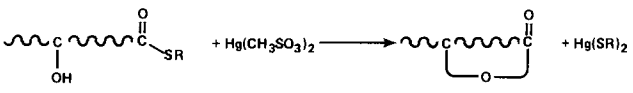


(52) (53) (54)

K_2CO_3 provides the monocyclic lactone *(53)* in excellent yields[71].

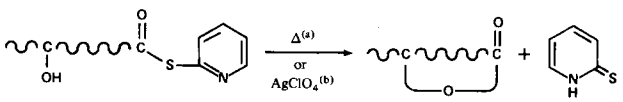
The other important aspect is the effect of the numerous substituents of the seco-acid. As already elaborated in Section 4, most of the "polyoxo" macrolide antibiotics are conformationally rigid molecules, and inspection of their CPK atomic models further predicts that the corresponding seco-acids would retain, to a large extent, the rigidity of the macrolides because of the bulky substituents. Thus the rotational freedom along most of the C—C bonds of the chain would be suppressed—a condition that favors an intramolecular cyclization. These considerations lead to an encouraging, nonetheless extremely risky prediction. Our project, a synthesis of methymycin *(1)* (see Section 5.2.1), was initiated against this background a few years ago, despite the adverse situation that the seco-acid could only be obtained by synthesis and not through a conversion of the natural product (world supply at that time was *ca.* 500 mg).

In the meantime intensive studies in this sector have led to the development of three efficient methods for the synthesis of the ester (and lactone). One of them (Method 1) utilizes activation of a hydroxycarboxylic thiol ester *(55)* with a thiophilic, soft metal ion such as Hg^{II} or Cu^{II}[72]. Another



(55) Method 1 (56)

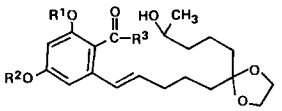
method is *Corey*'s "double activation" method[73], patterned after *Mukaiyama*'s procedure for formation of peptide linkages (Method 2)[74, 75]. Prolonged refluxing of a dilute solution of the thiol ester *(57)* in a relatively high-boiling, inert solvent such as xylene or toluene is normally required to complete the lactonization. However, $AgClO_4$ considerably accelerates this reaction, as reported by *Gerlach* (Method 3)[76], and thus



(a) Method 2
(b) Method 3

(57) (56)

the cyclization is completed within an hour at room temperature. The effectiveness (and selectivity; see Section 5.3.1) of these newer methods becomes evident from the recent reports[72, 73] on high-yield lactonization of the seco-acid derivatives *(58a)* and *(58b)* of zearalenone *(10)*, as compared with a rather low-yield cyclization previously reported[77]. [*(58a)*, Method 1, 25 °C, 5 min: 90 % zearalenone dimethyl ether ethylene ketal; *(58b)*, Method 2, benzene, reflux, H^+: 75 % *(10)*]. The scope and limitations have now been relatively well defined and are discussed in some depth in Section 5.3.



(58a), $R^1 = R^2 = CH_3$, $R^3 = SC(CH_3)_3$

(58b), $R^1 = H$, $R^2 = THP$, $R^3 = OH$

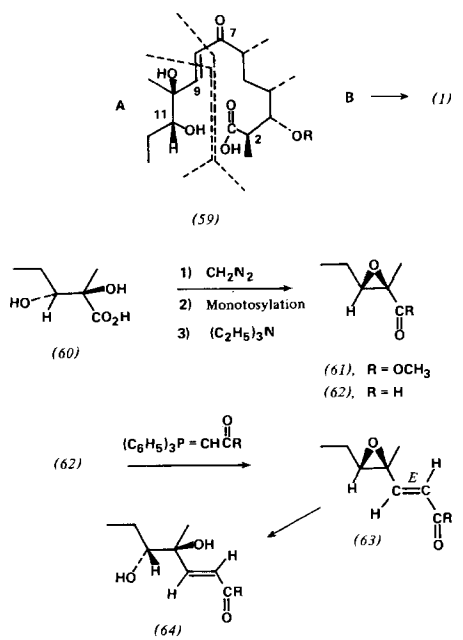
Having achieved the task of the lactone closure, one must consider the construction of the seco-acid. Although imaginative fragmentation reactions of a ring system to lead to an 11 to 15 C-atom seco-acid with the correct stereochemistry are not impossible, it appears more practical to dissect the seco-acid into two (or three) fragments. Since all of these fragments are chiral compounds, the problem arises of combining the proper set of each enantiomorphic isomers for the synthesis of a macrolide. There are at least three ways to achieve this: (Route 1) both segments are resolved or asymmetrically synthesized and combined, (Route 2) one segment is resolved and used as a resolving agent for the other, and (Route 3) the stereochemical information is directly transmitted to the other *via* chemical reactions. This last route is most attractive in that new chemistry would very likely emerge in pursuing this approach. Use of templates is highly tempting, and if one succeeds in this venture organic synthesis will be a step closer to the enzymatic reaction. Needless to say, the combination of the two (or three) segments which are often already highly sensitive toward both acid and base must be performed under mild conditions. Let us see how a few total syntheses have thus far been achieved.

5.2. Total Syntheses

At the time of writing this Review, syntheses of methymycin *(1)* (polyoxo macrolide), nonactin *(6)* (ionophoric macrolide), pyrenophorin *(12)*, vermiculine *(13)* in addition to zearalenone *(10)* and curvularin *(11)* (other macrolides) had been recorded, and those of several other, more complicated macrolides appear to be near completion.

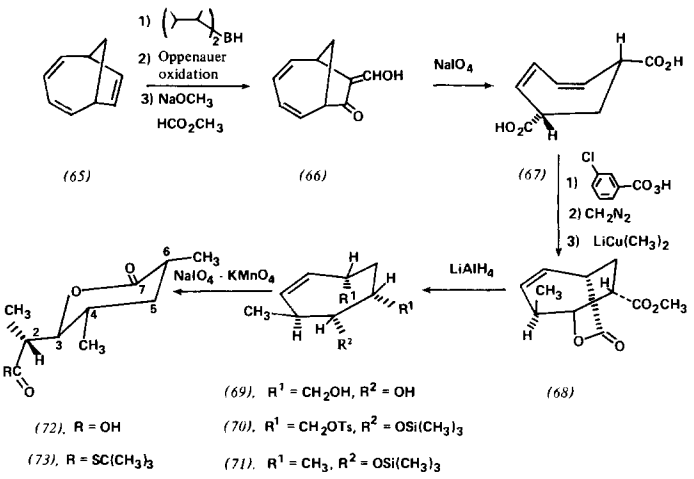
5.2.1. Methymycin[17]

The scheme used involves the condensation of optically pure segment A [C(9) through C(11)] and racemic segment B [C(1) through C(7)], to provide the seco-acid *(59)*. Segment A was prepared in a straightforward manner. Readily available (+)-(2*R*,3*R*)-2,3-dihydroxy-2-methylvaleric acid *(60)*[78] was converted by a standard route into the epoxy-ester *(61)*,



which upon reduction with $(i\text{-}C_4H_9)_2AlH$ yielded the corresponding aldehyde *(62)*. Wittig reaction of *(62)* with an acylmethylenephosphorane provided an *E*-α,β-unsaturated ketone *(63)* (R = CH_3, for example) which underwent epoxide ring opening under mild acidic conditions to the corresponding dihydroxyketone *(64)* with retention of configuration at the γ position. The neutral conditions of the Wittig reaction and the stereochemical course of the ring opening qualify *(62)* as a synthetic unit.

The construction of segment B is a little more involved and uses bicyclo[4.2.1]nona-2,4,7-triene *(65)* as starting material[79]. Selective hydroboration, oxidation, and formylation of *(65)* yielded a hydroxymethylene compound *(66)*,



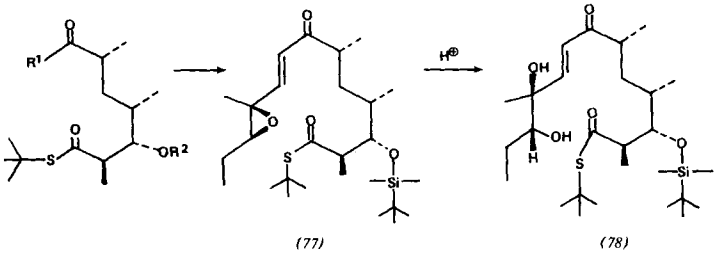
which was oxidatively cleaved to give *cis*-dicarboxylic acid *(67)*. Subsequent reactions on *(67)*, epoxidation, esterification, and finally methylation with $LiCu(CH_3)_2$, all proceeded reasonably well to afford a key intermediate lactonic ester *(68)*. $LiAlH_4$ reduction converted *(68)* into the corresponding triol *(69)*. The two primary hydroxy groups were tosylated, and the secondary one was trimethylsilylated to produce *(70)*. Lithium dihydrocuprate[80], a reagent developed for the reduction of tosylates and halides into hydrocarbons, cleanly removed the tosyl groups (without elimination of the homoallylic tosyl group), and the resulting cycloheptene *(71)* was subjected to the Lemieux-Rudloff oxidation to afford, after acidification, a C_{10}-acid *(72)* identical with a key degradation product of methynolide previously obtained by *Prelog*[81] and *Djerassi*[2].

The confirmation of the stereochemistry of a synthetic intermediate at this stage is highly desirable, and *(72)* also provides a means of distinguishing between the two carboxylic acids, one of them being masked as a δ-lactone. The 2,2-dimethylpropanethiol ester which tolerates quite well both mild acidic and basic conditions was used for the protection and later activation of the C(1)-carboxylic acid of *(72)*. Since the δ-lactone is at least several hundred times more readily hydrolyzed with alkali than a normal methyl ester[82], the thioate *(73)* very rapidly consumed 0.95 equivalent of KOH at 20 °C to afford the hydroxycarboxylate *(74)*, which was then transformed into the imidazolide *(75)*. Treatment of *(75)* in a dilute solution (0.01 M) with 1 equivalent of salt-free methylene(triphenyl)-phosphorane in benzene led to the desired Wittig reagent *(76)*[83, 84]. Model experiments using the imidazolide of 2-deu-

terio-2-ethylhexanoic acid confirmed that no epimerization occurred under these conditions. Refluxing a toluene solution of (±)-*(76)* (1 equivalent) and (+)-aldehyde *(62)* (3 equivalents) brought about successful condensation to yield a diastereoisomeric (presumably 1 : 1) mixture of epoxythiol esters *(77)* which was converted on mild acid treatment into the desired methynolide seco-acid derivative *(78)*.

The crucial step of lactonization was achieved by employing Method 1 (described earlier in Section 5.1.3). Treatment with $Hg(CF_3CO_2)_2$ or preferably $Hg(CH_3SO_3)_2$ in the presence of Na_2HPO_4 at room temperature effected cyclization to *(79)* in 30% yield. Compound *(79)* was quantitatively converted into *(80)* with tetrabutylammonium fluoride[85].

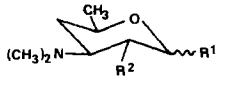
The final stage of the methymycin synthesis involved glycosylation of the aglycone with desosamine *(81)*. The presence



(74), R^1 = OK, R^2 = H

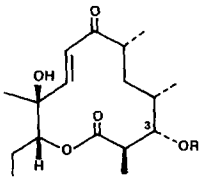
(75), $R^1 = C_3H_3N_2$, $R^2 = Si(CH_3)_2C(CH_3)_3$

(76), $R^1 = CH{=}P(C_6H_5)_3$, $R^2 = Si(CH_3)_2C(CH_3)_3$



(81), R^1 = β-OH, R^2 = OH

(82), R^1 = α-Br, R^2 = $OCOCH_3$



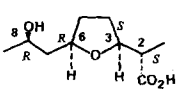
(79), R = $Si(CH_3)_2C(CH_3)_3$

(80), R = H

of the dimethylamino group in *(81)* and also the congested substituents around the C(3) hydroxy group of *(80)* restricted the selection of reagents and reaction conditions applicable for this operation. However, use of α-bromo-2-acetyldesosamine hydrobromide *(82)*·HBr and lutidine (which is too weak to liberate the amine which normally induces complicated side reactions) successfully led to a 5:1 mixture of β- and α-glycosides of methynolide. Deacetylation with methanol and triethylamine and separation of the β-isomer from the α-isomer completed the synthesis of *(1)*.

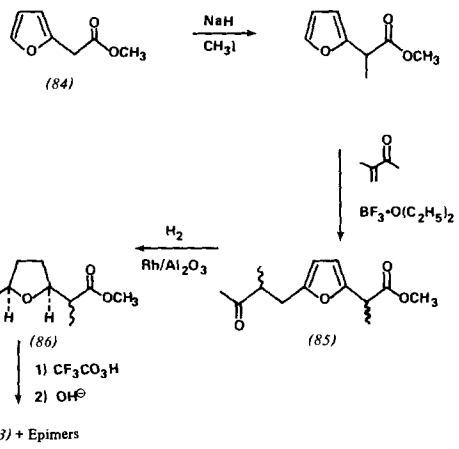
5.2.2. Nonactin *(7)*

This 32-membered ionophoric macrolide is comprised of four nonactic acid *(83)* subunits arranged in an alternating enantiomorphic (+ − + −) order. Therefore *(7)* is an achiral molecule. The structure of *(7)* immediately suggests a logical synthetic approach, consisting of (i) the preparation of *(83)*, (ii) tetramerization of its enantiomers in the proper sequence, and finally (iii) lactonization to the macrocycle *(7)*. Of several schemes reported for the first step, one starting with furan or a furan derivative and later creating the *cis*-stereochemistry at the C(3) and C(6) positions of *(83)* is most representative and has been used by four groups. *Beck* and *Henseleit*[86] utilized as starting material methyl furan-2-acetate *(84)* which, after monomethylation, was condensed with 3-methyl-3-buten-2-one to provide a 2,5-disubstituted furan *(85)*. Catalytic



(83)

(+)-(2*S*, 3*S*, 6*R*, 8*R*)-Nonactic acid



(84)

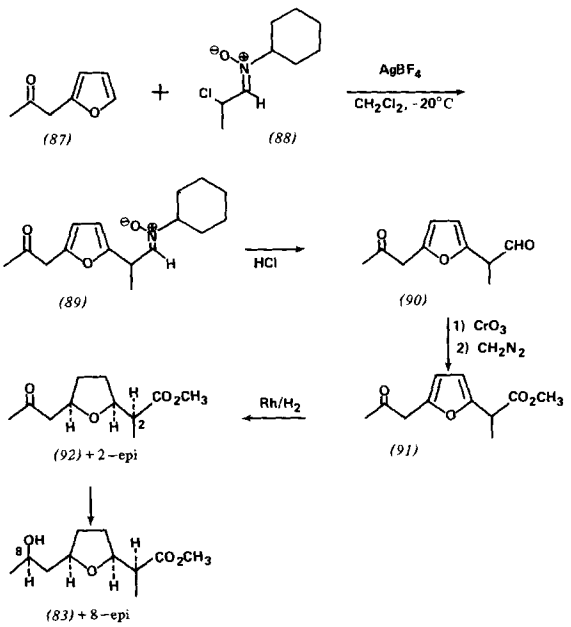
(86)

(85)

(83) + Epimers

hydrogenation of *(85)* with Rh introduced *cis*-oriented hydrogen atoms at the 2- and 5-positions of the furan and led to a mixture of four stereoisomers *(86)*. Subsequent conversion of the acetyl group into a hydroxy group afforded *(83)* and its diastereoisomers.

The scheme adopted by *Gerlach* and *Wetter*[87] also suffers from a similar drawback: non-stereoselective introduction of the two chiral centers of the side chains. Condensation of



(87)

(88)

(89)

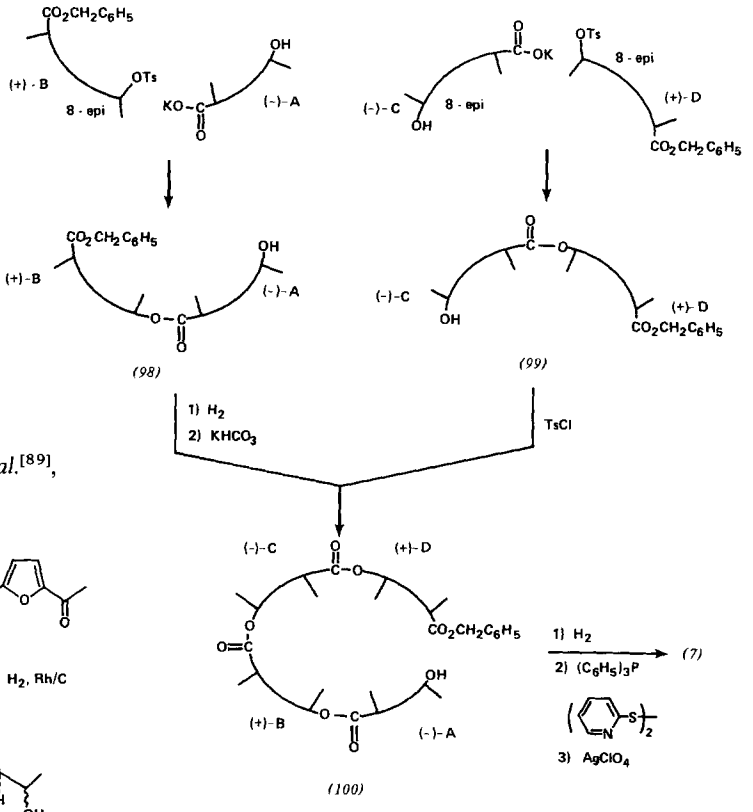
(90)

(92) + 2-epi

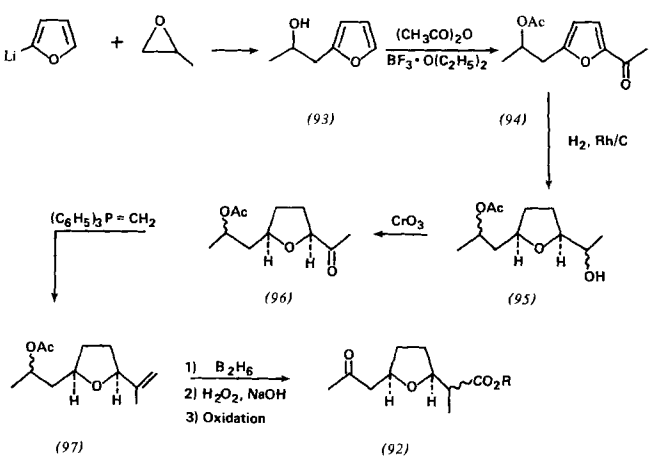
(91)

(83) + 8-epi

acetonylfuran *(87)* with chloronitrone *(88)*[88] and subsequent hydrolysis of the condensate *(89)* and oxidation of aldehyde *(90)* gave a ketoester *(91)*. The ensuing operations, catalytic hydrogenation and sodium borohydride reduction, led to the formation of four separable compounds isomeric at the 2- and 8-positions of *(83)*.

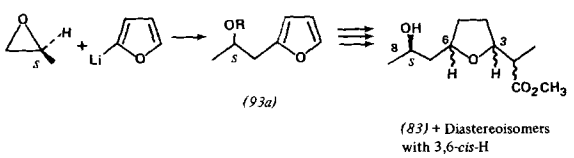


A further synthetic variant, reported by *White et al.*[89], involves intermediates *(93)*—*(97)* and leads to *(92)*.



Somewhat earlier, *Schmidt et al.*[20,90] described a method in which (−)-(*S*)-propylene oxide (rather than the racemate) [obtained from (+)-L-lactic acid] was used as starting material. Through a sequence of reactions, similar to those described above and preserving the original chiral center, they managed to obtain (−)-(2*R*,3*R*,6*S*,8*S*)-nonactic acid [(−)-*(83)*], and its three isomers: (2*S*,3*R*,6*S*,8*S*), (2*R*,3*S*,6*R*,8*S*), and (2*S*,3*S*,6*R*,8*S*). A Walden inversion proceeded smoothly on treatment of the 8-tosylate of this last isomer with potassium acetate to yield (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid [(+)-*(83)*]. In this way, a series of compounds, (+)-*(83)*, (−)-*(83)*, and their 8-epimers were prepared.

The non-selectivity encountered in the above four schemes[91] is not as discouraging as it appears, because the

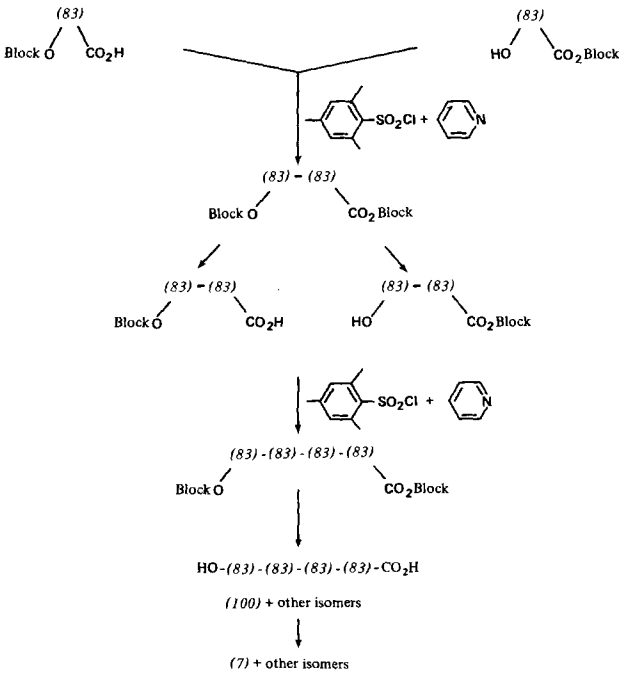


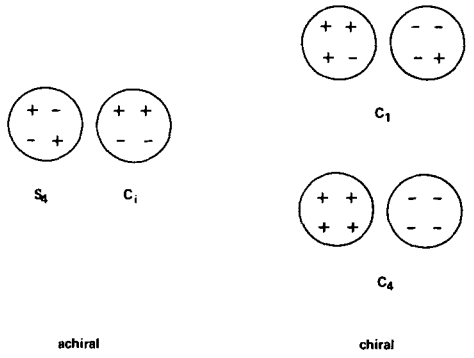
(83) + Diastereoisomers with 3,6-*cis*-H

2-epimers can be equilibrated to give a mixture of the normal and epi-series (which are separable). Moreover, 8-epi-*(83)* can be used for the synthesis of *(7)*.

The second and third steps of the nonactin synthesis proceeded in the following way[20]: an S_N2 displacement of the tosylate of (+)-8-epi compound (B) with the (−)-nonactate anion (A) and similarly that of D (= B) with (−)-8-epi-hydroxy-nonactate anion (C) afforded two esters *(98)* and *(99)*, respectively. After debenzylation of *(98)* and tosylation of *(99)*, the two fragments were condensed in the same manner as above. The final lactonization of the resulting tetra-ester *(100)* proceeded, after hydrogenolysis of the benzyl ester, in 20% yield by use of the Gerlach procedure (Method 3).

Gerlach et al.[21] started with racemic *(83)*, properly blocking and deblocking the carboxylic acid (*tert*-butyl and CF_3CO_2H) and the OH groups (benzyl and hydrogenolysis), and forming the ester linkage with the aid of 2,4,6-benzenesulfonyl chloride and pyridine to obtain a mixture of statistically

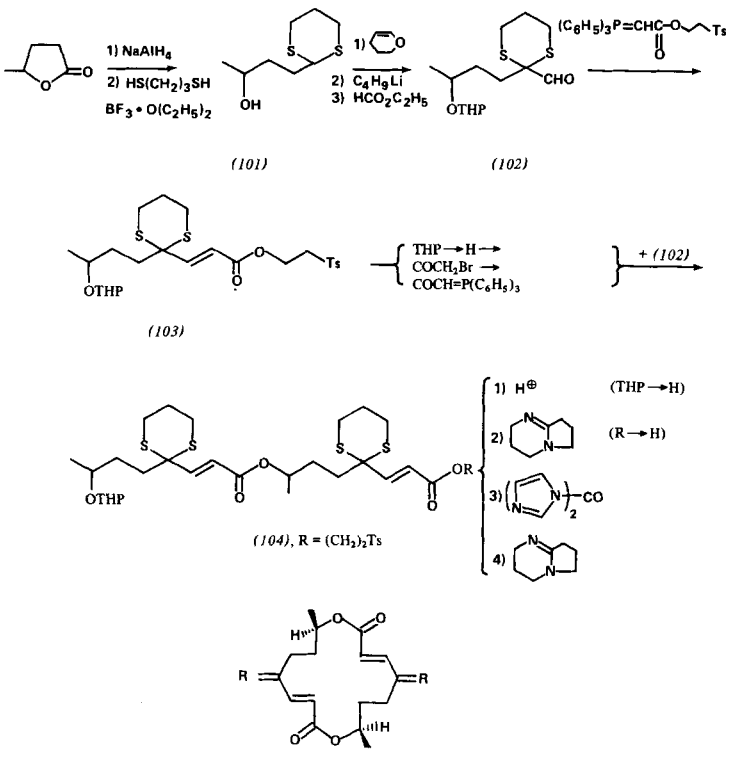




possible stereoisomers corresponding to *(100)*. Cyclization of the mixture using their method gave rise to several cyclic isomers in 20% yield, from which racemic *(7)* (of symmetry S_4) was isolated. The other possible isomers, an achiral compound of C_i, and two racemates of C_1 and C_4 symmetry, had apparently also been formed in this cyclization.

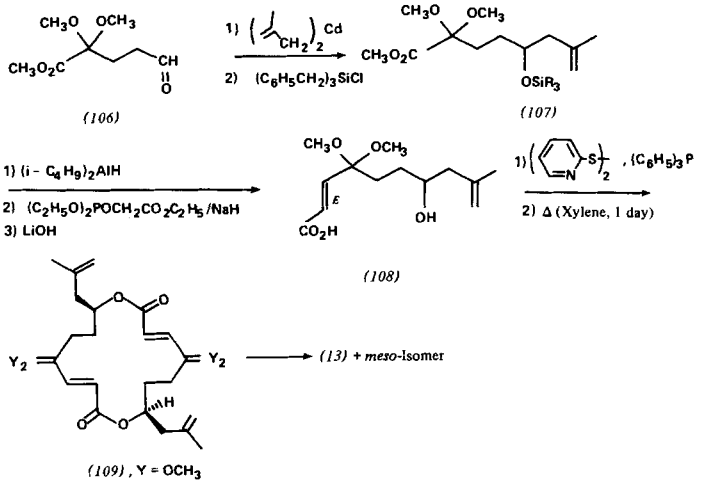
5.2.3. Pyrenophorin *(12)* and Vermiculine *(13)*

Since these 16-membered diolides which are composed of two identical hydroxyacids are optically active, the two chiral centers of each component must have the same absolute configuration. *Colvin, Purcell,* and *Raphael*[118] were able to synthesize *(12)*. The authors emphasized the importance of the



β-tosylethyl group for the protection of the carboxylic acid[92,93], which was liberated from *(104)* without cleavage of the central ester linkage. Treatment of the hydroxyacid corresponding to *(104)* with carbonyldiimidazole cleanly afforded the imidazolide of the hydroxyacid (the hydroxy group normally is less reactive to this reagent), which underwent base-catalyzed lactonization[94]. The generation of the keto

groups provided a separable mixture of (±)- and *meso-(12)*. This synthesis, first reported in 1972, could be somewhat simplified in view of other more recent techniques already described above. It appears possible to achieve one-step double lactonizations, as exemplified in the following synthesis of vermiculine. *Corey et al.*[119] condensed the aldehyde *(106)* (which was prepared by partial reduction of the corresponding glutarate) with bis(methallyl)cadmium to yield compound



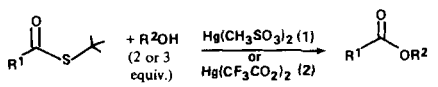
(107), in which the terminal methylene group served as a masked ketone and imparted base-stability to subsequent intermediates. A standard two-carbon chain extension of *(107)* provided a key intermediate *(108)*, and refluxing a xylene solution of its 2-pyridinethiol ester effected double cyclization to give a mixture of stereoisomeric diolides *(109)*. Further operations including OsO_4-$NaIO_4$ oxidation converted *(109)* into (±)-vermiculine *(13)* and its *meso*-isomer.

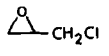
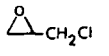
5.3. Further Remarks on Macrolide Synthesis

The total syntheses described in Section 5.2 reveal the two important problems of macrolide synthesis: ester and lactone formation, and control of the stereochemistry. Rather extensive studies have been performed in order to define the scope and limitations of several potentially useful reactions (see Section 5.1.3). A summary of this development is given in the following sections.

5.3.1. Ester and Lactone Formation

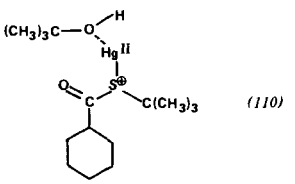
Method 1 (Section 5.1.3), utilizing a thiophilic metal ion to activate a thiol ester, offers some distinctive advantages. Firstly, as is described in the synthesis of methymycin *(1)* [see the processes for converting *(73)* into *(78)*], the 2,2-dimethylpropanethiol ester serves as an excellent protecting group, surviving both relatively mild alkaline and acidic conditions. Its stability toward OH^- and H^+ is comparable to that of normal alkyl esters. (However, the thiol ester does react readily with an amine in conformity with the hard-soft principle.) Secondly, reaction of a metal ion, such as Hg^{II}, with the thiol ester formally creates a trivalent sulfur molecule, a highly reactive species, and thus ester (and lactone) formation proceeds very rapidly at room temperature or below. More importantly, bulky substituents or double bonds located near



R¹	R²	Reagent	Buffer	Yield [%]
		1 or 2	Na_2HPO_4 (or none)	100 %
		1		90 %
		1 or 2		85 %
		1	Na_2HPO_4	90 %

the reaction centers—namely the hydroxy and acyl groups—do not impede the reaction[72, 95]. Thus *tert*-butyl pivalate and *tert*-butyl crotonate are prepared in excellent yields.

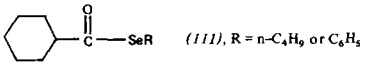
In the absence of alcohols, *tert*-butyl cyclohexanemethanethioate reacts with $Hg(CF_3CO_2)_2$ to form cyclohexanecarboxylic trifluoroacetic anhydride. Reaction of this anhydride with *tert*-butyl alcohol to give the ester, however, proceeds *ca.* 10 times slower than the above Hg^{II}-catalyzed ester formation[96]. Since intermediacy of the corresponding ketene has been ruled out[96], it would appear that the metal-catalyzed ester formation proceeds mostly through coordination of the alcohol to the metal. The possible intermediate *(110)* subsequently collapses into the ester and mercuric salts with retention of stereochemistry at carbon a to the carboxy group. The present method is not free from disadvantages: the electrophilicity of Hg^{II} toward



(110)

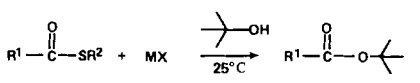
reactive alkenes[97] may be a problem sometimes. However, in most cases the reactivity of Hg^{II} with sulfur exceeds significantly that with ordinary or electron-deficient (C=C—C=O) double bonds, and we have thus far encountered only one case (cyclization of cytochalasin-B seco-acid, *vide infra*) where this problem is detrimental to the execution of successful lactonization, free from side reactions.

There are two obvious ways of modifying the procedure. Because of the comparatively weak bonding between carbon and selenium, selenol esters such as *(111)*[98] appeared to be good candidates for a more reactive species than the thiol ester. However, conversion of these *Se*-esters into *O*-esters

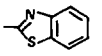
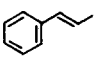
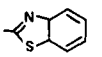


(111), R = n-C_4H_9 or C_6H_5

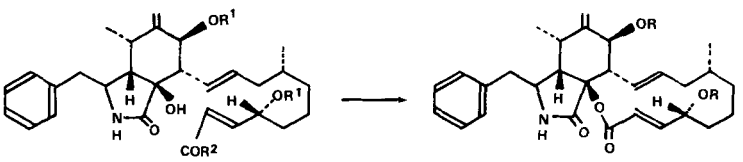
with transition metal cations which are inert to the C=C bond, [*e.g.*, Ag^I, Cu^I] were rather discouraging, and we have concluded that selenol esters do not offer any advantages for this purpose over thiol esters. Moreover, Hg^{II} was still needed to effect the reaction.



(112) *(113)*

R¹	R²	MX	Solvent	Time	Yield [%]
		$Cu(CF_3SO_3)$	C_6H_6/THF	10 min	95
		$Ag(CF_3CO_2)$	C_6H_6	10 min	100
		$Cu(CF_3SO_3)$	C_6H_6/THF	5 h	80
		$Cu(CF_3SO_3)_2$ $Ag(CF_3CO_2)$ $AgBF_4$	CH_3CN C_6H_6 (Δ) C_6H_6 (Δ)	1.5 h 1.5 h 1 h	24 100 <5
		$Ag(CF_3CO_2)$ $Cu(CF_3SO_3)$ $Cu(CF_3SO_3)_2$	C_6H_6 (Δ) C_6H_6/THF CH_3CN	1.5 h 5 h 30 min	100 90 100

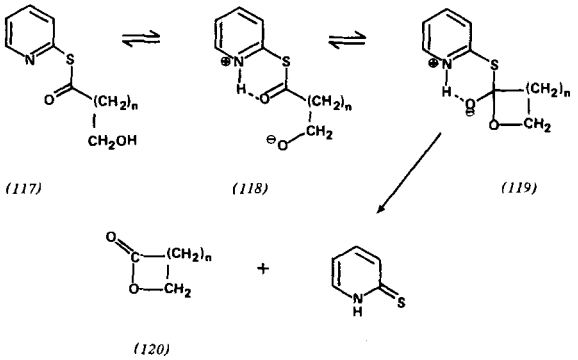
Another modification involves a variation of R^1 and R^2 in *(112)* and also that of MX. The more acidic the reacting thiol R^2SH is, the less thiophilic the metal cation needs to be to effect the reaction, and in many cases Cu^I, Cu^{II}, and Ag^I were even superior to Hg^{II}. The presence of electro-inductive groups such as the C=C bond and protected hydroxy groups somewhat retards the ester formation. All these observations appear to conform with the hard and soft acid and base principle of *Pearson*. Further it is now clear that *Gerlach*'s method (Method 3, Section 5.1.3), the use of $AgClO_4$ or $AgBF_4$ to activate 2-pyridinethiol esters, is fully in accord with this



(114), $R^1 = CH_3CO$, $R^2 = OH$
(115), $R^1 = CH_3CO$, $R^2 = SC_6H_5$

(116), R = H

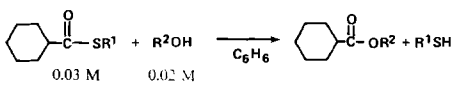
trend. In this way we have recently succeeded in cyclizing diacetylcytochalasin-B seco-acid *(114)* to the corresponding lactone, which yields cytochalasin-B *(116)* upon mild alkaline hydrolysis[95]. The ester *(115)* and $Ag(CF_3CO_2)$ (but not $AgClO_4$) have been the only combination able to achieve this task. (For the preparation of thiol esters see [74, 96, 99–101].)

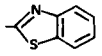


(117) *(118)* *(119)*

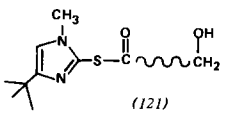
(120)

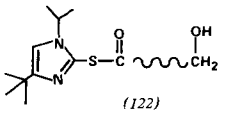
In contrast to Method 1, *Corey*'s "double activation" procedure (Method 2, Section 5.1.3) does not necessitate use of an external reagent to activate the functional group; cyclization (*e.g. (117)* to *(120)*) is accomplished by heating a solution of the 2-pyridinethiol ester of a hydroxyacid for a prolonged period of time. Several pieces of evidence point to the intermediacy of *(119)* in this lactonization[102]. If one accepts this mechanism, then it follows that a thiol ester substituted heavily near the reaction centers (hydroxy and acyl groups) would encounter a high energy barrier in the process leading to *(119)*. We have confirmed this inference: the rate of ester formation is progressively retarded as the steric hindrance increases, and is extremely slow with *tert*-butyl alcohol, although addition of Ag^I completes the reaction within 10



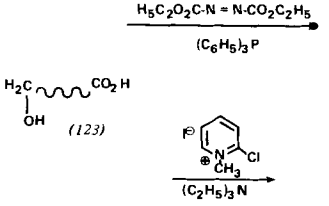
R^1	R^2	T [°C]	Time (h)	Yield of O-Ester [%]
	n-$C_9H_{19}CH_2$—	25	4	51
			20	96
		50	1	63
			4	91
	n-C_4H_9—CH(—CH_3)—	80	1	49
			4	98
	$(CH_3)_3C$—	80	24	18
			72	38
	n-$C_9H_{19}CH_2$—	50	1	7
			20	18
	n-C_4H_9—CH(—CH_3)—	80	2	2
			30	6
	$(CH_3)_3C$—	80	24	0

minutes. This steric retardation of the reaction constitutes a major drawback to Method 2. We have failed to cyclize the seco-acids of methynolide and cytochalasin derivatives [*(59)* and *(114)*, resp.] by this method. In fact, in most of the examples thus far reported[103] substances possessing either a primary hydroxy or primary carboxylic acid group were cyclized, whereas in model studies straight chain aliphatic ω-hydroxyacids are employed. Some improvement has been made, however, and the latest version of this method[104] involves the use of esters of the type *(121)* and *(122)*, which undergo cyclization 100 times faster than the corresponding 2-pyridinethiol ester. Other cyclization reactions include the


(121)


(122)

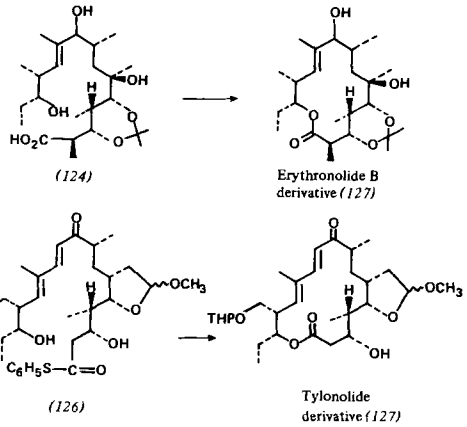
reaction of diethyl azocarboxylate and triphenylphosphane with an aliphatic hydroxyacid *(123)*[105] and use of 2-chloro-*N*-methylpyridinium iodide and triethylamine[106].



(120)

Staab's imidazolide method, which was successfully utilized in the synthesis of pyrenophorin *(12) (vide supra)* and in a model study for erythronolide B[107], requires a catalytic amount of strong base, which normally destroys sensitive "polyoxo" macrolide seco-acids and/or causes epimerization unless they are properly protected.

Other examples of the lactonization of seco-acids derived from natural macrocyclic compounds are: *(124)*→*(125)*

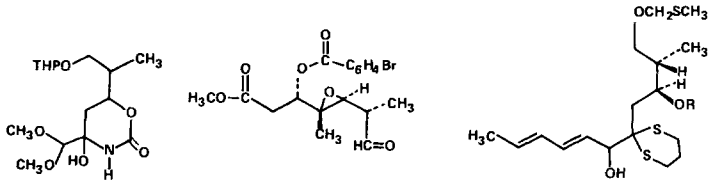


(Method 2, yield not specified)[103a], *(126)*→*(127)* (Method 1, 17%)[101] and the successful cyclizations, according to Method 2, of bistetrahydropyranyl ethers of A-brefeldinoic seco-acid to the corresponding brefeldin A derivative (70%) [cf. *(14)*], of *N*-benzyloxycarbonylcarpamic acid to bisbenzyloxycarbonylcarpaine (> 50%), and of vertalin seco-acid to vertaline (67%)[103a].

5.3.2. Stereochemical Considerations

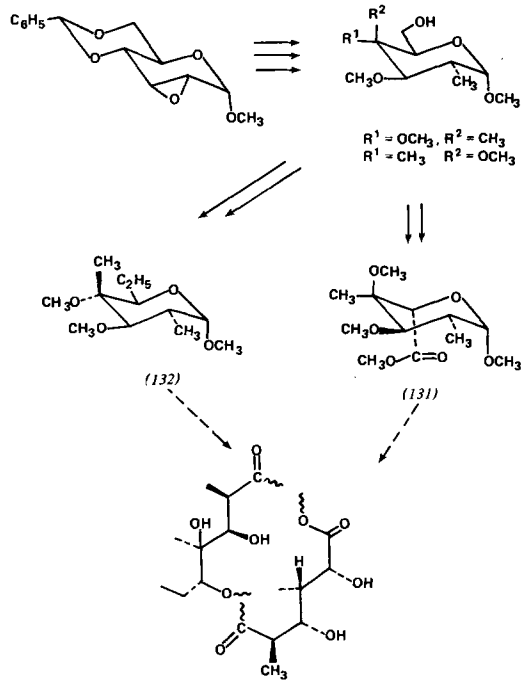
The subunit of pyrenophorin *(12)* or vermiculine *(13)* contains only a single chiral center and no effort has been made in the synthesis to selectively combine the two identical enantiomers of the subunit. Nonactin *(7)* obviously presents more stereochemical problems. Of the four asymmetric centers of nonactic acid *(83)*, only two (possibly three) were stereospecifically introduced in synthetic intermediates. Tetramerization of (+)- or (−)-*(83)* adopted either Route 1 (see Section 5.1.3) or a random combination of (±)-*(83)*, followed by chromatographic separation of the desired macrocycle (±)-*(7)* from other isomers. In the synthesis of methymycin *(1)* both fragments A and B were stereospecifically or selectively synthesized and were combined by Route 2. Although a few newer methodologies permitted efficient execution of some crucial transformations involved in the scheme, the overall control of stereochemistry relies upon conventional, well-known techniques which utilize a ring system to establish the *cis* or *trans* relationship of two specific substituents. Can we "stretch" this type of approach to a more complicated system? Can we devise a new methodology to create a chiral center in an aliphatic acid in a manner a step closer to the enzymatic process? These are questions we are seriously asking in the synthesis of tylosin *(5)*, a 16-membered macrolide antibiotic. These questions arise when we consider a few processes, (1) addition of one propionate unit to a preformed chiral fragment, (2) matching two different subunits, and in particular (3) creation of a new asymmetric center or centers concurrently with this matching.

Two years ago two groups reported syntheses of fragments, *(128)*[108], *(129)*[109], and *(130)*[110], from which it was



(128) *(129)* *(130)*

intended to form the 19-membered lactam of maytansine *(9)*. Clearly it is not a simple matter to link these fragments together in the proper manner. The view that polyoxo macrolide antibiotics are "big" cyclic sugars naturally suggests the idea that a sequence of transformations of commonly available monosaccharides would yield fragments required for a macrolide synthesis. This approach becomes particularly attractive for erythronolide A, whose structure possesses hidden symmetry. *Hanessian* and *Rancourt* have prepared the C(1)—C(6) *(131)* and C(9)—C(13) *(132)* fragments of erythronolide A



from glucose through a sequence of some ten steps[111]. This approach is neat and clever, and if macrolide syntheses were commercially important and viable, this would be the route to be chosen.

It is our view that synthetic organic chemists are still challenged by the above, as yet unsolved, fundamental problems associated with stereochemistry and when one accepts this challenge, new chemistry will undoubtedly emerge.

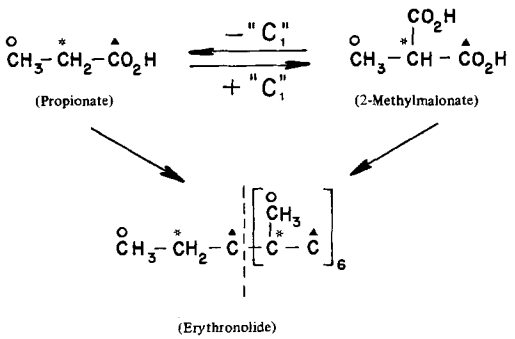
6. Biochemistry[*]

6.1. Biogenesis

Five representative "polyoxo" macrolides [*(1)*—*(5)*] are described in Section 2.1. Although there are common features in the biogenesis of all five, there are many differences. Early studies were mainly concerned with erythromycin A *(3)* and are summarized in several review articles[23, 112–114]. Apparently, these "polyoxo" macrolide antibiotics and also the polyenes (Section 2.2) and the bridge system of the ansamycins (Section 2.4) are formed from simple metabolic intermediates like acetate, propionate, malonate, 2-methylmalonate, butyrate (or 2-ethylmalonate), much in the same manner as saturated long-chain fatty acids are synthesized. Monomers with activated carboxyl groups (thiol esters of coenzyme A or a polyenzyme synthase) condense in rapid stepwise fashion with their carboxylated derivatives (malonate, 2-methylmalonate, and 2-ethylmalonate derivates) to yield a long-chain polyoxo fatty acid which after a minimum of one biological reduction can form a lactone. Structural analysis of the known macrolides shows that the process of chain extension or growth proceeds independently of whether modification of the β-oxo function introduced at each step of chain extension occurs or not. This feature distinguishes the formation of macrolide lactones from that of saturated fatty acids, but it would appear that the latter is the special case.

Most of the lipid-derived structures found in nature are built from carbon chains derived from the same monomers cited above (as well as others) and their structures show the retention of variable amounts of these same oxygen atoms. It seems that most lipids, including those of the macrolide group, are formed by General Fatty Acid Synthases (GFAS's) and the saturated acids (*e.g.*, palmitic) found in cell membranes and neurological tissues are formed by Specialized or Saturated Fatty Acid Synthases (SFAS's). (These abbreviations will be used here together with the abbreviated names of the substrates believed to be used by the synthase.)

The aglycones (erythronolides) of the erythromycins are synthesized by a GFAS:Pr, 2-MeMal; all available evidence shows that they are made from one *pr*opionate and six *2-meth*-

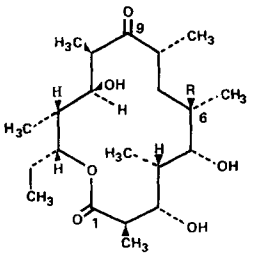


(Propionate) (2-Methylmalonate)

(Erythronolide)

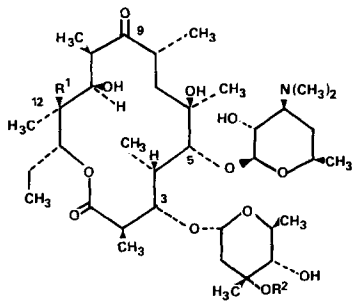
*yl*malonate units. This conclusion came from work using radioactive substrates and has been confirmed by ^{13}C-NMR studies which have added proof for the stepwise route of synthesis[115, 116]. Erythronolide B *(19c)* is the final lactone formed prior to glycoside formation. Its presence as well as that of its penultimate precursor, 6-deoxyerythronolide B *(133)*, was shown initially by studies with blocked mutants of *Streptomyces erythreus*[117, 118]. A most interesting soluble hydroxylase system which is dependent on a cytochrome P_{450} component is required for the transformation of *(133)* into *(19c)*[119]. The work with mutants also showed that a neutral monoglycoside, 3-*O*-mycarosyl-erythronolide B is the next isolable intermediate. This structure accepts either activated

[*] This section is contributed by *J. W. Corcoran.*

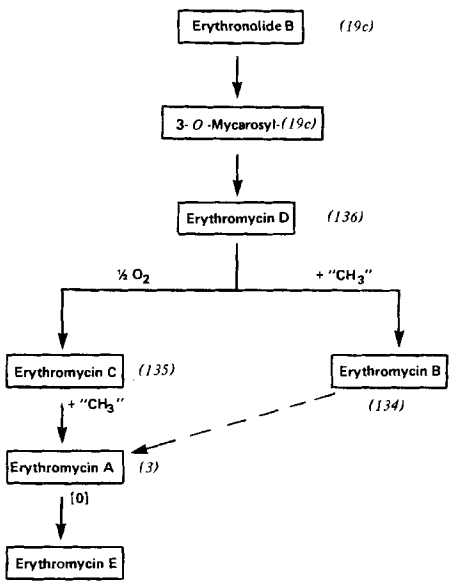


Erythronolide B *(19c)*, R = OH
6-Deoxyerythronolide B *(133)*, R = H

D-desosamine or some precursor yielding the first biologically active bis-glycoside, erythromycin D *(136)*[120–122]. This

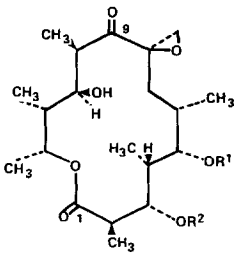


Erythromycin	R^1	R^2	
A	OH	CH_3	*(3)*
B	H	CH_3	*(134)*
C	OH	H	*(135)*
D	H	H	*(136)*



intermediate *(136)*, the key substance in the biosynthesis, can be either hydroxylated to yield erythromycin C *(135)*[123] or directly receive an activated methyl group from *S*-adenosyl-L-methionine to give erythromycin B *(134)*[124]. The same transmethylase will react with *(135)* to give the common A form *(3)*[125] of erythromycin. Under some conditions, *(134)* may be hydroxylated to the A form *(3)* directly, although this has yet to be demonstrated with the cell-free enzyme system used to elucidate the terminal steps in erythromycin formation. Oxidative degradation of erythromycin A *(3)* occurs, yielding at least one further substance, the E form, with an ortho ester linkage between oxidized L-cladinose and C(3) of the ring[126].

There is some biosynthetic "crossover" between closely related pathways in the macrolide area. Thus *S. erythreus* modified lactones derived from erythronolide B *(19c)* often accept L-mycarose. The products are novel monoglycosides which usually do not serve as acceptors for D-desosamine[127]. In general this has not proved to be a useful route to new antibiotics. A notable exception is the transformation of the 11-*O*-methyl ether of erythronolide B *(19c)* into 11-*O*-methylerythromycin B[128]. A second exception is the case of the 9-oxime of erythronolide A, where, in a mixed fermentation using *S. antibioticus* which is normally a producer of oleandomycin *(137)*, a new antibiotic is formed. It is 3-*O*-oleandrosyl-



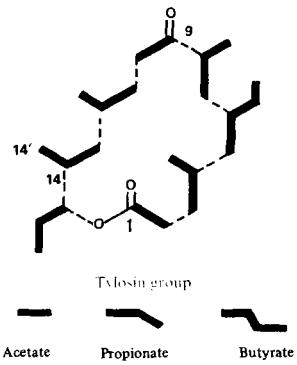
Oleandomycin *(137)*
R^1 = Desosaminyl
R^2 = Oleandrosyl

5-*O*-desosaminyl erythronolide A 9-oxime, which contains the typical sugar residues of oleandomycin and the lactone ring of erythromycin A[129].

Additional examples of "interspecies" cross-over are the formation of mycaminosyl derivatives of narbonolide and 9-dihydronarbonolide when these 14-membered aglycones are added to cultures of *Streptomycetes* that normally produce 16-membered macrolides[130]. *Martin et al.* have also isolated derivatives of erythronolide B *(19c)* in which non-branched neutral sugars are present instead of L-mycarose[131]. Clearly the future should see much more use of mixed fermentations which produce "hybrid" macrolide structures.

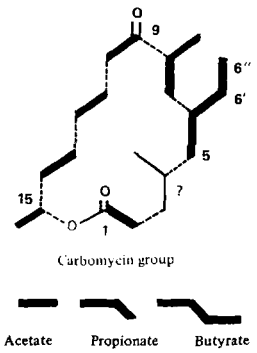
A large number of other macrolides similar to the erythromycins include, *inter alia*, methymycin *(1)*, pikromycin *(2)*, narbomycin [12-deoxy-*(2)*], and oleandomycin *(137)*. These antibiotics are not exclusively derived from propionate/2-methylmalonate but contain one unit that originates from acetate/malonate. This conclusion is based on isotopic and NMR evidence. The reasons for this are obscure, but a given microbial strain gives a single predominant product together with trace amounts of other possible products which differ more in oxygen atom substitution patterns from the major component than in the carbon skeleton of the lactone[132]. The finding that *S. Venezuelae* can form either the 12-membered methymycin system or the 14-membered pikromycin structure according to the culture medium is fascinating and awaits a rational explanation[133] (cf. discussion of the magnamycin-type of macrolide, *vide infra*).

The 16-membered macrolides tend to either of two structural extremes. The tylosin group (*e.g.*, rosamycin and cirramycin) are largely derived from propionate with the added feature that one biogenetic unit comes from butyrate/2-ethylmalonate (GFAS: Pr, Mal, 2-MeMal, 2-EtMal)[134, 135]. These structures are thus biogenetically somewhat similar to the erythromycin group. The methyl position of the butyrate is oxidized to an



aldehyde group in most known cases (except for platenolides, *vide infra*). The sugars of tylosin *(5)* are similar to those of erythromycin, but are present as a disaccharide, and a third sugar residue is attached to a hydroxylated methyl group [C(14')].

The other group of 16-membered macrolides is typified by carbomycin A (magnamycin) *(4)* and includes, *inter alia*, the leucomycins [cf. *(16)*], niddamycin, platenomycin, spiramycin, *etc.* These structures are formed biologically from acetate/malonate with the use of only one propionate/2-methylmalonate unit and the same butyrate/2-ethylmalonate building block as that for the tylosin group. The origin of C(3) and C(4) of the carbomycin ring system is as yet unclarified[136]. In the case of tylosin these same two positions are derived from 2-methylmalonate, and thus "can in principle" be formed from an acyl intermediate. This portion of the macrolide ring system seems more variable than the other,



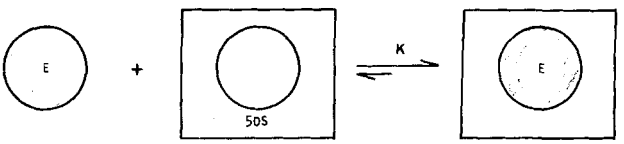
and perhaps is formed after the 15-oxo or 15-hydroxy acid leaves the GFAS responsible for its formation (cf. ref. [112]). Such variability might also explain how either a 12- or 14-membered lactone could stem from a common producing organism (cf. methymycin *(1)*, *vide infra*). The platenolides[137] differ from most 16-membered macrolide aglycones in retaining the methyl group [C(6'')] of the butyrate/2-ethylmalonate precursor which constitutes C(5), C(6), C(6') and C(6''). They are produced by blocked mutants of *S. platensis* which normally produces the platenomycins, 16-member macrolides of the carbomycin type with an aldehyde group at C(6'')[138].

Very few cell-free studies have been carried out on the enzymes involved in the biogenesis of 16-membered macrolides. Hence it is difficult to do more than speculate on the steps involved in assembling these complex molecules. Sugar-free lactones have been identified both in normal fermentations and in fermentations with blocked mutants, and it is likely, as with erythromycin, that some sugar-free lactone is released from the GFAS system, which then accepts either the preformed disaccharide L-mycarosyl-D-mycaminose plus the third sugar (when present) or all the sugars in stepwise fashion. The times of acylation of the L-mycarosyl moiety and the ring system are also unknown.

6.2. Mode of Action

The mode of action of the macrolides was initially studied with erythromycin A *(3)*, and a comparison has been made with a limited number of other macrolides[24,139-141]. Also, a large number of semi-synthetic macrolide antibiotics have been studied, mostly in comparison with erythromycin[141-144]. There appears to be general agreement that all macrolide antibiotics affect protein synthesis in susceptible bacteria—mostly the gram-positive group. However, cell-free studies have shown that erythromycin inhibits protein synthesis in systems from gram-negative bacteria. When the intracellular concentration of the antibiotic is high enough (*ca.* 10^{-4} M), intact cells of both groups are inhibited. The difference seems to lie in their ability to accumulate the drug, and there even seems to be some "barrier" to this process in highly sensitive gram-positive cells[145]. The mechanism of accumulation has not been studied.

Erythromycin A *(3)* inhibits the growth of bacteria and the mechanism of action involves a stoichiometric binding of high affinity of one molecule of the erythromycin to a highly specific "site" on the 50S ribosomal subunit. It appears that this occurs only, or at best, when the 50S unit is in the free state, and that the erythromycin/50S ribosomal adduct is able to form ribosomal assemblies (70S and polysomes) which may function in the synthesis of bacterial protein. On the average, however, these assemblies do not behave normally and overall cellular protein synthesis is disturbed[140,145].



E = Erythromycin. For *Bacillus subtilis* 168, $K \approx 3 \times 10^{-7}$ l/mol [140].

There is some controversy as to which part of the ribosome cycle is the primary target of the disturbance. Some macrolides appear to inhibit the action of peptidyl synthetase, an enzyme activity which promotes the formation of a new aminoacyl bond in the growing polypeptide chain. Other studies, especially those with erythromycin, have suggested that the primary disfunction in protein synthesis concerns the GTP-dependent translocation[146]. This may be an academic difference, since the assays used to study the mode of action are extremely non-physiological and very much influenced by experimental design. The study of erythromycin action used radioactive antibiotics of high specific activity, and most comparisons with other macrolides have depended on their ability to displace this erythromycin from its binding site on the 50S ribosomal unit[140,141]. Thus far this activity has agreed well with independent studies of the potency of the second macrolide.

In principle, the macrolide antibiotics should be capable of inhibiting mammalian mitochondrial protein synthesis, as this process is very similar to that in bacteria. Apparently erythromycin (and presumably other useful macrolides) is unable to penetrate the mitochondrial membrane and for

Table 1. Macrolide antibiotics.

	Ring size	Structural determination	Structural modification	Total/ partial synthesis	Bio- synthesis	Miscellaneous
"Polyoxo" macrolides						
Albocycline [b]	14	[147—149]				
Aldgamycin	16	[150, 151]	[150, 151]	[152] [f]		
Angolamycin	16	[153]				[153]
Carbomycin	16	[154]				[57b, 154]
Chalcomycin	16					[57b, 57c]
Cirramycin	16					[57b]
Erythromycin	14	[51—54, 157—159] [d] [129, 155, 156] [e]	[119, 126, 155, 157, 160—181]	[18] [111]	[121, 126, 131, 158—159]	[120, 129, 139, 142—145, 161, 170, 172—174, 176, 178, 179, 183—194]
Espinomycin	16					[195]
Josamycin	16		[196, 197]			[186]
Kujimycin	14		[198]			[198, 199]
Lankacidin [b]	17	[200, 201]	[201—205]		[202]	[203, 204, 206—209]
Lankamycin	14	[210] [d], [211]	[211]			
Leucomycin	16	[42] [e], [43, 57a] [d], [212]	[154, 212—216]	[43]	[136]	[57b, 57c, 136, 142, 154, 186, 188, 216—218]
Maridomycin	16	[219—221]	[196, 220—228]			[196, 219, 222, 225, 228—231]
Megalomycin	14	[232, 233]	[232—234]			[235, 236]
Methymycin	12			[17]		[237]
Midecamycin	16	[238]	[238]			
Narbomycin	14		[239]			[130]
Neomethymycin	12					[237]
Neutramycin	16					[57b]
Niddamycin	16		[43, 154]			[154]
Oleandomycin	14				[240]	[184, 186, 187]
Pikromycin	14	[55] [d], [56] [e], [241]			[239, 242]	[132, 237]
Platenomycin	16				[137, 138, 243—245]	
Rosamycin	16	[246]			[135]	[135, 247, 248]
Spiramycin	16					[57b, 57c, 184, 187, 249, 250]
Tylosin	16	[26c, 153]	[26c, 251]	[101]	[134]	[57b, 57c, 184, 251]
SF-837	16	[252—254]	[253—256]			[252, 255, 257]
XK-41	14	[258]	[258]			[259]
YC-17	12	[260]	[260]			
YL-704	16	[261—265]	[261, 263, 264]			[265—267]
Polyene macrolides [c]						
Amphotericin B (7)	38	[268] [e], [269]	[270—272]			[270, 273—279]
Azacolutin (7)						[277]
Candicidin (7)			[270]		[280]	[270, 273, 277, 279, 281]
Candidin (7)	38	[282]				
Candihexin (6)						[283, 284]
Candimycin (7)						[273]
Chainin (5)	28	[285]				
Cogomycin (5)	28	[286]				
Dermostatin (6)	36	[287]				
Filipin (5)	28					[281, 288]
Flavofungin (5)	30					[281, 289]
Flavomycin (5)		[290—291]				
Flavomycoin (5)						[281, 289]
Hamycin (7)						[277]
Heptamycin (7)						[277]
Lagosin (5)	28					[281]
Lucensomycin (4)	26	[269, 292]				[281]
Mediocidin (6)						[273, 279]
Mycoheptin (7)			[270]			[270, 277]
Mycotrienin (3)						[281]
Nystatin (4)	38	[293, 269]	[270]			[270, 273, 279, 281]
Perimycin (7)	38	[294]			[295]	[277]
Pimaricin (4)	26	[269, 292]	[270, 296]			[270, 273, 279, 281]
Rimocidin (4)	28	[297]	[297]			[281]
Tetramycin (4)		[298]				[281, 298]
Tetrin (4)	26	[299, 300]				
Trichomycin (7)			[270]			[270, 273, 277, 279]
2814 P (5)						[281]
5001 P (6)						[281]
Ionophoric macrolides						
Boromycin	28	[29b] [e]	[29b]			
Dinactin	32					[301—303]
Isodinactin	32					[304]
Isotrinactin	32					[301—303, 305]

Table 1 (continued).

	Ring size	Structural determination	Structural modification	Total/ partial synthesis	Bio- synthesis	Miscellaneous
Monactin	32					
Nonactin	32	[306—308] [e]		[20, 21, 86, 87, 89]		[301—303, 305, 309—310]
Tetranactin	32	[311] [e]				[303, 312—314]
Trinactin	32					[301—303]
Ansa macrolides						
Colubrinol	19		[315]			
Damavaricin	23		[316, 317]		[316]	[316, 317]
Geldanamycin	19				[318]	
Halomycin B	25	[319]	[320]			
Maytansine	19	[9, 45] [e], [32, 321]	[321, 322]	[108—110, 323]		[32]
Mikamycin B	19					[324]
Naphthomycin	29	[325]				
Protostreptovaricin	23	[326]				
Rifamycin	25	[30a, 327, 332], [328—331] [d]	[30c, 30d, 329, 333—339]	[320]	[30b, 340]	[332—346]
Streptovaricin	23	[347, 349, 350], [348, 351] [e]	[352, 353]	[316]	[354]	[353, 355]
Tolypomycin						[356—360]
Other macrolides						
Aplysiatoxin	14	[361]				
Aspicilin	17	[362]				
Axenomycin	34	[363, 364]				
Brefeldin A	13	[365] [e]		[182]	[366]	[365]
Chlorothricin	14	[367] [e], [368]	[368]			
9-Decanolide	10					[369]
(*Z*)-4-Decen-9-olide	10					[369]
Evorin		[370]	[370]			
11-Hydroxy-5-tetradecen-13-olide	15					[369]
9-Oxotridecanolide	13			[371]		
Macrolidine	14	[372]				
Milbemycin	16	[373]				
Primycin	36	[374—376]				
Pyrenophorin	16	[35b]		[18]		
Roridin	18				[377, 378]	[379, 380]
Trichothecane	18				[381]	
Venturicidine	20	[382] [e]	[382]			
Vermiculine	16	[36a] [e], [36b]		[19]		
Verrucarin	18				[377, 378]	[379, 380]
Vertisporin	18	[383, 384]				
Virginiamycin	23					[385, 386]
Zearalenone	14			[72, 73]		[33]

[a] The "polyoxo" macrolides are listed by family name only. There are thus many more individual compounds than these listed here. For example, there are at least 11 leucomycin variations and 3 spiramycins. Some families have a common aglycone but have various sugars attached which modify their physiological activity. The spiramycins, neospiramycins and the forocidins share a common 16-membered aglycone.—Acumycin, amaromycin, azalomycin, bandamycin, forocidin, griseomycin, macrocin, megacidin, miamycin, neospiramycin, relomycin, sekazin, tertimycin. B-58941 see [12—16]. Ring size: 16 or unknown.

[b] From the point of view of chemical and biological properties, these antibiotics might be intermediate in position between the "polyoxo" and the polyene macrolides.

[c] The figure in brackets following the name of the polyene macrolide is the number of conjugated double bonds present in the aglycone—aurenin (5) (ring size: 24), crytocidin (6), hepcin (7), hexamycin (6), monicamycin (7), Ac_2 435 (4), MM 8 (3), PA 150 (7), PA 153 (5), PA 166 (4), 2814 H (7) see [12—16].

[d] Conformational analysis.

[e] X-Ray analysis.

[f] Sugar part.

this reason it is not a cytotoxic agent[140]. This is in contrast to some other antibiotics with a similar mode of action (*e.g.*, chloramphenicol).

Clinical resistance to erythromycin is fairly common. Several possibilities exist as to its mechanism. In certain cases, mutation leads to a change in the binding constant for the erythromycin/50S ribosome adduct. In others, the erythromycin seems to "induce" an enzyme (an adenine methylase) that introduces a methyl-adenine moiety into the ribosomal RNA and this in turn affects the ability of the antibiotic to bind to the ribosome. No resistant microorganism has shown enzymatic destruction of erythromycin or other macrolides.

7. Concluding Remarks

We believe that the preceding sections have covered most of the significant developments in this area over the past seven years. The number of natural macrolides defined in a broad sense will undoubtedly increase and the emergence of new types of compounds is a distinct possibility. Powerful instrumental techniques are now at our disposal and will help elucidate the structures, configuration, and conformation of newly discovered substances very efficiently and almost automatically. In the field of synthesis, despite recent notable successes, there are important, as yet unsolved problems asso-

ciated with the stereochemistry of macrolide molecules (see Section 5.3). Obviously the biochemistry of macrolide antibiotics is extremely complicated, and understanding biological phenomena at the molecular level requires extensive research. The macrolides, because of their importance to chemistry, biochemistry, and medicine, will continue to attract both academic and practical interest for many years to come.

Since the submission of this paper several other publications in this sector have appeared in the literature. These will be reserved for a future review article.

The authors wish to express their appreciation to M. Aratani, W-K Chan, A. Greiner, Y. Hayase, and R. Sobczak who have aided in the compilation of the references cited in this article and also to those who have made their unpublished results available to us. Two of the authors (SM and GSB) are grateful to the National Research Council of Canada for financial assistance.

Received: March 14, 1977 [A 177 IE]
German version: Angew. Chem. *89*, 602 (1977)

[1] *H. Brockmann, W. Henkel*, Naturwissenschaften *37*, 138 (1950); Chem. Ber. *84*, 284 (1951).
[2] *C. Djerassi, J. A. Zderic*, J. Am. Chem. Soc. *78*, 6390 (1956).
[3] *P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., O. Weaver, U. C. Quarck, R. R. Chauvette, R. Monahan*, J. Am. Chem. Soc. *79*, 6062 (1957).
[4] *P. F. Wiley, M. V. Sigal, Jr., O. Weaver, R. Monahan, K. Gerzon*, J. Am. Chem. Soc. *79*, 6070 (1957).
[5] *R. B. Woodward*, Angew. Chem. *69*, 50 (1957).
[6] A minor structural correction was made. a) *M. E. Kuehne, B. W. Benson*, J. Am. Chem. Soc. *87*, 4660 (1965); b) *R. B. Woodward, L. S. Weiler, P. C. Dutta, ibid. 87*, 4662 (1965).
[7] A propionate unit was missing in the structure proposed for pikromycin by a) *H. Brockmann, R. Oster*, Chem. Ber. *90*, 605 (1957); b) *R. Anliker, K. Gubler*, Helv. Chim. Acta *40*, 119 (1957).
[8] The correct formulation of pikromycin was made by a) *H. Muxfeldt, S. Shrader, P. Hansen, H. Brockmann*, J. Am. Chem. Soc. *90*, 4748 (1968); b) *R. W. Rickards, R. M. Smith, J. Majer*, Chem. Commun. *1968*, 1049.
[9] For example, maytansine isolated from *Maytenus ovatus Loers* is defined as an Ansa macrolide by *S. M. Kupchan, Y. Komada, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, R. F. Bryan*, J. Am. Chem. Soc. *94*, 1354 (1972). However, *Prelog* [10] pointed out "Obwohl die aliphatische Brücke in diesen Verbindungen und in Ansamycinen auf eine biogenetische Verwandtschaft mit Makroliden hinweisen, ist für sie der neuerdings vorgeschlagene gemeinsame Name "ansa-Makrolide" nicht empfehlenswert, da er den falschen Eindruck erweckt, es handle sich um vielgliedrige Lactone."
[10] *V. Prelog, W. Oppolzer*, Helv. Chim. Acta *56*, 2279 (1973).
[11] For instance see: a) *A. Achenbach, W. Karl*, Chem. Ber. *108*, 772 (1975); b) *K. L. Rinehart, Jr., J. C. Cook, Jr., K. H. Maurer, U. Rapp*, J. Antibiot. *27*, 1 (1974); c) *L. A. Mitscher, H. D. H. Showalter, R. L. Foltz, ibid. 26*, 55 (1973).
[12] For 16-membered antibiotics, see *S. Ōmura, A. Nakagawa*, J. Antibiot. *28*, 401 (1975).
[13] *W. Keller-Schierlein*, Fortschr. Chem. Org. Naturst. *30*, 313 (1973).
[14] *W. D. Celmer*, Pure Appl. Chem. *28*, 413 (1971).
[15] *W. Keller-Schierlein, H. Gerlach*, Fortschr. Chem. Org. Naturst. *26*, 161 (1968).
[16] *M. Berry*, Q. Rev. Chem. Soc. *17*, 343 (1963).
[17] a) *S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, G. S. Bates*, J. Am. Chem. Soc. *97*, 3512 (1975); b) *S. Masamune, H. Yamamoto, S. Kamata, A. Fukuzawa, ibid. 97*, 3513 (1975).
[18] *E. W. Colvin, T. A. Purcell, R. A. Raphael*, J. Chem. Soc. Chem. Commun. *1972*, 1031; J. Chem. Soc. Perkin I *1976*, 1718.
[19] *E. J. Corey, K. C. Nicolaou, T. Toru*, J. Am. Chem. Soc. *97*, 2287 (1975).
[20] a) *J. Gombos, E. Haslinger, H. Zak, U. Schmidt*, Tetrahedron Lett. *1975*, 3391; b) *U. Schmidt, J. Gombos, E. Haslinger, H. Zak*, Chem. Ber. *109*, 2628 (1976).
[21] *H. Gerlach, K. Oertle, A. Thalmann, S. Servi*, Helv. Chim. Acta *58*, 2036 (1975).
[22] For syntheses of various sugars, see: a) *J. S. Brimacombe*, Angew. Chem. *83*, 261 (1971); Angew. Chem. Int. Ed. Engl. *10*, 236 (1971); b) *H. Grisebach, R. Schmid*, Angew. Chem. *84*, 192 (1972); Angew. Chem. Int. Ed. Engl. *11*, 159 (1972); c) *H. Paulsen, H. Redlich*, Angew. Chem. *84*, 1100 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1021 (1972).
[23] For instance, see *R. Morin, M. Gorman* in "Kirk-Othmer Encyclopedia of Chemical Technology", Vol. 12, 2nd Ed., Wiley, New York 1967, p. 632.
[24] For instance, see *D. Vazquez* in *J. W. Corcoran, F. E. Hahn*: Antibiotics III. Mechanism of Action of Antimicrobial and Antitumor Agents. Springer, New York 1975, p. 459.
[25] *S. Ōmura, M. Tishler, A. Nakagawa, Y. Hironaka, T. Hata*, J. Med. Chem. *15*, 1011 (1972).
[26] a) *R. B. Morin, M. Gorman*, Tetrahedron Lett. *1964*, 2339; b) *R. B. Morin, M. Gorman, R. L. Hamill, P. V. Demarco, ibid. 1970*, 4737; c) *H. Achenbach, W. Regel, W. Karl*, Chem. Ber. *108*, 2481 (1975).
[27] a) *W. Mechlinski, C. P. Schaffner, P. Ganis, G. Avitabile*, Tetrahedron Lett. *1970*, 3873; b) *E. Borowski, J. Zieliński, T. Ziminski, L. Falkowski, P. Kołodziejczyk, J. Golik, E. Jereczek, H. Adlercreutz, ibid. 1970*, 3909.
[28] a) *H. Gerlach, V. Prelog*, Justus Liebig Ann. Chem. *669*, 121 (1963); b) *J. Dominguez, J. D. Dunitz, H. Gerlach, V. Prelog*, Helv. Chim. Acta *45*, 129 (1962).
[29] a) *J. D. Dunitz, D. M. Hawley, D. Miklos, D. N. J. White, Yu. Berlin, R. Marušić, V. Prelog*, Helv. Chim. Acta *54*, 1709 (1971); b) *W. Marsh, J. D. Dunitz, D. N. J. White, ibid. 57*, 10 (1974).
[30] a) *W. Oppolzer, V. Prelog*, Helv. Chim. Acta *56*, 2287 (1973); b) *M. Brufani, D. Kluepfel, G. C. Lancini, J. Leitich, A. S. Mesentsev, V. Prelog, F. P. Schmook, P. Sensi, ibid. 56*, 2315 (1973); c) *W. Kump, H. Bickel, ibid. 56*, 2323 (1973); d) *W. Kump, H. Bickel, ibid. 56*, 2348 (1973).
[31] *K. L. Rinehart, Jr.*, Acc. Chem. Res. *5*, 57 (1972).
[32] *S. M. Kupchan, Y. Komoda, A. R. Branfman, R. G. Dailey, Jr., V. A. Zimmerly*, J. Am. Chem. Soc. *96*, 3706 (1974).
[33] For a recent review see: a) *M. T. Shipchandler*, Heterocycles *3*, 471 (1975); b) *C. A. Peters, R. N. Hurd*, J. Med. Chem. *18*, 215 (1975).
[34] *H. D. Munro, O. C. Musgrave, P. Templeton*, J. Chem. Soc. *C 1967*, 947; *C. O. Musgrave, ibid. 1956*, 4301.
[35] a) *S. Nozoe, K. Hirai, K. Tsuda, K. Ishibashi, M. Shirasaka, J. F. Grove*, Tetrahedron Lett. *1965*, 4675; b) *J. F. Grove*, J. Chem. Soc. *C 1971*, 2261.
[36] a) *R. K. Boeckman, Jr., J. Fayos, J. Clardy*, J. Am. Chem. Soc. *96*, 5954 (1974); b) *P. Sedmera, J. Vokoun, M. Podojil, Z. Vaněk, J. Fuska, P. Nemec, I. Kuhr*, Tetrahedron Lett. *1973*, 1347.
[37] a) *V. Betina, P. Nemec, Š. Kovač, A. Kjaer, R. H. Shapiro*, Acta Chim. Scand. *19*, 519 (1965); b) *E. Härri, W. Loeffler, H. P. Sigg, H. Stahrlin, Ch. Tamm*, Helv. Chim. Acta *46*, 1235 (1963); c) *V. L. Singleton, N. Bohonos*, Agr. Biol. Chim. (Japan) *28*, 77 (1964); d) X-ray structure analysis: *H. P. Weber, D. Hauser, H. P. Sigg*, Helv. Chim. Acta *54*, 2763 (1971).
[38] *M. Binder, Ch. Tamm*, Angew. Chem. *85*, 369 (1973); Angew. Chem. Int. Ed. Engl. *12*, 370 (1973).
[39] a) *S. B. Carter*, Endeavour *113*, 77 (1972); b) *S. B. Carter*, Nature *213*, 261 (1967); c) Aldrich Chemical Company, Technical Information on The Cytochalasans, January 1975, quotes several references concerning the biological activity of these compounds.
[40] *J. L. Robert, Ch. Tamm*, Helv. Chim. Acta *58*, 2501 (1975).
[41] *M. Hiramatsu, A. Furusaki, T. Noda, K. Naya, Y. Tomiie, I. Nitta, T. Watanabe, T. Take, J. Abe, S. Ōmura, T. Hata*, Bull. Chem. Soc. Jpn. *43*, 1966 (1970).
[42] *A. Ducruix, C. Pascard, A. Nakagawa, S. Ōmura*, J. Chem. Soc. Chem. Commun. *1976*, 947.
[43] Also see *L. A. Freiberg, R. S. Egan, W. H. Washburn*, J. Org. Chem. *39*, 2474 (1974).
[44] An X-ray structure analysis is in progress.
[45] *R. F. Bryan, Ch. J. Gilmore, R. C. Haltiwanger*, J. Chem. Soc. Perkin II *1973*, 897.
[46] For a summary of the work up to 1971, see ref. [14] of this review.
[47] a) *J. Dale*, J. Chem. Soc. *1963*, 93; b) *J. D. Dunitz, E. F. Mayer, Jr.*, Helv. Chim. Acta *48*, 1441 (1965); c) *M. Saunders*, Tetrahedron *23*, 2105 (1967).
[48] *W. D. Celmer*, Antimicrob. Agents Chemother. *1965*, 144.
[49] *D. R. Harris, S. G. McGeachin, H. H. Mills*, Tetrahedron Lett. *1965*, 679.
[50] a) *T. J. Perun, R. S. Egan*, Tetrahedron Lett. *1969*, 387; b) *T. J. Perun, R. S. Egan, P. H. Jones, J. R. Martin, L. A. Mitscher, B. J. Slater*, Antimicrob. Agents Chemother. *1969*, 116.
[51] *R. S. Egan, T. J. Perun, J. R. Martin, L. A. Mitscher*, Tetrahedron *29*, 2525 (1973).
[52] *J. G. Nourse, J. D. Roberts*, J. Am. Chem. Soc. *97*, 4584 (1975). It is our view that the C(11)—OH and C(1)=O are a little too far apart to be strongly hydrogen-bonded.

[53] a) *Y. Terui, K. Tori, K. Nagashima, N. Tsuji*, Tetrahedron Lett. *1975*, 2583; b) *S. Ōmura, A. Neszmélyi, M. Sangaré, G. Lukacs, ibid. 1975*, 2939.

[54] *R. S. Egan, J. R. Martin, T. J. Perun, L. A. Mitscher*, J. Am. Chem. Soc. 97, 4578 (1975).

[55] *H. Ogura, K. Furuhata, H. Kuwano, N. Harada*, J. Am. Chem. Soc. 97, 1930 (1975).

[56] *C. Tsai, J. J. Stezowski, R. E. Hughes*, J. Am. Chem. Soc. *93*, 7286 (1971).

[57] a) *S. Ōmura, A. Nakagawa, N. Yagisawa, Y. Suzuki, T. Hata*, Tetrahedron *28*, 2839 (1972); *S. Ōmura, A. Nakagawa, A. Neszmélyi, S. D. Gero, A.-M. Sepulchre, F. Piriou, G. Lukacs*, J. Am. Chem. Soc. *97*, 4001 (1975); c) *A. Neszmélyi, S. Ōmura, G. Lukacs*, J. Chem. Soc. Chem. Commun. *1976*, 97.

[58] a) *I. J. Borowitz, G. Gonis*, Tetrahedron Lett. *1964*, 1151; b) *I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, G. J. Williams*, J. Org. Chem. *31*, 3032 (1966); c) *I. J. Borowitz, R. D. Rapp, ibid. 34*, 1370 (1969).

[59] *I. J. Borowitz, G. J. Williams, L. Gross, R. D. Rapp*, J. Org. Chem. *33*, 2013 (1968). For other ring systems, see: *I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, S. Ueng, ibid. 38*, 1234 (1973).

[60] *I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, R. D. G. Rigby*, J. Org. Chem. *37*, 581 (1972).

[61] *J. F. Bagli, H. Immer*, Can. J. Chem. *46*, 3115 (1968).

[62] a) *J. R. Mahajan, H. C. Araújo*, Synthesis *1975*, 54; b) *J. R. Mahajan, H. C. Araújo, ibid. 1976*, 111.

[63] *J. R. Mahajan*, Synthesis *1976*, 110.

[64] *E. Vedejs, J. P. Hagen*, J. Am. Chem. Soc. *97*, 6878 (1975).

[65] a) *F. M. Dean, B. K. Park*, J. Chem. Soc. Chem. Commun. *1975*, 142; b) *R. Clinging, F. M. Dean, L. E. Houghton*, J. Chem. Soc. *C 1970*, 897.

[66] *E. J. Corey, H. A. Kirst*, J. Am. Chem. Soc. *94*, 667 (1972).

[67] a) *E. J. Corey, E. Hamanaka*, J. Am. Chem. Soc. *86*, 1641 (1964); b) *E. J. Corey, E. Hamanaka, ibid. 89*, 2758 (1967).

[68] *W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. P. Peppard, P. Pesnelle, C. Suter*, J. Am. Chem. Soc. *97*, 4973 (1975).

[69] *K. E. Wilson*, Ph. D. Thesis, University of Alberta 1973.

[70] a) *M. Stoll, A. Rouvé, G. Stoll-Comte*, Helv. Chim. Acta *17*, 1289 (1934); b) *M. Stoll, A. Rouvé, ibid. 18*, 1087 (1935); c) *M. Sisido*, Macromolecules *4*, 737 (1971).

[71] *C. Galli, L. Mandolini*, Gazz. Chim. Ital. *105*, 367 (1975).

[72] *S. Masamune, S. Kamata, W. Schilling*, J. Am. Chem. Soc. *97*, 3515 (1975).

[73] *E. J. Corey, K. C. Nicolaou*, J. Am. Chem. Soc. *96*, 5614 (1974).

[74] a) *T. Mukaiyama, R. Matsueda, H. Maruyama*, Bull. Chem. Soc. Jpn. *43*, 1271 (1970); b) *T. Mukaiyama*, Synth. Commun. *2*, 243 (1972).

[75] Pyridine-2-thiol esters were first used for the amide formation by *K. Lloyd, G. T. Young*, J. Chem. Soc. Chem. Commun. *1968*, 1400; J. Chem. Soc. *C 1971*, 2890.

[76] *H. Gerlach, A. Thalmann*, Helv. Chim. Acta *57*, 2661 (1974).

[77] a) *D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, N. L. Wendler*, Tetrahedron *24*, 2443 (1968); b) *I. Vlattas, I. T. Harrison, L. Tökés, J. H. Fried, A. D. Cross*, J. Org. Chem. *33*, 4176 (1968).

[78] *L. D. Bergel'son, E. V. Dyatlovitskaya, M. Tichy, V. V. Voronkova*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 1612.

[79] *L. G. Cannell*, Tetrahedron Lett. *1966*, 5967.

[80] a) *S. Masamune, P. A. Rossy, G. S. Bates*, J. Am. Chem. Soc. *95*, 6452 (1973); b) *S. Masamune, G. S. Bates, P. E. Georghiou, ibid. 96*, 3686 (1974); *E. C. Ashby, T. F. Korenowski, R. D. Schwartz*, J. Chem. Soc. Chem. Commun. *1974*, 157.

[81] *R. Anliker, D. Dvornik, K. Gubler, H. Heusser, V. Prelog*, Helv. Chim. Acta *39*, 1785 (1956).

[82] *Y. Pocker, E. Green*, J. Am. Chem. Soc. *98*, 6197 (1976), *96*, 166 (1974), *95*, 113 (1973) and references quoted therein.

[83] *H. A. Staab, H. Bräunling*, Justus Liebigs Ann. Chem. *654*, 119 (1962).

[84] *H. A. Staab, N. Sommer*, Angew. Chem. *74*, 294 (1962); Angew. Chem. Int. Ed. Engl. *1*, 270 (1962).

[85] *E. J. Corey, A. Venkateswarlu*, J. Am. Chem. Soc. *94*, 6190 (1972).

[86] *G. Beck, E. Henseleit*, Chem. Ber. *104*, 21 (1971).

[87] *H. Gerlach, H. Wetter*, Helv. Chim. Acta *57*, 2306 (1974).

[88] *S. Shatzmiller, P. Gygax, D. Hall, A. Eschenmoser*, Helv. Chim. Acta *56*, 2961 (1973).

[89] *M. J. Arco, M. H. Trammell, J. D. White*, J. Org. Chem. *41*, 2075 (1976).

[90] a) *J. Gombos, E. Haslinger, H. Zak, U. Schmidt*, Monatsh. Chem. *106*, 109 (1975); b) *H. Zak, U. Schmidt*, Angew. Chem. *87*, 454 (1975); Angew. Chem. Int. Ed. Engl. *14*, 432 (1975); c) *J. Gombos, E. Haslinger, A. Nikiforov, H. Zak, U. Schmidt*, Monatsh. Chem. *106*, 1043 (1975).

[91] For some selectivity, see [90c].

[92] *A. W. Miller, C. J. M. Stirling*, J. Chem. Soc. *C 1968*, 2612.

[93] *S. Masamune, N. Nakamura, J. Spadaro*, J. Am. Chem. Soc. *97*, 918 (1975).

[94] *H. A. Staab, A. Mannschreck*, Chem. Ber. *95*, 1284 (1962).

[95] *S. Masamune, W. Schilling, Y. Hayase*, unpublished results.

[96] Synthesis of 2-benzothiazole thioesters: *S. Masamune, W. K. Chan, Y. Sugihara*, unpublished results.

[97] *H. O. House:* Modern Synthetic Reactions. 2nd Ed. W. A. Benjamin, Menlo Park, Calif., 1972. Chap. 7.

[98] Syntheses: (1) Reaction of cyclohexanecarboxylic acid with either C_6H_5SeCl or diphenyl diselenide in the presence of tri-*n*-octylphosphane; (2) reaction of cyclohexanecarboxylic acid chloride or imidazolide with C_6H_5SeOTl or C_4H_9SeOTl; (3) reaction of cyclohexanecarboxylic acid diethylphosphoric acid anhydride with one of the above thallium(I) salts.

[99] *S. Masamune, S. Kamata, J. Diakur, Y. Sugihara, G. S. Bates*, Can. J. Chem. *53*, 3693 (1975).

[100] *G. S. Bates, J. Diakur, S. Masamune*, Tetrahedron Lett. *1976*, 4423.

[101] *S. Masamune, Y. Hayase, W. K. Chan, R. L. Sobczak*, J. Am. Chem. Soc. *98*, 7874 (1976).

[102] *E. J. Corey, D. J. Brunelle, P. J. Stork*, Tetrahedron Lett. *1976*, 3405.

[103] a) *E. J. Corey, K. C. Nicolaou, L. S. Melvin, Jr.*, J. Am. Chem. Soc. *97*, 653, 654 (1975); b) *E. J. Corey, P. Ulrich, J. M. Fitzpatrick, ibid. 98*, 222 (1976).

[104] *E. J. Corey, D. J. Brunelle*, Tetrahedron Lett. *1976*, 3409.

[105] *T. Kurihara, Y. Nakajima, O. Mitsunobu*, Tetrahedron Lett. *1976*, 2455.

[106] *T. Mukaiyama, M. Usui, K. Saigo*, Chem. Lett. (Japan) *1976*, 49.

[107] *J. D. White, S. N. Lodwig, G. L. Trammell, M. P. Fleming*, Tetrahedron Lett. *1974*, 3263.

[108] a) *A. I. Meyers, C. C. Shaw*, Tetrahedron Lett. *1974*, 717; b) *A. I. Meyers, C. C. Shaw, D. Horne, L. M. Trefonas, R. J. Majeste, ibid. 1975*, 1745.

[109] *A. I. Meyers, R. S. Brinkmeyer*, Tetrahedron Lett. *1975*, 1749.

[110] *E. J. Corey, M. G. Bock*, Tetrahedron Lett. *1975*, 2643.

[111] *S. Hanessian, G. Rancourt*, Can. J. Chem., in press. Also see *M. Miljković, Dj. Glišin*, J. Org. Chem. *40*, 3357 (1975) and references quoted therein.

[112] *J. W. Corcoran, M. Chick* in *J. F. Snell:* Biosynthesis of Antibiotics. Academic Press, New York 1966, p. 149.

[113] *Z. Vanek, J. Majer* in *D. Gottlieb, P. D. Shaw:* Antibiotics. II. Biosynthesis. Springer, Berlin 1967, p. 154.

[114] *J. R. Martin, A. W. Goldstein:* Progress in Antimicrobial and Anticancer Chemotherapy. Vol. 2. University Park Press, Baltimore 1970, p. 1112.

[115] *J. G. Nourse*, Ph. D. Thesis, University of California, Los Angeles 1974.

[116] *J. B. McAlpine, J. R. Martin, J. G. Nourse, J. D. Roberts, J. W. Corcoran*, unpublished results.

[117] *J. R. Martin, W. Rosenbrook*, Biochemistry *5*, 2852 (1966).

[118] *J. R. Martin, T. J. Perun, R. L. Girolomi*, Biochemistry *6*, 435 (1967).

[119] *A. M. Vygantas, J. W. Corcoran*, Fed. Proc. *33*, 1233 (1974).

[120] *J. Majer, J. R. Martin, J. W. Corcoran*, 14th Interscience Conference on Antimicrob. Agents and Chemotherapy, Abstract 200, Sept. 1974, San Francisco.

[121] *J. W. Corcoran, J. Majer*, Fed. Proc. *34*, 589 (1975).

[122] *J. Majer, J. R. Martin, R. S. Egan, J. W. Corcoran*, J. Am. Chem. Soc., in press.

[123] *A. M. Vygantas, J. W. Corcoran*, unpublished results.

[124] *J. W. Corcoran* in *J. H. Hash:* Methods in Enzymology. Vol. 63. Academic Press, New York 1975, p. 487.

[125] *T. S. McAlpine, J. W. Corcoran*, Fed. Proc. *30*, 1168 (1971).

[126] *J. R. Martin, R. S. Egan, A. W. Goldstein, P. Collum*, Tetrahedron *31*, 1985 (1975).

[127] *J. R. Martin*, unpublished results.

[128] *J. B. McAlpine, J. R. Martin*, unpublished results.

[129] *R. A. LeMahieu, H. A. Ax, J. F. Blount, M. Carson, W. Despreaux, D. L. Pruess, P. Scannell, F. Weiss, R. W. Kierstead*, J. Antibiot. *29*, 728 (1976).

[130] *I. Maezaqa, A. Kinumaki, M. Suzuki*, J. Antibiot. *29*, 1203 (1976).

[131] *P. Collum, R. S. Egan, A. W. Goldstein, J. R. Martin*, Tetrahedron *32*, 2375 (1976).

[132] *J. Majer, J. B. McAlpine, R. S. Egan, J. W. Corcoran*, J. Antibiot. *29*, 769 (1976).

[133] *S. E. DeVoe, H. B. Renfroe, W. K. Hausmann*, Antimicrob. Agents Chemother. *1964*, 125.

[134] *S. Ōmura, A. Nakagawa, H. Takeshima, J. Miyazawa, C. Kitao, F. Piriou, G. Lukacs*, Tetrahedron Lett. *1975*, 4503.

[135] *A. K. Ganguly, B. K. Lee, R. Brambilla, R. Condon, O. Sarre*, J. Antibiot. *29*, 976 (1976).

[136] *S. Ōmura, A. Nakagawa, H. Takeshima, K. Atusmi, H. Miyazawa, F. Pirious, G. Lukacs*, J. Am. Chem. Soc. *97*, 6600 (1975).

[137] *T. Furumai, M. Suzuki*, J. Antibiot. *28*, 783 (1975).

[138] *T. Furumai, K. Takeda, M. Suzuki*, J. Antibiot. *28*, 789 (1975).

[139] *J. W. Corcoran* in *S. Mitsuhashi:* Drug Action and Drug Resistance in Bacteria. University Park Press, Baltimore 1971, p. 177.

[140] *N. L. Oleinick* in *J. W. Corcoran, F. E. Hahn:* Antibiotics IV. Mechanism of Action of Antimicrobial and Antitumor Agents. Springer, New York 1975, p. 396.

[141] *J. M. Wilhelm, N. L. Oleinick, J. W. Corcoran*, Antimicrob. Agents Chemother. *1968*, 236.
[142] *S. Pestka, A. Nakagawa, S. Ōmura*, Antimicrob. Agents Chemother. *1974*, 606.
[143] *S. Pestka, R. A. LeMahieu, P. Miller*, Antimicrob. Agents Chemother. *1974*, 489.
[144] *S. Pestka, R. A. LeMahieu*, Antimicrob. Agents Chemother. *1974*, 479.
[145] *K. L. Arora, J. Majer, M. R. Chevallier, J. W. Corcoran*, 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City 1971.
[146] *N. L. Oleinick, J. W. Corcoran*: Progress in Antimicrobial and Anticancer Chemotherapy. Vol. 1, University of Tokyo Press, Tokyo 1970, p. 202.
[147] *N. Nagahama, I. Takamori, K. Kotera, M. Suzuki*, Chem. Pharm. Bull. (Tokyo) *19*, 649 (1971).
[148] *N. Nagahama, I. Takamori, M. Suzuki*, Chem. Pharm. Bull. (Tokyo) *19*, 655 (1971).
[149] *N. Nagahama, I. Takamori, M. Suzuki*, Chem. Pharm. Bull. (Tokyo) *19*, 660 (1971).
[150] *H. Achenbach, W. Karl*, Chem. Ber. *108*, 780 (1975).
[151] *H. Achenbach, W. Karl*, Chem. Ber. *108*, 759 (1975).
[152] *H. Paulsen, B. Sumfleth, H. Redlich*, Chem. Ber. *109*, 1362 (1976).
[153] *A. Kinumaki, M. Suzuki*, J. Antibiot. *25*, 480 (1972).
[154] *S. Rakhit, K. Singh*, J. Antibiot. *27*, 221 (1974).
[155] *R. A. LeMahieu, J. F. Blount, R. W. Kierstead*, J. Antibiot. *28*, 705 (1975).
[156] *A. Hempel, M. Bogucka-Ledochowska, Z. Dauter, E. Borowski, Z. Kosturkiewicz, A. Michniewicz*, Tetrahedron Lett. *1975*, 1599.
[157] *E. J. Corey, L. S. Melvin, Jr.*, Tetrahedron Lett. *1975*, 929.
[158] *J. R. Martin, T. J. Perun, R. S. Egan*, Tetrahedron *28*, 2937 (1972).
[159] *J. R. Martin, R. S. Egan, T. J. Perun, W. Goldstein*, Tetrahedron *29*, 935 (1973).
[160] *P. H. Jones, T. J. Perun, E. K. Rowley, E. J. Baker*, J. Med. Chem. *15*, 631 (1972).
[161] *H. Bojarska-Dahlig, W. Sławinski, D. Roslik-Kaminska, A. Schaeffer, A. Sipak-Krzysiak, E. Dzilinski, I. Skibinska, T. Prussak-Wieckowska, W. Kotula, R. Kadłubowski, A. Kurnatowska*, J. Antibiot. *29*, 907 (1976).
[162] *R. A. LeMahieu, M. Carson, R. W. Kierstead, L. M. Fern, E. Grunberg*, J. Med. Chem. *17*, 953 (1974).
[163] *E. J. Corey, L. S. Melvin, Jr., M. F. Haslanger*, Tetrahedron Lett. *1975*, 3117.
[164] *P. Kurath, J. R. Martin, J. Tadanier, A. W. Goldstein, R. S. Egan, D. A. Dunnigan*, Helv. Chim. Acta *56*, 1557 (1973).
[165] *J. Tadanier, P. Kurath, J. R. Martin, J. B. McAlpine, R. S. Egan, A. W. Goldstein, S. L. Mueller, D. A. Dunnigan*, Helv. Chim. Acta *56*, 2711 (1973).
[166] *J. Tadanier, J. R. Martin, R. S. Egan, A. Goldstein, E. Hirner, F. Fischer*, J. Am. Chem. Soc. *95*, 592 (1973).
[167] *J. Tadanier, J. R. Martin, R. S. Egan, A. Goldstein, R. Stanaszek, E. Hirner, F. Fischer*, J. Am. Chem. Soc. *95*, 593 (1973).
[168] *T. J. Perun, J. R. Martin, R. S. Egan*, J. Org. Chem. *39*, 1490 (1974).
[169] *R. S. Egan, L. A. Freiberg, W. H. Washburn*, J. Org. Chem. *39*, 2492 (1974).
[170] *J. Tadanier, J. R. Martin, R. S. Egan, A. W. Goldstein, R. S. Stanaszek, E. Hirner, F. Fischer*, J. Org. Chem. *39*, 2495 (1974).
[171] *P. Kurath, R. S. Egan*, Helv. Chim. Acta *54*, 523 (1971).
[172] *R. Fernandez-Munoz*, J. Antibiot. *26*, 107 (1973).
[173] *E. H. Massey, B. S. Kitchell, L. D. Martin, K. Gerzon*, J. Med. Chem. *17*, 105 (1974).
[174] *K. Krowicki*, J. Antibiot. *27*, 626 (1974).
[175] *K. Krowicki, A. Zamojski*, J. Antibiot. *26*, 569 (1973).
[176] *K. Krowicki, A. Zamojski*, J. Antibiot. *26*, 575 (1973).
[177] *K. Krowicki, A. Zamojski*, J. Antibiot. *26*, 582 (1973).
[178] *K. Krowicki, A. Zamojski*, J. Antibiot. *26*, 587 (1973).
[179] *R. Ryden, G. H. Timms, D. M. Prime, E. Wildsmith*, J. Med. Chem. *16*, 1059 (1973).
[180] *G. H. Timms, E. Wildsmith*, Tetrahedron Lett. *1971*, 195.
[181] *E. Wildsmith*, Tetrahedron Lett. *1972*, 29.
[182] *E. J. Corey, K. C. Nicolaou, L. S. Melvin, Jr.*, J. Am. Chem. Soc. *97*, 654 (1975).
[183] *H. Otaya, S. Okamoto, E. Inoue, Y. Adachi, S. Machihara, M. Yoshimura*, J. Antibiot. *24*, 155 (1971).
[184] *M. Ogata, H. Atobe, H. Kushida, K. Yamamoto*, J. Antibiot. *24*, 443 (1971).
[185] *M. C. Flickinger, D. Perlman*, J. Antibiot. *28*, 307 (1975).
[186] *K. Ubukata, M. Konno, R. Fujii*, J. Antibiot. *28*, 681 (1975).
[187] *E. Kitanaka, K. Ochiai, Y. Hamasu, M. Nakao, S. Nakazawa*, J. Antibiot. *25*, 679 (1972).
[188] *S. Ōmura, Y. Hisonaka, A. Nakagawa, I. Umezawa, T. Hata*, J. Antibiot. *25*, 105 (1972).
[189] *J. A. Yurchenco, M. W. Hopper, T. D. Vince, G. H. Warren*, J. Antibiot. *29*, 460 (1976).
[190] *K. Wakabayashi, S. Kamei*, J. Antibiot. *27*, 729 (1974).
[191] *H. Otaya, S. Machihara*, J. Antibiot. *26*, 84 (1973).
[192] *L. A. Mitscher, H. D. H. Showalter*, J. Chem. Soc. Chem. Commun. *1972*, 796.
[193] *T. Nishino, S. Nakazawa*, J. Antibiot. *26*, 362 (1973).
[194] *H. Teraoka*, J. Antibiot. *24*, 302 (1971).
[195] *I. Machida, S. Shiotsu, K. Yokota, T. Kawanaka, K. Honda*, 178th Scientific Meeting of the Japanese Antibiotic Research Assoc., Tokyo 1971.
[196] *K. Nakahama, T. Kishi, S. Igarasi*, J. Antibiot. *27*, 433 (1974).
[197] *T. Osono, K. Moriyama, M. Murakami*, J. Antibiot. *27*, 366 (1974).
[198] *S. Ōmura, S. Namiki, M. Shibata, T. Muro, S. Machida*, J. Antibiot. *24*, 717 (1971).
[199] *J. Sawada, S. Namiki, M. Onodera, S. Ōmura, I. Tanaka*, J. Antibiot. *27*, 639 (1974).
[200] *S. Harada, T. Kishi*, Chem. Pharm. Bull. (Tokyo) *22*, 99 (1974).
[201] *S. Harada*, Chem. Pharm. Bull. (Tokyo) *23*, 2201 (1975).
[202] *K. Hatano, S. Harada, T. Kishi*, J. Antibiot. *28*, 15 (1975).
[203] *S. Harada, S. Tanayama, T. Kishi*, J. Antibiot. *26*, 658 (1973).
[204] *S. Harada, T. Yamazaki, K. Hatano, K. Tsuchiya, T. Kishi*, J. Antibiot. *26*, 647 (1973).
[205] *K. Nakahama, S. Harada, S. Igarasi*, J. Antibiot. *28*, 390 (1975).
[206] *E. Higashide, T. Fugono, K. Hatano, M. Shibata*, J. Antibiot. *24*, 1 (1971).
[207] *T. Fugono, S. Harada, E. Higashide, T. Kishi*, J. Antibiot. *24*, 23 (1971).
[208] *S. Harada, T. Kishi, K. Mizuno*, J. Antibiot. *24*, 13 (1971).
[209] *K. Tsuchiya, T. Yamazaki, Y. Takeuchi, T. Oishi*, J. Antibiot. *24*, 29 (1971).
[210] *J. R. Martin, R. S. Egan, A. W. Goldstein, S. L. Mueller, W. Keller-Schierlein, L. A. Mitscher, R. L. Foltz*, Helv. Chim. Acta *59*, 1886 (1976).
[211] *R. Muntwyler, W. Keller-Schierlein*, Helv. Chim. Acta *55*, 460 (1972).
[212] *S. Ōmura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakubowski, M. Tishler*, J. Antibiot. *27*, 147 (1974).
[213] *N. N. Girotra, A. A. Patchett, N. L. Wendler*, Tetrahedron *32*, 991 (1976).
[214] *N. N. Girotra, N. L. Wendler*, Tetrahedron Lett. *1975*, 227.
[215] *S. Ōmura, A. Nakagawa, K. Suzuki, T. Hata*, J. Antibiot. *27*, 370 (1974).
[216] *A. Nakagawa, K. Suzuki, K. Iwasaki, K. Kaji, S. Ōmura, A. Jakubowski, M. Tishler*, Chem. Pharm. Bull. (Tokyo) *24*, 1749 (1976).
[217] *Y. Balducci, G. P. Boday*, J. Antibiot. *27*, 516 (1974).
[218] *S. Ōmura, Y. Suzuki, A. Nakagawa, T. Hata*, J. Antibiot. *26*, 794 (1973).
[219] *M. Muroi, M. Izawa, M. Asai, T. Kishi, K. Mizuno*, J. Antibiot. *26*, 199 (1973).
[220] *M. Muroi, M. Izawa, T. Kishi*, Chem. Pharm. Bull. (Tokyo) *24*, 450 (1976).
[221] *M. Muroi, M. Izawa, T. Kishi*, Chem. Pharm. Bull. (Tokyo) *24*, 463 (1976).
[222] *H. Ono, S. Harada, T. Kishi*, J. Antibiot. *27*, 442 (1974).
[223] *K. Nakahama, T. Kishi, S. Igarasi*, J. Antibiot. *27*, 487 (1974).
[224] *K. Nakahama, S. Igarasi*, J. Antibiot. *27*, 605 (1974).
[225] *K. Nakahama, M. Izawa, M. Muroi, T. Kishi, M. Uchida, S. Igarasi*, J. Antibiot. *27*, 425 (1974).
[226] *N. Kunishige, K. Kawamura, M. Muroi, T. Kishi*, Chem. Pharm. Bull. (Tokyo) *23*, 3075 (1975).
[227] *M. Shibata, M. Uyeda, S. Mori*, J. Antibiot. *29*, 824 (1976).
[228] *M. Shibata, M. Uyeda, S. Mori*, J. Antibiot. *28*, 434 (1975).
[229] *H. Ono, T. Hasegawa, E. Higashide, M. Shibata*, J. Antibiot. *26*, 191 (1973).
[230] *M. Kondo, T. Oishi, K. Ishifuji*, J. Antibiot. *26*, 206 (1973).
[231] *M. Muroi, M. Izawa, T. Kishi*, J. Antibiot. *27*, 449 (1974).
[232] *R. S. Jaret, A. K. Mallams, H. F. Vernay*, J. Chem. Soc. Perkin I *1973*, 1389.
[233] *R. S. Jaret, A. K. Mallams, H. Reimann*, J. Chem. Soc. Perkin I *1973*, 1374.
[234] *A. K. Mallams*, J. Chem. Soc. Perkin I *1973*, 1369.
[235] *T. Saito, S. Mitsuhashi*, J. Antibiot. *24*, 850 (1971).
[236] *J. A. Waitz, E. L. Moss, Jr., E. M. Oden, M. J. Weinstein*, J. Antibiot. *24*, 310 (1971).
[237] *I. Maezawa, A. Kinumaki, M. Suzuki*, J. Antibiot. *27*, 84 (1974).
[238] *S. Omoto, K. Iwamatsu, S. Inouye, T. Niida*, J. Antibiot. *29*, 536 (1976).
[239] *I. Maezawa, T. Hori, A. Kinumaki, M. Suzuki*, J. Antibiot. *26*, 771 (1973).
[240] *J. R. Martin, R. S. Egan, A. W. Goldstein, S. L. Mueller, S. A. Hirner, R. S. Stanaszek*, J. Antibiot. *27*, 570 (1974).
[241] *H. Ogura, K. Furuhata, H. Kuwane*, Tetrahedron Lett. *1971*, 4715.
[242] *S. Ōmura, H. Takeshima, A. Nakagawa, J. Miyazawa*, J. Antibiot. *29*, 316 (1976).
[243] *T. Furumai, M. Suzuki*, J. Antibiot. *28*, 775 (1975).
[244] *T. Furumai, M. Suzuki*, J. Antibiot. *28*, 770 (1975).
[245] *T. Furumai, Y. Seki, K. Takeda, A. Kinumaki, M. Suzuki*, J. Antibiot. *26*, 708 (1973).
[246] *H. Reimann, R. S. Jaret*, Chem. Commun. *1970*, 1270.

[247] *J. A. Waitz, C. G. Drube, E. L. Moss, Jr., M. J. Weinstein*, J. Antibiot. *25*, 647 (1972).
[248] *G. H. Wagman, J. A. Waitz, J. Marquez, A. Murawski, E. M. Oden, R. T. Testa, M. J. Weinstein*, J. Antibiot. *25*, 641 (1972).
[249] *M. Nakao, E. Kitanaka, K. Ochiai, S. Nakazawa*, J. Antibiot. *25*, 60 (1972).
[250] *M. Nakao, S. Nakazawa*, J. Antibiot. *27*, 970 (1974).
[251] *J. M. Wal, G. F. Bories*, J. Antibiot. *26*, 687 (1973).
[252] *T. Niida, T. Tsuruoka, N. Ezaki, T. Shomura, E. Akita, S. Inouye*, J. Antibiot. *24*, 319 (1971).
[253] *T. Tsuruoka, S. Inouye, T. Shomura, N. Ezaki, T. Niida*, J. Antibiot. *24*, 526 (1971).
[254] *S. Inouye, T. Tsuruoka, T. Shomura, S. Omoto, T. Niida*, J. Antibiot. *24*, 460 (1971).
[255] *T. Tsuruoka, N. Ezaki, T. Shomura, S. Amano, S. Inouye, T. Niida*, J. Antibiot. *24*, 476 (1971).
[256] *S. Inouye, T. Shomura, T. Tsuruoka, S. Omoto, T. Niida, K. Umemura*, Chem. Pharm. Bull. (Tokyo) *20*, 2366 (1972).
[257] *T. Tsuruoka, T. Shomura, N. Ezaki, H. Watanabe, E. Akita, S. Inouye, T. Niida*, J. Antibiot. *24*, 452 (1971).
[258] *R. S. Egan, S. L. Mueller, L. A. Mitscher, I. Kawamoto, R. Okachi, H. Kato, S. Yamamoto, S. Takasuwa, T. Nara*, J. Antibiot. *27*, 544 (1974).
[259] *I. Kawamoto, R. Okachi, H. Kato, S. Yamamoto, I. Takahashi, S. Takasawa, T. Nara*, J. Antibiot. *27*, 493 (1974).
[260] *A. Kinumaki, M. Suzuki*, J. Chem. Soc. Chem. Commun. *1972*, 744.
[261] *M. Suzuki, I. Takamori, A. Kinumaki, Y. Sugawara, T. Okuda*, Tetrahedron Lett. *1971*, 435.
[262] *M. Suzuki, I. Takamori, A. Kinumaki, Y. Sugawara, T. Okuda*, J. Antibiot. *24*, 904 (1971).
[263] *A. Kinumaki, I. Takamori, Y. Sugawara, M. Suzuki, T. Okuda*, J. Antibiot. *27*, 107 (1974).
[264] *A. Kinumaki, I. Takamori, Y. Sugawara, Y. Seki, M. Suzuki, T. Okuda*, J. Antibiot. *27*, 117 (1974).
[265] *M. Suzuki, I. Takamori, A. Kinumaki, Y. Sugawara, T. Okuda*, Tetrahedron Lett. *1971*, 435.
[266] *A. Kinumaki, I. Takamori, Y. Sugawara, N. Nagahama, M. Suzuki, Y. Egawa, M. Sakurazawa, T. Okuda*, J. Antibiot. *27*, 102 (1974).
[267] *T. Furumai, Y. Shimizu, K. Takeda, N. Matsuzawa, K. Tani, T. Okuda*, J. Antibiot. *27*, 95 (1974).
[268] *P. Ganis, G. Avitabile, W. Mechlinski, C. P. Schaffner*, J. Am. Chem. Soc. *93*, 4560 (1971).
[269] *C. N. Chong, R. W. Richards*, Tetrahedron Lett. *1972*, 5053.
[270] *L. Falkowski, J. Golik, P. Kotodziejczyk, J. Pawlak, J. Zielinski, T. Ziminski, E. Borowski*, J. Antibiot. *28*, 244 (1975).
[271] *N. Monji, W. Mechlinski, C. P. Schaffner*, J. Antibiot. *29*, 438 (1976).
[272] *W. Mechlinski, C. P. Schaffner*, J. Antibiot. *25*, 256 (1972).
[273] *D. P. Bonner, W. Mechlinski, C. P. Schaffner*, J. Antibiot. *25*, 261 (1972).
[274] *W. Monji, D. P. Bonner, Y. Hashimoto, C. P. Schaffner*, J. Antibiot. *28*, 317 (1975).
[275] *D. P. Bonner, W. Mechlinski, C. P. Schaffner*, J. Antibiot. *28*, 132 (1975).
[276] *N. I. Goldstein, A. H. McIntosh, P. B. Fisher, K. Maramorosch, C. P. Schaffner*, J. Antibiot. *29*, 656 (1976).
[277] *F. E. Pansy, W. P. Jambor, J. Wilber-Murphy, H. H. Gadebusch*, J. Antibiot. *25*, 405 (1972).
[278] *H. A. B. Linke, W. Mechlinski, C. P. Schaffner*, J. Antibiot. *27*, 155 (1974).
[279] *C. P. Schaffner, W. Mechlinski*, J. Antibiot. *25*, 259 (1972).
[280] *C. M. Liu, L. E. McDaniel, C. P. Schaffner*, J. Antibiot. *25*, 116 (1972).
[281] *I. Haupt, E. Schuhmann, R. Geuther, H. Thrum*, J. Antibiot. *29*, 44 (1976).
[282] *E. Borowski, L. Falkowski, J. Golik, J. Zielinski, T. Ziminski, W. Mechlinski, E. Jereczek, P. Kotodziejczyk, H. Adlercreutz, C. P. Schaffner, S. Neelakantan*, Tetrahedron Lett. *1971*, 1987.
[283] *J. F. Martin, L. E. McDaniel*, J. Antibiot. *27*, 610 (1974).
[284] *L. E. McDaniel*, J. Antibiot. *29*, 195 (1976).
[285] *R. C. Pandey, N. Narasimhachari, K. L. Rinehart, Jr., D. S. Millington*, J. Am. Chem. Soc. *94*, 4306 (1972).
[286] *V. Pozsgay, J. Tamas, G. Czira, T. Wirthlin, A. Levai*, J. Antibiot. *29*, 472 (1976).
[287] *R. C. Pandey, K. L. Rinehart, Jr., D. S. Millington, M. B. Swami*, J. Antibiot. *26*, 475 (1973).
[288] *I. P. Katzenstein, A. M. Spielvogel, A. W. Norman*, J. Antibiot. *27*, 943 (1974).
[289] *V. Pozsgay*, J. Antibiot. *28*, 344 (1975).
[290] *R. Schlegel, H. Thrum*, J. Antibiot. *24*, 360 (1971).
[291] *R. Schlegel, H. Thrum*, J. Antibiot. *24*, 368 (1971).
[292] *K. Dornberger, H. Thrum, G. Engelhardt*, Tetrahedron Lett. *1976*, 4469.
[293] *E. Borowski, J. Zielinski, L. Falkowski, T. Ziminski, J. Golik, P. Kotodziejczyk, E. Jereczek, Y. Shenin, T. Kotienko, M. Gdulewicz*, Tetrahedron Lett. *1971*, 685.
[294] *P. Kotodziejczyk, J. Zielinski, J. Pawlak, J. Golik, L. Falkowski, E. Borowski*, Tetrahedron Lett. *1976*, 3603.
[295] *C. M. Liu, L. E. McDaniel, C. P. Schaffner*, J. Antibiot. *25*, 187 (1972).
[296] *H. Brik*, J. Antibiot. *29*, 632 (1976).
[297] *L. Falkowski, J. Golik, J. Zielinski, E. Borowski*, J. Antibiot. *29*, 197 (1976).
[298] *K. Dornberger, R. Fugner, G. Bradler, H. Thrum*, J. Antibiot. *24*, 172 (1971).
[299] *R. C. Pandey, V. F. German, Y. Nishikawa, K. L. Rinehart, Jr.*, J. Am. Chem. Soc. *93*, 3738 (1971).
[300] *K. L. Rinehart, Jr., W. P. Tucker, R. C. Pandey*, J. Am. Chem. Soc. *93*, 3747 (1971).
[301] *Ch. U. Zust, P. U. Fruh, W. Simon*, Helv. Chim. Acta *56*, 495 (1973).
[302] *W. E. Morf, W. Simon*, Helv. Chim. Acta *54*, 2683 (1971).
[303] *L. L. Smith*, J. Antibiot. *28*, 1000 (1975).
[304] *Y. Nawata, M. Haneda, N. Nomura, K. Ando*, Tetrahedron Lett. *1974*, 1581.
[305] *P. V. Fruh, J. T. Clerc, W. Simon*, Helv. Chim. Acta *54*, 1445 (1971).
[306] *K. Neupert-Laves, M. Dobler*, Helv. Chim. Acta *59*, 614 (1976).
[307] *M. Dobler*, Helv. Chim. Acta *55*, 1371 (1972).
[308] *M. Dobler, R. P. Phizackerleyz*, Helv. Chim. Acta *57*, 664 (1974).
[309] *R. Buchi, E. Pretsch, W. Simon*, Helv. Chim. Acta *54*, 2327 (1976).
[310] *E. Pretsch, M. Vašák, W. Simon*, Helv. Chim. Acta *55*, 1098 (1972).
[311] *K. Ando, Y. Murakami, Y. Nawata*, J. Antibiot. *24*, 418 (1971).
[312] *K. Ando, H. Oishi, S. Hirano, T. Okutomi, K. Suzuki, H. Okazaki, M. Sawada, T. Sagawa*, J. Antibiot. *24*, 347 (1971).
[313] *K. Suzuki, Y. Nawata, K. Ando*, J. Antibiot. *24*, 675 (1971).
[314] *M. Haneda, Y. Nawata, T. Hayashi, K. Ando*, J. Antibiot. *27*, 555 (1974).
[315] *M. C. Wani, H. L. Taylor, M. E. Wall*, J. Chem. Soc. Chem. Commun. *1973*, 390.
[316] *K. L. Rinehart, Jr., F. J. Antosz, P. V. Deshmukh, K. Katinuma, P. K. Martin, B. I. Milavetz, K. Sasaki, T. R. Witty, L. H. Li, F. Reusser*, J. Antibiot. *29*, 201 (1976).
[317] *K. Sazaki, T. Naito, T. Satomi, K. Onodera*, J. Antibiot. *29*, 147 (1976).
[318] *R. D. Johnson, A. Haber, K. L. Rinehart, Jr.*, J. Am. Chem. Soc. *96*, 3316 (1974).
[319] *A. K. Ganguly, S. Szmulewicz, O. Z. Sarre, D. Greeves, J. Morton, J. McGlotten*, J. Chem. Soc. Chem. Commun. *1974*, 395.
[320] *A. K. Ganguly, P. Kabasakalian, S. Kalliney, O. Sarre, S. Szmulewicz, A. Westcott*, J. Org. Chem. *41*, 1258 (1976).
[321] *S. M. Kapchan, A. R. Branfman, A. T. Sneden, A. K. Verma, R. G. Dailey, Jr., Y. Komoda, Y. Nagao*, J. Am. Chem. Soc. *97*, 5294 (1975).
[322] *S. M. Kapchan, Y. Komoda, G. J. Thomas, H. P. Hinz*, J. Chem. Soc. Chem. Commun. *1972*, 1065.
[323] *W. J. Elliott, J. Fried*, J. Org. Chem. *41*, 2469 (1976).
[324] *C. H. Kim, N. Ōtake, H. Yonehara*, J. Antibiot. *27*, 903 (1974).
[325] *T. H. Williams*, J. Antibiot. *28*, 85 (1975).
[326] *P. V. Deshmukh, K. Kakinuma, J. J. Ameel, K. L. Rinehart, Jr., P. F. Wiley, L. H. Li*, J. Am. Chem. Soc. *98*, 870 (1976).
[327] *E. Martinelli, G. G. Gallo, P. Antonini, R. J. White*, Tetrahedron *30*, 3087 (1974).
[328] *M. L. Casey, H. W. Whitlock*, J. Am. Chem. Soc. *97*, 6231 (1975).
[329] *M. F. Dampier, C. W. Chen, H. W. Whitlock, Jr.*, J. Am. Chem. Soc. *98*, 7064 (1976).
[330] *E. Martinelli, R. J. White, G. G. Gallo*, Tetrahedron *29*, 3441 (1973).
[331] *G. G. Gallo, E. Martinelli, V. Pagani, P. Sensi*, Tetrahedron *30*, 3093 (1974).
[332] *G. Lancini, G. Sartori*, J. Antibiot. *29*, 466 (1976).
[333] *A. N. Tischler, F. M. Thompson, L. J. Libertini, M. Calvin*, J. Med. Chem. *17*, 948 (1974).
[334] *A. N. Tischler, U. R. Joss, F. M. Thompson, M. Calvin*, J. Med. Chem. *16*, 1071 (1973).
[335] *R. Cricchio, G. Lancini, G. Tamborini, P. Sensi*, J. Med. Chem. *17*, 396 (1974).
[336] *R. Cricchio, G. Tamborini*, J. Med. Chem. *14*, 721 (1971).
[337] *M. F. Dampier, H. W. Whitlock, Jr.*, J. Am. Chem. Soc. *97*, 6254 (1975).
[338] *F. R. Quinn, J. S. Driscoll, C. Hansch*, J. Med. Chem. *18*, 332 (1975).
[339] *B. Inouye, Y. Uchinomi, T. Wachi*, J. Antibiot. *27*, 192 (1974).
[340] *E. Martinelli, R. J. White, G. G. Gallo, P. J. Beynon*, Tetrahedron Lett. *1974*, 1367.
[341] *J. Birner, P. R. Hodgson, W. R. Lane, E. H. Baxter*, J. Antibiot. *25*, 356 (1972).
[342] *M. Talpaert-Borlé, F. Campagnari, G. Discenza*, J. Antibiot. *28*, 580 (1975).
[343] *G. Lancini, R. Cricchio, L. Thiry*, J. Antibiot. *24*, 64 (1971).
[344] *H. Fuhrer*, Helv. Chim. Acta *56*, 2377 (1973).
[345] *D. Leibfritz*, Tetrahedron Lett. *1974*, 4125.
[346] *K. Saito, S. Mitsuhashi*, J. Antibiot. *25*, 477 (1972).
[347] *K. L. Rinehart, Jr., M. L. Maheshwari, F. J. Antosz, H. H. Mathur, K. Sasaki, R. J. Schacht*, J. Am. Chem. Soc. *93*, 6273 (1971).

[348] A. H.-J. Wang, I. C. Paul, K. L. Rinehart, Jr., F. J. Antosz, J. Am. Chem. Soc. 93, 6275 (1971).
[349] K. L. Rinehart, Jr., F. J. Antosz, J. Antibiot. 25, 71 (1972).
[350] K. Kakinuma, B. I. Milavetz, K. L. Rinehart, Jr., J. Org. Chem. 41, 1358 (1976).
[351] A. H.-J. Wang, I. C. Paul, J. Am. Chem. Soc. 98, 4612 (1976).
[352] K. Sasaki, K. L. Rinehart, Jr., F. J. Antosz, J. Antibiot. 25, 68 (1972).
[353] K. Sasaki, T. Naito, T. Satomi, Y. Momoki, J. Antibiot. 29, 199 (1976).
[354] B. Milavetz, K. Kakinuma, K. L. Rinehart, Jr., J. P. Rolls, W. J. Haak, J. Am. Chem. Soc. 95, 5793 (1973).
[355] K. L. Rinehart, Jr., W. M. J. Knöll, K. Kakinuma, F. J. Antosz, I. C. Paul, A. H.-J. Wang, J. Am. Chem. Soc. 97, 196 (1975).
[356] T. Kishi, H. Yamana, M. Muroi, S. Harada, M. Asai, T. Hasegawa, K. Mizuno, J. Antibiot. 25, 11 (1972).
[357] T. Hasegawa, J. Antibiot. 25, 25 (1972).
[358] T. Hasegawa, E. Higashide, M. Shibata, J. Antibiot. 24, 817 (1971).
[359] M. Shibata, T. Hasegawa, E. Higashide, J. Antibiot. 24, 810 (1971).
[360] M. Kondo, T. Oishi, K. Tsuchiya, J. Antibiot. 25, 16 (1972).
[361] Y. Kato, P. J. Scheuer, J. Am. Chem. Soc. 96, 2245 (1974).
[362] S. Huneck, K. Schreiber, Tetrahedron 29, 3687 (1973).
[363] F. Arcamone, G. Franceschi, B. Gioia, S. Penco, A. Vigevani, J. Am. Chem. Soc. 95, 2009 (1973).
[364] F. Arcamone, W. Barbieri, G. Franceschi, S. Penco, A. Vigevani, J. Am. Chem. Soc. 95, 2008 (1973).
[365] H. P. Weber, D. Hauser, H. P. Sigg, Helv. Chim. Acta 54, 2763 (1971).
[366] B. E. Cross, P. Hendley, J. Chem. Soc. Chem. Commun. 1975, 124.
[367] M. Brufani, S. Cerrini, W. Fedeli, F. Mazza, R. Muntwyler, Helv. Chim. Acta 55, 2094 (1972).
[368] R. Muntwyler, W. Keller-Schierlein, Helv. Chim. Acta 55, 2071 (1972).
[369] B. P. Moore, W. V. Brown, Aust. J. Chem. 29, 1365 (1976).
[370] A. Klásek, F. Šantavy, A. M. Duffield, T. Reichstein, Helv. Chim. Acta 54, 2144 (1971).
[371] I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, S. N. Ueng, J. Org. Chem. 38, 1234 (1973).
[372] R. T. Brown, A. A. Charalambides, J. Chem. Soc. Chem. Commun. 1974, 553.
[373] H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano, A. Saito, Tetrahedron Lett. 1975, 711.
[374] J. Aberhart, R. C. Jain, T. Fehr, P. de Mayo, I. Szilagyi, J. Chem. Soc. Perkin I 1974, 816.
[375] T. Fehr, R. C. Jain, P. de Mayo, O. Motl, I. Szilagyi, L. Baczynskyj, D. E. F. Gracey, H. L. Holland, D. B. MacLean, J. Chem. Soc. Perkin I 1974, 836.
[376] D. E. F. Gracey, L. Baczynskyj, T. I. Martin, D. B. MacLean, J. Chem. Soc. Perkin I 1974, 827.
[377] B. Muller, R. Achini, Ch. Tamm, Helv. Chim. Acta 58, 453 (1975).
[378] R. Achini, B. Muller, Ch. Tamm, Helv. Chim. Acta 57, 1442 (1974).
[379] W. Breitenstein, Ch. Tamm, Helv. Chim. Acta 58, 1172 (1975).
[380] B. Muller, Ch. Tamm, Helv. Chim. Acta 58, 483 (1975).
[381] D. Arigoni, D. E. Cane, B. Muller, Ch. Tamm, Helv. Chim. Acta 56, 2946 (1973).
[382] M. Brufani, L. Cellai, C. Musu, W. Keller-Schierlein, Helv. Chim. Acta 55, 2329 (1972).
[383] S. Hayakawa, E. Kondo, Y. Wakisaka, H. Minato, K. Katagiri, J. Antibiot. 28, 550 (1975).
[384] H. Minato, T. Katayama, K. Tori, Tetrahedron Lett. 1975, 2579.
[385] P. Crooy, R. De Neys, J. Antibiot. 25, 371 (1972).
[386] M. B. Roberfroid, P. A. Dumont, J. Antibiot. 25, 30 (1972).

Principles of Osmotic Desalination

By K. W. Böddeker[*]

Salt solutions can be separated into pure water and concentrated salt solution by reverse osmosis using semipermeable membranes. The distinct features and limitations of osmotic separations are developed from a consideration of the pertinent solution properties and the conditions inherently to be met by the membranes, seen as interacting barrier phase in a process which substantially separates water from water.

1. Introduction

Osmosis is a natural phenomenon directed at equalizing concentration differences of solutions with common solvent. Reverse osmosis, by an analogous mechanism, increases solution concentration differences and thus is a separation phenomenon. Both effects depend on the presence of a semipermeable barrier which is permeable to the solvent but more or less completely impermeable to the solute. Generally speaking, therefore, the terms osmosis and reverse osmosis indicate directions of solvent flow across a semipermeable barrier separating two solutions of different concentration: from dilute to concentrated (osmosis) or from concentrated to dilute (reverse osmosis). The discussion of osmotic effects amounts to an analysis of the driving forces for solvent flow.

The importance of osmotic effects is best illustrated by noting that the cell walls of living tissue have semipermeable properties, *i.e.* they are permeable to water (life being an aqueous system) and impermeable—or in a sophisticated way partially permeable—to the solutes of the cell or body fluids. Osmosis has been called the physics of life.—Reverse osmosis, using artificial semipermeable membranes, is a barrier separation process best known in its application to the desalination of brackish waters and seawater. The discussion to follow will therefore deal with aqueous electrolyte solutions.

As a barrier separation process reverse osmosis belongs to the general class of filtration operations, of which it forms one limiting case on a scale whose opposite end is the classification of gravel on a sieve. The difference in operation between a semipermeable membrane and a sieve, however, is rooted far deeper than is suggested by simply picturing a perforated wall with pore sizes ranging down to molecular dimensions. The unique feature of reverse osmosis is that it does not really involve the separation of a dissolved species from the solvent but actually differentiates between thermodynamic activities of the solvent itself: water is separated from water. The properties of the dissolved species—including their size—are quite irrelevant except for their effect on the activity

[*] Dr. K. W. Böddeker
Institut für Werkstofftechnologie und Chemie
Gesellschaft für Kernenergieverwertung in Schiffbau und Schiffahrt mbH
Postfach 160, D-2054 Geesthacht (Germany)

of the solvent. A clear recognition of this situation could have spared much futile speculation on the salt rejecting capability of pores invoked to retain the notion of a "filter". In the proximity of "ideal" semipermeability no pores are needed, for water may pass a barrier phase by diffusion.

2. Osmotic Properties of Aqueous Solutions

Regardless of the mode of transport, any separation relies on some physical difference between the species to be separated, from size in ordinary filtration to minute mass effects in diffusive isotope separation. In reverse osmosis, then, the relevant difference is not that between salt and water—obviously large—but the much more subtle difference between water containing salt and pure water. This difference reveals itself in the so-called colligative properties, namely osmotic pressure, lowering of vapor pressure, elevation of boiling point, and lowering of freezing point, which are strictly properties of the solvent reflecting the change in free energy or chemical potential of the solvent as its activity is (invariably) lowered on introduction of solute:

$$\mu = \mu^0 + RT \ln a_w \tag{1}$$

μ^0 is the standard potential of the pure solvent at $a_w = 1$. Again, the nature of the solute is of no relevance as the colligative properties depend upon particle concentration only (ions in the case of electrolytes).

The lowering of potential at $a_w < 1$ (which, by dimension, is "energy" or "work") represents the minimum thermodynamic energy required to desalt water by removing pure water isothermally from an essentially infinite body of salt solution. As applied to seawater, for example, which contains about 3.5 % of total dissolved salt (TDS), the minimum energy requirement at room temperature is nearly 0.7 kWh per metric ton of water. At a recovery of 50 % the figure is around 1 kWh per ton. In actual seawater desalination by reverse osmosis the energy requirement is an order of magnitude higher, and still higher in distillation. Any cost figures quoted as being below this minimum are wishful thinking.

The physical boundary between the solution and pure water which localizes the chemical potential difference between adjoining regions of different activity is, of course, the semipermeable membrane. It will allow water to cross under the driving force of its own chemical potential drop, but represents something like an infinite resistance (if ideally semipermeable) to the potential difference of the solute. Since the solution always has a lower potential than the pure solvent the direction of flow is into the solution, as if drawn by the solute: osmosis. If the solution, *i.e.* the potential sink, is confined in volume, the solvent influx will result in a pressure increase. This well-known phenomenon, which, for example, makes ripe fruit burst after a shower, establishes a link between solute concentration and pressure. Both affect the activity of the solvent; however, whereas solutes lower the solvent potential, external pressure raises it.

The formal connection between concentration and pressure is best visualized by a model experiment in which one mole of water is first allowed to pass by osmosis from the pure water side into a solution (wherein it occupies the partial molar volume $\bar{v}$), and subsequently is driven out again by applying a pressure p. The work involved is $p\bar{v}$, and the complete expression for the chemical potential of the solvent becomes

$$\mu = \mu^0 + RT \ln a_w + p\bar{v} \tag{2}$$

Allowing now also for pressure differences across the semipermeable membrane, the direction of solvent flow apparently depends on the relative magnitude of the two effects. Reverse osmosis then is the situation in which the lowering of potential due to solute concentration is over-compensated by an external (hydrostatic) pressure, resulting in a net solvent flow away from the solution. Desalination by reverse osmosis is thus a misnomer since it actually is a de-watering scheme (as, incidentally, is distillation). Or, by the same token, a method to concentrate a solution (isothermally) (see Fig. 1).

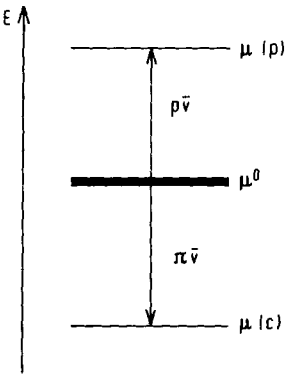


Fig. 1. The chemical potential of water. μ^0 = standard potential of pure water; p = external pressure, π = osmotic pressure. $\bar{v}$ = partial molar volume.

Of particular interest is the equilibrium situation in which the two opposing effects of solute concentration and pressure just balance each other. The corresponding pressure is, by definition, the osmotic pressure of the solution, π. It is one of the colligative properties of the solvent and as such is properly expressed in terms of the solvent activity. With $p = \pi$ at $\mu = \mu^0$ Eq. (2) gives for the osmotic pressure

$$\pi = -\frac{RT}{\bar{v}} \ln a_w \tag{3}$$

At $a_w = 1$ (pure water) the osmotic pressure is zero. Using this equation (or analogous expressions for the other colligative properties) the activity of the solvent—which is a somewhat hidden quantity—is experimentally accessible. Of more importance, however, is a direct relation between the analytical solute concentration and the corresponding osmotic pressure. For dilute solutions such a relationship may be constructed by observing that both the solvent activity and its mole fraction (x_1 for solvent concentration) are close to unity, implying that $\ln a_w \approx \ln x_1$. Simple mathematics then leads to the mole fraction of the solute (x_2, which, for dilute solutions, is proportional to other concentration units)

$$\ln a_w \approx \ln x_1 = \ln(1 - x_2) \approx -x_2 \tag{4}$$

As far as the approximation "dilute" holds, the desired relation between osmotic pressure and solute concentration is as follows:

$$\pi = \frac{RT}{\bar{v}} x_2 \text{ or } \pi\bar{v} = RTx_2 \quad (5)$$

This is the van't Hoff limiting law for osmotic pressure. It resembles the ideal gas law, giving rise to the alluring but erroneous notion that the osmotic pressure has the same kinetic origin as gas pressure, *viz.* particles bouncing against the walls of their container. In fact, as follows from a consideration of surface tension, electrolytes in solution even tend to stay away from the solution boundaries (an observation leading at one time to the suggestion that all that is required to desalt water is to skim its surface).

Since the colligative properties are a function of particle concentration, numerical calculations have to account for electrolyte dissociation (ν = number of moles of ions produced per molar entity of salt at "infinite dilution"). Furthermore, using molality to express the solute concentration (m_2 = moles of solute per kg of solvent, one kg of water representing 55.5 moles), the customary equation for the osmotic pressure is

$$\pi = \frac{RT\nu m_2}{\bar{v}\ 55.5}\phi \quad (6)$$

in which ϕ is the empirical "osmotic coefficient" correcting the naive expression (5) for ionic interactions (for example, incomplete dissociation at "actual dilution"). Its value has been tabulated for most salts of interest in desalination. At the concentrations in question here, it usually differs little from unity[1].

In the context of the approximations used here, even seawater with a total salt content of about 3.5 % may be considered a dilute solution. Its osmotic pressure at room temperature is about 26 bar, at 2 °C about 23 bar. Such pressures, of course, are encountered in the depths of the oceans, ready-made (in principle) to drive a perpetual fountain of fresh water in a device known as an "osmotic pump". This is a pipe open at the top but capped by a semipermeable membrane at the bottom, lowered straight down into the ocean (which, for all practical purposes, is a solution of uniform concentration and temperature, with a surface density close to 1.03 g/cm^3). A pressure difference of 23 bar across the membrane is reached at a depth of around 230 m; it corresponds to the osmotic pressure of the seawater. Any excess pressure on further lowering the pipe is reverse-osmotically compensated by fresh water rising inside the pipe, always maintaining a constant Δp of 23 bar at $\Delta\mu = 0$ across the membrane. Since the density of the fresh water is lower than that of seawater (both, of course, increasing with increasing depth), the fresh water inside the pipe does not simply remain at the 230 m-mark but actually rises until—at a calculated depth of the pipe of 8750 m—it reaches the surface[2].

In practice, pressurizing pumps are more convenient. Even then the desalination of seawater by single-pass reverse osmosis, though demonstrated on a pilot plant scale, is still more challenge than business. Solutions with lower salt concentrations and lower osmotic pressures are easier to handle. A physiological sodium chloride solution, which is adjusted to the osmotic pressure of the blood (7.6 bar) has an NaCl concentration (0.95 %) comparable to that of a "thick" brackish water—at present, the realm of applied reverse osmosis.

The osmotic pressure of the feed water is something like a basic design factor for the reverse osmosis process. First of all, there is obviously no reversal of solvent flow until the osmotic pressure is exceeded by an external pressure acting on the solution. This places an upper limit on the solution concentration that may reasonably be treated by this process. Secondly, while ordinary filtration may be carried out to the point of dehydration, reverse osmosis has to work against an increasing osmotic pressure as solvent is removed from a finite feed water reservoir. This limits the practical yield or recovery of the process and, by implication, renders the designed output a function of the initial feed water concentration.

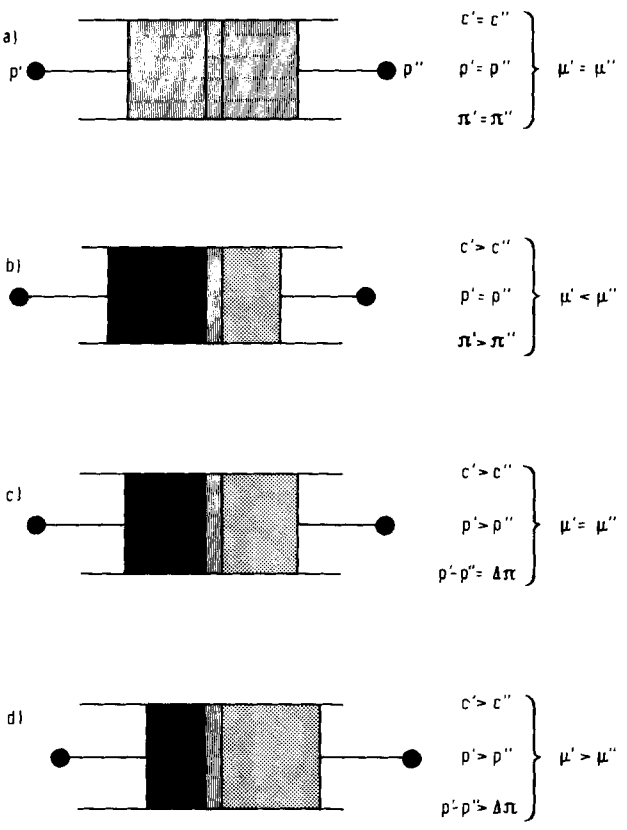


Fig. 2. Summary of the osmotic situations. a) Natural equilibrium, b) osmotic volume flow, c) osmotic equilibrium, d) reverse osmosis.

A summary of the four osmotic situations is presented in Figure 2[3]. It is understood that solvent flow from a given solution can likewise be effected by lowering the activity (raising the osmotic pressure) of the counter solution beyond the point of flow reversal, by concentrating the counter solution with anything soluble. This is the principle of dialysis at ambient pressure (osmotic extraction). If "anything soluble" is a nutrient, like saccharose, the principle might be useful for supplementing emergency water at sea in an osmotic flow extractor[4]. Another suggestion aims at producing hydro-electricity from the Dead Sea, osmotically linked to the Jordan River: Dead Sea water, being pumped to a hydroturbine, "absorbs" the Jordan through semipermeable membranes, thereby increasing—as in the above flow extractor—not the pressure head, but the total liquid volume delivered[5].

3. Membranes and Membrane Model

The discussion so far has assumed an "ideal semipermeable membrane" governed by the activity of the solvent only, with no inference as to the mechanism of transport or selection across the membrane. The next best real thing to the ideal limit is a "diffusion controlled solubility membrane", the model of which is pictured as a homogeneous (*i.e.* pore-free) phase in which all solution components are soluble to various degrees and have a certain diffusive mobility[6]. Even the model version of this membrane expressly allows for salt passage, as dictated by reality. Selectivity is interpreted as arising from differences in solubility and mobility of the components in the membrane phase, that is, in terms of measurable and even adjustable membrane properties. The only assumption involved in the model treatment is that there is no coupling between the flow of water and of salt through the membrane, thus allowing the transport of the two to be considered independently. Although this model is still a limiting case confined to "dense" membranes of high salt rejecting capacity, it comes very close to describing real membranes of this type. Any sizeable departure from simple solution-diffusion behavior is indicative of a pore flow mechanism and should be regarded as ultrafiltration (or else as a membrane imperfection) rather than reverse osmosis.

By combining the osmotic principles with the tangible features of the solution-diffusion model, the equations of flow constituting the "instructions for use" of applied reverse osmosis may now be derived. In a general way the diffusive flow (or flux) F_i of a species i through a homogeneous membrane is given by the concentration of that species *in* the membrane phase (c_i), its mobility *in* the membrane phase ($m_i = D_i/RT$, with diffusion coefficient D_i), and the driving force acting on that species across the membrane (grad μ_i, the gradient of the chemical potential within the membrane boundaries)[7]:

$$F_i = c_i \times m_i \times \operatorname{grad} \mu_i \tag{7}$$

Viewing this relation as a generalized ohmic law, the product $c_i \times m_i$ represents the "conductivity" of the membrane phase. The potential is represented by external concentration and pressure differences, with the thickness of the membrane in between included in the conductivity part (Δy, the geometry of the conductor). For the present purpose Eq. (7) thus becomes

$$\underset{\text{flux}}{F_i} = \underset{\text{conductivity}}{\frac{c_i D_i}{RT\Delta y}} \times \underset{\text{potential}}{\Delta\mu_i} \tag{8}$$

The specific features of reverse osmosis emerge on analysis of the driving forces involved, $\Delta\mu_i$. For the solvent, indicated by the subscript i = 1, this is straightforward: The activity term of Eq. (2) can be expressed by the corresponding osmotic pressure according to Eq. (3) to yield

$$\mu_1 = \mu_1^0 - \pi\bar{v}_1 + p\bar{v}_1 \qquad (2), (3)$$

and

$$\Delta\mu_1 = \bar{v}_1(\Delta p - \Delta\pi) \tag{9}$$

For the chemical potential of the solute, subscript i = 2, (as for any component of a mixture) an equation analogous to Eq. (2) applies, *i.e.*

$$\mu_2 = \mu_2^0 + RT\ln c_2 + p\bar{v}_2 \tag{2'}$$

Partial differentiation of μ_2 with respect to c_2 and p (observing that $\partial\mu/\partial p = \bar{v}$, and with $\mathrm{d}\ln c = c^{-1}\mathrm{d}c$) yields

$$\Delta\mu_2 = \frac{RT}{c_2}\Delta c_2 + \bar{v}_2\Delta p \tag{10}$$

By coincidence, the partial molar volumes of water and sodium chloride, $\bar{v}_1$ and $\bar{v}_2$, are nearly the same, 18 ml/mole (neglecting compressibility). If a high concentration difference is maintained across the membrane, as is the case in high rejection reverse osmosis, the contribution of pressure to the driving force is negligible, amounting to roughly 1 % of the total solute potential difference.—The concentration c_2 refers to the *external* solution, whereas $c_i = c_2$ in Eq. (8) is the salt concentration *within* the membrane. The ratio $c_{membrane}/c_{solution}$ is in effect a distribution coefficient between membrane phase and solution phase, denoted K.

By incorporating these driving forces into the general flow equation (8) the transport equations for water and salt in the approximation of the solution-diffusion model take on the form[6]:

$$\text{Water (solvent):}\quad F_1 = \frac{c_1 D_1}{RT\Delta y}\bar{v}_1(\Delta p - \Delta\pi) \tag{11}$$

$$\text{Salt (solute):}\quad F_2 = \frac{D_2 K}{\Delta y}\Delta c_2 \tag{12}$$

The immediate results of this treatment may be summarized as follows: a) the rate of permeation of water is linearly dependent on the excess pressure over and above the osmotic pressure of the feed; b) the rate of permeation of salt is completely independent of the pressure; it is a function of the salt concentrations only, or more precisely, of the salt concentration at the respective solution-membrane interface; c) there is no interdependence between the two flows: neither does the permeating water carry salt, nor is the permeating salt accompanied by water.

A peculiarity of reverse osmosis becomes apparent when the salt rejection is considered (R). Next to the permeate flow rate (F_1) it is the most important quantity characterizing a separation process. It is conveniently defined in terms of the analytical salt concentrations of feed (') and permeate ('') as

$$R = \frac{c_2' - c_2''}{c_2'}; \qquad R \times 100 \triangleq \% \tag{13}$$

or as the desalination ratio c_2'/c_2''. Since, according to the model, the rate of salt permeation is independent of the pressure-driven water permeation, the rejection increases with increasing pressure, simply because an increase in water flux results in a correspondingly lower analytical salt concentration on the product side. In contrast to ordinary filtration, even if pressure-assisted, the "success" of reverse osmosis separa-

tions can thus be influenced by the operating pressure, which so far is the only process variable outside the inherent membrane properties. The rejection, incidentally, is independent of the membrane thickness, since the permeate salt concentration is given by the ratio of the two flows [Eq. (14)].

A graphical presentation of flows and resultant rejection in the simplified scheme of this, as it is, near-realistic model is given in Figure 3. As an orientational aid, order-of-magnitude values pertaining to the desalination of seawater by current reverse osmosis technology are included. (In terms of specific output, the membrane area is roughly comparable to the heat exchange surface of distillation plants.) Again, both F_1 and R are pressure dependent, but F_2 is not.

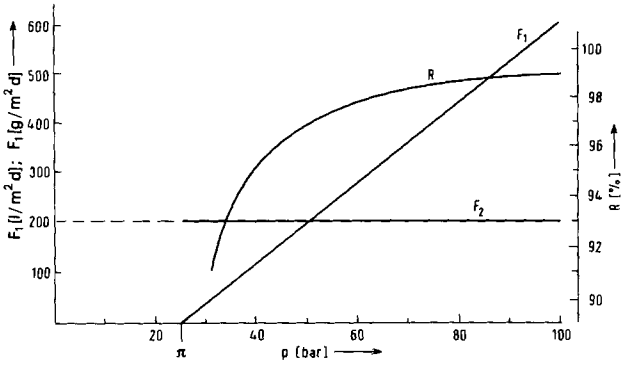


Fig. 3. Seawater desalination in the approximation of the solution-diffusion model. F_1, F_2 diffusive flow of water and salt, respectively; R = salt rejection; p = external pressure; π = osmotic pressure.

As a rule, the operating pressure of applied reverse osmosis is 3π, that is, it is adjusted to the salt content of the feed water to meet rejection requirements (about 75 bar in case of seawater). The salt concentration "seen" by a membrane in operation is, unfortunately, higher than the bulk concentration, c_2', because rejected salt accumulates at the solution-membrane interface as desalted water is withdrawn. The adverse effects of this "concentration polarization" are best seen by referring to the flow equations: As the osmotic pressure increases the net pressure (effective pressure) decreases with consequent reduction in flux [Eq. (11)]; secondly, a concentration build-up at the solution-membrane interface raises the level of salt passage, [Eq. (12)]. Essentially, the process of reverse osmosis separation is a polarization in itself, with much the same effects occurring gradually along the feed flow passage across any serial pattern of membrane surface. The only way to control concentration polarization is to maintain a reasonably high feed velocity across the membranes—which is a problem of hydraulic design.

It appears from this treatment that diffusion-controlled reverse osmosis may be of universal application conceptually, but faces some peculiar limitations when it comes to practical separations. First of all, as already mentioned, the process is confined to dilute solutions, there is no chance to desalt the Dead Sea (osmotic pressure > 200 bar) by reverse osmosis. It is perhaps more than coincidence that membrane performance is at its best at "physiological" salt concentrations (around 1 %), for this suggests that artificial (technical) membranes are not altogether different (though certainly less refined) than biological membranes. By a similar argument, and on first sight unexpectedly, it is not even desirable to do much better than nature: The higher the permeation rate of water through the membrane, the steeper the increase in concentration polarization. For hydraulic reasons, present-day apparatus will not handle more than about $2\,m^3$ of product water per square meter of membrane area and day. With certain brackish water membranes this limit is already being approached; seawater membranes rarely exceed a production rate of $500\,l/m^2\,d$. A final limitation, which only reluctantly has been accepted as a basic problem of reverse osmosis, concerns the fact that natural waters invariably contain particulate matter, living and dead, accumulating in a surrounding of high electrolyte concentration at the solution-membrane interface. It is the diminution in time-dependent flux due to membrane fouling which limits the availability of technical reverse osmosis installations.

4. Membrane Properties

Returning again to the conceptually possible, an intriguing question is whether, given a suitable transport model, membranes may be tailored to specific separation problems. If the solution-diffusion model does not really tell us how a membrane functions (much less so any "black box" treatment), it does provide some guidance in the orderly search for osmotic membranes. This involves two problem areas, which must be investigated separately: Finding a (polymeric) material that will discriminate permeability-wise between the solution components under consideration,—and making this material into a film of realistic productive capacity and mechanical strength.

In terms of the flow equations [Eqs. (11, 12)] the "conductivity" of a candidate membrane material for solvent and solute is represented by the permeabilities $c_1 D_1$ and KD_2, respectively, determined by absorption-desorption experiments. The most thoroughly investigated families of compounds for purposes of osmotic desalination are the cellulose acetates and the aromatic polyamides, the permeabilities of which towards water and sodium chloride are given in Table 1[8,9].

Table 1. Water and salt permeabilities in homogeneous membrane films. CA = cellulose diacetate; CTA = cellulose triacetate; PA = an aromatic polyamide.

Membrane	Acetyl [%]	H_2O c_1 [g/cm³]	H_2O D_1 [cm²/s]	NaCl K [a]	NaCl D_2 [cm²/s]
CA	33.6	0.29	5.7×10^{-6}	0.17	2.9×10^{-8}
CA	37.6	0.20	2.9×10^{-6}	0.060	4.3×10^{-9}
CA	39.8	0.16	1.6×10^{-6}	0.035	9.4×10^{-10}
CTA	43.2	0.12	1.3×10^{-6}	0.015	3.9×10^{-11}
PA	—	0.49	1.5×10^{-6}	0.2	1.2×10^{-10}

[a] K = (g NaCl/cm³ film)/(g NaCl/cm³ solution).

Selectivity rests primarily with the relative mobilities, which—in the case of the cellulose acetates—are also the most sensitive towards degree of acetylation with consequent effect on the potential salt rejection.—The permeation rate of water is directly related to the water content of the membrane phase, c_1, thus limiting the candidate membrane materials to hydrophilic polymers. Since it eventually governs the output of the process, the fractional water content is a highly important design variable. It is also open to some terminological confusion: A membrane material may contain two kinds

of water, *viz.* primary water as molecular constituent of the polymer matrix, and secondary water in the form of droplets or pore fluid, as in a sponge. While the total liquid transport clearly depends on both kinds, primary water will not enhance salt passage whereas secondary water does. With no coupling between the flows of water and salt, as postulated by the solution-diffusion model, the water term of Eq. (11) and Table 1 is strictly primary, the onset of pore formation with increasing total water content registering as a sudden increase in salt flow[10]. The occasional reference to the total (analytical) water concentration as "porosity" is, therefore, quite misleading.

Given the permeability data it is possible to calculate a "theoretical" or "intrinsic" salt rejection of a candidate membrane material for assumed conditions of concentration and pressure. The permeate salt concentration, c_2'', is determined by the relative flows of salt and water, *i.e.*

$$c_2'' = \frac{F_2}{F_1} c_1'' \tag{14}$$

implying that the salt rejection is independent of the membrane thickness, Eq. (13). The resultant expression in terms of the present model is

$$R = \left[1 + \frac{K D_2 R T}{c_1'' D_1 \bar{v}_1 (\Delta p - \Delta\pi)}\right]^{-1} \tag{15}$$

where c_1'' is the water concentration of the permeate, essentially 1.0 g/cm^3. For example, a membrane of CA-39.8 (cf. Table 1) applied to a 3.5 % sodium chloride solution at a gross pressure of 100 bar has a theoretical salt rejection of 99.8 %,—intrinsically, that is[11].

If the search for suitable osmotic materials has at least some rational basis, making membranes thereof remains largely an empirical task—it is an art illuminated by scattered experience. Since the flow of water, Eq. (11), is inversely proportional to the membrane thickness (Δy) with no effect on rejection, the efforts concentrate on making the membranes as thin as possible without incurring imperfections. This is achieved by a most disparate set of recipes, always to the effect that the membranes are reduced to a skin-layer covering one surface of an otherwise porous substrate film. If "integral-asymmetric", the layered structure emerges in a closed manufacturing process involving one and the same polymer throughout; if "composite-asymmetric", the skin-layer constituting the membrane proper is applied separately, either in the form of an ultra-thin homogeneous polymer film or by coverage with a polymeric or reactive monomeric solution. With integral-asymmetric membranes, of which the now classical cellulose acetate membranes of *Loeb-Sourirajan*[12] are a typical example, skin thickness ranges down to perhaps 1000 Å (0.1 μm); composite membranes, in particular the recent aromatic polyamide varieties[13], may reach an effective thickness of 200 Å. These are in fact the most promising classes of compounds (and the only ones to be used commercially) out of a vast and varied number of candidates evaluated to date[14]. Their success is not exclusively due to their superior intrinsic properties, but is likewise a result of the fact that these properties may be realized in the configuration of a membrane.

The concept of the "intrinsic membrane" is deceptive, for it completely ignores all manufacturing and operational circumstances. Experimentally, it is approximated by the "initial performance" of a laboratory membrane in short term reverse osmosis tests with clean salt solutions under conditions of zero recovery. The "actual performance" of production membranes is subject, not only to the limitations inherent in an osmotic separation, but also to the engineering design of the apparatus in which they are used.

The principal design concepts of applied reverse osmosis—referred to as module concepts—are summarily represented

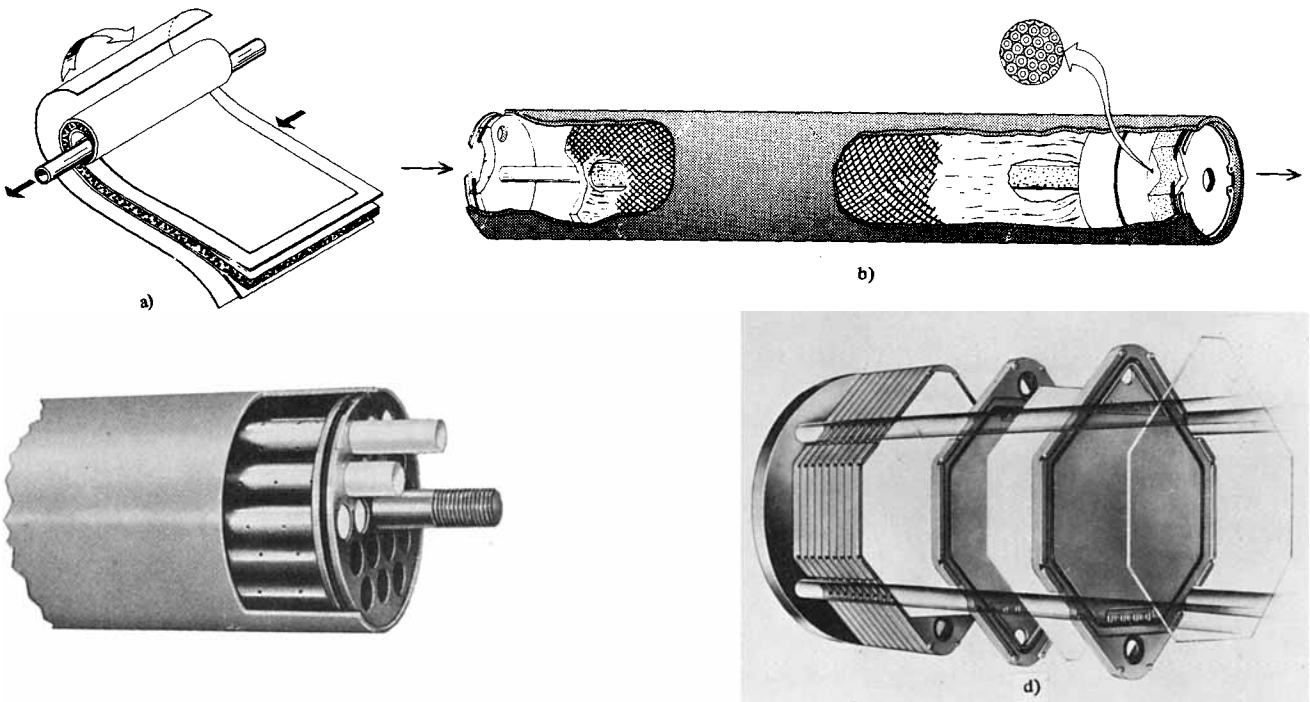


Fig. 4. Principal design concepts of applied reverse osmosis. Closed systems with prefabricated elements of a) spiral wound flat membranes or b) bundled hollow fibers; open systems with accessibly mounted membranes in c) tubular form or as d) flat sheets in serial arrangement [15].

in Figure 4[15]. The various designs are more than just geometrical isomers of membrane accomodation, each implying a certain mode of operation, and each adapting differently to environmental water conditions. Generally speaking, closed systems (Fig. 4a and 4b) requiring an elaborate feed water pretreatment are preferably used under conditions which favor a continuous quantity operation, while open systems (Fig. 4c and 4d) are less sensitive towards difficult feed water conditions and more versatile in small scale operation.

5. Conclusion

Reverse osmosis represents a highly attractive separation principle, whose somewhat uncertain credibility as a technical unit operation is due, not to a lack of basic development, but to overoptimism in projecting the intrinsically possible onto the harsh reality of actual feed waters. Future developments will have to focus on overall reliability rather than selectively on miracle membranes.

Received: March 8, 1977 [A 181 IE]
German version: Angew. Chem. 89, 624 (1977)

[1] *R. A. Robinson, R. H. Stokes*: Electrolyte Solutions. 2nd edit. Butterworths, London 1970.
[2] *O. Levenspiel, N. de Nevers*, Science *183*, 157 (1974).
[3] *K. W. Böddeker, H. Strathmann*, Chem. unserer Zeit *8*, 105 (1974).
[4] *J. O. Kessler, C. D. Moody*, Desalination *18*, 297 (1976).
[5] *S. Loeb*, J. Membr. Sci. *1*, 49 (1976).
[6] *U. Merten*: Desalination by Reverse Osmosis. MIT Press, Cambridge, Mass. 1966.
[7] *R. Schlögl*, Jahrb. Max-Planck-Ges. *1969*, 135.
[8] *H. K. Lonsdale, U. Merten, R. L. Riley*, J. Appl. Polym. Sci. *9*, 1341 (1965).
[9] *M. A. Frommer, J. S. Murday, R. M. Messalem*, Eur. Polym. J. *9*, 367 (1973).
[10] *H. Strathmann, U. v. Mylius*, Proc. 5th Int. Symp. Fresh Water from the Sea 4, 189 (1976).
[11] *R. L. Riley, H. K. Lonsdale, C. R. Lyons, U. Merten*, J. Appl. Polym. Sci. *11*, 2143 (1967).
[12] *S. Loeb, S. Sourirajan*, Adv. Chem. Ser. *38*, 117 (1962).
[13] *R. L. Riley et al.*, Proc. 1st Desalination Congr. of the American Cont. 1976, Paper II-1.
[14] *L. Dresner, J. S. Johnson, Jr.* in *K. S. Spiegler, A. D. K. Laird*: Principles of Desalination. 2nd Edit. Academic Press, New York, in preparation.
[15] Fig. 4a: UOP/Ajax; Fig. 4b: DuPont; Fig. 4c: PCI/Harwell; Fig. 4d: GKSS.

Molecular States and Molecular Orbitals[1, 2]

By Hans Bock[*]

Dedicated to Professor Erich Hückel on his 80th birthday and on the occasion of the 450th Anniversary of the foundation of Marburg University.

Molecules change their properties on acquisition or loss of energy. The state of a molecule can be characterized by the difference between its energy and that of the preceding initial state or that of the subsequent final state, as well as by the respective charge distribution. Molecules in their various energy states each display a particular structure and characteristic properties, and it is these entities which the chemist uses as synthetic building blocks.—The best model hitherto available for describing molecular states is the molecular orbital representation. Molecular orbitals are especially suitable for comparing mutually corresponding molecular states of similar compounds, and thus provide a manifold and stimulating overview of large areas of chemistry.—An attempt will now be made to point out important characteristic parameters of molecular states and to explain the rules governing their description by molecular orbitals, while circumventing mathematical barriers. A principal objective is the comparison of states of "chemically related" molecules with regard to the connection, the arrangement, and the potential of their atoms. The simple models employed for this purpose, whose inherent limitations and potential expansions are discussed, have meanwhile become valuable tools in the hand of the chemist.

Between 1789 and 1793, Georg Christoph Lichtenberg made the following entry in his Sudelheft No. I: "Wir sehen in der Natur nicht Wörter, sondern immer nur Anfangsbuchstaben von Wörtern, und wenn wir alsdann lesen wollen, so finden wir, daß die neuen sogenannten Wörter wiederum bloß Anfangsbuchstaben von anderen sind".[**]

1. To Measure or to Calculate?

The tetra-atomic molecule thioformaldehyde $H_2C{=}S$[3], detected in interstellar space, can be prepared pure by thermal elimination of HCl from methanesulfenyl chloride and subsequent deposition of NH_4Cl with ammonia (Fig. 1:A) and subjected to spectroscopic analysis (Fig. 1:B). Computer simulation of an almost superposable photoelectron spectrum[4] (Fig. 1:C) takes about 2 CPU hours (IBM 360/91).

Procedures such as PNO/CI (*P*seudo*n*atural *O*rbital/*C*onfiguration *I*nteraction) and CEPA (*C*oupled *E*lectron *P*air *A*pproach) developed by *Meyer*[5], or the GF method (many-

[*] Prof. Dr. H. Bock
Chemische Institute der Universität, Anorganische Chemie II
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

[**] "In Nature we see not words but only the first letters of words, and when we wish to read we find that the new so-called words are once again mere first letters of other words".

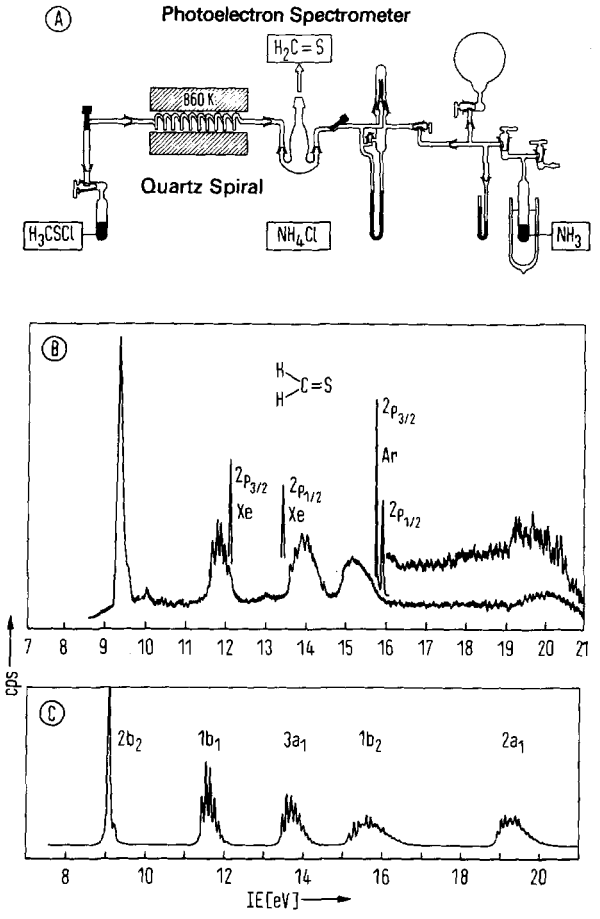


Fig. 1. For gas-phase preparation (A) of thioformaldehyde [3], methanesulfenyl chloride is passed through a quartz spiral heated to 860 K. Hydrogen chloride can be removed from the resulting gas mixture by deposition as ammonium chloride on reaction with ammonia introduced from a storage system *via* a fine-control valve. The reaction conditions such as furnace temperature or ratio of the gaseous reactants H_3CSCl to NH_3 are best adjusted with the aid of a photoelectron spectrometer, *i.e.* on the basis of the appearance and disappearance of the known ionization bands of HCl and NH_3. The PE spectrum (B) also provides a check on the purity of $H_2C{=}S$. Additional calculation [3, 4] of the ionization band pattern (C), a "fingerprint" of the molecule, also permits unequivocal identification of the reaction product $H_2C{=}S$.

body Green Functions)[4] utilized for reproduction of the PE spectrum (Fig. 1:C) permit calculation of some state data of gaseous, *i.e.* isolated, molecules up to the size of, say, *para*-difluorobenzene $C_6H_4F_2$[6] with a surprising degree of accuracy, *e.g.* ionization energies to within deviations of less than ± 0.3 eV[7].

Thus it is possible today to reproduce individual properties, especially those of small molecules, to within the limits of experimental error[7, 8] by calculation; or, generalizing, to satisfactorily approximate solutions of the Schrödinger equation by numerical methods[9]. This achievement has various consequences[10] which will come to affect the interrelationships between experimental practice and the application of theoretical tools. Some of these aspects[10] are presented in the simplified flowsheet of Figure 2[2c, d].

The provocative question "To measure or to calculate?" is probably best answered by pointing out how successful and stimulating a combination of the two can be. Thus correlation of experimental and calculated data, and especially the comparison of measured data for given states of chemically related molecules, will continue to promote the chemist's

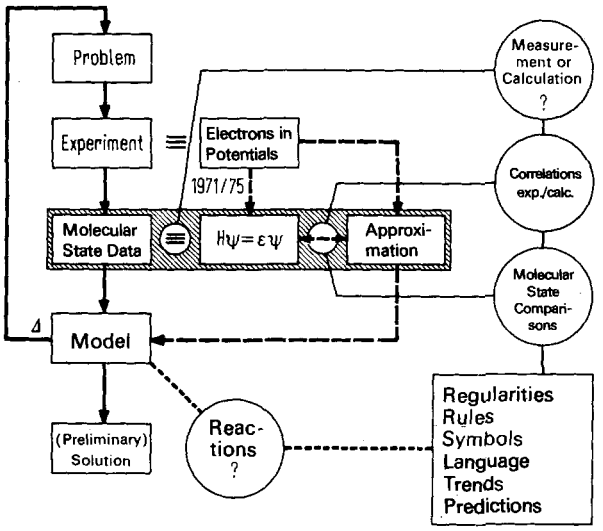


Fig. 2. Experimental investigation of a chemical problem (→) leads to individual experimental data which are generally compared with other results, *i.e.* verified by comparison with an (empirical) model. This cycle can be advantageously coupled with a loop (----→) in which the observations, after correlation with the behavior of electrons in potential fields, can be described in appropriate approximations, thus providing important information about the basic properties and scope of models. In particular, acting as their own computer, molecules "print out" complete solutions of the Schrödinger equation $H\psi=\varepsilon\psi$ (which cannot be solved exactly for many-particle systems) in the form of their measured data. Even simple approximations such as those proposed by *E. Hückel* in his epoch-making [11] work on π-systems [12] permit comparison of numerous individual data and derivation of far-reaching consequences and predictions from the resulting models.—The recent breakthrough achieved in numerically approximating solutions of the Schrödinger equation with newly developed calculating procedures [9] also enhances the importance of other correlations between experimental and calculated quantities and of comparisons between states of chemically related molecules. This could represent the starting point for a more intense development of a metatheory [10] providing a unified description of regularities, permitting manifold predictions, and also yielding models suitable for application to reaction courses as more and more detailed knowledge becomes available.

understanding of the substances with which he is dealing. In addition, however, greater effort could be invested in the development of a metatheory which facilitates an overall view of the material and energetic multiplicity by describing regularities and setting up rules, provides a unified set of symbols and a common language, reveals tendencies, and supports predictions to a greater extent than was formerly possible[10]. More attention should also be directed to theoretical calculation of quantities not readily accessible to experimental determination, *e.g.* on energy or reaction surfaces[13]. This would provide a means of incorporating the reactivity of chemical compounds in improved models as increasingly detailed knowledge becomes available concerning the course of reactions.

The following remarks about molecular states and their description by molecular orbitals, together with the examples largely selected according to their didactic value, are intended to arouse the preparative chemist's interest in exploiting the tools put at his disposal by theory.

2. Properties of Molecules in Their Various States

If energy is supplied to or withdrawn from a molecule it goes into another state. If, in addition, electrons are acquired or released during this transition then molecular ions, which may also be radicals, are formed as new particles which can themselves exist in numerous states of various energies. The

energy differences can be recorded by a variety of measuring techniques (cf., *e.g.*, Fig. 3) and show that the total energy of the individual molecular states increases on going from those of a stable radical anion $M^{\bullet\ominus}$ *via* those of the neutral molecule M to those of the radical cation $M^{\bullet\oplus}$ (Fig. 3).

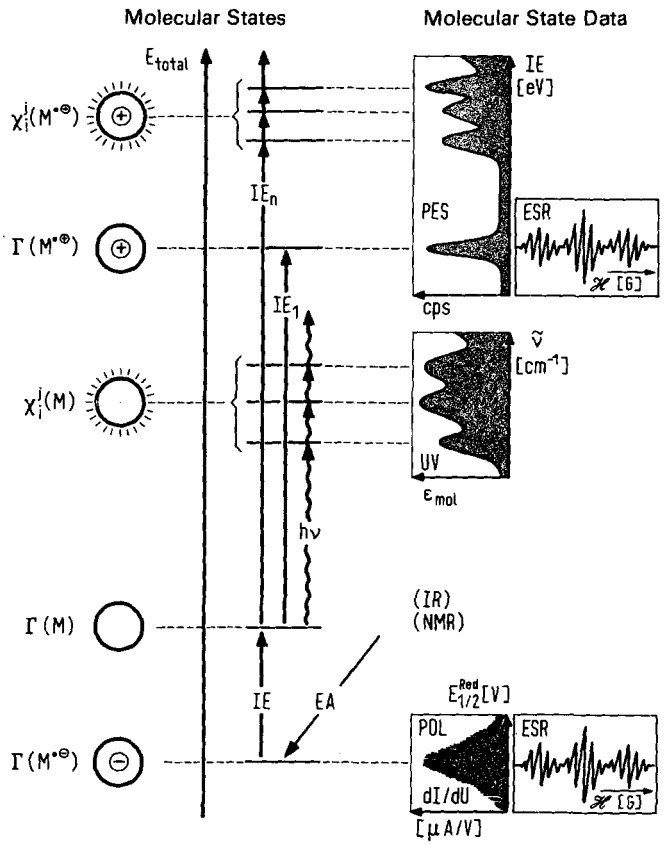


Fig. 3. A neutral molecule M in its ground state $\Gamma(M)$ can take up certain amounts of energy; thus on absorption of UV radiation $E = h\nu$ it is transferred into one of the numerous electronically excited states $\chi_i^j(M)$. Larger amounts of energy may lead to loss of an electron, for example to form the radical cation $M^{\bullet\oplus}$: the first ionization energy IE_1 generates its ground state $\Gamma(M^{\bullet\oplus})$; the higher ionization energies $IE_{n(>1)}$ likewise observable in the photoelectron spectrum (PES) produce its electronically excited states $\chi_i^j(M^{\bullet\oplus})$. In contrast, on acceptance of electrons to form a stable radical anion $M^{\bullet\ominus}$, *i.e.* given a positive electron affinity EA, the total energy becomes more negative; the ionization reaction $\Gamma(M^{\bullet\ominus}) \rightarrow \Gamma(M) + e^{\ominus}$ requires energy. In solution, radical anions can be stabilized by ion-pair formation with the counterion and by solvation; their energy difference relative to M can be measured polarographically (POL) as the half-wave reduction potential $E_{1/2}^{Red}$. Information concerning the spin-, and hence charge-density in the radical ions $M^{\bullet\oplus}$ and $M^{\bullet\ominus}$ can be gained from high-resolution electron spin resonance (ESR) spectra. For the nomenclature of molecular states, cf. ref. [14].

Radical cation states of molecules are especially suitable for an introductory discourse: they can be observed by the straightforward and direct technique of photoelectron spectroscopy[2c–e, 15], are characterized by a typical electron hole, and as shown below can usually be interpreted on the basis of simple models. A wealth of information about the properties of radical cations can be gleaned from PE spectra[2e, 15b, c]; this will be illustrated by clear-cut examples of relatively small molecules which in some cases experience only slight structural deviations (Figs. 4 and 6) and in others even undergo changes in structural type (Figs. 5 and 6).

In the PE spectrum of HBr[15a, 16] (Fig. 4) the first two ionizations can be assigned to the bromine electron pairs perpendicular to the molecular axis. Two radical cation states $^2\Pi_{3/2}$ and $^2\Pi_{1/2}$ result which are, however, not "degenerate",

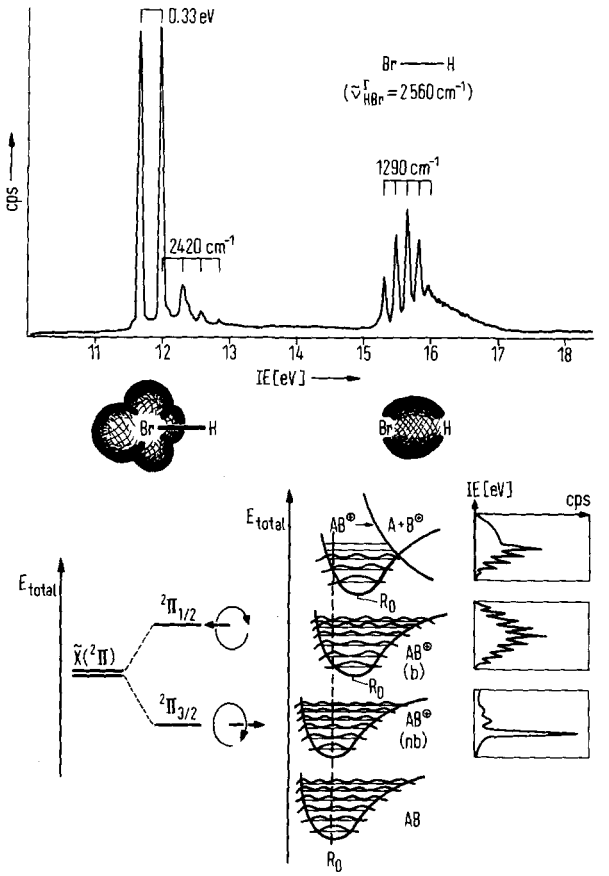


Fig. 4. In the photoelectron spectrum of HBr [15a, 16] a total of 4 ionizations are observed—corresponding to the presence of 8 valence electrons. Of the three lowest energy ionizations shown, the bands at 11.68 and 12.01 eV can be assigned to the Br electron pairs, and that at 15.60 eV to the BrH bond: in the nomenclature of spectroscopy [14] the two (spin/orbit) coupled radical cation states are designated as $^2\Pi_{3/2}$ and $^2\Pi_{1/2}$, and the simple one as $^2\Sigma^+$. They differ, among other things, in their stretching frequencies $\tilde{\nu}_{HBr}^{\oplus}$, which are hardly changed ($^2\Pi$) and almost halved ($^2\Sigma^+$), respectively, relative to that of the uncharged molecule $\tilde{\nu}_{HBr}$. This result can be interpreted, together with the differing band shapes, in terms of the potential energy curves as follows: if the equilibrium distance R_0 remains unchanged during the vertical transition to the radical cation state, *i.e.* if an (almost) nonbonding electron (nb) is ionized, then $\tilde{\nu}_{AB}^{\oplus} \approx \tilde{\nu}_{AB}$ and owing to the most frequent $0 \rightarrow 0$ transition a needle-shaped principal band will result. If R_0 increases, *i.e.* if a bonding electron (b) is removed, then $\tilde{\nu}_{AB}^{\oplus}$ becomes smaller relative to $\tilde{\nu}_{AB}$ and the most frequent vertical transition now appears near the center of the band. If the resulting radical cation $AB^{\oplus}$ is unstable, *e.g.* towards dissociation into $A^{\bullet} + B^{\oplus}$, then the vibrational fine structure vanishes—the curve of the dissociative state and that of the binding state cross in the potential energy diagram—as in the present case for $HBr^{\bullet\oplus}$, which decomposes into $H^{\bullet} + Br^{\oplus}$ at 15.85 eV [16].

i.e. of equal energy, but owing to different kinds of orientation of spin and orbit angular momentum[15b, c, 17] are split by 0.33 eV (Fig. 4). The vibrational fine structure recognizable following the second main band exhibits a frequency which is only slightly lower than the stretching frequency in the neutral HBr molecule: hence the electron hole arising on ionization of a "nonbonding" electron from the bromine electron pairs hardly exerts any significant effect on the force constants $f_{HBr}^{\oplus} \sim f_{HBr}$, and the equilibrium distance $R_0^{\oplus}$ accordingly remains practically unchanged compared with R_0[16]. In contrast, the third PE band, assignable to ionization from the σ_{HBr} bond, displays an approximately halved radical cation vibrational frequency $\tilde{\nu}_{HBr}^{\oplus}$ (Fig. 4)—corresponding to a diminished force constant $f_{HBr}^{\oplus}$ and an increased equilibrium distance $R_0^{\oplus}$ in this state. That each individual molecular state exhibits characteristic properties and possibly a specific

reactivity, is apparent from the dissociation $HBr^{\oplus} \rightarrow H^{\bullet} + Br^{\oplus}$ occurring in the third radical cation state above 15.85 eV—recognizable from the disappearance of vibrational fine structure (Fig. 4).

The experimental data for $HBr^{\bullet\oplus}$ demonstrate that molecular states have different kinds of charge distributions depending upon their energy, and hence also different properties including different kinds of reactions. In molecules containing more than two atoms, the overall structure, which is not necessarily linear, can therefore change according to the state, as will now be exemplified in more detail for certain radical cation states of disilane (Fig. 5) and ammonia (Fig. 6).

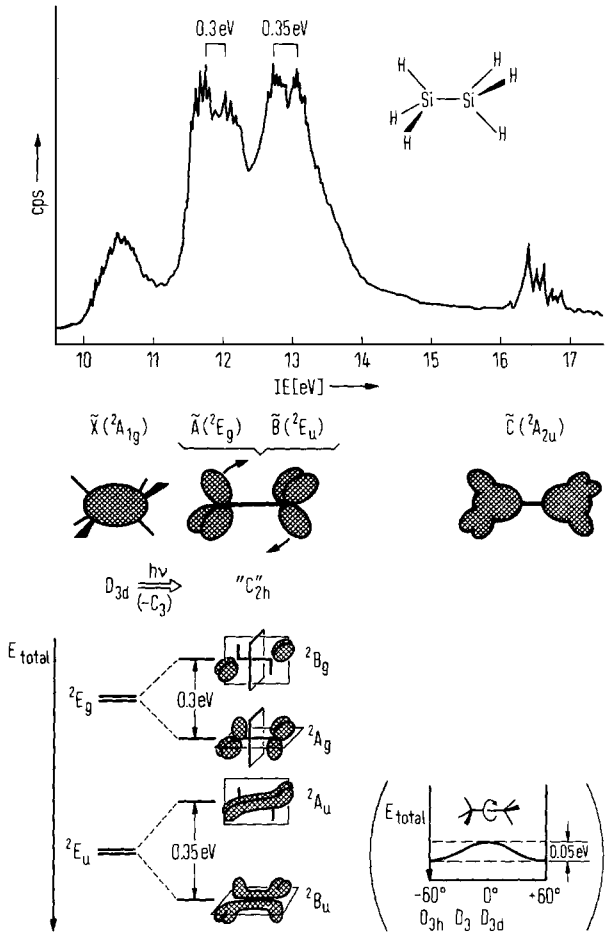


Fig. 5. In the photoelectron spectrum of Si_2H_6 [18] 7 ionizations are expected, corresponding to 14 valence electrons. Of these ionizations 2 each should lead, in the preferred staggered conformation of D_{3d} symmetry, to energetically degenerate radical cation states. Thus a total of 5 PE bands are predicted, assignable to the following $H_3Si—SiH_3^{\bullet\oplus}$ states given in the order of increasing energy (concerning nomenclature, cf. [14, 19]): σ_{SiSi} ionization $\rightarrow \tilde{X}(^2A_{1g})$, σ_{SiH_3} ionization $\rightarrow \tilde{A}(^2E_g)$ and $\tilde{B}(^2E_u)$, and the ionizations having large $3s_{Si}$ components $\rightarrow \tilde{C}(^2A_{2u})$ and $\tilde{D}(^2A_{1g})$, with the latter outside the range of measurement. It is observed, however, that the second and third PE bands are split by 0.3 and 0.35 eV, respectively. This is because the energetic equality of the degenerate states $\tilde{A}(^2E_g)$ and $\tilde{B}(^2E_u)$ is removed by a "Jahn-Teller distortion" of $H_3Si—SiH_3^{\bullet\oplus}$: two SiH bonds probably bend, the threefold symmetry axis vanishes ($-C_3$), the structure of the resulting radical cation belongs to the C_{2h} symmetry group, and the degenerate states split ($^2E_g' \rightarrow {}^2B_g + {}^2A_g$; $^2E_u \rightarrow {}^2A_u + {}^2B_u$). The splitting of the second and third PE bands cannot be attributed to a conformational rotation ($D_{3d} \rightarrow D_3 \rightarrow D_{3h}$) about the SiSi bond since the threefold axis and thus the degeneracy would be retained in the process; furthermore, the rotational barrier amounts to only 0.05 eV [18].

Assuming the species to have the same structure as the neutral molecule, the disilane radical cation $H_3Si—SiH_3^{\bullet\oplus}$ is expected to display two sets of two degenerate states of equal energy: the pertinent bands should therefore have double intensity but only one maximum. However, the PE spectrum of disilane (Fig. 5) tells a different story: the second and third PE bands are split by 0.3 and 0.35 eV, respectively[18]. This observation cannot be attributed to a conformational change since the degeneracy of the states would be conserved on rotation about the SiSi bond and the energy barrier for such a rotation is a mere 0.05 eV. Rather, a structural change must have taken place which destroys the threefold axis, *e.g.* by analogy with the $H_3C—CH_3^{\bullet\oplus}$ cation[18], by deformation of SiSiH angles (Fig. 5). Restructuring of the $\tilde{A}(^2E_g)$ and $\tilde{B}(^2E_u)$ states of the disilane cation is not a unique occurrence: degenerate radical cation states of non-linear molecules are generally unstable towards such a "Jahn-Teller distortion". The energy gap arising on removal of degeneracy can exceed 1 eV[15b,c].

Information like this read off from PE spectra is open to generalization: during mono-ionization from the ground state of a molecule having n valence electrons to generate one of the possible $n/2$ radical cation states (Fig. 3), both the molecular structure and other molecular properties can undergo drastic changes. This is impressively demonstrated by a comparison of vibrational frequencies of the tetraatomic molecules NH_3, PH_3, and PF_3 and those of their radical cations $NH_3^{\bullet\oplus}$, $PH_3^{\bullet\oplus}$, and $PF_3^{\bullet\oplus}$[2e, 20] (Fig. 6).

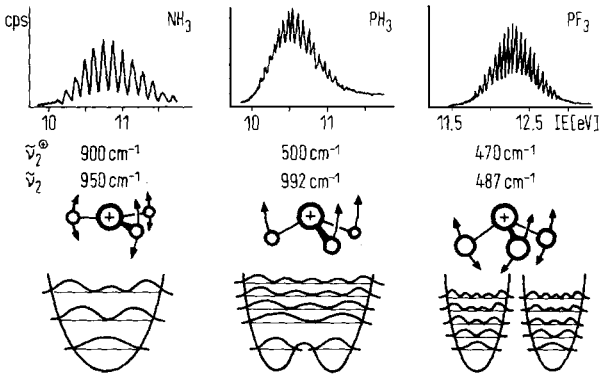


Fig. 6. The first band of the photoelectron spectra of NH_3, PH_3, and PF_3 [20], which is assigned to ionization from the n_N or n_P electron pair, exhibits a marked vibrational fine structure. Some 20 peaks are recognizable, from which the frequency of the symmetrical deformation $\nu^{\oplus}$ of the radical cation can be determined to within $\pm 20\,cm^{-1}$. On comparison of $\tilde{\nu}^{\oplus}$ with the ground state frequency of the neutral molecule $\tilde{\nu}$, a constant (NH_3, PF_3) or halved value (PH_3) is found [2e, 20]. Constant values result when no molecular inversion occurs, as a consequence of flattening of the molecular skeleton yielding the planar $NH_3^{\bullet\oplus}$ species or of an excessively high inversion barrier in pyramidal $PF_3^{\bullet\oplus}$. Halving of frequency [21] occurs at low inversion barriers, *e.g.* in the flattened pyramid of $PH_3^{\bullet\oplus}$. In the potential energy diagrams (cf. Fig. 4), these results are described in terms of a common potential trough ($NH_3^{\bullet\oplus}$), two extensively overlapping potential troughs ($PH_3^{\bullet\oplus}$), or two completely separate potential troughs ($PF_3^{\bullet\oplus}$) [2e, 20].

The first ionization of the pyramidal compounds XH_3 and XF_3 occurs from the electron pairs n_x[2e, 20–22]. Comparison of the symmetrical deformation vibrations of the neutral molecule (Fig. 6: $\tilde{\nu}_2$) and the radical cation (Fig. 6: $\tilde{\nu}_2^{\oplus}$) demonstrates just how diverse the changes in properties can be, which arise on removal of an almost nonbonding electron: in the planar[20] species $NH_3^{\bullet\oplus}$ no inversion can occur and the (slightly lower frequency) deformation vibration can be described by a single potential trough (Fig. 6). The ionization $PH_3 \rightarrow PH_3^{\bullet\oplus} + e^{\ominus}$ widens the HPH angle from 93.3° to about 110°[20]; the halving of frequency observed in the PE spectrum (Fig. 6: $\tilde{\nu}_2^{\oplus} \approx \frac{1}{2}\tilde{\nu}_2$) is explicable as due to extensive interpenetration of the potential troughs corresponding to the two inverto-

mers[21b]. In contrast, the molecular structure is largely retained on electron ejection from $PF_3 \rightarrow PF_3^{\bullet\oplus} + e^{\ominus}$, and the high inversion barrier describable by two distinct potential troughs[20] prevents frequency halving of the symmetrical deformation vibration $\nu_2^{\bullet\oplus}$.

Even in the case of constant electron occupancy in the initial and final states a supply of energy might effect a drastic redistribution of charge: frequently cited structural modifications[21c, 22] accompanying transitions into other electronic states include the mutual twisting of the two halves of the molecule of ethylene and the bending of acetylene in the lowest excited state, as well as the bending of carbon dioxide or the stretching of water on absorption in the vacuum UV region (Fig. 7).

From the sheer number of structural modifications of molecules known to occur on uptake of energy and—more generally—from the accompanying modifications of molecular properties caused by redistribution of charge it follows that:

The chemist's synthetic building block with a particular structure and characteristic properties is always a molecule in a state of specific energy and charge distribution.

Reactions are likewise not typical for a molecule but—as already emphasized for $HBr^{\bullet\oplus}$ (Fig. 4)—for a particular molecular state. This is strikingly confirmed by the different kinds of reaction pathways emanating from different kinds of photochemically excited states[23], *e.g.* from the $^3(n\rightarrow\pi^*)$ triplet state and from the $^1(\pi\rightarrow\pi^*)$ singlet state of adamantanethione[24] (Fig. 8).

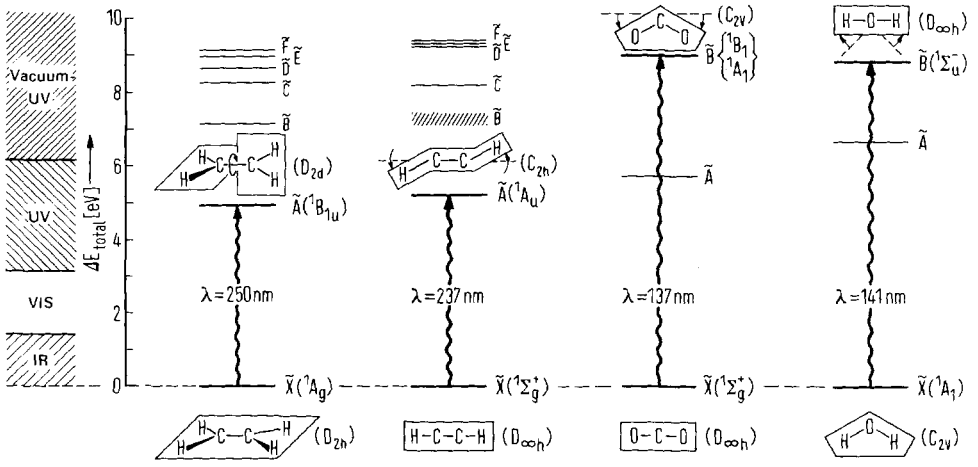


Fig. 7. The structure of a molecule can also be modified after energy transfer through a photon if the number of electrons remains constant (cf. Figs. 3 to 6). Thus ethylene is twisted on $\pi\rightarrow\pi^*$ excitation in the UV region; at the minimum of the potential energy curve of the excited state $\tilde{A}(^1B_{1u})$ [14] the two H_2C halves of the molecule are mutually perpendicular (D_{2d} symmetry). Linear in its ground state $\tilde{X}(^1\Sigma_g^+)$, acetylene is doubly bent in the first electronically excited state $\tilde{A}(^1A_u)$. Excitation with short-wave light ($\lambda = 137$ nm) bends carbon dioxide; in contrast, water is stretched in its 2nd excited state $\tilde{B}(^1\Sigma_u^-)$ in the vacuum UV region. In the other states shown ($\tilde{A}, \tilde{B}, \tilde{C}, \tilde{D}$...) there is either no structural change [21, 22] or the geometry of the excited state is (still) unknown.

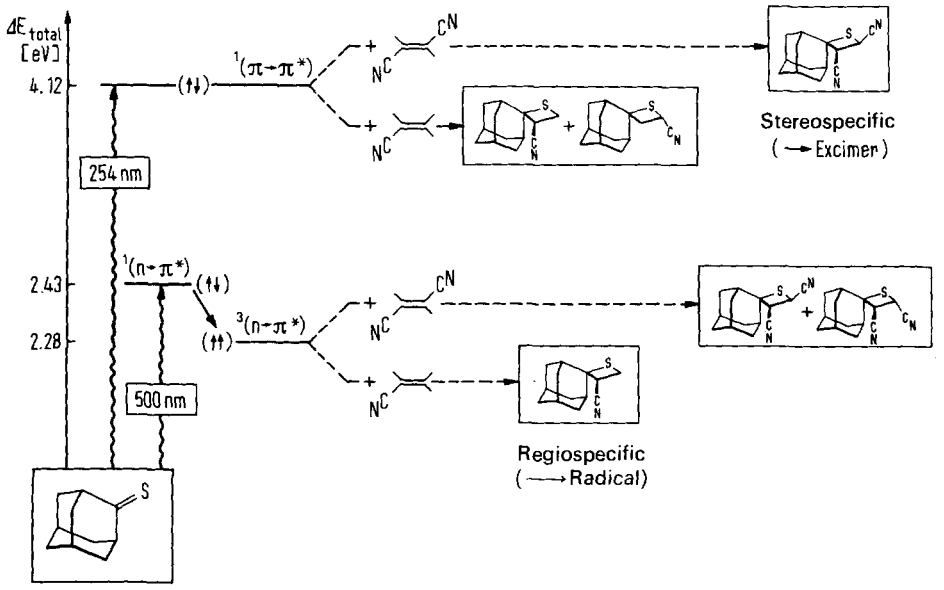


Fig. 8. Adamantanethione exhibits $^1(\pi\rightarrow\pi^*)$ and $^1(n\rightarrow\pi^*)$ electronically excited states separated by 1.69 eV; the latter undergoes radiationless transition into the lower-energy triplet state $^3(n\rightarrow\pi^*)$ with two unpaired ($\uparrow\uparrow$) electron spins [24]. Reaction with acrylonitrile or fumaronitrile on irradiation with 254-nm light ($\pi\rightarrow\pi^*$) or 500-nm light ($n\rightarrow\pi^*$) therefore lead to different reaction types and reaction products [24]: the $^3(n\rightarrow\pi^*)$ diradical reacts regiospecifically with acrylonitrile *via* the radical intermediate of most favorable energy. In the $^1(\pi\rightarrow\pi^*)$ singlet state with paired electron spins ($\uparrow\downarrow$) addition of fumaronitrile occurs stereospecifically *via* an excimer complex [24].

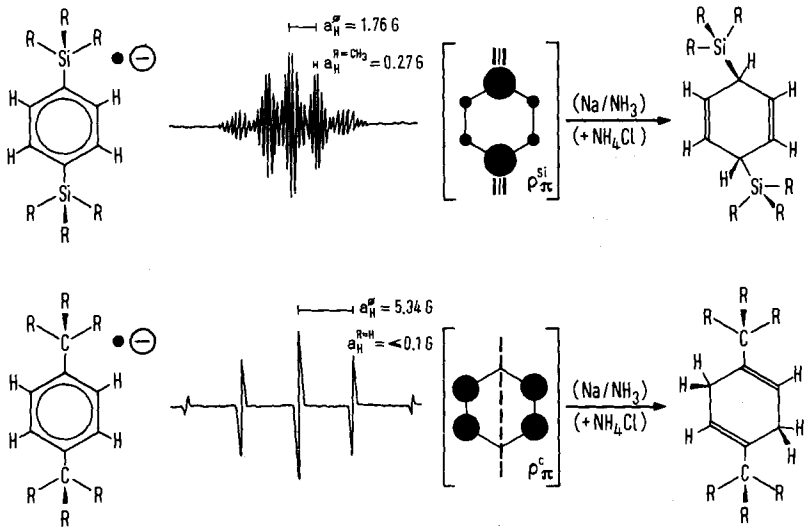


Fig. 9. 1,4-Bis(trimethylsilyl)benzene can be reduced to the radical anion by potassium in dimethoxyethane. Its ESR spectrum [25] displays the quintet of 4 phenyl protons with a gap of 1.76 G between the corresponding signals, which are further split by the 18 equivalent methyl protons ($R = CH_3$) (intensity ratio outer line: inner line = 1:48620). The *p*-xylene radical anion ($R = H$), on the other hand, yields an ESR spectrum which, while revealing a more strongly split quintet of the 4 phenyl protons, gives no evidence for additional coupling with the methyl protons: hence the substitution sites must lie in a nodal plane in which the spin density ρ_π is approximately equal to zero. The charge density is consequently also low and preparative protonation by treatment with NH_4Cl after prior Birch reduction (Na/NH_3) accordingly proceeds exclusively a positions 2 and 5. As indicated by the drop in the phenyl proton coupling constant a_H^{ar} from 5.34 to 1.76 G, the electron density in these positions is lower in the trimethylsilyl derivative which is protonated solely in positions 1 and 4 [26] where a high spin, and hence a high charge density is now evidenced by the clearly resolved coupling of the methyl protons $a_H^{R=CH_3}$.

As shown by the excitation and reaction scheme for adamantanethione, the reactions starting from the $^3(n\rightarrow\pi^*)$ triplet state proceed by a radical mechanism[24] and involve the radical intermediate of most favorable energy: they are therefore regiospecific but not stereospecific. In contrast, formation of an excimer complex is observed to follow excitation into the $^1(\pi\rightarrow\pi^*)$ singlet state[24]: acrylonitrile is not longer added regiospecifically, while fumaronitrile does undergo stereospecific addition.

Experimental evidence for the variety of reactions for various charge distributions is supplied by, *e.g.*, combined ESR[25] and preparative studies[26] on the reduction of 1,4-dialkyl- and of 1,4-bis(trimethylsilyl)benzene derivatives (Fig. 9).

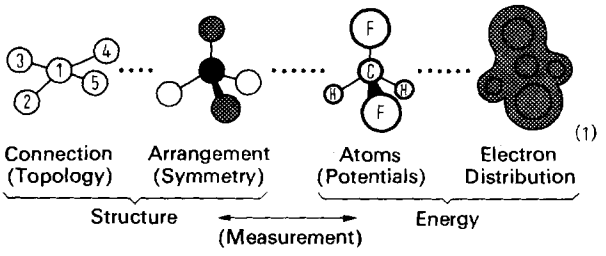
From the ESR spectra of benzene radical anions (Fig. 9) we can deduce coupling constants a_H^π which are directly proportional to the π-spin populations ρ_π at the relevant π centers[27,28]. They furnish the following information about the distribution of the additional electron in variously substituted reference compounds: in the trimethylsilyl derivative the substitution sites 1 and 4 bear the greatest charge, whereas in the *p*-xylene radical ion these positions lie in a nodal plane of negligible spin density (Fig. 9). The ESR evidence can be tested and exploited preparatively: protonation with NH_4Cl after prior Birch reduction with Na/NH_3 always occurs at the centers of greatest electron density. In full accord with the charge distribution estimated from the ESR spectra, the 1,4-bis(trimethylsilyl) compound is hydrogenated only in positions 1 and 4 to yield the corresponding cyclohexadiene, whereas the *p*-xylene radical anion is protonated solely at positions 2 and 5[26] (Fig. 9).

These examples, selected from a wealth of similar ones, document that the molecules in their individual states exhibit specific properties, including a specific reactivity. The number of building blocks available for chemical syntheses is multiplied several-fold by this energetic diversification: the number of 10^7 compounds so far known to result from variation of constituent elements and connections has to be increased for molecules containing N atoms and n valence electrons to include $3N-6$ vibrational modes, at least $n/2$ ionizations, far more than $(\frac{n}{2})^2$ electronic excitations, as well as states arising by other processes. In order to gain some kind of overview of such an enormous variety, to recognize inherent trends and regularities, and to formulate predictions the chemist needs a model containing the parameters of importance for molecular states (Fig. 3) in suitable form, and which is also flexible and open to extension (Fig. 2).

The best model hitherto available for a comprehensive description of molecular states is the molecular orbital representation[29].

3. Description of Molecular States by Molecular Orbitals

What demands does the chemist place on a model for molecular states? As illustrated for H_2CF_2, it must contain the number of atoms, their connection (topology) and their arrangement (symmetry):



(1)

Furthermore, potentials have to be defined for the individual centers, representing various kinds of atoms, in such a way that the resulting electron distribution reproduces all important details of molecular structure such as distances and conformation. The energy must be included in the model as a parameter of molecular state, and changes in characteristic molecular properties should be determinable as a consequence of changes in energy (Fig. 3). For the chemist it is important that such a model permits comparison of experimental data applying to corresponding states of chemically related molecules (Fig. 2).

In simple molecular orbital models, whose utility and limitations will now be considered for various examples, the procedure is to determine the distribution or motion of an electron in the time-averaged field of the atomic nuclei and the other electrons of a molecule. In order to answer the question "when and with what probability will an electron be located at which site?", the $3N$-dimensional total function resulting for N electrons is approximated by a product of three-dimensional functions having particular qualities[30-32]. The (one-electron)

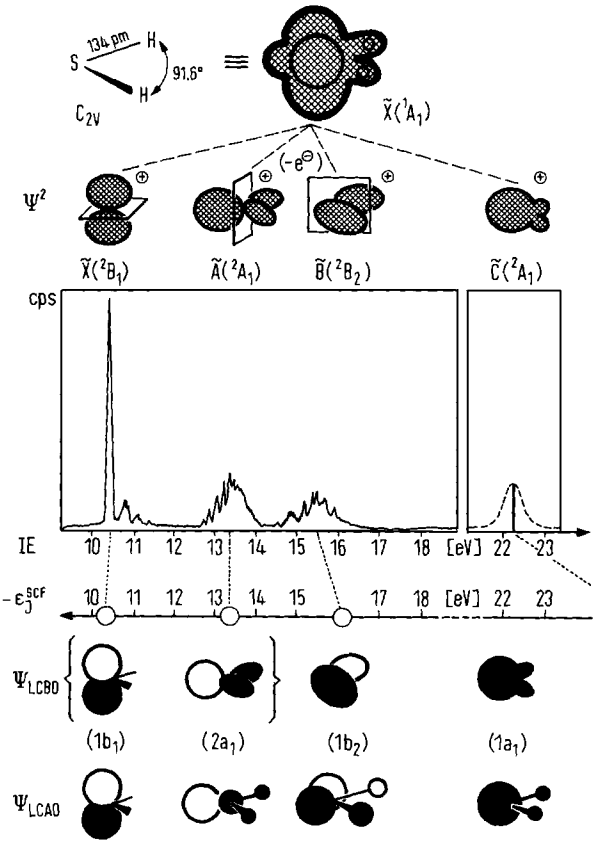


Fig. 10. In the gas phase the HSH molecule has a C_{2v} structure; the electron density distribution in the ground state $\tilde{X}(^1A_1)$ is totally symmetric and almost spherical. Ionization of one of the 8 valence electrons leads to the ground state $\tilde{X}(^2B_1)$ or one of the three excited states [14, 19] $\tilde{A}(^2A_1)$, $\tilde{B}(^2B_2)$, or $\tilde{C}(^2A_1)$ of the radical cation $HSH^{\bullet\oplus}$, which exhibit 0 or 1 zero site planes with respect to the resulting electron hole. All four states of $HSH^{\bullet\oplus}$ are observed in the PE spectrum between 10.47 and 22.2 eV in the HeII region [35]. The ionization energies can be satisfactorily correlated with SCF orbital energies according to *Koopmans* ($IE_n^v = -\varepsilon_j^{SCF}$) [36]. The relevant orbital diagrams can be qualitatively depicted by symmetry-adapted linear combinations (*LC*) of *B*ond *O*rbitals ψ_{LCBO} or of *A*tomic *O*rbitals ψ_{LCAO}. The resulting molecular orbitals ψ frequently change their sign (○|●); the resulting nodal planes of C_{2v} symmetry types (b_1), (a_1), and (b_2) are retained as zero site planes (⊛|⊛) in the squared functions [2]. These can be compared with the electron-hole zero site planes of the radical cation states such as would result from the difference electron densities of the HSH ground state and the individual $HSH^{\bullet\oplus}$ radical cation states.

molecular orbitals thus obtained are especially suitable for discussions of one-electron properties such as the states of radical cations $M^{\bullet\oplus}$ arising on ionization of an electron, in which the electronic interaction and electron distribution still resemble those in the ground state of the neutral molecule M. In such cases *Koopmans'* theorem[33] is valid

$$\Delta E_{total} = IE_n^v \equiv -\varepsilon_j^{SCF} \qquad (2)$$

according to which the vertical ionization energies IE_n^v measured by photoelectron spectroscopy, *i. e.* the energy differences between the particular states ΔE_{total} for ejection of an electron $M + h\nu \rightarrow M^{\bullet\oplus} + e^{\ominus}$ (Fig. 3), can be correlated with calculated (one-electron) orbital energies $-\varepsilon_j^{SCF}$ of "*S*elf *C*onsistent *F*ield" quality[32-34]. Let us therefore begin our description of molecular states by molecular orbitals with the didactically advantageous example of the four states of the triatomic radical cation $HSH^{\bullet\oplus}$ resulting on valence electron ionization and discussible in terms of theorem (2) (Fig. 10).

Ejection of a valence electron from the HSH molecule, which exhibits an almost spherical charge distribution in the ground state, leads to four states of the radical cation $HSH^{\bullet\oplus}$ observable in the PE spectrum. In these states the distribution of the electron hole can be described by calculating the difference electron density between the initial state and pertinent final state (Fig. 10): evidently, zero site planes can result whose positions relative to the molecular skeleton are reflected by the symmetry classification[19] of the radical cation state[14]. If *Koopmans'* theorem (2) applies—*i. e.* if the redistribution of charge (relaxation) and changes in the mutually dependent motion of electrons (correlation) accompanying the ionization process are negligibly small[15b,c]—then the electronic arrangements (configurations) in the individual states can be described by a single set of molecular orbitals ψ. Such a set can be approximately constructed by linear combination of bond or atomic orbitals (Fig. 10). There result symmetry-adapted molecular orbitals ψ which are themselves not experimental observables; however, their squares ψ^2 can be correlated with experimental electron densities. The electron-hole zero site planes in the radical cation states apparently correspond to those of the squared functions ψ^2 and thus to the nodal planes resulting from changes of sign in the molecular orbitals ψ (Fig. 10). The utility of such molecular orbitals ψ or of their squares ψ^2, sketched by hand or plotted by computer, will now be demonstrated by PE spectroscopic comparison of the iso-valence electronic compounds HSH and HOH (Fig. 11).

HSH and HOH differ primarily in the higher effective nuclear potential of the oxygen and in the larger HOH angle. Under the assumption, corroborated in the following, that no essential structural change will occur on ionization to the radical cation ground state $\tilde{X}(^2B_1)$[32], the potential difference can be accounted for by shifting one of the two PE spectra along the ionization energy scale (Fig. 11). The angle opening effects which then become clearly recognizable were correctly predicted by *Walsh* in 1953[37]—ten years before the discovery of PE spectroscopy: $\Delta IE_{1,2}$ decreases and $\Delta IE_{2,3}$ increases. This situation is a consequence of the optimum electron distribution in the individual radical cation states, which depends upon the given potential and can be qualitatively interpreted with the aid of the relevant molecular orbi-

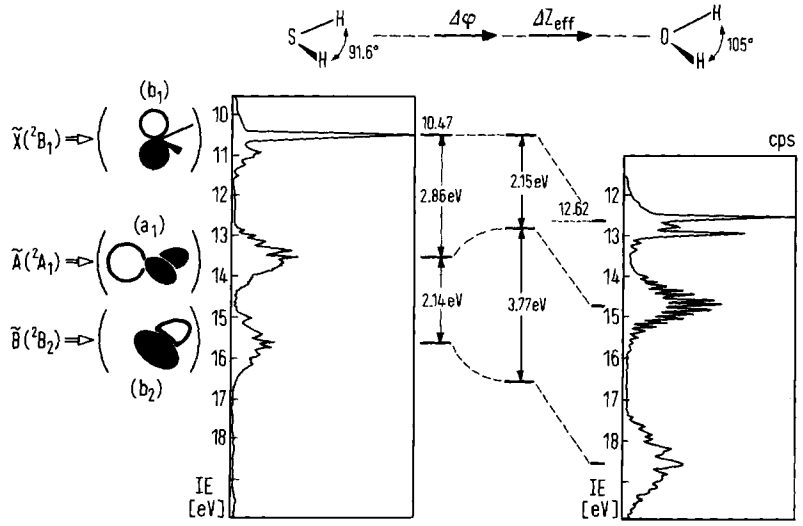


Fig. 11. On comparison of the first three radical cation states $\tilde{X}(^2B_1)$, $\tilde{A}(^2A_1)$, and $\tilde{B}(^2B_2)$ of the iso-valence electronic triatomic molecules HSH and HOH particular attention has to be focused on the change of the bond angle $\Delta\varphi$ and the differing effective nuclear charge ΔZ_{eff} of sulfur and oxygen. Assuming the first ionization, assigned to the nonbonding electron pair, to constitute a suitable internal standard, ΔZ_{eff} can be compensated by a relative shift of the PE spectra [35] by $12.62-10.47=2.15$ eV. The opening of the angle $\Delta\varphi$ can be discussed on the basis of the molecular orbitals (b_1), (a_1), and (b_2) as follows [37]: diminution of the bonding interaction and augmentation of the antibonding interaction in (a_1) raises (destabilizes) this orbital, while diminution of the antibonding interaction in (b_2) lowers (stabilizes) that orbital. There results an experimental Walsh diagram [37] which permits comparison of the radical cation states of the chemically related molecules HSH and HOH.

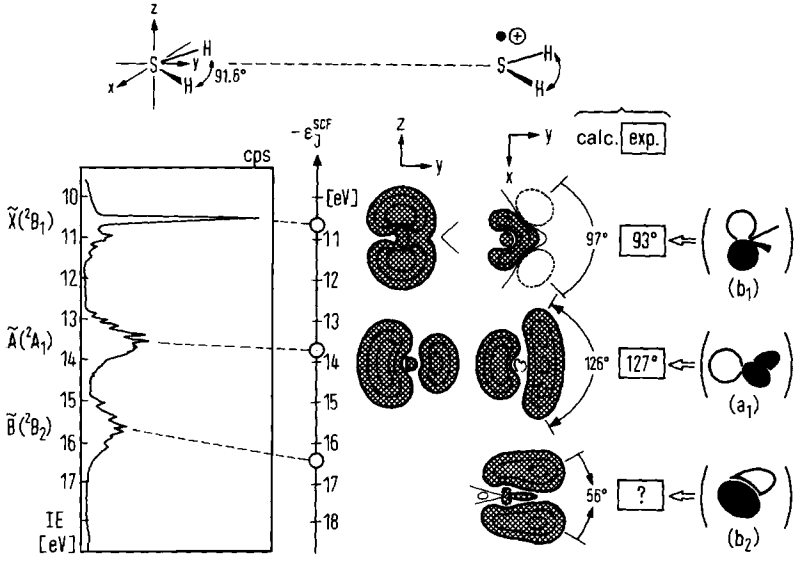


Fig. 12. The radical cation $HSH^{\bullet\oplus}$ expectedly shows structural changes (cf. Figs. 4 to 6) in some of its states. In the ground state $\tilde{X}(^2B_1)$ the angle φ remains almost constant relative to HSH. For the 1st electronically excited state $\tilde{A}(^2A_1)$ an opening to 127° is found spectroscopically [35] and for the 2nd excited state a closing to 56° is calculated [36]. The distribution of the unpaired electron, corresponding to that of the electron hole, follows from the spin population contour diagrams in the zy and xy planes calculated for optimized geometry [36]; negative spin densities are merely shown as dashes. There is satisfactory overall agreement between experimental and calculated data $IE=-\varepsilon_j^{SCF}$ and φ (*ab initio* open shell with STO 3G basis set [36]). Qualitative molecular orbital considerations predict the following angle changes in the $HSH^{\bullet\oplus}$ states: roughly constant according to (b_1) because of the node in the HSH plane; widened according to (a_1) by reduced antibonding interaction and analogously narrowed according to (b_2).

tals[37]: if the bonding interactions characterized by like signs in a molecular orbital increase then the orbital is stabilized, and if the antibonding interactions characterized by a change in sign increase then destabilization occurs (Fig. 11). Conversely, the applicability of such perturbation arguments to the comparison of states of chemically related compounds *via* molecular orbitals according to (2) shows that we are dealing with comparable states having comparable properties; it therefore supports the assignment of the PE spectra and can be extended to other AH_2 compounds which may also have a different number of electrons[37]. In sum, correlation diagrams according to *Walsh*[37], which reproduce changes in

orbital energies accompanying changes in structural parameters, furnish a far-reaching overview of numerous molecular states.

The perturbation arguments also permit prediction of structural modifications in the individual radical cation states of a particular molecule, if these relax towards the potential minima after vertical excitation (cf. Fig. 4): if ionization generates a radical cation state whose representative molecular orbital—now occupied by only one electron—is dominated by strong bonding or antibonding interactions then structural changes mitigating these interactions are expected. The optimum charge distribution in the individual states can be discussed in these terms as will also be demonstrated for $HSH^{\bullet\oplus}$ as example (Fig. 12).

The calculated optimum charge distributions in the individual $HSH^{\bullet\oplus}$ states[36], rationalizable in terms of qualitative molecular orbital perturbation arguments, are in accord with spectroscopic structural parameters[35]: ionization of the nonbonding sulfur electron pair leaves the HSH angle unchanged; in the subsequent first excited state it is opened to 127°. In this context, it should be mentioned as a further example of changes occurring in energetically higher states (cf. Figs. 4 to 7) that both spectroscopic evidence[35] and calculations[36] show the water radical cation $HOH^{\bullet\oplus}$ to be linear in the first electronically excited state (cf. Fig. 12: $\tilde{A}(^2A_1)$).

The above discussion of radical cation states of HSH and HOH (Figs. 10, 11, and 12) demonstrates that *ab initio* SCF spin populations and the "qualitative" molecular orbitals in qualitative agreement therewith, satisfactorily describe the electron distribution and structure, respectively, and thereby facilitate extensive comparison of these chemically related molecules. A further example will illustrate the feasibility of such a state correlation also for characteristic molecular subunits such as π bonds and the way in which the symmetry-adapted qualitative MO models can be energetically parametrized with the experimentally determined energy differences between the states. The π-ionization energies of norbornene, norbornadiene, isopropylidenenorbornadiene, and isopropylidenenorbornane determined by PE spectroscopy represent the starting point of our discussion[38] (Fig. 13).

Three π ionizations are expected and observed in the PE spectrum of isopropylidenenorbornadiene[38] (Fig. 13: $M^{\bullet\oplus}$).

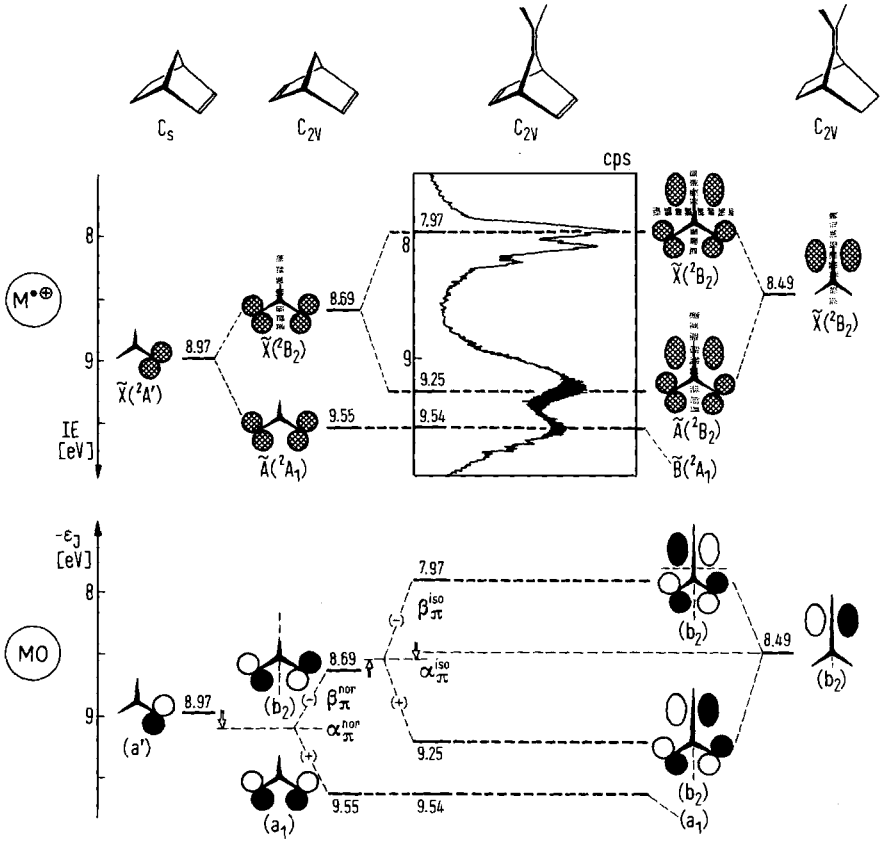


Fig. 13. Comparison of radical cation states $M^{\bullet\oplus}$ of chemically related molecules is a valuable aid in the assignment of PE spectra such as that of isopropylidenenorbornadiene: the first ionization of norbornene (C_s symmetry) and of isopropylidenenorbornane (C_{2v} symmetry) leads to the π-radical cation ground state $\tilde{X}(^2A')$ and $\tilde{X}(^2B_2)$, respectively. Norbornadiene has two $\pi^{\bullet\oplus}$ states, $\tilde{X}(^2B_2)$ and $\tilde{A}(^2A_1)$. Of the three π states of isopropylidenenorbornadiene the highest one $\tilde{B}(^2A_1)$ has the same energy as the $\tilde{A}(^2A_1)$ state of norbornadiene; the two lower ones $\tilde{X}(^2B_2)$ and $\tilde{A}(^2B_2)$ are of the same symmetry type and are split to lower and higher ionization energies relative to the $\tilde{X}(^2B_2)$ states of norbornadiene and isopropylidenenorbornane of equal symmetry.—This situation can be transparently illustrated with π molecular orbitals MO [38, 39]: in norbornadiene the two π orbitals (a_1) and (b_2) split about an average value α_π^{nor} which roughly corresponds to the π level of norbornane ($\Downarrow$). Of the two norbornadiene π orbitals only (b_2) has the correct symmetry to mix with the $\pi(b_2)$ orbital of isopropylidenenorbornane, which leads to the two $\pi(b_2)$ molecular orbitals split about the average value ($\Uparrow\Downarrow$) α_π^{iso}. The third π molecular orbital (a_1) cannot interact with any other orbital of same symmetry and therefore its orbital energy expectedly resembles that of the $\pi(a_1)$ orbital of norbornadiene. The interaction parameters β_π^{nor} and β_π^{iso} can be determined from the PE spectroscopic ionization energies (see text).

The radical cation ground state exhibits a relatively low energy, and the two excited states lie close together. Comparison with the $\pi^{\bullet\oplus}$ states of other bicyclo[2.2.1] hydrocarbons reveals how the varying energy differences can be interpreted: doubling the number of π electrons on going from norbornene to norbornadiene leads to states of type $^2A_1$ and $^2B_2$ and introduction of another exocyclic double bond of the same symmetry type to splitting of the two $^2B_2$ states about their average value. This state correlation can be translated into through-space interaction[39] within the framework of a qualitative MO model (Fig. 13: MO) and described by construction of linear combinations of appropriate symmetry. Only π orbitals of same symmetry mix with each other—in full accord with the PE spectroscopic finding that the same ionization energy must be expended to generate the $^2A_1$ states of norbornadiene and isopropylidenenorbornadiene (Fig. 13: $M^{\bullet\oplus}$).

The qualitative MO model whose molecular orbitals reflect the symmetry classification[19] of the radical cation states (Fig. 13) can be energetically parametrized as follows: The Coulomb integrals α_π[40], which represent the energy of electrons in a given potential, can be determined in the present case by taking the average of the π-ionization energies of norbornadiene or of the two $^2B_2$ states of norbornadiene and isopropylidenenorbornane (Fig. 13: α_π^{nor} and α_π^{iso}). In many calculation procedures—*e.g.* the HMO approximation—overlap integrals S are not explicitly accounted for but included by definition in the interaction parameter β[40]. The latter can be calculated from the determinant (3), which contains the connection of individual centers or of subunits in the system and permits calculation of the pertinent eigenvalues ε_J[40] by insertion of the relevant ionization energies. For instance, the interaction of the two π units in norbornadiene with $\alpha_\pi^{nor} = (8.69+9.55)/2 = 9.12\,eV$ and with $\varepsilon = IE_1 = 8.69\,eV$ (Fig. 13) is given by

$$\begin{vmatrix} \alpha_\pi^{nor}-\varepsilon & \beta_\pi^{nor} \\ \beta_\pi^{nor} & \alpha_\pi^{nor}-\varepsilon \end{vmatrix} = 0;$$

$$\beta_\pi^{nor} = -\sqrt{(\alpha_\pi^{nor}-\varepsilon)^2} \qquad (3)$$
$$= -\sqrt{(9.12-8.69)^2} = -0.43\,eV$$

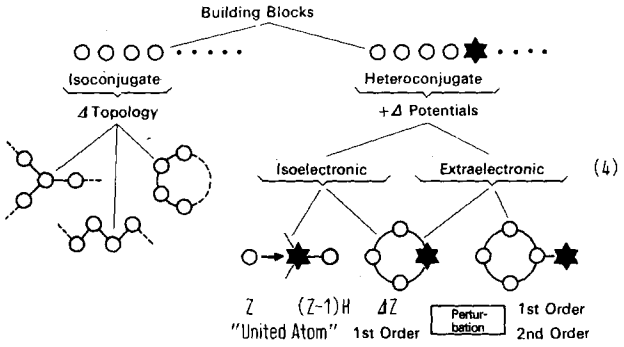
When calculating the analogous parameters β_π^{iso} for isopropylidenenorbornadiene it must be borne in mind that three π subunits are interacting[40]. The resulting parameters α_π and β_π command more general interest because they can be compared with values for other π systems[2c] and can be inserted in qualitative MO models[41] for analogous compounds.

The satisfactory description of radical cation states by molecular orbitals (Figs. 9 to 13) confirms that the requirements specified above (1) concerning the reproduction of atom connection and arrangement, as well as electron distribution in the existing potentials, are fulfilled. Even the qualitative linear combinations of bond orbitals which are readily compatible with chemical intuition can be symmetry-adapted[19] and parametrized in a transparent way with experimental state data. The predictions of such simple MO models can be supported by the results of calculations of varying degrees of sophistication right up to the numerical reproduction of state data (Fig. 1). As repeatedly emphasized, there is one particular application of particular interest to the chemist:

Mutually corresponding states of chemically related molecules can advantageously be compared on the basis of molecular orbitals.

4. Comparison of Molecular States Based on Molecular Orbitals

Practically every chemist attempts to organize his set of individual compounds by some definition of chemical relatedness, *e.g.* by principles of homology or by substituent effects. Starting from (1), the following classifications are recommended for molecular state comparison:



Depending upon the relative change, the distinction between iso- and hetero-conjugate, and between iso- and extra-electronic systems is of course a flexible one. The extent of perturbation often also determines the scope of a model, and, within this scope, its quality, *i.e.* the deviations in correlations between observed and calculated quantities.

From thousands of published state comparisons some exemplifying (4) will now be presented. They are chosen to illustrate how entire classes of compounds can be surveyed by application of a network of general rules (cf. Fig. 2).

4.1. Topology-Based Comparison of States

In the approximate solution of the Schrödinger equation applying the variation principle, a secular determinant of type (3) is passed[40] which incorporates the topology of the molecule (4). Thus in the HMO approximation[28] for unbranched polyene chains (Fig. 14) the principal diagonal contains the energy terms $(\alpha-\varepsilon)$ and the adjacent diagonals contain the π interactions β_π assumed to be equal between the connected centers ①–②, ②–①, ②–③ ... (μ)–(μ−1). The solutions of the corresponding eigenvalue polynomials can be derived in closed form[28] (Fig. 14).

From the HMO eigenvalue schemes of linear π systems (Fig. 14) one infers for their state comparison: neutral compounds with odd-numbered polyene chains in which one electron occupies the non-bonding molecular orbital of eigenvalue $\varepsilon_J^{HMO} = \alpha$, are radicals with a doublet ground state. In compounds with even-numbered π systems, the energy difference $\Delta E = h\nu_\pi$ between the ground state and the first $(\pi \rightarrow \pi^*)$ excited state can be compared, in a crude approximation, with the distance between the inner molecular orbitals $\Delta\varepsilon_J^{HMO}$, and the color of polyenes thereby satisfactorily predicted. Moreover, all unbranched polyene chains belong to the alternant π systems[28, 42–44], whose molecular orbitals show pairwise correspondence (Fig. 14: $\varepsilon_J^{HMO} = \varepsilon_{n-J+1}^{HMO}$) and always display

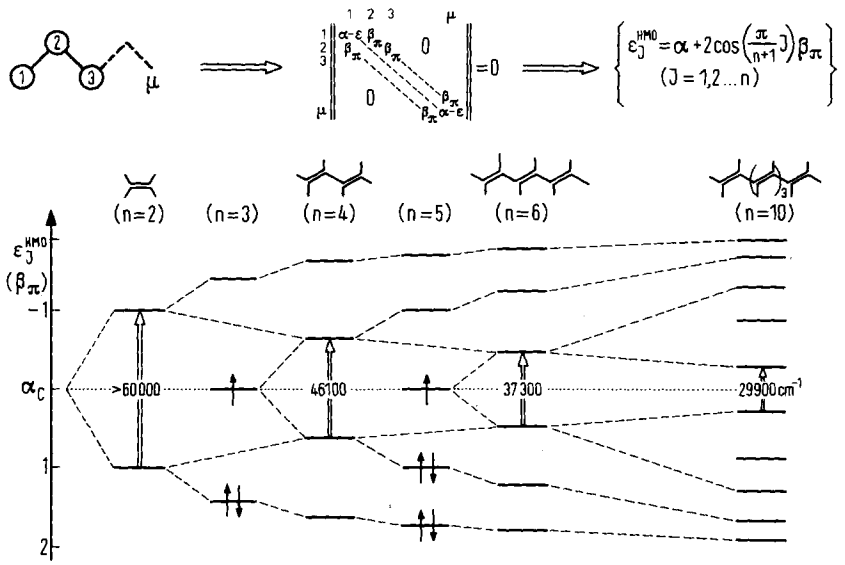


Fig. 14. The HMO model [28] for linear π-electron systems with $\mu = n$ centers, assumes in a simplifying way that all π interactions β_π are equal. A closed formula for the eigenvalues ε_J^{HMO} can be derived *via* the determinant [40] || || containing the connections of the individual centers. The eigenvalue schemes in units of the parameter (β_π) permit a comparative discussion of numerous properties of linear polyenes. Thus all odd-numbered compounds are radicals owing to the occupation of the non-bonding molecular orbital $\varepsilon_J^{HMO} = \alpha$ by only one electron (↑). For even-numbered π systems the distance between the inner orbitals decreases with increasing number of centers and a linear regression is obtained for the wave number $\tilde{\nu}_\pi$ [cm^{-1}] of the longest wavelength absorption, *i.e.* $\tilde{\nu}_\pi = 14800 + 25400\,\Delta\varepsilon_J^{HMO}$ [28], from which the color of long-chain polyenes can be predicted. From the alternancy, *i.e.* from the pairwise arrangement of the molecular orbitals ψ_J and ψ_{n-j+1} relative to α_C, it follows, among other things [28], that the charges q_μ at all centers μ amount to $q_\mu = 1$ and, therefore, the π-dipole moment μ_π must be identical to zero, $\mu_\pi = 0$.

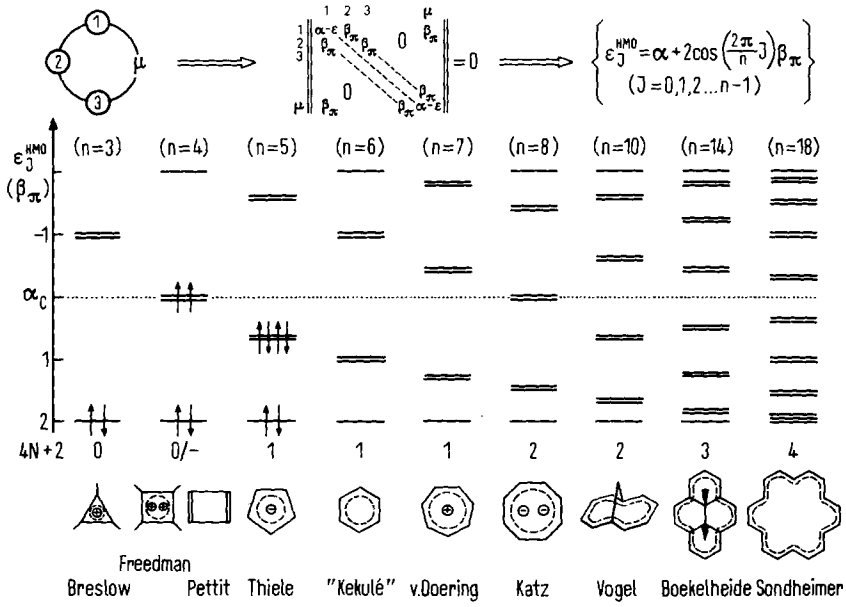


Fig. 15. For cyclic π-electron systems [28] the interactions β_π occurring on ring closure 1—μ have to be included in the HMO determinant [40] || || in addition to the linear systems (Fig. 14). The general formula resulting for the eigenvalue ε_J^{HMO} furnishes energy-level schemes in units of β_π which display the following features: regardless of the number of centers $J = n$, an eigenvalue $\varepsilon_0^{HMO} = \alpha + 2\beta$ is always obtained for $J = 0$; pairs of degenerate eigenvalues $\varepsilon_J^{HMO} = \varepsilon_{n-J}^{HMO}$ result from the cosine term for values $0 < J < n-1$; and finally $\varepsilon_{n-1}^{HMO} = \alpha - 2\beta$ follows for $J = n-1$ in all even-numbered, and hence alternant, primeters. On introducing the electrons one recognizes that closed shells with spin-paired electrons (↑↓) are obtained only if their number satisfies the Hückel rule $4N+2$. The corresponding compounds may be charged, exhibit characteristic properties, and have been systematically synthesized in large numbers [45].

a π charge $q_\mu^{HMO} = 1$ at all centers μ; hence a π dipole moment $\mu_\pi = 0$ is predicted for the compounds in the ground state[28].

The classical example for ground state comparisons with the aid of MO models is found in cyclic π systems known as perimeters[28,42–45]. Their topologically determined secular determinants[40] additionally contain the π interactions $\beta_{1\mu}$ and $\beta_{\mu 1}$ owing to cyclization of the chain by connecting centers 1 and μ (Figs. 14 and 15). The resulting polynomials again yield general solutions ε_J^{HMO} (Fig. 15).

As follows from the HMO eigenvalue schemes (Fig. 15), stable nonradical π systems with closed valence shells are obtainable only if $4N+2$ electrons ($N = 0, 1, 2, 3\ldots$) are sup-

plied. This conclusion, reached by *E. Hückel*[46], led to one of the greatest successes of MO theory: not only was the tropylium ion $C_7H_7^{\oplus}$, for example, predicted in 1931[46], long before it was ever isolated (1954) as a salt, but a large number of compounds such as [10]-, [14]-, and [18]annulenes (Fig. 15) have been systematically synthesized since 1950 as a consequence of the $(4N+2)$ rule[28, 42–46]. Numerous other observations on the ground states of molecules having π perimeters find a ready explanation[28, 42–46]: these include the Jahn-Teller distortion $D_{4h} \rightarrow D_{2h}$ of the cyclobutadiene diradical, and the oxidizability of its tetraphenyl derivative to the dication, or the flattening of the boat conformation of cyclooctatetraene on reduction to the dianion. On the other hand, caution should be exercised when dealing with all more or less arbitrary and artificial supplementary definitions of "aromatic", "nonaromatic", or even "antiaromatic" character of compounds[28, 47].

It should also be pointed out that even-numbered perimeters are also alternant systems[28, 42–44]. The fascinating topological criterion for alternancy can be formulated such that labeling of the individual centers of a system with "*" or "○" leads only to "*—○" connections. Among the numerous consequences of such a connection[28, 42–44], the pairwise occurrence of the molecular orbitals ψ_J and ψ_{n-J+1} for linear π-electron systems (Fig. 14) or ψ_{n-J} for even-numbered cyclic π-electron systems (Fig. 15) is especially striking. In this context one might also emphasize that the calculated virtual unoccupied molecular orbitals can also be correlated with experimental data, as demonstrated here for ESR, PE, and ET spectra (Fig. 16, 17, and 18).

The ESR coupling constants $a_X^{\ominus}$ and $a_X^{\oplus}$ of radical ion ground states (Fig. 3) can usually be satisfactorily correlated with calculated spin populations $\rho_\mu^{\ominus,\oplus}$, *i.e.* with the squares of the coefficients $c_{J\mu}^2$ from the relevant linear combinations $\psi_J = \sum_\mu c_{J\mu}\phi_\mu$[40], which represent the electron densities, according to the relation derived by *McConnell*[27]

$$a_{\mu,X}^{\ominus,\oplus} = |Q_X|\rho_\mu^{\ominus,\oplus} = |Q_X|c_{J\mu}^2| \tag{5}$$

Only in the case of alternant systems, owing to the pairing properties of ψ_J and ψ_{n-J+1} or ψ_{n-J}, are the radical cation and radical anion ground states of one and the same molecule expected, and found experimentally, to display (almost) the same spin populations and thus (almost) the same coupling constants (Fig. 16)[27].

On correlation of σ ionization energies with bond orbital models[19], all the orbitals of the latter are doubly occupied. For radical cation states of alternant σ systems, owing to the pairwise correspondence of the eigenvalues ε_J and ε_{n-J+1} or ε_{n-J}, it is expected and observed PE spectroscopically that the σ ionization energies of, say, methylpolysilanes[48] are equally distributed to both sides of a reference state (Fig. 17).

The PE ionization pattern of decamethyltetrasilane corresponds to the fully occupied eigenvalue scheme of the chain with $n=3$ (Fig. 14), and that of dodecamethylcyclohexasilane

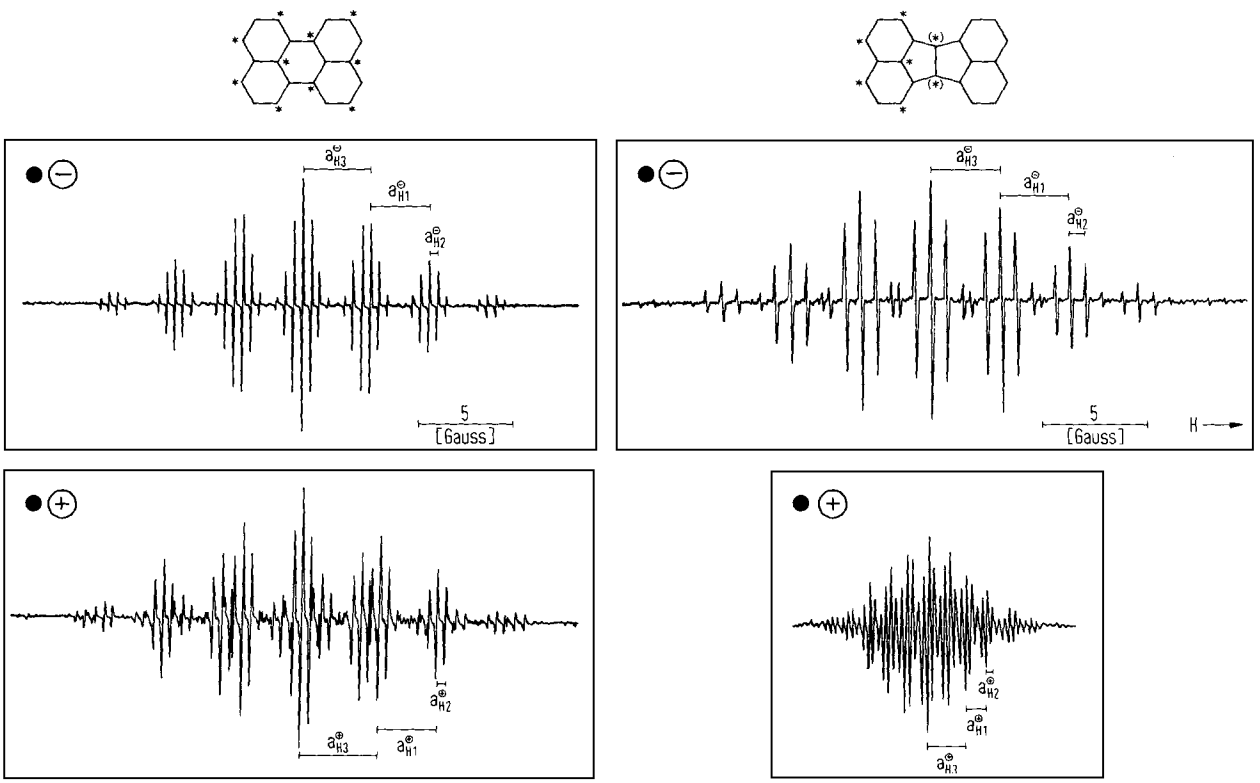


Fig. 16. In alternant π systems, *i.e.* those whose centers can be alternately starred, the pairing properties of their molecular orbitals ψ_J and ψ_{n-J+1} (Fig. 14: linear systems) or ψ_{n-J} (Fig. 15: even-numbered cyclic systems) imply that the coefficients $c_{J\mu}$ of the linear combinations $\psi_J = \sum_\mu c_{J\mu}\phi_\mu$ [40] differ in sign but not in magnitude [28, 42—44]. The squares of the coefficients $c_{J\mu}^2$, which can be correlated (5) with the ESR coupling constants $a_{\mu,X}^{\ominus,\oplus}$, are identical. The ESR spectra of the radical cation and the radical anion are therefore expected to be equal for the same alternant compound, but to differ considerably for nonalternant compounds, *e.g.* those with odd-numbered rings (*—*). This is indeed the case, as demonstrated by the ESR spectra of the radical ions of perylene and acenaphtho[1,2-*a*]acenaphthylene [27].

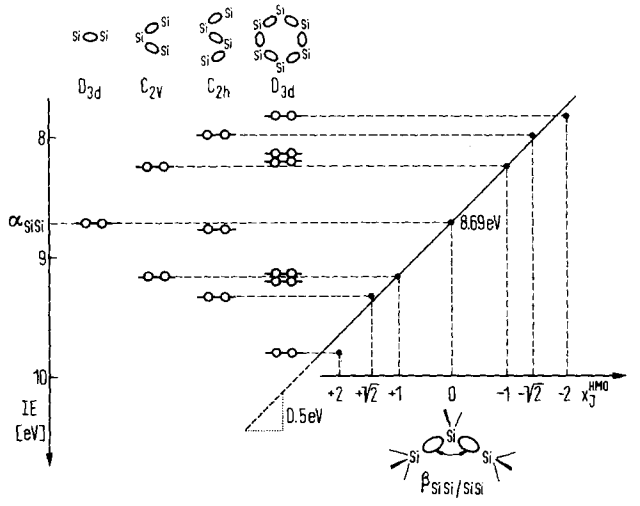


Fig. 17. Comparison of the lowest PE ionization energies of methylpolysilanes $R(SiR_2)_nR$ and $(SiR_2)_n$ yields as center of gravity α_{SiSi} the 1st ionization energy of hexamethyldisilane. The splitting patterns correspond to the HMO eigenvalue schemes of isoconjugate (4) chains (Fig. 14) and rings (Fig. 15) with fully occupied orbitals; insofar as they are not already included in the parameter α_{SiSi}, the SiC and CH orbital components can, to a good approximation, be neglected. Correlation with the eigenvalue coefficien x_j^{HMO} defined according to $\varepsilon=\alpha+x_j^{HMO}\beta$ leads to a regression line with only a slight standard deviation; its slope affords the interaction parameter $\beta_{SiSi/SiSi}=0.5$eV. The alternancy of the SiSi bond skeleton is already included in the HMO model: if Koopmans' theorem (2) is extended to $\Delta\varepsilon_j^{HMO}\sim\Delta IE_n$, the object/mirror image arrangement of the ionization energies about the disilane center of gravity fully confirms the above premise.

to that of the perimeter with $n=6$ (Fig. 15). Comparison of the radical cation states of methylpolysilanes on the basis of an LCBO-MO model is at the same time a good example of parametrization of the Coulomb integral α and resonance integral β[40] with the aid of ionization energies (Fig. 17).

The topological concept of alternancy can also be illustrated for certain isoconjugate π systems by inclusion of the radical anion states[49]. The energy differences from the ground state of the neutral molecule up to the resonance states generated by transient take-up of an electron are accessible by the refined[49] experimental technique of electron transmission spectroscopy (ETS)[50] (Fig. 18).

If electron transmission spectroscopy is regarded as complementary to photoelectron spectroscopy, and if the electron affinities taken from the ET spectra[50] are compared with unoccupied orbitals in an extension of (2) and contrasted with the ionization energies[15], there results the pairwise correspondence of orbital energies relative to a common center of gravity expected (Fig. 18) for alternant linear and cyclic π systems (Figs. 14 and 15).

Summarizing: Comparisons of states on the basis of topologically designed MO models emphasize the connection of the centers in the molecule, are of considerable utility owing to their extensively generalizable predictions—consider *E. Hückel's* $(4N+2)$ rule[46]—and also lead to further insights, as shown for the example of "alternancy"[28,42-44]. These insights apply strictly only to isoconjugate systems (4) such as unsaturated hydrocarbons[28,42-46] and, approximately, to σ systems with characteristic subunits such as peralkylated polysilanes[18,48], boranes[51], or interhalogen compounds[28,52]. However, the basic principles can also be transferred to hetero systems, *e.g.* after modification by the potential perturbations mentioned in Section 4.2.

4.2. Potential-Based Comparison of States

Although they may contain different kinds of building blocks, hetero-conjugate molecules *(4)* can nevertheless display the same kind of connection, comparable geometry (1), and possibly the same number of (valence) electrons. As already discussed for HSH and HOH (Figs. 10 to 12), however, the varying potentials of the central atoms lead to a different electron distribution, and thus to deviating molecular properties. If the changes remain in the range of validity of the

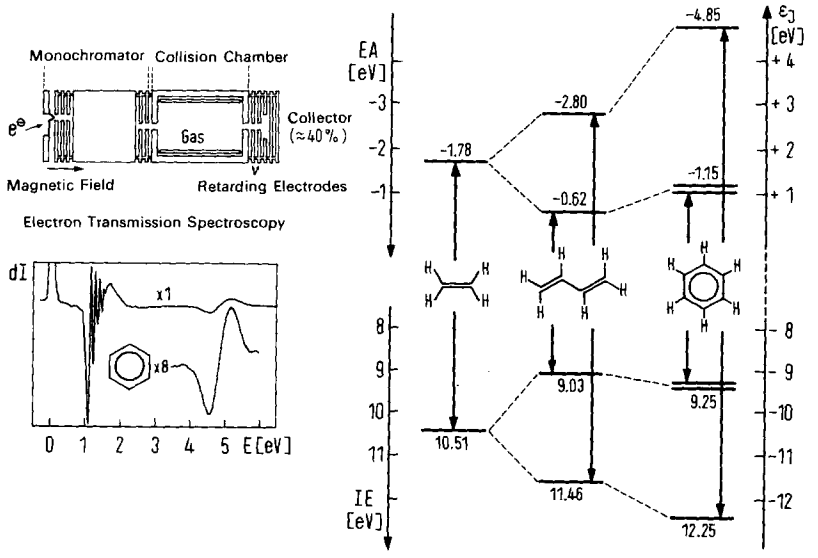


Fig. 18. On recording an electron transmission spectrum, a monochromatic electron beam of variable energy is scattered by the gaseous compound [49, 50]. The resonance (current) fluctuations dI measurable in the unscattered residual transmission beam indicate the intermediate formation of short-lived radical anions. If the electron affinities *EA* [eV] of the resonance states thus determined are plotted together with the PE ionization energies *IE* [eV] on an orbital energy scale ε_j [eV] one obtains the object/mirror image arrangement of the energy differences between the states expected from the alternancy of the π systems (Figs. 14 and 15).

MO model used, then the perturbations[28, 39, 42] can be profitably used for comparison of molecular states.

Potential-based models, which compare the states of chemically related molecules with (largely) similar structures on the basis of changes in potential, may open up interesting vistas. This is demonstrated, for instance, by the photoelectron spectra of the isoelectronic species AH_n of a group (constant n), and also within a period of the system of elements (Fig. 19), with one proton after the other with nuclear charge $Z=1$ being withdrawn from the nucleus Z. An approximation of this kind is designated as the "united atom" model (4) and is also known as *Grimm*'s "hydride shift" rule[54]. In the place of the ambiguously definable and far too imprecise quantity "electronegativity"[55], a suitable parameter for comparing the effective potential is the average ionization energy of all n valence electrons of the central atom $\overline{IE}^{\text{atom}}_{\text{valence}} = [IE_1(A)+IE_1(A^{\oplus})+IE_1(A^{\oplus\oplus})\ldots+IE_1(A^{+n-1})]/n$[56] which also serves for estimating effective nuclear charges according to *Slater*[28, 31] (Fig. 19).

The determining influence of the core potential of the central atom A in the compounds AH_n is clearly revealed by a comparison of the atomic and molecular ionization energies $\overline{IE}^{\text{atom}}_{\text{valence}}/IE^{\text{v}}_n(AH_n)$ (Fig. 19). Thus the sum of all PE ionization energies for argon and water are almost identical. Two regions are easily recognized: the energetically higher states with s holes and the band of the p-type radical cation states, which are to be assigned to the ionizations of electron pairs n_A or to the symmetry-adapted bond combinations σ_{AH} (Figs. 4 and 10). It appears, for example, that the AH_2 compounds display energetic centers of gravity which rise slower than the ns_A ionization energies (Fig. 19), corresponding to the expectation that s electrons, being on average closer to the nucleus, are more susceptible to changes in potential at center A.

In topology-determined systems, potential changes by substituents within the scope of the model can profitably be described as perturbations. One distinguishes between first- and second-order perturbations—as discussed here for the two highest occupied, degenerate benzene orbitals $\pi(e_{1g})$[28, 42, 43] (Fig. 20).

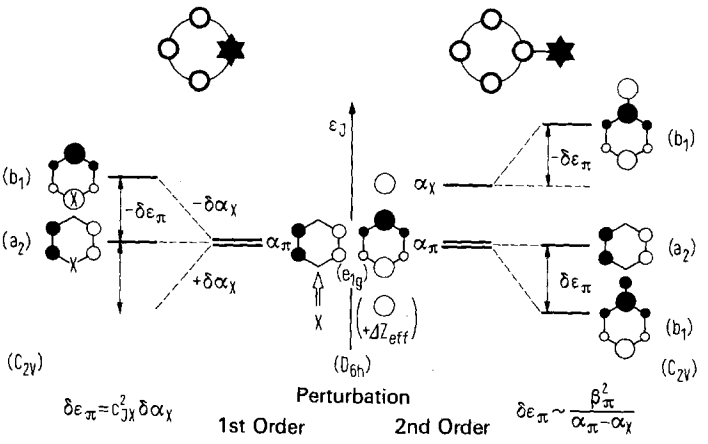


Fig. 20. Substitution in and on the benzene ring lowers the molecular symmetry, *e.g.* $D_{6h}\rightarrow C_{2v}$, thereby removing the degeneracy of the e_{1g} orbital.

1st order perturbation occurs in the HMO approximation [28] *via* a change in potential $-\delta\alpha_X$ (X = donor) or $\delta\alpha_X$ (X = acceptor) and leads to a raising $-\delta\varepsilon_\pi$ or lowering $\delta\varepsilon_\pi$ of the perturbed molecular orbital, whose composition is regarded approximately as unchanged. On substitution in a nodal plane, *i.e.* coefficient at center $c_{JX}=0$[57], $\delta\varepsilon_\pi$ remains equal to zero (cf., however, Fig. 23). 1st order perturbations are frequently isoelectronic (4), *i.e.* an atom X or a group of atoms X–(Y) at the center concerned is replaced by another atom or another group of atoms of different nuclear charge Z_X.

2nd order perturbation occurs in the HMO approximation [28] on mixing of orbitals of the same symmetry class, *i.e.* construction of the linear combination $\psi=c_J\psi_J\pm c_K\psi_K$ for the complete system. The change in orbital energies $\pm\delta\varepsilon_\pi$ is directly proportional to the square of the perturbing interaction β^2_{JK} and inversely proportional to the separation of the orbitals $\alpha_\pi-\alpha_X$. 2nd order perturbations are usually extra-electronic (4), *i.e.* the system is extended by one or more centers.

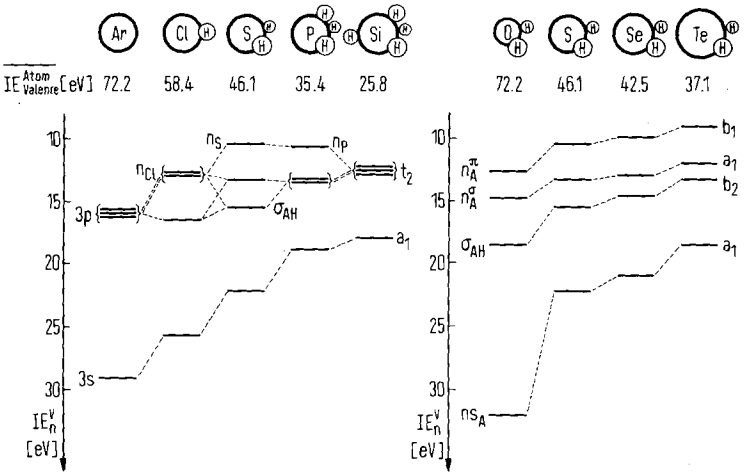


Fig. 19. Comparison of PE spectroscopic ionization energies IE^{v}_n [53] for 3rd row AH_n species, starting from the 3s and from 3p states of the argon atom shows: the 3s electrons in the proximity of the nucleus become more readily ionizable with decreasing effective nuclear charge, represented here by the average ionization energy of the valence electrons of atom A $\overline{IE}^{\text{atom}}_{\text{valence}}$ [56]. The p electrons, which are on average farther away from the nucleus, expectedly prove less susceptible to the influence of the potential of atom A; their levels split to the radical cation states typical of the compounds which are assignable to ionizations from n_A electron pairs or symmetry-adapted combinations of σ_{AH} bonds (Figs. 4 and 10).—In the hydrogen compounds AH_2 of group 6 the energy of the radical cation states $AH_2^{\oplus}$ decreases on going from O to Te, the rate of decrease being all the greater the higher the ionization energy IE^{v}_n, and thus the influence of the effective nuclear charge ($\overline{IE}^{\text{atom}}_{\text{valence}}$).

PE spectroscopy furnishes—*via* Koopmans' theorem (2)—didactically excellent examples of 1st and 2nd order perturbation[2d]: these include phosphabenzene[2e, 58] and 1,4-bis(methylthio)benzene[2c, 59] and their homologous derivatives (Figs. 21 and 22).

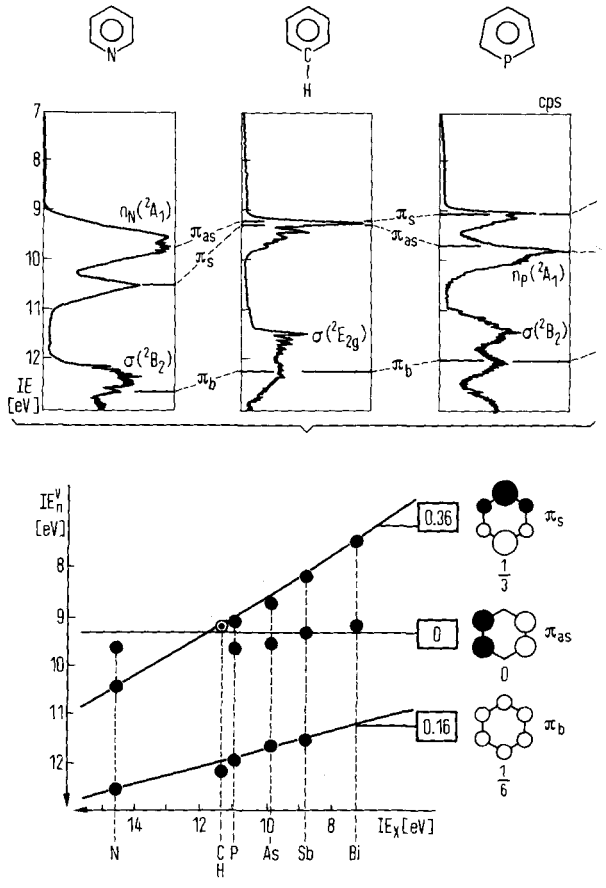


Fig. 21. In the PE spectra of benzene and its hetero derivatives C_5H_5X with X = N, P, As, Sb, Bi [58], the three π ionizations are observed below 12 eV and, in addition, radical cation states which are assigned to the electron pair $n_X(^2A_1)$ and to the benzene skeleton $\sigma(^2B_2)$ [58]. In the benzene π orbitals the coefficients [57] at the substitution centers are 1/3 (π_s), 0 (π_{as}), and 1/6 (π_b). On correlation of the 1st order perturbations due to the potential changes $\delta\alpha_X$—approximated by the valence ionization energies IE_X ($^4S_{3/2} \rightarrow {}^3P_0$) of the atoms X—with the PE ionization energies of the C_5H_5X molecules then, according to (2) $\Delta IE \sim \Delta\varepsilon_J$ and to $\delta\varepsilon_J = c_{J\mu}^2 \delta\alpha_X$ (Fig. 20), regression lines result as expected with slopes of about 1/3, 0, and 1/6. This molecular state comparison at the same time confirms the PE band assignment for the π ionizations.

The radical cation state comparison of benzene and its aza, phospha, arsa, stiba, and bismuta derivatives[58] demonstrates the elegance, quality, and utility of potential-based 1st order perturbation models as follows (Fig. 21): of the three model parameters two are accessible by comparison with experimental data, the difference in eigenvalues $\delta\varepsilon_\pi$ according to Koopmans' theorem (2) from differences in molecular π ionization energies, and the perturbations of the potential $\delta\alpha_X$ from the 1st ionization energies of the atoms X[56]. The varying slopes of the resulting regression lines expectedly correspond to the various orbital contributions[57] $c_{\pi X}^2$ at the substitution center X (Fig. 21). The quality of the regression (6) is very good[58], and one of the possible applications should be to predict the 1st ionization energy of the hitherto unknown species silabenzene:

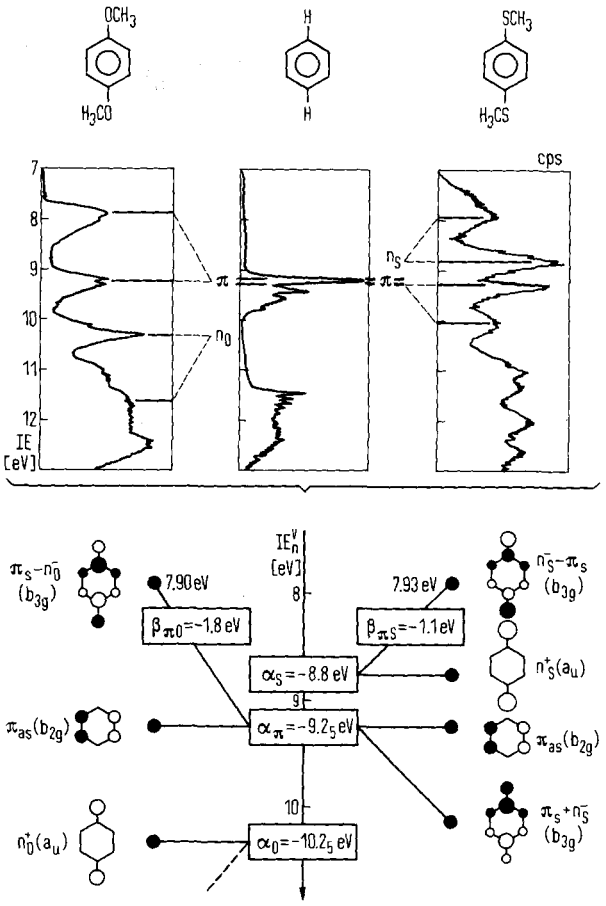
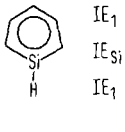


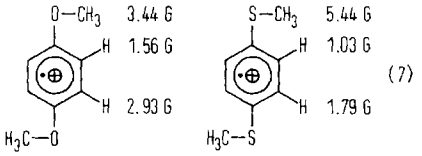
Fig. 22. The PE spectra of benzene and its *p*-bis(methylthio)- and *p*-dimethoxy derivatives contain ionizations to $\pi^{*\oplus}$ states as the lowest 2, 4, and 3 ionizations. In the MO model, *e.g.* for the dithio π system, $n_S^+(a_u) \equiv \alpha_S$ and $\pi_{as}(b_{2g}) \equiv \alpha_\pi$ represent internal standards which are of unique symmetry type and do not mix with any other orbitals in the same energy region. Mixing of symmetry-equivalent orbitals $n_S^- \pm \pi_s(b_{3g})$ leads to mirror image splitting $\pm\delta\varepsilon_\pi$. Parameters $\beta_{\pi X} = -\sqrt{(IE_2 - IE_1)(IE_3 - IE_1)}$ show that $2p_C/2p_O$ interaction effects a larger 2nd order perturbation than $2p_C/2p_S$ interaction.



$$IE_1 = 5.24 + 0.362\ IE_{Atom}\ [57]$$
$$IE_{Si} = 8.15\ eV\ [56] \qquad (6)$$
$$IE_1 \approx 8.2\ eV$$

External extraelectronic (4) substitution on the benzene ring, *e.g.* with XCH_3 groups whose electron pairs n_X extend the π system, can usually be satisfactorily described by 2nd order perturbation models. *Para*-disubstituted benzene derivatives[58] constitute an appropriate example (Fig. 22): mixing of the symmetry-equivalent orbitals can be parametrized with PE ionization energies, the orbitals of unique symmetry class serving as internal standards α_S and α_π. It warrants mention that numerical agreement of the 3rd ionization energy of the dithio compound (α_π) and the 1st benzene π-ionization energy, *i.e.* the constancy of the π_{as} orbitals confirms the applicability of a 2nd order perturbation model. Parametrization by analogy with (3) yields $\beta_{\pi O} > \beta_{\pi S}$, and thereby provide the information that the π interaction $2p_C/2p_O$ causes a larger perturbation than $2p_C/3p_S$.

Considering the many known examples it is pointed out that perturbation models, once established, also reflect other molecular properties suitable for modeling: thus the measured ESR spin populations of the corresponding radical cations



(7)

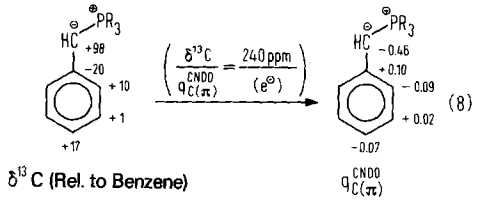
must, according to the McConnell relation (5), at least qualitatively reproduce the orbital mixing ratio $\pi_s \pm n_{\tilde{X}}$ (Fig. 22). Accordingly, a large ring contribution π_s is expected and observed for the dimethoxy derivative, but a large electron pair contribution n_s for the bis(methylthio) derivative[59].

1st and 2nd Order perturbation models of the kind discussed in this section are commonly encountered in the literature, *e.g.* for unsaturated hydrocarbons[28, 38, 41, 42, 60] (cf. also Fig. 13), their halo[61] or pseudohalo derivatives[62], and also for saturated hydrocarbons and their derivatives[17, 63]. The parameters α_X and β_{XY} determinable from experimental data—especially ionization energies—can also be used in other models and are therefore of predictive value (6) with regard to model-determined molecular properties of chemically related compounds.

4.3. Computer-Assisted Comparison of States

The question "to calculate or to measure?" has already been answered in Section 1 by pointing out just how successful and stimulating a combination of the two turns out to be. Computer assistance is usually also valuable for setting up models for comparison of states, a whole arsenal of various procedures[64] presently being available—ranging from the optimum parametrization of MO models from a set of experimental data[62,63] *via* EHMO[65] (*E*xtended *H*ückel *MO*) as the simplest σ calculation procedure[64] and numerous so-called semi-empirical procedures[64] such as CNDO (*C*omplete *N*eglect of *D*ifferential *O*verlap) and INDO[34, 66] (*I*ntermediate *N*eglect of *D*ifferential *O*verlap) or MINDO[67] (*M*inimum *N*eglect of *D*ifferential *O*verlap) to *ab initio* calculations[64, 68]. In the HMO approximation[28, 42], for example, the complete secular determinant[40] containing all the centers and all the interactions is solved instead of the incomplete perturbation determinant of type (3). Experience shows computational aids to be indispensable for molecules of low symmetry and special cases, *e.g.* for extreme perturbations[69] (Fig. 23).

In the PE spectrum of the phenyl-substituted phosphorus ylide (Fig. 23) the characteristic benzene band at 9.25 eV (shown as dashed line) that would have to be assigned to the π_{as} ionization (Figs. 20 to 22) is conspicuously absent. The suspected gross perturbation of the benzene π system by the neighboring "ylidic" carbon electron pair $n_c^{\ominus}$ is clearly revealed by CNDO calculations (Fig. 23): the computer-simulated C—C connection of the two molecular moieties without allowing for π interaction raises the two benzene $\pi(e_{1g})$ orbitals to different degrees by σ charge transfer. Additional splitting leads to the final sequence of molecular orbitals. As may be gathered from the PE spectrum (Fig. 23), the π_{as} molecular cation state is stabilized by 0.9 eV relative to benzene by the neighboring carbanion center—this is one of the strongest substituent effects known[2e]. The model derived by CNDO simulation of an experimentally inaccessible intermediate can be substantiated by state comparisons with other phosphorus ylides; the charges $q_{C(\pi)}^{CNDO}$ also calculated for the benzylidene carbon atoms by the CNDO program correlate satisfactorily with ^{13}C-NMR data[69]:



(8)

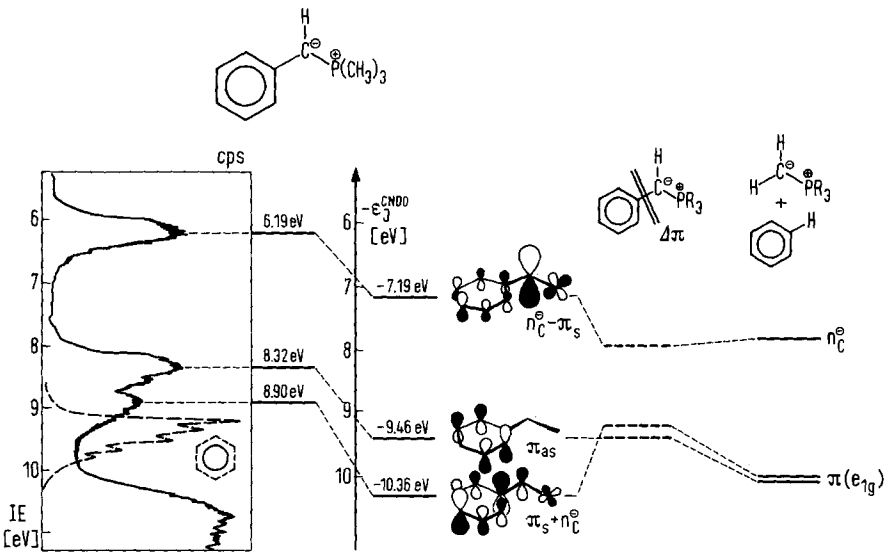


Fig. 23. The PE spectrum of benzylidenetrimethylphosphorane surprisingly no longer shows a band typical for benzene derivatives at 9.25 eV (---) [69]. This finding becomes understandable in the light of CNDO calculations: if the partial systems benzene and methylenetrimethylphosphorane are connected together without permitting π interaction (Δπ) then a considerable raising of the π_s orbital, and also of the π_{as} orbital, is calculated. π interaction mixes the initial orbitals $n_c^{\ominus} \pm \pi_s$, whereas π_{as} remains unchanged. The PE ionization energies are assigned thus: IE_1 ($n_c^{\ominus} - \pi_s$), IE_2 (π_{as}), and IE_3 ($\pi_s + n_c^{\ominus}$). The benzene radical cation state represented by the orbital π_{as} is therefore stabilized to the extent of 9.25 − 8.32 = 0.93 eV by the ylide substituent.

As demonstrated by the perturbation model (Fig. 23), the phenyl ring acts as an acceptor and assists in distributing the neighboring carbanion charge over the ylide molecule.

Generally speaking, state comparisons *via* computer-assisted perturbation models were, and still are, frequently utilized for detecting dominating effects and possibly defining them as model parameters—for example, the concepts of through space and through bond interactions[39, 70] (cf. also Fig. 13[38]) or of hyperconjugation[2c, 71]. As a rule, the computer programs used also calculate further data for comparison such as in (8). Among these data, particular interest attaches to the total energies E_{tot} and the charges q_μ on the individual centers μ, which, in the HMO approximation for example, are made up of the contributions of the individual orbitals ψ_J each occupied by b_J electrons:

$$E_{tot}^{HMO} = \sum_J b_J \varepsilon_J \qquad (b_J = 0,1,2) \qquad (9)$$
$$q_\mu^{HMO} = \sum_J b_J c_{J\mu}^2$$

These data are obtained independently by semiempirical procedures[34, 42, 64] and can be profitably employed in computer-assisted perturbation models. Ylides have already been discussed as examples for charge distribution q_μ^{CNDO}[69] (cf. (8) and Fig. 23); the use of EHMO total energies will be illustrated by a description of the cage structure of S_4N_4[72] (Fig. 24).

The starting point for a discussion of the S_4N_4 cage structure[72] is provided by the molecular orbitals of the [8]perimeter (Fig. 15). Perturbation by S and N potentials merely removes the degeneracy of the nonbonding orbital pair, owing to the position of the nodal planes. Each nitrogen atom contributes one π electron, and each sulfur atom two π electrons; filling with a total of twelve π electrons affords a reactive triplet state with two unpaired electrons. A stable singlet state could be achieved if the highest orbital could be lowered, by additional transannular interactions, beneath the next-highest pair (Fig. 24). Among several possible deformations, EHMO calculations show the D_{2d} structure with S—S bonds to have the lowest total electron energy[72]. This calculated result agrees with the S_4N_4 structure determined by X-ray methods. The computer-assisted perturbation model is also valid for the ground state of other cage compounds such as P_4S_7, in which the P—P connection leads to a greater interatomic distance, and permits understanding of further molecular properties: thus addition of the Lewis acid $SbCl_5$ generates a perturbation sufficient to stabilize opening to the singlet ground state[72] (Fig. 24). A planar structure was predicted by the MO model[72] for the dication $S_4N_4^{2\oplus}$ in 1970—in full accord with the recently published X-ray structure analysis[73].

Quite intentionally, the examples cited so far have not aimed at closest possible numerical reproduction of experimental data by calculated values (Fig. 1), but were instead selected to provide an insight into the dynamic behavior of molecules under the influence of perturbations for comparisons of states of chemically related compounds. For the sake of completeness, however, it should be mentioned that the comparison of experimental data and model quantities has not only often permitted parametrization of the latter (cf., *e.g.*, Fig. 13 and (3), Figs. 17, 21, or 22), but frequently leads to significant correlations for calculated model quantities, permitting

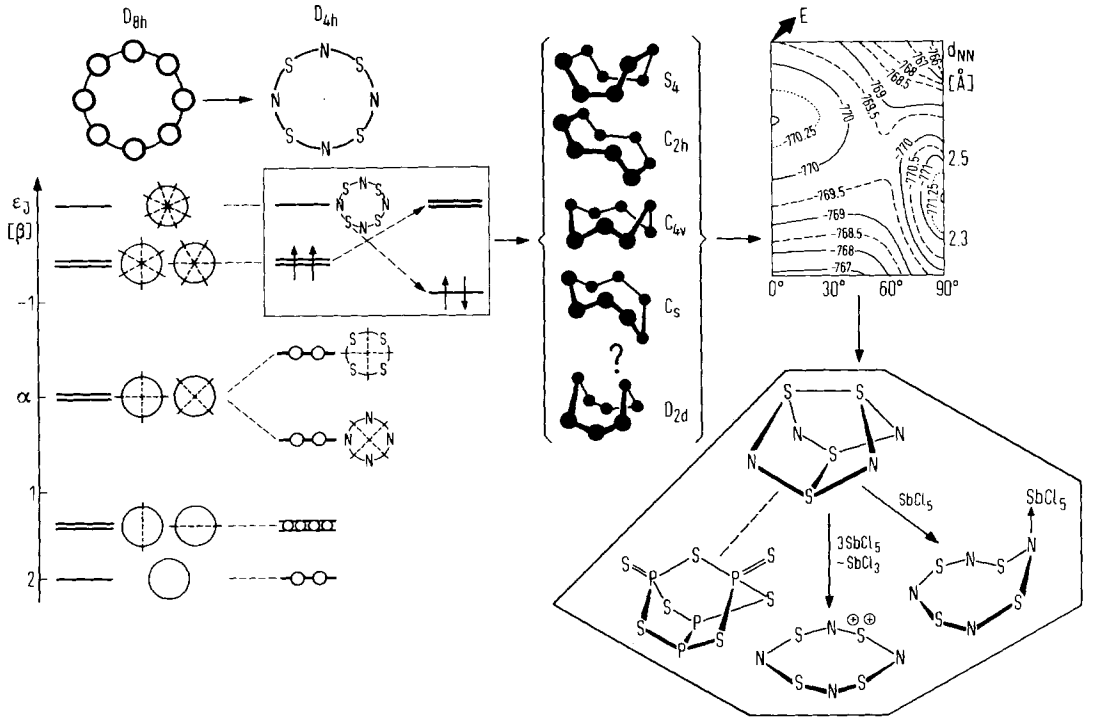
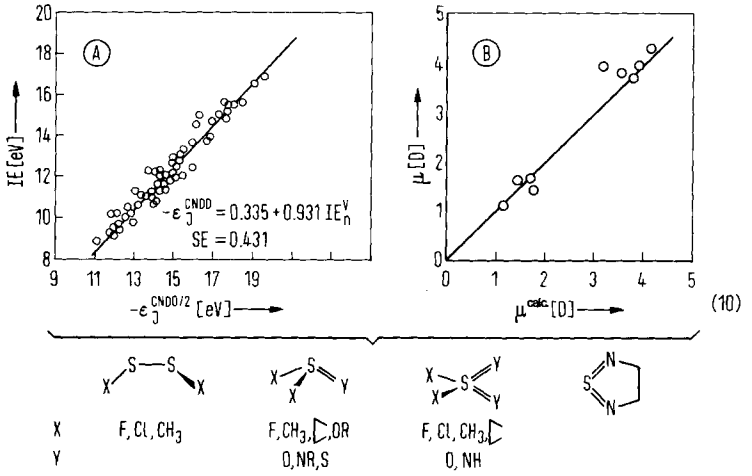


Fig. 24. The MO description of the three-dimensional cage structure of S_4N_4 [72] starts from the isoconjugate [8]perimeter (Fig. 15). Lowering of the symmetry $D_{8h} \rightarrow D_{4h}$ merely removes the degeneracy of the orbitals $\varepsilon_{4,5} = \alpha$ by different 1st order perturbation (Fig. 20). Occupation by 1N and 2S electrons shows that a planar S_4N_4 molecule would have to be a diradical. Between the numerous possible structural distortions, which would either interchange the uppermost orbitals or cancel the degeneracy of the second from top pair of orbitals, no adequate qualitative distinction seems possible. Calculation of an energy surface E_{tot}^{EHMO} as a function of distances such as d_{NN} shows that a D_{2d} cage should be the most stable S_4N_4 structure. The model can also be applied to other cage molecules such as P_4S_7 or to cage opening by perturbation in the $SbCl_5$ adduct. X-Ray structure analysis recently proved [73] the cation $S_4N_4^{2\oplus}$ to be planar—as would be expected from occupation of the eigenvalue scheme by two electrons less.

predictions within their confidence limits. Points to watch will become clear in simultaneous correlations of energy $-\varepsilon_J^{CNDO}/IE_n^V$ according to *Koopmans* (2) and of dipole moments $\mu^{calc.}/\mu^{exp.}$ covering 15 sulfur compounds of four different types, some exhibiting extreme substituents (F) and some with extreme ring strain ($\sphericalangle$CSC *ca.* 50°)[74].



(10)

The regression line of the Koopmans correlation (10: A) neither passes through the origin nor exhibits a slope of 1, and its standard deviation is relatively large. The known gas-phase dipole moments are correlated directly with the calculated values: the regression line (10: B) of slope 1 passes through the origin. Taken together, the two correlations show the calculation procedure used to be suitable, within the limitations mentioned[28], for interpretation and for prediction of model properties of such sulfur compounds. However, the reader is earnestly warned against all fortuitous numerical coincidences based on single "hit and run" calculations without extensive testing of confidence limits (10), or in which "home-spun" parameters defined more or less arbitrarily, like "aromaticity", are backed up with some kind of calculated figures.

To summarize:

By virtue of their inherent concepts (topology, symmetry), of their input parameters (potentials, number of electrons), and of their flexibility (perturbation), molecular orbital models provide a manifold and stimulating overview of types and classes of compounds.

5. Limits of the Molecular Orbital Description of Molecular States

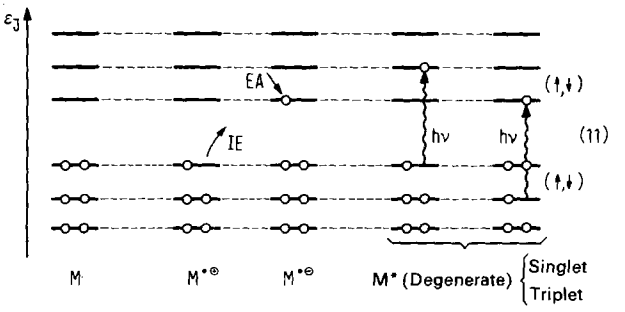
Experimental molecular state data and calculated molecular orbital parameters can be correlated in various ways: energy differences such as ionization or excitation energies can be compared with eigenvalues (cf. (2), (10), or Figs. 10, 13, 17, 18) or their differences (cf. Figs. 14, 20, 21, 22). Changes in charge such as demonstrated by ESR spin populations or resulting from substituent perturbations can be correlated with squared eigenfunctions (cf. (5), (7), or Figs. 12, 16, 20, 21). Furthermore, "summed-up" parameters such as total energies or total charges (9) provide a basis for discussing numerous other molecular properties such as structures (Fig. 24), dipole moments (10), or NMR signal shifts (8). However, the accompanying loss of transparency often leads to the limits of easily tractable MO models. Beyond these limits, the description of molecular states on a molecular orbital basis has made enormous progress within the discipline of theoretical chemistry—even reaching as far as the reproduction of spectra of small molecules (Fig. 1). In what cases should the average consumer of quantum chemistry become cautious and consult a theory producer?

All the MO models presented are based on the implicit assumption that the distribution or motion of an electron can be described within the time-averaged field of the atomic nuclei and the other electrons of a molecule (1). Such one-electron MO models describe the properties of molecules in a particular state, in each case on the basis of a single electronic configuration (11): for instance, all radical cation states according to *Koopmans* by means of a single set of molecular orbitals (Fig. 25).

In conclusion, the limited validity and some possible extensions of one-electron MO models will be illustrated for important aspects: change in electron energy with or without changes in the number of electrons, structural changes or reactions, and the description of large molecules of low symmetry.

5.1. Changes in Electron Energy Due to Changes in the Number of Electrons

One-electron MO models for molecules M with closed electron shells in the ground state (11: M) generally also permit



(11)

description of the properties of radical ions (11: $M^{\bullet\oplus}$ and $M^{\bullet\ominus}$) with a modified number of electrons (Fig. 25). Numerous correlations of various experimental data with calculated parameters of the respective singly occupied molecular orbital

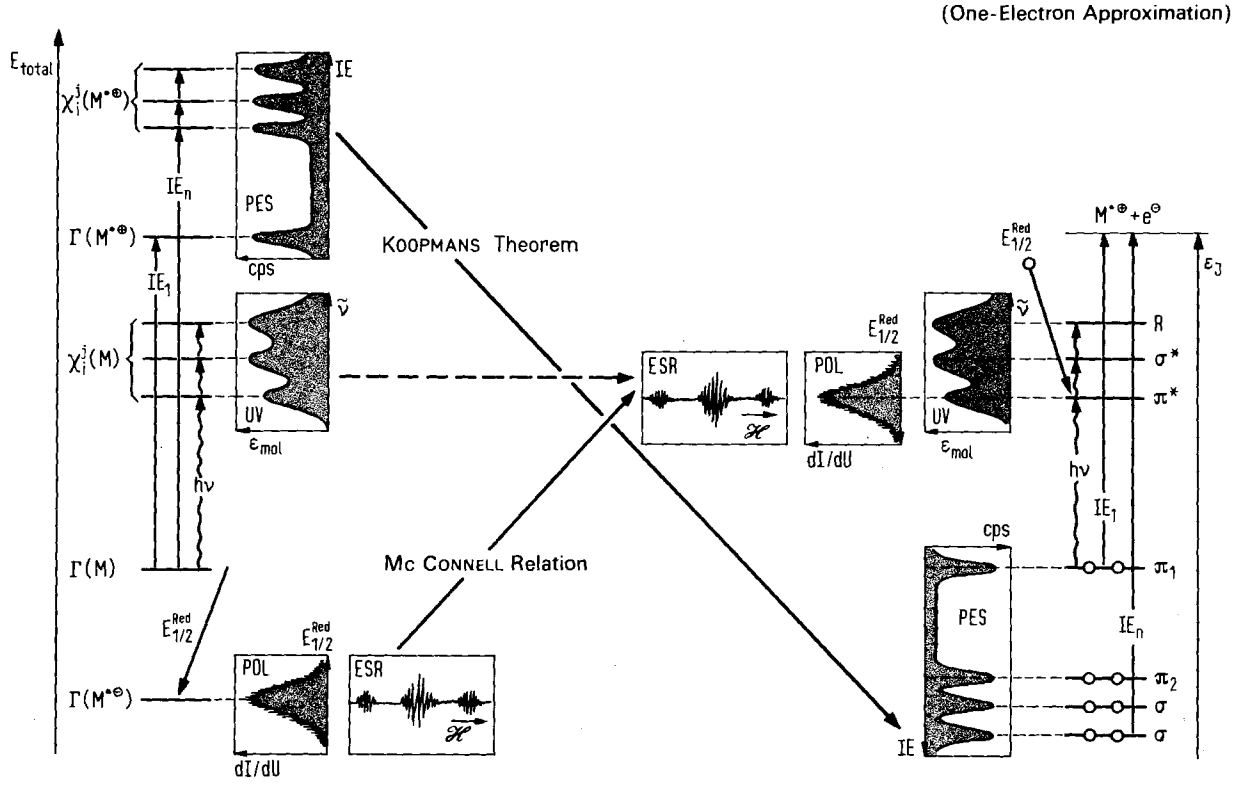


Fig. 25. Energy differences between, and charge distributions in the various states of a molecule can be determined by a variety of experimental methods, of which some are mentioned (cf. Fig. 3). Interpretation of experimental data with one-electron MO models is based on the fundamental assumption of Koopmans' theorem $IE_n^v = -\varepsilon_j^{SCF}$ (2) or the McConnell relation $a^{\bullet\oplus,\ominus}_{\mu,X} = |Q| c^2_{J\mu}$ (5), *i.e.* that the electron distribution can be established with a single electron configuration. Ionization energies or half-wave reduction potentials can then be compared with the eigenvalues ε_J, ESR coupling constants with the squares of the orbital coefficients $c_{J\mu}$ at the centers μ of the singly occupied molecular orbital ψ_J of type σ, π, π^*, σ^* or R. In some (a few) cases the UV excitation energies $\Delta E = h\nu$ can be expressed as the eigenvalue differences $\Delta\varepsilon_J$ between the initial and final orbitals (cf. Fig. 14). The limitations of describing states by one-electron MO models are clearly apparent from the crossovers (→) of the individual correlations.

confirm[27, 28, 42–44] that the electron distribution can usually be described satisfactorily by a single electron configuration (11: $M^{\bullet\oplus}$ and $M^{\bullet\ominus}$).

The applicability of one-electron approximations requires not only a comparable molecular structure but also that changes in the charge distribution (relaxation) and in mutually dependent electron motions (correlation) may together be neglected[15b]. Thus the molecular structure remains essentially constant during the *ca.* 10^{-16} s duration of vertical ionization (cf. Fig. 4: HBr potential curves), and the deviations from Koopmans' theorem appearing in a particular method of calculation will be all the smaller the less the charge distribution and electron correlation change during the ionization process[33]. Far better agreement with experimental data is yielded by the many-electron approximative solutions of the Schrödinger equation mentioned in the introduction (cf. Fig. 1), in which the total energies of the individual states are calculated separately and subtracted from one another according to (2): calculated values ΔE_{total} and vertical ionization energies IE_n^v generally differ by less than ± 0.3 eV[3–7]. Nevertheless, application of these highly sophisticated methods to larger molecules still remains in the precinct of the theoretician.

5.2. Changes in the Electron Energy not Involving Changes in the Number of Electrons

As documented by many of our examples (Figs. 10, 13, 18, 21, or 23), ionizations can usually be described, starting from a single electron configuration (11: $M^{\bullet\oplus}$), by one of the so-called canonical orbitals[64] which are adapted to the symmetry of the molecule and satisfy Koopmans' theorem (2). The electron hole generated can thus be characterized according to the orbital type and the electronic interaction regarded approximately as unchanged. For excitations in which the number of electrons remains constant, *i. e.* none of the electrons is ejected, a description of the molecular state based on just a single electron configuration (11: M) is generally inadequate (Fig. 26).

As in the case of the blue compound bis(trimethylsilyl)diimine[76] (Fig. 26), the ionization energies are usually reproduced satisfactorily by MO calculations *via* Koopmans' theorem (2), while reproduction of the excitation energies usually requires consideration of the modified electronic interaction—in the present case electron repulsion is approximately accounted for by Coulomb terms J as well as spin pairing effects by exchange terms K[77].

Generally, one-electron MO approximations, *i.e.* those which treat electrons as being independent of one another, are unsuitable for describing electronically excited states $\chi_i^j(M)$ of neutral molecules; simple regressions between UV maxima and eigenvalue differences, as shown in Figure 14, therefore represent exceptions valid only for certain excited states of particular series of compounds[28, 44]. Thus it is impossible, with a single electronic configuration, to establish either the energy differences between singlet and triplet states (11: ↑↓ and ↑↑) or the different excitation energies to such states of like symmetry (11: $h\nu \neq h\nu'$), for which degeneracy would be predicted

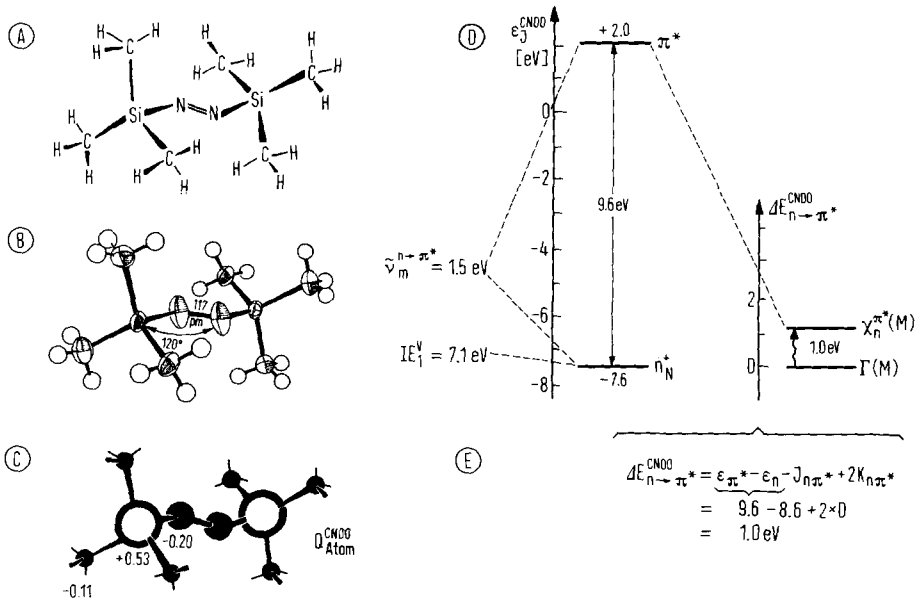
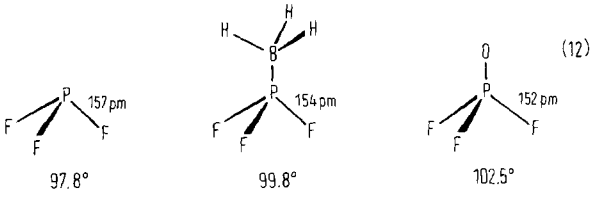


Fig. 26. *Bis(trimethylsilyl)diimine* (A) *is a blue (!) azo compound* [76], *whose long-wave* $n\rightarrow\pi^*$ *band appears at the edge of the IR spectral range, which exhibits a first ionization energy of only 7.1 eV, and whose unusually short NN bond length (B) amounts to only 117 pm (azobenzene 125 pm,* N≡≡N 111 pm). The MO description in terms of the charges Q_{atom} (C) suggests that silicon ($Q_{Si}^{CNDO} = +0.53$) acts as a strong electron donor towards nitrogen ($Q_N^{CNDO} = -0.2$). The CNDO calculations also satisfactorily reproduce the first ionization energy $IE_1^V = 7.1$ eV (D); the eigenvalue of the highest occupied orbital n_N^+ amounts to $\varepsilon_{30}^{CNDO} = 7.6$ eV. The $n\rightarrow\pi^*$ excitation energy $E_m^{n\rightarrow\pi^*} = 1.5$ eV, on the other hand, cannot be related to the gap $\Delta\varepsilon = 9.6$ eV to the lowest unoccupied π^* orbital. Only after approximate consideration of the modified electronic interaction [17], as expressed in the large Coulomb term $J_{n\pi^*}$, can the $n\rightarrow\pi^*$ excitation energy be roughly reproduced (E) with $\Delta E_{n-\pi^*}^{CNDO} = 1.0$ eV.

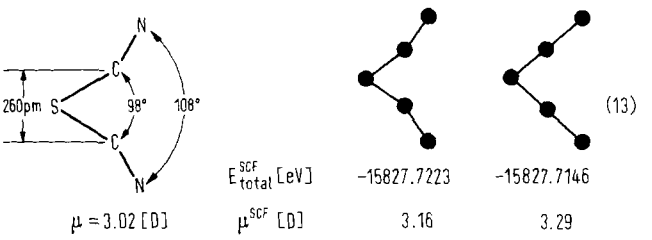
without inclusion of configurational mixing[31, 32, 44, 78, 79]. Numerous other experimental results such as negative spin densities (Fig. 12) can only be explained after inclusion of electronic interaction.

5.3. Changes in the Electron Energy Accompanying Changes in Molecular Structure

Molecular orbital models are usually based on a given, unchanged molecular geometry—frequently an illegitimate assumption[37]. Rather, changes in the structure of a molecule are known to occur on transition to another molecular state (Figs. 5, 6, 7, 12 or 24) and also within series of chemically closely related compounds (cf. *e.g.* Fig. 11). In many cases, *Gillespie*'s electron pair repulsion model[80] proves very useful in discussing possible changes; thus, along the series



widening of the FPF angle and shortening of the FP bond can be explained by increasing electron withdrawal F→P, which is also observed in the PE spectra[2e]. Precise calculation of the geometry of states requires considerable computational effort because the differences between large energy contributions ΔE_{total} have to be calculated. The bending of the S—C—N bond in $S(CN)_2$ is illustrative[81]:



Obviously, the $S(CN)_2$ structure as determined by microwave spectroscopy, and also the dipole moment, are satisfactorily reproduced by *ab initio* calculation with an extensive basis[81]; the slight SCN bending can be attributed to the calculated electron density between the two carbon atoms. However, the minor differences in total energy on bending (13: $\Delta E_{total}^{SCF} = 0.0077$ eV) show how much caution should be exercised when considering numerical data, *e.g.* from semiempirical procedures.

In polyatomic molecules, structure determinations via the minimum of the total energy require calculation of a multidimensional energy surface; attempts are made to avoid prohibitive costs, *e.g.* by fixing some coordinates, using fast computer programs, and optimization of coordinates (Fig. 27).

The total energy surface for rotation of SH about the CS axis in thiphenol[27], comprising 595 individual CNDO calculations (Fig. 27), and also considering deflections of C—SH, requires some 2 hours of computing time on a medium-size computer. It may be seen that no other conformation is preferred apart from the minima in the total energy for planar geometry. In spite of reservations towards individual numerical results from semiempirical calculations, such a comparison of total energies should, in general, correctly reproduce the energetically favored conformers.

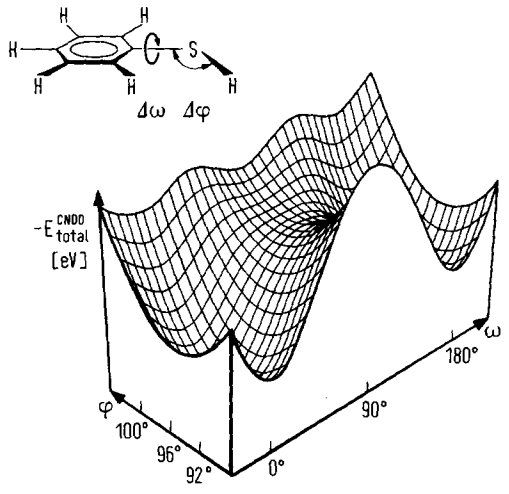


Fig. 27. The total energy surface for SH rotation in thiophenol [82], is made up of $17 \times 35 = 595$ individual CNDO calculations. In addition to twisting about the CS axis (Δω), deflections of C—S—H (Δφ) have also been considered, especially on passing of the *ortho* hydrogen atoms of the benzene ring. It is seen that no minima of the CNDO total energy occur except for planar arrangements ($\omega = 0°$ and 180°).

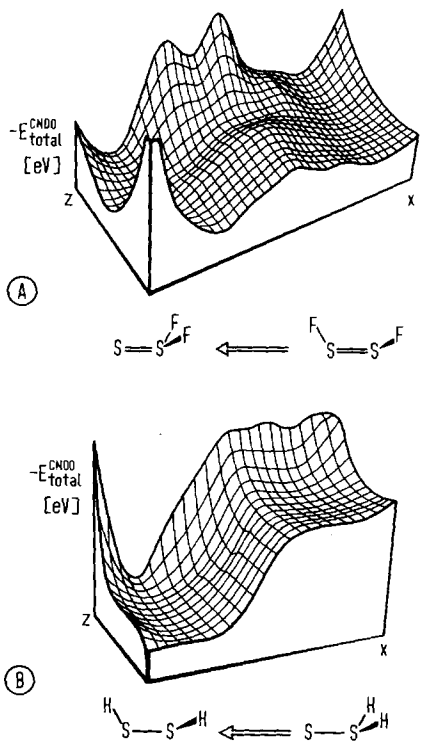


Fig. 28. The two isomers FSSF and F_2SS can be prepared separately; F_2SS is the thermodynamically more stable of the two. This situation—like PE ionization energies (10: A) or dipole moments (10: B)—is reproduced by CNDO calculations. On this basis, the isomerization energy surface FSSF⇆F_2SS(A) can be approximated assuming the occurrence of an intramolecular 1,2 fluorine shift: the FSS fragment is considered fixed and the second fluorine atom migrates along the SS axis x through 12 sectional planes z each with 144 screening points. The geometry is completely optimized only in the region of the minima; configuration interaction is neglected. The surface made up of 1728 CNDO total energies clearly exhibits the energetically preferred potential valley corresponding to isomerization. Close to the saddle point a shallow minimum is calculated for an almost planar three-membered ring arrangement F—S(—F)···S. The CNDO total energy for the more stable isomer F_2SS is only slightly more negative than that for FSSF; a relatively high barrier is found between the two. Corresponding energy surfaces for the H_2S_2 system, and likewise for Cl_2S_2 too [74], predict the XSSX isomer with C_2 symmetry to be the thermodynamically and kinetically stable species.

5.4. A Special Case: Molecular Reactions

As sketched out in the previous Section, changes in the geometry of molecules can often be satisfactorily approximated by point-for-point calculation and comparison of the total energy. Intensive efforts are currently being invested in the calculation of such energy surfaces also for molecular reactions in many places[13, 83, 84]. One of the many prerequisites of such calculations is that either experimental information about the detailed reaction course is available, *e.g.* from molecular beam studies[83], or plausible assumptions are possible, as for the presumably intramolecular isomerizations of compounds S_2X_2[74] (Fig. 28).

Accepting the various assumptions and simplifications given the following conclusions concerning the isomerizations $XSSX \rightleftarrows X_2SS$ can be drawn from the calculated energy surfaces[74] (Fig. 28), in complete accord with experimental evidence: both F_2S_2 isomers must be isolable; F_2SS is more stable than FSSF; only the HSSH and ClSSCl isomer, respectively, should be capable of existence in the H_2S_2 and Cl_2S_2 systems.

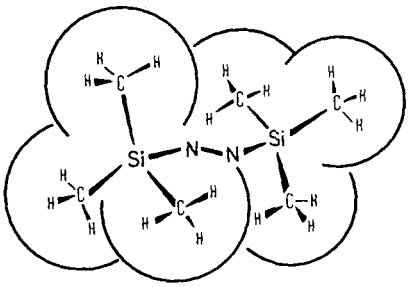
What general statements can be put forward concerning reactions between molecules of medium size $K_kL_lM_m + R_rS_sT_t \rightarrow$? For instance, how do the successful collisions occur in the gas phase? What is the structure of the molecular collision complex at the saddle point of maximum energy? Are there any intermediates? How is the course of reaction affected by the environment, *e.g.* in a solvent or at a catalyst? Numerous questions require experimental elucidation[83]—apart from further development of suitable calculating procedures[83, 84] (Fig. 2).

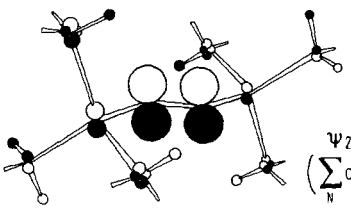
In this context, some attempts at mapping reaction coordinates warrant mention: thus comparison of X-ray structure analyses furnishes information about mutually coupled changes in molecular structures, such as angular deviation as a function of distance[85]; the "hyperspace" $H_2 + H^{\oplus}$ has already been calculated[84]; *ab initio*[68, 83] and MINDO/NDDO procedures[67, 83] compete with each other[86, 87], *e.g.* in calculation of hydrocarbon reactions; a qualitative illustrative model for reactions from singlet and triplet excited states[88] proves to be useful[23]; and, last but not least, the orbital symmetry rules of *Woodward* and *Hoffmann*[90], which are based on configuration diagrams[89], have found wide application in organic chemistry[91].

5.5. Large Molecules of Low Symmetry

A further limitation of MO models is that characteristic orbitals are generally no longer obtained for molecules with more than 15 to 20 atoms and structures of low symmetry. In particular, proximate (canonical[75]) orbitals of the same symmetry class usually undergo extensive mixing. For instance, the 28-atom molecule of bis(trimethylsilyl)diimine (Fig. 2) is calculated to have the following orbital as the seventh-from-highest of 30 occupied molecular orbitals:

Although ψ_{24} appears to represent the π_{NN} bond[24], its contributions at the nitrogen centers $\sum_N c^2_{24,N}$ amount to only about





(14)

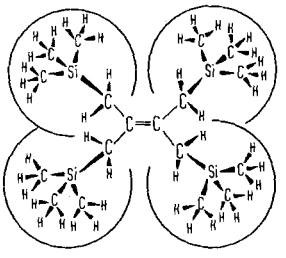
50 %[76]. Integrated quantities such as the total atomic charges (9) are often much more suitable for describing the states of such molecules. Thus the calculated high electron densities in the NN bond of azo compounds such as bis(trimethylsilyl)-diimine (Fig. 26), which are due to Si→N polarization, can be correlated with the low first ionization energies[76].

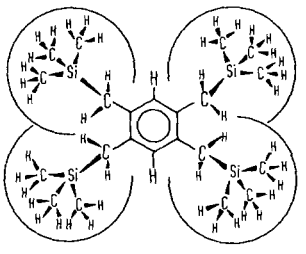
This example also marks a boundary beyond which a direct qualitative discussion of molecular states offers several advantages. For instance, comparably low first ionization energies are predicted for the 66- and 72-atom ethylene and benzene derivatives in the gas phase (Fig. 29) as a consequence of their identical substitution pattern of four tetrahedrally arranged $(H_3C)_3SiCH_2$ groups, and of the excellent stabilization of the roughly spherical radical cations. Similarly ESR spectra with extensive coupling are predicted as a result of complete delocalization of the electron hole over the molecule on oxidation in solution[92]—regardless of whether the central π system is ethylene or benzene, comparable 1st ionization energies and radical cation spin populations are observed for the similarly substituted molecules $[(H_3C)_3SiCH_2]_2$-π-$[CH_2Si(CH_3)_3]_2$ (Fig. 29). These compounds are already very large for a conventional description of their states in terms of molecular orbitals; nevertheless, in this case too—as in the discussions of Sections 5.1 and 5.4—there is a possibility of extending the available methods, for example by applying calculating techniques developed for the solid state.

6. Conclusion and Outlook

The selection of examples presented in this report should corroborate the following statement:

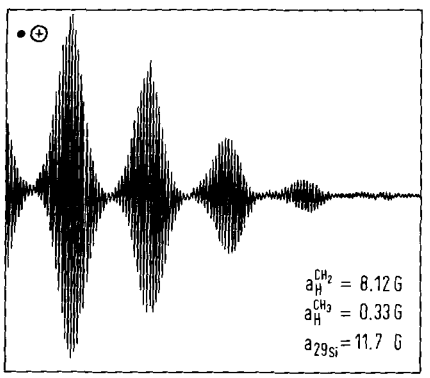
Chemical building blocks with defined structure and properties are molecules in particular states which can be characterized by their energy and their charge distribution. The best models yet available for their description are molecular orbitals, which are especially suitable for comparison of corresponding molecular states of chemically related compounds. By virtue of their inherent topology and symmetry, the potentials and numbers





$IE_1 = 7.15$ eV

$IE_1 = 7.10$ eV



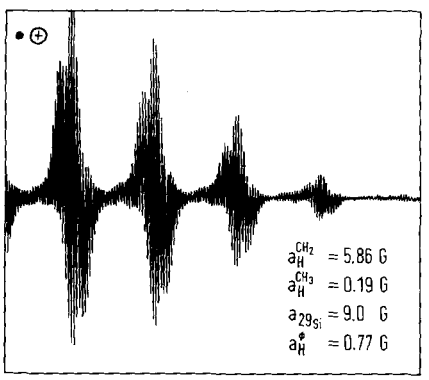


Fig. 29. In the tetrakis(trimethylsilylmethyl)-substituted ethylene and benzene derivatives $C_{18}H_{44}Si_4$ and $C_{22}H_{46}Si_4$ the central systems are surrounded in similar manner by four $(H_3C)_3SiCH_2$ groups. The energy differences between the ground states of the neutral molecule and the radical cation are in close agreement at 7.10 and 7.15 eV [92]. Their ESR spectra (1850 and 1988 lines, respectively) are characterized by the nonet of the methylene protons, of which five groups of signals are shown starting from the midpoint of the spectrum. The coupling constants for the 36 methyl protons $a_H^{CH_3}$, for the ^{29}Si doublet ($I^{29}_{Si} = 1/2$, abundance 4.70%) and the phenyl protons $a_H^{\oplus}$ can be confirmed by spectral simulation [92]. Obviously, $a_H^{CH_2}$ and a^{29}_{Si} decrease on switching from the ethylene derivative to the large benzene compound, providing further evidence for complete delocalization of the unpaired electron over the entire molecule.

of electrons to be inserted, and their flexibility towards perturbations, they provide a manifold and stimulating overview covering wide areas of chemistry.

How will molecular states be interpreted ten years from now? Ten years ago expeditions had just started into the *terra incognita* of σ molecular skeletons, with photoelectron spectra and all-electron calculations as navigational aids. Time and again, MO models have done great service in the interpretation of new experimental data—some 20 years ago in the case of the newly developed ESR technique and likewise just recently in the novel chemical application of electron transmission spectroscopy. The stimulation of preparative work by MO models is manifested by all those studies which are based on the stability of cyclic compounds with $(4N+2)$ electrons or on orbital symmetry in concerted reactions. The snowball-like increase in application of MO models during the past 15 years is a classical example of the influence of large computers in the natural sciences, and even the very next generation of computers can provide fresh impetus for advances and innovations in calculating procedures.

Last but not least, MO models offer—in the face of the increasing complexity and incredibly fast expansion of chemical sciences—an opportunity of gaining, and retaining, a general understanding and overall view of chemistry.

This is an appropriate place to express my gratitude to Professor Edgar Heilbronner, who introduced me to the "HMO model and its application". The work of the Frankfurt group cited above would not have been possible without the untiring efforts of dedicated co-workers, especially Dr. Hartmut Alt (deceased), Dr. Hans Seidl, Dr. Bahman Solouki, Dr. Klaus Wittel, Dr. Gerhard Wagner, Dr. Herbert Stafast, Dr. Walter Ensslin, Georg Brähler, Wolfgang Kaim, Shamsher Mohmand, Karl-Alexander Ostoja-Starzewski, and Abbas Tabatabai. Generous support of our work by the Deutsche Forschungsgemeinschaft, the State of Hesse, Hoechst AG, the Fonds der Chemischen Industrie, the Max-Buchner-Stiftung, and the Stiftung Volkswagenwerk is gratefully acknowledged. Scientific contacts with numerous colleagues have always had a stimulating effect; for suggestions and critical discussion comments I wish to thank especially Prof. E. Heilbronner, Dr. K. Wittel, Prof. G. Binsch, Prof. W. Kutzelnigg, Dr. P. Rosmus, and Dr. A. Semkow.

Received: June 29, 1977 [A 180 IE]
German version: Angew. Chem. *89*, 631 (1977)

[1] Based on a lecture delivered at the invitation of the Gesellschaft Deutscher Chemiker on the occasion of the Chemiedozententagung, Marburg, March 22, 1977.

[2] 6th Essay on "Molecular Properties and Models".—The following articles are to be considered as the 1st to 5th essays, respectively: a) "Color and Constitution of the Azo Compounds", Angew. Chem. *77*, 469 (1965); Angew. Chem. Int. Ed. Engl. *4*, 457 (1965); b) "Die Störung von π-Systemen als Molekülsonde für Substituenteneffekte", Jahrb. Akad. Wiss. Göttingen *1969*, 13; c) "Photoelectron Spectra of Nonmetal Compounds and Their Interpretation by MO Models" (with *B. G. Ramsey*), Angew. Chem. *85*, 773 (1973); Angew. Chem. Int. Ed. Engl. *12*, 734; d) "Photoelectron Spectroscopy: An Experimental Approach to Teaching Molecular Orbitals" (with *P. Mollère*), J. Chem. Educ. *51*, 506 (1974); e) "Photoelectron Spectra and Bonding in Phosphorus Compounds", Pure Appl. Chem. *44*, 343 (1975).

[3] *B. Solouki, P. Rosmus, H. Bock*, J. Am. Chem. Soc. *98*, 6054 (1976) and references cited therein; cf. also *H. Bock, S. Mohmand, B. Solouki, E. Block, L. K. Revelle*, J. Chem. Soc. Chem. Commun. *1977*, 287.

[4] *W. v. Niessen, L. S. Cederbaum, W. Domke, H. Diercksen*, J. Chem. Phys. *66*, 4893 (1977); concerning the GF procedure, cf. *L. S. Cederbaum*, Theor. Chim. Acta *31*, 239 (1973); J. Phys. *B8*, 290 (1975).

[5] *W. Meyer*, Int. J. Quantum Chem. *55*, 341 (1971); J. Chem. Phys. *58*, 1017 (1973); cf. also *R. Ahlrichs, W. Kutzelnigg, ibid. 62*, 1225 (1975); *M. Jungen, R. Ahlrichs*, Theor. Chim. Acta *17*, 339 (1970).

[6] *W. v. Niessen, G. H. F. Diercksen, L. S. Cederbaum*, Chem. Phys. Lett. *45*, 295 (1977).

[7] Further [3] examples are: $H_2C{=}C{=}S$ [*H. Bock, B. Solouki, G. Bert, P. Rosmus*, J. Am. Chem. Soc. *99*, 1663 (1977); *P. Rosmus, B. Solouki, H. Bock*, Mol. Phys., in press] as well as H_3CCl and H_3SiCl [*P. Rosmus, A. Semkow, H. Bock*, unpublished].

[8] Cf., *e.g.*, Nachr. Chem. Tech. *23*, 24 (1975).

[9] For a survey, see *H. F. Schaefer III*, "Molecular Electronic Structure Theory: 1972—1975", Annu. Rev. Phys. Chem. *1976*, 264.

[10] Discussion at the CNRS Symposium "Theoretische Chemie" at Obersteigen, October 1976: *E. Heilbronner*, personal communication.

[11] *F. Hund*, Angew. Chem. *89*, 89 (1977); Angew. Chem. Int. Ed. Engl. *16*, 87 (1977).

[12] *E. Hückel*, Z. Phys. *60*, 423 (1930); *70*, 204 (1931); *72*, 310 (1931).

[13] Cf. *J. B. Collins, J. D. Dill, E. D. Jemmis, Y. Apeloig, P. v. R. Schleyer, R. Seeger, J. A. Pople*, J. Am. Chem. Soc. *98*, 5419 (1976); *J. J. Dannenberg*, Angew. Chem. *88*, 602 (1976); Angew. Chem. Int. Ed. Engl. *15*, 519 (1976).

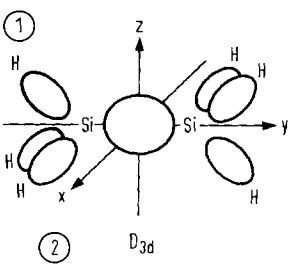
[14] Molecular states are generally designated Γ for the ground state and χ_i^j for electronically excited states generated by excitation $i \rightarrow j$; the charge is also given (in parentheses), *e.g.* as $M^{\bullet\oplus}$, M, or $M^{\bullet\ominus}$.—IUPAC rules have been published [Pure Appl. Chem. *21*, 29 (1970)] for specific cases. The individual states of a particle M or $M^{\bullet\oplus}$ are denoted therein by $\tilde{X}$ (ground state) and successively by $\tilde{A}$, $\tilde{B}$, $\tilde{C}$... (excited states), and also by their multiplicity $m=s+1$, *i.e.* the number s of spin-uncoupled electrons (singlet: $s=0$, $m=1$; doublet: $s=1$, $m=2$, *etc.*) as well as their symmetry type within the symmetry group of the molecular structure [19].

[15] From the wealth of review literature about photoelectron spectroscopy the following have been selected (with contents): a) *D. W. Turner, C. Baker, A. D. Baker, C. R. Brundle:* Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970 (reproductions of numerous spectra, literature covered up to 1969); b) *C. R. Brundle, M. B. Robin* in *F. C. Nachod, J. J. Zuckerman:* Determination of Organic Structures by Physical Methods. Vol. III. Academic Press, New York 1971, pp. 1ff. (introduction with the aid of selected examples); c) *J. H. D. Eland:* Photoelectron Spectroscopy. Butterworths, London 1974 (principles, information from PE spectra, general interpretation, literature covered up to 1972); d) *J. P. Maier*, Annu. Rep. Prog. Chem. *B 71*, 75 (1974) (survey of recent developments). Cf. also refs. [2c, 2e].

[16] *H. J. Lempka, T. R. Passmore, W. C. Price*, Proc. Roy. Soc. London *A 304*, 53 (1968).

[17] Cf. *F. Brogli, E. Heilbronner*, Helv. Chim. Acta *54*, 1423 (1971); *K. Wittel, H. Bock, R. Manne*, Tetrahedron *30*, 651 (1974); references cited therein.

[18] *H. Bock, W. Ensslin, F. Fehér, R. Freund*, J. Am. Chem. Soc. *98*, 668 (1976); references cited therein. The Jahn-Teller distortion $D_{3d} \rightarrow C_{2h}$



③							⑦	⑧
② D_{3d}	E	$2C_3$	$3C_2$	i	$2S_3$	$3\sigma_d$	$\sum \chi_\Gamma \chi_{ir}$	"SO"
A_{1g}	1	1	1	1	1	1	24	2
A_{2g}	1	1	-1	1	1	-1	0	0
E_g	2	-1	0	2	-1	0	12	1
⑥ A_{1u}	1	1	1	-1	-1	-1	0	0
A_{2u}	1	1	-1	-1	-1	1	12	1
E_u	2	-1	0	-2	1	0	12	1
⑤ Γ	7	2×1	3×1	1	2×1	3×3		
			④					

⑨ $\Gamma \doteq 2 \times A_{1g} + 1 \times A_{2u} + 1 \times E_g + 1 \times E_u$

of the iso(valence)electronic ethane radical cation is calculated by *A. Richartz, R. J. Buenker, P. J. Bruna, S. Peyerimhoff*, Mol. Phys., in press. Cf. also the survey by *C. Sandorfy:* Chemical Spectroscopy and Photochemistry in the Vacuum Ultraviolet. Reidel, Dordrecht 1974.

[19] For designation of symmetry of states the reader is referred to the introduction in ref. [21c] and to *F. A. Cotton:* Chemical Applications of Group Theory, Wiley-Interscience, New York 1966. A simple procedure for determining the symmetry of all radical cation states of a molecule is illustrated for the case of disilane (see Scheme at foot of p. 635):
① Definition of the coordinate system and bond classification; change in sign occurs for units such as π bonds or electron pairs extending over more than one center. Performance of all symmetry operations ③ belonging to the symmetry group ② of the molecule in order to determine the number ④ of "bond basis functions" transforming into "+" or "−" themselves. The product of the resulting characters ④ of the "reducible" representation Γ⑤ and the characters of the individual "irreducible representations" ⑥ of the group concerned ② are added together ⑦ and divided by the number of symmetry operations ⑧ performed. One obtains the symmetry types ⑨ of all radical cation states that can be generated by (mono)ionization of the valence electrons of molecule ①.

[20] *A. W. Potts, W. C. Price*, Proc. Roy. Soc. London *A 326*, 165 (1972); *L. J. Aarons, M. F. Guest, M. B. Hall, I. H. Hillier*, J. Chem. Soc. Faraday Trans. II *69*, 643 (1973), discuss the results of *J. P. Maier, D. W. Turner, ibid. 68*, 11 (1972). Cf. also *R. D. Baechler, K. Mislow*, J. Am. Chem. Soc. *93*, 773 (1971).

[21] The standard work on electronically and vibrationally excited molecular states is *G. Herzberg:* Molecular Spectra and Molecular Structure, comprising the three volumes: a) Vol. I: Spectra of Diatomic Molecules. Van Nostrand, New York 1950; b) Vol. II: Infrared and Raman Spectra of Polyatomic Molecules. Van Nostrand, New York 1955; c) Vol. III: Electronic Spectra of Polyatomic Molecules. Van Nostrand, New York 1966 (the tables on pp. 583ff. provide a comprehensive survey of the excited states of numerous molecules, with symmetry characterization).

[22] Cf. *M. B. Robin:* Higher Excited States of Polyatomic Molecules, Vol. I and II. Academic Press, New York 1974, 1975 (encyclopedia with over 1000 references).

[23] Cf. *G. Quinkert*, Angew. Chem. *87*, 851 (1975); Angew. Chem. Int. Ed. Engl. *14*, 790 (1975).

[24] *A. H. Lawrence, C. C. Liao, P. de Mayo, V. Ramamurthy*, J. Am. Chem. Soc. *98*, 2219, 3573 (1976); *A. Couture, K. Ho, M. Hoshino, P. de Mayo, R. Suan, W. R. Ware, ibid. 98*, 6218 (1976); *P. de Mayo*, Acc. Chem. Res. *9*, 52 (1976).

[25] *F. Gerson, J. Heinzer, H. Bock, H. Alt, H. Seidl*, Helv. Chim. Acta *51*, 707 (1968). The *p*-xylene radical anion spectrum was first published by *J. R. Bolton, A. Carrington*, Mol. Phys. *4*, 497 (1961).

[26] *H. Alt, E. R. Franke, H. Bock*, Angew. Chem. *81*, 538 (1969); Angew. Chem. Int. Ed. Engl. *8*, 525 (1969).

[27] Cf. *F. Gerson:* Hochauflösende ESR-Spektroskopie. Verlag Chemie, Weinheim 1967.

[28] Cf. *E. Heilbronner, H. Brock:* Das HMO-Modell und seine Anwendung, Vols I and II. Verlag Chemie, Weinheim 1968 and 1970; The HMO Model and its Application, Vols. I and II. Verlag Chemie, Weinheim, and Wiley, Chichester, 1976.

[29] Review: *W. C. Price, S. S. Chissick, T. Ravensdale:* Wave Mechanics—the first fifty years. Butterworths, London 1973.

[30] An important condition [31, 32] is *Pauli*'s principle of antisymmetry: The overall (wave) function of a many-electron system must be antisymmetric on simultaneous exchange of site and spin coordinates $\vec{x}_i$ of two electrons $\psi(\vec{x}_1,\vec{x}_2,\vec{x}_3\ldots)=-\psi(\vec{x}_2,\vec{x}_1,\vec{x}_3\ldots)$. Two electrons of a system therefore cannot exhibit identical coordinates $x_1=x_2=x$ since $\psi(x,x,x_3)=0$ would then hold.

[31] Among the many introductions to the principles of quantum mechanics, one of the most recent ones is: *W. Kutzelnigg:* Einführung in die Theoretische Chemie, Vol. I. Verlag Chemie, Weinheim 1975.

[32] A comprehensible qualification of spectroscopic states and their discussion on the the basis of electron configurations is found in *K. Wittel, S. McGlynn*, "The Orbital Concept in Molecular Spectroscopy", Chem. Rev. 1977, in press.

[33] *T. Koopmans*, Physica *1*, 104 (1933). The scope is discussed, *e.g.*, in [15b, c] and by *E. Heilbronner* in *R. Daudel, B. Pullman:* The World of Quantum Chemistry. Reidel, Dordrecht 1974, pp. 211ff.

[34] Cf. *J. A. Pople, D. L. Beveridge:* Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.

[35] *A. W. Potts, W. C. Price*, Proc. Roy. Soc. London *A 326*, 181 (1972).

[36] The SCF orbital energies are calculated by *B. Roos, P. Siegbahn*, Theor. Chim. Acta *21*, 368 (1971), and the potential surfaces and spin populations of the individual radical cation states by *H. Sakai, S. Yamabe, T. Yamabe, K. Fukui, H. Kato*, Chem. Phys. Lett. *25*, 541 (1974).

[37] *A. D. Walsh*, J. Chem. Soc. *1953*, 2260; cf. also *R. Buenker, S. D. Peyerimhoff*, Chem. Rev. *74*, 127 (1974); references cited therein.

[38] *E. Heilbronner, H. D. Martin*, Helv. Chim. Acta *55*, 1490 (1972); references cited therein.

[39] *R. Hoffmann*, Acc. Chem. Res. *4*, 1 (1971); references cited therein.

[40] Approximate solution of the Schrödinger equation $H\psi=\varepsilon\psi$ is discussed at length, *e.g.*, in ref. [31]. For the simplest case with most extensive simplifications—a homonuclear two-center system in the HMO approximation—the procedure [28] is as given below: in order to solve the differential equation with the two unknown eigenfunctions ψ and eigenvalue ε, an approximate linear combination $\psi^0_{1,2}=c_1\phi_1\pm c_2\phi_2$ is assumed which is made up of atomic orbitals ϕ and initially unknown coefficients c for each of the two centers. The best possible fit of ψ^0 to ψ within the framework of the approximation procedure, *i.e.* determination of the coefficients c_1 and c_2, is performed with the expanded and rearranged equation:

$$\varepsilon^0_{1,2}=\frac{\langle\psi^0_{1,2}|H|\psi^0_{1,2}\rangle}{\langle\psi^0_{1,2}|\psi^0_{1,2}\rangle}\approx\frac{\langle c_1\phi_1\pm c_2\phi_2|H|c_1\phi_1\pm c_2\phi_2\rangle}{\langle c_1\phi_1\pm c_2\phi_2|c_1\phi_1\pm c_2\phi_2\rangle}$$

the individual integrals being defined as parameters in the following way:

Type	$\langle\phi_i\|H\|\phi_j\rangle$	$\langle\phi_i\|\phi_j\rangle$
$i=j$	α_i (Coulomb)	1 (Normalization)
$i\neq j$	β_{ij} (Resonance)	S_{ij} (Overlap)

Determination of the energy minimum as a function of the coefficients $\delta\varepsilon/\delta c=0$ leads, *via* a system of so-called secular equations $\{\}$ and the corresponding secular determinant $\|\ \|$, initially to the eigenvalues $\varepsilon_{1,2}$:

$$\left.\begin{aligned}c_1(\alpha_1-\varepsilon)\pm c_2(\beta_{12}-S_{12}\varepsilon)&=0\\ c_1(\beta_{21}-S_{21}\varepsilon)\pm c_2(\alpha_2-\varepsilon)&=0\end{aligned}\right\}\Rightarrow\left\|\begin{matrix}\alpha_1-\varepsilon & \beta_{12}-S_{12}\varepsilon\\ \beta_{21}-S_{21}\varepsilon & \alpha_2-\varepsilon\end{matrix}\right\|=0$$

$$\psi^0_1=c_{11}\phi_1+c_{12}\phi_2 \qquad \varepsilon^0_{1,2}=\frac{\alpha\pm\beta}{1\pm S}$$
$$\psi^0_2=c_{21}\phi_1-c_{22}\phi_2$$

Insertion of the eigenvalues $\varepsilon_{1,2}$ into the secular equations finally affords the coefficients $c_{1,2}$ and hence the molecular orbitals $\psi_{1,2}$.

[41] Cf. *F. Brogli, E. Heilbronner, J. Ipaktschi*, Helv. Chim. Acta *55*, 2447 (1972); *R. Gleiter, E. Heilbronner, L. A. Paquette, G. L. Thompson, R. E. Wingard jr.*, Tetrahedron *29*, 565 (1973).

[42] a) *M. J. S. Dewar, R. C. Dougherty:* The PMO Theory of Organic Chemistry. Plenum, New York 1975; b) *M. J. S. Dewar:* The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[43] *A. Streitwieser jr.:* Molecular Orbital Theory for Organic Chemists. Wiley, New York 1961 (complete bibliography up to 1960).

[44] *L. Salem:* The Molecular Orbital Theory of Conjugated Systems. Benjamin, New York 1966 (literature up to 1965).

[45] Cf. "Aromaticity", Spec. Publ. 21, Chem. Soc. London 1967.

[46] *E. Hückel*, Z. Phys. *70*, 204 (1931); *76*, 628 (1932); Z. Elektrochem. Angew. Phys. Chem. *42*, 657 (1936).

[47] Cf. *G. Binsch*, Naturwissenschaften *60*, 369 (1973); *M. J. Goldstein, R. Hoffmann*, J. Am. Chem. Soc. *93*, 6193 (1971).

[48] *H. Bock, W. Ensslin*, Angew. Chem. *83*, 435 (1971); Angew. Chem. Int. Ed. Engl. *10*, 404 (1971); cf. also ref. [18].

[49] *P. D. Burrow, K. D. Jordan*, Chem. Phys. Lett. *36*, 594 (1976); *K. D. Jordan, J. A. Michejda, P. D. Burrow, ibid. 42*, 227 (1976); J. Am. Chem. Soc. *98*, 1295, 7189 (1976).

[50] *L. Sanche, G. J. Schulz*, J. Chem. Phys. *58*, 479 (1973); *I. Nenner, G. J. Schulz, ibid. 62*, 1747 (1975).

[51] *W. N. Lipscomb:* Boron Hydrides. Benjamin, New York 1963.

[52] *E. E. Havinga, E. H. Wiebenga*, Recl. Trav. Chim. Pays-Bas *78*, 724 (1959); *E. H. Wiebenga, E. E. Havinga, K. H. Boswijk*, Adv. Inorg. Chem. Radiochem. *3*, 133 (1961).

[53] *A. W. Potts, W. C. Price*, Proc. Roy. Soc. London *A 326*, 165 (1972); cf. also refs. [16, 35].

[54] *Cf., e.g.*, Holleman-Wiberg: Lehrbuch der Anorganischen Chemie, 81–90 Editions de Gruyter, Berlin 1976, pp. 734, 1137.

[55] The electronegativity is defined by *Pauling* and *Mulliken* as an energy, and by other authors as a force or a dimensionless ratio. The entire range of chemistry is embraced by $\Delta EN=3.54$ units (Fr 0.86 and Ne 4.40 [54]) and the effect of the central atom in various substituent groups (C in CH_3, CN, or CF_3) is not accounted for. Cf. *J. Hinze*, Fortschr. Chem. Forsch. *9*, 448 (1968).

[56] Cf. "Ionization Potentials and Ionization Limits Derived from the Analyses of Optical Spectra", NS RDS-NBS 34, Nat. Bur. Stand. Washington 1970.

[57] Orbital diagrams as shown in Fig. 20 are advantageously [28] drawn such that the radii of the circles round the sites are numerically equal to the coefficients $c_{J\mu}$. The areas of the circles $F=\pi c^2_{J\mu}$ are then directly proportional to the squares of the coefficients $c^2_{J\mu}$.

[58] C. Batich, E. Heilbronner, V. Hornung, A. J. Ashe III, D. T. Clark, U. T. Cobley, D. Kilcast, I. Scanlan, J. Am. Chem. Soc. 95, 928 (1973); for bismutabenzene: J. Bastide, E. Heilbronner, J. P. Maier, A. J. Ashe III, Tetrahedron Lett. 1976, 411. Cf. also A. J. Ashe III, F. Burger, M. Y. El-Sheik, E. Heilbronner, J. P. Maier, J.-F. Muller, Helv. Chim. Acta 59, 1944 (1976); and references cited therein.
[59] H. Bock, G. Wagner, J. Kroner, Chem. Ber. 105, 3850 (1972); Tetrahedron Lett. 1971, 3713; references cited [especially W. E. Forbes, P. D. Sullivan, Can. J. Chem. 46, 317 (1968)].
[60] Cf. F. Brogli, E. Heilbronner, J. Wirz, E. Kloster-Jensen, R. G. Bergmann, K. P. C. Vollhardt, A. J. Ashe III, Helv. Chim. Acta 58, 2620 (1975); M. Beez, G. Bieri, H. Bock, E. Heilbronner, ibid. 56, 1028 (1973); W. Ensslin, H. Bock, G. Becker, J. Am. Chem. Soc. 96, 2757 (1974); H. Bock, G. Wagner, K. Wittel, J. Sauer, D. Seebach, Chem. Ber. 107, 1869 (1974).
[61] Cf. E. Heilbronner, V. Hornung, J. P. Maier, E. Kloster-Jensen, J. Am. Chem. Soc. 96, 4252 (1974); K. Wittel, H. Bock, Chem. Ber. 107, 317 (1974); C. R. Brundle, M. B. Robin, N. A. Kuebler, H. Basch, J. Am. Chem. Soc. 94, 1451, 1466 (1972).
[62] H. Stafast, H. Bock, Tetrahedron 32, 855 (1976).
[63] Cf. J. N. Murrell, M. Schmidt, J. Chem. Soc. Faraday Trans. II 1972, 1709; H. Stafast, H. Bock, Z. Naturforsch. B 28, 746 (1973); R. N. Dixon, J. N. Murrell, B. Narayan, Mol. Phys. 20, 611 (1971); references cited.
[64] Cf. the survey of original publications in O. Sinanoglu, K. B. Wiberg: Sigma Molecular Orbital Theory. Yale University Press, New Haven 1970, or the review in [42b].
[65] R. Hoffmann, J. Chem. Phys. 39, 1397 (1963).
[66] J. A. Pople, D. P. Santry, G. A. Segal, J. Chem. Phys. 43, 129, 136 (1965); 44, 3289 (1966).
[67] M. J. S. Dewar, G. Klopman, J. Am. Chem. Soc. 89, 3089 (1967).
[68] W. J. Hehre, Acc. Chem. Res. 9, 399 (1976).
[69] K. A. Ostoja-Starzewski, H. Bock, J. Am. Chem. Soc. 98, 8456 (1976).
[70] As representative of numerous articles [39] one may cite: R. Hoffmann, A. Imamura, W. J. Hehre, J. Am. Chem. Soc. 90, 1499 (1968).
[71] Literature surveys are found in [2c] and in C. G. Pitt, J. Organomet. Chem. 61, 49 (1973); cf. also W. Ensslin, H. Bock, G. Brähler, J. Am. Chem. Soc. 96, 2757 (1974); R. Hoffmann, L. Radom, J. A. Pople, P. v. R. Schleyer, W. J. Hehre, L. Salem, ibid. 94, 6221 (1972).
[72] R. Gleiter, J. Chem. Soc. A 1970, 3174.
[73] R. J. Gillespie, D. R. Shin, J. D. Tyrer, J. Chem. Soc. Chem. Commun. 1977, 253.
[74] B. Solouki, H. Bock, Inorg. Chem. 16, 665 (1977).
[75] Cf. W. Kutzelnigg, Angew. Chem. 85, 564 (1973); Angew. Chem. Int. Ed. Engl. 12, 559 (1973).
[76] H. Bock, K. Wittel, M. Veith, N. Wiberg, J. Am. Chem. Soc. 98, 109 (1976); references cited therein.
[77] E. Haselbach, A. Schmelzer, Helv. Chim. Acta 54, 1575 (1971).
[78] M. Klessinger, "Mehrelektronen-Modelle in der organischen Chemie", Fortschr. Chem. Forsch. 9, 354 (1968); references cited therein.
[79] J. N. Murrell: The Theory of the Electronic Spectra of Organic Molecules. Methuen, London 1963.
[80] R. J. Gillespie, Angew. Chem. 79, 885 (1967); Angew. Chem. Int. Ed. Engl. 6, 819 (1967); Molecular Geometry. Van Nostrand Reinhold, London 1972; Molekülgeometrie. Verlag Chemie, Weinheim 1975.
[81] P. Rosmus, H. Stafast, H. Bock, Chem. Phys. Lett. 34, 275 (1975).
[82] H. Bock, A. Tabatabai, unpublished; A. Tabatabai, Diplomarbeit, Universität Frankfurt 1976.
[83] The discussion conference "Potential Energy Surfaces" held Sept. 8—10, 1976 at Brighton/England is reported by the Faraday Society in Faraday Discuss. Chem. Soc. 62 (1977). Lectures and discussions concerned both recent experimental results about reaction pathways and further development of theoretical approaches to their description, e.g. by energy surfaces.
[84] B. Lin, J. Chem. Phys. 58, 1925 (1973); cf. also ref. [9].
[85] H. B. Bürgi, J. D. Dunitz, E. Shefter, J. Am. Chem. Soc. 95, 5065 (1973); H. B. Bürgi, Angew. Chem. 87, 461 (1975); Angew. Chem. Int. Ed. Engl. 14, 460 (1975).
[86] M. J. S. Dewar, J. Am. Chem. Soc. 97, 6591 (1975); Chem. Br. 11, 97 (1975); cf. also [83].
[87] W. J. Hehre, J. Am. Chem. Soc. 97, 5308 (1975); J. A. Pople, ibid. 97, 5306 (1975); cf. also [83, 84].
[88] L. Salem, C. Rowland, Angew. Chem. 84, 86 (1972); Angew. Chem. Int. Ed. Engl. 11, 92 (1972); W. G. Dauben, L. Salem, N. J. Turro, Acc. Chem. Res. 8, 41 (1975); references cited therein.
[89] H. C. Longuet-Higgins, W. E. Abrahamson, J. Am. Chem. Soc. 87, 2045 (1965).
[90] R. B. Woodward, R. Hoffmann, Angew. Chem. 81, 797 (1969); Angew. Chem. Int. Ed. Engl. 8, 781 (1969).
[91] N. Trong Anh: Die Woodward-Hoffmann-Regeln und ihre Anwendung. Verlag Chemie, Weinheim 1972.
[92] H. Bock, W. Kaim, J. Organomet. Chem. 135, C 14 (1977); Tetrahedron Lett. 1977, 2343; cf. also Abstr. 10th Organosilicon Symp. Windsor/Canada, April 1976.

COMMUNICATIONS

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

1-Aryl-4-methoxyarsacyclohexadiene→2-Arylarsabenzene Rearrangement—An Organoelement Analog of the Cyclohexadienol→Benzene Rearrangement

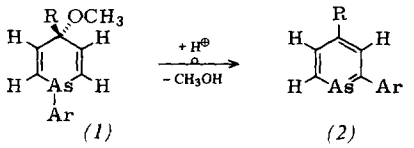
By *Gottfried Märkl* and *Rainer Liebl*[*]

The cyclohexadienol→benzene rearrangement[1] has been demonstrated on numerous occasions[2]. In the present communication we report the first analogous organoelement rearrangement.

The pronounced tendency of phospha- and arsacyclohexadienes to rearrange into phospha- and arsabenzenes is well known[3]. We have now been able to show that the 4-substituted 1-aryl-4-methoxyarsacyclohexadienes *(1)*[4], readily

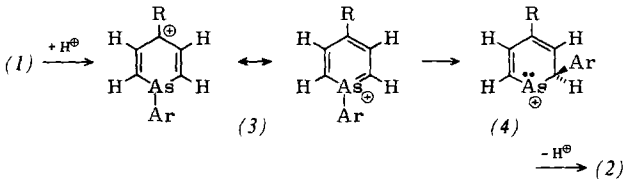
[*] Prof. Dr. G. Märkl, R. Liebl
Chemisches Institut der Universität
Universitätsstrasse 31, D-8400 Regensburg 1 (Germany)

accessible by cycloaddition of arylarsanes to 3-substituted 3-methoxy-1,4-pentadiynes, smoothly rearrange to give the 4-substituted 2-arylarsabenzenes *(2)* in good yields on reaction with catalytic amounts of strong acids, *e.g.* *p*-toluenesulfonic acid in boiling benzene, or with boron trifluoride ether in benzene at room temperature. The rearrangement *(1)*→*(2)* thus constitutes a novel, preparatively extremely facile entry to the arsabenzenes.



(1) *(2)*

The initial step is cleavage of allyl ether from *(1)*, which is additionally facilitated by the heteroatom. Most likely the pyridinium ion analogs, the previously unknown 1-arylarsabenzenium ions *(3)* (1-arylarseninium ions) of tetravalent arsenic with coordination number 3[5], are formed first and then undergo the 1,2 aryl shift to give *(4)*, and finally deprotonation to give the arsabenzenes *(2)*.



(3) *(4)*

The intermediate *(4)* has the structure of a σ-complex formed as product of the electrophilic aromatic substitution of the arsabenzene ring (in position 2) and thus provides strong supporting evidence for the existence of non-aromatic complexes derived from arsabenzenes. Electrophilic aromatic substitution reactions of arsa- or phosphabenzenes have so far not been reported in the literature.

That also the difficultly accessible 4-substituted 1-arylarsacyclohexadien-4-ols undergo acid catalyzed rearrangement in the expected fashion to give the 2-arylarsabenzenes was demonstrated with 1,4-diphenylarsa-2,5-cyclohexadien-4-ol, which under analogous reaction conditions rearranges to 2,4-diphenylarsabenzene in 85% yield. Since the arsabenzenes cannot be arylated or alkylated in position 2[7] similarly to the Ziegler alkylation and arylation of pyridine[6] by reaction with organometallic compounds RLi or RMgX, the rearrangement mentioned here constitutes the first preparatively useful method for the synthesis of 2-arylarsabenzenes[8]. Some examples are listed in Table 1.

Procedure

2,4-Diphenylarsabenzene *(2a)*: A solution of *(1a)* (1.60 g, 5.0 mmol) (as a mixture of *cis/trans* isomers, in which the amount of one component is about 90—95%)[4] in anhydrous benzene (50 ml) is boiled under reflux in the presence of 20 mg *p*-toluenesulfonic acid for 3 h. The cooled reaction mixture is washed several times with water, dried over $MgSO_4$, and the solvent removed in a water-jet vacuum. Distillation of the residue in a rotating bulb-tube (air-bath temperature 180°C) at 10^{-3} torr affords 1.36 g *(2a)* (94%) as a pale yellow oil, which crystallizes on rubbing with petroleum ether in the presence of some ethyl acetate. Colorless crystals (from ethyl acetate/petroleum ether), m.p. 75—77°C. All operations must be carried out under highly-pure nitrogen.

Received: June 10, 1977 [Z 760 IE]
German version: Angew. Chem. *89*, 670 (1977)

CAS Registry numbers:
(1) (R = C_6H_5, Ar = C_6H_5), 63428-62-6; *(1)* (R = C_6H_5, Ar = *p*-$CH_3C_6H_4$), 63428-61-5; *(1)* (R = CH_3, Ar = C_6H_5), 63428-60-4; *(1)* (R = C_2H_5, Ar = C_6H_5), 63428-59-1; *(1)* (R = C_6H_{11}, Ar = C_6H_5), 63428-58-0; *(1)* (R = $(CH_3)_3C$, Ar = *p*-$CH_3C_6H_4$), 63428-57-9; *(1)* (R = $(CH_3)_3C$, Ar = C_6H_5), 63428-56-8; *(2)* (R = C_6H_5, Ar = C_6H_5), 63466-40-0; *(2)* (R = C_6H_5, Ar = *p*-$CH_3C_6H_4$), 63428-55-7; *(2)* (R = CH_3, Ar = C_6H_5), 63428-54-6; *(2)* (R = C_2H_5, Ar = C_6H_5), 63428-53-5; *(2)* (R = C_6H_{11}, Ar = C_6H_5), 63428-52-4; *(2)* (R = $(CH_3)_3C$, Ar = *p*-$CH_3C_6H_4$), 63428-51-3; *(2)* (R = $(CH_3)_3C$, Ar = C_6H_5), 63428-50-2

[1] *H. Plieninger, G. Keilich*, Angew. Chem. *68*, 618 (1956); Chem. Ber. *91*, 1891 (1958).
[2] *P. de Mayo:* Molecular Rearrangements, Vol. 2. Wiley-Interscience, New York 1964, pp. 1028—1035.
[3] *G. Märkl, D. E. Fischer*, Tetrahedron Lett. *1972*, 4925; *1973*, 223; *G. Märkl, J. B. Rampal, ibid.*, in press.
[4] *G. Märkl, R. Liebl*, Synthesis, in press.
[5] The 1-arylphosphabenzenium ions analogous to *(3)* could possibly be prepared as reactive intermediates: *G. Märkl, A. Merz, H. Rausch*, Tetra-

Table 1. 2-Arylarsabenzenes *(2)* synthesized by rearrangement from *(1)*.

R	Ar	Yield [%] [a]	M.p. [°C]	MS (rel. int. [%]) [b]	^{1}H-NMR ($CDCl_3$) [c]	UV [nm] (ε) (Ethanol)
C_6H_5	C_6H_5	94	75—77	$[M-CH_3]^+$ (21); $[M-As]^+$ (32)	H^6: 9.63 (d); H^5: 8.00 (d); H^3: 8.18 (s)	315 (19900); 271 (33400); 233 (17800)
C_6H_5	*p*-$CH_3C_6H_4$	62	47—48	$[M-CH_3]^+$ (25); $[M-As]^+$ (29)	H^6: 9.71 (d); H^5: 7.99 (d); H^3: 8.17 (s); CH_3: 2.32 (s)	315 (13600); 279 (24200); 235 (12500)
CH_3	C_6H_5	86	Oil	$[M-CH_3]^+$ (44); $[M-As]^+$ (28)	H^6: 9.60 (d); H^5: 7.66 (d); H^3: 7.88 (s); CH_3: 2.33 (s)	298 (7000); 257 (21700)
C_2H_5	C_6H_5	74	Oil	$[M-CH_3]^+$ (12); $[M-C_2H_5]^+$ (31); $[M-As]^+$ (16)	H^6: 9.63 (d); H^5, Phenyl-H: 7.23—7.80 (m); H^3: 7.83 (s); CH_2: 2.66 (q); CH_3: 1.20 (t), J_{HH} = 7 Hz	298 (10900); 257 (25600)
c-C_6H_{11}	C_6H_5	80	Oil	$[M-C_6H_{10}]^+$ (17)	H^6: 9.52 (d); H^5, Phenyl-H: 7.00—7.70 (m); Cyclohexyl-H: 1.60—2.80 (m)	297 (9800); 256 (17900)
$(CH_3)_3C$	*p*-$CH_3C_6H_4$	92	51—53	$[M-CH_3]^+$ (56); $[M-C_4H_8]^+$ (25)	H^6: 9.65 (d), H^5: 8.00 (d); H^3: 8.12 (s); CH_3: 2.33 (s); $(CH_3)_3C$: 1.35 (s)	298 (7100) 259 (21900)
$(CH_3)_3C$	C_6H_5	93	Oil	$[M-CH_3]^+$ (76)	H^6: 9.46 (d), H^5: 7.74 (d); H^3: 7.90 (s); $(CH_3)_3C$: 1.13 (s)	296 (8100); 257 (26000)

[a] Distillation under pure nitrogen in a rotating bulb-tube (Büchi GKR-50) at 10^{-3} torr. All the compounds described gave correct elemental analyses.
[b] Measurement with Varian MAT CH5; in each case M^+ occurs with 100% rel. intensity.
[c] H^5, H^6: AB spectrum; J_{AB} = 12 Hz [compounds *(2a)*, *(2b)*, *(2e)*] or 11 Hz.

hedron Lett. *1971*, 2989; *K. Dimroth*, Fortschr. Chem. Forsch. *38*, 1 (1973); *G. Märkl*, Phosphorus Sulfur *3*, 77 (1977).
[6] *K. Ziegler, H. Zeiser*, Ber. Dtsch. Chem. Ges. *63*, 1847 (1930); Justus Liebigs Ann. Chem. *485*, 174 (1931).
[7] *J. Advena*, Dissertation, Universität Regensburg 1973; see also *A. J. Ashe III, T. W. Smith*, Tetrahedron Lett. *1977*, 407.
[8] The synthesis of 2-phenylarsabenzene described by *A. J. Ashe III, W. T. Chan, E. Perozzi* (Tetrahedron Lett. *1975*, 1083) is impaired by the poor accessibility of the 2-phenylstanna-2,5-cyclohexadiene as precursor.

Pentacarbonyl(dimesitylgermanediyl)chromium(0)[**]

By *Peter Jutzi* and *Wolfgang Steiner*[*]

Carbene analogous diorganogermylenes are extremely reactive species that are stabilized by formation of polygermanes and by insertion reactions[1]. Following the synthesis of complexes containing GeX_2 ligands (X = halogen, SR)[2], we have now been able to prepare a diarylgermylene complex.

Reaction of pentacarbonyl(tetrahydrofurandichlorogermanediyl)chromium(0) [compound *(1)*][3] with mesitylmagnesium bromide affords pentacarbonyl(dimesitylgermanediyl)-chromium(0) [compound *(2)*] in *ca.* 50% yield:

$$(CO)_5Cr{\leftarrow}GeCl_2{\cdot}THF + 2\ MesitylMgBr \longrightarrow$$

(1)

$$(CO)_5Cr{\leftarrow}Ge\left[\begin{array}{c}CH_3\\ \\ CH_3 \quad\quad CH_3\end{array}\right]_2 + \ldots$$

(2)

Complex *(2)* is isolable as a red crystalline powder which is surprisingly air-stable and only slightly sensitive towards hydrolysis. Noteworthy is its thermal stability (DTA: dec. pt. 80 °C). *(2)* readily dissolves in hydrocarbons, chlorinated hydrocarbons, carbon disulfide and, without complexation, also in tetrahydrofuran and diethyl ether. Its structure follows from elemental analysis and spectroscopic data. Mass spectrum and molecular weight determination (cryoscopically in benzene) confirm the complex to be monomeric.

The dimesitylgermylene ligand should be a good π acceptor. This is indeed evidenced by the position of the long-wave A_1 vibration in the νCO region. Assignment of the νCO vibrations is based on the assumption of local C_{4v} symmetry for the $Cr(CO)_5$ moiety [IR in CH_2Cl_2 (comp.): 2075 (m, A_1), 1995 (s, A_1), 1945 (s, E) cm^{-1}].

The germylene complex *(2)* can readily be transformed into the nitrogen-germanium ylide complex *(3)* with pyridine:

$$(2) + Pyridine \longrightarrow (CO)_5Cr{\leftarrow}Ge\left[\begin{array}{c}CH_3\\ \\ CH_3 \quad\quad CH_3\end{array}\right]_2$$

with a pyridine ring coordinated to Ge via N

(3)

Compound *(3)*: pale yellow needles, m.p. 114 °C; IR in CH_2Cl_2 (comp.): 2065 (m, A_1), 1945 (s, A_1), 1925 (s, E) cm^{-1}. No reaction takes place with bulky bases such as triphenylphosphane or benzothiazole.

Presumably steric effects are responsible for the unexpected stability of the dimesityl germylene complex *(2)*. Attempts to synthesize the analogous diphenylgermylene complex have so far met without success.

Procedure

Synthesis of *(2)*: A THF-solution of mesitylmagnesium bromide (10 mmol) is added dropwise with stirring to a solution of *(1)* (2.03 g, 5 mmol) in THF (50 ml) at −20 °C. The reaction solution is warmed to room temperature and stirred for 1 h. After removal of all the volatile components *in vacuo*, the remaining brown oil is chromatographed on silica gel (Merck 60) with benzene/petroleum ether 50/70 (1:1). The red zone contains the desired product. Recrystallization from petroleum ether 50/70 at −78 °C affords the analytically pure complex *(2)*. Yield: 1.22 g (48 %).—^{1}H-NMR (in CH_2Cl_2): δ = 6.8 (s, 4 aryl-H), 2.4 (s, 12 methyl-H), 2.3 (2, 6 methyl-H).

Synthesis of *(3)*: A solution of *(2)* (2.52 g, 5 mmol) in benzene (50 ml) is treated with pyridine (0.40 g, 5 mmol). After removal of solvent the yellow residue is recrystallized twice from petroleum ether 50/70. Yield: 3.01 g (91 %).—^{1}H-NMR (in CH_2Cl_2): δ = 6.85 (s, 4H), 2.3 (s, 18H), 7.2—7.9 (m, 5 pyridine-H).

Received: June 23, 1977 [Z 769 IE]
German version: Angew. Chem. *89*, 675 (1977)

CAS Registry numbers:
(1), 60260-16-4; *(2)*, 63428-34-2; *(3)*, 63466-36-4; mesitylmagnesium bromide, 2633-66-1

[1] *I. Satgé, M. Massol, P. Rivière*, J. Organomet. Chem. *56*, 1 (1973).
[2] *P. Jutzi, W. Steiner*, Angew. Chem. *88*, 720 (1976); Angew. Chem. Int. Ed. Engl. *15*, 684 (1976).
[3] *P. Jutzi, W. Steiner*, Chem. Ber. *109*, 3473 (1976).

[*] Doz. Dr. P. Jutzi, Dipl.-Chem. W. Steiner
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

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

Anomalous Nucleophilic Substitution in (Chloromethyl)silane: 1,2-Hydride Shift[**]

By *Hubert Schmidbaur* and *Beate Zimmer-Gasser*[*]

(Chloromethyl)silane is the β-Si analog of ethyl chloride:

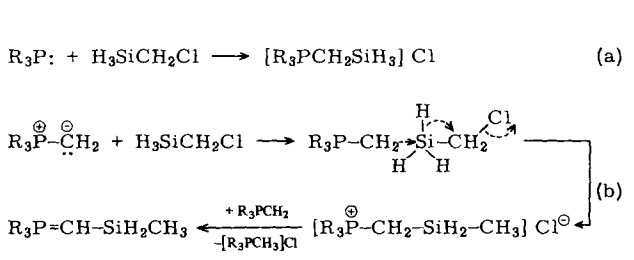
$$\overset{\delta+}{H_3Si}-\overset{}{CH_2}-\overset{\delta-}{Cl} \qquad\qquad \overset{\delta+}{H_3C}-\overset{}{CH_2}-\overset{\delta-}{Cl}$$

Spectroscopic investigations[1] have shown the "silaethyl chloride" to have a markedly reduced C—Cl polarity. Hence, in many cases substitutions in such a species ought to proceed differently from in the case of the "pure" alkyl compound. Whereas the previously studied quaternizations of phosphanes[2] showed no anomalies on account of the modest affinity of the phosphorus toward silicon [Reaction (a)], the first examples of the suspected alternative reaction mechanism [Reaction (b)] have now been observed in reactions with phosphorus ylides.

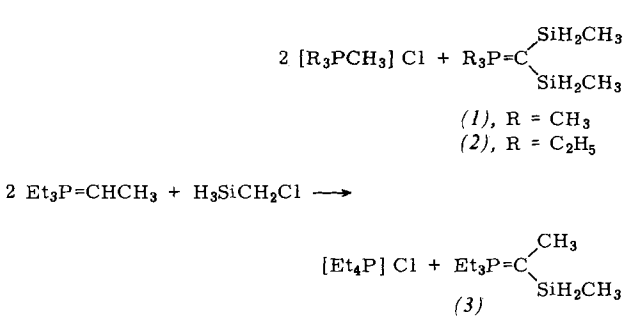
In contrast to trialkylphosphanes, the trialkyl(methylene)-phosphoranes have, in their ylidic carbanions, a nucleophilic center showing a high affinity toward silicon, the atom which it attacks preferentially on reaction with H_3SiCH_2Cl. The increase in coordination number of the silicon to 5 leads to destabilization of the Si—H bond, so that a hydride shift to the neighboring C-atom can follow with displacement of the Cl atom.

[*] Prof. Dr. H. Schmidbaur, Dipl.-Chem. B. Zimmer-Gasser
Anorganisch-chemisches Institut der Technischen Universität
Arcisstr. 21, D-8000 München 2 (Germany)

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



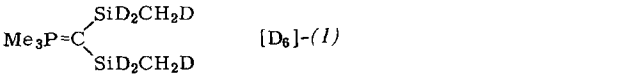
The [(methylsilyl)methyl]phosphonium salt thus formed is transformed by transylidation with further ylide[3] into the [(methylsilyl)methylene]phosphorane end product. Since this reaction with H_3SiCH_2Cl can take place twice (until complete silylation of the ylide function), $Me_3P{=}CH_2$ and $Et_3P{=}CH_2$ respectively afford the bis(silyl)methylenephosphoranes *(1)* and *(2)* in almost quantitative yields. With $Et_3P{=}CHCH_3$ the reaction must terminate at the stage of the monosilyl compound *(3)*.



(1), R = CH_3
(2), R = C_2H_5

(3)

For proof of the 1,2 shift according to Eq. (b) we have synthesized D_3SiCH_2Cl and investigated its reaction with $Me_3P{=}CH_2$. NMR analysis of the product [D_6]-*(1)* confirmed the origin of one of the $SiCH_3$ hydrogen atoms from the SiH_3 group.



In the light of these findings a series of previously unexplained observations can now be clarified. For example, the instability or non-existence of silylmethyl-alkali metal and Grignard compounds $H_3SiCH_2^{\ominus}M^{\oplus}$ and of silylated ylides $H_3Si{-}CH{=}PR_3$[2,4]. Moreover, the prediction that alkylations of silylalkyl halides do not proceed in the usual sense, finds experimental support in the reaction of H_3SiCH_2Cl with *n*-butyllithium, which does not lead to pentyl- but to butylmethylsilane. This finding confirms the substitution mechanism suggested above and shows, as do experiments with fluorides and alkoxides as nucleophiles, that it is in no way restricted to ylidic reaction partners, but represents a general reaction principle.

Procedure

A solution of the ylide (20 mmol) in Et_2O (20 ml) is added dropwise at −78 °C to a stirred solution of $ClCH_2SiH_3$[5] (20 ml) in Et_2O (20 ml). The phosphonium salt formed immediately is filtered off and ether removed from the filtrate by evaporation. The resulting residue is then purified by distillation. B.p. [°C/torr]: *(1)* $30/10^{-1}$ (65/10); *(2)* $56/10^{-1}$; *(3)* $79/10^{-1}$.

^{1}H-NMR (C_6D_6, TMS ext.): *(1)* δCH_3P 1.2, d, 9H, $^2J_{HCP}$ 12.75 Hz; δCH_3Si 0.55, t, 6H, $^3J_{HSiCH}$ 3.75; δSiH 4.9, dq, 4H, $^3J_{HSiCP}$ 12.75. *(2)* δCH_3Si 0.55, t, 6H, $^3J_{HSiCH}$ 3.75; δSiH 4.9, dq, 4H, $^3J_{HSiCP}$ 11; A_3B_2X-multiplet for PC_2H_5, 15H. *(3)* δCH_3Si 0.55, t, 3H, $^3J_{HCSiH}$ 3.75; δCH_3C 1.9, d, 3H, $^3J_{HCCP}$ 19.8; δSiH 5.0, dq, 2H, $^3J_{HSiCP}$ 4.5; A_3B_2X multiplet for PC_2H_5, 15H. [D_6]-*(1)* δCH_3P 1.1, d, 9H, $^2J_{HCP}$ 12.75; $\delta SiCH_2D$ 0.4, tquin, 4H, $^2J_{HCD}$ 2.4, $^3J_{HCSiD}$ 0.75.—$^{31}P\{^1H\}$-NMR (benzene, H_3PO_4 ext.): *(1)* δP 5.2, s; [D_6]-*(1)* δP 5.6, s; *(2)* δP 28.2, s; *(3)* δP 24.9, s.

Received: July 5, 1977 [Z 779a IE]
German version: Angew. Chem. 89, 678 (1977)

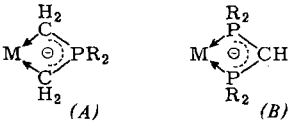
CAS Registry numbers:
(1), 63528-37-0; [D_6]-*(1)*, 63528-38-1; *(2)*, 63528-39-2; *(3)*, 63528-40-5; $Me_3P{=}CH_2$, 14580-91-7; $Et_3P{=}CH_2$, 17847-84-6; $Et_3P{=}CHCH_3$, 17847-85-7; D_3SiCA_2Cl, 18157-07-8; $ClCH_2SiH_3$, 10112-09-1; [Me_3PCA_3]Cl, 1941-19-1; [Et_3PCH_3]Cl, 63528-41-6; [Et_4P]Cl, 7368-65-2

[1] *H. Schmidbaur, B. Zimmer-Gasser, F. H. Köhler, W. Buchner*, Z. Naturforsch. *B32*, 481 (1977).
[2] *H. Schmidbaur, W. Malisch*, Chem. Ber. *103*, 3007 (1970); *H. Schmidbaur, B. Zimmer-Gasser*, Z. Naturforsch. *B32*, 603 (1977).
[3] *H. Schmidbaur*, Acc. Chem. Res. *8*, 62 (1975).
[4] *H. Schmidbaur, W. Wolf*, Chem. Ber. *108*, 2842 (1975).
[5] *H. D. Kaesz, F. G. A. Stone*, J. Chem. Soc. *1957*, 1433.

Diphosphinomethanide/Phosphoniumbismethylide: A Novel Ligand Combination for Transition Metals[**]

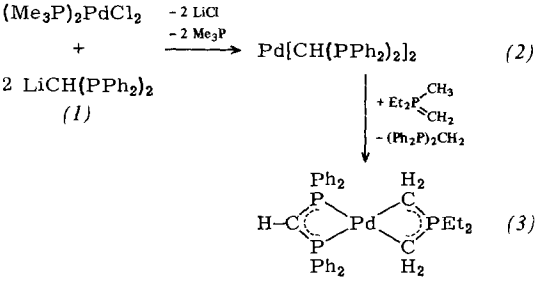
By *Hubert Schmidbaur* and *Johann R. Mandl*[*]

Under suitable conditions phosphorus ylides react with almost all metal centers to give metallocyclic compounds of type A, which on account of their interesting properties[1] have been the subject of numerous studies. In contrast, little is known about the related diphosphinomethanide complexes of type B, of which only a few of the previously reported[3] examples have been satisfactorily characterized structurally.



We have now found that the *combination of both ligand systems* leads to novel coordination compounds having a notably high tendency to formation and high thermal stability. The methods of synthesis and typical properties of such compounds are demonstrated here using a mononuclear palladium(II)- and a dinuclear gold(I)-complex as examples.

Reaction of $(Me_3P)_2PdCl_2$ with lithiated bis(diphenylphosphino)methane *(1)*[2] in tetrahydrofuran leads to formation of the orange-yellow insoluble palladium(II) bis[bis(diphenylphosphino)methanide] *(2)*, which reacts with diethylmethyl(methylene)phosphorane[4] with displacement of bis(diphenyl-



[*] Prof. Dr. H. Schmidbaur, Dr. J. R. Mandl
Anorganisch-chemisches Institut der Technischen Universität
Arcisstr. 21, D-8000 München 2 (Germany)

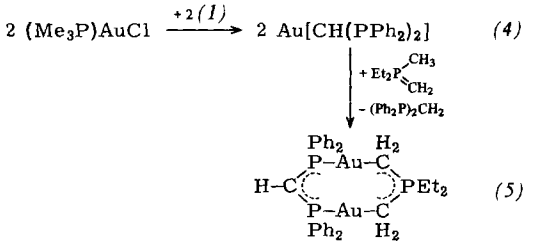
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

phosphino)methane to give the ylide/phosphinomethanide complex *(3)*.

The yellow crystalline diamagnetic product shows mass and IR spectra which reveal quite clearly the close relation to the precursor *(2)* on the one hand and to ylide complexes on the other.

^{1}H- and ^{1}H{^{31}P}-NMR spectra, but above all the ^{31}P{^{1}H}-NMR spectrum, support the proposed structure *(3)*; the latter shows a structurally diagnostic doublet/triplet pattern (2:1), which confirms the symmetrical bonding of the ligands.

In an analogous way reaction of $(Me_3P)AuCl$ and *(1)* affords the lemon-yellow insoluble gold(I) bis(diphenylphosphino)-methanide *(4)*, which is characterized by its ^{197}Au Mössbauer spectrum as a polymeric Au^I derivative with the metal atoms in a uniform environment (IS = 4.09, QS = 9.25 mm/s; 4 K)[5]. *(4)* reacts with the ylide to form the eight-membered heterocycle *(5)*, in which, unlike in *(3)*, neither the ylide nor the diphosphinomethanide assume a chelating function, serving instead as bridges between the metal atoms.



The colorless, crystalline compound *(5)*, which is soluble in benzene, was identified, like *(3)*, by mass, IR, and NMR spectra[6].

Procedure:

(1)→(2)→(3): To a suspension of $(Me_3P)_2PdCl_2$ (330 mg, 1 mmol) in THF (10 ml) is added a solution of *(1)* (2 mmol) in THF (20 ml). After 3 h the orange-yellow precipitate is filtered off, washed with THF and pentane, and dried at 60 °C/0.1 torr: Yield 830 mg (98 %) *(2)*, dec. pt. 190 °C.—A suspension of *(2)* (2.18 g, 2.5 mmol) in benzene (10 ml) is treated with $MeEt_2PCH_2$ (2.5 mmol) and stirred for 30 minutes. After removal of solvent the residue is taken up in toluene; *(3)* is then precipitated by addition of pentane. Yield 740 mg (50 %), m.p. 150 °C; MS: *m/e* = 608 [M^+(^{106}Pd)].

^{1}H-NMR ([D$_8$]-toluene, TMS int.): δC_2H_5 0.83 and 0.47, A_3B_2X, 10H; $\delta PdCH_2$ −0.35, m, 4H; δCH 2.9, "t", 1H, J_{HCP} 3 Hz; δC_6H_5 5.85, m, 20H.—^{31}P-NMR ([D$_8$]-toluene, H_3PO_4 ext.): δPPd 21.2, d, 2P; δPEt_2 −25.3, t, 1P, J_{PCPdP} 8.

(1)→(4)→(5): To a suspension of $(Me_3P)AuCl$ (308 mg, 1 mmol) in 10 ml THF is added a solution of the equivalent amount of *(1)* in THF. The yellow precipitate is washed with THF and pentane and then dried at 60 °C/0.1 torr. Yield 490 mg (85 %) *(4)*, dec. pt. 240 °C.—A suspension of *(4)* (480 mg, 0.82 mmol) in benzene (10 ml) is treated with 50 mg (0.43 mmol) $MeEt_2PCH_2$. After decoloration the solution is filtered and the filtrate evaporated down. *(5)* is precipitated by addition of pentane. Yield 275 mg (75 %), m.p. 186 °C (from toluene/pentane); MS: *m/e* = 894 [M^+]; IR: ν(AuC) = 550, ν(AuP) = 388 cm^{-1}.

^{1}H-NMR (C_6D_6, TMS ext.): δCH_3 0.87, dt, 6H, J_{HCCH} 7 Hz, J_{HCCP} 18; δCCH_2 1.25, m, masked by $\delta AuCH_2$ 1.10, d, J_{HCP} 9 (together 8H); δCH 2.50, "t", 1H, J_{HCP} 4.5; δC_6H_5 7.70, m, 20H.—^{31}P-NMR ([D$_8$]-toluene, H_3PO_4 ext.): δPAu −23.2, d, 2P; δPEt_2 −27.8, t, 1P, J_{PCAuP} 12.

Received: July 5, 1977 [Z 779b IE]
German version: Angew. Chem. *89*, 679 (1977)

CAS Registry numbers:
(1), 28926-61-6; *(2)*, 63528-02-9; *(3)*, 63528-03-0; *(4)*, 63528-04-1; *(5)*, 63528-05-2; $(Me_3P)_2PdCl_2$, 25892-38-0; $(Me_3P)AuCl$, 15278-97-4; $MeEt_2PCH_2$, 44514-33-2

[1] *H. Schmidbaur*, Acc. Chem. Res. *8*, 62 (1975); *E. Kurras, U. Rosenthal, H. Mennenga, G. Oehme*, Angew. Chem. *85*, 913 (1973); Angew. Chem. Int. Ed. Engl. *12*, 854 (1973); *H. Schumann, S. Hohmann*, Chem. Ztg. *100*, 365 (1976); *L. E. Manzer*, Inorg. Chem. *15*, 2567 (1976).—For analogous sulfur compounds see *H. Schmidbaur, W. Richter*, Z. Anorg. Allg. Chem. *429*, 222 (1977); *P. Bravo, G. Fronza, C. Ticozzi*, J. Organomet. Chem. *118*, C 78 (1976).

[2] *K. Issleib, H. P. Abicht*, J. Prakt. Chem. *312*, 456 (1970); *K. Issleib, H. P. Abicht, H. Winkelmann*, Z. Anorg. Allg. Chem. *388*, 89 (1972).

[3] *A. Camus, N. Marsich, G. Nardin, L. Randaccio*, J. Organomet. Chem. *60*, C 39 (1973).

[4] *H. Schmidbaur, W. Tronich*, Chem. Ber. *101*, 595 (1968).

[5] We thank Doz. Dr. *F. E. Wagner*, Physik-Department der TU München, for measuring the spectrum.

[6] Elemental analysis gave correct values for *(2)*—*(5)*.

Carbodiimides as Source of Isocyanide and Carbonyl Ligands[**]

By *Wolf Peter Fehlhammer, Andreas Mayr*, and *Michael Ritter*[*]

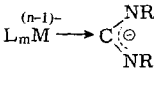
Application of the Ugi reaction[1] to carbamoylmetal compounds (*C*-metalated formamides) leads to *isocyanide complexes* under extremely mild conditions[2]. Deprotonated carbamoyl complex species[3a], as formed by simple addition of isocyanates to carbonylmetalates[3b], may also be used as starting material. This synthetic principle, which is apparently of general validity for heteroallenes X=C=NR[4], is demonstrated for *carbodiimides*. In the presence of electron-rich metal compounds this heteroallene also proves to be a productive source of novel *carbene complexes*.

The reaction between carbonylmetal anion and carbodiimide, which requires from a few minutes at −78 °C [(I), *(1a)*] to several weeks at room temperature [(I), *(2b)*], can be followed by IR spectroscopy. The disappearance of the ν_{as}(NCN) band of the free carbodiimide is accompanied by

$$RN{=}C{=}NR + L_mM^{n-} \longrightarrow [L_mMC(NR)_2]^{n-} \quad (1)$$

L_mM = $Cr(CO)_5$ *(1)*, $C_5H_5Fe(CO)_2$ *(2)*
R = C_6H_5 *(a)*, C_6H_{11} *(b)*

the appearance of new bands in the region of 1500—1600 cm^{-1} which we assign to ν(N···C···N) vibrations of an adduct of the *C*-metalated formamidine type *(3)*. At the same time the ν(CO) bands shift to higher wavenumbers, indicating delocalization of the negative charge over the entering allene system.



Protonation of this adduct with HCl in tetrahydrofuran leads to the diaminocarbene complexes *(4)* and *(5)*, thus supporting formulation *(3)*.

[*] Dr. W. P. Fehlhammer, Dipl.-Chem. A. Mayr, M. Ritter
Institut für Anorganische Chemie der Universität Erlangen-Nürnberg
Egerlandstrasse 1, D-8520 Erlangen (Germany)

[**] Isonitrile Syntheses at the Metal, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 2: [2].

$(OC)_5CrC(NHR)_2$ (4) $[\eta^5\text{-}C_5H_5Fe(CO)_2\{C(NHR)_2\}]Cl$ (5)

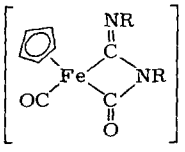
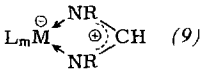
As expected, on reaction with phosgene *(1a)* is split into the isocyanide complex *(6)* and $NC_6H_5^{2-}$, which occurs as phenyl isocyanate.

$$(1a) \xrightarrow[-2\,NaCl,\,-C_6H_5NCO]{COCl_2} (OC)_5CrC{\equiv}NC_6H_5 \quad (6)$$

This reaction clearly demonstrates the analogy between *(3)* and *N,N'*-disubstituted ureas, which react with phosgene to give two molecules of isocyanate[5]. Surprising, and inconsistent with the intermediacy of *(3)*, however, is the formation of the diisocyanide complex *(7)*.

$$(2) \xrightarrow[-NaCl,\,-CO_2]{COCl_2} [\eta^5\text{-}C_5H_5Fe(CO)(C{\equiv}NR)_2]Cl \quad (7)$$

For this reason we assume *(2)*, which can be isolated as yellow sodium salt, to have the chelate structure *(8)*, resulting from a primary product *(3)* by intramolecular nucleophilic attack of a carbodiimide nitrogen at the neighboring carbonyl ligand. In agreement with the suggested structure *(8)* the IR solution spectrum of *(2)* shows only one ν(CO) band (1886 cm^{-1}) accompanied by a remarkably intense structured band at *ca.* 1550 cm^{-1} [ν(N···C···N)+ν(C=O, carboxamide)].

Na [] *(8)*  *(9)*

A similar $\overline{FeC(NHR)N(R)C(NHR)}$ four-membered ring—product of addition of methylamine *via* two *cis* RNC ligands in hexakis(methyl isocyanide)iron(II)—has been confirmed X-ray crystallographically[6]. Most likely the isomerization carbamoyl(isocyanide)→carbonyl(carbene) complex[7] observed on addition of amine to $Mn(CO)_4(CNR)_2^+$ also proceeds *via* a four-membered ring as intermediate.

The reaction behavior of the iron adducts follows from their carboxamide structure *(8)*. Thus, protonation leads to cleavage of the four-membered ring at the CN carboxamide bond[3b], whereas phosgene attacks the exocyclic CO bond[2], causing ring opening in the formamidine moiety. In that case the carbodiimide molecule is completely used up for the construction of two isocyanide ligands, and the C atom required for mass balance is provided by a CO ligand.

Previously, complexes of type *(7)* were obtained only by substitution reactions, which naturally afford mixed products. The reaction of carbodiimides with carbonylmetalates and acids allows their direct synthesis and at the same time opens up a convenient entry to complexes such as *(4)* and *(5)*, which hitherto could not be synthesized by alternative routes.

Carbodiimides behave "quasi-ambivalent" toward metals: only the most electron-rich metal compounds obviously are capable of interacting with the weakly electrophilic carbodiimide carbon. In contrast, coordination to metals in higher oxidation states proceeds *via* one or even both nitrogen atoms, as observed, *e.g.*, in insertion products of type *(9)*[8].

Procedure

Adduct (2a): A solution of diphenylcarbodiimide (20 mmol) in THF (50 ml) is added with stirring at −78 °C to a solution of $Na[\eta^5\text{-}C_5H_5Fe(CO)_2]$ (20 mmol) in *ca.* 200 ml THF[9]. The mixture is allowed to warm to room temperature, stirred for a further 15 minutes, and then re-cooled to −78 °C.

$[\eta^5\text{-}C_5H_5Fe(CO)_2\{C(NHC_6H_5)_2\}]PF_6$ *(10a):* 50 mmol HCl in ether is added dropwise with stirring to a solution of *(2a)*. The mixture is evaporated to dryness, dissolved in water, and treated with NH_4PF_6 solution. Recrystallization of the resulting precipitate affords 5.5 g (53 % based on $[CpFe(CO)_2]_2$) ocher-colored crystals, m.p. 125 °C.

$[\eta^5\text{-}C_5H_5Fe(CO)(CNC_6H_5)_2]PF_6$ *(11a):* A 1 M solution of phosgene in THF (20 ml) is added dropwise with stirring to a solution of *(2a)* and the product isolated as in the case of *(10a)*. Recrystallization from ethanol yields 6.1 g (63 %) light-brown crystals, m.p. 142 °C.

Received: June 27, 1977 [Z 775 IE]
German version: Angew. Chem. 89. 660 (1977)

CAS Registry numbers:
(1a), 63428-75-1; *(1b)*, 63428-74-0; *(2a)*, 63428-73-9; *(2b)*, 63428-73-8; *(4a)*, 63466-39-7; *(4b)*, 63428-71-7; *(5a)*, 63428-70-6; *(5b)*, 63428-69-3; *(6)*, 14782-94-6; *(7a)*, 63428-68-2; *(7b)*, 63428-67-1; *(8a)*, 63428-66-0; *(8b)*, 63428-65-9; *(10a)*, 63428-64-8; *(11a)*, 55451-30-4; $Na[C_5H_5Fe(CO)_2]$, 12152-20-4

[1] Cf. *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann*, Angew. Chem. *77*, 492 (1965); Angew. Chem. Int. Ed. Engl. *4*, 472 (1965).
[2] *W. P. Fehlhammer, A. Mayr*, Angew. Chem. *87*, 776 (1975); Angew. Chem. Int. Ed. Engl. *14*, 757 (1975).
[3] a) *W. P. Fehlhammer, A. Mayr*, unpublished; b) *R. J. Angelici*, Acc. Chem. Res. *5*, 335 (1972).
[4] The splitting off of S^{2-} from isothiocyanate adducts of carbonylmetalate ions proceeds particularly smoothly: *W. P. Fehlhammer, A. Mayr*, unpublished.
[5] *H. Ulrich, A. A. R. Sayigh*, Angew. Chem. *78*, 761 (1966); Angew. Chem. Int. Ed. Engl. *5*, 704 (1966).
[6] *J. Miller, A. L. Balch, J. H. Enemark*, J. Am. Chem. Soc. *93*, 4613 (1971).
[7] *T. Sawai, R. J. Angelici*, J. Organomet. Chem. *80*, 91 (1974).
[8] *S. D. Robinson, A. Sahajpal*, J. Organomet. Chem. *117*, C111 (1976).—Insertion of dimethylcarbodiimide into the metal-hydrogen bond of $H_2Fe(CO)_4$, however, leads to the bis(methylamino)carbene complex: *K. Öfele*, private communication; cf. also *K. Öfele, C. G. Kreiter*, Chem. Ber. *105*, 529 (1972).
[9] *J. E. Ellis, E. A. Flom*, J. Organomet. Chem. *99*, 263 (1975).

Repetitive Peptide Synthesis with Insoluble Polymer-Bound Reagents and Solubilizing Macromolecular Peptide Carriers[**]

By *Gerhard Heusel, Günter Bovermann, Walter Göhring*, and *Günther Jung*[*]

For chain lengthening, peptides bound C-terminally to soluble polymeric carriers react quantitatively with activated *N*-protected amino acid esters which are bound to an insoluble matrix. We used the crystallizable polyoxymethylene introduced by *Bayer* and *Mutter*[1] for peptide synthesis as solubilizing peptide carrier and the N_α-*tert*-butyloxycarbonylamino acid ester of 2-nitrophenol[2] and 1-hydroxybenzotriazole[3] bound to crosslinked polystyrene as insoluble polymeric reagent (see Fig. 1).

[*] Prof. Dr. G. Jung, Dipl.-Chem. G. Bovermann, Dr. W. Göhring, Dipl.-Chem. G. Heusel
Institut für Organische Chemie der Universität
Auf der Morgenstelle, D-7400 Tübingen (Germany)

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

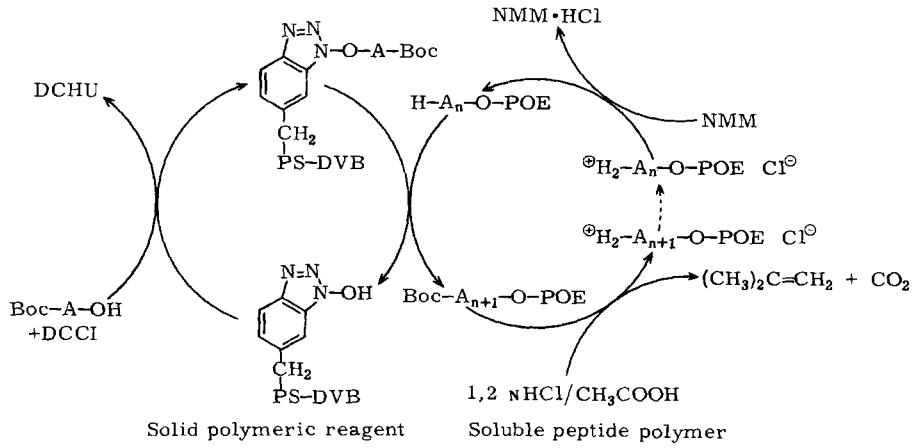


Fig. 1. Reaction scheme for peptide synthesis by coupling of polymer reagent with soluble peptide polymers. A = amino acid, Boc = *tert*-butyloxycarbonyl, DCCI = dicyclohexylcarbodiimide, DCHU = dicyclohexylurea, NMM = *N*-methylmorpholine, POE = polyoxyethylene, PS-DVB = 2% crosslinked polystyrene-divinylbenzene.

The synthesis of some oligopeptides[4] shows that, surprisingly, no complications arise in the inhomogeneous reactions of the two polymers. The advantages of the liquid-phase synthesis[1] (no reduced solubility of the growing fully-protected peptide chain, precise control of conversions) and the polymeric reagents (maintenance of supply of activated, *N*-protected building units, regeneration, favorable process engineering in batch or continuous column processes) are retained. Our repetitive peptide synthesis leads to fundamental simplification and improvement, since for the first time in peptide coupling, neither are side-products formed, nor do excess coupling components have to be removed.

General procedure:

A mixture of amino acid polyoxyethylene ester with free amino groups (molecular mass 6000, loading at least 0.2 mmol g. H-A-O-POE) in CH_2Cl_2 (5 ml) and *N*-Boc-amino acid-1-hydroxybenzotriazole ester bound to solid polystyrene (5 g) (loading about 1 mmol/g) is stirred for 2 h at 20 °C; the pH is maintained at 7—8 with *N*-methylmorpholine (NMM). The solution of the peptide-polymer Boc-A_2-O-POE is removed from the polymeric reagent by filtration. After determination of the coupling yield by titration or dansylation of the liberated amino groups, recoupling is continued until less than 0.1% free amino groups are detectable. After removal of solvent the Boc group of the dipeptide polymer is cleaved in the usual way with 1.2 N HCl/glacial acetic acid. The next coupling to the *N*-protected tripeptide polyoxyethylene ester can then be carried out. Considerably shorter coupling times and smaller excess quantities of reagent are required with the polymer-bound 1-hydroxybenzotriazole derivatives than with the corresponding 2-nitrophenol derivatives[4] (Fig. 2).

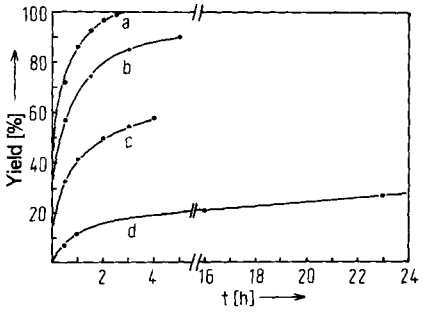


Fig. 2. Comparison of the coupling of Boc-L-Ala-O-(polystyrenehydroxybenzotriazole) with H-L-Val-O-POE of mol. masses 6000 (a), 10000 (b), and 20000 (c), and of Boc-L-Ala-O-(polystyrene-2-nitrophenol) with H-L-Val-O-POE of mol. mass 6000 (d). A threefold excess of polymeric reagent was used in each case.

Received: July, 1977 [Z 787 IE]
German version: Angew. Chem. 89, 681 (1977)

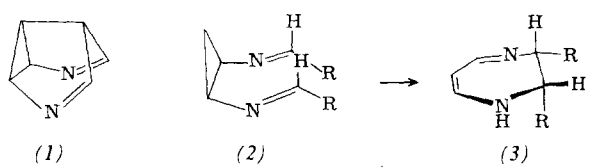
[1] *M. Mutter, E. Bayer*, Angew. Chem. *86*, 101 (1974); Angew. Chem. Int. Ed. Engl. *13*, 88 (1974).
[2] *R. Kalir, M. Friedkin, A. Patchornik*, Eur. J. Biochem. *42*, 151 (1974).
[3] *R. Kalir, A. Warshawsky, M. Fridkin, A. Patchornik*, Eur. J. Biochem. *59*, 55 (1975).
[4] *G. Jung, G. Bovermann, W. Göhring, G. Heusel* in: Peptides: Chemistry, Structure and Biology. Proc. 4th Amer. Pept. Symp. Ann Arbor Science Publ. 1975, p. 433.

Degenerate Cope Rearrangement of the 2,6-Bisazoniabicyclo[5.1.0]octa-2,5-diene Dication[**]

By *Helmut Quast* and *Josef Stawitz*[*]

In memoriam Professor Hans Schmid

None of the non-classical semibullvalenes and diazasemibullvalenes with delocalized, bishomoaromatic ground states as proposed by *Hoffmann*[1] and *Dewar*[2], has yet been synthesized. In the search for realistic models for one of these compounds, 3,7-diazasemibullvalene *(1)*[2], we recently investigated the Cope rearrangement of the bisimines *(2)* resulting in the diazepines *(3)*[3]. We report here on the Cope rearrangement of 2,6-bisazonia-bicyclo[5.1.0]octa-2,5-diene dications *(7)*.



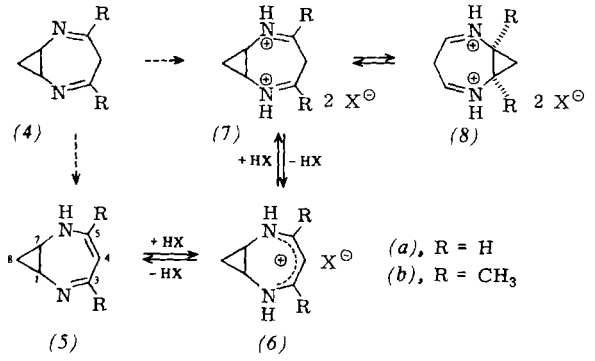
(1) *(2)* *(3)*

Diaza-3,4-homotropilidenes *(4)*, which are closely related to 3,7-diazasemibullvalene *(1)*, should not exist as such but are expected to tautomerize to their more stable tautomers *(5)*[4]. Their double protonation should however regenerate the structure *(4)* and produce the dications *(7)* having the structural prerequisites for a Cope rearrangement.

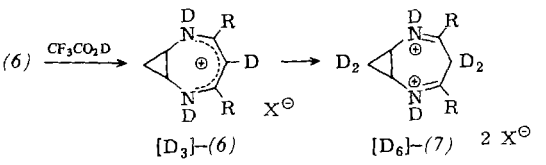
[*] Prof. Dr. H. Quast, Dipl.-Chem. J. Stawitz
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie. The results are taken from the planned dissertation of *J. Stawitz*.

(5b) (92%) is obtained in aqueous, acetate-buffered solution from the dihydrochloride of *cis*-1,2-cyclopropanediamine[5] and 2,4-pentanedione after 45 h at 75 °C, followed by basification and ether extraction; it is formed as pale yellow crystals (m.p. 161—164 °C) which sublime at 100—120 °C/10^{-5} torr. The structure of *(5b)* and its perchlorate *(6b)*, X = ClO_4, is based on IR, UV, ^{1}H-NMR (Table 1) and mass spectra.



The unsubstituted *(6a)* is less readily accessible than *(6b)* since the formation of a formal dimer with a 14-membered ring[6] competes with the ring closure yielding *(6a)*. Indeed the 14-membered ring[6] alone is formed from *cis*-1,2-cyclopropanediamine and malondialdehydedianil perchlorate[3,4] which has successfully been used in the synthesis of 2,3-dihydro-1*H*-1,4-diazepines having unsubstituted 5-, 6- and 7-positions, such as *(3)*. Only in rather dilute solution (5×10^{-3} to 6×10^{-3} M) in water/ethanol (1:1) did the sodium salt of malondialdehyde and the dihydrochloride of *cis*-1,2-cyclopropanediamine afford the cation *(6a)* free from dimer and decomposition products. It was isolated as the tetraphenylborate (yield 49%) which crystallized from dioxane, together with one mol of dioxane, as light-sensitive, pale yellow crystals with m.p. 226—228 °C. Its structure was established by IR, UV and ^{1}H-NMR spectra (Table 1).



as is shown by the intact ABX_2 spectra of the cyclopropyl protons. Accordingly, under these conditions D^+ may add to *(6)*, but the Cope rearrangement of the dications, which are present only in minimal amounts, apparently cannot yet compete with the reverse reaction. Addition of an equal volume of [D_2]-sulfuric acid to the solution of [D_3]-*(6a)* in [D]-trifluoroacetic acid results in the immediate disappearance of the AB part of the spectrum which only exhibits two equally intense singlets for 1-H, 7-H and 3-H, 5-H and thus proves formation of [D_6]-*(7a)* as the result of a rapid, degenerate Cope rearrangement.

The Cope rearrangement of *(7b)* should be rendered more difficult by the two methyl groups on the cyclopropane ring[7] of *(8b)*. Indeed the formation of [D_6]-*(7b)* requires more severe conditions, namely the warming of [D_3]-*(6b)* in [D]-trifluoromethanesulfonic acid.

The ^{1}H-NMR spectra of the dications *(7a)* and *(7b)* (Table 1) in trifluoromethanesulfonic acid are temperature dependent. The AB spectrum of the protons 4-H and 4'-H of *(7b)* is already broadened at 30 °C, this being especially evident in the low-field half of the spectrum. At 90 °C, only a broad singlet is observed for one of the two protons while the signal of the other proton at lower field can no longer be recognized. The reason for this is the difference in the rates of exchange of the protons 4-H and 4'-H with trifluoromethanesulfonic acid which, at the higher temperatures, are comparable with the ^{1}H-NMR time scale. In contrast, the ABX_2 spectrum of the cyclopropane protons of *(7b)* remains unchanged up to 90 °C. There is even a certain sharpening of the ABX_2 spectrum.—In the ^{1}H-NMR spectrum of *(7a)* in trifluoromethanesulfonic acid, already at 30 °C only the broad signal of one of the two protons 4-H and 4'-H can be recognized. Their rate of exchange with trifluoromethanesulfonic acid approximately corresponds to that of *(7b)* at 90 °C. Contrary to the changes observed with *(7b)*, in the case of *(7a)* an increase in temperature causes a broadening of *all* signals due to the rapid, degenerate Cope rearrangement; the fine structure of the ABX_2 spectrum also disappears. Above 100 °C slow decomposition begins. The ^{1}H-NMR spectra of *(7a)* and [D_6]-*(7a)* can be used to estimate a coalescence tempera-

Table 1. Chemical shifts and coupling constants (Hz) in the 90 MHz ^{1}H-NMR spectra of 2,6-diazabicyclo[5.1.0]octa-2,4-diene *(5)* and of the cations *(6)* and *(7)* derived therefrom. The data of the ABX_2 spectra of the cyclopropane protons were optimized using the LAOCOON III program.

Cpd.	Solvent	Cyclopropane protons						Other protons			
		8-H *(endo)*	8'-H *(exo)*	1-H, 7-H	$J_{8,8'}$	$J_{8,1} = J_{8,7}$	$J_{8',1} = J_{8',7}$	3-R, 5-R	4-H	4'-H	NH
								R = H			
(5a)	$CDCl_3$ [a]	0.51	1.87	3.04	−4.78	6.35	8.57	6.84 (d, J = 7.6)	4.61 (t)	—	
(6a)	CF_3CO_2H [b]	1.18	2.20	3.44	−6.23	6.07	7.65	7.36 (t, J = 8.0)	5.23 (t)	—	8.34 [d]
(7a)	CF_3SO_3H [c]	1.89	2.50	4.22	−7.75	6.47	9.10	8.76 [d] (d, J = 5.6)	4.86 [d]		
								$R = CH_3$			
(5b)	$CDCl_3$ [a]	0.39	1.63	2.93 [e]	−4.57	5.92	8.08	1.98 (s)	4.62 (s)	—	5.26
(6b)	CF_3CO_2H [b]	0.99	1.94	3.39	−6.07	6.00	7.67	2.31 (s)	5.14 (t, J = 1.88)	—	8.29
(7b)	CF_3SO_3H [c]	1.71	2.12	3.98	−7.83	5.85	8.66	2.90 (s)	4.26 (AB, J = 15.2)	4.95 [d]	

[a] Internal standard TMS = 0.
[b] Internal standard [2,2,3,3-D_4]-3-trimethylsilylpropionic acid = 0.
[c] External standard TMS (50 percent in CCl_4).
[d] Broadened.
[e] 7-H still coupled with 6-H.

2,3-Dihydro-1*H*-1,4-diazepinium cations, *e.g.* *(3)*·H^+, already show rapid H/D exchange at their 1-, 4- and 6-positions[4] in [D]-trifluoroacetic acid. If the two methylene groups in *(7)* were to become equivalent due to a Cope rearrangement, then in deuterated strong acids the [D_6]-bisazonia-3,4-homotropilidene dications [D_6]-*(7a)* and [D_6]-*(7b)* should be formed from *(6a)* and *(6b)*, respectively.

In [D]-trifluoroacetic acid however, only the trideuterated cations [D_3]-*(6)* are observed in the ^{1}H-NMR spectra,

ture of 110±10°C for the signals of 1-H, 7-H and 3-H, 5-H and thus an activation barrier of $\Delta G_c^{\neq} = 73 \pm 2$ kJ/mol ($\Delta\nu = 409$ Hz) for the degenerate Cope rearrangement (assuming that all of *(7a)* is present as the dication). The activation barrier is thus clearly larger than that of 3,4-homotropilidene[8] but very similar to that of disubstituted 3,4-homotropilidenes[9].

Received: June 14, 1977 [Z 759 IE]
German version: Angew. Chem. 89, 668 (1977)

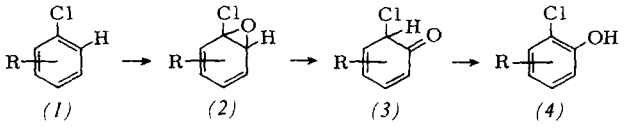
CAS Registry numbers:
(5a), 63466-72-8; *(5b)*, 63466-73-9; *(6a)*, 63466-74-0; [D_3]-*(6a)*, 63466-77-3; *(6b)*, 63466-78-4; [D_3]-*(6b)*, 63466-80-8; *(7a)*, 63466-82-0; [D_6]-*(7a)*, 63466-84-2; *(7b)*, 63466-86-4; [D_6]-*(7b)*, 63466-88-6; *cis*-1,2-cyclopropanediamine dihydrochloride, 63466-89-7; 2,4-pentanedione, 123-54-6; Na salt of malondialdehyde, 24382-01-5

[1] *R. Hoffmann, W. D. Stohrer*, J. Am. Chem. Soc. *93*, 6941 (1971).
[2] *M. J. S. Dewar, D. H. Lo*, J. Am. Chem. Soc. *93*, 7201 (1971); *M. J. S. Dewar, Z. Náhlovská, B. D. Náhlovský*, Chem. Commun. *1971*, 1377.
[3] *H. Quast, J. Stawitz*, Tetrahedron Lett. *1977*, 2709.
[4] *D. Lloyd, H. P. Cleghorn, D. R. Marshall*, Adv. Heterocycl. Chem. *17*, 1 (1974).
[5] Cf. *H. Quast, J. Stawitz*, Tetrahedron Lett. *1976*, 3803.
[6] *H. Quast, J. Stawitz, K. Peters, H. G. von Schnering*, unpublished.
[7] *M. C. Flowers, H. M. Frey*, Proc. Roy. Soc. (London) *A 257*, 122 (1960); *W. D. Good*, J. Chem. Thermodyn. *3*, 539 (1971).
[8] *H. Günther, J.-B. Pawliczek, J. Ulmen, W. Grimme*, Chem. Ber. *108*, 3141 (1975); *R. Bicker, H. Kessler, W. Ott*, ibid. *108*, 3151 (1975).
[9] *H. Kessler, W. Ott*, J. Am. Chem. Soc. *98*, 5014 (1976).

Formation of Chlorophenols by Microbial Transformation of Chlorobenzenes[1]

By *Karlheinz Ballschmiter, Charlotte Unglert*, and *Peter Heinzmann*[*]

Only chloropyrocatechols have hitherto been described as products of the microbial degradation of chlorobenzenes[2]. We have now investigated the microbial transformation of the monochloro- to pentachlorobenzenes *(1)* (Table 1) into chlorophenols *(4)*.



(1) *(2)* *(3)* *(4)*

Table 1. Microbial transformation of chlorobenzenes *(1)* into chlorophenols *(4)* (experimental conditions see text).

Chlorobenzenes *(1)*	Chlorophenols *(4)*	Ratio [a]	Chlorobenzenes *(1)*	Chlorophenols *(4)*	Ratio [a]
(1a) 1-	*(4a)* 2-			*(4g)* 2,3,4-	7
	(4b) 2,3-	2	*(1e)* 1,2,3-	*(4h)* 2,3,6-	1
(1b) 1,2-	*(4c)* 3,4-	1		*(4i)* 3,4,5-	[b]
	(4d) 2,6-	[b]		*(4j)* 2,4,5-	
	(4e) 2,4-	6	*(1f)* 1,2,4-	*(4k)* 2,4,6-	
(1c) 1,3-	*(4f)* 2,5-	1	*(1g)* 1,3,5-	*(4k)* 2,4,6-	
	(4d) 2,6-	[b]	*(1h)* 1,2,3,4-	*(4l)* 2,3,4,5-	
(1d) 1,4-	*(4e)* 2,4-	3	*(1i)* 1,2,3,5-	*(4m)* 2,3,4,6-	
	(4f) 2,5-	1	*(1j)* 1,2,4,5-	*(4n)* 2,3,5,6-	
			(1k) 1,2,3,4,5-	[c]	

[a] Ratio after 24 h; [b] detected after 100 h; [c] not detectable.

We used mixed cultures of soil bacteria—preferably gram negative, polar flagellated rods—precultured on benzene. In the mineral salt solution (pH = 6.8) the bacteria had access to further benzene as a source of C. 200 mg of benzene and 50 mg of one of the chlorobenzenes *(1a)* to *(1k)* were allowed to diffuse from a hard paraffin layer (2 g) into 200 ml nutrient medium, whereupon the concentration of the chlorobenzene in solution finally amounted to 10^{-6} to 10^{-7} M (*ca.* 20 to 200 ppb). After 24, 100, 240, and 500 hours' incubation at 28 °C the cells and nutrient medium were worked up for chlorophenols[3]. The chlorophenols were extractively esterified with acetic anhydride in 0.1 M K_2CO_3 solution and identified by comparison of the retention indices of the esters with those of authentic compounds (glass capillary gas chromatography with ^{63}Ni electron-capture detector; Carlo Erba, Model 2300)[4]. Combined GC-MS using glass capillaries enabled additional confirmation of structure.

The degradation of benzene to phenol and its further hydroxylation to diphenols was investigated in the same experimental setup. The reaction products phenol, pyrocatechol, resorcinol and hydroquinone were identified by comparison of the retention indices of their pentafluorobenzyl ethers[5] with those of the authentic substances. Usually it is assumed that dioxygenases are responsible for the microbial degradation of benzene[6].

Microbial degradation of the chlorobenzenes *(1)* can be assumed to proceed *via* attack by a monooxygenase, since the observed distribution of isomers can only be rationalized in terms of an intermediary chlorinated cyclohexadiene epoxide *(2)*. With epoxides as intermediates, a migration of the chloro substituents is possible[7].

After a while diphenols can be detected in the joint degradation of chlorobenzenes and benzene *(vide supra)*. Their mode of formation is still unclear.

The hydroxylation shows structural specificity. In four experiments with different cultures only 2-chlorophenol was formed from chlorobenzene. All chlorophenols up to 3,4-dichloro- and 3,4,5-trichlorophenol are formed by attack at the *ortho* position to the chlorine of a —CCl=CH group.

In assessing the occurrence of phenol and chlorophenols as pollutants not only their direct release into the environment must be taken into consideration but also their formation by microbial transformation of benzene and chlorobenzenes.

Received: June 6, 1977 [Z 783 IE]
German version: Angew. Chem. 89, 680 (1977)

CAS Registry numbers:
(1a), 108-90-7; *(1b)*, 95-50-1; *(1c)*, 541-73-1; *(1d)*, 106-46-7; *(1e)*, 81-61-6; *(1f)*, 120-82-1; *(1g)*, 108-70-3; *(1h)*, 634-66-2; *(1i)*, 634-90-2; *(1j)*, 95-94-3; *(1k)*, 608-93-5; *(4a)*, 95-57-8; *(4b)*, 576-24-9; *(4c)*, 95-77-2; *(4d)*, 87-65-0; *(4e)*, 120-83-2; *(4f)*, 583-78-8; *(4g)*, 15950-66-0; *(4h)*, 933-75-5; *(4i)*, 609-19-8; *(4j)*, 95-95-4; *(4k)*, 88-06-2; *(4l)*, 4901-51-3; *(4m)*, 58-90-2; *(4n)*, 935-95-5

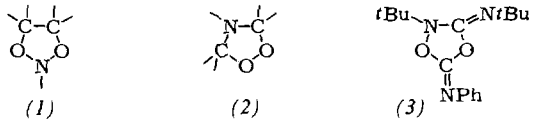
[*] Prof. Dr. K. Ballschmiter [+], Ch. Unglert, Dr. P. Heizmann [**]
Abteilung für Analytische Chemie der Universität
Oberer Eselsberg, D-7900 Ulm (Germany)
[+] Author to whom correspondence should be addressed.
[**] New address: C.O.F. Hoffmann-La Roche AG, F/BP Phakin, CH-4005 Basel (Switzerland).

[1] Microbiological Degradation of Aromatics, Part 4. This work was supported by the Bundesministerium für Forschung und Technologie.—Part 3: *K. Ballschmiter, Ch. Unglert, H. J. Neu*, Chemosphere *6*, 51 (1977).
[2] *D. T. Gibson, J. R. Koch, C. L. Schuld, R. E. Kallio*, Biochemistry *7*, 3795 (1968); *K. Haider, G. Jagnow, R. Kohnen, S. U. Lim*, Arch. Microbiol. *96*, 183 (1974); *C. M. Tu, ibid. 108*, 259 (1976).
[3] *H. J. Neu, K. Ballschmiter*, Chemosphere, *6*, 419 (1977).
[4] *M. Zell, H. J. Neu, K. Ballschmiter*, Z. Anal. Chem., in press.
[5] *K. Ballschmiter, U. Niederschulte, H. Thamm, H. J. Neu*, Chemosphere *5*, 367 (1976).
[6] *K. Kieslich:* Microbial Transformations of Non-Steroid Cyclic Compounds. Thieme, Stuttgart 1976; *H. J. Knackmus*, Chemiker-Ztg. *5*, 213 (1975), and references cited therein.
[7] *J. W. Daly, D. M. Yerina, B. Witkop*, Experientia *28*, 1129 (1972).

Synthesis of a Stable 1,3,4-Dioxazolidine[**]

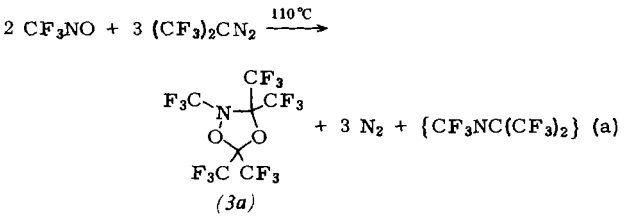
By *Jürgen Varwig* and *Rüdiger Mews*[*]

Whereas 1,3,2-[1] and 1,2,4-dioxazolidines[2], compounds *(1)* and *(2)* respectively, are well documented, to our knowledge only the thermally unstable 1:1:1 adduct of *tert*-butyl isocyanide, 2-methyl-2-nitrosopropane and phenyl isocyanate has so far been assigned the 1,3,4-dioxazolidine structure *(3)*—purely on the basis of its mass spectrum[3].



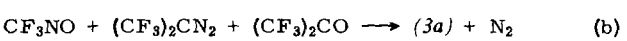
(1) *(2)* *(3)*

We have now been able to synthesize the 2,2,4,5,5-pentakis-(trifluoromethyl)-1,3,4-dioxazolidine *(3a)* in 25% yield from bis(trifluoromethyl)diazomethane and trifluoronitrosomethane:



(3a)

Apparently hexafluoroacetone is formed as intermediate product in this reaction, the yield of *(3a)* being almost doubled due to reaction according to eq. (b):



The product *(3a)* is a water-clear liquid, b.p. 85°C. The new compound is extraordinarily stable, both thermally and chemically; concentrated alkalis and acids decompose it only slowly. *(3a)* was characterized by elemental analysis and by IR and mass spectra; ^{19}F- and ^{13}C-NMR spectra afforded proof of its structure[4]. The ^{19}F-NMR spectrum shows three signals in the intensity ratio 2:2:1 [$\delta(2,5\text{-}CF_3^A) = -73.37$, mult.; $\delta(2,5\text{-}CF_3^B) = -76.70$, sept., $J_{F(A)F(B)} = 4.2$ Hz; $\delta(NCF_3) = -64.58$, sept., $J_{FF(A)} = 9.18$ Hz], which do not permit unequivocal differentiation between *(3a)* and its 1,3,2-isomer *(1a)*, since similar intensity and coupling ratios are expected for *(1a)* for hindered inversion at nitrogen[5]. The ^{13}C-NMR spectrum, however, shows two nonequivalent quarternary carbon atoms [$\delta(C\text{-}2) = -100.89$, sept., $J_{CF} = 37.5$ Hz; $\delta(C\text{-}5) = -91.26$, sept., $J_{CF} = 36.1$ Hz] each bearing two trifluoromethyl groups [$\delta(2,5\text{-}C^A) = -119.76$, quart., $^1J_{CF} = 288.2$ Hz; $\delta(2,5\text{-}C^B) = -120.07$, quart., $^1J_{CF} = 288.3$ Hz; plus $\delta(NC) = -119.23$, quart., $^1J_{CF} = 270.0$ Hz.

Procedure

A mixture of $(CF_3)_2CN_2$ (17.8 g, 0.1 mol) and CF_3NO (9.9 g, 0.1 mol) is stirred in an autoclave at 110°C for 24 h. The product mixture is fractionally condensed *in vacuo* (−80°C, liq. air) and the contents of the trap (−80°C) finally distilled; yield 10.4 g (25%) colorless *(3a)*.—Analogous reaction of $(CF_3)_2CN_2$ (3.0 g, 0.017 mol), $(CF_3)_2CO$ (2.8 g, 0.017 mol) and CF_3NO (1.7 g, 0.017 mol) affords 3.7 g (53%) *(3a)*.—IR [gas, cm^{-1}]: 1382 w, 1348 w, 1305 s, 1280 vs, 1259 vs, 1230 s, 1202 m, 1170 s, 1123 s, 1091 m, 1002 m, 990 s, 923 w, 769 w, 752 w, 742 w, 723 m. MS [70 eV, (rel. int.)]: $m/e = 415$ M^+ (14), 69 CF_3 (100).

Received: July 4, 1977 [Z 777 IE]
German version: Angew. Chem. 89, 675 (1977)

CAS Registry numbers:
(3a), 63527-91-3; bis(trifluoromethyl)diazomethane, 684-23-1; trifluoronitrosomethane, 334-99-6; hexafluoroacetone, 684-16-2

[*] Priv.-Doz. Dr. R. Mews, Dr. J. Varwig
Anorganisch-chemisches Institut der Universität
Tammannstrasse 4, D-3400 Göttingen (Germany)

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

[1] Cf. *e.g. J. L. Charlton, C. C. Liao, P. de Mayo*, J. Am. Chem. Soc. *93*, 2463 (1971).
[2] *N. Durán*, J. Org. Chem. *39*, 1791 (1974); *E. G. E. Hawkins*, J. Chem. Soc. *C 1971*, 160.
[3] *F. D. Greene, J. F. Pazos*, J. Org. Chem. *34*, 2269 (1969).
[4] We thank Prof. *H. Lackner*, Universität Göttingen, and Dr. *M. Fild*, Technische Universität Braunschweig, for recording the ^{13}C-NMR spectra.
[5] The phosphorus analog of *(1a)*, prepared for comparison from $[(CF_3)_2COLi]_2$ and CF_3PCl_2 in tetrahydrofuran, shows three signals in the ^{19}F-NMR spectrum [$\delta(4,5\text{-}CF_3^A) = -66.7$, mult.; $\delta(4,5\text{-}CF_3^B) = -65.8$ mult.; $\delta(PCF_3) = -65.0$, dubl. of sept., $J_{CF_3\text{-}P} = 75.0$ Hz, $J_{CF_3\text{-}CF_3^B} = 6.2$ Hz]; the ^{31}P-NMR spectrum shows a quartet of septets [$\delta = +174.4$, $J_{P\text{-}CF_3^B} = 18.8$ Hz]. As in the case of the 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane [*B. Fontal, H. Goldwhite*, Tetrahedron *22*, 3275 (1966)] no inversion is observed at the phosphorus.

Reaction of Alkenylfurans with Ethyl Diazoacetate

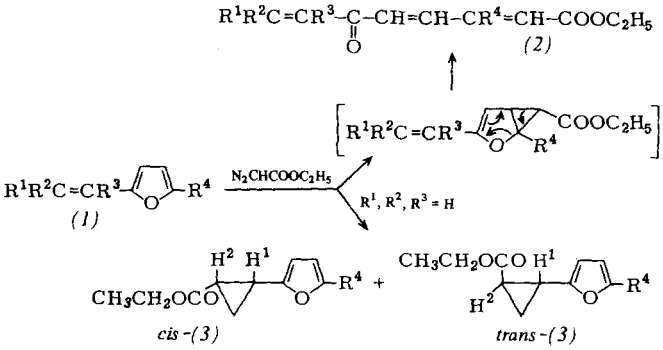
By *Oleg M. Nefedov, Viacheslav M. Shostakovsky*, and *Alexander E. Vasilvizky*[*]

Dedicated to Professor G. Wittig on the occasion of his 80th birthday

Whereas alkenylarenes (vinylbenzene, vinylnaphthalene) react with ethyl diazoacetate with exclusive formation of cyclopropane compounds, the alkenylfurans 2-isobutenylfuran *(1a)*, 2-(1-propenyl)furan *(1b)*[1] and 2-(1-methyl-1-propenyl)furan *(1g)* react with this reagent to give ethyl esters *(2)* of acyclic oxoalkatrienecarboxylic acids. The formation of the ester *(2)* can be explained by participation of the double bond of the furan ring[2] remote from the alkenyl substituent.

Neither the reaction temperature nor the manner of decomposition of the ethyl diazoacetate (catalysis, thermolysis or photolysis) influences the reaction path (Table 1). The properties of some of the esters *(2)* are listed in Table 2.

In contrast, reaction of 2-vinylfuran *(1c)* and 2-methyl-5-vinylfuran *(1d)* with ethyl diazoacetate leads mainly, and of 5-chloro-2-vinylfuran *(1e)* and 5-bromo-2-vinylfuran *(1f)*



(1) *(2)* *cis*-*(3)* *trans*-*(3)*

[*] Prof. Dr. O. M. Nefedov, Dr. V. M. Shostakovsky, Dipl.-Chem. A. E. Vasilvizky
N. D. Zelinsky Institute of Organic Chemistry, USSR Academy of Sciences
Leninsky prospect, 47, Moscow 117913 (USSR)

Table 1. Reaction of the alkenylfurans *(1)* with ethyl diazoacetate giving oxoalkatrienecarboxylates *(2)* and/or 2-(2-furyl)cyclopropanecarboxylates *(3)*. Also quoted are ratios of the rate constants for the addition of diazoacetate to the double bond in the furan ring remotely situated from the alkenyl substituents (K_F), to the vinyl group (K_V), and to added cyclohexene (K_C). K_F/K_C and K_V/K_C are each mean values from three experiments.

	(1)				Catalysis [a]				Thermolysis [b]				Photolysis [c]			
	R^1	R^2	R^3	R^4	Yield [%] *(2)*	Yield [%] *(3)*	$\frac{K_F}{K_C}$	$\frac{K_V}{K_C}$	Yield [%] *(2)*	Yield [%] *(3)*	$\frac{K_F}{K_C}$	$\frac{K_V}{K_C}$	Yield [%] *(2)*	Yield [%] *(3)*	$\frac{K_F}{K_C}$	$\frac{K_V}{K_C}$
a	CH_3	CH_3	H	H	47	29	2.48	0.76	33	16	2.36	1.04	14.5	6.8	1.54	0.72
b	CH_3	H	H	H	46	26	1.92	1.07	34	24	1.38	0.97	13.7	7.2	1.16	0.61
c	H	H	H	H	5.4	52	0.19	2.01	4.9	47	0.28	2.96	6.5	35	0.37	2.00
d	H	H	H	CH_3	4.8	68	0.27	3.32	8.1	52	0.62	3.14	4.1	42	0.18	1.82
e	H	H	H	Cl	0	36	0	1.04	0	42	0	1.76	0	18	0	0.60
f	H	H	H	Br	0	22	0	0.92	0	26	0	1.34	0	12	0	0.29
g	CH_3	H	CH_3	H	58	—	—	—	—	—	—	—	—	—	—	—

[a] Thermocatalytic decomposition of ethyl diazoacetate in the presence of anhydrous $CuSO_4$ and 5- to 10-fold excess of *(1)* at temperatures of 50°C up to the boiling point, mostly at 50—70°C.
[b] Thermolysis at 60—110°C and, depending upon the boiling point of *(1)*, also up to 165°C.
[c] 350 W mercury lamp at 20°C.

Table 2. Properties of the esters *(2a)*, *(2b)* and *(2g)*.

(2)	M.p. [°C]	UV λ_{max} [nm]	UV lgε	IR (C=C, C=O) [cm^{-1}]	M.p. (2,4-DNPH) [°C] [a]
(2a) [b]	84	10100	210	1580, 1615, 1628, 1665, 1708	181
		28200	294		
		187	385		
(2b)	83	30000	286	1595, 1620, 1645, 1660, 1705	136
(2g)	92	8400	210	1590, 1628, 1640, 1652, 1712	184
		24000	287		
		300	355		

[a] 2,4-DNPH = 2,4-dinitrophenylhydrazone.
[b] Adduct with maleic anhydride, prepared in boiling xylene (5 h), m.p. 172°C (from benzene).

exclusively, to the formation of ethyl esters of 2-(2-furyl)cyclopropanecarboxylic acids *(3)*. The adducts are 2.5—3:1 mixtures of *trans*- and *cis*-isomers (GLC and NMR data)[3]. Configurations of the isomers *(3)* were assigned by analysis of the ^{1}H-NMR spectra (multiplets of $—CH_2—O—$, H^1 and H^2) taking into account the magnetic anisotropy of the furan ring[4].

The different behavior of *(1a)*, *(1b)* and *(1g)*, on the one hand, and of *(1c)* to *(1f)* on the other, toward ethyl diazoacetate, correlates with the fact that the ratio of rate constants for addition to the vinyl double bond and for addition to the double bond remote from substituents in the furan ring decreases with increasing number of methyl substituents on the vinyl group. It can be largely explained in terms of steric factors. As competition reactions show (cf. Table 1), the double bond of the furan ring (remote from alkenyl substituents) in *(1a)* and *(1b)* is more reactive than the double bond in hexene.

Though the relative rate constants for the addition of ethyl diazoacetate to the double bond remote from alkenyl substituents do indeed depend upon the electronic character of the substituents [see *(1c)* and *(1d)* in Table 1], big differences in the values cannot be explained by steric and electronic factors only. Apparently the observed effect is connected with the ease with which the furan ring forms complexes.

Received: June 7, 1977 [Z 762 IE]
German version: Angew. Chem. *89*, 674 (1977)

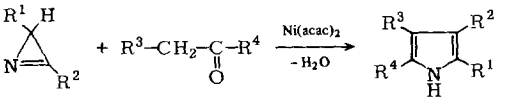
CAS Registry numbers:
(1a), 10504-11-7; *(1b)*, 10599-55-0; *(1c)*, 1487-18-9; *(1d)*, 10504-13-9; *(1e)*, 63269-95-4; *(1f)*, 63269-96-5; *(1g)*, 55276-11-4; *(2a)*, 63269-97-6; *(2a)*, adduct with maleic anhydride, 63269-98-7; *(2a)*, 2,4-DNPH, 63269-99-8; *(2b)*, 33879-87-7; *(2b)*, 2,4-DNPH, 33879-88-8; *(2c)*, 54520-25-1; *(2d)*, 63270-00-8; *(2e)*, 63270-01-9; *(2f)*, 63270-02-0; *(2g)*, 63270-03-1; *(2g)*, 2,4-DNPH, 63270-04-2; *cis-(3c)*, 63270-05-3; *trans-(3c)*, 63270-06-4; *cis-(3d)*, 63270-07-5; *trans-(3d)*, 63270-08-6; *cis-(3e)*, 63270-09-7; *trans-(3e)*, 63270-10-0; *cis-(3f)*, 63270-11-1; *trans-(3f)*, 63270-12-2; ethyl diazoacetate, 623-73-4

[1] *O. M. Nefedov, V. M. Schostakovsky, M. Ya. Samoilova, M. I. Kravchenko*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 1590.
[2] According to *J. Novak, F. Šorm*, Collect. Czech. Chem. Commun. *23*, 1126 (1958).
[3] In the case of *(3c)* the ratio of *trans*- and *cis*-isomers is 2.5:1 (GLC, NMR). The isomers were separated thin-layer chromatographically ($SiO_2 \cdot n H_2O$, eluted with hexane/ether (10:1)).
[4] ^{1}H-NMR of *trans-(3c)*: δ = 4.05 (q, —O—CH_2—), 2—2.5 (m, H^1), 1.65—2.0 (m, H^2); *cis-(3c)*: 3.9, 2.2—2.7, and 1.65—2.05.

Nickel(II)-Catalyzed Synthesis of Pyrroles from 2*H*-Azirines and Activated Ketones[**]

By *Pedro Faria dos Santos Filho* and *Ulf Schuchardt*[*]

3-Phenyl- and 2,3-diphenyl-2*H*-azirine[1], *(1a)* and *(1c)* respectively, react with dimedone at 145°C to give the pyrroles *(3d)* and *(3f)*[2]. We have now found that this reaction can be extended to a large number of activated ketones and that it is catalyzed by nickel(II) compounds.



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

The catalysis proves advantageous in that side-reactions are avoided. With sufficiently activated CH_2 groups in the ketone *(2)*, reaction with the azirine *(1)* proceeds to completion, even at room temperature; the pyrrole *(3)* can be precipitated in analytically pure form and in quantitative yield by addition of water (Table 1).

The versatility of this synthesis when *(2)* is sufficiently enolized would seem to be limited only by the number of known 2*H*-azirines *(1)*.

(3a), *(3c)*, *(3g)*, and *(3k)* were first prepared by *Knorr et al.* by reduction of the α-nitrosocarbonyl compounds with zinc dust in acetic acid in the presence of the corresponding ketone *(2)*[3]. We synthesized *(3b)*, *(3e)*, and *(3f)* in a similar

[*] Prof. Dr. U. Schuchardt, P. Faria dos Santos Filho
Universidade Estadual de Campinas, Instituto de Química, C. P. 1170
13.100 Campinas, S. P. (Brazil)

[**] This work was supported by the Fundação de Amparo à pesquisa do Estado de São Paulo (FAPESP).

Table 1. Synthesized pyrroles *(3)*. All products were characterized on the basis of their ^{1}H-NMR, IR, and mass spectra.

Cpd.	R^1	R^2	R^3	R^4	m.p. [°C]	Yield [%]
(3a)	H	C_6H_5	$COCH_3$	CH_3	156	quant.
(3b)	CH_3	C_6H_5	$COCH_3$	CH_3	133	quant.
(3c)	C_6H_5	C_6H_5	$COCH_3$	CH_3	135	quant.
(3d)	H	C_6H_5	$COCH_2C(CH_3)_2CH_2$		245	quant.
(3e)	CH_3	C_6H_5	$COCH_2C(CH_3)_2CH_2$		287	quant.
(3f)	C_6H_5	C_6H_5	$COCH_2C(CH_3)_2CH_2$		300	quant.
(3g) [a]	H	C_6H_5	$COCH_3$	C_6H_5		80
	H	C_6H_5	COC_6H_5	CH_3		20
(3h)	H	C_6H_5	CN	C_6H_5	280	quant.
(3i)	C_6H_5	C_6H_5	CN	C_6H_5	222	quant.
(3k) [b]	H	C_6H_5	$CO_2C_2H_5$	CH_3	104	50
(3l) [b]	H	C_6H_5	$CO_2C_2H_5$	C_6H_5	106	50

[a] Mixture of isomers (4 : 1).
[b] Purified by chromatography on neutral Al_2O_3 in acetone/petroleum ether (1 : 1).

way in order to confirm their structures. However, in some cases purification of the product was demanding, and the yields were at most 50 %. It could be shown that the three-membered ring is opened only at the N=C double bond, and that an opening at the C—C single bond, as observed in the photolysis of *(1)*[1], does not occur. The reaction also proceeds *via* cleavage of N=C bond at 145 °C in the absence of catalyst. We prepared *(3a)*, *(3c)*, *(3f)*, and *(3l)* in this way, but the yields were less than 50 %; for purification of the products, chromatography on neutral aluminum oxide was necessary.

2,2-Dimethyl-3-phenyl-2*H*-azirine does not react with *(2)* in the presence of bis(2,4-pentanedionato)nickel at room temperature. The H atom in position 2 of *(1)* therefore seems to play an essential role in the reaction.

The reaction is not catalyzed by acids ($HClO_4$, $BF_3 \cdot Et_2O$). Reaction of *(1a)* with sodium acetylacetonate affords *(3a)* in only *ca.* 10% yield, the main products of the reaction being unidentified oligomers. The sodium salt of *(2)*, $R^3 = CO_2Et$, $R^4 = Ph$, reacts with *(1a)* to give 3-benzoyl-4-phenyl-2-oxopyrroline[4]; however, on reaction of this ketone *(2)* with *(1a)* in the presence of catalytic amounts of Ni^{II}, we obtained *(3l)*.

The reaction *(1)*+*(2)*→*(3)* is also catalyzed by other transition metal compounds.

General procedure

Bis(2,4-pentanedionato)nickel (15—20 mg, *ca.* 0.06 mmol) is added at room temperature to a solution of azirine *(1)* (5 mmol) and activated ketone *(2)* (5 mmol) in acetone (10 ml). After an induction period of 10—15 min the solution warms to 35—40 °C. For completion of reaction the mixture is stirred for 2–3 h at room temperature. The pyrrole *(3)* is then quantitatively precipitated with *ca.* 30 ml water. Precipitation with petroleum ether is also possible, but in the case of *(3a)*, for example, the yield is reduced owing to its significant solubility.

Received: June 21, 1977 [Z 765 IE]
German version: Angew. Chem. *89*. 672 (1977)

CAS Registry numbers:
(1a), 7654-06-0; *(1b)*, 16205-14-4; *(1c)*, 16483-98-0; *(2)* ($R^3 = COCH_3$; $R^4 = CH_3$), 123-54-6; *(2)* (R^3, $R^4 = COCH_2C(CH_3)_2CH_2$), 126-81-8; *(2)* ($R^3 = COCH_3$; $R^4 = C_6H_5$), 93-91-4; *(2)* ($R^3 = CN$; $R^4 = C_6H_5$), 614-16-4; *(2)* ($R^3 = CO_2C_2H_5$; $R^4 = CH_3$), 141-97-9; *(2)* ($R^3 = CO_2C_2H_5$; $R^4 = C_6H_5$), 94-02-0; *(3a)*, 63324-73-2; *(3b)*, 63324-74-3; *(3c)*, 32559-50-5; *(3d)*, 10131-09-6; *(3e)*, 63324-75-4; *(3f)*, 31210-91-0; *(3g)* isomer 1, 63324-76-5; *(3g)* isomer 2, 59009-58-4; *(3h)*, 59009-62-0; *(3i)*, 63324-77-6; *(3k)*, 3274-63-3; *(3l)*, 63324-78-7; bis(2,4-pentanedionato)nickel, 3264-82-2

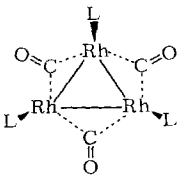
[1] *D. J. Anderson, A. Hassner*, Synthesis *1975*, 483.
[2] *N. S. Narasimham, H. Heimgartner, H.-J. Hausen, H. Schmid*, Helv. Chim. Acta *56*, 1351 (1973). The alternative structure of a tetrahydroisoindole for *(3f)* reported therein should be corrected on the basis of our findings.
[3] *L. Knorr, H. Lange*, Ber. Dtsch. Chem. Ges. *35*, 2998 (1902).
[4] *S. Sato, H. Kato, M. Ohta*, Bull. Chem. Soc. Jpn. *40*, 2936 (1967).

Reactivity of η^5-Indenylrhodium(I) Complexes; Cyclocotrimerization of Alkynes with Alkenes[**]

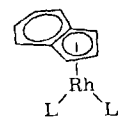
By *Peter Caddy, Michael Green, Edmund O'Brien, Lesley E. Smart*, and *Peter Woodward*[*]

$[MoX(CO)_3(\eta^5\text{-}C_9H_7)]$ (X = halogen) has a higher reactivity towards ligand substitution than the corresponding $\eta^5\text{-}C_5H_5$ system[1]. This difference is explicable in terms of the "slippage" of the indenyl ligand ($\eta^5\text{-}C_9H_7 \rightarrow \eta^3\text{-}C_9H_7$). The possible general synthetic consequences of this kinetic observation in the synthesis of transition metal organic compounds have been examined[1].

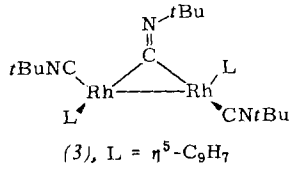
$[Rh(C_2H_4)_2(\eta^5\text{-}C_5H_5)]$ does not react with carbon monoxide, whereas the η^5-indenyl analog reacts instantaneously at room temperature to give $[Rh(CO)_2(\eta^5\text{-}C_9H_7)]$[2] ($\nu_{CO}$ = 2048 s, 1990 s cm^{-1}) in quantitative yield. Prolonged photolysis of $[Rh(CO)_2(\eta^5\text{-}C_5H_5)]$ affords two isomers of $[Rh_3(CO)_3(\eta^5\text{-}C_5H_5)_3]$, albeit only in low yield[3], while in refluxing heptane dicarbonyl(η^5-indenyl)rhodium is converted selectively in high yield into the dark-green trimer *(1)*[4] [ν_{CO} (CH_2Cl_2) 1852 s, 1805 s cm^{-1}].



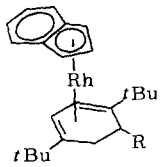
(1), L = $\eta^5\text{-}C_9H_7$



(2), L = *t*BuNC
(4), L = 
(5), L = CH_2=CH-CN
(6), L_2 = 
(7), L_2 = 
(8), L_2 =  (1,3-η^2)



(3), L = $\eta^5\text{-}C_9H_7$



(9), R = H; *(10)*, R = CN

tert-Butyl isocyanide (2 mmoles) rapidly displaces ethylene from $[Rh(C_2H_4)_2(\eta^5\text{-}C_9H_7)]$ to form *(2)* [ν_{NC} (Nujol) = 2125 s, 2090 s, 2055 s cm^{-1}], which in solution is slowly converted into the red crystalline dinuclear complex *(3)* [ν_{NC} (Nujol) = 2120 s, 2080 s, 1750 m, 1720 m cm^{-1}; ^{1}H-NMR (C_6D_6, 32 °C): τ = 8.8 (s, *t*BuN)]. Excess *tert*-butyl isocyanide forms $[Rh(\sigma\text{-}C_9H_7)(t\text{BuNC})_4]$ [ν_{NC} (Nujol) = 2175 w,

[*] Dr. M. Green, Dr. L. E. Smart, Dr. P. Woodward, P. Caddy, E. O'Brien
Department of Inorganic Chemistry, University of Bristol
Bristol BS8 1TS (England)

[**] This work was supported by the Science Research Council.

2120 cm^{-1}]. The ^{1}H-NMR spectrum of *(3)* indicates rapid bridged to terminal isocyanide exchange (cf. [5]). Ethylene can also be readily displaced from $[Rh(C_2H_4)_2(\eta^5\text{-}C_9H_7)]$ at room temperature by methylenecyclopropane, acrylonitrile and 1,3-dienes such as isoprene, cyclohexadiene or 1,3,5-cycloheptatriene forming respectively the crystalline complexes *(4)*, *(5)*, *(6)*, *(7)* and *(8)*. Similar reactions cannot, of course, be achieved with the $\eta^5\text{-}C_5H_5$ system[6].

The facile reaction of the η^5-indenyl complex with alkynes is of interest in terms of its relevance to recent comments[7] on the cyclocotrimerization of alkynes and alkenes. Reaction of $[Rh(C_2H_4)_2(\eta^5\text{-}C_9H_7)]$ with an excess of 3,3-dimethyl-1-butyne results in the rapid catalytic cyclotrimerization of the alkyne to 1,2,4-tri-*tert*-butylbenzene[8]. However, if the reaction is run at low alkyne concentration the complex (1,4-di-*tert*-butylcyclohexa-1,3-diene)(η^5-indenyl)rhodium *(9)* is obtained as yellow crystals, the diene being readily displaced by carbon monoxide.

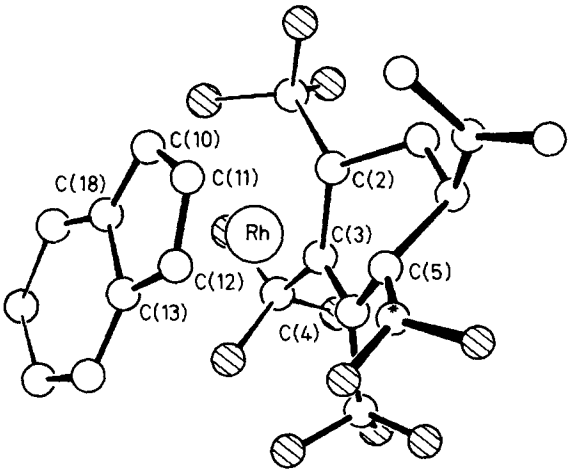
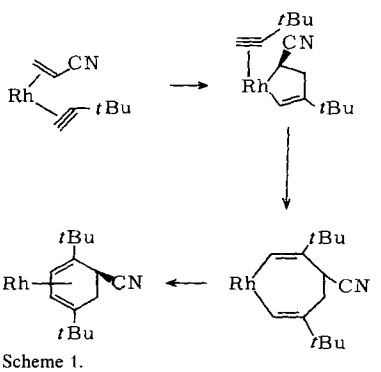


Fig. 1. Molecular structure of (η^5-indenyl)[5-isopropenyl-1,2,3,4-tetrakis(trifluoromethyl)-1,3-cyclohexadiene]rhodium(I) *(11)*. Space group Pbca, $a=16.962(3)$, $b=29.618(4)$, $c=8.596(4)$ Å, $V=4318.1$ Å^3, $Z=8$; Syntex four circle diffractometer; 2879 independent reflections ($I_0 \geq 1.0\sigma I$); $2.9° \leq 2\theta \leq 50°$ (Mo-K_α radiation); $R=0.063$. Rh—C(2): 2.15, Rh—C(3): 2.07, Rh—C(4): 2.09, Rh—C(5): 2.10, Rh—C(10): 2.18, Rh—C(11): 2.19, Rh—C(12): 2.18, Rh—C(13): 2.32, Rh—C(14): 2.31 Å; estimated mean standard deviation 0.01 Å.—For clarity the fluorine atom at * has been omitted.

Similarly, bis(acrylonitrile)(η^5-indenyl)rhodium *(5)* reacts with 3,3-dimethyl-1-butyne to give the cyano-substituted analog *(10)*. The reaction can also be extended to electronegatively substituted alkynes. Thus the isoprene complex *(6)* reacts at room temperature with hexafluoro-2-butyne to give *(11)* in the form of yellow orthorhombic crystals. According to X-ray structure analysis (see Fig. 1) the 1,3-diene part of the C_6-ring is planar; but the two carbon atoms originating from the isoprene bend away from the rhodium at a dihedral angle of *ca.* 132°. The propenyl group lies *endo* to the metal. The indenyl group is η^5-bonded to the Rh, but the atoms C(18) and C(13) are at greater bond distances from the rhodium than are C(10), C(11) and C(12).



Scheme 1.

Although the cyclocotrimerization of two alkyne molecules with an alkene molecule to form cyclohexa-1,3-diene derivatives has been the subject of a number of studies, with one exception[9] only the organic product has been isolated. The results reported here suggest the intermediacy of metallo-2-cyclopentenes[9] rather than metallocyclopentadienes[7], and that the incorporated alkene (ethylene or acrylonitrile) remains bonded to the metal throughout the reaction (see Scheme 1).

Received: June 13, 1977 [Z 763 IE]
German version: Angew. Chem. *89*, 671 (1977)

CAS Registry numbers:
(1), 63466-35-3; *(2)*, 63466-37-5; *(3)*, 63428-35-3; *(4)*, 63428-36-4; *(5)*, 63428-38-6; *(6)*, 63428-31-5; *(7)*, 63428-40-0; *(8)*, 63428-39-1; *(9)*, 63466-38-6; *(10)*, 63428-48-8; *(11)*, 63428-47-7; $[Rh(C_2H_4)_2(\eta^5\text{-}C_9H_7)]$, 63428-46-6; $[Rh(\sigma\text{-}C_9H_7)(t\text{-}BuNC)_4]$, 63428-45-5

[1] *A. J. Hart-Davis, C. White, R. J. Mawby*, Inorg. Chim. Acta *4*, 1441 (1970).
[2] All new compounds described have been characterized by elemental analysis, mass- and NMR-spectroscopy.
[3] *O. S. Mills, E. F. Paulus*, J. Organomet. Chem. *10*, 331 (1967); *E. F. Paulus, E. O. Fischer, H. P. Fritz, H. Schuster-Woldan, ibid. 10*, P3 (1967); *E. F. Paulus*, Acta Crystallogr. *25 B*, 2206 (1969).
[4] a) Preliminary experiments have shown that *(1)*, in contrast to its η^5-cyclopentadienyl analog [4], is highly reactive towards ligand substitution, *e.g.* by alkynes; b) *R. J. Lawson, J. R. Shapley*, J. Am. Chem. Soc. *98*, 7433 (1976).
[5] *J. Evans, B. F. G. Johnson, J. Lewis, J. R. Norton*, J. Chem. Soc. Chem. Commun. *1973*, 79.
[6] The barrier to ethylene rotation in the η^5-indenyl complex (10.5 ± 0.4 kcal/mol) is lower than in the corresponding η^5-cyclopentadienyl complex (15.0 ± 0.2 kcal/mol).
[7] *H. Suzuki, K. Itoh, Y. Ishii, K. Simon, J. A. Ibers*, J. Am. Chem. Soc. *98*, 8494 (1976).
[8] At high acetylene concentrations 2-butyne and 3,3-dimethyl-1-butyne form interesting catalytically-active dinuclear species. *M. Green, P. Caddy, L. E. Smart*, unpublished.
[9] *Y. Wakatsuki, T. Kuramitsu, H. Yamazaki*, Tetrahedron Lett. *1974*, 4549; J. Am. Chem. Soc. *96*, 5284 (1974).

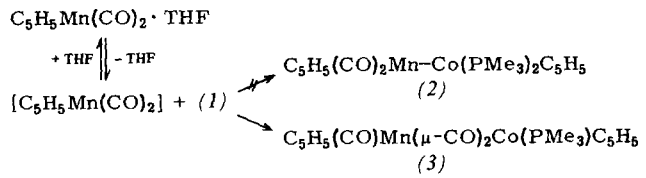
Synthesis and Reactivity of Hetero Dinuclear Complexes Containing a Mn—Co Bond[1]

By *Konrad Leonhard* and *Helmut Werner*[*]

The compound $C_5H_5Co(PMe_3)_2$ *(1)*[2] recently synthesized by us is an extraordinarily strong nucleophile. It reacts not only with Brønstedt acids and with alkyl and acyl halides to give complex cations containing very stable Co—H and Co—C bonds[2] but also with Lewis acids such as $SnCl_4$, $ZnCl_2$, or $HgCl_2$ with formation of 1:1 adducts containing a metal-metal bond[3].

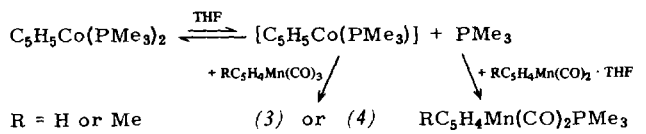
In order to test the reactivity of *(1)* toward Lewis acidic *transition metal* ligand fragments we have investigated the reaction of the cobalt compound with $C_5H_5Mn(CO)_2 \cdot THF$ (generated photochemically *in situ*, and present in THF solution together with $C_5H_5Mn(CO)_3$). Surprisingly, instead of the expected "adduct" *(2)* of the Lewis base $C_5H_5Co(PMe_3)_2$ and the Lewis acid $[C_5H_5Mn(CO)_2]$ we obtained the dinuclear complex *(3)*. Its composition and structure[4] are confirmed by elemental analysis, mass spectrum, IR, and NMR data (Table 1).

[*] Prof. Dr. H. Werner, Dr. K. Leonhard
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)



$MeC_5H_4(CO)Mn(\mu\text{-}CO)_2Co(PMe_3)C_5H_5$ *(4)* could be synthesized in an analogous way.

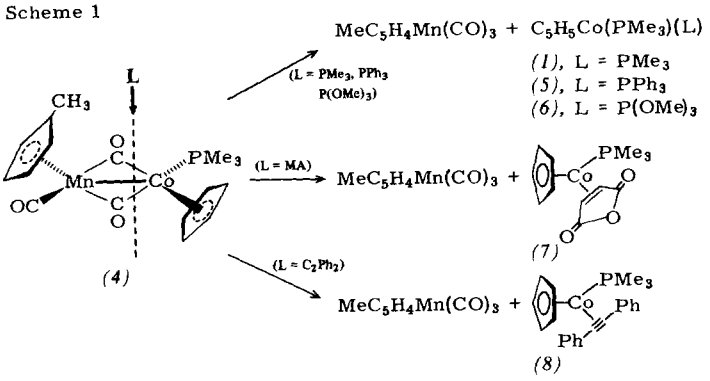
We interpret the formation of the dinuclear complex in terms of intermediary formation of the 16-electron species $[C_5H_5Co(PMe_3)]$ (possibly solvated by THF) and subsequent reaction of this very reactive fragment with the inert tricarbonyl $RC_5H_4Mn(CO)_3$ (R = H, Me). This interpretation, which might seem very unusual at first sight, is supported by the finding that addition of $C_5H_5Mn(CO)_3$ to a *previously* irradiated solution of $MeC_5H_4Mn(CO)_3$ in THF (in which $MeC_5H_4Mn(CO)_2 \cdot THF$ is present as well as $MeC_5H_4Mn(CO)_3$ and *subsequent* reaction of this solution with *(1)* leads to formation of an isolable mixture of *(3)* and *(4)*, in which complex *(3)* predominates.



The formation and reactivity of 16e species of the type $[C_5H_5CoL]$ also underscores the result of the reaction of $C_5H_5Co(CO)_2$ with $MeC_5H_4Mn(CO)_2 \cdot THF$/ $MeC_5H_4Mn(CO)_3$. A (*Co—Mn*)-dinuclear complex is *not* formed, but a mixture of $(C_5H_5)_3Co_3(CO)_3$ and $(C_5H_5)_4Co_4(CO)_2$, thus indicating that the intermediate $[C_5H_5Co(CO)]$ reacts more rapidly with itself (or with $C_5H_5Co(CO)_2$) than with $MeC_5H_4Mn(CO)_3$. The Co_3- and Co_4-clusters so formed have already been synthesized photochemically[5, 6a].

(3) and *(4)* show pronounced reactivity toward Lewis bases L. For example, reaction of *(4)* with trimethylphosphane (in acetone or benzene at 30—50 °C) leads *quantitatively* to $MeC_5H_4Mn(CO)_3$ and *(1)*. In contrast, the *photolysis* of *(4)* in the presence of PMe_3 (in THF at room temperature) affords $MeC_5H_4Mn(CO)(PMe_3)_2$[7] and $C_5H_5Co(CO)PMe_3$. All other thermal reactions of *(3)* or *(4)* with L lead also to the complexes $RC_5H_4Mn(CO)_3$ (R = H, Me) and $C_5H_5Co(PMe_3)L$ *(5)—(8)*; particularly interesting is the reaction of the π donors maleic anhydride (MA) and tolane. "Mixed" cyclopentadienyl-bis(phosphane)- and -(phosphane)(phosphite)cobalt complexes such as *(5)* and *(6)* are to our knowledge unknown. These compounds could be useful starting materials for studies concerned with elucidating the mechanism of Co-catalyzed cyclotrimerizations of alkynes[8].

Scheme 1



We ascribe the *unsymmetrical* cleavage of the $Mn(\mu\text{-}CO)_2Co$ bridge fragment in *(3)* and *(4)* on reaction with Lewis bases (Scheme 1) to the *difference* in the metal atoms and their electron configurations. For equal distribution of the bonding electrons of the Mn—CO—Co bridges (taking into account a metal-metal single bond) the manganese would formally have 17 electrons and the cobalt 19 electrons in the valence shell. A "normal" 18e arrangement at both metal atoms would then be achieved, if 75 % of the two bonding electrons (= 1.5e) of each CO bridge belonged to the Mn and 25 % (= 0.5e) to the Co. As a consequence one would expect the Co—μ-CO bonds to be weaker than the Mn—μ-CO bond, as reflected by the reaction behavior of *(3)* and *(4)*. *Cotton et al.*[6] have demonstrated the presence of unsymmetrical CO bridges in the carbonylcyclopentadienylmetal complexes $(C_5H_5)_3Co_3(CO)_3$ and $(C_5H_5)_2V_2(CO)_5$; an unsymmetrical CO-bridge between two *different* metals has been found in $[FeCo(CO)_8]^-$ by *Bau et al.*[9].

Table 1. Spectroscopic data of the dinuclear complexes *(3)* and *(4)*.

(3): MS (70 eV): *m/e* (above 0.3 % I_{rel}) 404 (6.9; M^+), 376 (0.3; −CO), 348 (1.2; −2CO), 320 (8.8; −3CO), 204 (20.6; $C_5H_5Mn(CO)_3^+$), 200 (18.2; $C_5H_5CoPMe_3^+$), 176 (4.4; $C_5H_5Mn(CO)_2^+$), 148 (21.2; −CO), 124 (36.8; $C_5H_5Co^+$), 120 (100; $C_5H_5Mn^+$). IR (THF): $\nu CO = 1902$, 1757 cm^{-1}. ^1H-NMR ([D_6]-acetone, room temperature, 100 MHz): $\delta = 4.83$ (5 H of C_5H_5Co; s), 4.60 (5 H of C_5H_5Mn; s), 1.10 (9 H; d; $J_{PH} = 10$ Hz).

(4): MS (70 eV): *m/e* (above 0.1 % I_{rel}) 418 (0.5; M^+), 362 (0.1; −2CO), 334 (0.7; −3CO), 218 (20.8; $MeC_5H_4(CO)_3^+$), 200 (10.4; $C_5H_5CoPMe_3^+$), 190 (30.1; $MeC_5H_4Mn(CO)_2^+$), 162 (25.1; −CO), 134 (100; −2CO), 124 (23.0; $C_5H_5Co^+$). IR (THF): $\nu CO = 1898$, 1752 cm^{-1}. ^1H-NMR ([D_6]-acetone, room temperature, 100 MHz): $\delta = 4.82$ (5 H; s), 4.38 (4 H; s), 2.03 (3 H; s), 1.11 (9 H; d; $J_{PH} = 9.9$ Hz).

Procedure

A solution of $MeC_5H_4Mn(CO)_3$ (1 mmol) in THF (200 ml) is irradiated with a mercury vapor lamp (Philips HPK 125 W) until evolution of gas has subsided. After switching off the lamp, the solution is treated with 1 mmol $MeC_5H_4Mn(CO)_3$ and 1 mmol *(1)* and then stirred for 16 h at room temperature. The oily residue obtained after removal of solvent *in vacuo* is washed several times with hexane and then recrystallized from THF/hexane: *(4)*, blue-black crystals, dec. pt. 121 °C; yield 330 mg (79 % w.r.t. *(1)*).

Received: June 23, 1977 [Z 771 IE]
German version: Angew. Chem. 89, 656 (1977)

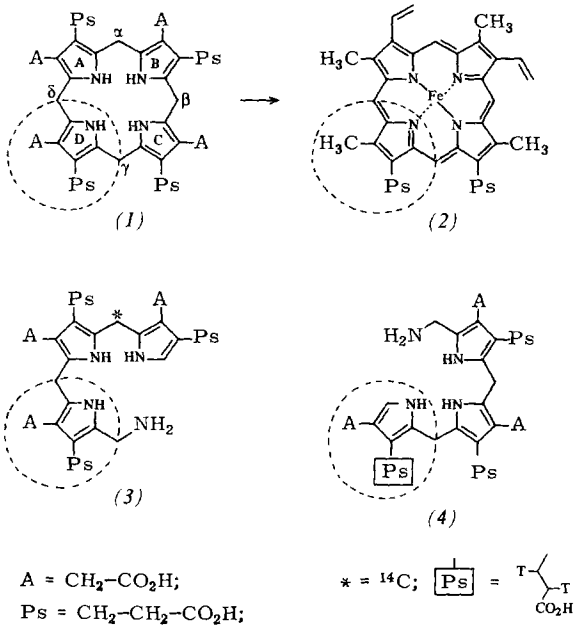
CAS Registry numbers:
(1), 63413-01-4; *(3)*, 63413-02-5; *(4)*, 63413-03-6; *(5)*, 63413-04-7; *(6)*, 63413-05-8; *(7)*, 63413-06-9; *(8)*, 63413-07-0; $C_5H_5Mn(CO)_3$, 12079-65-1; $MeC_5H_4Mn(CO)_3$, 12108-13-3

[1] Basic Metals, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Bayer AG, Leverkusen.—Part 4: Ref. [3].
[2] *H. Werner, W. Hofmann*, Chem. Ber., in press.
[3] *K. Dey, H. Werner*, J. Organomet. Chem., in press.
[4] A crystal structure analysis is currently being carried out by Prof. *I. Bernal*, University of Houston.
[5] *R. B. King*, Inorg. Chem. 5, 2227 (1966); *K. P. C. Vollhardt, J. E. Bercaw, R. G. Bergman*, J. Organomet. Chem. *97*, 283 (1975); *W. S. Lee, H. H. Brintzinger, ibid. 127*, 87 (1977).
[6] a) *F. A. Cotton, J. D. Jamerson*, J. Am. Chem. Soc. *98*, 1273 (1976); b) *F. A. Cotton, B. A. Frenz, L. Kruczynski, ibid. 95*, 951 (1973); *F. A. Cotton*, Progr. Inorg. Chem. *21*, 1 (1976).
[7] *H. Werner, B. Juthani*, J. Organomet. Chem. *129*, C 39 (1977).
[8] *D. R. McAlister, J. E. Bercaw, R. G. Bergman*, J. Am. Chem. Soc. *99*, 1666 (1977).
[9] *H. B. Chin, M. B. Smith, R. D. Wilson, R. Bau*, J. Am. Chem. Soc. *96*, 5285 (1974).

Total Synthesis of [^{14}C]- and [^{3}H]-Labeled Tripyrrole Precursors for Heme Biosynthesis[1]

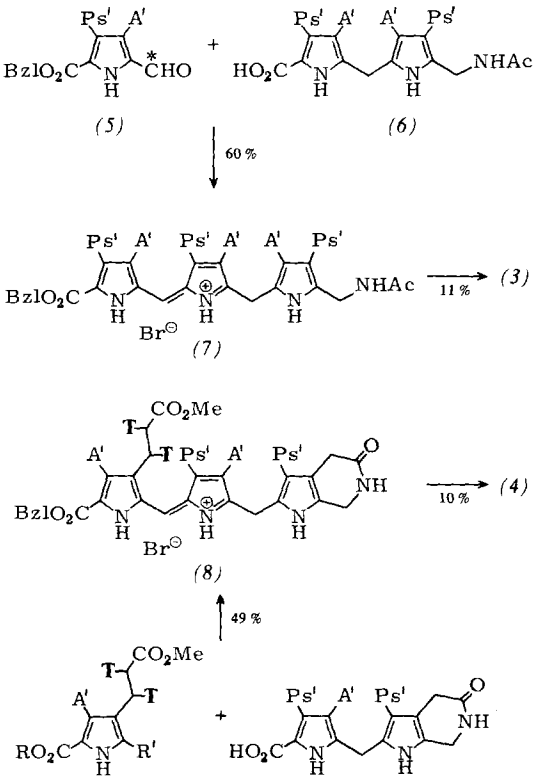
By *Burchard Franck, Gregor Fels, Günter Ufer,* and *Arend Rowold*[*]

As has been demonstrated for heme *(2)*[2] and vitamin B_{12}[3] and is probably also the case for chlorophyll[4], uroporphyrinogen III *(1)* is a precursor of and key compound in the biosynthesis of biologically active porphyrins. Uroporphyrinogen III *(1)* is characterized by inversion of pyrrole nucleus D (in the dotted circle), together with its side chains. Isotopically labeled, biogenetically significant tripyrroles[5] are of importance for the elucidation of the biosynthesis of *(1)* from linear, oligopyrrole precursors, as well as for elucidation of the physiologically important "pyrrole inversion". We will now report the first total syntheses of the [^{14}C]- and [^{3}H]-labeled tripyrroles *(3)* and *(4)* respectively; each of them contains a terminal, inverted pyrrole nucleus and, of all the eight possible isomeric tripyrroles, these could well be the precursors preferred for biosynthesis.



On account of the complicated structure and high reactivity of the tripyrroles *(3)* and *(4)*, pathways for their syntheses were selected which, with extensive use of the convergence principle[6], yielded the stable well-protected depot compounds *(7)* and *(8)* from which *(3)* and *(4)* could be liberated by easy, mild reactions. Radioisotopes with different radiation energies were used to label the two tetrapyrroles so that when they were mixed, the individual rates of incorporation [of *(3)* and *(4)*] could be directly determined by measuring the radioactivities of the biosynthetic product, heme *(2)*. The positions of the labels were chosen so that the ^{14}C- and ^{3}H-isotopes (a) could be introduced into *(3)* and *(4)* respectively as late as possible in the multi-step synthesis, (b) would not be lost during biogenetic conversions, and (c) could be located in heme *(2)* by simple degradation.

The ^{14}C-labeled reactant for the synthesis of the tripyrrole *(7)* was pyrrolecarbaldehyde *(5)* which was obtained by Vilsmeier formylation with [^{14}CO]-dimethylformamide/$POCl_3$[7].



(5) was condensed with the dipyrrole derivative *(6)* with simultaneous decarboxylation in a single step (HBr/MeOH) to give the trinuclear compound *(7)*: m.p. 92—93 °C; FD-MS (12 kV): $m/e = 902$ (58 %, $M^{\oplus} - HBr$); ^{1}H-NMR ($CDCl_3$): $\delta = 13.22, 12.91, 10.36$ (3 s, 3 pyrrole-NH). Tritiated pyrrolecarbaldehyde *(9a)* condensed with the dipyrrole derivative *(10)* under the same conditions to yield *(8)*: m.p. 153—155 °C; FD-MS (11 kV): $m/e = 829$ ($M^{\oplus} - HBr + H$); ^{1}H-NMR ($CDCl_3$): $\delta = 11.36$ (2H), 10.02 (1H) (3 pyrrole-NH). The tritium was introduced catalytically into the pyrrolylacrylic ester *(9b)* with 5 Ci T_2/Pd and a 73 % yield of radioactivity. Subsequent transesterification and selective oxidation with sulfuryl chloride lead to the formation of *(9a)*.

The labeled tripyrroles *(3)* and *(4)* were prepared from the hydrobromides *(7)* and *(8)* respectively, with the yields specified, in four steps; these steps were conversion to the free base (NH_3), hydrogenolysis of the benzyl ester (H_2/Pd), decarboxylation (CF_3CO_2H, 0 °C), and alkaline saponification (2 N KOH, 20 °C).

Experimental

(7): A solution of *(5)* (418 mg, 1.08 mmol; 2.5 mCi) and *(6)* (624 mg, 1.08 mmol) in 25 ml methanol was mixed with 47 % HBr (0.8 ml) and stirred for 4 h at 20 °C. After 21 days in the refrigerator *(7)* (664 mg, 60 %) containing 1.45 mCi (58 %) had crystallized out.

Received: June 23, 1977 [Z 770a]
German version: Angew. Chem. *89*, 676 (1977)

[*] Prof. Dr. B. Franck, Dipl.-Chem. G. Fels, Dipl.-Chem. G. Ufer, Dr. A. Rowold
Organisch-Chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

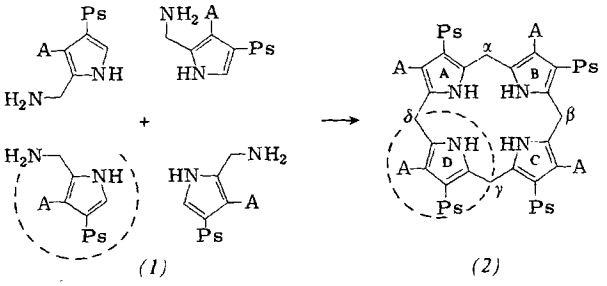
CAS Registry numbers:
(1), 1976-85-8; *(2)*, 14875-96-8; *(3)*, 63448-77-1; *(4)*, 63448-78-2; *(5)*, 63448-79-3; *(6)*, 63448-80-6; *(7)*, 63448-81-7; *(8)*, 63448-82-8; *(9a)*, 63448-83-9; *(9b)*, 63448-84-0; *(10)*, 50622-69-0

[1] Tetrapyrrole Biosynthesis, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: *B. Franck, A. Rowold, Ch. Wegner, H.-G. Eckert*, Phil. Trans. R. Soc. London *B 273*, 181 (1976).
[2] *B. Franck, D. Gantz, F.-P. Montforts, F. Schmidtchen*, Angew. Chem. *84*, 433 (1972); Angew. Chem. Int. Ed. Engl. *11*, 421 (1972).
[3] *A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, P. J. Whitman, R. J. Cushley*, J. Am. Chem. Soc. *94*, 8267 (1972).
[4] *O. T. G. Jones*, Phil. Trans. R. Soc. London *B 273*, 207 (1976); see also the bibliography given in *D. Ranganathan, S. Ranganathan*: Art in Biosynthesis. Vol. I, Academic Press, New York 1976, p. 40.
[5] *B. Frydman, R. B. Frydman*, Acc. Chem. Res. *8*, 201 (1975); *R. B. Frydman, A. Valasinas, S. Levy, B. Frydman*, FEBS Lett. *38*, 134 (1974).
[6] *S. Turner*: The Design of Organic Synthesis. Elsevier, Oxford 1976, p. 70; *L. Velluz, J. Valls, J. Mathieu*, Angew. Chem. *79*, 774 (1967); Angew. Chem. Int. Ed. Engl. *6*, 778 (1967).
[7] *B. Franck, D. Gantz, F. Hüper*, Angew. Chem. *84*, 432 (1972); Angew. Chem. Int. Ed. Engl. *11*, 420 (1972).

Heme Biosynthesis from [^{14}C]- and [^{3}H]-Labeled Tripyrroles[1]

By *Burchard Franck, Gregor Fels*, and *Günter Ufer*[*]

The blood pigment heme [*(5)*, T=H] is biosynthesized *via* uroporphyrinogen III *(2)*[3] from four molecules of porphobilinogen *(1)*[2] under inversion of one of the pyrrole nuclei (in the dotted circle)[4]. The course of the condensation reaction yielding *(2)* from *(1)* and the point at which the vital[5] "pyrrole inversion" takes place are still uncertain[6, 7]. Tripyrroles have often been discussed as intermediates in heme biosynthesis. We have now been able to obtain informative experimental findings from biosynthetic studies with the [^{14}C]- and [^{3}H]-labeled tripyrroles, *(3a)* and *(4a)*[1], respectively.



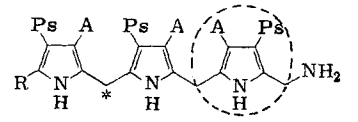
(1) *(2)*

A = CH_2–CO_2H; Ps = CH_2–CH_2–CO_2H

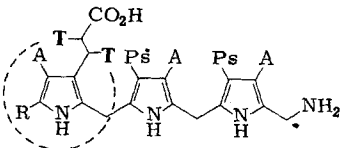
Previous investigations of heme biosynthesis from isomeric dipyrroles and oligopyrroles gave inconsistent results[6, 8]. This can be attributed to the small quantities (nmol) of substances used, to variation in the enzyme activity in comparison experiments and a tendency for the reactive oligopyrroles to take part in non-enzymatic condensation ("chemical blank")[7]. In order to avoid such drawbacks, the multi-step syntheses of *(3a)* and *(4a)* were carried out in the mmol range. The two pyrroles were labeled with different isotopes so that they could compete for the heme-synthesizing enzyme in one experiment. A reliable determination of the "chemical blank"[8] was made possible by the observation that the carboxytripyrroles *(3b)* and *(4b)* which are also synthesized do not react with the enzyme system but behave as the tripyrroles *(3a)* and *(4a)* respectively in the chemical condensation.

[*] Prof. Dr. B. Franck, Dipl.-Chem. G. Fels, Dipl.-Chem. G. Ufer
Organisch-Chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

(3)



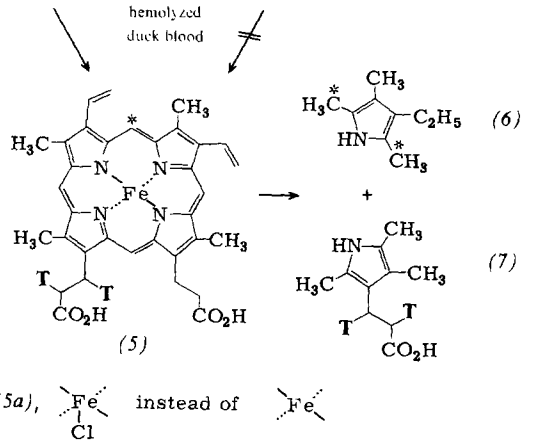
(4)



a: R = H; *b*: R = CO_2H; * = ^{14}C

(3a) + *(4a)* *(3b)* + *(4b)*

hemolyzed duck blood



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

(5a), instead of

In 17 separate experiments various quantities (0.5–4 mg) of mixtures of the tripyrroles *(3a)* and *(4a)* and of their carboxy derivatives *(3b)* and *(4b)* were incubated for 5 or 24 h at 32 °C with 25 ml of hemolyzed duck blood[3, 9]. The subsequently isolated hemin *(5a)* (90—117 mg) was purified until its level of radioactivity was constant.

Table 1. Competitive incorporation of the ^{14}C- and ^{3}H-labeled tripyrroles *(3a)* and *(4a)* and of *(3b)* and *(4b)* into hemin after 5 h.

Radioactivity of the tripyrroles [μCi]	Radioactivity of the hemin [μCi]	Incorporation of the radioactivity of the tripyrroles into hemin
(3a) ^{14}C: 2.37	^{14}C: 0.0122	^{14}C: 0.51 %
(4a) ^{3}H: 5.07	^{3}H: 0.0118	^{3}H: 0.23 %
(3b) ^{14}C: 4.09	^{14}C: 0.00034	^{14}C: 0.008 %
(4b) ^{3}H: 23.8	^{3}H: 0.00191	^{3}H: 0.008 %

The experimental results shown in Table 1 demonstrate that the two tripyrroles *(3a)* and *(4a)* are converted into heme significantly—*(3a)*, however, 2.2-fold faster. It follows from the low incorporation values of the "unnatural" carboxytripyrroles *(3b)* and *(4b)* that the "chemical blanks" can be neglected under the experimental conditions used.

The competitive incorporation of *(3a)* and *(4a)* has thus shown that, in addition to the preferred biosynthetic precursor, the enzyme system of duck blood can also use isomeric oligopyrroles. This could result in a partial diffusion of the ^{14}C- and ^{3}H-labeling of the tripyrroles *(3a)* and *(4a)* in the heme. It was confirmed by the chemical degradation of the hemin *(5a)*. The phyllopyrrole *(6)* formed after methylating cleavage (HI/CH_2O) contained, in addition to ^{14}C, 31 % of the ^{3}H-radioactivity of the hemin *(5a)* and the phyllopyrrolecarboxylic acid *(7)* contained, in addition to ^{3}H, 35 % of the ^{14}C-radioactivity.

As is the case with other natural products, the enzyme can use not only one but several intermediates for heme biosynthesis although these intermediates may be utilized with different efficiencies. This fact explains the apparently contradictory findings with other precursors[6-8].

Received: June 23, 1977 [Z 770b]
German version: Angew. Chem. 89, 677 (1977)

CAS Registry numbers:
(3a), 63448-77-1; *(3b)*, 63448-85-1; *(4a)*, 63448-78-2; *(4b)*, 63448-86-2; *(5a)*, 63527-98-0; *(6)*, 63448-87-3; *(7)*, 63448-88-4

[1] Tetrapyrrole Biosynthesis. Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 6: *B. Franck, G. Fels, G. Ufer, A. Rowold*, Angew. Chem. *89*, 676 (1977); Angew. Chem. Int. Ed. Engl. *16*, 651 (1977).
[2] *E. I. B. Dresel, J. E. Falk*, Biochem. J. *63*, 80 (1956).
[3] *B. Franck, D. Gantz, F.-P. Montforts, F. Schmidtchen*, Angew. Chem. *84*, 433 (1972); Angew. Chem. Int. Ed. Engl. *11*, 421 (1972).
[4] *A. R. Battersby, G. L. Hodgson, E. Hunt, E. McDonald, J. Saunders*, J. Chem. Soc. Perkin I *1976*, 273.
[5] Failure of "pyrrole inversion" to occur results in the formation of uroporphyrinogen I which cannot be converted to heme *(5)* and is the cause of an inborn, lethal blood disease (erythropoetic porphyria).
[6] *B. Frydman, R. B. Frydman, A. Valasinas, E. S. Levy, G. Feinstein*, Phil. Trans. R. Soc. London *B 273*, 137 (1976).
[7] *A. R. Battersby, E. McDonald* in *K. M. Smith*: Porphyrins and Metalloporphyrins. Elsevier, Oxford 1975, p. 61.
[8] *A. R. Battersby, E. McDonald, D. C. Williams, H. K. W. Wurziger*, Chem. Soc. Chem. Commun. *1977*, 113.
[9] *S. Granick*, J. Biol. Chem. *232*, 1101 (1958).

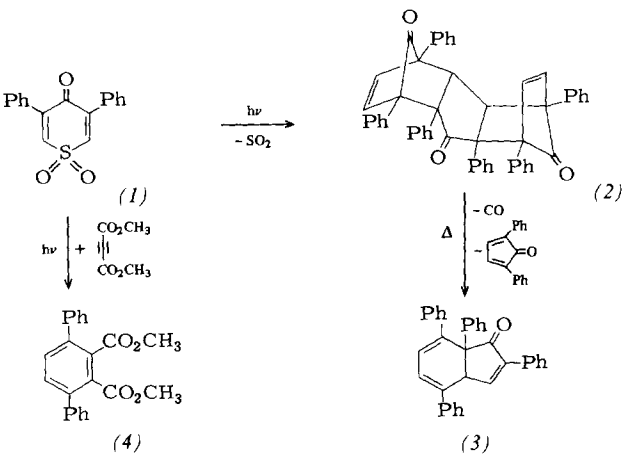
A Trimeric Cyclopentadienone Derivative by Photolysis of 3,5-Diphenyl-4*H*-thiopyran-4-one 1,1-Dioxide with Daylight

By *Walter Ried* and *Hubert Bopp*[*]

Dedicated to Professor Friedrich Asinger on the occasion of his 70th birthday

Depending upon the nature of substitution, cyclopentadienone derivatives are known either as monomers or, through Diels-Alder reaction, as dimers[1]. The action of daylight on 3,5-diphenyl-4*H*-thiopyran-4-one 1,1-dioxide *(1)*, both in the solid state as well as in solution, led *via* the previously unknown 2,5-diphenylcyclopentadienone to formation of a trimer *(2)* by a double Diels-Alder reaction. Formation of a dimeric Diels-Alder product, as is usual for monomeric unstable cyclopentadienone derivatives, could not be observed. A photochemical synthetic route to monomeric substituted cyclopentadienones has been described by *Ishibe et al.*[2]: Irradiation of 2,6-bis(alkylthio)-3,5-diphenyl-4*H*-thiopyran-4-ones with a mercury lamp leads to loss of sulfur and formation of stable monomers.

The pentacyclic compound *(2)* is present in the *trans* form[3] and can be decarbonylated by briefly heating it to 190°C. The bicyclic product *(3)*[4], which can be regarded as normal decarbonylated dimeric cyclopentadienone, is formed. Confirmation of this retro-Diels-Alder reaction is provided by the decomposition of *(2)* in the mass spectrometer, since occurrence of the fragment $m/e = 435$ as base peak in the spectrum is consistent with the stability of *(3)*, while no fragment is observed that would correspond to the tricyclic decarbonylation product.



The ease of SO_2-extrusion from 4*H*-thiopyran-4-one 1,1-dioxides depends decisively upon the choice of substituents. Whereas, *e.g.* the 2,6-diphenyl[5] and the 3,5-dimethyl derivative[6] are completely stable in daylight, in the case of 3,5-diphenyl derivatives extrusion of SO_2 already begins after *ca.* 10 min. The 2,5-diphenylcyclopentadienone that is formed can be trapped with suitable dienophiles. It reacts with dimethyl acetylenedicarboxylate with loss of CO to give dimethyl 3,6-diphenylbenzene-1,2-dicarboxylate *(4)*[2].

t-1, t-4, c-5, c-8, t-8a, c-9a-Hexaphenyloctahydro-r-1,4:t-5,8-dimethanofluorene-9,10,11-trione (2): A solution of *(1)*[7] (2.96 g, 0.01 mol) in $CHCl_3$ (10 ml) is exposed to daylight for 10 d at room temperature. The solvent is removed in a rotary evaporator and the residue recrystallized from CH_3OH/acetone. 1.7 g (73 %) of colorless crystals, m.p. 143 °C (red coloration and decomposition).—IR (KBr): C=O 1770 (s), 1690 (s) C=C 1590 (s) cm^{-1}. UV (CH_2Cl_2): $\lambda_{max}(\varepsilon) = 232\ (3.5 \times 10^4)$, 260 (sh) nm ($1.6 \times 10^4$). ^{1}H-NMR ($CDCl_3$): $\delta = 4.32$ d (2), $J = 3$ Hz; 6.5 d (2), $J = 6$ Hz; 6.82 d (2), $J = 6$ Hz; 7.2—7.7 m (30). MS: $m/e = 696$ (2 %), M^+; 435 (100 %).

2,4,7,7a-Tetraphenyl-3a,7a-dihydroinden-1-one (3): *(2)* (1 g, 1.4 mmol) is heated in an oil-bath at 190 °C for 15 min. After cooling, the residue is recrystallized from acetone. 400 mg (64 %) pale yellow crystals, m.p. 186 °C.—IR (KBr): C=O 1705 (s), C=C 1590 (s) cm^{-1}. UV (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ 230 (2.5×10^4), 335 nm (1×10^4). ^{1}H-NMR ($CDCl_3$): $\delta = 4.08$ d (1), $J = 2$ Hz; 6.65 and 6.82 AB-dd (2), $J = 7$ Hz; 7.1—7.7 m (21).

Dimethyl 3,6-diphenylbenzene-1,2-dicarboxylate (4): A solution of *(1)* (296 mg, 1 mmol) and dimethyl acetylenedicarboxylate (284 mg, 2 mmol) in $CHCl_3$ (10 ml) is exposed to daylight at room temperature. Separation of the reaction solution by column chromatography on silica gel (eluent benzene/ethyl acetate 10:1) affords—together with small amounts of *(2)*—160 mg (46 %) *(4)* as colorless crystals m.p. 192 °C (after recrystallization from methanol).

Received: June 27, 1977 [Z 773 IE]
German version: Angew. Chem. 89, 659 (1977)

CAS Registry numbers:
(1), 63448-89-5; *(2)*, 63448-90-8; *(3)*, 63448-91-9; *(4)*, 1169-58-0; dimethyl acetylenedicarboxylate, 762-42-5

[1] *M. A. Ogliaruso, M. Romanelli, E. S. Becker*, Chem. Rev. *65*, 261 (1965).
[2] *N. Ishibe, M. Odani, R. Tanuma*, J. Chem. Soc. Perkin Trans. I *1972*, 1203.
[3] The exact stereochemistry has not yet been determined. In investigations on dimeric cyclopentadienone derivatives (*B. Fuchs, B. Pazhenchevsky, M. Pasternak*, Tetrahedron Lett. *1972*, 3051 and references cited therein) the *endo* form has always been confirmed, so most likely the *endo-trans-endo* form is favored over the *exo-trans-exo* form in *(2)*. The *endo-trans-exo* form can be ruled out on the basis of spectroscopic data.

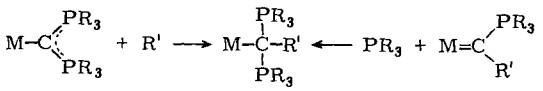
[*] Prof. Dr. W. Ried, Dipl.-Chem. H. Bopp
Institut für Organische Chemie der Universität, Laboratorium Niederrad
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

[4] D. W. Jones, J. Chem. Soc. Perkin Trans. I 1973, 1951, has described isomeric dihydrotetraphenylinden-1-ones.
[5] F. Arndt, P. Nachtwey, J. Pusch, Ber. Dtsch. Chem. Ges. 58, 1633 (1925).
[6] Y. Gaoni, Tetrahedron Lett. 1976, 2167.
[7] L. A. Paquette, L. D. Wise, J. Am. Chem. Soc. 90, 807 (1968).

Bis[trimethylphosphorio(-onio)]methanide, A "Semi-Ylidic" Ligand in Transition Metal Complexes[**]

By *Fritz R. Kreissl, Karl Eberl,* and *Peter Stückler*[*]

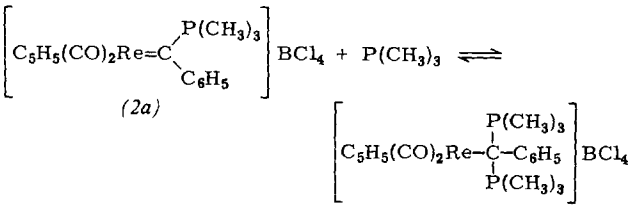
Transition metal complexes of type *(3)* ought to be accessible, either by addition of an organyl to the ylide carbon atom in bis-ylide complexes *(1)*, or by addition of a phosphane to the sp^2 carbon atom in metal-substituted phosphorus ylides *(2)*.



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

M = metal carbonyl moiety

Occurrence of a comparable complex $[(CO)_5W{-}CH(PPh_3)_2]Cl$[1] as intermediate in the reaction of $(CO)_5WC(PPh_3)_2$ with HCl has been postulated but not isolated. We now report the first isolation and characterization of the phenylbis[trimethylphosphorio(-onio)]methanide complex *(3a)*, formed in the reaction of dicarbonyl(η-cyclopentadienyl)[α-(trimethylphosphoranediyl)benzyl]rhenium tetrachloroborate *(2a)*[2] with trimethylphosphane in dichloromethane.



(2a) *(3a)*

The thermolabile compound *(3a)*[3], which crystallizes with one molecule of CH_2Cl_2, is readily soluble in acetone but practically insoluble in ether or pentane. At room temperature it rapidly loses phosphane with regeneration of *(2a)*. The position of the two νCO bands of *(3a)* [KBr: 1885 and 1805 cm^{-1}] indicates a large σ-donor/π-acceptor ratio for the "semi-ylidic ligand". The ^{1}H-NMR spectrum shows four signals of relative intensity 5:2:5:18, which are assigned to the phenyl (δ = 8.03 and 7.53), methylene chloride (5.83), cyclopentadienyl (5.20), and *P*-methyl (2.38) protons; due to ^{31}P-^{1}H coupling the latter signal appears as an $A_9XX'A'_9$ system with $N = 12.0$ Hz[4] and proves the magnetic equivalence of all PCH_3 groups. The constitution of *(3a)* follows from the $^{13}C\{^1H\}$-NMR spectrum (CD_3COCD_3, −40 °C, δ rel. CD_3COCD_3 = 206.5 ppm, coupling constants in Hz): CO 208.01, C_6H_5 139.07 (2.4), 134.33 (7.3), 128.07, 127.64, C_5H_5 85.24, CH_2Cl_2 54.38, PCH_3 16.79 ($N = 61.0$), Re—C 6.16 (22.0 Hz). In contrast to the CO ligands, two aryl signals and the ylide carbon show triplet splitting, which rules out an attack by the phosphane on rhenium and clearly evidences formation of a semi-ylidic ligand. This finding also confirms the AXX′ system with $N = 61.0$ Hz expected for the PCH_3 carbon atom[5]. The $^{31}P\{^1H\}$-NMR spectrum (CD_3COCD_3) shows only one singlet at δ = 36.61, which once again underlines the equivalency and the ylidic character of the two phosphorus atoms.

Procedure

All operations must be carried out in anhydrous (Na, P_4O_{10}) solvents saturated with N_2. A solution of *(2a)*[2] (1.23 g, 2.0 mmol) in dichloromethane (20 ml) is treated with trimethylphosphane (0.25 g, 3.30 mmol) at −78 °C. A colorless precipitate is formed. After treatment with 20 ml ether and 20 ml pentane the supernatant liquor is decanted off and the residue washed with 5 × 10 ml pentane and 5 × 10 ml ether. Removal of solvent in a high vacuum (−78 °C, 48 h) furnishes colorless crystals; yield *ca.* 1.2 g (86 %).

Received: June 27, 1977 [Z 772 IE]
German version: Angew. Chem. 89, 657 (1977)

CAS Registry numbers:
(2a), 63428-44-4; *(3a)*, 63428-42-2; $P(CH_3)_3$, 594-09-2; ^{13}C, 14762-74-4

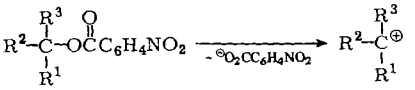
[1] W. C. Kaska, D. K. Mitchell, R. F. Reichelderfer, J. Organomet. Chem. 47, 391 (1973).
[2] F. R. Kreissl, P. Stückler, E. W. Meinecke, Chem. Ber., in press; F. R. Kreissl, P. Friedrich, Angew. Chem. 89, 553 (1977); Angew. Chem. Int. Ed. Engl. 16, 543 (1977).
[3] The corresponding manganese compound was prepared in the same way.
[4] R. K. Harris, Can. J. Chem. 42, 2275 (1964).
[5] D. A. Redfield, J. H. Nelson, L. W. Cary, Inorg. Nucl. Chem. Lett. 10, 727 (1974).

[*] Dr. F. R. Kreissl [+], Dipl.-Chem. K. Eberl, Dr. P. Stückler
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)
[+] Author to whom correspondence should be addressed.
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Steric Enhancement of Chemical Reactivity. The Molecular Structure of Tris(*tert*-butyl)methyl *p*-Nitrobenzoate

By *Pei-Tak Cheng, S. C. Nyburg, Chacko Thankachan,* and *Thomas T. Tidwell*[*]

Significant steric accelerations have been observed both in reactions leading to formation of carbenium ions and in fragmentations to free radicals. Examples include carbenium ion formation by the solvolysis of *p*-nitrobenzoate esters or chlorides, and free radical formation from peresters, diazenes, and hexasubstituted ethanes[1–3]. Bulky substituents on these



reactants lead to rate accelerations that are sometimes quite large and the origin of these accelerations has been the subject of considerable discussion.

[*] Prof. Dr. T. T. Tidwell, Dr. P.-T. Cheng, Prof. Dr. S. C. Nyburg, C. Thankachan
Department of Chemistry, University of Toronto
Toronto, Ontario M5S 1A1 (Canada)

The rate enhancing factor which originally received the most attention was the mutual repulsion of the bulky groups R^1, R^2, R^3 in the ground state ("*B*ack-strain" effect) assumed to be relieved as the central carbon approached a trigonal geometry in the transition state. More recently it has been emphasized that as the bond to the leaving group lengthens in the transition state the repulsion between the alkyl groups and the leaving group ("*F*ront-strain" effect)[3a] will also be reduced; this may have major effects on the reactivity both in carbonium ion and free radical formation, but direct evidence for this phenomenon has so far not been obtained.

We have now determined the molecular structure of tris(*tert*-butyl)methyl *p*-nitrobenzoate *(1)* by X-ray crystallography, which vividly demonstrates the effects of both *B*- and *F*-strain (Fig. 1).

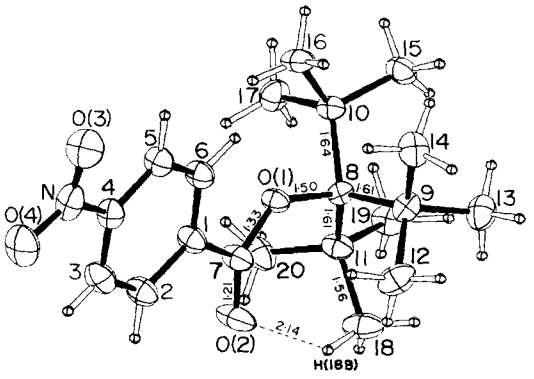


Fig. 1. ORTEP drawing of *p*-$NO_2C_6H_4C(O)OC[C(CH_3)_3]_3$ with bond distances given in Ångstroms (the average C—Me distance is 1.55 Å).

The crowding of the *tert*-butyl groups results in lengthening of the C8—C bonds to an average value of 1.62 Å, opening of the C—C8—C angles to an average value of 114°, and closing of the O—C8—C angles to an average value of 105°. There is also steric interference between the *tert*-butyl groups and the *p*-nitrobenzoate moiety, as evidenced by the H18B—O2 distance of 2.14 Å and the H16A—H6 distance of 2.20 Å. This interaction opens the C11—C8—O angle to 112.5°, whereas the other C—C8—O angles are 98.7 and 102.6°[4]. The C—O1—C angle is also opened to 132.8° by this crowding.

The bond angles of *(1)*, tris(*tert*-butyl)methane *(2)*[5], bis(*tert*-butyl)methyl oxalate *(3)*[6a], and bis(*tert*-butyl)methane *(4)*[6b] are listed in Table 1 for comparison.

Two competing effects may be envisaged to vary the relative geometry around the central carbon atoms of *(1)* and *(2)*: The increased steric pressure of the *p*-nitrobenzoate group in *(1)* will tend to compress the C—C—C angles, while the enhanced electronegativity of the oxygen in *(1)* would tend to increase the p character in the carbon orbital and hence increase these angles. The result of these competing effects for *(1)* is a 3.0° increase in the average X—C8—C angles, and a 2.2° decrease in the average C—C8—C angles.

Molecular mechanics has been used to calculate the geometries of the hydrocarbons *(2)* and *(4)*[5b,6b], and shows promise in predicting reaction rates of *p*-nitrobenzoates, chlorides, and peresters[3,7]. However, so far these methods have utilized hydrocarbons to simulate the reactants and fully formed intermediates with an sp^2 radical or cationic center to simulate the transition state. But, as the present study shows, ground state interactions between the leaving group and the rest of the molecule must also be taken into consideration.

Received: June 20, 1977 [Z 774 IE]
German version: Angew. Chem. 89, 658 (1977)

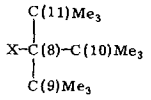
CAS Registry numbers:
(1), 20818-90-0; *(2)*, 35660-96-9; *(3)*, 53074-75-2; *(4)*, 1070-87-7

[1] *P. D. Bartlett, T. T. Tidwell*, J. Am. Chem. Soc. *90*, 4421 (1968); *T. T. Tidwell*, J. Org. Chem. *39*, 3533 (1974); *J. A. Ernst, C. Thankachan, T. T. Tidwell, ibid. 39*, 3614 (1974); references cited therein.

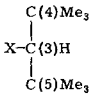
[2] *W. Duismann, R. Hertel, J. Meister, Ch. Rüchardt*, Justus Liebigs Ann. Chem. *1976*, 1820; *W. Duismann, Ch. Rüchardt, ibid. 1976*, 1834; *A. Schulz, Ch. Rüchardt*, Tetrahedron Lett. *1977*, 849; *H.-D. Beckhaus, Ch. Rüchardt*, Chem. Ber. *110*, 878 (1977); references cited therein.

[3] a) *J. Slutsky, R. C. Bingham, P. v. R. Schleyer, W. C. Dickason, H. C. Brown*, J. Am. Chem. Soc. *96*, 1969 (1974); b) *W. Parker, R. L. Tranter, C. I. F. Watt, L. W. K. Chang, P. v. R. Schleyer, ibid. 96*, 7121 (1974); *J. L. Fry, R. C. Badger, ibid. 97*, 6276 (1975); references cited therein.

Table 1. Comparative bond angles of tris(*tert*-butyl)methyl and bis(*tert*-butyl)methyl derivatives.



(1), X = $O_2CC_6H_4NO_2$
(2), X = H



(3), X = $O_2C_2O_2CHtBu_2$
(4), X = H

	(1)	*(2)*		*(3)*	*(4)*
X—C8—C9	102.6	101.6 [a]	X—C3—C4	105.8 [a]	112.1 [a]
X—C8—C10	98.7		C4—C3—C5	124.0 [a]	128.0 [a]
X—C8—C11	112.5				
	104.6 [a]				
C9—C8—C10	113.8	116.0 [a]			
C9—C8—C11	115.4				
C10—C8—C11	112.1				
	113.8 [a]				

[a] Average value.

[4] Cf. bond angles and bond lengths in *tert*-butoxy ester groups: C—C—C 112, O—C—C 107°; O—C 1.48, C—C 1.52 Å [*M. Cesari, L. D'Ilario, E. Giglio, G. Perego*, Acta Crystallogr. *B31*, 49 (1975); references cited therein].

[5] a) *H. B. Bürgi, L. S. Bartell*, J. Am. Chem. Soc. *94*, 5236 (1972); b) *ibid. 94*, 5239 (1972).

[6] a) *G. Adiwidjaja, J. Voss*, Chem. Ber. *109*, 761 (1976); b) *L. S. Bartell, W. F. Bradford*, J. Mol. Struct. *37*, 113 (1977).

[7] *R. C. Bingham, P. v. R. Schleyer*, J. Am. Chem. Soc. *93*, 3189 (1971).

Synthesis of Perdeuteriobenzo[*a*]pyrene[**]

By *Josette C. Seibles, Don M. Bollinger,* and *Milton Orchin*[*]

Benzo[*a*]pyrene is one of the most extensively studied chemical carcinogens[1]. There is substantial evidence implicating the electronically excited states of this and other polynuclear aromatic hydrocarbons in the initiation of the neoplastic process[2, 3]. When the hydrogens of aromatic hydrocarbons are replaced by deuterium, the photophysical properties are affected[4]. Perdeuteriated polycyclic arenes may thus be employed to test those hypotheses of chemical carcinogenesis which invoke the intermediacy of electronic excited states[5]. In one such study it was found that perdeuterio-7,12-dimethylbenz[*a*]anthracene was approximately twice as carcinogenic as the undeuterated compound[3].

Perdeuterated polycyclic arenes are currently prepared by two quite different procedures[6]. A suspension of the arene in D_2O is heated in the presence of reduced platinum in an autoclave at about 350 °C for several days, or, the exchange can be achieved in a homogeneous catalytic system. In the latter procedure the arene is dissolved in [D_6]-benzene, the exchange catalyst $C_2H_5AlCl_2$ is added and the solution is heated at about 90 °C for about 7 days[7]. In our procedure, the homogeneous exchange with [D_6]-benzene is achieved in 6 h using $AlBr_3$ as a catalyst.

Aluminum tribromide is vacuum sublimed and stored under nitrogen. To a 5 ml glass ampoule are added 2 ml of [D_6]-benzene and 1 µl of pure bromine. Approximately 20 mg of freshly sublimed $AlBr_3$ is added (in a dry box) to the preweighed reddish-orange solution in the ampoule, whereupon the solution turns yellow. The ampoule is capped and removed from the dry box, cooled in dry ice/acetone and flame sealed. The sealed ampoule is then heated (stirring is not necessary) in an oil bath in which it is immersed to about the liquid content level at 100 °C for 2 hours. The ampoule is opened (in a dry box) and its contents transferred by Pasteur pipette or syringe to a second 5 ml ampoule containing 100 mg of benzo[*a*]pyrene. A deep red color develops. The ampoule is sealed as before and heated in an oil bath without stirring at 110 °C for 6 h. The ampoule is cooled, opened, and 4—5 drops of distilled water added. The benzene layer is removed and transferred to a small round bottom flask. The reaction flask is washed several times with small additional amounts of benzene and the combined benzene solution evaporated to dryness *in vacuo*. The brown-yellow residue is transferred to a sublimation apparatus and vacuum sublimed. The light yellow sublimate is removed from the cold finger with a few ml of acetone and the acetone solution evaporated by a stream of nitrogen. The residue (87 mg) consist of pure benzo[*a*]pyrene containing 94.7 atom percent deuterium.

The deuterium content was determined by low voltage (7 eV) mass spectrometry using a Hitachi Perkin Elmer RMU7 mass spectrometer coupled with a VG Data System adapted to a PDP8 computer. Appropriate precautions to account for isotopic composition[8] were taken and analysis of the data (Amdahl 470 computer) afforded both atom percent and mole percent deuterium incorporation. The rate data (Table 1) indicate that six hours is probably the optimum time at 110 °C for maximum ^2H incorporation and minimum tar formation. These data were obtained by using a separate sample for each time interval. Using essentially the same procedure we also have prepared perdeuterated benz[*a*]anthracene, pyrene, chrysene, perylene, fluoranthene, carbazole, and triphenylene.

Further work is in progress to determine the rates of deuteration and dedeuteration at the various positions in benzo[*a*]pyrene.

Received: June 27, 1977 [Z 776 IE]
German version: Angew. Chem. *89*, 667 (1977)

CAS Registry numbers:
Perdeuteriobenzo[*a*]pyrene, 63466-71-7; [D_6]-benzene, 1076-43-3; benzo[*a*]-pyrene, 50-32-8

Table 1. Rate of deuteration of benzo[*a*]pyrene (100 mg; 2 ml C_6D_6; 1 µl Br_2; 20 mg Al_2Br_6 at 110 °C).

Reaction time [min]		5	15	30	60	90	180	360
D-content of product [Atom-%]		2.7	11.1	34.8	66.1	73.7	89.8	94.7
Deuterated species $C_{20}D_xH_{12-x}$								
m/e	*x*							
252	0	69.3	25.0	6.8	4.2	3.0		
253	1	29.1	36.8	7.1	3.5	2.0		
254	2	1.4	23.3	7.6	1.8	1.1		
255	3	0.2	10.7	12.4	1.6	0.6		
256	4		3.4	17.8	1.7	0.5		
257	5			20.3	2.6	0.7		
258	6			15.0	4.6	2.3		
259	7			8.8	8.9	6.2	0.5	
260	8			3.4	16.6	14.1	2.6	0.3
261	9				21.5	23.3	8.8	2.4
262	10				19.6	25.2	22.4	10.6
263	11				10.9	16.7	38.6	34.2
264	12				2.5	4.8	27.1	52.5

[*] Prof. M. Orchin, J. C. Seibles, and D. M. Bollinger
Department of Chemistry, University of Cincinnati
Cincinnati, Ohio 45221 (USA)

[**] We wish to acknowledge: the advice of Dr. *Lawrence Seibles* in setting up the computer program; the National Science Foundation for help (GP-8490) with the purchase of the mass spectrometer; assistance from *Roger Hurst* in the operation of the instrument; and the award of a Fellowship from the National Fellowships Fund to J. C. S.

[1] Committee on Biologic Effects of Atmospheric Pollutants: Particulate Polycyclic Organic Matter. National Academy of Sciences, Washington 1972.

[2] *H. H. Seliger, J. P. Hamman,* J. Phys. Chem. *80*, 2296 (1976); *J. P. Hamman, H. H. Seliger,* Biochem. Biophys. Res. Commun. *70*, 675 (1976); *E. Cavalieri, M. Calvin,* Photochem. Photobiol. *14*, 641 (1971); *R. H. Steele, L. C. Cusachs, S. P. McGlynn,* Int. J. Quantum Chem. Symp. *1S*, 179 (1967); *L. Santamaria, G. G. Giordano* in *F. Urbach:* Biological Effects of UV Radiation. Pergamon, New York 1969, p. 569 ff.; *L. Santamaria, G. G. Giordano, M. Alfisi, F. Cascione,* Nature *210*, 824 (1966); *S. S. Epstein, M. Small, H. Falk, N. Mantel,* Cancer Res. *24*, 855 (1964).

[3] *N. P. Buu-Hoi, N. B. Giao,* Naturwissenschaften *58*, 371 (1971).

[4] *C. H. Hutchison, B. W. Mangum,* J. Chem. Phys. *32*, 1261 (1960); *M. R. Wright, R. P. Frosch, G. W. Robinson, ibid. 33*, 934 (1960); *G. D. Johnson, L. M. Logan, I. G. Ross,* J. Mol. Spectrosc. *14*, 198 (1964); *G. M. Breuer, E. K. C. Lee,* J. Chem. Phys. *51*, 3615 (1969); *R. Benson, N. E. Geactinov, ibid. 60*, 3251 (1974); *J. B. Birks, T. D. S. Hamilton, J. Najbar,* Chem. Phys. Lett. *39*, 445 (1976); *J. C. Miller, K. U. Breakstone,*

J. S. Meek, S. J. Strickler, J. Am. Chem. Soc. 99, 1142 (1977); J. L. Charlton, B. R. Henry, J. Mol. Spectrosc. 55, 420 (1975).
[5] A. U. Khan, M. Kasha, Trans. Ann. N. Y. Acad. Sci. 171, 24 (1970); N. P. Buu-Hoi, S. S. Sung, Naturwissenschaften 57, 135 (1970); S. S. Sung, N. P. Buu-Hoi, C. R. Acad. Sci. C 270, 2052 (1970); J. B. Birks, Nature 190, 232 (1961); L. C. Cusachs, R. H. Steele, Int. J. Quantum Chem. Symp. 1S, 175 (1967).
[6] For a review see: M. Orchin, D. M. Bollinger, Struct. Bonding 23, 167 (1975).
[7] M. A. Long, J. L. Garnett, R. F. W. Vining, J. Chem. Soc. Perkin Trans. II, 1298 (1975).
[8] K. Biemann: Mass Spectrometry. Organic Chemical Applications. McGraw-Hill, New York 1962, Chapter 5.

Radical Cation of [2.2](9,10)Anthracenophane as a Model for Dimeric Anthracene Radical Cations[**]

By *Fabian Gerson, Gerd Kaupp,* and *Hiroaki Ohya-Nishiguchi*[*]

Oxidation of benzenoid hydrocarbons affords under certain conditions dimeric radical cations in which the π-spin population is evenly distributed between two equivalent aromatic moieties[1-3]. The most reasonable suggestion for the unknown structure of such paramagnetic species would be that the two π-systems involved lie in parallel planes, one above the other. Since no inclusion of solvent molecules is expected, the interplanar distance should amount to *ca.* 3 Å.

Suitable models for the dimers in question are therefore cyclophanes of D_{2h} symmetry, a distinct favorite being [2.2](9,10)anthracenophane *(1)*[4]. This compound not only contains two nearly parallel anthracene moieties in an essentially eclipsed arrangement and with an average distance of 3 Å[5], but it also readily forms a relatively stable radical cation $(1)^{\oplus\cdot}$. The ESR spectrum of such a radical cation is shown in Figure 1, along with that of the radical anion $(1)^{\ominus\cdot}$. The pertinent proton coupling constants are listed in Table 1, where they are compared with the analogous data for the radical ions and dimeric cations of anthracene *(2)* and its 9,10-dimethyl derivative *(3)*[2,3,6].

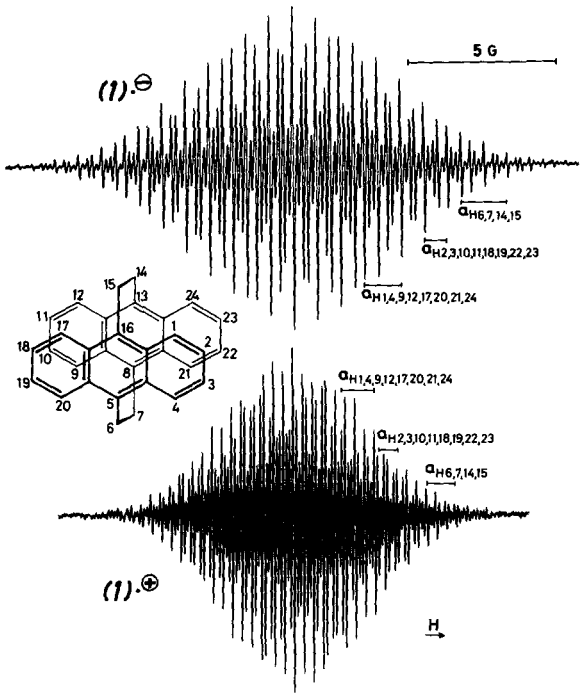


Fig. 1. ESR spectra of the radical ions of [2.2](9,10)anthracenophane *(1)*. Top: anion $(1)^{\ominus\cdot}$. Solvent: DME; counterion: $K^{\oplus}$; −10°C. Bottom: cation $(1)^{\oplus\cdot}$. Solvent: CH_3NO_2/CF_3COOH (*ca.* 10%)/$(CF_3CO)_2O$ (*ca.* 5%); counterion: $CF_3COO^{\ominus}$; +10°C.

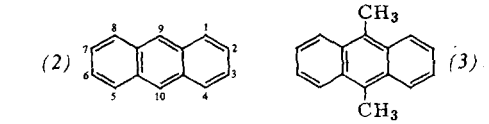


Table 1. Proton coupling constants (G) for the radical ions of [2.2](9,10)anthracenophane *(1)*, anthracene *(2)* and 9,10-dimethylanthracene *(3)*, in addition to those for the dimeric radical cations of *(2)* $[(2)_2^{\oplus}]$ and *(3)* $[(3)_2^{\oplus}]$.

Position:	1, 4, 9, 12, 17, 20, 21, 24	2, 3, 10, 11, 18, 19, 22, 23	6, 7, 14, 15	Ref.
$(1)^{\ominus}$	1.26	0.78	1.56 [a]	[7a]
$(1)^{\oplus}$	1.10	0.65	0.98 [a]	
Position:	**1, 4, 5, 8**	**2, 3, 6, 7**	**9, 10**	**Ref.**
$(2)^{\ominus}$	2.74	1.51	5.34	[2]
$(2)^{\oplus}$	3.08	1.38	6.50	[2]
$(2)_2^{\oplus}$	1.42	0.71	3.25	[2]
$(3)^{\ominus}$	2.90	1.52	3.88 [b]	[6]
$(3)^{\oplus}$	2.54	1.19	8.00 [b]	[6]
$(3)_2^{\oplus}$	1.22	0.66	3.51 [c]	[3]

[a] Eight methylene protons. [b] Six methyl protons. [c] Twelve methyl protons.

Assignment of the values 1.56 and 0.98 G to the eight equivalent methylene protons in $(1)^{\ominus}$ and $(1)^{\oplus}$, respectively, has been confirmed by the studies of the radical ions produced from [2.2](9,10)anthracenophane deuterated in all aromatic positions $(1-d_{16})$ (Fig. 2).

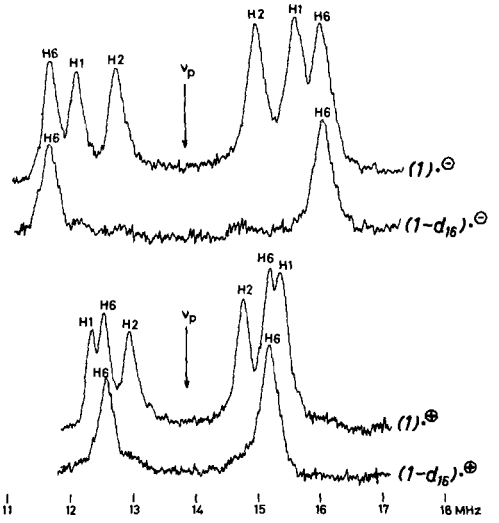


Fig. 2. ENDOR spectra of the radical ions of [2.2](9,10)anthracenophane *(1)* and its ring deuterated derivative $(1-d_{16})$. Top: anions $(1)^{\ominus\cdot}$ and $(1-d_{16})^{\cdot\ominus}$. Solvent: DME; counterion: $K^{\oplus}$; −80°C. Bottom: cations $(1)^{\oplus\cdot}$ and $(1-d_{16})^{\cdot\oplus}$. Solvent: CH_2Cl_2/CF_3COOH (*ca.* 10%)/$(CF_3CO)_2O$ (*ca.* 5%); counterion: $CF_3COO^{\ominus}$; −90°C. ν_p = free proton frequency.

The experimental finding that the coupling constants of the ring protons in $(1)^{\oplus\cdot}$, 1.10 and 0.65 G, strongly resemble the corresponding values in $(2)_2^{\oplus}$ and, in particular, those

[*] Prof. Dr. F. Gerson, Dr. H. Ohya-Nishiguchi
Physikalisch-chemisches Institut der Universität
Klingelbergstrasse 80, CH-4056 Basel (Switzerland)
Doz. Dr. G. Kaupp
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

[**] This work was supported by the Swiss National Foundation (Project 2.523.76) and by the Fonds der Chemischen Industrie.

in $(3)_2^{\oplus}$ points to almost identical π-spin distributions. Moreover, this result indicates that the structures of $(1)^{\cdot\oplus}$ and of both dimeric radical cations are also similar, since markedly differing spatial arrangements of the two anthracene-π-systems would lead to large differences in the coupling constants of the ring protons. (Cf., *e.g.*, Ref. [7]). Thus, the values presented in Table 1 provide an experimental support for the structures of $(2)_2^{\oplus}$ and $(3)_2^{\oplus}$ in which the two aromatic moieties are in an essentially eclipsed position and with an interplanar distance of *ca.* 3 Å.

It is noteworthy that the coupling constant of the methylene protons in $(1)^{\cdot\oplus}$ is considerably smaller than in $(1)^{\cdot\ominus}$, this decrease being presumably due to different conformational preferences.

Experimental

[2.2](9,10)Anthracenophane *(1)* was prepared according to a slightly modified[8] procedure of *Golden*[4]. The synthesis of the hexadecadeuterio derivative $(1-d_{16})$ started with perdeuterioanthracene which was converted into 1,2,3,4,5,6,7,8-octadeuterio-9,10-bis(chloromethyl)anthracene by the method of *Miller et al.*[9]. The latter compound yielded $(1-d_{16})$ in a reaction analogous to that described for *(1)*[4, 8].

The radical anion $(1)^{\cdot\ominus}$ was produced by reduction of *(1)* with potassium in 1,2-dimethoxyethane (DME), while the radical cation $(1)^{\cdot\oplus}$ resulted from oxidation of *(1)* in a mixture containing methylene chloride or nitromethane, trifluoroacetic acid (*ca.* 10%), and its anhydride (*ca.* 5%).

Received: July 4, 1977 [Z 780 IE]
German version: Angew. Chem. *89*, 666 (1977)

CAS Registry numbers:
(1), 5672-97-9; $(1)^{\cdot\ominus}$, 34819-23-3; $(1-d_{16})^{\cdot\ominus}$, 63533-44-8; $(1)^{\cdot\oplus}$, 63569-05-1; $(1-d_{16})^{\cdot\oplus}$, 63598-03-8; $(2)^{\cdot\ominus}$, 34509-92-7; $(2)^{\cdot\oplus}$, 34512-28-2; $(2)_2^{\oplus}$, 63528-16-5; $(3)^{\cdot\ominus}$, 34512-39-5; $(3)^{\cdot\oplus}$, 34526-95-9; $(3)_2^{\oplus}$, 63528-15-4; perdeuterioanthracene, 1719-06-8; 1,2,3,4,5,6,7,8-octadeuterio-9,10-bis(chloromethyl)-anthracene, 63528-36-9

[1] *I. C. Lewis, L. S. Singer*, J. Chem. Phys. *43*, 2712 (1965); *H. van Willigen, E. de Boer, J. T. Cooper, W. F. Forbes, ibid. 49*, 1190 (1968); *W. F. Forbes, J. T. Cooper*, Can. J. Chem. *46*, 1158 (1968); *T. C. Chiang, A. H. Reddoch*, J. Chem. Phys. *52*, 1371 (1970).
[2] *O. W. Howarth, G. K. Fraenkel*, J. Am. Chem. Soc. *88*, 4514 (1966); J. Chem. Phys. *52*, 6258 (1970).
[3] *F. Gerson, H. Ohya-Nishiguchi*, unpublished results.
[4] *J. H. Golden*, J. Chem. Soc. *1961*, 3741.
[5] Such a distance is indicated by molecular models of *(1)* and the X-ray structural data for [2.2]paracyclophane: *K. Longsdale, H. J. Milledge, K. V. Krishna Rao*, Proc. Roy. Soc. A *255*, 82 (1960).
[6] *J. R. Bolton, A. Carrington, A. D. McLachlan*, Mol. Phys. *5*, 31 (1962).
[7] a) *F. Gerson, W. B. Martin, Jr., Ch. Wydler*, J. Am. Chem. Soc. *98*, 1318 (1977); b) *J. Bruhin, F. Gerson, W. B. Martin, Jr., Ch. Wydler*, Helv. Chim. Acta, in press.
[8] *G. Kaupp*, Liebigs Ann. Chem. *1973*, 844.
[9] *M. W. Miller, R. W. Amidon, P. O. Tawney*, J. Am. Chem. Soc. *77*, 2845 (1955).

An Olefin with Unusually Large C—C=C Angles[**]

By *Otto Ermer*[*]

Experimental evaluation of the range over which the potential functions of force field calculations are valid[1] requires the investigation of severely strained molecules. We report here on the results of a crystal structure analysis of 2,2,5,5-tetramethyl-7,8;9,10-dibenzobicyclo[4.2.2]deca-3,7,9-triene *(1)* [Fig. 1a, b], a compound with high angle strain.

[*] Dr. O. Ermer
Abteilung für Chemie der Universität
Universitätsstrasse 150, D-4630 Bochum (Germany)

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

Calculations have shown that unsubstituted all-*cis*-bicyclo[4.2.2]deca-3,7,9-triene has an unusually large C—C=C angle of 137.8° at the double bond C(3)—C(4)[2]. For the 2,2,5,5-tetramethyl derivative *(2)* [Fig. 1c] a still somewhat higher value of 138.9° is calculated which exceeds the corresponding reference angle of 122.3° by 16.6°. The favored calculated conformations of these two olefins show C_{2v}-symmetry and not C_s-symmetry corresponding to a conformation *(3)* [Fig. 1d] as might be concluded from the consideration of Dreiding models.

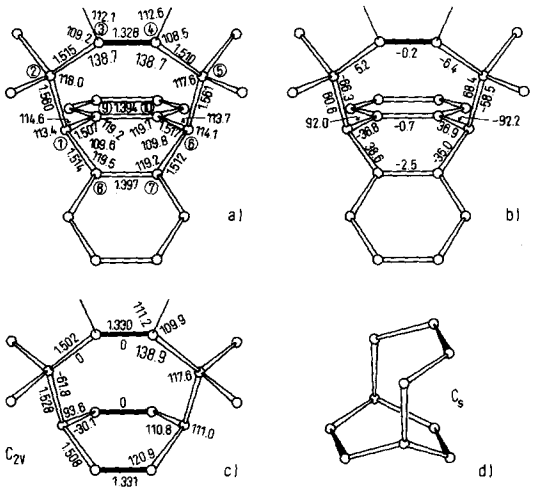


Fig. 1. a) Observed bond lengths [Å] and angles [°] and b) torsion angles [°] for the bicyclodecatriene framework of *(1)*; estimated average standard deviations: CC 0.003 Å, CCC 0.2, HCC 1.1, CCCC 0.4°. c) Calculated geometry of *(2)*. Distances and torsion angles are shown on the left-hand side of the diagram and bond angles on the right-hand side; corresponding information for the very similar geometry of the unsubstituted bicyclo[4.2.2]decatriene is given in [2]. d) Conformation *(3)* of bicyclodecatriene with favorable bond angles yet unfavorable torsion angles. *(3)* does not correspond to a potential energy minimum.

The crystal structure analysis of the dibenzo derivative *(1)* was performed in order to check the results of our force field calculations. The experimental results are of general interest as both our force field and those of other authors contain quadratic angle deformation potentials without anharmonicity corrections[1] whose suitability for the description of such large angle deformations as in the present case is questionable. The presence of the two benzene rings in *(1)* does not significantly impair the comparison between experimental and calculated results (see below).

Crystal data of *(1)*[3]: $a=9.132(5)$, $b=9.360(5)$, $c=12.914(6)$ Å; $\alpha=112.02$, $\beta=91.17(3)$, $\gamma=122.32(3)°$; space group $P\bar{1}$; $Z=2$. The intensities of 2997 independent reflections were measured on a Nonius three-circle diffractometer ($0.098\,Å^{-1}<\sin\theta/\lambda<0.617\,Å^{-1}$; graphite monochromator, MoKα-radiation, $\lambda=0.71069$ Å). A structural model was derived from a sharpened Patterson function of the crystal. 2239 reflections with $F_o>3\sigma(F_o)$ were used for the refinement of the carbon atoms (anisotropic temperature factors). The hydrogen atoms were refined with fixed carbon atom parameters excluding the reflections with $\sin\theta/\lambda>0.45\,Å^{-1}$ [1073 reflections; common isotropic temperature factors for the methyl hydrogen atoms (3.2 $Å^2$) and the remaining hydrogen atoms (1.4 $Å^2$)]. The final, conventional *R*-value was 0.048. Important structural parameters are given in Figure 1.

In the crystal, *(1)* has approximate C_{2v}-symmetry, although there are significant differences which tend towards a geometry analogous to *(3)* (cf. torsion angles in Fig. 1b). These differences could be due to crystal packing forces since they occur

mainly along the normal coordinate of the lowest calculated vibrational frequency of *(2)*[2] which amounts to only 51 cm^{-1}. The C—C=C angles at the planar, olefinic double bond of *(1)* are both 138.7° (Fig. 1a); to the best of our knowledge, these are the largest angles of this kind observed so far. The neighboring H—C=C and H—C—C angles (112 and 109°, respectively) are compressed accordingly. The length of the severely deformed double bond is normal (1.328 Å). The calculated results for *(2)* agree satisfactorily with these experimental findings (Fig. 1).

It is well known that, combined with excessive thermal motion parameters, apparent shortenings of bond lengths and increases of bond angles may result from crystal structure analyses. The large bond angles observed in the present case are not due to such an effect as is evident from the normal bond lengths and thermal parameters; the largest eigenvalue of the thermal motion tensors of C(2) to C(5) amounts to 4.8 $Å^2$.

The main reason for the approximate (exact in the calculations) C_{2v}-symmetry of the bicyclodecatriene framework lies in its favorable torsion angles as compared with conformation *(3)* which contains two eight-membered rings with unfavorable boat and chair conformations[2]. The severe opening of the two C—C=C angles and the less pronounced widening of the C—C—C ring angles at the quaternary carbon atoms are a consequence of the fact that the atoms C(1) to C(6) form an almost planar (exactly planar in the calculations) hexagon in which the olefinic double bond faces the long side C(1)...C(6).

A comparison between Figs. 1a, b and Fig. 1c, as well as the results from force field calculations for *(2)* with modified potential constants [increased reference lengths for C(7)—C(8) and C(9)—C(10); reduced rotation barrier around the C—C single bonds of the six-membered ring], indicate that the geometry of the olefinic double bond is only very slightly influenced by the fused benzene rings. A more significant influence may be noted for the non-aromatic, six-membered ring which is calculated to be somewhat flatter in *(2)* than that observed in the crystals of *(1)* (Figs. 1b and 1c). The bond lengths C(1)—C(2) and C(5)—C(6) measured for *(1)* exceed the corresponding calculated values for *(2)* by 0.03 Å. However, in view of largely normal non-bonded distances only small repulsive interactions are likely to occur between the benzene rings and the methyl groups.

A combination of energetically favorable changes of torsion angles around C—C single bonds may thus give rise to enormous changes of bond angles. Furthermore, the comparison of experimental and calculated results allows the conclusion that harmonic deformation potentials are useful for the description of relatively large widenings of C—C=C angles of up to about 17°. There are indications[4] that this also holds for similarly large widenings of C—C—C angles. It remains to be shown to what extent in such cases energetic and vibrational properties may be treated with simple, quadratic angle deformation potentials.

Received: June 14, 1977 [Z 778 IE]
German version: Angew. Chem. 89, 665 (1977)

CAS Registry numbers:
(1), 63527-89-9; *(2)*, 63527-90-2

[1] See *e.g. C. Altona, D. H. Faber*, Top. Curr. Chem. *45*, 1 (1974); *O. Ermer*, Struct. Bonding *27*, 161 (1976).
[2] *O. Ermer*, J. Am. Chem. Soc. *98*, 3964 (1976).
[3] *N. C. Yang, J. Libman*, J. Am. Chem. Soc. *94*, 1405 (1972). I thank Dr. *J. Libman*, Rehovot, for providing a sample of *(1)* and Dr. *G. C. Verschoor*, Leiden, for the intensity measurements.
[4] *O. Ermer*, to be published.

Crystal Structure of Barium Disilicide at High Pressures[**]

By *Jürgen Evers, Gilbert Oehlinger*, and *Armin Weiss*[*]

In the course of our high pressure studies on the behavior of disilicides and digermanides MSi_2 and MGe_2 of reactive divalent metals (M = Yb, Ca, Eu, Sr, Ba)[1] a high-pressure (HP)-modification of barium disilicide has been found. This phase is formed when $BaSi_2$ is heated to 1000 °C at 40 kbar in a belt apparatus[2]. On quenching to ambient conditions the HP-modification is storable as a metastable phase in the absence of air and moisture for several months without any noticeable change. Heating to approximately 400 °C at normal pressure (NP) leads to its complete retransformation into the orthorhombic NP-phase[3].

The powder diagram of the HP-phase can be indexed trigonal showing the characteristic sequence of reflections for the $EuGe_2$-type structure[4]. Crystallographic data are listed in Table 1. At low Θ-values very weak superlattice reflections were observed which were neglected in the trigonal indexing. Best agreement between observed and calculated intensities (27 reflections, Mo K_α radiation) was achieved with $z_{Si} = 0.432$; the minimum for the reliability facotr Q_R is flat (Table 2).

Table 1. Comparison of the crystallographic data of the high pressure (HP) and low pressure (NP) modifications of $BaSi_2$.

	HP-Phase	NP-Phase
Symmetry	trigonal	orthorhombic
Space group	D_{3d}^3-P$\bar{3}$m1	D_{2h}^{16}-Pnma (or C_{2v}^9-Pna2_1)
Axes [nm]	$a = 0.4047 \pm 0.0003$ $c = 0.5330 \pm 0.0005$	$a = 0.892 \pm 0.006$ $b = 0.675 \pm 0.006$ $c = 1.157 \pm 0.006$
Cell volume [nm^3]	0.07560	0.6966
Density [g/cm^3]		
exp.	4.2_6	3.54
calc.	4.251	3.68
Number of formula units	1	8
Atomic positions	1 Ba in 1a 2 Si in 2d	4 Ba^1 in 4c, 4 Ba^2 in 4c 4 Si^1 in 4c, 4 Si^2 in 4c, 8 Si^3 in 8d

Table 2. Reliability factor Q_R as a function of the parameter z_{Si} of the silicon atoms.

z_{Si}	0.400	0.425	0.430	0.432	0.434	0.450	0.475	0.500
Q_R	0.12_4	0.07_7	0.07_6	0.07_4	0.07_5	0.08_1	0.09_8	0.11_2

The $EuGe_2$-type structure in disilicides is already known from single crystal investigations on the NP-phase $Ca_{0.5}Sr_{0.5}Si_2$[5]. This type of structure differs from the AlB_2 type mainly with respect to the planarity of the metalloid atom layers; they are corrugated in the $EuGe_2$ type and planar in the AlB_2 type. Planar layers in the HP-phase of $BaSi_2$ would lead to Si—Si distances similar to those found in the HP-modification of $CaSi_2$[1b].

The packing density is about 13% higher in the HP-phase of $BaSi_2$ than in the NP-phase ($(V_{HP} - V_{NP})/V_{NP} = -0.13$). Referred to the elements silicon and barium the volume contraction for the HP-phase is 20%, for the NP-phase 7%. In the NP-phase the silicon atoms form isolated tetrahedra. According to the symmetry of the space group Pnma these tetrahedra are tilted against each other, the Ba-atoms lying

[*] Dr. J. Evers, G. Oehlinger, Prof. Dr. A. Weiss
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

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

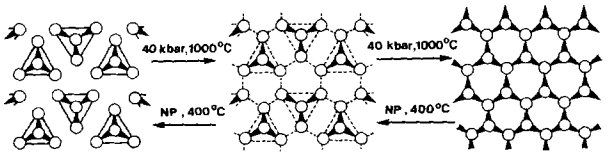


Fig. 1. Reconstruction of isolated Si_4-tetrahedra in NP—$BaSi_2$ into corrugated Si-layers in HP-$BaSi_2$ and *vice versa*.

between them. In the HP-phase the corrugated Si-layers could be reconstructed from the Si_4-tetrahedra by only slight displacements of the silicon atoms as illustrated schematically in Figure 1. In both modifications all the silicon atoms have three nearest Si-neighbors. However the $Si^{Si}Si$ bond angle is increased from approximately 60° in the NP-phase to $111.6°$ in the HP-phase. The Si—Si bond lengths are 0.24_5 nm in the HP-modification. The shortest Ba—Si distance is 0.32_8 nm, the shortest Ba—Ba distance 0.405 nm.

Received: June 23, 1977 [Z 768 IE]
German version: Angew. Chem. 89, 673 (1977)

CAS Registry numbers:
$BaSi_2$, 1304-40-1

[1] a) *J. Evers, A. Weiss*, GdCH-Festkolloquium on the occasion of Prof. *W. Klemm*'s 80th birthday, Münster, February 1976; *J. Evers, G. Oehlinger, A. Weiss*, 3. Eur. Crystallogr. Meeting, Zürich, September 1976; b) J. Solid State Chem. *20*, 173 (1977).
[2] *K.-J. Range, R. Leeb*, Z. Naturforsch. *B30*, 889 (1975).
[3] *K. H. Janzon, H. Schäfer, A. Weiss*, Angew. Chem. 75, 451 (1963); Angew. Chem. Int. Ed. Engl. 2, 393 (1963); Z. Anorg. Allg. Chem. *372*, 87 (1970).
[4] *E. I. Gladyshevskii*, Dopov. Akad. Nauk Ukr. RSR 2, 209 (1964).
[5] *B. Eisenmann, K. H. Janzon, C. Riekel, H. Schäfer, A. Weiss*, Z. Naturforsch. *B22*, 102 (1967).

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Elemental sulfur and its reactions are surveyed by *Roland Mayer*. Sulfur has a pronounced tendency to react with itself and to form S—S bonds. Depending upon the external conditions, either chain or cyclic molecules can arise, which contain between two and over 10^5 sulfur atoms. S—S bonds can be homolyzed (by action of heat, radiation, or chemical energy) or heterolyzed (on nucleophilic attack). In particular, CH acids as well as organo-metallic, -boron, -silicon, -phosphorus, and -sulfur compounds should be able to react with elemental sulfur but knowledge about such reactions is, in some cases, limited. Among the reactions of elemental sulfur, thermal and base-catalyzed reactions with C—H bonds, reactions with S—H bonds, and base-catalyzed oxidations of C—Cl bonds are described. [Elemental Sulfur and its Reactions in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 33—69; 54 references]

[Rd 962 IE]

The vulcanization of natural and synthetic rubber with sulfur is the topic of a review penned by *M. Porter*. Natural rubber and seven synthetic rubbers can be vulcanized at temperatures between 20 and 200 °C with sulfur or sulfur donors (*e.g.* tetraalkylthiuram disulfide or dithiobismorpholine). Activators (zinc oxide, higher fatty acids, nitrogen bases) and accelerators (derivatives of 2-mercaptobenzothiazole or of a dialkyldithiocarbamidic acid) are usually also required. Analysis of structural modifications occurring on vulcanization is hampered by low concentrations, by the insolubility of the products, and by the difficulty of measuring degrees of crosslinking. Our knowledge about the vulcanization process has therefore been gained principally from studies of the reactions of sulfur and sulfur donors with olefins. [Vulcanization of Rubber in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 71—118; 91 references]

[Rd 963 IE]

Electronic energy transfer processes in organic molecules are reviewed by *N. J. Turro*. The article considers the most important processes which could contribute to an event of the kind

$$D^* + A \rightarrow D + A^*$$

the asterisk denoting an excited state, and the use of such processes to stabilize polymers or render them degradable. [Energy Transfer Processes. Pure Appl. Chem. *49*, 405—429 (1977); 26 references]

[Rd 969 IE]

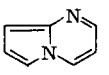
Polymers which become electrical conductors on irradiation represent the theme of an article by *J. M. Pearson*. Such materials have potential uses in electrophotography and for the development of inexpensive photocells for converting the sun's energy into electrical energy. However, only very few of the systems studied so far are active enough to compete with presently used inorganic materials. The reason lies mainly in the poor mobility of the charge carriers in organic polymers. Like the ease of generation of the charge carriers, it depends upon the electronic and morphological structure of the polymers. [Photoconductive Polymers. Pure Appl. Chem. *49*, 463—477; 42 references]

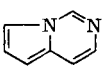
[Rd 972 IE]

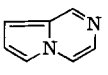
The photooxidation of polymers is surveyed by *F. H. Winslow*. The light-induced oxidative degradation of polyolefins comprises a combination of radical and non-radical processes: singlet oxygen reacts with the polymer to form hydroperoxides

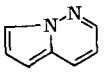
which decompose to radicals and thus lead to Norrish-type chain cleavage reactions. [Photooxidation of High Polymers. Pure Appl. Chem. *49*, 495—502 (1977); 25 references]
[Rd 973 IE]

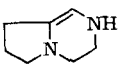
Pyrrolodiazines with a bridgehead nitrogen, *i.e.* compounds of type *(1)* to *(4)*, are treated in a progress report by *D. E. Kuhla* and *J. G. Lombardino*. A systematic account is given of syntheses, reactions, spectral properties, and hydrogenated derivatives. The hexahydro compound *(5)* is of industrial importance as a strongly basic catalyst without nucleophilic


(1)


(2)


(3)


(4)


(5)

properties. [Pyrrolodiazines with a Bridgehead Nitrogen. Adv. Heterocycl. Chem. *21*, 1—63 (1977); 241 references]
[Rd 974 IE]

BOOK REVIEWS

Handbuch der Textilhilfsmittel (Handbook of Textile Auxiliary Agents). Edited by *A. Chwala* and *V. Anger* in collaboration with *Ch. Chwala*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., xvi, 1158 pp., 316 figs., 175 tables, bound, DM 440.—.

The task that the editors set before themselves, namely to bring out a new edition of *Chwala*'s "Textilhilfsmittel", required an entirely new concept for the book. In the interest of readers, an exhaustive treatment of the wide-ranging theme and the more important literature could be mastered only by drawing in competent specialists. This problem has been solved in the new edition in a remarkable manner, with the collaboration with 53 specialist authors.

The arrangement of this Handbook is clear and logical. The introductory chapters give the theoretical principles needed to understand textile auxiliary agents, with particular emphasis on the structural principles and the physicochemical properties of surface-active agents, but also with practical indications of interest to those working in this field. A detailed section is concerned with the structure of natural and synthetic textile fibers, providing a review of their construction and composition as well as of their chemical, physical, and dyeing characteristics. The main part of the book contains individual sections covering the whole spectrum of textile auxiliary agents and their application from the spinning process through intermediate treatments to the final preparation for the customer and the care of textiles. As examples we shall mention only the fiber preparation and coning oils, antistatics, bleaches and bleaching aids, sizes, finishing agents, high grade finishing agents, softeners, hydrophobic and oleophobic agents, optical brighteners, and flame-protection agents. Much space is devoted to dyeing and printing which present a diversity of problems. Special chapters deal with fiber-specific aids, of which we may mention wool protection and carbonizing agents, scouring and mercerizing agents, antimicrobiotics, and pest repellants.

A section on the use of organic solvents in initial preparation and final finishing demonstrates that recent trends are also taken into account, even if they have not yet achieved major importance. It should be specially emphasized that, along with the basic theme of the book—textile auxiliary agents and their application—special problems are also treated; for example, there are chapters on biological degradation of surfactants and on analysis; this underlines the importance of ecological knowledge for the use of textile finishing aids.

The description of an efficient system and its use with reference to a commercial product from a company with which the author is closely connected should generally be avoided in favor of an objective treatment. However, a review of the most important commercial products and their manufacturers is of value.

Treatment of many auxiliary agents, *e.g.* surfactants, in several sections, usually considered as duplication of effort, proves on closer examination to be a didactic advantage.

The literature references collected at the end of the individual chapters make it possible for interested readers to gain entry into primary literature. In a new edition it would be useful to consider the patent literature in each chapter; this should be attempted not only on the grounds of homogeneity but also because of the importance of patents as sources of information.

The publishers should be congratulated for the careful and readable printing and satisfactory make-up. The book can be recommended without any reservations.

Helmut Diery [NB 383 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Liquid Chromatography in Practice. By *P. A. Bristow*. hetp, Cheshire 1977. 265 pp., paper, £ 10.20.—ISBN 0-9504833-0-3

Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel. Edited by *R. Wegler*. Band 5: Herbizide. Springer-Verlag, Berlin 1977. xxi, 752 pp., bound, DM 198.—.—ISBN 3-540-08178-X

Blutzuckersenkende Sulfonamide. Standort der modernen Substanzen im Vergleich zu älteren Antidiabetika. By *E. Haupt*. From the series "reprotext". Verlag Chemie, Weinheim 1977. 169 pp., paper, DM 34.—.—ISBN 3-527-25744-6

Ligand Field Energy Diagrams. By *E. König* and *S. Kremer*. Plenum Press, New York 1977. viii, 454 pp., bound, $ 59.40.—ISBN 0-306-30946-7

The Chemical Physics of Surfaces. By *S. R. Morrison*. Plenum Press, New York 1977. xvii, 415 pp., bound, $ 39.50.—ISBN 0-306-30960-2

Encyclopedia of Chemical Processing and Design, Vol. 3: Aluminum to Asphalt, Design. Edited by *J. J. McKetta* and *W. A. Cunningham*. Marcel Dekker, New York 1977. xii, 493 pp., bound, SFrs. 300.— (Subscr.-Price SFrs. 250.—).— ISBN 0-8247-2453-4

Semiempirical Methods of Electronic Structure Calculation. Part B: Applications. Edited by *G. A. Segal*. Vol. 8 of the series "Modern Theoretical Chemistry". Edited by *W. H. Miller, H. F. Schaefer III, B. J. Berne*, and *G. A. Segal*. Plenum Press, New York 1977. xvii, 308 pp., bound, $ 47.40.—ISBN 0-306-33508-5

Thermodynamic Network Analysis of Biological Systems. By *J. Schnakenberg*. Springer-Verlag, Berlin 1977. viii, 143 pp., paper, DM 38.—.—ISBN 3-540-08133-4

Chemistry and Physics of Carbon, Vol. 13. Edited by *Ph. L. Walker* and *P. A. Thrower*. Marcel Dekker, New York 1977. viii, 295 pp., bound, SFr. 107.—.—ISBN 0-8247-6359-9

Synergetics. Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry and Biology. By *H. Haken*. Springer-Verlag, Berlin 1977. xii, 325 pp., bound, DM 72.—.—ISBN 3-540-07885-1

Vibrational Spectra and Structure, Vol. 6. Edited by *J. R. Durig*. Elsevier Scientific Publishing Company, Amsterdam 1977. xiv, 397 pp., bound, Dfl. 146.00.—ISBN 0-444-41588-2

Structure and Bonding. Edited by *J. D. Dunitz, P. Hemmerich, J. A. Inbers, C. K. Jørgensen, J. B. Neilands, D. Reinen*, and *R. J. P. Williams*. Vol. 32: Novel Chemical Effects of Electronic Behaviour. Springer-Verlag, Berlin 1977. iv, 171 pp., bound, DM 62.—.—ISBN 3-540-08014-7

Toxicology of Trace Elements. By *R. A. Goyer* and *M. A. Mehlman*. Vol. 2 of the series "Advances in Modern Toxicology". Edited by *M. A. Mehlman*. Hemisphere Publishing Corporation, Washington/John Wiley & Sons, New York 1977. xiv, 303 pp., bound, $ 31.00.—ISBN 0-470-99049-X

Topics in Applied Physics. Edited by *H. K. V. Lotsch*. Vol. 18: Ultrashort Light Pulses. Edited by *S. L. Shapiro*. Springer-Verlag, Berlin 1977. xi, 389 pp., bound, DM 97.—.— ISBN 3-540-08103-8

Chemistry and Properties of Crosslinked Polymers. Edited by *S. S. Labana*. Academic Press, New York 1977. xiii, 581 pp., bound, $ 29.50.—Proceedings of the ACS Symposium "Chemistry and Properties of Crosslinked Polymers", San Francisco, Aug. 31—Sept. 2, 1976.—ISBN 0-12-432250-3

Prostaglandin Synthesis. By *J. S. Bindra* and *R. Bindra*. Academic Press, New York 1977. xiii, 522 pp., bound, $ 24.00.— ISBN 0-12-099460-7

Advanced Organic Chemistry, Part B: Reactions and Synthesis. By *F. A. Carey* and *R. J. Sundberg*. Plenum Press, New York 1977. xxiii, 521 pp., bound, $ 47.40.—ISBN 0-306-35117-X

Elementary Reaction Kinetics. By *J. L. Latham* and *A. E. Burgess*. Butterworths, London 1977. 3rd Edit., 182 pp., paperback *ca.* £ 2.95.—ISBN 0-408-461020

Principles of Physical Chemistry. By *R. M. Rosenberg*. Oxford University Press, New York 1977. xix, 743 pp., bound, £ 15.75.

Filtration. Principles and Practices, Part I. By *C. Orr*. Vol. 10 of the series "Chemical Processing and Engineering". Edited by *L. F. Albright, R. N. Maddox*, and *J. J. McKetta*. Marcel Dekker, New York 1977. vii, 534 pp., bound, SFrs. 145.—.—ISBN 0-8247-6283-5

Surface Characteristics of Fibers and Textiles, Part II. Edited by *M. J. Schick*. From the series "Fiber Science Series". Edited by *L. Rebenfeld*. Marcel Dekker, New York 1977. xii, 669 pp., bound, $ 34.50.—ISBN 0-8247-6531-1

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone (06201) 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P.O. Box 1260 1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English

Volume 16 · Number 10
October 1977
Pages 663–734

The Electro-Optical Kerr Effect in Conformational Analysis

New analytical methods (10)

By Manuel James Aroney[*]

Birefringence induced in a material by application of an electric field is known as the Kerr effect. The great sensitivity of this property to variations of molecular geometry and environment has made it the basis of a potent method for studying the conformations of molecules. It has, in addition, been effectively applied to investigations of the geometry of solvation and of solute aggregation. An outline is presented of the general technique of measurement of the Kerr effect, the extraction of directed effective polarizabilities of solute molecules and of structural groups, the calculation of theoretical Kerr constants for candidate structures of molecules, and the procedures used to determine solute conformations. The scope and limitations of the method are illustrated by specific conformational problems drawn from the literature. In the case of highly flexible molecules analysis of the measured Kerr constant is inhibited by uncertainties in conformational energy data. This paper is concerned mainly with the specification of detailed conformational features of molecules. Reference is made, however, to the utilization of pulsed orienting fields to study shapes and dimensions of biological macromolecules.

1. Introduction

If a strong, uniform electric field is applied to an aggregation of molecules in the gas or liquid state, a degree of order is imposed through interaction of the permanent and induced electric moments with the field **E**. A statistical equilibrium is attained in which the orienting interactions are counterbalanced by random thermal motion. The molecular system in the field becomes optically anisotropic. The refractive index measured in the direction of the field ($n_{\parallel}$) differs from that perpendicular to the field ($n_{\perp}$) and the substance is said to be birefringent. Experimentally the effect is usually studied by passing through the partly ordered system a beam of monochromatic, plane-polarized light arranged so that the plane of polarization is inclined 45° to **E**. The incident light vector can be regarded as the sum of two components in phase, which are respectively parallel and perpendicular to **E**. Since $n_{\parallel}$ and $n_{\perp}$ are unequal, the light components in these directions traverse the medium at different velocities and emerge out of phase; the light beam is now elliptically polarized (Fig. 1). The phase difference δ in radians is related to the birefringence Δn ($=n_{\parallel}-n_{\perp}$) by the equation

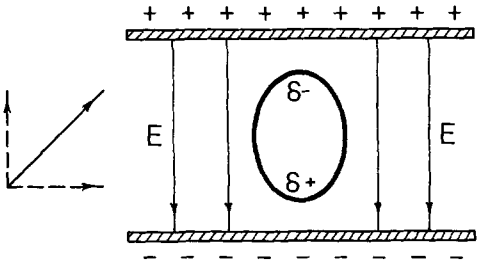


Fig. 1. Plane polarized light entering an "ordered" system of molecules. $n_{\parallel} \neq n_{\perp}$.

$$\delta = 2\pi l(n_{\parallel}-n_{\perp})/\lambda = 2\pi B l E^2 \qquad (1)$$

where l is the length of the light path through the birefringent medium; λ is the wavelength of the light; and B is the "Kerr constant" of the substance. This relation, derived from experi-

[*] Prof. Dr. M. J. Aroney
Department of Inorganic Chemistry, University of Sydney
Sydney, New South Wales 2006 (Australia)

ment, is called Kerr's Law after *John Kerr* who first reported the effect in 1875[1].

2. Measurement of the Kerr Effect

For gases and non-conducting liquids the Kerr constant B can conveniently be determined using the basic experimental arrangement shown in Figure 2[2]. A monochromatic light beam from ML is collimated by a lens L and passed through a polarizing Glan-Thompson prism P to give light polarized 45° to the static electric field E applied across two parallel electrodes of known dimensions in a Kerr cell KC; A is a second Glan-Thompson prism which is crossed with reference to P; PM is a photomultiplier. With the dielectric in the Kerr cell but no field applied, the light emerging from KC remains plane polarized and is absorbed by the analyzing prism A. If a high voltage is applied across KC (*ca.* $10^6\,V\,m^{-1}$ for a non-dipolar, non-conducting liquid such as benzene) the light emerges elliptically polarized; the intensity of light which penetrates the analyzer and is registered on the photomultiplier can be used, in conjunction with the incident light intensity, to determine the phase difference δ. Alternatively, a compensating device C (a mica sheet or a second Kerr cell containing a standard[3]) which causes a known phase change can be inserted between the Kerr cell and the analyzer and used to determine δ. Fuller descriptions of the components are given in ref. [2]. An alternative and highly sensitive method utilizes a quarter wave plate to convert the ellipticity into an optical rotation which is nulled by a Faraday coil arrangement[4]. The measurement of δ and thence B for a substance is normally made using light in the visible region but remote from absorption bands to avoid anomalous dispersion effects. Since B for a substance is dependent on λ [eq. (1)], the wavelength of light used for the measurement should be quoted. Pulsed voltages of short duration are also used to generate orienting fields. Pulsed birefringence techniques are generally less sensitive than static field compensation methods but they are more widely applicable in that they enable studies to be extended to conducting media[2, 5, 6].

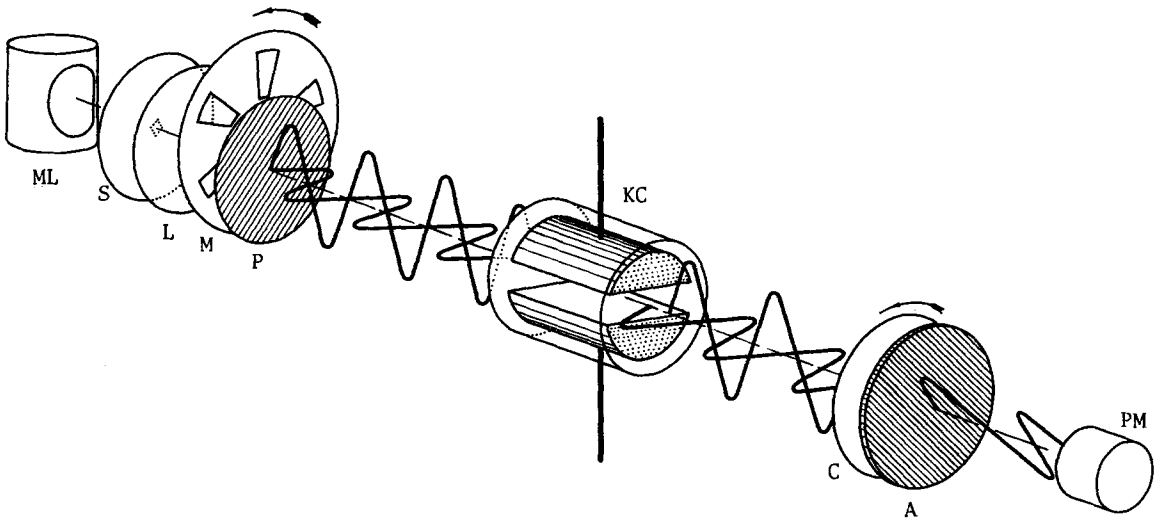


Fig. 2. Apparatus for measurement of the Kerr effect. ML monochromatic light source, S aperture, L lens, M modulator, P polarizer, KC Kerr cell, C compensator, A analyzer, PM photomultiplier.

The Kerr effect of a molecular substance is often expressed as the molar Kerr constant ${}_mK$ which is defined as

$${}_mK = 6\lambda n B M/(n^2+2)^2(\varepsilon_r+2)^2 d \qquad (2)$$

where n is the refractive index, ε_r the relative permittivity, M the molar weight, and d the density. The relation was initially applied to dilute gases. Physically ${}_mK$ is a measure of the difference, per unit field, of molecular refractions[*] $R_\parallel$ and $R_\perp$ measured parallel and perpendicular to the field direction[7]. For molecules in solution in a non-polar solvent the apparent solute molar Kerr constant at infinite dilution, designated ${}_\infty({}_mK_2)$, can be extracted from measurements of B, ε_r, d and n, for a graded series of dilute solutions[7].

3. Theoretical Concepts

3.1. Molecular Polarizability Anisotropy

Any molecule subjected to a uniform static electric field E undergoes deformation of its electrons and small displacements of the atoms relative to one another. A dipole moment **m** is induced in the molecule (additional to the *permanent* moment $\boldsymbol{\mu}$ which it may already possess) and, providing the field is not too great, the magnitude of the induced moment is in direct proportion to that of the applied field intensity.

$$m = \alpha E = (\alpha_E + \alpha_A) E \qquad (3)$$

The constant of porportionality α (*i.e.* the moment induced per unit field) is known as the mean polarizability of the molecule. It is composed of α_E and α_A, the electron and atom polarizabilities, respectively. With optical frequency fields only the electrons are sufficiently mobile to respond to the field and the induced moment now arises almost completely from α_E. The quantity α_E is directly related to the molar electron polarization ${}_EP$ of a substance by the well-known Lorentz-Lorenz equation[8]

$${}_EP = N_A \alpha_E / 3\varepsilon_0 \qquad (4)$$

where the constants N_A and ε_0 refer in turn to Avogadro's number and to the permittivity of a vacuum; ${}_EP$ is estimated

[*] The physical property of molecular refraction is defined by the relation $R_\lambda = (n_\lambda^2 - 1)M/(n_\lambda^2+2)d$. [8]

from refractivity (R_i) wavelength dispersion measurements by extrapolation procedures used to eliminate any atom polarization contribution[9].

The electrons in a molecule are generally not equally polarizable in all directions, *e. g.* the deformability of benzene electrons in the aromatic plane would be expected to be greater than that perpendicular to the aromatic plane. Thus we say that the polarizability of a molecule is *anisotropic* in that it varies with direction with reference to the molecular framework. A molecule may be regarded as having an *ellipsoid of polarizability* defined by the semi-axes b_1, b_2, b_3 in the directions of the principal axes *1*, *2*, and *3*. Thus b_1 is the moment induced by an electric field of unit intensity applied along the *1* axis; similarly b_2 and b_3 are moments induced by unit field along the axes *2* and *3*, respectively. The principal axes are such that one of them corresponds to the direction of maximum polarizability, another to the direction of minimum polarizability, and the three are mutually orthogonal (Fig. 3). The locations of the principal axes can sometimes be deduced from

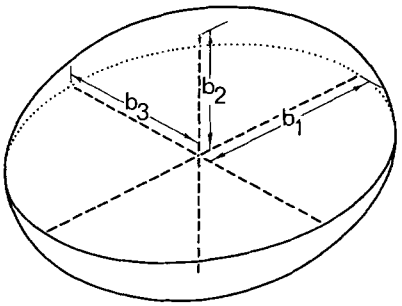


Fig. 3. Molecular polarizability ellipsoid.

symmetry considerations—an axis of symmetry must coincide with one, and a plane of symmetry must contain two, of the principal axes. It follows from eq. (4) that

$$_{E}P = N_A(b_1+b_2+b_3)/9\varepsilon_0 \qquad (5)$$

since α_E is the mean value of b_1, b_2, and b_3.

3.2. Interpretation of the Kerr Effect

The Kerr effect may be explained in terms of a partial orientational ordering by the applied field of molecules which are anisotropically polarizable[10, 11]. Thus the material as a whole becomes optically anisotropic and doubly refracting. Figure 4 shows the preferred molecular orientations for three specific types of interaction: (a) non-polar molecules such as benzene which tend to align themselves with the greatest polarizability axis, and hence the maximum induced moment, parallel to the field; (b) polar molecules with the permanent electric moment μ directed along the major polarizability axis; (c) polar molecules in which μ is located perpendicular to the major axis. Methyl chloride and chloroform are examples of (b) and (c), respectively. Since permanent moments are *ca.* 10^5 times greater than induced moments, the orientative action of a field on a polar molecule is overwhelmingly controlled by the disposition of μ within the molecular framework. This means that B and $_{m}K$ may, for polar molecules, be algebraically positive or negative depending on the location

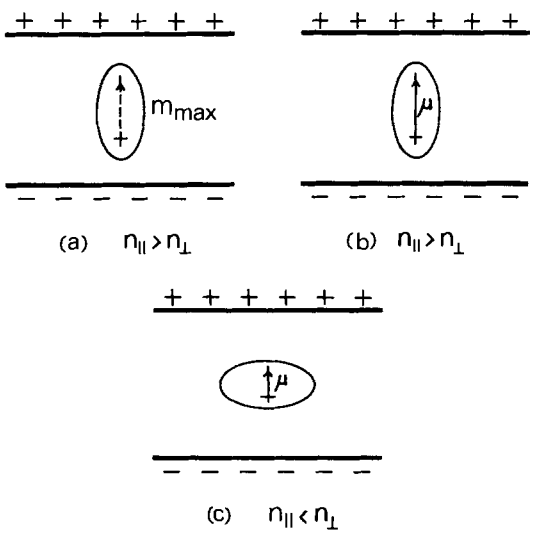


Fig. 4. Orientative action of a uniform electric field on non-polar (a) and polar molecules (b) and (c). For explanation see text.

of μ relative to the polarizability axes. For non-polar molecules the Kerr effect is positive but usually smaller in magnitude than for polar molecules. Of course if the molecules were isotropically polarizable (*i. e.* $b_1 = b_2 = b_3$) then the effect would be zero. Hence it is seen that the magnitude and sign of the Kerr constant must be related to the molecular polarizability anisotropy and to the magnitude and location of the permanent electric moment. Quantitatively this is expressed by eq. (6) which is a modified form[2] of the classical equations of *Langevin* and *Born*.

$$\begin{aligned} {}_{m}K = (N_A/810kT\varepsilon_0)\{({}_{D}P/{}_{E}P)[(b_1-b_2)^2+(b_2-b_3)^2+(b_3-b_1)^2] \\ +(kT)^{-1}[(b_1-b_2)(\mu_1^2-\mu_2^2)+(b_2-b_3)(\mu_2^2-\mu_3^2) \\ +(b_3-b_1)(\mu_3^2-\mu_1^2)]\} \end{aligned} \qquad (6)$$

The molar distortion polarization $_{D}P$ is the sum of the molar electron and atom polarizations $({}_{E}P + {}_{A}P)$[12]. For polar organic substances the ratio $_{D}P/{}_{E}P$ is usually taken as 1.1 which is a satisfactory approximation since the second part of eq. (6) nearly always far outweighs the first. In cases where a more precise knowledge of the ratio is needed, $_{D}P$ is obtained by methods that are standard for dipole moment measurements[12]. The terms μ_1, μ_2, μ_3 are the vector components of the permanent moment along the principal axes *1*, *2*, and *3*, respectively; k is the Boltzmann constant; and T is the absolute temperature. For non-polar molecules the equation is simplified since terms involving μ_1, μ_2, and μ_3 vanish.

The derivation of eq. (6) assumes that polarizability is a linear function of the applied field intensity [(as in eq. (3)]. *Buckingham* and *Pople*[13] have modified the Langevin-Born approach to allow for a field-dependent polarizability:

$$m = \alpha E + \frac{1}{2}\beta E^2 + \frac{1}{6}\gamma E^3 + \cdots \qquad (7)$$

m is the induced moment; α is the normal low field polarizability; β, γ... are *hyperpolarizability* terms which describe the additional (non-linear) effects of strong fields. Both treatments apply strictly to molecules in the gas state at low pressure. The simpler (modified) Langevin-Born interpretation has been extensively used to derive "*effective*" *solute electron polarizabili-*

ties b from ${}_{\infty}({}_{m}K_2)$ measurements in non-polar solvents. Analysis of such data using the Buckingham-Pople approach is prohibitively complex for most molecules. The latter theory does, however, explain the observation of very small positive Kerr constants, attributed to field-induced distortions (γ term), for molecules such as carbon tetrachloride.

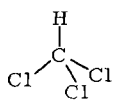
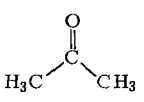
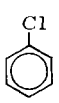
3.3. Principal Polarizabilities of Molecules as Solutes

For molecules such as ammonia, chloroform, or benzene, which have a three- or higher-fold symmetry axis, two of the principal polarizabilities (those in a plane perpendicular to that symmetry axis) are equal and the ellipsoid is one of revolution. In such cases eq. (5) and (6) can be used to solve for b_1, b_2, b_3. In the more general case where $b_1 \neq b_2 \neq b_3$, a third equation is necessary. This can be obtained from Rayleigh light scattering experiments.

If a beam of unpolarized monochromatic light is passed through a system of anisotropically polarizable gas molecules, the light scattered at 90° to the incident light path is imperfectly polarized. The degree of depolarization Δ_u[*] is related to the "molecular anisotropy" δ^2 of the molecules by $\delta^2 = 10\Delta_u/(6-7\Delta_u)$. From Δ_u measurements of solutions may be extracted the solute ${}_{\infty}\delta_2^2$ (at infinite dilution in non-polar solvents). The latter is related, by the derivation of *Le Fèvre* and *Rao*[14], to the effective solute polarizabilities b through eq. (8):

$$ {}_{\infty}\delta_2^2 = [(b_1-b_2)^2+(b_2-b_3)^2+(b_3-b_1)^2]/(b_1+b_2+b_3)^2 \qquad (8) $$

Table 1. Molecular principal polarizabilities [10^{40} b/C m^2 V^{-1}] [a] [b].

Molecule	b_1	b_2	b_3	Ref.
	5.66	4.57	4.57	[15]
	7.4$_9$	10.0	10.0	[14]
	7.80	7.61	5.36	[14]
	8.27	9.89	5.97	[16]
	12.4	12.4	8.2$_8$	[17]
	16.4	14.0	9.1$_3$	[18]

[a] Expressed in SI units; the conversion factor to the c.g.s., e.s.u. system is: 1 C m^2 V^{-1} = 0.8988 × 10^{16} cm^3.
[b] From measurements at $\lambda = 589$ nm.

[*] Δ_u is measured as the ratio of the intensities of the light polarized in a horizontal plane (*i.e.* the plane defined by the incident and scattered beams) to that polarized in a vertical plane.

Eq. (5), (6), and (8) constitute three independent equations only if $\mu \neq 0$. It is implicit also that the symmetry of polar molecules should be such as to allow μ to be located with reference to the principal axes. Some examples of molecular principal polarizabilities so derived are listed in Table 1.

3.4. Polarizabilities of Bonds and Structural Groups

Bonded atom pairs and functional groups are known to have characteristic refractivities and mean polarizabilities[8, 19]. Directional polarizabilities have been attributed to individual bonds and groups and these can be deduced from analysis[8] of experimentally determined principal polarizabilities of molecules of known geometry. A selection of such values is given in Table 2. The term b_L for a bond represents the polarizability along the internuclear (longitudinal) axis; b_T and b_V (transverse and vertical polarizabilities) are normal to this axis. For example, an aliphatic C—C link is axially symmetric so that $b_L \neq b_T = b_V$; for C=O all three polarizabilities are unequal and, in cases like this, b_T is located in the plane of the trigonal carbon valencies with b_V perpendicular to this plane.

Table 2. Bond and group directional polarizabilities [10^{40} b/C m^2 V^{-1}] [a].

Bond or Group (AB)	b_L(AB)	b_T(AB)	b_V(AB)	Bond environment	Ref.
C—H	0.72	0.72	0.72	cyclohexane and related hydrocarbons	[20] [b]
C—C	1.08	0.29	0.29		
C=C	3.12	0.81	0.86	1,1-dichloro-ethylene	[21]
C—N	0.89	0.57	0.57	trimethylamine	[22] [c]
C=O	2.56	1.56	0.51	acetone	[23] [c]
N—H	0.45	0.98	0.98	ammonia	[22] [c]
C—Cl	3.54	2.45	2.45	methyl chloride	[2] [c]
C_{ar}—Cl	4.7	2.2	1.7	chlorobenzene	[2] [c]
C—Br	5.17	3.45	3.45	methyl bromide	[2] [c]
C_{ar}—Br	6.9	2.7	2.4	bromobenzene	[2] [c]
C—C≡N	4.05	1.95	1.95	acetonitrile	[2] [c]
C_6H_5	11.7	11.7	7.5$_5$	benzene	[17] [d]

[a] From data at $\lambda = 589$ nm (1 C m^2 V^{-1} = 0.8988 × 10^{16} cm^3).
[b] *Le Fèvre, Orr,* and *Ritchie* [20] justified the isotropic b(C—H) values as appropriate for this scheme rather than the anisotropic α(C—H) estimates derived from Raman intensity studies of methane in the vapor state [24, 25].
[c] The polarizabilities quoted include, by the method of their derivation, contributions from the unshared electron pairs.
[d] b_L and b_T are the in-plane polarizabilities for the phenyl group.

It has been shown[2, 8] that this scheme of bond and group b values can be used to predict anisotropic polarizabilities and Kerr constants of molecules *providing the data are applied to molecular situations analogous to those from which they were derived.* The bond data are of course not constant throughout all molecular environments, *e.g.* conjugation in the halobenzenes results in C_{ar}—halogen polarizabilities which differ from those of the corresponding methyl halides[18]. In situations where bond polarizabilities are not accessible from Kerr effect measurements, approximate estimates may be obtained from empirical and semi-empirical relationships using atomic and bond dimensions[17, 26], vibration frequencies[27], or δ-function potentials[28].

4. The Kerr Effect Applied to Conformational Studies

The Kerr effect technique has been applied to a wide range of problems of conformation and configuration. In excess of three hundred publications have appeared in the literature on this subject since 1953. Substantive summaries of results are given in ref.[2, 8, 29, 30]. The procedure usually adopted involves measurement of the molar Kerr constant of the substance under investigation as a solute, *i.e.* the ${}_{\infty}({}_{m}K_2)$, and subsequent comparison with theoretical ${}_{m}K$ values computed for possible stereostructures. The approach is similar in principle to that used with dipole moments but the Kerr effect is much more versatile in that its application is not restricted to conformational situations requiring changes of relative disposition of *dipolar* groups. The techniques are often used in a complementary manner. Other physical methods, notably NMR and IR spectroscopy, frequently provide data which facilitate analysis of the Kerr effect through defining and/or limiting the range of conformational possibilities.

4.1. Calculation of Theoretical Molar Kerr Constants

The following data are needed to calculate the molar Kerr constant ${}_{m}K$ of a specific geometric form of a molecule: (a) the anisotropic polarizabilities of all component bonds or groups, (b) the permanent electric moments of all dipolar bonds or groups.

The molecular polarizability for a structure of specified geometry can be computed by additivity of the directed polarizabilities of the component structural units (cf. Table 2). The method may be illustrated with the simple case of an angular molecule A_2B composed of two A—B groups each having the polarizabilities b_L(A—B), b_T(A—B), b_V(A—B) (see Fig. 5). By symmetry the molecular principal axes *1* and *2* can be located as shown in Figure 5; *3* is perpendicular to the A_2B plane.

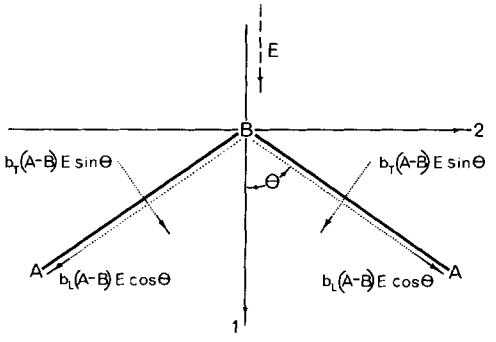


Fig. 5. Moments induced through polarization of the structural groups A—B by an electric field **E** applied in the direction of the axis *1*.

An electric field **E** of unit intensity, imagined to act along the molecular *1* axis has field components $E\cos\theta$ along the longitudinal axis of each A—B bond and moments b_L(A—B)$E\cos\theta$ are induced along these axes. The field has vector components $E\sin\theta$ along the transverse axis of each A—B bond and induces moments b_T(A—B)$E\sin\theta$ along each of these axes. The resultant induced moment for the molecule is $2b_L$(A—B)$\cos^2\theta + 2b_T$(A—B)$\sin^2\theta$ (electric field strength is unity) and this is directed along the *1* axes. Thus we have calculated the molecular b_1 which, by definition, is the moment induced along *1* by unit field acting in that direction. Similarly if the unit field is imagined to apply in turn along the *2* and *3* axes then b_2 and b_3 can be calculated by vector summation of the induced group moments. The procedure is the reverse of that used to obtain the bond and group polarizabilities (Section 3.4) from molecular principal polarizabilities. It is important to note that an electric field applied along a principal axis induces an overall resultant moment which is collinear with that axis. If the field were applied in a direction other than that of a principal axis, the resultant induced moment vector for the molecule would *not* coincide with the field.

With more complicated structures it is usually not possible to identify the locations of the molecular principal axes. We then choose any convenient set of orthogonal axes *X*, *Y*, *Z* within the molecule. A unit electric field imagined to act along *X* polarizes each structural group but the vector resultant of all induced moments for the molecule does not lie along *X* since this is not a principal axis. The resultant induced moment has vector components along *X*, *Y*, and *Z*, which are designated b_{xx}, b_{xy}, b_{xz}, respectively. Similarly, if a unit field were applied along *Y*, moments b_{yx}, b_{yy}, b_{yz} would be induced along *X*, *Y*, and *Z*; and finally if the unit field were directed along *Z*, moments b_{zx}, b_{zy}, b_{zz} would be induced along *X*, *Y* and *Z*. Thus the molecular polarizability specified with respect to our chosen set of axes *X*, *Y*, *Z*, has nine components, b_{xx}, b_{xy}, *etc.* Mathematically, or by trial and error, we can find that set of *X*, *Y*, *Z* axes for which all terms except b_{xx}, b_{yy}, b_{zz}, are zero. We know then that we have the principal polarizabilities b_1, b_2, b_3 and, as well, the location of the principal axes within the molecule. The latter information enables us to resolve all component group *permanent* electric moments along the principal axes to obtain μ_1, μ_2, μ_3. Substitution of the calculated quantities b_i and μ_i (i=1 to 3) in eq. (6) yields the theoretical molar Kerr constant for that geometric form of the molecule under study[*].

Two points should be noted: (a) Polarizability corrections are introduced into the additivity scheme if small exaltations are observed, *i.e.* if the experimental mean polarizability is found to exceed that expected from component group summation. Such exaltations, reflecting increased electron mobility in conjugated and hyperconjugated systems, are included in the calculations as additional increments of polarizability directed along the axis of maximum electromeric shift[8]. The group polarizability additivity scheme cannot, at this stage of knowledge, reasonably be applied to molecules such as conjugated polyenes in which extensive resonance interactions occur. (b) The permanent electric moment of a molecule under investigation is also measured. In many cases this assists in the analysis of molecular conformations from dipole vector

[*] We recognize here that polarizability is a symmetric tensor. It is more elegantly represented (with reference to a chosen set of reference axes *X*, *Y*, *Z*) in matrix form.

$$\mathbf{b} = \begin{bmatrix} b_{xx} & b_{xy} & b_{xz} \\ b_{yx} & b_{yy} & b_{yz} \\ b_{zx} & b_{zy} & b_{zz} \end{bmatrix} \xrightarrow[\text{transformation}]{\text{axes}} \begin{bmatrix} b_1 & 0 & 0 \\ 0 & b_2 & 0 \\ 0 & 0 & b_3 \end{bmatrix}$$

It is common practice in structural work to obviate the need for the axes transformation and to use instead a more general form of eq. (6) to calculate the theoretical ${}_{m}K$ directly from the terms b_{xx}, b_{xy}, *etc.* and μ_x, μ_y, μ_z— eq. (30), (35), (36) of ref. [8].

considerations alone. Often μ (observed) can be used to deduce μ_1, μ_2, μ_3 for eq. (6).

4.2. Some Applications

The method is best illustrated by considering some recent examples.

4.2.1. Carboxylic Esters

Many techniques including that of the Kerr effect have been applied to the study of the conformations of carboxylic esters—see review[31]. Recent investigations concern unsaturated esters. Vinyl formate, for example, was found to have an experimental dipole moment of 5.07[*] and $_\infty(_mK_2)$ of 48.1[*] in carbon tetrachloride solution[32]. Model conformations were specified by the interplanar angles θ and ϕ (see Fig. 6); θ is the dihedral angle between the O=C—$\overset{*}{O}$ and C—$\overset{*}{O}$—C planes and ϕ is that between the C=C—$\overset{*}{O}$ and C—$\overset{*}{O}$—C planes. The uniplanar s-*cis*-s-*trans* reference structure has both θ and ϕ equal to zero. From bond dipole additivity the predicted moments range from a minimum of 5.01 ($\theta=0°$) to a maximum of 11.67 ($\theta=180°$) clearly indicating that in solution the molecule has a s-*cis* $\theta=0$ geometry. This form is stabilized through antiparallel arrangement of C$\overset{*}{O}$C and C=O group dipoles. The molecular dipole moment is not sensitive to rotations ϕ. The calculated molar Kerr constant does, however, vary with ϕ since the vinyl group is anisotropically polarizable. Theoretical $_mK$ values for conformations defined by particular values of ϕ (retaining θ as 0°) are as follows:

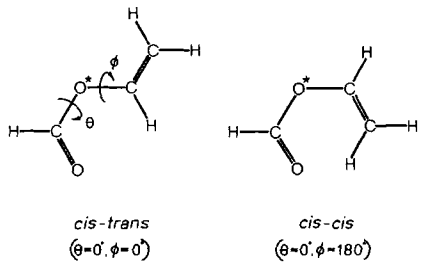


Fig. 6. Conformational models of vinyl formate.

ϕ	0°	30°	60°	90°	120°	150°	180°
$_mK$ (calc.)	+49	+38	+21	+22	+51	+90	+109

Agreement between observed and calculated Kerr constants occurs for structures with $\phi=ca.$ 0° or *ca.* 120°. The former is favored because of conjugative stabilization. It was concluded that vinyl formate in solution has a preferred s-*cis*-s-*trans* conformation ($\theta=0°\pm10$, $\phi=0°\pm10$). This result was reinforced by *ab initio* molecular orbital calculations[32] and is in accord with the result of an earlier microwave spectral study of the vapor[33]. A similar conclusion was drawn for vinyl acetate[32].

[*] Dipole moments and molar Kerr constants are given throughout in SI units as $10^{30}\,\mu$/C m and $10^{27}\,_mK/m^5\,V^{-2}\,mol^{-1}$, respectively. Conversion factors for comparisons with data in e.s.u. are: 1 C m = 0.2998×10^{30} D; $1\,m^5\,V^{-2}\,mol^{-1} = 0.8988\times10^{15}$ e.s.u. mol^{-1}.

4.2.2. Diaryl Disulfides

The skew configuration of the disulfide bridge in compounds R_2S_2 in solution has been verified by dipole moment and microwave dielectric loss measurements[34, 35]. For diphenyl disulfide the angle θ between the two R—S—S planes was determined as 85° from the measured dipole moment (6.07). The experimental $_\infty(_mK_2)$ was then analyzed to deduce that the phenyl groups are positioned such that each C_6H_5 is virtually coplanar with the adjacent $C_{ar}SS$ plane.

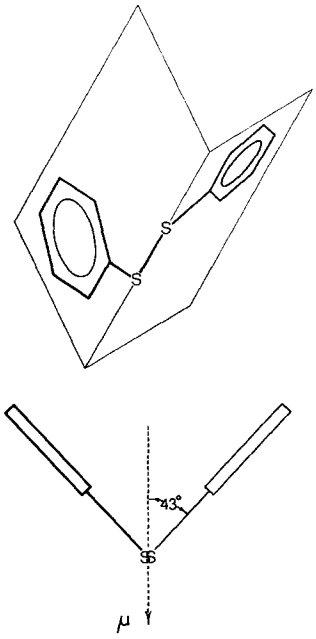


Fig. 7. Conformation of diphenyl disulfide.

The result is definitive since the observed value (−12.8) is close to the calculated value for the above model (−16) (see Fig. 7) and all rotations of one or both phenyl groups away from that model lead to a rapid increase in $_mK$ (calc.); *e.g.* for both phenyl groups perpendicular to their adjoining $C_{ar}SS$, $_mK$ (calc.) is 186. Di(4-pyridyl)- and di(2-pyridyl)-disulfide have also been shown, by similar arguments, to have skew structures in solution ($\theta=ca.$ 74°) with the pyridyl and contiguous $C_{py}SS$ groups nearly coplanar[36].

The approach outlined above has been applied as well to specifying solute conformations of the aromatic diketones such as benzil[37], di(2-pyridyl)-[38], di(1-naphthyl)- and di(2-naphthyl)diketones[39].

4.2.3. Conformational Equilibria

For molecules which exist in solution as equilibrium mixtures of two or more conformational isomers[40], the measured solute molar Kerr constant can be regarded as an average value connected with the molar Kerr constants of the individual forms by the relation

$$_\infty(_mK_2)=\sum_{i=1}^{n}N_i(_mK_i) \qquad (9)$$

where N_i is the molar fraction of the ith conformer and $_mK_i$ is the molar Kerr constant of that conformer. The analogous expression for dipole moments is given by eq. (10).

$$\mu^2_{exp.} = \sum_{i=1}^{n} N_i \mu_i^2 \quad (10)$$

The following condition also applies

$$\sum_{i=1}^{n} N_i = 1 \quad (11)$$

Equations (9) and (11) were used to determine *trans/gauche* ratios for molecules like the *n*-propyl halides[41] the dipole moments of which, unlike those of 1,2-dihalogenoethanes, are insensitive to conformational change. It must be assumed, however, that the geometry of each rotamer can be reasonably specified. Early work on conformational equilibria in the nitrogen heterocycles morpholine, piperazine, *etc.* (summarized in ref. [8]) did not take into account the strong solvent effect of benzene (see Section 4.3) and is being revised using molar Kerr constants and bond polarizability data from "non-interacting" solvent environments. More recently *Huang et al.*[42,43] examined a number of substituted ethanes in which the dipole moments as well as the molar Kerr constants vary appreciably with rotation about the ethane C—C bond. Equations (9)—(11) were used to interpret the experimental data in terms of two basic variables: the percentage of *gauche* population (χ) and the dihedral angle (θ) which defines the *gauche* conformer. For 2,2,3,3-tetramethylbutanedinitrile in carbon tetrachloride at 25° they found $\chi = 18\,\%$, $\theta = 85°$ and ΔE (the internal energy difference between the isomers) = 5.5 kJ mol^{-1} (see Fig. 8). *Huang et al.* sometimes use a graphical

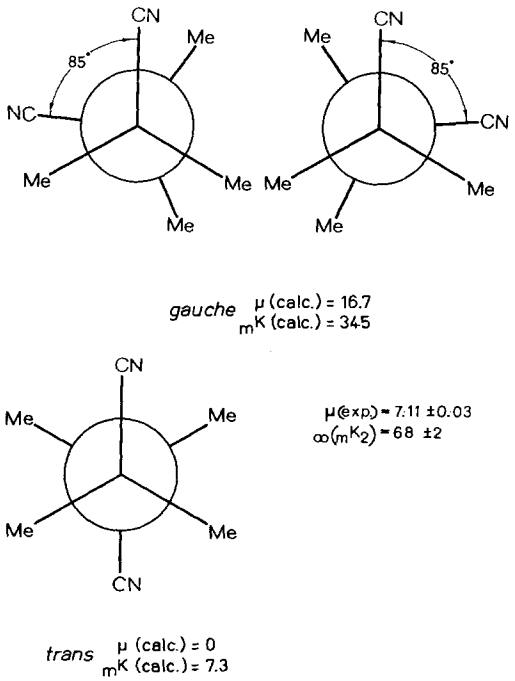


Fig. 8. Conformational isomers of 2,2,3,3-tetramethylbutanedinitrile.

procedure to derive χ and θ for such molecules. This is illustrated in ref.[43] with regard to 1,2-dibromopropane but the conclusions for this molecule are somewhat uncertain because the calculated molar Kerr constants for the two *gauche* conformers are not equivalent. The epihalohydrins (2-(halomethyl)oxiranes) provide examples of conformational equilibria between three characterized low energy forms[44]. Conformer distributions were obtained on this basis from the experimental dipole moments and molar Kerr constants by solution of equations (9)—(11)[45]. *Arbuzov et al.*[30,46] have extended such considerations to include light scattering studies (Δ_u in Section 3.3) which provide another conformation-dependent parameter. They describe a three dimensional graphical analysis, involving all three measured quantities, which they use to determine conformational equilibria in molecules such as the tetrahalonorcaranes (see Fig. 1 of ref.[46]). It is clear, however, that the method is in general limited in its application to molecules which have relatively few rotational isomers.

4.2.4. Substituted Cyclopropanes

The cyclopropyl group, because of its unsaturated character, has the ability to conjugate with adjacent π-electron systems. Phenylcyclopropane, for example, is known to have a resonance stabilized "bisected" structure (specified by $\phi = 0°$) with a mutually orthogonal disposition of the phenyl and cyclopropyl group planes[47], *i.e.* the C_6 group plane includes the CCC angle bisector (broken line in Fig. 9). Calculation shows

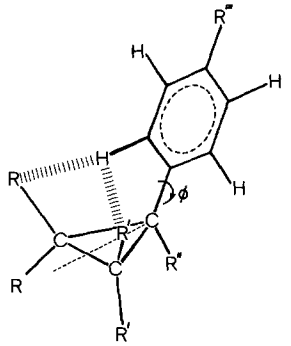


Fig. 9. Conformations ϕ of substituted arylcyclopropanes.

that the theoretical $_mK$ for this molecule is only slightly sensitive to rotations ϕ about the C(phenyl)—C(cyclopropyl)[48] bond. If polar groups are substituted in the cyclopropane ring, however, $_mK$ (calc.) acquires a wide range of values for $0° \leq \phi \leq 180°$. This occurs because rotations ϕ are associated with changes of orientation of the molecular dipole moment relative to the highly anisotropically polarizable aromatic group. A typical calculation, that for 1,1-dichloro-2-phenylcyclopropane, is reproduced graphically in Figure 10 as the theoretical $_mK(\phi)$ plotted against ϕ[49]. It is seen that the measured $_\infty(_mK_2)$ agrees with the calculated value if $\phi = ca.\ 60°$ or alternatively

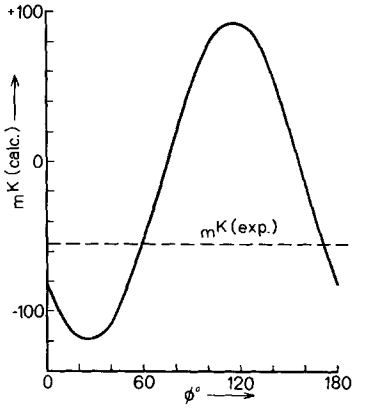


Fig. 10. Theoretical $_mK$ values for conformations $0° \leq \phi \leq 180°$ of 1,1-dichloro-2-phenylcyclopropane: ϕ is the angle of rotation from the bisected form (for which $\phi = 0°$) away from the CCl_2 group. (R = Cl, R′ to R‴ = H.)

ca. 170°; the latter model is precluded on steric grounds. There are, however, alternative interpretations[*].

The procedure adopted was to calculate analogous but independent ${}_{m}K(\phi)$ functions for a number of *para*-substituted 1,1-dichloro-2-phenylcyclopropanes. It was found that simultaneous agreement between theoretical and observed molar Kerr constants for the series is achieved only if $\phi = 60° \pm 5$. The variation of molecular geometry with different groups R, R′, R″ and R‴ (in Fig. 9) was investigated. It was shown that $\phi = ca.\ 6°$ for 1,1-difluoro-2-phenylcyclopropane[45] whereas the *cis*-halogen of the chloro- and bromo-analogs ($\phi = 67° \pm 6$ for the latter[48]) deflects the phenyl group beyond the eclipsed position with reference to the cyclopropyl methylene group. In the case of 1,1-dichloro-2-mesitylcyclopropane $\phi = ca.\ 76°$. By contrast with phenylcyclopropane, ϕ for *N*-phenylaziridine[50] was found to be *ca.* 90° (stabilized in this form by delocalization of the N-lone pair electrons into the phenyl ring).

This approach has been applied also to determining solute conformations of cyclopropyl methyl ketone[51] (bisected s-*cis* form as found also for the vapor by microwave spectroscopy[52]); cyclopropyl substituted-phenyl ketones[51], substituted bicyclopropyls[53], and aryl oxiranes[45]. Current work is directed to studying interactions between electron donor substituent groups and three-membered rings and the transmission of conjugation in polysubstituted cyclopropanes.

4.2.5. Substituted Pentafluorobenzenes

Specification of the pentafluorophenyl group polarizabilities[54] enabled the measured molar Kerr constants of decafluorobiphenyl, decafluorobenzophenone, and molecules of general formula C_6F_5R (R = OH, NH_2, CHO, $COCH_3$, OCH_3, SCH_3, CH_2CN) to be analyzed[55, 56]. The first of these is non-dipolar but the calculated molar Kerr constant varies rapidly with change of mutual disposition of the two C_6F_5 groups since they are highly anisotropically polarizable. A plot of ${}_{m}K$(calc.) against the dihedral angle ϕ is shown in Figure 11; $\phi = 0°$ for planar geometry. The experimental ${}_{\infty}({}_{m}K_2)$ in cyclohexane is 43.2 in agreement with that predicted for $\phi = ca.\ 62°$. This is close to the solute conformation (*ca.* 60°) from UV spectral studies in ethanol[57], the solid state structure (62°) from X-ray analysis[58], and the vapor state conformation (70°) by electron diffraction[59].

The results for molecules C_6F_5R are summarized in Table 3[56]; ϕ refers to the rotation of R from the resonance favored "planar" form. With each molecule C_6F_5R, ${}_{m}K(\phi)$ values were calculated for $0° \leq \phi \leq 90°$; the range is illustrated in columns 3 and 4. The ϕ estimates of column 5 designate, in each case, that conformation for which theoretical and measured molar Kerr constants are in agreement; in effect they represent average conformations. Column 6 lists similar ϕ values for

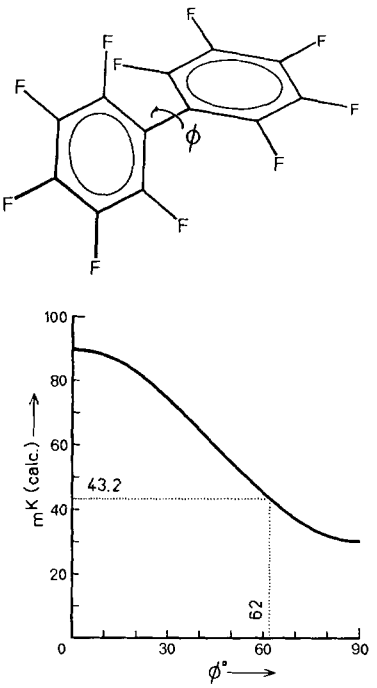


Fig. 11. Calculated molar Kerr constants for conformations ϕ of decafluorobiphenyl.

Table 3. Molar Kerr constants and conformations ϕ for molecules C_6F_5R in cyclohexane solution.

R in C_6F_5R	${}_{\infty}({}_{m}K_2)$ [a] (obs.)	${}_{m}K$(calc.) [a] ($\phi = 0°$)	${}_{m}K$(calc.) [a] ($\phi = 90°$)	$\phi°$ (C_6F_5R) [b]	$\phi°$ (C_6H_5R) [b] [c]
OH	186	199	− 59	*ca.* 0	*ca.* 0
NH_2 [d]	423	431	542	*ca.* 0	0
CHO	103	181	−154	28 ± 6	0
$COCH_3$	−113	341	−269	58 ± 7	0
OCH_3	124	185	48	47 ± 5	*ca.* 18
SCH_3	112	240	80	64 ± 5	*ca.* 23
CH_2CN	−357	512	−524	68 ± 4	*ca.* 32

[a] $10^{27}\ {}_{m}K/m^5\ V^{-2}\ mol^{-1}$.
[b] Measured and calculated Kerr constants are in complete agreement at this value of ϕ.
[c] Quoted from earlier papers; original sources are given in ref. [56].
[d] The H···H line is parallel to the C_6 ring for $\phi = 0°$.

the corresponding C_6H_5R molecules determined also from Kerr effect data. Each of the molecules C_6H_5OH, C_6F_5OH, C_6H_5CHO, and $C_6H_5COCH_3$ was shown to exist in solution as a virtually planar form; for $C_6H_5NH_2$ and $C_6F_5NH_2$ the amino group disposition is given by $\phi = ca.\ 0°$. Anisole and *para*-substituted anisoles are, from Kerr effect evidence, planar or near-planar depending on the nature of the *para*-substituent[60]. An approximately planar structure for anisole was recently suggested from ^{1}H-NMR spectra of nematic solutions by *Emsley et al.*[61]; it should be noted, however, that these authors incorrectly quoted the Kerr effect results of ref. [60]. *Emsley et al.*[62] also examined pentafluorobenzaldehyde (in nematic solution) which, they deduce, has a planar "equilibrium structure". The ϕ values for C_6F_5R, where R = OCH_3, SCH_3, or CH_2CN, exceed those for the corresponding C_6H_5R compounds indicating greater steric/electrostatic repulsions of *ortho*-fluorine, relative to hydrogen, for each of these R groups. With R = CHO or $COCH_3$ the larger ϕ values in the pentafluorophenyl compounds are attributable to greater repulsions of R with *ortho* F and, in addition, to decreased

[*] The ${}_{\infty}({}_{m}K_2)$ should properly be regarded as the mean value for a population of conformations in torsional oscillation about one or more energetically favored geometric forms, *i.e.*

$$\langle {}_{m}K \rangle = \int_{-\pi}^{+\pi} {}_{m}K(\phi) \cdot \exp[-U(\phi)/kT]\,d\phi \Big/ \int_{-\pi}^{+\pi} \exp[-U(\phi)/kT]\,d\phi$$

$U(\phi)$ is the potential-energy function which determines the distribution amongst the various possible molecular conformations. This equation is not often applied since $U(\phi)$ functions are generally uncertain and speculative (see, however, Section 4.2.6).

resonance energy arising from inductive depletion of the aromatic π-system by the fluorine atoms.

4.2.6. Kerr Constants of Amides and Peptides

Flory et al.[63] have attempted to interpret the measured molar Kerr constants of some amides and peptides in dioxane solution using estimates of conformational energy data. With *N*-methylpropionamide, for example, theoretical ${}_mK$ values were calculated for rotations ψ of the CH_2—CH_3 group in the range $0° \leq \psi \leq 180°$ (see Fig. 12). The amide group was assumed to remain in the planar *trans* configuration. The average theoretical molar Kerr constant was computed by summing values of ${}_mK$(calc.) weighted according to conformational energies; the latter were calculated for various values of ψ as sums of non-bonded interactions and intrinsic torsional potentials for rotation about the central C—C bond[64]. Close agreement was obtained between the theoretical $\langle {}_mK \rangle$ and that from experiment. In the case of *N*-ethylacetamide, however, the experimental result is appreciably larger than that similarly calculated for rotations of the *N*-ethyl group. For each of the molecules the conformational energies are minimal when the rotating CH_2—CH_3 group is approximately perpendicular to the amide group plane. The approach was extended to glycyl, L-alanyl, and L-leucyl peptides of the type CH_3—CO—NH—CHR—CO—NH—CH_3 (where the peptide unit is defined by two torsional angles) and to oligoglycines and oligo-L-alanines. It was shown that the calculated average molar Kerr constants are sensitively dependent on conformational energies, but these, however, are not known at present with sufficient accuracy to allow quantitative calculations of $\langle {}_mK \rangle$ to be made. *Flory et al.*[63] also concluded that "the Kerr constant is an especially acute index of the average conformation".

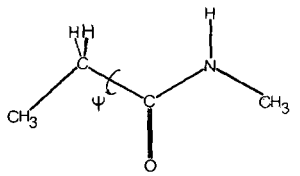


Fig. 12. Conformations ψ of *N*-methylpropionamide.

4.2.7. The Cotton-Mouton Effect

Another approach recently applied to conformational analysis involves the measurement of magnetic field induced birefringence (Cotton-Mouton effect) of diamagnetic organic molecules. The experimental method is identical to that of the Kerr effect except that the molecules in the cell are subjected to a strong uniform magnetic induction (*ca.* 2 Tesla). The molecules tend to be oriented by the magnetic field because of their magnetic anisotropy. Since each molecule is anisotropically polarizable the partly ordered system of molecules becomes optically anisotropic and birefringent. The molar Cotton-Mouton constant ${}_mC$, an intrinsic property of a molecule, is related to both the magnetic anisotropy and to the polarizability anisotropy [see eq. (1) and (4) of ref. [65]].

The procedure adopted in this work is analogous to that used in interpreting the Kerr effect in terms of solute conformations. The measured solute ${}_mC$ is compared with theoretical ${}_mC$(calc.) values for different possible geometric forms. The calculations are based on additivity of component group magnetic anisotropy and polarizability anisotropy data (as in Section 4.1). The Cotton-Mouton effect technique is generally not as sensitive a structural probe as that of the Kerr effect. This need not be the case, however, with some non-dipolar aromatic molecules such as 9-phenylanthracene or 1,3,5-triphenylbenzene where the range of calculated Cotton-Mouton constants for possible stereostructures exceeds that of the corresponding Kerr constants. With 9-phenylanthracene, for example, ${}_mC$(calc.) varies with rotations ϕ of the 9-phenyl group from 515 (for $\phi = 0°$, *i.e.* the planar form[*]) to 213 ($\phi = 90°$); the ${}_mK$(calc.) ranges from 244 ($\phi = 0°$) to 119 ($\phi = 90°$). The theoretical ${}_mC(\phi)$ and ${}_mK(\phi)$ functions when compared with the measured ${}_mC$ and ${}_mK$ (248 and 134, respectively, in carbon tetrachloride solution) each indicate an average conformation of $70° \pm 6$, a result in close agreement with the interplanar angle of 68° obtained from analysis of the electron spin resonance spectrum of the 9-phenylanthracene radical anion[66].

4.3. Solute-Solvent Interactions

With solutes in dilute solution, a non-linear concentration dependence of the electric birefringence may arise from solute-solute associations as for aniline[67] or through conformational changes induced by the reaction field of the medium[68,69] (the dielectric characteristics of the medium would vary of course with solute concentration). For structural investigations solute molar Kerr constants are determined at infinite dilution ideally in non-polar, "inert", and near-isotropically polarizable solvents, *e.g.* cyclohexane. Carbon tetrachloride has also been much used although it is known to interact with solutes such as amines[50,70]. For solutions in benzene, however, time-averaged non-random distributions of the highly anisotropically polarizable solvent molecules about the solute can result in apparent solute ${}_\infty({}_mK_2)$ values quite different to those from "innocent" solvents. The ${}_\infty({}_mK_2)$ of chloroform, for example, is -26.9 in carbon tetrachloride and -45.5 in benzene. The negative Δ_mK increment suggests that the benzene molecules within the solvent-cluster about $CHCl_3$ are organized such that the polarizability perpendicular to the solute dipole axis is augmented to a greater extent than in a direction parallel to that axis. This is compatible with *favored* transient $CHCl_3 \cdot C_6H_6$ associations, involving π-hydrogen bonding, in which the chloroform dipole moment lies perpendicular to the plane of the benzene molecule[71].

The Kerr constant of a solute, in common with its nuclear magnetic resonance spectrum, can be markedly affected by stereospecific interactions with aromatic solvents[72]. An extreme example is provided by the neutral metal complex *N*,*N*,*N*′,*N*′-tetramethylethylenediaminezinc(II) chloride for which the following apparent ${}_\infty({}_mK_2)$ values have been recorded: -7 (in "inert" solvent), -2450 (in benzene), $+5560$ (in hexafluorobenzene)[72]. Kerr effect measurements in benzene and other aromatic solvents present difficulties of interpretation as far as the analysis of solute conformations is

[*] Molar Cotton-Mouton constants are given here in SI units as $10^{26}\ {}_mC/m^5\ A^{-2}\ mol^{-1}$; $1\ m^5\ A^{-2}\ mol^{-1} = 0.6333 \times 10^{10}$ e.m.u. mol^{-1}.

concerned, but they undoubtedly provide a sensitive and potent method for investigating the geometry of solvation.

5. Electric Birefringences of Solutes in Water

Utilization of pulsed-voltage techniques has allowed extension of Kerr effect studies to conducting media. Small molecules and simple ionic species in water have not been much studied. A major difficulty is that of theoretical interpretation of the measured data, reflecting the inadequacy of existing dielectric theory. The experimental technique for such measurements is described in ref. [2]. A square-wave voltage pulse is applied to the molecular system which becomes birefringent. The light transmitted through the crossed prisms and the voltage applied are both simultaneously displayed on a double-beam oscilloscope (see Fig. 6.11 of ref. [2] for examples). The light intensity, measured as the height of the steady-state birefringence trace, is linearly dependent on E^4 if Kerr's law is obeyed. The Kerr constants B ($\lambda = 633\,\text{nm}$) for pure water and for a number of organic solvents were recently determined by this technique using voltage pulses of 70 μs duration and fields up to $15 \times 10^5\ \text{V m}^{-1}$ [73]. The extraction of anisotropic polarizabilities of glycine, *dl*-alanine, and α-aminoisobutyric acid from measured B values in water had earlier been attempted by *Orttung* and *Meyers*[74].

The electric birefringence technique has been much used in recent years for stereostructural investigations of biologically important macromolecules[5, 6, 75]. The duration of the orienting square voltage pulse is adjusted so that maximum orientation of the macromolecules is attained (evidenced by the horizontal section of the birefringence trace), but to minimize electrolysis, heating, and degradation, the pulse time must not be unnecessarily long. Macromolecular solutes commonly exhibit three regions of birefringence (Fig. 13): the build-up Δn_R (once the field is applied), the steady-state Δn_0, and the decay Δn_D (on sudden removal of the field). At high fields, saturation birefringence Δn_S may be attained, *i.e.*, a limiting value of the measured Δn with increase of the field intensity, and Kerr's law is no longer obeyed. The quantity Δn_S is related to the apparent solute polarizability anisotropy[76]. A complicating factor in such interpretations, particularly with solutions of polyelectrolytes, is the "interfacial polarizability" arising through displacement of counter-ions along the macro-ion by the applied field[77, 78]. *Benoit*[79] has shown that the birefringence decay of a monodisperse solution of particles of cylindrical symmetry is given by

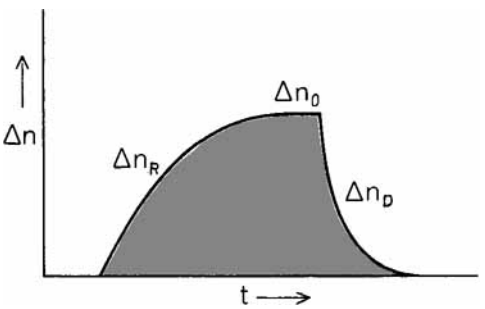


Fig. 13. Representation of the time dependent electric birefringence trace.

$$\Delta n_D = \Delta n_0 e^{-6\Theta t} = \Delta n_0 e^{-t/\tau} \quad (12)$$

where Δn_D is the birefringence at time t after removal of the field; Δn_0 is the birefringence value at the instant the pulse is quenched; Θ is a constant (the rotary diffusion constant); τ is the relaxation time of the particles. The term Θ is related to the particle dimensions[6]. For cylindrical, rod-like particles of length $2l$ and breadth $2m$

$$\Theta = 3kT[\ln(2l/m) - 0.8]/8\pi\eta l^3 \quad (13)$$

where η is the viscosity of the solvent. Thus the length of a long, rigid macromolecule can be deduced if an estimate of the axial ratio l/m is known, *e.g.* from viscosity measurements. The analysis of birefringence decay curves is, however, a complex and uncertain procedure with polydisperse solutes[75] or with flexible particles where the relaxation may occur by orientations of segments of the macromolecule. *Fredericq* and *Houssier*[6] have recently given an account of the dynamic electric birefringence technique as applied to biological macromolecules; they detail investigations on viruses, nucleic acids, nucleoproteins, fibrous proteins, and globular proteins. The interpretation is very rarely in terms of precise conformational features but the technique is of great value in exploring changes of shape and dimensions of biopolymers in solution with variation of temperature, pH, concentration, ionic strength, or of the applied field intensity.

6. Conclusion

The electro-optical Kerr effect is the basis of a highly sensitive yet relatively uncomplicated technique which has been extensively used to investigate the conformational preferences of molecules in non-polar solvents. The method has, in addition, been applied to the study of the geometry of solvation, solute aggregation[80], and the shapes and dimensions of biopolymers in solution. Problems of theoretical interpretation remain to be overcome particularly for polar and conducting dielectrics. The technique is gaining wider use despite the non-availability of commercial instruments.

I am grateful to Professor R. J. W. Le Fèvre, F. R. S. for his inspiration past and present, to Professor Dr. W. Lüttke for his very considerable encouragement, and to my many Sydney friends and colleagues, notably Dr. R. S. Armstrong, Dr. M. P. Bogaard, Dr. K. E. Calderbank, Dr. J. M. Eckert, Mr S. W. Filipczuk, Dr. R. K. Pierens, and Dr. G. L. D. Ritchie, for valued discussion. I thank also the Australian Research Grants Committee for financial support.

Received: August 31, 1976 [A 184 IE]
revised: November 23, 1976
German version: Angew. Chem. *89*, 725 (1977)

[1] *J. Kerr*, Philos. Mag. *50*, 337, 446 (1875).
[2] *C. G. Le Fèvre, R. J. W. Le Fèvre* in *A. Weissberger*: Techniques of Chemistry. Vol. 1/IIIC. Wiley, New York 1972, p. 399.
[3] *L. L. Boyle, A. D. Buckingham, R. L. Disch, D. A. Dunmur*, J. Chem. Phys. *45*, 1318 (1966).
[4] *A. D. Buckingham, H. Sutter*, J. Chem. Phys. *64*, 364 (1976).
[5] *C. T. O'Konski* in *N. Bikales*: Encyclopedia of Polymer Science and Technology. Vol. 9. Wiley, New York 1968, p. 551.
[6] *E. Fredericq, C. Houssier*: Electric Dichroism and Electric Birefringence. Clarendon Press, Oxford 1973.

[7] *C. G. Le Fèvre, R. J. W. Le Fèvre*, Rev. Pure Appl. Chem. *5*, 261 (1955).
[8] *R. J. W. Le Fèvre*, Adv. Phys. Org. Chem. *3*, 1 (1965).
[9] *R. J. W. Le Fèvre:* Dipole Moments. 3rd edition. Methuen, London 1953.
[10] *P. Langevin*, Radium (Paris) 7, 249 (1910).
[11] *M. Born*, Ann. Phys. (Paris) *55*, 177 (1918).
[12] *C. P. Smyth:* Dielectric Behavior and Structure. McGraw-Hill, New York 1955.
[13] *A. D. Buckingham, J. A. Pople*, Proc. Phys. Soc. *A 68*, 905 (1955).
[14] *R. J. W. Le Fèvre, B. Purnachandra Rao*, J. Chem. Soc. *1957*, 3644.
[15] *C. G. Le Fèvre, R. J. W. Le Fèvre*, J. Chem. Soc. *1954*, 1577.
[16] *C. G. Le Fèvre, R. J. W. Le Fèvre, B. Purnachandra Rao, M. R. Smith*, J. Chem. Soc. *1959*, 1188.
[17] *R. J. W. Le Fèvre, L. Radom*, J. Chem. Soc. *B 1967*, 1295.
[18] *R. J. W. Le Fèvre, B. Purnachandra Rao*, J. Chem. Soc. *1958*, 1465.
[19] *A. I. Vogel, W. T. Cresswell, G. H. Jeffery, J. Leicester*, J. Chem. Soc. *1952*, 514.
[20] *R. J. W. Le Fèvre, B. J. Orr, G. L. D. Ritchie*, J. Chem. Soc. *B 1966*, 273.
[21] *R. Bramley, C. G. Le Fèvre, R. J. W. Le Fèvre, B. Purnachandra Rao*, J. Chem. Soc. *1959*, 1183.
[22] *R. S. Armstrong, M. J. Aroney, K. E. Calderbank, R. K. Pierens*, Aust. J. Chem. *30*, 1411 (1977).
[23] *C. G. Le Fèvre, R. J. W. Le Fèvre, B. Purnachandra Rao*, J. Chem. Soc. *1959*, 2340.
[24] *T. Yoshino, H. J. Bernstein*, J. Mol. Spectrosc. *2*, 241 (1958).
[25] *R. S. Armstrong, R. J. H. Clark*, J. Chem. Soc. Faraday Trans. II *72*, 11 (1976).
[26] *R. J. W. Le Fèvre*, Proc. Chem. Soc. *1958*, 283.
[27] *R. J. W. Le Fèvre*, Proc. Chem. Soc. *1959*, 363.
[28] *W. H. Nelson*, J. Phys. Chem. *76*, 1502 (1972), and references cited therein.
[29] *H. A. Stuart:* Molekülstruktur. Springer, Berlin 1967.
[30] *A. N. Vereshchagin, S. G. Vul'fson, B. A. Arbuzov*, Izv. Akad. Nauk SSSR, Ser. Khim. *1974*, 1026.
[31] *G. I. L. Jones, N. L. Owen*, J. Mol. Struct. *18*, 1 (1973).
[32] *M. J. Aroney, E. A. W. Bruce, I. G. John, L. Radom, G. L. D. Ritchie*, Aust. J. Chem. *29*, 581 (1976).
[33] *V. M. Rao, R. F. Curl*, J. Chem. Phys. *40*, 3688 (1964).
[34] *M. J. Aroney, R. J. W. Le Fèvre, R. K. Pierens, H. L. K. The*, Aust. J. Chem. *21*, 281 (1968).
[35] *M. J. Aroney, S. W. Filipczuk, D. V. Radford*, J. Chem. Soc. Perkin Trans. II *1975*, 695.
[36] *C. L. Cheng, G. L. D. Ritchie*, Aust. J. Chem. *26*, 1785 (1973).
[37] *P. H. Cureton, C. G. Le Fèvre, R. J. W. Le Fèvre*, J. Chem. Soc. *1961*, 4447.
[38] *R. J. W. Le Fèvre, P. J. Stiles*, J. Chem. Soc. *B 1966*, 420.
[39] *E. A. W. Bruce, P. H. Gore, S. D. Gupta, I. G. John, G. L. D. Ritchie*, Aust. J. Chem. *27*, 2663 (1974).
[40] *E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morrison:* Conformational Analysis. Interscience, New York 1965.
[41] *R. J. W. Le Fèvre, B. J. Orr*, J. Chem. Soc. *1965*, 5353; *B 1966*, 37.
[42] *L. H. L. Chia, H. H. Huang, P. K. K. Lim*, J. Chem. Soc. *B 1969*, 608.
[43] *L. H. L. Chia, E. Huang, H. H. Huang*, J. Chem. Soc. Perkin Trans. II *1973*, 766.
[44] *C. J. Macdonald, W. F. Reynolds*, Can. J. Chem. *48*, 1046 (1970).
[45] *H. J. Stootman*, Ph. D. Thesis, University of Sydney 1974.
[46] *B. A. Arbuzov, S. G. Vul'fson, A. P. Timosheva, A. N. Vereshchagin*, Izv. Akad. Nauk SSSR, Ser. Khim. *1973*, 1386.
[47] *L. V. Vilkov, N. I. Sadova*, Dokl. Akad. Nauk SSSR *162*, 565 (1965).
[48] *M. J. Aroney, K. E. Calderbank, H. J. Stootman*, J. Chem. Soc. Perkin Trans. II *1973*, 2060.
[49] *R. S. Armstrong, M. J. Aroney, A. Hector, P. Hopkins, R. J. W. Le Fèvre, W. Lüttke*, J. Chem. Soc. *B 1971*, 1499.
[50] *R. S. Armstrong, M. J. Aroney, R. J. W. Le Fèvre, W. Lüttke, H. J. Stootman*, J. Chem. Soc. *B 1971*, 2104.
[51] *M. J. Aroney, K. E. Calderbank, H. J. Stootman*, J. Chem. Soc. Perkin Trans. II *1973*, 1365.
[52] *P. L. S. Lee*, Diss. Abstr. Int. *B 32*, 5131 (1972).
[53] *M. J. Aroney, K. E. Calderbank, H. J. Stootman*, Aust. J. Chem. *27*, 1563 (1974).
[54] *M. J. Aroney, G. Cleaver, R. J. W. Le Fèvre, R. K. Pierens*, J. Chem. Soc. Perkin Trans. II *1974*, 3.
[55] *M. J. Aroney, K. E. Calderbank, G. Cleaver, R. K. Pierens*, unpublished results.
[56] *M. J. Aroney, G. Cleaver, R. J. W. Le Fèvre, R. K. Pierens*, J. Chem. Soc. Perkin Trans. II *1976*, 1854.
[57] *D. E. Fenton*, Chem. Ind. (London) *1969*, 695.
[58] *N. N. Neronova*, Zh. Strukt. Khim. *9*, 147 (1968).
[59] *A. Almenningen, A. O. Hartmann, H. M. Seip*, Acta Chem. Scand. *22*, 1013 (1968).
[60] *M. J. Aroney, R. J. W. Le Fèvre, R. K. Pierens, M. G. N. The*, J. Chem. Soc. *B 1969*, 666.
[61] *J. W. Emsley, J. C. Lindon, J. M. Street*, J. Chem. Soc. Perkin Trans. II *1976*, 805.
[62] *J. W. Emsley, J. C. Lindon, D. S. Stephenson*, J. Chem. Soc. Perkin Trans. II *1975*, 1508.
[63] *R. T. Ingwall, E. A. Czurylo, P. J. Flory*, Biopolymers *12*, 1137 (1973).
[64] *R. T. Ingwall, P. J. Flory*, Biopolymers *12*, 1123 (1973).
[65] *C. L. Cheng, D. S. N. Murthy, G. L. D. Ritchie*, J. Chem. Soc. Faraday Trans. II *68*, 1679 (1972).
[66] *L. O. Wheeler, K. S. V. Santhanam, A. J. Bard*, J. Phys. Chem. *71*, 2223 (1967).
[67] *M. J. Aroney, R. J. W. Le Fèvre, L. Radom, G. L. D. Ritchie*, J. Chem. Soc. *B 1968*, 507.
[68] *R. J. W. Le Fèvre, G. L. D. Ritchie, P. J. Stiles*, Chem. Commun. *1966*, 846.
[69] *R. J. W. Le Févre, G. L. D. Ritchie, P. J. Stiles*, J. Chem. Soc. *B 1967*, 819.
[70] *R. J. W. Le Fèvre, L. Radom, G. L. D. Ritchie*, J. Chem. Soc. *B 1969*, 913.
[71] *R. J. W. Le Fèvre, D. V. Radford, G. L. D. Ritchie, P. J. Stiles*, J. Chem. Soc. *B 1968*, 148.
[72] *R. S. Armstrong, M. J. Aroney, R. K. Duffin, R. J. W. Le Fèvre, H. J. Stootman*, J. Chem. Soc. Perkin Trans. II *1973*, 1272, 1362.
[73] *M. J. Aroney, M. R. Battaglia, R. Ferfoglia, D. Millar, R. K. Pierens*, J. Chem. Soc. Faraday Trans. II *72*, 724 (1976).
[74] *W. H. Orttung, J. A. Meyers*, J. Phys. Chem. *67*, 1911 (1963).
[75] *B. R. Gerber, A. Minakata, L. D. Kahn*, J. Mol. Biol. *92*, 507 (1975).
[76] *C. T. O'Konski, K. Yoshioka, W. H. Orttung*, J. Phys. Chem. *63*, 1558 (1959).
[77] *C. T. O'Konski*, J. Phys. Chem. *64*, 605 (1960).
[78] *K. Kikuchi, K. Yoshioka*, Biopolymers *15*, 583 (1976); and references cited therein.
[79] *H. Benoit*, Ann. Phys. (Paris) *6*, 561 (1951).
[80] *M. S. Beevers*, Mol. Cryst. Liq. Cryst. *31*, 333 (1975); and references cited therein.

Oxometallates with Planar Coordination

By Hanskarl Müller-Buschbaum[*]

Oxo compounds whose coordination polyhedra have a planar structure are a rarity in solid state chemistry. The present state of this research area provides a wealth of interesting principles concerning one-, two-, and three-dimensional linkage of square-planar structural units. In certain cases the environment of these units in solids requires new conceptual models for the chemical bonding.

1. Introduction

During the last 15 years solid state chemistry has been enriched by a series of oxometallates with planar-coordinated ions such as Ni^{2+}, Cu^{2+}, Cu^{3+}, Pd^{2+}, Pt^{2+}, and Au^{3+}. Interest attaches not only to the chemical properties of these compounds but also to their structure, which has been studied by modern methods. The present article is intended as a review of the remarkable diversity of their characteristic structural principles—there have been only isolated investigations of their physical properties. Since important characteristics of the linkage of planar polyhedra[**] to one another are encountered in the halooxocuprates, this class of compounds has been included in the present review. While some of these substances exhibit deviations from the strictly planar coordination of the Cu^{2+} because the halogen provides a partial octahedral supplement to the planar metal-oxygen coordination, only those halooxocuprates will be included in which the copper in the planar bases of the distorted octahedra is surrounded by oxygen in quasiplanar manner.

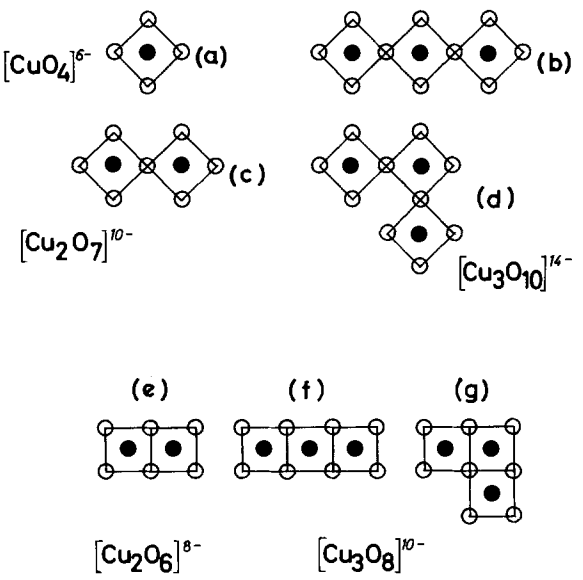


Fig. 1. Model representations of one-dimensional linking of square-planar polyhedra. (a) to (d) corner linking, (e) to (g) edge-linking (formulated for Cu^{2+}).

[*] Prof. Dr. Hk. Müller-Buschbaum
Institut für anorganische Chemie der Universität
Olshausenstrasse 40/60, D-2300 Kiel (Germany)

[**] If two corners of a regular octahedron are removed further and further from each other, or if a tetrahedron is compressed, these classical coordination polyhedra pass into planar configurations. Since such transitions are fluxional and the planar environment is a limiting case, the designation "square-planar polyhedron" is justified.

In this review the oxometallates are divided into the following two groups irrespective of their historical development: planar-coordinated oxometallates with one- or two-dimensional linkage of square-planar polyhedra, and planar-coordinated oxometallates with three-dimensional linkage of square-planar polyhedra.

In addition, two-dimensional linkage of the polyhedra can be subdivided characteristically into those in which the linkage is by the corners and those where it is by the edges, whereas the much more complicated three-dimensional linkage must still be presented *en bloc*. All the compounds belong to the class of solids *i. e.* their characteristic structure is restricted to the solid state and can be recognized only on consideration of the crystal structure. In the illustrations selected here the important structural principles are emphasized for clearer recognition.

2. Planar-Coordinated Oxometallates with One- or Two-Dimensional Bonding of Square-Planar Coordination Polyhedra

2.1. Square-Planar Polyhedra Occurring in Isolation

Figure 1 illustrates isolated, simply constructed, planar polyhedra. Cu^{2+} is regularly used as an example for the formulation of the chemical composition of anionic structural units, since oxocuprates provide examples of most of the structure types. The environmental relationships in the crystal structure are intentionally left out of consideration in this presentation. As can be seen from Figure 1, for structural units $[M_xO_y]$ with $x_{max}=3$ there are already seven possible, two-dimensional, isolated coordination polyhedra with exclusively corner or edge linkage. Of these seven possibilities only two have so far been observed in oxo compounds: the isolated square-planar structural unit (Fig. 1a) $[CuO_4]^{6-}$ found in Bi_2CuO_4[1-3] and Bi_2PdO_4[3,4]; and the edge-linked double square (Fig. 1e) $[Au_2O_6]^{6-}$ that is contained in the compounds Li_3AuO_3[5] and $Na_6Au_2O_6$[6] described by *Hoppe et al.*

Figure 2 shows, for Bi_2CuO_4, that in a tetragonal structure isolated square-planar structural units are stacked along the z-axis with a 45° twist. This structure is reminiscent of the almost identical arrangement of ligands in complexes such as $[Ni(CN)_4]^{2-}$. Bi^{3+} serves formally only as the linking element. In spite of its orthorhombic symmetry, Bi_2PdO_4[3,4] shows only very small deviations from Bi_2CuO_4, and these will not be discussed here any further. Nevertheless, these two compounds should be regarded as oxocuprate and oxopalladate and not as oxobismuthates, for which the formulations would be $CuBi_2O_4$ and $PdBi_2O_4$. This view follows from

experience with alkaline earth metal oxocuprates, where it can be seen that the Cu^{2+} is always square-planar coordinated even if it functions as a component in an anionic structural group[7].

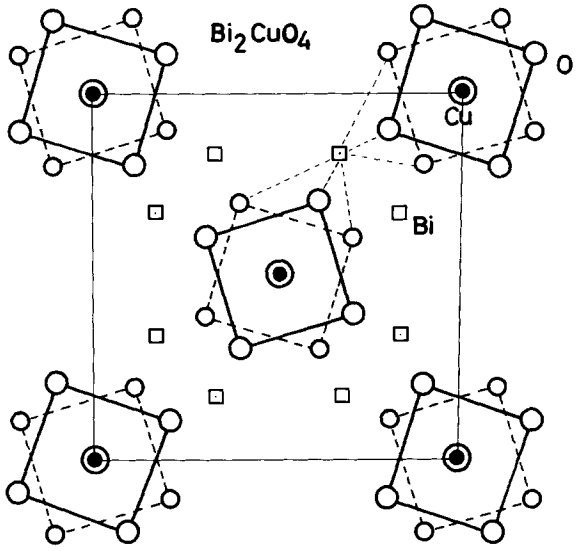


Fig. 2. Characteristic arrangement of square-planar CuO_4 polyhedra in Bi_2CuO_4; projective representation of the atomic distribution along [001] [2].

Li_3AuO_3 is a representative of double squares occurring in isolation[5], its typical structure being shown in Figure 3. The emphasized structural units $[Au_2O_6]^{6-}$, which are directly comparable with the structural units in dimeric gold chloride Au_2Cl_6, are here also stacked in an axial direction and are linked together only by tetrahedrally coordinated Li^+ ions. The compounds $Na_6Au_2O_6$[6] and Li_3CuO_3[8] are isotypic with Li_3AuO_3.

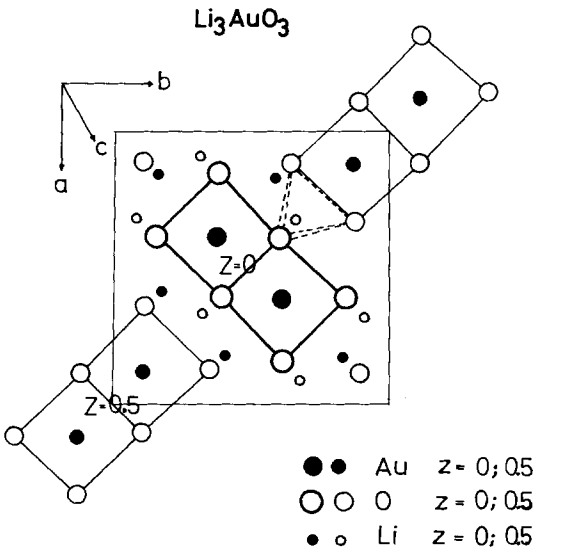


Fig. 3. Arrangement of $[Au_2O_6]^{6-}$ structural groups in Li_3AuO_3; projective representation of the atomic arrangement along [001] [5].

Although there is an apparent analogy between the structure of the solid compounds Bi_2CuO_4, Bi_2PdO_4, Li_3AuO_3, Li_3CuO_3, and $Na_6Au_2O_6$ and the well known structures of complexes or molecules, it cannot be derived therefrom under what conditions it would be possible to prepare other compounds with the still missing polyhedral groupings shown in Figure 1.

2.2. Infinite Linking of Square-Planar Coordination Polyhedra Having Exclusively Edge Linkage

2.2.1. One-Dimensional Infinite Chains

If for this type of polyhedra linkage we again chose to limit ourselves to the characteristic size of structural unit $[M_xO_y]$ with $x_{max}=3$, we obtain the polyhedral groupings shown in Figure 4. These begin with an extended isolated chain (Fig. 4a) and end with two flat arrangements of the structural unit $[Cu_3O_4]^{2-}$ (Figs. 4e and 4f). There are a number of interesting examples of the isolated extended chain shown in Figure 4a:

We shall first refer to Li_2CuO_2 and the compounds Li_2PdO_2, Na_2PtO_2, Li_2NiO_2, and Li_5AuO_4 isotypic with it. Li_2CuO_2 was first mentioned by *Scholder*[9] and was first obtained pure by *Klemm*, *Wehrmeyer* and *Bade*[10]. *Den Os*[11] designed the first model that described the structure. Finally, *Hoppe* and *Rieck*[12] determined the structure reproduced in Figure 5; this investigation yielded distinctly different parameters, especially for Li^+ and showed that the extended chains arranged in parallel, as emphasized in Figure 5, are a compromise with tetrahedral cross-linking through Li^{2+}, leading to stretching of the square polyhedra in the direction of the chain as well as to distortion of the tetrahedral coordination of O^{2-} around the Li^+.

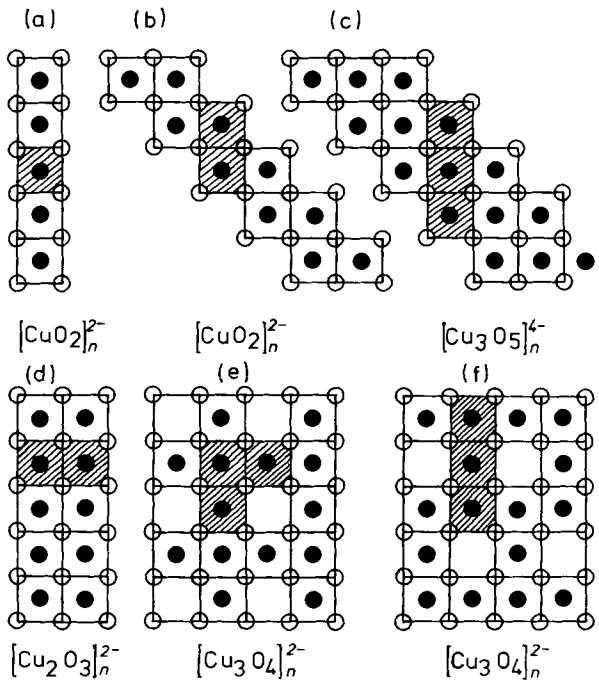


Fig. 4. Model representations of two-dimensional edge-linking of square-planar polyhedra (formulated for Cu^{2+}).

Directly comparable with Li_2CuO_2 are Li_2NiO_2[13] and the compound Li_2PdO_2, first prepared by *Scheer*[14] and investigated by X-ray analysis by *Dubey*, *Gard*, *Glasser*, and *West*[15] in ignorance of the already known crystal structure. Li_2PdO_2 has the structural characteristics described for Li_2CuO_2. What is remarkable, however, is that Na_2PtO_2 is isotypic with Li_2CuO_2, as observed by *Urland* and *Hoppe*[16]: Na^+ still has

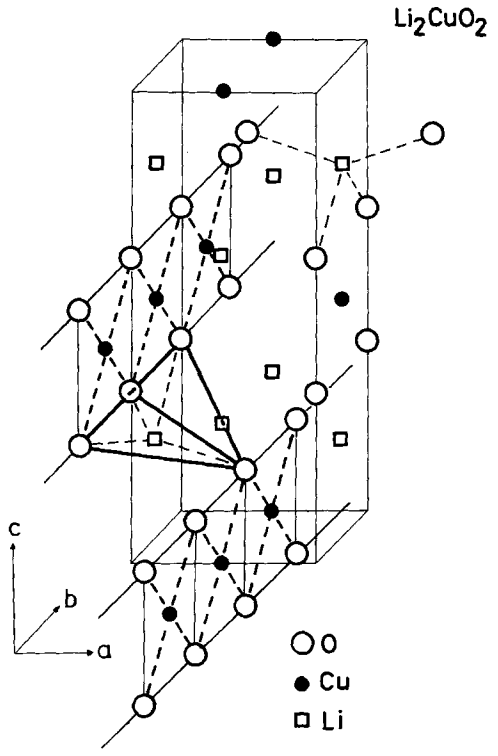


Fig. 5. Perspective representation of the arrangement of extended chains in Li_2CuO_2. The tetrahedral coordination of Li^+ is indicated [12].

tetrahedral oxygen coordination in spite of its relatively large dimensions, but the distortion of these tetrahedra and the stretching of the square-planar polyhedra around Pt^{2+} assume large values, so that the ideally right-angled O—Pt—O and Pt—O—Pt bonds are modified to 81 and 99°, respectively. Finally, the structural type Li_2CuO_2 includes a compound of formula Li_5AuO_4[5], which has the peculiarity that, statistically, part of the Li^+ occupies the metal positions in the stretched chains in common with Au^{3+} (cf. Fig. 5); the molecular formula Li_5AuO_4 should accordingly be altered to $Li_4(Li_{0.5}Au_{0.5})_2O_4$ or $Li_2(Li_{0.5}Au_{0.5})O_2$, whereby it becomes understandable also from the stoichiometry why the arrangement of the polyhedra is the same as in Li_2CuO_2.

However, the examples above do not exhaust the crystal chemistry of stretched chains of square-planar polyhedra. Figure 6 shows that, like Li_2CuO_2, the compounds $KCuO_2$, $RbCuO_2$, and $CsCuO_2$[10, 17, 18], as well as $RbAuO_2$[5] and probably $CsAuO_2$[5], also form stretched chains running parallel to one another, although these are not displaced in the lengthwise direction by half a polyhedron length. From these fine differences arise the trigonal-prismatic holes, emphasized in Figure 6, for K^+ (and Rb^+ and Cs^+, where relevant) which bind the stretched chains to one another. Clarification of the crystal structure by *Hoppe* and *Wasel-Nielen*[5] provided proof of the planar coordination of Cu^{3+} predicted by *Klemm*[10, 17] from magnetic measurements. Supplementing the structures shown in Figure 6, it is shown in Figure 7b that the parallel chains produced by crystallographic identity periods (*i.e.* without translation) can in the simplext case yield cubic polyhedra for large metal ions; this spatial arrangement of parallel stretched chains of polyhedra has been observed in $KAuO_2$[5]. If the right-angled $[AuO_2]_n^-$ chains arranged parallel to one another are distorted triclinically, there then results the cross-linking through octahedra observed with $NaCuO_2$[10, 19] (Fig. 7a). In addition to the findings reproduced in Figures 6 and 7, investigation of the crystal structure of K_2PdO_2[20, 21] shows that in parallel chains (cf. Fig. 22), and despite the same translation of the chains as in Li_2CuO_2 (cf. Fig. 5), not only tetrahedral but also prismatic holes for the linking alkali metal ions are produced.

The structural principles illustrated in Figures 6 and 7 give a substantially complete picture of isolated chains of edge-linked planar structural units. It remains to be shown that stretched chains of square-planar polyhedra arranged in parallel can, by chain cross-linking, afford all the coordination polyhedra of simple structure (tetrahedra, octahedra, trigonal prisms, and cubes) (a) on arrangement in crystallographically

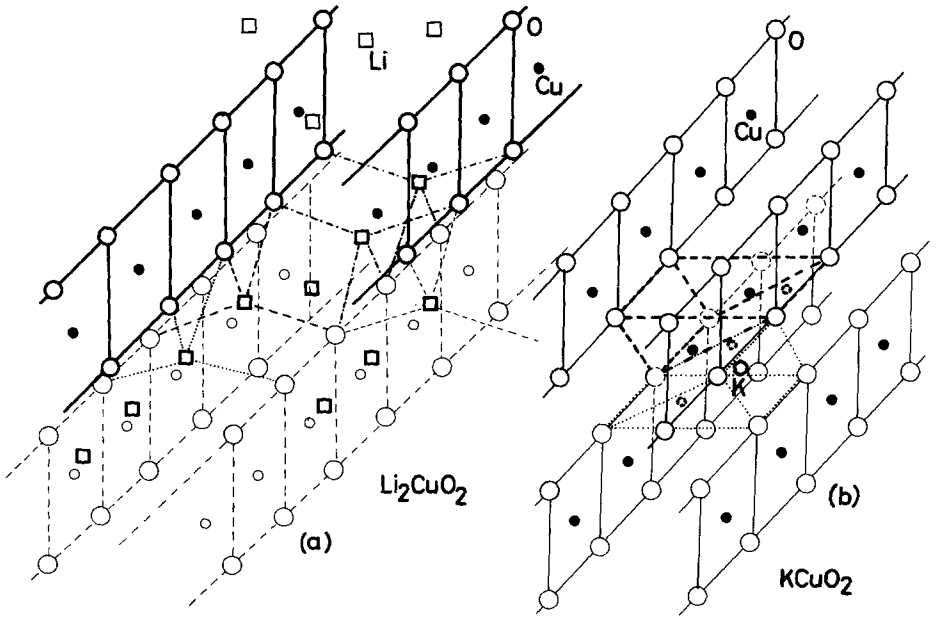


Fig. 6. Perspective representation of extended edge-linked chains in Li_2CuO_2 (a) with tetrahedral and in $KCuO_2$ (b) with trigonal-prismatic cross-linking [12, 18].

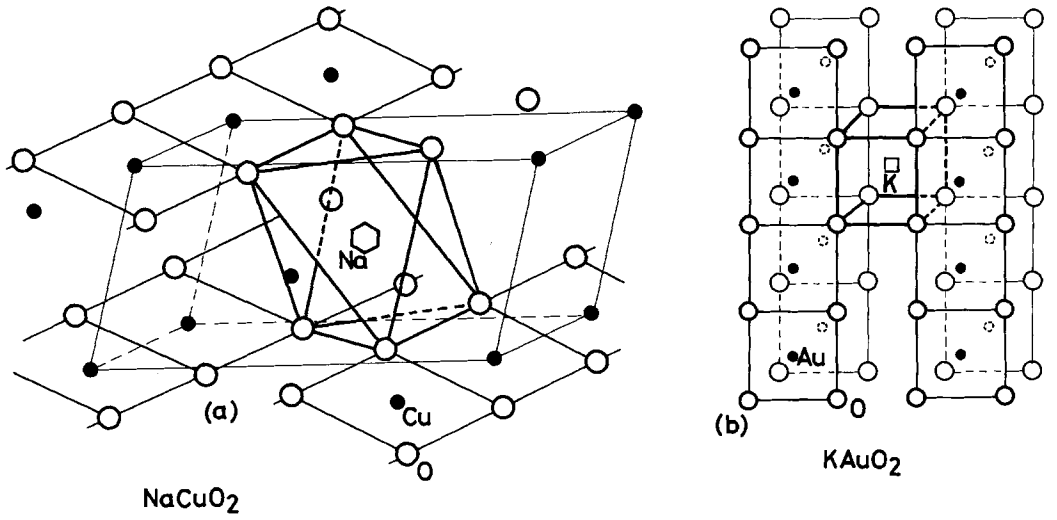


Fig. 7. Perspective representation of linear extended edge-linked chains in $NaCuO_2$ (a) with octahedral and in $KAuO_2$ (b) with cubic cross-linking [5, 19].

identical positions, and (b) by two-dimensional and (c) three-dimensional translation.

After the isolated stretched chains we turn to the zigzag chains of edge-linked square-planar polyhedra (Fig. 4b). Two isotypic compounds $SrCu_{0.75}Ni_{0.25}O_2$[22] and $SrCuO_2$[23] containing isolated zigzag chains have been known for some years. Figure 8 shows that every two rows of trigonal prisms (shaded triangles) of O^{2-} around Sr^{2+}, if linked in the long dimension, produce zigzag chains in the solid crystal structure. For a long time it seemed impossible to replace the Cu^{2+} in $SrCuO_2$ totally by Ni^{2+}, but recently we were able to prepare $SrNiO_2$ single crystals by a high-temperature/high-pressure technique (CO_2 laser, O_2 autoclave)[24], and this again confirmed the structure of $SrCuO_2$.

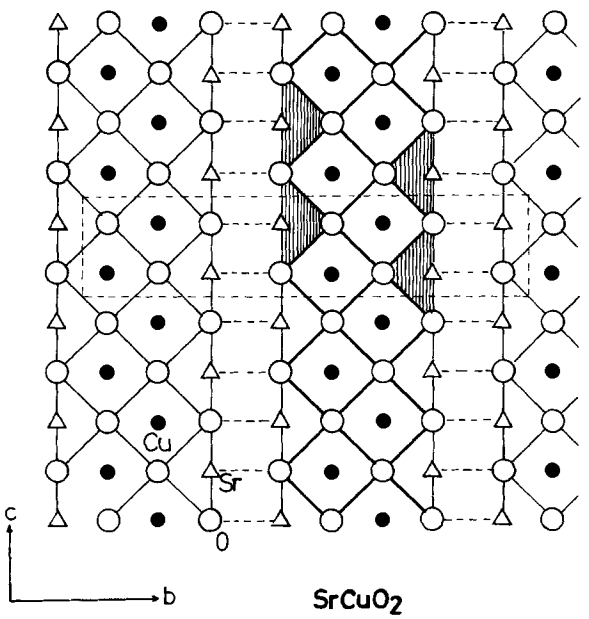


Fig. 8. Projective atomic distribution along [100] for $SrCuO_2$. The hatched surfaces are the view onto the triangular surfaces of trigonal prisms. One of the isolated square-planar zigzag chains is emphasized [22].

2.2.2. Formation of Two-Dimensional Planar Networks

The edge-linked patterns of Figures 4c and 4d are still hypothetical and until recently this was also true of the planar network formation of structural units $[Cu_3O_4]_n^{4-}$ (Figs. 4e and 4f). Recently we succeeded in preparing and determining the crystal structure of the chlorooxocuprate $Ba_2Cu_3O_4Cl_2$[25] and of the compounds $Sr_2Cu_3O_4Cl_2$[26], $Ba_2Cu_3O_4Br_2$[27, 28], and $Sr_2Cu_3O_4Br_2$[29] isotypic with it; this, surprisingly, gave the structural pattern shown in Figure 4e which was formulated previously by *Teske*[31]. Only half of the Cu^{2+} in these halooxocuprates is square-planar-coordinated; the other half of the square Cu/O polyhedra still present is supplemented by halogen to yield greatly tetragonally elongated octahedra. It should, however, be noted that all the oxygen in the four above-named compounds $M_2Cu_3O_4X_2$ belongs to the coordination sphere of the Cu^{2+}, an arrangement that justifies assigning these compounds to the edge-linked, two-dimensionally planar-coordinated oxo compounds (cf. Fig. 9). From the perspective representation in Figure 9 it can be seen that each Ba^{2+} is coordinated to four O^{2-} ions of a square (not occupied by Cu) in the $[Cu_3O_4]_n^{2-}$ pattern and also to four halide ions, thus forming a square antiprism. This halogen-barium configuration is also the reason why only the network scheme 4e is realizable for a $[Cu_3O_4]_n^{2-}$ group and not the other mode of linkage shown in Figure 4f[27]. The principle of alternating supplementation of square-planar Cu/O polyhedra by halide ions to give elongated octahedra is indicated separately in Figure 9 as a projection on the *a/b* plane; it can be seen that the regular pattern of square-planar structural groups is overlaid by a specific succession of octahedrally supplemented polyhedra corresponding exactly to those in $Sr_2CuO_2Cl_2$[32, 33], $Ca_2CuO_2Cl_2$[30, 33], $Sr_2CuO_2Br_2$[34], and $Ca_2CuO_2Br_2$[30]. Since these compounds for their part fall almost into the K_2NiF_4 type, there is also a loose relationship between the compounds $M_2Cu_3O_4X_2$ and the K_2NiF_4 type.

Figure 10 shows the typical great elongation at the apices of the octahedra in the structural types $M_2CuO_2X_2$ and $M_2Cu_3O_4X_2$ (M = Sr, Ba; X = Cl, Br), while the square-planar

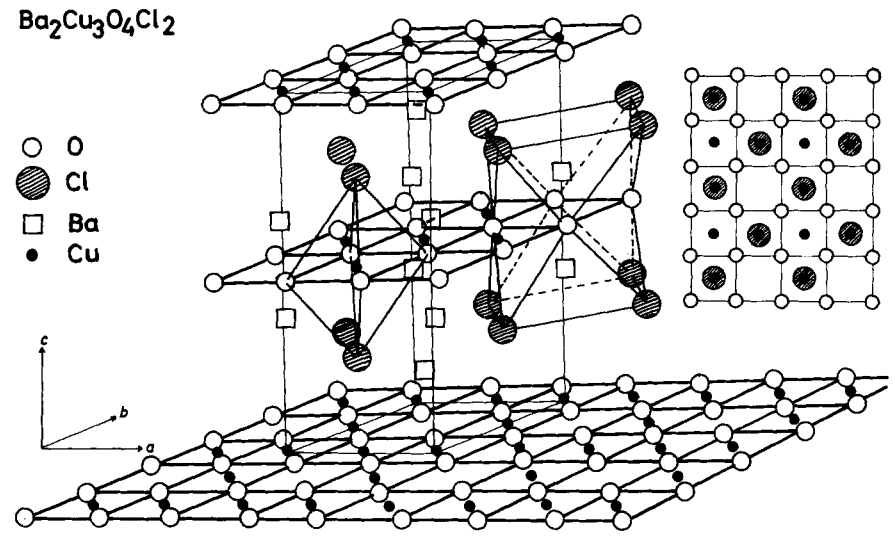


Fig. 9. Perspective representation of the atomic distribution in $Ba_2Cu_3O_4Cl_2$. The planar two-dimensional structure pattern, a planar polyhedron supplemented by Cl^- to afford an octahedron, and the coordination of Ba^{2+} are emphasized. The scheme for a series of alternating squares and octahedra is reproduced in projection on the right [25].

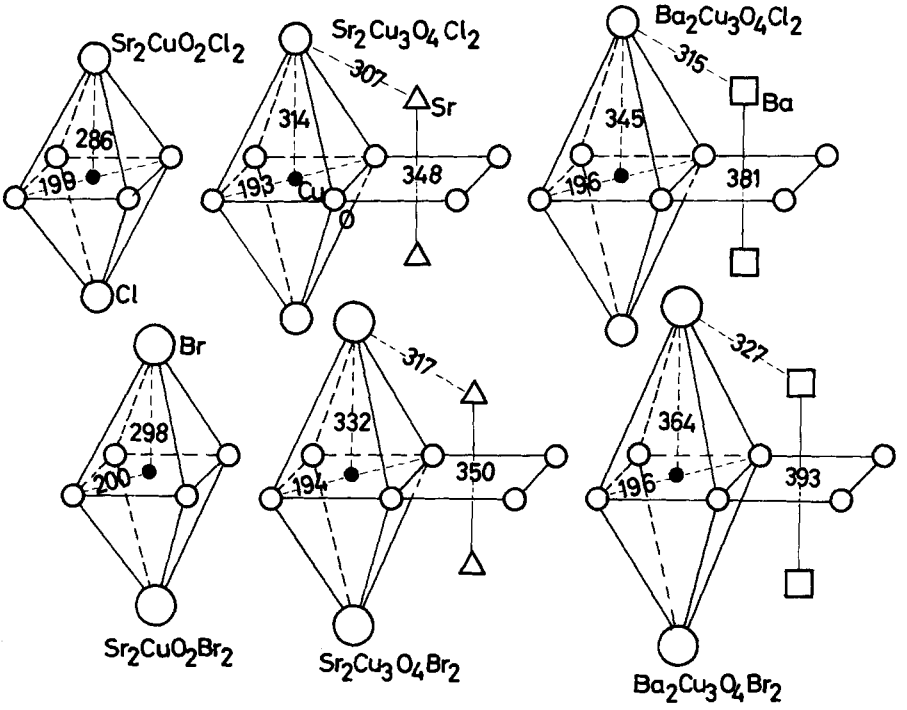


Fig. 10. Octahedral coordination polyhedra completed by halogen in the compounds $M_2CuO_2X_2$ and $M_2Cu_3O_4X_2$ (M = Sr, Ba, (Ca); X = Cl, Br). The distances are given in pm units [25—30, 32, 33].

Cu/O coordination remains almost constant. From the geometric relation in the crystal structure between metal ions (M—M) on the one hand and the experimentally determined separations d(Sr—Cl(Br)) and d(Ba—Cl(Br)) (cf. Fig. 10) on the other, it can be deduced that in the compounds $M_2Cu_3O_4X_2$ the large tetragonal distortion of the $[CuO_4X_2]$ octahedra cannot be explained by means of the Jahn-Teller effect alone; determining influence attaches rather to the relative atomic distances typical of the crystal structure, a feature that is discussed further for compounds $M_2CuO_2X_2$ in Section 2.3.2.

2.3. Infinite Linkages of Square-Planar Polyhedra with Exclusive Corner Linkage

2.3.1. One-Dimensional Infinite Chains

Figure 11 shows examples of edge-linking of square-planar structural groups. The simplest case in this type of linkage is the isolated one dimensional infinite chain (Fig. 11 a) which is present in the compounds Sr_2CuO_3[35], Ca_2CuO_3[36], and Sr_2PdO_3[37]. This rare form of a linear arrangement of isolated planar polyhedra, hitherto restricted to one crystal struc-

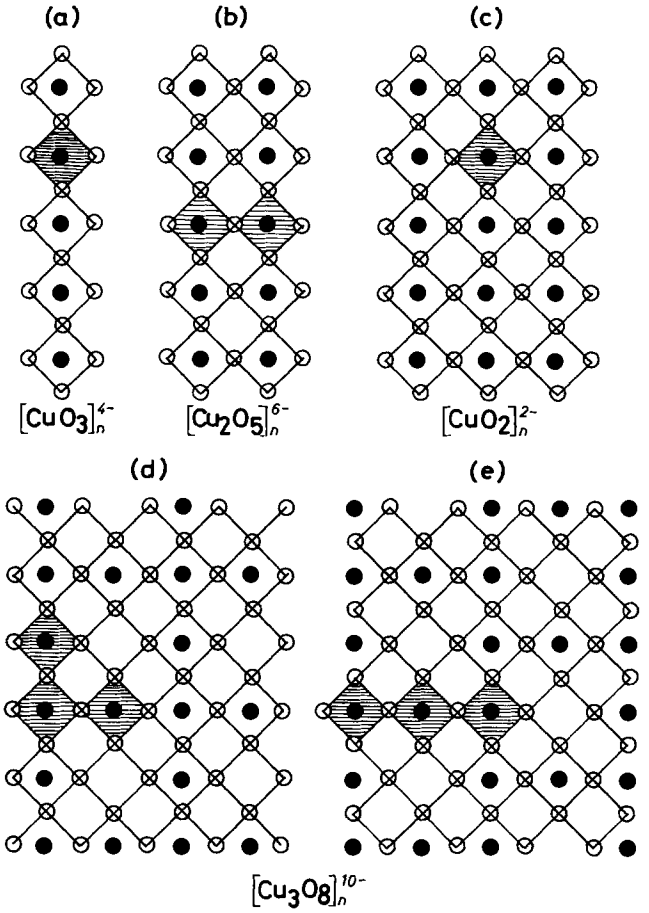


Fig. 11. Model illustrations of two-dimensional edge-linking of square-planar polyhedra (formulated for Cu^{2+}).

ture, is produced in the last-designated compounds by means of an Sr/O or Ca/O framework. Figure 12 shows in projection and perspective that the isolated corner-linked $[CuO_3]_n^{4-}$ chains span the triangular faces of trigonal prisms linked at every long edge.

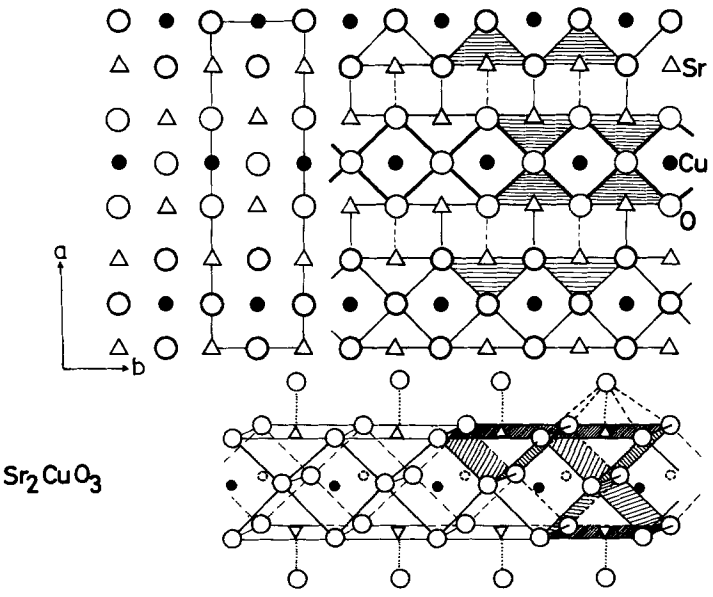


Fig. 12. Projective and perspective representation of the arrangement of polyhedra in Sr_2CuO_3. The hatched surfaces characterize trigonal prisms around Sr^{2+}; the isolated, extended, corner-linked, chain of planar $[CuO_3]^{4-}$ polyhedra is emphasized [35, 36].

In Sr_2CuO_3[35] each Cu/O polyhedron is exactly square and planar; in Ca_2CuO_3[36], because of the different atomic separations d(Cu—O) = 189 pm (2×) and 196 pm (2×), the polyhedra are merely planar. Finally, by a single-crystal X-ray structure study of Sr_2PdO_3[38] it was shown that, owing to the lowering of symmetry, even the central position of the Pd^{2+} in the planar polyhedron can be lost.

2.3.2. Two-Dimensional Planar Network Formation

The planar structural pattern of Figure 11 c has only recently been recognized, although many compounds with this polyhedral network have long been known. Thus, on the basis of X-ray powder diffraction all compounds of the chemical composition RE_2CuO_4 (RE = Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}) were erroneously assigned to the K_2NiF_4 type[39–42], until *Müller-Buschbaum* and *Wollschläger*[43] proved on Nd_2CuO_4 single crystals that the Cu^{2+} in these is square-planar-coordinated and not octahedrally as in the K_2NiF_4 type. This surprising finding was later confirmed by an X-ray study of single crystals of Sm_2CuO_4[44], Gd_2CuO_4[45], and Eu_2CuO_4[46], which showed that octahedral coordination of the Cu^{2+} (K_2NiF_4 type) must also be rejected for these compounds.

Figure 13 shows the characteristic structure of Nd_2CuO_4. Comparison with the previously assumed K_2NiF_4 type[43] shows that the position of only one oxygen atom in this crystal structure needs to be altered, as a result of which Cu^{2+} is still only square-planar coordinated by O^{2-}. For the large cation (here Nd^{3+}) the trigonal-prismatic environment changes to cubic. Four of the eight neighbors of Nd^{3+} do not belong to the Cu^{2+} coordination sphere, and this explains why a stoichiometric composition such as Nd_2CuO_4 can nevertheless contain $[CuO_2]^{2-}$ groups. Nd_2CuO_4 was the first oxometallate in which it was observed that square-planar anionic structural units $[CuO_2]^{2-}$ are cross-linked not by ions but by cationic structural groups $[Nd_2O_2]^{2+}$. Figure 13 also shows that rejection of the K_2NiF_4 type is not valid for all rare earth metal oxocuprates: thus, La_2CuO_4[45] is the only compound in this series that contains not planar- but octahedrally-coordinated Cu^{2+}. This compound is thus not an oxometallate with planar structural units, but it must be mentioned here that it is the only compound containing Cu^{2+} undoubtedly in anionic structural units in spite of the octahedral coordination. Thus, the structure of La_2CuO_4 contradicts the thesis formulated in Section 2.1 above, namely that Cu^{2+} as a component of anionic structural groups is always square-planar-coordinated. Although this is so far the only exception, it is difficult to understand under what circumstances Cu^{2+} is planar- or non-planar-coordinated in oxometallates.

Compounds $M_2CuO_2X_2$ (M = Ca, Sr; X = Cl, Br) require discussion in connection with our consideration of oxocuprates that may be of the Nd_2CuO_4 or the K_2NiF_4 crystal-structure type. If one neglects the orthorhombic distortion of the crystal symmetry and the concomitant displacement (recognizable in Fig. 13) of the octahedron base in La_2CuO_4, the arrangement of octahedra and prisms is the same in La_2CuO_4 as in $M_2CuO_2X_2$. This makes it possible to discuss the experimentally observed large tetragonal elongation of the Cu/O octahedra. Figure 14 shows, for compounds of the type $M_2CuO_2X_2$

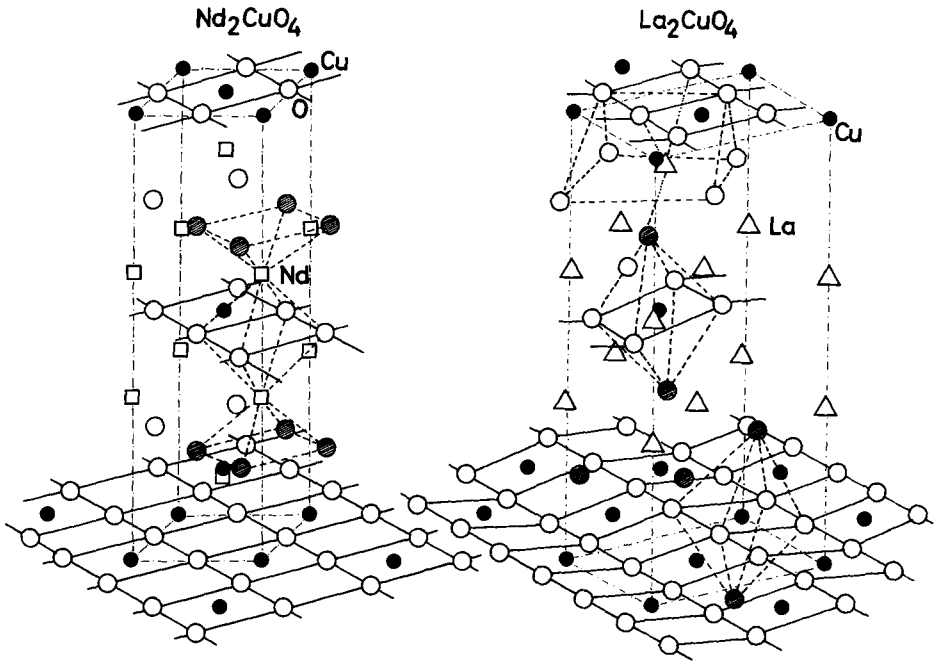


Fig. 13. Perspective representation of the two-dimensional linking of planar Cu/O polyhedra in Nd_2CuO_4, and the octahedral coordination (differing from it) of Cu^{2+} in La_2CuO_4 [43, 45].

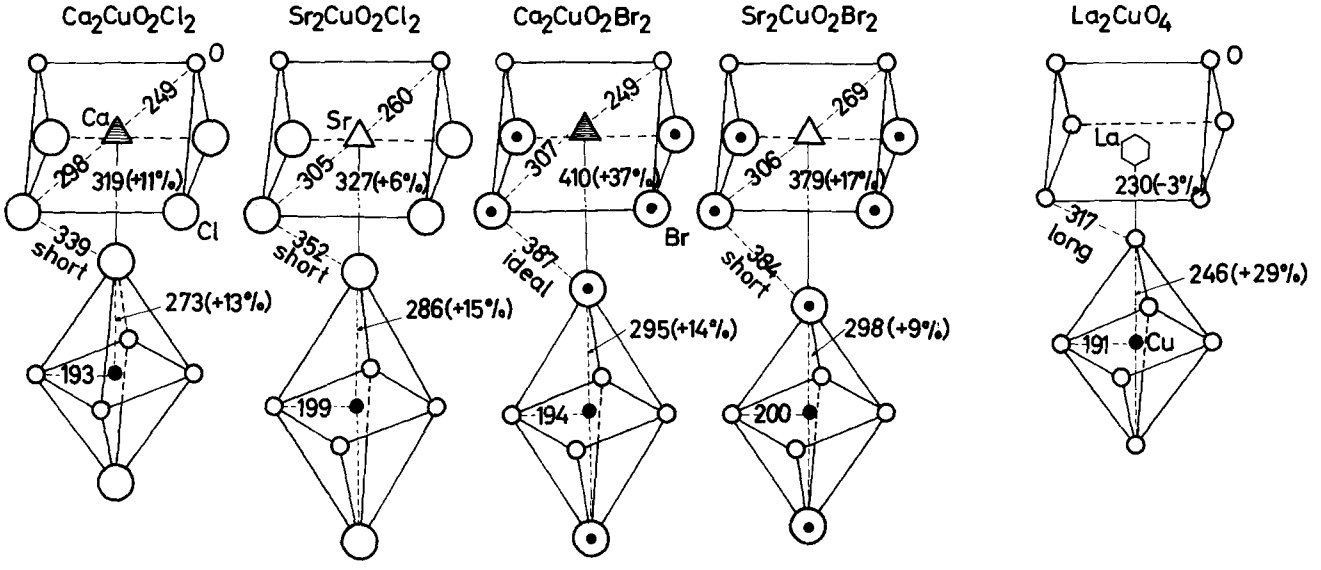


Fig. 14. Coordination polyhedra around Cu^{2+}, Ca^{2+}, and Sr^{2+} and their linkage in compounds of the type $M_2CuO_2X_2$ (M = Ca, Sr; X = Cl, Br). The analogous arrangement in La_2CuO_4 is added for comparison. The distances are in pm units [30, 32, 34, 35].

and for La_2CuO_4, the mode of linkage and the distance relationships between an octahedron around Cu^{2+} and the prismatic coordination of Ca^{2+}, Sr^{2+}, and La^{3+}. It can be seen that the distance between the Cu^{2+} and the peak or foot of the octahedron in halooxocuprates is about 14%, and in La_2CuO_4 about 29%, greater than the sum of the radii of the ions taking part in the bonding. In spite of the relatively short halogen-halogen separation (cf. Fig. 14), the Ca^{2+}/Sr^{2+}-halogen bonds in compounds of the type $M_2CuO_2X_2$ are in some cases considerably too long, so that undoubtedly a superposition of structural geometric effects falsifies the tetragonal Jahn-Teller distortion of the CuO_4X_2 octahedron or places it in doubt. The comparable distances in La_2CuO_4 are considerably different. Figure 14 shows that, in spite of the short separation $d(La^{3+}—O^{2-}) = 230$ pm in the direction of octahedral elongation, the apices of the CuO_6 octahedron are unusually greatly elongated which unequivocally indicates a Jahn-Teller effect at the Cu^{2+} ion. A recently concluded study of La_2NiO_4[34] confirms the assumption made here: since Ni^{2+} with the d^8 configuration does not undergo Jahn-Teller distortion, the octahedral elongation of about 18% observed for La_2NiO_4 is an effect due to the crystal structure; the higher degree of octahedral distortion in La_2CuO_4 must thus be considered as a Jahn-Teller-active contribution.

Each new structural type of planar-coordinated oxometallate raises the question as to which of the known structural principles nature has used in the formation of the compound. For substances with the formula $M_2CuO_2X_2$ (M = Ca, Sr;

X=Cl, Br) and for La_2CuO_4 this is the K_2NiF_4 type. For compounds of the general formula $M_2Cu_3O_4X_2$ (M=Sr, Ba; X=Cl, Br) (cf. Section 2.2.2) some influence of the K_2NiF_4 structural principles could also be detected. We shall now show that the structure types of Nd_2CuO_4, Sr_2CuO_3, and $SrCuO_2$ are simple variations of the K_2NiF_4 type. The original papers should be consulted for more complete understanding.

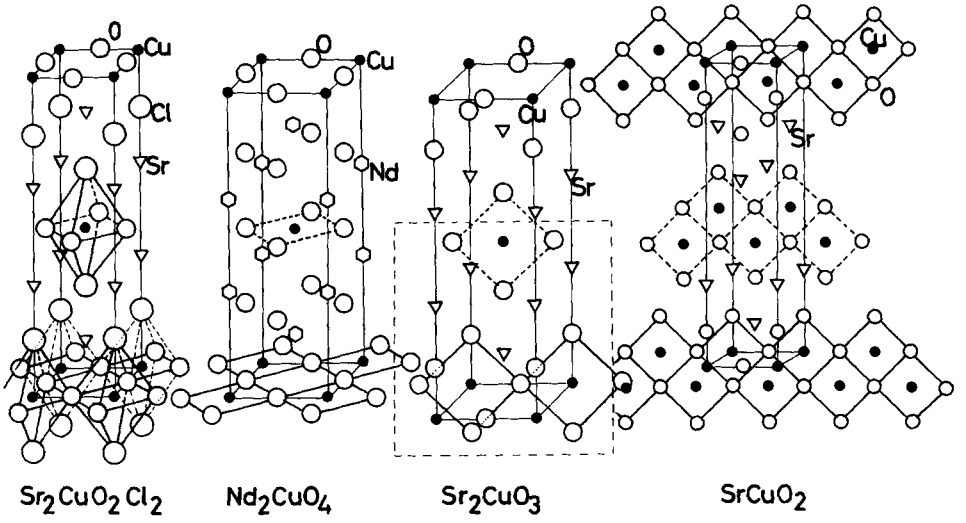


Fig. 15. Perspective representation of the relationships of the K_2NiF_4 structural type (exemplified by $Sr_2CuO_2Cl_2$) to Nd_2CuO_4, Sr_2CuO_3, and $SrCuO_2$ [24, 32, 43].

Figure 15 summarizes the results, and for comparison the distorted K_2NiF_4 type of $Sr_2CuO_2Cl_2$ is presented. If now, as explained previously, each position that forms a peak or foot of the octahedron on the *c*-axis is moved sideways, then one obtains around the Cu^{2+} the planar configuration shown in Figure 11c which is characteristic of the Nd_2CuO_4 type. If instead, starting again from the K_2NiF_4 type, an oxygen atom is formally removed from within the *a/a* plane, then the octahedral coordination again changes to square-planar around the Cu^{2+}, as is found in Sr_2CuO_3. That means that the structural type of Sr_2CuO_3 with its characteristic extended chain (cf. Fig. 11a) can be derived in a very simply way from the K_2NiF_4 type. Finally, the $SrCuO_2$ type can also be derived very simply from the Sr_2CuO_3 type by choosing a suitable section (Fig. 15, the broken line in Sr_2CuO_3)[24]. For this purpose the structural unit denoted by the broken line in Figure 15 is rotated through 180°, placed on an identical unit, and translated by *a*/2; the result is the isolated, edge-linked zigzag chain of Figure 4b. These examples show that the oxometallates with planar coordination polyhedra of known structure types can be referred back to three-dimensional coordination.

2.4. Two-Dimensional Infinite Linking of Square-Planar Polyhedra with Mixed Corner- and Edge-Linking

Figure 16 shows three designs for mixed corner- and edge-linking, the first of which, containing $[Cu_2O_3]^{2-}$ groups, has been observed in $CaCu_2O_3$[47] and $MgCu_2O_3$[48]. These oxocuprates form a two-dimensional infinite Cu/O network (cf. Fig. 17) which already is markedly wavy in the *a/b* plane (section perpendicular to Fig. 17)[47]. Thus, not only are the two compounds examples of the structural pattern in Figure 16, but also, because of the marked waviness of this $[Cu_2O_3]^{2-}_n$ network, they lie at the boundary of planar-coordinated oxometallates showing a spatial arrangement of planar polyhedra. Since, moreover, both compounds allow the octahedron peak and foot to be recognized, with graduated differences for Cu^{2+}, they also form a transition to the oxocuprates that

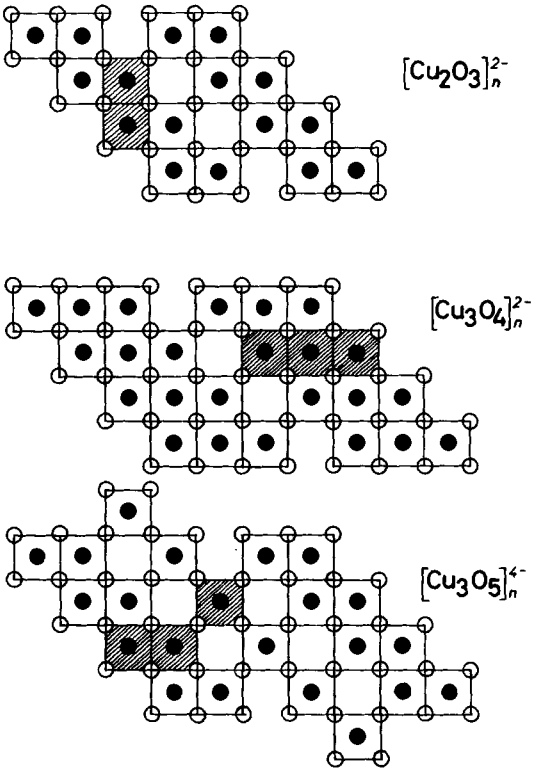


Fig. 16. Model representations of two-dimensional mixed edge and corner linkage of square-planar polyhedra (formulated for Cu^{2+}).

no longer contain planar-coordinated Cu^{2+}. Figure 18 shows that in $CaCu_2O_3$ the Cu—O separations are widely different in the planar base and in the peak or foot of the octahedron, whereas in $MgCu_2O_3$ they are so similar that the octahedral

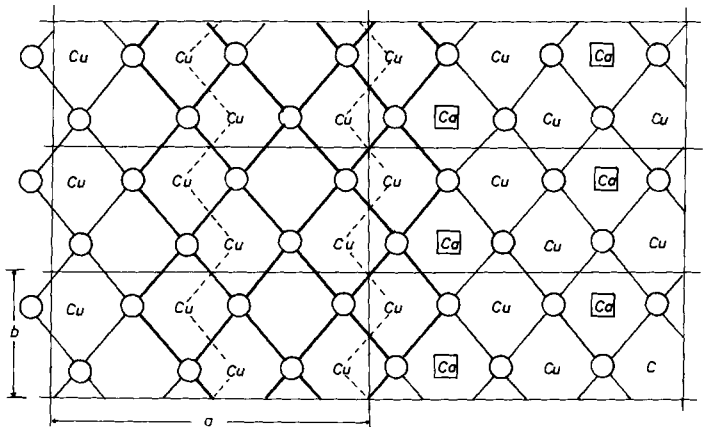


Fig. 17. Projective representation of flat, two-dimensional, endless linking of zigzag chains of square-planar polyhedra in $CaCu_2O_3$ [47].

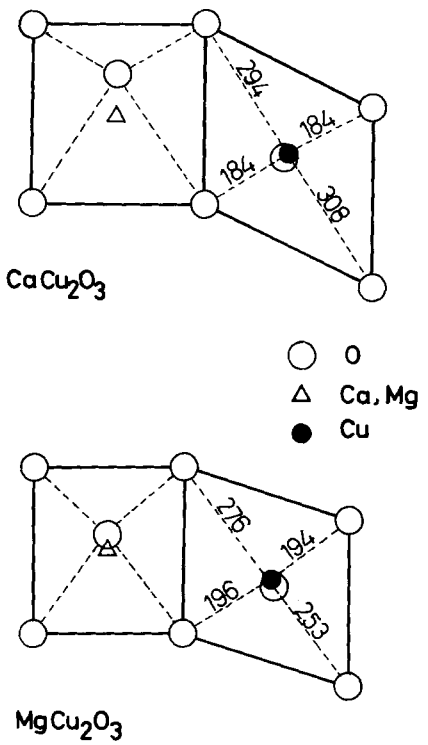


Fig. 18. Characteristic coordination polyhedra around Cu^{2+} and Ca^{2+} or Mg^{2+} in $CaCu_2O_3$ or $MgCu_2O_3$. The distances are given in pm units [48].

coordination of Cu^{2+} is evident. The harmonious transition recognizable in both compounds, from purely planar- to octahedral-coordinated Cu^{2+}, is a very good example of the change in the role of the copper from a component in anionic structural units to the function of a Cu^{2+} cation. Between the limiting states of 1) Cu^{2+} as component of anionic structural groups and 2) Cu^{2+} as cation there lies the intermediate region of mixed oxides, to which $MgCu_2O_3$ can be assigned with perhaps some justification; this supports *Zemann*'s view[49] that $MgCu_2O_3$ can be regarded as an NaCl variant in which half of the octahedra are distorted.

3. Oxometallates with Square-Planar Structural Groups in Three-Dimensional Linkage

Since systematics similar to those for the one- and two-dimensionally linked square-planar structural groups cannot at present be formulated for the three-dimensional case, this group of compounds will be arranged according to increasing degree of linkage. The Section ends with a discussion of compounds with isolated, three-dimensionally linked polyhedra.

The transition from one- and two-dimensional frameworks built up from planar polyhedra to three-dimensional linkage is not sharp but fluid. Similarly to $CaCu_2O_3$[47], in which an indication of the third dimension can be recognized in the waviness of its planar $[Cu_2O_3]_n^{2-}$ framework, the oxonicolate $BaNiO_2$ contains angled chains of the $[NiO_2]_n^{2-}$ type. This structure was clarified by *Lander*[50, 51], although it is still disputed[52–55]. The arrangement of the square-planar polyhedra in the compound $Ba_3Cu_2O_4Cl_2$ was shown in a recent study[56] to be definitely three-dimensional. Figure 19 demonstrates how an elongated, edge-linked chain, angled at nearly 90° runs through the crystal structure. In this chain, almost as in $Ba_2Cu_3O_4Cl_2$[25], every other planar polyhedron is supplemented on one side by halogen; the literature[56] should be consulted for a discussion of the Cu—Cl distance and the arrangement of the three different coordination polyhedra around the Ba^{2+}, not readily recognizable in Figure 19, which are necessary to link these isolated angled chains.

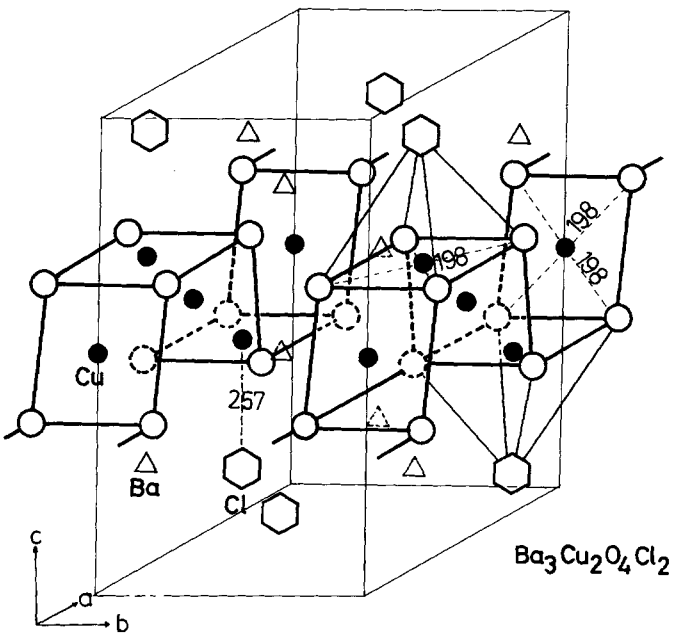


Fig. 19. Perspective representation of the angular edge-linked Cu/O chains in $Ba_3Cu_2O_4Cl_2$ [56].

As a special case, and therefore not mentioned in the Introduction, a (2+2)-coordination around Tl^{3+} in the compound $Sr_4Tl_2O_7$[57] contributes to the three-dimensional linkage of planar polyhedra. Although the different atomic separations d(Tl—O) = 208 pm (2×) and 250 pm (2×) previously led the discussion toward a strongly distorted (2+2)-coordination such as is recognizable in mercury compounds[57], here the planar character of the Tl/O polyhedra serves to include this compound in the discussion of planar-coordinated ions. $Sr_4Tl_2O_7$ is so far the only example of the perpendicular arrangement of linear, crossing, corner-linked chains shown in Figure 20. Owing to the crossing there appears a quasicyclic linkage of perpendicular planar polyhedra. The "rings" are

composed of $[Tl_2O_7]^{8-}$ structural units angled to about 90° to one another.

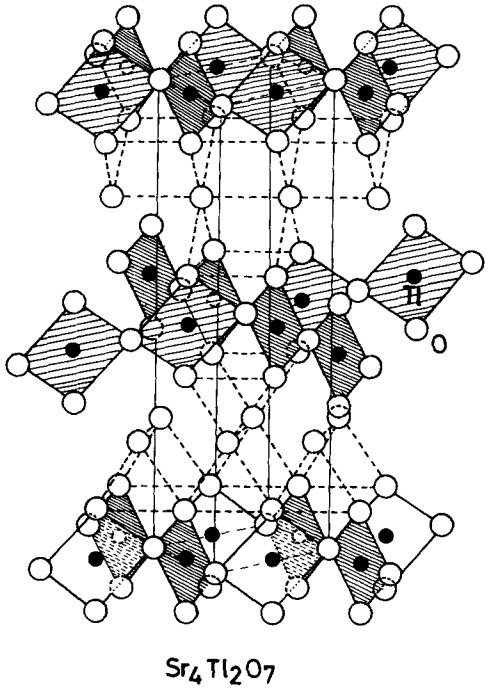


Fig. 20. Perspective representation of the quasi-square-planar (2+2)-Tl/O coordination in $Sr_4Tl_2O_7$. For the sake of clarity the positions of Sr^{2+} are not indicated; they lie within the hatched trigonal prisms [57].

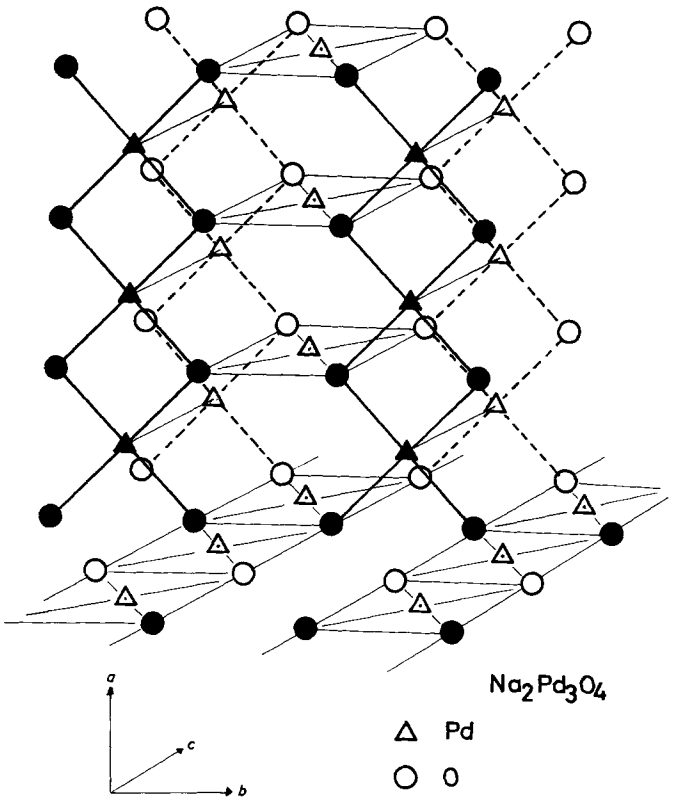


Fig. 21. Perspective representation of part of the linking of polyhedra in $Na_2Pd_3O_4$. The characteristic arrangement of linear extended edge-linked chains and their three-dimensional linkage by isolated square-planar polyhedra is shown [58].

An interesting kind of three-dimensional linkage of square-planar polyhedra was found by *Hoppe* and *Wilhelm*[58] in the compound $Na_2Pd_3O_4$. Figure 21 shows that in $Na_2Pd_3O_4$ elongated parallel chains, such as have been described for $KAuO_2$ (cf. Section 2.2.1), are cross-linked by individual square polyhedra around Pd^{2+}. In this compound we find a coexistence of linear chains and quasi-isolated single polyhedra that are not, as could be inferred from Figure 21, linked together unidimensionally and *ad infinitum* along [001]. Viewed in this way, there is a remarkable parallel between the three-dimensional linkage in $Na_2Pd_3O_4$ on the one hand and in $KCuO_2$ and K_2PdO_2 on the other. These three compounds have in common a combination of extended edge-linked chains with trigonal prisms around the alkali metal ion. Figure 22 shows the way in which trigonal prisms can

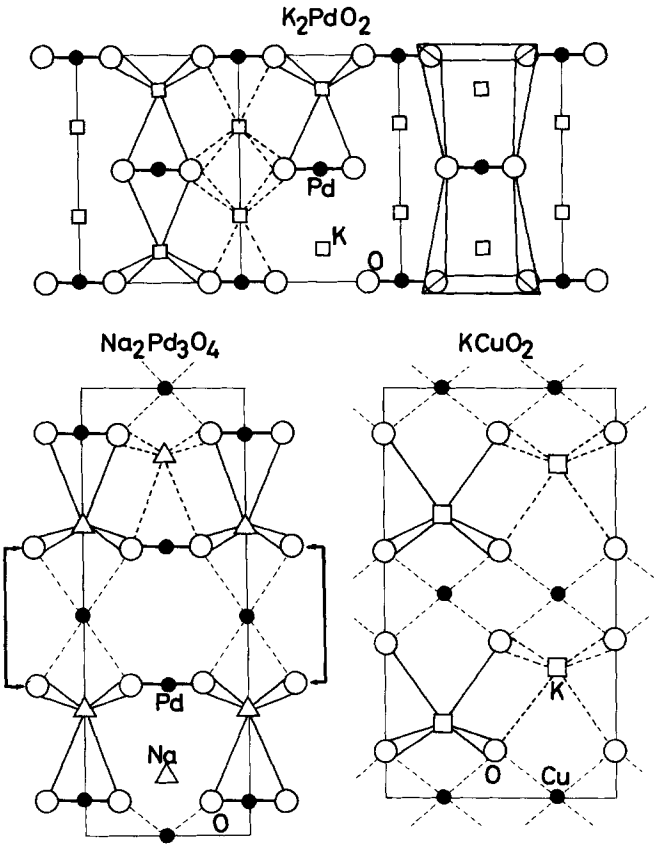


Fig. 22. Projective representation of the cross-linking of extended chains of planar polyhedra by trigonal-prismatic structural units in K_2PdO_2, $Na_2Pd_3O_4$ and $KCuO_2$ [21, 58, 18].

link parallel chains. K_2PdO_2 and $Na_2Pd_2O_4$ differ from $KCuO_2$ only in the orientation of the chain with identical arrangement of the prisms, this being due to the square structural units within the chains. On this basis it is easy to derive, for example, the structure of $Na_2Pd_3O_4$ from that of K_2PdO_2: if the cross-linking by isolated squares is removed from $Na_2Pd_3O_4$ (bracket in Fig. 22), then formally "Pd_2O_2" is removed from the formula unit $Na_2Pd_3O_4$ and together with the new chemical composition Na_2PdO_2 one obtains the polyhedral arrangement of K_2PdO_2. $KCuO_2$ contains a chain whose course is twisted by about 90° from that in K_2PdO_2 (cf. Fig. 22); in this case there is no sign of extension toward three-dimensional linkage.

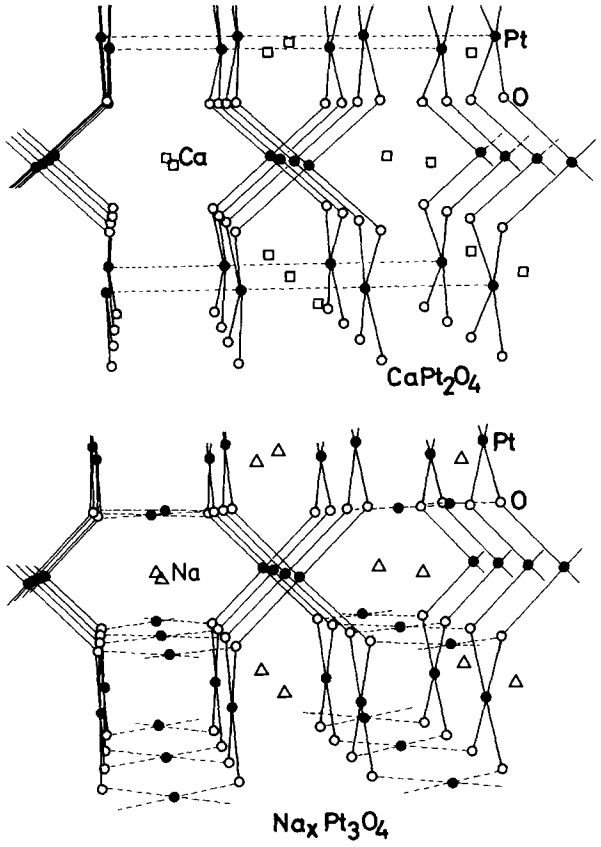


Fig. 23. Perspective representation of the three-dimensional linking of polyhedra in $CaPt_2O_4$ and $Na_xPt_3O_4$. Only the framework structure of square-planar polyhedra is shown [59].

The compound $CaPt_2O_4$[59] can be regarded as the precursor of a perfect three-dimensionally linked framework composed of individual square-planar polyhedra, such as were found in the interesting platinum bronzes of type $Na_xPt_3O_4$[60, 64]. A series of compounds such as $NaPd_3O_4$[61], $CaPd_3O_4$[62], $SrPd_3O_4$[66], $CdPd_3O_4$[63], $CdPt_3O_4$[59], $Cd_{0.3}Pt_3O_4$[59], $Ni_xPt_3O_4$[65], and $Pt_{0.4}Pt_3O_4$[68] is isotypic with $Na_xPt_3O_4$. Figure 23 shows the structure of $CaPt_2O_4$ and $Na_xPt_3O_4$. The high electrical conductivity due to the structure of the bronzes and the ability of the $[Pt_3O_4]$ framework to incorporate cations in widely varying amounts into the cubic holes are worth noting. In each case the partially tetravalent character of the platinum in Pt_3O_4 is changed to Pt^{2+}, a consideration that permits exclusively the oxidation state Pt^{2+} to be assigned to the $[Pt_3O_4]_n^{2-}$ framework in $Pt_{0.4}Pt_3O_4$[68].

Some very recently discovered oxocuprates and halooxocuprates contain limited areas of three-dimensional structural groups. Their peculiarity lies in the fact that these isolated structural groups are themselves constructed of square-planar coordinated Cu^{2+}. A characteristic example is provided by the compound $Ba_9Cu_7O_{15}Cl_2$[67] with a wealth of unusual coordinations. To provide a clearer picture, the interesting arrangements of polyhedra for Ba^{2+} and for the planar coordinated Cu^{2+} have been picked out in Figure 24 from the complicated over-all structure of this compound. A cyclic closed structural group $[Cu_6O_{12}]^{12-}$ can be recognized, which is constructed of planar polyhedra. Still more remarkable is the particle marked Cu_I in Figure 24: it has biplanar 12-fold coordination. This arrangement is reminiscent of the sandwich structures in molecular and complex chemistry. The Ba^{2+} occurs with 6-fold coordination to oxygen, supplemented by two Cl^-, in a previously unknown coordination polyhedron.

At present the most remarkable compound in the series of alkaline earth metal oxocuprates(II) is $BaCuO_2$[69]. Although the simple chemical composition does not lead us to expect anything unusual, this compound has no relation at all to the previously known $SrCuO_2$. In a large unit cell there are in all 90 $BaCuO_2$ formula units, so arranged that along the diagonal of the cubic space six-membered rings are formed from square-planar Cu/O polyhedra. These isolated structural units have been discussed in more detail above for $Ba_9Cu_7O_{15}Cl_2$ (Fig. 24). $BaCuO_2$ also has a 26-gon, formally constructed from Cu/O squares; the 26-gon is emphasized in Figure 25 as an important structural characteristic. This 26-gon occupies positions (000) and (1/2 1/2 1/2) and is linked by a complicated polyhedral framework around Ba^{2+}.

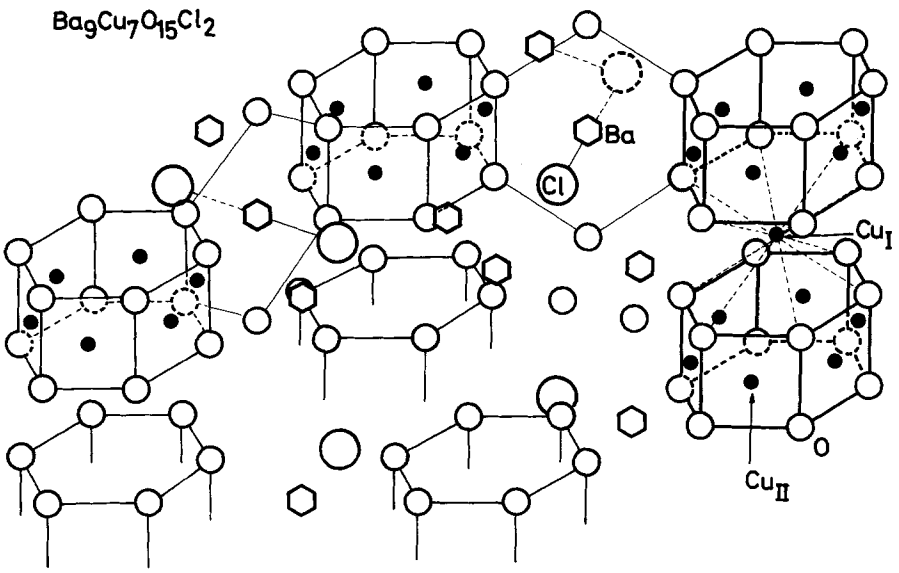


Fig. 24. Perspective representation of part of the linking of polyhedra in $Ba_9Cu_7O_{15}Cl_2$. The six-membered rings of square-planar polyhedra around position Cu_{II}, the biplanar 12-fold coordination around position Cu_I, and the (6+2)-coordination of O^{2-} and Cl^- (novel for Ba^{2+}) are emphasized [67].

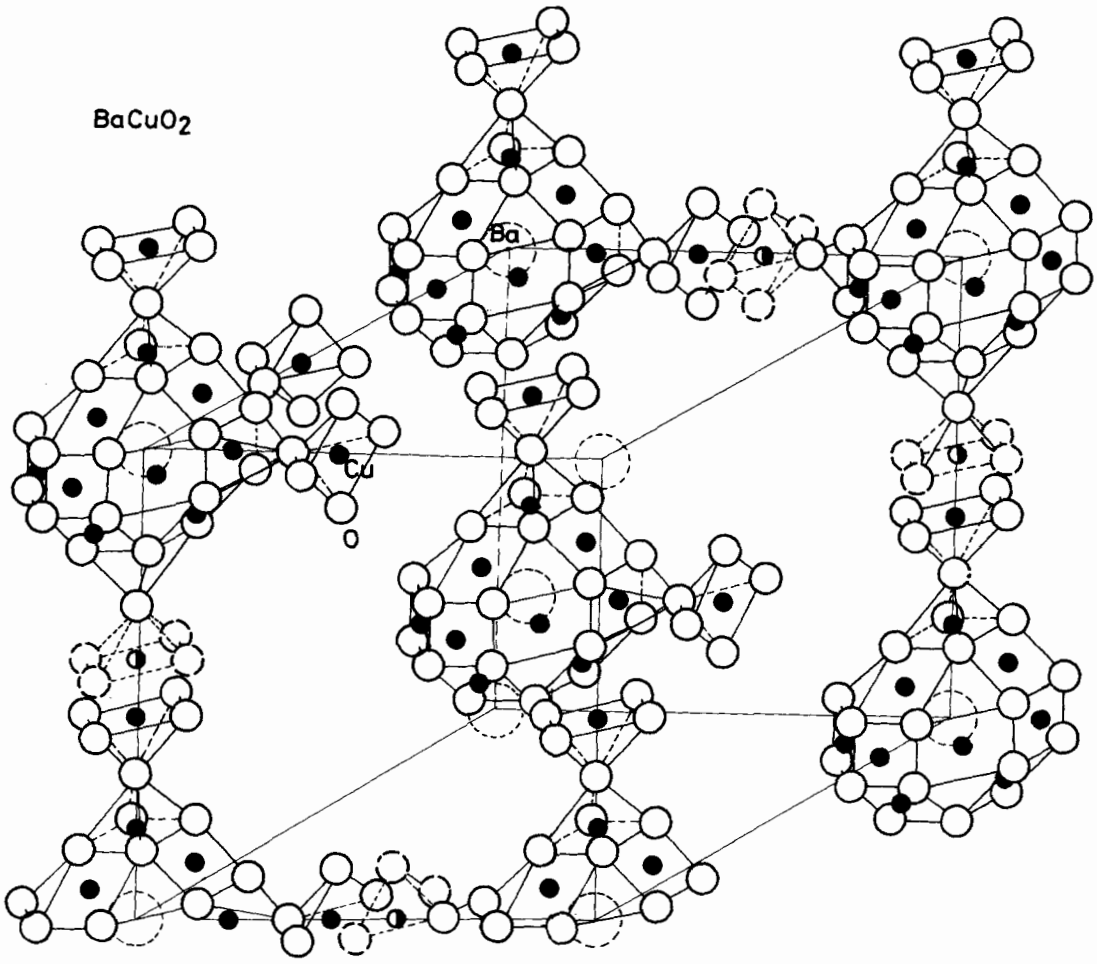


Fig. 25. Perspective representation of the 26-gon constructed from planar Cu/O polyhedra in $BaCuO_2$. Occupation of this quasispherical hollow body by Ba^{2+} is emphasized. Tetragonal pyramids around Cu^{2+} represented only by dotted lines denote a random distribution [69, 70].

The center of the 26-gon is $BaCuO_2$ is occupied by Ba^{2+}, which has the coordination number CN = 24 to O^{2-}, a number never observed before. In recently completed investigations of two structurally related halooxocuprates $Ba_{44}Cu_{45}O_{87}Cl_4$ and $Ba_{88}Cu_{88}O_{175}Br_2$[70], Cl^- or Br^-, respectively is observed at the center of the 26-gon instead of Ba^{2+}. This exchange is possible only because there appears to be an almost spherical coordination sphere with point-like distribution of positive and negative charges. It must, however, be pointed out that these environmental relationships are at present difficult to understand, in view of present concepts of chemical bonding, as in the sandwich-like incorporation of Cu^{2+} in $Ba_9Cu_7O_{15}Cl_2$ (cf. Fig. 24). For further detail, such as a Jahn-Teller distortion of some Cu^{2+} positions on occupation of the 26-gon by Br^- the literature[70] should be consulted.

This section would be incomplete without a reference to *Zemann*'s previous review of the crystal chemistry of copper[71]. Comparison of that review with the results presented above will demonstrate the appreciable progress made during the last 15 years, particularly for compounds with planar-coordinated ions.

4. Outlook

Oxo- and halooxometallates with planar coordination polyhedra are a recently discovered group of compounds, and few of their physical properties are known. Thus, only after further physical measurements will it be possible to answer questions about their electrical, optical, and magnetic behavior, about the chemical bonding, and about thermodynamic stability, questions that are important in connection with their practical application. Therefore, after recording the already known facts we shall turn to a few problems that still lie in the realm of speculation.

On the basis of presently available experimental material the structural systematics for one- and two-dimensional linking of planar-coordinated oxo compounds in the solid state can be considered as largely known. For the three-dimensional linking of planar-coordinated ions we need many more examples so that here too the basic structural principles may be recognized. What is certain is that the tetragonal elongation of the octahedra around Cu^{2+} in solids can seldom be unequivocally explained by the Jahn-Teller theory. In particular the halooxocuprates(II) show that crystal-chemical aspects (distribution of all atoms in each unit cell with consideration of the bond lengths, particle size, polarizability, *etc.*) are responsible for the elongated octahedra around Cu^{2+}. The few known examples of isotypic oxoniccolates(II) afford evidence against the validity of the argument that "Jahn-Teller effects determine the structural type". Oxo- and halooxoniccolates(II) are thus of great importance for theoretical understanding of deformed coordination polyhedra. Finally, it is remarkable that com-

pounds of the type $M_xPt_3O_4$ have a good electrical conductivity[72], which should be strongly anisotropic because of the stacking of square-planar structural groups at quasimetallic distances d(Pt—Pt) = 279—284 ppm. Oxometallates with these properties are comparable with the one-dimensional electrical conductors that are interesting physicists. In this connection the question arises whether oxocuprates(II), in which anisotropic metal-metal interactions could be expected on the basis of their known crystal structure, should be assigned to the group of one-dimensional conductors. It has been shown that in Bi_2CuO_4 the planar CuO_4 polyhedra are stacked unidimensionally (cf. Fig. 2) with distances d(Cu—Cu) = 290 pm longer than those in metallic copper. According to the band model, anisotropic conductivity in the stacking direction could arise on partial oxidation of Cu^{2+} to Cu^{3+}; however, the customary concepts about electron occupation of the 3d orbital of copper speak against this view. In the planar configuration Cu^{2+} has the ninth 3d electron always in the energetically unfavorable $d_{x^2-y^2}$-orbital. Even if partial oxidation to Cu^{3+} produced mobility of the charge carriers in the valence band, according to MO theory only the one $d_{x^2-y^2}$-electron can be affected. However, the orientation of this ($d_{x^2-y^2}$) orbital perpendicular to a one-dimensional metal chain excludes conductivity in the chain direction. In parallel with this, one must ask whether Bi_2PdO_4, which is related to Bi_2CuO_4 and contains a planar-coordinated d^8-element (Pd^{2+}), may not after all be a one-dimensional conductor.

Unlike Bi_2CuO_4, $Ba_3Cu_2O_4Cl_2$ contains an unfolded chain with partially planar-coordinated Cu^{2+}; the copper distances d(Cu—Cu) = 243 pm (cf. Fig. 19) are abnormally short. This compound thus contains one-dimensional isolated quasimetallic zigzag chains. Here too, according to concepts of orbital overlap along the zigzag chain only interactions of the d_{xy}- or d_{z^2}-orbital are possible, and neither of these is concerned in partial oxidation of the valence band of copper[73], *i.e.* electrical conductivity is excluded. For better understanding of such bonding it is important to measure the electrical conductivity as it is to prepare an isotypic compound $Ba_3Pd_2O_4Cl_2$, to which the same consideration might not apply.

The uncertainties in the prediction of conductivity are due not least to insufficient knowledge of the chemical bonding in these solid substances. On the one hand there are undisputed strong covalent interactions between Cu^{2+} and O^{2-}, which justify consideration of the situation according to the rules of MO theory, but on the other hand the observed coordination relationships seem explicable only on the basis of electrostatic interactions. Consider two examples.

In the compound $Ba_9Cu_7O_{15}Cl_2$ the situation of Cu_I (cf. Fig. 24) relative to the bonding of its $12\,O^{2-}$ neighbors is quite uncertain. If we apply orbital-overlap arguments it is not clear whether O^{2-} is bonded by $p_{x,y}$ to Cu_{II} and by p_z to Cu_I, or whether Cu_I is bonded by $12\,sp^3$ hybrid orbitals of oxygen with distances d(Cu_I—O) = 326 pm. It seems equally unsatisfactory to assume purely electrostatic interactions, since the identically charged but larger Ba^{2+} ion could, from the energy point of view, fill this large hole better than copper, whereas experimentally this is found not to occur.

Clearly, the inclusion of Ba^{2+}, Cl^-, and Br^- into the 26-gon of the $BaCuO_2$ crystal structure can be explained only by pure coulombic interactions (cf. Fig. 25). But how is one to visualize the bonds when ions occur at the center of a sphere with a uniform distribution of positive and negative charges on the surface? What is it that enables a Ba^{2+} ion to accept pointwise the $24\,O^{2-}$ particles on the surface of a 26-gon while refusing to accept 18 equidistant Cu^{2+} particles? If it seems reasonable to ascribe this to the different number of positive and negative charges, then the inclusion of Cl^- or Br^- becomes inexplicable.

These two examples show that the nature of the chemical bonding in solids must be reconsidered fundamentally if its growing separation from bonds in isolated molecules is not to continue.

Received: November 22, 1976 [A 183 IE]
German version: Angew. Chem. *89*, 704 (1977)
Translated by Express Translation Service, London

[1] *J. C. Boivin, D. Thomas, G. Tridot*, C. R. Acad. Sci. Ser. *C 276*, 1105 (1973).
[2] *R. Arpe, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *426*, 1 (1976).
[3] *R. Arpe*, Dissertation, Universität Kiel 1977.
[4] *R. Arpe, Hk. Müller-Buschbaum*, Z. Naturforsch. *B31*, 1708 (1976).
[5] *H.-D. Wasel-Nielen, R. Hoppe*, Z. Anorg. Allg. Chem. *375*, 43 (1970).
[6] *H. Klassen, R. Hoppe*, Naturwissenschaften *63*, 387 (1976).
[7] *H.-P. Christian, Hk. Müller-Buschbaum*, Z. Naturforsch. *B30*, 175 (1974).
[8] *H. N. Migeon et al.*, Rev. Chim. Miner. *12*, 203 (1975).
[9] *R. Scholder*, Angew. Chem. *70*, 583 (1958).
[10] *W. Klemm, G. Wehrmeyer, K. Bade*, Z. Elektrochem. *63*, 56 (1959).
[11] *D. P. den Os*, Dissertation, University of Leiden 1962.
[12] *R. Hoppe, H. Rieck*, Z. Anorg. Allg. Chem. *379*, 157 (1970).
[13] *H. Rieck, R. Hoppe*, Z. Anorg. Allg. Chem. *392*, 193 (1972).
[14] *J. J. Scheer*, Dissertation, Universität Leiden 1956.
[15] *B. L. Dubey, J. A. Gard, F. P. Glasser, A. R. West*, J. Solid State Chem. *6*, 329 (1973).
[16] *W. Urland, R. Hoppe*, Z. Anorg. Allg. Chem. *392*, 23 (1972).
[17] *K. Wahl, W. Klemm*, Z. Anorg. Allg. Chem. *270*, 69 (1952).
[18] *K. Hestermann, R. Hoppe*, Z. Anorg. Allg. Chem. *367*, 249 (1969).
[19] *K. Hestermann, R. Hoppe*, Z. Anorg. Allg. Chem. *367*, 261 (1969).
[20] *H. Sabrowsky, R. Hoppe*, Naturwissenschaften *53*, 501 (1966).
[21] *H. Sabrowsky, W. Bronger, D. Schmitz*, Z. Naturforsch. *B29*, 10 (1974).
[22] *Hk. Müller-Buschbaum, H. Mattausch*, Z. Anorg. Allg. Chem. *377*, 144 (1970).
[23] *C. Teske, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *379*, 234 (1970).
[24] *H. Pausch, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *426*, 184 (1976).
[25] *R. Kipka, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *419*, 58 (1976).
[26] *B. Grande, Hk. Müller-Buschbaum*, Z. Naturforsch. *B31*, 405 (1976).
[27] *R. Kipka, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *424*, 1 (1976).
[28] *R. Kipka*, Dissertation, Universität Kiel 1977.
[29] *B. Grande, Hk. Müller-Buschbaum*, Z. Naturforsch. *B31*, 405 (1976).
[30] *B. Grande, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *429*, 88 (1977).
[31] *C. Teske*, Dissertation, Universität Giessen 1970.
[32] *B. Grande, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *417*, 68 (1975).
[33] *B. Grande*, Dissertation, Universität Kiel 1977.
[34] *B. Grande, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem., in press.
[35] *C. Teske, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *371*, 325 (1969).
[36] *C. Teske, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *379*, 234 (1970).
[37] *H.-D. Wasel-Nielen, R. Hoppe*, Z. Anorg. Allg. Chem. *375*, 209 (1970).
[38] *B. Grande*, Diplomarbeit, Universität Kiel 1974.
[39] *M. Foex, A. Nancheron, M. Line*, C. R. Acad. Sci. *250*, 3028 (1960).
[40] *M. Foex*, Bull. Soc. Chim. Fr. *1961*, 109.
[41] *R. Frushour, K. Vorres*, A.E.C. Accession No. 46—246 Rept. Bo. TID-22-207, Paper E (1965).
[42] *V. F. Sawschenko, Ya. S. Rubinschik*, Vestn. Akad. Nauk Beloruss. SSR Ser. Khim. *1969*, 44.
[43] *Hk. Müller-Buschbaum, W. Wollschläger*, Z. Anorg. Allg. Chem. *414*, 76 (1975).
[44] *W. Wollschläger*, Diplomarbeit, Universität Kiel 1974.
[45] *B. Grande, Hk. Müller-Buschbaum, M. Schweizer*, Z. Anorg. Allg. Chem. *428*, 120 (1977).
[46] *M. Schweizer*, Diplomarbeit, Universität Kiel 1975.
[47] *C. Teske, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *370*, 134 (1969).
[48] *H. Drenkhahn, Hk. Müller-Buschbaum*, Z. Anorg. Allg. Chem. *418*, 116 (1975).
[49] *J. Zemann* (Wien), private communication.
[50] *J. J. Lander*, J. Am. Chem. Soc. *73*, 2450 (1951).
[51] *J. J. Lander, L. A. Wooten*, J. Am. Chem. Soc. *73*, 2452 (1951).
[52] *R. Hoppe* (Giessen), private communication.

[53] H. Mattausch, Diplomarbeit, Universität Kiel 1970.
[54] M. Arjomand, D. J. Machin, J. Chem. Soc. Dalton Trans. 1975, 1055.
[55] H. Krischner, K. Torkar, B. O. Kolbesen, J. Solid State Chem. 3, 349 (1971).
[56] R. Kipka, Hk. Müller-Buschbaum, Z. Anorg. Allg. Chem. 422, 231 (1976).
[57] R. v. Schenck, Hk. Müller-Buschbaum, Z. Anorg. Allg. Chem. 396, 113 (1973).
[58] M. Wilhelm, R. Hoppe, Z. Anorg. Allg. Chem. 409, 60 (1974).
[59] D. Cahen, J. A. Ibers, M. H. Mueller, Inorg. Chem. 13, 110 (1974).
[60] J. Waser, E. D. McClanahan, J. Chem. Phys. 19, 413 (1951); 20, 199 (1952).
[61] J. J. Scheer, A. E. van Arkel, R. Heyding, Can. J. Chem. 33, 683 (1955).
[62] R. C. Wnuk, T. R. Touw, B. Post, IBM J. Res. Dev. 8, 185 (1964).
[63] O. Muller, R. Roy, Adv. Chem. Ser. 98, 28 (1971).
[64] D. Bergner, R. Kohlhaas, Z. Anorg. Allg. Chem. 401, 15 (1973).
[65] D. Cahen, J. A. Ibers, R. D. Shannon, Inorg. Chem. 11, 2311 (1972).
[66] H. D. Wasel-Nielen, R. Hoppe, Z. Anorg. Allg. Chem. 375, 209 (1970).
[67] R. Kipka, Hk. Müller-Buschbaum, Z. Naturforsch. B31, 1067 (1976).
[68] B. Grande, Hk. Müller-Buschbaum, J. Inorg. Nucl. Chem. 39, 1084 (1977).
[69] R. Kipka, Hk. Müller-Buschbaum, Z. Naturforsch. B32, 121 (1977).
[70] R. Kipka, Hk. Müller-Buschbaum, Z. Naturforsch. B32, 124 (1977).
[71] J. Zemann, Fortschritte Mineral. 39, 59 (1961).
[72] D. Cahen, J. A. Ibers, J. B. Wagner, Jr., Inorg. Chem. 13, 1377 (1974).
[73] We thank Prof. Reinen for valuable discussions concerning this problem.

Some Aspects of Antibiotics Research[**]

By Hans Zähner[*]

The era of spectacular developments in the field of antibiotics appears to be over. Ever greater efforts are needed to find ever fewer new antibiotics. The view that well-considered hypotheses can lead as successfully as proven results to further research is supported by the establishment of five theses. "Non-classical" screening methods and the search for secondary metabolites with unusual properties can provide a rich harvest.

Introduction

Antibiotics have been intensively investigated for more than 30 years. The successes, which in the early years followed one another in quick succession, have now become rarer. The effort required for progress has increased and the optimism has waned; some believe that the approach to new antibiotics is now asymptotic and that searching further for them is no longer worthwhile. Against this mood of skepticism I wish to put forward five theses, which have on purpose been phrased provocatively.

Thesis 1: Only a small part of the conceivable fields for the introduction of antibiotics has so far been covered.

Table 1 shows, in greatly simplified form, the relationship between the fields already covered and the partially covered to open fields.

Antibiotics are of course also used today in the fields designated here as open, but the latter are nevertheless thus described because the antibiotics used there are not satisfactory in every respect. For example, large quantities of antibiotics are used in animal feeds: insofar as they are used also in human medicine, they must be replaced. In practice, the only field described as wholly closed concerns infections by gram-positive bacteria in human medicine. The fields of protozoa, worms, and viruses are completely open; for the fields of tumors and systemic mycoses, antibiotics are only partially satisfactory.

One of the reasons for the uneven coverage of the various fields is that the correlation between the first screening tests and the desired action at the point of application is of very variable quality; the weaker this correlation, the more time-consuming and expensive is the work and the smaller is the prospect of success. The high cost of finding and preparing the antibiotics is, however, offset by the great economic interest.

Table 1. Possible fields for the introduction of antibiotics.

Fields covered	Fields partially covered	Open fields
Medical applications	Medical applications	Medical applications
Gram-negative bacteria	Gram-negative bacteria including multiresistant bacteria	Protozoa Systemic mycoses Worms Viruses Tumors
Nonmedical applications	Nonmedical applications	Nonmedical applications
	Phytopathogenic fungi	Phytopathogenic bacteria Phytopathogenic viruses Insects and mites Nematodes Snails Nutritive uses

According to a compilation by *Berdy*[1], 4076 antibiotics were known at the end of 1972. Each group concerned with the search for new antibiotics comes inescapably to the view that the proportion of new substances to those investigated is decreasing. For example, in the years 1954/55 we found one to three new antibiotics for every 1000 Actinomycetes strains tested, and only one out of 20 antibiotics actually investigated was new[2]. By 1958 the proportion of new antibiotics had fallen to less than one per thousand strains tested, and

[*] Prof. Dr. H. Zähner
Institut für Biologie II der Universität
Auf der Morgenstelle 28, D-7400 Tübingen (Germany)

[**] Based on a lecture at the Fifth International Fermentation Symposium, Berlin, July 1976.

not even every fiftieth antibiotic selected for study was new. These observations, together with the very large number of antibiotics described by then, have led to the view that we already know a large proportion of all existing antibiotics. To oppose this view I wish to present Thesis II.

Thesis II: Only a small fraction of the natural antibiotics has so far been found

Up to a few years ago all antibiotics laboratories were using the same test methods and to some extent even the same test organisms. Only recently has the spectrum of the test methods become substantially wider. The classical methods are derived mainly from *Waksman*, and can be characterized by the following points:

there is an attempt to correlate the first test with later application as closely as possible;
all the tests depend on growth-inhibition or killing of the test organism;
all the tests are carried out under optimal conditions, *i.e.* with complex nutrient media;
all the tests are diffusion tests.

Two factors are decisive for the results of an antibiotic screening: the microorganisms and the test methods. Although this statement may be trivial, it has not been taken sufficiently into account, at least as far as the test methods are concerned. If one departs from the classical tests (see above), then quite a different selection of substances is obtained. In many antibiotics indications there is no satisfactory correlation between the first test and the desired action at the point of application. If this failure is regarded as a virtue and no account is taken of any correlation between the first test and the later application, *i.e.* if the first test is used only as a guide to the isolation of a new metabolite, then the other criteria of the classical test can also be disregarded.

The extent to which the test decides what will be found may be illustrated here by some examples from our own experience. Antifungal substances are still sought mostly by the classical method, with yeasts or fungal spores in a plate diffusion test; with actinomycetes one finds in this way a large number of polyenes as well as cycloheximide and antimycins. If the growth-inhibition criterion is replaced by the criterion of abnormal growth of the hyphae[3] or inhibition of zygospore formation[4], one then finds a wholly different spectrum of antifungal antibiotics from actinomycetes, namely compounds *(1)* to *(3)*.

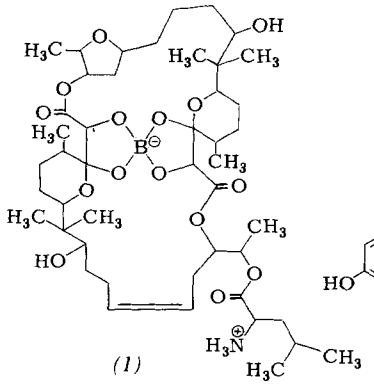
From its action, boromycin *(1)*[5], the first boron-containing natural product, belongs to the ionophoric antibiotics[7]. Its structure was clarified by *Prelog et al.*[6].

Venturidicin B *(2)* is an antifungal macrolide[8] whose structure was determined by *Keller-Schierlein et al.*[9]. Nikkomycin *(3)*, a nucleoside antibiotic related to the polyoxines[10], inhibits chitin synthesis[11].

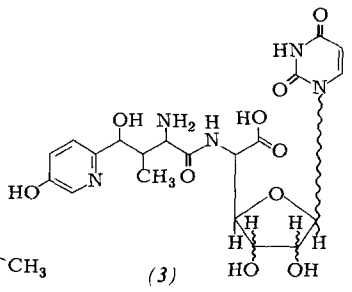
Simple and chemically well-defined media are used in the search for substances that show activity only in such simple media, and replacing the optimal complex nutrient media by such simpler ones leads to numerous antimetabolites[12] on the one hand and to some unusual new antibiotics on the other; examples of the latter are *(4)* to *(7)*.

Manumycin *(4)*[13] is an antibiotic that interferes with protein synthesis of prokaryotic cells[14]. α- *(5)* and β-lipomycin *(6)*[15], together with oleficin[16], constitute a new group of antibiotics that interfere with lipids[17].

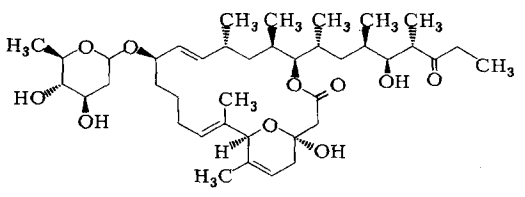
Chlorothricin *(7)*[18] is an unusual chlorine-containing macrolide that acts as an antagonist of acetyl-CoA[19] instead of inhibiting protein synthesis like the usual macrolides.



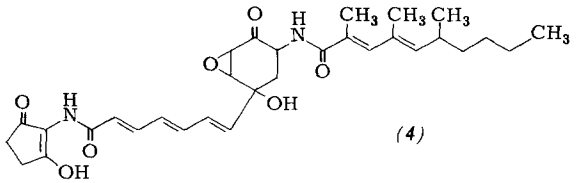
(1)



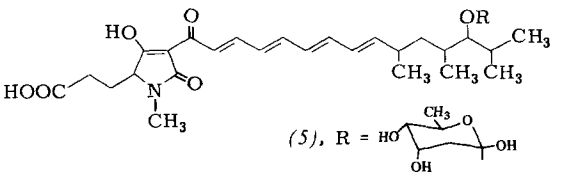
(3)



(2)

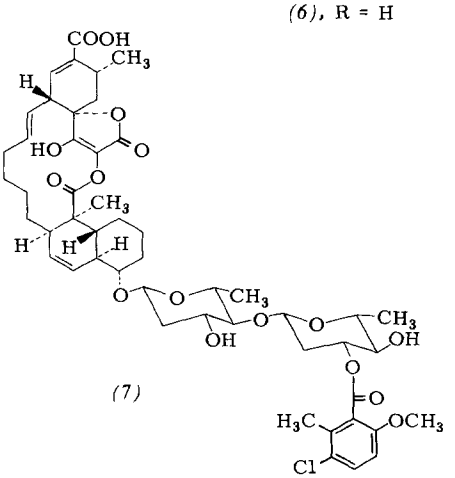


(4)



(5), R =

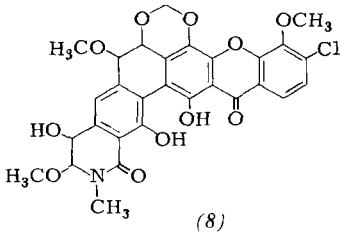
(6), R = H



(7)

If we now transfer our attention to antibiotics that diffuse only slowly—for which unfortunately there is still no generally

applicable test—we again find antibiotics that differ from those selected by the classical test procedures. As an example we may cite lysolipin I *(8)*[20] which, together with albofungin[21], forms a group of antibiotics whose mode of action and possible application have so far been little studied.



(8)

The modifications indicated above open up only a small fraction of the possible variations of the classical test procedures. New test methods are advantageously selected in such a way as to facilitate the identification or exclusion of known antibiotics. Examples of "nonclassical" screening are collected in Table 2.

Table 2. Some possibilities of "nonclassical" screening for microbial metabolites.

1. Search for antibiotics effective only under conditions nonoptimal for the test organisms, *e.g.* only on simple and chemically well-defined media or at nonoptimal temperatures
2. Use of permeation-damaged test organisms, *e.g.* extreme R-forms of *Enterobacteriaceae* or stable L-forms [a]
3. Use of extremely sensitive wild strains with consideration of antibiotics that are effective only against these "oversensitive" strains (narrow-spectrum antibiotics)
4. Search for antibiotics effective only in conjunction with detergents or ethylenediaminetetraacetic acid, *i.e.* antibiotics that require "help" for penetration
5. Cell-free systems of certain enzymes, *e.g.* proteases, dopa-decarboxylases, neuramidases, or chitin-synthetases and systems in which cell-free protein synthesis will occur, serve as indicators of activity
6. Application of criteria other than growth inhibition or death, *e.g.* action on differentiation and morphogenesis
7. Application of reactions for specific chemical groups as criteria, *e.g.* for reducing groups, amines, alkaloids, chlorine-containing or sulfur-containing metabolites
8. Application of methods from the field of "microbial transformation" [b]

[a] R-forms are gram-negative bacteria with incomplete lipopolysaccharides, L-forms are bacteria with either severely damaged or no cell wall.
[b] "Microbial transformation" means here the modification of organic compounds by microorganisms.

The new test methods indicated in Table 2 greatly increase the number of metabolites still to be discovered, although in such processes the boundary between antibiotics and other microbial metabolites begins to fade. If we combine the large number of possible new test methods with the almost unlimited number of microorganisms and consider that mutations increase the number of variations still further, we arrive at the thesis at the beginning of this section: so far we know only a small fraction of the natural antibiotics.

Thesis III: The problems of antibiotic transport have been neglected far too long

Antibiotics can be divided schematically into two groups: Group I, membranophilic antibiotics, and Group II, nonmembranophilic antibiotics.

The antibiotics of Group I attach themselves to or penetrate the cell wall of bacteria or fungi and there exert their activity; these antibiotics must not penetrate into the interior of the cell. To this group belong, among others, all the ionophoric antibiotics, polymyxins, colistins, lipomycins, and lysolipin I.

The antibiotics of Group II must penetrate into the cell, since their site of action is in the cell interior. Group II consists of antibiotics that attack primarily nucleic acid synthesis, protein synthesis, or the synthesis of metabolic intermediates. Examples are actinomycins, anthracyclines, tetracyclines, macrolides, aminoglycosides, and rifamycins, as well as chloramphenicol, cycloserine, and phosphonomycin. In the case of the gram-negative bacteria these antibiotics must pass through two membranes: the outer membrane and the cytoplasmic membrane.

The same possibilities are available for the uptake of antibiotics[22] of Group II into the cell as for the uptake of substrates, namely: a) active transport, b) facilitated diffusion, and c) passive diffusion.

We shall concern ourselves in detail with active transport further below. The second possible mode of uptake, namely facilitated diffusion, cannot yet be exemplified; on theoretical grounds, however, it must be assumed that such systems require the uptake of large, not very lipophilic molecules. The third possibility, namely passive diffusion, is not conceivable according to the liquid mosaic model of membrane structure, at least not for large antibiotic molecules such as vancomycins, avilamycin/everinomycin, actinomycins, *etc.*

Owing to the several systems of active transport the bacterial cell can take up substrates even from highly dilute solutions. Failing such a system of active transport, *e.g.* as a result of mutation, much higher concentrations of the relevant substrate must be offered up to the cell to maintain the normal growth rate. Since antibiotics are sometimes active in extremely low concentrations, and in individual cases their enrichment in the cell has also been demonstrated, the suspicion arises that some of the antibiotic enters the cell by active transport; nevertheless, proof of enrichment is not yet proof of active transport, for even passive diffusion can lead to enrichment if there is a specific bonding site in the cell.

The transport systems for the substrates of bacterial cells are astonishingly specific. Since it cannot be assumed that special transport systems are set up for antibiotics, the question arises, which of the transport systems of the bacterial cell is drawn upon for this purpose. In other words, which substrate-transport system is misused by the antibiotic? Transport by way of the D-alanine system[23] has been demonstrated for cycloserine, and it has been shown that phosphonomycin is taken up both by means of the transport system for glycerophosphate and by means of an inducible transport system for glucose 6-phosphate[24]. Bacilysin can enter the cell by means of a dipeptide transport system[25]. The utilization of "normal" transport systems for the uptake of antibiotics will be illustrated here by three examples.

1. The Sideramine-Sideromycin Transport System

The sideramines, *e.g.* ferrichrome *(9)* and ferrioxamine B *(11)*, are microbial iron-transport compounds that are very soluble in water and permit optimal access of iron to the cell. Practically all microorganisms secrete either sideramines or related iron-complexing agents into the medium. Among

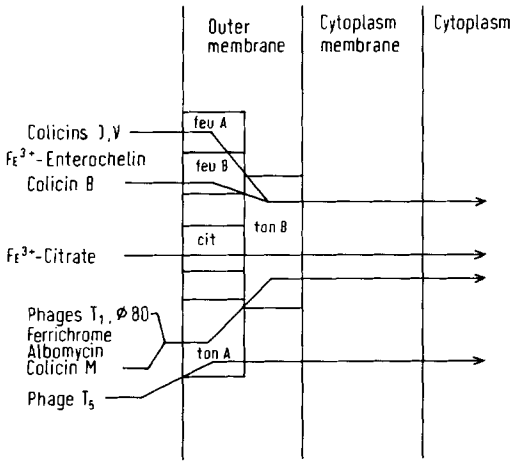
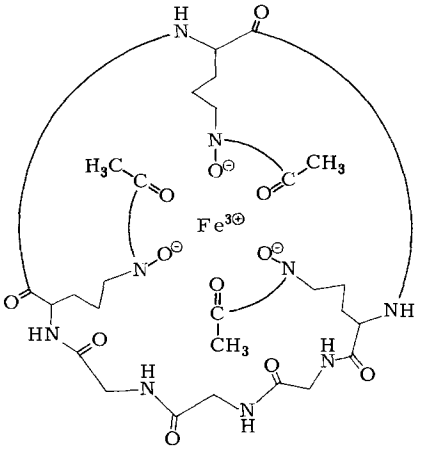


Fig. 1. System of Fe^{3+} transport in *Escherichia coli* [29]. For explanation see text.

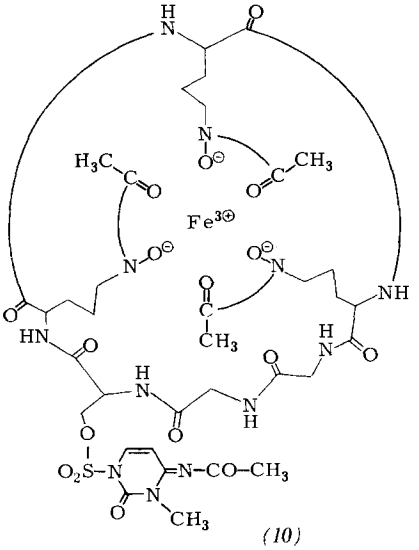
the sideromycins are included albomycin *(10)* and ferrimycin A_1 *(12)*. The antagonism between sideramines and sideromycins[26] rests on antagonism in transport[27,28]. *Hantke* and *Braun*[29] have investigated in detail the conditions for iron transport in *E. coli*, and have shown that ferrichrome *(9)* and albomycin *(10)* compete for bonding to the product of the gene ton A. The very complicated situation of the iron transport in *E. coli* is reproduced in Figure 1.

The product of the gene ton B is involved as well as the product of gene ton A in the ferrichrome uptake system. These gene products are proteins of the outer membrane of *E. coli* (from a chemical viewpoint these proteins deserve further investigation), whereas the genes ton A and ton B have already been mapped on the *E. coli* chromosome. This uptake system is used also by phages T_1 and ϕ 80 and by colicin M.

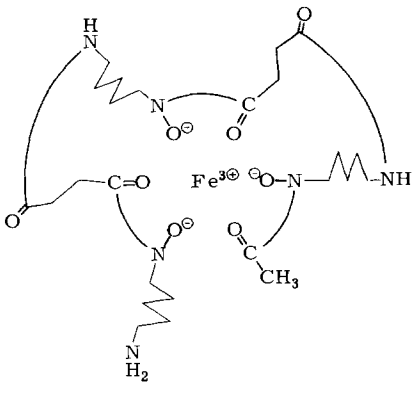
According to recent studies by *Wolf* and *Dengler*[34], the sideromycins inhibit protein synthesis in *E. coli* by inhibiting the transfer of certain amino acids to tRNA. The mode of the action of sideromycins thus has nothing to do with the antagonism to sideramines, *i.e.* to competition in transport.



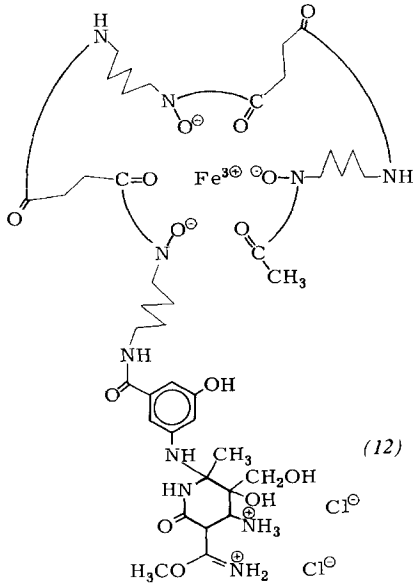
(9)



(10)



(11)



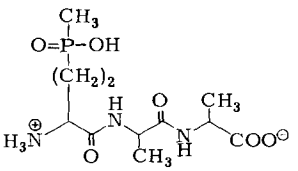
(12)

Sideramines are being investigated to an increasing extent[35], and a marked specificity in their formation and, in partial correspondence therewith, a specificity of transport, have become evident[36]. It is particularly interesting to note that specific sideramine-transport systems occur in organisms that themselves do not form sideramines. For example, *E. coli* synthesizes enterochelin as an iron-transport compound, but has a bonding protein specific for ferrichrome and can utilize the iron from ferrichrome. Higher cells too, *e.g.* bone marrow cells, are able to transport sideramines specifically and at mutually differing rates, and to utilize their iron for heme synthesis[37].

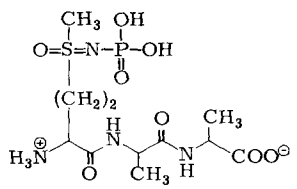
The close structural relationship between sideramines and sideromycins becomes clear if we contrast ferrichrome *(9)*[30] and albomycin *(10)*[31] with ferrioxamine B *(11)*[32] and ferrimycin A_1 *(12)*[33]. Ferrimycin A_1 *(12)* contains the complete molecule of ferrioxamine B *(11)*; the additional part has a molecular weight of more than 400. Albomycin *(10)* inhibits gram-negative and gram-positive bacteria; in both bacterial groups its action is antagonized by ferrichrome *(9)* and related sideramines. Ferrimycin A_1 *(12)* inhibits only gram-positive bacteria, and correspondingly ferrioxamine B *(11)* hinders the action of albomycin *(10)* only in gram-positive and not in gram-negative bacteria.

2. The Oligopeptide-Transport System

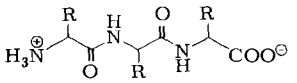
Payne and *Gilvarg*[39] have described a transport system for oligopeptides in *E. coli*. This system, which probably occurs widely in bacteria, transports tripeptides of the type *(15)*, tetrapeptides, and in some cases even pentapeptides, almost independently of their composition. We were recently able to show[38] that the tripeptide antibiotics phosphinothricylalanylalanine *(13)*[40] and phosphonomethioninesulfoximinylalanylalanine *(14)*[41] are conveyed by this transport system into the cell where they act as inhibitors of glutamine synthetase. In the cell they are split by a peptidase, with liberation in each case of the active component, which is always an unusual phosphorus-containing amino acid. Failure of the oligopeptide-transport system leads in *E. coli* to resistance to the two antibiotics.



(13)



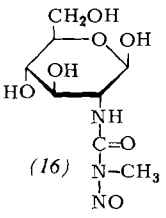
(14)



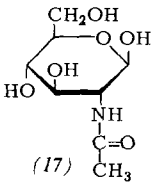
(15)

3. Transport of Antibiotics by the Phosphoenolpyruvate: Sugar-Phosphotransferase System

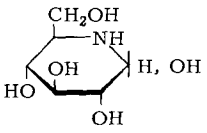
Schindler[42] has recently proved that streptozotocin *(16)*[43] and nojirimycin *(18)*[44] enter the cell by means of the phosphoenolpyruvate: sugar-phosphotransferase system[45]. This transferase system contains several enzymes. The protein designated as enzyme II recognizes the relevant sugar and is thus specific for certain sugars, whereas the remaining portions—enzyme I and a protein designated HPr—are the same irrespective of the sugars transported by the system. It is not yet clear whether phosphorylation occurs during the transport of streptozotocin *(16)* and nojirimycin *(18)*, or whether these antibiotics use the sugar-recognizing enzyme II and then penetrate into the cell more or less passively.



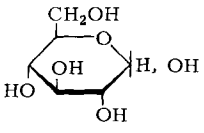
(16)



(17)



(18)



(19)

In the case of active antibiotic transport described above there is a clear relationship between the antibiotics, *e.g. (16)* and *(18)*, and the corresponding substrates, here *N*-acetylglucosamine *(17)* and D-glucose *(19)*, respectively. The same is true of the transport routes of cycloserine and phosphonomycin. For antibiotics of complicated structure no relationship to specific substrates can be seen, and proof of active transport is hardly possible in such cases. Nevertheless, it would be worthwhile to look for other actively transported antibiotics and to investigate their transport systems in detail. Further progress should follow better understanding of the antibiotic transport:

If it were known what transport system introduces complicated molecules into the cell, this system could perhaps also be misused for the transport of inhibitors of a different kind.

If the resistance is a resistance to penetration, as in the case of tetracyclines, it could perhaps be overcome by coupling the antibiotic with a carrier. In narrow-spectrum antibiotics the spectrum could perhaps be appreciably broadened by making derivatives designed to improve the transport properties.

Thesis IV: Antibiotics are secondary metabolites whose importance to the producer cell should be sought at the levels of primary metabolism, regulation, transport, and differentiation or morphogenesis rather than in defense against competitors

The wide distribution of antibiotics and the variety of their structures and points of attack lead repeatedly to the question

of the importance of antibiotics to the producer cell. In textbooks antibiotics are regarded as of major significance in competition between microorganisms, even if it is not assumed that microorganisms form antibiotics in order to keep other organisms away from the body. Several items of evidence lead us to doubt the "defense theory of antibiotics":

Many antibiotic-producing organisms are just as sensitive to their own antibiotics as are their competitors.

Some antibiotics are first produced at the end of the logarithmic phase of growth, often in connection with spore formation; if the spores are sensitive to the producer's own antibiotic, then clearly this must be degraded or inactivated by other organisms before germination is possible.

Only in exceptional cases can the presence of an antibiotic in its natural ecological niche be demonstrated.

The action spectrum of the antibiotics formed rarely coincides with the spectrum of the competitors.

We have declared antibiotics to be secondary metabolites that more or less accidentally possess antibiotic action. Next, we shall discuss the role of secondary metabolism. Are secondary metabolites really only waste products of primary metabolism or uneliminated residues of phylogenetic development[46]?

The development of organisms occurs at the levels of primary metabolism, metabolic regulation, material transport, differentiation, and morphogenesis. The driving force for further development is the interplay of increasing variation due to mutation with decreasing variation due to selection. Quite recently *Eigen* and *Winkler*[47] worked out afresh this interplay character of evolution. The extremely rigorous boundary conditions—the need to maintain reproductive and competitive capabilities—lead to the result that there is very little margin for the interplay between mutation and selection. One can thus imagine that latitude exists where the boundary conditions are less severe.

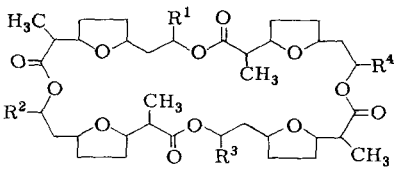
An example may clarify the gross difference in latitude between the primary and secondary metabolism. In primary metabolism a change in a product leads at once to death of the cell unless the new product can take over all the functions of the original product. In contrast, in secondary metabolism a product can be changed in any desired way so long as the change does not have an adverse effect at any of the above five levels. This has the result that in secondary metabolism there are often variations on a theme, *e.g.* a single strain may produce twenty anthracyclines.

This latitude of secondary metabolism should not be considered as isolated from the five levels of primary metabolism, metabolic regulation, material transport, differentiation, and morphogenesis. On the one hand the building units and various enzymes for secondary metabolism are derived from these levels, and on the other hand their results are taken up into a level if they are advantageous there. There are many substance groups that stand between secondary metabolism and one of the levels. Two examples will illustrate this point, and at the same time show the "fortuitousness" of antibiotic activity.

Sideramines, *e.g. (9)* and *(11)*, are assigned to iron transport; they occur in nature in great variety. On the one hand, there is a considerable specificity in sideramine formation, and on the other hand most sideramine-producers form many similar sideramines. For example, ferrioxamines A_1, A_2, B, C, D_1, D_2, E, F, and G can be isolated from the same Actinomyces strain[32]. Sideramines show the characteristics of both secondary metabolism (specificity of formation, variation) and of primary metabolism (function in iron transport). Of the nine ferrioxamines only the iron-free ferrioxamine E is active; it has been previously described as an antibiotic under the name nocardamine[48]. Its activity rests on the fact that it is a very strong iron-complexing agent and that many organisms are unable to remove the iron from the nocardamine-iron complex. The number of actinomycetes whose main component is ferrioxamine B (an antibiotically inactive component) is considerably greater than the number of actinomycetes that have nocardamine (iron-free ferrioxamine E) as the main component. It seems more or less accidental that, in addition to fulfilling its function in iron-transport in the producer cell, nocardamine also exerts an antibiotic effect on other microorganisms. In the fungal sideramine series of more than twenty individuals only one compound manifests antibiotic activity, namely deferritriacetylfusigen[49].

The observation that only one or a few members of a naturally occurring variation has or have antibiotic activity could be made much more frequently if antibiotic activity were not made the guideline for the isolation of secondary metabolites.

The second example is provided by the macrotetrolides *(20)*[50]. These are ionophoric antibiotics that have so far



(20a), $R^1 = R^2 = R^3 = R^4 = CH_3$, Nonactin
(20b), $R^1 = R^2 = R^3 = CH_3$, $R^4 = C_2H_5$, Monactin
(20c), $R^1 = R^3 = CH_3$, $R^2 = R^4 = C_2H_5$, Dinactin
(20d), $R^1 = CH_3$, $R^2 = R^3 = R^4 = C_2H_5$, Trinactin

been reported from only one, admittedly large, series of actinomycetes. Other microorganisms yield other ionophoric antibiotics. Biophysicists have found in them excellent models for the study of ion transport; whether they fulfil the same function in the producer cell is still an open question.

By using the nonactin-producing *Streptomyces griseus* as an example we can show that the producer may reap an advantage from its ability to produce such substances; mutants without this capability are at a disadvantage when the sodium-potassium ratios in the medium are unfavorable in comparison with the macrotetrolide producers[51]. Moreover, there are *Streptococcus faecalis* mutants[52] with a disturbed alkali-metal-ion transport; the wild strain also produces an ionophoric antibiotic[53], but it is not yet known whether this is absent from the above mutants. These ionophoric antibiotics show all the characteristics of secondary metabolites (specificity of formation, variation) and also play a part in the ion-economy of the producer; the antibiotic activity is connected with this more or less accidentally.

For some few examples it has been found[53] that at least part of the information for antibiotic synthesis can reside in the plasmids and not in the chromosome. Following this discovery it has been discussed how large is the proportion that resides in the plasmids compared with the total information on secondary metabolism. If this proportion is significant, then also on the genetic level the boundary conditions for the mutation/selection interplay would be less stringent in the secondary-metabolism area than in other areas. Plasmids can be duplicated more easily than portions of chromosomes and they can also reproduce outside the predecessor-successor chain. The transferability of plasmids to other organisms could appreciably accelerate the development and dissemination of a new possibility.

The hypothesis proposed here about the function of secondary metabolism as the "latitude" of phylogenetic development ascribes much greater importance to it than did earlier hypotheses. Secondary metabolism is thus the field where future developments will occur.

If secondary metabolism is in fact the "latitude" of biochemical evolution, then new metabolites, including new antibiotics, are continually being formed, and in numbers greater than we can describe. Thesis II as originally proposed, that we know only a small fraction of natural antibiotics, would then need to be amplified: we shall never isolate more than a small proportion of natural antibiotics.

Thesis V: Biological engineering processes also have their dangers

Here I should like to draw special attention to some dangers of the new possibilities offered by biological engineering in general and by antibiotics research in particular.

1. Highly impure water runs to waste from biological engineering processes. To purify it sufficiently for addition to the usual biological clarification plants requires more than mere neutralization or dilution; very probably special biological purification procedures will have to be included. Direct discharge into drainage systems or the sea must be ruled out.

2. Microorganisms can trigger off allergies. This is the case particularly with fungal spores, but also with certain constituents of microorganisms. These points must be borne in mind in the introduction of new biological engineering processes or in the reorganization of existing processes.

3. Microorganisms generally produce secondary metabolites, not only the desired ones, but often also undesirable and previously unknown ones. Most of the bio-engineering processes now in use have not yet been sufficiently investigated for the occurrence of undesirable secondary metabolites. Until proved innocent, each strain of *Penicillium* or *Aspergillus* should be examined for the formation of the extremely carcinogenic aflatoxins or other mycotoxins[53]. Most of the substrates used in biological engineering are ideal nutrient media for these fungi and are often massively contaminated with them. The control on mycotoxins must also be extended to the substrates of other processes if there is a possibility that one of the mycotoxins can make human contact[55].

4. In biological engineering processes increasing use is made of strains whose pathogenicity to man, animals, or plant life, and whose capacity to damage wood, textiles, or foodstuffs have been little studied. If, for example, we were to begin worldwide cultivation of edible fungi that have previously been grown only regionally, then a careful watch should be kept to see whether in their new environment they are not phytopathogenic or do not destroy wood. If the physiological properties of microorganisms are changed by mutation, *e.g.* the temperature optimum, then the pathogenicity must be rechecked. Changes in the action spectrum of weakly pathogenic strains should be taken into account just as much as the pathogenicity for a certain species.

It is true that the above-mentioned dangers are less spectacular in their effects than those that can arise from genetic engineering[54], but the likelihood of their occurrence is considerably higher. It is our responsibility to meet this danger with circumspection and care and to help to ensure that undesirable developments do not occur.

The work described in this article was carried out mainly within the framework of Sonderforschungsbereich 76 "Chemical Biology of Microorganisms". I am indebted to the Deutsche Forschungsgemeinschaft for generous aid, and to the many collaborators and partners without whose help this work could not have been accomplished.

Received: October 25, 1976 [A 178 IE]
German version: Angew. Chem. *89*, 696 (1977)
Translated by Express Translation Service, London

[1] *J. Berdy*, Adv. Appl. Microbiol. *18*, 309 (1974).
[2] This result accords with the data from *H. B. Woodruff, L. E. MacDaniel* in *S. T. Cowan, E. Rowatt:* The Strategy of Chemotherapy, 8th Symp. Soc. Gen. Microbiol., London 1958.
[3] Description of test arrangements: *R. Hütter, W. Keller-Schierlein, J. Nüesch, H. Zähner*, Arch. Mikrobiol. *51*, 1 (1965).
[4] Description of test arrangements: *H. Kneifel, W. A. König, G. Wolf, H. Zähner*, J. Antibiot. *27*, 20 (1974).
[5] *R. Hütter, W. Keller-Schierlein, F. Knüsel, V. Prelog, G. C. Rodgers, P. Suter, G. Vogel, W. Voser, H. Zähner*, Helv. Chim. Acta *50*, 1533 (1967).
[6] *J. D. Dunitz, D. M. Hawley, D. Miklos, D. N. J. White, Yu. Berlin, R. Marušić, V. Prelog*, Helv. Chim. Acta *54*, 1709 (1971).
[7] *W. Pache, H. Zähner*, Arch. Microbiol. *67*, 156 (1969).
[8] *M. Brufani, W. Keller-Schierlein, W. Löffler, I. Mansperger, H. Zähner*, Helv. Chim. Acta *51*, 1293 (1968), first description of venturicidin B. Venturicidin A: *A. Rhodes, K. H. Fantes, B. Boothroyd, M. P. McGonagle, R. Grosse*, Nature *192*, 952 (1961); *P. Langcake, R. B. Beechey, C. R. Lindop, S. G. A. Wickins, D. P. Lepworthy, D. E. Wiggins, J. M. Broughall*, Trans. Biochem. Soc. *2*, 202 (1974).
[9] *M. Brufani, S. Cerrini, W. Fedeli, C. Musu, L. Cellai, W. Keller-Schierlein*, Experientia *27*, 604 (1971); *M. Brufani, L. Cellai, C. Musu, W. Keller-Schierlein*, Helv. Chim. Acta *55*, 2329 (1972).
[10] *K. Isono, K. Asahi, S. Suzuki*, J. Am. Chem. Soc. *91*, 7490 (1969).
[11] *U. Dähn, H. Hagenmaier, H. Höhne, W. A. König, G. Wolf, H. Zähner*, Arch. Microbiol. *107*, 143 (1976).
[12] *D. L. Pruess, J. P. Scannell*, Adv. Appl. Microbiol. *17*, 19 (1974).
[13] *F. Buzetti, E. Gäumann, R. Hütter, W. Keller-Schierlein, L. Neipp, V. Prelog, H. Zähner*, Pharm. Acta Helv. *38*, 871 (1963); *K. Schröder, A. Zeeck*, Tetrahedron Lett. *1973*, 4995.
[14] *H. Wolf*, Tübingen, private communication.
[15] *B. Kunze, K. Schabacher, H. Zähner, A. Zeeck*, Arch. Microbiol. *86*, 147 (1972); *K. Schabacher, A. Zeeck*, Tetrahedron Lett. *1973*, 2691.
[16] *J. Gyimesi, I. Ott, I. Koszka, K. Magyar*, J. Antibiot. *24*, 278 (1971); *Gy. Horváth, J. Gyimesi, Zs. Méhesfalvi-Vajna*, Tetrahedron Lett. *1973*, 3643.
[17] *B. Kunze*, Dissertation, Universität Tübingen 1975.
[18] *W. Keller-Schierlein, R. Muntwyler, W. Pache, H. Zähner*, Helv. Chim. Acta *52*, 127 (1969); *R. Muntwyler, J. Widmer, W. Keller-Schierlein, ibid. 53*, 1544 (1970); *R. Muntwyler, W. Keller-Schierlein, ibid. 55*, 2071 (1972); *M. Brufani, S. Cerrini, W. Fedeli, F. Mazza, R. Muntwyler, ibid. 55*, 2094 (1972); *A. Gerhard, R. Muntwyler, W. Keller-Schierlein, ibid. 58*, 1323 (1975).

[19] *P. W. Schindler, H. Zähner*, Arch. Microbiol. *82*, 66 (1972); Eur. J. Biochem. *39*, 591 (1973); *P. W. Schindler, ibid. 51*, 579 (1975); *P. W. Schindler, M. C. Scrutton, ibid. 55*, 543 (1975).

[20] *H. Drautz, W. Keller-Schierlein, H. Zähner*, Arch. Microbiol. *106*, 175 (1975); Abstr. Fifth Int. Fermentation Symp., Berlin 1976, p. 233. Structure determination: *W. Keller-Schierlein, M. Dobler* (Zürich), unpublished data.

[21] *A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. N. Omelchenko, V. V. Onoprienko, G. I. Petrenko, S. A. Popravko*, Tetrahedron Lett. *1972*, 1751; *A. I. Gurevich, T. N. Deshko, G. A. Kogan, M. N. Kolosov, V. V. Kudryashova, V. V. Onoprienko, ibid. 1974*, 2801; *A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. N. Omelchenko, V. V. Onoprienko, G. I. Petrenko, I. I. Chervin, G. I. Yakovlev*, Sov. J. Bioorg. Chem. *1*, 62 (1975); *A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. V. Onoprienko, G. I. Petrenko, I. I. Chervin, G. I. Yakovlev, ibid. 1*, 67 (1975).

[22] *T. J. Franklin* in *B. Spencer:* Industrial Aspects of Biochemistry. Federation Eur. Biochem. Soc. Vol. 30, Part II, Amsterdam 1974; Crit. Rev. Microbiol. *30*, 253 (1973), was the first to draw urgent attention to these questions and to collect previous data.

[23] *R. J. Wargel, G. A. Shadur, F. C. Neuhaus*, J. Bacteriol. *105*, 1028 (1971).

[24] *F. M. Kahan, J. S. Kahan, P. J. Cassidy, H. Kropp*, Ann. N. Y. Acad. Sci. *235*, 364 (1974).

[25] *M. Kenig, E. P. Abraham*, J. Gen. Microbiol. *94*, 37 (1976); *M. Kenig, E. Vandamme, E. P. Abraham, ibid. 94*, 46 (1976).

[26] *H. Bickel, E. Gäumann, W. Keller-Schierlein, V. Prelog, E. Vischer, A. Wettstein, H. Zähner*, Experientia *16*, 129 (1960); *H. Zähner, R. Hütter, E. Bachmann*, Arch. Microbiol. *36*, 325 (1960).

[27] *J. Nüesch, F. Knüsel* in *D. Gottlieb, P. D. Shaw:* Antibiotics. Vol. 1. Springer, Berlin 1967.

[28] *F. Knüsel, W. Zimmermann* in *J. W. Corcoran, F. E. Hahn:* Antibiotics. Vol. 3. Springer, Berlin 1975.

[29] *K. Hantke, V. Braun*, FEBS Lett. *49*, 301 (1975). Figure 1 is supplemented by still unpublished work by *V. Braun* and *K. Hantke*.

[30] Ferrichrome; first description: *J. B. Neilands*, J. Am. Chem. Soc. *74*, 4846 (1952); elucidation of structure: *S. J. Rogers, A. J. Warren, J. B. Neilands*, Nature *200*, 167 (1963); synthesis: *B. Maurer, W. Keller-Schierlein*, Helv. Chim. Acta *52*, 388 (1969); *W. Keller-Schierlein, B. Maurer, ibid. 52*, 603 (1969).

[31] Albomycin, first description: *G. F. Gause, M. G. Brazhnikova*, Nov. Med. (Moskau) *23*, 35 (1951); the identity with grisein [*D. M. Reynolds, A. Schatz, S. A. Waksman*, Proc. Soc. Exp. Biol. *64*, 50 (1947)] was proved by *E. O. Stapley, R. E. Ormond*, Science *125*, 587 (1957); structure determination: *O. Mikeš, J. Turková, F. Šorm*, Collect. Czech. Chem. Commun. *28*, 1747 (1963); *J. Turková, O. Mikeš, F. Šorm, ibid. 30*, 118 (1965); *31*, 2444 (1966). Doubts about the formula: *H. Maehr, R. G. Pitcher*, J. Antibiot. *24*, 830 (1971).

[32] Ferrioxamin B, first description: *H. Bickel, R. Bosshardt, E. Gäumann, P. Reusser, E. Vischer, W. Voser, A. Wettstein, H. Zähner*, Helv. Chim. Acta *43*, 2118 (1960); structure determination: *H. Bickel, G. E. Hall, W. Keller-Schierlein, V. Prelog, E. Vischer, A. Wettstein, ibid. 43*, 2129 (1960); synthesis: *V. Prelog, A. Walser, ibid. 45*, 631 (1962).

[33] Ferrimycin A_1, first description: *H. Bickel, E. Gäumann, G. Nussberger, P. Reusser, E. Vischer, W. Voser, A. Wettstein, H. Zähner*, Helv. Chim. Acta *43*, 2105 (1960); structure determination: *H. Bickel, P. Mertens, V. Prelog, J. Seibl, A. Walser*, Tetrahedron Suppl. 8, Part I, 171 (1966).

[34] *H. Wolf, D. Dengler* (Tübingen), unpublished work.

[35] *J. B. Neilands:* Microbial Iron Metabolism. Academic Press, New York 1974; summary: *H. Diekmann, E. Krezdorn*, Arch. Microbiol. *106*, 191 (1975); *R. E. Morre, Th. Emery*, Biochemistry *15*, 2719 (1976); *Th. Emery, ibid. 15*, 2723 (1976) (as examples of new original papers).

[36] *G. Winkelmann, H. Zähner*, Arch. Microbiol. *88*, 49 (1973); *G. Winkelmann, A. Barnekow, D. Ilgner, H. Zähner, ibid. 92*, 285 (1973); *G. Winkelmann, ibid. 98*, 39 (1974); *C. Wiebe, G. Winkelmann*, J. Bacteriol. *123*, 837 (1975).

[37] *A. Barnekow, G. Winkelmann, H. Zähner*, Arch. Microbiol. *100*, 329 (1974); *A. Barnekow, G. Winkelmann*, Exp. Hematol. (Copenhagen) *4*, 70 (1976).

[38] *H. Diddens, H. Zähner, E. Kraas, W. Göring, G. Jong*, Eur. J. Biochem. *66*, 11 (1976).

[39] *J. W. Payne, Ch. Gilvarg*, Adv. Enzymol. *35*, 187 (1971); *J. W. Payne*, Front. Biol. *37*, 283 (1975); Adv. Microb. Physiol. *13*, 55 (1976).

[40] *E. Bayer, K. H. Gugel, K. Hägele, H. Hagenmaier, S. Jessipow, W. A. König, H. Zähner*, Helv. Chim. Acta *55*, 224 (1972); *Y. Kondo, T. Shomura, Y. Ogawa, T. Tsuruoka, H. Watanabe, K. Totzukawa, T. Suzuki, C. Moriyama, J. Yoshida, S. Inouje, T. Niida*, Sci. Rep. Meiji Seika Kaisha *13*, 34 (1973); *Y. Ogawa, T. Tsuruoka, S. Inouje, T. Niida, ibid. 13*, 42 (1973); *Y. Ogawa, J. Yoshida, S. Inouje, T. Niida, ibid. 13*, 49 (1973); *13*, 54 (1973); *N. Ezaki, S. Amano, K. Fukushima, S. Inouje, T. Niida, ibid. 13*, 60 (1973).

[41] *D. L. Preuss, J. P. Scannell, H. A. Ax, M. Kellett, F. Weiss, T. C. Demny, A. Stempel*, J. Antibiot. *26*, 261 (1973).

[42] *P. Schindler* (Tübingen), unpublished work.

[43] Streptozotocin, a Streptomyces antibiotic active against bacteria, is now used in many laboratories for inducing experimental diabetes in animals. First description: *J. J. Vavra, C. DeBoer, A. Dietz, L. J. Hanka, W. T. Sokolski*, Antibiot. Annu. *1959/60*, 230; *R. R. Herr, T. E. Eble, M. E. Bergy, H. K. Jahnke, ibid. 1959/60*, 236; structure and synthesis: *R. R. Herr, H. K. Jahnke, A. D. Argoudelis*, J. Am. Chem. Soc. *89*, 4808 (1967).

[44] *T. Niida, K. Hamamoto, T. Shomura*, J. Antibiot. *20*, 62 (1967); *N. Ishida, K. Kumagai, T. Niida, T. Tsuruoka, H. Yumoto, ibid. 20*, 66 (1967); *S. Inouye, T. Tsuruoka, T. Niida, ibid. 19*, 288 (1966); *T. Niwa, S. Inouye, T. Tsuruoka, Y. Koaze, T. Niida*, Agric. Biol. Chem. *34*, 966 (1970).

[45] For a review of this transferase system see *W. Boos*, Annu. Rev. Biochem. *43*, 123 (1974).

[46] The problem of secondary metabolism has been discussed much more intensively in connection with the constituents of plants than of microbial metabolites; see, *e.g. M. Luckner:* Der Sekundärstoffwechsel in Pflanze und Tier. G. Fischer Verlag, Jena 1969.

[47] *M. Eigen, R. Winkler:* Das Spiel. Naturgesetze steuern den Zufall. Piper Verlag, München 1975.

[48] *A. Stoll, A. Brack, J. Renz*, Schweiz. Z. Pathol. Bakteriol. *14*, 225 (1951); *A. Stoll, J. Renz, A. Brack*, Helv. Chim. Acta *34*, 862 (1951); *W. Keller-Schierlein, V. Prelog, ibid. 44*, 1981 (1961).

[49] According to *H. Anke*, J. Antibiotics *30*, 125 (1977), deferritriacetylfusigen exhibits antibiotic activity comparable to that of nocardamine. Triacetylfusigen was first obtained by *H. Diekmann, H. Zähner*, Eur. J. Biochem. *3*, 213 (1967), by acetylation of deferrifusigen and was recently reported as a natural product by *H. Diekmann, E. Krezdorn*, Arch. Microbiol. *106*, 191 (1975); *R. E. Moore, Th. Emery*, Biochemistry *15*, 2719 (1976).

[50] Summary: *W. Keller-Schierlein, H. Gerlach*, Fortschr. Chem. Org. Naturst. *26*, 161 (1968); for synthesis of nonactin see *H. Gerlach, K. Oertle, A. Thalmann, S. Servi*, Helv. Chim. Acta *58*, 2036 (1975).

[51] *R. Kanne, U. Klein-Vogler, H. Zähner*, Arch. Mikrobiol. *93*, 205 (1973); *R. Kanne, H. Zähner*, Z. Naturforsch. *31c*, 115 (1967).

[52] *F. M. Harold, J. R. Baarda*, Biochemistry *6*, 3107 (1967); *F. M. Harold, R. L. Harold, J. R. Baarda, A. Abrams, ibid. 6*, 1777 (1967).

[53] *H. Schrempf, H. Bujard, D. A. Hopwood, W. Goebel*, J. Bacteriol. *121*, 416 (1975).

[54] *P. Berg, D. Baltimore, H. W. Boyer, S. N. Cohen, R. W. Davis, D. S. Hogness, D. Nathans, R. Roblin, J. D. Watson, S. Weissmann, N. D. Zinder*, Science *185*, 332 (1974).

[55] Review of mycotoxins: *A. Ciegler, S. Kadis, S. J. Ajl:* Microbial Toxins. Vol. 4. Academic Press, New York 1971.

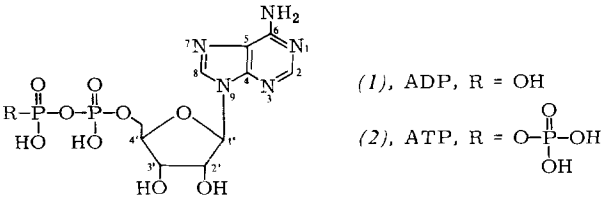
Investigations of Mitochondrial Adenine Nucleotide Translocation by Means of Nucleotide Analogs

By Eckhard Schlimme, Karl Siegfried Boos, Dubo Bojanovski, and Joachim Lüstorff[*]

ATP and ADP are transferred across the inner mitochondrial membrane by means of a carrier (translocator), an inner membrane integral lipoprotein. Translocation of the adenine nucleotides occurs in two steps: specific binding and transport. By using substrate analogs with modified adenine, phosphate, or ribose moieties it is possible to check which structural properties of the substrate are essential for binding and transport.

1. Physiological Importance of the Adenine Nucleotide Carrier

Membrane bound processes are of fundamental importance for the function of living systems. In this context substrate transport is of special interest. For example, transfer of the adenine nucleotides adenosine 5′-*O*-triphosphate (ATP) and



adenosine 5′-*O*-diphosphate (ADP) across the inner membrane of the mitochondrion (Fig. 1a) is the key process in energy metabolism of aerobic cells. (The outer membrane is permeable to compounds of low molecular weight and can therefore be left out of consideration here.) Thereby, ADP is transferred[1–4] from the cytosolic side to the matrix side (*i.e.* from "outside" to "inside"), where oxidative phosphorylation occurs according to the reaction:

$$\text{ADP} + \text{Monophosphate} \rightleftarrows \text{ATP} + H_2O$$

By this phosphorylation process the energy liberated in numerous catabolic reactions is "chemically stored" in the

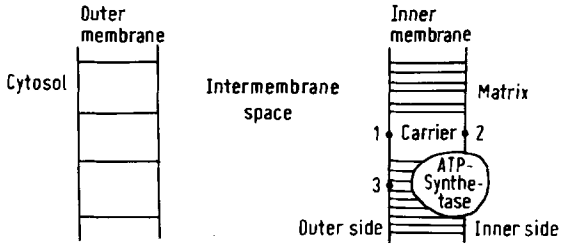


Fig. 1b. Schematic graph of the inner mitochondrial membrane
1: Carrier-dependent (specific) binding of ATP and ADP to the outer (cytosolic) side of the inner membrane; inhibitor is atractyloside;
2: Carrier-dependent (specific) binding of ATP and ADP to the inner (matrix) side of the inner membrane; inhibitor is bongkrekic acid;
3: Carrier-independent (unspecific) binding of ATP and ADP to the outer (cytosolic) side of the inner membrane; not inhibited by atractyloside.

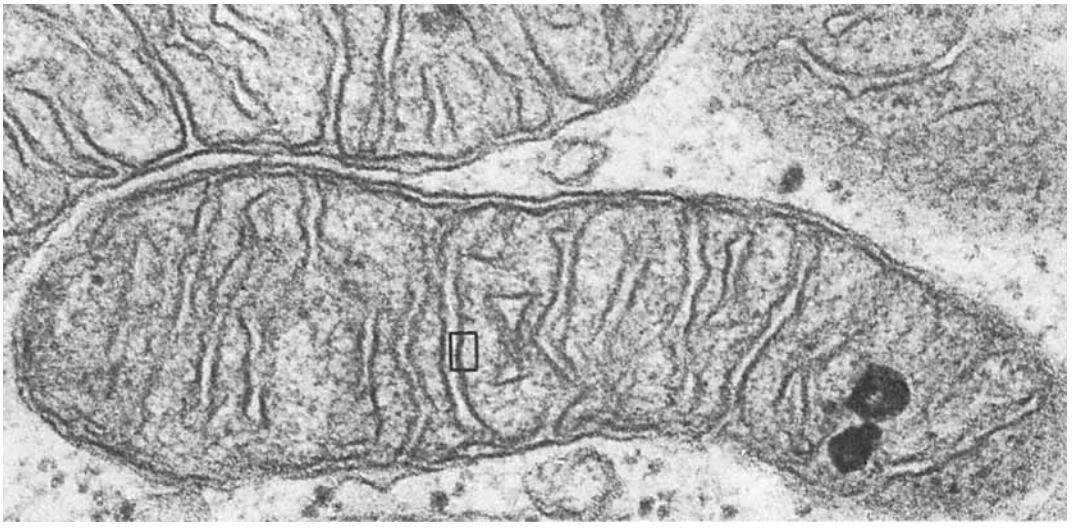


Fig. 1a. Electron-micrograph of a mitochondrion from a cell of mouse gall-bladder epithelium. The outer and the inner membrane surround the intermembrane space, while the inner membrane with numerous foldings (cristae) encloses the matrix space. The mitochondrion is surrounded with cytosol. The inset of the figure shows a segment of the inner membrane (cf. Fig. 1b).
(Micrograph courtesy of Prof. *Enrico Reale*, Medizinische Hochschule Hannover, Abteilung Elektronenmikroskopie.)

[*] Prof. Dr. Dr. E. Schlimme, Dipl.-Biochem. K. S. Boos
Laboratorium für Biologische Chemie im Fachbereich Naturwissenschaften der Universität—Gesamthochschule
Warburger Strasse 100, Bauteil J, D-4790 Paderborn (Germany)
Dr. D. Bojanovski, Dr. J. Lüstorff
Institut für Klinische Biochemie und Physiologische Chemie der Medizinischen Hochschule
Hannover (Germany)

ATP molecule *via* the respiratory chain to which the ATP-synthetase (F1-ATPase)—located on the matrix side—is coupled[5, 6]. ATP is then transported from the matrix to the cytosolic side, *i. e.* from "inside" to "outside". A substrate/product exchange thus occurs across the membrane.

This transport across the membrane can be specifically prevented by inhibitors (Fig. 1b). Atractyloside[7] and carboxyatractyloside, two cyclic triterpene glycosides from *Atractylis gummifera*, block the transport from the cytosolic side ($K_D \simeq 10^{-7}$—10^{-8} mol/l)[2,3,8-11], whereas bongkrekic acid, a lipophilic tricarboxylic acid from *Pseudomonas cocovenenans*, inhibits the transport mainly from the matrix side ($K_D \simeq 10^{-8}$ mol/l)[2, 3]. Other inhibitors are long-chain acyl-coenzyme-A esters, in particular palmitoyl-coenzyme-A[12-18]; their inhibitory effect may be physiologically important for the regulation of the adenine nucleotide transport.

The mode of action of the inhibitors pointed towards a carrier mediated active transport of ATP and ADP. This carrier molecule, which was isolated and characterized[19-29], is an integral component of the inner membrane (see Section 2) and represents about 10%[19-29] of the total mitochondrial protein. Some characteristic data for this transport system are summarized in Table 1.

The adenine nucleotide carrier preferentially transfers ADP from the cytosolic to the matrix side[2, 3]; in the reverse direction ATP transport is preferred[35, 36]. The translocation system thus operates asymmetrically, the asymmetry being due to the different postulated conformations of the carrier when oriented to the cytosolic ("c" state) and to the matrix side ("m" state) of the membrane, respectively[26, 28]. This property of the carrier system in particular guarantees rapid regulation of the cellular ATP level, the maintenance of which is a prerequisite for a steady state of energy-consuming processes. These are coupled either directly to ATP as the source of energy or to other nucleoside triphosphates (GTP, ITP, CTP, UTP) for whose syntheses ATP is again required as a donor of phosphoryl groups. The driving force of all of these processes is the free energy of hydrolysis of the nucleoside triphosphates. Under standard conditions (and at pH 7.0) the free energy for the hydrolysis of ATP is $\Delta G = -30.7$ kJ/mol; *in situ* this value can deviate widely from the standard value, and it can also vary within different cell compartments.

In addition to their function as central energy "transmitter" of the cell, adenine nucleotides in their role as allosteric effectors play an important role in regulation of the cell metabolism and are also substrates for anabolic processes.

Table 1. Some characteristic data for the mitochondrial adenine nucleotide translocator *in situ*.

Michaelis-Menten constants (K_M) [30—33]

K_M (ADP extramitochondrial, 2—5°C): 1—10 μmol/l
K_M (ATP extramitochondrial, 2—5°C): 1—150 μmol/l [a]

Maximal rate of translocation V

[μmol·min^{-1} per g of mitochondrial protein] [30—33]
V(ADP): 5 (2°C), 20 (5°C)
V(ATP): 2 (2°C), 7 (5°C)

Turnover [2, 34]

40—60 min^{-1} (2°C)
1600—2000 min^{-1} (20°C)

Activation energy [30, 31]

below 10°C: 176 kJ/mol
above 10°C: 69 kJ/mol

Topological findings

2×10^{13} translocator molecules per cm^2 of surface (inner mitochondrial membrane, rat liver) [34]

Molar ratio translocator: cytochrome a = (1.5—2.0):1 (rat liver mitochondria); = (2.5—3.0):1 (rat heart mitochondria) [2]

[a] Dependent on the energy state of the mitochondrion [32].

2. Structure and Mode of Action of the Carrier

Methods for the isolation and *in-vitro* characterization of the mitochondrial adenine nucleotide carrier were developed recently in several independent laboratories[20, 21, 24, 25, 27]. A review is given in Table 2.

According to the experimental findings, the macromolecule isolated from the inner membranes of heart and liver mitochondria (MW 29000 and 26000 respectively), as the substrate-

Table 2. Isolation and characterization of the mitochondrial adenine nucleotide translocator.

Solvent	Isolation technique	Molecular weight	Characterization	Ref.
Heart mitochondria (beef) Cholate	Ammonium sulfate fractionation	29000	Incorporation of the isolated protein into phospholipid vesicles; thereby reconstitution of the exchange activity for ATP and ADP	[19, 25]
Triton X 100	Solubilization of mitochondria after binding of carboxyatractyloside; column chromatography on hydroxylapatite and agarose	29000 carboxyatractyloside-binding protein: MW 55000 (dimer)	Binding of carboxyatractyloside; carboxyatractyloside specifically replaceable by bongkrekic acid and ADP: immunological differentiation between the c- and m-conformations of the translocator protein	[22, 24—26, 28]
Liver mitochondria (rat) Brij 56	Soluble protein fraction in the exclusion volume of Sephadex G 25	—	Atractyloside-sensitive binding of ADP	[20]
Triton X 100 Emulphogen BC 720	Affinity chromatography on atractyloside-agarose	50000 to 60000	Binding of atractyloside	[21]
Sodium dodecyl sulfate	Affinity chromatography on carboxyatractyloside-agarose	26000 60000 (dimer)	Binding of atractyloside and inhibition of the ATP/ADP translocation in digitonin particles by antibodies against the isolated translocator protein	[23, 27]

and inhibitor-binding component, is an essential structural constituent of the adenine nucleotide carrier. The active carrier[26] is possibly the dimeric form of the isolated macromolecule[21,23,26,27]. Its translocation activity is largely characterized by interactions with the hydrophobic lipid environment. The carrier is a lipoprotein[27,37,38] consisting of: protein 85%, phospholipids 14%, and triacylglycerol 1%[27,38]; small-angle X-ray measurements on the isolated macromolecule[39] indicate a membrane-spanning structure with a largest distance of 7.3 nm and a radius of gyration of 3.1 nm.

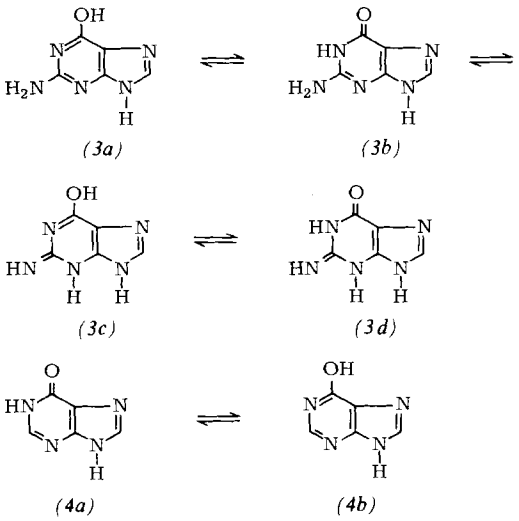
Translocation of the substrates (S) ATP and ADP catalyzed by this carrier system (C) occurs in a reaction sequence of the type:

$$S_a + C \rightleftarrows S_a C \rightleftarrows CS_i \rightleftarrows C + S_i$$

Association or dissociation reactions take place on both sides of the membrane (a = outer; i = inner). Transport of the substrate across the membrane can in principle be accomplished by two different means: 1) the nucleotide-carrier complex rotates within the membrane (rotation mechanism) so that the nucleotide ends up on the other side of the membrane; 2) the nucleotide is transferred from one side of the membrane to the other through a channel (pore mechanism) as a result of a conformational change of the nucleotide-carrier complex. Both processes are energy-dependent[26,29,40,41]. The general ideas about membrane transfer reactions[42-44], as well as the present knowledge of the structure of the adenine nucleotide carrier[27-29,38-47], favor a "pore mechanism" as the mode of ATP and ADP transport across the inner mitochondrial membrane.

3. Substrate Specificity of the Carrier

The carrier system is highly specific for ATP and ADP. None of the naturally occurring ribo- or deoxyribo-nucleoside 5-*O*'-tri(di)phosphates of guanine *(3)*, GTP, GDP, and dGTP, dGDP, of hypoxanthine *(4)*, ITP, IDP, and dITP, dIDP, of uracil, UTP, UDP, and of thymine, dTTP, dTDP, and of cytidine, CTP, CDP, dCTP, dCDP, are substrates for mitochondrial nucleotide transport[2,20,45].



(3a) *(3b)*

(3c) *(3d)*

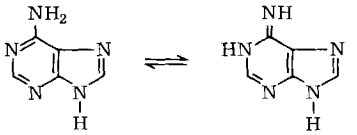
(4a) *(4b)*

These findings emphasize again the role of ATP as the main donor of phosphoryl groups in the aerobic cell.

As in the field of enzyme-catalyzed reactions[46,47], substrate analogs proved to be of exceptional utility in the investigation of carrier-nucleotide interactions, especially those bound to the carrier but inappropriate for transportation. The two step nature of the process (binding and transport) can be experimentally proved by means of such analogs; furthermore, it can be shown which structural[48,49] properties of the adenine nucleotide molecule are essential for the specific binding (first step) and which are additionally required for inducing the transfer (second step).

3.1. Base-Modified Substrate Analogs

As mentioned above, replacement of adenine *(5)* in the nucleotide tri(di)phosphate by another purine or pyrimidine base leads to a loss of specific binding to the carrier. This may be due to the different electron distributions in the heterocyclic systems or to the different substitutions. In aqueous solutions guanine *(3)* and hypoxanthine *(4)* exist in the lactam forms *(3b)* and *(4a)*, while adenine exists in the amino form *(5a)*[50,51]. The different tautomeric equilibria and ionizations in the aqueous phase give rise to large physical differences between adenine on the one hand and guanine and hypoxanthine on the other.



(5a) *(5b)*

Figure 2 shows the reference systems for the orientation of heterocycle and sugar residue. The importance of an intact adenine base for binding to the carrier molecule and/or for

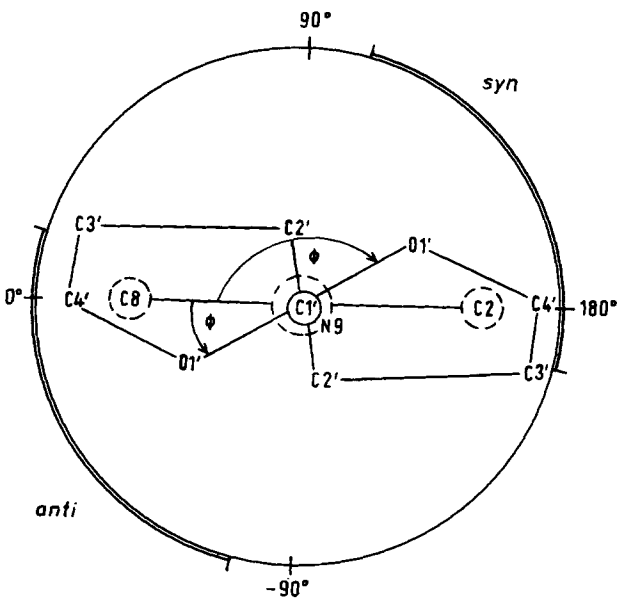


Fig. 2a. The position of the purine base relative to the sugar is described by the torsion angle φ (O1'—C1'—N9—C8) (cf. Fig. 3a). The base can be *syn*- or *anti*-positioned, where for a *syn*-conformation the angle φ is defined as 150±45° and for an *anti*-conformation as −30±45° [51, 52].

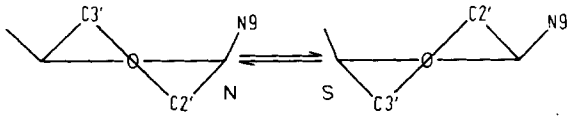


Fig. 2b. Pseudorotation (puckering) of the ribofuranose ring is described by the conformer equilibrium N(C2'-*exo*,C3'-*endo*)⇌S(C2'-*endo*,C3'-*exo*) [51, 53—56].

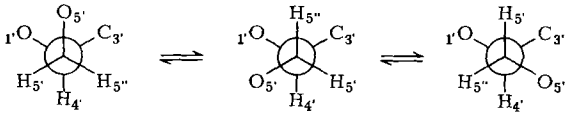


Fig. 2c. Newman projection along the exocyclic C5'—C4' bond shows the three rotamer positions *gauche,gauche (gg)*, *gauche,trans (gt)*, and *trans,-gauche (tg)* [51, 53—56].

the transport process is shown by the investigation of base-modified adenine nucleotide analogs; a summary is given in Table 3.

translocated by the adenine nucleotide carrier[45]. Structural changes in the phosphate chain that do not influence the number of charges are generally tolerated by the carrier molecule much better than are changes in the base (Table 4).

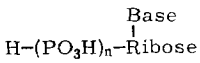
3.3 Substrate Analogs Containing Modified Sugar Moieties

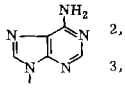
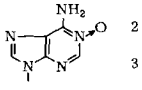
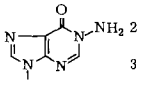
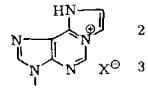
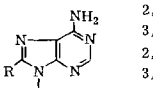
The N⇄S equilibrium (pseudorotation, puckering; cf. Fig. 2) of the ribose ring[51, 53–56] has a considerable influence on the nucleotide conformation[51, 54–56]. For this reason the behavior of adenine nucleotide analogs with modified sugar moieties (Table 5) points to the importance of the nucleotide conformation for the interactions of ATP and ADP with the mitochondrial adenine nucleotide carrier.

4. Conclusions from the Studies with Substrate Analogs

Which conclusions can now be drawn from the findings presented in Tables 3 to 5 concerning the molecular require-

Table 3. Substrates and base modified substrate analogs of type



Nucleotide Base	n	Conformation (cf. Fig. 2)	Translocator Binding [%] [a]	Translocator Rate of transport [b]	Remarks
(1) 	2, ADP	*anti* > *syn* ($\phi = -20°$) [51—60]	100 [1, 2]	20 [1, 2]	
(2)	3, ATP	N (47 %)⇌S (53 %) *gg* > *tg*.*gt*	100 [1, 2]	7 [1, 2]	
(6) 	2		50 [61—64]	0.6 [61, 62] – [63, 64] [c]	*(6)* is not a substrate of oxidative phosphorylation [49, 63]. *(6)* and *(8)* are substrates of the CF1-coupling factor of photophosphorylation in chloroplasts [66]
(7)	3				
(8) 	2		– [65]	– [65]	
(9)	3				
(10) 	2		+ [67, 68]	– [67], + [68]	*(11)* is dephosphorylated by F1-ATPase [68]. *(10)* is a substrate of the CF1-coupling *(10)* factor [69]
(11)	3				
(12) 	2, R = Br	*syn* [51, 57, 70, 71] ($\phi = +120°$) [58] *tg* ≈ *gt* > *gg*	30 [48]	– [48]	*(12)* is not a substrate in the photophosphorylation reaction [66]. *(14)* and *(15)* show UV light-sensitive irreversible binding to the translocator and block the ATP/ADP exchange [72]
(13)	3, R = Br				
(14)	2, R = N_3		+ [72]	– [72]	
(15)	3, R = N_3				

[a] Under saturation conditions (5°C) with 1.6 μmol per g of mitochondrial protein = 100%. "+" means "bound", "–" means "not-bound". [b] Maximal rate of translocation for externally offered nucleotides (5°C) [μmol·min^{-1} per g of mitochondrial protein]. "+" means "transported", "–" means "not transported". [c] Results are not derived from measurements with radioactively labeled analogs.

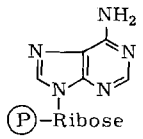
3.2. Substrate Analogs with Modified Phosphate Chains

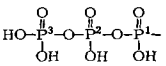
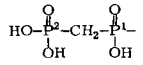
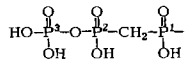
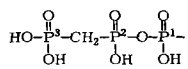
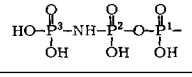
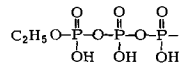
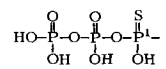
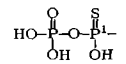
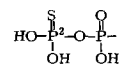
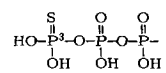
For carrier-specific binding of the adenine nucleotides ATP ($pK_a = 6.97$ for ATP^{4-}/ATP^{3-}) and ADP ($pK_a = 6.65$ for ADP^{3-}/ADP^{2-}) at least three negative charges are required[34]. Unlike adenosine 5'-*O*-di-, -tri-, and -tetraphosphate, therefore, adenosine 5'-*O*-monophosphate (AMP) is not

ments of the membrane integral carrier with respect to its substrate?

Modifications of the phosphate chain have only moderate influence on specific binding of the nucleotide to the carrier on the cytosolic side, provided that the number of negative charges remains unchanged. Structural changes in the adenine are tolerated as long as the adenine character of the hetero-

Table 4. Substrates and phosphate chain modified substrate analogs of type

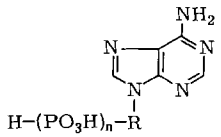


	Nucleotide Ⓟ	Structure of the phosphate chain	Translocator: Binding [%] [a]	Translocator: Rate of transport [b]	Remarks
(2)		P—O = 1.61 Å [47] ∢P—O—P = 130° [47]	100 [1, 2]	7 [1, 2]	
(16)		P—C = 1.79 Å [47] ∢P—C—P = 117° [47]	+ [73]	+ [73]	Neither is *(16)* phosphorylated by F1-ATPase [c] nor are *(17)* and *(18)* dephosphorylated [73]
(17)					
(18)					
(19)		P—N = 1.68 Å [47] ∢P—N—P = 127° [47]	+ [74, 75]	+ [74, 75]	*(19)* is not dephosphorylated by F1-ATPase, but inhibits competitively the dephosphorylation of ATP, no effect on ADP phosphorylation [76]
(20)		P—P = 3 Å [47]	+ [77]	+ [77]	*(20)* is not a substrate of F1-ATPase [77] [d]
(21)			+ [78]	− [78]	
(22)		van der Waals radii: O = 1.40 Å S = 1.83 Å electronegativities: O = 3.5 S = 2.5 thione thiol P=S > P—SH	+ [49, 79]	10 [49, 79]	*(22)* to *(24)* are not substrates of F1-ATPase [49, 80] or of ATP-P_i exchange [80]. Inhibition of mitochondrial respiration [49, 79] is due to inhibition of ATP synthetase [80—82] when coupled to complex IV of the respiratory chain [82]. Only the B isomer [e] of *(23)* is an inhibitor of oxidative phosphorylation of ADP. The A isomer of *(23)* is substrate of photophosphorylation in chloroplasts, whereas the B isomer of *(23)* as well as *(24)* is not a substrate for this reaction [66]
(23)					
(24)					
(25)					

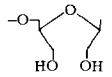
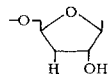
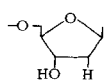
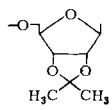
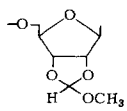
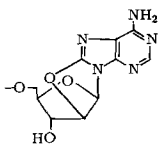
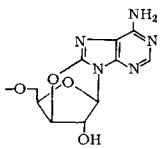
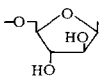
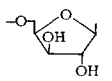
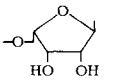
[a, b] Cf. footnotes to Table 3. [c] Possible explanation: In *(16)* P^2 is less electrophilic than in ADP; furthermore, in *(16)* the P—C bond is longer than the corresponding P—O bond in ADP. [d] Possible explanation: In *(20)* P^2 is less electrophilic than in ADP; furthermore, in *(20)* the P—P bond is shorter than the corresponding P—O bond in ADP. [e] The two diastereoisomers were separated enzymatically [46, 83] and by liquid chromatography [84]. The absolute configuration has so far not been determined.

cycle—including the amino group at C6—is retained, as can be concluded particularly from comparison of the structurally isomeric analogs *(6)* to *(9)* (Table 3). Thus, after substitution of the C8 hydrogen—as in *(12)* to *(15)* (Table 3)—the carrier specific binding is not lost, although the *syn*⇄*anti* isomerization of the nucleobase (Fig. 2) is prevented in favor of a sterically preferred *syn*-conformation[51, 57, 70, 71]. If, however, the sugar is covalently bound to the adenine base, as in *(36)* to *(39)* (Table 5), then the position of the nucleobase relative to the sugar is fixed. Because of this fixed position of the base, the hydrophobic interactions between nucleotide and active center of the carrier molecule are decreased in the case of *(36)* to *(39)* compared to *(12)* to *(15)*, so that the analogs *(36)* and *(37)* show only very weak specific binding while the analogs *(38)* and *(39)* display no specific binding at all. Replacement of the 3′- [*(28)* and *(29)*] or the 2′-hydroxyl group [*(30)* and *(31)*] by hydrogen has qualitatively as little effect on specific binding as an inversion of the *trans*-2′- or 3′-hydroxyl group of the ribose into the corresponding *cis*-configuration [*(40)* and *(41)*, *(42)* and *(43)*] or as cleavage of the C2′/C3′ bond of the ribose ring in *(26)* and *(27)*. If, however, both hydroxyl groups are chemically blocked [*(32)*

Table 5. Substrates and sugar-modified substrate analogs of type



$H-(PO_3H)_n-R$

Nucleotide R	n	Conformation (cf. Fig. 2)	Translocator: Binding [%] [a]	Translocator: Rate of transport [b]	Remarks
(26) 	2	N⇄S equilibrium abolished; neither the *syn*- nor the *anti*-orientation of the adenine base is favored; no hindrance to rotation around the C1′—C2′ or the C4′—C3′ axis [86]	15 [33, 62, 85]	– [33, 62, 85]	*(26)* is bound to CF1 coupling factor but is not photophosphorylated [87]
(27)	3				
(28) 	2	*anti*>*syn* [c] Distribution of rotamers: $gg \simeq tg \simeq gt$ [55, 56]	50 [88, 89]	3 [88, 89]	*(28)* is substrate of F1-ATPase [90] and of CF1 coupling factor [87]
(29)	3				
(30) 	2	*anti*>*syn* [c] N (29 %) ⇄ S (71 %) $gg < tg \simeq gt$ [55, 56]	30 [88, 89]	– [88, 89]	*(30)* is not a substrate of oxidative phosphorylation [90], but is photophosphorylated by CF1 coupling factor [87]
(31)	3				
(32) 	2	Restricted pseudorotation of the ribose [91, 92]	– [90]	– [90]	In equimolar concentrations *(32)* and *(34)* inhibit ADP induced state-3 respiration [93] to about 25 % [94] [d]
(33)	3				
(34) 	2				
(35)	3				
(36) 	2	Rigid fixation of the adenine base in the *syn*/*anti* boundary region "high" *anti* ($\phi = -122°$) [96] C2′-*endo*,*gt* favored	20 [89, 95]	– [89, 95]	
(37)	3	Rigid fixation of the adenine base in an *anti*-position ($\phi = -72°$) [98] C3′-*endo*, *gt* favored			
(38) 	2		– [89, 97]	– [89, 97]	
(39)	3				
(40) 	2	*anti*>*syn* [58, 99] *gt*>*gg*, *tg*	12 [89, 90]	– [89, 90]	
(41)	3				
(42) 	2	*anti*>*syn* [100] C3′-*endo*, *gt* favored	9 [89]	– [89]	
(43)	3				
(44) 	2	*anti*>*syn* [89] C2′-*endo*, *tg* favored	– [89]	– [89]	
(45)	3				

[a, b] Cf. footnotes to Table 3.

[c] The *anti*-conformation in *(28)* and *(29)* is stabilized by electrostatic attraction between C2′—OH and N3. Due to lack of stabilization in *(30)* and *(31)* the position of the adenine base is shifted toward *syn* ($\phi = -63°$) [58].

[d] Caused by incorporation into the lipophilic regions of the mitochondrial membrane due to the lipophilic character of *(32)* and *(34)*, thus reducing the activity of the translocator.

to *(35)*], or if there is an inversion at C4′ [*(44)* and *(45)*], the specific binding is completely lost.

Regarding the question how the binding step of a nucleotide is molecularly coupled to the second step of nucleotide transfer, following points of view can be taken into consideration:

Adenine nucleotide analogs existing in a (not covalently fixed) *syn*-conformation are bound to the carrier but do not

stimulate transfer across the membrane. The analogs *(36)* and *(37)* with covalently fixed adenine rings in the *syn/anti* boundary region are as little transferred after binding as are the analogs *(38)* and *(39)* containing a covalently fixed *anti*-conformation. For induction of the second step there must thus be a certain freedom of rotation around the C1′/N9 linkage in the *anti*-region ($-30° \pm 45°$, cf. Fig. 2).

The influence of the conformation on the transport of adenine nucleotides is demonstrated by analogs *(26)* and *(27)*. Chemically they are almost identical to the natural substrates, but differ markedly in their conformations. Ring-opening of the ribose prevents stabilization of the *anti-gauche*, *gauche*-conformation in which ADP and ATP preferentially occur (Fig. 3a). The analog *(27)* (Fig. 3b) is considerably more flexible in its structure; for energetic reasons the conformation equivalent to that of the natural substrate cannot be achieved in the carrier-nucleotide complex, and the transfer does not occur[33].

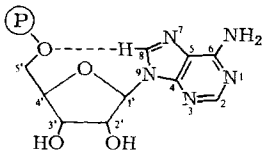


Fig. 3a. Conformation of ATP. Ⓟ = H—$(PO_3H)_3$.

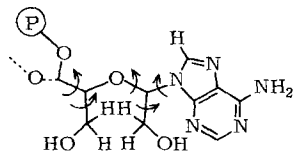


Fig. 3b. Conformation of *(27)*. Ⓟ = H—$(PO_3H)_3$.

A decisive function in establishing the transport is played by the 2′-hydroxyl group, very probably by means of hydrogen bridge formation to the complementary position in the carrier molecule. This group must be present in the *trans*-position; as *(40)* and *(41)* show, a 2′-hydroxyl group in the *cis*-position cannot fulfill this function. Replacement of the 3′-hydroxyl group by hydrogen, however, as in *(28)* and *(29)*, is tolerated.

We are indebted to all who have helped us by stimulation and criticism. We are grateful to the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung Nordrhein-Westfalen, and the Fonds des Verbandes der Chemischen Industrie for financial assistance. We thank Professor Walther Lamprecht for working facilities at the Medizinische Hochschule Hannover during the building operations at Paderborn.

Received: October 8, 1976 [A 172 IE]
German version: Angew. Chem. *89*, 717 (1977)
Translated by Express Translation Service, London

[1] *M. Klingenberg, E. Pfaff* in *J. M. Tager, S. Papa, E. Quagliariello, E. C. Slater:* Regulation of Metabolic Processes in Mitochondria. Biochim. Biophys. Library Vol. 7. Elsevier, Amsterdam 1966, p. 180.
[2] *P. V. Vignais, P. M. Vignais, G. Lauquin, F. Morel*, Biochimie *55*, 763 (1973).
[3] *M. Klingenberg, B. Scherer, L. Stengel-Rutkowski, M. Buchholz, K. Grebe* in *G. F. Azzone, L. Ernster, S. Papa, E. Quagliariello, N. Siliprandi:* Mechanisms in Bioenergetics. Academic Press, London 1973, p. 257.
[4] *A. Kemp jr., T. A. Out*, Proc. K. Ned. Akad. Wet. Ser. C, *78*, No. 2, p. 143, 155 (1975).
[5] *E. C. Slater*, 6th Keilin Memorial Lecture, Meeting Biochem. Soc., Cambridge (UK) 1974, Vol. 2, p. 1149.
[6] *E. C. Slater, J. Rosing, D. A. Harris, R. O. van de Stadt, A. Kemp jr.* in *G. F. Azzone, M. Klingenberg, E. Quagliariello, N. Siliprandi:* Membrane Proteins in Transport and Phosphorylation. North-Holland, Amsterdam 1974, p. 137.
[7] *M. Lefranc*, C. R. Acad. Sci. *67*, 954 (1868).
[8] *R. Santi, M. Bistocchi, A. Bruni*, Proc. 4. Int. Congr. Biochem., Wien 1958.
[9] *A. Bruni, S. Luciani, A. R. Contessa*, Nature *201*, 1219 (1964).
[10] *E. Pfaff, M. Klingenberg, H. W. Heldt*, Biochim. Biophys. Acta *104*, 312 (1965).
[11] *H. H. Winkler, A. L. Lehninger*, J. Biol. Chem. *243*, 3000 (1968).
[12] *L. Wojtczak, H. Zaluska*, Biochem. Biophys. Res. Commun. *28*, 76 (1967).
[13] *S. V. Pande, M. C. Blanchaer*, J. Biol. Chem. *246*, 402 (1971).
[14] *A. Shug, E. Lerner, C. Elson, E. Shrago*, Biochem. Biophys. Res. Commun. *43*, 557 (1971).
[15] *R. A. Harris, B. Farmer, T. Ozawa*, Arch. Biochem. Biophys. *150*, 199 (1972).
[16] *W. J. Vaartjes, A. Kemp jr., J. H. M. Souverijn, S. G. Van den Bergh*, FEBS Lett. *23*, 303 (1972).
[17] *F. Morel, G. Lauquin, J. Lunardi, J. Duszynski, P. V. Vignais*, FEBS Lett. *39*, 133 (1974).
[18] *C. H. Ho, S. V. Pande*, Biochim. Biophys. Acta *369*, 86 (1974).
[19] *H. G. Shertzer, E. Racker*, J. Biol. Chem. *249*, 1320 (1974).
[20] *R. W. Egan, A. L. Lehninger*, Biochem. Biophys. Res. Commun. *52*, 195 (1974).
[21] *G. Brandolin, C. Meyer, G. Defaye, P. M. Vignais, P. V. Vignais*, FEBS Lett. *46*, 149 (1974).
[22] *M. Klingenberg, P. Riccio, H. Aquila, B. Schmiedt, K. Grebe, P. Topitsch* in *G. F. Azzone, M. Klingenberg, E. Quagliariello, N. Siliprandi:* Membrane Proteins in Transport and Phosphorylation. North-Holland, Amsterdam 1974, p. 229.
[23] *D. Bojanovski, E. Schlimme, C. S. Wang, P. Alaupovic*, Abstr. Commun. 11th Meeting Fed. Eur. Biochem. Soc., Paris 1975, No. 1156.
[24] *P. Riccio, H. Aquila, M. Klingenberg*, FEBS Lett. *56*, 129, 133 (1975).
[25] *H. G. Shertzer, E. Racker*, J. Biol. Chem. *251*, 2446 (1976).
[26] *M. Klingenberg, H. Aquila, P. Riccio, B. B. Buchanan, W. Eiermann, H. Hackenberg* in *E. Quagliariello, S. Papa, F. Palmieri, E. C. Slater, N. Siliprandi:* Electron Transfer Chains and Oxidative Phosphorylation. North-Holland, Amsterdam 1975, p. 431.
[27] *D. Bojanovski, E. Schlimme, C. S. Wang, P. Alaupovic*, Eur. J. Biochem. *71*, 539 (1976).
[28] *B. B. Buchanan, W. Eiermann, P. Riccio, H. Aquila, M. Klingenberg*, Proc. Natl. Acad. Sci. USA *73*, 2280 (1976).
[29] *P. V. Vignais*, Biochim. Biophys. Acta *456*, 1 (1976).
[30] *E. D. Duée, P. V. Vignais*, J. Biol. Chem. *244*, 3920 (1969).
[31] *E. Pfaff, H. W. Heldt, M. Klingenberg*, Eur. J. Biochem. *10*, 484 (1969).
[32] *J. H. M. Souverijn, P. J. Weijers, G. S. P. Groot, A. Kemp jr.*, Biochim. Biophys. Acta *305*, 185 (1970).
[33] *K. S. Boos, E. Schlimme, D. Bojanovski, W. Lamprecht*, Eur. J. Biochem. *60*, 451 (1975).
[34] *M. Klingenberg*, Essays Biochem. *6*, 119 (1970).
[35] *J. Duszynski, L. Wojtczak*, Abstr. 10 IUB Congr. Biochem., Hamburg 1976, p. 347.
[36] *M. Klingenberg*, Ciba Found. Symp. *31*, 105 (1975).
[37] *T. L. Spencer, J. K. See, F. L. Bygrave*, Biochim. Biophys. Acta *423*, 365 (1976).
[38] *D. Bojanovski, E. Schlimme, M. Bojanovski, C. S. Wang, P. Alaupovic, W. Folkhard, I. Pilz* in *H. Peters:* Protides of Biological Fluids. Proc. 25th Colloquium. Pergamon Press, Oxford, in press.
[39] *W. Folkhard, I. Pilz, D. Bojanovski, E. Schlimme*, Abstr. Meeting Fed. Eur. Biochem. Soc., Copenhagen 1977, No. 304.
[40] *H. Aquila, W. Eiermann, M. Klingenberg*, Abstr. Symp. Biochem. Membrane Transport, Zürich 1976, P 400, p. 62.
[41] *M. Klingenberg, H. Aquila, R. Krämer*, Abstr. Symp. Biochem. Membrane Transport, Zürich 1976, L 44, p. 21.
[42] *J. S. Singer, G. L. Nicolson*, Science *175*, 720 (1972).
[43] *J. S. Singer*, Annu. Rev. Biochem. *43*, 805 (1974).
[44] *A. Dutton, E. D. Rees, J. S. Singer*, Proc. Natl. Acad. Sci. USA *73*, 1532 (1976).
[45] *M. Weidemann, J. J. Erdelt, M. Klingenberg*, Eur. J. Biochem. *16*, 313 (1970).
[46] *F. Eckstein*, Angew. Chem. *87*, 179 (1975); Angew. Chem. Int. Ed. Engl. *14*, 160 (1975).
[47] *R. Yount*, Adv. Enzymol. *43*, 1 (1975).

[48] *E. Schlimme, K. W. Stahl*, Hoppe-Seylers Z. Physiol. Chem. *355*, 1139 (1974).
[49] *E. Schlimme, W. Lamprecht, F. Eckstein, R. W. Goody*, Eur. J. Biochem. *40*, 485 (1973).
[50] *Y. P. Wong, K. L. Wong, D. R. Kearns*, Biochem. Biophys. Res. Commun. *49*, 1580 (1972).
[51] *P. O. P. Tso:* Basic Principles in Nucleic Acid Chemistry. Academic Press, New York 1974, Vol. 1, p. 453ff.
[52] *J. Donohue, K. N. Trueblood*, J. Mol. Biol. *2*, 363 (1960).
[53] *H. D. Lüdemann, O. Röder, E. Westhof, E. von Goldammer, A. Müller*, Biochem. Struct. Mechanism *1*, 121 (1975).
[54] *C. H. Lee, F. E. Evans, R. H. Sarma*, J. Biol. Chem. *250*, 1290 (1975).
[55] *D. B. Davies, S. S. Danyluk*, Biochemistry *13*, 4417 (1974).
[56] *D. B. Davies, S. S. Danyluk*, Biochemistry *14*, 543 (1975).
[57] *S. S. Tavale, H. M. Sobell*, J. Mol. Biol. *48*, 109 (1970).
[58] *M. Sundaralingam*, Ann. N. Y. Acad. Sci. *255*, 3 (1975).
[59] *W. Saenger*, Angew. Chem. *85*, 680 (1973); Angew. Chem. Int. Ed. Engl. *12*, 591 (1973).
[60] *O. Kennard, N. W. Isaacs, J. C. Coppola, A. J. Kirby, S. Warren, W. D. S. Motherwell, D. G. Watson, D. L. Wampler, D. H. Chenery, A. C. Larson, K. A. Kerr, L. Riva di Sanseverino*, Nature *225*, 333 (1970).
[61] *E. Schlimme, G. Schäfer*, FEBS Lett. *20*, 659 (1972).
[62] *E. Schlimme*, Nieders. Ärztebl. *46*, 656 (1973).
[63] *G. Jebeleanu, N. G. Ty, H. H. Mantsch, O. Bârzu, G. Niac, I. Abrudan*, Proc. Natl. Acad. Sci. USA *71*, 4630 (1974).
[64] *H. H. Mantsch, J. Goia, M. Kezdi, O. Bârzu, M. Dansoreanu, G. Jebeleanu, N. G. Ty*, Biochemistry *14*, 5593 (1976).
[65] *E. Schlimme, W. Fröhlich*, unpublished results (1977).
[66] *H. Strotmann, S. Bickel-Sandkötter, K. Edelmann, J. Lüstorff, E. Schlimme, K. S. Boos, F. Eckstein*, unpublished.
[67] *M. Klingenberg*, Hoppe-Seylers Z. Physiol. Chem. *355*, 759 (1974).
[68] *R. S. Kaplan, P. S. Coleman*, FEBS Lett. *63*, 179 (1976).
[69] *D. Vandermeulen, Gooindjee*, FEBS Lett. *57*, 272 (1975).
[70] *J. M. Delabar, W. Guschlbaur*, Biochimie *54*, 1041 (1972).
[71] *E. Westhof, O. Röder, J. Croneiss, H. D. Lüdemann*, Z. Naturforsch. *30C*, 131 (1975).
[72] *G. Schäfer, E. Schrader, G. Rowohl-Quishoudt, S. Penades, M. Rimpler*, FEBS Lett. *64*, 185 (1976).
[73] *E. D. Duée, P. V. Vignais*, Biochem. Biophys. Res. Commun. *30*, 546 (1968).
[74] *R. G. Yount, D. Babcock, D. Ojala, W. Ballantyne*, Biochemistry *10*, 2484 (1971).
[75] *M. Klingenberg, K. Grebe, B. Scherer*, FEBS Lett. *16*, 253 (1971).
[76] *H. Penefsky*, J. Biol. Chem. *249*, 3579 (1974).
[77] *P. V. Vignais, J. Setondji, J. P. Ebel*, Biochimie *53*, 127 (1971).
[78] *K. W. Stahl, E. Schlimme, F. E. Köster*, Naturwissenschaften *61*, 38 (1974).
[79] *E. Schlimme, G. Schäfer, R. S. Goody, F. Eckstein* in *G. F. Azzone, L. Ernster, S. Papa, E. Quagliariello, N. Siliprandi:* Mechanism in Bioenergetics. Academic Press, London 1973, p. 89.
[80] *J. Lüstorff, E. Schlimme, F. Eckstein, W. Lamprecht*, Hoppe-Seylers Z. Physiol. Chem. *355*, 1400 (1974).
[81] *J. Lüstorff, K. S. Boos, E. Schlimme*, Abstr. 10 IUB Congr. Biochem., Hamburg 1976, p. 338.
[82] *J. Lüstorff*, Dissertation, Technische Universität Hannover 1976.
[83] *F. Eckstein, R. S. Goody*, Biochemistry *15*, 1685 (1976).
[84] *K. W. Stahl, E. Schlimme, F. Eckstein*, FEBS Lett. *40*, 241 (1974).
[85] *K. S. Boos*, Diplomarbeit, Technische Universität Hannover 1974.
[86] *F. von der Haar, E. Schlimme, M. Gomez-Guillen, F. Cramer*, Eur. J. Biochem. *24*, 296 (1971).
[87] *K. S. Boos, J. Lüstorff, E. Schlimme, H. Hesse, H. Strotmann*, FEBS Lett. *71*, 124 (1976).
[88] *K. S. Boos, E. Schlimme*, Hoppe-Seylers Z. Physiol. Chem. *357*, 290 (1976).
[89] *K. S. Boos*, Dissertation, Technische Universität Hannover 1977.
[90] *K. S. Boos, J. Lüstorff, E. Schlimme*, Abstr. Symp. Biochem. Membrane Transport, Zürich 1976, P 401, p. 62.
[91] *O. Röder, H. D. Lüdemann, E. von Goldammer*, Eur. J. Biochem. *53*, 517 (1975).
[92] *P. C. Manor, W. Saenger, D. B. Davies, K. Jankowski, A. Rabczenko*, Biochim. Biophys. Acta *340*, 472 (1974).
[93] *R. W. Estabrook*, Methods Enzymol. *10*, 41 (1968).
[94] *E. Schlimme, J. Lüstorff, K. S. Boos, U. Oppermann*, unpublished results (1976).
[95] *K. S. Boos, J. Lüstorff, E. Schlimme, M. Ikehara*, Abstr. 10 IUB Congr. Biochem., Hamburg 1976, p. 288.
[96] *M. Ikehara, T. Maruyama*, Tetrahedron *31*, 1369 (1975).
[97] *K. S. Boos, E. Schlimme, M. Ikehara*, Abstr. Meeting Fed. Eur. Biochem. Soc., Copenhagen 1977, No. 301.
[98] *M. Ikehara*, Biochemistry *11*, 830 (1972).
[99] *E. Darzynkiewicz, M. Remin, A. Dworak, D. Shugar*, Cancer Biochem. Biophys. *1*, 85 (1975).
[100] *M. Remin, E. Darzynkiewicz, A. Dworak, D. Shugar*, J. Am. Chem. Soc. *98*, 367 (1976).

COMMUNICATIONS

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

Phase-Transfer Catalyzed Alkylation of Diphenylphosphinic Amide—A New Versatile Synthesis of Primary and Secondary Amines[**]

By *Andrzej Zwierzak* and *Iwona Podstawczyńska*[*]

Although wide applicability of Gabriel synthesis for the preparation of primary amines has been well documented, no general alkylative procedure for the synthesis of primary as well as secondary amines has so far been reported.

We have found that readily accessible diphenylphosphinic amide *(1)*[1] in contrast to dialkylphosphoramidates, can

[*] Prof. Dr. A. Zwierzak [+], Dipl.-Chem. I. Podstawczyńska
Institute of Organic Chemistry, Technical University (Politechnika)
Żwirki 36, PL-90-924 Lodz 40 (Poland)
[+] Author to whom correspondence should be addressed.

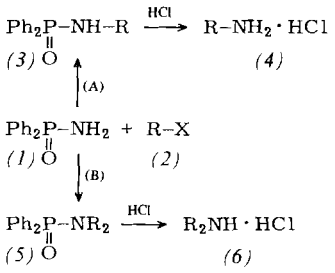
[**] Organophosphorus Esters, Part 14.—Part 13: *T. Gajda, A. Zwierzak*, Synthesis *1977*, in press.

Table 1. Substituted diphenylphosphinic amides *(3)*, *(5)* and *(5')*, and amine hydrochlorides *(4)*, *(6)* and *(6')*. All compounds synthesized gave correct elemental analyses and ^{1}H-NMR spectra and were identified by comparison with authentic material.

	R		*(3)* Yield [%]	*(3)* M.p. [°C]	*(4)* Yield [%]	*(4)* M.p. [°C]
a	C_2H_5		80	103—105	96	79—81
b	n-C_3H_7		78	81.5—83	97	154—155
c	n-C_4H_9		91	84—85.5	93	194
d	CH_2=CH—CH_2		57	85—86.5	95	104—109
e	C_6H_5—CH_2		45	92—94	96	243—244
	R	**R'**	*(5), (5')* Yield [%]	*(5), (5')* M.p. [°C]	*(6), (6')* Yield [%]	*(6), (6')* M.p. [°C]
f	C_2H_5		91	138—139.5	92	214—216
g	n-C_3H_7		85	46	95	273—274
h	n-C_4H_9		82 [a]	oil [e]	97	282—284
i	CH_2=CH—CH_2		77	oil	97	161—162
j	C_6H_5—CH_2		79 [a]	120.5—122	95	255
k	C_2H_5	n-C_3H_7	93 [b]	47—49	95	223—224
l	C_2H_5	i-C_4H_9	55 [c]	69—71	93	207—209
m	C_6H_5	CH_3	96 [b]	115—117	94	119—122
n	C_6H_5	C_2H_5	92 [b]	103—105	96	172—174
o	C_6H_5	i-C_3H_7	92 [b]	180—181.5	95	102—104
p	C_6H_5	C_6H_5—CH_2	91 [c]	177—179	95	196—197
q	C_6H_5	CH_2=CH—CH_2	90 [c]	126—128.5	94	109.5—110
r	*cyclo*-C_6H_{11}	n-C_4H_9	49 [d]	75—77	93	287—289
s	*cyclo*-C_6H_{11}	CH_2=CH—CH_2	94 [d]	69—72.5	94	174.5—177
t	*cyclo*-C_6H_{11}	C_6H_5—CH_2	64 [d]	123—125	98	282—283

[a] 3 mol *(2)* per mol *(1)*. [b] 2 mol *(2)* per mol *(3)*. [c] 1 mol *(2)* per mol *(3)*. [d] 10 Mol-% catalyst; reaction time 6 h. [e] According to the ^{31}P-NMR spectrum contains 15% *(3c)*.

be selectively mono- or dialkylated under the conditions of phase-transfer catalysis (for examples see Table 1). *N*-Alkyldiphenylphosphinic amides *(3)*, obtained by selective monoalkylation of *(1)* or prepared by conventional aminolysis of diphenylphosphinic chloride[2], can undergo further alkylation under the conditions similar to those reported for dialkyl *N*-alkylphosphoramidates[3] to give symmetrically *(5)* or unsymmetrically *(5')* *N,N*-disubstituted diphenylphosphinic amides. Possibilities of alkylation are, however, limited practically to primary alkyl halides as alkylating agents. Due to its remarkable acid lability the protecting diphenylphosphinic



group can be almost quantitatively removed from the alkylation product *(3)*, *(5)* or *(5')* by treatment of the latter with gaseous HCl in THF at room temperature[3].

The alkylation-deprotection two-step procedure can be utilized for the preparation of hydrochlorides of primary *(4)* and secondary *(6)* or *(6')* amines thus offering a substantial extension to conventional variants of the Gabriel synthesis. The use of diphenylphosphinoyl as protecting group for transformation of primary into secondary amines is superior to the previously described procedure[3].

Procedures

Monoalkylation of diphenylphosphinic amide *(1)* (Method (A)): A solution of alkyl bromide (0.02 mol) in benzene (15 ml) was added dropwise over a period of 1.5 h to the vigorously stirred and refluxed mixture of *(1)* (0.02 mol), 50% aqueous solution of NaOH (50 ml), benzene (50 ml), and tetra-*n*-butylammonium hydrogen sulfate (0.34 g, 5 mol%). Stirring was continued at the reflux temperature for 1.5 h. Benzene (50 ml) was then added, the organic layer separated, washed with water (3 × 30 ml), dried, and evaporated *in vacuo* to give crude *(3)*, which crystallized on cooling. Analytically pure samples of *(3)* were obtained by recrystallization from benzene/hexane.

Dialkylation of *(1)* (Method (B)): A mixture of *(1)* (0.02 mol), alkyl bromide (0.08 mol), toluene (50 ml), 50% aqueous solution of NaOH (50 ml), and tetra-*n*-butylammonium hydrogen sulfate (0.34 g, 5 mol%) was refluxed with vigorous stirring for 4 h. Toluene (50 ml) was then added and the product worked-up as in Method (A) to give crude *(5)*. The same procedure was applied for alkylation of *N*-alkyldiphenylphosphinic amides *(3)*. According to NMR data all crude products *(5)* and *(5')* did not contain any appreciable amounts of impurities.

Received: July 4, 1977 [Z 781 IE]
German version: Angew. Chem. 89, 737 (1977)

CAS Registry numbers:
(1), 5994-87-6; *(2)* (R = C_2H_5), 74-96-4; *(2)* (R = n-C_3H_7), 106-94-5; *(2)* (R = n-C_4H_9), 109-65-9; *(2)* (R = CH_2=CH—CH_2), 106-95-6; *(2)* (R = C_6H_5—CH_2), 100-39-0; *(2)* (R' = i-C_4H_9), 78-77-3; *(2)* (R' = CH_3), 74-83-9; *(2)* (R' = i-C_3H_7), 75-26-3; *(3a)*, 63528-17-6; *(3b)*, 6230-69-9; *(3c)*, 24625-67-0; *(3d)*, 63328-18-7; *(3e)*, 27127-08-8; *(3m)*, 6190-28-9; *(3r)*, 6941-20-4; *(4a)*, 557-66-4; *(4b)*, 556-53-6; *(4c)*, 3858-78-4: *(4d)*, 10017-11-5; *(4e)*, 3287-99-8; *(5f)*, 56372-47-5; *(5g)*, 63528-19-8; *(5h)*, 63528-20-1; *(5i)*, 63528-21-2; *(5j)*, 27127-09-9; *(5'k)*, 63528-22-3; *(5'l)*, 63534-38-3; *(5'm)*, 63528-23-4; *(5'n)*, 56616-08-1; *(5'o)*, 63528-24-5; *(5'p)*, 27826-13-7; *(5'q)*, 63528-25-6; *(5'r)*, 63528-26-7; *(5's)*, 63528-27-8; *(5t)*, 63528-28-9; *(6f)*, 660-68-4; *(6g)*, 5326-84-1; *(6h)*, 6287-40-7; *(6i)*, 6147-66-6; *(6j)*, 20455-68-9; *(6'k)*, 36550-63-7; *(6'l)*, 63528-29-0; *(6'm)*, 2739-12-0; *(6'n)*, 4348-19-0; *(6'o)*, 23576-78-5; *(6'p)*, 2290-89-3; *(6'q)*, 31663-62-4; *(6'r)*, 61278-99-7; *(6's)*, 63528-30-3; *(6't)*, 16350-96-2

[1] *I. N. Zhmurova, I. Y. Voitsekhovskaya, A. V. Kirsanov*, Zh. Obshch. Khim. *29*, 2083 (1959); *T. Koizumi, P. Haake*, J. Am. Chem. Soc. *95*, 8073 (1973).
[2] *D. A. Tyssee, L. P. Bausher, P. Haake*, J. Am. Chem. Soc. *95*, 8066 (1973).
[3] *A. Zwierzak, J. Brylikowska-Piotrowicz*, Angew. Chem. *89*, 109 (1977); Angew. Chem. Int. Ed. Engl. *16*, 107 (1977).

$[\eta^5\text{-}C_5H_5Mo(CO)_3HgMo]_4$, a Metal Cluster with Cubane Structure

By *Josef Deutscher, Suheil Fadel*, and *Manfred L. Ziegler*[*]

In the synthesis of $C_5H_5Mo(CO)_3C_4H_7$ from the dimer $[C_5H_5Mo(CO)_3]_2$, 2-butenyl chloride and sodium amalgam by a procedure described in the literature[1], an as yet unknown by-product can be isolated under suitable conditions: to our knowledge tetrakis(tricarbonyl-η^5-cyclopentadienyldimolybdenummercury), $[C_5H_5Mo(CO)_3HgMo]_4$ *(1)*, is the first metal cluster with cubane structure to have a cubane framework composed only of metal atoms (Mo, Hg).

The novel compound *(1)* was characterized by elemental analysis, ^{1}H-NMR and IR spectra as well as by X-ray structure analysis. *(1)* shows three bands [CH_2Cl_2: 2020 (vs), 1943 (sh), 1930 (vs) cm^{-1}] in the region of the CO stretching frequencies. In the ^{1}H-NMR spectrum, only one signal is found at $\delta = 5.5$; this must be assigned to the cyclopentadienyl rings. Crystal structure analysis[2] provided the molecular structure shown in Figure 1. The corners of the slightly deformed cubic skeleton are occupied alternatively by molybdenum and mercury atoms; a $Mo(C_5H_5)(CO)_3$ group is found at each of the four Hg atoms.

The cluster-forming molybdenum is unusually coordinated, it merely forms three bonds with the mercury atoms. The possibility of a hydride ligand at the molybdenum can be ruled out on the basis of the ^{1}H-NMR spectrum. The molybdenum of the $Mo(C_5H_5)(CO)_3$ group obeys the 18 electron rule. The cyclopentadienyl rings are statistically arranged; since they are not subject to restrictions imposed by symmetry conditions or structural factors, free rotation would appear to be possible.

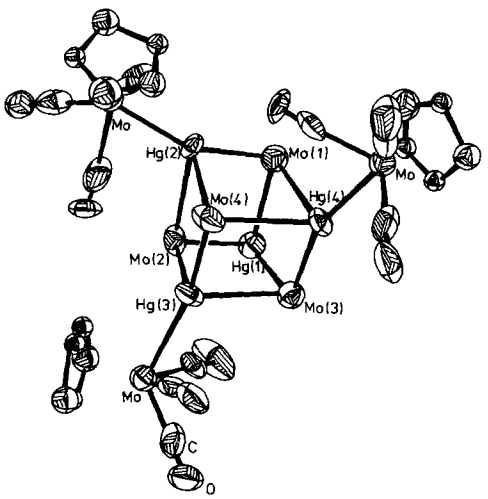


Fig. 1. ORTEP representation of the cubane *(1)*; the $Mo(CO)_3(C_5H_5)$ group at Hg(1) has been omitted for reasons of clarity. Only one position of the statistically distributed cyclopentadienyl rings is given. The thermal ellipsoids correspond to a probability of 50 %.

Bond lengths [pm]		Angles [°]	
Hg(3)—Mo	269.2(3)	Mo(1)—Hg(1)—Mo(3)	90.83(9)
Hg(1)—Mo(1)	319.2(3)	Mo(1)—Hg(1)—Mo(2)	80.84(8)
Hg(1)—Mo(2)	316.2(3)	Mo(1)—Hg(1)—Mo	103.62(9)
Hg(1)—Mo(3)	255.9(3)	Mo(2)—Hg(1)—Mo(3)	86.00(9)
		Hg(2)—Mo(1)—Hg(4)	93.8 (1)
		Hg(2)—Mo(1)—Hg(1)	99.9 (1)
		Hg(1)—Mo(1)—Hg(4)	88.18(8)

[*] Prof. Dr. M. L. Ziegler, Dipl.-Chem. J. Deutscher, Dipl.-Chem. S. Fadel
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1 (Germany)

In describing the cluster it is also possible to postulate that there are two tetrahedra composed of either mercury or molybdenum atoms and with an identical center of gravity, which are displaced through an angle of 90° with respect to each other.

In the case of the known cubanes and dicubanes, non-metals as well as metals are involved in the formation of the cube (*e.g.* $[CH_3HgOSi(CH_3)_3]_4$[3] and $Zn_7O_8(CH_3)_{14}$[4]), but the cubane skeleton of *(1)* consists solely of mercury and molybdenum.

Experimental Procedure

5 g (≈ 10 mmol) $[C_5H_5Mo(CO)_3]_2$ is dissolved in 150 ml tetrahydrofuran and poured into a three-necked flask fitted with a draincock and containing sodium amalgam [15 ml (≈ 1 mol) Hg and 0.6 g (25 mmol) Na]. The contents of the flask are stirred for 12 h at room temperature. Unreacted sodium amalgam is removed and 17 g (0.2 mol) 2-butenyl chloride is added dropwise to the solution, which is then stirred for another 24 h. The color of the solution changes from yellow-green to red-brown. After removal of the solvent by evaporation, the remaining brown grease is taken up in 200 ml CH_2Cl_2, concentrated to 50 ml in a rotary evaporator and subjected to a column chromatographic separation (silica gel 0.05—0.2, 5 × 100 cm, eluting agent CH_2Cl_2). Yellow, orange ($C_5H_5Mo(CO)_3C_4H_7$) and red ($[C_5H_5Mo(CO)_3]_2$) bands are observed. A yellow crystalline solid can be isolated from the solution of the first yellow band, which is then recrystallized from CH_2Cl_2/CH_3Cl (1:3). Yield 10 % *(1)*, m.p. 200 °C (decomp.).—All operations must be carried out under a N_2 atmosphere.

Received: July 14, 1977 [Z 792 IE]
German version: Angew. Chem. *89*, 746 (1977)

CAS Registry numbers:
(1), 63848-12-4; $[C_5H_5Mo(CO)_3]_2$, 12091-64-4

[1] *J. J. Eisch, R. B. King*, Inorg. Chem. *2*, 1031 (1963).
[2] Yellow crystals (from CH_2Cl_2), acentric tetragonal space group D_{2d}^4 – $P\bar{4}2_1c$, $a = b = 1209.5 \pm 0.3$, $c = 1565.9 \pm 0.8$ pm, $Z = 8$, $d_{ber} = 3.153$ g/cm^3. 1172 independent, non-zero reflections were measured with an automatic, single crystal diffractometer (Siemens-AED) and were corrected in the customary way; $R = 5.0$ %.
[3] *H. Schmidbaur, M. Bergfeld, F. Schindler*, Z. Anorg. Allg. Chem. *363*, 73 (1968).
[4] *M. L. Ziegler, J. Weiss*, Angew. Chem. *82*, 931 (1970); Angew. Chem. Int. Ed. Engl. *9*, 905 (1970).

Dicyanophosphide

By *Alfred Schmidpeter* and *Franz Zwaschka*[*]

According to the "cyano displacement principle"[1] the elements E, which precede the halogens by n places in the periodic system should, by taking up n cyano groups, form the pseudohalogens $E(CN)_n$. In the first short period this rule is obeyed up to $n = 3$, *e.g.* by the formation of pseudohalide ions $E(CN)_n^-$, but up to now the series in the second short period did not continue beyond $n = 1$.

[*] Prof. Dr. A. Schmidpeter, Dipl.-Chem. F. Zwaschka
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

n =	3	2	1	0
	$C(CN)_3$	$N(CN)_2$	OCN	F
		$P(CN)_2$	SCN	Cl

The dicyanophosphide ion which continues this series has now been synthesized by reacting phosphorus tricyanide with dialkyl phosphites ($R=CH_3$, C_2H_5):

$$P(CN)_3 + HPO(OR)_2 + Et_3N \longrightarrow Et_3NH^+P(CN)_2^- + NCPO(OR)_2 \quad (1)$$

$$P(CN)_3 + NaPO(OR)_2 \longrightarrow Na^+P(CN)_2^- + NCPO(OR)_2 \quad (2)$$

However, neither its triethylammonium salt *(1)* nor its sodium salt *(2)* is stable in solution, but the salt of the crown ether-sodium complex *(3)* is stable as such and in solution.

In the reaction which we have found, phosphorus tricyanide behaves as an interpseudohalogen compound, NC—$P(CN)_2$, with "positive cyanogen" which is taken over nucleophilically by the dialkylphosphite anion (and the trialkyl phosphite, see below). With reverse polarity, however, phosphorus tricyanide reacts with the dialkylphosphite in the absence of a base:

$$P(CN)_3 + HPO(OR)_2 \longrightarrow HCN + (NC)_2P\text{-}PO(OR)_2 \quad (4)$$

The (dialkylphosphoryl)phosphorus dicyanide *(4)* [$\delta^{31}P=14$ (to low field, $PO(OEt)_2$, d) and -121 (to high field, $P(CN)_2$, d); $J_{PP}=88$ Hz] cannot be considered as an intermediate in the reaction formulated above since it is not cleaved by subsequent addition of CN^- to $P(CN)_2^-$ and $NCPO(OR)_2$.

The dicyanophosphide ion ($\delta^{31}P=-193$) is bent, as is the isoelectronic molecule $S(CN)_2$[2]; a transfer of charge into the cyano groups is however revealed by the lower CN and higher PC stretching frequencies as compared with those of $P(CN)_3$[3] and $CH_3P(CN)_2$[4] ($\nu_{as}PC=616$, $\nu_sPC=630$, $\nu_{as}CN=2097$, $\nu_sCN=2120\,cm^{-1}$).

$$N\equiv C-\overset{\ominus}{P}-C\equiv N \;\leftrightarrow\; N\equiv C-P=C=N^{\ominus} \xrightarrow{+CH_3I} CH_3P(CN)_2 \;\text{(}\not\rightarrow\text{ } CH_3NCPCN\text{)}$$

The dicyanophosphide ion could thus react ambivalently; the nucleophilicity at the σ^2P outweighs by far that at the σ^1N atom with the result that the anion reacts with methyl iodide to produce exclusively methylphosphorus dicyanide *(5)* (this corresponds to the *S*-methylation of the thiocyanate ion). The same compound is also formed directly from phosphorus tricyanide and trimethyl phosphite in a CN/CH_3 exchange accompanied by a Michaelis-Arbusov rearrangement:

$$P(CN)_3 + P(OCH_3)_3 \longrightarrow [NCP(OCH_3)_3^+P(CN)_2^-] \longrightarrow CH_3P(CN)_2 + NCPO(OCH_3)_2 \quad (5)$$

[18]Crown-6-sodium dicyanophosphide (3)

3.0 g $NaPO(OC_2H_5)_2$ and 5.0 g [18]crown-6 in 40 ml tetrahydrofuran were combined with 2.1 g $P(CN)_3$ in 20 ml tetrahydrofuran at room temperature and cooled to -20°C. The crystals which separated out were collected on a cooled frit under moisture-free conditions: 3.8 g (53 %).

Methylphosphorus dicyanide (5)

3.0 g $P(CN)_3$ and 3.4 g $P(OCH_3)_3$ in 30 ml CCl_4 are briefly warmed at 40 °C until the reaction starts and the suspension becomes clearer. After 30 min most of the solvent has evaporated off, the remaining oil is cooled and the crystals of *(5)* are removed. M.p. 70 to 72 °C (from CCl_4), $\delta^{31}P=-82$, cf. [4]; approximately 50 %. $NCPO(OCH_3)_2$[5] remains as the filtrate, $\delta^{31}P=-18$; it is contaminated by the residual $CH_3P(CN)_2$ which cannot be entirely removed by vacuum distillation.

Received: July 15, 1977 [Z 793 IE]
German version: Angew. Chem. *89*, 747 (1977)

CAS Registry numbers:
(1), 63731-06-6; *(2)*, 63765-56-0; *(3)*, 63731-77-1; *(4)*, R = Et, 63731-05-5; *(5)*, 27388-03-0; $P(CN)_3$, 1116-01-4; $P(OCH_3)_3$, 20502-88-9

[1] *L. Birckenbach, K. Huttner*, Z. Anorg. Allg. Chem. *190*, 1 (1930), following "Grimm's hydride displacement principle", *H. G. Grimm*, Z. Elektrochem. Ang. Phys. Chem. *31*, 474 (1925).
[2] *L. Pierce, R. Nelson, C. Thomas*, J. Chem. Phys. *43*, 3423 (1965).
[3] *J. Goubeau, H. Haeberle, H. Ulmer*, Z. Anorg. Allg. Chem. *311*, 110 (1961).
[4] *L. Maier*, Helv. Chim. Acta *46*, 2667 (1963).
[5] Houben/Weyl: Methoden der organischen Chemie, Vol. XII/2. Thieme, Stuttgart 1964, p. 298.

Thioheteroanions—Unusual Metal-Ligand Interaction and Reactions

By *Achim Müller* and *Sabyasachi Sarkar*[*]

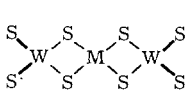
Whereas heteropolyanions have been known for a long time[1], heteroanions of the type $[Ni(WS_4)_2]^{2-}$ were first reported only in recent years[1,2]. These complexes—which in contrast to heteropolyanions contain simple monomeric anions as ligands—are interesting because of their strong electron delocalization between the metal centers of different valence states[3]. From the strong reduction in electron density at the Co center[4], as *e.g.* in $[Co(WS_4)_2]^{2-}$ *(1)*, one should expect species of this type to react with free ligands such as NO, in spite of a nearly regular tetrahedral site symmetry of Co ($[Co(NCS)_4]^{2-}$ does not react!). This metal→ligand electron delocalization (pseudo intramolecular redox reaction) thwarted all previous attempts to isolate complexes like $[Fe^{II}(WS_4)_2]^{2-}$ and $[Fe^{II}(MoS_4)_2]^{2-}$ in a pure form[5], which contain the same or similar "heteroelements" as the nitrogenase[3]. Reactions of thioheteroanions were hitherto unknown.

The reaction products of the thioheteroanions, namely the brown-red derivatives $[Co(NO)(WS_4)_2]^{2-}$ *(2)*, $[Fe(NO)(WS_4)_2]^{2-}$ *(3)* and $\{Fe(NO)(MoS_4)_2\}^{2-}$ *(4)* as well as $[Fe(WS_4)_2]^{2-}$ *(5)* (green) and $\{Fe(MoS_4)_2\}^{2-}$ *(6)* (brown-violet, not pure) have now been isolated as the tetraphenylphosphonium salts and have been characterized by elemental analyses, powder diffractograms, IR-, VIS-, ESR-, PE(ESCA)-spectral studies, and by magnetic measurements. *(2)*, *(3)* and *(5)* are soluble in CH_2Cl_2.

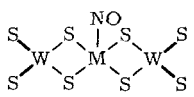
The ν(WS)-bands of *(2)*, *(3)*, and *(5)* show the characteristic splitting pattern for *bidentate* thiometallato-complexes of the

[*] Prof. Dr. A. Müller, Dr. S. Sarkar [**]
Institut für Chemie der Universität
Postfach 500500, D-4600 Dortmund 50 (Germany)
[**] Alexander-von-Humboldt-Foundation Fellow.

degenerate vibrations of the free ligand (assignment confirmed by metal-isotope studies; see Table 1). These monomeric complex anions contain the structural units shown below[6]:



(M = Fe)



(M = Fe, Co)

(thick lines depict the stronger WS_{term}-bonds), whereas the stronger electron delocalization in the thiomolybdato complexes of iron (due to the lower lying unoccupied MO's in MoS_4^{2-} in comparison with those in WS_4^{2-})[2] causes weakening of the terminal MoS-π-bonds and thus a higher electron density at the terminal sulfur. Hence, the coordination ability of the terminal sulfur increases and consequently leads to "polymerisation" of the thioheteroanions. This can be recognized in the IR spectra of compounds *(4)* and *(6)*, which, in contrast to *(2)*, *(3)* and *(5)*, are X-ray amorphous [diffuse reflection (2θ) for Cu-K_α at 8.7, 12.7, 19.0 and 42.3° or 6.5, 12.5, 20 and 44°, respectively][7].

From our results one would expect that the thioheteroanions should also fix other interesting ligands. The strong electron delocalization in thioheteroanions compared to that in the other complexes with sulfur-containing ligands can be seen from the data listed in Tables 1 and 2. Extremely strong metal-ligand interactions also occur in ene-1,2-dithiolato complexes (the data of one have been given for comparison).

Table 1. Main IR bands (tetraphenylphosphonium salts as solids, nujol, cm^{-1}) [a].

	ν(NO)	$\nu(MS)_{term}$	$\nu(MS)_{br}$
$[Co(WS_4)_2]^{2-}$ *(1)*	—	491, 484	442, 434
$[Co(NO)(WS_4)_2]^{2-}$ *(2)*	1674 (1617) [b]	491, 483	445
$[Fe(WS_4)_2]^{2-}$ *(5)*	—	493, 484	450, 438
$[Fe(NO)(WS_4)_2]^{2-}$ *(3)*	1715 (1633) [c]	487	450, 443
$\{Fe(MoS_4)_2\}^{2-}$ *(6)*	—		448, 434. 350, 330 [d]
$\{Fe(NO)(MoS_4)_2\}^{2-}$ *(4)*	1704		455, 436, 353. 335/325 [e]

[a] Weak δ(NO) and ν(MN) bands cannot be determined unequivocally.
[b] Corresponding value in $[(C_6H_5)_4P]_2[Co(NO)\{S_2C_2(CN)_2\}_2]$.
[c] Corresponding value in $[(C_6H_5)_4P]_2[Fe(NO)\{S_2C_2(CN)_2\}_2]$.
[d] Additional band at 480 cm^{-1} (substance not pure).
[e] Additional band at 404 cm^{-1}.

Experimental

$[(C_6H_5)_4P]_2[Co(NO)(WS_4)_2]$ *(2)*: NO (diluted with Ar in the ratio of *ca.* 1:10) was passed through a solution of tetraphenylphosphonium-bis(tetrathiotungstato)cobalt *(1)* (0.75 g) in CH_2Cl_2 (20 ml) for 10 min; the color of the solution changed from green to brown-red. After filtering this solution to remove traces of solid particles, the complex *(2)* was precipitated as a brown crystalline solid in almost quantitative yield by adding *n*-pentane (20 ml)[9].

$[(C_6H_5)_4P]_2[Fe(NO)(WS_4)_2]$ *(3)*: Prepared analogously to *(2)* from a solution of *(5)* (0.5 g) in oxygen-free CH_2Cl_2 (15 ml). The precipitate of *(3)* obtained on adding *n*-pentane (20 ml) was dissolved in CH_2Cl_2 and recrystallized as deep-red crystals in almost quantitative yield by adding methanol.

$[(C_6H_5)_4P]_2\{Fe(NO)(MoS_4)_2\}$ *(4)*: Prepared analogously to *(3)* (reaction time with NO 20 min!), but *n*-pentane was added after filtration of the reaction mixture and the process of reprecipitation was repeated by extracting the compound with CH_2Cl_2 and precipitating with *n*-pentane. Yield *ca.* 60 %.

$[(C_6H_5)_4P]_2[Fe(WS_4)_2]$ *(5)*: A solution of $(NH_4)_2WS_4$ (0.7 g) in H_2O (50 ml) was added slowly with stirring to an aqueous, O_2-free solution of $FeSO_4 \cdot 7H_2O$ (0.38 g), $[(C_6H_5)_4P]Cl$ (0.75 g) and $N_2H_4 \cdot 2HCl$ (50 mg). The resulting precipitate was filtered under Ar and washed with water, ethanol, and ether. Yield *ca.* 70 %.

$[(C_6H_5)_4P]_2\{Fe(MoS_4)_2\}$ *(6)*: Prepared analogously to *(5)* without adding $N_2H_4 \cdot 2HCl$, which reduces MoS_4^{2-}. Not isolated in pure form.

Received: May 20, 1977 [Z 795 IE]
Supplemented: July 18, 1977
German version: Angew. Chem. *89*, 748 (1977)

CAS Registry numbers:
(1), 63714-43-2; *(2)*, 63714-41-0; *(3)*, 63714-51-2; *(4)*, 63714-49-8; *(5)*, 63714-39-6; *(6)*, 63714-37-4

[1] *F. A. Cotton, G. Wilkinson:* Advanced Inorganic Chemistry. Wiley-Interscience, New York 1972.
[2] *A. Müller, E. Diemann*, Chem. Commun. *1971*, 65; see *E. Diemann, A. Müller*, Coord. Chem. Rev. *10*, 79 (1973).
[3] *A. J. Thomson*, Nachr. Chem. Tech. Lab. *25*, 238 (1977).
[4] The ESR-spectrum of *(1)* in $[(C_6H_5)_4P]_2[Zn(WS_4)_2]$ measured at 5.3 K shows only a small deviation from tetrahedral symmetry for CoS_4 ($g_1 = 2.054$, $g_2 = 2.035$, $g_3 = 2.002$) as well as a small value for the orbital reduction factor from the g_{av}-value (high electron delocalization!). The same conclusion results from the electron absorption spectrum (extremely high ε value for the pseudo d→d transition at 12400 cm^{-1}: *ca.* $5 \cdot 10^3$ l mol^{-1} cm^{-1}!) as well as from the μ_{eff}-values. The interesting band with high intensity (transition probably with L→M charge transfer character) will be assigned with a MO calculation.
[5] *A. Müller, E. Diemann, H. H. Heinsen*, Chem. Ber. *104*, 975 (1971). *A. Müller, E. Ahlborn, H. H. Heinsen*, Z. Anorg. Allg. Chem. *386*, 102 (1971).

Table 2. Comparison of characteristic data of the heteroanion *(3)* and of its enedithiolato analog.

	$[Fe(NO)(WS_4)_2]^{2-}$ *(3)*	$[Fe(NO)\{S_2C_2(CN)_2\}_2]^{2-}$ [8]
ESR [a]: g_{av}	2.022	2.028
ESR [a]: A_N [G]	15.0	15.3
VIS: "d→d" [cm^{-1}]	≈15000 [b]	14600, 23700
PE(ESCA) ΔN1s [eV]	−2 [c]	
μ_{eff} [μ_B]	(2.5) [d]	1.84

[a] In CH_2Cl_2 solution; characteristic triplet due to $^{14}N(I=1)$ superhyperfine interaction.
[b] Shoulder (CH_2Cl_2).
[c] Difference to $[Fe(CN)_5NO]^{2-}$ corresponding to the higher ν(NO) frequency in the nitroprusside.
[d] For problematic nature see [8].

[6] The bidentate coordination concluded from our spectroscopic observation was later confirmed by X-ray structure determinations on $[Ni(MoS_4)_2]^{2-}$ (*I. Søtofte*, Acta Chem. Scand. *A 30*, 157 (1976)) and on $[Zn(WS_4)_2]^{2-}$ (*I. Paulat-Böschen, B. Krebs, A. Müller, E. Königer-Ahlborn, H. Dornfeld*, Inorg. Chem., in press).

[7] Determination of the structure (approximate) will be made by the method of radial distribution functions.
[8] *J. A. McCleverty, N. M. Atherton, J. Locke, E. J. Wharton, C. J. Wiscom*, J. Am. Chem. Soc. *89*, 6082 (1967).
[9] On prolonged passage of NO further reaction takes place to give the structurally less interesting dinitrosyl complex, $[Co(NO)_2WS_4]$; see *F. N. Tebbe, E. L. Muetterties*, Inorg. Chem. *9*, 629 (1970); *A. R. Hendrickson, R. K. Y. Ho, R. L. Martin, ibid. 13*, 1279 (1974) in the case of other sulfur-containing ligands.

Isodiazomethane Complexes[**]

By *Wolf Peter Fehlhammer, Peter Buračas*, and *Klaus Bartel*[*]

An "isomeric diazomethane" was first reported in 1934 by *Müller* and *Kreutzmann*[1a]. Its isocyanide character remained unrecognized for a long time. It was as late as 1968 before *Müller et al.* reported on the characterization of this species, which could not be isolated as a pure substance[1b].

We have now succeeded in the stabilization, in metal complexes, of this parent compound of the Bredereck *N*-isocyanodialkylamines[2a] which can also be regarded as the amide of the unknown isofulminic acid CNOH[2b].

1) Solid PdI_2 is suspended in a solution of isodiazomethane in ether[3] with cooling (−10°C). After filtration and concentration of the solution, diiodobis(isodiazomethane)palladium(II) crystallizes with 2 molecules of diethyl ether *(1)* in the form of orange-red platelets.

$$H_2CN_2 \xrightarrow[2)\ H_2O]{1)\ LiCH_3} CNNH_2 \xrightarrow[Et_2O]{PdI_2} I_2Pd(-C{\equiv}N-NH_2)_2 \cdot 2\ Et_2O \qquad (1)$$

The presence of an isocyanide complex with a metal-carbon bond is indicated by a weak IR absorption at 2240 cm^{-1} which we attribute to the ν_{NC} vibration of the coordinated isodiazomethane. The observed increase by $\approx +100\ cm^{-1}$ in the ν_{NC} frequency of isodiazomethane ($\nu_{NC} = 2140\ cm^{-1}$) on coordination to palladium(II) is of the usual order of magnitude for complexes of the type $Hal_2M(CNR)_2$[4a] and $Hal_2M(CNNR_2)_2$[4b] ($M = Pd^{II}, Pt^{II}$).

The solvent molecules in *(1)* apparently contribute to the stabilization of the compound. If they are removed by high vacuum, *(1)* decomposes to a dark brown powder which gives only unresolved peaks in the region of the ν_{NH} and ν_{NC} vibrations of the IR spectrum, presumably indicating the presence of separated cyano and ammine ligands[5]. *Müller et al.* isolated substances with analogous IR spectra while trying to incorporate isodiazomethane into Co^{II} and Ni^{II} complexes[6].

2) The isodiazomethane ligand in pentacarbonyl(isodiazomethane)chromium(0) *(3)* is generated at the protecting metal. Analytically pure *(3)* can be obtained in excellent yields [b) > 90 %] by protolysis of the Si—N bonds in *(2)*[7] and subsequent sublimation (50°C, high vacuum).

$$(OC)_5Cr-C{\equiv}N-N(SiMe_3)_2 \xrightarrow[b)\ CF_3CO_2H/CH_2Cl_2]{a)\ HCl/Benzene} (OC)_5Cr-C{\equiv}N-N\begin{matrix}H\\H\end{matrix}$$
(2) *(3)*

Embedded in this stable coordination compound isodiazomethane can be conveniently handled; this should be of benefit in the further investigation of its physical and chemical properties.

The signal of the molecular ion in the mass spectrum of *(3)* is of medium intensity (base line for $[CrCNNH_2]^+$). As expected, the ^1H-NMR spectrum ($CDCl_3$, TMS ext.) shows only a broad singlet at $\delta = 5.17$. The compound $(OC)_5Cr-N{\equiv}C-NH_2$ *(4)*, which is isomeric with *(3)*, was synthesized for comparison; in contrast to *(3)* (m.p. 91 °C), this compound proved to be extremely thermolabile (dec. pt. <40°C). The stabilities of the complexes are thus the reverse of those of the free ligands.

Received: July 20, 1977 [Z 798 IE]
German version: Angew. Chem. *89*, 752 (1977)

CAS Registry numbers:
$I_2Pd(-C{\equiv}N-NH_2)_2$, 63714-47-6; *(2)*, 63714-46-5; *(3)*, 63714-45-4; *(4)*, 63714-44-3; H_2CN_2, 334-88-3; PdI_2, 7790-38-7

[1] a) *E. Müller, W. Kreutzmann*, Justus Liebigs Ann. Chem. *512*, 264 (1934); b) *E. Müller, P. Kästner, R. Beutler, W. Rundel, H. Suhr, B. Zeeh, ibid. 713*, 87 (1968).
[2] a) *H. Bredereck, B. Föhlisch, K. Walz*, Justus Liebigs Ann. Chem. *686*, 92 (1965); b) fulminic acid has the structure of a formonitrile oxide H—CNO: *W. Beck, K. Feldl*, Angew. Chem. *78*, 746 (1966); Angew. Chem. Int. Ed. Engl. *5*, 722 (1966); *W. Beck, P. Swoboda, K. Feldl, R. S. Tobias*, Chem. Ber. *104*, 533 (1971).
[3] *E. Müller, D. Ludsteck*, Chem. Ber. *87*, 1887 (1954).
[4] a) Cf. *e.g. B. Crociani, T. Boschi, U. Belluco*, Inorg. Chem. *9*, 2021 (1970); b) *W. P. Fehlhammer*, unpublished work.
[5] This decomposition is due to cleavage of the N—N bond of the coordinated ligand, as is generally observed with *N*-isocyanodialkylamine complexes: *W. P. Fehlhammer*, unpublished.
[6] *E. Müller, R. Beutler, B. Zeeh*, Justus Liebigs Ann. Chem. *719*, 72 (1968).
[7] *(2)* can be synthesized from $Cr(CO)_5 \cdot THF$ and bis(trimethylsilyl)aminoisocyanide [*N. Wiberg, G. Hübler*, Z. Naturforsch. *B31*, 1317 (1976)]. We thank Prof. *Wiberg* and Dr. *Hübler* for providing this substance.

Trifluoromethylamine, CF_3NH_2[**]

By *Gerhard Klöter, Walter Lutz, Konrad Seppelt*, and *Wolfgang Sundermeyer*[*]

In spite of its instability, the hitherto unknown compound trifluoromethylamine has now been synthesized by two different pathways. The first pathway corresponds to the preparation of trifluoromethanol[1]: transformation of the known *N*-dichloro derivative[2] into the amine. The second pathway entails cautious cleavage of *tert*-butyl trifluoromethylcarbamate obtainable from trifluoromethyl isocyanate[3].

$$CF_3-N{=}SF_2 \xrightarrow[-SF_4]{+2\ ClF} CF_3-NCl_2 \xrightarrow[-2\ Cl_2]{+3\ HCl/-100^\circ C}$$

$$CF_3-NH_2 \cdot HCl \xrightarrow{Base/-40^\circ C} CF_3NH_2$$

$$CF_3-N{=}C{=}O + HO-tC_4H_9 \longrightarrow CF_3-NH-\overset{O}{\overset{\|}{C}}-O-tC_4H_9$$

$$\xrightarrow[-CO_2,\ -ClC(CH_3)_3]{+HCl/-25^\circ C} CF_3-NH_2(\cdot HCl)$$

[*] Dr. W. P. Fehlhammer, Dipl.-Chem. P. Buračas, Dr. K. Bartel
Institut für Anorganische Chemie der Universität Erlangen-Nürnberg
Egerlandstrasse 1, D-8520 Erlangen (Germany)

[**] Metal Complexes of Functional Isocyanides, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft. Part 2: *W. P. Fehlhammer, K. Bartel, W. Petri*, J. Organomet. Chem. *87*, C 34 (1975).

[*] Priv.-Doz. Dr. K. Seppelt, G. Klöter, Dipl.-Chem. W. Lutz, Prof. Dr. W. Sundermeyer
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1 (Germany)

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

The amine can be liberated from the initially formed amine hydrochloride by the action of a base (quinoline, pyridine, diethylamine, or trimethylamine).

CF_3NH_2 is a colorless solid which melts with decomposition at -21 °C, but can be partly sublimed without decomposition. It was characterized by the mass spectrum [$m/e = 85$, $CF_3NH_2^+$, and numerous fragments], IR spectrum [gas; cm^{-1}: 3484 m ($\nu_{as}NH_2$), 3407 m (ν_sNH_2), 1611 s (δNH_2), 1310 vs, 1106 vs, 1038 s (νCF and νCN), *etc.*], Raman spectrum [solid; cm^{-1}: 1647 (15), 1372 (12), 1315 (7), 1272 (8), 914 (8), *etc.*], ^{1}H-NMR [broad quartet at $\delta = 6.73$, $J_{HF} = 10.6$ Hz and ^{19}F-NMR spectrum [sharp triplet at $\delta = 48.9$, $J_{HF} = 10.4$ Hz].

The compound has unexpected physical properties. While the recently discovered trifluoromethanol CF_3OH is more volatile than CH_3OH, CF_3NH_2 is less volatile than CH_3NH_2 (b.p. 50 °C, extrap.) and also has a notably high melting point. Hydrogen bonding can be ruled out on the basis of the gas phase IR spectrum. In fact, an HNH angle of 110.0° can be calculated with an approximation formula[4] from the splitting of the two very sharp NH_2 stretching vibrations. The fine structure of the NMR signals shows that the molecule also fails to associate in solution. Valuable information should come from crystal structure analysis which will, however, be complicated by the sensitivity of the substance.

Owing to the inductive effect of fluorine, CF_3NH_2 is a weaker base than CH_3NH_2. This has its parallels in the increase in acidity on going from CH_3OH to CF_3OH. Acidic properties like those observed for the related compound H_2NTeF_5[5] have not yet been found either for CF_3NH_2 or for H_2NSF_5[6].

The simplest primary perfluoroalkylamine decomposes at room temperature to give polymeric products of the general formula $(FCN)_x(CF_2NH)_y$ and hydrogen fluoride. In the gaseous state, on the other hand, decomposition leads to FC≡N and HF.

Received: July 22, 1977 [Z 800 IE]
German version: Angew. Chem. 89, 754 (1977)

CAS Registry numbers:
CF_3CF_3—N=SF_2, 1512-14-7; CF_3—NCl_2, 13880-73-4; CF_3—NH_2·HCl, 63689-56-5; CF_3—NH_2, 61165-75-1; CF_3—N=C=O, 460-49-1; HO-*t*-C_4H_9, 75-65-0; CF_3—NH—CO—O-*t*-C_4H_9, 63689-57-6

[1] *K. Seppelt*, Angew. Chem. *89*, 325 (1977); Angew. Chem. Int. Ed. Engl. *16*, 322 (1977).
[2] *R. A. DeMarco, J. M. Shreeve*, Chem. Commun. *1971*, 788.
[3] *W. Lidy, W. Sundermeyer*, Chem. Ber. *109*, 1491 (1976).
[4] *H.-J. Götze*, personal communication.
[5] *K. Seppelt*, Inorg. Chem. *12*, 2837 (1973).
[6] *A. F. Clifford, C. C. Duncan*, Inorg. Chem. *5*, 692 (1966).

A Cobalt-Catalyzed One-Step Synthesis of Annelated Pyridines[**]

By *Alaric Naiman* and *K. Peter C. Vollhardt*[*]

The pyridine nucleus as incorporated into a more complex structural framework is ubiquitous in heterocyclic molecules of synthetic and medicinal interest. We wish to report a new approach to the synthesis of such moieties based on the cobalt-catalyzed cooligomerization of diacetylenes[1] with nitriles. This method allows in one step the formation of oligoheterocyclic systems with pronounced chemo- and regioselectivity, and it is tolerant of functional groups and medium sized (seven-membered) rings[2]. Thus, commercial cyclopentadienyl cobalt dicarbonyl under high dilution conditions catalyzes the cooligomerization of diynes *(1)* or *(8)* with a variety of substituted nitriles *(2)* to give heterocycles *(3)*—*(7)* with remarkable selectivity and in good yield[3]. The formation of the 5,6,7,8-tetrahydroisoquinolines *(4)* is particularly valuable, since this class of compounds is not otherwise easily accessible[4].

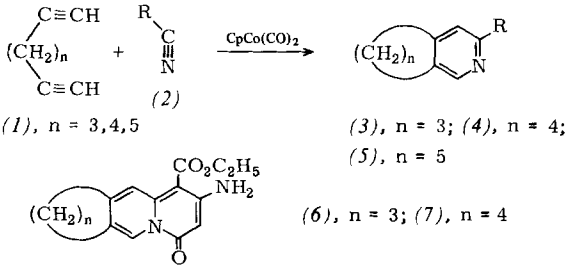


Table 1. Compounds synthesized.

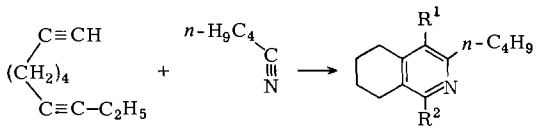
(2)	R	*(3)*—*(7)*	*n*	Yield [%]
(2a)	*n*-C_4H_9	*(3a)*	3	67
(2b)	C_6H_5	*(3b)*	3	56
(2a)	*n*-C_4H_9	*(4a)*	4	77
(2b)	C_6H_5	*(4b)*	4	70 [5]
(2c)	CH_3	*(4c)*	4	81 [6]
(2d)	CH_2OCH_3	*(4d)*	4	62
(2e)	$CO_2C_2H_5$	*(4e)*	4	5.9 [7]
(2f)	$CH_2CO_2C_2H_5$	*(4f)*	4	47
(2g)	CH_2CH_2CN	*(4g)*, *(4h)*	4	[a]
(2h)	C_6F_5	*(4i)*, *(4j)*, *(4k)*	4	2.7 [b, c] [8]
(2i)	$C(CH_3)_3$	*(4l)*	4	47
(2a)	*n*-C_4H_9	*(5a)*	5	43
(2b)	C_6H_5	*(5b)*	5	54
(2f)	$CH_2CO_2C_2H_5$	*(6)*	3	37 [d]
(2f)	$CH_2CO_2C_2H_5$	*(7)*	4	22 [d]

[a] Products *(4g)* and *(4h)* with R = CH_2CH_2CN (yield 30%) and CH_2CH_2-3-(5,6,7,8-tetrahydro)isoquinolyl (yield 19%).
[b] Mixture of the products *(4i)*, *(4j)*, and *(4k)* with R = C_6F_5, C_6F_4H and $C_6F_3H_2$ (3.5 : 5.5 : 1).
[c] Analyzed by GC/mass spectroscopy on a Du Pont 492-1 instrument interfaced with a Varian Aerograph Model No. 204 (linear temperature programmer) equipped with a 20′ + 0.03″ glass capillary column (*ca.* 600 cm × 0.1 cm) packed with 3% Dexsil 300 on 80/100 gas chrom Q.
[d] With excess *(2f)*.

Several results are particularly noteworthy. 1. In contrast to previous work[1, 2], large excess of any one reactant (in particular nitrile) is unnecessary and does not lead to improved yields. This permits the efficient utilization of starting materials. 2. Cyclization of *(1)*, $n = 3$ or 4, with excess cyanoacetic ester results in the novel 7,8-annelated 2-amino-4-oxo-4H-quinolizine-1-carboxylates *(6)* and *(7)*, respectively, formed *via* the 3-(tetrahydroisoquinoline)acetates [cf. *(4f)*] by condensation with a second equivalent of nitrile. 3. Pronounced regioselectivity is observed in the reaction of 1,7-decadiyne *(8)* with valeronitrile *(2a)* resulting in the preferred formation of product *(4m)*, at the expense of *(4n)* (17 : 1 ratio)[9]. 4. Despite the functional group tolerance of the reaction, strongly electron-withdrawing groups bound directly to cyano carbon appear to be disadvantageous.

[*] A. Naiman, Prof. Dr. K. Peter C. Vollhardt
Department of Chemistry, University of California, and the Materials and Molecular Research Division, Lawrence Berkeley Laboratory
Berkeley, California 94720 (USA)

[**] This work was supported by the National Institutes of Health (GM 22479), the National Science Foundation (CHE76-01783), (in part) by Cancer Research Funds of the University of California, and the A. P. Sloan Foundation. We thank Prof. *H. Rapoport* for useful discussions, and Dr. *R. P. Philp* and Mr. *S. C. Brown* for recording GC/MS data.



(8) *(2a)* *(4m)*, R^1 = H, R^2 = C_2H_5; 73%
(4n), R^1 = C_2H_5, R^2 = H; 4.1%

The pronounced chemospecificity of the reaction may derive from the ligand selectivity of a Co^{III} species, as it (formally) exists in an intermediate cobaltacyclopentadiene derived from *(1)* or *(8)*. Thus, whereas the better back-bonding Co^{I} nucleus in starting catalyst prefers complexation to the CC triple bonds of *(1)* and *(8)*, the subsequently formed metallocycle selects for the better σ-donor nitrile to give pyridine and not benzene as the final product.

Procedure

Ethyl 3-(5,6,7,8-tetrahydroisoquinoline)acetate (4f): A solution of 1,7-octadiyne *(1)*, $n=4$, (650 µl, 5.00 mmol), cyanoacetic ester *(2f)* (531 µl, 5.00 mmol) and $(C_5H_5)Co(CO)_2$ (63 µl, 0.50 mmol) in xylene (15 ml) was added over 117 h (by syringe pump) to *o*-xylene (15 ml) warmed to reflux under N_2 (all reagents deoxygenated).

After removal of solvent under reduced pressure, the reaction mixture was chromatographed on silica gel (60 g; ether elution). The crude product was microdistilled (85—105 °C/0.01 torr) to give a clear oil, analytically pure (510 mg = 47.1 %).

Received: May 31, 1977 [Z 803 IE]
revised: July 20, 1977
German version: Angew. Chem. *89*, 758 (1977)

CAS Registry numbers:
(1) (*n*=3), 2396-63-6; *(1)* (*n*=4), 871-84-1; *(1)* (*n*=5), 2396-65-8; *(2a)*, 110-59-8; *(2b)*, 100-47-0; *(2c)*, 75-05-8; *(2d)*, 1738-36-9; *(2e)*, 623-49-4; *(2f)*, 105-56-6; *(2g)*, 110-62-1; *(2h)*, 773-82-0; *(2i)*, 630-18-2; *(3a)*, 63797-41-1; *(3b)*, 63797-43-3; *(4a)*, 63797-40-0; *(4b)*, 53937-37-4; *(4c)*, 37009-20-4; *(4d)*, 63797-44-4; *(4e)*, 63797-26-2; *(4f)*, 63797-27-3; *(4g)*, 63797-28-4; *(4h)*, 63797-29-5; *(4i)*, 63797-30-8; *(4j)*, 63797-31-9; *(4k)*, 63797-32-0; *(4l)*, 63797-33-1; *(4m)*, 63797-34-2; *(4n)*, 63797-35-3; *(5a)*, 63797-36-4; *(5b)*, 63797-37-5; *(6)*, 63797-38-6; *(7)*, 63797-39-7; *(8)*, 63815-29-2; dicarbonyl(cyclopentadienyl)cobalt, 12078-25-0

[1] For applications of this methodology in the synthesis of complex carbocycles, see: *W. G. L. Aalbersberg, A. J. Barkovich, R. L. Funk, R. L. Hillard III, K. P. C. Vollhardt*, J. Am. Chem. Soc. *97*, 5600 (1975); *R. L. Hillard III, K. P. C. Vollhardt*, Angew. Chem. *87*, 744 (1975); Angew. Chem. Int. Ed. Engl. *14*, 712 (1975); J. Am. Chem. Soc. *99*, 4058 (1977); *R. L. Funk, K. P. C. Vollhardt*, J. Chem. Soc. Chem. Commun. *1976*, 833; J. Am. Chem. Soc. *98*, 6755 (1976); *99*, 5483 (1977); *K. P. C. Vollhardt*, Acc. Chem. Res. *10*, 1 (1977).

[2] The cocyclization of monoacetylenes with nitriles in the presence of cobalt catalysts leads to random cyclizations of low product and regioselectivity and/or yield, resulting in complex mixtures: *A. Naiman, K. P. C. Vollhardt*, unpublished results; see also: *Y. Wakatsuki, H. Yamazaki*, J. Chem. Soc. Chem. Commun. *1973*, 280; Tetrahedron Lett. *1973*, 3383; Synthesis *1976*, 26; *H. Bönnemann, R. Brinkmann, H. Schenkluhn, ibid. 1974*, 575; *H. Bönnemann, R. Brinkmann, ibid. 1975*, 600.

[3] All new compounds prepared gave correct spectral and analytical data.

[4] *F. W. Vierhapper, E. L. Eliel*, J. Org. Chem. *40*, 2729 (1975).

[5] *P. Schiess, C. Monnier, P. Ringele, E. Sendi*, Helv. Chim. Acta *57*, 1676 (1974).

[6] *E. Ochiai, M. Takahashi*, Itsuu Kenkyusho Nempo *1971*, 15.

[7] *R. M. Anderson, G. R. Clemo, G. A. Swan*, J. Org. Chem. *19*, 2579 (1954).

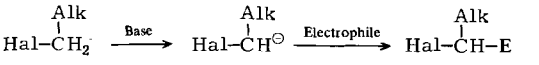
[8] For a similar finding, see: *S. A. Gardner, E. F. Tokas, M. D. Rausch*, J. Organometal. Chem. *92*, 69 (1975).

[9] This contrasts with the finding that in some cases the sterically more hindered benzenes are formed in cocyclizations of diynes with monoacetylenes: *R. L. Hillard III, K. P. C. Vollhardt*, Angew. Chem. *89*, 413 (1977); Angew. Chem. Int. Ed. Engl. *16*, 399 (1977).

Versatile Principle for the Synthesis of Functionalized Hydrocarbons *via* Organoarsenic Compounds[**]

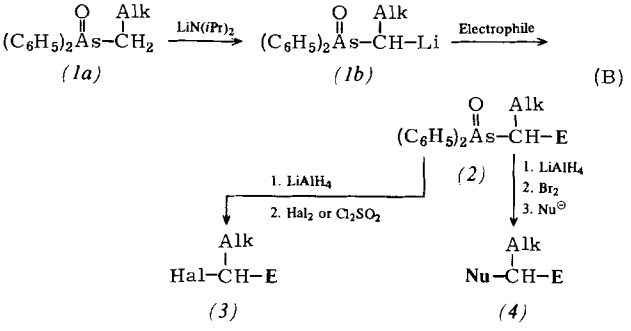
By *Thomas Kauffmann, Rolf Joussen*, and *Annegret Woltermann*[*]

Among the unattainable reactions of organic chemistry, that according to equation (A) would be extremely useful since the halogen in the final product could be replaced by a variety of other substituents[1]. The substitute reaction (B) described below utilizes the ability of organoarsenic groups to act as halogen equivalents.



(A)

Like *methyl*diphenylarsane oxide[2], the higher homologs *(1a)* preparable therefrom can be metalated in the methylene group α to the As atom by lithium diisopropylamide. The resulting compounds *(1b)* provide numerous entries to functionalized hydrocarbons: after reaction with electrophiles (Table 1), the diphenylarsane oxide moiety can be quantitatively reduced to the arsane and then replaced by halogen (Cl, Br, I) (Table 2). As demonstrated by two examples, the latter reaction can also be combined with nucleophilic substitution reactions in a one-pot procedure (Table 3). Sulfonyl chloride



(B)

Table 1. Reactions *(1a)* → *(2)*.

Alk	Electrophile	E	Product *(2)* Yield [%]	M.p. [°C]
C_2H_5	I—CH_3	CH_3	72	84 (Et_2O/THF 95:5)
C_3H_7	O=$C(C_6H_5)_2$	$C(C_6H_5)_2OH$	45	214—215 ($CHCl_3$)
C_4H_9	Br—$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	51	181 (Et_2O/THF 95:5)
C_4H_9	O=$C(C_6H_5)_2$	$C(C_6H_5)_2OH$	93	210 ($CHCl_3$)
C_4H_9	CO_2	COOH	64	126 (Et_2O/THF 95:5)

[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. R. Joussen, A. Woltermann
Organisch-chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

[**] New Reagents, Part 5. This work was supported by the Ministry of Science and Research of North Rhine-Westphalia and the Fonds der Chemischen Industrie.—Part 4: *Th. Kauffmann, R. Joussen, A. Woltermann*, Chem. Ber., in press.

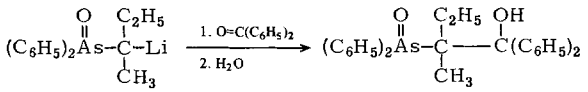
was found to be particularly useful as a reagent for replacing the diphenylarsane group by chlorine (heating equimolar amounts to 132 °C in chlorobenzene).

Table 2. Reactions *(2)* → *(3)* [3].

Alk	E	Reagent	Hal	Yield [%]
C_2H_5	CH_3	Cl_2SO_2	Cl	77
C_2H_5	CH_3	Br_2	Br	93
C_2H_5	CH_3	I_2	I	95
C_4H_9	COOH	Br_2	Br	56

Table 3. Reactions *(2)* → *(4)* [3].

Alk	E	Nucleophile	Nu	Yield [%]
C_2H_5	CH_3	KOH	OH	64
C_2H_5	CH_3	$NaSC_6H_5$	SC_6H_5	71



(5) *(6)*

The structures of the hitherto unreported compounds are confirmed by elemental analysis and ^{1}H-NMR and mass spectra.

Procedure: sec-Butyl phenyl sulfide from diphenylpropylarsane oxide

Transformation of diphenylpropyl arsane oxide into *sec*-butyldiphenylarsane oxide (72 %; m.p. 84 °C, from ether/THF 95:5) by methyl iodide and reduction to the arsane (not isolated) were accomplished by analogy with a recently published procedure[2]. A solution of bromine (16 g, 100 mmol) in chlorobenzene (50 ml) is added dropwise at room temperature to a solution of the arsane (15.0 g, 50 mmol) in chlorobenzene (125 ml). The reaction mixture is heated under reflux for 1.5 h, thiophenol (16.5 g, 150 mmol) and NaOH (6.0 g, 150 mmol) are added at room temperature, and heating under reflux then continued for 24 h. After removal of solvent in a rotary evaporator, fractional distillation affords *sec*-butyl phenyl sulfide [*ca.* 5.9 g (71 %); b.p. 104—105 °C/25 torr; lit. value 90—91 °C/4 torr[4]].

Received: July 6, 1977 [Z 805a IE]
German version: Angew. Chem. *89*, 759 (1977)
Publication delayed at authors' request

CAS Registry numbers:
(1a), Alk = C_2H_5, 57831-41-1; *(1a)*, Alk = C_3H_7, 57831-42-2; *(1a)*, Alk = C_4H_9, 61025-00-1; *(1b)*, Alk = C_2H_5, 63866-91-1; *(1b)*, Alk = C_3H_7, 63866-92-2; *(1b)*, Alk = C_4H_9, 63866-93-3; *(2)*, Alk = C_2H_5, E = CH_3, 63866-84-2; *(2)*, Alk = C_3H_7, E = $C(C_6H_5)_2OH$, 63866-94-4; *(2)*, Alk = C_4H_9, E = $(CH_2)_3CH_3$, 63866-95-5; *(2)*, Alk = C_4H_9, E = $C(C_6H_5)_2OH$, 63866-96-6; *(2)*, Alk = C_4H_9, E = COOH, 63866-97-7. Table 2 (compounds *(3)*, from top): 78-86-4; 78-76-2; 513-48-4; 616-05-7. Table 3 (compounds *(4)*, from top): 78-92-2; 14905-79-4. *(5)*, 63866-98-8; *(6)*, 63866-83-1; lithium diisopropylamide, 4111-54-0; I—CH_3, 74-88-4; O=$C(C_6H_5)_2$, 119-61-9; Br—$(CH_2)_3$—CH_3, 109-65-9; CO_2, 124-38-9; *sec*-butyldiphenylarsane oxide, 63866-84-2; KOH, 1310-58-3; $NaSC_6H_5$, 930-69-8

[1] H/Li exchange is possible for sp^3-hybridized C atoms with at least two chlorine atoms. However, it leads to thermally highly labile compounds. Cf. *G. Köbrich*, Angew. Chem. *84*, 557 (1972); Angew. Chem. Int. Ed. Engl. *11*, 473 (1972).

[2] *Th. Kauffmann, H. Fischer, A. Woltermann*, Angew. Chem. *89*, 52 (1977); Angew. Chem. Int. Ed. Engl. *16*, 53 (1977).

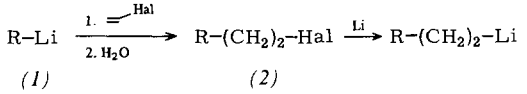
[3] Products *(3)* and *(4)* have been described in the literature.

[4] *W. H. Taylor*, J. Am. Chem. Soc. *58*, 2649 (1936).

2C-Chain Elongation of Lithioalkanes with Diphenylvinylarsane and Phenyl Vinyl Selenide[**]

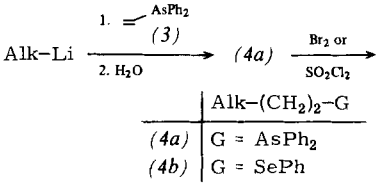
By *Thomas Kauffmann, Holger Ahlers, Hans-Joachim Tilhard,* and *Annegret Woltermann*[*]

Chain elongations of organolithium compounds according to the following scheme (Hal = Cl, Br) are precluded by the unattainability of step *(1)* → *(2)*:



(1) *(2)*

The addition of lithioalkanes to *diphenylvinylarsane (3)*[1] constitutes a replacement for *(1)* → *(2)*, for the diphenylarsanyl group of the resulting primary alkyl(diphenyl)arsanes *(4a)* can readily be replaced by Br or Cl atoms[2], which are in turn replaceable by lithium as shown in the reaction scheme[3]. In the case of the adduct *(4a)*, Alk = nC_4H_9, $As(C_6H_5)_2$/Br exchange is 96 % complete (heating with 1 mol. equiv. of Br_2 in chlorobenzene at 132 °C for 2.5 h) and $As(C_6H_5)_2$/Cl exchange is 90 % complete (mixing of reactants at room temperature in CCl_4, distillation of solvent, and heating to 185 °C for 2.5 h).



	Alk–$(CH_2)_2$–G
(4a)	G = $AsPh_2$
(4b)	G = SePh

We also succeeded in adding alkyllithium compounds to *phenyl vinyl selenide*. However, diphenylvinylarsane is greatly superior to phenyl vinyl selenide as an electrophilic chain elongation reagent since poorer yields are obtained, both in the addition step (Table 1) and on exchange of the C_6H_5Se group of primary alkyl phenyl selenides for a Br atom[4] (for Alk = nC_4H_9 reaction is 44 % complete after warming with 1 mol. equiv. of Br_2 in ethanol/H_2O (5:1) to 80 °C for 0.5 h)[5].

Table 1. Addition of lithioalkanes to *(3)* or H_2C=CH—SeC_6H_5.

Adduct	Alk	Conditions	Yield [%]	B.p. [°C/torr]
(4a)	C_2H_5	[a]	37	87/0.05
(4a)	nC_4H_9	[a]	95	102/0.6
(4a)	sC_4H_9	[b]	71	107/0.2
(4a)	tC_4H_9	[b]	57	110/0.5
(4b)	nC_4H_9	[c]	72	64/0.1
(4b)	sC_4H_9	[c]	25	80/0.3
(4b)	tC_4H_9	[c]	25	47/0.05

[a] Reaction of equimolar amounts in tetrahydrofuran at room temperature for 1/4 to 2 h.
[b] Reaction of equimolar amounts in ether at 0 °C followed by warming to room temperature for 1/2 h.
[c] Reaction in ether at room temperature for 1/2 to 1 h.

[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. H. Ahlers, Dipl.-Chem. H.-J. Tilhard, A. Woltermann
Organisch-chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

[**] New Reagents, Part 6. This work was supported by the Ministry of Science and Research of North Rhine-Westphalia and by the Fonds der Chemischen Industrie.—Part 5: *Th. Kauffmann, R. Joussen,* and *A. Woltermann*, Angew. Chem. *89*, 759 (1977); Angew. Chem. Int. Ed. Engl. *16*, 709 (1977).

The structures of the hitherto undescribed compounds (all compounds in Table 1) follow unequivocally from the spectra (MS, ^{1}H-NMR, IR) and elemental analysis.

Procedure:

Diphenylvinylarsane (1.28 g, 5 mmol) dissolved in THF (75 ml) is added dropwise to *n*-butyllithium (5 mmol) in THF (75 ml) at room temperature. After 30 min, the reaction mixture is hydrolyzed with H_2O, the aqueous phase extracted with chloroform (3 × 75 ml), and the dried organic phases evaporated. Distillation of the oily residue affords *n*-hexyldiphenylarsane [1.48 g (95 %), b.p. 102 °C/0.6 torr].

Received: July 6, 1977 [Z 805b IE]
German version: Angew. Chem. *89*, 760 (1977)
Publication delayed at authors' request

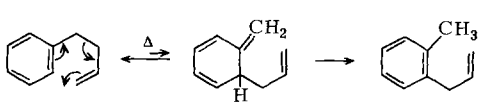
CAS Registry numbers:
(1), Alk = C_2H_5, 811-49-4; *(1)*, Alk = nC_4H_9, 109-72-8; *(1)*, Alk = sC_4H_9, 598-30-1; *(1)*, Alk = tC_4H_9, 594-19-4; *(3)*, 61193-58-6; *(4a)*, Alk = C_2H_5, 38563-45-0; *(4a)*, Alk = nC_4H_9, 63866-85-3; *(4a)*, Alk = sC_4H_9, 63866-86-4; *(4a)*, Alk = tC_4H_9, 63866-87-5; *(4b)*, Alk = nC_4H_9, 63866-88-6; *(4b)*, Alk = sC_4H_9, 63866-89-7; *(4b)*, Alk = tC_4H_9, 63866-90-0; phenyl vinyl selenide, 35167-28-3; $As(C_6H_5)_2$/Br, 3095-87-2; $As(C_6H_5)_2$/Cl, 712-48-1

[1] Compounds Alk-CH_2—CHLi—$As(C_6H_5)_2$ command little interest as reagents owing to their modest nucleophilicity.
[2] Cf. *Th. Kauffmann, H. Fischer, A. Woltermann*, Angew. Chem. *89*, 52 (1977); Angew. Chem. Int. Ed. Engl. *16*, 53 (1977).
[3] Cf., *e.g., B. J. Wakefield:* The Chemistry of Organolithium Compounds. Pergamon, Oxford 1974. The action of lithium leads to coupling in the case of alkyl iodides.
[4] Exchange for a Cl atom has not yet been accomplished.
[5] *M. Sevrin, W. Dumont, L. Hevesi, A. Krief*, Tetrahedron Lett. *1976*, 2647, achieved *ca.* 20 % C_6H_5Se/Br exchange with primary alkyl phenyl selenides.

Carbo-Claisen Rearrangement of 8-*endo*-Phenylbicyclo[5.1.0]octa-2,4-dienes[**]

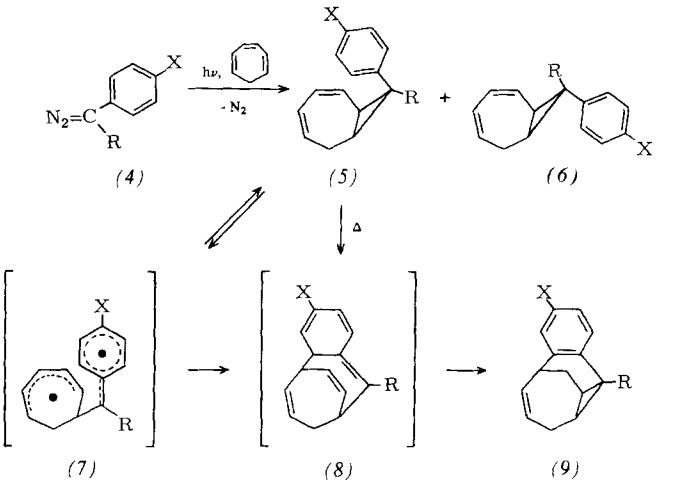
By *Gerhard Maas* and *Manfred Regitz*[*]

In contrast to the Claisen rearrangement of allyl phenyl ethers, the Cope rearrangement of a 1,5-hexadiene whose double bond belongs to an aromatic system as in *(1)*, known as the "carbo-Claisen rearrangement"[1], normally defies attempts at direct observation. This is because the only way in which the primary product *(2)* of the sigmatropic [3,3] shift can undergo rearomatization, apart from the reverse reaction to *(1)*, is by a thermally forbidden 1,3 hydrogen shift to form *(3)*. The isomerization *(1)* → *(3)* is therefore only observed in the presence of a strong base, which presumably catalyzes the step *(2)* → *(3)*[2].



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

We have found that the 8-*endo*-phenyl substituted bicyclo[5.1.0]octa-2,4-dienes *(5)*, formed together with minor amounts of the *exo* isomer *(6)* on photolytic decomposition of the diazo compounds *(4a)*—*(4e)*[3] in cycloheptatriene, isomerize to the tricyclic compounds *(9)* at as low a temperature as *ca.* 130 °C. Their structures are established by the ^{1}H-NMR spectra and X-ray structure analysis[4] of *(9b)*.



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

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

(a): R = $PO(OCH_3)_2$, X = H
(b): R = $PO(OCH_3)_2$, X = OCH_3
(c): R = CO_2CH_3, X = H
(d): R = $PO(C_6H_5)_2$, X = H
(e): R = C_6H_5, X = H

The transformation *(5)* → *(9)* can be interpreted as a carbo-Claisen rearrangement of *(5)* to *(8)*, which is subsequently stabilized in a thermally allowed 1,5-homodienyl hydrogen shift with regeneration of the aromatic system to give *(9)*.

The isomerization *(5a)* → *(9a)* was examined by ^{1}H-NMR spectroscopy in the temperature range 119.2—146.8 °C; it is found to be a first-order reaction with $k = (6.4 \pm 3.5) \times 10^{11} \exp[(29.3 \pm 0.4)RT]$ and $\Delta S^{\neq} = -7.1 \pm 0.9$ cal K^{-1} mol^{-1} (for a mean temperature of 133 °C). These data do not permit any decision whether the formation of *(8)* is concerted or proceeds *via* the diradical *(7)*; however, evidence favoring participation of *(7)* comes from the known ease of homolytic ring opening of vinylcyclopropanes[5] and from the observation that *(5e)* rearranges to the tricyclic about twice as fast as *(5a)*—*(5d)*.

Procedure:

A solution of *(4a)* (11.32 g, 50 mmol) in cycloheptatriene (180 ml) is irradiated for 22 h (Philips HPK 125 W). The excess of cycloheptatriene is distilled off, and the oily residue dissolved in ether (30 ml). Colorless *(5a)* (2.50 g) of m.p. 121 °C is obtained at 0 °C. Chromatography of the filtrate on silica gel (360 g, Woelm 0.2—0.5 mm) with ethyl acetate (3100 ml) and ethyl acetate/methanol 9 : 1 (800 ml) affords colorless compound *(6a)* (0.54 g, 4 %), m.p. 129 °C (ether), and a further crop of *(5a)* (1.31 g; total yield 3.81 g, 26 %).

A solution of *(5a)* (1.50 g) in xylene (10 ml) is heated under reflux for 9.5 h. The reaction mixture is evaporated down *in vacuo*, the residue treated with activated charcoal/chloroform, and after filtration the solvent is again removed and the residue recrystallized twice from ether/petroleum ether 30—75 °C (1 : 1): yield of *(9a)*, 1.0 g (67 %); m.p. 69 °C. IR (KBr): 3030, 3005, 2963, 2925, 2855 (CH/CH_2), 1655, 1607 (C=C), 1255 (PO), 1063, 1038, 1028 cm^{-1} (POC). ^{1}H-NMR ($CDCl_3$): $\delta = 1.70$—2.95 (CH_2 and CH-cyclopropane), 3.28—3.55 (CH-benzyl), 3.65 and 3.79 (each d, $^3J_{PH} = 10.8$ Hz, OCH_3), 5.39 and 5.98 (each dd, CH-olefin), 6.85—7.30 (m, 3 H-aromatic), 7.80—8.10 ppm (1 H-aromatic). A correct elemental analysis is obtained.

[*] Prof. Dr. M. Regitz, Dr. G. Maas
Fachbereich Chemie der Universität
Pfaffenbergstrasse 95, D-6750 Kaiserslautern (Germany)

[**] Carbenes, Part 16.—Part 15: *G. Maas, M. Regitz, W. Illger*, Chem. Ber. *111* (1978).

Received: August 3, 1977 [Z 809 IE]
German version: Angew. Chem. 89, 763 (1977)

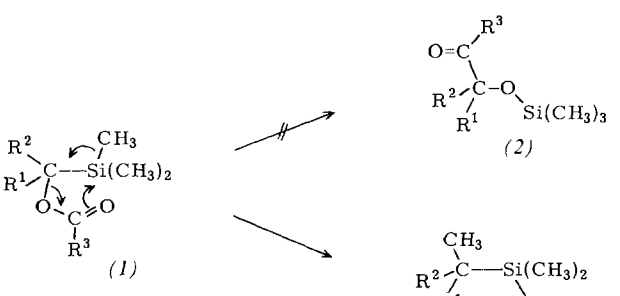
CAS Registry numbers:
(4a), 16965-72-3; (5a), 58576-61-7; (5b), 63798-06-1; (5c), 63798-07-2; (5d), 63798-08-3; (5e), 63798-09-4; (6a), 63864-77-7; (9a), 63798-10-7; (9b), 63798-11-8; (9c), 63798-03-8; (9d), 63798-04-9; (9e), 63798-05-0; cycloheptatriene, 544-25-2

[1] Review: G. Maier: Valenzisomerisierungen, 1st Edit. Verlag Chemie, Weinheim 1972, pp. 52, 180.
[2] W. v. E. Doering, R. A. Bragole, Tetrahedron 22, 385 (1966).
[3] (4a) and (4b): H. Scherer, A. Hartmann, M. Regitz, B. D. Tunggal, H. Günther, Chem. Ber. 105, 3357 (1972); (4c) by analogy with the ethyl ester; M. Regitz, F. Menz, ibid. 101, 2622 (1968); (4d): M. Regitz, W. Anschütz, ibid. 102, 2916 (1969); (4e): H. Staudinger, E. Anthes, F. Pfenninger, Ber. Deut. Chem. Ges. 49, 1928 (1916).
[4] (9b) forms orthorhombic crystals, $Pna2_1$, with $a = 1223.5(7)$, $b = 1416.8(8)$, $c = 898.3(8)$ pm, $\alpha = \beta = \gamma = 90°$, $Z = 4$, $d_{calc} = 1.37\ g\,cm^{-3}$. The structure was solved by direct methods and refined to $R = 0.030$ for 754 reflections with $F_o > 4\sigma(F_o)$.
[5] The activation energy for the vinylcyclopropane/cyclopentene rearrangement is 49.7 kcal mol^{-1}, but can be reduced to values around 30 kcal mol^{-1} by radical-stabilizing substituents, see, e.g.: J. S. Swenton, A. Wexler, J. Am. Chem. Soc. 93, 3066 (1971); J. M. Simpson, H. G. Richey, Tetrahedron Lett. 1973, 2545; G. H. Richey, D. W. Shull, ibid. 1976, 575.

Thermal Rearrangement of Silylmethyl Acetates[1]

By *Manfred T. Reetz* and *Norbert Greif*[*]

Two routes are formally open for dyotropic rearrangements[2] of compounds of type *(1)* to form a strong Si—O bond: a silyl-acyl or an acyloxy-methyl exchange[3] to the more stable valence isomers *(2)* and *(3)*, respectively. Heating of *(1a, b)* at 130—195 °C in inert solvents gives *(3a, b)* in almost quantitative yield.



(a): $R^1 = R^2 = C_6H_5$, $R^3 = CH_3$
(b): $R^1 = R^2 = C_6H_5$, $R^3 = CF_3$
(c): $R^1 + R^2$ = 2,2'-Biphenyldiyl, $R^3 = CH_3$

We attempt to interpret the mechanism of this smooth valence isomerization[4] with the aid of the following findings:

1) Crossover experiments prove that both the methyl and also the acetoxy groups undergo intramolecular migration to an extent exceeding 95%.

2) The rate of rearrangement is practically independent of solvent polarity: k_{rel} for *(1a)*→*(3a)*: 1.0 (benzene); 0.9 (acetonitrile); 1.3 (propylene carbonate).

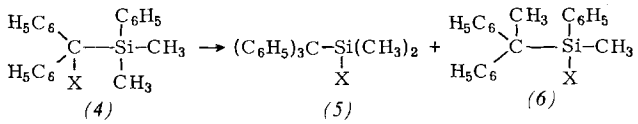
3) The activation parameters for *(1a)*→*(3a)* in benzene are: $\Delta H^{\neq} = 33.1 \pm 0.8$ kcal mol^{-1}, $\Delta S^{\neq} = -5.3 \pm 1$ cal mol^{-1} K^{-1}; in acetonitrile they are: $\Delta H^{\neq} = 34.0 \pm 0.8$ kcal mol^{-1}; $\Delta S^{\neq} = -3.6 \pm 1$ cal mol^{-1} K^{-1}.

4) The trifluoroacetate rearranges faster than the acetate: $k_{(1b)}/k_{(1a)} = 564$.

5) The fluorene derivative *(1c)* is stable under the reaction conditions; only on raising the temperature (230 °C) does slow decomposition set in.

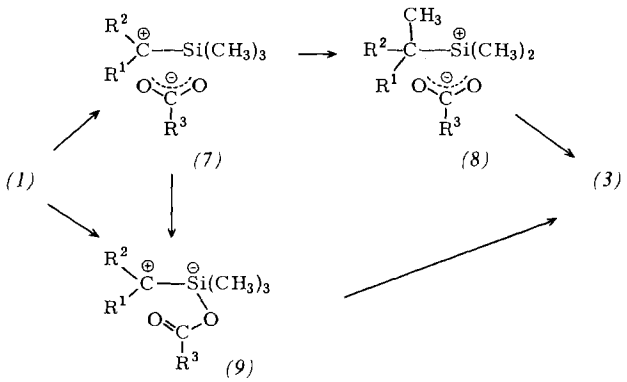
6) Replacement of the trimethylsilyl group in *(1a)* by a [D_9]-trimethylsilyl group leads to a secondary kinetic isotope effect of $k_H/k_D = 0.81 \pm 0.05$.

7) In the acetate *(4a)* both the methyl and the phenyl groups migrate to form *(5a)* and *(6a)* in the ratio 60:40 (yield >90%), while in the bromide *(4b)* only a quantitative migration of the methyl groups is observed to give *(5b)*[5].



(a): X = OC(O)CH$_3$
(b): X = Br

The entropy of activation for *(1a)*→*(3a)* and the unexpectedly high thermal stability of *(1c)* can be rationalized neither by a concerted dyotropic process nor by a two-step free-radical mechanism. An ionic mechanism involving contact ion pairs *(7)* and *(8)* also appears unlikely on account of the lack of solvent dependence. Without precedent, and yet in accord with our findings, is a rate-determining intramolecular migration of the nucleofugal group to the silicon to form an inverted ylide *(9)*, which transforms *via* a fast 1,2 shift into *(3)*. The differing behavior of *(4a)* and *(4b)* could be the result of stereoelectronic factors at pentavalent silicon. The results of solvent studies could be interpreted by assuming the formal positive charge at the cationic center of *(9)* to be delocalized as a result of hyperconjugation with pentacoordinate silicon. The question whether negatively charged hypervalent groups can stabilize carbenium ions has not previously been posed in general terms. However, it is known that compounds of pentacoordinate silicon are stable only if electronegative ligands effect a d-orbital contraction[7]. In this connection, carbenium ions are ideal substituents.



Two-step dyotropic mechanisms forming inverted ylides are therefore conceivable for related rearrangements[3, 5]—this working hypothesis is currently being tested.

Received: August 4, 1977 [Z 811 IE]
German version: Angew. Chem. 89, 765 (1977)

CAS Registry numbers:
(1a), 63832-90-6; (1b), 63832-91-7; (1c), 63832-92-8; (3a), 63832-93-9; (3b), 63848-87-3; (4a), 63832-94-0; (4b), 62092-84-6; (5a), 63832-95-1; (5b), 62092-85-7; (6a), 63832-96-2

[*] Doz. Dr. M. T. Reetz, Dr. N. Greif
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

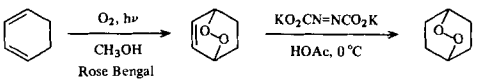
[1] Dyotropic Rearrangements, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 13: M. T. Reetz, N. Greif, Chem. Ber. 110, 2958 (1977).

[2] For a definition, see *M. T. Reetz*, Tetrahedron *29*, 2189 (1973).
[3] Related halogen-halogen as well as hylogen- or acetoxy-phenyl exchange reactions in silicon compounds are known, but have not been studied with regard to their mechanism: *W. I. Bevan, R. N. Haszeldine, J. Middleton, A. E. Tipping*, J. Organomet. Chem. *23*, C17 (1970); *A. G. Brook, P. F. Jones*, J. Chem. Soc. Chem. Commun. *1969*, 1323.
[4] *N. Greif*, Dissertation, Universität Marburg 1977.
[5] The selective thermal transformation of *(4b)* into *(5b)* has recently be utilized preparatively: *D. J. Ager, I. Fleming*, J. Chem. Res. (S) *1977*, 6.
[6] Inverted ylides with hypervalent sulfur have recently been isolated: *A. J. Arduengo, E. M. Burgess*, J. Am. Chem. Soc. *99*, 2376 (1977).
[7] *E. A. V. Ebsworth* in *A. G. MacDiarmid*: The Bond to Carbon. Dekker, New York 1968, p. 14.

2,3-Dioxabicyclo[2.2.2]octane by Selective Reduction of Double Bonds with Azodicarboxylate[**]

By *Waldemar Adam* and *Henny J. Eggelte*[*]

The peroxide linkage is one of the most susceptible towards reductive cleavage by a variety of reductants. It is, therefore, not surprising that in the catalytic hydrogenation of unsaturated peroxides the peroxide bond as well as the double bond are reduced. If the problem of concurrent peroxide bond reduction could be circumvented in a general and efficient way, this would implement a novel entry into hitherto unknown saturated cyclic peroxides by reduction of the corresponding unsaturated precursors, which are readily available by singlet oxygenation[1] of suitable cyclic 1,3-diene substrates. Azodicarboxylate is a mild and double bond-specific reductant[2], ideally suited to solve the above synthetic problem. The strategy and execution is outlined below for the two-step conversion of 1,3-cyclohexadiene *(1)* into the previously unknown 2,3-dioxabicyclo[2.2.2]octane *(3)*.



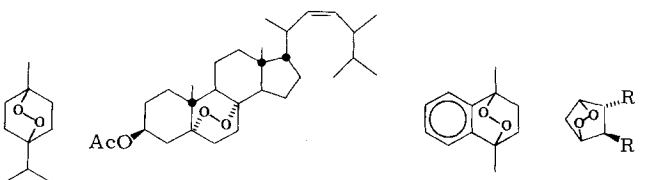
(1) *(2)* *(3)*

On treatment of the unsaturated cyclic peroxide *(2)*, prepared by photo-oxygenation of *(1)*[3], with excess azodicarboxylate in methanol at 0°C[4], the saturated cyclic peroxide *(3)* was obtained in 48% yield (m.p. 117—118°C from hexane)[5]. On reaction with ethanolic potassium hydroxide the peroxide *(3)* is isomerized to the known 4-hydroxycyclohexanone in high yield, and on catalytic hydrogenation over Pd-C gives quantitatively the known *cis*-1,4-cyclohexanediol. It is important to mention that submission of pure *(3)* to the azodicarboxylate reduction conditions did not lead to reduction of the peroxide linkage to give the diol.

The generality of the azodicarboxylate reduction could be demonstrated by preparing dihydroascaridole *(4)*, epidioxyergosterol acetate *(5)*, and 1,2,3,4-tetrahydro-1,4-dimethyl-1,4-epidioxynaphthalene *(6)*. Thus, the known dihydroascaridole *(4)* was obtained quantitatively from ascaridole, and identified by its characteristic NMR and IR data.

[*] Prof. Dr. W. Adam (NIH Career Development Awardee, 1975—1980), Dr. H. J. Eggelte
Department of Chemistry
University of Puerto Rico
Rio Piedras, Puerto Rico 00931 (USA)

[**] Cyclic Peroxides, Part 58. Acknowledgments are made to the Donors of the Petroleum Research Fund (Grant 8341-AC-1,4), administered by the American Chemical Society, the National Science Foundation (Grant CHE-72-04956-A03) and the National Institutes of Health (Grants GM-22119-02, GM-00141-02, and RR-8102-03).—Part 57: *W. Adam et al.*, to be published.



(4) *(5)* *(6)* *(7)*

Ascaridole is one of the few cyclic peroxides for which catalytic hydrogenation does not sever the peroxide linkage[6]. The previously unknown ergosterol derivative *(5)*[7a] with saturated Ring B has now been synthesized for the first time. Even the unstable 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene, prepared by photo-oxygenation of 1,4-dimethylnaphthalene[8], could be reduced essentially quantitatively to the novel cyclic peroxide *(6)*[7b]. It is interesting to note that despite the excess azodicarboxylate that was used, the side chain double bond of *(5)* was not reduced. Strained double bonds show a greater reactivity towards azodicarboxylate reduction[2].

In the reduction of epidioxycyclopentene with azodicarboxylate only isomerization products could be isolated. Readily accessible peroxides of type *(7)* could simplify the prostaglandin synthesis.

General Reduction Method

To a 50 ml, round-bottom flask, provided with magnetic spinbar, are charged 5 mmol of the endoperoxide to be reduced and 15 mmol dipotassium azodicarboxylate in 10 ml absolute methanol. While stirring magnetically and cooling by means of an ice bath, a solution of 30 mmol acetic acid in 3 ml absolute methanol is added dropwise within 30 min. After stirring for 3 h at 30°C, the solvent is rotoevaporated (0°C/10 torr), and the residue taken up in 20 ml H_2O and extracted twice with 20 ml CH_2Cl_2. The combined CH_2Cl_2 extracts are washed once with saturated aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and rotoevaporated (0°C/10 torr). The crude product is purified by recrystallization.

Received: August 1, 1977 [Z 808 IE]
German version: Angew. Chem. *89*, 762 (1977)

CAS Registry numbers:
(1), 592-57-4; *(2)*, 6671-70-1; *(3)*, 280-53-5; *(4)*, 5718-73-0; *(5)*, 59476-71-0; *(6)*, 63797-42-2; 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene, 35461-84-8; dipotassium azodicarboxylate, 4910-62-7

[1] *W. Adam*, Chem.-Ztg. *99*, 142 (1975); Angew. Chem. *86*, 683 (1974); Angew. Chem. Int. Ed. Engl. *13*, 619 (1974).
[2] *H. O. House*: Modern Synthetic Reactions. W. A. Benjamin, Menlo Park, Cal., 1972.
[3] *(2)*: yield 41%, m.p. 85—86°C; *C. Kaneko, A. Sugimoto, S. Tanaka*, Synthesis *1974*, 876: m.p. 88.5°C.
[4] *J. W. Hamersma, E. I. Snyder*, J. Org. Chem. *30*, 3985 (1965).
[5] The pure substance (by TLC) deteriorates on standing at room temperature within a few days. It was, therefore, not possible to obtain elemental analytic data. ^{1}H-NMR (CCl_4, TMS): δ = 1.4—1.9 (m, 4H), 1.9—2.5 (m, 4H), 3.9 (m, 2H); IR (CCl_4): 2960, 2940, 2890, 2855, 1460, 1445, 1430, 1305, 1225, 1030, 950 cm^{-1}; MS: *m/e* = 114 (71%), 81 (100), 67 (41), 57 (85), 43 (88) (P + 1 = 6.62%, P + 2 = 0.68%, calc. 6.72% and 0.59%, resp.).
[6] *H. Paget*, J. Chem. Soc. *1938*, 829.
[7] a) *(5)*: yield 90%, m.p. 209—210°C (from methanol); ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.8—1.2 (CH_3; 18H), 1.2—2.5 (CH, CH_2, $COCH_3$; 27H), 4.9 (m, 1H), 5.15 (m, 2H); IR ($CHCl_3$): 2955, 2870, 2800, 1730, 1440, 1365, 1350, 1250, 1025, 960, 900 cm^{-1}; MS: *m/e* = 472 (1%); correct elemental analysis; b) *(6)*: m.p. 93—94°C (from hexane); ^{1}H-NMR ($CDCl_3$, TMS): δ = 1.60 (s, 6H), 1.70 (m, 2H), 2.30 (m, 2H), 7.28 (m, 4H); IR (CCl_4): 3075, 3030, 2990, 2940, 2890, 2850, 1590, 1470, 1460, 1380, 1335, 1260, 1180, 1075 cm^{-1}; MS: *m/e* = 190 (6%), 158 (93), 143 (100), 128 (50), 115 (25), 91 (36), 76 (25), 43 (62); correct elemental analysis.
[8] *H. H. Wasserman, D. L. Larsen*, J. Chem. Soc. Chem. Commun. *1972*, 253.

Binding of Urease to Anodized Sheet Aluminum

By *Peter Grunwald, Walter Gunsser,* and *Siegfried Scheer*[*]

The fixation of proteins to water-insoluble materials has become an important field of study in chemistry and related disciplines[1]. Preference is often given to inorganic carriers because they cannot be degraded by bacteria. The binding of an enzyme to the carrier may be covalent or adsorptive and usually entails a loss of activity. Criteria for the quality of such a preparation include not only the residual activity but, above all, the potential for repeated use and the thermal stability.

In our studies on the adsorption of proteins on inert metal oxides we found in the case of the enzyme urease that anodized sheet aluminum is very suitable for this application.

Figure 1 shows the dependence of enzyme activity on the conditions of anodization. While the reaction rate is still relatively low under the conditions of the well known G-S process (hatched area), the activity of the adsorbate increases by almost two powers of ten on surpassing a certain sulfuric acid concentration (current density). Scanning electron micrographs (Fig. 2) show the surface of an Al sheet before and after loading with urease. The structure of the aluminum hydroxide surface reveals the texture of the sheet aluminum used.

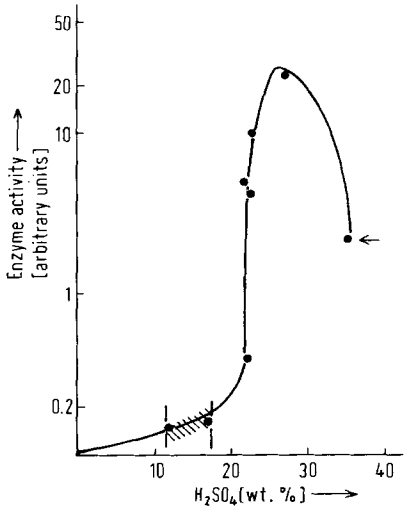
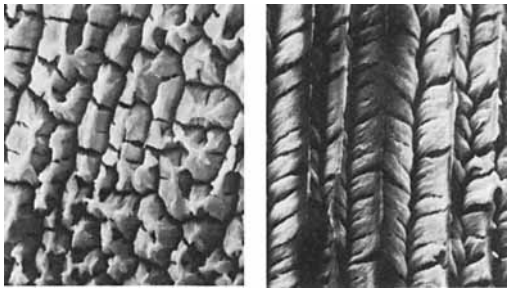


Fig. 1. Activity of anodized sheet aluminum as a function of the sulfuric acid concentration; the activities were determined by conductometry.



a) b)

Fig. 2. Scanning electron micrograph (magnification 2000 X) of an anodized layer a) before and b) after charging with urease from the region beyond the optimum activity (arrow in Fig. 1).

The thermal stability of urease fixed by adsorption to these anodization layers compared with that of the free enzyme in solution, whose optimum temperature is about 65 °C, is remarkable (see Fig. 3). Specific features of the temperature dependence of urease are apparently retained in the adsorbate, such as the anomalous course of urease-catalyzed hydrolysis of urea described by *Talsky*[2a] as well as different activation energies within different temperature ranges [50.8 kJ mol^{-1} (5—20 °C), 24 kJ mol^{-1} (20—41 °C), 45.1 kJ mol^{-1} (41—96 °C)]. The activation energies for hydrolysis of urea in the presence of dissolved urease are 49 kJ mol^{-1} (0—22 °C)[3] and 36.5 kJ mol^{-1} (20—40 °C)[2b]; we were able to confirm both values for the enzyme we used for absorption as 49 kJ mol^{-1} (0—21 °C) and 36.5 kJ mol^{-1} (20.5—50 °C). Relative to the free enzyme, the adsorbate has a significantly lower activation energy in the middle temperature range.

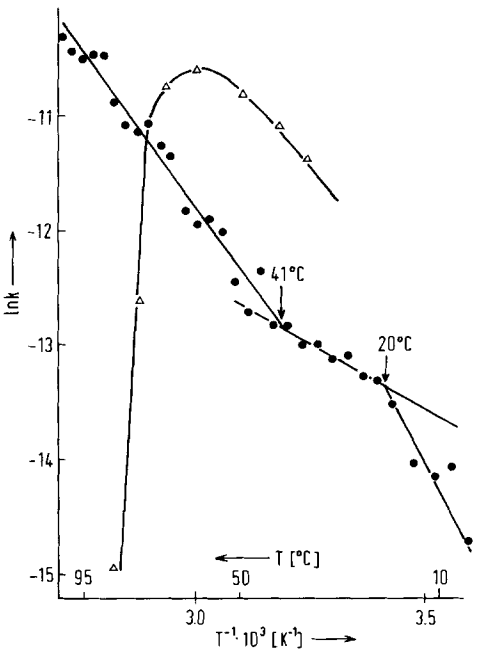


Fig. 3. Temperature dependence of the hydrolysis of urea for dissolved urease —△—△—△— and urease adsorbed on anodized aluminum —●—●—●—.

The temperature dependence of urea hydrolysis was determined over the entire temperature range of 2 to 98 °C (30 measurements) on the same preparation, thus adequately demonstrating the possibility of repeated use of this carrier-bound enzyme. If the supply of urease is not too high the adsorbed enzyme exhibits greater activity than that in the free state. Comparison with conventional inorganic carrier materials[4] shows that anodized sheet aluminum well satisfies the criteria initially mentioned.

Received: July 22, 1977 [Z 807 IE]
German version: Angew. Chem. *89*, 761 (1977)

CAS Registry numbers:
Urease, 9002-13-5; Al, 7429-90-5

[*] Dr. P. Grunwald [+], Prof. Dr. W. Gunsser, cand. HL S. Scheer
Institut für Physikalische Chemie der Universität
Laufgraben 24, D-2000 Hamburg 13

[+] To whom correspondence should be addressed.

[1] *H. D. Orth, W. Brümmer*, Angew. Chem. *84*, 319 (1972); Angew. Chem. Int. Ed. Engl. *11*, 249 (1972); cf. also Nachr. Chem. Tech. *21*, 236 (1973).
[2] a) *G. Talsky*, Angew. Chem. *83*, 553 (1971); Angew. Chem. Int. Ed. Engl. *10*, 548 (1971); b) *G. Talsky, W. Klunker*, Z. Physiol. Chem. *348*, 1372 (1967).
[3] *I. W. Sizer*, J. Bacteriol. *41*, 511 (1941).
[4] *H. H. Weetall, R. A. Messing* in *M. L. Hair*: The Chemistry of Biosurfaces, Vol. 2. Dekker, New York 1972, pp. 563ff.

Crystal and Molecular Structure of *cyclo*-Heptasulfur (δ-S_7)[1]

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

Together with S_8, *cyclo*-heptasulfur is a principal component of molten[2] and gaseous[3] sulfur, and can be prepared by extraction of quenched sulfur melts[2] or by condensation of $(C_5H_5)_2TiS_5$ with S_2Cl_2[4]. An incomplete X-ray structure analysis (*xy* projection of the molecule) was interpreted in terms of a puckered seven-membered ring[5], and internuclear distances of 200—215 pm[6a] were deduced from the Raman spectrum. However, the precise molecular structure is not known.

We found by Raman spectroscopy that S_7 crystallizes in at least four modifications which differ significantly from one another primarily in their lattice vibrations, and also in the stretching and bending regions, with regard to the wave numbers and relative intensities of the lines. We have obtained single crystals of one of these modifications, which we call δ-S_7, by evaporation of a CS_2 solution at $-78\,^{\circ}C$[7] and subjected them to X-ray analysis at $-110\,^{\circ}C$. Since the modification is a low-temperature form, whose crystals rapidly disintegrate to a powder at 25 °C, the substance was handled at temperatures below $-50\,^{\circ}C$.

de Jong-Bouman and precession diagrams revealed the monoclinic space group $P2_1/n$ with $Z=8$, $a=1510.5(5)$, $b=599.8(7)$, $c=1509.6(5)$ pm, $\beta=92.15(5)^{\circ}$, $d_{calc.}=2.182\,g\,cm^{-3}$ ($-110\,^{\circ}C$). Using an automatic Siemens single crystal diffractometer, 2263 symmetry-independent reflections up to $\theta=25^{\circ}$ were recorded with $Mo_{K\alpha}$ radiation; 20 reflections were classified as unobserved ($I\leq 2\sigma$). The phase problem was solved by direct methods and the structure refined to an R value of 7.0 % with anisotropic temperature factors (absorption correction, $\mu=20.8\,cm^{-1}$).

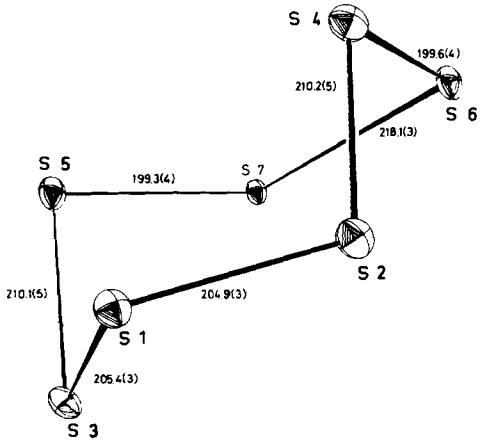


Fig. 1. Molecular shape, numbers of atoms, and internuclear distances [pm] of δ-S_7; standard deviations in parentheses (the values apply to molecule I).

One of the molecules in the asymmetric unit cell is depicted in Figure 1. Although the molecules occupy general sites, the molecular symmetry is approximately C_s. The internuclear distances are identical to within the simple standard deviation; among the angles, however, the differences are considerably greater (Table 1). The bond lengths deviate from the spectroscopically predicted values by at most 3 pm[6a] and thus confirm the theory of bond interaction in sulfur chains, explaining the alternancy of the internuclear distances[6], upon which the prediction is based.

Table 1. Valence and torsional angles [°] in δ-S_7; standard deviations in parentheses.

Valence angle at atom no.	Molecule I	Molecule II	Torsional angle at bond between atoms no:	Molecule I	Molecule II
1:	106.3(1)	105.9(1)	1—2:	−75.2	−74.4
2:	101.5(1)	102.8(1)	1—3:	75.8	75.4
3:	102.5(1)	102.1(1)	2—4:	107.6	107.2
4:	105.6(1)	105.0(1)	3—5:	−107.0	−108.0
5:	105.1(1)	105.4(1)	4—6:	−84.3	−85.6
6:	106.9(1)	106.5(1)	5—7:	83.6	82.5
7:	107.5(1)	107.5(1)	6—7:	−0.3	2.4

The shape of the δ-S_7 molecule resembles that of S_7I^+[8] and can be formally derived from that of S_8 by excision of one atom and connection of the resulting chain ends by an unusually long bond. The large internuclear distance of this bond is primarily due to the small S4-S6-S7-S5 torsional angle of *ca.* 1°, which normally corresponds to a maximum of the torsional potential[6b]. However, as a result of the bond weakening, the adjacent bonds are strengthened: they are the shortest ones in the molecule, the same effect having also been observed in other sulfur rings (S_8O, S_7I^+, S_7O). Simple MO considerations show that a four-center bond occurs between atoms 4 to 7, which is responsible for the almost coplanar arrangement of these atoms. This geometry, and hence C_s symmetry, are therefore also predicted for the free (gaseous) S_7 molecule. The average distance between atoms 4 and 5 is 335.5(3) pm.

As a consequence of the alternating bond lengths, the average SS distance of 206.8 pm is only slightly greater than that in S_6, S_8, and S_{12} (205 pm[6b]), so that the average bond energy can differ only slightly from that of the other rings. The average value of the bond angles (105.1°) lies exactly halfway between those of S_6 (102.2°) and S_8 (108.0°). The smallest intermolecular distances (339.7 pm) correspond to those found for other sulfur rings[9]. Particularly effective packing of the S_7 molecules in the lattice leads to a high density, which together with that of S_6 ($2.18\,g\,cm^{-3}$[9]) surpasses that in all other forms of sulfur (1.94—2.09 $g\,cm^{-3}$).

Received: July 5, 1977 [Z 802a IE]
German version: Angew. Chem. *89*, 756 (1977)

CAS Registry number:
δ-S_7, 21459-04-1

[*] Prof. Dr. R. Steudel, Dipl.-Chem. F. Schuster
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)
Dipl.-Chem. R. Reinhardt
Institut für Kristallographie der Freien Universität
Takustrasse 6, D-1000 Berlin 33 (Germany)

[1] Sulfur Compounds, Part 49. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 48: *R. Steudel, F. Rose, R. Reinhardt, H. Bradaczek*, Z. Naturforsch. *B32*, 488 (1977).
[2] *R. Steudel, H.-J. Mäusle*, Angew. Chem. *89*, 114 (1977); Angew. Chem. Int. Ed. Engl. *16*, 112 (1977); and unpublished results.
[3] *H. Rau, T. R. N. Kutty, J. R. F. Guedes de Carvalho*, J. Chem. Thermodyn. *5*, 833 (1973); and references cited therein.
[4] *M. Schmidt, B. Block, H. D. Block, H. Köpf, E. Wilhelm*, Angew. Chem. *80*, 660 (1968); Angew. Chem. Int. Ed. Engl. *7*, 632 (1968).
[5] *I. Kawada, E. Hellner*, Angew. Chem. *82*, 390 (1970); Angew. Chem. Int. Ed. Engl. *9*, 379 (1970).
[6] a) *R. Steudel*, Spectrochim. Acta *31 A*, 1065 (1975); b) Angew. Chem. *87*, 683 (1975); Angew. Chem. Int. Ed. Engl. *14*, 655 (1975).
[7] This modification forms block-shaped, tetragonal-bipyramidal, and sarcophage-like crystals and differs from α-, β-, and γ-S_7 in that the most intense Raman line in the 20—600 cm^{-1} region lies at 400 cm^{-1} (−100 °C, spectrometer Cary 82, spectral slit width 2 cm^{-1}, krypton laser 647.1 nm).
[8] *J. Passmore, P. Taylor, T. Whidden, P. White*, J. Chem. Soc. Chem. Commun. *1976*, 689.
[9] *J. Donohue*: The Structures of the Elements. Wiley, New York 1974.

Bond Interaction in Sulfur Rings: Crystal and Molecular Structure of *cyclo*-Heptasulfur Oxide, S_7O[1]

By *Ralf Steudel*, *Richard Reinhardt*, and *Torsten Sandow*[*]

S_7O arises on oxidation of S_7 with CF_3CO_3H and forms orange-yellow crystals which are stable only at low temperatures[2]. In contrast to other sulfur rings (S_6, S_7, S_8, S_8O, S_9, S_{10}, S_{12}), S_7O fails to show any Raman lines in the stretching region of SS single bonds (410—500 cm^{-1}), *i.e.* all the bonds must be considerably longer or shorter than the SS single bond length (206 pm[3a]). In order to establish the reason for this unusual bonding we have carried out an X-ray structure analysis on a single crystal at −110 °C.

de Jong-Bouman and precession diagrams revealed the monoclinic space group $P2_1/n$ with $Z=4$, $a=1296.3(7)$, $b=872.3(9)$, $c=660.1(5)$ pm, $\beta=88.73(9)°$, $d_{calc.}=2.140\ g\,cm^{-3}$ (−110 °C). Using an automatic single-crystal diffractometer 4110 independent reflections up to $\theta=30°$ were measured with $Mo_{K\alpha}$ radiation and corrected in the usual way; 85 reflections were classified as unobserved ($I \leq 2\sigma$). The proposed structure (direct methods) could be refined with anisotropic temperature factors to $R=0.068$. An absorption correction ($\mu=19.25\ cm^{-1}$) has yet to be performed.

The asymmetric unit contains one molecule whose internuclear distances and bond and torsional angles are given in Figure 1 and Table 1. Exceptionally small intramolecular contacts are observed between atoms S4···S5 (332.8 pm) and S7···O1 (295.2 pm). The smallest intermolecular SO and SS distances are S5···O1 (288.6 pm) and S5···S7 (325.3 pm).

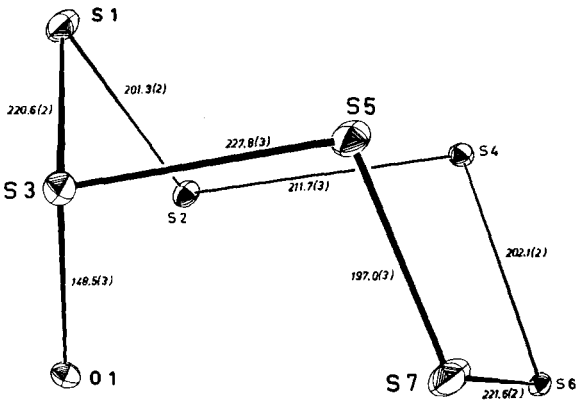


Fig. 1. Conformation, numbering, and internuclear distances [pm] of S_7O; standard deviations in parentheses.

Table 1. Valence and torsional angles [°] in S_7O; standard deviations in parentheses.

Valence angles		Torsional angles	
S2—S1—S3	100.21(6)	S3—S1—S2—S4	−79.4
S1—S2—S4	101.76(7)	S2—S1—S3—S5	79.3
S1—S3—S5	98.80(6)	S1—S2—S4—S6	112.0
S2—S4—S6	106.57(7)	S1—S3—S5—S7	−112.3
S3—S5—S7	99.86(8)	S2—S4—S6—S7	−82.1
S4—S6—S7	106.70(8)	S3—S5—S7—S6	87.6
S5—S7—S6	105.45(8)	S4—S6—S7—S5	−6.2
S1—S3—O1	106.74(8)	S2—S1—S3—O1	−25.6
S5—S3—O1	101.45(8)	S7—S5—S3—O1	−3.1

[*] Prof. Dr. R. Steudel, Dipl.-Chem. T. Sandow
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)
Dipl.-Chem. R. Reinhardt
Institut für Kristallographie der Freien Universität
Takustrasse 6, D-1000 Berlin 33 (Germany)

The conformation of the S_7O molecule corresponds to expectations based on comparison with S_7[1] and S_7I^+[4]. The average SS distance of 211.7 pm is larger than in S_7 (206.8 pm), which is attributable to bond weakening by the exocyclic oxygen atom as first observed in S_8O[5]. The torsional angles S4—S6—S7—S5 (−4°) and S7—S5—S3—O1 (−3°), which are energetically unfavorable for SS bonds[3a], lead to the extremely large internuclear distances of the S3—S5 and S6—S7 bonds. The bonds adjacent to the long ones are shortened by the influence of bond interaction[3], the shortest bond plainly lying next to the longest one, as also found in S_8O[5], S_7I^+[4], S_7[1], and S_{20}[6].

It is shown in Figure 2 that a relation exists between the internuclear distance between two divalent sulfur atoms d_2 in neutral sulfur rings[7] and the arithmetic mean of the

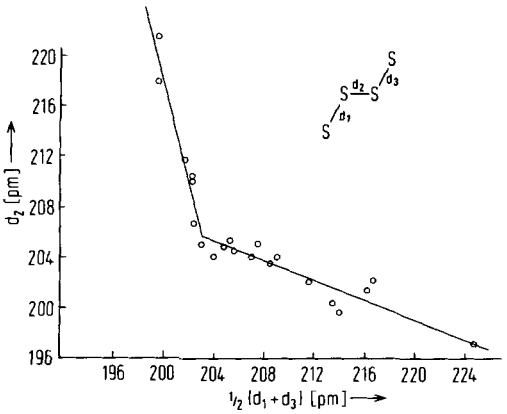


Fig. 2. Dependence of the internuclear distance d_2 of the SS bond upon the arithmetic mean of the internuclear distances d_1 and d_3 of the neighboring bonds in the compounds S_7, S_7O, S_8, S_8O, S_{12}, S_{20}, and $S_nO_6^{2-}$ ($n=4$—6). For large values of 0.5 (d_1+d_3), the distance d_2 approaches to 189 pm, the bond length in S_2.

internuclear distances d_1 and d_3 of the two adjacent bonds. The rings having bonds of equal length (S_6, S_8, S_{12}) lie near the discontinuity of the curve. On extrapolation of d_2 to the van der Waals distance of 340 pm[3a], *i.e.* for the case of homolytic cleavage of a bond in the S_n ring, it is seen that the internuclear distances d_1 and d_3 of the terminal bonds of the resulting diradical $\cdot S_n \cdot$ must be about 196 pm, *i.e.* correspond to multiple bonds. The resulting increase in bond energy facilitates homolysis and also explains why nonionic compounds with cumulated SS bonds are thermally very sensitive and often decompose at as low a temperature as 50—150 °C.

Received: July 5, 1977 [Z 802b IE]
German version: Angew. Chem. *89*, 757 (1977)

CAS Registry number:
S_7O, 60828-66-2

[1] Sulfur Compounds, Part 50.—Part 49: *R. Steudel, R. Reinhardt, F. Schuster*, Angew. Chem. *89*, 756 (1977); Angew. Chem. Int. Ed. Engl. *16*, 715 (1977).

[2] *R. Steudel, T. Sandow*, Angew. Chem. *88*, 854 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976).

[3] a) *R. Steudel*, Angew. Chem. *87*, 683 (1975); Angew. Chem. Int. Ed. Engl. *14*, 655 (1975); b) Spectrochim. Acta *31 A*, 1065 (1975).

[4] *J. Passmore, P. Taylor, T. Whidden, P. White*, J. Chem. Soc. Chem. Commun. *1976*, 689.

[5] *P. Luger, H. Bradaczek, R. Steudel, M. Rebsch*, Chem. Ber. *109*, 3441 (1976).

[6] *M. Schmidt, E. Wilhelm, T. Debaerdemaeker, E. Hellner, A. Kutoglu*, Z. Anorg. Allg. Chem. *405*, 153 (1974).

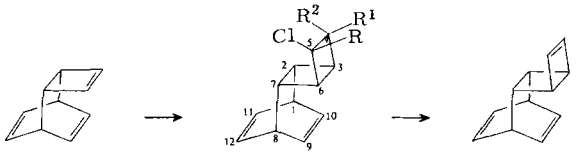
[7] The values for the S_4^{2+} and S_7I^+ ions are shifted towards the origin owing to the additional bond energy [3a]; however, an analogous relation apparently also applies to S_7I^+.

(3—6-η-Tricyclo[6.2.2.0^{2,7}]dodeca-3,5,9,11-tetraene)-tricarbonyliron, a Stable Transition Metal Complex of "*o,p'*-Dibenzene"[**]

By *Wolfram Grimme* and *Ernst Schneider*[*]

[4+2]-Cycloreversions with elimination of benzene—favored by aromatic resonance in the transition state—proceed quite readily and are of synthetic importance[1]. In such reactions benzene can take on the role both of the diene as well as that of the dienophile[2]. In the Diels-Alder dimer of benzene, "*o,p'*-dibenzene" *(4)*[3a], it is present in both functions and consequently the rate of decomposition for this compound should, to a first approximation, increase quadratically. The preparation of *(4)* has hitherto been precluded by its low stability, whereas the dimer of the [2+2]-cycloaddition, "*anti-o,o'*-dibenzene"[3], could be isolated at 0°C.

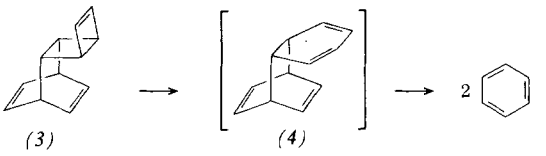
Since their release from transition metal complexes at low temperature has proved a useful method for the liberation[4a] and isolation[4b] of labile olefins we have tried to synthesize π-complexes of *(4)*. To do this, a stable valence isomer of *o,p'*-dibenzene had to be bonded to a metal and subsequently thermally rearranged. The Dewar isomer *(3)*, which is readily accessible *via* a conventional route, appeared to be the most suitable candidate for this purpose:



(1) *(2a)*, R = Cl, R^1–R^2 = O *(3)*
(2b), R = H, R^1–R^2 = O
(2c), R = R^1 = H, R^2 = OH
(2d), R = R^1 = H, R^2 = O_3SCH_3

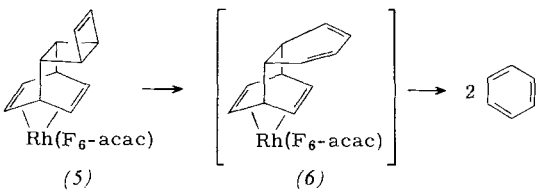
Cycloaddition of dichloroketene[5a] to tricyclo[4.2.2.0^{2,5}]-deca-3,7,9-triene *(1)*[5b] affords the tetracyclic ketone *(2a)* [60%; m.p. 102°C; ^{1}H-NMR (CCl_4): δ=6.57—6.20 (m, H-9,10,11,12), 3.87 (m, H-1,8), 3.23 (dd, *J*=5 and 2.5 Hz, tgα=0.4[6], H-3), 2.70—2.42 (m, tgα=0.13, H-6,7), 2.15 (ddd, *J*=6.5, 4 and 2.5 Hz, tgα=0.26, H-2); IR (KBr): ν_{CO}=1807 cm^{-1}], whose partial dechlorination with tri-*n*-butylstannane in cyclohexane gives the monochloroketone *(2b)* [78%; m.p. 89°C; ^{1}H-NMR ($CDCl_3$): δ=6.63—6.23 (m, H-9,10,11,12), 5.03 (dd, *J*=8 and 2.5 Hz, H-5), 3.83 (m, H-1,8), 3.03 (m, H-3), 2.60 (m, H-6,7), 2.12 (m, H-2)]. In the subsequent reduction with sodium tetrahydridoborate in 80% dioxane at 0°C the base-sensitive chlorocyclobutanol *(2c)* is not purified but immediately esterified with methanesulfonyl chloride/triethylamine in ether to *(2d)*. The elimination reaction with sodium in liquid NH_3/ether[7] finally leads to the *anti*-tetracyclo[6.2.2.0^{2,7}.0^{3,6}]dodeca-4,9,11-triene *(3)*, which is purified by low-pressure chromatography on silica gel with pentane [43% from *(2b)*; ^{1}H-NMR (CCl_4); δ=6.30 (t, *J*=4.5 Hz, H-9,10,11,12), 6.07 (t, *J*=1.5 Hz, H-4,5), 3.47 (m, H-1,8), 2.62 (m, H-3,6), 2.18 (m, H-2,7); IR (in substance): $\nu_{C=C}$=1587 cm^{-1} (s), 1553 (s)].

On warming to 100°C *(3)* decomposes in a first-order reaction to benzene. The rate constant $k=(2.24\pm0.04)\times10^{-5}$ s^{-1} determined at 110.2°C is a little greater than that for the isomerization of bicyclo[2.2.0]hex-2-ene[8] and would suggest that the fragmentation is initiated by opening of the bicyclohexene moiety. Attempts to trap the intermediate *(4)* with maleic anhydride or tetracyanoethylene at 110°C have so far been unsuccessful.



(3) *(4)*

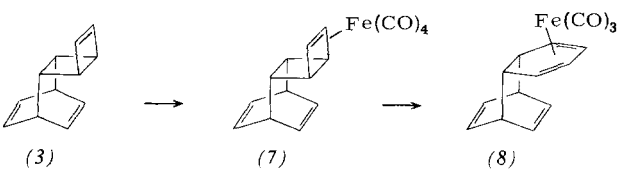
Boiling of *(3)* with dicarbonyl(hexafluoropentane-2,4-dionato)rhodium[9] in *n*-hexane for 1.5 h and subsequent sublimation (80°C/10^{-3} torr) yields orange needles of the complex *(5)* [83%; dec. pt. 132°C; ^{1}H-NMR (C_6D_6): δ=6.17 (s, F_6-acac), 5.99 (m, H-4,5), 3.42 (m, H-1,8,9,10,11,12), 2.55 (m, H-3,6), 1.45 (m, H-2,7); MS: *m/e*=466 (M^+), 388 ($M^+-C_6H_6$), 181 ($-F_6$-acac), 103 (Rh^+), 78 ($C_6H_6^+$)]. Heating of *(5)* to 110°C in degassed [D_6]-benzene leads to decomposition with formation of benzene. This reaction is not first-order, but proceeds autocatalytically; after 70 min no more complex *(5)* is present. Since tricyclo[4.2.2.0^{2,5}]deca-7,9-diene(hexafluoropentane-2,4-dionato)rhodium (m.p. 117°C) is stable up to 190°C under the same conditions it would appear that decomposition of *(5)* likewise begins with opening of the bicyclohexene moiety, but that stabilization of the ligand is inadequate in the initially formed *o,p'*-dibenzene complex *(6)*.



(5) *(6)*

Reaction of the Dewar dibenzene *(3)* with $Fe_2(CO)_9$ in hexane at 50°C does not lead to the expected η^4-tricarbonyliron, but exclusively to the η^2-tetracarbonyliron complex *(7)*, which can be purified by chromatography (alumina/pentane), recrystallization (pentane, −20°C) and sublimation (50°C/10^{-3} torr) [40%; m.p. 74°C; ^{1}H-NMR (C_6D_6): δ=6.35 (t, *J*=3 Hz, H-11,12), 6.11 (t, *J*=4.5 Hz, H-9,10), 3.42 (s, H-4,5), 3.37 (m, H-1,8), 2.12 (s, H-3,6), 2.05 (m, H-2,7); MS: *m/e*=324 (M^+), 268 (M^+-2CO), 240 ($-CO$), 212 ($-CO$), 134 ($-C_6H_6$), 78 ($C_6H_6^+$), 56 (Fe^+)].

Following the work of *Pettit et al.*[10] on the facilitated disrotatory opening of tricyclo[4.2.0.0^{2,5}]octenes in their tetracarbonyliron complexes, we heated *(7)* in degassed benzene to 100°C and found that complete transformation took place within one hour: the tricarbonyliron complex of the *o,p'*-dibenzene *(8)* was formed and some of the starting complex *(7)* was cleaved into the ligand *(3)* and $Fe(CO)_5$ by liberated CO. Recrystallization (pentane, −20°C) and sublimation (70°C/10^{-2} torr) afforded pure *(8)* [45%; dec. pt. 128°C; ^{1}H-NMR (C_6D_6): δ=6.30 (t, *J*=3.5 Hz, H-11,12), 6.20 (t, *J*=3.5 Hz, H-9,10), 4.35 (AA'XX' half spectrum, H-4,5), 3.03 (m, H-1,8), 2.70 (AA'XX' half spectrum, H-3,6), 1.50 (s, H-2,7); MS: *m/e*=296 (M^+), 268 (M^+-CO), 240 ($-CO$), 212 ($-CO$), 134 ($-C_6H_6$), 78 ($C_6H_6^+$), 56 (Fe^+)]. Oxidative cleavage with



(3) *(7)* *(8)*

[*] Dr. W. Grimme, Dr. E. Schneider
Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)

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

ceric ammonium nitrate in acetone at room temperature affords benzene as the sole organic product, thus proving the ease of decomposition of the primarily liberated *o,p'*-dibenzene.

The greater stability of *(8)* compared to that of the rhodium complex *(6)* and of norbornadienonetricarbonyliron[11] can be explained as follows: In the latter-mentioned complexes the metal fixes the bent bicyclo[2.2.*n*]diene moiety, which must be flattened in the transition state with scission of the bond to the metal. In *(8)*, on the other hand, the metal remains bound to the cyclohexadiene ring, with the result that the double bond that is formed does not gain the resonance energy of benzene[12].

Received: July 27, 1977 [Z 801 IE]
German version: Angew. Chem. *89*, 754 (1977)

CAS Registry numbers:
(1), 21604-76-2; *(2a)*, 63784-75-8; *(2b)*, 63784-74-7; *(2c)*, 63784-73-6; *(2d)*, 63784-72-5; *(3)*, 63784-71-4; *(5)*, 63797-21-7; *(7)*, 63797-20-6; *(8)*, 63797-19-3; dichloroketene, 4591-28-0; dicarbonyl(hexafluoropentane-2,4-dionato)-rhodium, 18517-12-9; $Fe_2(CO)_9$, 15321-51-4; $Fe(CO)_5$, 13463-40-6

[1] Cf. *H. Kwart, K. King*, Chem. Rev. *68*, 415 (1968).
[2] *E.g.* the compounds



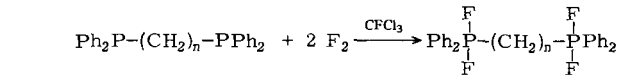
already decompose at 25 °C: a) *W. G. Dauben, G. T. Rivers, R. J. Twieg, W. T. Zimmerman*, J. Org. Chem. *41*, 887 (1976); b) *A. R. Rye, D. Wege*, Aust. J. Chem. *27*, 1943 (1974).
[3] a) *J. A. Berson, R. F. Davis*, J. Am. Chem. Soc. *94*, 3658 (1972); b) *H. Röttele, W. Martin, J. F. M. Oth, G. Schröder*, Chem. Ber. *102*, 3985 (1969).
[4] a) *G. F. Emerson, L. Watts, R. Pettit*, J. Am. Chem. Soc. *87*, 131 (1965); b) *W. Grimme, K. Seel*, Angew. Chem. *85*, 514 (1973); Angew. Chem. Int. Ed. Engl. *12*, 507 (1973); *C. R. Graham, G. Scholes, M. Brookhart*, J. Am. Chem. Soc. *99*, 1180 (1977).
[5] a) *L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, P. Mollet*, Tetrahedron *27*, 615 (1971); b) *M. Avram, E. Sliam, C. D. Nenitzescu*, Justus Liebigs Ann. Chem. *636*, 184 (1960); cf. also ref. [2a].
[6] Assignment of signals and configuration was made from the shifts $\Delta\delta$ by tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium as a function of $[Eu(FOD)_3]/[(2a)]$. tgα is the slope of this linear relationship.
[7] *vic*-Mesyloxychlorocyclobutanes eliminate under the same conditions as the dichloro analogs: *E. L. Allred, B. R. Beck, K. J. Voorhees*, J. Org. Chem. *39*, 1426 (1974).
[8] *M. J. Goldstein, R. S. Leigh, M. S. Lipton*, J. Am. Chem. Soc. *98*, 5717 (1976).
[9] *F. Bonati, G. Wilkinson*, J. Chem. Soc. *1964*, 5517.
[10] *W. Slegeir, R. Case, J. S. McKennis, R. Pettit*, J. Am. Chem. Soc. *96*, 287 (1974).
[11] *J. M. Landesberg, J. Siezkowski*, J. Am. Chem. Soc. *90*, 1655 (1968).
[12] The same effect stabilizes the ketone tautomer of phenol in its tricarbonyliron complex: *A. J. Birch, P. E. Cross, J. Lewis, D. A. White, S. B. Wild*, J. Chem. Soc. *A 1968*, 332.

Oligo(difluorophosphoranes) by Direct Fluorination of Tertiary Phosphanes

By *Ingo Ruppert* and *Volker Bastian*[*]

Although the first gas-phase chlorination of tertiary phosphanes was described as long ago as 1876[1], no such halogenation with fluorine has yet been reported. The reason may lie in the suspected failure of regioselective fluorination to compete successfully with cleavage of the PC and/or CH bond[2]. However, our preliminary experiments with triphenylphosphane showed quantitative conversion into the difluorophosphorane.

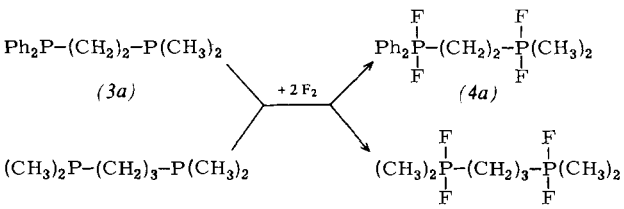
The general validity of direct fluorination will now be illustrated for the example of tertiary oligophosphanes whose difluorides were formerly accessible in isolated cases only by the action of SF_4[3a] or hydrofluorination of phosphoric imides[3b]. Passage of a current of fluorine (max. 20 ml/min) diluted with an inert gas (N_2, He, Ar; *ca.* 100 ml/min) through a suspension of perphenylated polymethylenebisphosphane *(1)* in $CFCl_3$ furnishes the bis(difluorophosphorane) *(2)* as reaction product in good yield, independently of the length of the methylene bridge.



(1) *(2)*

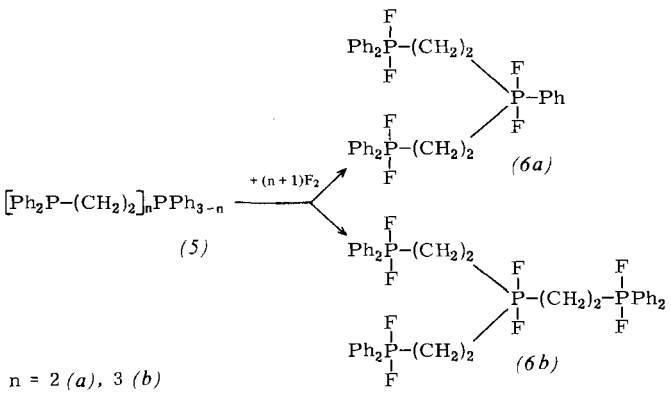
n = 1 *(a)*, 2 *(b)*, 3 *(c)*, 4 *(d)*

The concentration of fluorine given is an upper limit. If it is exceeded local ignition occurs at the gas inlet tube and decomposition of the substrate ensues. However, under the mild conditions chosen the methylene protons are not attacked even in the presence of an excess of fluorine. Phosphanes bearing terminal methyl groups such as *(3a)* and *(3b)* are likewise fluorinated mainly at the phosphorus[4], *i.e.* the procedure is not restricted to resistant phenyl substituents.



(3a) *(4a)* *(3b)* *(4b)*

The synthesis of the oligo(difluorophosphoranes) *(6a)* and *(6b)* constitutes a further impressive demonstration of the scope of oxidative direct fluorination[5].



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

n = 2 *(a)*, 3 *(b)*

The modest yields obtained in these cases are due less to side reactions during the actual fluorination than to greater sensitivity of the products to hydrolysis which interferes with their isolation and purification.

The constitution of the difluorophosphoranes is confirmed by correct elemental analysis and characteristic fragment ions[6], and above all by NMR studies. The $^{31}P\{^1H\}$ spectra exhibit an overall triplet pattern[7], showing that two fluorine atoms coordinate each λ^5-phosphorus atom and thereby ruling

[*] Dr. I. Ruppert, Dr. V. Bastian
Anorganisch-chemisches Institut der Universität
Max-Planck-Strasse 1, D-5300 Bonn

Table 1. Preparative and NMR spectroscopic data [a] of the compounds prepared.

	Yield [%]	M.p. [b] [°C]	^{19}F-NMR δ [c]		^{1}J(PF) [Hz]	^{31}P{^{1}H}-NMR δ [c]		^{1}J(PF)	^{3}J(PP) [Hz]
(2a)	78	118	−27.8 (dm)		656	−45.2 (tm)		650	
(2b)	89	132	−40.8 (dm)		648	−42.4 (tm)		640	
(2c)	89	63	−40.0 (dm)		644	−42.0 (t)		642	
(2d)	71	114	−39.9 (dm)		645	−41.3 (t)		642	
(4a)	93	65	−40.1 (dm)	Ph_2PF_2	640	−45.7 (td)	Ph_2PF_2	643	103
			−18.0 (dm)	Me_2PF_2 [d]	550	−14.1 (td)	Me_2PF_2 [d]	546	
(4b)	40	60	−17.4 (dm) [d]		550	−12.8 (t) [d]		543	
(6a)	46	55	−40.3 (dm)	Ph_2PF_2	650	−44.0 (td)	Ph_2PF_2	650	100
			−39.0 (dm)	$PhPF_2$	635	−31.1 (tt)	$PhPF_2$	632	
(6b)	23	82	−42.7 (dm)	Ph_2PF_2	650	−46.8 (td)	Ph_2PF_2	650	89
			−41.8 (dm)	PF_2	620	−18.8 (tq)	PF_2	630	

[a] The ^{19}F- (Varian A 56/60, 56.4 MHz, $CFCl_3$ int.) and ^{31}P{^{1}H}-NMR spectra (Jeol C 60/HL, 24 MHz, H_3PO_4 ext.) were recorded in conc. $CHCl_3$ solution. Owing to pronounced multiplicity arising by PP coupling, ^{31}P{^{1}H}-PFT spectra with a more favorable signal to noise ratio were also recorded for *(4a)*, *(6a)*, and *(6b)* (Varian CFT 20, phosphorus head, 32 MHz).
[b] In sealed capillary with partial decomposition.
[c] Signal multiplicities in the usual notation, *e.g.* (td) = triplet with doublet fine structure.
[d] In alkyl-substituted difluorophosphoranes, HF-exchange (result of partial hydrolysis) leads, in some cases, to diffuse signal summits. However, this exchange phenomenon can be suppressed by low-temperature measurement.

out phosphonium structures; if nonequivalent phosphorus centers are present in the molecule then a significant fine structure of the individual triplet peaks is observed [^{3}J(PP), cf. Table 1]. The ^{19}F-NMR spectra show the complementary signal multiplicity: a quasi-doublet (dm) due to the λ^5-phosphorus atom with unresolved fine structure arising from long-range coupling with ^{1}H, ^{31}P, as well as ^{19}F *via* the methylene bridge.

Procedure

A current of diluted fluorine (max. 20 ml F_2 to 100 ml of Ar per minute, amount of fluorine determined by a rotameter system[9]) is passed into a magnetically stirred suspension or solution [*(3a)*, *(3b)*] of oligophosphane[8] (25 mmol) in $CFCl_3$ (150 ml, dried over P_4O_{10}) (Solidex glass flask with gas tube and low temperature cooler, −90 °C circulatory cooling with cryostat). Depending upon the solubility of the phosphane, reaction is complete after passage of 60—80 mmol of F_2 (excess), as checked by ^{31}P-NMR spectroscopy. In the case of *(2a)* and *(2b)* the product is recrystallized from boiling CH_3CN after filtration. Otherwise, the solids (oxide and/or HF adduct) are removed from the solution, $CFCl_3$ distilled off, and the residue recrystallized from hot *n*-heptane [*(2d)*], sublimed *in vacuo* [*(4b)*], or repeatedly frozen out of *n*-pentane/ether (5:1) [*(2c)*, *(4a)*, *(6a)*, and *(6b)*].

Received: August 3, 1977 [Z 810 IE]
German version: Angew. Chem. *89*, 763 (1977)

CAS Registry numbers:
(1a), 2071-20-7; *(1b)*, 1663-45-2; *(1c)*, 15383-58-1; *(1d)*, 7688-25-7; *(2a)*, 26040-41-5; *(2b)*, 55339-52-1; *(2c)*, 63883-61-4; *(2d)*, 63883-60-3; *(3a)*, 42495-77-2; *(3b)*, 39564-18-6; *(4a)*, 63883-59-0; *(4b)*, 55339-53-2; *(5a)*, 23582-02-7; *(5b)*, 23582-03-8; *(6a)*, 63883-58-9; *(6b)*, 63883-57-8; F_2, 7782-41-4

[1] *A. Michaelis*, Justus Liebigs Ann. Chem. *181*, 351 (1876).
[2] Only recently was the remarkable stability of element-carbon bonds toward molecular fluorine mentioned in the literature *E. K. S. Liu*, *R. J. Lagow*, J. Am. Chem. Soc. *98*, 8270 (1976).
[3] a) *T. A. Blazer*, *J. K. Gregor*, *R. Schmutzler*, Z. Naturforsch. *B24*, 1081 (1969); *R. Schmutzler*, Inorg. Chem. *3*, 421 (1964); b) *R. Appel*, *I. Ruppert*, Chem. Ber. *108*, 919 (1975); *R. Appel*, *R. Milker*, *I. Ruppert*, Z. Anorg. Allg. Chem. *429*, 69 (1977).
[4] In contrast, we detected the expected side-chain fluorination in experiments performed with $(CH_3)_3P$ at a maximum concentration of 40 ml F_2 and 100 ml He per minute. In addition to varying amounts of $(CH_3)_3PF_2$, dealkylation to form hexafluorophosphate can also be observed.
[5] Although more involved, the method appears to be not only of phenomenological interest in view of the price of SF_4.
[6] Molecular ions recorded with only weak intensity, if at all, in the mass spectrum.
[7] The symmetrically substituted bis(difluorophosphoranes) *(2a)* and *(2b)* having a short $(CH_2)_n$ bridge show the substructure of a XX'AA'X''X''' ^{31}P/^{19}F spin system of four chemically but not magnetically equivalent fluorine (X) and two phosphorus atoms (A).
[8] Preparation: *(1a—d)*: *K. Sommer*, Z. Anorg. Allg. Chem. *376*, 37 (1970); *(3a)*: *R. B. King*, *J. C. Cloyd*, *P. K. Hendrick*, J. Am. Chem. Soc. *95*, 5083 (1973); *(3b)*: *A. Wold*, *J. K. Ruff*, Inorg. Synth. *14*, 17 (1973); *(5a, b)*: *R. B. King*, *P. N. Kapoor*, J. Am. Chem. Soc. *93*, 4158 (1971).
[9] *V. Bastian*, Dissertation, Universität Bonn 1976.

Dependence of the Calcium Isotope Effect upon the Electrolyte Concentration in Ion-Exchange Chromatography[**]

By *Klaus G. Heumann*, *Ferdinand Gindner*, and *Helmut Klöppel*[*]

Enriched stable calcium isotopes are of topical interest[1] primarily for labeling experiments in medical research. With the set aim of chemical pre-enrichment of calcium isotopes and elucidation of the origins of separation effects we have studied the dependence of the calcium isotope effect upon several parameters during ion exchange in inorganic electrolyte systems. Our previous findings suggested that the behavior of isotopes in electrolyte systems is comparable with that of a homologous series of elements—such as the alkaline earth metals[2].

All experiments were performed in a column packed with the strongly acidic sulfonic acid exchanger resin Dowex 50W-X12 (H^+ form, 200—400 mesh, Bio-Rad) at 20 °C. In each case a 60-mg sample of calcium of natural isotope abundance was applied in the form of $CaCl_2$ or $Ca(ClO_4)_2$ and eluted with HCl or $HClO_4$ of various concentrations (HCl: 3, 6, 9 M; $HClO_4$: 3, 5, 6 M) at a rate of about 15 ml/h. The calcium content of the eluate collected fractionwise was established

[*] Prof. Dr. K. G. Heumann, F. Gindner, Dipl.-Ing. H. Klöppel
Institut für Chemie der Universität
Universitätsstrasse 31, D-8400 Regensburg (Germany)

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

by atomic absorption spectrometry and the isotopic ratios $^{44}Ca/^{40}Ca$ and $^{48}Ca/^{40}Ca$ by thermal ionization mass spectrometry.

The equilibrium constant $K_c = 1 + \varepsilon$ (ε isotope effect of an equilibrium stage), *e.g.* for the isotope exchange reaction (resin: exchanger phase, sol: solution)

$$^{48}Ca^{2+}_{resin} + {}^{40}Ca^{2+}_{sol} \rightleftharpoons {}^{48}Ca^{2+}_{sol} + {}^{40}Ca^{2+}_{resin}$$

can be determined from the elution curve and the dependence of the measured isotopic ratio upon the amount of calcium eluted by a standard procedure[3].

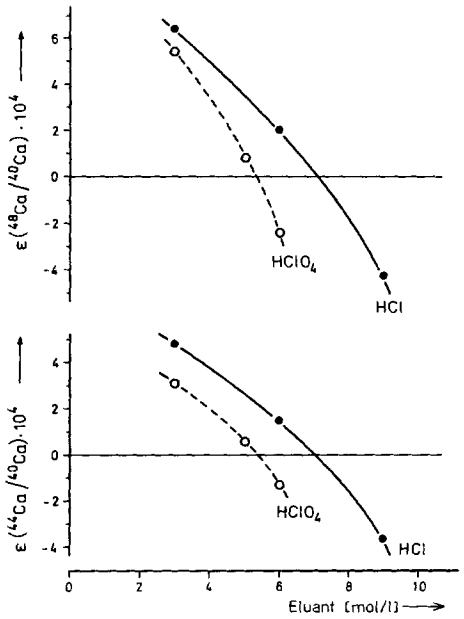


Fig. 1. Dependence of the calcium isotope effect ε upon the concentration and the anion of the eluant.

Figure 1 shows a pronounced dependence to exist between the isotope effect ε for the $^{44}Ca/^{40}Ca$ and for the $^{48}Ca/^{40}Ca$ ratio and both the concentration and the anion of the eluant. As the concentration increases, ε decreases—very high electrolyte concentrations can even effect inversion of the isotope effect. The inversion point lies at a concentration of *ca.* 5 M on use of $HClO_4$, and at 7 M for HCl. The dependence of the value of ε upon the concentration of the eluant is greater for the isotope pair $^{48}Ca/^{40}Ca$ than for the pair $^{44}Ca/^{40}Ca$. It is observed that $\varepsilon(^{48}Ca/^{40}Ca)$ is greater than $\varepsilon(^{44}Ca/^{40}Ca)$ by a factor of about $\sqrt{2}$ (corresponding to the square root of the ratio of the mass differences). Thus we have also found a drop in the ε value with increasing eluant concentration in the case of calcium, resembling that already detected in an analogous anionic system with the $^{37}Cl/^{35}Cl$ isotopic pair[2b]. However, an inversion of the isotope effect in the same system has not been reported before. The results of the calcium isotope study can be compared with those for alkali and alkaline earth metals obtained in similar exchange reactions. While the use of moderate electrolyte concentrations in the latter case leads to more selective binding of elements with increasing Pauling ionic radius—and hence decreasing radius of the hydrated ion—to a sulfonic acid exchange resin[4], an inversion of selectivity is observed with highly concentrated electrolyte solutions[5]. The results of our experiments are best compared with those of *Whitney* and *Diamond*[5b], who found an inversion of Cs^+/Na^+ selectivity on a sulfonic acid exchange resin at an HCl concentration of *ca.* 7 M but at an $HClO_4$ concentration of only 2 M. This inversion of selectivity can be explained in terms of more and more pronounced dehydration of the ions at high electrolyte concentrations and the consequent change in effective ionic radius. The point of inversion of Cs^+/Na^+ selectivity occurring at higher electrolyte concentrations in the HCl system is due to the greater anion-cation interaction of dehydrated Na^+ with the Cl^- ion as against the ClO_4^- ion.

The similarities between the isotopic series of calcium and the series of alkali metals demonstrate that—at least in the case of "hard" ions—isotopes in electrolyte systems behave in the same way as homologous elements. Hence it must be assumed that the isotopes have different effective ionic radii.

Our experiments show that it is fundamentally possible within certain limits to determine both the direction and the magnitude of an isotope effect by varying the concentration and the nature of eluant. This is of considerable significance for the preconcentration of stable isotopes. Furthermore, it should now be easier to understand some of the previously reported isotope effects whose direction and magnitude were not always perfectly clear.

Received: July 22, 1977 [Z 799 IE]
German version: Angew. Chem. *89*, 753 (1977)

CAS Registry numbers:
^{40}Ca, 14092-94-5; ^{44}Ca, 14255-03-9; ^{48}Ca, 13981-76-5

[1] *B. E. Jepson, R. DeWitt*, J. Inorg. Nucl. Chem. *38*, 1175 (1976).
[2] a) *K. G. Heumann, K. H. Lieser*, Z. Naturforsch. *B 27*, 126 (1972); *K. G. Heumann, R. Hoffmann, W. Luecke, ibid. B 30*, 497 (1975); b) *K. G. Heumann, R. Hoffmann*, Angew. Chem. *88*, 54 (1976); Angew. Chem. Int. Ed. Engl. *15*, 55 (1976).
[3] *E. Glueckauf*, Trans. Faraday Soc. *54*, 1203 (1958).
[4] Cf. *F. W. E. Strelow*, Anal. Chem. *32*, 1185 (1960).
[5] a) *R. M. Diamond*, J. Am. Chem. Soc. *77*, 2978 (1955); *W. A. Platek, J. A. Marinsky*, J. Phys. Chem. *65*, 2113 (1962); b) *D. C. Whitney, R. M. Diamond*, Inorg. Chem. *2*, 1284 (1963).

Inclusion of Anions in Macrotricyclic Quaternary Ammonium Salts[**]

By *Franz P. Schmidtchen*[*]

In contrast to the large variety[1] of compounds which form complexes with cations, there are only a few known synthetic host molecules (abiotic receptors[2]) for organic and inorganic anions[3]. Since at least two thirds of all enzymes act on negatively charged substrates or cofactors, the construction and complexation behavior of abiotic receptors for anions should provide interesting comparisons with substrate binding to enzyme pockets and to cell wall receptors.

The binding of anions to the host molecules *(12)* to *(14)* should be predominantly due to electrostatic attraction.

Whereas *(12)* is obtained by quaternization (methyl *p*-toluenesulfonate) of the known[4] aminopolyether, we synthesized the quaternary ammonium salts *(13)* and *(14)* by the following scheme: Alkylation of tosyl amide with the ε-bromo ester *(1)* (NaH/DMSO) and subsequent hydrolysis yielded the dicarboxylic acid *(2)* (50 %) which was converted to its acyl chloride *(3)* (95 %) by oxalyl chloride. Condensation of *(3)* with hexamethylenediamine under high dilution conditions

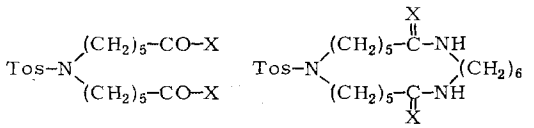
$$Br\text{-}(CH_2)_5\text{-}COOCH_3$$

(1)

[*] Dr. F. P. Schmidtchen
Lehrstuhl für organische Chemie und Biochemie der Technischen Universität
Arcisstrasse 21, D-8000 München (Germany)

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

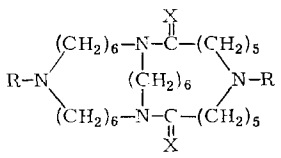
afforded the cyclic amide *(4)* (40 %) which was reduced to the amine *(5)* (95 %) with diborane in THF. Condensation of *(5)* with *(3)* at high dilution gave the bicyclic amide



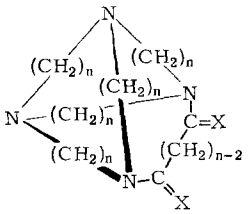
(2), X = OH
(3), X = Cl

(4), X = O
(5), X = H_2

(6) (50 %). The carboxamide groups were successively reduced with diborane [*(7)*, 90 %] and the tosyl groups split off with lithium in liquid ammonia [*(8)*, 90 %]. Ring closure between the two secondary amino groups of *(8)* was achieved by reaction with adipoyl chloride to give the tricyclic amide *(9)* (40 %) which could, in turn, be reduced with diborane/THF to the tetrahedral tetramine *(10)* (65 %). The tetramine *(11)* was obtained by the same method. The structure of these cage molecules was established by elemental analysis, ^{1}H-, ^{13}C-NMR, and mass spectra.

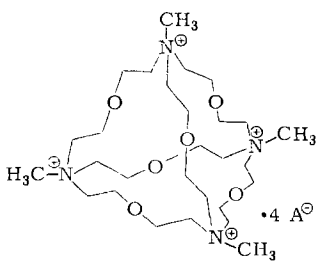


(6), X = O, R = Tos
(7), X = H_2, R = Tos
(8), X = H_2, R = H

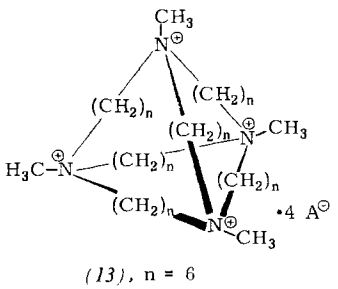


(9), X = O, n = 6
(10), X = H_2, n = 6
(11), X = H_2, n = 8

Quaternization with methyl fluorosulfate or methyl *p*-toluenesulfonate in nitromethane converted *(10)* and *(11)* into the tetraammonium salts *(13)* and *(14)* which were obtained as crystals (fluorosulfates) or colorless oils (tosylates). Crystalline tetrafluoroborates were produced from the oils by anion exchange.



(12)
$A^{\ominus}$ = $^{\ominus}O_3S$–C$_6$H$_4$–CH_3



(13), n = 6
(14), n = 8
$A^{\ominus}$ = $FSO_3^{\ominus}$, $BF_4^{\ominus}$, $^{\ominus}O_3S$–C$_6$H$_4$–CH_3

The "cavity molecules" *(12)*, *(13)*, and *(14)* allow, for the first time, inclusion complex formation with anions to be studied independently of the configuration and protonation equilibria at the nitrogen atoms[3]. Examination of models shows that, with the maximum possible cavity radii [*(12)* 1.95 Å; *(13)* 2.3 Å; *(14)* 3.8 Å], compound *(12)* can bind, of the halides (ionic radii; Cl^- 1.81 Å; Br^- 1.96 Å; I^- 2.28 Å), chloride and bromide whereas *(13)* and *(14)* should also be able to take up iodide.

The 1:1 complexes were rapidly formed on addition of 100 mol-% alkali metal halide to solutions of the cage molecules *(12)*, *(13)*, and *(14)* in water or 95 % methanol. In the ^{1}H-NMR spectrum a downfield shift of the α and β methylene signals is observed, while the signals of the methyl groups experience a weak diamagnetic shift. However, the signals are not split, showing that the symmetry of the ligands is preserved in the complexed state. In aqueous solution, *(13)* also binds acetate ions and *(14)* binds the HPO_4^{2-} anion.

Comparison of the stability constants of the halide complexes (Table 1) demonstrates that the bromide and iodide complexes are considerably more stable than the chloride complexes. Since the solvation shell of the anion must be stripped off when it enters the cavity of the molecule, the more strongly solvated anion should form the more labile complexes. The observed order of stabilities thus agrees with these predictions. The same effect must also be partially responsible for the higher stability of the complexes in the more weakly solvating solvent (95 % methanol). On the other hand, it can be inferred from the low selectivity of bromide and iodide complex formation with *(13)* and *(14)*, that changes in ligand conformation also influence the stability. *(13)* and *(14)* are apparently not completely rigid cages and electrostatic attraction does not seem to be the sole force responsible for complex formation. If this were the case then the halide complexes of *(14)* should be weaker than those of *(13)*. Presumably, *(14)* is especially flexible, with the result that its equilibrium conformation will be drastically changed on transfer to a solvent having a lower polarity than water. The bromide and iodide complexes of *(13)* and *(14)* are, as yet, the most stable inclusion compounds of these two anions in aqueous solution.

Table 1. Stability constants ($\lg K_s$) of the inclusion complexes [a] of halides with *(12)*, *(13)*, and *(14)* in water and 95 % methanol.

Anion	Solvent	Complex with *(12)*	*(13)*	*(14)*
Cl^-	H_2O	1.0 [b]	1.3 [b]	<0.5 [c]
Br^-	H_2O	1.8 [b]	2.45 [b]	2.45 [c]
	95 % CH_3OH	2.7 [c]	3.7 [c]	3.9 [c]
I^-	H_2O		2.2 [c]	2.4 [c]
	95 % CH_3OH		3.1 [c]	5.0 [c]

[a] Measured using halide electrodes with ligand concentrations of $5 \cdot 10^{-3}$ mol/l.
[b] KNO_3 as supporting electrolyte.
[c] KF as supporting electrolyte.

Received: June 27, 1977 [Z 797 IE]
German version: Angew. Chem. *89*, 751 (1977)

CAS Registry numbers:
(1), 14273-90-6; *(2)*, 63702-61-4; *(3)*, 63730-77-8; *(4)*, 63702-62-5; *(5)*, 63702-63-6; *(6)*, 63702-64-7; *(7)*, 63702-65-8; *(8)*, 63730-74-5; *(9)*, 63702-66-9; *(10)*, 63702-67-0; *(11)*, 63702-68-1; *(12)*-chloride, 63702-69-2; *(12)*-bromide, 63702-70-5; *(13)*-chloride, 63702-71-6; *(13)*-bromide, 63702-72-7; *(13)*-iodide, 63702-73-8; *(14)*-chloride, 63702-74-9; *(14)*-bromide, 63730-76-7; *(14)*-iodide, 63702-75-0; tosyl amide, 70-55-3; oxalyl chloride, 79-37-8; hexamethylenediamine, 124-09-4

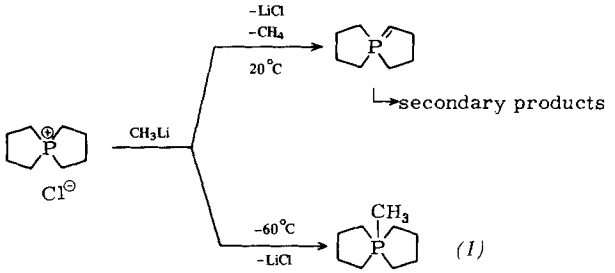
[1] *J. M. Lehn*, Struct. Bonding (Berlin) *16*, 1 (1973); *D. J. Cram et al.*, J. Am. Chem. Soc. *99*, 2564 (1977).
[2] *R. C. Hayward*, Nachr. Chem. Tech. Lab. *25*, 15 (1977).
[3] *E. Graf, J. M. Lehn*, J. Am. Chem. Soc. *98*, 6403 (1976), and references cited therein.
[4] *E. Graf, J. M. Lehn*, J. Am. Chem. Soc. *97*, 5022 (1975).

5-Methyl-5λ⁵-phosphaspiro[4.4]nonane—The Simplest Pentaalkylphosphorane Yet Obtained[**]

By *Hubert Schmidbaur*, *Peter Holl*, and *Frank H. Köhler*[*]

While there is still no evidence for the existence of unsubstituted phosphorane PH_5, stepwise progress is nevertheless being made towards the simplest pentaorganophosphorane systems PR_5[1]. Having successfully prepared pentamethylarsorane[2] and its alkoxy derivative[3] our search for monocyclic phosphoranes met with failure, although alkoxy compounds did prove to be accessible[4].

Meanwhile, by careful selection of the reaction conditions we have now been able to suppress the otherwise unavoidable formation of the ylide[6] on reaction of 5λ⁵-phosphoniaspiro[4.4]nonane chloride[5] with methyllithium and to force methylation of the phosphorus atom to give the pentaalkyl compound *(1)*:



(1)

Compound *(1)* is a colorless liquid which can be distilled unchanged and is hardly sensitive to air; in low concentration it gives off a blossom-like scent. The molecular mass was confirmed by the mass spectrum, which contains the molecular ion and also reveals fragmentation to *P*-methylphospholane. Pentacoordination of the phosphorus atom follows from the large ^{31}P-NMR upfield shift ($\delta = -91.7$). Owing to the complicated nature of the ^{1}H-NMR spectrum, which undergoes hardly any simplification in the $\{^{31}P\}$ version, particular importance attaches to the $^{13}C\{^1H\}$-NMR spectrum: at room temperature the doublet of the CH_3 group is accompanied by a doublet due to the four α-CH_2 groups and a doublet due to the β-CH_2 groups. Off-resonance experiments confirm this assignment by additional q,t,t splitting.

The molecular geometry of *(1)* is not expected to be that of an ideal trigonal bipyramid or a square pyramid because the two phospholane units have distinct angular preferences. Structural studies on related spirocyclic *oxa*phosphoranes nearly all indicate considerable deviations from these standard geometries[7]. It is therefore hardly surprising that low-temperature ^{1}H- and ^{13}C-NMR spectra of *(1)* fail to show any splitting of the CH_2 signals, in line with some kind of distribution between equatorial or axial positions, even at −105 °C. A decision in favor of a square planar structure, which appears somewhat more likely in the light of the above findings, or whether the activation energies of the polytopic rearrangement are extremely low, will have to await completion of the electron diffraction structural elucidation currently in progress.

Procedure:

5λ⁵-Phosphoniaspiro[4.4]nonane iodide is prepared according to ref. [5] and transformed into the chloride. $^{13}C\{^1H\}$-NMR (CD_2Cl_2, converted to TMS, 305 K): $\delta CH_2(\alpha)$ 22.6, d, J(PC) 46.4 Hz; $\delta CH_2(\beta)$ 25.4, d, J(PCC) 7.3[8].—To a suspension of the chloride (1.45 g, 8.1 mmol) in ether (20 ml) is slowly added dropwise at −60 °C a solution of methyllithium (10 mmol) in ether (25 ml), stirring is continued for 6 h at −40 °C, LiCl is filtered off after warming of the reaction mixture, and the solvent is removed at 0 °C/60 torr. Distillation at 46 °C/1 torr furnishes *(1)* (0.62 g (48 %), m.p. ≈ −40 °C).

^{1}H-NMR ([D_8]toluene, TMS ext., 305 K): δCH_3 1.44, d, 3H, J(HCP) 10.35 Hz; δCH_2(α and β) 0.88—1.83, m, 16H. The spectrum is almost unchanged at 180 K.—$^{13}C\{^1H\}$-NMR ([D_8]toluene, converted to TMS, 305 K): δCH_3 19.6, d, J(PC) 65.9; $\delta CH_2(\alpha)$ 33.3, d, J(PC) 41.5; $\delta CH_2(\beta)$ 23.0, d, J(PCC) 9.8 Hz. Off resonance: q,t,t. The spectrum is practically unchanged at 180 K.—$^{31}P\{^1H\}$-NMR (H_3PO_4 ext.): $\delta = -91.7$, s. MS (15 eV): m/e 158, M^+; 102, $(CH_2)_4PCH_3^+$ (100 %).

Received: July 15, 1977 [Z 794 IE]
German version: Angew. Chem. 89, 748 (1977)

CAS Registry numbers:
(1), 63702-97-6; 5λ⁵-phosphoniaspiro[4.4]nonane chloride, 63702-96-5; ^{13}C, 14762-74-4

[1] Literature survey: *H. Schmidbaur*, Adv. Organomet. Chem. *14*, 205 (1976).
[2] *K. H. Mitschke, H. Schmidbaur*, Chem. Ber. *106*, 3645 (1973).
[3] *H. Schmidbaur, W. Richter*, Angew. Chem. *87*, 204 (1975); Angew. Chem. Int. Ed. Engl. *14*, 183 (1975).
[4] *H. Schmidbaur, P. Holl*, Chem. Ber. *109*, 3151 (1976); *H. Schmidbaur, H. Stühler, W. Buchner, ibid. 106*, 1238 (1973); *H. Schmidbaur, W. Buchner, F. H. Köhler*, J. Am. Chem. Soc. *96*, 6208 (1974).
[5] *N. J. Derkach, A. V. Kirsanov*, Zh. Obshch. Khim. *38*, 331 (1968).
[6] *B. D. Cuddy, J. C. F. Murray, B. J. Walker*, Tetrahedron Lett. *1971*, 2397.
[7] Cf. *P. Narayanan, H. M. Berman, F. Ramirez, J. F. Marecek, Y. Chaw, V. A. V. Prasad*, J. Am. Chem. Soc. *99*, 3336 (1977); *R. R. Holmes, J. A. Deiters, ibid. 99*, 3318 (1977).
[8] We are grateful to Dipl.-Chem. *H. P. Scherm* for recording this spectrum.

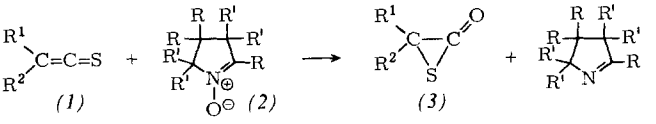
[*] Prof. Dr. H. Schmidbaur, Dipl.-Chem. P. Holl, Univ.-Doz. Dr. F. H. Köhler
Anorganisch-chemisches Institut der Technischen Universität
Arcisstrasse 21, D-8000 München 2 (Germany)

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

α-Thiolactones from Thioketenes

By *Ernst Schaumann* and *Ulrich Behrens*[*]

While the chemistry of α-lactams has been thoroughly studied[1] and α-lactones have been detected in solution[2], α-thiolactones *(3)* have not previously been reported. We have now found the oxidation of thioketenes *(1)*[3] bearing bulky substituents with nitrones of the 1-pyrroline 1-oxide type *(2)* to provide a facile entry to *(3)*.



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

(1a), *(3a)*: $R^1 = CH(CH_3)_2$, $R^2 = C(CH_3)_3$
(1b), *(3b)*: $R^1 = R^2 = C(CH_3)_3$
(1c), *(3c)*: $R^1 + R^2 = -C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$

(2a): R = CH_3, R' = H
(2b): R = H, R' = CH_3

[*] Prof. Dr. E. Schaumann [+]
Institut für Organische Chemie und Biochemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)
Dr. U. Behrens
Institut für Anorganische und Angewandte Chemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)
[+] To whom correspondence should be addressed.

Table 1. Conditions of synthesis, yields, physical and important IR data of *(3)*–*(6)*, *(9)*.

	T [°C]	Reaction duration	Solvent	Yield [%]	M.p. [°C]	IR [cm^{-1}]
(3a)	0	3 h	ether [b]	45 [d]	Oil	1800 (C=O)
(3b)	25	8 w	none [b]	36 [d]	65–76 (dec.)	1810, 1785 (C=O)
(3c)	20	3 h	ether [a]	92 [d]	107–111 (dec.)	1785 (C=O)
	20	4 h	ether [b]	84 [d]		
(4)	75	9 h	CCl_4	88	Oil [e]	1130 (C=S)
(5)	65	2 h	CH_3OH [c]	60	114–118	2590 (SH), 1720 (ester C=O)
(6)	20	3 h	ether	13 [d]	117–120	2550 (SH), 1635 (amide C=O)
(9)	35	14 h	ether [b]	59 [d]	56–58	1140, 1055 (S=O)

[a] Reaction with *(2a)*. [b] Reaction with *(2b)*. [c] Addition of a catalytic amount of conc. sulfuric acid. [d] Isolated by preparative layer chromatography on silica gel PF 254 [eluant dichloromethane/petroleum ether (1:9) or ethyl acetate/petroleum ether (1:9)]. [e] Red, b.p. 92°C/19 torr.

The thiolactones *(3)* clearly differ in all their data from the classical oxidation products of *(1)*, *i.e.* the thioketene *S*-oxides[4]. A C=O stretching vibration (Table 1) observed at high wave numbers and a carbonyl signal in the ^{13}C-NMR spectrum ($\delta = 186.9$ for *(3c)* in $CDCl_3$) are in full accord with structure *(3)*. Structural proof was provided by an X-ray structure determination[5] on *(3c)* (cf. Fig. 1). In keeping with their spiro-type connection the six-membered ring and the three-membered ring, which coincides with the crystallographic plane of symmetry, are at right angles to each other, with the sulfur in a quasi-equatorial position. The ring strain in the three-membered ring is apparently relieved to a considerable extent by the sulfur atom, as is demonstrated by the extremely long S—C^2 bond and the small bond angle at the sulfur.

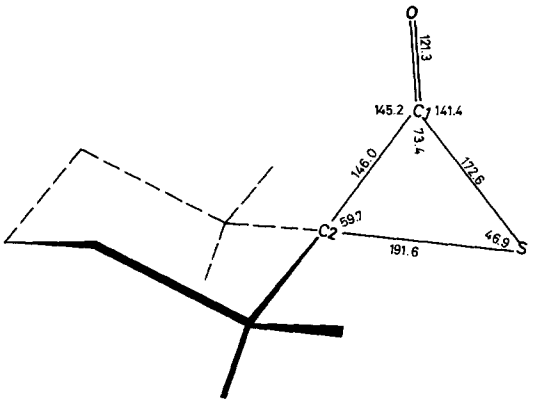
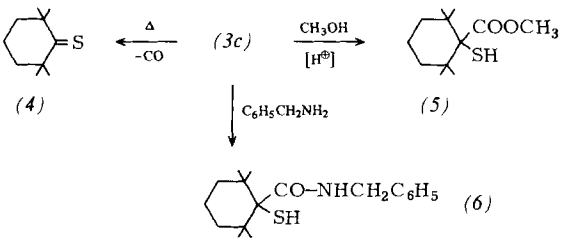
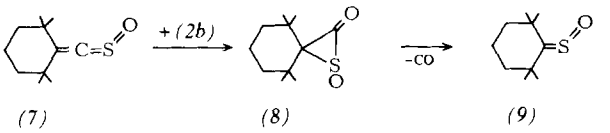


Fig. 1. Important bond lengths [pm] (standard deviation 0.8 pm) and angles [°] (standard deviation 0.7°) in *(3c)*.

On heating, compound *(3c)* (studied as a typical member of the class) underwent qualitative decarbonylation to the thioketone *(4)* (half-reaction time 1.5 h in acetonitrile, 2.9 h in tetrachloromethane at 75 °C). It is relatively stable to hydrolysis and solvolysis, probably as a result of the bulky alkyl group; only on heating is sulfur liberated to form derivatives of the ketene corresponding to *(1c)*. Addition products of *(3)* are obtained only with methanol and benzylamine: on the basis of their IR data (Table 1) and degradation reactions they are to be formulated as α-mercapto carboxylic acid derivatives *(5)* and *(6)*. Thus *(3)* reacts *via* 1,2 ring cleavage, whereas α-lactams[1] and the α-lactone corresponding to *(3b)*[2a] are preferentially attacked at the 1,3 bond by protic reagents.



The course of the reaction with the heteroallenes *(1)*, which differs from the usual behavior of the nitrones[6], is again observed in the reaction of the thioketene *S*-oxide *(7)*[4] with



(2b). However, the α-thiolactone *S*-oxide *(8)* cannot be isolated but, unlike *(3)*, eliminates CO to give the thioketone oxide *(9)* *in situ*.

Received: July 18, 1977 [Z 796 IE]
German version: Angew. Chem. *89*, 750 (1977)

CAS Registry numbers:

(1a), 54439-99-5; *(1b)*, 16797-75-4; *(1c)*, 54440-00-5; *(2a)*, 6931-11-9; *(2b)*, 10135-38-3; *(3a)*, 63702-81-8; *(3b)*, 63702-82-9; *(3c)*, 63702-83-0; *(4)*, 63702-84-1; *(5)*, 63702-85-2; *(6)*, 63702-86-3; *(7)*, 63702-87-4; *(8)*, 63702-88-5; *(9)*, 63702-89-6

[1] *I. Lengyel, J. C. Sheehan*, Angew. Chem. *80*, 27 (1968); Angew. Chem. Int. Ed. Engl. 7, 25 (1968).
[2] a) *R. Wheland, P. D. Bartlett*, J. Am. Chem. Soc. *92*, 6057 (1970); b) *W. Adam, J.-C. Liu, O. Rodriguez*, J. Org. Chem. *38*, 2269 (1972).
[3] *E. Schaumann, W. Walter*, Chem. Ber. *107*, 3562 (1974).
[4] *E. Schaumann, W.-R. Klein*, unpublished.
[5] $a = 1139.1(5)$, $b = 911.7(4)$, $c = 962.1(4)$ pm, $\beta = 146.69(1)°$, space group Cm, $Z = 2$, 656 independent diffraction data ($F > 3\sigma$); $R = 0.047$. Measurement: $\theta/2\theta$ scan technique on a four-circle single crystal diffractometer (Hilger-Watts) with monochromated $Mo_{K\alpha}$ radiation. Solution: Patterson method.
[6] *D. St. C. Black, R. F. Crozier, V. C. Davis*, Synthesis *1975*, 205.

Bis(trifluoromethyl)disulfane Oxide $CF_3S(O)SCF_3$[**]

By *Willy Gombler*[*]

Organyl disulfane oxides (-thiosulfinates) of the type RS(O)SR have been well documented[1], and since the disco-

[*] Dr. W. Gombler
Lehrstuhl für Anorganische Chemie II der Universität
Postfach 102148, D-4630 Bochum 1 (Germany)

[**] Experimental work performed at the Universities of Saarbrücken and Bochum.

very and characterization of allicin (R = allyl), the antibacterial component of garlic, the biological activities of dialkyldisulfane oxides have also been demonstrated[1]. All the previously synthesized disulfane oxides (and trisulfane oxides[2]) disproportionate at room temperature:

$$2\,RS(O)SR \rightarrow RSSR + RS(O)_2SR$$

Disulfane oxides containing perhaloalkyl groups could hitherto not be synthesized. Thus, reaction of $Hg(SCF_3)_2$ with $CF_3S(O)Cl$ did not afford the desired compound $CF_3S(O)SCF_3$ *(1)*, but CF_3SSCF_3 *(2)* and $CF_3S(O)_2SCF_3$ *(3)*[3]. The hydrolysis of CF_3SCl *(4)*[4] and the reaction of *(4)* with Ag_2O or Ag_2CO_3[5] led to the same result. All recent attempts to prepare compounds containing the $CF_3S(O)S$ group have also remained unsuccessful[6]. We have now been able to obtain *(1)* in 65 % yield by hydrolysis of $CF_3SF_2SCF_3$ *(5)*[7] at low temperature in the presence of KF as HF-trapping agent.

$$\underset{(5)}{CF_3SF_2SCF_3} \xrightarrow[-50\,^\circ C,\ KF]{H_2O} \underset{(1)}{CF_3S(O)SCF_3}$$

The product *(1)* is unexpectedly stable at room temperature (unchanged after 3 months in a sealed glass tube); it is a colorless liquid which solidifies at −138 °C whose vapor pressure is given by $\log p\,[\mathrm{torr}] = 7.5462 - 1605.98/T$ (extrapolated boiling point 71.1 °C, $\Delta H_v = 30.8$ KJ/mol, $\Delta S_v = 89.2$ J/mol·K). *(1)* disproportionates into *(2)* and *(3)* within 1—2 days in the presence of HF, and within about 3 weeks in the presence of *(4)*. Having characterized *(1)* it has now been possible to establish by NMR spectroscopy that the hydrolysis of *(4)* as well as the reaction of *(4)* with Ag_2CO_3 also proceed *via (1)*. Compound *(1)* was characterized spectroscopically (Tables 1 and 2) and by molecular weight determinations. The spectra were compared with those of *(3)*.

Table 1. ^{19}F- and ^{13}C-NMR data of *(1)*, *(2)*, and *(3)*.

	313.7	336.9	311.3	327.1	314.9
	CF_3SSCF_3	$CF_3S(O)SCF_3$		$CF_3S(O)_2SCF_3$	
		1.5		5 [a]	
$\delta(^{19}F)$	−46.6	−69.5	−34.2	−76.8 [a]	−36.3 [a]
$\delta(^{13}C)$	128.5	125.6	129.7	116.0	122.9

Positive δ values: downfield shift relative to $CFCl_3$ and TMS, respectively; J in Hz.
[a] *R. A. De Marco, J. M. Shreeve*, Inorg. Chem. *12*, 1896 (1973).

Table 2. IR, Raman, and mass spectroscopic data of *(1)*.

IR (cm^{-1}, rel. int.): 1220 vs, 1180 vs, 1105 vs, 758 m, 454 m.
Raman (cm^{-1}, rel. int.): 1190—1250 br (3), 1173 (22), 1117 (12), 765 (59), 752 (28), 579 (6), 562 (5), 548 (1), 485 (36), 460 (30), 364 (18), 329 (14), 262 (65), 250 (100), 207 (10), 148 (32), 119 (5).
MS (*m/e*, rel. int.): 218 (2), 202 (4), 149 (24), 133 (3), 117 (7), 114 (2), 101 (2), 98 (2), 82 (100), 76 (14), 69 (92), 64 (16), 63 (21), 60 (12), 50 (6), 48 (10), 44 (10), 31 (6).

Experimental

A fresh sample of *(5)* is prepared in a high vacuum apparatus. This is allowed to react with 8 g (59 mmol) *(4)* and 50 g (210 mmol) anhydrous HgF_2[7]. *(4)* and *(2)* are removed from the crude product at −78 °C by pumping until it is almost colorless (NMR spectroscopic identification of *(5)* at −50 °C). The yield of *(5)* with negligible contamination by residual *(2)* is *ca.* 5.8 g (24 mmol). *(5)*, which may not be warmed to more than −30 °C, is now condensed with the aid of liquid nitrogen into a glass condensation vessel [K] containing 6 g (103 mmol) finely ground KF and 0.6 g (33 mmol) H_2O. [K] is kept at −50 °C for 24 h and, if necessary, gently shaken. Any SiF_4 that is formed is then pumped off at −78 °C, [K] warmed to −50 °C and the product condensed into a receiver (−196 °C) except for the excess water. The separation of readily volatile *(2)* is achieved by batch removal of the gas phase, which is in equilibrium with the liquid at −50 °C (partial pressures at −50 °C: *(2)* 10.7, *(1)* 0.2 torr).

Yield of *(1)* 3.4 g (65 %), contamination with *(2)* 5 %. Molecular weight determination (Regnault): 217.5 (calc. 218.1).

Received: July 11, 1977 [Z 785 IE]
German version: Angew. Chem. *89*, 740 (1977)

CAS Registry numbers:
(1), 63548-94-7; *(2)*, 372-64-5; *(3)*, 358-15-6; *(4)*, 421-17-0; *(5)*, 26391-89-9

[1] Cf. *E. Block, J. O'Connor*, J. Am. Chem. Soc. 96, 3921 (1974); and references cited therein.
[2] *R. Steudel, J. Latte*, Chem. Ber. *110*, 423 (1977).
[3] *D. T. Sauer, J. M. Shreeve*, Inorg. Chem. *10*, 358 (1971).
[4] *R. N. Haszeldine, J. M. Kidd*, J. Chem. Soc. *1955*, 2901.
[5] *A. Haas, M. E. Peach*, Z. Anorg. Allg. Chem. *338*, 299 (1965).
[6] *C. A. Burton, J. M. Shreeve*, Inorg. Chem. *16*, 1039 (1977).
[7] *F. Seel, W. Gombler*, Angew. Chem. *81*, 789 (1969); Angew. Chem. Int. Ed. Engl. *8*, 773 (1969); *W. Gombler*, Z. Anorg. Allg. Chem., in press.

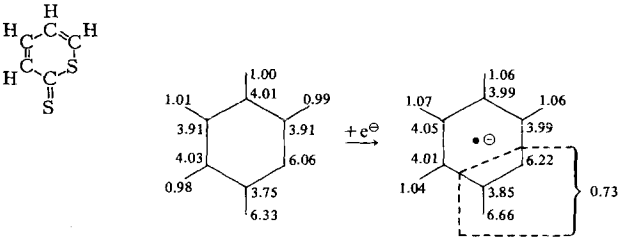
Thiathione Radical Anions: Are $(—S)_2C{=}S$ Groups Electron Traps?[1, 2]

By *Hans Bock, Georg Brähler, Abbas Tabatabai, Andrzej Semkow*, and *Rolf Gleiter*[*]

Dialkyl thioketones can be electrochemically reduced to their radical anions $R_2C{=}S^{\bullet\ominus}$[3,4]. We also succeeded in inserting an additional electron into electron-rich thia- and dithiathiones such as trithione[2]:



Our studies were prompted by the photoelectron-spectroscopic finding that thiocarbonyl difluoride $F_2C^{\oplus}—S^{\ominus}$ possesses a polar π_{CS} bond[5], as well as by the results of INDO open shell calculations[6], according to which thiapyran-α-thione, for instance, and its radical anion should exhibit the following total charge distribution:



[*] Prof. Dr. H. Bock, Dipl.-Chem. G. Brähler, Dipl.-Chem. A. Tabatabai, Dr. A. Semkow
Institut für Anorganische Chemie der Universität
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)
Prof. Dr. R. Gleiter
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt (Germany)

An electron hole is seen to be postulated at the thiocarbonyl carbon atom in the neutral molecule, and in the radical anion the additional unpaired electron should be located predominantly in the (SCS) region.

The ESR spectrum of the radical anion of thiapyran-α-thione (Fig. 1a) expectedly shows 16 lines of equal intensity for the 4 nonequivalent hydrogen atoms and can be simulated—except for the anisotropism arising in the mixture of solvents used at low temperature with the coupling constants given in Table 1 (Fig. 1b).

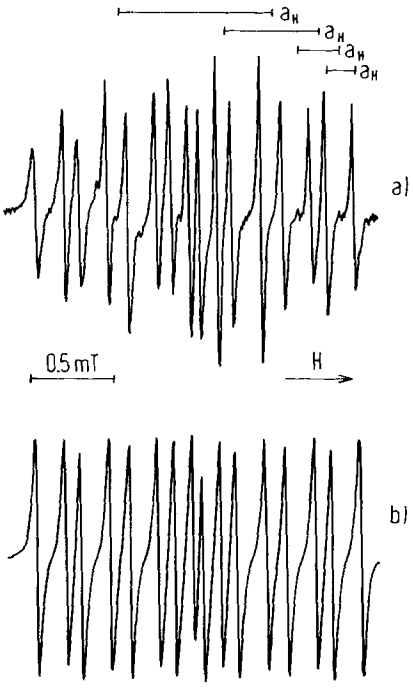
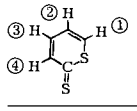
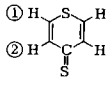
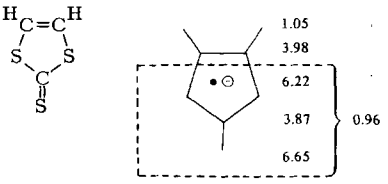


Fig. 1. a) ESR spectrum of the thiapyran-α-thione radical anion at 210 K in acetonitrile/dimethylformamide (DMF) and b) its simulation.

Table 1. Thiathione radical anions: recording temperature T of the ESR spectrum, measured ($a_{H,\mu}$) and calculated ($a_{H,\mu}^{INDO}$) coupling constants for the hydrogen atoms at the various centers μ.

Compound	T [K]	μ	$a_{H,\mu}$ [mT]	$a_{H,\mu}^{INDO}$ [mT]
	210	①	0.158	0.187
		②	0.246	0.437
		③	0.514	0.837
		④	0.861	1.052
	250	①	0.726	0.837
		②	0.241	0.410
	200	①	0.950	1.054
		②	0.274	0.481
	200	①	0.056	0.043

In view of the semiempirical INDO open shell calculation, the measured and calculated ESR coupling constants are in satisfactory agreement[7] and therefore permit spectral assignment (Fig. 1). The small coupling in the isotrithione radical anion is remarkable; according to the McConnell relation $a_{\pi,\mu} = |Q|\rho_{\pi,\mu}$ this corresponds to an only small spin population at the ethylene carbon atoms. The INDO open-shell total charges



also suggest that trithiocarbonate units in planar radical anions can act as "electron traps"[8].

Received: July 13, 1977 [Z 791 IE]
German version: Angew. Chem. 89, 745 (1977)

CAS Registry numbers:
Table 1 (left-hand column, from top to bottom): 63609-38-1; 63609-39-2; 63588-75-0; 63588-76-1

[1] Part 14 of "Radical Ions" and Part 23 of "The Electronic Structure of Sulfur Compounds".—Parts 13 and 24, respectively: *H. Bock, W. Kaim*, Nachr. Chem. Tech. Lab. *25*, 306 (1977), and *R. Bartetzko, R. Gleiter*, Inorg. Chem., in press.

[2] Diplomarbeit *A. Tabatabai*, Universität Frankfurt 1976; Dissertation *G. Brähler*, Universität Frankfurt 1977.

[3] *G. A. Russell, J. L. Gerlock, G. R. Underwood*, J. Am. Chem. Soc. *94*, 5209 (1972), $(F_3C)_2C{=}S^{\bullet\ominus}$.

[4] *C.-P. Klages, J. Voss*, Angew. Chem. *89*, 744 (1977); Angew. Chem. Int. Ed. Engl. *16*, 726 (1977), have succeeded in generating dialkyl thioketyls such as $[(H_3C)_3C]_2C{=}S^{\bullet\ominus}$ for the first time. We are grateful to Dr. *Voss* for communicating this result.

[5] *K. Wittel, A. Haas, H. Bock*, Chem. Ber. *105*, 3865 (1972).

[6] *A. Semkow*, unpublished. The INDO parameters are taken from *P. E. Stevenson, D. L. Burkey*, J. Am. Chem. Soc. *96*, 3061 (1974). Cf. also *A. Ohno, K. Nakamura, M. Uohama, S. Oka, T. Yamabe, S. Nagata*, Bull. Chem. Soc. Jpn. *48*, 3718 (1975).

[7] The regression line $a_H^{INDO} = 1.09\ a_H^{exp} + 0.10$ has a standard deviation of 0.108 mT [2].

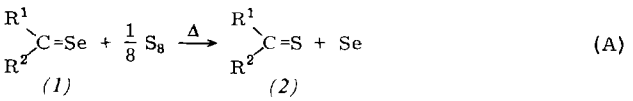
[8] *H. Bock, G. Brähler, D. Dauplaise, R. Gleiter, J. Meinwald*, unpublished.

Preparation of Thiocarbonyl Compounds Containing Isotopic Sulfur Labels[**]

By *Claus-Peter Klages* and *Jürgen Voss*[*]

The possibility of substituting the sulfur of a thiocarbonyl group by isotopes is of considerable utility in studies on the physical properties and chemical reactions of thiocarbonyl compounds by mass spectrometry, vibrational, NMR, and ESR spectroscopy, and by tracer methods. Conventional preparations of thiocarbonyl compounds[1] employ sulfur in the form of hydrogen sulfide, tetraphosphorus decasulfide, or carbon disulfide. Yields based on these reagents are generally low, making the incorporation of commercially available *elemental* sulfur isotopes extremely involved and very expensive.

We have now found a convenient method of preparing semimicro amounts of three classes of thiocarbonyl derivatives



(A)

[*] Prof. Dr. J. Voss, Dipl.-Chem. C.-P. Klages
Institut für Organische Chemie und Biochemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)

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

(Table 1) in very good yield: the final step consists in exchange of selenium for elemental sulfur.

Our experiments were instigated in order to obtain ^{33}S-enriched compounds for ESR spectroscopic studies on their radical anions[2].

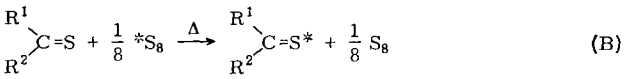
Transformation of selenocarbonyl compounds *(1)*[3] into the thiocarbonyl derivatives *(2)* is accomplished merely by heating with sulfur in the absence of solvent in an evacuated ampoule. After cooling the product is dissolved in a suitable solvent, the solution treated with activated charcoal and filtered through a layer of basic alumina. Amount of reactant *n*, reaction time *t*, reaction temperature *T*, solvent used for isolation S, and yields are listed in Table 1 (the data refer to a 1.4-fold excess of sulfur).

Table 1. Thiocarbonyl compounds *(2)* prepared by exchange of selenium.

	R^1	R^2	*n* [mmol]	*t* [min]	*T* [°C]	S	Yield [%]
(2a)	$C(CH_3)_3$	$C(CH_3)_3$	0.2	120	140	Hexane	80
(2b)	C_6H_5	OC_2H_5	0.6	180	140	CCl_4	95
(2c)	C_6H_5	$N(CH_3)_2$	0.5	20	120	CH_2Cl_2	90

The resulting products are pure according to NMR and IR spectroscopy. Possible contamination by elemental sulfur can be removed by chromatography if necessary. The excess of sulfur can be lowered; however, the reaction time for complete conversion at a given temperature will then increase [*e.g.* $t = 6$ h for *(1a)* with a 1.1-fold excess, $T = 140$ °C].

By analogy with reaction (A), sulfur-sulfur exchange is also possible (B). This was established for thiocarbonamides and thiocarboxamides by use of ^{35}S[4].



(B)

We found that 2,2,4,4-tetramethylpentane-3-thione *(2a)* can be substituted according to (B). A mixture of *(2a)* (0.32 mmol) and $^{34}S_8$ (0.15 mmol, 51.7 % enrichment) was heated to 140 °C. After 72 h, the thioketone was shown by its mass spectrum to contain 20 % of ^{34}S. A ^{34}S content of 19.2 % is calculated for complete equilibration. Thus it is possible, using a large excess of enriched sulfur, to label thioketones directly.

Received: July 4, 1977 [Z 790a IE]
German version: Angew. Chem. *89*, 743 (1977)

CAS Registry numbers:
(1a), 56956-23-1; *(1b)*, 57701-22-1; *(1c)*, 13120-03-1; *(2a)*, 54396-69-9; *(2b)*, 936-61-8; *(2c)*, 15482-60-7

[1] *M. J. Janssen* in *S. Patai*: The Chemistry of Carboxylic Acids and Esters. Wiley-Interscience, New York 1969, p. 705; *W. Walter, J. Voss* in *J. Zabicky*: The Chemistry of Amides. Wiley-Interscience, New York 1970, p. 383; *D. Paquer*, Int. J. Sulfur Chem. *7*, 269 (1972); *8*, 173 (1973); *D. H. R. Barton, F. S. Guziec jun., J. Shahak*, J. Chem. Soc. Perkin Trans. I *1974*, 1794.

[2] Cf. *C.-P. Klages, J. Voss*, Angew. Chem. *89*, 744 (1977); Angew. Chem. Int. Ed. Engl. *16*, 726 (1977).

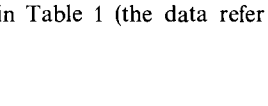
[3] Preparation of starting compounds: *(1a)*: *T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, F. S. Guziec jun.*, J. Chem. Soc. Perkin Trans. I *1976*, 2079; *(1b)*: *D. H. R. Barton, S. W. McCombie, ibid. 1975*, 1574; *(1c)*: *K. A. Jensen, P. H. Nielsen*, Acta Chem. Scand. *20*, 597 (1966).

[4] *C. Suarez Contreras*, An. Quim. *64*, 819 (1968); Chem. Abstr. *70*, 56896j (1969); *T. Sato*, Radioisotopes *23*, 145 (1974); Chem. Abstr. *81*, 49237u (1974).

ESR Spectroscopic Studies on the Radical Anion of [^{33}S]-2,2,4,4-Tetramethylpentane-3-thione[**]

By *Claus-Peter Klages* and *Jürgen Voss*[*]

Radical anions of thioamides and thionic, as well as dithioic, esters generated by electrochemical means have long been studied by ESR spectroscopy. We have now also generated dialkyl thioketyls *(1)*[1] for the first time, and now report di-*tert*-butyl thioketyl *(1a)*, its ESR spectrum, and our conclusions regarding the electronic and geometrical structure of this species.



(1a), X = S, $R^1 = R^2 = C(CH_3)_3$
(1b), X = S, R^1, $R^2 = -C(CH_3)_2CH_2C(CH_3)_2-$
(2), X = O, $R^1 = R^2 = C(CH_3)_3$

Di-*tert*-alkyl thioketones can be reduced electrochemically to the radical anions in a reversible one-electron step in polar aprotic solvents in the presence of tetraalkylammonium supporting electrolytes.

As expected from the lower strength of the CS π bond, compared with the CO π bond, the negative half-wave potential $E_{1/2}$ for thioketones lies at lower values than for the analogous ketones: while the radical anion of 2,2,4,4-tetramethylpentan-3-one *(2)* cannot be generated in acetonitrile in the accessible range of potentials, the corresponding thioketyl *(1a)* is formed at $E_{1/2} = -2.25$ V (*vs.* 0.1 N $AgNO_3$ (CH_3CN)/Ag).

Figure 1 shows the ESR spectrum of [^{33}S]-di-*tert*-butyl thioketyl. The corresponding thioketone was prepared from the selenoketone and elemental [^{33}S]-sulfur (16.7 % ^{33}S) by a new procedure[2].

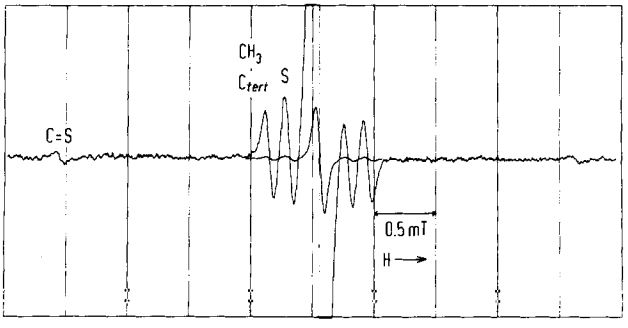


Fig. 1. ESR spectrum of radical anion *(1a)* with ^{13}C and ^{33}S satellites.

The satellite lines of the radical anions with a ^{33}S or ^{13}C atom can be recorded at higher amplification. The measured parameters are compared with those of *(2)* in Table 1.

Table 1. Coupling constants [mT] and *g* values of *(1a)* and *(2)*.

	(1a)	*(2)*
g	2.0061	2.003 [3]
$a^C_{C=X}$	4.19	5.27 [4]
$a^C_{C\text{-}tert}$	0.80	0.77 [4]
$a^C_{CH_3}$	0.80	0.77 [4]
a^X	0.16	−1.11 [4]
$a^H_{CH_3}$	—	0.012 [4]

[*] Prof. Dr. J. Voss, Dipl.-Chem. C.-P. Klages
Institut für Organische Chemie und Biochemie der Universität
Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)

[**] Thioketyls, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Owing to the greater anisotropism of the g tensor, the ESR signals of thioketyls are broader than those of the ketyls. Coupling of the methyl protons of *(1a)* is therefore not resolved under the given conditions. Assignment of the satellite signals is based upon intensities and comparison with the spectrum of the thioketyl having a natural isotopic abundance. Only the components with $m_I = \pm 3/2$ are visible in the quadruplet due to ^{33}S coupling.

A positive sign is deduced for $a^{C}_{C=S}$ from variations in line width in the thiocarbonyl ^{13}C doublet[5]. Our studies on *(1b)* yielded a sulfur coupling constant of $a^{S} \approx +0.2\,mT$[1]; by analogy we assume *(1a)* to have $a^{S} > 0$.

Comparison of the coupling constants $a^{C}_{CH_3}$ and $a^{C}_{C\text{-}tert}$ in *(1a)* with those in *(2)* and in some substituted di-*tert*-butylmethyl radicals[6] shows that the spin population at the thiocarbonyl C atom ρ^{π}_{C} is about 0.8 to 0.9. Hence di-*tert*-butyl thioketyl resembles an alkyl radical more closely than a thiyl radical. This result confirms an INDO calculation by *Ohno et al.*[7]. The measured coupling constants can be reproduced by known or plausible $\sigma-\pi$ parameters[1]. There is accordingly no need to postulate a pyramidal configuration for *(1)*, as assumed for ketyls[8a] and the *tert*-butyl radical[8b], even though this possibility cannot be entirely ruled out.

Received: July 4, 1977 [Z 790b IE]
German version: Angew. Chem. *89*, 744 (1977)

CAS Registry number:
(1a), 63588-77-2

[1] Planned Dissertation by *C. P. Klages*, Universität Hamburg. The perfluorinated species $[CF_3{-}CS{-}CF_3]^{\ominus}$ has already been reported by *G. A. Russell, J. L. Gerlock, G. R. Underwood*, J. Am. Chem. Soc. *94*, 5209 (1972).

[2] *C.-P. Klages, J. Voss*, Angew. Chem. *89*, 743 (1977); Angew. Chem. Int. Ed. Engl. *16*, 725 (1977).

[3] Generated with potassium in tetrahydrofuran: *N. Hirota, S. I. Weissman*, J. Am. Chem. Soc. *82*, 4424 (1960).

[4] Generated with potassium-sodium alloy in dimethoxyethane: *G. A. Russell, G. R. Underwood*, J. Phys. Chem. *72*, 1074 (1968).

[5] *N. M. Atherton*: Electron Spin Resonance. Wiley, New York 1973, pp. 339ff.

[6] *D. Griller, K. U. Ingold*, J. Am. Chem. Soc. *96*, 6715 (1974).

[7] *A. Ohno, K. Nakamura, M. Uohama, S. Oka, T. Yamabe, S. Nagata*, Bull. Chem. Soc. Jpn. *48*, 3718 (1975).

[8] a) *G. R. Underwood*, Mol. Phys. *22*, 729 (1971); b) *J. B. Lish, L. F. Williams, O. E. Wood*, J. Am. Chem. Soc. *98*, 227 (1976); *P. J. Krusic, P. Meakin, ibid. 98*, 228 (1976); however, see also: *T. A. Claxton, E. Platt, M. C. R. Symons*, Mol. Phys. *32*, 1321 (1976); and references cited therein.

N-Imidoyl Isocyanides[**]

By *Gerhard Höfle* and *Bernd Lange*[*]

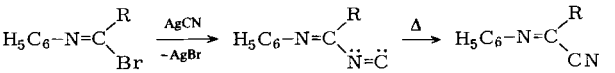
Successful preparation of the first *N*-acyl isocyanides from carboxylic acid iodides and silver cyanide[1] raised the question whether structurally related isocyanides could be prepared according to the same principle.

We have found that the *N*-phenylimidoyl bromides *(1a)* and *(1b)* undergo rapid reaction with silver cyanide in $CHCl_3$ to give the imidoyl isocyanides *(2a)* and *(2b)*, respectively.

[*] Priv.-Doz. Dr. G. Höfle, Dipl.-Chem. B. Lange
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

[**] Reactions of Organic Halogen Compounds with Silver Cyanide, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 3: [1].

The structures of the compounds are confirmed by their IR spectra, which show an intense isocyanide absorption at 2110 and 2100 cm^{-1} and a C=N absorption at 1632 and 1660 cm^{-1}, respectively. In the ^{13}C-NMR spectrum[2] of *(2a)* a signal for the isocyanide group is observed in the expected range at $\delta = 169.3$.

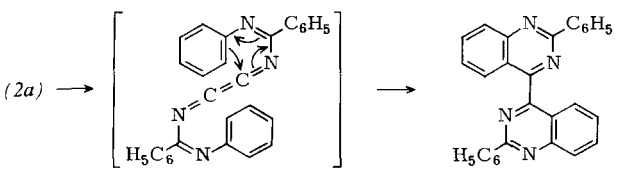


(1a), R = C_6H_5 *(2)* *(3)*
(1b), R = $C(CH_3)_3$

Compared to the *N*-acyl isocyanides, the *N*-imidoyl isocyanides are distinctly more stable in dilute solution; thus *(2a)* is transformed into the thermodynamically more stable imidoyl cyanide *(3)* only in the course of days, *(2b)* in several hours. However, if the solutions are concentrated at room temperature or reaction of the imidobromide is carried out in boiling chloroform formation of the imidoyl cyanides *(3)* predominates[3].

Isolation of an *N*-imidoyl isocyanide in pure form has so far been realized only in the case of the diphenyl derivative *(2a)*, which is obtained in 85 % yield in the form of yellow crystals on low-temperature crystallization from petroleum ether. It melts at 60 °C and has a weak aromatic isonitrile odor. It can be stored at room temperature for a few days, and at −20 °C indefinitely. On melting it decomposes, giving mainly *(3a)*. Hydrolysis with dilute HCl leads to benzanilide in good yields, and reaction with methanol affords mainly *N*-phenylbenzimino esters.

According to mass spectral data the expected trimerization of *(2)*, in analogy to the *N*-acyl isocyanides, does not take place, even under the most varied conditions. In contrast, in the thermal transformation of *(2a)* into *(3a)* varying amounts (10 to 30 %) of a by-product are observed which could be identified by an authentic synthesis as 2,2′-diphenyl-4,4′-bisquinazoline *(5a)*. We interpret its formation in terms of an initial head-to-head dimerization of *(2a)* to give the heterocumulene *(4a)*, which by double electrocyclic ring closure and subsequent oxidation can elude trimerization[5]. Attempts to transform β-styryl isocyanides into 2,2′-bisisoquinolines in the same way have so far failed.



(2a) *(4a)* *(5a)*

Experimental

Synthesis of *(2a)*: 1.34 g (5.15 mmol) *N*-phenylbenzimidoyl bromide is added to a solution of AgCN[1] (1.7 g, 12.7 mmol) in anhydrous CH_2Cl_2 (20 ml). After 10 minutes' stirring at 20 °C the silver salt is filtered off and the filtrate evaporated down at 0 °C/0.1 torr. The orange-red residue is extracted several times with petroleum ether. On cooling the concentrated petroleum extract from 0 °C to *ca.* −60 °C, 0.90 g (85 %) *(2a)* crystallized out, m.p. 60 °C.

Synthesis of *(5a)*: A solution of AgCN (1.34 g, 10 mmol) and *N*-phenylbenzimidoyl bromide (1.04 g, 4.0 mmol) in anhydrous benzene (25 ml) is heated under reflux for 4 h. The silver salts are separated by filtration and washed several times with hot benzene. The combined filtrates are concentrated and

then treated with petroleum ether. This affords 0.26 g (32 %) *(5a)*, m.p. 293–294 °C. 0.31 g (38 %) *(3a)* can be obtained from the petroleum ether solution by distillation.

Received: July 4, 1977 [Z 789 IE]
German version: Angew. Chem. *89*, 742 (1977)

CAS Registry numbers:
(1a), 40168-06-7; *(1b)*, 63588-82-9; *(2a)*, 63588-83-0; *(2b)*, 63588-84-1; *(3a)*, 4686-14-0; *(5a)*, 60538-88-7; AgCN, 506-64-9

[1] *G. Höfle, B. Lange*, Angew. Chem. *89*, 272 (1977); Angew. Chem. Int. Ed. Engl. *16*, 262 (1977).

[2] Bruker WH 270 at 67.88 MHz in $CDCl_3$ at 30 °C; ^{13}C enrichment in the isocyanide group 90 %; halfwidth of signal 10 Hz at $\delta = 169.3$. On cooling, a coalescence of this signal at *ca.* −10 °C is followed at −50 °C by its replacement by two new signals of comparable intensity at $\delta = 146.3$ and 157.2, which can be assigned to the *E*- and *Z*-isomers. Unusual, however, is that *both* signals are shifted to higher field. The possibility that we observed the dimer *(4a)*, likely to be present in the equilibrium, is ruled out by the low-temperature IR spectrum.

[3] This thermolability casts doubt upon the isolation [4] of *N*-alkylformimidoyl isocyanides in admixture with the corresponding cyanides. The IR and ^{13}C-NMR data [4] (2120 cm^{-1} and $\delta_{-NC} = 157.7$, resp.) suggest that these compounds are actually alkyl isocyanides originating from base-catalyzed HCN elimination from the *N*-alkylformimidoyl cyanides.

[4] *J. H. Boyer, J. Kooi*, J. Chem. Soc. Perkin I, *1975*, 1743; *J. H. Boyer, J. Dunn, J. Kooi*, J. Am. Chem. Soc. *98*, 1099 (1976).

[5] A cyanide-catalyzed dimerization of *(2a)* by way of a 2-phenylquinazoline can be ruled out since added 2-(*m*-tolyl)quinazoline is neither consumed nor incorporated in *(5a)*.

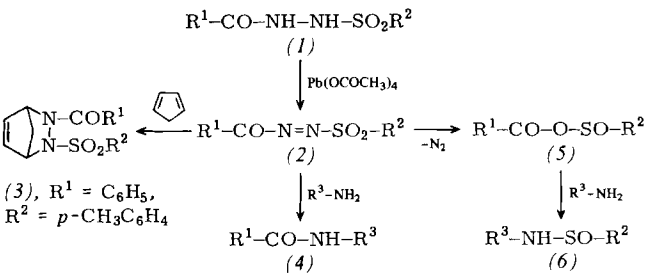
N-Acyl-*N'*-arylsulfonyldiazenes; Detection and Use in the Synthesis of Amides

By *Hansjürgen Gölz, Bernd Glatz, Georges Haas, Günter Helmchen*, and *Hans Muxfeldt* (deceased)[*]

While *N,N'*-diacyldiazenes are in many cases stable and readily accessible, to our knowledge the *N,N'*-disulfonyl- and *N*-acyl-*N'*-sulfonyldiazenes (excepting azobissulfates) have so far not been reported[1]. Owing to the pronounced nucleofugal character of the sulfonylazo group[2] these compounds ought to represent an interesting new class of acylating agents.

We have now been able to demonstrate the existence of a compound of type *(2)*, *viz.* *N*-benzoyl-*N'*-tosyldiazene *(2a)* (cf. Scheme 1 and Table 1). Oxidation of the hydrazide *(1a)* with lead tetraacetate in the presence of cyclopentadiene at −78 °C leads to formation of the cycloadduct *(3)*[3] in 33 % yield, and on addition of boron trifluoride ether in 53 % yield[4] (cf. experimental procedure). In order to estimate the lifetime of *(2a)* the temperature and the interval of time between completion of oxidation and addition of cyclopentadiene were varied. Oxidation at −50 °C and addition of cyclopentadiene after 30 minutes leads to 40 % *(3)*, whereas oxidation at −30 °C and addition of cyclopentadiene after 10 minutes leads to only traces of *(3)*. Consequently, at temperatures below *ca.* −50 °C *(2a)* is sufficiently stable for its isolation.

[*] Dr. H. Gölz, Dr. B. Glatz, Dr. G. Helmchen [+], Prof. Dr. H. Muxfeldt (deceased)
Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität
Pfaffenwaldring 55, D-7000 Stuttgart 80 (Germany)
Dr. G. Haas [**]
Ciba-Geigy AG
CH-4000 Basel (Switzerland)
[+] Author to whom correspondence should be addressed.
[**] Formerly at Cornell University, Ithaca, N. Y.



Scheme 1

Table 1. Carboxamides *(4)* and sulfinamides *(6)* prepared (see experimental) from hydrazides *(1)* and benzylamine ($R^3 = CH_2C_6H_5$) by oxidation with lead tetraacetate.

Reactant	R^1	R^2	T [°C]	Products yield [%]			
(1a)	C_6H_5	*p*-$CH_3C_6H_4$	−60	*(4a)*	>98	—	
(1b)	C_6H_5	C_6H_5	25	*(4a)*	75	*(6a)*	5
(1c)	CH_3	*p*-$CH_3C_6H_4$	−60	*(4b)*	77	*(6b)*	2
(1c)	CH_3	*p*-$CH_3C_6H_4$	25	*(4b)*	51	*(6b)*	12
(1d)	$(CH_3)_3C$	*p*-$CH_3C_6H_4$	−80	*(4c)*	>98	—	
(1d)	$(CH_3)_3C$	*p*-$CH_3C_6H_4$	−50	*(4c)*	89	*(6b)*	9
(1d)	$(CH_3)_3C$	*p*-$CH_3C_6H_4$	25	*(4c)*	28	*(6b)*	42
(1e)	$(CH_3)_3C$	2,4,6-$(CH_3)_3C_6H_2$	−60	*(4c)*	92	*(6c)*	5
(1e)	$(CH_3)_3C$	2,4,6-$(CH_3)_3C_6H_2$	25	*(4c)*	9	*(6c)*	76

N-Acyl-*N'*-arylsulfonyldiazenes *(2)* can acylate amines. Thus, oxidation of the hydrazides *(1a)*—*(1e)* with lead tetraacetate in the presence of benzylamine below −60 °C leads to the carboxamides *(4)*[5] in good yields, together with small amounts of the sulfinamides *(6)* (cf. Table 1 and experimental procedure). The amount of *(6)* can reach significant proportions if the reaction is carried out at room temperature. It follows from our present studies and from numerous other data[6] that the ratio *(6)*/*(4)* increases with increasing temperature and increasing bulkiness of R^1 and R^2. Electronic effects have comparatively little influence in this respect[6].

The results can be interpreted in terms of Scheme 1. The diazenes *(2)* stable at −60 °C react cleanly with amines to give carboxamides; however, at higher temperatures competing elimination of nitrogen leads to the mixed anhydrides *(5)*. These are preferentially attacked at the sulfur atom by amines[7]. This is confirmed by predominant formation of the sulfinamide *(6e)* from *(1e)* at room temperature; in this instance the situation is especially sterically unfavorable for attack at the sulfur atom.

Experimental

2-Benzoyl-3-tosyl-2,3-diaza-5-norbornene (3): A solution of lead tetraacetate (4.0 mmol) in dichloromethane (25 ml) is added dropwise during 1 h at −78 °C to a solution of *(1a)* (880 mg, 3.03 mmol), cyclopentadiene (30.3 mmol), and boron trifluoride ether (1.54 mmol) in THF/acetonitrile (1/1) (50 ml). After a further 4 h at −78 °C the solution is allowed to warm over a period of *ca.* 20 h to room temperature. The crude product obtained after treatment with ether, extraction with sodium hydrogen carbonate solution, drying (sodium sulfate) and removal of organic phase by evaporation is chromatographed on 300 g silica gel (chloroform/acetone 95/5, 15 ml fractions). Fractions 64 to 80 yielded 564 mg (53 %) *(3)*, colorless crystals, m.p. 148—149 °C, after recrystallization from ethyl acetate/hexane.

Carboxamides (4): A solution of lead tetraacetate (1 mmol) in dichloromethane (10 ml) is added dropwise during 20 min to a solution of hydrazide *(1)* (1 mmol) and benzylamine (5 mmol) in THF (for temperature see Table 1). After 2 h

at the same temperature the reaction mixture is treated with ether and extracted with 1 N hydrochloric acid, 1 N sodium hydroxide, and water. The crude product obtained after drying and evaporation of the ether phase is recrystallized or chromatographed on silica gel for determination of the *(4)*/*(6)* ratio.

Received: July 12, 1977 [Z 788 IE]
German version: Angew. Chem. 89, 742 (1977)

CAS Registry numbers:
(1a), 3064-19-5; *(1b)*, 6631-28-3; *(1c)*, 4837-35-8; *(1d)*, 10565-50-1; *(1e)*, 63548-95-8; *(2a)*, 63548-96-9; *(2b)*, 63548-97-0; *(2c)*, 63548-98-1; *(2d)*, 63548-99-2; *(2e)*, 63549-00-8; *(3)*, 63549-01-9; *(4a)*, 1485-70-7; *(4b)*, 588-46-5; *(4c)*, 26209-45-0; *(6a)*, 6829-91-0; *(6b)*, 6873-90-1; *(6c)*, 63549-02-0; cyclopentadiene, 542-92-7; benzylamine, 100-46-9

[1] Reviews: *H. Bock*, Angew. Chem. 77, 469 (1965); Angew. Chem. Int. Ed. Engl. 4, 457 (1965); *S. Patai*: The Chemistry of the Hydrazo, Azo and Azoxy Groups. Wiley, New York 1975, Parts I and II.
[2] *W. R. Bamford, T. S. Stevens*, J. Chem. Soc. *1952*, 4735.
[3] All the isolated compounds described here were unequivocally characterized by elemental analysis and spectroscopy (^{1}H-NMR, IR, MS).
[4] Attempts to trap *N,N'*-ditosyldiazene, possibly formed analogously from *N,N'*-ditosylhydrazine by oxidation at −75 °C, with cyclopentadiene, were unsuccessful; cf. [6].
[5] Carboxamides are prepared by oxidation of acylhydrazines and *N*-acyl-*N'*-phenylhydrazines: *Y. Wolman, P. M. Gallop, A. Patchornik*, J. Am. Chem. Soc. *83*, 1263 (1961); *H. B. Milne, W. Kilday*, J. Org. Chem. *30*, 64 (1965).
[6] *H. Götz*, Dissertation, Universität Stuttgart 1976.
[7] The intermediate *(5a)* formed from sodium *p*-toluenesulfinate and benzoyl chloride in ethanol correspondingly yields chiefly ethyl *p*-toluenesulfinate; cf. *M. Kobayashi*, Bull. Chem. Soc. Jpn. *39*, 967 (1966).

The Te-O-Fe System: $Te(OTeF_5)_6$[**]

By *Dieter Lentz, Hans Pritzkow*, and *Konrad Seppelt*[*]

The accidental discovery[1] and subsequent elucidation of the structure[2] of *trans*-$F_2Te(OTeF_5)_4$ *(4)* motivated interest in the directed synthesis of higher tellurium oxide fluorides utilizing the oxidative action of xenon(II) derivatives. It was essential, in the first place, to establish the ultimate steric accommodation of a tellurium atom and whether the octahedral construction remains valid. As will be demonstrated in the present communication, the covalent chemistry of tellurium can be developed quite extensively.

First of all, $Te(OTe_5)_4$ *(1)* was synthesized (m.p. 89 °C, subl. 110 °C/10^{-2} mbar, 99.5 % yield) and then oxidized with $Xe(OTeF_5)_2$[3] to $Te(OTeF_5)_6$ *(2)* (95 % yield).

$$3\ TeF_4 + 4\ B(OTeF_5)_3 \longrightarrow 4\ BF_3 + 3\ Te(OTeF_5)_4 \qquad (1)$$

$$(1) + Xe(OTeF_5)_2 \xrightarrow{100\,^\circ C} Xe + Te(OTeF_5)_6 \qquad (2)$$

(2) is the largest oxide fluoride of tellurium so far reported, and, with respect to its mass, one of the heaviest of all inorganic molecular compounds.

Compound *(2)* is a colorless solid having the extremely high melting melting point of 242 °C; nevertheless, despite its high relative molecular mass of 1559.2 it can be sublimed at 110 °C/10^{-2} mbar. It crystallizes in at least two forms [triclinic $P\bar{1}$, $a = 9.096(2)$, $b = 9.132(2)$, $c = 8.878(3)$ Å, $\alpha = 100.22(2)$, $\beta = 99.96(3)$, $\gamma = 115.41(2)°$, $Z = 1$; rhombohedral, $a = 10.524(2)$ Å, $\alpha = 50.09(2)°$, $Z = 1$], but in each case in a pure molecular lattice.

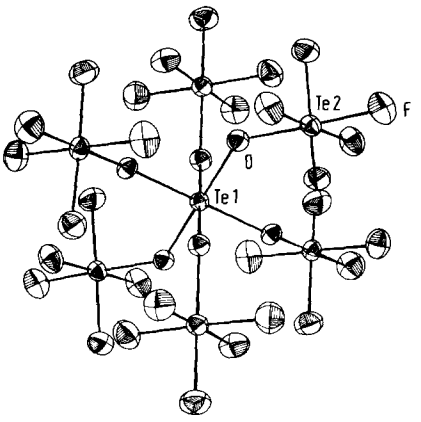


Fig. 1. Crystal structure of $Te(OTeF_5)_6$, triclinic modification, $R = 0.029$.

It can be seen in Figure 1 how the large $OTeF_5$ ligands perfectly occlude the central atom, due to the TeOTe angle of 138°. The high melting point naturally arises from the spherical shape of the molecule. Spatial compactness is much better here than in the case of $U(OTeF_5)_6$[4], since in the latter the U-O-Te angle reaches almost 180°.

On the other hand, $Te(OTeF_5)_4$ *(1)* reacts with XeF_2 and with F_2 to give a mixture of products.

$$(1) + XeF_2 \xrightarrow[-\,Xe]{20\,^\circ C} \begin{cases} cis\text{-}F_2Te(OTeF_5)_4 & (3) \\ FTe(OTeF_5)_5 & (5) \\ trans\text{-}F_4Te(OTeF_5)_2 & (6) \end{cases}$$

$$(1) + F_2 \xrightarrow{20\,^\circ C} \begin{cases} cis\text{-}F_2Te(OTeF_5)_4 & (3) \\ trans\text{-}F_2Te(OTeF_5)_4 & (4) \\ FTe(OTeF_5)_5 & (5) \end{cases}$$

The product *cis*-$F_2Te(OTeF_5)_4$ *(3)* (m.p. −12 °C, b.p. 63 °C/3 mbar) is shown by its ^{19}F spectrum to be the isomer of the already known *trans*-compound *(4)*: the spectrum shows two different pairs of $OTeF_5$ groups ($\delta_A = 51.5$, $\delta_{A'} = 51.6$, $\delta_{B_4} = \delta_{B'_4} = 39.7$). It is still unclear why only the *cis* isomer is formed in the reaction with XeF_2, while fluorination with elemental fluorine also gives the *trans* isomer.

The fivefold substituted compound $FTe(OTeF_5)_5$ *(5)* occurs as by-product (m.p. 48 °C, b.p. 90—100 °C/5 mbar), and, as expected, in the ^{19}F-NMR spectrum it shows different $OTeF_5$ signals in the intensity ratio 1:4 ($\delta_A = 48.0$, $\delta_{A'} = 48.1$, $\delta_{B_4} = \delta_{B'_4} = 36.9$).

Finally, an old structural problem could be solved by directed synthesis:

$$TeF_4 + Xe(OTeF_5)_2 \xrightarrow{20\,^\circ C} Xe + (trans)F_5TeO\text{–}TeF_4\text{–}OTeF_5\ (6)$$

$$+\ (cis)F_5TeO\text{–}\underset{\displaystyle O}{\underset{|}{TeF_4}}\ \ (7)$$
$$\qquad\qquad\qquad

be separated by fractional crystallization. In the ^{19}F-NMR spectrum the *trans* compound *(6)* shows equivalence of the four fluorine atoms ($\delta = 20.7$) while the *cis* compound *(7)* shows a typical A_2B_2 spectrum ($\delta_A = 27.7$, $\delta_B = 35.9$). Up to 150 °C the isomers do not transform into one other. Comparison of the physical data shows that *Robinson* in 1956 had indeed obtained exclusively the *cis* compound. The sulfur analog $F_5SO\text{-}SF_4\text{-}OSF_5$ is so far known only in the *cis* form[6].

All reactions proceed almost quantitatively, and we found no evidence for the frequently observed occurrence of polymeric $(TeOF_4)_n$[1, 7].

The new compounds are astonishingly stable toward hydrolysis. They have been unequivocally characterized (elemental analysis, mass spectrum, IR, Raman and NMR spectra); their data are in agreement with the given structures.

Received: July 12, 1977 [Z 786 IE]
German version: Angew. Chem. 89, 741 (1977)

CAS Registry numbers:
(1), 63599-48-4; *(2)*, 63569-52-8; *(3)*, 63598-93-6; *(4)*, 60788-81-0; *(5)*, 63599-47-3; *(6)*, 63569-53-9; *(7)*, 63598-94-7; $B(OTeF_5)_3$, 40934-88-1; $Xe(OTeF_5)_2$, 25005-56-5; TeF_4, 15192-26-4; XeF_2, 13709-36-9; F_2, 7782-41-4.

[1] *K. Seppelt*, Chem. Ber. *110*, 1470 (1977).
[2] *H. Pritzkow, K. Seppelt*, Angew. Chem. *88*, 846 (1976); Angew. Chem. Int. Ed. Engl. *15*, 771 (1976).
[3] *F. Sladky*, Monatsh. Chem. *101*, 1559, 1571 (1970).
[4] *K. Seppelt*, Chem. Ber. *109*, 1046 (1976); *L. K. Templeton, D. M. Templeton, N. Bartlett, K. Seppelt*, Inorg. Chem. *15*, 2720 (1976).
[5] *R. Campell, P. L. Robinson*, J. Chem. Soc. *1956*, 3454.
[6] *C. I. Merrill, G. H. Cady*, J. Am. Chem. Soc. *85*, 909 (1963).
[7] *F. Sladky, H. Kropshofer, O. Leitzke*, J. Chem. Soc. Chem. Commun. *1973*, 134.

Diastereoselective Synthesis of the Aporphine Alkaloid (+)-Cataline. Hydroxylation with Vanadium(V) Trifluoride Oxide[**]

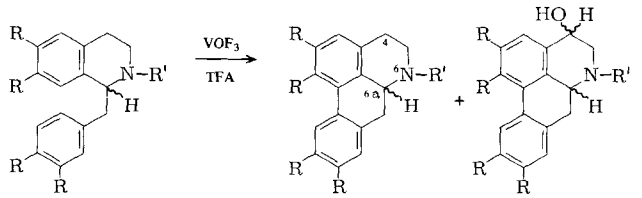
By *Johannes Hartenstein* and *Gerhard Satzinger*[*]

Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday

The use of vanadium(V) oxide compounds for the intramolecular oxidative coupling of benzylisoquinolines has recently claimed considerable preparative interest[1]. On oxidative coupling of (±)-laudanosine, (±)-*(1a)*, with VOF_3 (2 mol. equiv.) in trifluoroacetic acid (TFA) at −15 °C we surprisingly obtained racemic cataline (4-hydroxyglaucine), (±)-*(3a)*, in *ca.* 40 % yield: m.p. 152—153 °C; hydrobromide: m.p. 212—215 °C (dec.)[2, 3]. Small amounts of (±)-glaucine, (±)-*(2a)*, could also be identified[1].

Careful chromatographic investigation of the reaction product showed that practically only one of the two possible diastereomeric pairs of *(3a)* had been formed.

Similarly, in the reaction of (±)-tetrahydropapaverine, (±)-*(1b)* with VOF_3 in trifluoroacetic acid, after chromatography of the reaction product on basic aluminum oxide (Activity III) with chloroform/triethylamine (99/1, v/v) as eluent we obtained not only (±)-norglaucine, (±)-*(2b)* [yield *ca.* 30 %; hydrobromide: m.p. 252—253 °C (dec.)] but also (±)-*N*-norcataline, (±)-*(3b)*[2] [m.p. 93—95/152—160 °C (ether), yield



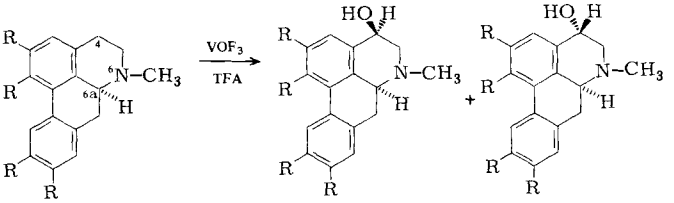
(±)-*(1a)*, (±)-*(1b)* (±)-*(2a)*, (±)-*(2b)* (±)-*(3a)*, (±)-*(3b)*

(a), R' = CH_3; *(b)*, R' = H
R = CH_3O

38 %, trifluoroacetate: m.p. 200—205 °C (dec.); *O,N*-diacetyl-(±)-*(3b)*: m.p. 194—196 °C (ether)].

Use of optically active (−)-tetrahydropapaverine, (−)-*(1b)*[4], led to (+)-*N*-norglaucine, (+)-*(2b)*, and (+)-*N*-norcataline, (+)-*(3b)*, (see Table 1).

Concerning the mode of formation of the 4-hydroxyporphines of type *(3)* under the reaction conditions mentioned we have carried out the reaction of (+)-glaucine, (+)-*(4)*, and of (−)-glaucine with VOF_3 (2 mol. equiv.) in trifluoroacetic acid between −15 °C and room temperature, and likewise *via* regio- and stereoselective reaction obtained (+)-cataline, (+)-*(5)*, and (−)-cataline, respectively, in *ca.* 50 to 60 % yield; $[\alpha]_D^{22} = +139.7$ and $-147.7°$, respectively ($c = 1$, $CHCl_3$) (see Table 1).



(+)-*(4)* (+)-*(5)* (+)-*(6)*

6a-H: α-Position
R = CH_3O

On chromatographic separation of the reaction product on basic aluminum oxide (Activity III) small amounts (< 2 % yield) of the respective diastereomeric *cis*-4-hydroxyaporphine, (+)-*(6)*, and its antipode could also be isolated and characterized (see Table 1).

In contrast to the smooth 4-hydroxylation with VOF_3, reaction of glaucine with $Pb(OAc)_4$ in glacial acetic acid at room temperature[6] leads mainly to the oxoaporphine *O*-methylatheroline.

Table 1. Some data for compounds (+)-*(2b)*, (+)-*(3b)*, (+)-*(5)* and (+)-*(6)* and their derivatives.

(+)-(6a*S*)-*(2b)*, NMR ($CDCl_3$): $\delta = 6.66$ (8-H, s), 6.80 (3-H, s), 8.19 (11-H, s); hydrobromide: m.p. 246—248 °C (248—250 °C [5a]), $[\alpha]_D^{22} = +97.3°$ ($c = 1$, MeOH) (+99° ($c = 1$, MeOH) [5a]); *N*-acetyl-(+)-*(2b)*: m.p. 185—186 °C (173—174 °C [5b]), $[\alpha]_D^{22} = +356.3°$ ([α]$_D$ = 367° ($c = 0.5$, EtOH) [5b])

(+)-(4*S*,6a*S*)-*(3b)*, NMR ($CDCl_3$): $\delta = 4.52$ (4-H, m, unresolved), 6.73 (8-H, s), 6.89 (3-H, s), 8.10 (11-H, s); m.p. 160—162 °C (EtOH), $[\alpha]_D^{22} = +106.7°$ ($c = 1$, $CHCl_3$); *O,N*-diacetyl-(+)-*(3b)*: m.p. 235—236 °C, $[\alpha]_D^{22} = +286.3°$ ($c = 1$, $CHCl_3$)

(+)-(4*S*,6a*S*)-*(5)*, NMR ($CDCl_3$): $\delta = 2.60$ (N—CH_3, s), 4.47 (4-H, dd, unresolved, X part of an AMX system), 6.72 (8-H, s), 6.92 (3-H, s), 8.03 (11-H, s), m.p. 180—182 °C

(+)-(4*R*,6a*S*)-*(6)*, NMR ($CDCl_3$): $\delta = 2.43$ (N—CH_3, s), 4.80 (4-H, dd, resolved, AMX system with $J_{AM} = 10.7$, $J_{AX} = 6.2$, $J_{MX} = 9.5$ Hz), 6.68 (8-H, s), 7.04 (3-H, s), 8.03 (11-H, s), m.p. 188—189 °C, $[\alpha]_D^{22} = +97.3°$ ($c = 1$, $CHCl_3$)

[*] Dr. J. Hartenstein [+], Dr. G. Satzinger
Gödecke Forschungsinstitut, Chemische Forschung und Entwicklung
Postfach 569, D-7800 Freiburg (Germany)
[+] Author to whom correspondence should be addressed.
[**] We thank *G. Pohlmann* for careful experimental assistance.

Experimental

(+)-Cataline, (+)-*(5)*: A solution of (+)-*(4)* (1 g) in trifluoroacetic acid (TFA) is treated dropwise with stirring at −15 °C with a solution of VOF_3 (0.7 g) in TFA (25 ml) (deep blue to red-violet coloration). The mixture is stirred for 2 h at −15 to −10 °C and, after removal of the cold-bath, for a further 1 h at room temperature. The TFA is then removed at 20 °C/70 torr and the residue treated with cold aqueous NH_3 solution and extracted with $CHCl_3$. After drying over Na_2SO_4 and removal of solvent the residue is taken up in ether and filtered. Subsequent crystallization affords 646 mg (61 %) (+)-*(5)*.

Received: June 23, 1977 [Z 784 IE]
German version: Angew. Chem. *89*, 739 (1977)

CAS Registry numbers:

(±)-*(1a)*, 1699-51-0; (±)-*(1b)*, 26642-09-1; (−)-*(1b)*, 4747-98-2; (±)-*(2a)*, 5630-11-5; (±)-*(2b)*, 39945-40-9; (±)-*(2b)*·HBr, 63569-46-0; (+)-*(2b)*, 21848-62-4; (+)-*(2b)*·HBr, 63599-49-5; (+)-*(2b)* *N*-acetyl deriv., 14787-63-4; (±)-*(3a)*, 57236-98-3; (±)-*(3a)*·HBr, 63569-47-1; (±)-*(3a)* acetate, 63598-88-9; (±)-*(3b)*, 63569-48-2; (±)-*(3b)*·HBr, 63569-49-3; (±)-*(3b)* Trifluoroacetate, 63569-50-6; (±)-*(3b)* *O,N*-diacetyl deriv., 63569-51-7; (+)-*(3b)*, 63598-89-0; (+)-*(3b)* *O,N*-diacetyl deriv., 63598-90-3; (+)-*(4)*, 475-81-0; (−)-*(4)*, 38325-02-9; (+)-*(5)*, 38764-84-0; (+)-*(5)* acetate, 38726-63-5; (−)-*(5)*, 63598-91-4; (+)-*(6)*, 63598-92-5; VOF_3, 13709-31-4

[1] *S. M. Kupchan, Om P. Dhingra, Chang-Kyu Kim*, J. Org. Chem. *41*, 4049 (1976), and literature cited therein.

[2] All the compounds synthesized were characterized by IR, NMR, MS, and partly by elemental analysis. Yields refer to crystallized products.

[3] a) (+)-Cataline, (+)-*(5)*, was isolated from *Glaucium Flavum Cr. var. Vestitum*; *I. Ribas, J. Sueirasu, L. Castedo*, Tetrahedron Lett. *1972*, 2033. b) Our synthesis of cataline was carried out at the beginning of 1974; *J. Hartenstein, G. Satzinger*, DOS 2625116.1 (1976), Goedecke AG; c) *D. Hoshino, H. Hara, M. Ogawa, B. Umezana* have reported an alternative synthetic entry to (±)-cataline: J. Chem. Soc. Chem. Commun. *1975*, 306; Chem. Pharm. Bull. (Japan) *23*, 2578 (1975); d) Acetylation affords the acetate having m.p. 169—170 °C. For (+)-catalin acetate a melting point of 91—92 °C has been quoted [3a].

[4] *H. Corrodi, E. Hardegger*, Helv. Chim. Acta *39*, 889 (1956).

[5] a) *M. Tomita, S.-T. Lu, S.-J. Wang, C.-H. Lee, H.-T. Shih*, Yakugaku Zasshi *88*, 1143 (1968); Chem. Abstr. *70*, 48850b (1969); b) *C. Casagrande, G. Ferrari*, Farmaco *25*, 442 (1970).

[6] *L. Castedo, R. Suan, A. Mourino*, Heterocycles *3*, 449 (1975).

$Co_5(CO)_{11}(PR_2)_3$, A Novel Type of Pentanuclear Cluster[**]

By *Egbert Keller* and *Heinrich Vahrenkamp*[*]

The reaction of complexes of secondary phosphanes with π-allyl complexes involving elimination of propene has previously led to phosphorus-bridged dinuclear and trinuclear complexes containing metal-metal bonds[1]. We have now tried to utilize this reaction scheme for the synthesis of a compound containing a Co—Ni bond. On reacting η^3-$C_3H_5Co(CO)_3$ with $(CO)_3Ni—PMe_2H$ we surprisingly obtained the pentanuclear cobalt cluster $Co_5(CO)_{11}(PMe_2)_3$ *(1)*. The mechanism of formation of this product is unclear; its formation is, however, consistent with our observation[1] that the aggregation of polynuclear base-bridged complexes increases with decreasing number of terminal ligands.

The composition and structure of the new compound *(1)*[2] could be unequivocally determined only by a crystal structure analysis[3]. As seen in Figure 1, the arrangement of the cobalt atoms has to be described as an edge-bridged trigonal pyramid in which the lengths of the Co—Co bonds in the central $Co_3(CO)_6$ unit are 2.41—2.47 Å, of those bridged by phosphorus to the outer Co atoms 2.76—2.81 Å, and of the unbridged Co—Co bonds 2.89 and 2.92 Å. The nonbonding Co···Co distance is 3.21 Å.

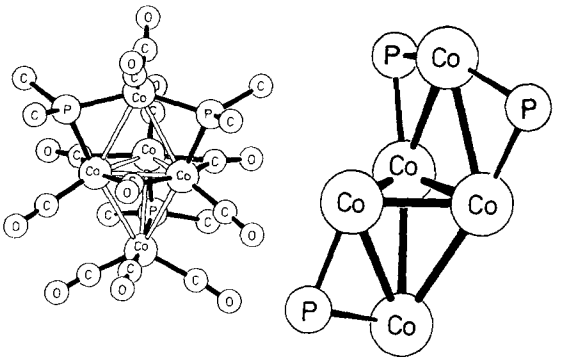
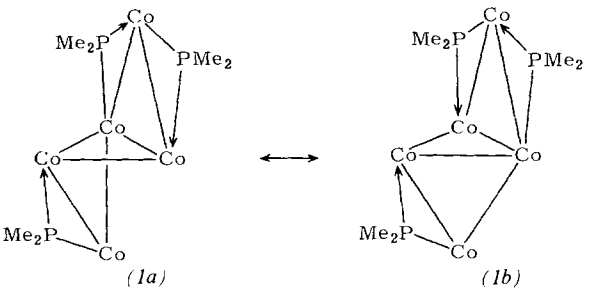


Fig. 1. Molecular structure (left) and heavy-atom skeleton (right) of $Co_5(CO)_{11}[P(CH_3)_2]_3$ *(1)*.

The structure and bonding of *(1)* are in many respects unusual. Firstly, *(1)* is the first Lewis-base-bridged cluster containing more than four metal atoms[4]. Further, such an edge-bridged trigonal pyramid in pentanuclear clusters is new; previously only the trigonal bipyramid[4, 5], the tetragonal pyramid[4, 6], and the double triangle[7] have been observed. Finally, the metal-metal bonds in *(1)* are explainable neither by simple application of the 18-electron rule nor by the skeleton electron counting method[8]. Only the valence bond notation with the two resonance formulas *(1a)* and *(1b)* provides a somewhat acceptable picture of the bonding. It gives all cobalt atoms the krypton configuration and assigns the bond order $^1/_2$ to the unbridged Co—Co bonds. It is then understandable that these two bonds are distinctly longer than normal unbridged Co—Co bonds.



The structure of *(1)* is a further example showing that phosphorus bridging leads to unusual polynuclear complex geometries[1, 9]. A systematization of these geometries, however, requires the discovery of further examples.

Experimental:

A mixture of $(CO)_3Ni—PMe_2H$ (4.0 g, 20 mmol) and η^3-$C_3H_5Co(CO)_3$ (3.7 g, 20 mmol) is stirred for 1 d without solvent. 280 ml of gas (propene, CO) is evolved. The highly viscous oil remaining after removal of 1.9 g of volatile reaction products (mainly $Ni(CO)_4$) is extracted with benzene (20 ml) and the extract chromatographed on a silica gel column (2 × 100 cm). Initial elution with benzene/hexane (1:4) gives a dark-green compound which has not yet been identified. Next, with benzene/hexane (1:2) a dirty-green fraction is obtained which after concentration by evaporation and subsequent slow recrystallization from benzene affords 220 mg (7 %) of black *(1)*, m.p. 166—167 °C (dec.).

Received: July 8, 1977 [Z 782 IE]
German version: Angew. Chem. *89*, 738 (1977)

[*] Prof. Dr. H. Vahrenkamp, Dipl.-Chem. E. Keller
Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the University Computing Center at Freiburg.

CAS Registry numbers:

(1), 63588-51-2; $(CO)_3Ni—PMe_2H$, 63548-46-9; η^3-$C_3H_5Co(CO)_3$, 12144-85-3

[1] *B. C. Benson, R. Jackson, K. K. Joshi, D. T. Thompson*, Chem. Commun. *1968*, 1506; *E. Keller, H. Vahrenkamp*, Chem. Ber. *110*, 430 (1977); Angew. Chem. *89*, 568 (1977); Angew. Chem. Int. Ed. Engl. *16*, 542 (1977).

[2] Correct elemental analyses, ^1H- and ^{31}P-NMR, IR, and mass spectra were obtained.

[3] Monoclinic, $P2_1/c$, $Z=4$; $a=9.974(4)$, $b=15.192(2)$, $c=18.981(3)$ Å, $\beta=105.79(3)°$; 3617 reflections corrected for absorption, $R=0.041$.

[4] Cf. *P. Chini, G. Longoni, V. G. Albano*, Adv. Organomet. Chem. *14*, 285 (1976); *H. Vahrenkamp*, Struct. Bonding *32*, 1 (1977).

[5] *C. R. Eady, B. F. G. Johnson, J. Lewis, B. E. Reichert, G. M. Sheldrick*, J. Chem. Soc. Chem. Commun. *1976*, 271.

[6] *K. Jödden, H. G. von Schnering, H. Schäfer*, Angew. Chem. *87*, 594 (1975); Angew. Chem. Int. Ed. Engl. *14*, 570 (1975).

[7] *H. Vahrenkamp, L. F. Dahl*, Angew. Chem. *81*, 152 (1969); Angew. Chem. Int. Ed. Engl. *8*, 144 (1969).

[8] *K. Wade*, Adv. Inorg. Chem. Radiochem. *18*, 1 (1976).

[9] *R. J. Haines, R. Mason, J. A. Zubieta, C. R. Nolte*, J. Chem. Soc. Chem. Commun. *1972*, 990.

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Polymerizations proceeding *via* free radicals and initiated by light have become increasingly important in recent years owing to their practical significance in the printing industry and in the production of printed circuits and coatings. *A. Ledwith* gives an account of the polymerizations of methyl methacrylate initiated by various amine-fluorenone combinations and light. [Photoinitiation of Polymerisation. Pure Appl. Chem. *49*, 431—441 (1977); 36 references]

[Rd 970 IE]

Thiols (mercaptans), as all chemists know, have an extremely unpleasant odor. This repulsive property may have precluded a thorough study of this class of compounds, although no organism is able to live without them. In a review, *A. Ohno* and *S. Oae* compare and contrast the physical properties of the thiols with those of their oxygen analogs, describe the syntheses and reactions of thiols, and discuss some of their biological functions. [Thiols in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 119—187; 250 references]

[Rd 964 IE]

Thiocarbonyl and carbonyl groups differ in the following properties: 1) The π electrons of a thiocarbonyl group are more strongly localized at the sulfur than the π electrons of a carbonyl group at the oxygen. The thiocarbonyl C atom therefore carries a greater positive charge than the carbonyl C atom.—2) Unpaired electrons on the thiocarbonyl sulfur are more readily removed than those on the carbonyl oxygen, *i.e.* the thiocarbonyl group is more easily ionized than the carbonyl group.—3) The thiocarbonyl group has a greater volume than the carbonyl group.—*A. Ohno* compares the reactions of thiocarbonyl and carbonyl compounds from this vantage point. [Thiones in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 189—229; 145 references]

[Rd 965 IE]

Tellurophene *(1)* and related compounds is the title of a survey by *F. Frinquelli, G. Marino*, and *A. Taticchi*. The term "related compounds" not only covers derivatives of tellurophene but also applies to furan, thiophene, and selenophene,

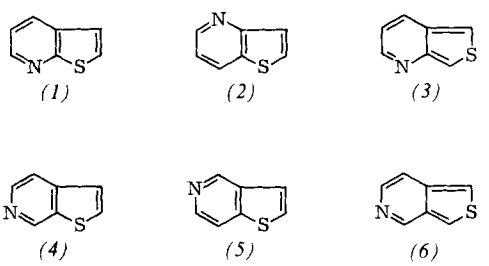


(1)

whose properties are compared quantitatively with those of tellurophene. [Tellurophene and Related Compounds. Adv. Heterocycl. Chem. *21*, 119—173 (1977); 109 references]

[Rd 976 IE]

Thienopyridines, *i.e.* compounds of type *(1)* to *(6)*, command theoretical interest as systems having one ring with a surfeit of π electrons and the other with a deficiency of π electrons. Numerous substances of this class have also been synthesized in the search for new pharmaceuticals; apart from derivatives of type *(1)* and *(2)*, which occur in high-sulfur oil shales,



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

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

thienopyridines have not yet been found in nature. *J. M. Barker* has written a review of the syntheses, reactions, and properties of these compounds. [The Thienopyridines. Adv. Heterocycl. Chem. *21*, 65—118 (1977); 150 references]

[Rd 975 IE]

Chronologie Chemie 1800—1970 (Chronology of Chemistry 1800—1970). By *S. Neufeldt*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., vii, 359 pp., 19 figs., 4 tables, linen, DM 78.—.

Neufeldt's "Chronology of Chemistry 1800—1970" will be welcomed both by chemists and by historians of science. It is a wide-ranging reference work standing half-way between a presentation of the history of chemistry and a chronological tabulation of findings and discoveries. It should be found in every school library, in every library of a chemical college or research institute, and on the desks of science historians, teachers and lecturers of chemistry.

Dates provide the main arrangement of the most important discoveries, theories, syntheses, processes, and apparatus (as well as occasionally the more important institutions), and they also serve for crossreferences. In each section arranged under a year the names of the innovators as subtitle are picked out in bold print, while the innovation itself is presented in three to eighteen lines of text and is emphasized within the text by an italicized keyword. The events described are "characterized by their content and nature, and are provided with references to previous knowledge as well as their importance; laws and rules are formulated, formulas and equations are written out wherever possible, and synthesis routes are indicated" (page V). There follow brief bibliographic references to the original publications, to previous work mentioned in the text, and to directly dependent subsequent innovations and further advances; but unfortunately only a few references to historical papers or books occur. Eighteen "highlights" have been extracted from the chronological arrangement, and for those Appendix I gives a detailed description with an illustration. "Important steps in the development of chemical nomenclature" are described in Appendix IV (why is *Cannizzaro*'s name missing from the item "1860 Karlsruhe Chemical Congress"?), which is divided into inorganic and organic chemistry; this gave the opportunity to mention *Lavoisier*'s contributions under the dates 1787 and 1789, whereas the date 1800 seems to have been a rather arbitrary choice for the starting point of chemistry proper.

Other Appendices contain the names of Nobel prizewinners for physics, chemistry, and physiology or medicine (each up to 1975) and the achievements for which the prize was awarded; the names of the scientists who bore or bear the order "Pour le mérite" for science and technology; chemical societies; a "Chronological list of a selection of the oldest scientific journals (up to 1900)", as well as a "Selection of (*s.c.* monographic) literature on the history of chemistry" (up to 1974).

No lexicological method is perfect, since it can never be applied to the whole material. It is somewhat confusing that the names of several persons are often given together as keywords under one date, persons who either made different contributions (*e.g.* 1800: *Ritter*, *Cruickshank*; electrolytic decomposition of water and cathodic separation of metals) or made advances that supplemented each other (*e.g.* 1934: *Butenandt*, *Marker* [1940], *Pincus* [1956]; isolation of crystalline progesterone, conversion of sapogenins into progesterone, and investigations on oral contraceptives, respectively). There are also other difficulties with the system, as in the organization of important institutions. For example, *e.g.* "1911: *A. v. Harnack* [the first President] and *O. Hahn* [the first postwar President after renaming]" as the keyword for the organization of the Kaiser-Wilhelm-Gesellschaft (Max-Planck-Gesellschaft).

The dating usually follows the date of appearance of the first publication, but here too there have been decisions that could lead to different dates and thus to confusion. X-Rays were discovered in December 1895; *Röntgen* submitted his work ("Vorläufige Mitteilung") on December 28th, and it was accepted by the Sitzungsberichte der Physicalisch-Medizinischen Gesellschaft in Würzburg of the year 1895, but the journal didn't appear before January 1896 (recorded in *Neufeldt*'s book under 1895); on November 19th, 1807 *Davy* reported the discovery of sodium and potassium before the Royal Society; the lecture was published as the first contribution in the Philosophical Transactions of 1808 (put by *Neufeldt* under 1808). In December 1938 *O. Hahn* and *F. Strassmann* discovered nuclear fission of uranium (why was *Strassmann*'s name not mentioned, especially since it was in fact he who provided the analytical proof?), but the paper appeared only on 6th January 1939 (listed by *Neufeldt* under 1939). Since *I. Noddack*'s paper of 1934 is listed in this section and recorded as the first reference to nuclear fission, the editorial comment in Naturwissenschaften 27 (No. 13) 1939 concerning her pretension printed there should have been noted together with this pretension itself.

The notions above are, however, minor criticisms that do not detract from the excellent total impression of this work, the contents of which are made accessible by author and subject indexes.

Fritz Krafft [NB 382 IE]

Atmospheric Chemistry. By *J. Heicklen*. Academic Press, London—New York 1976. 1st edit., xiv, 406 pp., numerous figures and tables, bound £ 27.00.

This book aims at giving a comprehensive account of the chemical processes taking place in the upper and lower atmosphere.

The structure of the atmosphere, its chemical composition in individual altitude zones, and the primary photochemical processes are first treated in the introductory chapter. The next two chapters deal with the chemical reactions in the upper atmosphere, *i.e.* the stratosphere, the mesosphere, and the ionosphere. Here the treatment follows essentially the view of the Brussels aeronomist *M. Nicolet*, with whom the author collaborated for many years. The theory is strongly emphasized, but unfortunately much less emphasis is given to the results of measurements, so that the impression is one of an uncritical treatment of the material.

The remaining two-thirds of the book deal with the problems of atmospheric pollution. After a chapter on the sources and the effects of atmospheric pollutants there is a section on the chemical processes taking place in the oxidation of hydrocarbons. Three chapters follow on the chemistry of chemical smog, on the reactions of ozone and singlet oxygen, and on the homogeneous oxidation of sulfur dioxide. Two concluding chapters treat very briefly the possible processes of aerosol formation and measures for limiting the emission of pollutants.

In the general representation of this material *Heicklen* writes overwhelmingly from the standpoint of reaction kinetics. This has the advantage that the reaction mechanisms are described in detail, but on the other hand a number of other important aspects are dealt with too briefly. The biochemical sources of trace atmospheric gases, the transport of trace constituents in the troposphere, and the chemical composition and distribution of atmospheric aerosols to mention only a few topics, are not treated. Furthermore, the author cannot be absolved from the charge of using some obsolete material. On the subject of the distribution of CO with geographic latitude more extensive and more reliable data are now available;

the (unpublished) first results from 1969, which are given on page 161, are therefore superseded.

The book contains remarkably few printing errors and can be recommended to all those who would like a detailed account of atmospheric gas reactions. The price is reasonable.

Peter Warneck [NB 380 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Grundlagen der enzymatischen Analyse. Edited by *H. U. Bergmeyer* in collaboration with *K. Gawehn*. Verlag Chemie, Weinheim 1977. xvi, 260 pp., paper, DM 44.—.—ISBN 3-527-25677-6

Characterization of Metal and Polymer Surfaces. Edited by *Lieng-Huang Lee*. Academic Press, New York 1977.
Vol. 1: Metal Surfaces. xiv, 517 pp., bound, $ 26.50.—ISBN 0-12-442101-6
Vol. 2: Polymer Surfaces. xv, 465 pp., bound, $ 24.00.—ISBN 0-12-442102-4

Advances in Photochemistry, Vol. 10. Edited by *J. N. Pitts, Jr., G. S. Hammond*, and *K. Gollnick*. John Wiley & Sons, New York 1977. ix, 475 pp., bound, $ 37.50.—ISBN 0-471-02145-8

Mass Spectrometry, Vol. 4. Senior Reporter: *R. A. W. Johnstone*. The Chemical Society, London 1977. xii, 357 pp., bound, DM 114.80. ISBN 0-85186-288-8—A volume in the series "Specialist Periodical Reports"

Interfacial Synthesis. Vol. 1: Fundamentals. Edited by *F. Millich* and *C. E. Carraher, Jr.* Marcel Dekker, New York 1977. xi, 298 pp., bound, SFrs. 113.—.—ISBN 0-8247-6372-6

IUPAC: 25th International Congress of Pure and Applied Chemistry (Jerusalem, 1975). Edited by *Y. Marcus* and *L. Ben-Dor*. Pergamon Press, Oxford 1977. 73 pp., bound, $ 18.75.—ISBN 0-08-020952-1

IUPAC: Marine Natural Products (Aberdeen, 1975). Edited by *R. H. Thomson*. Pergamon Press, Oxford 1976. 44 pp., bound, DM 28.—.—ISBN 0-08-021242-5

IUPAC: Colloquium Spectroscopicum Internationale—XVIII (Grenoble, 1975). Edited by *J. P. Robin*. Pergamon Press, Oxford 1976. pp. 45—126, bound, DM 28.—.—ISBN 0-08-021569-6

IUPAC: Industrial Waste Water and Wastes—2 (Stockholm, 1975). Edited by *B. Goransson*. Pergamon Press, Oxford 1977. pp. 135—209, bound, $ 35.00.—ISBN 0-08-020954-8(Y)/0-08-021057-0(R)

Inorganic Chemistry of the Main-group Elements, Vol. 4. Senior Reporter: *C. C. Addison*. The Chemical Society, London 1977. xi, 454 pp., bound, £ 26.00.—ISBN 0-85186-782-0.—A volume in the series "Specialist Periodical Reports"

Vom Wasser, Band 48. Issued by the Fachgruppe Wasserchemie in der Gesellschaft Deutscher Chemiker. Editor responsible for text: *W. Husmann*. Verlag Chemie, Weinheim 1977. viii, 322, A107 pp., bound, DM 98.—.—ISBN 0083-6915

Physikalische Methoden in der Chemie (Collective Authorship). Vol. 3 of "Ausgewählte Lehrabschnitte der Chemie". Edited by *L. Kolditz*. From the series "Studienbücherei". VEB Deutscher Verlag der Wissenschaften, Berlin 1977. 326 pp., bound, *ca.* DM 19.80.

Geometrie und elektronische Struktur von Molekülen. By *C. A. Coulson* (deceased). Vol. 53 of the series "taschentext". Verlag Chemie/Physik Verlag, Weinheim 1977. 103 pp., paper, DM 16.80.—ISBN 3-527-21044-X (Verlag Chemie); 3-876-64544-1 (Physik Verlag)

Fundamentals of Integrated GC-MS. Part III: The Integrated GC-MS Analytical System. By *B. J. Gudzinowicz, M. J. Gudzinowicz*, and *H. F. Martin*. Vol. 7 of "Chromatographic Science Series". Marcel Dekker, New York 1977. vii, 603 pp., bound, SFrs. 190.00.—ISBN 0-8247-6431-5

Organophosphorus Chemistry, Vol. 8. Senior Reporter: *S. Trippett*. The Chemical Society, London 1977. xi, 289 pp., bound, £ 22.00.—ISBN 0-85186-076-1—A volume in the series "Specialist Periodical Reports"

Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten (Maximale Arbeitsplatz-Konzentrationen). Edited by *D. Henschler*. Verlag Chemie, Weinheim. 5th instalment 1976/77. xxv, 111 pp., loose-leaf edition, DM 48.—.

Gmelin Handbuch der Anorganischen Chemie. Main work, System No. 31: Radium und Isotope. Supplementary volume 2: Element und Verbindungen. Springer-Verlag, Berlin 1977. xiv, 305 pp., bound, DM 651.—.—ISBN 3-540-93335-2

Gmelin Handbuch der Anorganischen Chemie. Supplementary work, Vol. 42: Borverbindungen. Part 11: Carborane 3. Springer-Verlag, Berlin 1977. xiv, 207 pp., bound, DM 493.—.—ISBN 3-540-93336-0

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone (06201) 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 11
November 1977
Pages 735 – 806

Fluorinated Isocyanates and Their Derivatives as Intermediates for Biologically Active Compounds

By Engelbert Kühle and Erich Klauke[*]

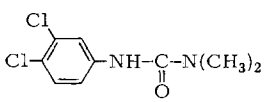
Dedicated to Professor Otto Bayer on the occasion of his 75th birthday

Fluorinated aromatic isocyanates are valuable intermediates for the production of herbicides and insecticides. Unexpected rearrangements during the synthesis of 2-(trifluoromethyl)phenyl isocyanates provide an entry to *N*-trifluoromethylaminobenzoyl fluorides, a novel class of compounds having fungicidal properties. Carbamoyl fluorides, the products of HF addition to isocyanates, undergo ready sulfenylation. Use of these intermediates for the synthesis of *N*-sulfenylcarbamate insecticides led to the discovery of the new principle of detoxification of carbamates by sulfenylation.

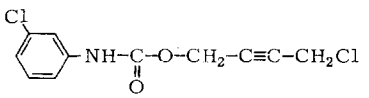
1. Introduction

The active constituents of modern pesticides are not all esters of phosphorus acids—derivatives of carbonic acid also play a considerable role. This very extensive class of compounds is dominated by those derived from aliphatic or aromatic isocyanates.

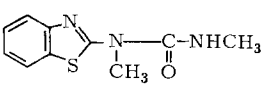
Examples of compounds having pronounced general or selective herbicidal activity[1] are found in the 3,4-disubstituted *N*-alkyl-*N'*-phenylurea derivative *(1)*, the *N*-phenylurethane *(2)*, and the urea *(3)* bearing heterocyclic substituents.



(1)

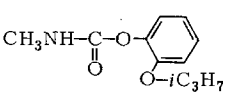


(2)

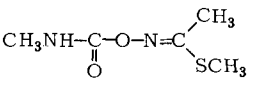


(3)

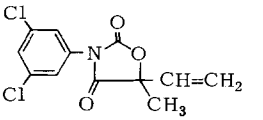
Like phosphoric esters, aryl *N*-methylcarbamates, *e.g. (4)*, and *O*-(*N*-methyl-carbamoyl)oximes *(5)* act as strong cholinesterase inhibitors and are used as insecticides because of this property[2].



(4)



(5)



(6)

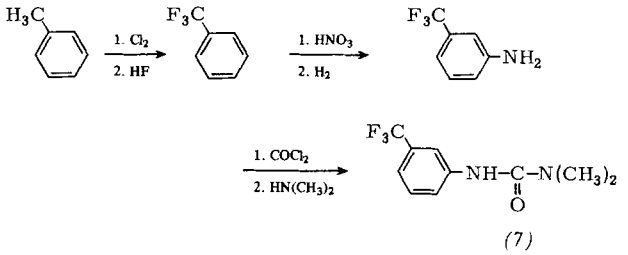
Finally, the existing range of fungicides has recently been extended by specific botrytis agents, such as *(6)*, which are all derived from 3,5-dichlorophenyl isocyanate[3].

2. Fluorinated Isocyanates as Intermediates for Herbicides

Several years ago *N*,*N*-dimethyl-*N'*-[3-trifluoromethylphenyl]urea (common name Fluometuron)*(7)* became known as a derivative of a fluorinated isocyanate and has meanwhile

[*] Dr. E. Kühle, Dr. E. Klauke
Bayer AG, Zentrale Forschung WHL
D-5090 Leverkusen (Germany)

become a market leader among cotton herbicides, particularly in the USA and the USSR. Compound *(7)* is accessible from toluene by classical methods[1].

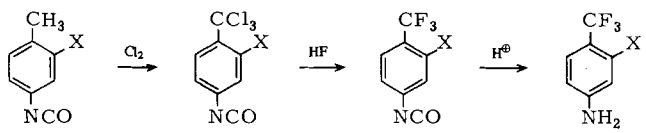


(7)

The isomers of the *para* and *ortho* series cannot be synthesized in this way.

The classical protecting group for a primary amine is an acyl group; the subsequent reactions will determine whether it should be an acetyl group (*e.g.* for nitration) or a phthaloyl group (*e.g.* for halogenations). In recent years the smallest possible "acyl group", *viz.* the carbonyl group, has found increasing application in chlorinations[4], *i.e.* the primary amine is protected in the form of the isocyanate on chlorination.

Starting from readily available 4-tolyl- or 3-chloro-4-tolyl isocyanate *(8)* side-chain chlorination affords the corresponding 4-trichloromethylphenyl isocyanate *(9)* and subsequent chlorine/fluorine exchange with anhydrous hydrofluoric acid furnishes the required 4-(trifluoromethyl)phenyl isocyanates *(10)*[5]. If desired, 4-trifluoromethylanilines *(11)* can be liberated from *(10)* by acid hydrolysis.



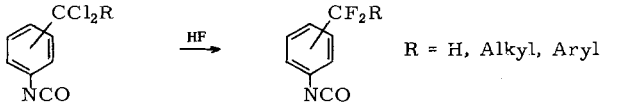
(8) *(9)* *(10)* *(11)*

X = H, Cl

The reaction scheme is not applicable to the *ortho* series since the action of hydrofluoric acid then leads to rearrangement (cf. Section 3). 2-(Trifluoromethyl)phenyl isocyanate can be produced from the trichloromethyl compound by direct fluorination with SbF_3[6].

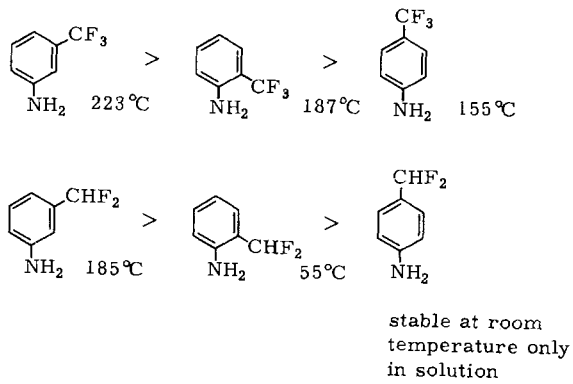
Side-chain fluorination with an excess of hydrofluoric acid proceeds very smoothly and almost quantitatively at temperatures between 0 and 60 °C, depending upon the other substituents present. Operation between definite temperature limits and appropriate dosing of the anhydrous hydrofluoric acid permit directed synthesis of intermediates of chlorine/fluorine exchange; products are the dichloromonofluoro- and monochlorodifluoro derivatives.

Apart from the CCl_3 group, the CCl_2R moiety with R = H, alkyl, or aryl can also be fluorinated with hydrofluoric acid[7].



Suitable starting compounds for these intermediates are substituted benzylidene chlorides or the products of reaction between benzaldehydes, acetophenones, and benzophenones with PCl_5[8].

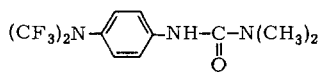
It is appropriate at this juncture to compare the stability of CF_3- and CHF_2-substituted anilines. The temperature of incipient decomposition is given in Scheme 1 as a measure of thermal stability (determined by differential thermal analysis).



Scheme 1

Potential intermediates for herbicides are not limited to isocyanates having fluoroalkyl groups linked directly to the phenyl ring but also include those in which a heteroatom such as oxygen or sulfur is located between the fluoroalkyl and phenyl units.

N,N-Dimethyl-*N'*-[4-bis(trifluoromethyl)aminophenyl]-urea (with an inserted nitrogen atom) exhibits only slight herbicidal activity[8a].

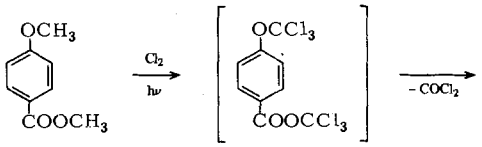


Among the trifluoromethoxyphenyl and trifluoromethylthiophenyl isocyanates, we have concerned ourselves primarily with the 3- and 4-substituted compounds containing, in some cases, a further chlorine atom in position 3 and 4, respectively.

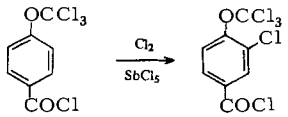
In the following Sections we shall consider the synthesis of three selected isocyanates whose dimethylureas exhibit a highly selective herbicidal action in various plant cultures.

2.1. Synthesis of *N'*-[3-Chloro-4-(trifluoromethoxy)phenyl]-*N,N*-dimethylurea *via* the Isocyanate

4-Hydroxybenzoic acid, readily accessible on an industrial scale by the Kolbe-Schmidt reaction, is converted directly into methyl 4-methoxybenzoate *(12)* by methylation. Per-



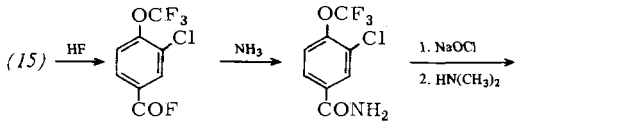
(12) *(13)*



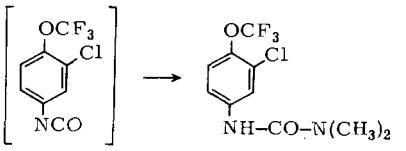
(14) *(15)*

chlorination of the side chain thence affords the thermally unstable ester *(13)* which undergoes stabilization to 4-trichloromethoxybenzoyl chloride *(14)* by elimination of phosgene[8b]. Subsequent ring chlorination in the presence of a catalyst then leads to the 3-chloro-4-(trichloromethoxy) derivative *(15)*. An appropriate catalyst is $SbCl_5$ which also has a catalytic action in the subsequent fluorination step.

Thus *(15)* affords 3-chloro-4-trifluoromethoxybenzoyl fluoride *(16)* which in turn cleanly gives the benzamide *(17)* with ammonia. Treatment of *(17)* with NaOCl in an alkaline medium at 10 to 20 °C is conducted as a one-pot reaction; the desired urea *(18)* is then formed directly in high purity *via* Hoffmann degradation in the presence of dimethylamine at about 40—50 °C. There is no need to isolate the isocyanate[9].



(16) *(17)*



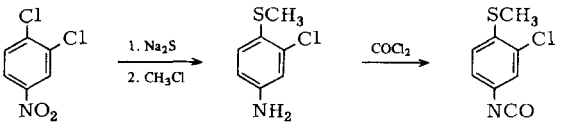
(18)

The urea derivative *(18)*[10,11] shows very good selective herbicidal activity on pre-emergence or post-emergence application to cotton. At an application of 1 kg/ha this product is superior to other ureas, especially towards grasses. Moreover the compound shows good selectivity in corn, potatoes, sorghum, and peanuts.

The acute toxicity of compound *(18)* can be regarded as low or insignificant. The LD_{50} values for oral application to rats is 797 mg/kg; maximum amounts and concentrations, respectively, were tolerated without symptoms on dermal and aerosol exposure. The compound is without irritant properties on skin and mucous membranes. No cumulative toxic effects were observed in subacute animal experiments on application with feed or as aerosols.

2.2. Synthesis of *N'*-[3-Chloro-4-chlorodifluoromethylthiophenyl]-*N*,*N*-dimethylurea *via* the Isocyanate

In a one-pot reaction, 3,4-dichloro-1-nitrobenzene *(19)* is first transformed into 3-chloro-4-mercaptoaniline by treatment



(19) *(20)* *(21)*



(22) *(23)*

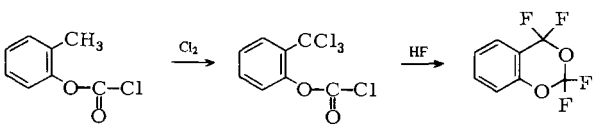
with sodium sulfide and methylated directly with methyl chloride to give the 4-methylthio compound *(20)*. The isocyanate *(21)* obtained therefrom is chlorinated in the side chain, fluorinated at room temperature to give the desired chlorodifluoromethylthio compound *(22)*, and converted into the urea *(23)* with dimethylamine.

The urea *(23)*[12], known as Thiochloromethyl, is used for weed control in sown and transplanted rice. It is well tolerated by the rice, being mainly active against Dicotyledoneae and algae. The product can be used in both the pre-emergence and the post-emergence modes. This urea is also very suitable for use as a component of commercially available grass herbicides based on thiolcarbamates (*e.g.* Benzthiocarb)[13]. The 4-trifluoromethylthio compound analogous to the urea *(23)* shows the same range of activity, but requires more involved production technology since the last chlorine atom can only be replaced by fluorine under pressure (side reactions)[14].

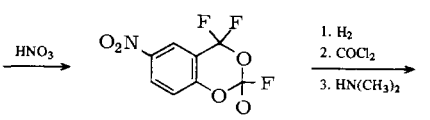
The active component *(23)* has a moderate acute oral toxicity in laboratory animals (*e.g.* LD_{50} oral, rat = 432 mg/kg). No symptoms were observed on application of 500 mg/kg to the skin of rats. High concentrations were tolerated without symptoms for exposure periods of four hours. The compound has no damaging effect on the skin of rabbit and man, or on the eye of a rabbit. No cumulative toxic effects were observed in subacute animal experiments on application with feed or as an aerosol.

2.3. Synthesis of *N*,*N*-Dimethyl-*N'*-(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)urea *via* the Isocyanate

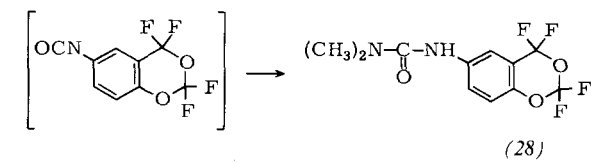
As the third example, a herbicidal urea will be presented which contains a phenyl group with a difluoromethyleneoxydifluoromethyleneoxy bridge. In order to synthesize the urea *(28)*, *o*-cresol is chlorinated in the form of its chloroformate *(24)* to give the trichloromethyl compound *(25)*. On subsequent fluorination *(25)* cyclizes to the stable benzodioxine derivative *(26)*, which can be cleanly nitrated in position 6 to give *(27)*[15]. Further steps of the process leading to the urea *(28)* are straightforward.



(24) *(25)* *(26)*



(27)



(28)

This urea also shows good selectivity in several crops, *e.g.* in potatoes (4 kg/ha) and in cotton (2—4 kg/ha)[16].

2.4. Other Fluorinated *N,N*-Dimethyl-*N'*-phenylureas Having Herbicidal Activity

Section 2 will now close with a brief characterization of other ureas, classified according to their fluorine-containing substituent.

CF_3 Substitution[5]: The active compounds of this series, exhibiting a good selective action in cotton, should be viewed in relation to Fluormeturon *(7)*. The *para* isomer has roughly the same activity, while the 3-chloro-4-trifluoromethylphenyl derivative has a somewhat superior action against weeds.

CF_2H Substitution[7, 17]: In contrast to the above series, the 4-chloro-3-difluoromethylphenyl derivative occupies the leading position in the scale of herbicidal efficacy; selectivities are present in cotton, peanuts, corn, and potatoes. The 3-chloro-4-difluoromethyl isomer can be used as a selective agent in corn and grain. The herbicidal activity of the 4-difluoromethyl derivative is only modest, probably owing to its instability; the *m*-isomer on the other hand, can be used in rape.

CF_3O Substitution[10, 11]: Apart from the urea *(18)*, which is significantly more active and also more reliable in its cotton selectivity than Fluometuron *(7)*, only the 3-chloro-4-chlorodifluoromethoxy compound has an action comparable with that of Fluometuron in cotton and corn. Surprisingly, the chlorine-free representatives of this series develop only a weak herbicidal activity.

CF_2HO Substitution[17a, 17b]: Among the compounds substituted in this way, mention should be made of the 3-chloro-4-difluoromethoxy derivative, which is superior to *(7)*, but less active than *(18)*, and is also less selective than *(18)* in cotton.

CF_3S Substitution[12, 14]: In this series too, the ring-chlorinated compounds have greater biological activity than the unchlorinated derivatives. However, crops are also affected adversely, with the result that rice is the only crop for which practical application is feasible. The best product is the above-mentioned urea *(23)*.

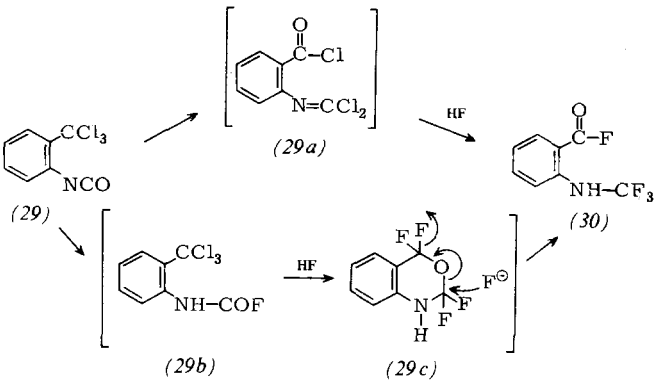
CF_2HS Substitution[17b]: The herbicidal activity of the 4-difluoromethylthio and the 3-chloro-4-difluoromethylthio compound is unusually strong; unfortunately their selectivities leave much to be desired.

Summarizing: in each of the series presented above, the compounds having the best herbicidal activity and greater selectivity are nearly always the ones bearing a chlorine atom in position 3 in addition to the fluorinated substituent in position 4.

3. 2-[*N*-Trifluoromethylamino]benzoyl Fluorides as Intermediates for Fungicides and Bactericides

As already mentioned, attempts to synthesize trifluoromethylphenyl isocyanates from the trichloromethyl compounds with anhydrous hydrofluoric acid fail in the *ortho* series. For instance, in the case of *(29)* a novel rearrangement involving oxygen migration gives *N*-trifluoromethylanthraniloyl fluoride *(30)*[17c] (Scheme 2).

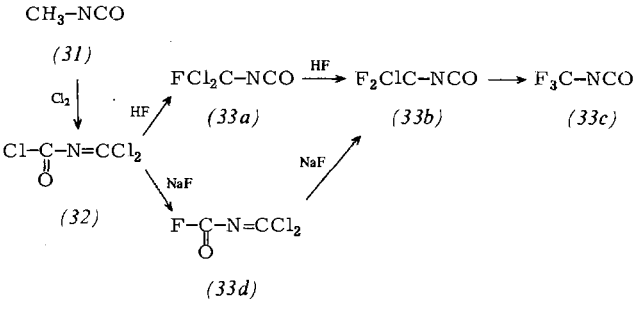
With regard to our discussion of Scheme 2, it should be mentioned that isomerization of *(29)* to *(29a)*, giving contents up to 50 %, can be accomplished merely by thermal treatment. Owing to the high temperatures employed in the production of *(29)*, there is always a certain amount of *(29a)* present



Scheme 2

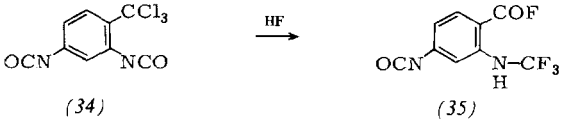
in *(29)*. This isomeric structure provides a ready explanation for the fluorination product *(30)* formed by chlorine/fluorine exchange and subsequent HF addition to the N=C double bond. Another interpretation of the reaction course involves a primary HF/isocyanate adduct, the carbamoyl fluoride *(29b)* having a strongly polarized carbonyl bond, which cyclizes to *(29c)* on chlorine/fluorine exchange [cf. the synthesis of the stable compound *(26)*]. In HF as reaction medium, $F^{\ominus}$ addition leads to ring opening and stabilization to give *(30)*.

If compound *(29)* is regarded as the phenylog of trichloromethyl isocyanate, CCl_3NCO, then the rearrangement shown in scheme 2 appears particularly surprising. Perchlorination of methyl isocyanate *(31)* does not give an isocyanate but exclusively the chlorocarbonyl isocyanide dichloride *(32)*[4]. Only on preparing the corresponding fluorinated products does re-isomerization occur to give isocyanates *(33a)*—*(33c)*. The direction of isomerization is the opposite of that in the phenylogous series.



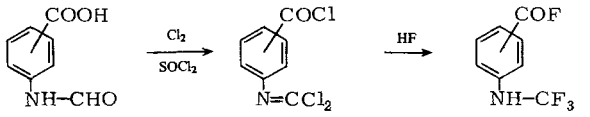
The monochlorinated compound should be mentioned as a curiosity—depending upon the fluorination reagent it can appear as *(33a)* or *(33b)*. Surprisingly, these two compounds are not in equilibrium with each other, and differ considerably in their physical properties.

The rearrangement *(29)*→*(30)* proceeds unaffected by other ring substituents. Thus, even 4-trichloromethyl-1,3-phenylene diisocyanate *(34)* rearranges with retention of an NCO group to *(35)*.



What do we know about the *N*-trifluoromethylaminobenzoyl fluorides of the *meta* and *para* series which cannot be synthesized in the same way?

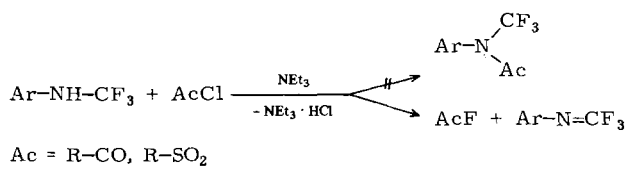
These isomers are accessible by a "classical" route starting from *m*- and *p*-aminobenzoic acids, which react in the form of their formyl compounds *(36)* with chlorine in thionyl chloride to form the chlorocarbonylphenyl isocyanide dichlorides *(37)*[18]. The products *(37)* yield the desired compounds *(38)* on treatment with hydrofluoric acid[19].



(36) *(37)* *(38)*

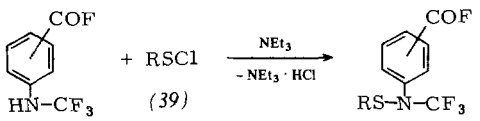
The basicity of the NH group in *N*-trifluoromethylaminobenzoyl fluorides is severely diminished by the electronegative CF_3 moiety. On the basis of their reactivity the compounds are better classified as "orthofluorides" of carbamic acids.

The *N*-trifluoromethylamino compounds form true salts with tertiary amines. However, they are of only very limited use as nucleophilic reactants. For instance, they can no longer be alkylated. On attempted acylation with acid chlorides of carboxylic and sulfonic acids in the presence of a tertiary amine they generally exert a fluorinating action. Acid fluorides are formed, while the *N*-trifluoromethylamines are transformed into isocyanide difluorides or their dimers[20].



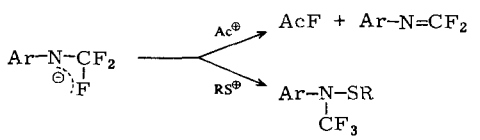
Ac = R–CO, $R–SO_2$

In contrast *N*-trifluoromethylaminobenzoyl fluorides *(38)* and sulfenyl chlorides *(39)* give the desired sulfenamides *(40)*[21] under the same conditions.



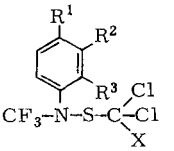
(38) *(39)* *(40)*

The remarkable behavior of the sulfenyl chlorides in this reaction can be adequately explained in terms of the concept of hard and soft acids and bases. The soft sulfenyl cation attacks the soft nitrogen atom of the *N*-trifluoromethylamine while hard acyl cations preferably react with the hard fluoride ion.



In view of the expected biological, and especially fungicidal activity of the reaction products, we have treated *N*-trifluoromethylaminobenzoyl fluorides with trichloromethane- and, in particular, dichlorofluoromethanesulfenyl chloride[22]. A selection of these intermediates is presented in Table 1[21].

Table 1. *N*-Sulfenylated aminobenzoyl fluorides of type *(40)*.

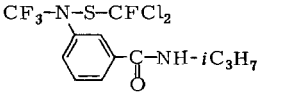


(40)

R^1	R^2	R^3	X	[°C/torr]
H	H	COF	Cl	148—151/13
H	H	COF	F	132—136/13
CF_3	H	COF	F	116—124/13
H	COF	H	F	118—125/11
Cl	COF	H	F	142—147/13
CH_3	COF	H	F	140—145/15
OCH_3	COF	H	F	160—167/13
COF	H	H	F	123—128/11
COF	Cl	H	F	155—158/27
COF	NO_2	H	F	128—129/0.15

These novel sulfenylaminobenzoyl fluorides *(40)* can be transformed into numerous acid derivatives. They can be readily hydrolyzed to the free carboxylic acids with formic acid while retaining the sulfenamide structure[23]. Moreover, a wide range of esters[24], thioesters, amides[25] and hydroxamic acids[26] have been examined since practically all the reaction products possess fungicidal, and in some cases also antimycotic and bactericidal properties.

In this context, attention should be directed to *N*-isopropyl-3-[*N*-dichlorofluoromethylthio-*N*-trifluoromethylamino]-benzamide *(41)*, which has a pronounced biological activity and a wide spectrum of fungicidal action[27]. The biological activity is directed predominantly towards Peronosporaceae. Field tests conducted over several years under conditions close to those encountered in practice revealed not only a high acute efficacy, but also certain eradicating action and a relatively long duration of action. Within the phytopathologically important group of the Peronosporaceae, compound *(41)* is active both towards Phytophthora species and towards fungi of the Bremia, Peronospora, Pseudoperonospora, and Plasmopara genera. Furthermore, several trials have also shown it to exhibit acaricidal side effects. Potential applications are shown in Table 2.



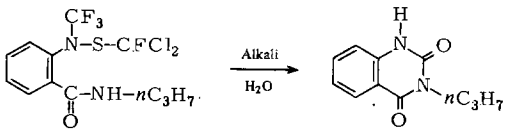
(41)

Table 2. Activity of compound *(41)* towards Peronosporaceae and other harmful fungi.

Fungus	Culture	Amount of *(41)* [kg/ha]	[%]
Phytophthora infestans	Potatoes	1.25	
	Tomatoes		0.05—0.1
Phytophthora parasitica	Eggplant (Aubergine)		0.08
Bremia lactucae	Lettuce		0.05—0.1
Peronospora destructor	Onions		0.15
Pseudoperonospora cubense	Cucumbers		0.05—0.1
Pseudoperonospora humuli	Hops		0.05—0.1
Plasmopara viticola	Grapevine		0.075—0.1
Alternaria spp.	Apples, Pears Tomatoes, Cabbage		0.075—0.1
Colletotrichum spp.	Vegetables, Coffee		
	Wine		0.05—0.1
Venturia spp.	Apples, Pears		0.075

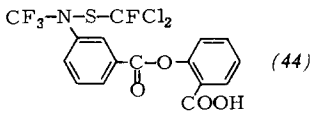
The oral LD_{50} of compound *(41)* is 3086 mg/kg for male rats. Application of 500 mg/kg to the skin of rats is tolerated without symptoms. The LC_{50} for four hours' exposure to an aerosol is 250 mg/m³ air. Compound *(41)* does not irritate the skin of rabbits, but does cause significant damage to the mucous membranes of the eye. No cumulative toxic effects were observed in rats after repeated oral administration or repeated aerosol exposure.

The isomer *(42)* shows the same spectrum of biological activity as compound *(41)*. Depending upon the quality of the active component, however, *(42)* may cause crop damage in the field. Combined gas chromatography/mass spectrometry showed that this compound can easily be degraded to 2,4-dioxo-3-propyltetrahydroquinazoline *(43)* by alkali. Admixture of only 2% of compound *(43)*[28], already known as a herbicide, to pure *(42)* has a phytotoxic effect.



(42) *(43)*

Surprising biological activity is found in aryl esters of *N*-sulfenylated *N*-trifluoromethylaminobenzoic acid whose aryl group contains an additional carboxyl group, *i.e.* derivatives of hydroxybenzoic acids. These compounds have a high fungicidal and also bactericidal efficacy on use in organic materials[29]. The reaction product *(44)* obtained from 3-[*N*-dichlorofluoromethylthio-*N*-trifluoromethylamino]benzoyl fluoride and salicylic acid (Eulan Asept P®) has proved of considerable value.



(44)

This product[30] is used for antimicrobial finishing of textiles. Owing to its broad spectrum of activity towards fungi and bacteria and to its ease of application, compound *(44)* is used for hygienic finishing of fabrics to suppress the spread of pathogenic microbes on the textile and in its soil phase. Such treatment is employed mainly on textiles (carpeting, rugs, upholstering, fabrics, *etc.*) used by many people (in hotels, hospitals, homes) and not frequently laundered.

A concentration of 0.5—0.75% of compound *(44)* suffices for general applications, while 1—1.5% is recommended for floorcovering material in hospitals in order to provide an added safety factor against pyogens (Pseudomonas pyocyanea). The antimicrobial action of *(44)* is still present in polyamide fibers and wool even after several washings or shampooings.

A biological application has also been found for the same compound *(44)*, *i.e.* for maintaining the freshness of cut flowers[31]. It is active towards microorganisms which block the channels of the plant stem by slime formation; moreover, it also inhibits the growth of microorganisms in vase water. The compound exhibits a good conserving effect in numerous plant species (roses, carnations, chrysanthemums, *etc.*) over a long period of time. Good results have also been obtained with branches from flowering shrubs (*e.g.* forsythia).

The active ingredient *(44)* has an oral LD_{50} of 882 mg/kg in rats. On cutaneous application to rats, 500 mg/kg were tolerated without symptoms. In a four-hour exposure of rats to aerosols, LC_{50} was found to be 135 mg/m³ air. Applied neat, the compound irritates the skin and mucous membranes of rabbits.

4. *N*-Sulfenylated Carbamic Esters as Insecticides and Fungicides

If the *N*-trifluoromethylamino compounds described in Section 3 are considered as adducts of HF to isocyanide difluorides then corresponding addition compounds should be preparable from isocyanates and isothiocyanates.

$$R{-}N{=}CF_2 + HF \longrightarrow R{-}NH{-}CF_3$$

$$R{-}N{=}C{=}O + HF \longrightarrow R{-}NH{-}\underset{\underset{O}{\|}}{C}{-}F \qquad (45)$$

$$R{-}N{=}C{=}S + HF \dashrightarrow R{-}NH{-}\underset{\underset{S}{\|}}{C}{-}F$$

While no thiocarbamoyl fluorides can be prepared by reaction of hydrofluoric acid with isothiocyanates[31a], isocyanates and hydrofluoric acid do afford carbamoyl fluorides *(45)*[32] which exhibit considerable thermal stability in contrast to monosubstituted carbamoyl chlorides.

In their reactivity, the carbamoyl fluorides resemble *N*-trifluoromethylamines, at least as far as acylation reactions are concerned. The action of acyl or sulfonyl chlorides on carbamoyl fluorides *(45)* in the presence of a *tert*-amine merely leads to cleavage of the carbamoyl fluoride to the isocyanate. In contrast, sulfenyl chloride reacts under the same conditions to give *N*-sulfenylated carbamoyl fluorides *(46)*. A selection is shown in Table 3.

$$\underset{(45)}{R{-}NH{-}COF} + AcCl \xrightarrow[-\,NEt_3\cdot HCl]{NEt_3} R{-}N{=}C{=}O$$

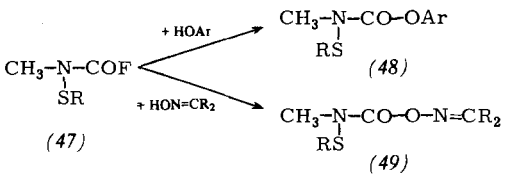
$$\underset{(45)}{R{-}NH{-}COF} + R'SCl \xrightarrow[-\,NEt_3\cdot HCl]{NEt_3} \underset{\underset{R'S}{|}}{R{-}N{-}}COF \qquad \underset{(46)}{}$$

Table 3. *N*-Sulfenylated carbamide fluorides of type *(46)* [33, 34, 34a].

	R—N(R'S)—COF	*(46)*	
R	R'	B.p. [°C/torr]	M.p. [°C]
CH_3	CCl_2F	57—60/11	
CH_3	CCl_3	86—89/11	38—39
CH_3	C_6H_5	128—130/16	
CH_3	4-Cl—C_6H_4	85—90/0.1	
CH_3	3-CF_3—C_6H_4	118—120/11	
CH_3	$N(CH_3)$—CO—$N(CH_3)_2$	88—90/15	
CH_3	$N(CH_3)$—SO_2—$N(CH_3)_2$	137/0.2	
CH_3	$N(C_6H_5)$—SO_2—$N(CH_3)_2$		84—85
CH_3	COO-iC_3H_7	105—107/10	
CH_3	4-NH—SO_2—C_6H_4—Cl		65
c-C_6H_{11}	CCl_2F	124—129	
C_6H_5	CCl_2F	133—136/12	53—55
4-CH_3—C_6H_4	CCl_2F	147—150/12	
3,4-$Cl_2C_6H_3$	CCl_2F	175—177/10	
CH_3	$N(CH_3)_2$	55—57/5	
CH_3	Morpholino		48—50

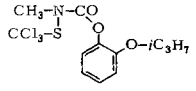
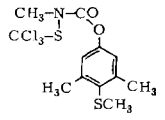
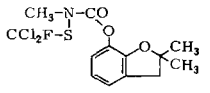
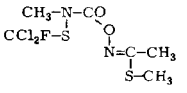
As is apparent from Table 3 we have concerned ourselves primarily with sulfenylation products of *N*-methylcar-

bamoyl fluorides *(47)*, because these intermediates are suitable for the production of highly active insecticides, *viz.* *N*-sulfenylated aryl carbamates *(48)* and carbamoyl oximes *(49)*.



Like the *N*-trifluoromethylamines described in Section 3, *N*-methylcarbamoyl fluoride was treated preferably with trichloromethane- or dichlorofluoromethane-sulfenyl chloride with a view to obtaining biologically active end products. Only those representatives were subjected to reaction with phenols or oximes, whose *N*-methylcarbamates are known to be insecticides. Some examples are presented in Table 4.

Table 4. *N*-Sulfenylated carbamates *(50)* to *(52)* [of type *(48)*] and carbamoyloximes *(53)* [of type *(49)*] and their parent compounds without the *N*-(trihalomethylthio)-substituents. The LD_{50} values refer to the rat.

N-Sulfenylation product	LD_{50} [mg/kg]	Parent compound "common name"	LD_{50} [47] [mg/kg]
(50) 	2000	Propoxur	100
(51) 	500	Methiocarb	100
(52) 	200	Carbofuran	5
(53) 	250	Methomyl	25

The biological data of compounds *(50)* to *(53)* cannot be discussed at length in this article. The following features have been established[35–38]:

a) The sulfenylated products *(50)* to *(53)* show about the same insecticidal activity as their parent compounds listed in Table 4.
b) The sulfenyl compounds are significantly stronger acaricides than the parent compounds.
c) Possible phytotoxic activity of the parent compounds in various crops is reduced in the case of the sulfenyl derivatives.
d) Particular importance attaches to the fact that the toxicity of the sulfenylated products towards warm-blooded animals is generally lower than that of the parents by a factor of 5 to 20 (see Table 4)[38a].

Despite their advantages, we have turned our attention away from this particular class of compounds, which were subsequently also studied by other research teams[38], because all these trihalomethansulfenyl-substituted *N*-methylcarbamates have some degree of irritating action on the skin or mucous membranes.

Our continued studies on other sulfenyl chlorides, particularly aromatic sulfenyl chlorides and those belonging to the sulfonamide series, have confirmed the general principle of "detoxification by sulfenylation".

Meanwhile, other workers have also successfully introduced a sulfenyl group into known biologically active groups, *e.g.* in formamidines[39] and ureas[40].

Whereas sulfenylated *N*-methylcarbamates based upon *N*-trihalomethanesulfenyl chlorides are accessible only *via* the fluorides of type *(47)*, an alternative synthetic pathway is open for other sulfenylated *N*-methylcarbamates, *i.e.* direct sulfenylation of *N*-methylcarbamates proceeding under analogous conditions[41,42,42a].

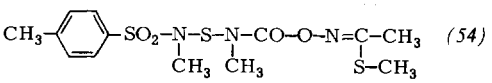
$$CH_3–NH–CO–OR + R'SCl \xrightarrow[-NEt_3 \cdot HCl]{NEt_3} CH_3–\underset{\underset{SR'}{|}}{N}–CO–OR$$

R = Aryl or $-N=CR_2''$
R' ≠ Trihalomethyl
(48), (49)

Although direct sulfenylation of *N*-methylcarbamates with trichloromethanesulfenyl chloride is claimed in an earlier patent, the reaction could not be repeated[43].

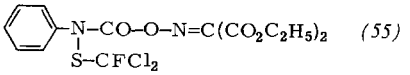
The sulfenylated *N*-methylcarbamates obtained from arene or sulfonamidesulfenyl chlorides show essentially the same biological behavior as observed in trihalomethylsulfenyl compounds (roughly equal insecticide activity but better acaricidal action than with the parent compounds having the CH_3NH instead of the $CH_3N(SR)$ group, disappearance of possible damage to crops, greatly diminished toxicity to warm-blooded animals). However, in contrast to the sulfenyl compounds described above, the new compounds do not act as skin irritants.

The biological action will be considered in greater detail for the example of compound *(54)*[44]. Compound *(54)*


(54)

(LD_{50} = 843 mg/kg rat, per os) has much more favorable toxicological data than its parent compound Methomyl (see Table 4). The spectrum of action of *(54)* is shifted relative to that of Methomyl; the principal application of *(54)* lies in the protection of cotton and vegetable crops against attack by various caterpillars. Its initial action is established somewhat slower, but its long term action is very good. Like Methomyl, *(54)* also exhibits a systemic action. It is better tolerated by plants than Methomyl.

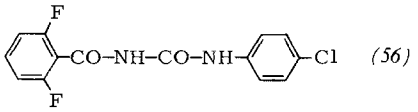
In the further course of our studies we also discovered sulfenylated carbamates having pronounced microbicidal or fungicidal properties[45]. Thus compound *(55)* is suitable as a wood preservative or for use in paints.


(55)

5. Outlook

The acylureas have been found to have a completely new mode of insecticidal action. They are not cholinesterase inhibi-

tors, but interfere with molting of the insects, stopping chitin formation and thus inhibiting development. An example taken from this series is Diflubenzuron *(56)*[46].



(56)

This field of study is undergoing rapid development, and once again underlines the significance of fluorinated isocyanates as starting materials for the synthesis of biologically active materials.

In addition to all the ladies and gentlemen at Bayer AG whose names appear in the literature references, we wish to thank the following colleagues for their cooperation: Dr. H. Tarnow for chemical engineering contributions, Dr. Oehlmann for spectroscopic studies, and Dr. I. Hammann, Dr. L. Eue, Dr. H. Kaspers, Dr. J. Niggemann, and Ing. A. Fuss for a comprehensive discription of the biological results used in this article. The toxicological data were kindly supplied by Dr. G. Kimmerle.

Received: June 8, 1977
supplemented: July 6, 1977 [A 186 IE]
German version: Angew. Chem. *89*, 797 (1977)

[1] *R. Wegler:* Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel. Springer, Berlin 1970, Vol. 2, p. 227, 241ff.
[2] Cf. [1], Vol. 1, p. 220ff.
[3] *E. Sturm* in: Ullmanns Encyklopädie der technischen Chemie. Verlag Chemie, Weinheim 1976, 4. Edit., Vol. 12, p. 1ff.
[4] *H. Holtschmidt*, Angew. Chem. *74*, 848 (1962); Angew. Chem. Int. Ed. Engl. *1*, 623 (1962).
[5] *E. Klauke, E. Kühle, H. Hack, L. Eue*, DBP 1668003 (1967), Bayer AG.
[6] *G. Büttner, E. Klauke*, DOS 2133467 (1971), Bayer AG.
[7] *E. Klauke, E. Kühle, L. Eue, H. Hack*, DBP 1768634 (1968), Bayer AG.
[8] *E. Klauke, E. Kühle*, DOS 1768635 (1968), Bayer AG.
[8a] Cf. *F. S. Fawcett, W. A. Sheppard*, J. Am. Chem. Soc. *87*, 4341 (1965).
[8b] *E. Klauke, H. Schwarz, F. Döring*, DOS 2325089 (1973), Bayer AG.
[9] *J. Hempel, E. Klauke*, DOS 2129200 (1971), Bayer AG.
[10] *E. Klauke, E. Kühle, L. Eue*, DBP 1909521 (1969), Bayer AG.
[11] *O. Scherer, G. Hörlein, H. Schönowsky*, DOS 1542889 (1966), Hoechst AG.
[12] *E. Klauke, E. Kühle, L. Eue*, DBP 2003143 (1970), Bayer AG.
[13] *E. Kühle* in: Ullmanns Encyklopädie der technischen Chemie. Verlag Chemie, Weinheim 1976, 4. Edit., Vol. 12, p. 597ff.
[14] *E. Kühle, E. Klauke, L. Eue, H. Hack*, DBP 1668004 (1967), Bayer AG.
[15] *K. U. Alles, E. Klauke, D. Lauerer*, Justus Liebigs Ann. Chem. *730*, 16 (1966).
[16] *H. U. Alles, E. Klauke, E. Kühle, L. Eue, H. Hack*, DOS 1768244 (1968), Bayer AG.
[17] *O. Scherer, G. Schneider, P. Langelüddecke*, DOS 1938578 (1969), Hoechst AG.
[17a] *J. Hempel, E. Kühle, E. Klauke, L. Eue*, DOS 2126930 (1971), Bayer AG.
[17b] *G. Hörlein, P. Langelüddecke, A. Studeneer*, DOS 2123185 (1971), Hoechst AG.
[17c] *E. Kühle, E. Klauke*, Kem.-Kemi *1*, 596 (1974).
[18] *E. Kühle, B. Anders, G. Zumach*, Angew. Chem. *79*, 663 (1967); Angew. Chem. Int. Ed. Engl. *6*, 649 (1967).
[19] *E. Kühle*, Angew. Chem. *81*, 18 (1969); Angew. Chem. Int. Ed. Engl. *8*, 20 (1969).
[20] *E. Kühle, E. Klauke*, DOS 1568553 (1966), Bayer AG.
[21] *E. Klauke, E. Kühle*, DBP 1293754 (1966), Bayer AG.
[22] *E. Kühle, E. Klauke, F. Grewe*, Angew. Chem. *76*, 807 (1964).
[23] *E. Kühle, E. Klauke*, DOS 1810580 (1968), Bayer AG.
[24] *E. Kühle, E. Klauke, I. Hammann, H. Scheinpflug*, DOS 2257345 (1972), Bayer AG.
[25] *E. Kühle, E. Klauke, M. Plempel*, DBP 1543615 (1966), Bayer AG.
[26] *E. Kühle, E. Klauke, H. Kaspers, H. Scheinpflug*, DOS 2311983 (1973), Bayer AG.
[27] *H. Kaspers, H. Scheinpflug, E. Kühle, E. Klauke*, DBP 2064596 (1970), Bayer AG.
[28] *A. Zeidler, A. Fischer, G. Scheurer*, Z. Naturforsch. *B24*, 740 (1969).
[29] *E. Kühle, E. Klauke, B. Hamburger, F. Steinfatt*, DBP 1919180 (1969), Bayer AG.
[30] *H. Klesper*, Text.-Prax. Int. *1973*, No. 10, p. 1.
[31] *J. Niggemann, E. Klauke, E. Kühle*, Dt. Pat.-Anm. 2654349.7 (1976), Bayer AG.
[31a] Cf. *H. Lübbers*, DOS 2425414 (1974), Hoechst AG.
[32] *G. D. Buckley, H. A. Piggott, A. J. E. Welch*, J. Chem. Soc. *1945*, 864.
[33] *E. Kühle, E. Klauke*, DBP 1297095 (1967).
[34] *N*-sulfenylated carbamide chlorides have in the meantime become accessible by phosgenation of sulfenamides; cf. *J. E. Moore*, DOS 2362686 (1973), Chevron Res. Comp.
[34a] *D. E. Thurman*, DOS 2628575 (1976), Union Carbide Corp.
[35] *E. Kühle, E. Klauke, I. Hammann, B. Hamburger, P. E. Frohberger, W. Behrenz*, DOS 1922929 (1969), Bayer AG.
[36] *E. Kühle, I. Hammann*, DOS 2016623 (1970), Bayer AG.
[37] *G. Zumach, E. Kühle, I. Hammann, W. Behrenz*, DOS 2045441 (1970), Bayer AG.
[38] *J. A. Durden, T. D. J. D'Silva*, DOS 2425211 (1974), Union Carbide Corp.
[38a] *A. L. Black, Y. C. Chiu, T. R. Fukuto, TA. Miller*, Pest. Biochem. Physiol. *3*, 435 (1973).
[39] *V. L. Rizzo*, DOS 2425748 (1974), The Upjohn Co.
[40] *D. Hainaut, J. Demoute*, DOS 2256275 (1972), Roussel-Uclav.
[41] *G. K. Kohn, M. Brown*, DOS 1949234 (1969), Chevron Res. Comp.
[42] *P. Siegle, E. Kühle, I. Hammann, W. Behrenz, B. Homeyer*, DOS 2344175 (1973), Bayer AG.
[42a] *A. L. Black, Y. C. Chiu, M. A. H. Fahmy, T. R. Fukuto*, J. Agric. Food Chem. *21*, 747 (1973).
[43] Fr. Pat. 1493581 (1966), Chimetron S. A. R. L.
[44] *P. Siegle, E. Kühle, W. Behrenz, I. Hammann*, DOS 2254359 (1972), Bayer AG.
[45] *E. Kühle, E. Klauke, B. Hamburger, H. Scheinpflug*, DOS 2243626 (1972), Bayer AG.
[46] *K. Wellinga, R. Mulder*, DOS 2123236 (1971), Philips Duphar.
[47] These toxicity values are taken from [1], Vol. 1, p. 234ff.

Synthesis and Reactions of *N*-Chlorocarbonyl Isocyanate

By Hermann Hagemann[*]

Dedicated to Professor Otto Bayer on the occasion of his 75th birthday

Cl—CO—N=C=O (*N*-chlorocarbonyl isocyanate) is prepared in 90% yield by partial hydrolysis of the addition product of phosgene and cyanogen chloride. Many derivatives of the iminocarboxylic acid parent compound can be obtained from this highly reactive species. Both the acid chloride and the isocyanate group are amenable to reactions exhibiting overall selectivity, and this opens the way, *inter alia*, to a simple preparative synthesis of isocyanates from alcohols, phenols, thiols, and thiophenols. Combination of the two functional groups and their peculiar symmetry, which becomes evident, *e.g.* in the HCl adduct, facilitates ready cyclization of *N*-chlorocarbonyl isocyanate under very mild conditions.

1. Introduction

Following several publications in which modes of formation[1] and reactions[1a, 2] of *N*-chlorocarbonyl isocyanate were described, the present article deals with our syntheses, already patented in 1968[3], and with the diverse chemistry of this C_2-compound which has meanwhile become available on a technical scale.

2. Preparation of *N*-Chlorocarbonyl Isocyanate from Cyanogen Chloride, Phosgene, and Water

The addition products of cyanogen chloride and strongly electrophilic reagents are in some cases formed under very mild conditions[4]. The best known example is probably chlorosulfonyl isocyanate *(1)*, which can be prepared from sulfur trioxide and cyanogen chloride[5].

$$ClCN + SO_3 \rightarrow ClSO_2{-}NCO \quad ClCO{-}NCO$$
$$(1) \qquad (2)$$

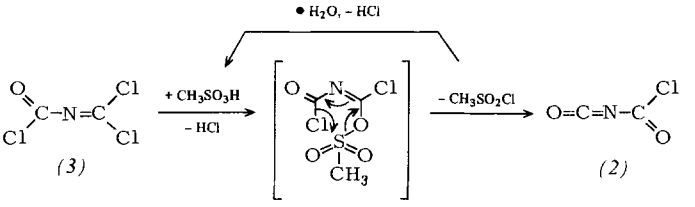
The analogous reaction to yield *N*-chlorocarbonyl isocyanate *(2)* does not, however, occur because the electrophilic character of carbon dioxide is too weak. A detour by way of the more strongly electrophilic carbonic acid derivative phosgene provides a simple access to the desired compound.

If phosgene and cyanogen chloride are passed at 150°C and 55 bar over an active charcoal catalyst the addition product *N*-chlorocarbonyl isocyanide dichloride *(3)* is formed[6], a compound that had been obtained earlier by chlorination of methyl isocyanate[7].

$$CH_3{-}NCO \xrightarrow[-3\,HCl]{+3\,Cl_2} \underset{Cl}{\overset{O}{\overset{\|}{C}}}{-}N=\underset{Cl}{C}{<}^{Cl} \xleftarrow[55\,bar]{150\,^\circ C} COCl_2 + ClCN$$
$$(3)$$

Addition over the active charcoal catalyst is carried out in a plant operating semicontinuously, an excess of phosgene being used to suppress as far as possible the trimerization of the cyanogen chloride and the formation of a product from two moles of cyanogen chloride and one mole of phosgene.

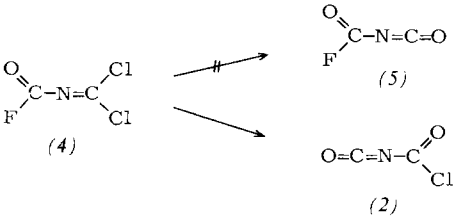
Partial hydrolysis of *(3)* by methanesulfonic acid leads to *N*-chlorocarbonyl isocyanate *(2)* in 90% yield[8], although this product reacts rapidly and irreversibly with methanesulfonic acid.



By suitable temperature control the partial hydrolysis can be largely resolved into two partial steps, so that the reaction between methanesulfonic acid and *N*-chlorocarbonyl isocyanate *(2)* is suppressed. The first step occurs already at 20°C with elimination of hydrogen chloride. The hypothetical intermediate *(3a)* is cleaved at a slightly higher temperature into *(2)* and methanesulfonyl chloride; the latter can be recovered in >90% yield and after conversion into methanesulfonic acid can be returned to the cycle.

Whether, in the partial hydrolysis, *(3)* reacts by way of a four-membered transition state as the isocyanide dichloride[9] or as *N*-(chlorocarbonyl)imidoyl chloride[8], as formulated above, cannot be decided from the formation of *(2)*. The six-membered ring transition state *(3a)* is favored by the fact that *N*-chlorocarbonyl isocyanate *(2)* and not *N*-fluorocarbonyl isocyanate *(5)* is formed from *N*-fluorocarbonyl isocyanide dichloride *(4)* under the same conditions.

The isocyanate group is thus apparently formed from the *N*-fluorocarbonyl group and not from the isocyanide dichloride grouping[10].



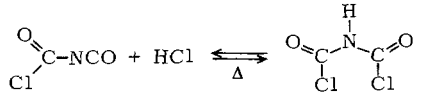
[*] Dr. H. Hagemann
Wissenschaftliches Hauptlaboratorium der Bayer AG
D-5090 Leverkusen (Germany)

The product *(2)* is a water-clear liquid that can be stored indefinitely in the absence of moisture; it boils at 64°C (63.6°C[1a]).

3. Reactions of *N*-Chlorocarbonyl Isocyanate

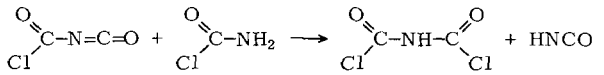
3.1. General Considerations

The diversity of the chemical reactions of *(2)* arises on the one hand from the combination of two functional groups known to be especially reactive and, on the other hand, from the inherent symmetry of the molecule, which is manifested in its adduct with hydrogen chloride, *viz.* *N*-(chlorocarbonyl)carbamoyl chloride *(6)*. Compound *(6)*, the dichloride of iminodicarboxylic acid, redissociates on melting at 88—89°C.



(2) *(6)*

Because of this symmetry one cannot conclude, for instance from product analysis, whether *(2)* reacts with weak nucleophiles such as water or alcohol primarily at the acid chloride or at the isocyanate grouping.

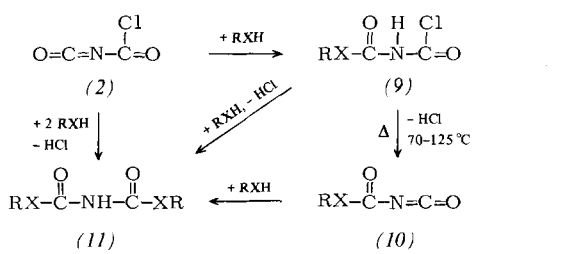


(2) *(7)* *(6)* *(8)*

Furthermore, the formation of *N*-(chlorocarbonyl)carbamoyl chloride *(6)* from *(2)* and an excess of water, and the absence of carbamoyl chloride *(7)* from reaction products, do not justify the conclusion that there could not have been primary addition of water to the isocyanate group[1a]. Carbamoyl chloride *(7)* is known[11] to eliminate HCl even at room temperature, whereas under these conditions *(2)* adds HCl in a strongly exothermic reaction, so that in the presence of *(2)* the chloride *(7)* escapes detection owing to formation of *(6)* and *(8)* (→cyanuric acid).

3.2. Reaction with Alcohols, Thiols, Phenols, Thiophenols, Secondary Amines, and Sulfonamides

The preparation of the *N*-carbonyl-substituted carbamoyl chlorides *(9)* is effect by the reaction of the above nucleophiles (RXH) with a supply of *(2)*. Here again, however, it is not immediately necessary to assume that the apparently plausible selective addition of the nucleophile to the isocyanate group has in fact initially occurred, since the hydrogen chloride arising on substitution of the acid chloride group would be trapped at once by the isocyanate group under the reaction condition (*ca.* 20°C), and the same products would be obtained.



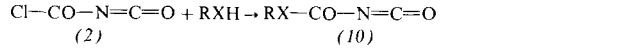
(2) *(9)* *(11)* *(10)*

R,R' = Alkyl, Aryl

a, RX = RO; *b*, RX = RS; *c*, RX =  ; *d*, RX = 

The primary products *(9)* lose hydrogen chloride at 70—125°C, thus being transformed into the relevant isocyanates *(10)*[12]. Some examples of the reaction *(2)*→*(10)* are collected in Table 1.

Table 1. Isocyanates of type *(10)* from *(2)* and nucleophiles [a].



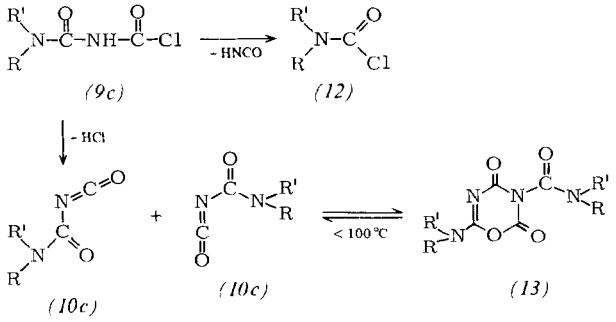
(2) *(10)*

RX	Type	B.p. [°C/torr]	Yield [%] [b]	Ref.
CH_3O	*(10a)*	97/760	70	[12d]
C_2H_5O	*(10a)*	114/760	76	[12d]
n-$C_8H_{17}O$	*(10a)*	113/11	85	[12d]
C_6H_5O	*(10a)*	100/15	90	[12d]
CH_3S	*(10b)*	125/760	66	[12d]
C_4H_9S	*(10b)*	88/15	88	[12d]
$C_{12}H_{25}S$	*(10b)*	111/0.04	77	[12d]
C_6H_5S	*(10b)*	115/11	73	[12d]
o-Cl—$C_6H_4(C_2H_5)N$	*(10c)*	98/0.03	86	
$C_6H_5(C_4H_9)N$	*(10c)*	116/0.4	72	
$(CH_3)_2N$	*(10c)*	62/17	43	
$(C_3H_7)_2N$	*(10c)*	64/0.02	52	
p-CH_3—$C_6H_4SO_2(i$-$C_3H_7)N$	*(10d)*	148—150/0.1	91	[12f]
$CH_3SO_2(C_6H_5$—$CH_2)N$	*(10d)*	142/0.12	85	[12f]
$CH_3SO_2(C_2H_5)N$	*(10d)*	93/0.08	78	[12f]
$CH_3SO_2(C_6H_{11})N$	*(10d)*	114/0.08	80	[12f]

[a] The structures of the isocyanates *(10)* are proved by elemental analyses, spectra, numerous solid iminodicarboxylic acid derivatives, and comparison with authentic samples.
[b] The yields, which in many cases are not optimized, refer to the product isolated by distillation.

The primary products from *(2)* and some secondary amines show partially divergent behavior. Whereas mixed aliphatic-aromatic allophanoyl chlorides *(9c)*, R = alkyl, R' = aryl, afford the isocyanates *(10c)* with elimination of hydrogen chloride as described above, on thermolysis of purely aliphatic allophanoyl chlorides *(9c)*, R = R' = alkyl, fission into HNCO and dialkylcarbamoyl chlorides *(12)* to the extent of about 50% is observed.

The isocyanates *(10c)* from *(2)* and secondary amines have a further peculiarity that has been described by *Zinner* and *Isensee*[12e]. Unlike the other isocyanates of general formula *(10)*, they dimerize very readily to 1,3,5-oxadiazinediones *(13)* without the addition of a catalyst. This [4+2]-cycloaddition is reversible even under very mild conditions, and thus the well-crystallizing dimers permit a simple separation of



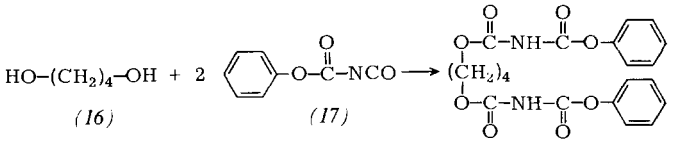
(9c) *(12)* *(10c)* *(10c)* *(13)*

the isocyanates *(10c)* from the carbamoyl chlorides *(12)* that boil at almost the same temperatures.

The symmetrical iminodicarboxylic acid derivatives *(11)* can be obtained in one step from *(2)* and the nucleophile RXH reacted in a molar ratio of 1:2. Almost any desired asymmetric compound of general formula *(14)* can be prepared by treating the primary products *(9)* or the isocyanates *(10)* with a second nucleophile.

RX—CO—NH—CO—XR′ *(14)*

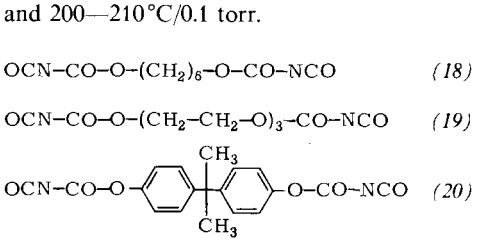
Polyfunctional mixed aliphatic-aromatic iminodicarboxylic esters *(15)* are phenol-capped highly reactive polyisocyanates that are suitable for thermal crosslinking of polymeric lacquers containing hydroxyl groups[13]; these esters *(15)* are prepared, *e.g.*, by the reaction of polyhydroxy compounds *(16)* with the phenyoxycarbonyl isocyanate *(17)*, a compound of type *(10a)* that is readily accessible from *(2)* and phenol.



(16) *(17)* *(15)*

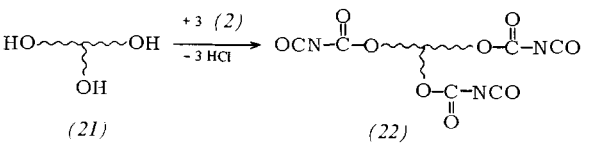
3.3. Reaction with Diols and Polyols

1,6-Hexanediol, triethylene glycol, and α,α-dimethyl-4,4′-methylenediphenol (bisphenol A) lead on reaction with *(2)* to the diisocyanates *(18)*—*(20)*. The yields are 90, 85, and 90%, and the boiling points 123°C/0.09 torr, 170°C/0.1 torr, and 200—210°C/0.1 torr.



(18), *(19)*, *(20)*

The reaction *(2)* → *(10)* proceeds very smoothly even with polyethers *(21)* containing several hydroxyl groups and opens a particularly simple route to high-molecular (molecular weight *ca.* 2000), very reactive polyisocyanates *(22)*. By analogy with polyurethane chemistry, polyiminodicarboxylic



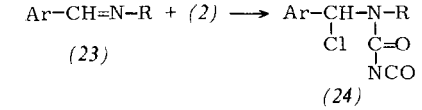
(21) *(22)*

esters of very widely variable properties are obtainable from the di- and polyisocyanates by reaction with polyol systems[14]. Here one needs as starting material for the isocyanate component only a di- or polyhydroxy compound and no di- or polyamine as in the preparation of the isocyanate components for polyurethanes.

3.4. Reaction with Azomethines, Aldehydes, Ketones, Vinyl Esters, Cyanates, and Epoxides

A selective reaction of the chlorocarbonyl group of *(2)* can be achieved with some polar π-bonds and with the C—O bond of epoxides.

From azomethines of general formula *(23)* there thus arise carbamoyl isocyanates with an *N*-(chloroalkyl)amide partial structure *(24)*[15].

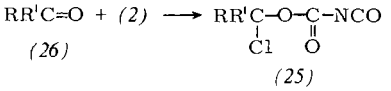


(23) *(24)*

Ar = C_6H_5; R = CH_3, *i*-C_3H_7, *c*-C_6H_{11}, C_6H_5
Ar = *p*-Cl-C_6H_4; R = CH_3

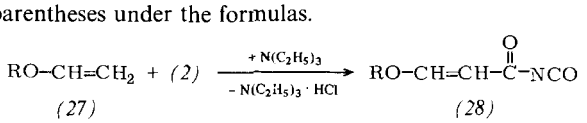
The basic character of the amide-nitrogen is weakened by the neighboring chlorine atom, and this is probably why the isocyanates *(24)* do not have any tendency to dimerize comparable with that of the chlorine-free *N*,*N*-disubstituted carbamoyl isocyanates of type *(10c)* (cf. Section 3.2).

The adducts *(25)* of carbonyl compounds *(26)* and *N*-chlorocarbonyl isocyanate *(2)* can be isolated in yields of between 25 and 80%. This reaction has been carried out with chloral and benzaldehyde as aldehydes and with acetone, ethyl methyl ketone, and cyclohexanone as ketones[2b].



(26) *(25)*

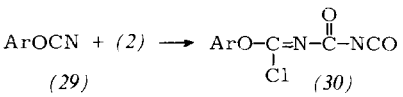
The 1:1 adducts of vinyl ethers *(27)* and *(2)* can be converted by triethylamine into 3-alkoxyacryloyl isocyanates *(28)* with elimination of hydrogen chloride[2a]; the yields are given in parentheses under the formulas.



(27) *(28)*

R = C_2H_5(36%), *i*-C_3H_7(39%), C_4H_9(43%)

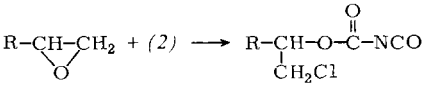
Aryl esters *(30)* of *N*-(isocyanatocarbonyl)chloroformimidic acid are accessible by the addition of the acid chloride group of *(2)* to the CN triple bond of aromatic cyanates *(29)*[2c]; the yields in the examples cited under the formulas are 55—60%.



(29) *(30)*

Ar = C_6H_5, *p*-CH_3-C_6H_4, *p*-Cl-C_6H_4

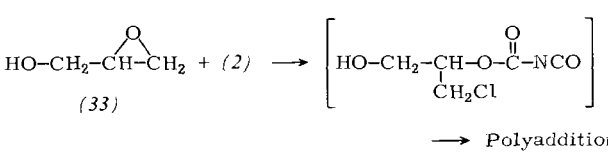
1-(Chloromethyl)alkoxycarbonyl isocyanates *(31)* are formed in 55—60% yield by the ring-opening addition of *(2)* to epoxides *(32)*[16].



(32) *(31)*

R = H, C_6H_5, CH_3, C_2H_5, $ClCH_2$

Epoxides containing an additional hydroxyl group in the molecule, such as *(33)*—the simplest representative of this series, undergo polyaddition on reaction with *(2)*.

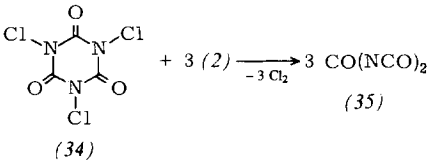


(33)

3.5. Reaction with *N,N',N''*-Trichloroisocyanuric Acid

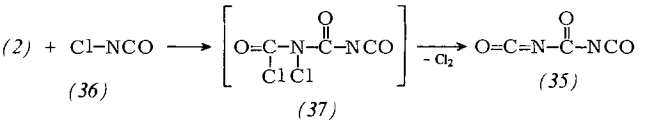
Compounds with negatively polarized chlorine, *e.g.* acid chlorides, and compounds with positively polarized chlorine, *e.g.* *N*-chloro compounds, can react with each other *via* elimination of chlorine. However, high temperatures and often also Friedel-Crafts catalysts are required for this purpose[17].

One of the most readily accessible and easily handled *N*-chloro compounds is trichloroisocyanuric acid *(34)*, which can also be regarded as a trimer of *N*-chloro isocyanate *(36)*. Unlike all other acid chlorides, *(34)* can be induced to react with *(2)* at as low a temperature as *ca.* 40 °C *via* elimination of chlorine; at somewhat higher temperature the reaction gives carbonyl diisocyanate *(35)* in 86 % yield[18].



(34) *(35)*

The special position of *(2)* among acid chlorides with respect to its reactivity must presumably be explained by the participation of the isocyanate group, as described above for the reaction of *(2)* with alcohols. The initial step would then be addition of the *N*-chloro compound *(34)* to the isocyanate group of *(2)*, affording *(37)* (formulated for the sake of clarity with $^1/_3$ trichloroisocyanuric acid = *(36)*).

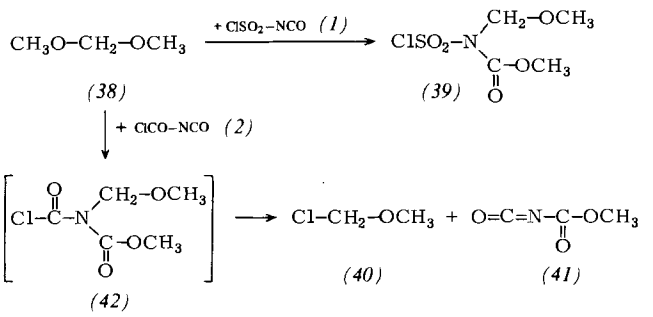


(36) *(37)* *(35)*

On reaction of *(2)* with alcohols, a new isocyanate group arises from the primary product *(9)* by elimination of hydrogen chloride; in the present case, it is formed with the elimination of chlorine.

3.6. Reaction with Dimethoxymethane

It seems reasonable to compare additions to *N*-chlorocarbonyl isocyanate *(2)* with the extensively investigated additions to *N*-chlorosulfonyl isocyanate *(1)*[5]. The primary step is similar in both cases, but the properties of the carbonyl group permit surprising, stabilizing, secondary reactions that are not open to compounds containing the sulfonyl group.



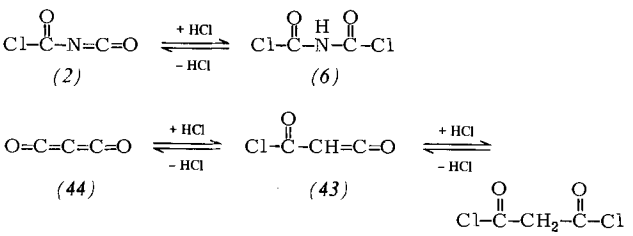
(38) *(39)* *(42)* *(40)* *(41)*

Compound *(1)* gives an insertion product *(39)* with dimethoxymethane (methylal) *(38)*. The reaction of *(2)* with *(38)* leads, however, to chloromethyl methyl ether *(40)* and methoxycarbonyl isocyanate *(41)*; once again *(2)* probably undergoes an initial insertion reaction [to give *(42)*]; however, this primary product achieves stability by fission to *(40)* and *(41)*.

3.7. Syntheses of Heterocycles

In spite of the great reactivity of both functional groups in chlorocarbonyl isocyanate *(2)*, reaction may occur at one or other of these groups, depending on the nature of the other reactant, thus making the compound particularly suitable for heterocycle syntheses.

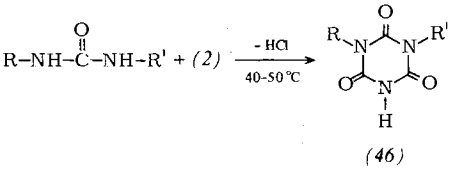
N-(Chlorocarbonyl)carbamoyl chloride *(6)* can be regarded as azamalonyl dichloride. The formal close relationship with the reactive malonic acid derivatives leads us to expect that *(6)* will also be suitable as a building block in heterocycle syntheses. Compound *(2)* is the aza analog of the hitherto unisolated chlorocarbonyl ketene *(43)*, the adduct of carbon suboxide *(44)* and hydrogen chloride[19].



(2) *(6)* *(44)* *(43)*

3.7.1. Heterocycles from *(2)* and R—NH—$(X)_n$—NH—R'

One of the best known heterocycle syntheses, the preparation of barbiturates from malonic acid derivatives and ureas, can readily be adapted for *(2)*. *N,N'*-Disubstituted ureas *(45)* cyclize with *(2)* even in boiling dichloromethane with thermal elimination of hydrogen chloride, to yield disubstituted isocyanurates *(46)* (Table 2). The synthesis conditions are so mild that even thermally sensitive substituents such as *tert*-butyl survive the reaction unaltered[20].



(46)

Whereas in the cyclization to *(46)* hydrogen chloride is eliminated under very mild conditions even without the aid of an acid-binding material, hydrogen chloride elimination does not occur under similar conditions in the reaction of *N,N'*-disubstituted thioureas *(47)*. However, the initial products *(48)* can easily be converted into monothioisocyanurates *(49)* (Table 3) by water or an alcohol/water mixture. The

Table 2. Disubstituted isocyanurates of type *(46)* from *(2)* and *(45)* [20a].

R	R'	M.p. [°C]	Yield [%]
3,4-Cl_2—C_6H_3	CH_3	233	94
i-C_3H_7	*i*-C_3H_7	163	98
CH_2=CH—CH_2	CH_2=CH—CH_2	148	86
c-C_6H_{11}	CH_3	214	98
C_6H_5	CH_3	240	84
CH_3	CH_3	219	85
t-C_4H_9	*t*-C_4H_9	189	75

heterocycles *(49)*—unlike *(46)*—should apparently be regarded as weak bases, while *(48)* are their easily hydrolyzable salts.

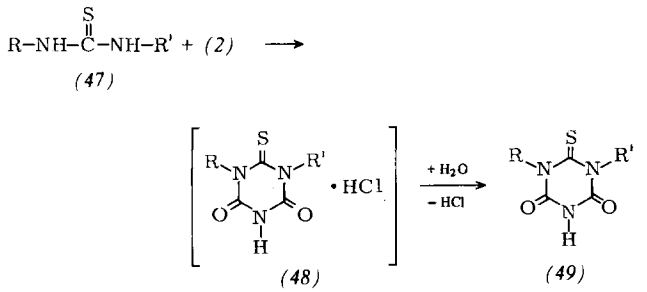


Table 3. Disubstituted monothioisocyanurates of type *(49)* from *(2)* and *(47)* [20a].

R	R′	M.p. [°C]	Yield [%]
C_6H_5	n-C_4H_9	164	72
CH_3	CH_3	194—195	95
c-C_6H_{11}	CH_2=CH—CH_2	140	36
C_6H_5	CH_3	217	42

For reaction with still more strongly basic cyclization components *(50)* it is preferable to use derivatives of *(2)* such as *(17)* in order to have a better leaving group. Five-, six-, and seven-membered heterocycles *(51)* recorded in Table 4 are obtained from hydrazines *(50)*, $n=0$, aminals *(50)*, $n=1$, and ethylenediamines *(50)*, $n=2$, respectively.

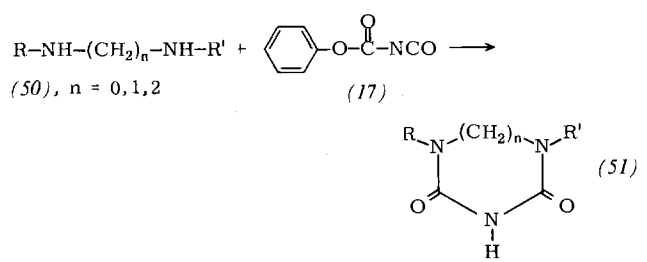


Table 4. Heterocycles of type *(51)* from the *(2)*-derivative *(17)* [or similar compounds *(10a)*] and *(50)* [21].

R	R′	n	M.p. [°C]	Yield [%]
C_6H_5	H	0	262—263	96
p-Cl—C_6H_4	H	0	283	75
p-CH_3—C_6H_4	H	0	276—278	68
CH_3	H	0	243	30
C_6H_5	CH_3CO	0	175	87
o-CH_3O—CO—C_6H_4	o-CH_3O—CO—C_6H_4	1	190	50
CH_3	CH_3	2	202—204	83
$C_6H_5CH_2$	$C_6H_5CH_2$	2	206—208	79
α-Pyridylmethyl	α-Pyridylmethyl	2	152	77
c-C_6H_{11}	c-C_6H_{11}	2	218—222	67
C_4H_9	C_4H_9	2	140—142	80

3.7.2. Heterocycles from *(2)* and ArOH, ArNHR, or $ArNR_2$

If the two acylatable centers in the cyclization components for *(2)* have very different nucleophilicities, then in many cases intermediate products can be isolated. Examples of especially stable intermediates are the adducts of phenols and *(2)* mentioned in Section 3.2, namely the phenyl ester chlorides of iminodicarboxylic acid of type *(9a)*. However, these compounds cyclize at higher temperatures in the presence of catalytic amounts of iron(III) chloride in an intramolecular Friedel-Crafts reaction that yields benzoxazinediones *(52)* (Table 5). The isocyanate *(10a)*, R = R′ = R″ [≡ *(17)*], obtained without $FeCl_3$ from *(9a)*, R = R′ = R″ = H, is thermally stable but is smoothly cyclized by iron(III) chloride.

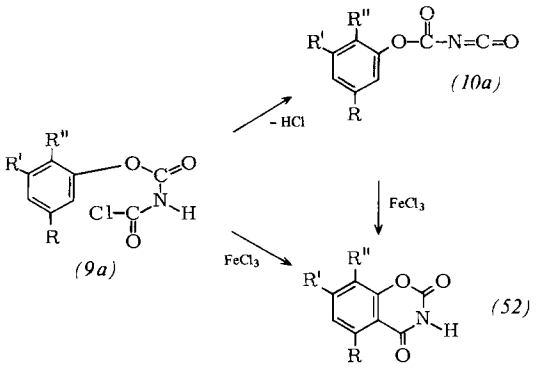


Table 5. Benzoxazinediones of type *(52)* from *(2)* and phenols [22].

R	R′	R″	M.p. [°C]	Yield [%]
H	H	H	226—227	89
CH_3O	H	H	216—217	86
CH_3	CH_3	CH_3	257—259	84
H	—(CH=CH)$_2$—		280	76
H	H	Br	243	22

A similar situation arises with the addition products of mixed aliphatic-aromatic secondary amines and *(2)*, *viz.* allophanoyl chlorides *(9c)* (see Section 3.2). They can be converted as desired into either the carbamoyl isocyanates *(10c)* or (under pressure in autoclaves) into the quinazolinediones *(53)* isomeric therewith (Table 6).

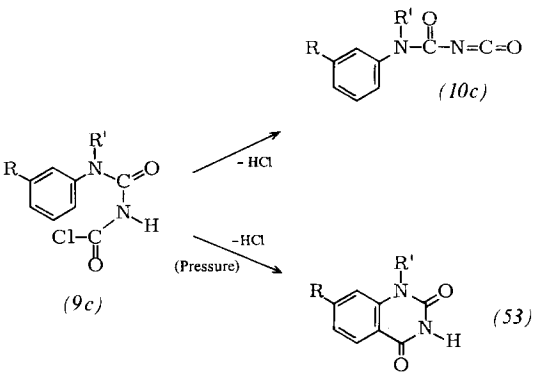
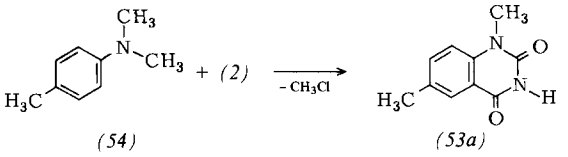


Table 6. Quinazolinediones *(53)* from *(2)* and mixed aliphatic-aromatic secondary amines [22].

R	R′	M.p. [°C]	Yield [%]
H	CH_3	243—244	34
H	C_2H_5	215	62
H	n-C_4H_9	125—128	62
H	i-C_4H_9	160	45
CH_3	n-C_4H_9	159—163	60

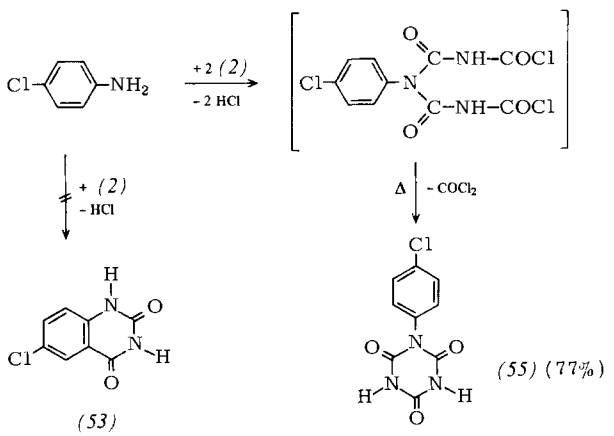
The same type of heterocycle *(53)* is obtained from *N*,*N*,4-trimethylaniline *(54)*. In place of hydrogen chloride, methyl chloride is eliminated from this tertiary amine in a kind of von Braun degradation. *(53a)* is formed in 80% yield and melts at 275 °C. The yields are good only from *p*-substituted dimethylanilines.

The reaction of primary aromatic amines with *(2)* does not give the heterocycles of type *(53)*, but instead leads,



(54) (53a)

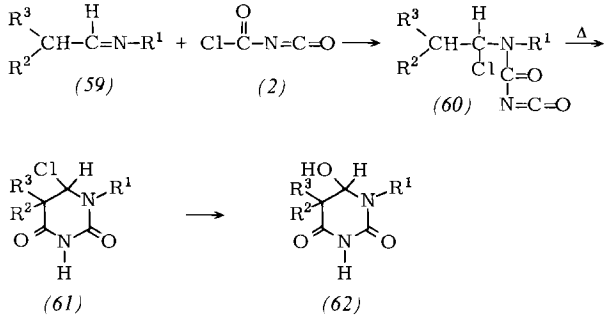
with addition of two moles of (2) and elimination of phosgene, to monosubstituted isocyanurates (55).



(53) (55) (77%)

Like their open-chain analogs[24], such cyclic *N*-(chloroalkyl)amides are readily substituted by nucleophiles at the C-6 atom: heating with water or water/ethanol leads to (62).

If *N*,*N'*-disubstituted amidines (63) are used in place of the azomethines (59), then compounds (64) with salt-like character are formed; replacement of $A=CR^2R^3$ by $A=NR^1$



(59) (2) (60) (61) (62)

makes it possible for the resonance-stabilized cation to be formed in the cyclization with (2).

Particularly stable salts of this type are obtained when trisubstituted cyclic thioureas (65) are used as the reactants

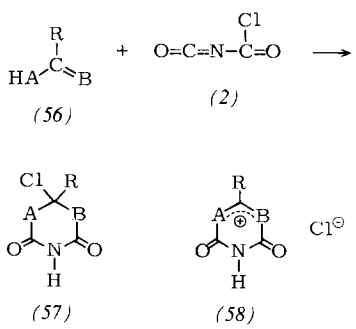
Table 7. 6-Chloro-5,6-dihydropyrimidine-2,4-diones (61) from (2) and azomethines (59) as well as hydroxy-compounds (62) from (61) [23].

			(61)		(62)	
R^1	R^2	R^3	M.p. [°C]	Yield [%]	M.p. [°C]	Yield [%]
c-C_6H_{11}	CH_3	CH_3	198	92	213	92
c-C_6H_{11}	$-CH_2-CH=CH-(CH_2)_2-$		211	91	213	98
CH_3	CH_3	CH_3	205—207	57	180	66
CH_3	$-CH_2-CH=CH-(CH_2)_2-$		190	44	192	60
$C_6H_5-CH_2$	CH_3	CH_3	86—88	70	204	39
i-C_3H_7	CH_3	CH_3	161—163	78	203	92

The yields are also good from aliphatic primary amines if the hydrochlorides are used instead of the free amines to suppress the formation of biuret that might easily occur.

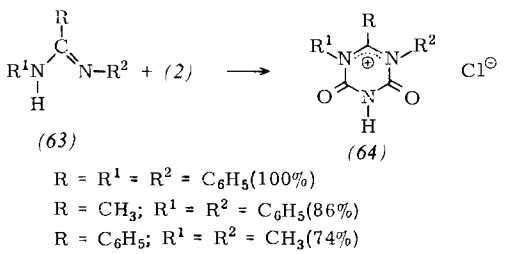
3.7.3. Heterocycles from (2) and HA—CR=B

In the cyclization of (2) with compounds of the general formula (56) two types of product can be expected: 1) the cyclic chloroalkylamides (57) with activated but still predominantly homopolar-bonded chlorine; and 2) the salt-like compounds (58) in which the positive charge is particularly well delocalizable.



(56) (2) (57) (58)

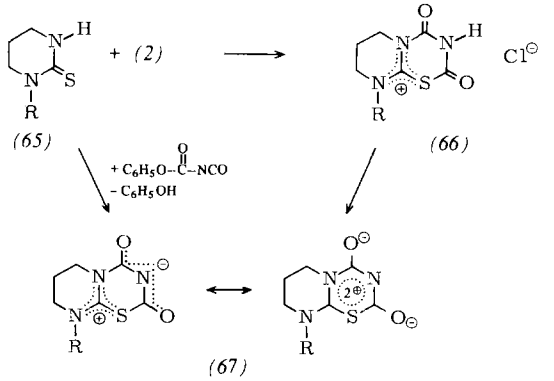
The addition of (2) to azomethines (59), which are derived from disubstituted acetaldehyde [(56), $A=CR^2R^3$; $B=NR^1$], does not stop at the isocyanate stage (60); instead rapid cyclization to 6-chloro-5,6-dihydropyrimidine-2,4-diones (61) occurs at *ca.* 90°C (Table 7).



(63) (64)

R = R^1 = R^2 = C_6H_5(100%)
R = CH_3; R^1 = R^2 = C_6H_5(86%)
R = C_6H_5; R^1 = R^2 = CH_3(74%)

HA—CR=B. The salts (66) can be dehydrochlorinated to six-membered mesionic "arenes" (67). Such mesoionic heterocycles can here, as in the amidine series, be prepared in a single step by treating compounds (65) or (63) with isocyanates RO—CO—NCO (10a) (see Table 1)[25]. Examples of (67) are the compounds

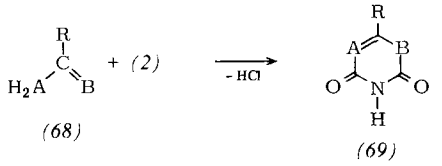


(65) (66) (67)

with R = CH_3, i-C_3H_7, n-C_4H_9, and c-C_6H_{11}; they melt at 210—211, 190, 114, and 208 °C, respectively.

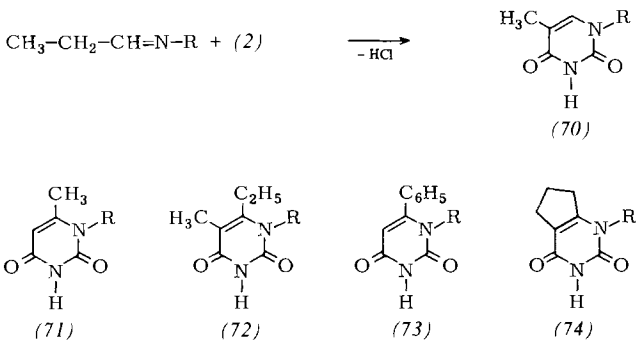
3.7.4. Heterocycles from (2) and H_2A—CR=B

The generalized reaction (68)→(69) describes the most widely variable type of cyclization. Unlike compounds HA—CR=B (56), in compounds (68) there are two H atoms in the position α to the double bond. Thus, the cyclization products corresponding to (57) can react further with β-elimination of hydrogen chloride and the formation of a double bond, so affording (69). In such reactions A may represent nitrogen or a substituted carbon atom, and B oxygen, sulfur, or a substituted nitrogen; A and R, or B and R, may together belong to a common ring system. Compounds (68) include, for example, azomethines, amidines, ketones, amides and thioamides, isoureas and isothioureas, β-dicarbonyl compounds, pyrazolones, iminoethers, oxazolines, and thiazolines.



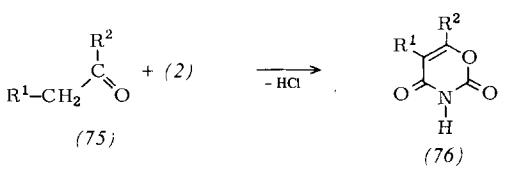
(68) (69)

Among the most interesting from the preparative point of view are the azomethines with two or three hydrogens in the β-position to the nitrogen atom. By their use one obtains, even at room temperature, very good yields in the series of biologically highly active uracils. For example, the use of propionaldehyde as the starting material for the azomethine components leads to thymines (70), the use of acetone leads to the isothymines (71), diethyl ketone to the 6-ethyl-5-methyluracils (72), and acetophenone to the 6-phenyluracils (73). Bicyclic uracils (74) are obtained from azomethines and cyclic ketones.



(70) (71) (72) (73) (74)

Such reactions provide an exceedingly simple route to a large number of uracil derivatives, some of which are too difficult to prepare in other ways; in two German patent applications, Nos. 2126148 and 2142317, over a hundred examples are listed together with yields and melting points[26].



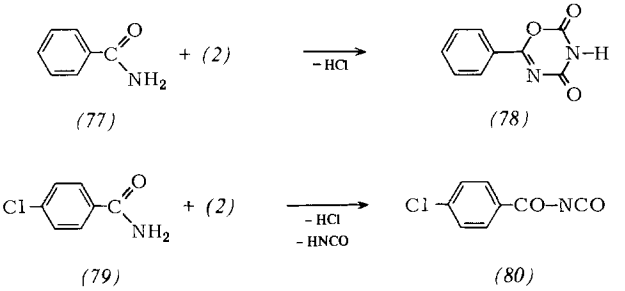
(75) (76)

Table 8. Disubstituted 1,3-oxazine-2,4-diones (76) from (2) and ketones (75).

R^1	R^2	M.p. [°C]	Yield [%]
—$(CH_2)_4$—		152—154	35
H	p-Cl—C_6H_4	244—246 (dec.)	50
H	C_6H_5—CH=CH	265—267	56
H	C_6H_5	229—230	55
CH_3	C_6H_5	177—178	47
n-C_3H_7	C_6H_5	146.5—148	54
H	$(CH_3)_3C$	193—194	50
C_2H_5O—CO	CH_3	99—100	77
CH_3	C_2H_5	146—147	51
CH_3CO	CH_3	122—124	68

Ketones of general formula (75) can be treated in a similar way, yielding 1,3-oxazine-2,4-diones (76) (Table 8)[27].

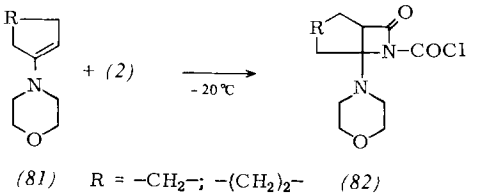
A small change in the nucleophilic character of the centers controlling the ring formation can completely transform the course of the reaction; while benzamide (77) and (2) cyclize smoothly to the phenyloxadiazinedione (78) (m.p. >360 °C, yield >90 %), p-chlorobenzoyl isocyanate (80) is almost the sole product when p-chlorobenzamide (79) is used. The nucleophilicity of the carboxamide group is apparently so weakened that the expected primary product decomposes before it can cyclize.



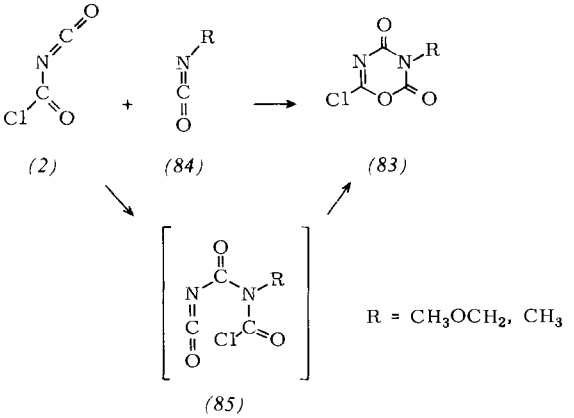
(77) (78) (79) (80)

3.7.5. Cycloadditions Involving (2)

The marked tendency of N-chlorosulfonyl isocyanate (1) to undergo cycloadditions with even relatively apolar olefinic double bonds has not yet been observed with (2). On use of the strongly polar double bond of enamines (81), however, the [2+2]-cycloadducts (82) have recently been obtained[2d].



(81) R = $-CH_2-$; $-(CH_2)_2-$ (82)



(2) (84) (83) (85) R = CH_3OCH_2, CH_3

Formation of adducts *(83)*[28], corresponding in result to a [2+4]-cycloaddition between *(2)* and aliphatic isocyanates *(84)*, can also be explained by assuming intermediates *(85)*. The addition of acid chlorides to the C=N double bond of isocyanates is a known reaction[29].

Received: June 10, 1977 [A 185 IE]
German version: Angew. Chem. *89*, 789 (1977)
Translated by Express Translation Service, London

[1] a) *W. Gottardi, D. Henn*, Monatsh. Chem. *101*, 11 (1970); b) *C. Jäckh, W. Sundermeyer*, Chem. Ber. *106*, 1752 (1975).
[2] a) *V. J. Gorbatenko, N. W. Melnitschenko*, Zh. Org. Khim. *11*, 2227 (1975); b) *V. J. Gorbatenko, L. F. Lur'e, L. J. Samarai, ibid. 12*, 1963 (1976); c) *ibid. 12*, 2473 (1976); d) *L. A. Lazukina, V. J. Gorbatenko, L. F. Lur'e, V. P. Kukhar', ibid. 13*, 290 (1977).
[3] *H. Hagemann, D. Arlt*, Belg. Pat. 731350 (1969), Bayer AG, German Pat. Appl. P 176817.7 (1968).
[4] a) *R. G. R. Bacon, R. S. Irvin, J. M. Pollock, A. D. E. Pullin*, J. Chem. Soc. *1958*, 764; b) *D. Pawellek*, Angew. Chem. *78*, 908 (1966); Angew. Chem. Int. Ed. Engl. *5*, 845 (1966); c) *H. Hagemann, D. Arlt, I. Ugi, ibid. 81*, 572 (1969) and *8*, 606 (1969), respectively; d) *H. Hagemann*, DOS 2126540 (1972), Bayer AG.
[5] a) *R. Graf*, Chem. Ber. *89*, 1071 (1956); b) Angew. Chem. *80*, 179 (1968); Angew. Chem. Int. Ed. Engl. *7*, 172 (1968).
[6] a) *H. Hagemann*, DOS 1668011 (1970), Bayer AG; b) *H. Hagemann*, DBP 1900542 (1970), Bayer AG.
[7] *H. Holtschmidt*, Angew. Chem. *74*, 848 (1962); Angew. Chem. Int. Ed. Engl. *1*, 623 (1962).
[8] *H. Hagemann*, Angew. Chem. *85*, 1058 (1973); Angew. Chem. Int. Ed. Engl. *12*, 999 (1973).
[9] *D. Arlt*, Synthesis *1970*, 21.
[10] *E. Klauke*, unpublished.
[11] *R. J. Slocombe, E. E. Hardy, J. U. Sunders, R. L. Jenkins*, J. Am. Chem. Soc. *72*, 1888 (1950).
[12] a) *O. Diels, B. Wolf*, Chem. Ber. *39*, 688 (1906); b) *W. Klebert, E. Müller*, DOS 1518806 (1969), Bayer AG; c) *A. J. Speziale, L. R. Smith, J. E. Fedder*, J. Org. Chem. *30*, 4306 (1965); d) *H. Hagemann*, DOS 1793088 (1972), Bayer AG; e) *G. Zinner, G. Isensee*, Chem.-Ztg. *97*, 73 (1973); f) *H. Hagemann*, DOS 2449365 (1976), Bayer AG.
[13] *H. Hagemann, J. Pedain, E. Zankl*, DOS 2048658 (1972), Bayer AG.
[14] *H. Hagemann*, DOS 2300541 (1974), Bayer AG.
[15] *H. Hagemann, K. Ley*, Angew. Chem. *84*, 1062 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1011 (1972).
[16] *H. Hagemann*, DOS 1931283 (1971), Bayer AG.
[17] *V. P. Kukhar', M. V. Shevschenko, N. A. Kirsanova*, Zh. Org. Khim. *9*, 1815 (1973).
[18] *H. Hagemann*, DOS 2408069 (1975), Bayer AG.
[19] *Th. Kappe, E. Ziegler*, Angew. Chem. *86*, 529 (1974); Angew. Chem. Int. Ed. Engl. *13*, 491 (1974).
[20] a) *H. Hagemann*, DOS 1927921 (1970), Bayer AG; b) *E. M. Smolin, L. Rapoport: s*-Triazines and Derivatives. Interscience, New York 1959, pp. 397ff.; c) Brit. Pat. 928637 (1963), Olin-Mathieson Chemical Corporation; d) *P. A. Argabright*, French Pat. 1582371 (1969).
[21] *H. Hagemann*, DOS 2036172 (1972), Bayer AG.
[22] *H. Hagemann, A. v. König*, DOS 2261739 (1974), Agfa-Gevaert AG.
[23] *H. Hagemann, K. Ley*, Angew. Chem. *84*, 1063 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1011 (1972).
[24] *H. Hellmann*, Angew. Chem. *69*, 466 (1957).
[25] a) *H. Hagemann, K. Ley*, Angew. Chem. *84*, 1063 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1012 (1972); b) *W. Stadlbauer, Th. Kappe*, Chem. Ber. *109*, 3661 (1976).
[26] a) *H. Hagemann, K. Ley*, DOS 1959705 (1971), Bayer AG; b) *K. Ley, G. Aichinger, A. Botta, H. Hagemann, E. Niemers*, DOS 2126148 (1972), Bayer AG; c) *K. Ley, G. Aichinger, H. Hagemann, E. Niemers, F. Hoffmeister*, DOS 2142317 (1973), Bayer AG.
[27] *G. Jäger, H. Hagemann, K. Findeisen, A. v. König, A. Poot, J. v. Besauw*, DOS 2520956 (1976), Agfa-Gevaert AG.
[28] *H. Disselnkötter, H. Hagemann*, unpublished.
[29] a) *H. Hagemann, K. Ley*, DOS 1932830 (1971), Bayer AG; b) *H. Disselnkötter*, DOS 1793287 (1972), Bayer AG.

Entanglement of Thread Molecules and Its Influence on the Properties of Polymers

By Martin Hoffmann[*]

Dedicated to Professor Otto Bayer on his 75th birthday

This article shows the extent to which the entanglement of threadlike molecules can influence many of the properties of deformable polymers and of solutions of macromolecular substances. Thus, the molecular concept of entanglement leads to quantitative predictions of the dependence of the entanglement number on the nature of the polymer, its concentration, and extension. Experimental values of the relaxation modulus confirm these predictions for melts and solutions. The influence of entanglement on relaxation and flow processes leads to very simple relationships for the magnitudes of the structural viscosity and the shear stress at which the structural viscosity starts to become measurable. Osmotic pressures, light scattering intensities, and diffusion coefficients of concentrated solutions can be derived quantitatively from the conformational constraints due to entanglement. Entanglement is effective above a concentration at which the three-dimensional coils fill the solution volume, and probably also at lower concentrations. At very high concentrations entangled structures may be formed which drastically reduce the number of possible conformations. The swelling and extension behavior of cross-linked deformable polymers can be understood only if entanglement is taken into account.

1. Introduction

In dilute solutions[1] and in melts[2] long threadlike molecules demonstrably assume a conformation resembling a three-dimensional coil: for a polystyrene sample of molecular weight $M=1\times10^6$ in toluene solution the diameter of the coil is about 100 nm. Such coils are approximately spherical and in this case have a volume V of about 3×10^8 ml per mole. The polymer concentration in the coil is M/V and here amounts to about 0.3 wt-%. In solutions containing more than 0.3 wt-% of such a polymer the coils may interpenetrate or escape interpenetration by shrinkage. The coils are energetically preferred, *i. e.* stable, conformations; they rapidly return to their original shape after deformation (rubber-elasticity[3]). As a result, they shrink only little on concentrating the solutions, and they are so large in melts that, with such threadlike molecules and because of the high polymer concentration in the melt, the number of molecules contained in the volume of one coil must be of the order of 10^2. If several coils interpenetrate with retention of the coil conformation, then chain fragments must touch one another during the continual movement of the chains (conformational changes); in some cases the movement is such that one chain twines round the other so that further movement is hindered. Such contact between two chains acts briefly as a chain junction made by main valences.

This concept of physical cross-linking by entanglement was first formulated several decades ago (for a review see [4]), but was accepted only slowly as a basis for theoretical interpretation of the properties of polymers and their solutions[4–6]. Such conformational interaction of polymer molecules does not arise from any specific interaction by secondary valence forces between them and therefore occurs generally in solutions and melts, as well as in partly crystalline and cross-linked polymers. Since entanglement influences many of the properties of high-molecular substances and their solutions, the underlying principles and effects will now be surveyed and formulated quantitatively for noncrystalline systems.

2. The Molecular Model

The shape of long molecules essentially resembles a random flight path, being formed by joining rigid chain fragments of given length (segments) to one another in such a way that the direction of the last segment is completely independent of the direction of the previous one and all directions occur with equal probability[7]. These segments of length l replace equally long chain fragments regarded as rigid (straight or possibly curved). The distance h between the ends of a sufficiently long chain of Z segments is then on average a vector of length $l\sqrt{Z}$. If Z is large, the chain can be divided into subchains each with Z_i members, and each subchain obeys chain statistics (*i. e.* $h_i=l\sqrt{Z_i}$). The vectors h_i at the junctions are on average perpendicular to one another, as is easily appreciated by considering the case of $Z=2Z_i$; here $h=l\sqrt{Z}$ and $h_i=l\sqrt{Z/2}$, so that $h=\sqrt{2}\cdot h_i$ is the diagonal of a square of side length h_i.

For the description below, which is correct to an order of magnitude, the segment model can be simplified to the string-of-beads model; thus, we assume that the segments are compact balls that in a melt adopt a close packing and become deformed so as to eliminate empty spaces. The segment molecular weight M_S can then be employed to calculate how many segments are contained in 1 cm³ of the melt of density ρ ($N_A\approx6\times10^{23}$);

$$N_S=\frac{\rho N_A}{M_S} \tag{1}$$

[*] Dr. M. Hoffmann
Bayer AG, Zentrale Forschung, Wissenschaftliches Hauptlabor
5090 Leverkusen (Germany)

On estimating how many bonds are required for the direction of a polymethylene chain to be continued with equal probability in each spatial direction (a requirement of the segment model), one obtains a segment molecular weight M_S of around 170, in agreement with estimates from measured coil dimensions[8]; thus for polyethylene N_S is approximately 3×10^{21}.

Next, we can calculate how many contacts between different chains occur in 1 cm^3 of this melt. Figure 1 shows two macromolecules A and B in a melt, the two chains being in contact at segment a of chain A. The segment a has twelve nearest neighbor sites, of which two are occupied by neighboring portions of chain A. In addition, back-coiling of chain A causes further p nearest neighbor sites of segment a to be occupied by chain A.

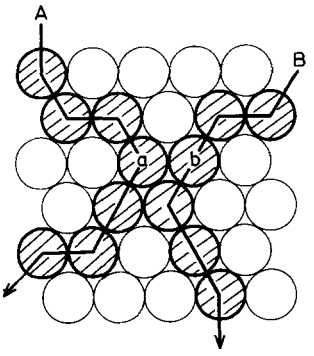


Fig. 1. Two thread molecules A and B whose spherical segments in the melt adopt close packing (represented two-dimensionally).

When estimating the back-coiling number p, it must be remembered that the third segment (counting from a) can occupy, out of the twelve possible places, those four that are adjacent to a, so that $4/12=0.33$ neighboring sites of a are occupied. This treatment can be continued for further segments, considering then the positions of the third segment. The residence probability P of a more distant segment at a site adjacent to a can be calculated by the known statistical function[10] for chain-end separations (α is *Flory*'s expansion factor[10]):

$$P(x,y,z)\mathrm{d}x\mathrm{d}y\mathrm{d}z = \left(\frac{3}{2\pi Z l^2 \alpha^2}\right)^{3/2} \exp\left[-\frac{3}{2Z l^2 \alpha^2}(x^2+y^2+z^2)\right]\mathrm{d}x\mathrm{d}y\mathrm{d}z \qquad (2)$$

For $l=1$ each of the twelve neighboring sites has the volume $\mathrm{d}x\mathrm{d}y\mathrm{d}z=1$ and in eq. (2) the exponent $-3/(2Z\alpha^2)$. The summation over all values of $12P(Z_i)$, leading to p, should already be stopped, however, when Z_i is still small: entanglements are continually being untied and new ones formed; the network chains of the entanglement network, *i.e.* the portions of the chain between entanglement points, contain in the melt relatively few segments [see eq. (17)], of which certainly only a small proportion can be attached at segment a without severely straining the residual part of the network chain. Contact of chain A at segment a with distant segments of the same chain should therefore be regarded as contact between different chains. In solutions the network chains comprise many more segments than in melts, so that p can then be greater than in melts; $p\approx1$ has been estimated for the latter.

If one considers that chain A coils back to segment a from two directions, one finds that, of the twelve neighboring sites of segment a in the melt, $2+2p\approx4$ sites are occupied by segments of the neighboring portions of chain A. The remaining $12-4=8$ sites adjacent to segment a can now be occupied by segments of other chains. If chain B occupies such a position with segment b, then a and b have four nearest neighbors in common, of which on average $4\times4/12$ are occupied by chain A and the same number by chain B. Chain B thus occupies $1+(4/3)=2.3$ of the sites adjacent to a. The eight sites at a which are free for contact with other chains can thus be occupied by $8/2.3=3.5$ foreign chains. On counting all N_K contacts of the various chains in 1 cm^3 of the melt, each contact refers to two segments and is therefore counted twice, giving the contact number N_K as[9]:

$$N_K = \frac{3.5}{2} N_S \qquad (3)$$

For polyethylene therefore, in conjunction with eq. (1), $N_K=5\times10^{21}$.

It still remains to be shown which of these contacts should be regarded as entanglements. Entanglements should be contacts that withstand many changes of chain conformation and thus are so long-lived that they act as cross-linking sites, permitting rubber-elastic deformations of the melts. Figure 2 shows such a contact position of chains A and B. In this presentation[9] the chains are symbolized only by the vectors h_i of the subchains, which here have the designations A_1, A_2, B_1, and B_2. In the outer part of Figure 2, these vectors end in further entanglements of the chains A and B. Had the contact of chains A and B taken the form shown in Figure 1, it would have been rapidly broken by the usual conformational changes. On average, such changes leave unaltered the length of the vectors A_1, A_2, B_1, B_2 and angle α (on average a right angle) between A_1 and A_2 and the angle β between B_1 and B_2. Having fixed the lengths of the vectors A_i and B_i, as well as α and β, the allowed conformational changes thus correspond to rotating chain A (or B) around the vector h_A (or h_B). It is now simple to formulate the conditions under which contact between chains A and B is not destroyed by such rotations. In so doing, it must be borne in mind that h_A and h_B can assume any position in space. The contact is not destroyed if the following geometric conditions are fulfilled (for $\alpha=\beta=90°$):

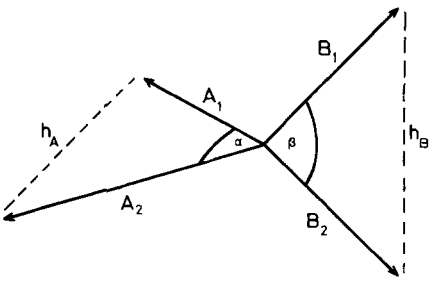


Fig. 2. Two thread molecules A and B touch at one point. Their subchains are symbolized by the vectors A_1 and B_1. The vectors h_A and h_B join the end points of two chain fragments that are themselves situated at further entanglement points [9].

a) Chain B touches chain A in the internal angle of the vectors A_1 and A_2. This happens with a probability $W_a=1/4$ ($=90°/360°$).

b) Vector B_1 lies above and vector B_2 below the plane of the vector A_1 and A_2: $W_b = 1/2$.

c) In cases where the plane containing A_i is at right angles to that of B_i: B_1 points in directions in space that correspond to the octant lying diagonally "opposite" the internal angle between A_1 and A_2: $W_c = 1/4$. W_c is not changed when the plane of A_i is not at a right angle to that of B_i.

The fraction $W = W_a \times W_b \times W_c = 0.031$ of all N_K contacts is therefore long-lived. Such contacts are entanglements that are only destroyed when neighboring contacts are also released in a cooperative process.

This argument can be extended to all cases in which the angles α and/or β are not 90°.

If $\beta = 90°$, then W_2 is always 1/2 and $W_1 = \alpha/360$, and further $W_3 = (180-\alpha)/360$. The probability $W_{\alpha\beta}$ then amounts to:

$$W_{\alpha\beta} = \frac{8}{360^4}[\alpha(180-\alpha)\cdot\beta(180-\beta)] \tag{4}$$

α and β can assume any values between 0 and 180°, so that the probabilities are proportional to $\sin\alpha$ and $\sin\beta$, respectively, the maximum of the frequency distribution of statistical conformations lies at 90°, and half of all cases have angles between 60 and 120°. If $W_{\alpha\beta}$ is multiplied by the corresponding values of the frequencies of α and β and averaged, the result is $W_R = 2/\pi^4 = 0.021$. Furthermore, W_R is not changed when the vectors A_1, A_2, B_1, B_2 are allowed to have different lengths. If, however, the entanglements are sufficiently long-lived, then A_i and B_i "forget" to which chain they belong and thus on average point to the corners of a tetrahedron. The frequency distribution of the angles then has a maximum at 109.5°, so that the probability $\bar{W}$ falls to $\bar{W}_{109.5} = 0.018$[9]. The entanglement number N_v is then:

$$N_v = 0.018\, N_K \tag{5}$$

For polymethylene eqs. (4) and (3) give $N_v = 9 \times 10^{19}$.

The preceding derivation neglects the effect of end groups and thus assumes infinitely long molecules. If the network chains of the entanglement network have a molecular weight M_c and the molecules have a molecular weight M, then networks can be formed[3] only if the condition known for cross-linking polymerizations[11] is fulfilled for the construction of a continuous network:

$$2M_c \leq M \tag{6}$$

In the derivation of eq. (5) it was also considered unimportant that some of such entanglements are more easily broken than others. Thus, the entanglement number calculated according to eq. (5) includes entanglement for which the pair of values α and β or the position of chain A relative to chain B only just fulfil the geometric requirements for entanglement. Even small diffusion movements of neighboring entanglement points can break such entanglements, so that they will certainly be shorter-lived than the others.

Furthermore, no consideration was given to how easily the chains could slide over one another and to how far the end of the chain is separated from the entanglement of interest. Diffusion of a chain end could break an entanglement near to this end faster than a more distant one[9]. Such considerations will be taken up in Section 4 below.

We would add here that, even in the absence of any long-term relaxation, the entanglement number N_v given by eq. (5) is lowered if the entanglement network is subjected to shear or deformation[12]. Deformation causes changes in the angles α and β and thus in the geometric requirements for entanglement. The tetrahedral entanglement (Fig. 3) is broken if sufficiently strong uniaxial stretching occurs in directions that do not lie in the part of the spherical shell drawn in the figure (or in the opposite direction), for then the stretching directions make an angle smaller than 90° with one or more of the relevant chain vectors. Thus, purely geometrically and in a very short time, a large stretch reduces the number of entanglement points per unit volume to the fraction X:

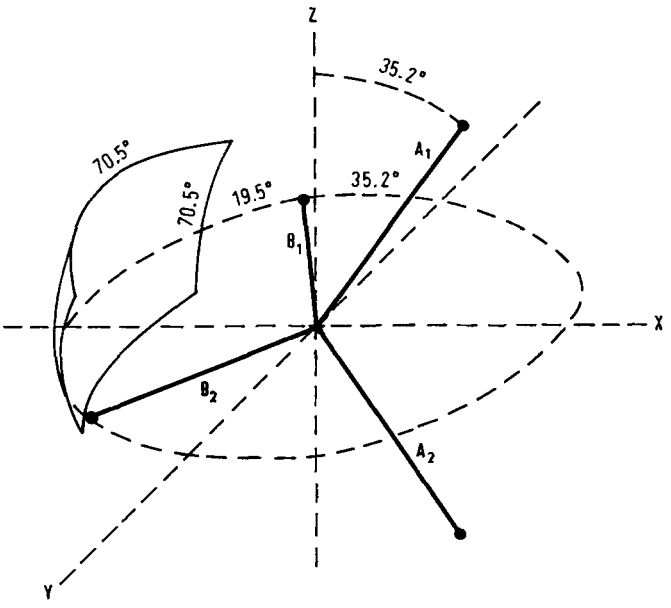


Fig. 3. As a result of stretching the spatial directions and lengths of the vectors at a (tetrahedral) contact of two chains are deformed, so that the entanglement no longer has the same probability $W_{\alpha\beta}$ [see Eq. (4)] as before the stretching [12].

$$X = \frac{\alpha}{180}\sin\left(\frac{180-\beta}{2}\right) \tag{7}$$

If one averages over all α and β corresponding to their frequency, one obtains[12] for a maximum of the frequency distribution 90° $\bar{X} = 0.33$ and for 109.5° an almost identical value. If one now permits even a slight relaxation or slip of the sometimes very unevenly stretched network chains at the entanglement points, then the number of residual entanglement points decreases almost to zero.

Furthermore, it is important to know how small extensions reduce the entanglement number N_v. The ends of the vectors A_1, A_2, B_1, and B_2 can occupy any desired point on the surface of a sphere of radius $|A|$. On deformation (extension ratio $\lambda = L/L_0$) such a sphere is transformed into an ellipsoid of rotation ($a = |A|\cdot\lambda$, $b = |A|/\sqrt{\lambda}$), so that on average each vector assumes a greater length $|A_\lambda|$[3]:

$$|A_\lambda|^2 = |A|^2\left(\frac{\lambda^2}{3} + \frac{2}{3\lambda}\right) \tag{8}$$

The coordinate x (in the stretching direction) and y of each vector end-point have thus changed into $x' = x \cdot \lambda$ and $y' = y/\sqrt{\lambda}$, so that an angle γ formed initially by the x-axis and such a vector ($\tan\gamma = y/x$) changes to γ' ($\tan\gamma' = y'/x' = \tan\gamma/\lambda^{1.5}$). If one puts the length $|A_\lambda|$ into the equation for the ellipsoid of rotation one obtains the relevant angle α' between two vectors as $\tan(\alpha'/2) = \pm 1/\lambda^{1.5}$. Before the stretching, the angles α and β amount on average to 90° and are transformed into smaller or greater angles α' and β'. As a result, $W_{\alpha\beta}$ [eq. (4)] decreases to $W_{\alpha'\beta'}$, *i.e.* the entanglement number N_v falls to N'_v. The factor f_λ ($= W_{90,90,\lambda}/W_{90,90,\lambda=1}$) gives the fraction of entanglements that are still present at λ (relative to the number at $\lambda = 1$) (Fig. 4a). The elastic restoring force of an entanglement network (referred to the cross section of the stretched specimen) is therefore not, as in main-valence networks, proportional to $\lambda^2 - 1/\lambda$ [see eq. (9)], but is instead proportional to $f_\lambda(\lambda^2 - 1/\lambda)$. Figure 4b shows the course of this function. Above a certain extension the restoring force should decrease on further extension. The entanglement network thus breaks on deformations around $\lambda = 2$. The experimentally observed extension law for non-cross-linked, very slowly relaxing polymers confirms that the entanglement number N_v decreases with λ in the manner derived here[12]. Moreover, the shear stress at which structural viscosity occurs shows that entanglement networks break at specific extensions (see Section 5).

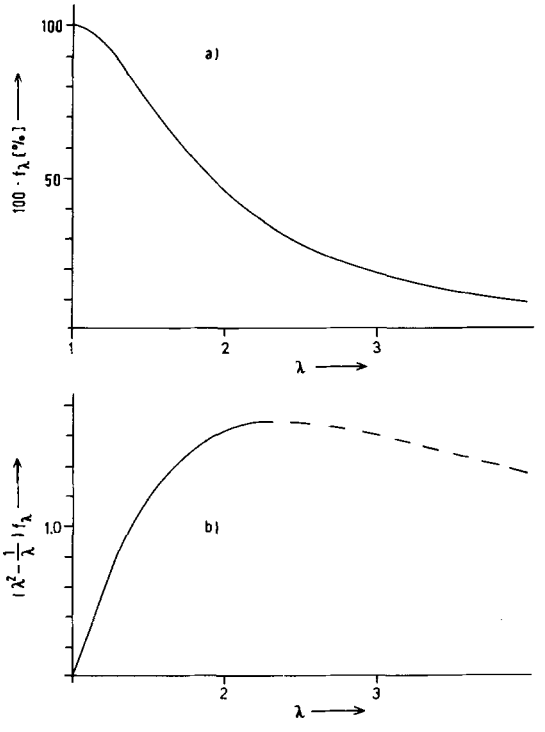


Fig. 4. a) The percentage of active entanglements as a function of the extension ratio λ. $f_\lambda = W_{90,90,\lambda}/W_{90,90,\lambda=1}$ is not exactly $1/\lambda$ as required by the Mooney-Rivlin equation [19]. b) The restoring force σ_r of an entanglement network divided by the relaxation modulus G_r (at $\lambda = 1$) in dependence on the extension ratio λ [cf. eq. (9)]. If λ is larger than corresponds to the curve maximum, an equilibrium retractive force is no longer established: the sample flows by a mechanism different to the usual one, where the conformational changes destroy and rebuild entanglements even at low τ. The relationship applies for all polymers.

The above considerations neglect the fact that in entanglement networks of undiluted polymers (and in very concentrated solutions) the network chains lead to a network junction that, although a neighbor along the chain, is not the junction nearest in space but in fact one further removed (Fig. 5) (see also Section 8). If such a network is stretched, volume elements of interest become more remote in the stretching direction.

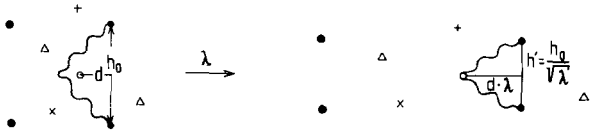


Fig. 5. At high concentrations the distances between the entanglement points are smaller than those between the ends of the network chains. Then several simple networks seem to interpenetrate (different point symbols for each network). If such a system is deformed, contacts are established that were not previously present; these contacts are not broken during extension, thus acting as additional entanglement points [12].

Since the contour length of the network chains remains unchanged, the network chain finally contacts a spatially close network junction[12] (Fig. 5). Even a small extension can lead in this way to larger entanglement numbers, estimated[11] as $(5/3)N_{v,\lambda=1}$. After a small extension, therefore, the $N_{v,\lambda=1}$ in eq. (5) should be replaced by $(5/3)N_{v,\lambda=1}$.

3. Conclusions from the Molecular Model and Their Experimental Testing with the Aid of the Relaxation Modulus

Equation (5), the result of the molecular model, can be tested by investigating whether melts have highly elastic properties. As shown in Figure 6, it is in fact found experimentally that above the softening temperature a rapid deformation is followed by restoring forces σ that remain constant for a longer time (plateau of the relaxation modulus in the rubber region of the relaxation). Use of the extension ratio $\lambda = L/L_0$ permits calculation of the relaxation moduli E_r or $G_r = 3E_r$ (G_r = shear modulus in experiments with $f_\lambda \approx 1$)[3]:

$$\sigma_r = G_r\left(\lambda^2 - \frac{1}{\lambda}\right) = 2N_v kT\left(\lambda^2 - \frac{1}{\lambda}\right)\left(1 - \frac{2M_c}{M_n}\right) \qquad (9)$$

At sufficiently high molecular weights G_r is proportional to $2N_v$, the number of network chains per cm³ of the melt, and it has a finite value only when the molecular weight M_n (M_n = number-average molecular weight of the polymer) of the polymer exceeds $2M_c$ (Fig. 6).

However, at appreciably larger M, G_r is independent of M. This result is to be expected from the description of entanglement given above, because at $M < 2M_c$ the known requirement for network formation [see eq. (6)] is not fulfilled. On the other hand, if $2M_c \ll M$, the entanglement number does not depend on the molecular weight because the small number of chain ends does not influence the relaxation modulus.

For polyethylene melts at 120°C one obtains according to eq. (9) a modulus G_r of about 1.1×10^6 Pa, and thus an entanglement number $N_v = 8 \times 10^{19}$ at 25°C. The agreement of this value with that estimated from eq. (4) is much too good in view of the uncertainty in the segment size, the crude approximations of the molecular model used here, and the uncertainty in the conversion from 120 to 25°C. The experiment thus confirms the molecular model at least to within

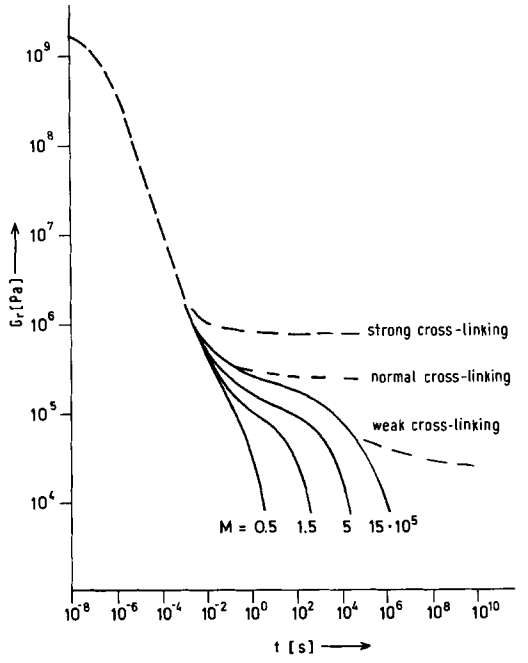


Fig. 6. Restoring forces σ_r arise after momentary stretching of *cis*-1,4-polyisoprene, which decrease as the load-application time is increased. In non-cross-linked samples of molecular weight $M > 2 \times 10^4$ it is observed that G_r (the relaxation modulus calculated from the restoring force) remains nearly constant for a certain time (the plateau of the modulus in the rubber elastic region of the relaxation). G_r is there almost independent of the molecular weight and of weak cross-linking by main valences [14].

an order of magnitude and encourages us in our search for further conclusions.

In proceeding further it must be remembered that the segment model correctly represents the conformations of a chain of CH_2 groups linked together at the usual valence angles. The auxiliary quantity "segment" is used only to simplify the statistics. In reality the spheres considered here are the CH_2 groups of the polymethylene chain and these are joined together with specific valence angles. If to a polymethylene melt we add oligomers or solvent molecules having the size of one segment (or the size of the CH_2 groups), not changing the chain conformation by special interactions with the polymer, then the solvent molecules will occupy some neighboring sites of each segment and thus reduce the number of contacts between different chains (contact number N_K). The probability of pairs of segments from different chains occurring is known to be proportional to the square of the volume fraction φ of the polymer, provided that the back-coiling number p is not dependent on φ:

$$N_{K,\varphi} = N_{K,1} \cdot \varphi^2 \tag{10}$$

Since, furthermore, the geometric conditions of chain conformation at entanglement points are not changed by the presence of solvent molecules, it follows from eq. (10) and (5) that the entanglement number is[9]:

$$N_{v,\varphi} = N_{v,1} \cdot \varphi^2 \tag{11}$$

Table 1. Relaxation moduli G_r, critical shear stresses τ_w (see text), molecular weights for network chains M_c, and molar volumes V_g of the repeating unit for the entanglement networks in linear polymers, in dependence on the volume fraction φ and temperature.

Polymer	T [°C]	V_g [ml·mol^{-1}]	φ	G_r [Pa 10^{-4}]	τ_w [Pa 10^{-4}]	$M_{c,1}$
Polymethylene	+25	31	1	90	—	2500
Polybutadiene (Li)	+25	32	1	55	≈70	4300
Polyisoprene (*cis*-1,4)	+25	37	1	32	≈30	7300
Polyisobutylene	+25	62	1	20	≈30	11000
Polydimethylsiloxane	+25	72	1	10	11.0	25000
Poly(vinyl acetate)	+25	73	1	10	8.0	30000
Polystyrene	+25	97	1	5.5	9.0	45000
Poly(butyl acrylate)	+25	129	1	4.0	3.0	65000
Poly(2-ethylhexyl acrylate)	+25	203	1	3.0	3.0	80000
Poly(dodecyl methacrylate)	+25	285	1	1.7	1.1	140000
Polyisoprene (Li)	−51		1	28		
($M = 1.7 \times 10^6$)	−22		1	29		
	+25	37	1	30	17	
	+84		1	29		
in toluene	+25		0.59	10.5	5.3	
	+25		0.44	7.9		
	+25		0.32	3.5	1.5	
	+25		0.26	1.45		
	+25		0.20	0.70		
	+25		0.19	0.90		
	+25		0.17	0.55	0.4	
	+25		0.11	0.13	0.15	
	+25		0.055	0.012	0.015	
Polystyrene	+25	97	0.21	0.56	0.40	
($M_v = 6 \times 10^6$, $U_M \approx 0.3$)	+25		0.13	0.28	0.15	
in toluene	+25		0.12	0.24	0.15	
	+25		0.059	0.055	0.045	
	+25		0.028	0.006	0.008	
in decalin	+25		0.12	0.16	0.14	
	+25		0.058	0.035	0.03	
	+25		0.028	0.005		
Polystyrene	+25	97	0.25	0.76	0.70	
($M = 1.15 \times 10^6$)	+25		0.12	0.06	0.14	
in toluene						
in decalin	+25	97	0.25	0.75	0.60	
	+25		0.12	0.050	0.14	

Table 1 shows that the relaxation modulus G_r, which according to eq. (9) is a measure of the entanglement number N_v, does in fact depend on the square of the volume fraction φ of the high-molecular components in solutions and polymer mixtures[9]. The same result can be derived from the right-hand side of Figure 7 ($f_t \sim G_r$). Fractions with molecular weights $M < M_{c,\varphi=1}$ thus lower the entanglement density of a polymer.

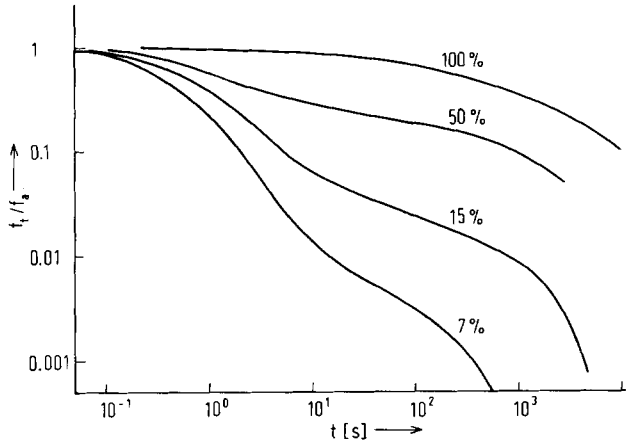


Fig. 7. Restoring forces arising after momentary (5 ms) deformation of mixtures of two molecularly homogeneous ($U_M < 0.02$) polyisoprenes (Li) ($M_1 = 2 \times 10^6$, $M_2 = 1.4 \times 10^5$) plotted as a function of the load-application time at 22 °C. f_t/f_a has the following meaning: $f = \sigma/\lambda$ is the restoring force referred to the initial cross-section of the sample, and f_a is the same for all samples (3.0 bar $= G_r$; eq. (9)). According to eq. (9), $\sigma_r \sim G_r$. The components relax at different rates, which leads to the stepwise nature of the relaxation curves of such mixtures [9]. The numbers on the curves are the proportions of M_1 in the mixtures.

When we next consider melts of chains whose side groups are so large that they occupy neighboring sites of a segment, and thus decrease the entanglement number N_v, we see that, as in eq. (11), the square of the volume fraction of backbone chains determines the entanglement number. If $V_{g,PE}$ is the molar volume of an ethylene unit and V_g that of the repeating unit of a vinyl polymer with side groups, then we should find that[9]:

$$N_v = 8 \times 10^{19} \left(\frac{V_{g,PE}}{V_g} \right)^2 = \frac{0.75 \cdot 10^{23}}{V_g^2} \tag{12}$$

Figure 8 and Table 1 show that eq. (12) is also confirmed by experiment[9]. In these calculations we used the molar volume V_g of the repeating unit of the polymers or the molar volume of a chain fragment of constant length, this fragment corresponding to a repeating unit in the case of vinyl polymers. In eq. (12) it is assumed that the backcoiling number p does not depend on the structure of the polymer; special hindrance to rotation is also disregarded.

In place of the number N_v of entanglement points in 1 cm^3 we may use M_c, the molecular weight of the network chains in the entanglement network (ρ = density of the polymer). From equations (9), (11), and (12):

$$G_{r,\varphi} = 2 N_{v,\varphi} kT \left(1 - \frac{2 M_{c,\varphi}}{M_n} \right) = \frac{\rho \varphi RT}{M_{c,\varphi}} - \frac{2 \rho \varphi RT}{M_n}$$

$$= \frac{2.1 \times 10^6 \times T \times \varphi^2}{V_g^2} - \frac{2 \rho \varphi RT}{M_n} \text{ [Pa]} \tag{13}$$

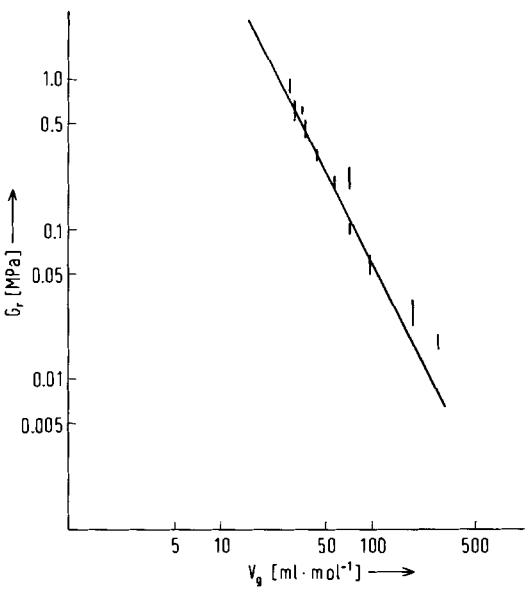


Fig. 8. Relaxation moduli G_r, measured according to Fig. 6, of various polymers (for individual values see Table 1) plotted as a function of the molar volume V_g of a chain fragment whose length corresponds to a repeating unit of the vinyl polymers [9].

$$M_{c,\varphi} = \frac{\rho \varphi N_A}{2 N_{v,\varphi}} = \frac{4.1 \times \rho V_g^2}{\varphi^2} = \frac{M_{c,1}}{\varphi} \tag{14}$$

A proportionality between $M_{c,\varphi}$ and $1/\varphi$ was earlier derived by *Bueche* by a different route and was tested experimentally[5].

At this point we should turn to yet another consequence of the molecular model, concerning the segment size. Eq. (3) shows the relation between the segment number N_S and the contact number N_K in chains without side groups. According to eq. (12) side groups reduce the contact number proportionally to $(V_{g,PE}/V_g)^2$. It is now possible to define an apparent segment size by assuming spherical segments (larger than in polyethylene because the spheres now contain the side groups) and apply eq. (3) for the calculation of the segment number. The segment number in melts is then given by:

$$N_{S,m} = \frac{N_K}{1.75} = \frac{N_{K,PE}}{1.75} \cdot \left(\frac{V_{g,PE}}{V_g} \right)^2 = \frac{1.67 \times 10^{24}}{V_g^2} = \frac{N_A}{V_{S,m}} \tag{15}$$

It follows that the molecular weight of the segment $M_S = V_S \rho$ in melts is:

$$M_{S,m} = 0.36 \times \rho \times V_g^2 \tag{16}$$

Experimentally, it has been found that eq. (16) is confirmed, although the factor 0.36 is better replaced by 0.2[9].

Now, since according to eq. (13) the molecular weight $M_{c,1}$ of the network chain in the melt is also proportional to V_g^2, the network chains of different polymers in the melt all contain the same number of segments[9]:

$$\frac{M_{c,1}}{M_{S,m}} = \frac{4.1}{0.36 \text{ to } 0.2} = 11 \text{ to } 21 \tag{17}$$

For nonideal solutions eq. (14) must be modified when the distance h between the ends of a molecule in such solutions is greater by the Flory expansion factor[13] α than in ideal

solutions (denoted by a subscript θ): $h=h_\theta\cdot\alpha$. The volume occupied by a chain fragment of molecular weight M_c in the form of a coil is then increased by the factor α_c^3 over that in ideal solvents, so that correspondingly more foreign chains pass through this coil and form entanglements. Moreover, in each volume element there are α_c^3 as many chains, because at a given total concentration the more coils must overlap, *i.e.* interpenetrate, the greater the coils are at a given molecular weight, so that the total concentration may everywhere be attained. Finally, the segment length also increases, under the usual assumptions ($Z_0 l_0^2 \alpha^2 = Z l^2$ and $Z_0 l_0 = Z l$) by the factor α_c^2. The segment molecular weight M_S thus similarly increases by about α_c^3, so that N_K and hence N_v should decrease by α_c^3. In all, α_c thus changes eq. (14) to[14]:

$$M_{c,\varphi} = \frac{M_{c,\theta,\varphi}}{\alpha_{c,\varphi}^3} = \frac{M_{c,\theta,1}}{\varphi \times \alpha_\varphi^3} = \frac{M_{c,1}}{\varphi}\cdot\left(\frac{\alpha_{c,1}}{\alpha_{c,\varphi}}\right)^3 = \frac{M_{c,1}}{f(\varphi)} \tag{18}$$

$$\left(\frac{\alpha_{c,\varphi}}{\alpha_{c,1}}\right)^3 = \frac{f(\varphi)}{\varphi} = \frac{G_{r,\varphi} + \dfrac{2\rho\varphi RT}{M_n}}{\left(G_{r,1} + \dfrac{2\rho\varphi RT}{M_n}\right)\varphi^2} \tag{19}$$

The experimental relaxation moduli confirm (see Table 1 and Figs. 9 and 19) the influence of the efficiency of the solvent and thus the influence of α_c.

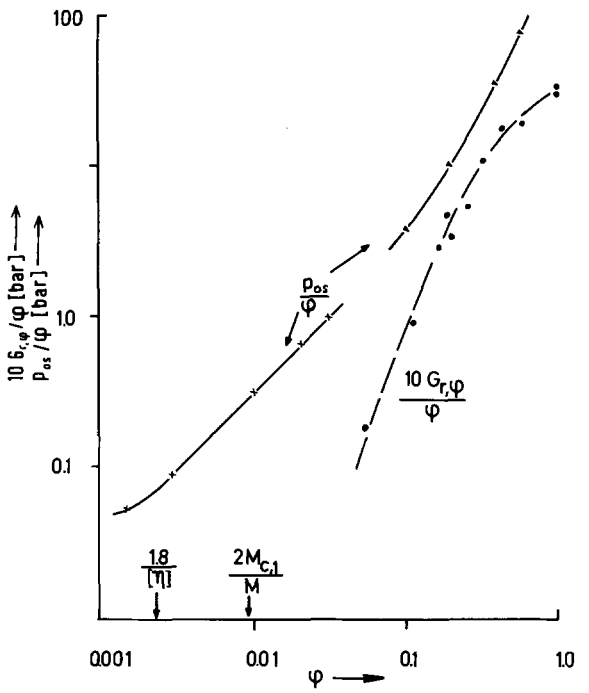


Fig. 9. Relaxation moduli $G_{r,\varphi}$ divided by the concentration φ (=volume fraction) plotted as a function of the concentration for mixtures of polyisoprene (Cariflex IR 305, $M_w = 1.7\times10^6$, $U_M < 0.1$) and toluene, as measured from the relaxation behavior 15—3000 ms after momentary (5 ms) compression or shear and extrapolated to $t=0$ (Hottinger technique, display oscillograph). The osmotic pressures p_{os}, also plotted were measured with an automatically compensating osmometer [14] (left-hand branch of the curves) or taken from the literature [29].

According to experimental investigations of structural viscosity[15] and relaxation modulus (see Table 1) in a temperature interval of about 100°C, the temperature dependence of $M_{c,1}$ is negligibly small. The modulus plateau can therefore hardly be due to an equilibrium between association and dissociation of the polymer chains[31].

4. Influences of Entanglement on Relaxation and Flow Processes

All the investigations described so far show that the entanglement number is an intrinsic property of each polymer and is thus independent of time. Since, however, according to Figure 7 restoring forces disappear in the course of time and melts or solutions can flow, it must be assumed that the entanglement numbers measured correspond to a dynamic equilibrium between disentanglement and renewed entanglement. The underlying processes are not specific associations and dissociations of the polymer chains but the usual conformational changes of the chains, diffusion of chain ends through entanglement loops[6], and cooperative and nearly simultaneous conformational changes at several neighboring entanglement points[4-6]. It is found that polystyrene powder ($M_w \approx 10^5$), produced by spraying of dilute solutions into vacuum, has the usual flow behavior immediately after pressing in vacuum, *i.e.* about 40 min after the spraying. Thus, the entanglement network must have formed in the course of this time. Other experiments show that large dissolved molecules diffuse away from one another in milliseconds after instantaneous fission; then the fragments display the usual light scattering[16]. The conformations clearly change so fast that even complicated structures such as entanglement networks are formed sufficiently rapidly. Further information on this is provided by a study of strain relaxation and of flow.

Figure 7 shows relaxation measurements made on mixtures of polyisoprenes with a heterogeneity index of about 1.1. It is evident that these mixtures form two kinds of entanglement networks. At short times one finds moduli that correspond to the usual moduli for polyisoprenes (Fig. 6), independently of the composition of the mixture or its molecular weight M_w (weight average molecular weight). This means that the two types of molecules have formed a common network whose network density is independent of the composition of the mixture. At long times, however, there is a second plateau of the relaxation moduli that shows much smaller moduli and depends strongly on the concentration of the high-molecular fraction and can therefore be assigned only to entanglement of the larger molecules. At this time all the entanglement positions in which short molecules take part have changed their conformation, their contribution to the restoring force being lost because the chains have formed an equal number of new entanglements with the use of undeformed chain fragments. The entanglements of the larger molecules remain; these are broken only after longer times, because there must be a cooperative process involving many entanglement points simultaneously—or at least coordinated in time and space—and this cooperation requires the more points, the larger is the molecule concerned.

Bueche[5] and others (for a review see [4]) have used the concept of entanglement in theories of flow. Accordingly, the maximal relaxation time t_r in the rubber-elasticity region of the relaxation and the viscosity η proportional to it depend extensively on the molecular weight M and the concentration φ (volume fraction)[17]:

$$t_r = \text{const.}\,\eta = \text{const.}\; M^{3.5}\cdot\varphi^4 \tag{20}$$

Figure 7 gives the times in which the entanglement networks of molecules of various sizes undergo strain relaxation to one-tenth of its original value; these times are approximately in the ratio $(M_2/M_1)^{3.5}$, thus confirming eq. (20). Furthermore, the step heights obey approximately the expected law, namely eq. (13). On the other hand, concentration dependence of t_r in this experiment appears to be considerably weaker than predicted by eq. (20); the reason for this is that the process cannot be described by a single relaxation time, and the maximal relaxation times t_r for disappearance of the last traces of a restoring force cannot yet be measured with accuracy.

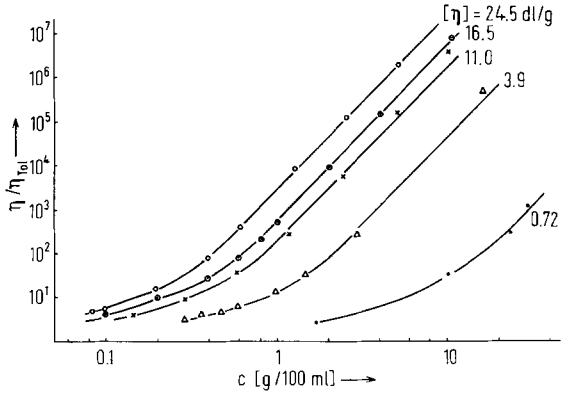


Fig. 10. Relative viscosity η/η_{tol} (from flow curves extrapolated to shear stress $\tau = 0$) plotted as a function of the concentration for polystyrene fractions of various molecular weights. $[\eta]$ = limiting viscosity in [dl/g] in toluene at 25 °C. Above a critical concentration the viscosity of the solutions increases with c^4. The critical concentration decreases with increasing molecular weight.

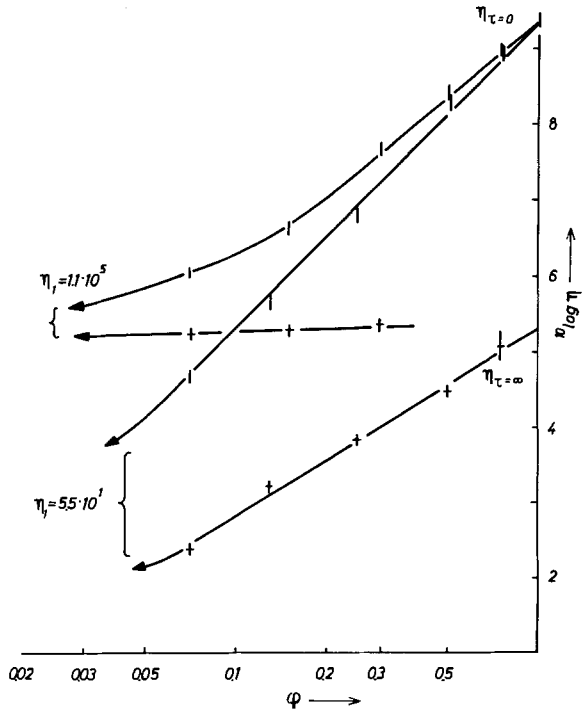


Fig. 11. Flow curves for mixtures of two polyisoprenes (Li, $M_1 = 1.4 \times 10^5$ or 1.2×10^4; $M_2 = 2 \times 10^6$, $U_M < 0.1$) give viscosities $\eta_{\tau=0}$ and $\eta_{\tau=\infty}$ extrapolated to shear stresses $\tau = 0$ and $\tau = \infty$, respectively, which are here plotted as a function of the concentration (= volume fraction φ) [17]. The $\eta_{\tau=\infty}$ is extrapolated as if the viscosity η_1 of the lower-molecular component were independent of τ and at sufficiently small η_1 is proportion to φ^2. At sufficiently small η_1, however, $\eta_{\tau=0}$ is proportional to φ^4. $\eta_1 = 1.1 \times 10^5$ refers to $M_1 = 1.4 \times 10^5$; $\eta_1 = 5.5 \times 10^1$ refers to $M_1 = 1.2 \times 10^4$.

However, many investigations of the flow of solutions confirm the concentration dependence expressed in eq. (20) (Figs. 10 and 11). Naturally, this is only so if the prerequisites for eq. (20) are satisfied, *i.e.* if the expansion factor α and the back-coiling number p as well as the segment mobility are none of them strongly dependent on φ[9, 17].

The flow behavior of melts and solutions containing entangled molecules also shows other effects of entanglement. It is found that the molecular volume V_g of the repeating unit of the vinyl polymers has an appreciable influence[17]:

$$\eta_v = f(T - T_g) \times \frac{M^{3.5} \cdot \varphi^4}{V_g^{7.5}} \cdot 1.7 \times 10^{-5} \text{ [Pa·s]} \quad (21)$$

The factor $f(T - T_g)$ describes the influence of the strongly temperature-dependent segment mobility. In the absence of entanglement the viscosity is far less influenced by M, φ, and V_g[17]:

$$\eta = f(T - T_g) \times \frac{M^{1.45} \cdot \varphi^2}{V_g^{3.5}} \cdot 2.5 \times 10^{-4} \text{ [Pa·s]} \quad (22)$$

Thus, eq. (21) holds for the dependence of the viscosity on molecular weight at molecular weights M that fulfil the network-formation condition [eq. (6)], whereas eq. (22) applies if M is smaller. This kink or transition in the $\log\eta - \log M$ relationship has been shown to appear in many polymers and solutions[4, 5, 17, 21].

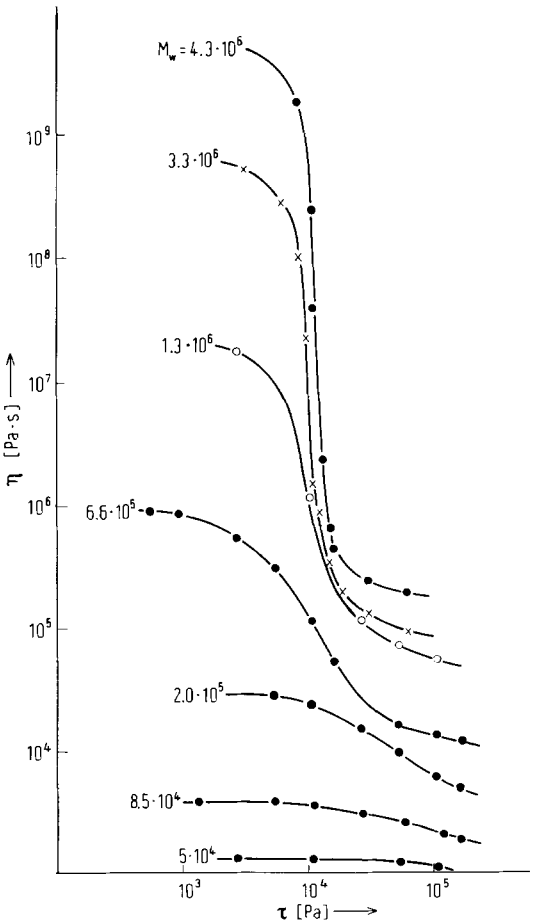


Fig. 12. Flow curves of unbranched polydodecyl methacrylates at 25 °C. The flow curves of these polymers can be measured down to the vicinity of the second Newtonian region without fracture of the melt [17].

A further consequence of entanglement is the appearance of a structural (non-Newtonian) viscosity that is much stronger than in systems where the thread molecules do not entangle. If melts or solutions that follow eq. (21) are made to flow under higher shear forces, their viscosity decreases with increasing shear stress τ (Fig. 12). At very high shear stresses the viscosity reaches values that correspond to those of eq. (22)[17], so long as the melt does not previously collapse (melt fracture). The quotient of the viscosities η_v and η constitutes a suitable measure of the magnitude of the structural viscosity:

$$\frac{\eta_{\tau=0}}{\eta_{\tau=\infty}} = \frac{\eta_v}{\eta} = 1.54 \times 10^{-2} \frac{M^2 \varphi^2}{V_g^4} = \left(\frac{M}{M_{c,\varphi}}\right)^2 \tag{23}$$

Figure 13 shows flow curves for polyisoprene mixtures[9] at low shear stresses. Measurements on solutions[18] and on the mixtures of Figure 13 are shown in Figure 14 to conform, at least approximately, to eq. (23) which, as previously, is formulated for constant expansion factors α_c and constant back-coiling numbers p. The influence of the basic molar volume V_g is not clearly visible for the few polymers studied,

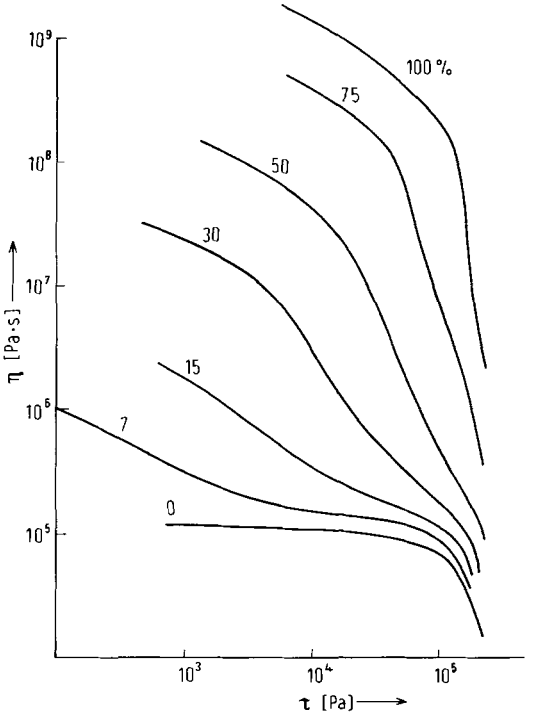


Fig. 13. Flow curves of mixtures of homogeneous ($U_M < 0.1$) polyisoprenes ($M_1 = 1.6 \times 10^6$; $M_2 = 1.4 \times 10^5$) at 25 °C. Addition of the component with a high molecular weight raises the viscosity $\eta_{\tau=0}$ and produces a structural viscosity and an inflection point in the flow curves in the region of $\tau < 10^5$ Pa, this inflection not being observed with homogeneous polymers [9]. The numbers on the curves give the proportion (percentage) of M_1.

apparently because other factors such as differences in *Bueche*'s slipping factor[5] may play a part. The constants derived experimentally[17] for eq. (23) agree with the constants obtained differently for eq. (14), in fact much too well in view of the large limits of error in the construction of eq. (23). The size $\eta_{\tau=0}/\eta_{\tau=\infty}$ of the structural viscosity is thus simply equal to the square of the number of network chains per molecule, which is a clear indication of a cooperative process. The experimental result does not confirm other theoretical claims so well[4, 5].

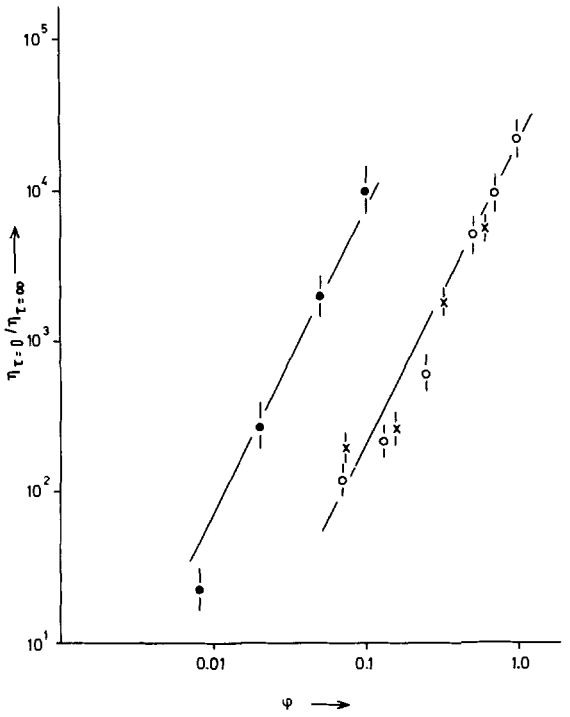


Fig. 14. $\eta_{\tau=0}/\eta_{\tau=\infty}$ as a measure of the magnitude of the structural viscosity plotted against the concentration φ for polystyrenes ($M = 1.4 \times 10^7$, $U_M \leq 0.3$) in toluene (●), and for polyisoprene ($M = 1.7 \times 10^6$, $U_M \leq 0.1$) in polyisoprenes of lower molecular weight (○; see Fig. 13) as well as in toluene (+) at 25 °C. The concentration dependence sufficiently confirms eq. (23).

To obtain a visible structural viscosity of the melts it is necessary to use various shear stresses, suited to the individual polymer. For a more precise discussion we use the shear stress τ_w found at the inflection point of the plots of $\log\eta$ *versus* $\log\tau$. Figure 12 shows that the τ_w are almost independent of M, so that τ_w may be regarded as a property of entanglement networks. Furthermore, the τ_w follow laws similar to those for G_r[9, 17]. Eq. (24) summarizes the results for several polymers at various concentrations (see also Table 1):

$$\tau_w = \frac{5.5 \times 10^8 \cdot \varphi^2}{V_g^2} \approx G_r\,[\mathrm{Pa}] \tag{24}$$

This finding can be interpreted as showing that the same distortion of the entanglement network is always sufficient to reduce its effect on viscosity by a certain fraction, confirming the considerations of the dependence of the number of active entanglements on the extension, which lead to the assumption that $\tau_w \approx 1.6\,G_r$ (see Fig. 4). The collapse of the entanglement network becomes evident when, at high shear stresses, melt fracture occurs. Consequently, these critical shear stresses are proportional to φ^2/V_g^2[17, 18] so long[32] as no stretch crystallization occurs.

Moreover, it can be assumed that under the influence of an applied load, *i.e.* deformation of the chain fragments taking part in entanglement, the diffusion steps or conformational changes leading to a removal of the load are preferred to others and so accelerate the disentanglement of the stressed network chains[6, 4], but leave the process of new entanglement unaffected. A gradual decrease of entanglement could therefore occur during relaxation after large deformations.

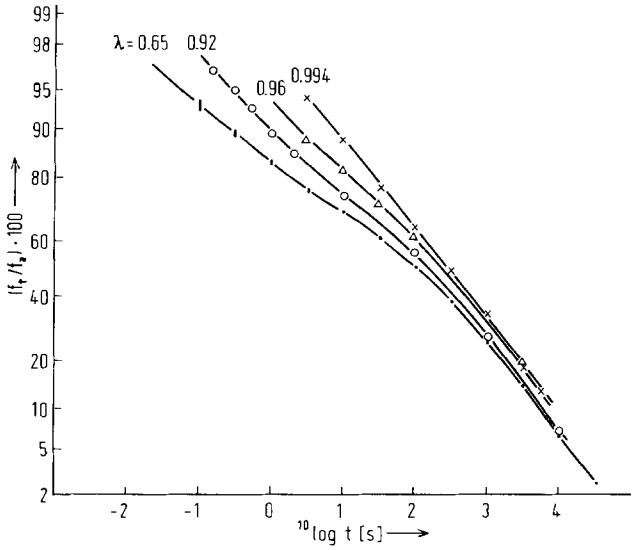


Fig. 15. Rate of strain relaxation (as a percentage) in a non-crosslinked polyisoprene ($M/M_0 \approx 130$) after momentary (5 ms) compression increases with increasing deformation as a result of the nonlinear form of eq. (9) and for the same reason as causes structural viscosity (see text). λ = extension ratio. $f_a = \sigma_a/\lambda$ can be calculated for $\lambda \geq 0.92$ by means of eq. (9) with $G_{r,a} = 3.0$ bar·cm^{-2}.

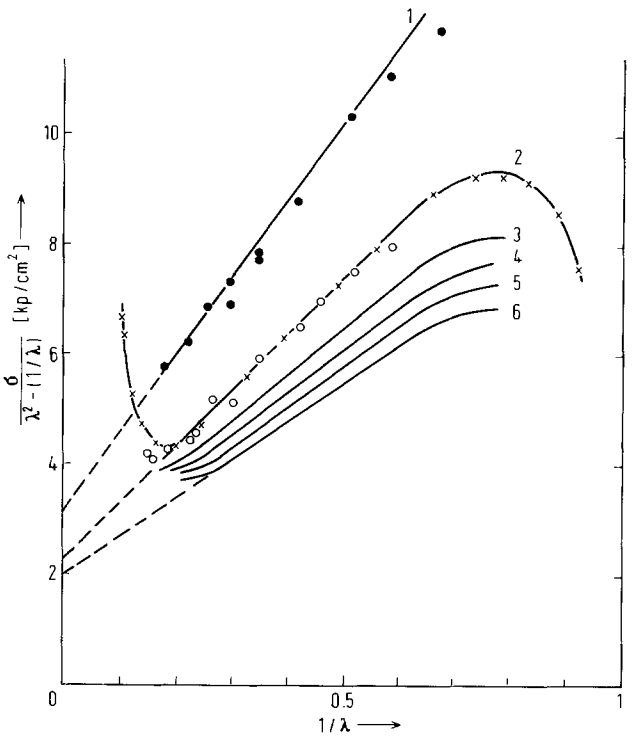


Fig. 16. As described by Mooney-Rivlin-Saunders [19], the quotients of the stress σ (referred to the cross-section of the stretched sample) and $\lambda^2-(1/\lambda)$ (λ = extension ratio) are plotted against $1/\lambda$. The intercept $2C_1$ on the left-hand ordinate is a measure of the main-valence cross-linking; that on the right, $2C_2$, is a measure of the concentration of entanglements active under the measurement conditions. $2C_2$ decreases with increasing duration of stress [12]. Curves 1 to 6: $d\lambda/dt = 13$, 1.25, 0.12, 0.025, 6.25×10^{-3}, 1.25×10^{-3}.

The same causes as lead to the appearance of structural viscosity lead to the fact that the relative rate of stress relaxation is greater after large than after small elongations: According to Figure 15, the halflife of mechanical relaxation decreases with increasing deformation[9].

5. Influence of Entanglement on the Extension of Cross-Linked Materials

The fact that the effective entanglement number depends on the extension is also important for the properties of materials such as rubber[12] that are cross-linked by main valences. Figure 6 shows their relaxation behavior in comparison with that of non-cross-linked material. With slightly to medium cross-linked samples we find, at short loading times, relaxation moduli that correspond to those of non-cross-linked polymers. Only after prolonged loading times does cross-linking by main valences become noticeable, so that analytic stretching experiments are often carried out with extended loading times. On the other hand, in chemically weakly cross-linked samples and with brief and slight (*e.g.* periodic) deformations, restoring forces are found that arise only from the entanglement network and, according to Figure 6, are usually greater than expected on the basis of the weak main-valence cross-linking. Since, however, according to Fig. 4, entanglements are made ineffective by strong deformations, even with short-lasting load applications one can, by using strong deformations, recognize the restoring forces that arise from the main-valence cross-linking. At large extensions one then finds the extension behavior predicted by the theory for main-valence networks[12]. With medium extension rates and deformations one must divide the restoring forces by the Mooney-Rivlin-Saunders procedure[19] into $2C_1$, the fraction due to the main-valence network, and $2C_2$, the fraction due to the entanglements (Fig. 16).

The ordinate intercept of the straight part of the curve at $\lambda = 1$ is $2C_2$, and that at $\lambda = \infty$ is $2C_1$. The fraction $2C_2$ decreases, as expected, when the loading times are increased, and also if the sample is swollen, as would be expected from the strong concentration dependence of the entanglement number shown by eq. (13). The experiments confirm the following law[12]:

$$\frac{2C_{1,\varphi}}{\varphi^{1/3}} + \frac{2C_{2,\varphi}}{\varphi^2} = \frac{5}{3} G_{r,\varphi=1} \tag{25}$$

In the rubber region of relaxation behavior the breaking stresses and maximal extensions also rise with increasing rate of extension, because with short loading times (rapid stretching) the restoring forces affect more contacts and entanglements than with long times.

Finally, the maximum degree of swelling of cross-linked samples is influenced by entanglement of the thread molecules because entanglement changes the thermodynamic properties of the solutions. In the usual swelling equations a value of the interaction parameter (Flory-Huggins parameter) χ_1 should then be used[14], which is influenced by the effects of entanglement, as will now be shown.

6. Significance of Entanglement for the Thermodynamic Properties of Solutions

If melts or solutions become rubber-elastic by the entanglement of thread-like molecules and thus possess an entropy-determined memory, and if the entanglement density depends

on the concentration, then on dilution of such a network an entropy change ΔS occurs that differs from the entropy change for unentangled dissolved polymers[20, 14]. This can have a considerable bearing on the thermodynamic properties of such systems and will be formulated here, because previous formulations[21] of statistical thermodynamics cannot yet be used for experimental testing.

If a chain comprising b bonds or Z segments (of bonding number b_s and length $l=1$) is fastened at one end in such a way that the orientation of the first segment with respect to the anchoring is defined, then that chain can assume ω_0 conformations, which can be calculated when the rotation potential has three minima and thus each bond can be oriented in a total of three spatial directions[3]:

$$\omega_0 = 3^b = 3^{b_s Z} \tag{26}$$

If such a chain is fastened at both ends, *e.g.* at entanglement points, then only a fraction of the previously permissible conformations is possible. This can easily be understood by considering a chain of two segments. The end points of the second segment mark out evenly the surface of a sphere of radius l. On average, the first and the second segment make an angle of 90° to each other. If we specify that this angle is strictly retained, so that the chain ends always maintain the statistical mean value of their separation, then the end of the second segment can occupy only positions on an arc and no longer on the whole surface of the sphere.

If the separation h of the ends of the chain considered in eq. (26) has the statistical mean value, then $h_0^2 = Z l^2$; and with $l=1$ and eq. (2) the conformation number ω_e of the chain fixed at both ends[3] is given by:

$$\omega_e = \omega_0 \cdot \left(\frac{3}{2\pi Z \alpha^2}\right)^{3/2} \cdot e^{-3/2} = \frac{\omega_0 \cdot 0.074}{Z^{1.5} \cdot \alpha^3} \tag{27}$$

In the case of greater entanglement each polymer molecule with its Z segments is divided into $m+1=(M/M_c)+1$ parts, of which $m-1$ parts are network chains with Z/m segments and two parts are end fragments with $Z/2m$ segments. The total number of conformations of such a chain is ω_m:

$$\omega_m = \left(\frac{3^{Zb_s/m} \cdot 0.074}{(Z/m)^{1.5} \cdot \alpha_c^3}\right)^{m-1} \cdot (3^{Zb_s/2m})^2 = \omega_0 \cdot \left(\frac{0.074}{(Z/m)^{1.5} \cdot \alpha_c^3}\right)^{m-1} \tag{28}$$

For calculating the dependence of ω_m on concentration we require the concentration dependences of m and α_c. According to eq. (18) we have:

$$m_\varphi = \frac{M}{M_{c,\varphi}} = m_1 \times \left(\frac{\alpha_{c,\varphi}}{\alpha_{c,1}}\right)^3 \times \varphi = m_1 \cdot f(\varphi) \tag{29}$$

The concentration dependence of $\alpha_{c,\varphi}^3$ follows according to eq. (19) from that of $G_{r,\varphi}$, φ, and $f(\varphi)$:

$$\frac{d\alpha_{c,\varphi}^3}{d\varphi} = \frac{\alpha_{c,\varphi}^3}{\varphi}\left(\frac{\varphi f'(\varphi)}{f(\varphi)} - 1\right) = \frac{\alpha_{c,\varphi}^3}{\varphi}\left(\frac{d\ln G_{r,\varphi}}{d\ln\varphi} - 2\right) \tag{30}$$

The entropy S_φ of the network of N_2 polymer molecules and N_1 solvent molecules can now be obtained[14]:

$$S_\varphi = k N_2 \ln \omega_{m,\varphi}$$
$$= k N_2 \{b_s Z \ln 3 + (m_\varphi - 1)[\ln 0.074 - 1.5 \ln(Z/m_\varphi) - \ln \alpha_{c,\varphi}^3]\} \tag{31}$$

At least in the case where $\alpha_{c,\varphi}=1$, eq. (31) agrees with other formulations for network-formation entropy[21].

In addition to the entropy of mixing $S_\varphi - S_1$ derived from eq. (31), a further term $-kN_1\ln(1-\varphi)$ must be introduced into the equation for the free energy of mixing (subscript M), since this describes the amount of entropy that should be assigned to a giant molecule containing $N_2 \cdot Z$ segments (the entanglement network)[22]:

$$\Delta G_M = \Delta H_M - T\Delta S_M = k T_1 N_1 \varphi - T[S_\varphi - S_1 - k N_1 \ln(1-\varphi)] \tag{32}$$

The osmotic pressure p_{os} can now be calculated by substituting eq. (31) into eq. (32) and by partial differentiation[22]:

$$p_{os} = -\frac{N_A}{V_1} \cdot \left(\frac{\partial \Delta G_M}{\partial N_1}\right)_{N_2} \tag{33}$$

V_1 is the molar volume of the solvent, $N_A = 6 \times 10^{23}$, and k is Boltzmann's constant. To carry out the differentiation we need $d\alpha_{c,\varphi}^3/d\varphi$ [eq. (30)], $\alpha_{c,\varphi}^3$ [eq. (19)], and finally the quantity $(\partial\varphi/\partial N_1)_{N_2}$:

$$\left(\frac{\partial \varphi}{\partial N_1}\right)_{N_2} = -\frac{N_1}{V_2 N_2}\varphi^2 \tag{34}$$

We now obtain a relationship for p_{os} that involves not only the known term containing the Flory-Huggins parameter χ_1[22], but also a further term that depends on the relaxation modulus $G_{r,\varphi}$ of the solution, *i.e.* on its entanglement number N_v [see eq. (9)]. $f(\varphi)$ is the experimentally determinable function defined in eq. (18).

$$\begin{aligned} p_{os} = \frac{RT}{V_1}[&-\ln(1-\varphi) - \varphi - \chi_1 \varphi^2] + \\ &+ G_{r,\varphi}\left[\frac{d\ln G_{r,\varphi}}{d\ln\varphi} - 1\right]\left\{1.5 \ln \frac{M_{c,1}}{M_S} - \ln 0.074 - 1.5\ln\varphi\right. \\ &- 0.5 \cdot \ln\left(\left[\frac{G_{r,\varphi} + 2\rho\varphi RT/M_n}{G_{r,1}\cdot\varphi^2}\right] \cdot \alpha_{c,1}^3\right) \\ &\left. - 0.5\left[1 + \frac{1}{1 + (2\rho\varphi RT/M_n G_{r,\varphi})}\right]\left[2.5 - \frac{(1 + 2\rho\varphi RT/M_n G_{r,\varphi})}{[(d\ln G_{r,\varphi}/d\ln\varphi) - 1]}\right]\right\} \end{aligned} \tag{35}$$

In the last term the part beginning with $1/(1+\cdots)$ describes the usually small influence of the unentangled end fragments of the network. Eq. (35) is valid only for the case of an entanglement network and must not be extrapolated to $\varphi = 0$, *i.e.* to a very dilute solution.

With the experimental value of $G_{r,\varphi}$ we can calculate, by means of eq. (35) the portion of the osmotic pressure that corresponds to the term with $G_{r,\varphi}$. This pressure differs little at $\varphi < 0.1$ from the experimentally measured pressure (see Tables 2 and 3), so that we must conclude that at concentrations below 10% the first term on the right in eq. (35) is appreciably smaller than the term with $G_{r,\varphi}$. The parameter χ_1 must therefore have values of around 0.50, *e.g.* 0.51 for polystyrene in toluene and 0.57 for polystyrene in decalin.

Table 2. Osmotic pressures of concentrated solutions at 25°C, given as rise heights d of the solvent at 25°C [η] = viscosity.

Polymer	M_w	U_M	Solvent	c [g·ml^{-1}]	d [cm]	[η] [ml/g]
Polystyrene	$9.0 \cdot 10^5$	<0.02	Toluene	1.5	0.07	230
				3	0.20	
				6	0.65	
				9	1.25	
				18	5.4	
	$9.0 \cdot 10^5$	<0.02	Dimethylformamide	20	2.55	119
				30	5.18	
				40	9.35	
	$9.0 \cdot 10^5$	<0.02	Methyl ethyl ketone	25	2.8	117
				35	6.8	
				55	19.9	
	$9.0 \cdot 10^5$		Decalin	5	0.19	98
				10	0.47	
				20	1.50	
				40	5.30	
Polybutadiene (Li)		<0.02	Toluene	2	0.58	221
				4	1.25	
				5	1.73	
				10	4.93	
				18	20.57	
				40	119	
Polyisoprene (Li) (IR 305)		<0.1	Toluene	5	0.91	750
				10	3.57	
				20	16.31	
Polyisobutylene		0.3	Toluene	4	0.21	296
				6.7	0.56	
				10	1.07	
				15	2.45	
				30	10.22	
Poly(vinyl acetate)		0.3	Toluene	29.6	7.75	101
				30	8.0	
Polydimethylsiloxane		0.3	Toluene	20	6.9	110
				30	15.8	
Poly(butyl methacrylate)		0.3	Toluene	20	7.94	74
				30	17.55	
Poly(2-ethylhexyl acrylate)		0.3	Toluene	30	12.28	100
Poly(dodecyl methacrylate)		0.3	Toluene	10	0.70	320
				20	3.40	
				30	8.58	
Polyisoprene (Li)		<0.1	Cyclohexane	0.5	0.13	730
				1.0	0.44	
				2.0	1.68	
Polyisobutylene		0.3	Cyclohexane	10	2.35	580
				20	11.6	
Crepe [a]		0.3	Benzene	10	2.74	720
				20	13.45	

[a] Polyisoprene (*cis*-1,4).

Table 3. Comparison of calculated and measured osmotic pressures.

Polymer	Solvent	φ	$G_{r,\varphi}$ [Pa·10^{-2}]	$\frac{d \ln G_{r,\varphi}}{d \ln \varphi}$	p_{os} (calc.) eq. (35) [bar]	p_{os} (exp.) [bar]	$\chi_{1,corr.}$	p_{os} (calc.) eq. (41) [bar]
Polystyrene ($M_v = 8 \times 10^6$)	Toluene	0.25	79	1.5	0.39	2.0	0.50	—
		0.12	24	1.9	0.19	0.29	0.51	—
		0.06	5.5	2.2	0.066	0.063	0.52	0.080
		0.028	0.6	3.1	0.016	0.013	0.53	0.017
		0.01	—	—	—	0.0016	—	0.0020
	Decalin	0.25	80	1.9	0.55	1.5	0.51	—
		0.12	16	2.0	0.15	0.12	0.55	—
		0.06	3.7	2.3	0.051	0.015	0.58	0.0124
		0.028	0.5	2.7	0.011	0.0019	0.58	0.013
		0.01	—	—	—	0.00012	—	0.00009
Polystyrene ($M_v = 1.1 \times 10^6$)	Toluene	0.25	76	1.8	0.45	2.0	0.50	—
		0.12	6	4.3	0.18	0.29	0.51	—
		0.06	—	—	—	0.063	—	0.054
	Decalin	0.25	75	2.2	0.61	1.5	0.51	—
		0.12	5	4.4	0.16	0.12	0.56	—
		0.06	—	—	—	0.015	—	—
Polyisoprene (Li, $M_v = 1.7 \times 10^6$)	Toluene	0.50	900	2.0	6.1	27	0.42	—
		0.20	88	2.8	1.35	2.0	0.51	—
		0.10	10	3.3	0.25	0.39	0.48	—
		0.05	0.9	3.5	0.038	0.083	0.44	0.19
		0.01	—	—	—	0.0032	—	0.0062

A theoretical formulation[24], corresponding to the lattice theory[23], presumes that at high concentrations and with a homogeneous segment distribution the osmotic pressure is independent of the molecular weight and is proportional to the square of the concentration, but with these corrected χ_1 values this theory gives pressures that are much too low. For the same reason, the excluded-volume theory cannot explain the experimental values, especially as according to this theory the pressures would be expected to depend on the molecular weight. Experiment[20] shows (Fig. 17) that above a critical concentration φ^* the concentration dependence can no longer be described by the virial coefficients of this theory.

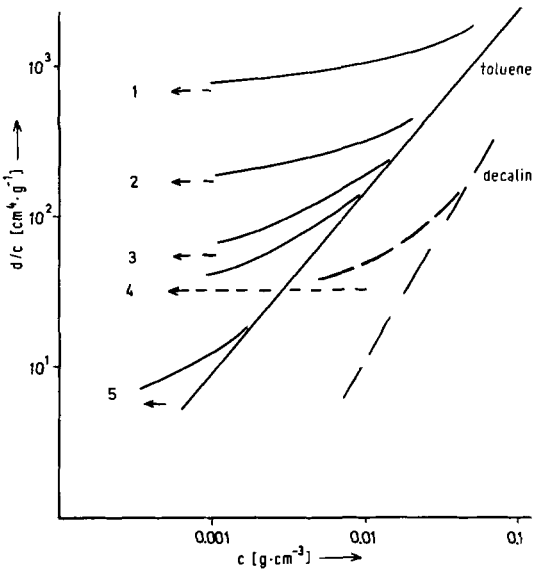


Fig. 17. Osmotic pressure p_{os} (represented as the rise height d of the solvent for $\rho = 0.87$) plotted against the concentration c in toluene (polymers 1 to 5) [20] and in decalin (*cis-trans* mixture) (polymer 5) at 25 °C for the following polystyrenes: 1, $M_w = 4.1 \times 10^4$, $U_M < 0.02$; 2, $M_w = 1.7 \times 10^5$, $U_M < 0.02$; 3, $M_w = 4.7 \times 10^5$, $U_M < 0.02$; 4, $M_2 = 9 \times 10^5$, $U_M < 0.02$; 5, $M_w = 1.4 \times 10^7$, $U_M \leq 0.3$. At sufficiently high concentrations the values reach the limiting straight line with all molecular weights.

The term including $G_{r,\varphi}$ in eq. (35) is almost proportional to φ^2. The same is true of $\chi_1 \varphi^2$, so that the two terms can be treated together by means of an effective parameter $\chi_{1,eff}$. The $\chi_{1,eff}$ measured at high concentrations thus contain an entropy component that is derived from the entanglement network and in nonideal solutions is dependent on concentration, because there $G_{r,\varphi}/\varphi^2$ is not quite constant but decreases with increasing concentration. $\chi_{1,eff}$ thus increases.

Eq. (35) is also important for light scattering R_0 (in the direction of the primary beam) and for diffusion in concentrated solutions, as shown by the following relationships[25, 26] (K^* = light scattering constant):

$$\frac{K^* \cdot c}{R_0} = \frac{1}{RT} \cdot \left(\frac{\partial p_{os}}{\partial c}\right)_T \tag{36}$$

$$D = \frac{M}{f} \cdot \left(\frac{\partial p_{os}}{\partial c}\right)_T \tag{37}$$

Since according to eqs. (35) and (13) p_{os} is independent of M and is proportional to the square of the concentration, it follows that $K^* c/R_0$ is independent of M and proportional to c, *i.e.* R_0 is independent of both M and c[20, 14] (Fig. 18). Then the diffusion coefficient D measured in concentrated solution is also proportional to c, whereas the value obtained by measurement in the supernatant dilute solution in an overlaying experiment is almost independent of c[20]. Thus, the

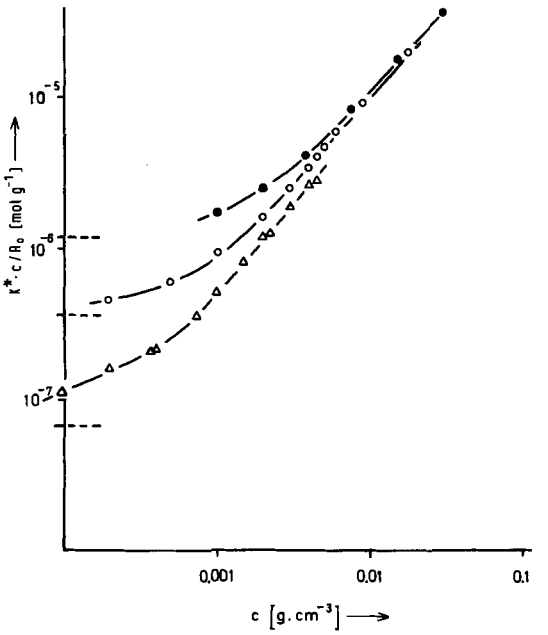


Fig. 18. Light scattering R_0 (extrapolated to the direction of primary beam) as a function of the concentration c for polystyrenes of various molecular weights ($U_M \leq 0.3$) in toluene at 25 °C. At sufficiently high concentrations the scattering becomes independent of the molecular weight and of the concentration [20].

concentrated solution increases its volume, *i.e.* it swells like a cross-linked polymer. Permeation of low-molecular substances through polymers, diffusion in melts (adhesion), and sedimentation are also altered by the formation of an entanglement network, as can be recognized from the preceding discussions. Finally, the effects of entanglement on the demixing behavior of concentrated solutions, *e.g.* on concentration of the concentrated phase and on swelling of substances cross-linked by main valences, can also be formulated by means of the equations given above. In an approximate manner, an effective interaction parameter $\chi_{1,eff}$ can be used for this purpose[14].

7. Effects of Entanglement at Medium and Low Concentrations

It now remains to demonstrate at what concentrations φ^{**} a solution begins to form an entanglement network. Figures 9 and 19 show that an osmotic pressure independent of the molecular weight can be observed already at small concentrations where one cannot detect the very small rubber elastic modulus arising from an entanglement network. The limiting concentration for the formation of an entanglement network follows from equations (9) and (18):

$$\varphi^{**} = \frac{2 M_{c,1}}{M_n} \cdot \left(\frac{\alpha_{c,1}}{\alpha_{c,\varphi}}\right)^3 \tag{38}$$

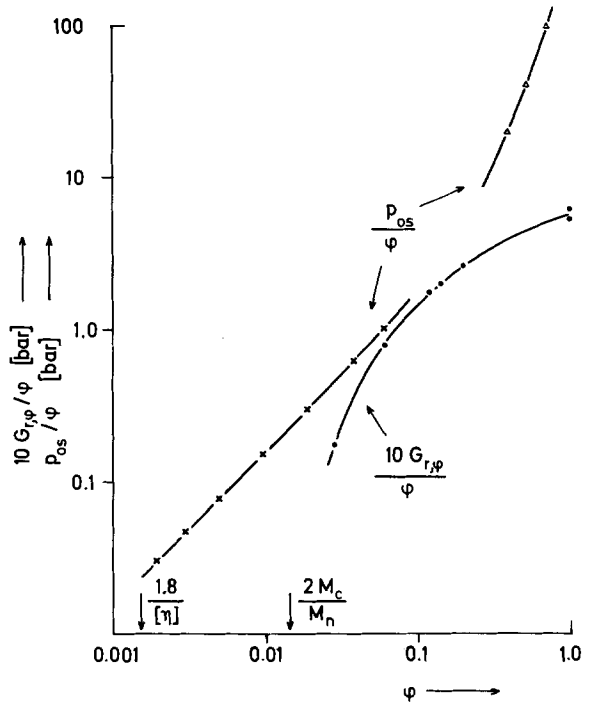


Fig. 19. Diagram plotted analogously to Fig. 9, showing $G_{r,\varphi}/\varphi$ and p_{os}/φ for polystyrene ($M_w = 8 \times 10^6$, $M_n = 5.5 \times 10^6$) in toluene at 25 °C. The left-hand branch of p_{os}/φ was determined as in Fig. 9; the right-hand branch comes from the literature [30] ($M_n = 2.9 \times 10^5$).

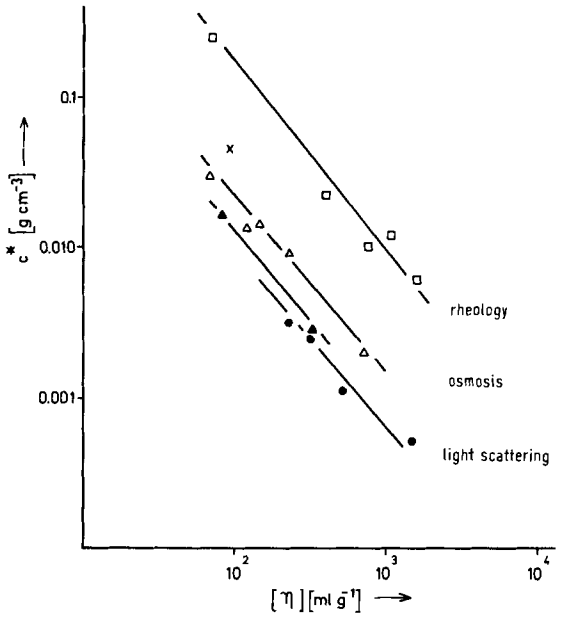


Fig. 20. Critical concentrations c^* above which the osmotic pressure p_{os} or the light scattering R_0 is independent of M, or the viscosity of the solutions rises with φ^4, plotted against the limiting viscosity $[\eta]$ for polystyrenes in toluene at 25 °C (△, ●, □), in cyclohexane at 35 °C (▲), and in decalin (*cis-trans* mixture) at 25 °C (×).

If then in accordance with eq. (13) $G_{r,\varphi}/\varphi$ is plotted against φ, one observes that, for polystyrene with $M_n \approx 6 \times 10^6$ in toluene or decalin, $G_{r,\varphi}$ disappears at $\varphi^{**} \approx 0.02$. The critical concentrations following from measurements of elasticity (see Fig. 19 for $G_{r,\varphi} \to 0$) correspond well with those from rheology (Fig. 10). Their value is somewhat higher than expected and could be explained by $\alpha_{c,\varphi} < 1$ (see below), but in any case it is far above the critical concentrations measured osmotically or by light scattering (see Figs. 9, 19, and 20). Furthermore, the critical concentrations measured osmotically are inversely proportional to $[\eta]$ according to Figure 20 and thus contrary to eq. (38). The value corresponds to a state of the solution where the coils just fill the volume of the solution. For spherical coils of diameter h this concentration would be:

$$\varphi^* = 0.74 \times \frac{2.5}{[\eta]} = \frac{1.85}{[\eta]} \tag{39}$$

The values obtained in good solvents follow this relationship very closely. Clearly mere mutual contact between the coils causes disturbances that raise the osmotic pressure above the value calculated by the excluded-volume theory (second virial coefficients dependent on the molecular weight) and, contrary to this theory, make the osmotic pressure independent of the molecular weight.

The cause of the disturbances is that at the concentrations in question the coils begin to interpenetrate; during this process entanglements occur between the end fragments of the chains, which may be found mainly in the outer regions of the coils[27]. Such entanglements are not subject to the statistics that led to eq. (9), so that M_c, the molecular weight of the network chains, is larger, and φ^* is smaller, than expected. At this stage the entanglements need not lead to a complete network but may only bind several coils together, thereby considerably restricting the number of possible conformations. The molecules can reduce these disturbances by shrinkage, so long as the increase in free energy due to shrinkage does not exceed the increase due to entanglement. Presumably some shrinkage occurs in the neighborhood of φ^*, which in the neighborhood of φ^{**} is largely superseded by stronger entanglement. On shrinkage, the free energy of the N_2 molecules in the network increases[28]:

$$\frac{\partial \Delta G}{\partial \alpha_K} = -6 c_M kT \left(\frac{1}{2} - \chi_1\right) \frac{\sqrt{M} N_2}{\alpha_K^4} + \frac{\partial \Delta G_{el}}{\partial \alpha_K} = 3 N_2 kT \left(\alpha_K - \frac{1}{\alpha_K} - \frac{\alpha_0^5 - \alpha_0^3}{\alpha_K^4}\right) \tag{40}$$

In expression (40) c_M is a constant, $\alpha_K = \alpha/\alpha_0$ is a relative expansion factor (<1) in the shrunken molecule and α_0 is the expansion factor (>1) before the shrinkage, the latter factor depending on interactions with the solvent. From the assumption $\alpha_K^3 = \varphi^*/\varphi$ that is arguable in the vicinity of φ^*, the pressure can be calculated as:

$$p_{os} = \frac{RT}{M} c \left[2 - \left(\frac{\varphi^*}{\varphi}\right)^{2/3} + (\alpha_c^5 - \alpha_0^3) \cdot \frac{\varphi}{\varphi^*}\right] + \frac{RT}{V_1} [-\ln(1-\varphi) - \varphi - \chi_1 \varphi^2] \tag{41}$$

According to Table 3 this expression agrees sufficiently well with the experimental values for polystyrene in toluene, polyisoprene in toluene, and polystyrene in decalin in the neighborhood of φ^* for $\chi_1 = 0.5$. The $\alpha_{c,\varphi} < 1$ discussed in respect of eq. (38) also supports this hypothesis.

Thus for a quantitative interpretation of the experimental pressures the relationship $\alpha_K = \varphi^*/\varphi$ must be assumed, *i.e.*

a strong dependence of α on concentration. As the usually assumed decrease of α over the whole concentration range to $\alpha=1$ in the melt is much smaller, this concentration dependence does not suffice to explain the osmotic pressure.

It is possible that entanglements exert their effect even at concentrations below φ^* thus influencing the second virial coefficients A_2 of the osmotic pressure. Specifically, it is remarkable that, according to Table 2 and Figure 17 (where it is designated by d/c), the reduced osmotic pressure p_{os}/φ is greater than $\lim_{\varphi\to 0} p_{os}/\varphi$ by the same percentage, independently of the solvent efficiency at the same φ/φ^*. In fact, theories of the excluded volume do not take into account the conformation restrictions due to contacts between two chains or distant chain fragments, at least not explicitly. The parameter χ_1 derived from A_2 or from the expansion factor α_0 (in dilute solutions) may therefore contain an entropy contribution due to conformational disturbances.

8. Abnormal Effects of Entanglement at Very High Concentrations

At concentrations above 20 % conformational changes may be subject to hindrance[114], which has not been discussed above. At large entanglement numbers N_v the distance of the ends of the network chains of the entanglement network is greater than the distance between spatially neighboring network junctions, in polystyrene for example 1.4×10^{-6} cm as opposed to 0.45×10^{-6} cm (see Fig. 5). Consequently, the $m-1$ subchains of a chain cannot be arranged as freely as is assumed in eq. (27).

It is not easy to calculate the hindrance[21c], so it must be estimated[114]. Starting from one entanglement (network junction) a network chain (Z_c segments) passes through several (namely n) lattice planes of such disturbing network junctions. The twelve nearest neighbors divide the totality of spatial directions into g groups of directions of almost equal size. The network chain decides in favor of one of them and thus reduces the number of its possible conformations to the fraction $1/g$. It carries out this limitation $n=(M_c/M^*)-1$ times, so that the numerator in eq. (27) must be increased by the factor g^n. M^* is the molecular weight of a coiled chain fragment whose ends have the same distance as the spatially neighboring network junctions.

Reckoning that network junctions acting in this way may include both the entanglement points N_v and, to a smaller degree (factor $j<1$), the $n/2$ quasi-network points assigned to the n segments of the network chains, we obtain

$$N_{v,\mathrm{eff}}=N_v(1+jn/2) \tag{42}$$

and the distance separating the ends of the chain fragments of molecular weight M^* becomes:

$$h^*=K_{h,\theta}M^{*1/2}=\frac{l}{N_v^{1/3}(1+jn/2)^{1/3}} \tag{43}$$

For $j\ll 1$, therefore:

$$n=M_{c,1}{}^{1/3}\times(\rho N_A/2)^{2/3}\times K_{h\theta}^2\times\frac{\varphi^{2/3}}{[f(\varphi)]^{1/3}}=n_1\times\frac{\varphi^{2/3}}{[f(\varphi)]^{1/3}} \tag{44a}$$

and for $j=1$:

$$n=\frac{M_{c,1}\times(\rho N_A/2)^2\times K_{h,\theta}^6\times\varphi^2}{(j/2)^2 f(\varphi)}=n_1\times\frac{\varphi^2}{f(\varphi)} \tag{44b}$$

The number n is then introduced into eq. (31), giving:

$$S_\varphi=kN_2\{\ln\omega_0+(m\varphi-1)[\ln 0.074-1.5\ln(Z/m\varphi)-\ln\alpha_{c,\varphi}^3-n\ln g]\} \tag{45}$$

The bracket at $G_{r,\varphi}$ in eq. (35) then receives for $jn/2\ll 1$ a term proportional to

$$\varphi^{2/3}/[f(\varphi)]^{1/3}\approx\varphi^{1/3}$$

and for $jn/2\gg 1$ a term that is proportional to φ[114].

As a result, p_{os} now increases more steeply with φ than the second term in eq. (35) would lead us to expect. In addition, at high φ the first term in eq. (35) has a large influence on p_{os}, independently of the value of the parameter χ_1.

The n portions of the network chains which may disturb the conformational changes of the chains need not also act elastically, at least not at small deformations where the number n is not altered by deformation. Figures 9 and 19 show that at very high concentrations the experimentally determined relaxation modulus has an almost normal dependence on concentration, and thus it is not possible to draw any conclusions about the conformational hindrance considered here from measurements of elasticity.

9. Final Remarks

The concept of entanglement of thread molecules is confirmed by many experimental findings and lucidly explains some important properties of melts and concentrated solutions, *i.e.* of noncrystalline systems.

Chain entanglement certainly also occurs in partially crystalline polymers. This explains why polymers that have been stretched, *i.e.* deformed in the crystalline state, shrink on melting: the sample regains the form that it had before being stretched. The entanglement network has clearly withstood the crystallization and the deformation of the partially crystalline material and on melting appears as a deformed network with a restoring force corresponding to its modulus G_r [see eq. (13)] and the deformation due to stretching.

Some effects of entanglement still remain to be treated more precisely—*e.g.* those occurring in phase separation, in intramolecularly cross-linked molecules (the effect of cross-linking so far observed for such cases is surprisingly small[120]), and in the chemical reactivity of the groups and structure components (*e.g.* double bonds) situated at entanglement positions.

In any event, in discussions of the properties of polymers it should always be borne in mind that entanglement can strongly affect the properties of soft polymers and solutions.

Received: 6th May 1966 [A 182 IE]
German version: Angew. Chem. 89, 773 (1977)
Translated by Express Translation Service, London

[1] *H. G. Elias:* Makromoleküle. Hüthig & Wepf, Basel 1972.

[2] *R. G. Kirste, W. A. Kruse, J. Schelten*, Makromol. Chem. *162*, 299 (1972).
[3] a) *A. V. Tobolsky*: Properties and Structure of Polymers. Wiley, New York 1960; b) Revised edition by *M. Hoffmann*, Berliner Union, Stuttgart 1967, pp. 118f.
[4] *W. W. Graessley*, Adv. Polym. Sci. *16*, 1 (1974).
[5] a) *F. Bueche*: Physical Properties of Polymers. Interscience, New York 1962, p. 61; b) J. Chem. Phys. *20*, 1959 (1952); *25*, 599 (1956).
[6] *M. Hoffmann*, Rheol. Acta *6*, 92 (1967).
[7] *P. J. Flory*: Principles of Polymer Chemistry. Cornell Univ. Press, New York 1953, p. 402.
[8] *H. A. Stuart*: Die Physik der Hochpolymeren. Springer, Berlin 1953, Vol. 2, p. 655.
[9] *M. Hoffmann*, Rheol. Acta *6*, 377 (1967).
[10] See ref. [7], p. 405; *W. Kuhn, F. Grün*, Kolloid-Z. *101*, 248 (1942); cf. *P. J. Flory*, Angew. Chem. *87*, 787 (1975).
[11] See ref. [3a], p. 94.
[12] *M. Hoffmann*, Kolloid-Z. Z. Polym. *250*, 197 (1972).
[13] See ref. [7], p. 425; *P. J. Flory, T. G. Fox, Jr.*, J. Am. Chem. Soc. *73*, 1904 (1951); J. Polym. Sci. *5*, 745 (1950).
[14] *M. Hoffmann, H. Krömer, R. Kuhn*: Polymeranalytik. Thieme, Stuttgart 1977, Vol. 1.
[15] *M. Hoffmann, K. Rother*, Makromol. Chem. *80*, 95 (1964).
[16] *G. Dobrowolski, W. Schnabel*, Makromolekulares Colloquium, Freiburg, March 3, 1977.
[17] *M. Hoffmann*, Makromol. Chem. *153*, 99 (1972).
[18] *M. Hoffmann*, Rheol. Acta *6*, 82 (1967).
[19] *M. Mooney*, J. Appl. Phys. *11*, 582 (1940); *R. S. Rivlin, D. W. Saunders*, Philos. Trans. R. Soc. London *A243*, 251 (1951).
[20] *M. Hoffmann*, Makromol. Chem. *174*, 167 (1973).
[21] a) *A. S. Lodge*, Rheol. Acta 7, 379 (1968); b) *R. Takserman-Krozer, A. Ziabicky*, J. Polym. Sci. A2, 7, 2005 (1969); A2, *8*, 321 (1970); c) *F. S. Edwards*, Proc. Phys. Soc. London *85*, 613 (1965); *91*, 513 (1967); *92*, 9 (1967); Discuss. Faraday Soc. *49*, 43 (1970); J. Phys. A*6*, 1169, 1186 (1973).
[22] See ref. [7], pp. 577, 512; *P. J. Flory*, J. Chem. Phys. *18*, 108 (1950).
[23] *M. L. Huggins*, J. Phys. Chem. *46*, 151 (1942).
[24] *M. Daoud, J. P. Cotton, B. Farnoux, G. Janninck, G. Sarma, H. Benoit, R. Duplessix, C. Picot, P. de Gennes*, Macromolecules *8*, 804 (1975).
[25] *P. Debye*, J. Phys. Colloid Chem. *51*, 18 (1947).
[26] *G. V. Schulz*, Z. Phys. Chem. *193*, 168 (1944).
[27] See ref. [5a], p. 19; *P. Debye, F. Bueche*, J. Chem. Phys. *11*, 470 (1943); *A. Ishihara*, J. Phys. Soc. Jpn. *5*, 201 (1950).
[28] See ref. [7], p. 599.
[29] *G. Gee, L. R. G. Treloar*, Trans. Faraday Soc. *38*, 147 (1942); *G. Gee, W. I. C. Orr, ibid. 42*, 507 (1946).
[30] *C. E. H. Bawn, R. F. J. Freeman, A. R. Kamallidin*, Trans. Faraday Soc. *46*, 677 (1950).
[31] *J. Furukawa, H. Inagaki*, Kautsch. Gummi Kunstst. *29*, 744 (1976).
[32] *U. Eisele*, Lecture at the IISRP Conference Williamsburg (USA) 1976.

Flexible Drug Molecules and Dynamic Receptors[**]

By R. J. P. Williams[*]

When a small flexible drug molecule binds to its likewise mobile receptor (protein, membrane *etc.*) the shape and function of both can change. The study of the nature and extent of these changes by several independent methods gives an insight into the mode of action of drugs. The static lock and key model will most probably have to be revised or be replaced by the nebulous concept of dynamic states.

1. Introduction

The basic problem of drug action in biological systems is easily formulated. In order to interact with a biological system any drug must first bind and may then react, whence a comprehensive minimal two-stage reaction path can be written

$$D + L \underset{k_b}{\overset{k_f}{\rightleftarrows}} DL \xrightarrow{k_{DL}} D^1L^1 \ldots \quad (1)$$

where D is the drug which undergoes a rapid reversible binding to a biological receptor L, *i.e.* a protein, DNA, RNA or a membrane *etc.*, giving DL. This reaction has an equilibrium binding constant

$$\frac{k_f}{k_b} = K_{DL} = [DL]/[D][L]$$

and there can be many successive steps of this kind before the 'final' binding condition is reached. The second step in the above simplified scheme [eq. (1)], which may or may not be a required part of action, is an irreversible chemical combination of D in the form D^1 with a part of the biological system L^1, where L^1 may be a protein, RNA, DNA, a membrane *etc.* which has incorporated D (or D^1). L and L^1 could be the same receptor site of course. The reaction rate constant in its simplest form is a first order rate constant, k_{DL}, but again many such steps could be involved.

My analysis of drug action will be based upon the structural features of these reaction paths starting from the structures of D and L themselves. By structural features I imply the whole series of conformational states through which the two species D and L must go in order to reach some final state DL or D^1L^1. Recently the nature of such pathways has been stressed by *Feeney, Roberts* and *Burgen*[1], who were motivated by their observations, using nuclear magnetic resonance (NMR) spectroscopy, on the mobility of certain drug and hormone molecules. My independent and parallel interest in the problem of conformational mobility has arisen through studies of both small and large molecules in solution also using sophisticated NMR methods for conformational analysis. In the past the solution structures of D and L (which

[*] Prof. Dr. R. J. P. Williams
Inorganic Chemistry Laboratory
South Parks Road, Oxford OX1 3QR (England)

[**] This article is based on the Merck, Sharp and Dohme Scientific Lecture 1976 given in London. It was also given in outline at the Belgian Chemical Society Meeting in Namur, 1976.

are the ones to be discussed in a drug/receptor interaction) have often been assumed to be known once X-ray *crystal* structures had been completed. This approach ignores the statistical occupancy and the time dependencies of many different conformations of a molecule in solution and may well have led to over-precise thinking about the general need for structural fitting, *e.g.* as in the notions of lock-and-key and induced fit. Examples illustrate the point.

The study of different penicillins in the crystalline state by X-ray crystallography showed that there were two possible ring conformers and that different substituents on the four-membered ring led to a switch from one conformation to the other (Fig. 1). We have studied the conformation of some of the same penicillins in aqueous solution by NMR probe

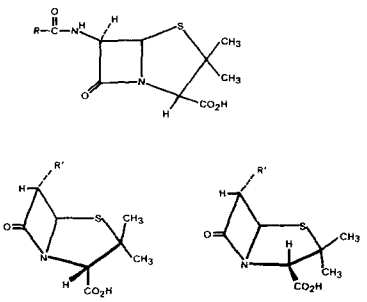


Fig. 1. General formula of penicillins; spatial arrangement of the atoms in crystalline penicillin G and ampicillin.

methods[2] but our results show clearly that there is little if any dependence of structure of the penicillins in solution on substitution of its rings (see Fig. 1). We also noted that the data suggested that although one conformation was dominant there was a smaller percentage of the other conformation in fast equilibrium with it. In principle the rate constants for conformational flipping of the molecules could have been determined too. We are forced to ask which particular structure if any is important for drug action and, has the nature and rate of conformational mobility an importance of its own?

A rather general inspection of drug molecules shows in fact that only a limited number of drugs have rigid frames and obviously their conformations in the bound state are easily described from crystal or solution studies (but see below). In all other cases there are different conformations open to the drug molecule and these may well be in rapid equilibrium, as in the case of the penicillins. We need to consider the relative energies of these different conformations (open to the drug in the unbound state) since, presuming that only a limited set of the conformational forms are bound by the receptor, there is a population bias against the drug being bound in these forms in direct proportion to the probability of achieving the limited conformation set in the free state. Drug design might then be based partly on fitting, but if we are dealing with a conformationally mobile drug, partly on the restriction of conformational freedom of the (free) drug. However, this last approach could fail too for the very flexibility of the drug might also be an unavoidable requirement in order to achieve final binding or reaction, and in this case a knowledge of the conformational mobility of the drug would be essential in an understanding of action. In the above Scheme [eq. (1)] certain steps, k_f, would represent necessary movements on the way to a final binding site—a wriggling of the drug to a 'best' site. Drug design might have to be based on selected dynamic properties of a molecular frame as well as upon the possibility of providing a particular structure to fit a supposedly rigid receptor. Finally it will be shown in this article that the large molecules which form receptors are not necessarily more rigid than the small molecule drugs, and the same statistical fluctuations and time-dependent changes must be analyzed for them. This motion also has an influence upon the constants in eq. (1).

The obvious need for a careful analysis of the mobilities of drugs and receptors before indulging in a discussion of their interaction leads me to turn away from drug action for a while and to describe recently obtained knowledge of structures in solution and of the dynamics of these molecular conformations.

2. General Comments about Rigidity of Small Molecules in Solution

Apart from the conformations of penicillins in solution we have examined the conformations of a series of amino-acids, some small peptides, some sugars, and a series of nucleotides, where there is obviously a much greater variety of possible mobility[3,4]. The general impression gained from these studies is that even though there must be mobility in the small molecules (rotation about single bonds with limited steric hindrance) certain "conformational families" or a very small set of families peculiar to each group of molecules in turn are overwhelmingly favored, possibly through the solvation by water. A family of conformations is to be thought of as a relatively small group of structures related to one another by minor changes in bond angles. We can illustrate the point by reference to the simple nucleotides but rather than making direct reference to the deduced nucleotide conformations, derived from NMR spectroscopic data, I shall use a comparison of the experimental NMR information so that experiment and interpretation are not confused.

Our experimental procedure starts from an examination and an assignment of the NMR spectrum of a molecule in solution in as much detail as possible. This means that each ^1H, ^{13}C, ^{31}P, ^{19}F nucleus in the molecule is studied as far as is possible, but here I shall describe ^1H-NMR data in large part. These spectra in themselves contain coupling constant data derived from spectral fine structure and the coupling constants are related to the relative position in space of coupled protons. For example, in such a system of atoms as $C(H^1)$—$C(H^2)$ the geometric relationship of H^1 and H^2 can be uncovered. Restrictions upon free rotation about C—C bonds are then obvious in a qualitative and sometimes in a semi-quantitative way. Again proton relaxation times of the spectral signals can be used to calculate the non-bonded H—H distances and further data on small local regions of the conformation comes from the study of the nuclear Overhauser effect. All these methods have been used for some time by a large number of research workers. The considerable extension of the conformational analysis which we have made is to examine the NMR spectra of the small molecule in the presence of bound (in fast exchange) paramagnetic ions (see Fig. 2). The NMR spectra are found to be perturbed in two ways: 1) shifts of absorption lines (δ) arise if the paramagnetic center has

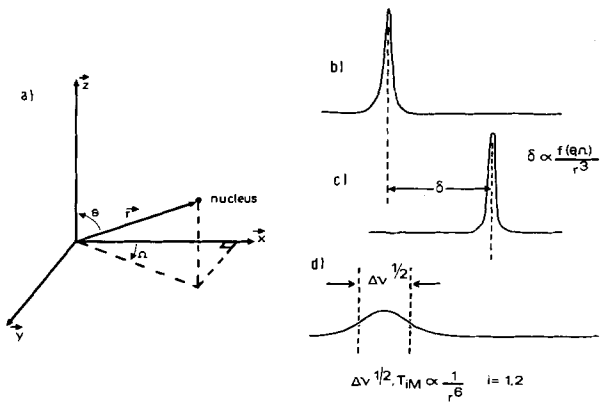


Fig. 2. The effect of a paramagnetic reagent placed at the origin of space (a) upon the line position (shift b→c) and line of width (broadening b→d) of an NMR spectrum (see ref. [3]). The broadening of lines is directly related to T_{2m}, and the shift is given as δ for the most general rhombic field case. In an axial field, $\Omega = 0$.

a fast electron relaxation time; 2) changes in relaxation time, *e.g.* broadening of lines *(B)* arise when the paramagnetic center has a long electron relaxation time. The equations

$$\delta = A(3\cos^2\theta - 1)/r^3 \tag{2}$$

$$B = C\ \frac{1}{r^6} \tag{3}$$

show that δ is a vector quantity depending upon the distance, r, of the nucleus under inspection from the paramagnetic probe atom, and upon the angle θ between the principal axis of the paramagnetic probe and the direction from probe to the nucleus (see Fig. 2), while B is a scalar quantity. In the equations A and C are constants independent of the nucleus under study. (The above shift equation [eq. (2)] assumes that the bound paramagnetic ion generates an axially symmetric magnetic field. Details of the methods and measurements which allow the field to be so defined are given elsewhere[3].) Let us assume that the site of binding of the paramagnetic ion to the molecule under study can be determined (which is the case), then these shift and relaxation measurements give directly a set of conformational parameters, δ and B, just as coupling constants are conformational parameters and they can be used empirically as comparative molecular conformation data on very many different atoms which are separated by considerable distances. Of course all the different NMR methods add together to give the largest number of conformational parameters, and together should be used in the definition of structure[*].

[*] All NMR methods provide data which refer to the average conformation. It is a matter of convenience whether we search to describe the average in terms of a single conformation with non-idealized bond-lengths and bond angles [2, 3, 5] or in terms of combinations of two, or three, or four idealized conformations *etc.* It has often been the case that averaged conformations have been analyzed using sums of two or three conformers where the contributing conformers introduced are those suggested by theoretical energy calculations in the gas phase. As shown by *Feeney et al.* [7] it is always possible to fit NMR data by such a procedure. Even though it is certain that better fits of experimental parameters can be obtained by using such semi-theoretical approaches, since larger numbers of variables are introduced, than using single conformation fitting the fit must be suspect as the theory does not apply to solvated species. Thus it is essential that many *independent* methods are used to check structural representations of molecules in solution, *e.g.* coupling constants, relaxation data, shift data, and nuclear Overhauser effects, using first *one* and only later combinations of *two* conformations.

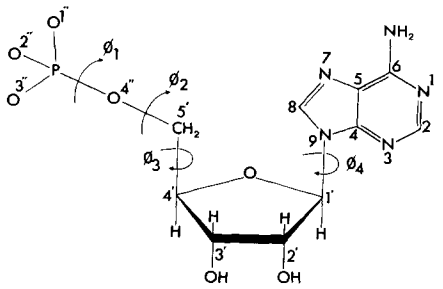


Fig. 3. 5'-Adenosine monophosphate (5'-AMP); bonds about which there is apparent free rotation are indicated by arrows.

Table 1. NMR shifts (δ) of nucleotide sugar protons by lanthanoid(III)-containing probes given as the ratio $R = \delta(i\text{-H})/\delta(5'\text{-H})$ [9] [see Fig. 2, Fig. 3 and Eq. (2)].

Nucleotide	pH	$R = \delta(i\text{-H})/\delta(5'\text{-H})$			
		i = 1'	i = 2'	i = 3'	i = 4'
5'AMP	2.0	0.09	0.24	0.40	0.32
	7.6	0.09	0.26	0.38	0.34
5'-GMP	9.0	0.11	0.27	0.38	0.33
5'-CMP	2.0	0.10	0.20	0.40	0.32
	7.6	0.08	0.21	0.38	0.31
5'-UMP	2.0	0.07	0.20	0.38	0.32
	7.6	0.08	0.25	0.37	0.32
5'-d-TMP	2.3	0.08	0.30	0.37	0.35

Table 1 gives shift data for the protons of some nucleotides (Fig. 3). The observed shift δ(*i*-H) of the NMR signal of a proton *i*-H due to presence of a bound lanthanide(III) ion is expressed by the ratio R of this observed shift relative to the shift of a chosen proton, here δ(5'-H) of the 5'-H proton (see Fig. 2). The paramagnetic lanthanide ions have been used to generate the shifts but a wide variety of reagents can be employed. A striking result is that, almost within experimental error limits, all the nucleotides give the same set of conformation parameters. Broadening (relaxation) and coupling constant data are also almost invariant which can only mean that independent of the base (pyrimidine or purine) and of the sugar (oxy- or deoxyribose), the general conformational outline of nucleotide (including mobility averaging) is fixed, and it is surprisingly closely related to the single conformation observed in crystals. (As an aside we observed that although the crystal structures of deoxy- and oxy-uracil monophosphate were different from that of deoxy- and oxy-cytidine monophosphate this difference was not seen in solution and it may well be that the difference seen is an "artefact" of crystallization as in the case of the penicillin.) These results were deduced independently from coupling constant data alone by *Sundaralingam*[6] who has gone so far as to state that the nucleotides must be relatively rigid in solution.

As there is clearly a high degree of constraint in the mobility of these molecules the relative stability of the observed (averaged) set of conformations seen in these nucleotides must be due in part to the nature of water as a solvent. If we change solvent we observe a different stable conformational family. In dimethyl sulfoxide the (average) conformation of the nucleotide monomers is different from that found in water, and in some aqueous systems we find that even salt and denaturants such as urea also affect the conformations of small molecules, as indicated by probe measurements[3]. We

note that receptor sites may be very unlike water in their "solvation" properties and may prefer energetically a quite different conformational family from that found in aqueous solution. All these data tell us nothing about the nature of other non-preferred conformations or the rate of flipping to lowly populated conformational states, although we may presume this flipping is fast since we see no separate signals for different states (but of course we do not know that such states of low probability exist). In fact many conformations widely different from those determined by NMR methods of analysis could be reached and for 1 % of the time almost any conformation X could be present and it would go undetected by these solution methods. However, if X is the desired conformation for action there is then a factor of 100 against its formation for this particular molecule and it must be possible to build a better molecule, drug, for binding alone where this mobility factor is considerably reduced.

The implications of these findings for the study of drugs is simple but has not been clearly stated before:

1. Only for those drugs which have *rigid* frames (Table 2), are we able to neglect mobility, but even here we must consider the aqueous (or other) solvation environment. For example our study of cyclic 3',5'-adenosine monophosphate (3',5'-cAMP) gave the same structure for the two rings containing the phosphate and the sugar (X-ray structure analysis), and we may assume that this frame is relatively rigid[8]. The

Table 2. Rigid and flexible drug molecules [a].

Relatively rigid	Flexible	Moderately flexible
Quinine (Many alkaloids)	Straight-chain alcohols	Penicillins Chloramphenicol
	Nitrogen mustards (*N*-methylbis(2-chloroethyl)amine) and derivatives	
Sulfonamides		Streptomycin
	Linear polypeptides	
Steroids		Mepacrine
Tetracyclines		Phenothiazine
Morphine		Nicotine
Cocaine		

[a] It is of great interest to make molecular models of drugs and attempt to visualize the number of different static and dynamic modes of action which they could have.

receptor could bind exactly this frame, but just because the hydration remains unknown it is conceivable that it is the hydrated form of the molecule which generates action when the stereochemistry of the receptor site can *not* be deduced from the solution or crystal structure studies of the small molecule.

2. Other drug molecules may be much more mobile (Table 2); for example, we have been unable to determine a "structure" for 2',3'-cAMP by our methods, a fact which suggests that the NMR data can not be represented by a single conformation family[9]. For such a molecule (drug) which has considerable mobility between two or more rather different conformational families knowledge of the conformations observed in crystals or in solution is of much more limited value for we do not know not only the hydration but which or how many conformationally different steps are required in each of the steps of equation (1), and we do not know which are the important conformations in the final condition. The problem becomes even more serious as we turn to molecules of increasing size, and we note that it is not just a problem of drug binding alone but is perhaps a general feature of biological activity.

3. From our studies, the orientation of the base in 3',5'-cAMP is clearly not fixed relative to the two rings of the cyclic system to the same degree as was found in the simple nucleotides 5'- or 3'-AMP[8]. Thus it may be easy for this part of 3',5'-cAMP to wriggle or corkscrew its way to a required binding site, receptor. Thus, whether a molecule binds or not can depend upon whether it can reach a certain site or not, for the receptor site need not be on an open surface[**]. Impressions as to the importance of molecular dynamics for drug action are strongly supported by the inspection of hormones.

2.1. Hormones and Peptide Hormones

On first inspection it is surprising that small molecules such as adrenaline, 5-hydroxytryptamine, and acetylcholine should be used as hormones and transmitters, for these molecules contain only a very small rigid unit—if they contain a rigid unit at all—and rather few sites (*e.g.* —OH or $-NH_2$ groups) by which they can be recognized selectively. The molecules also contain some bonds about which rotation is relatively easy. Given the requirement for virtually specific action of a hormone a much more rigid molecule would seem to be appropriate. However, if we consider that a molecule has to "wriggle" to reach its site of action then rapid on/off reactions using a series of different conformations could be required[1]. Thus as above a compromise may be reached between a good match of hormone and binding surface in some final state and a mobility required in order to reach the site. This compromise will include a loss of some binding capability which is governed by the adverse statistical weighting of conformers in free and bound forms. It is not easy to work out an optimum system for such fast and selective binding but, as it may be that the actual binding site is closely related to the heavily weighted conformation in solution, it will still pay in designing drugs which compete with hormones or transmitters to try first conformational matching with these states.

It is remarkable too how many larger hormones are not like 3,5'-cAMP or sterols, which must have very limited conformational mobilities. Instead many of them are apparently disordered linear polymers ranging from tripeptides to higher peptides such as glucagon, which have molecular weights

[**] A change of attitude may now be required on the part of chemists who are engaged in the design of drug molecules. The outline "shape" of a molecule, at 0 K, when examined by instantaneous methods (time constant $< 10^{-13}$ s) will conform to bond angle and bond length predictions based upon our knowledge of simple molecules such as methane. However for a mobile molecule/mobile receptor interaction it could well be that a rather different space-filling model would be more appropriate: for example, methane would become a simple ball and an indole ring would be represented by a flattened spinning disc. Dynamics in these cases involves rotational movement about various axes, but no translation. However, translation could also be important and perhaps we should seek for tunnels and channels in receptors which may have gates at which "wriggling" motions may be involved in site interactions. The shape of these channels must be such that given wriggling the whole molecule can pass through, but such a shape is clearly not closely related to any single molecular structure.

of >10000. These molecules must be flexible to a very high degree, and in fact this mobility has been confirmed by NMR measurements. The longer the chain of these hormones the smaller the probability of a correct matching between the hormone and receptor assuming that the receptor recognizes all the hormone. It would seem that fast action should then belong to small or rigid hormone molecules while slower action, but perhaps very highly selective control, should belong to longer flexible molecules, all static and dynamic ways of achieving selectivity having then been found (Table 3).

Table 3. Naturally occurring rigid and flexible small molecules and hormones [a].

Relatively rigid	Flexible	Moderately flexible
Alkaloids	Spermine	Vassopressin
Sterols	Glutathione	Oxytocin
Auxins	Corticotropins (ACTH)	Nucleotides
Thyroxine	Releasing hormone	Vitamins E and K
Trypsin inhibitor	Many lipids	Bacetracin
Heme	Glucagon	Folic acid
Coenzyme B_{12}	Melanocyte-stimulating hormones	Polysaccharides ATP

[a] It is assumed that steric hindrance as in thyroxine, ring formation as in vasopressin, and cross-linking as in the trypsin inhibitor make a part of a molecule effectively rigid.

Particularly interesting in this respect is the recent work on insulin, which illustrates conformational mobility of at least one tenth of the peptide[10]. Here it is the cooperative effect of metal ion and anion binding, at different sites, which causes a rearrangement of the peptide. Using NMR methods we have confirmed that a corresponding conformational switch of insulin occurs in solution with addition of the same reagents[11]. The changes are anion-, cation- (*i. e.* salt) and temperature-dependent. This result throws doubt again on the detailed use of crystal structures in the discussion of the action of such hormones—except for the regions of immobilized (rigid) surface (see the trypsin inhibitor in Section 2.2). The observations can also be used to describe the synergism of two small-molecule "drugs", here X^+ (Zn^{2+}) and Y^- (Cl^- or I^-), on a receptor surface (insulin) when it is seen that there can be large conformational effects in some regions of the large molecule and that also general changes may occur to a smaller degree over larger regions of the molecule (see Section 2.2).

2.2. Small Molecules: Summary

Table 3 lists a variety of molecules found in biological systems. Apart from peptides and polynucleotides[9,12] we have looked at such molecules as adenosine triphosphate (ATP)[13] and vitamin B_{12}[14] by the same conformational methods using paramagnetic probes. In the last two cases the structures found in solution are again relatively closely related to those in the solid state and we class these molecules as largely rigid. Other molecules such as polyamines and long chain fatty acids must have a much greater mobility and Table 3 puts them into a different group. Not all control peptide molecules of higher molecular weight are of the mobile kind such as is glucagon. The nature of the trypsin inhibitors which are quite large peptides but not simple linear polymers and which must act rapidly, suggest that they are rather rigid, for their —S—S cross-links and internal β-pleated sheet restrict the conformation very greatly[15,16]. The rigidity of the trypsin inhibitor is shown too by the fact that even some of the aromatic residues of amino-acid side chains do not flip freely despite the fact that this is a small molecule[16]. We stress that the possible combinations of rigid and flexible elements can lead to all kinds of intermediate behavior and different parts of large molecules can behave differently.

3. The Receptor Site: Introduction

The approach in the discussion of the structure of the receptor must be the same as that used in the study of small molecules. We must go from an examination of constrained molecules in crystals or free molecules in the solution phase to a semi-speculative knowledge of a receptor geometry and dynamics. Now we suspect that receptor sites are particular regions of proteins, DNA, RNA, membranes or polysacchar-

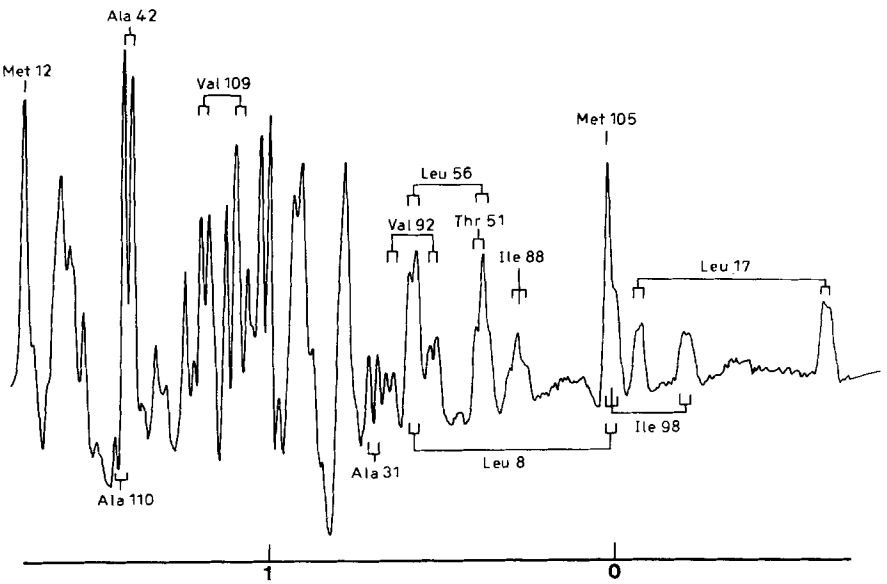


Fig. 4. Part of the ^{1}H-NMR spectrum of lysozyme with assignments (methyl groups in the given amino acids).

ides. What can we say about the structure of such large molecules in biological systems? First we turn to the examination of the nature of these large molecules in solution.

3.1. Proteins as Flexible Molecules

In the last few years, 1974—77, a change away from rigid pictures of the conformation of macromolecules has developed. We pioneered these studies in so far as the use of high resolution ^{1}H-NMR spectroscopy on proteins was concerned[17] (Fig. 4), while parallel work by *Sykes* and by *Wüthrich*[16] was underway on peptides, and many authors were carrying out ^{13}C-NMR studies. In other work a variety of techniques[18, 19] have been employed which also demonstrate motion, such as oxygen quenching of fluorescence and hydrogen exchange, but this work is restricted to the general discussion of the protein and it has not been possible to locate the mobility within the protein sequence. Our work shows clearly the nature of the motions and how they are distributed within proteins. The types of motion observed are:

1. Rotation and libration (sometimes restricted) about certain single bonds internal to the protein.
2. High mobility of protein side-chains on the surface.
3. General mobility of (hydrophobic) groups internal to proteins (breathing).
4. Occasional segmental movements of the main chain.
5. Some proteins are quite generally mobile *i.e.* close to random coil polymers. Table 4 gives some details of these motions.

Table 4. Protein motion.

Type of Motion	Observation
Expansion (Vibration)	Temperature dependence of ring current shifts relaxation times
Fast segmental motion	Insulin: transitions Heme: resonances (hemoglobin)
Surface motion	Lysine: correlation times
Slow motion of side chains	Tryptophan: oscillation Phenylalanine and tyrosine: flip Temperature dependence of resonance positions
Random coil motions	Relaxation times

3.2. Segmental Motion: Summary

In some proteins we must suppose that a part of the protein may be mobile while another part is not and that these parts can be of quite diverse sizes for different proteins[20–22]. *Vallee et al.* have stressed the mobility of the active site region of carboxypeptidase in solution[23] and it would appear that the effect is seen even in the crystals. This mobility effects a relatively small back-bone change, comparable with the type of change which occurs on the binding of oxygen to hemoglobin when the FG region undergoes perturbation. In the meantime quite a number of proteins have been examined and they would appear to fall into very different classes of behavior. Lysozyme, peroxidases, peptidases, carbonic anhydrase and cytochrome c show least conformational change of the main frame; kinases, concanavalin A, colicin Ia, and hemoglobin show rather larger changes; histones, chromagranin A, and phosvitin are very adaptable, flexible, chains (Table 5). Thus it seems that large molecules (receptors) show the same range of flexibility as small molecules. There must be some very rigid systems and some very mobile ones and all intermediate behavior patterns will emerge.

Table 5. Rigid and flexible large molecules [a].

Relatively rigid	Flexible	Moderately flexible
Cytochrome c	Phosvitin	Insulin
Neurotoxins [b]	Chromogranin A	DNA-binding proteins
Lysozyme	Histones	t-RNA
Peptidases	Glucagon	Kinases (?)
Nucleases	Myelin protein A. 1.	Antibodies (?)
	Vesiculin	Lipases

[a] Generally, extracellular proteins are rigid and are often crosslinked by S—S bridges. Intracellular proteins are more mobile especially if they are required to equilibrate between bound and unbound states involving DNA, RNA or membrane surfaces.
[b] Personal communication from Prof. *G. Petsko.*

The case of cytochrome c is of great interest[21]. Although it is known that the two oxidation states of cytochrome c have different physical properties *e.g.* solubility and chromatographic mobility we have been unable to detect differences in the interior of the molecule in the two oxidation states in solution. A similar result has been found in crystals. However we do observe that the binding of various anionic and cationic reagents on the surface of cytochrome c is different in the two oxidation states which proves that their surface energies are changed by the change in charge on the iron. Change in surface energy will be reflected by change in charge, conformation, and hydration, but present methods do not detect the surface states readily. Even so it is these surface states which will be important in protein/protein and at least initially in drug/protein interactions.

4. Small Molecule/Protein (Drug/Receptor) Combination

This article has stressed dynamic features of both drugs and receptors where drugs have been likened to many types of small molecules and receptors to many types of large polymers or assemblies. In discussing the combination of drug with receptor it is the dynamic features which we wish to keep to the forefront, although we realize that static matching has a very important and proven role to play. The discussion will proceed through examples, but before proceeding to these examples the states of the receptor and small molecule must be visualized as they approach one another. All the evidence provided above indicates that the small molecule will be fluctuating very rapidly between at best a small number of similar conformations and at worst a complete spectrum of very different states. The receptor surface may be equally mobile—especially in the case of sugars and lysines—but in other regions, pockets and grooves, may show limited mobility. An agonist drug might bind and then pass through these mobile regions, in some cases going to a site much deeper in the receptor while other, antagonist, molecules may just block access of the agonist to the deep-seated site. From here on we examine the bound drug/receptor sites.

4.1. Lysozyme-Saccharide Reactions

The "receptor site" of lysozyme is the enzyme binding groove for substrate. It is lined with readily recognizable (by NMR) tryptophan residues (Fig. 5), and it is these groups which we can follow most readily during the binding of the saccharide[24,25]. The NMR method is fast enough to follow steps which occur with time constants of $\leq 10^{-4}$ s, and its specificity allows a precise statement as to which groups move and, if sufficient care is taken, the movement itself can be defined with some precision (Fig. 6).

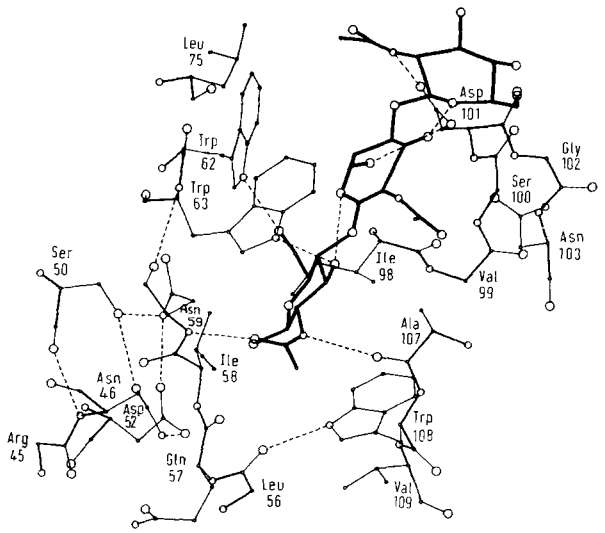


Fig. 5. The lysozyme pocket showing the binding of a trisaccharide (after [25]).

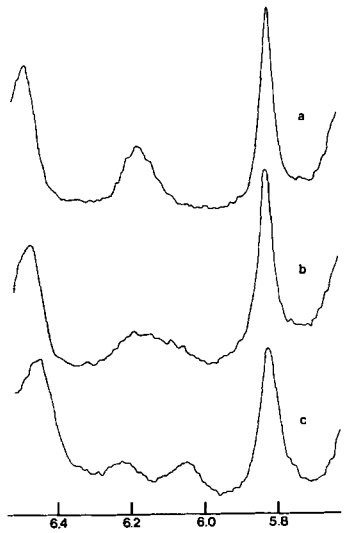
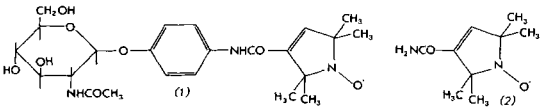


Fig. 6. Aromatic ^{1}H-NMR spectral region of hen lysozyme (3 mmol/l) at pH 5.3 in the presence of tris(*N*-acetylglucosamine) (4 mmol/l) showing the effect of temperature on the tryptophan $>$NH resonances at a) 37 °C, b) 45 °C, c) 55 °C.

In the initial state there is present say the disaccharide bis(*N*-acetylglucosamine), which is a semi-mobile molecule but which may well be largely constrained by interaction with water, so that perhaps 95 % of the molecules belong to a small family of conformers. The protein lysozyme has a groove which is undergoing some dynamic motion including fast motion of side chains such as valines and the slow movement of the tryptophans (see Fig. 10). In other words the two molecules generate a set of geometries, some compatible and some incompatible, and on binding they settle down into the final energetically most favorable bound state, which—as we have shown—has rather less mobility. The overall binding reaction path is then a succession of conformational states

$$E+S \rightarrow \sum ES(1) \rightarrow \sum ES(2) \rightarrow$$
$$\text{final state } (\textstyle\sum \text{ final conformations})$$

where the sum sign, Σ, covers all the dynamic states of a species. It is the dynamic nature of the initial and intermediate states of the reaction sequence which allows all the steps to the final condition to be rapid[24]. The observed greater rigidity in the last step (or stages) means that the reverse process, the first dissociation step, may have a slow step as its initial step. Ignoring the consequences of this description as far as enzyme action is concerned we note here that an inhibitor of the enzyme could be a molecule which reaches states $\Sigma ES(1)$ or $\Sigma ES(2)$ but cannot go through to the final state for reaction, when the inhibitor need not be a very good match for a substrate so long as it binds. As an almost trivial example CN^- is a very strong poison (drug) when it replaces O_2 in heme proteins. Sulfonamides do not match CO_2 or HCO_3^- very well but they bind in the pocket of carbonic anhydrase in place of CO_2. Thus the match of enzyme and substrate is not highly restricted and we visualize a series of poor, moderate and good matches to different states of the enzyme groove. A very interesting test of this situation has been observed by accident.



We wished to study the surface of lysozyme using the spin-labeled substrate 3-[4-(2-deoxy-2-acetylamino-1-glucosyloxy)-phenylcarbamoyl]-2,2,5,5-tetramethyl-3-pyrrolin-1-oxyl *(1)*[26]. However, we found that the binding was not through the *N*-acetylglucosamine moiety, which is a portion of the natural substrate, but was directly to the spin-label itself which binds in site C. The fit can not be perfect but the binding of the spin-label molecule *(2)* by itself, which was tested as a result of the above finding, showed that it is bound better than *N*-acetylglucosamine! Thus by accident a potential inhibitor (drug) has been uncovered which is chemically unlike the substrate but binds better than the substrate analog. No examination of the spin-label molecule *(2)* and the *N*-acetylglucosamine would have suggested the parallel. Detailed inspection of possible protein surfaces and the geometry of a molecule such as *N*-acetylglucosamine or even more so a steroid reveals how difficult it is for an enzyme to match precisely the space-filling and bonding capabilities of a substrate or a drug. Restricted mobility of the surface then becomes a very great advantage in assisting good (not excellent) matching. In fact I believe the matching has been rather over-stressed, for all that is required is good, relatively specific, *binding* and that the *kinetics* of this binding should be under control. In both respects mobility is highly valuable (Fig. 7).

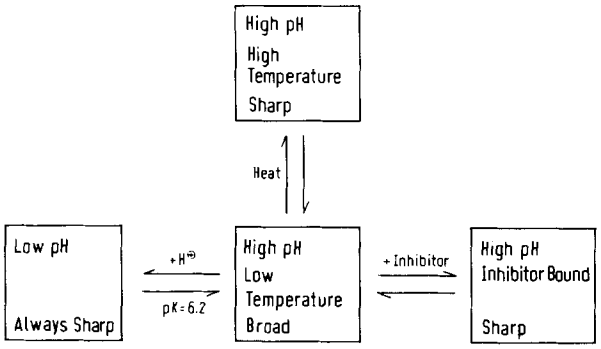


Fig. 7. Active center of lysozyme [25]. Overall survey of the conformational states of lysozyme in solution. Each block represents a conformational state and the linewidths referred to are those of the ^{1}H-NMR spectrum.

A somewhat more extensive rearrangement is seen on binding saccharides to concanavalin A[27]. Here binding results in such changes to the protein structure that two complete crystal structure analyses (protein with sugar and protein without sugar) were required. No evidence is available about the dynamics of the protein in this case. Note that here too a carefully labeled reagent, 1-(*o*-iodophenyl)-β-D-glucopyranoside, designed to find the sugar binding site, actually became bound to an abnormal site.

Another example of mobility at a receptor site has been uncovered by *Burgen et al.*[28]. They observed that the absorption spectrum of carbonic anhydrase (as the cobalt(II) enzyme) was changed by the addition of sulfonamides. The change is consistent with the reaction

$$\underset{\text{distorted geometry}}{\text{Co(II)(base}^-\text{)}} + \text{sulfonamide} \rightarrow \underset{\text{tetrahedral geometry}}{\text{Co(II)(sulfonamide}^-\text{)}}$$

for the 3- and 4-substituted sulfonamides; but the 2-substituted sulfonamide complex has an absorption spectrum lying between these extremes and thus indicating an "intermediate" geometry at the cobalt. There is general agreement that the metal site in carbonic anhydrases can flick between different coordination states. Although only a small change is apparent this metalloenzyme is comparable with such enzymes as peroxidase and cytochrome P-450 in that the coordination sphere of the metal is sensitive to drug binding (see also Table 6).

Table 6. Changes in metalloenzymes due to drug binding.

Enzyme	Metal	Drug	Change
Cytochrome P-450	Iron(III)	Sterol	Low-spin ⟷ high-spin
Peroxidase	Iron(III)	3-Indolepropionic acid	*g*-value changes
(Myoglobin	Iron(III)	HgI_3^-	Low-spin ⟷ high-spin)
(Hemoglobin	Iron(III)	Xe 1,3-di-phosphoglycerate	Low-spin ⟷ high-spin)
Carbonic anhydrase	Cobalt(II) [Zinc(II)]	Sulfonamides	Distortion of tetrahedral coordination

4.2. Peroxidase-Substrate Complexes

The complexes of peroxidase with substrates can be readily studied since some of the substrates—indoles and phenols—have NMR spectra which are easy to interpret. The indole ring is a rigid frame and we have examined such frames extensively in simple complexes, showing for example how they form plane-to-plane stacked molecular complexes with porphyrins[29]. We then used these methods in the study of peroxidase complexes[30].

Peroxidases are very large glycoproteins which have some obvious mobile features such as the saccharide side chains. In the native state they are high-spin Fe^{III} enzymes. Reaction with cyanide converts them into the low-spin state, whereas reaction with azide gives a mixture of the two forms (low-spin ⇄ high-spin) in equilibrium. *On the NMR time-scale* all these states

$$\text{Native (largely high-spin)} \rightleftharpoons \text{Azide (high-spin)} \rightleftharpoons \text{Azide (low-spin)}$$

are rapidly in equilibrium so that both the on/off reactions of azide and the spin-changes are very fast. In fact there is probably present some 5% of low-spin state in the native enzyme, as is the case in myoglobin and hemoglobin. As shown in Figure 8, high-spin and low-spin Fe^{III} heme complexes have rather different structures. We must suppose that iron(III) oscillates rapidly between the different states and that the protein chain linked directly to the iron through the proximal histidine also undergoes rapid changes[22, 31].

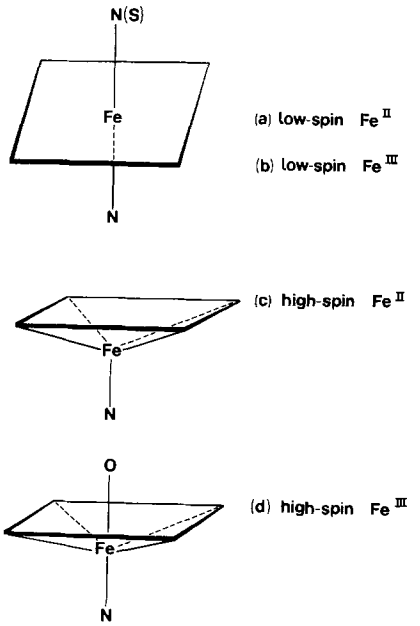


Fig. 8. Stereochemistry of the heme iron spin-states.

When an aromatic substrate binds to the protein it does not form a plane-to-plane stacked molecular complex like in the model reactions with porphyrins. Taking peroxidase complexes of 3-indolepropionic acid as an example we find that the indole system lies as is shown in Figure 9[30]. The indole derivative is bound only by weak Van der Waals interactions in the pocket of the enzyme. Binding of other substrates is in the same pocket but the relationship between these substrates and their binding sites and between the indoles and their binding sites differ considerably. We conclude that the site of binding is more like a small *mobile* oily pool than a lock and key fit. Thus it is anticipated that a large number of organic chemicals can act as inhibitors of these

enzymes. Maybe enzymes for detoxification behave in this rather general way, for similar features can be seen in the binding sites of cytochrome P-450 and of alcohol dehydrogenases.

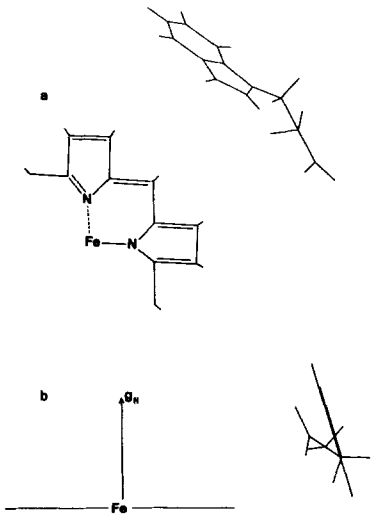


Fig. 9. The peroxidase complex of indolepropionic acid showing the disposition of heme and substrate, (a) and (b) are orthogonal views.

Now these oily pools in the proteins for taking up substrates need not be immediately accessible to the small molecules and it would be very interesting to observe exactly the time course of approach to the final state of binding. An inhibitor or a drug could act at any of the approach stages, or it could act indirectly by preventing the conversion of one form of a protein into another. Again it does not appear that the mobility within the oily drop is much altered by the insertion of the substrate even though the substrate binding affects the iron(III) site somewhat.

A good example of the wriggling of a group to reach such an "oily-drop" binding site is the uptake of the hydrophobic anion HgI_3^- into myoglobin. The binding site as observed by X-ray crystallography is at the back of the heme. There are gross restrictions to movement in this region of the protein and even quite small ligands cannot bind to the iron itself for this region of space is designed to accept oxygen only. We have studied the effect of the uptake of HgI_3^- on the properties of the Fe(III) form of myoglobin and have shown that there is a small change in the spin-state equilibrium (high-spin $\rightleftarrows$ low-spin) on binding. Thus the binding group (drug), here HgI_3^-, has to wriggle through the protein to its binding center where it alters the conformation of the protein slightly. Uptake of xenon (a very large atom) must take place by similar wriggling. Again the effects of oxygen on the fluorescence of proteins demand a similar conformational mobility allowing access by wriggling.

It is of interest to see how such binding could adjust the chemistry of the receptor. In the β-chains of hemoglobin[32] there is a sulfydryl group FG (β-93) which is on the helix which carries the Fe-linked histidine (proximal). *Perutz* has shown that the degree to which this sulfydryl is exposed depends upon the spin-state of the iron, for change of spin-state causes rotation of the helix. Thus we have the following dependencies: a) drug bound—more low-spin Fe, exposed —SH; b) drug absent—more high-spin Fe, hidden —SH.

The *effect* of a drug can occur (i) at its immediate site which may be a long way from the iron, *i.e.* 1,3-diphosphoglycerate, (ii) at the iron by way of the spin-state change—a considerable relay, (iii) at the —SH group which is an even greater distance away. Antagonists could block these processes while agonists could potentiate them in a quite different way. Moreover, there are several very different reagents which can act on the same process, *i.e.* O_2 uptake by hemoglobin, by binding at totally different sites, *e.g.* 1,3-diphosphoglycerate, xenon, HgI_3^-, CO, and sulfydryl reagents. The very different chemical behavior of these reagents as compared with O_2, the substrate which the drug challenges, shows that drug design can be quite impossibly difficult. Note too that it is the mobility of the receptor, here hemoglobin, which is responsible for all these different "drug" effects.

4.3. Wriggling and Gating

Another illustration of this "wriggling" principle can be given by examining again the mobility exhibited by the binding groove of lysozyme (Fig. 10). This groove contains two aminodicarboxylate residues, Glu 35 and Asp 52, of which Glu

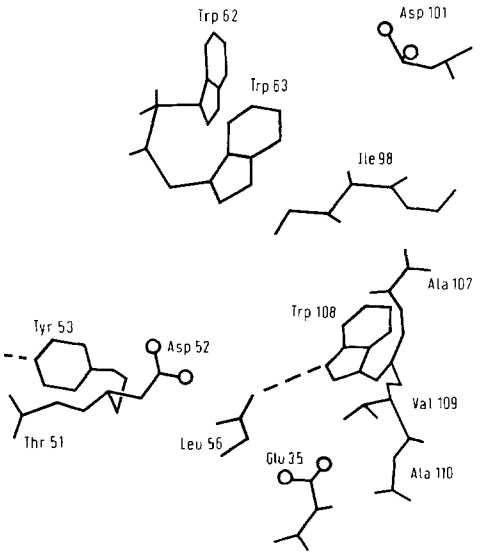
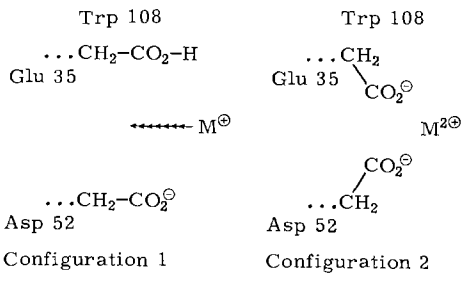


Fig. 10. The active site region of lysozyme; section of the crystal structure. *All* the amino acid residues can be detected in the NMR spectrum.

35 is held in the protonated form, against Trp 108. If a cation is bound in this region of the groove it may interact with sufficient strength that Glu 35 is ionized, and the resulting carboxylate group moves away from Trp 108 (configuration 2 in Scheme 1). In the case of weakly interacting cations this movement does not occur (configuration 1). We can therefore distinguish strongly interacting and weakly interacting cations. Now let us suppose that exactly the same structural relationship of two carboxylate groups occurs, not in lysozyme, but in a region of space *behind* which there is a second binding site for the cation. In the case of strong interaction (configuration 2) the actual binding at the two carboxylate centers would prevent (gate) access to this site. In the case of weak interaction (configuration 1) binding at the rear site would occur as the gate would remain open. Clearly the cations could act in very different ways. Gated reactions will always be associated with wriggling paths. Of course the same pattern can be imagined for the action of a cation such as acetylcholine.



Scheme 1

Another example concerns the passage of an ion, *e.g.* Li^+, through a membrane using an ionophore. There is a binding on/off reaction of metal and ionophore followed by a release. There is also an outward directed ion pump and we may suppose a site of action for Li^+ say in competition with Ca^{2+} or Mg^{2+}. It must be seen that the ionophore-governed steps are very important in the overall effect of lithium.

As we have stated above the mobility of the surfaces of proteins is much greater than that of the internal regions. Our measurements show that surface lysine and sugar side chains (in glycoproteins) have motions with correlation times of 10^{-9} s, *i.e.* as fast as collision diffusion rates. In an assembly of proteins there must be a pathway between the protein molecules which is diffusion restricted by the constraints imposed by the packing of the mobile side chains. The general point can be visualized from an examination of packing of proteins in crystals. Examination of these crystals shows that between protein molecules there are large channels of "disordered" solvent and protein side chains. Inhibitors and other quite large groups such as heavy atom labels diffuse down these channels quite readily to binding sites. But quite clearly there are restrictions on this diffusion which can be of almost any degree of selectivity. Thus only certain molecules will be able to reach particular regions of proteins in an assembly. It is possible to describe this as a "gating" of (drug) action, and the actual motion as "wriggling" to a site. The importance of this mobility of proteins extends to the binding reaction when an antibody combines with an antigen. *Huber et al.*[15] have suggested that the Fc fragment of the antibody is relatively mobile so that it changes conformation on receiving the antigen.

4.4. More Complicated Receptors

A protein or a group of proteins may or may not be the receptor site of a drug. Rather a drug may act on a similar type of large molecule, *e.g.* RNA or DNA, or it could act at a membrane or similar condensed phase. The effect of small molecules on a condensed phase should now be examined in the same way as we have examined their effect on large molecules. The parallels between these problems has been described in a recent review on phases in biological systems[33]. We use lipid phases, membranes, as an example.

4.5. Membranes

Fast tumbling of groups such as we have described in proteins is observed in artificial vesicle membranes of most lipids. For example lecithin vesicles give a high resolution NMR spectrum which shows that motion must be fast for the $-N(CH_3)_3^+$ group on the head and the methyl group on the tail of the fatty acid chains but is somewhat slower for the region around the glycerol group. When the size of the vesicle is changed or other molecules incorporated into it, or the temperature changed, or ions bound to the surface, these mobilities can undergo quite considerable changes. Turning to biological membranes we and others have observed that the ^{1}H-NMR spectrum of almost all *cell* membranes is very broad, even for membranes which contain a high percentage of lecithin, and it is not possible to detect in the NMR spectrum either the choline group on the head or the methyl group on the tail of the fatty acid chains. It is readily shown that inclusion of such molecules as cholesterol in the bilipid layer will cause a general reduction of the motion of the lipid sections of the molecule but the head-group remains free. We are therefore left with the problem that there are gross restrictions on mobility in real biological membranes which are not seen in vesicles. This restriction could be related to size, curvature of membrane surface, or to the binding of the head-groups.

The membrane lipids are also in rapid lateral motion, *i.e.* in the plane of the membrane. Inversion of lipids is however relatively slow; hence the membrane retains its asymmetry. The time scale for lateral movement is not vastly different from diffusion and it has frequently been supposed that drugs can influence this motion. The inversion has a time constant in the range of minutes. Thus although inversion is not important in any steady-state change and return, which takes place within seconds, the steady-state itself can change in response to ambient conditions. We proposed some years ago that it would be interesting to study this asymmetry with the paramagnetic binding probes, but the first actual study was made independently in Russia[34, 35]. A major problem—as in the study of proteins—was (and still is) the question of the structure and the structural dynamics of the membrane and what chemical factors control the dynamics. To this end we looked at the binding of probe ions to a variety of phosphate esters including phosphatidylcholines.

The first feature of binding is that the metal ions do not bind to the phosphate of a membrane phosphatidylcholine in the same way as they bind to phosphate esters such as phosphoglycerolcholine in water. If we use our standard procedures for the study of biological molecules we obtain the structure shown in Figure 11, in which the choline head-group stretches away from the bilipid membrane to a large degree. The result need not be analyzed in great detail, for there is surely much motion, but it is important to observe that the head-group of a lipid in a membrane does not behave in the same way as the dissociated free head-group, say phosphoglycerolcholine, behaves in aqueous solution. Secondly, the binding strength of cations at the two membrane surfaces (inside and outside) is not equal. Thirdly, as the cations bind selectively to different phospholipids they generate asymmetry in the membrane if their concentrations are different on the two sides of the membrane[36]. The effect of the metal binding on the mobility of the membrane has not yet been assessed. However, it will be recognized immediately that the action of a chemical (drug) on such a system is not likely to be dependent upon any one simple factor. Thus as with protein receptors we anticipate that an extremely complicated story

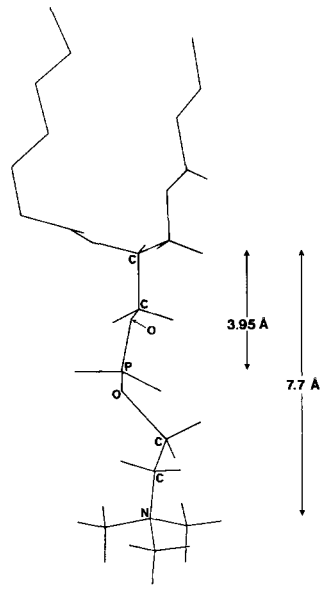


Fig. 11. The structure of phosphatidylcholine. Note that this structure has considerable mobility, and is for a cation-bound condition.

lies behind the drug action. Though it may be possible to follow drug-protein binding atom by atom, this possibility does not really exist in a membrane phase and we may have to be content with a more phenomonological functional thermodynamic approach. This would mean that drug design would remain very empirical. For example, fluidity in a cooperative liquid is open to a phase change of the sol ⇄ gel kind and it could be that a small quantity of an impurity could shift the sol ⇄ gel equilibrium and thus change the dynamics of the phase dramatically.

4.6. Mobility of Bound States

The conclusion seems inevitable that just as all degrees of molecular motion are to be found in drugs (small molecules) and in receptors (proteins, RNA, membranes) so in their combination we shall find all kinds of mobilities (Fig. 12), for the binding site of a drug can vary from a condition in which the best model is a molecule held on a rigid crystalline material to one in which the drug has partitioned from water into an organic medium. There cannot be a general theory of drug action, for this description covers the whole of solid state and solution chemistry with its wide variety of interactions which are expressed quantitatively only in terms of free energy changes. Recently we have been using NMR to examine whole organs and have found a remarkable variety of mobilities in different phases[37]. However, these features of cells cannot be discussed at length here; but in conclusion it should be pointed out that we must contend with many new problems when dealing with added chemicals (drugs) which can affect mobility, and static solid state models of fitting the geometry and chemistry of one surface to another may have to be supplanted by the more nebulous concepts of dynamic (solution) states.

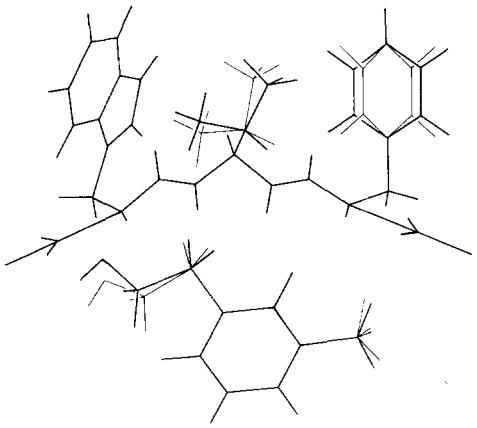


Fig. 12. Schematic diagram for a mobile protein (linked by arrows)—mobile drug interaction.

The work described in this article was made possible by grants from the Science and Medical Research Councils, England. The author wishes to acknowledge the great help he has received from fellow members of The Oxford Enzyme Group and from his students.

Received: November 8, 1976 [Z 187 IE]
German version: Angew. Chem. *89*, 805 (1977)

[1] *A. S. V. Burgen, G. C. K. Roberts, J. Feeney*, Nature *253*, 753 (1975); and references cited therein.
[2] *C. M. Dobson, L. O. Ford, S. E. Summers, R. J. P. Williams*, J. Chem. Soc. Faraday Trans. II *71*, 1145 (1975).
[3] *B. A. Levine, R. J. P. Williams*, Proc. Roy. Soc. (London) *345*, 5 (1975); *B. A. Levine, R. J. P. Williams* in *B. Pullman:* Environmental Effects on Molecular Structure and Properties. Reidel, Dordrecht 1976, p. 95ff.
[4] See *e.g. E. Bergmann, B. Pullman:* Molecular and Quantum Pharmacology. Reidel, Dordrecht 1974.
[5] *C. D. Barry, J. A. Glasel, R. J. P. Williams, A. V. Xavier*, J. Mol. Biol. *84*, 471 (1974).
[6] *C. Altona, M. Sundaralingam*, J. Am. Chem. Soc. *95*, 2333 (1973).
[7] *B. Birdsall, N. J. M. Birdsall, J. Feeney, J. Thornton*, J. Am. Chem. Soc. *97*, 2845 (1975).
[8] *C. D. Barry, D. R. Martin, R. J. P. Williams, A. V. Xavier*, J. Mol. Biol. *84*, 491 (1974).
[9] *C. Geraldes*, D. Phil. Thesis, Oxford 1976.
[10] *G. Bentley, E. Dodson, G. Dodson, D. Hodgkin, D. Mercola*, Nature *261*, 166 (1976).
[11] *G. Bentley, R. J. P. Williams, K. Williamson*, unpublished.
[12] *C. D. Barry, J. A. Glasel, A. C. T. North, R. J. P. Williams, A. V. Xavier*, Biochim. Biophys. Acta *262*, 101 (1972).
[13] *P. Transwell, J. M. Thornton, A. V. Korda, R. J. P. Williams*, Eur. J. Biochem. *57*, 135 (1975).
[14] *O. D. Hensens, H. A. O. Hill, J. Thornton, R. J. P. Williams*, Phil. Trans. Roy. Soc. (London) *B 273*, 353 (1976).
[15] *R. Huber, D. Kukla, W. Stiegemann, J. Deisenhofer, A. Jones:* Bayer Symposium V, Proteinase Inhibitors. Springer, Berlin 1973.
[16] *K. Wüthrich, G. Wagner*, FEBS Lett. 50, 265 (1975).
[17] *I. D. Campbell, C. M. Dobson, R. J. P. Williams*, Proc. Roy. Soc. (London) *345*, 23, 41 (1975).
[18] *K. Linderstrom-Lang, J. A. Schellmann* in *P. D. Boyer, H. Lardy, K. Myrbäck:* The Enzymes. Vol. 1. Academic Press, New York 1959, p. 443ff.
[19] *J. R. Lakowicz, G. Weber*, Biochemistry *12*, 4161 (1973).
[20] *A. Cave, C. M. Dobson, J. Parello, R. J. P. Williams*, FEBS Lett. *65*, 190 (1976).
[21] *G. R. Moore, R. J. P. Williams*, Coord. Chem. Rev. *18*, 125 (1956).
[22] *R. J. P. Williams*, Cold Spring Harbor Symp. Quant. Biol. *36*, 53 (1971).
[23] *J. T. Jahansen, B. L. Vallee*, Biochemistry *14*, 649 (1975).
[24] *C. M. Dobson, R. J. P. Williams*, FEBS Lett. *56*, 362 (1975).
[25] *T. Imoto, L. N. Johnson, A. C. T. North, D. C. Phillips, J. A. Rupley* in *P. D. Boyer:* The Enzymes. Vol. 7. Academic Press, New York 1972, p. 665.
[26] *J. Poulsen, C. M. Dobson, R. J. P. Williams*, unpublished.
[27] *J. W. Becker, G. N. Reeke, B. A. Cunningham, G. M. Edelman*, Nature *259*, 407 (1976).
[28] *R. W. King, A. S. V. Burgen*, Proc. Roy. Soc. (London) *B193*, 107 (1976).

[29] C. D. Barry, H. A. O. Hill, P. J. Sadler, R. J. P. Williams, Proc. Roy. Soc. (London) A 334, 493 (1973).
[30] P. S. Burns, R. J. P. Williams, P. E. Wright, J. Chem. Soc. Chem. Commun. 1975, 795.
[31] This problem has been studied in much detail recently by Prof. H. Frauenfelder (Hamburg Int. Biochemistry Meeting 1976).
[32] M. F. Perutz, L. F. Teneyck, Cold Spring Harbor Symp. Quant. Biol. 36, 295 (1971).
[33] R. J. P. Williams, Biochim. Biophys. Acta 416, 237 (1975).
[34] See H. Hauser, M. C. Phillips, B. A. Levine, R. J. P. Williams, Nature 261, 390 (1976).
[35] L. I. Barsukov, Y. E. Shapiro, A. V. Viktorov, A. F. Bystrov, A. D. Bergelson, Akad. Nauk USSR 208, 717 (1973).
[36] R. J. P. Williams, Physiol. Chem. Phys. 4, 427 (1972).
[37] A. Daniels, R. J. P. Williams, P. E. Wright, Nature 261, 321 (1976).

COMMUNICATIONS

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

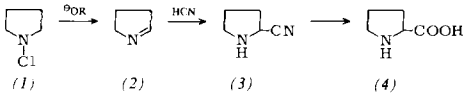
Simple Synthesis of Racemic Proline

By *Ulrich Schmidt* and *Hans Poisel*[*]

Dedicated to Professor Engelbert Broda on the occasion of his 65th birthday

Racemic proline has so far only been accessible by time-consuming multi-step syntheses[1]. We have now found a simple synthetic pathway starting from pyrrolidine:

N-Chlorination, preferably with *tert*-butyl hypochlorite, leads to *N*-chloropyrrolidine *(1)* which is not isolated but instead reacted directly with sodium methoxide to give 1-pyrroline *(2)*. This product trimerizes even in solution within a few hours and cannot be isolated[2]. However, we found it to be sufficiently stable in dilute solution to add reactive compounds. Hydrogen cyanide adds smoothly to 1-pyrroline to form the nitrile *(3)* whose hydrolysis affords racemic proline



(1) *(2)* *(3)* *(4)*

(4) in about 45% yield (based on pyrrolidine).

Hydrogen chloride must be eliminated from the *N*-chloropyrrolidine *(1)* prior to addition of hydrogen cyanide; direct reaction of *(1)* with cyanide in alkaline solution yields *N*-pyrrolidinecarbonitrile. For large scale preparations it is recommended that chlorination of the pyrrolidine be carried out in the two-phase system: ether (or toluene)/aqueous hypochlorite solution.

[*] Prof. Dr. U. Schmidt and Dr. H. Poisel
Organisch-Chemisches Institut der Universität
A-1090 Wien, Währingerstrasse 38 (Austria)

Racemic proline (4)

Pyrrolidine (7.1 g, 0.10 mol) and *tert*-butyl hypochlorite (12.0 g, 0.11 mol) are simultaneously added dropwise to stirred, ice-cooled ether (100 ml). After 5 min the colorless solution is extracted once with dilute HCl and twice with a small volume of water. The mixture is dried with sodium sulfate, treated with sodium (2.76 g, 0.12 mol) in methanol (70 ml) and refluxed for 25 min, whereupon NaCl is precipitated. After cooling, a solution of anhydrous hydrogen cyanide (10 ml, 0.26 mol) in ether (10 ml) is added and reaction allowed to continue overnight at room temperature. The solvent is removed in a rotary evaporator and the residue dissolved in methylene chloride, washed twice with water, and dried with sodium sulfate. Vacuum distillation yields 5.6 g (58%) of *(3)*, b. p. 77 °C/12 torr.—Compound *(3)* (5.5 g) is heated with 19% aqueous hydrochloric acid (100 ml) for 14 h at 100 °C in a bomb tube. After evaporation of the acid the residue is dissolved in water and decolorized with animal charcoal. After concentration the product is dried over sulfuric acid. Esterification of the salt mixture by *Fischer*'s method with HCl/ethanol affords 6.6 g (81%) of D,L-proline ethyl ester which is allowed to stand overnight with 20 ml of water. Removal of solvent leaves 5.0 g [76% based on *(3)*] of D,L-proline *(4)*.

Received: September 22, 1975 [Z 316 IE]
German version: Angew. Chem. 89, 824 (1977)
Publication delayed at authors' request

CAS Registry numbers:
(1), 19733-68-7; *(2)*, 5724-81-2; *(3)*, 57015-08-4; *(4)*, 609-36-9

[1] See, *e.g.*, *K. Hasse* and *A. Wieland*, Chem. Ber. 93, 1686 (1960); *K. H. Buechel* and *F. Korte*, *ibid.* 95, 2453 (1962); *R. A. Strojny*, *H. C. White*, and *E. Strojny*, J. Org. Chem. 27, 1241 (1962).
[2] *D. W. Fulhage* and *C. A. Van der Werf*, J. Am. Chem. Soc. 80, 6249 (1958).

Photochemical [2+2] Cycloaddition between Parallel CC and NN Double Bonds[**]

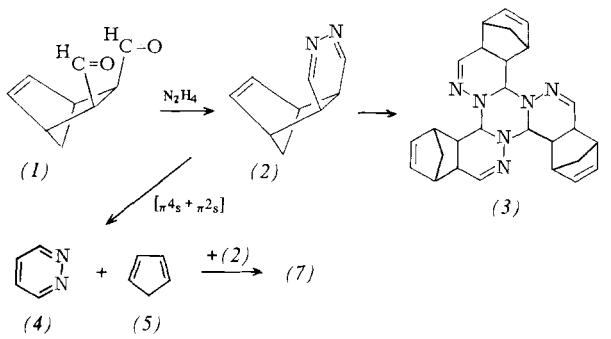
By *Wilfried Berning* and *Siegfried Hünig*[*]

Rigid polycyclic compounds containing two parallel C=C bonds are well known and their chemistry, particularly photochemical [2+2] cycloaddition to cage compounds, has been

[*] Prof. Dr. S. Hünig, Dr. W. Berning
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

[**] From the dissertation by *W. Berning*, Universität Würzburg 1977. This work was supported by the Fonds der Chemischen Industrie and the BASF AG, Ludwigshafen.

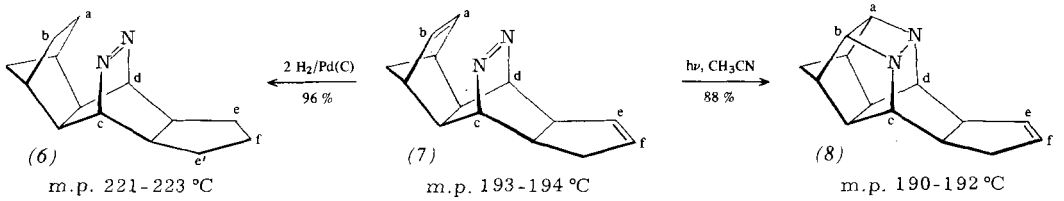
the subject of numerous investigations[1]. We now wish to report on the rigid molecule *(7)*, in which a C=C bond and an N=N bond are oriented parallel and spatially very close to each other. *(7)* is formed in 91 % yield according to the stoichiometry $2(1)+2N_2H_4 \rightarrow (4)+(7)$. Addition of hydrazine hydrochloride to a solution of the aldehyde *(1)*[2]



in 1 % acetic acid leads to almost instantaneous precipitation of *(7)* as colorless crystals. The expected amount of pyridazine *(4)* can be isolated from the concentrated filtrate. The reaction most likely proceeds as follows: The initially formed azine *(2)* suffers a $[\pi 4_s+\pi 2_s]$ cycloreversion generating cyclopentadiene *(5)* and *(4)*. Related cycloreversions proceed under similarly mild conditions[3]. In a Diels-Alder reaction with inverse electron demand further available *(2)* then adds to *(5)*, a particularly active dienophile in this case[4], to give the product *(7)*. Protonation of *(2)* could increase its activity still further. Evidence for this is provided by the fact that under neutral conditions the cleavage $(2) \rightarrow (4)+(5)$ does not take place and *(2)* trimerizes to the hexahydrotriazine *(3)*[5], which is transformed into *(7)* only in an acidic medium.

(7) can be smoothly hydrogenated to the saturated azo compound *(6)*. In *(6)* the *cis* azo group shows UV data resembling those of 2,3-diazabicyclo[2.2.2]oct-2-ene[6], whereas in *(7)* an interaction typical for parallel CC double bonds[1] is observed to take place between the two unsaturated groups (Table 1). The strong π-π interaction between parallel C=C and N=N bonds is also clearly discernable in the photoelectron spectrum[7a]. As is usual in the case of alicyclic azo compounds[8], *(6)* liberates nitrogen on heating or irradiation, giving unidentified products. In contrast, *(7)*, which is thermally stable up to *ca.* 250 °C, undergoes ring closure almost quantitatively on irradiation in acetonitrile to give *(8)*, and the typical UV absorption of the azo group disappears. Thus, not only a new type of cage compound has been formed but also the first $[\pi 2_s+\pi 2_s]$ photocyclization between non-activated C=C and N=N bonds has been accomplished which previously always failed because of rapid elimination of nitrogen.

A detailed analysis of the ^{1}H- and ^{13}C-NMR spectra[7b] confirms the structure and configuration of *(6)*—*(8)*[7c]. The signals for the positions a through f in *(6)*—*(8)* are especially characteristic (Table 1): In *(7)* the resonances of H_c, H_d and C_c, C_d appear in the typical region for NMR absorptions of H and C atoms in the α-position to an azo group[9a]; and as expected for an asymmetric compound two signals appear for each of these atoms. The anisotropy effect of the azo group gives rise to a distinct upfield shift for H_a, H_b (cf. norbornene: $\delta = 5.95$[9b]), while H_e, H_f are influenced to a somewhat lesser extent (cf. cyclopentene: $\delta = 5.60$[9b]). After elimination of the intramolecular interactions in the cage compound *(8)* the signals of H_e, H_f appear at lower field. Consistent with the required C_s symmetry of the hydrogenated compound *(6)* H_c, H_d and C_c, C_d respectively show only one signal; magnetic equivalence of C_a, C_b and C_e, $C_{e'}$ is likewise observed. The ^{1}H-NMR spectrum of *(8)* exhibits a new signal at $\delta = 4.2$ which is assigned to the diazetidine protons H_a, H_b (best comparable example in the literature: 4.35[10]). Furthermore, in *(8)* the signals of C_a, C_b appear at lower field in the aliphatic region, thus indicating their close proximity to the nitrogens.



Received: July 29, 1977 [Z 804 IE]
German version: Angew. Chem. 89, 825 (1977)

CAS Registry numbers:
(1), 63904-57-4; *(6)*, 63904-58-5; *(7)*, 63904-59-6; *(8)*, 63904-60-9; hydrazine hydrochloride, 14011-37-1

Table 1. Characteristic spectral data of *(6)*, *(7)* and *(8)*.

	(6)	*(7)*	*(8)*
^{1}H-NMR ($CDCl_3$), δ			
H_a, H_b	0.7–2.5 [a]	5.43 [b]	4.2
H_e, H_f	0.7–2.5 [a]	5.41 [b]	5.57 (H_e), 5.88 (H_f)
H_c, H_d	5.15	5.16/5.21	2.3–3.3 [a]
^{13}C-NMR ($CDCl_3$), δ			
C_a, C_b	27.9 [c]	132.2/132.3	69.9/70.1
C_e, C_f	30.7 (C_e, $C_{e'}$) [c], 26.6 (C_f)	132.0/129.6	131.7/130.3
C_c, C_d	69.3	67.7/69.6	59.6/61.9
UV (*n*-hexane), λ_{max} [nm] (ε)			
	384 (164)	396 (126)	–
	222 ($1.26 \cdot 10^3$)	216 ($1.73 \cdot 10^3$)	217 ($9.4 \cdot 10^2$)

[a] In a multiplet of the aliphatic protons.
[b] Assignment by decoupling experiments.
[c] Assignment unclear.

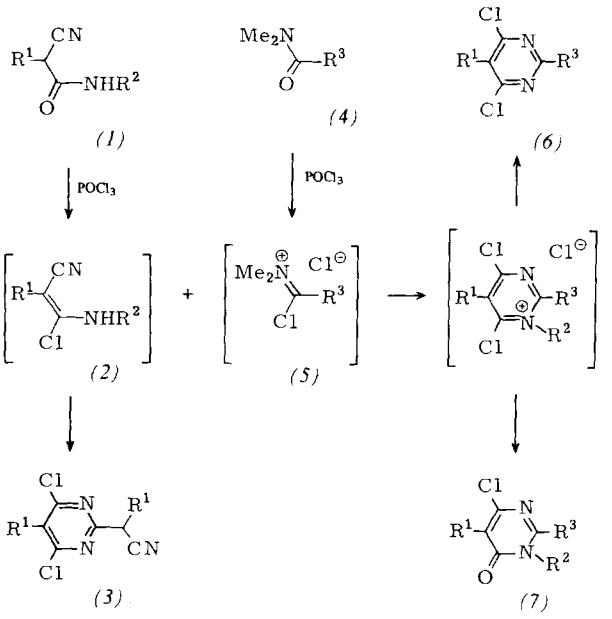
[1] *W. L. Dilling*, Chem. Rev. *66*, 373 (1966).
[2] Generated from the acetal: *K. Alder, H. Betzing, K. Heimbach*, Justus Liebigs Ann. Chem. *638*, 187 (1960).
[3] *A. R. Rye, D. Wege*, Aust. J. Chem. *27*, 1943 (1974); *W. S. Wilson, R. N. Warrener*, Tetrahedron Lett. *1970*, 5203; *P. Baumgartner, G. Hugel*, Bull. Soc. Chim. Fr. *1954*, 1005.
[4] *H. Wollweber* in Houben-Weyl-Müller: Methoden der organischen Chemie, Vol. V/1c. Thieme, Stuttgart 1970, p. 1041.
[5] Related example: *G. Maier, T. Sayrac*, Chem. Ber. *101*, 1354 (1968).
[6] *R. J. Boyd, J. C. Bünzli, J. P. Snyder, M. L. Heymann*, J. Am. Chem. Soc. *95*, 6478 (1973); *J. P. Snyder*, private communication, April 1977.
[7] a) *H.-D. Martin*, unpublished; b) we thank Dr. *M. Christl* for help in interpreting the spectra; c) elemental analysis, molecular weight determinations, and mass spectra are consistent with the empirical formulas.
[8] *P. S. Engel, C. Steel*, Acc. Chem. Res. *6*, 275 (1973).
[9] a) *A. A. R. Harper, J. Vaughan* in *S. Patai*: The chemistry of hydrazo, azo and azoxy-groups. Wiley, New York 1975, p. 243; b) *H. Günther*: NMR-Spektroskopie. Thieme, Stuttgart 1973, p. 371.
[10] *W. A. Thaler, B. Franzus*, J. Org. Chem. *29*, 2226 (1964).

A New Synthesis of Pyrimidines and Pyrimidinones[**]

By *R. L. N. Harris* and *J. L. Huppatz*[*]

N-Alkyl-2-cyanamides *(1)* undergo self-condensation on prolonged heating in $POCl_3$ to give the pyrimidines *(3)*. An intermediate in this reaction was thought to be the α-chloroenamine *(2)*[1]. We have now found that these intermediates are suitable substrates for an alternative pyrimidine synthesis in which the other component is itself an amide-acid chloride adduct *(5)*, generated from an *N,N*-dialkylamide *(4)* and $POCl_3$. Thus, reaction of a mixture of the amides *(1)* and *(4)* with $POCl_3$ at 100°C leads to pyrimidines *(6)*. Depending on the nature of R^2, pyrimidinones *(7)* may also be isolated. When the R^2 is a primary alkyl group, it is only partially lost during the condensation and a mixture of pyrimidines and pyrimidinones results. When R^2 is a secondary alkyl group, loss is usually complete and good yields of pyrimidines are obtained (Table 1).

Most conveniently, *N*-cyclohexylamides are used as component *(1)* since they are readily prepared in high yield by gently refluxing together the appropriate ethyl 2-cyanoalkanoate and a slight excess of cyclohexylamine. The esters themselves are obtained by reductive alkylation of ethyl cyanoacetate[2].



The reaction appears to depend for its success on the simultaneous generation of intermediates *(2)* and *(5)*; when the highly reactive amides *(4b)* or *(4c)* are used the reaction fails unless compound *(1)* is heated at 100°C with $POCl_3$ for 5 min before their addition.

Yields are best when R^3 is aryl, when the synthesis complements the usual base-catalyzed routes[3] to compounds *(6)* and *(7)*. The principal limitation is that an alkyl or aryl substituent must be present at the α-carbon of the precursor amide *(1)* (and thus at C-5 of the products) to avoid alternative self-condensation of *(1)*[4].

Experimental:

4,6-Dichloro-2-phenyl-5-propylpyrimidine (6d): Ethyl 2-cyanopentanoate[2] (31 g, 0.2 mol) and cyclohexylamine (21 g, 0.21 mol) were heated under gentle reflux for 5 h. After removal of ethanol and excess cyclohexylamine *in vacuo* (rotary evaporation) the mixture was allowed to cool and the resulting solid amide *(1e)* (40 g, 96 %) used without further purification in the following step. A portion crystallized for analysis from ethanol as colorless needles, m.p. 90—92°C. The foregoing amide *(1e)* (2.1 g, 0.01 mol) and *N,N*-dimethylbenzamide *(4a)* (1.5 g, 0.01 mol) were dissolved in $POCl_3$ (5 ml) and the mixture heated on a steam-bath overnight. The mixture was poured

Table 1. Pyrimidines *(6)* and pyrimidinones *(7)* from *N*-alkyl-2-cyanamides *(1)* and *N,N*-dialkylamides *(4)* [6].

Educts					Products								
	R^1	R^2		R^3		R^1	R^3		R^1	R^2	R^3	Yield [%]	M.p. [°C]
(1a)	Me	Me	*(4a)*	Ph	*(6a)*	Me	Ph					21	109–110
								(7a)	Me	Me	Ph	14	143–144
(1b)	sBu	Me	*(4a)*	Ph	*(6b)*	sBu	Ph					52	48–49
								(7b)	sBu	Me	Ph	21	68–69
(1c)	Et	iPr	*(4a)*	Ph	*(6c)*	Et	Ph					53	73–75 (74–75 [5])
(1d)	Et	C_6H_{11}	*(4a)*	Ph	*(6c)*	Et	Ph					55	
(1e)	Pr	C_6H_{11}	*(4a)*	Ph	*(6d)*	Pr	Ph					60	69–71 (67–70 [5])
(1e)	Pr	C_6H_{11}	*(4b)*	Me	*(6e)*	Pr	Me					25	oil
(1e)	Pr	C_6H_{11}	*(4c)*	H	*(6f)*	Pr	H					37	oil
								(7c)	Pr	C_6H_{11}	H	19	102–103

[*] Dr. R. L. N. Harris, Dr. J. L. Huppatz
CSIRO, Division of Plant Industry
P.O. Box 1600, Canberra City, A.C.T. (Australia)

[**] Amide-Acid Chloride Adducts in Organic Synthesis, Part 8.—Part 7: *R. L. N. Harris, J. L. Huppatz, J. N. Phillips*, Angew. Chem. *88*, 539 (1976); Angew. Chem. Int. Ed. Engl. *15*, 498 (1976).

with stirring into ice-water and the crude product extracted into chloroform. The chloroform extract was passed through a short (100 × 15 mm) column of silica gel and the residue after removal of solvent was recrystallized from methanol-water to give *(6d)* as long silky needles (1.6 g).

5-sec-Butyl-4,6-dichloro-2-phenylpyrimidine (6b) and *5-sec-Butyl-6-chloro-3-methyl-2-phenyl-4-pyrimidinone (7b): (1b)* (3.0 g, 0.02 mol) and *(4a)*, (3.0 g, 0.02 mol) were reacted together in $POCl_3$ as described above for *(6d)*. Chromatography of the product on silica gel using chloroform-petroleum ether (b.p. 60—80 °C) (1:1) as eluent gave *(6b)* as a pale yellow oil (2.9 g) which, after solidification, crystallized from ethanol in the form of colorless needles. Subsequent elution of the column with chloroform gave *(7b)* as a yellow oil (1.2 g), which solidified. Crystallization from a small quantity of petroleum ether (b.p. 60—80 °C) gave colorless prisms.

Received: July 18, 1977 [Z 806 IE]
German version: Angew. Chem. 89, 816 (1977)

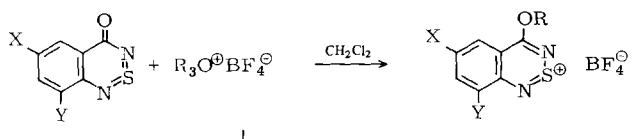
CAS Registry numbers:
(1a), 53260-43-8; *(1b)*, 63797-45-5; *(1c)*, 63797-46-6; *(1c)*, 63797-47-7; *(1e)*, 63797-48-8; *(4a)*, 611-74-5; *(4b)*, 127-19-5; *(4c)*, 68-12-2; *(6a)*, 33655-33-3; *(6b)*, 63797-49-9; *(6c)*, 33655-34-4; *(6d)*, 33655-35-5; *(6e)*, 63797-50-2; *(6f)*, 63797-51-3; *(7a)*, 63797-52-4; *(7b)*, 63797-53-5; *(7c)*, 63797-54-6; ethyl 2-cyanopentanoate, 6967-47-1; cyclohexylamine, 108-91-8

[1] *A. L. Cossey, R. L. N. Harris, J. L. Huppatz, J. N. Phillips*, Angew. Chem. *82*, 898 (1974); Angew. Chem. Int. Ed. Engl. *13*, 809 (1974).
[2] *E. D. Alexander, A. C. Cope*, J. Am. Chem. Soc. *66*, 886 (1944).
[3] *D. J. Brown*: The Pyrimidines. Interscience, New York 1962, Chap. 2—3.
[4] *A. L. Cossey, R. L. N. Harris, J. L. Huppatz, J. N. Phillips*, Aust. J. Chem. *29*, 1039 (1976).
[5] *S. Yanagida, M. Yokoe, M. Ohoka, S. Komori*, Bull. Chem. Soc. Jpn. *44*, 2182 (1971).
[6] The structures of all compounds reported are consistent with analytical, NMR and mass spectral data.

A Novel Heteroaromatic System: 2,1,3-Benzothiadiazinylium Derivatives[**]

By *Wolfgang Kosbahn* and *Helmut Schäfer*[*]

Analogously to pairs such as benzene/tropylium or thiophene/thiopyrylium, formal ring expansion of the well documented and extremely stable heterocycle 2,1,3-benzothiadiazole ("piazthiol")[1] affords the 2,1,3-benzothiadiazinylium ion *(2)*. We have now succeeded in preparing the first derivatives of this ring system from the benzothiadiazinones *(1)* by directed alkylation at the oxygen:



(1) *(2)*

	X	Y	R
(a)	H	H	CH_3
(b)	H	H	C_2H_5
(c)	Cl	H	C_2H_5
(d)	Cl	Cl	C_2H_5
(e)	NO_2	H	C_2H_5

[*] Dr. habil. W. Kosbahn, Dr. H. Schäfer
Arbeitsgemeinschaft für Strukturchemie der Technischen Universität
Arcisstr. 21, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Leibniz-Rechenzentrum München. The results were delivered in part in a lecture at the Chemiedozententagung in Marburg on March 25, 1977.

Like the already known unsubstituted compound *(1ab)*[2], the educts *(1c)* to *(1e)* are obtainable from the corresponding substituted 2-aminobenzamides by reaction with *N,N'*-bis(*p*-toluenesulfonyl)sulfur diimide in chloroform. The reaction with oxonium salts in dichloromethane proceeds at room temperature within a few minutes in the case of *(1ab)*, within a few days in the case of *(1d)*. The products *(2)* can be purified by dissolution in acetone and precipitation with diethyl ether [yields between 13% *(2e)* and 85% *(2a)*]. Their structure follows from the IR, ^{1}H-NMR and, in particular, from the ^{13}C-NMR spectra. Noteworthy is the strong deshielding influence of the N_2S^+ group on the atom C-6 located in the *p*-position; the substituent increment with about +15.5 ppm has almost the same value as the diazonium group[3].

The finely crystalline 2,1,3-benzothiadiazinylium salts *(2)* have decomposition points between 111 and 165 °C; they react slowly with water with evolution of SO_2.

(2b) reacts smoothly at room temperature with 1,3-dienes such as 2,3-dimethylbutadiene, 1,3-pentadiene or isoprene, whereby the double bond between N-1 and S functions as dienophile. The structure of the adducts (isolable in yields of *ca.* 65%) follows above all from the ^{13}C-NMR spectra. The ease of addition and its pronounced regioselectivity can be explained in terms of the frontier orbitals of the reactants: According to PPP and CNDO/S calculations[4] the lowest unoccupied molecular orbital (LUMO) of *(2)*, a π orbital, is almost completely localized on the atoms N-1 and S; this localization, a nodal plane between both atoms and the low energetic state of the LUMO enable optimum interaction with the highest occupied orbital (HOMO) of the diene in the sense of a normal Diels-Alder reaction[5].

Evidence for the "aromaticity"[6] of the new heterocyclic system *(2)* can be gained from its resonance energy. Resonance energies on an HMO basis have recently been re-defined[7]. For *(2)* calculation according to this definition yields a distinctly large resonance energy of 0.313 β (for comparison: naphthalene 0.389 β); the ring system *(2)* can therefore be regarded as being heteroaromatic.

Received: August 9, 1977 [Z 813 IE]
German version: Angew. Chem. 89, 826 (1977)

CAS Registry numbers:
(1ab), 33800-08-7; *(1c)*, 63904-41-6; *(1d)*, 63904-42-7; *(1e)*, 63904-43-8; *(2a)*, 63904-45-0; *(2b)*, 63904-47-2; *(2c)*, 63904-49-4; *(2d)*, 63904-51-8; *(2e)*, 63904-53-0; 2-amino-5-chlorobenzamide, 5202-85-7; 2-amino-3,5-dichlorobenzamide, 36765-01-2; 2-amino-5-nitrobenzamide, 16313-65-8; *N,N'*-bis(*p*-toluenesulfonyl)sulfur diimide, 851-06-9; trimethyloxonium tetrafluoroborate, 420-37-1; triethyloxonium tetrafluoroborate, 368-39-8; 2,3-dimethylbutadiene, 513-81-5; 1,3-pentadiene, 504-60-9; isoprene, 78-79-5; 2,3-dimethylbutadiene adduct with *(2b)*, 63904-54-1

[1] *O. Hinsberg*, Ber. Dtsch. Chem. Ges. *22*, 2895 (1889).
[2] *H. Grill, G. Kresze*, Justus Liebigs Ann. Chem. *749*, 171 (1971).
[3] *G. A. Olah, J. L. Grant*, J. Am. Chem. Soc. *97*, 1546 (1975).
[4] *W. Kosbahn*, unpublished.
[5] *K. N. Houk*, Acc. Chem. Res. *8*, 361 (1975).
[6] *G. Binsch*, Naturwissenschaften *60*, 369 (1973); *G. Maier*, Chem. Unserer Zeit 9, 131 (1975).
[7] *J. Aihara*, J. Am. Chem. Soc. *98*, 2750, 6840 (1976); *I. Gutman, M. Milun, N. Trinajstić*, *ibid.* *99*, 1692 (1977).

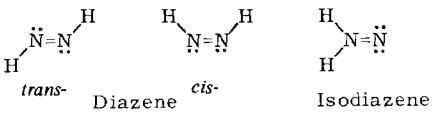
cis- and *trans*-Diazene (Diimine)[1]

By *Nils Wiberg, Gerd Fischer*, and *Heinz Bachhuber*[*]

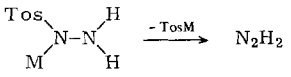
According to experimental findings[1] and quantum mechanical calculations[2] N_2H_2 can exist in two constitu-

[*] Prof. Dr. N. Wiberg, Dr. G. Fischer, Dr. H. Bachhuber
Institut für Anorganische Chemie der Universität
Meiserstr. 1, D-8000 München 2 (Germany)

tionally isomeric forms, diazene (diimine) and isodiazene (isodiimine); for the diazene two configurationally isomeric forms are conceivable, *trans*- and *cis*-diazene.



As shown by mass spectrometric investigations, in the thermolysis of alkali-metal tosylhydrazides[3] according to



two constitutionally isomeric species N_2H_2[1] are formed depending upon the nature of M and the pretreatment of the tosylhydrazide: lithium, sodium, potassium, and aged cesium tosylhydrazide lead to formation of an energy-poor, yellow N_2H_2 (diazene), which above *ca.* −180 °C mainly disproportionates into nitrogen and hydrazine; freshly prepared cesium tosylhydrazide leads to a colorless N_2H_2 species (isodiazene) which is richer in energy by about 13 kcal/mol (54 kJ/mol), readily isomerizes, and decomposes above *ca.* −240 °C into nitrogen, hydrogen and ammonia. Thermolysis of rubidium tosylhydrazide affords both sorts of N_2H_2.

According to IR spectroscopic measurements the energy-poorer diazene itself occurs in two configurationally isomeric forms. Thus, as we have previously observed, in the thermal decomposition of potassium tosylhydrazide mainly one N_2H_2 form (*cis*-diazene) is produced which on contact with cold surfaces transforms into the other form (*trans*-diazene). If the N_2H_2 gas is passed through a glass tube cooled with 'dry-ice' (−78 °C) onto an IR window cooled with liquid nitrogen (−196 °C) then—according to the IR spectrum—a mixed condensate of both isomers is obtained which, given a short cooling tube, chiefly contains *cis*-diazene, and given a long cooling tube exists mainly as *trans*-diazene. The temperature of the window also plays a role: at lower temperatures the *cis*-diazene is obtained, at higher temperatures the *trans*-diazene.

A typical IR spectrum of the N_2H_2 mixed condensate, which generally contains hydrazine[4] shows—besides bands of N_2H_4 and two further absorptions at 2935 and 2870 cm^{-1} that are possibly due to hydrogen bridge vibrations—two groups of bands which according to number and position[5] are evidently due to vibrations of *trans*- and *cis*-diazene. The intensity of the band for the *trans* isomer increases at the expense of the absorptions of the *cis* isomer if a long cooling tube (up to 10 m)[6] and/or a relatively warm IR window[6] is used (the spectrum of a mixed condensate containing mainly *trans*-diazene is illustrated in [3]), and *vice versa*. Should the changes in the IR spectrum arise merely as a result of differences in molecular aggregation of a configurational isomer then only the condensation temperature, but not the length of the cooling tube, could influence the spectrum of the N_2H_2 condensate.

IR vibration bands of solid diazene and dideuteriodiazene. The underlined wave numbers [cm^{-1}] are assigned to the *trans* form, the remainder to the *cis* form.

N_2H_2: 3116, 3109, 3025, 1347, 1333, 1304
N_2D_2: 2305, 2275, 1517, 1084, 989

Our interpretation of the data is supported by investigations on dideuteriodiazene, which on the grounds of the kinetic isotope effect should have a lower reactivity, *i.e.* a higher thermostability and stability towards isomerization. In fact the thermolysis gas from lithium [D_2]-tosylhydrazide contains astonishingly little N_2D_4[4]; also the low-temperature condensate consists of only one sort of N_2D_2, even after flowing through a longer glass tube cooled to −78 °C: The IR spectrum of the condensate shows only one group of relatively sharp bands, which according to number and position correspond to the *cis* form.

The two configurationally isomeric diazenes are distinguishable only on the basis of the IR spectra, but not the UV or mass spectra. Their electronic structure ought, therefore, to be very similar (cf.[2] and the almost identical electron spectrum of *trans* and *cis* azomethane[7]). Since no difference in the appearance energies of the molecular and fragment ions of the isomers can be detected mass spectrometrically (limit of error: ±1.5 kcal/mol) their energy content might be almost equal. The observed *cis*→*trans* isomerization would of course indicate that the *trans*-diazene is somewhat more stable than the *cis*-diazene. This is consistent with calculations[2], according to which isodiazene is considerably richer, but *cis*-diazene only slightly richer in energy than *trans*-diazene.

Received: August 4, 1977 [Z 815 IE]
German version: Angew. Chem. *89*, 828 (1977)

CAS Registry numbers:
trans-diazene, 15626-43-4; *cis*-diazene, 15626-42-3; isodiazene, 28647-38-3; Li tosylhydrazide, 38448-42-9; Na tosylhydrazide, 38448-43-0; K tosylhydrazide, 38448-44-1; Cs tosylhydrazide, 63915-11-7; Rb tosylhydrazide, 63915-12-8

[1] Part 22 of Diimine and Its Derivatives. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 21: *N. Wiberg, G. Fischer, H. Bachhuber*, Angew. Chem. *88*, 386 (1976); Angew. Chem. Int. Ed. Engl. *15*, 385 (1976).
[2] *R. Ahlrichs, V. Stämmler*, Chem. Phys. Lett. *37*, 77 (1976); *N. C. Baird, R. F. Barr*, Can. J. Chem. *51*, 3303 (1973); *G. Wagnière*, Theor. Chim. Acta *31*, 269 (1973).
[3] *N. Wiberg, G. Fischer, H. Bachhuber*, Chem. Ber. *107*, 1456 (1974).
[4] Owing to the high decomposibility of diazene the thermolysis gas of alkali-metal tosylhydrazides always contains the disproportionation product hydrazine, which can be separated from N_2H_2 only if the gas mixture is passed through very long glass tubes cooled with 'dry ice'.
[5] Considering vibration spectroscopic selection rules, 3 IR active absorptions are expected for *trans*-diazene, 5 for *cis*-diazene.
[6] Because of the decomposibility of diazene the temperature of the IR window should not exceed −180 °C; also the cooling tube should not be too long.
[7] *R. F. Hutton, C. Steel*, J. Am. Chem. Soc. *86*, 745 (1964).

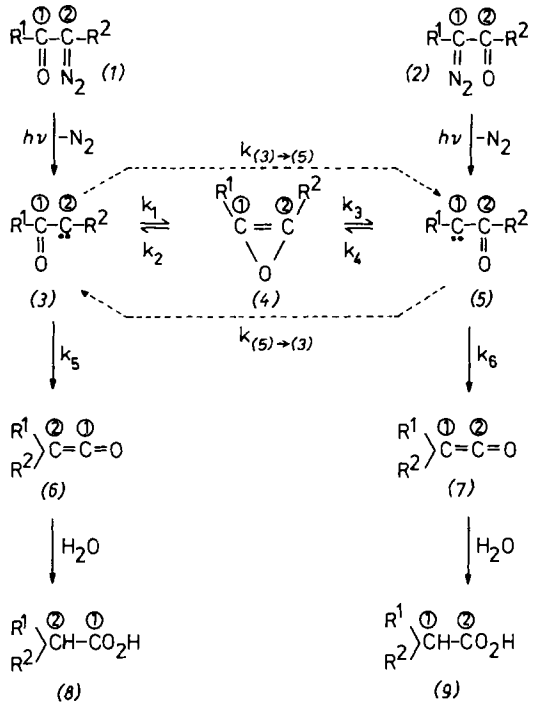
α-Oxocarbene-Oxirene Isomerization: Photolysis of [1-^{13}C]-2-Diazo-1-phenyl-1-propanone and [2-^{13}C]-1-Diazo-1-phenyl-2-propanone[**]

By *Klaus-Peter Zeller*[*]

The carbene-carbene rearrangement of α-oxocarbenes *via* potential antiaromatic oxirenes[1] has been demonstrated on numerous acyclic systems by carbon labeling[2] or competing carbene reactions[3]. Scheme 1 outlines the individual steps on using the labeling technique and the Wolff rearrangement as demonstration reactions.

[*] Priv.-Doz. Dr. K.-P. Zeller
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

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

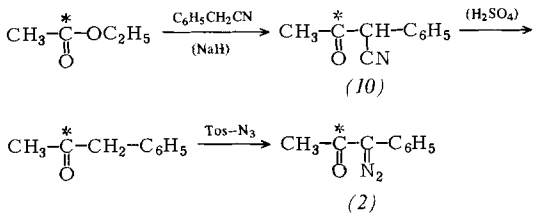


Scheme 1. The α-oxocarbene-oxirene equilibrium as accompanying reaction for the Wolff rearrangement.

If an α-diazoketone labeled on ① or ② [*(1)*, *(2)*] is used as starting compound, a carbene-carbene rearrangement *(3)*⇌*(4)*⇌*(5)* is confirmed when the labeling is distributed over both carbon atoms in the Wolff rearrangement product.

For closer examination of the kinetic model (Scheme 1) both entries to the α-oxocarbene-oxirene equilibrium by photolysis of the isomers, ^{13}C-labeled α-diazopropanones [1-^{13}C]-*(1)* and [2-^{13}C]-*(2)* ($R^1=C_6H_5$, $R^2=CH_3$) have now been monitored.

The diazoketone *(1)* can be obtained from [carbonyl-^{13}C]-benzoyl chloride and excess diazoethane solution[4]: $M^{+\bullet}=m/e$ 161, 84.5% ^{13}C in ①; IR $\tilde{\nu}$ [cm^{-1}]: 2075 (NN), 1570 (^{13}CO). For the synthesis of the isomeric compound *(2)*, [carbonyl-^{13}C]-ethyl acetate is first condensed with benzyl cyanide to give the nitrile *(10)*. Hydrolysis of *(10)* with sulfuric acid affords phenylacetone[5], which reacts with tosyl azide to give the labeled diazoketone *(2)*[6]: $M^{+\bullet}=m/e$ 161, 60.8 % ^{13}C in ②; IR $\tilde{\nu}$ [cm^{-1}] 2070 (NN), 1655 (CO).



(10)

(2)

Photolysis of *(1)* and *(2)* in aqueous dioxane leads to ^{13}C-labeled 2-phenylpropionic acid *(8)* and *(9)*, respectively, ($R^1=C_6H_5$, $R^2=CH_3$) in which the distribution of ^{13}C over the carboxy group and the tertiary C atom can be determined from the ^{13}C-NMR spectrum and the mass spectrometric fragmentation.

The PFT ^{13}C-NMR spectrum of unlabeled 2-phenylpropionic acid contains signals at δ (rel. TMS)=180.8 (CO_2H), 139.7, 128.6, 127.5 (C_{ar}), 45.3 (CH) and 17.9 (CH_3). The spectrum of the acid obtained from *(1)* shows that *ca.* 60% (irradiation with pyrex-filtered radiation from a Hanovia 450 watt medium-pressure lamp) or 68 % (mercury low-pressure burner) of the label has migrated from ① to ②. The same values are obtained from the intensities of the pronounced $[M-CO_2H]^+$ ions in the mass spectrum (*m/e* 105, C_8H_9 and *m/e* 106, $C_7{}^{13}CH_9$). In the acid obtained from *(2)* the proportion of the label migrating from ② to ① borders on the limit of detection of the two analytical methods.

Table 1. Photolysis of 1.3×10^{-2} M solutions of *(1)* and *(2)* in dioxane/water (13:2) at room temperature and on purging with pure nitrogen.

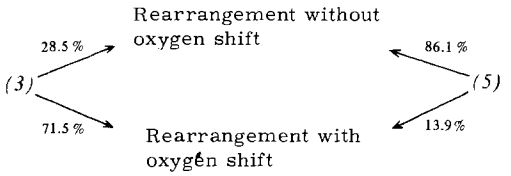
α-Diazoketone	^{13}C-Labeling	λ [nm]	Proportion of migrated labeling [%] [a]
(1) $R^1=C_6H_5$, $R^2=CH_3$	84.5 % in ①	>290	60.2
		254	68.3
(2) $R^1=C_6H_5$, $R^2=CH_3$	60.8 % in ②	>290	2.8
		254	4.4

[a] Mean value of three ^{13}C-NMR and five mass spectrometric measurements; mean deviation *ca.* ±2.

Consequently, the Wolff rearrangement product formed from *(1)* does not predominantly orginate from the primarily generated α-oxocarbene *(3)* but from the isomeric α-oxocarbene *(5)* formed by oxygen migration. On the other hand, in the photolysis of *(2)* the oxygen atom largely remains on the original carbon atom ②.

This finding points to a complicated dependence of the carbene-carbene rearrangement of α-oxocarbenes on the partial steps k_1 to k_6. The preferred formation of *(7)* [and subsequently of *(9)*], irrespective of whether the α-oxocarbene-oxirene equilibrium proceeds *via* *(1)*→*(3)* or *(2)*→*(5)*, is explained in part by the pronounced migration ability of the methyl group (R^2) compared to the phenyl group (R^1) in the photochemical Wolff rearrangement[1a, 7]. The drastic difference in the proportion of migrated oxygen, however, is only understandable if it is also assumed that the equilibrium *(3)*⇌*(4)*⇌*(5)* is strongly shifted towards *(5)*.

If k_1 and k_2 are summed to $k_{(3)\rightarrow(5)}$ and k_4 ad k_2 to $k_{(5)\rightarrow(3)}$ a kinetic evaluation from the 254 nm photolysis[8] yields the ratio $k_{(3)\rightarrow(5)}/k_5=2.5$ and $k_{(5)\rightarrow(3)}/k_6=0.16$ (cf. Scheme 1). Thence for the carbenes *(3)* and *(5)* we have the following proportions for rearrangement with and without oxygen shift:



Received: August 9, 1977 [Z 814 IE]
German version: Angew. Chem. 89, 827 (1977)

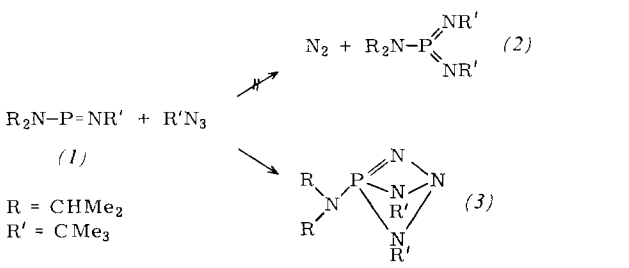
CAS Registry numbers:
(1) (unlabeled), 31164-01-9; [1-^{13}C]-*(1)*, 63904-55-2; *(2)* (unlabeled), 3893-35-4; [2-^{13}C]-*(2)*, 63904-56-3; [carbonyl-^{13}C]-benzoyl chloride, 52947-05-4; diazoethane, 1117-96-0; [carbonyl-^{13}C]-ethyl acetate, 3424-59-7; benzyl cyanide, 140-29-4; tosyl azide, 941-55-9

[1] Review: a) *H. Meier, K.-P. Zeller*, Angew. Chem. *87*, 52 (1975); Angew. Chem. Int. Ed. Engl. *14*, 32 (1975); b) *C. Wentrup*, Top. Curr. Chem. *62*, 173 (1976).
[2] *J. Fenwick, G. Frater, K. Ogi, O. P. Strausz*, J. Am. Chem. Soc. *95*, 124 (1973); *K.-P. Zeller, H. Meier, H. Kolshorn, E. Müller*, Chem. Ber. *105*, 1875 (1972); *K.-P. Zeller*, Tetrahedron Lett. *1977*, 707.
[3] *S. A. Matlin, P. G. Sammes*, J. Chem. Soc. Perkin Trans. II *1972*, 2623.
[4] *A. L. Wilds, A. L. Meader*, J. Org. Chem. *13*, 763 (1948).
[5] *P. L. Julian, J. J. Oliver*, Org. Synth. Collect. Vol. II, 391 (1943).
[6] *M. Regitz*, Chem. Ber. *98*, 1210 (1965).
[7] *R. Müller*, Diplomarbeit, Universität Tübingen 1977.
[8] It is assumed that *(3)* and *(5)* are in real equilibrium.

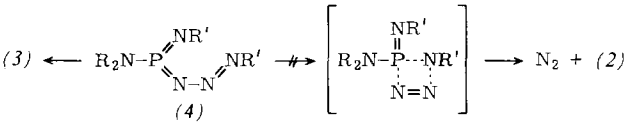
An Imino-Bridged Triaza-λ^5-phosphetine[**]

By *Edgar Niecke* and *Hans-Günther Schäfer*[*]

Reaction of *tert*-butyliminodi(isopropyl)aminophosphane[1] *(1)* with *tert*-butyl azide does not lead to the completely alkylated aminodiiminophosphorane *(2)*, but to a thermostable adduct *(3)* having a bicyclic structure.



We presume that *(3)* is formed by intramolecular [2+2] cycloaddition from an intermediate *(4)* corresponding to the Staudinger adducts of tertiary phosphanes and organic azides[2]. Formation of a four-membered ring transition state[3] leading to N_2 elimination is evidently suppressed by electronic and steric effects of the *N*-alkyl substituents.



The imino-bridged triaza-λ^5-phosphetine *(3)* is a yellow crystalline solid (m.p. 78 °C) which is practically insensitive to moisture. The composition and the monomolecularity of the compound in the liquid and gaseous phase are confirmed by elemental analysis, molecular weight determination, and mass spectrum[4]. The bicyclic structure of the adduct with phosphorus-nitrogen double bond in the ring is supported by[5]:

1) the equivalence of the two *tert*-butyl groups in the ^{1}H- and $\{^1H\}^{13}$C-NMR spectrum (Table 1);
2) the chemical shift of the ^{31}P-NMR signal ($\delta = +23.9$; ext. H_3PO_4) in the expected region for nitrogen-substituted phosphorus compounds of coordination number 4;
3) the P=N absorption at 1225 cm^{-1} in the IR spectrum, because of its characteristic position, intensity, and contour.

Temperature dependent ^{1}H- and $\{^1H\}^{13}$C-NMR measurements show that the two isopropyl groups are already anisochronic at room temperature ($T_c = 28$ °C). Model considerations suggest that this finding, evidencing hindered rotation about the phosphorus-nitrogen bond, results from a steric interaction with the *tert*-butyl groups bound to the ring.

Table 1. ^{1}H- and ^{13}C-NMR data [a] of *(3)*.

	$\delta_{^1H}$	J_{HP} [Hz]	$\delta_{^{13}C}$	J_{CP} [Hz]
PNC*Me*$_3$	+1.49	0.8	+31.2	7.5
PN*C*Me$_3$	–	—	+56.2	15.1
PN(CH*Me*$_2$)$_2$	+0.95	<0.3	+21.9	< 0.3
	+1.39	<0.3	+27.1	12.5
PN(*CH*Me$_2$)$_2$	+3.03	16	+44.3	±28.7 [b]
	+3.16	< 1	+47.4	∓ 8.2 [b]

[a] Measured at −10 °C as 30% solution in CH_2Cl_2 (^{1}H) or [D_8]toluene (^{13}C) with TMS as internal standard.
[b] At 45 °C the coupling constant of the two tertiary C atoms is 10.5 Hz.

[*] Priv.-Doz. Dr. E. Niecke, H.-G. Schäfer
Anorganisch-chemisches Institut der Universität
Tammannstrasse 4, D-3400 Göttingen (Germany)

[**] Part 13 of Investigations on Phosphazenes of Coordination Number 2 and 3. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 12: *E. Niecke, G. Ringel*, Angew. Chem. *89*, 501 (1977); Angew. Chem. Int. Ed. Engl. *16*, 486 (1977).

Procedure

tert-Butyliminodi(isopropyl)aminophosphane *(1)* (4 g, 19.8 mmol) is added dropwise with stirring to a solution of *tert*-butyl azide (4 g, 40.4 mmol) in 20 ml CS_2 under N_2 as protecting gas. The solution turns pale yellow. It is allowed to boil under reflux for 2 h, whereupon it becomes dark-yellow in color. After cooling to room temperature it is stirred for 40 h before the solvent and unconsumed azide are removed by distillation at 0 °C/10 torr. The remaining yellowish brown residue is taken up in 15 ml toluene and recrystallized twice at −78 °C. After 2 hours' drying at 40 °C/0.1 torr an analytically pure product *(3)* is obtained (5.8 g, 95 %).

Received: August 16, 1977 [Z 816 IE]
German version: Angew. Chem. *89*, 817 (1977)

CAS Registry numbers:
(1), 63950-84-5; *(3)*, 63950-85-6; *tert*-butyl azide, 13686-33-4

[1] *E. Niecke, O. J. Scherer*, Nachr. Chem. Tech. *23*, 395 (1975).
[2] *H. Bock, M. Schnöller*, Chem. Ber. *102*, 38 (1969); references cited therein.
[3] A correspondingly structured transition state appeared likely for the azide oxidation of tertiary phosphanes [2].
[4] MS (70 eV) in *m/e*: M = 301 (6 %), M − N(C_3H_7)$_2$ (100 %).
[5] A crystal structure analysis is currently being carried out.
[6] $Cl_2\overline{P{=}N{-}C(=O){-}NR}$: *M. V. Kotilo, G. I. Derkach*, J. Gen. Chem. USSR *39*, 437 (1969); $Cl_2P{=}N{-}C(CCl_3){=}N$; *V. P. Kukhar, T. N. Kasheva, E. S. Kozlov, ibid. 43*, 741 (1973); the structure of the second compound is doubtful [7].
[7] *G. Schöning, O. Glemser*, Chem. Ber. *109*, 2960 (1976).

Simple *de-novo* Synthesis of Reactive Pseudoglycals (Hex-2-enopyranosides)—Stereospecific α-Glycoside Coupling[**]

By *Richard R. Schmidt* and *Rolf Angerbauer*[*]

Pseudoglycals (hex-2-enopyranosides) are valuable key compounds for the synthesis of modified sugars and oligosaccharides[1]. While α-*erythro*-hex-2-enopyranosides and corresponding disaccharides *(1)* are readily accessible by alkoxylating allyl rearrangement of tri-*O*-acetylglucal, the α-*threo* compounds *(2)* can be obtained from tri-*O*-acetylgalactal only in poor yield[2]. We report here on a facile *de-novo* synthesis of compounds of type *(2)* *via* the reactive acetylated α-*threo*-hex-2-enopyranosyluronic acid esters *(3a)*, which can be conveniently converted with alcohols into α-glycosides, *e.g. (3b)* to *(3f)*.

Diels-Alder reaction of *trans,trans*-1,3-butadienylene diacetate[3] with *n*-butyl glyoxylate affords a 1:1 mixture of *(3a)*[4] and *(4a)*[4, 5] in a total yield of 75 %. The β-anomer of *(3a)*, initially formed according to the *cis*-addition principle, com-

[*] Prof. Dr. R. R. Schmidt, Dipl.-Chem. R. Angerbauer
Fachbereich Chemie der Universität
Postfach 7733, D-7750 Konstanz (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank BASF AG for supplying us with cyclooctatetraene.

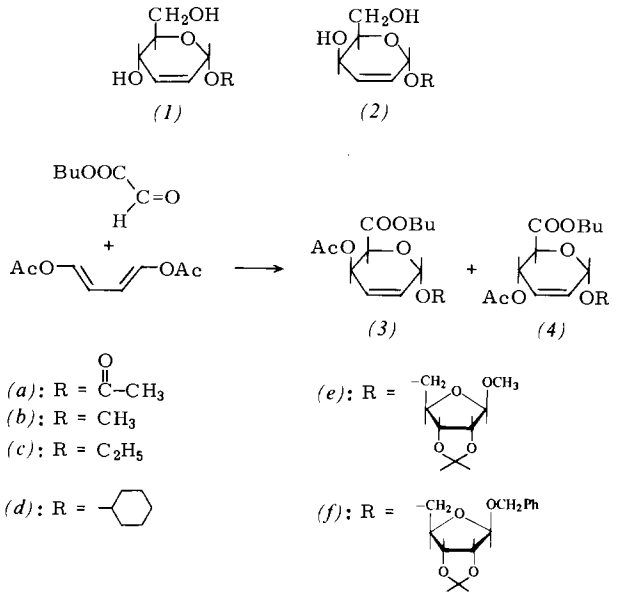


Table 1. Synthesized α-*threo*-hex-2-enopyranosides [a].

Cpd. [b]	Yield [%]	^{1}H-NMR data [c] 1-H	2-H	3-H	4-H	5-H	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
(3a)	37 [e]	6.47	6.06	6.28	5.33	4.73	3	10	5.5	3
(4a)	38 [e]	6.37	5.88–5.98		5.54	4.38	≈1.5	[d]	2	9.5
(3b)	98	5.07	5.99	6.14	5.27	4.72	2.5	10	5	3
(3c)	96	5.19	6.00	6.15	5.28	4.76	2.5	10	4.5	3
(3d)	98	5.31	5.96	6.12	5.27	4.78	2.5	10	5	3
(3e)	52	5.19	6.00	6.15	5.27	4.76	2.5	10	5	3
(3f)	50	5.19	5.96	6.15	5.27	4.76	2.5	10	4.5	3
(2d)	66	5.06	5.73	5.98	[d]	[d]	3	10	5	[d]
(2f)	76	4.96	5.75	6.02	[d]	[d]	3	10	5	[d]

[a] All compounds gave correct elemental analyses and mass spectra consistent with the structure.
[b] *(2d)*, m.p. 98°C; all other compounds are viscous oils.
[c] 100-MHz spectra in $CDCl_3$ with TMS as internal standard; δ values, coupling constants in Hz.
[d] Not determinable from the spectrum.
[e] Yields referred to 1,3-butadienylene diacetate used.

pletely isomerizes to *(3a)* under the reaction conditions; under milder conditions the β-anomer can be isolated in low yield.

(3a) reacts almost quantitatively with aliphatic alcohols and in good yields with D-ribose derivatives in anhydrous acetonitrile in the presence of boron trifluoride ether catalyst; it affords the glycoside uronic acid esters *(3b)* to *(3f)* (see Table 1). The stereospecificity is attributed to the anomeric effect and possibly to the influence of the carboxyl group[6]. Reduction of *(3d)* and *(3f)* with $LiAlH_4$ in ether gives the unsaturated α-glycoside *(2d)* and the α-disaccharide *(2f)*, respectively.

Procedure

A mixture of 1,3-butadienylene diacetate (9 g, 53 mmol), *n*-butyl glyoxylate (9 g, 69 mmol) and hydroquinone (20 mg) is dissolved in 10 ml anhydrous benzene and heated in an autoclave for 60 h at 125°C. The reaction mixture is then chromatographed on silica gel (eluent: benzene/acetone 9:1). Yield 5.9 g *(3a)* and 6.1 g *(4a)*.

Received: August 8, 1977 [Z 817 IE]
German version: Angew. Chem. *89*, 822 (1977)

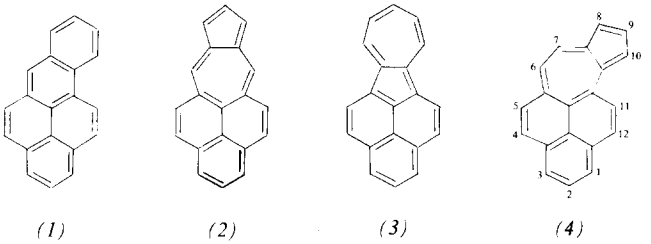
CAS Registry numbers:
(2d), 64035-97-8; *(2f)*, 64035-99-0; *(3a)*, 64035-87-6; *(3a)* (β-anomer), 64035-88-7; *(3b)*, 64035-89-8; *(3c)*, 64035-90-1; *(3d)*, 64035-91-2; *(3e)*, 64035-92-3; *(3f)*, 64035-93-4; *(4a)*, 64035-94-5; *trans,trans*-1,3-butadienylene diacetate, 15910-11-9; *n*-butyl glyoxylate, 6295-06-3; methanol, 67-56-1; ethanol, 64-17-5; cyclohexanol, 108-93-0; methyl 2,3-*O*-(1-methylethylidene) β-D-ribofuranoside, 4099-85-8; phenylmethyl 2,3-*O*-(1-methylethylidene) β-D-ribofuranoside, 23276-32-6

[1] *R. J. Ferrier*, Adv. Carbohydr. Chem. *20*, 67 (1965); *24*, 199 (1969); *B. Fraser-Reid*, Acc. Chem. Res. *8*, 192 (1975); references cited therein.
[2] *R. J. Ferrier, N. Prasad*, J. Chem. Soc. *C 1969*, 570; *J. Thiem, J. Schwentner*, Tetrahedron Lett. *1976*, 3117; *K. Heyns, J. I. Park*, Chem. Ber. *109*, 3262 (1976).
[3] Prepared from cyclooctatetraene according to the method of *R. M. Carlson, R. K. Hill*, Org. Synth. *50*, 24 (1970).
[4] D,L mixture.
[5] Analogously as described here for *(3a)*, the α-*erythro*-hex-2-enopyranosides of type *(1)* can by synthesized from *(4a)*: *R. R. Schmidt, R. Angerbauer*, unpublished work.
[6] *R. R. Schmidt, P. Hermentin*, Angew. Chem. *89*, 58 (1977); Angew. Chem. Int. Ed. Engl. *110*, 48 (1977).

Azuleno[4,5,6-*cd*]phenalene; A Novel Nonalternant Isomer of Benzo[*a*]pyrene[**]

By *Kazuhiro Nakasuji, Eishiro Todo*, and *Ichiro Murata*[*]

Polycyclic arenes such as benzo[*a*]pyrene *(1)*[1] are an important class of carcinogenic compounds. Our interest lies in the area of comparative studies on the properties of *(1)* and its nonalternant isomers. Azuleno[5,6,7-*cd*]phenalene *(2)*[2] is a carcinogen[3], while its nonalternant isomer, azuleno[1,2,3-*cd*]phenalene *(3)*[4], exhibits only weak carcinogenicity[5]. We have now synthesized azuleno[4,5,6-*cd*]phenalene *(4)*, which on account of the topology of its π-electron system [similar to that of *(2)*] and its molecular geometry [which closely resembles that of *(1)*] can be expected to display substantial biological activity.

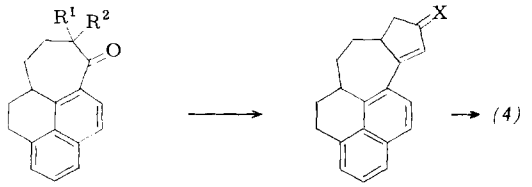


We selected the pentacyclic alcohol *(10)* as a precursor for our synthesis, reasoning that it might be converted to

[*] Dr. K. Nakasuji, E. Todo, Prof. Dr. I. Murata [+]
Department of Chemistry, Faculty of Science, Osaka University
Toyonaka, Osaka 560 (Japan)
[+] Author to whom correspondence should be addressed.

[**] The Chemistry of Phenalenium Systems, Part 26.—Part 25: *O. Hara, K. Tanaka, K. Yamamoto, T. Nakazawa, I. Murata*, Tetrahedron Lett. *1977*, 2435.

(4) by dehydrogenation in view of the known thermal stabilities of *(2)*[2] and *(3)*[4].



(5), $R^1 = R^2 = H$
(6), $R^1 = CO_2C_2H_5$, $R^2 = H$
(7), $R^1 = CO_2C_2H_5$, $R^2 = CH_2C{\equiv}CH$
(8), $R^1 = CO_2C_2H_5$, $R^2 = CH_2COCH_3$

(9), X = O
(10), X =

Ethoxycarbonylation of the tetracyclic ketone *(5)*[6] ($(C_2H_5O)_2CO$, NaH, diglyme, reflux 2 h) furnished 89% of the oxo ester *(6)*. Reaction of *(6)* with propargyl bromide ($NaOC_2H_5/C_2H_5OH$, reflux 2 h) gave the alkyne *(7)*, which was subjected to hydration in the usual way ($HgSO_4$, H_2SO_4, HOAc, 95 °C, 3 h) to give the diketo ester *(8)* in quantitative yield. Intramolecular aldol condensation (5% aq. KOH, dioxane, reflux 6 h) yielded a mixture of the stereoisomeric cyclopentenones *(9)* which on chromatographic separation (Al_2O_3, benzene) afforded the isomers *(9a)* and *(9b)* in 28% and 43% yield, respectively. Reduction of the mixture *(9)* with $LiAlH_4$ provided a mixture of the cyclopentenols *(10)* in 95% yield. Final conversion of *(10)* into *(4)* was achieved in 18% yield by heating *(10)* with sulfur in trichlorobenzene at 210—220 °C (for properties of intermediates see Table 1).

Table 1. Some properties of the compounds prepared.

(4), m.p. 168—169 °C (benzene/hexane); IR (KBr): $\tilde{\nu} = 3040$ w, 1610 w, 1575 m, 1525 m, 1440 m, 1390 m, 1345 m, 1185 m, 850 s, 740 s, 695 cm^{-1} m; λ_{max} (cyclohexane) = 250 nm ($\log\varepsilon = 4.17$), 354 (4.69), 397 (3.87), 409 (3.88), 432 (4.20), 458 (4.49), 714 (2.69), 792 (2.62), 840 (2.30), 900 (2.25); ^{1}H-NMR: 2 AB-quartets at $\delta = 8.65$ and 7.83 ($J_{6,7} = 10.0$ Hz, 7-H and 6-H) and at 9.15 and 8.11 ($J_{11,12} = 9.5$ Hz, 11-H and 12-H), 7.66 (dd, $J_{8,9} = 4.0$, $J_{8,10} = 2.0$ Hz, 8-H), 8.35 (br. d, $J_{9,10} = 4.0$ Hz, 10-H) [a], 7.75—8.25 (m, 1-H to 5-H, 9-H)

(6), colorless oil, ^{1}H-NMR: $\delta = 1.40$ (t, 3H, $J = 7$ Hz, $-CH_3$), 1.7—3.4 (m, 9H), 4.20 (q, 2H, $J = 7$ Hz, $-OCH_2-$), 7.0—7.8 (m, 5H), 12.6 (s, 1H, $\gtrless C-OH$)

(7), m.p. 138—139 °C; IR (Nujol): $\tilde{\nu} = 3250$ ($\equiv C-H$), 1720, 1660 cm^{-1} (C=O); ^{1}H-NMR: $\delta = 1.00$ (t, 3H, $J = 7.0$ Hz, $-CH_3$), 1.7—3.3 (m, 12H), 4.10 (q, $J = 7.0$ Hz, $-OCH_2-$), 7.1—7.9 (m, 5H)

(8), m.p. 130—131 °C; IR (Nujol): $\tilde{\nu} = 1720$, 1700, 1660 cm^{-1} (C=O); ^{1}H-NMR: $\delta = 1.13$ (t, 3H, $J = 7.0$ Hz, $-CH_3$), 1.7—2.5 (m, 5H), 2.12 (s, 3H, $-COCH_3$), 2.8—3.7 (m, 6H), 4.17 (q, 2H, $J = 7.0$ Hz, $-OCH_2-$), 7.3—7.8 (m, 5H)

(9a) [b], m.p. 130—133 °C; IR (Nujol): $\tilde{\nu} = 1690$ cm^{-1} (C=O); ^{1}H-NMR: $\delta = 1.6$—3.3 (m, 12H), 6.10 (s, 1H, $=CH-$), 7.0—7.7 (m, 5H)

(9b) [b], m.p. 96—97 °C; IR (Nujol): $\tilde{\nu} = 1680$ cm^{-1} (C=O); ^{1}H-NMR: $\delta = 1.6$—3.6 (m, 12H), 6.30 (s, 1H, $=CH-$), 7.0—7.7 (m, 5H)

(10), IR (CCl_4): $\tilde{\nu} = 3600$, 3340 cm^{-1} (OH)

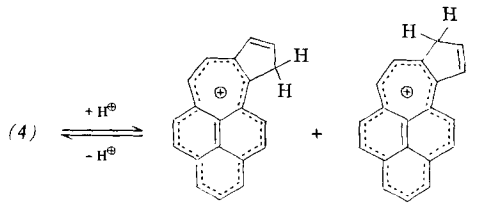
(11)·CF_3COO^-, ^{1}H-NMR: $\delta = 4.82$ (br. s, 2H), 7.70 (dt, $J = 5.5$ and 1.2 Hz, 1H), 7.75 (dt, $J = 5.5$ and 1.7 Hz, 1H), 8.66—9.62 (m)

(12)·CF_3COO^-, ^{1}H-NMR: $\delta = 4.51$ (br. s, 2H), 7.6—7.9 (m, 2H), 8.66—9.62 (m)

[a] Assignment of previously enumerated signals by double resonance experiments. Irradiation at $\delta = 9.15$ (11-H) and 8.65 (7-H) converted the signals at $\delta = 8.11$ and 7.83, respectively, into singlets. Irradiation at $\delta = 8.35$ (10-H) converted the double doublet at $\delta = 7.66$ into a doublet with $J = 4.0$ Hz.
[b] The stereochemistry has not been investigated.

Azuleno[4,5,6-*cd*]phenalene *(4)* crystallizes as stable green leaflets. Its structure was confirmed by elemental analysis and spectroscopic properties (Table 1). In the electronic spectrum three major bands can be discerned, as in the spectra of *(2)*[2] and *(3)*[4]. Due to the lack of a symmetry axis in *(4)* complete analysis of the ^{1}H-NMR spectrum could not be made.

The diamagnetic susceptibility of *(4)* (measured with a Cahn balance) is $\chi_M = 147 \pm 7$[7] which is comparable with the value found in the case of *(3)*[4].



(11) *(12)*

As would be expected for a compound containing an azulene moiety, *(4)* is markedly basic and is protonated reversibly in degassed trifluoroacetic acid to a mixture of the cations *(11)* and *(12)* in the ratio of 4:1. The preferential formation of *(11)* can be explained by the postulation that relief of the strain associated with a nonbonded interaction between hydrogens H-10 and H-11 of *(4)* provides the driving force for protonation at C-10. The pronounced basicity of *(4)* is attributed to the substantial thermodynamic stability of the cyclohepta[*cd*]phenalenium ion[8].

Studies on the carcinogenicity and mutagenicity of *(4)*, which will provide insight into the biological properties of polycyclic arenes, are currently in progress[9].

Received: August 8, 1977 [Z 818 IE]
German version: Angew. Chem. *89*, 821 (1977)

CAS Registry numbers:
(4), 64036-33-5; *(5)*, 53260-25-6; *(6)*, 64036-34-6; *(7)*, 64036-35-7; *(8)*, 64036-36-8; *(9a)*, 64036-37-9; *(9b)*, 64036-38-0; *(10)*, 64036-39-1; *(11)*, 64045-02-9; *(12)*, 64045-03-0

[1] See *e.g. D. M. Jerina, H. Yagi, O. Hemandez, P. M. Dansette, A. W. Wood, W. Levin, R. L. Chang, P. G. Wislocki, A. H. Conney* in *R. Freudenthal* and *P. Jones*: Polynuclear Aromatic Hydrocarbons. Raven Press, New York 1976, pp. 91—113.
[2] *Ch. Jutz, R. Kirchlechner*, Angew. Chem. *78*, 493 (1966); Angew. Chem. Int. Ed. Engl. *5*, 516 (1966); *Ch. Jutz, R. Kirchlechner, H.-J. Seidel*, Chem. Ber. *102*, 2301 (1969).
[3] *N. P. Buu-Hoi, D. P. Hien, Ch. Jutz*, Naturwissenschaften *54*, 470 (1976); *N. P. Buu-Hoi, N. B. Giao, Ch. Jutz, ibid. 57*, 499 (1970).
[4] *I. Murata, K. Nakasuji, K. Yamamoto, T. Nakazawa, Y. Kayane, A. Kimura, O. Hara*, Angew. Chem. *87*, 170 (1975); Angew. Chem. Int. Ed. Engl. *14*, 170 (1975).
[5] Private communication from Prof. *Y. Sakamoto*, Osaka University, Medical School.
[6] *I. Murata, K. Yamamoto, Y. Kayane*, Angew. Chem. *86*, 861 (1974); Angew. Chem. Int. Ed. Engl. *13*, 807 (1974). We wish to thank Dr. *K. Yamamoto* and Mr. *Y. Kayane* for the preparation of *(5)*.
[7] We thank Prof. *R. Kiriyama* and Dr. *T. Asai*, Osaka University, for carrying out this measurement.
[8] *I. Murata, K. Yamamoto, Y. Kayane*, Angew. Chem. *86*, 862 (1974); Angew. Chem. Int. Ed. Engl. *13*, 808 (1974).
[9] Prof. *T. Sugimura* and Dr. *M. Nagao*, Biochemical Division, National Cancer Research Institute, Tokyo (Japan) are currently engaged with the mutagenicity test of *(4)*.

Base-Stabilized Silyleneiron Complexes[1]

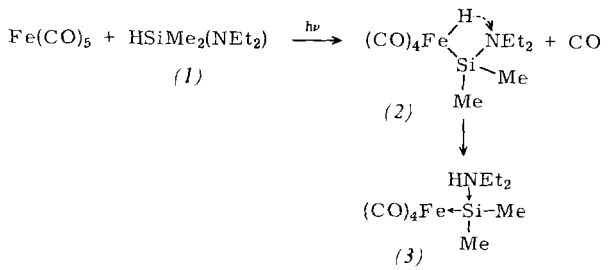
By *Günter Schmid* and *Eckhard Welz*[*]

While germylene, stannylene, and plumbylene complexes can be prepared with comparative ease, attempts to synthesize

[*] Prof. Dr. G. Schmid, Dipl.-Chem. E. Welz
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg (Germany)

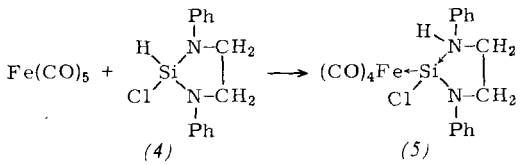
monomeric silylene complexes have so far met with only very limited success. The instability of divalent silicon and its tendency to assume the coordination number 4 led in most cases to formation of dimeric or trimeric complexes in which the silicon atoms bridge two metal atoms each and therefore fail to show silylene character. The dimeric complex $[(CO)_5WSiI_2]_2$ appears to deviate from this structural principle in that the iodine atoms are responsible for the bridging[2]. Although this complex is monomeric in basic solvents such as tetrahydrofuran, it was not possible to isolate stable $(CO)_5WSiI_2 \cdot B$ (B = basic solvent).

We have now succeeded in isolating the first base-stabilized silylene complexes *via* aminosilyl(carbonyl)iron hydrides.



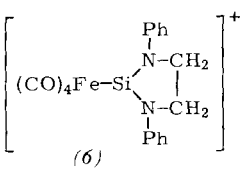
The silylated tetracarbonyliron hydride *(2)*, accessible from $Fe(CO)_5$ and diethylamino(dimethyl)silane *(1)*, is unstable under the reaction conditions and is transformed into the silylene complex *(3)*. This compound is stable for prolonged periods only at temperatures below −20 °C. The reason for the proton shift from iron to nitrogen in *(2)* lies in the greater basicity of the nitrogen atom compared with the iron.

The reaction can be applied to other aminosilanes, as demonstrated by the formation of the silylene complex *(5)* from $Fe(CO)_5$ and 2-chloro-1,3-diphenyl-1,3-diaza-2-silacyclopentane *(4)*.



Complex *(5)* is likewise stable for extended periods only below −20 °C.

The presence of NH bonds is established by a sharp NH stretching vibration at 3220 cm^{-1} in *(3)* and at 3185 cm^{-1} in *(5)*. In the ν(CO) region there appear [as also in the case of base-stabilized stannylene complexes $(CO)_4FeSnR_2 \cdot B$[3]] essentially three bands, of which that at longest wavelengths is split in the case of *(5)*: *(3)*: 1996 (s), 1900 (s, sh), 1868 cm^{-1} (vs, br.); *(5)*: 2050 (s), 1966 (s), 1925/1896/1880 cm^{-1} (vs). The mass spectrum of *(5)* shows, in addition to the molecular ion at $m/e = 442$ ($I_{rel} = 33.7\,\%$), two characteristic degradation series, one of which corresponds to stepwise elimination of CO as far as FeL^+ (97 %) (L = silylene ligand). The second degradation series begins with the



(6)

elimination of HCl from *(5)* to form the complex ion *(6)* [$m/e = 406$ (26.8 %)] which then likewise undergoes successive loss of CO as far as FeL'^+ (L' = 1,3-diphenyl-1,3-diaza-2-silacyclopent-2-yl) [$m/e = 294$ (97 %)]. The final product of both series is the free silylene cation L'^+ at $m/e = 238$ (100 %). The formation of the fragment $(CO)_4FeL'^+$ and the apparent high stability of the silylene cation L'^+ suggested preparative removal of HCl from *(5)* to form the 1,3-diaza-2-silacyclopentyl complex $(CO)_4FeL'$; however, reaction with amines and with butyllithium merely led to the decomposition of *(5)*.

Procedure

Synthesis of *(3)*: To an ice-cooled solution of Me_2SiHCl (10.5 g, 111.0 mmol) in light petroleum (300 ml) is added dropwise a solution of $HNEt_2$ (16.1 g, 220.1 mmol) in light petroleum (80 ml). After completion of addition, $[Et_2H_2N]Cl$ is filtered off and washed with light petroleum (2 × 40 ml), and the combined filtrates are then reacted with $Fe(CO)_5$ (22.0 g, 109.6 mmol). Upon UV irradiation (150 W mercury vapor immersion lamp) evolution of CO starts immediately. After 3 h, compound *(3)* (3.26 g) could be scratched off the lamp housing and a further crop of *(3)* (1.18 g) could be frozen out of the solution (−20 °C). Total yield: 4.44 g (13 %) of pale yellow, wax-like crystals.

Synthesis of *(5)*: One proceeds as for *(3)*, except that 2-chloro-1,3-diphenyl-1,3-diaza-2-silacyclopentane[4] (27.5 g, 100.0 mmol) is used instead of Me_2SiHCl. Yield: 57 % of *(5)* as a yellow product that is sparingly soluble in light petroleum.

The compositions of *(3)* and *(5)* were confirmed by elemental analyses and molecular weight determinations.

Received: August 24, 1977 [Z 824 IE]
German version: Angew. Chem. 89, 823 (1977)

[1] Silylene-Metal Complexes, Part 4.—Part 3: *G. Schmid, H.-J. Balk, J.* Organomet. Chem. *80*, 257 (1974).
[2] *G. Schmid, R. Boese*, Chem. Ber. *105*, 3306 (1972).
[3] *T. J. Marks, A. R. Newman*, J. Am. Chem. Soc. *95*, 769 (1973).
[4] Prepared in 96 % yield from 1,2-dianilinoethane, butyllithium, and HSiCl.

New Aliphatic Thioacylating Reagents; Preparation of *tert*-Butyl Esters of Aliphatic Dithiocarboxylic Acids *via* Bis(thioacyl) Sulfide

By *Shinzi Kato, Takashi Takagi, Tomonori Katada*, and *Masateru Mizuta*[*]

Sterically hindered esters of carboxylic or thiocarboxylic acids are best prepared by reaction of alkali metal alkoxides or thioalkoxides with acyl halides or anhydrides. However, application of this method for the preparation of the dithiocarboxylic acid analogs, particularly esters of type *(1)* (R = alkyl), was limited because of the difficulty of synthesizing aliphatic thioacyl chlorides and the unavailability of the aliphatic bis(thioacyl) sulfides *(3)*. We have now succeeded in preparing compounds *(1)*, like the aromatic analogs[1], from the aliphatic dithiocarboxylic acid and dicyclohexylcarbodimide, but at temperatures below −5 °C (see Table 1).



R = Alkyl

[*] Prof. Dr. S. Kato [+], T. Tagaki, T. Katada, Prof. Dr. M. Mizuta Department of Chemistry, Faculty of Engineering, Gifu University Kagamihara, Gifu 504 (Japan)
[+] To whom correspondence should be addressed.

Table 1. Physical properties of compounds of type *(1)* and *(3)*. IR (neat) for all compounds [except *(1b)*] $\tilde{\nu} = 1220\ cm^{-1}$.

	(1a)	*(1b)*	*(1c)*	*(3a)*	*(3b)*	*(3c)*
R	n-C_3H_7	i-C_3H_7	n-C_4H_9	n-C_3H_7	i-C_3H_7	n-C_4H_9
Yield [%]	94	93	92	16	20	18
B.p. [°C/torr]				51—53/4	73—75/4	85—86/7
UV/Vis λ_{max} (ε_{max})						
[nm] [a] π^*	349	351	349	306	305	306
	(11600)	(12000)	(10800)	(12950)	(11900)	(10200)
$n \rightarrow \pi^*$	516	517	516	478	478	478
	(20)	(23)	(18)	(16)	(14)	(17)
^{1}H-NMR [b]		1.34 (d, 12H, CH_3),		0.95 (t, 3H, CH_3),	1.24 (s, 6H, CH_3),	0.95 (t, 3H, CH_3), 1.9—1.2
δ-values		3.72 (m, 2H, CH)		2.0—1.3 (m, 2H, CH_2), 2.87 (t, 2H, CH_2)	3.32 (m, 1H, CH)	(m, 4H, CH_2), 2.90 (t, 2H, CH_2)

[a] In cyclohexane.
[b] *(1b)* in CCl_4, *(3a)*—*(3c)* in $CDCl_3$. Signals (singlets) of the *tert*-butyl groups: *(3a)* and *(3c)*: δ = 1.57, *(3b)*: δ = 1.58.

With the thioanhydrides *(1)* and the thiolates *(2)* it was possible to synthesize the sterically hindered esters of type *(3)*. Examples are listed in Table 1. The structures of compounds *(1)* and *(3)* are in accord with the results of elemental analysis, IR, UV, and ^{1}H-NMR spectroscopic data. The $n \rightarrow \pi^*$ band of *(3)* is shifted bathochromically by *ca.* 17—18 nm compared to that of sterically unhindered aliphatic dithioesters.

Experimental

Synthesis of *(3b)*: A solution of *(2)* (2.24 g, 20 mmol) in 10 ml of anhydrous ethanol was added dropwise over 30 min to an ice-cold solution of *(1b)* (cf. [1]) (2.06 g, 10 mmol) in 70 ml of dry n-hexane. After addition, the solution was stirred at room temperature for 5 h, washed with cold water, dried over Na_2SO_4, and then the solvent removed. Distillation of the resulting residue gave analytically pure *tert*-butyl dithioisobutyrate *(3b)*, an orange liquid, in 20% yield.

Received: August 8, 1977 [Z 819a IE]
German version: Angew. Chem. 89, 820 (1977)

CAS Registry numbers:
(1a), 64035-98-9; *(1b)*, 64035-95-6; *(1c)*, 64056-84-4; *(2)*, 29364-29-2; *(3a)*, 64035-82-1; *(3b)*, 64035-83-2; *(3c)*, 64035-84-3

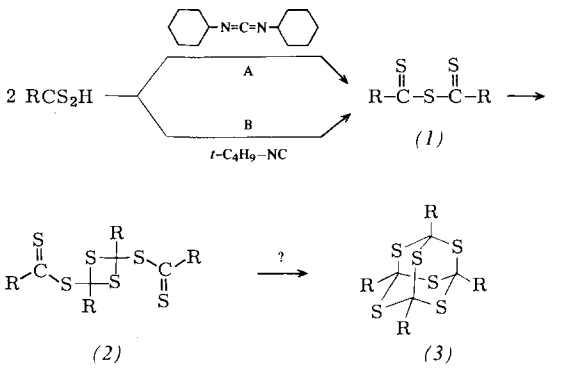
[1] *S. Kato, T. Katada, M. Mizuta*, Angew. Chem. *88*, 844 (1976); Angew. Chem. Int. Ed. Engl. *15*, 766 (1976).

2,4-Diisopropyl-1,3-dithietane-2,4-diyl Bis(dithioisobutyrate), a Dimeric Form of Bis(thioacyl) Sulfide

By *Shinzi Kato, Akira Hori, Takashi Takagi*, and *Masateru Mizuta*[*]

In a previous paper[1] we described the isolation of bis(thioacyl) sulfides *(1)* (Scheme 1, Route A), which are considered as important intermediates in the cyclization of dithio acids to hexathiaadamantanes *(3)*[2].

We now wish to report the synthesis of 2,4-diisopropyl-1,3-dithietane-2,4-diyl bis(dithioisobutyrate) *(2a)* from dithioisobutyric acid and *tert*-butyl isocyanide (Route B) *via* the thioanhydride *(1a)* and its dimerization. *(2a)* could likewise be an intermediate in thiaadamantane synthesis.



(a), R = i-C_3H_7

Scheme 1

An equimolar amount of *tert*-butyl isocyanide (1.29 g) is added dropwise over 5 min to an ice-cold solution of freshly distilled dithioisobutyric acid (1.86 g, 15.5 mmol) in anhydrous n-hexane (10 ml). The purple reaction mixture turns yellow within 10 min. Fractional recrystallization of the reaction mixture with n-hexane or ether affords an almost quantitative yield (95%) of *N-tert*-butylthioformamide; it was identified by comparison with authentic material. 0.36 g of yellow crystals (m.p. 145—146 °C) could also be isolated, and were shown to be *(2a)* [IR (KBr): $\tilde{\nu} = 1200\ cm^{-1}$; UV (cyclohexane): $\lambda_{max} = 323$ ($\varepsilon = 9600$) and 465 nm ($\varepsilon = 18$); ^{1}H-NMR ($CDCl_3$): δ = 1.05 (d, 6H, CH_3), 1.25 (d, 6H, CH_3), 2.75 (m, 1H, CH), 3.15 (m, 1H, CH); MS: $m/e = 412$ (M^+), 293 (M − i-Pr—CS), 206 (M/2), 174 (M − i-Pr—CS—S), 119 (i-Pr—CS—S), 87 (i-Pr—CS)].

It is interesting that the same yellow compound *(2a)* was obtained in 12.5% yield on stirring bis(dithioisobutyryl) sulfide *(1a)* (2.06 g, 10 mmol) in n-hexane (10 ml) for 5 h at room temperature. This finding and the observation[3] that the UV and visible spectra (in cyclohexane, $\lambda_{max} = 351$ and 517 nm) of the purple solution formed on reaction of dithioisobutyric acid with *tert*-butyl isocyanide were consistent with those of *(1a)*[1a] provide supporting evidence for the formation of *(2)* *via* *(1)*.

Received: August 8, 1977 [Z 819b IE]
German version: Angew. Chem. 89, 820 (1977)

CAS Registry numbers:
(1a), 64035-95-6; *(2a)*, 64035-96-7; dithioisobutyric acid, 35329-04-5; *tert*-butyl isocyanide, 7188-38-7; *N-tert*-butylthioformamide, 20278-31-3

[*] Prof. Dr. S. Kato [+], A. Hori, T. Tagaki, Prof. Dr. M. Mizuta
Department of Chemistry, Faculty of Engineering, Gifu University
Kagamihara, Gifu 504 (Japan)
[+] Author to whom correspondence should be addressed.

[1] a) *S. Kato, T. Katada, M. Mizuta*, Angew. Chem. *88*, 844 (1976); Angew. Chem. Int. Ed. Engl. *15*, 766 (1976); b) *S. Kato, T. Takagi, T. Katada, M. Mizuta, ibid. 89*, 820 (1977) and *16*, 786 (1977).
[2] *A. Fredga*, Ark. Kemi Mineral. Geol. *B25*, No. 8, p. 1 (1974); *K. A. Olsson*, Ark. Kemi *14*, 371 (1950); *K. A. Olsson, H. Baeckstrom, R.*

Engwall, ibid. 26, 219 (1966); *A. Fredga*, Int. J. Sulfur Chem. *C 7*, 1 (1972).

[3] The reaction of an isocyanide with a carboxylic acid produces an acid anhydride and a formamide; *J. U. Nef*, Justus Liebigs Ann. Chem. *270*, 267 (1892). We have observed the formation of bisacetyl sulfide on reaction of thioacetic acid and *tert*-butyl isocyanide.

Dichloro(porphyrinato)molybdenum(IV)—Synthesis and Structure

By *Tharcis Diebold*, *Bernard Chevrier*, and *Raymond Weiss*[*]

Most of the known porphyrinatomolybdenum derivatives are oxo compounds whose chemistry is dominated by the presence of very strong Mo=O bonding[1]. We now report the synthesis and structural characterization of the non-oxo dichloro(porphyrinato)molybdenum(IV) compounds $MoCl_2(P)$, where P = *meso*-tetra(*p*-tolyl)porphyrinate(2−) (TTP) or octaethylporphyrinate(2−) (OEP). Both compounds represent useful starting materials for the synthesis of other porphyrinatomolybdenum derivatives with a low valency central atom.

Gaseous hydrogen chloride was bubbled into a stirred benzene solution of Mo=O(P) (P = TTP or OEP) under scrupulously oxygen free conditions and at ambient temperature[1b,1c,2]. The dichloro compounds $Mo(Cl)_2P$ were then crystallized from the resulting brown solution by addition of pentane and identified by elemental analysis and by IR and NMR spectroscopy.

The far IR spectra each revealed an intense band at 330 cm^{-1} for the TTP complex and at 268 cm^{-1} for the OEP complex. These bands are ascribed to the asymmetric Mo—Cl vibration; when the dichloro compounds are allowed to react with potassium thiocyanate these bands are replaced by strong absorptions at 2020 cm^{-1} (TTP complex) and 2060 cm^{-1} (OEP complex).

Both dichloro(porphyrinato)molybdenum(IV) compounds are paramagnetic, as evidenced by the fact that their NMR spectra ($CDCl_3$, under argon) show large chemical shifts relative to tetramethylsilane: for the TTP derivative, a singlet (methyl-H) at $\delta = 2.46$, two doublets (phenyl-H) centered at $\delta = 7.71$ and 10.06 ($J = 8$ Hz) and a singlet (pyrrole-H) at $\delta = 17.54$; for the OEP derivative, a singlet (methine-H) at $\delta = -3.70$, a triplet (methyl-H) centered at $\delta = 3.26$ ($J = 7.3$ Hz), and a quadruplet (methylene-H) centered at $\delta = 14.61$ ($J = 7.3$ Hz).

Paramagnetic susceptibilities were measured at room temperature by the NMR method described by *Evans*[3]. The resulting moments μ_{eff}^{corr} of 2.90 μ_B for the TTP derivative and of 2.88 μ_B for the OEP derivative are consistent with a high-spin d^2 molybdenum configuration.

In CH_2Cl_2 each of the two compounds gave four visible absorptions: the TTP complex, at 550 nm ($\varepsilon \times 10^{-3} = 10$), 488 (28), 429 (105), and 360 (42); the OEP complex, at 574 (24), 530 (30), 406 (143), and 354 (57).

Well-formed crystals of the benzene solvate $Mo(Cl)_2TTP \cdot C_6H_6$ were obtained on allowing benzene/pentane solutions of the TTP complex (under argon) to stand for several weeks. These enabled an X-ray structure analysis to be carried out[4], the results of which are shown in Figure 1.

The two chlorine atoms are mutually *trans* relative to the porphyrin ligand, and the Cl(1)—Mo—Cl(2) bond angle is

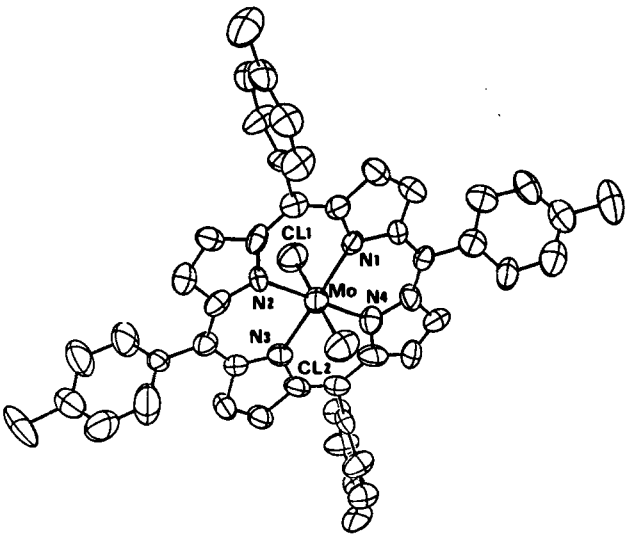


Fig. 1. Crystal structure of dichloro[*meso*-tetra(*p*-tolyl)porphyrinato]molybdenum(IV), $MoCl_2$ (TTP).

178.4(2)°. The mean plane of the four coordinating pyrrole nitrogen atoms contains the molybdenum atom. Coplanarity of molybdenum and nitrogens is also reflected in the angles at the molybdenum atom: ∢ N(1)—Mo—N(3) = 178.4(5)°, ∢ N(2)—Mo—N(4) = 179.3(5)°. The four Mo—N bond lengths are equivalent (2.07 ± 0.02 Å) and compare well with those in $Mo(O_2)_2TTP$[5] [2.096(4) Å] and in $(O{=}MoTTP)_2O$[1d] [2.094(3) Å]. The average bond angles are 90.0(5)° for N(1)—Mo—N(2), 89.6(3)° for Cl(1)—Mo—N, and 90.4(3)° for Cl(2)—Mo—N. Although the chlorine atoms are chemically equivalent, the two Mo—Cl distances appear to be slightly different. Thus the Mo—Cl(1) distance of 2.347(4) Å is longer than the Mo—Cl(2) distance of 2.276(4) Å. We cannot as yet offer a reasonable explanation for this finding.

The bond parameters for the porphinato core are in good agreement with those reported for several metalloporphyrins[6]. The individual pyrrole rings are almost planar. Their planes make dihedral angles of 2.9° (N-1), 3.7° (N-2), 1.6° (N-3) and 4.2° (N-4), respectively, with the mean plane of the four nitrogens. Also small angles of 4—5° occur between adjacent pyrroles. The departures from planarity observed here closely resemble those found in the so-called planar porphyrins and metalloporphyrins[7].

The tolyl groups are tilted with respect to the plane of the three neighboring carbons of the bridge positions between pyrroles; the angles are 83.9°, 78.3°, 85.0° and 65.5°.

Received: July 19, 1977 [Z 821 IE]
German version: Angew. Chem. *89*, 819 (1977)

CAS Registry numbers:
$MoCl_2(TTP) \cdot C_6H_6$, 64024-41-5; $MoCl_2(OEP)$, 64044-69-5; Mo=O(TTP), 64024-42-6; Mo=O(OEP), 32125-06-7

[*] Dipl.-Ing. Th. Diebold, Dr. B. Chevrier, and Prof. Dr. R. Weiss
Laboratoire de Cristallochimie associé au CNRS
Institut Le Bel, Université Louis Pasteur
4, rue Blaise Pascal, 67070 Strasbourg (France)

[1] a) *E. B. Fleischer, T. S. Srivastava*, Inorg. Chim. Acta *5*, 151 (1971); b) *J. W. Buchler, K. Rohbock*, Inorg. Nucl. Chem. Lett. *8*, 1073 (1972); c) *J. W. Buchler, L. Puppe, K. Rohbock, H. H. Schneehage*, Ann. N. Y. Acad. Sci. *206*, 116 (1973); Chem. Ber. *106*, 2710 (1973); d) *J. F. Johnson, W. R. Scheidt*, J. Am. Chem. Soc. *99*, 294 (1977).

[2] *W. E. Newton, D. C. Bravard, J. W. McDonald*, Inorg. Nucl. Chem. Lett. *11*, 553 (1975).

[3] *D. F. Evans*, J. Chem. Soc. *1959*, 2003.

[4] Philips diffractometer PW 1100 with Cu-K_α radiation. The structure was solved by the heavy-atom method and refined to convergence using anisotropic temperature factors for all nonhydrogen atoms: $MoCl_2N_4C_{48}H_{36} \cdot C_6H_6$, orthorhombic, space groups F_{dd2}, $a = 45.159(9)$, $b = 35.671(7)$, $c = 11.199(3)$ Å, $\rho_{calc} = 1.345$, $\rho_{obs} = 1.33$ g/cm^3 (flotation in

aqueous $ZnCl_2$ solution), $Z=16$, $R_1=0.052$, $R_2=0.063$, 1977 unique data ($I>3\sigma(I)$, $2\theta<126°$.
[5] *B. Chevrier, Th. Diebold, R. Weiss*, Inorg. Chim. Acta *19*, L57—L58 (1976).
[6] *J. L. Hoard* in *K. M. Smith*: Porphyrins and Metalloporphyrins. Elsevier, Amsterdam 1975, Chapter 8.
[7] *B. M. L. Chen, A. Tulinsky*, J. Am. Chem. Soc. *94*, 4144 (1972); *J. W. Lauher, J. A. Ibers, ibid. 95*, 5148 (1973); *D. L. Cullen, E. F. Meyer, Jr., ibid. 96*, 2095 (1974); *R. G. Little, J. A. Ibers, ibid. 96*, 4440 (1974); *97*, 5363 (1975); *F. S. Molinaro, J. A. Ibers*, Inorg. Chem. *15*, 2278 (1976).

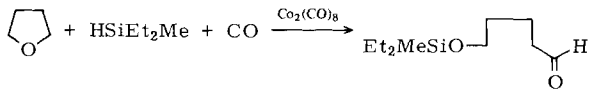
$Co_2(CO)_8$ Catalyzed Reactions of Cyclic Ethers with Hydrosilanes and Carbon Monoxide[1]

By *Yoshio Seki, Shinji Murai, Iwao Yamamoto*, and *Noboru Sonoda*[*]

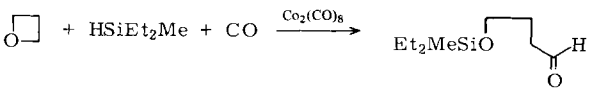
We recently reported a new reaction of olefins with hydrosilanes and carbon monoxide which leads to enol silyl ethers[2], and resembles that of hydroformylation. To test the applicability of the new hydrosilane reaction to compounds other than olefins, we have studied the reaction of cyclic ethers with hydrosilanes and carbon monoxide.

Hydroformylation of cyclic ethers is known to give hydroxyaldehydes as initial products[3]. The reaction, however, frequently suffers from undesirable side reactions or further reactions, since the hydroxyaldehydes are very labile compounds. For example, hydroformylation of tetrahydrofuran did not afford the expected 4-hydroxybutanal but yielded various products arising from further carbonylation[4], and the hydroformylation of cyclohexene oxide gave only a condensation product of the expected 2-hydroxycyclohexanecarbaldehyde[5].

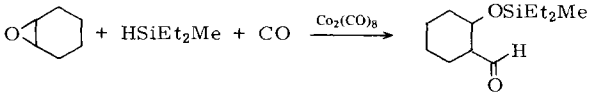
We have found that the reaction of tetrahydrofuran, oxetane, or 1,2-epoxycyclohexane with diethyl(methyl)silane and carbon monoxide in the presence of a catalytic amount of $Co_2(CO)_8$ gives the silyl-protected hydroxyaldehydes *(1)*—*(3)*, respectively, in reasonable yields[6].



(1), 53%



(2), 40%



(3), 51%

It is interesting to note that *Chalk*[7] has already reported the polymerization of tetrahydrofuran catalyzed by $Co_2(CO)_8$ and triethylsilane (1:2) and proposed opening of the tetrahydrofuran ring by a carbonyl(silyl)cobalt for the initiation step. No polymerization, however, was observed in the present reaction.

[*] Y. Seki, Prof. Dr. S. Murai [*], I. Yamamoto, Prof. Dr. N. Sonoda
Department of Petroleum Chemistry, Faculty of Engineering, Osaka University
Suita, Osaka 565 (Japan)
[*] To whom correspondence should be addressed.

Experimental

Synthesis of *(1)*: A solution of 4 ml (50 mmol) of tetrahydrofuran, 1.02 g (10 mmol) of diethyl(methyl)silane, and 0.068 g (0.2 mmol) of $Co_2(CO)_8$ in 20 ml of benzene was placed in a 100 ml stainless steel autoclave. The autoclave was flushed with N_2 (60 kg/cm^2) and CO (60 kg/cm^2), then charged with CO (60 kg/cm^2) and heated at 140°C with stirring. After 20 h, the autoclave was cooled and depressured. Analysis of the reaction mixture by GLC (Silicon OV-1, 5%, on Uniport KS, 3 m × 3 mm, 135°C) with *n*-tetradecane as an internal standard showed it to contain *(1)* in 53% yield. An analytical sample of *(1)* was obtained by fractional distillation (b.p. 120—130°C/30 torr) followed by preparative GLC (Silicon OV-1, 5%, on Uniport KS, 3 m × 8 mm, 140°C).

Received: August 16, 1977 [Z 822 IE]
German version: Angew. Chem. *89*, 818 (1977)

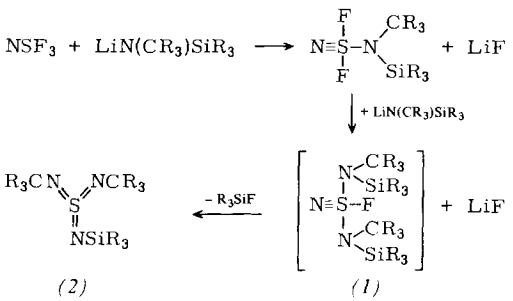
CAS Registry numbers:
(1), 64035-85-4; *(2)*, 64035-86-5; *(3)*, 64056-85-5; tetrahydrofuran, 109-99-9; diethylmethylsilane, 760-32-7; oxetane, 503-30-0; 7-oxabicyclo[4.1.0]heptane, 286-20-4

[1] Part 3 of Transition Metal Reactions of Silanes.—Part 2: [2].
[2] *Y. Seki, A. Hidaka, S. Murai, N. Sonoda*, Angew. Chem. *89*, 196 (1977); Angew. Chem. Int. Ed. Engl. *16*, 174 (1977); *Y. Seki, A. Hidaka, S. Makino, S. Murai, N. Sonoda*, J. Organomet. Chem., in press.
[3] *J. Falbe*: Carbon Monoxide in Organic Synthesis. Springer, Berlin 1970.
[4] *W. Reppe, H. Kroper, H. J. Pistor, O. Weissbarth*, Justus Liebigs Ann. Chem. *587*, 87 (1953).
[5] *L. Roos, R. F. Goetz, M. Orchin*, J. Org. Chem. *30*, 3023 (1965).
[6] This is important from the viewpoint of utility as synthetic intermediates. Efforts are being made to optimize the yields. Elemental analysis of all the new compounds gave the expected results. Spectral data: IR (without solvent) for *(1)* to *(3)*: 1725 cm^{-1} (C=O); ^{1}H-NMR (in CCl_4; each s, CHO) for *(1)*: 9.60, for *(2)*: 9.64, for *(3)*: 9.66.
[7] *A. J. Chalk*, Chem. Commun. *1970*, 847.

Tris(*tert*-butylimino)sulfur(VI) and Bis(*tert*-butylimino)(silylimino)sulfur(VI); The "Y-triene" Structure[**]

By *Oskar Glemser, Siegfried Pohl, Frank-M. Tesky*, and *Rüdiger Mews*[*]

Compounds containing tricoordinate sulfur(VI) have only rarely been reported. The only representatives of proven structure are SO_3 and its aza analogs $(R_3SiN{=})_3S$[1] and $(R_3SiN{=})_2S{=}O$[2]. As shown by these examples, the trimeth-



(2) *(1)*

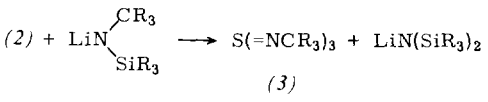
[*] Prof. Dr. O. Glemser, Dipl.-Chem. F.-M. Tesky, Priv.-Doz. Dr. R. Mews
Anorganisch-Chemisches Institut der Universität
Tammannstrasse 4, D-3400 Göttingen (Germany)
Dr. S. Pohl
Anorganisch-Chemisches Institut der Universität
Postfach 8640, D-4800 Bielefeld (Germany)

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

ylsilyl group can be used to stabilize small coordination numbers; the bulky *tert*-butyl group has the same effect[3].

We have now found that while the reaction of NSF_3 with $LiN(SiR_3)R'$ ($R=CH_3$, $R'=CH_3$, *i*-C_3H_7, C_6H_5) leads to polymeric products, that with $LiN(CR_3)SiR_3$ affords compounds of tricoordinate sulfur.

If the reaction is conducted at -70°C then only *(2)* can be isolated. At higher temperature and given an excess of $LiN(CR_3)SiR_3$ transamidation occurs to form the tris(*tert*-butyl) derivative *(3)*.



(2) + LiN(CR$_3$)(SiR$_3$) ⟶ S(=NCR$_3$)$_3$ + LiN(SiR$_3$)$_2$

(3)

The colorless compounds *(2)* (m.p. 11 °C) and *(3)* (m.p. 52.5 °C) could be characterized by their IR and Raman spectra [ν_{as} and ν_{sym} are tentatively assigned to the bands at 1215 and 1074 cm^{-1} for *(2)* and 1210 and 1059 cm^{-1} for *(3)*][4], mass spectra [*(2)*: E.I. (70 eV, principal fragments only): 261 M^+ (8.1), 246 $M-CH_3^+$ (57), 191 $M-R_3CN+H^+$ (99), 73 R_3Si^+ (100), 57 R_3C^+ (91); *(3)*: E.I.: 245 M^+ (1.3), 230 $M-CH_3^+$ (5.0), 175 $M-NCR_3+H^+$ (28.6), 174 $M-NCR_3^+$ (13.5), 57 CR_3^+ (100), F.I.: 245 M^+ (100), 174 $M-NCR_3^+$ (6.2)], ^{1}H-NMR spectra [*(2)*: $\delta(CH_3)_3Si=+0.18$, $\delta(CH_3)_3C=+1.33$; *(3)*: $\delta(CH_3)_3C=+1.34$], and the results of elemental analyses.

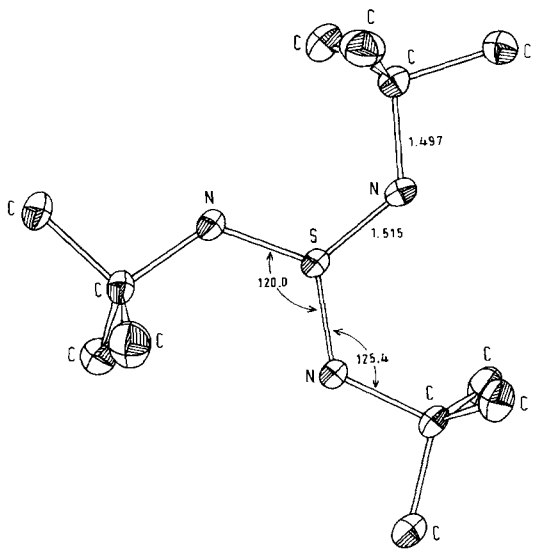


Fig. 1. Molecular structure of *(3)* with mean bond lengths (in Å) and bond angles (in °) (without H atoms, vibrational ellipsoids corresponding to 50% probability distributions).

Information about the crystal structure of the molecules is provided by an X-ray analysis performed on *(3)* at -130 °C[5] (see Fig. 1). It afforded the first proof of a trigonal planar coordination of sulfur(VI) in a solid. The S—N bond lengths are 1.508(4), 1.517(4), and 1.519(4) Å. The σ bonds between the sulfur and the nitrogen atoms are practically coplanar. This steric arrangement thus favors formation of $3p_\pi$(S)—$2p_\pi$(N) bonds. Similar bonding has been observed in the SN_3 skeleton of $(R_3SiN=)_3S$ ($R=CH_3$)[1], which is a liquid under normal conditions; its structure was also determined at -130 °C (S=N bond lengths: 1.504(3) Å)[6]. The C—C bond lengths in *(3)* have an average value of 1.522 Å, lying between 1.513(6) and 1.537(6) Å. The positions of all 27 H atoms could be determined.

Procedure

A solution of $LiN(CR_3)SiR_3$ with $R=CH_3$ (15.1 g, 0.1 mol) in tetrahydrofuran (200 ml) is added to a solution of NSF_3 (11 g, 0.106 mol) in tetrahydrofuran (50 ml) at -70 °C over a period of 2 to 3 h. After removal of volatile products, fractional distillation (oil-pump vacuum) affords *(2)* (2.0 g, 7.2% yield).

In contrast, passage of NSF_3 (31 g, 0.3 mol) into a suspension of $LiN(CR_3)SiR_3$ with $R=CH_3$ (99 g, 0.65 mol) in *n*-hexane (700 ml) at -15 °C within 2 to 3 h affords compound *(3)* (10 g, 19% yield). $(R_3Si)_2NH$, $R_3SiNHCR_3$, $(R_3CN)_2S$, $(R_3CN)_2C$, $R_3CN{=}SF_2{=}NSiR_3$, and $(R_3SiN)_2SF_2$ (R always CH_3) were identified as by-products.

Received: August 19, 1977 [Z 823 IE]
German version: Angew. Chem. *89*, 829 (1977)

CAS Registry numbers:
(2), 64011-16-1; *(3)*, 64011-17-2; NSF_3, 15930-75-3; $LiN(CMe_3)SiMe_3$

[1] *O. Glemser, J. Wegener*, Angew. Chem. *82*, 324 (1970); Angew. Chem. Int. Ed. Engl. *9*, 309 (1970).
[2] *O. Glemser, M. Feser, S. P. v. Halasz, H. Saran*, Inorg. Nucl. Chem. Lett. *8*, 321 (1972).
[3] *E. Niecke, O. J. Scherer*, Nachr. Chem. Tech. *23*, 395 (1975).
[4] The ν_{as} and ν_{sym} vibrations of the SN_3 skeleton in $S(=N-SiR_3)_3$ lie at 1280 and 1128.5 cm^{-1}: *A. Herbrechtsmeier, O. Glemser*, J. Mol. Spectrosc., in press.
[5] Owing to the low melting point of the compound all data were recorded at -130 °C. *(3)* forms triclinic crystals, $P\bar{1}$, with $a=9.362(3)$, $b=9.433(3)$, $c=10.746(4)$ Å, $\alpha=96.73(2)$, $\beta=102.55(2)$, $\gamma=120.14(2)$°, $V=772$ Å^3, $Z=2$. The structure was solved from the diffractometer data by a Patterson synthesis. Refinement with the structure data of 1907 reflections converged to an unweighted *R* value of 5.0%.
[6] *S. Pohl, B. Krebs, G. Henkel*, unpublished.

Infrared Rotatory Dispersion of Liquid-Crystalline Solutions of Chiral Molecules[**]

By *Ernst-Heiner Korte, Bernhard Schrader, Sauvarop Bualek*, and *Hans Jürgen Krabbe*[*]

In nematic phases the longitudinal axes of rod-shaped molecules are parallel. When a chiral "guest substance" is dissolved in such a phase the arrangement of molecules becomes twisted in the form of helices[1]. Such a solution exhibits the properties of cholesteric phases. These are distinguished by the fact that they selectively reflect circularly polarized light of wavelength λ_0 in the direction of their screw axis. λ_0 is proportional to the pitch *z* of the helical structure ($\lambda_0=n\cdot z$;

[*] Dr. E. H. Korte
Institut für Spektrochemie
Bunsen-Kirchhoff-Strasse 11, D-4600 Dortmund 1 (Germany)
Prof. Dr. B. Schrader [+]
Teilbereich Physikalische und Theoretische Chemie der Universität-GHS
Universitätsstr. 2, D-4300 Essen 1 (Germany)
Dr. S. Bualek
Department of Chemistry, Mahidol-University
Bangkok (Thailand)
Dr. H. J. Krabbe
VEW, Vereinigte Elektrizitätswerke Westfalen
Postfach 941, D-4600 Dortmund 1 (Germany)
[+] Author to whom correspondence should be addressed.

[**] This work was carried out at the Institut für Spektrometrie, Dortmund, and at the Universität Dortmund, with support from the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen, the Deutsche Forschungsgemeinschaft, the Deutscher Akademischer Austauschdienst and the Fonds der Chemischen Industrie.

n = refractive index), and the circular polarization corresponds to the handedness of the helix[2]. Inversely circularly polarized light of the same wavelength is transmitted. In the surrounding range of wavelengths a strong anomaly in the optical rotation occurs with the center at λ_0: a Reflection Cotton Effect. A positive Reflection Cotton Effect indicates a left-handed helical structure (M-helix) of the cholesteric phase, a negative effect a right-handed structure (P-helix). In induced cholesteric solutions the Reflection Cotton Effect usually lies in the IR region.

In order to test whether information about the molecular structure of chiral substances can be gained with the aid of this effect we have measured and evaluated the infrared rotatory dispersion of *ca.* 150 chiral compounds in the spectral region 2.5...50 μm[3f].

As solvent we used an equimolar mixture of MBBA and EBBA [*N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline and *N*-(*p*-ethoxybenzylidene)-*p*-*n*-butylaniline] and the nematic phase Licristal®IV [*p*-methoxy-*p'*-*n*-butylazoxybenzene, eutectic mixture of both isomers]. The concentration of chiral substance was in the region of *ca.* 1...10 mol percent, the sample temperature varied in the range within which the mesophase exists (*ca.* 15...75 °C). The infrared rotatory dispersion spectra were measured in NaCl or CsI cuvettes with an IR spectropolarimeter[3a]; a typical spectrum is shown in Figure 1. The essential characteristics of the method are:

1. Molecules with chiral centers or axes and helical molecules transform nematic into cholesteric phases[3b,c].
2. Enantiomers produce cholesteric phases having equal pitches but with opposite helical sense.
3. At low concentration ($x = 0.01...0.1$) the pitch z is inversely proportional to the mole fraction x of the chiral guest substance[3e]: $\lambda_0/n = z = 1/xP$; the proportionality factor P is called the "Helical Twisting Power"[4].
4. The quantity P is proportional to the optical purity[3e].
5. The pitch, but not the induced handedness, depends upon the temperature[3c].
6. A chiral substance (which does not form a liquid-crystalline phase), always induces the same handedness in a "host substance"[3c].
7. Besides the Reflection Cotton Effect, whose wavelength—as mentioned under 3—changes with the concentration, sharp dispersion anomalies appear at fixed positions in the region of the absorption bands of the host molecules[3d,5], so-called Absorption Cotton Effects. If the Reflection Cotton Effect does not lie in the accessible spectral region its position and sign can be deduced from the sign of the above Absorption Cotton Effect[3c,d].
8. The absolute configuration of dissolved chiral molecules can be elucidated from the infrared rotatory dispersion of the induced cholesteric solutions.

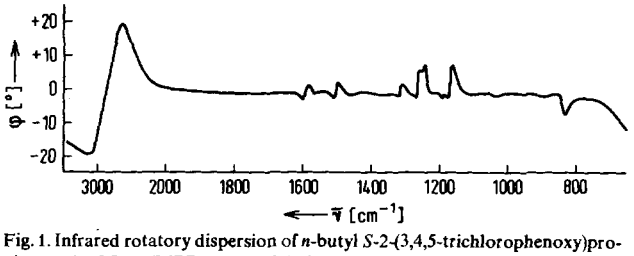


Fig. 1. Infrared rotatory dispersion of *n*-butyl *S*-2-(3,4,5-trichlorophenoxy)propionate in EBBA/MBBA ($x = 0.07$), layer thickness *ca.* 25 μm. A positive Reflection Cotton Effect appears at *ca.* 2900 cm^{-1}; a series of Absorption Cotton Effects in the region between 800 and 1600 cm^{-1} has a negative sign, all others have positive signs.

The infrared rotatory dispersion of induced cholesteric solutions indicates primarily properties of the helical molecular arrangement. Conclusions about the guest molecules are therefore independent of the previously known chiroptic methods, which are determined by electron excitation (ORD, CD) or normal vibrations (Raman circular intensity difference[6], vibrational circular dichroism[7]) of the chiral molecules.

The use of this new chiroptic method for the determination of absolute configurations is reported in the following communication[8].

Received: August 17, 1977 [Z 829a IE]
German version: Angew. Chem. 89, 830 (1977)

CAS Registry numbers:
n-Butyl *S*-2-(3,4,5-trichlorophenoxy)propionate, 64114-08-5

[1] *G. Friedel*, Ann. Phys. (Paris) *18*, 273 (1922); *A. D. Buckingham, G. P. Caesar, M. B. Dunn*, Chem. Phys. Lett. *3*, 540 (1968); *H. Stegemeyer, K. J. Mainusch, E. Steigner, ibid. 8*, 425 (1971).
[2] *H. de Vries*, Acta Crystallogr. *4*, 219 (1951).
[3] a) *E. H. Korte, B. Schrader*, Messtechnik *81*, 371 (1973); Appl. Spectrosc. *29*, 389 (1975); b) *E. H. Korte*, Dissertation, Universität Dortmund 1972; c) *S. Bualek*, Dissertation, Universität Dortmund 1975; d) *H. J. Krabbe*, Dissertation, Universität Dortmund 1977; e) *E. H. Korte, S. Bualek, B. Schrader*, Ber. Bunsenges. Phys. Chem. *78*, 876 (1974); f) details of the studies will be reported in J. Chem. Res. (M) *1977*.
[4] *H. Baessler, M. M. Labes*, J. Chem. Phys. *52*, 631 (1970).
[5] *B. Schrader, E. H. Korte*, Angew. Chem. *84*, 218 (1972); Angew. Chem. Int. Ed. Engl. *11*, 226 (1972); *G. Holzwarth, N. A. W. Holzwarth*, J. Opt. Soc. Am. *63*, 324 (1973).
[6] *L. D. Barron*, Annu. Rev. Phys. Chem. *26*, 381 (1975).
[7] *G. Holzwarth, E. C. Hsu, H. S. Mosher, T. R. Faulkner, A. Moscowitz*, J. Am. Chem. Soc. *96*, 251 (1974); *L. A. Nafie, T. A. Keiderling, P. J. Stephens, ibid. 98*, 2715 (1976).
[8] *H. J. Krabbe, H. Heggemeier, B. Schrader, E. H. Korte*, Angew. Chem. *89*, 831 (1977); Angew. Chem. Int. Ed. Engl. *16*, 791 (1977).

Relationship between the Infrared Rotatory Dispersion of Liquid-Crystalline Solutions of Chiral Molecules and Their Absolute Configuration[**]

By *Hans Jürgen Krabbe, Heinrich Heggemeier, Bernhard Schrader*, and *Ernst-Heiner Korte*[*]

In the preceding communication the characteristics of the infrared rotatory dispersion of induced cholesteric solutions were outlined[1]. We shall now demonstrate how conclusions about the absolute configuration of molecules having a chirality center can be drawn from the sign of the observed Reflection Cotton Effect.

The absolute configuration of chiral molecules was characterized by a sequence of ligand parameters in analogy to the Cahn-Ingold-Prelog nomenclature[2]. Various systems of ligand parameters were then investigated to establish whether a relationship existed between the absolute configuration

[*] Dr. H. J. Krabbe
VEW, Vereinigte Elektrizitätswerke Westfalen
Postfach 941, D-4600 Dortmund 1 (Germany)
Dipl.-Chem. H. Heggemeier, Prof. Dr. B. Schrader [+]
Teilbereich Physikalische und Theoretische Chemie der Universität—GHS
Universitätsstr. 2, D-4300 Essen 1 (Germany)
Dr. E. H. Korte
Institut für Spektrochemie
Bunsen-Kirchhoff-Str. 11, D-4600 Dortmund 1 (Germany)
[+] Author to whom correspondence should be addressed.

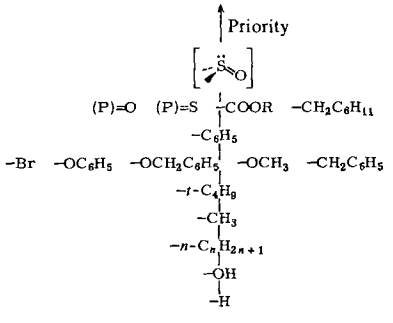
[**] This work was carried out at the Institut für Spektrometrie, Dortmund, and at the Universität Dortmund, and was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen, the Deutsche Forschungsgemeinschaft, the Deutscher Akademischer Austauschdienst, and the Fonds der Chemischen Industrie.—We thank Prof. Dr. *A. Fredga*, Uppsala, and Prof. Dr. *R. Luckenbach*, Mainz, für supplying model substances.

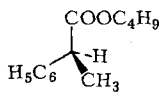
defined thereby and the helical sense induced, which would enable prediction of the absolute configuration of compounds of unknown structure. The ordering by atomic number used in the Cahn-Ingold-Prelog system is unsuitable in this respect. Using the "effective volume" of ligands as a basis we have empirically worked out a system for the interpretation of our measurements on substances having one chirality center. Table 1 shows the priority scheme of the ligands in previously investigated molecules. The determination of the absolute configuration proceeded as follows:

1. The four ligands a, b, c, d of a chirality center might according to Table 1 have the order of priority a > b > c > d. If a molecular model is oriented in such a way that the ligand d is furthest away from the observer then the molecular model is assigned the absolute configuration R_v when the sequence a, b, c is clockwise, otherwise the symbol S_v.

2. Molecules having the absolute configuration R_v give rise to a positive Reflection Cotton Effect in liquid-crystalline solution, those having configuration S_v a negative effect.

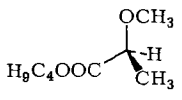
Table 1. Priority scheme for determination of the absolute configuration from the Reflection Cotton Effect.





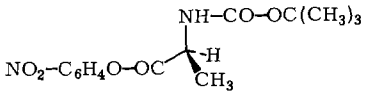
S
S_V
N

Butyl *S*-2-phenylpropionate



S
R_V
P

Butyl *S*-2-methoxypropionate



S
R_V
P

S-(+)-*N*-BOC-alanine-*p*-nitrophenyl ester

Fig. 1. Absolute configuration according to a) the Cahn-Ingold-Prelog system, b) R_v, S_v system, and c) the signs of the Reflection Cotton Effect for molecules with one chirality center.

So far over 100 compounds having a chirality center fit into this scheme[3]. The handedness of the induced helical structures for guest substances extrapolated by *Gottarelli et al.*[4] from measurements in the visible region can also be interpreted by a modified scheme corresponding to Table 1. Molecules with chirality centers in rings or with several chirality centers, and those with branched ligands or ligands which resemble the host molecules, cannot as yet be definitely classified by a systematic sequence.

Received: August 17, 1977 [Z 829b IE]
German version: Angew. Chem. *89*, 831 (1977)

CAS Registry numbers:
Butyl *S*-2-phenylpropionate, 64114-09-6; butyl *S*-2-methoxypropionate, 28310-92-1; *S*-*N*-(+)-Boc-alanine *p*-nitrophenyl ester, 2483-49-0

[1] *E. H. Korte, B. Schrader, S. Bualek, H. J. Krabbe*, Angew. Chem. *89*, 830 (1977); Angew. Chem. Int. Ed. Engl. *16*, 790 (1977).
[2] *R. S. Cahn, C. K. Ingold, V. Prelog*, Angew. Chem. *78*, 413 (1966); Angew. Chem. Int. Ed. Engl. 5, 385 (1966).
[3] *S. Bualek*, Dissertation, Universität Dortmund 1975; *H. J. Krabbe*, Dissertation, Universität Dortmund 1977; *J. Oelichmann*, Diplomarbeit, Universität Dortmund 1975; *H. Heggemeier*, Diplomarbeit, Universität Dortmund 1975. Details of the studies will be reported in J. Chem. Res. (M) 1977.
[4] *G. Gottarelli, B. Samori, S. Marzocchi, C. Stremmenos*, Tetrahedron Lett. *1975*, 1981; *G. Gottarelli, B. Samori, C. Stremmenos*, Chem. Phys. Lett. *40*, 308 (1976).

Dimeric Bis(di-*tert*-butylphosphino)stannanediyl: A Cyclic Phosphorus-Tin Ylide[**]

By *Wolf-Walther du Mont* and *Heinz-Jürgen Kroth*[*]

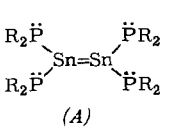
Reports on the stabilization of carbene-analogous stannylenes (stannanediyls) by bis(trimethylsilyl)methyl- and trimethylsilylamino substituents have evoked lively and in part controversial discussion on how and whether such stannylenes associate in solution or in the solid state, and whether the color of such compounds is caused by monomeric species[1].

We have now succeeded in synthesizing bis(di-*tert*-butylphosphino)stannanediyl *(1)*, the first stannylene substituted only with R_2P groups[2], by reaction of potassium di-*tert*-butyl phosphide with stoichiometric amounts of ethylphosphanedichlorostannanediyl[2] in toluene at −78 to −40 °C[3]:

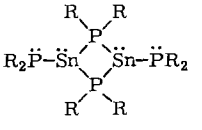
$$2\ KP(CMe_3)_2 + Et_3PSnCl_2 \longrightarrow 2\ KCl + Et_3P + [(Me_3C)_2P]_2Sn \qquad (1)$$

(1) readily dissolves in toluene, ethers and aliphatic hydrocarbons with deep red coloration of the solution. The pure compound is obtained as orange-red crystals in *ca.* 40 % yield on crystallization from pentane at −25 °C. Cryoscopic molecular weight determinations in benzene show that *(1)* is dimeric in this solvent (calc.: 409.1 (monomer), obs.: 765)[4].

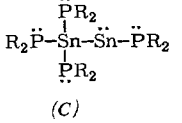
There are three possible alternative structures *(A)*–*(C)* for the dimeric compound:



(A)



(B)



(C)

[*] Dr. W.-W. du Mont, Dr. H.-J. Kroth
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-1000 Berlin 12 (Germany)

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

The formulation *(A)*, corresponding to the structure of dimeric $[(Me_3Si)_2CH]_2Sn$[5] in the solid state, is ruled out since two main signals with quite different chemical shifts and coupling constants $^1J(^{31}P^{117,119}Sn)$ appear in the ^{31}P-NMR spectrum of *(1)*. A distinction between the structure *(B)* and *(C)* is made possible by the ^{119}Sn-NMR spectrum of *(1)*, in which only *one* group of signals with doublet-of-triplet splitting is observed [$\delta(^{119}Sn)=328$, triplet $^1J(^{119}Sn^{31}P)=1800$ Hz, doublet $^1J(^{119}Sn^{31}P=1086$ Hz][6]. This splitting pattern is obviously compatible only with the structure *(B)* and at the same time enables a correct assignment of the ^{31}P resonances: $\delta(P_{ring})=19.1$, $^1J(^{31}P^{117/119}Sn)=1707/1782$ Hz; $\delta(P_{terminal})=67$, $^1J(^{31}P^{117/118}Sn)=1035/1071$ Hz. The ^1H-NMR signal of the terminal $(t\text{Bu})_2P$ groups appears as a sharp doublet [$\delta(^1H)=0.9$, $^3J(HP)=10.0$ Hz], superposing the group of signals of the $(t\text{Bu})_2P$ groups in the diphosphadistannetane ring [$(AX_n)_2$ spin system].

Assuming that the nonbonding electron pairs on the tin in *(1,B)* are stereochemically active, then there should still be the possibility of formation of *cis* and *trans* isomers for the R_2P ligands on the four-membered ring. In repeated syntheses of *(1)* we always obtained the same product. The kinetic stability of *(1)*, even in the presence of triethylphosphane or dimethoxyethane, shows that there are no rapid exchange equilibria. Evidence for the remarkable stability of the phosphorus(III)-tin(II) four-membered ring in *(1)* is also provided by the fact that attempts to introduce three di-*tert*-butylphosphino groups at tin(IV) have so far failed—presumably for steric reasons—while nucleophilic attack of the third phosphino group at the tin(II) in the dimerization of bis(di-*tert*-butylphosphino)stannanediyl to diphosphadistannetane apparently even proceeds with gain in energy.

Procedure

A 1 M solution of Et_3PSnCl_2 in toluene (4.5 ml) is added at -78 °C to a suspension of $KP(t\text{Bu})_2$ (1.88 g, 10 mmol) in toluene (50 ml) in the absence of oxygen and moisture and the mixture stirred for *ca.* 4 h at -40 °C. The resultant deep-red solution is filtered and the filtrate concentrated under reduced pressure to about a third of its original volume. For crystallization of *(1)* the solution is treated with 20 ml pentane and cooled to -25 °C. The crude product is recrystallized from pentane. Yield *ca.* 1 g (45%) orange-red, *(1)*, m.p. 148—150 °C (dec.).

Received: September 6, 1977 [Z 831 IE]
German version: Angew. Chem. *89*, 832 (1977)

CAS Registry numbers:
(1), 64146-55-0; $KP(t\text{-Bu})_2$, 64146-54-9; Et_3PSnCl_2, 64163-61-7; ^{119}Sn, 14314-35-3

[1] *D. H. Harris, M. F. Lappert*, J. Chem. Soc. Chem. Commun. *1974*, 895; *C. D. Schaeffer, J. J. Zuckerman*, J. Am. Chem. Soc. *96*, 7160 (1974); *M. Veith*, Angew. Chem. *87*, 287 (1975); Angew. Chem. Int. Ed. Engl. *14*, 263 (1975); *P. Foley, M. Zeldin*, Inorg. Chem. *14*, 2264 (1975); *D. Hänssgen, J. Kuna, B. Ross*, Chem. Ber. *109*, 1797 (1976); *M. F. Lappert, P. P. Power*, Adv. Chem. Ser. *157*, 70 (1976).

[2] *W.-W. du Mont*, 2nd Int. Conf. Organomet. Coord. Chem. Ge, Sn, Pb, Nottingham 1977, Abstr.

[3] Reactions of $Me_3Si—P(CMe_3)_2$ or $Li—P(CMe_3)_2$ with tin dihalides under comparable conditions always afford the stannylenes $(Me_3C)_2PSnX$: *W.-W. du Mont, H. Schumann*, Angew. Chem. *87*, 354 (1975); Angew. Chem. Int. Ed. Engl. *14*, 368 (1975); *W.-W. du Mont, B. Neudert*, Z. Anorg. Allg. Chem., in press.

[4] A very weak signal appears at $m/e=410$ in the mass spectrum of *(1)* at 70 °C/70 eV, but not the molecular ion of the dimer. Correct values were obtained in the elemental analysis.

[5] *D. E. Goldberg, D. H. Harris, M. F. Lappert, K. M. Thomas*, J. Chem. Soc. Chem. Commun. *1976*, 261.

[6] NMR pulse spectrometer Bruker SXP 33.55 MHz for ^{119}Sn, 36.44 MHz for ^{31}P. Positive sign corresponds to downfield shifts relative to Me_4Sn or 85% H_3PO_4.

A Novel Transformation of Diphenylcyclopropenone: Double Bond Cleavage in the Reaction with Platinum Complexes[**]

By *W. Eamon Carroll, Michael Green, Judith A. K. Howard, Michel Pfeffer*, and *F. Gordon A. Stone*[*]

Although cyclopropenone-metal complexes have been postulated[1] as intermediates in certain metal-catalyzed co-oligomerizations of acetylenes and carbon monoxide, relatively little has been reported on reactions of this important class of small-ring molecules with transition metal compounds. One interesting reaction involving zero-valent tertiary phosphane complexes of platinum results in the formation of platinacyclobutenone compounds *via* initial formation of an η^2-adduct between the metal and the carbon-carbon double bond of the cyclopropenone[2]. We now report a novel activation of diphenylcyclopropenone resulting in ring-opening *via* cleavage of the carbon-carbon double bond of the three-membered ring.

Reaction (toluene solution, 25 °C) of diphenylcyclopropenone with the trinuclear platinum complex $[Pt_3(t\text{BuNC})_6]$[3] gives a yellow crystalline diplatinum compound $[Pt_2\{\mu_2\text{-}(PhC)_2CO\}(t\text{BuNC})_4]$ *(1)* [ν_{max}(NC) 2168 and 2140 cm^{-1}]. The molecular structure was established by a single crystal X-ray diffraction study (Fig. 1)[4].

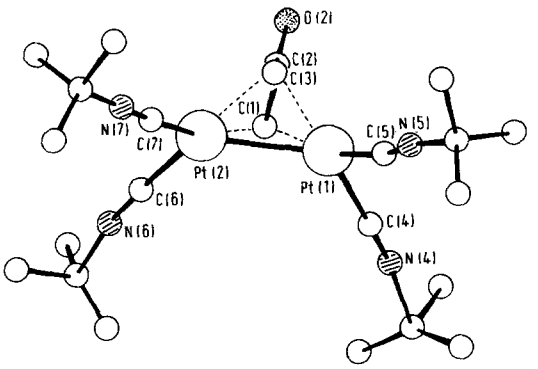


Fig. 1. Molecular structure of $[Pt_2\{\mu_2\text{-}(PhC)_2CO\}(t\text{BuNC})_4]$ *(1)*; the two phenyl groups are omitted for clarity.

The ring-opened fragment C(1)C(2)C(3) lies perpendicular to the Pt—Pt vector, with the carbon C(1) and C(3) atoms originally involved in the ring CC double bond now separated by 2.18(2) Å[5]. The two platinum atoms are in essentially square planar environments equidistant from C(1) and C(3) (mean Pt—C = 2.11 Å)[6]. The distance of C(2) from the platinum atoms (mean 2.50(2) Å) exceeds the sum of the covalent radii (1.99 Å) but some degree of bonding appears to be involved because ^{13}C-NMR studies reveal substantial coupling $J(^{195}Pt\text{-}^{13}C)$ between C(2) and the metal nuclei[7]. Moreover, the C(2)O(2) distance (1.26(2) Å) is unusually long and this lengthening is reflected in an abnormally low ν_{max}(CO) band at 1556 cm^{-1}.

Several other complexes similar to *(1)* have been synthesized. Treatment of $[Pt(cod)_2]$ (cod = cycloocta-1,5-diene)[8] with

[*] Dr. W. E. Carroll, Dr. M. Green, Dr. J. A. K. Howard, Dr. M. Pfeffer, Prof. Dr. F. G. A. Stone [+]
Department of Inorganic Chemistry
University of Bristol
Bristol BS8 1TS (England)

[+] Author to whom correspondence should be addressed.

[**] This work was supported by the U. K. Science Research Council. *M. P.* gratefully acknowledges a European Exchange Postdoctoral Fellowship of the Royal Society and C.N.R.S.

methyl vinyl ketone at −50°C in diethyl ether followed by addition of diphenylcyclopropenone gives yellow crystalline $[Pt_2\{\mu_2\text{-}(PhC)_2CO\}(cod)_2]$ *(2)*, $\nu_{max}(CO)$ 1570 cm^{-1}, m.p. 206°C (decomp.). Complex *(2)* reacts with *tert*-butyl isocyanide to give *(1)*, while treatment with HBF_4 gives the salt $[Pt_2\{\mu_2\text{-}(PhC)_2COH\}(cod)_2]BF_4$ *(3)*. Compound *(1)* can also be readily protonated at the oxygen atom yielding $[Pt_2\{\mu_2\text{-}(PhC)_2COH\}(tBuNC)_4]BF_4$ *(4)*.

Mechanistically it is interesting to contrast the CC double bond cleavage process observed in this study with the previous results which gave platinacyclobutenones[2]. It seems likely that an η^2-complex $[Pt\{\eta^2\text{-}PhC{=}C(Ph)C(O)\}L_2]$ ($L = Ph_3P$[2]; *t*BuNC, cod/2) is also initially formed in the reactions here described but with the weaker σ donors (*t*BuNC or cod) the rearrangement of the η^2-complex is slowed down sufficiently to permit attack by a second PtL_2 group on the bent σ orbitals of the C_3-ring with simultaneous breaking of the CC double bond and formation of a bridged dinuclear system[9].

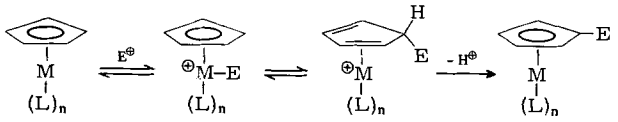
Received: July 19, 1977 [Z 812 IE]
German version: Angew. Chem. 83, 838 (1977)

[1] *C. W. Bird, E. M. Briggs, J. Hudec*, J. Chem. Soc. *C 1967*, 1862; and references cited therein.
[2] *W. Wong, S. J. Singer, W. D. Pitts, S. F. Watkins, W. H. Baddley*, J. Chem. Soc. Chem. Commun. *1972*, 672; *J. P. Visser, J. E. Ramakers-Blom*, J. Organomet. Chem. *44*, C 63 (1972).
[3] *M. Green, J. A. K. Howard, M. Murray, J. L. Spencer, F. G. A. Stone*, J. Chem. Soc. Dalton Trans. *1977*, 1509.
[4] Syntex-$P2_1$: monoclinic, space group $P2_1/n$, $Z = 4$, $a = 11.283(8)$, $b = 19.821(6)$, $c = 17.584(7)$ Å, $\beta = 90.23(4)°$; 4494 independent diffraction data ($I \geq 2\sigma(I)$); $R = 0.07$.
[5] This distance is identical with that found for the C—C separations in the cleaved cyclopropenium ion fragments in $[Pd_3\{\eta^3\text{-}C_3Ph(p\text{-}MeO\text{-}C_6H_4)_2\}_2(acac)_2]$ (*A. Keasey, P. M. Bailey, P. M. Maitlis*, J. Chem. Soc. Chem. Commun. *1977*, 178).
[6] The two sets of atoms {Pt(1), C(1), C(3), C(4), C(5)} and {Pt(2), C(1), C(3), C(6), C(7)} define planes with a dihedral angle of 72°, and show dihedral angles of 56° and 52°, respectively, with the plane defined by {C(1), C(2), C(3)}. The Pt—Pt distance 2.819(1) Å, although longer than in other diplatinum bridged species, is too short to discount metal-metal bonding.
[7] The $^{13}C\text{-}\{^1H\}$-NMR spectrum (δ values rel. Me_4Si, *J* in Hz) showed resonances at 86.6 [C(1) and C(3), *J*(PtC) 342] and 168.5 [C(2), *J*(PtC) 125]. Although ^{195}Pt coupling to C(1) and C(3) is larger than to C(2) the value of 125 Hz for the latter indicates strong interactions with the platinum atoms.
[8] *M. Green, J. A. K. Howard, J. L. Spencer, F. G. A. Stone*, J. Chem. Soc. Dalton Trans. *1977*, 271.
[9] Comparison with the numerous known bridged acetylene complexes of the type $[L_2M(\mu\text{-}RC_2R)ML_2]$ (M = Ni, Pt) suggest that the cyclopropenone fragment is functioning as a "homo-acetylene"; cf. *M. Green, D. M. Grove, J. A. K. Howard, J. L. Spencer, F. G. A. Stone*, J. Chem. Soc. Chem. Commun. *1976*, 759; *V. W. Day, S. S. Abdel-Meguid, S. Dabestani, M. G. Thomas, W. R. Pretzer, E. L. Muetterties*, J. Am. Chem. Soc. *98*, 8289 (1976).

An Unusually Facile Electrophilic Substitution at the Cyclopentadienyl Ring in a Half-Sandwich Complex[1]

By *Helmut Werner* and *Werner Hofmann*[*]

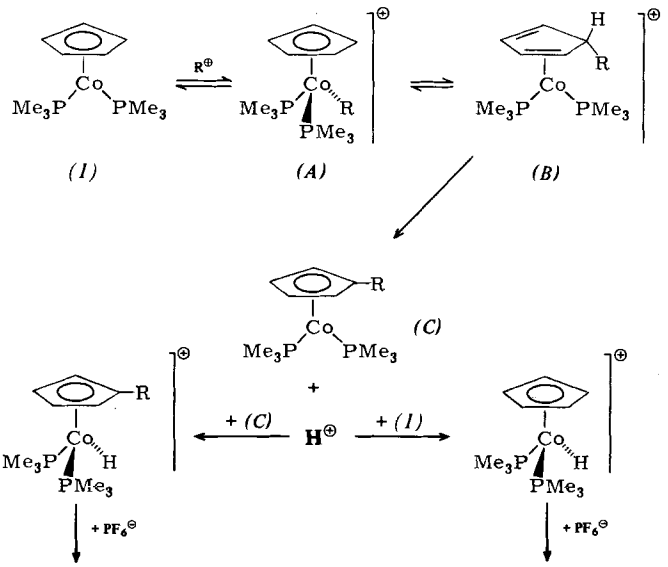
Concepts on the mechanism of electrophilic ring substitution in η-cyclopentadienylmetal complexes are still controversial. For reactions of ferrocene and of cyclopentadienyltricarbonylmanganese—the two compounds whose "aromatic behavior" has so far been investigated in most detail—initial attack of the electrophile E^+ at the metal center with subsequent linking of a C—E bond and elimination of H^+ has been most frequently postulated[2].



We have now been able to establish that this postulate is in fact correct in the case of ring substitution of a half-sandwich complex of type $C_5H_5ML_2$, namely $C_5H_5Co(PMe_3)_2$ *(1)*.

Compound *(1)* contains an extraordinarily nucleophilic metal center[3,4]. It reacts with MeI to give the salt $[C_5H_5(PMe_3)_2CoMe]I$, whose cation possesses a very stable methylcobalt bond[3]. On reaction with EtI, $[C_5H_5(PMe_3)_2\text{-}CoEt]I$ is formed. In contrast, reactions of *(1)* with alkyl halides RX (X preferably Br) which carry at least two methyl or ethyl groups on the C_α atom leads to *cationic hydridocobalt complexes containing an alkyl-substituted cyclopentadienyl ring.* They are isolated as PF_6 salts *(3)*—*(5)*. Depending upon the molar ratio *(1)*: RX, formation of $[C_5H_4R(PMe_3)_2CoH]^+$ can be accompanied by formation of the corresponding cation with an unsubstituted five-membered ring (isolated as PF_6 salt *(2)*)[5]. On using *equimolar* amounts of *(1)* and RX (in ether as solvent) a product ratio $[C_5H_4R(PMe_3)_2CoH]^+ : [C_5H_5(PMe_3)_2CoH]^+ = 70:30$ results when RX = *i*-C_3H_7Br, and a ratio of 50:50 when RX = *t*-C_4H_9Br. With a *threefold* excess of *i*-C_3H_7Br or *t*-C_4H_9Br, the ring-substituted cation is the *only* reaction product.

Scheme 1.



(3), R = *i*-C_3H_7
(4), R = *t*-C_4H_9
(5), R = $C(CH_3)_2C_2H_5$

The mechanism of the reaction of *(1)* with RX is outlined in Scheme 1. The initially formed intermediate *(A)* (which can be isolated when R = Me or Et[3]) rearranges to a 5-R(*endo*)-cyclopentadiene complex *(B)* if the alkyl groups R are bulky, and $C_5H_4RCo(PMe_3)_2$ is formed with elimination of a proton.

[*] Prof. Dr. H. Werner, Dipl.-Chem. W. Hofmann
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

The proton can then react either with this compound or with *(1)* in an oxidative addition, the latter reaction applying only if the initially formulated equilibria are not shifted completely to the side of the cationic species because of the selected molar ratio *(1)*:RX. That *steric* and not electronic effects are actually decisive for the rearrangement of *(A)* to *(B)* is evidenced by the observation that the cation $[C_5H_5(PMe_3)_2CoSnMe_3]^+$ formed from *(1)* and Me_3SnCl is kinetically completely inert[4], although the stability of Me_3Sn^+ (which would be a likely migrating particle) is distinctly greater than that of Me_3C^+.

Two alternative mechanisms—namely a direct attack of RX at the ring as well as formation of HX by β-elimination from RX—are ruled out on the following grounds:

1. Addition of R^+ to the ring would lead to initial formation of a cationic cyclopenta*diene* complex in which the group R assumes an *exo* position at the sp^3 hybridized C atom. Owing to the favorable steric conditions for interaction of the metal with the *endo*-H atom in such an intermediate the cation $[C_5H_4R(PMe_3)_2CoH]^+$ should be formed—even at a molar ratio of *(1)*:RX = 1:1. But this is not the case.
2. On formation of HX from RX (possibly catalyzed by *(1)*) the product ratio $[C_5H_4R(PMe_3)_2CoH]^+:[C_5H_5(PMe_3)_2CoH]^+$ should not be dependent upon the concentration of RX in the manner observed. The cation $[C_5H_5(PMe_3)_2CoH]^+$ would then have to be formed even with an excess of RX, but this is also not the case.

Reaction of *(1)* with Me_3SiCl leads to a paramagnetic product. Use of $Me_3SiOSO_2CF_3$ as silylating reagent leads to formation of the cation $[C_5H_4SiMe_3(PMe_3)_2CoH]^+$, which can be precipitated as the PF_6 salt *(6)*. The NMR data of *(6)* are listed—together with those of *(3)*–*(5)*—in Table 1.

Table 1. ^{1}H-NMR data of $[C_5H_4R(PMe_3)_2CoH]PF_6$ in CD_3NO_2 (δ values, TMS int.; *J* in Hz).

Complex	Cyclopentadienyl $H^{3,4}$	Cyclopentadienyl $H^{2,5}$	PMe_3	Co—H	J_{PH}	R
(3)	4.68 m	5.12 m	1.50 vt	−15.67 t	81	CH_3: 1.15 d; CH: 2.47 sept [J_{HH} = 6.6]
(4)	4.63 m	5.11 m	1.53 vt	−15.54 t	80	CH_3: 1.15 s
(5)	4.61 m	5.17 m	1.55 vt	−15.40 t	82	C—CH_3: 1.21 s; CH_2: [a]; CH_2—CH_3: 0.77 t [J_{HH} = 7.5]
(6)	4.72 m	5.40 m	1.51 vt	−16.23 t	83	CH_3: 0.17 s

[a] Masked by signal of the PMe_3 protons.

Table 2. ^{1}H-NMR data of $C_5H_4RCo(PMe_3)_2$ in C_6D_6 (δ values, TMS int.; *J* in Hz).

Complex	Cyclopentadienyl $H^{3,4}$	Cyclopentadienyl $H^{2,5}$	PMe_3	R
(7)	3.62 m	4.60 m	1.00 vt	CH_3: 1.25 d; CH: 2.62 sept [J_{HH} = 7.0]
(8)	3.58 m	4.65 m	1.05 vt	CH_3: 1.33 s
(9)	3.49 m	4.61 m	0.98 vt	C—CH_3: 1.21 s; CH_2: 1.57 q [J_{HH} = 7.0]; CH_2—CH_3: [a]
(10)	3.61 m	4.88 m	0.99 vt	CH_3: 0.30 s

[a] Masked by signal of the PMe_3 protons.

A quantitative transformation of the cationic hydrido complexes *(3)*–*(6)* into the corresponding neutral compounds *(7)*–*(10)* (Table 2) is possible with NaH in tetrahydrofuran.

$$[C_5H_4R(PMe_3)_2CoH]^+ + H^- \rightarrow C_5H_4RCo(PMe_3)_2 + H_2$$

(7), R = *i*-C_3H_7
(8), R = *t*-C_4H_9
(9), R = $C(CH_3)_2C_2H_5$
(10), R = $Si(CH_3)_3$

The extraordinarily mild reaction conditions for the ring substitution of *(1)* differ markedly from those which are necessary for the electrophilic substitution of $Fe(C_5H_5)_2$ or $C_5H_5Mn(CO)_3$. We attribute this to the *considerably higher basicity of the metal atom* of *(1)*, which at the same time also explains why a stable secondary product with a C_5H_4RM—H bond can be isolated in the reaction of this complex but not in the reactions of ferrocene and cyclopentadienyltricarbonylmanganese with RX.

Procedure

(3)—*(5)*: A threefold excess of alkyl bromide is added dropwise at −78°C to a solution of *(1)* (1 mmol) in ether (5 ml). On slowly thawing out, a light-brown precipitate forms which is extremely air-sensitive and is therefore dried directly in the reaction flask. Addition of NH_4PF_6 (2 mmol) to the solid residue followed by methanol (5 ml) leads to formation of light-yellow crystals, which are filtered off and washed with cold ethanol and ether. Recrystallization from acetone/ether affords the analytically pure PF_6 salt; yield 85–95 %.

(6): Preparation analogous to that above except that the ester $Me_3SiOSO_2CF_3$ is used instead of RBr; yield >95 %.

(7)—*(10)*: To the corresponding salt *(3)*—*(6)* (1 mmol) in a little THF (3—5 ml) is added NaH (*ca.* 3 mmol). After spontaneous evolution of gas has subsided the solvent is removed *in vacuo* and the residue extracted with pentane. Filtration and removal of the pentane affords a dark brown oil which is extremely air-sensitive. The yield is quantitative.

Received: August 8, 1977 [Z 826a IE]
German version: Angew. Chem. 89, 835 (1977)

CAS Registry numbers:
(1), 63413-01-4; *(2)*, 64508-16-3; *(3)*, 64508-14-1; *(4)*, 64508-12-9; *(5)*, 64508-39-0; *(6)*, 64508-37-8; *(7)*, 64508-26-5; *(8)*, 64508-25-4; *(9)*, 64508-33-4; *(10)*, 64521-04-6

[1] Basic Metals, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Bayer AG, Leverkusen.—Part 5: *K. Leonhard, H. Werner*, Angew. Chem. 89, 656 (1977); Angew. Chem. Int. Ed. Engl. 16, 649 (1977).
[2] *G. E. Coates, M. L. H. Green, K. Wade*: Organometallic Compounds, 3. Ed., Vol. II. Methuen, London 1968, Chap. 4.
[3] *H. Werner, W. Hofmann*, Chem. Ber., in press.
[4] *K. Dey, H. Werner*, J. Organomet. Chem. 137, C 28 (1977).
[5] For NMR data of *(2)* see ref. [3].

Detection of Rigid Rotamers in Disubstituted Cyclopentadienylcobalt Complexes[1]

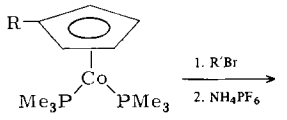
By *Werner Hofmann, Wolfgang Buchner*, and *Helmut Werner*[*]

In general, the barrier to rotation about the metal-to-ring bond in bis(η^5-cyclopentadienyl)metal complexes is very small;

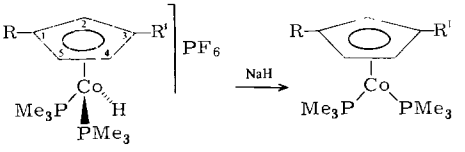
[*] Prof. Dr. H. Werner, Dr. W. Buchner, Dipl.-Chem. W. Hofmann
Institut für Anorganische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

for ferrocenes it is 2—5 kcal/mol[2]. Estimated values for other metallocenes and for cyclopentadienylmetal carbonyls are of the same order of magnitude. In the case of substituted monocyclopentadienyl complexes $C_5H_{5-n}R_nML_m$ it should be possible by choice of sufficiently bulky substituents R and voluminous (especially not rod-shaped) ligands L to hinder rotation about the metal-to-ring bond to such an extent that certain conformers can be frozen. We have now succeeded in demonstrating the first such frozen conformation for half-sandwich complexes of cobalt.

Monosubstituted derivatives of cyclopentadienylbis(trimethylphosphane)cobalt such as *(1)* and *(2)* are accessible *via* the intermediate $[C_5H_4R(PMe_3)_2CoH]X$[3]. The *disubstituted* cationic complexes *(3)*—*(5)* and the neutral compounds *(6)*—*(8)* can be obtained in an analogous way.



(1), R = *i*-C_3H_7
(2), R = *t*-C_4H_9



(3) - *(5)* *(6)* - *(8)*

(3), *(6)*: R = R' = *i*-C_3H_7
(4), *(7)*: R = *i*-C_3H_7, R = *t*-C_4H_9
(5), *(8)*: R = R = *t*-C_4H_9

In the case of *(3)* and *(6)* no fixed rotamers are detectable. In the temperature range from −60 to +25°C the ^{1}H- and ^{13}C-NMR spectra each show the very characteristic virtual triplet of spectral type $X_nAA'X'_n$ for protons[4] and AA'X for ^{13}C of the PMe_3 groups (X = ^{1}H or ^{13}C; A = ^{31}P), which is also observed for the complexes $C_5H_4RCo(PMe_3)_2$ and $[C_5H_4R(PMe_3)_2CoH]PF_6$ (R = H, *i*-C_3H_7, *t*-C_4H_9 *etc.*)[3] and whose appearance requires chemical equivalence of the two A nuclei. The triplet splitting of the signals of the cyclopentadienyl ring in *(3)* and in *(6)* by the two phosphorus atoms likewise affords proof of the equivalence of the phosphane ligands and thus of unhindered rotation about the metal-to-ring bond.

By way of contrast, the NMR data of *(5)* and *(8)* prove the presence of *rigid rotamers*—even at 100°C. Thus a typical AB pattern is observed for the two phosphorus ligands in the ^{31}P-NMR spectrum at −60°C which at higher temperature is no longer resolved owing to the quadrupole moment of cobalt. At 25 to 100°C, however, the non-equivalence of the PMe_3 ligands is very clearly revealed in the ^{1}H- and ^{13}C-NMR spectra: in no case is a virtual triplet observed, since the condition for a spectrum of the type $X_nAA'X'_n$ or AA'X is no longer fulfilled owing to the dissimilarity of the phosphorus atoms. On the contrary, the ^{1}H-NMR spectra show two doublets ($^4J_{PCoPCH}$ is very small) for PMe_3 protons, while the ^{13}C-NMR spectra show two doublets of doublets for the corresponding C atoms, each due to simple PH and PC coupling. The rigid structure of *(5)* and *(8)* (Table 1 and 2) is most evident from the different, no longer time averaged, phosphorus coupling constants of the ^{13}C- and ^{1}H-NMR signals of the corresponding ring atoms. From these data and the fact that two chemically non-equivalent *tert*-butyl groups are detectable for *(5)* it follows without doubt that *(A)* and *(B)* are the rotamers of *(5)* and *(8)* obtained in the synthesis, and are probably the most stable ones.

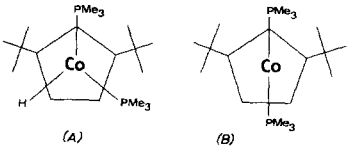
Table 1. ^{1}H-NMR data of *(3)*, *(5)*, *(6)* and *(8)* (δ values, TMS int.; *J* in Hz; 25°C, 100 MHz).

	Solvent	Ring-H		PMe_3	R	Co—H
(3)	CD_3NO_2		4.67, 3H, t, $^3J_{PH}=1.5$	1.55, 18H, vt $\|^2J_{PH}+{}^4J_{PH}\|=10.2$	2.64, 2H, sept, $J_{HH}=7.0$ 1.26, 6H, d, $J_{HH}=7.0$ 1.24, 6H, d, $J_{HH}=7.0$	−15.39, 1H, t, $J_{PH}=77$
(5)	CD_3NO_2		5.03, 1H, m 4.81, 1H, m 4.30, 1H, m	1.56, 9H, d, $J_{PH}=9.5$ 1.53, 9H, d, $J_{PH}=10.2$	1.23, 9H, s 1.20, 9H, s	−15.56, 1H, t, $J_{PH}=80$
(6)	C_6D_6	H^2:	3.40, 1H, txt, $^4J_{HH}=2.0$, $^3J_{PH}=3.0$	1.04, 18H, vt $\|^2J_{PH}+{}^4J_{PH}\|=7.2$	2.57, 2H, sept, $J_{HH}=6.6$ 1.27, 6H, d, $J_{HH}=6.6$	
		$H^{4,5}$:	3.79, 2H, dxt, $^4J_{HH}=2.0$, $^3J_{PH}=2.0$		1.23, 6H, d, $J_{HH}=6.6$	
(8)	C_6D_6	H^2:	3.37, 1H, txd, $^4J_{HH}=2.0$, $^3J_{PH}=6.0$	1.11, 9H, d, $J_{PH}=6.5$ 1.00, 9H, d, $J_{PH}=6.5$	1.28, 18H, s	
		$H^{4,5}$:	3.69, 2H, dxd, $^4J_{HH}=2.0$, $^3J_{PH}=4.5$			

Table 2. ^{13}C-NMR data of *(5)*, *(6)* and *(8)* (^{1}H-decoupled, δ values, TMS int.; *J* in Hz; 25°C, 22.636 MHz).

	Solvent	Ring-C		PMe_3	R	
(5)	[D6]-Acetone	$C^{1,3}$	121.44, bs [a] 117.24, bs [a]	22.69, dd, $^1J_{PC}=28.7$, $^3J_{PC}=1.5$	CMe_3: CCH_3:	[b] 31.64, s
		$C^{2,4,5}$	86.18, t, $J_{PC}=2.2$ 83.08, d, $J_{PC}=5.1$ 71.58, dd, $J_{P1C}=4.4$ $J_{P2C}=2.1$	21.27, dd, $^1J_{PC}=28.7$, $^3J_{PC}<1.5$		31.51, s
(6)	C_6D_6	$C^{1,3}$:	107.34, bs [a]	24.75, vt, $\|^1J_{PC}+{}^3J_{PC}\|=22$	$CHMe_2$: CCH_3:	28.00, s 26.05, s
		C^2:	74.85, t, $J_{PC}=2.2$			24.53, s
		$C^{4,5}$:	71.28, t, $J_{PC}=1.5$			
(8)	$C_6D_5CD_3$	$C^{1,3}$: C^2: $C^{4,5}$:	110.86, d, $J_{PC}=2.2$ 69.18, d, $J_{PC}=3.7$ 69.83, d, $J_{PC}=3.7$	24.37, dd, $^1J_{PC}=17.7$, $^3J_{PC}=3.0$ 23.47, dd, $^1J_{PC}=17.7$, $^3J_{PC}=3.0$	CMe_3: CCH_3:	29.21, s 32.00, s

[a] PC coupling not resolved; [b] masked by signal of the solvent.



The complexes *(4)* and *(7)* with mixed substituents fit into the series between *(3)*/*(6)* (freely rotating) and *(5)*/*(8)* (rigid). Two different types of phosphorus atoms are recognizable in the ^{31}P-NMR spectrum of *(7)* at -60 °C, thus indicating a frozen conformation (analogous to *(B)*). Above -10 °C a "thawing" of this arrangement and a slow rotation about the cobalt-to-ring axis is observed (change in the splitting of the NMR signals of the phosphane H and C atoms). Below -10 °C, for example, a doublet of doublets is observed in the ^{13}C-NMR spectrum at $\delta = 24.62$ with $^{1}J_{PC} = 17.3$ and $^{3}J_{PCoPC} = 5.5$ Hz, which at higher temperature converts into a virtual triplet ($\delta = 25.14$ with $|^{1}J_{PC} + {}^{3}J_{PCoPC}| = 22.8$ Hz, 50 °C, in [D$_6$]acetone). In the case of *(4)* no definite conclusions can be drawn from NMR data regarding hindered or restricted rotation about the cobalt-to-ring axis, since the two phosphorus atoms are bonded, as a result of unsymmetrical ring substitution, to a prochiral cobalt atom and are therefore non-equivalent in any case.

The question why two *tert*-butyl substituents (in *(5)* and *(8)*) hinder rotation of the cyclopentadienyl ring, whereas two isopropyl substituents (in *(3)* and *(6)*) do not, might be explained in terms of a "gear mechanism". When a 1,3-(t-C$_4$H$_9$)$_2$C$_5$H$_3$ ring is present it is obviously impossible on rotation about the metal-ring axis for the *tert*-butyl groups

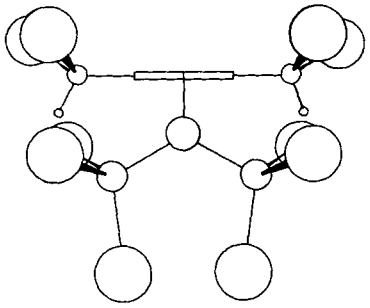


Fig. 1. Steric requirements for rotation according to the "gear mechanism" in compound *(6)* (schematic).

to get past the trimethylphosphane ligands—despite rotation about the C—CMe$_3$ bond. However, if one of the three methyl groups is replaced by an H atom (*i.e.* i-C$_3$H$_7$ instead of t-C$_4$H$_9$) then it appears possible that the two ring substituents are so oriented during the rotation that at the moment of sliding past a trimethylphosphane the H atom of the isopropyl group is directed inwards (cf. Fig. 1).

Received: August 8, 1977 [Z 826b IE]
German version: Angew. Chem. *89*, 836 (1977)

CAS Registry numbers:
(1), 64508-26-5; *(2)*, 64508-25-4; *(3)*, 64508-24-3; *(4)*, 64508-22-1; *(5)*, 64508-20-9; *(6)*, 64508-18-5; *(7)*, 64508-17-4; *(8)*, 64521-07-9; ^{13}C, 14762-74-4

[1] Stereochemical Studies on Coordination Compounds, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Bayer AG, Leverkusen.
[2] *M. Rosenblum*: Chemistry of the Iron Group Metallocens, Part I. Wiley-Interscience, New York 1965, p. 45.
[3] *H. Werner, W. Hofmann*, Angew. Chem. *89*, 835 (1977); Angew. Chem. Int. Ed. Engl. *16*, 794 (1977).
[4] *R. K. Harris*, Can. J. Chem. *42*, 2275 (1964).

Synthesis of Bridged 1,3,2λ^3,4λ^3-Diazadiphosphetidines

By *Rodney Keat* and *David G. Thompson*[*]

1,3,2λ^3,4λ^3-Diazadiphosphetidines of type *(1)* have recently attracted considerable attention[1]. Geometrical isomers of these heterocycles are characterized by exceptionally large ^{31}P chemical shift differences[1a–c, 4] and by differences in chemical reactivity[2].

We have now succeeded in "bridging" the 1,3-di-*tert*-butyl-2,4-dichloro-1,3,2λ^3,4λ^3-diazadiphosphetidine *(1)* to give the new crystalline bicyclic compounds *(4)*, *(5a)* and *(5b)*. The compounds were characterized by elemental analyses, mass spectra, and the spectral data shown in Table 1. Variable amounts of polymeric materials are also formed, but generally the proportion is much less than in the condensation of aromatic diols with 1,3,2λ^5,4λ^5-diazadiphosphetidines, where they are the exclusive products[3]. No bicyclic compound of type *(4)* was isolated on reaction of *N*,*N*′-dimethyltrimethylenediamine with *(1)*.

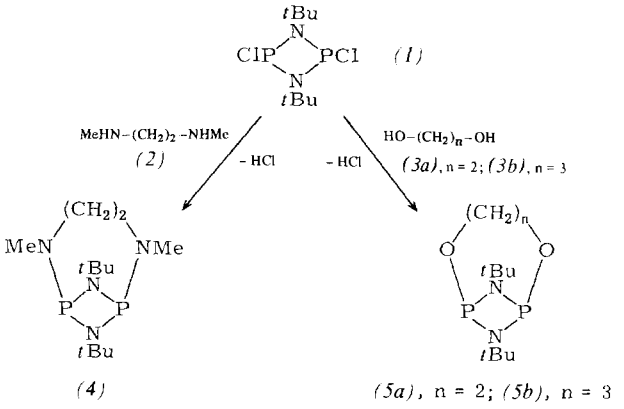


Table 1. Selected physical properties of the bicyclic compounds *(4)*, *(5a)* and *(5b)*.

	(4)	*(5a)*	*(5b)*
M.p. [°C]	36–38	65–67	182
B.p. [°C/torr]	73/0.1		
Yield [%]	20	23	20
δ_P (in CDCl$_3$)	155.0	177.5	135.4
δ_{ZCH_2} (in CDCl$_3$) [a]	3.12	4.17	3.97
$\lvert J_{PZCH_2} + J_{PNPZCH_2}\rvert$ [Hz] [a]	5.6 [b]	9.1	6.6
ν(P—N—P) asymm. [cm^{-1}] (in Nujol)	846	861	899

[a] Z = O or N.
[b] $|J_{PNCH_3} + J_{PNPNCH_3}| = 13.8$ Hz.

It is not clear what causes the large ^{31}P shift differences between geometrical isomers of diazadiphosphetidines of type *(1)*[4], but conformational changes within the diphosphetidine ring and the exocyclic (or bridging) groups are clearly implicated, especially when the difference in shift between *(5a)* and *(5b)* is considered.

Experimental

7,8-Di-tert-Butyl-2,5-dimethyl-2,5,7,8-tetraaza-1λ^3,6λ^3-diphosphabicyclo[4.1.1]octane (4): A solution of *(2)* (2.75 g, 31.2 mmol) in ether (30 ml) is slowly added with stirring at ambient temperature to a solution of *(1)* (4.30 g, 15.6 mmol)

[*] Dr. R. Keat, D. G. Thompson
Department of Chemistry, University of Glasgow
Glasgow G12 8QQ (U.K.)

in ether (120 ml). Removal of the precipitate and solvent affords a colorless oil which is purified by vacuum distillation.

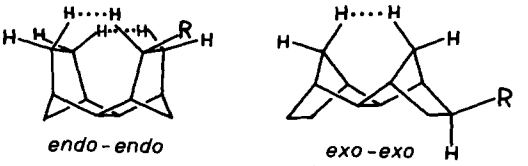
(5a): A mixture of *(3a)* (0.7 g, 11 mmol) and triethylamine (2.4 g, 12 mmol) in chloroform (30 ml) is added slowly to a solution of *(1)* (3.2 g, 12 mmol) in light petroleum (200 ml) at 0 °C. After removal of the salt and solvent the product is purified by two vacuum sublimations (*ca.* 50 °C/0.1 torr).

(5b) was prepared similarly to *(5a)* and recrystallized from pentane.

Received: August 10, 1977 [Z 820 IE]
German version: Angew. Chem. 89, 829 (1977)

[1] Recent papers on this topic include: a) *G. Bulloch, R. Keat, D. G. Thompson*, J. Chem. Soc. Dalton Trans. *1977*, 99; b) *E. Niecke, W. Flick, S. Pohl*, Angew. Chem. *88*, 305 (1976); Angew. Chem. Int. Ed. Engl. *15*, 309 (1976); c) *O. J. Scherer, G. Schnabl, ibid. 88*, 845 (1976) and *15*, 772 (1976); d) *W. Zeiss, H. Weis*, Z. Naturforsch. *B32*, 485 (1977).
[2] *R. Keat, D. G. Thompson*, unpublished work.
[3] *H.-G. Horn, M. Becke-Goehring*, J. Polym. Sci. A-1, 7, 959 (1969).
[4] Compare the ^{31}P shifts in isomeric forms of $(Me_2N—PN—tBu)_2$: 95.0 and 184.7 [1a] and in $(MeO—PN—tBu)_2$: 133.7 and 202.4 [2].

The structures of two racemic derivatives each of *(1)* and *(2)* have been determined [*(3)*—*(6)*; Table 1, Fig. 1][4].



(1), R = H
(3), R = 3,5-dinitrobenzoate
(4), R = hydrogenphthalate

(2), R = H
(5), R = 3,5-dinitrobenzoate
(6), R = *p*-nitrobenzoate

Unreasonable bond lengths and thermal motion parameters are obtained for the hydrocarbon residue of the poorly refinable structural model *(4)* (*R* = 0.131; Table 1). Similar effects, though less extreme are observed in *(6)*, while in the case of *(3)* normal thermal motion but again questionable bond lengths are obtained. In each case the aromatic substituents behave normally. Difference Fourier syntheses reveal partial disorders, presumably because the asymmetric units contain a random mixture of both enantiomers ("enantiomeric disorder"[5]). No disorder effects are perceptible in the *exo-exo* derivative *(5)*, which crystallizes non-centrosymmetrically.

Table 1. Crystallographic data of the structure analyses: cell constants and intensities measured on four-circle diffractometers (N_{tot}, number of independent reflections measured); space groups of *(3)* and *(6)* assumed centrosymmetric; determination of the structure of *(4)* by direct, otherwise by vector methods; heavy atoms anisotropically refined with N_{ref} reflections [$F_0 > 4\sigma(F_0)$ for *(3)* and *(4)*, $F_0 > 3\sigma(F_0)$ for *(5)* and *(6)*], H atoms isotropically with additional exclusion of reflections with $\sin\theta/\lambda > 0.45$ Å^{-1} (H atoms of *(4)* not refined); conventional *R* values for the N_{ref} reflections.

	(3)	*(4)*	*(5)*	*(6)*
Formula	$C_{19}H_{20}N_2O_6$	$C_{20}H_{22}O_4$	$C_{19}H_{20}N_2O_6$	$C_{19}H_{21}NO_4$
M.p. [°C]	149	198	165	110
a [Å]	6.243(0)	9.759(1)	13.914(3)	6.111(1)
b	11.357(1)	11.677(1)	5.891(1)	11.757(2)
c	13.673(1)	14.803(1)	10.840(2)	11.861(2)
α [°]	66.72(1)	90	90	103.64(2)
β	85.70(1)	104.35(1)	101.54(1)	90.66(2)
γ	75.36(1)	90	90	91.35(2)
Space group, *Z*	$P\bar{1}$, 2	$P2_1/c$, 4	Pc, 2	$P\bar{1}$, 2
d_m, d_x [g cm^{-3}]	1.44, 1.435	1.32, 1.326	1.40, 1.420	1.31, 1.313
λ [Å]	1.5418 (CuKα)	1.5418 (CuKα)	0.71069 (MoKα)	0.71069 (MoKα)
$\sin\theta_{max}/\lambda$ [Å^{-1}]	0.61	0.63	0.64	0.64
N_{tot}, N_{ref}	3255, 2611	3630, 2515	1911, 1312	3569, 2025
R	0.074	0.131	0.030	0.065

Structure of Two Highly Strained Tetracyclododecanes[**]

By *Otto Ermer*[*]

More than 15 years ago *Winstein et al.* prepared a series of highly strained polycyclic hydrocarbons and attempted to interpret abnormally high CH stretching modes by means of very simple force field considerations[1]. These compounds also represent suitable candidates for testing the much more refined force field calculations presently in use. We report here on crystal structure analyses of derivatives of *endo-endo*- and *exo-exo*-tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodecane [*(1)* and *(2)*, resp.] and compare the results with force field calculations[2]. Compounds *(1)* and *(2)* consist of fused norbornane moieties[3] and display unusually large C—C—C angles as a result of non-bonded repulsions between H atoms. The two angles C(1)—C(2)—C(3) and C(6)—C(7)—C(8) in the *endo-endo* isomer *(1)* exceed the tetrahedral angle by about 18° (Fig. 1a, b).

[*] Dr. O. Ermer
Abteilung für Chemie der Universität
Universitätsstr. 150, D-4630 Bochum (Germany)

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

With respect to bond angles and torsion angles the *endo-endo*-tetracyclododecane framework in the crystals of *(3)* has, to a good approximation, C_2 symmetry—but without greatly deviating from the higher C_{2v} symmetry. In view of substituent and crystal packing effects the agreement with the results of the force field calculations (Fig. 1a, b) is not self-evident, since the calculated C_{2v} conformation (transition state between enantiomeric C_2 minima) is only 0.08 kcal·mol^{-1} richer in energy than the C_2 minimum. The lowering of symmetry leads to a favorably "staggered" arrangement of the four inner H atoms on C(4), C(5), C(9), and C(10), enabling a slight closing-up of these C atoms accompanied by a reduction of angle strain. The small energy difference between the C_2 and C_{2v} geometries is expressed by a calculated smallest vibrational frequency of only 63 cm^{-1} for the C_2 minimum. As expected, the atomic displacements of the respective normal coordinate point towards the C_{2v} transition state (Fig. 1e).

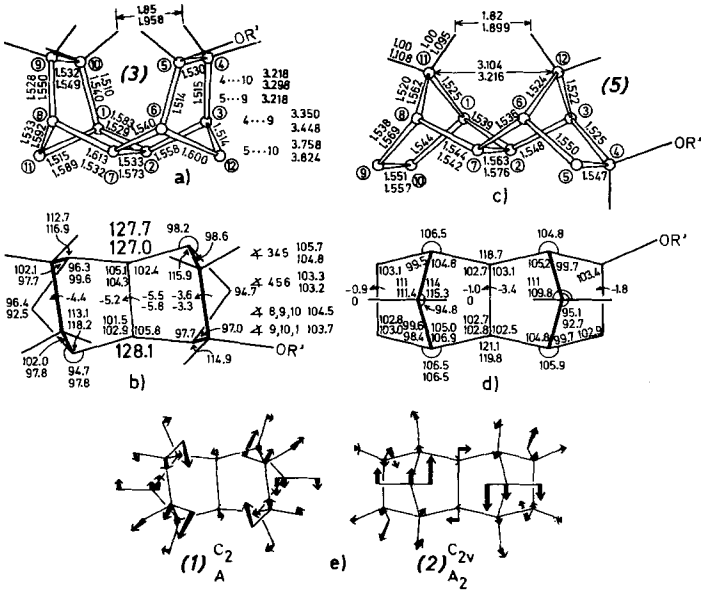


Fig. 1. a, c) Observed and calculated bond lengths [Å], and b, d) bond angles and torsion angles [°] for the tetracyclododecane moieties in *(3)* and *(5)*; the lower calculated values apply for gaseous *(1)* and *(2)* of symmetry C_2 and C_{2v}, respectively (only symmetry independent values given); estimated average standard deviations for *(5)*: CC 0.005, CH 0.04, HH 0.06 Å, CCC 0.3, CCH 2, HCH 3, CCCC 0.4°; observed geometrical parameters including H atoms represent C_2 and C_{2v}-averages, respectively; R' = 3,5-dinitrobenzoyl. e) Normal coordinates of the calculated smallest vibrational frequencies of *(1)* and *(2)* (63 and 69 cm^{-1}, respectively); atomic displacements drawn to scale apart from an arbitrary overall scale factor.

The *exo-exo*-tetracyclododecane framework in the crystals of *(5)* has, to a good approximation, C_{2v} symmetry. Once again the agreement with the calculations is remarkable, since a lowest frequency of 69 cm^{-1} is calculated for *(2)*, along whose normal coordinate (Fig. 1e) the distance between the two inner H atoms on C(11) and C(12) increases (corresponding frequency of norbornane 166 cm^{-1}). The deformation is similar to that in *(1)*, but the one inner H...H repulsion in *(2)* does not quite suffice for a lowering of symmetry.

The partial disorder in *(3)* does not allow a conclusive discussion of the geometric parameters in the *endo-endo*-tetracyclododecane skeleton. For example, the bond lengths C(3)—C(12) and C(6)—C(12), which are expected to be similar, differ by 0.086 Å. On the other hand, there is good agreement between the particularly interesting widely opened angles C(1)—C(2)—C(3) and C(6)—C(7)—C(8) with values of 127.7 and 128.1°, respectively, and the calculated value 127.0° (Fig. 1a, b). The angle deformation potentials of our force field are simple quadratic functions. As in the case of C—C=C angles[6] it would appear that also at sp^3 C-atoms harmonic potentials can be applied to the description of angle opening up to the high value of *ca.* 18°. Final clarification should be provided by the planned study of optically active derivatives of *(1)*, whose crystal structures we expect to be ordered.

The shortest inner H...H distances in *(3)* are 1.85 Å (C_2-average; Fig. 1a, b; calculated for *(1)*: 1.958 Å; also the more accurately observed distances C(4)...C(10) and C(5)...C(9) are shorter than calculated). *Winstein et al.* roughly estimated the very small value of 1.58 Å for *(1)* in order to explain an abnormally high νCH band at 3031 cm^{-1}[1]. We calculate 2976 cm^{-1} for the highest vibrational frequency of *(1)*. The above mentioned short H...H distances decrease markedly along the respective normal coordinate. The same applies for the normal coordinate of the highest calculated CH_2 angle deformation frequency of 1571 cm^{-1} (mainly deformation of the CH_2—CH_2 groups; corresponding frequency in norbornane 1465 cm^{-1}).

The results for the ordered crystals of *(5)* enable a more informative comparison with the calculations than in the case of *(3)*. The angles C(1)—C(2)—C(3) and C(6)—C(7)—C(8) with values of 118.7° and 121.1° are not opened to the extent they are in *(3)* (Fig. 1c, d; calculated for *(2)* 119.8°). The smallest inner H...H distance is 1.82 Å and again is shorter than the calculated value (1.899 Å; estimated[1] 1.50 Å). The same applies for the very short distance C(11)...C(12) of 3.104 Å. As for *(1)*, the observed highest vibrational frequency of 3052 cm^{-1}[1] is larger than our calculated value of 3007 cm^{-1}. The respective normal coordinate has similar character as in *(1)*, *i.e.* the two inner C—H bonds at C(11) and C(12) stretch synchronously. The largest CH_2 deformation frequency is calculated to be very high, 1686 cm^{-1} (the normal coordinate is characterized by simultaneous opening of the two H—C—H angles at C(11) and C(12) accompanied by substantial shortening of the inner H...H distance; analogous frequency of norbornane 1532 cm^{-1}).

The C—C bond lengths calculated for *(2)* are not in complete agreement with those observed in *(5)*. The C—C bonds emanating from C(11) and C(12) in *(5)* are on average 0.04 Å shorter than calculated for *(2)*, while the CCC angles at these atoms are somewhat larger (Fig. 1c, d). The four measured bond lengths of type C(1)—C(2) are also systematically shorter than calculated, albeit to a lesser extent. Apparent bond shortening by strong thermal motion can essentially be ruled out. Similarly as in norbornane the C—C bond lengths in *(1)* and *(2)* depend strongly on "stretch-bend" cross terms[3]. However, calculations with modified such terms did not lead to satisfactory results, so that further investigations are necessary which also should include experiments for a more accurate determination of the hydrogen positions. The comparison of the experimental findings with the partly deviating calculated results is important in a future re-optimization of our force field.

Received: August 11, 1977 [Z 827 IE]
German version: Angew. Chem. 89, 833 (1977)

CAS Registry numbers:
(1), 53862-33-2; *(2)*, 58865-53-5; *(3)*, 64550-39-6; *(4)*, 64490-42-2; *(5)*, 64490-41-1; *(6)*, 64490-40-0

[1] *D. Kivelson, S. Winstein, P. Bruck, R. L. Hansen*, J. Am. Chem. Soc. *83*, 2938 (1961).
[2] Force field and method of calculation: *O. Ermer, S. Lifson*, J. Am. Chem. Soc. *95*, 4121 (1973); *O. Ermer*, Struct. Bonding *27*, 161 (1976).
[3] Calculations on norbornane systems: *O. Ermer*, Tetrahedron *30*, 3103 (1974).
[4] I thank Dr. *D. Lenoir*, Munich, for preparing the tetracyclododecanols (R = OH) used as educts in these studies, Dr. *M. Draeger*, Mainz, and Dr. *C. Krüger*, Mülheim, for the intensity measurements, and *K. P. Schick* for work on the structure of *(4)*. The crystallographic calculations were carried out with the program system SHELX (*G. M. Sheldrick*, unpublished).
[5] *C. Altona, M. Sundaralingam*, Acra Crystallogr. *B28*, 1806 (1972).
[6] *O. Ermer*, Angew. Chem. *89*, 665 (1977); Angew. Chem. Int. Ed. Engl. *16*, 658 (1977).

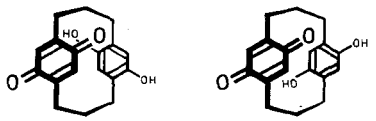
Diastereoisomeric [3.3]Paracyclophane Quinhydrones[1]

By *Heinz A. Staab* and *Claus P. Herz*[*]

Considerable differences in charge-transfer (CT) interactions have become apparent on comparing diastereomeric quinhy-

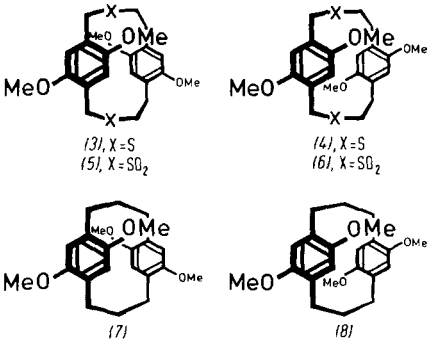
[*] Prof. Dr. H. A. Staab, Dr. C. P. Herz
Max-Planck-Institut für medizinische Forschung, Abteilung Organische Chemie
Jahnstrasse 29, D-6900 Heidelberg (Germany)

drones and other donor-acceptor systems of the [2.2]paracyclophane series[2]. Due to the strong deviations from ring planarity and the short transannular distances in [2.2]paracyclophanes, these results give only limited evidence for the orientation dependence of CT interactions in regular CT complexes. Donor-acceptor cyclophanes of the [3.3]paracyclophane series are better models for intramolecular simulation of normal CT interactions since their donor and acceptor units are almost planar and the distance between them (around 3.2 Å) is closer to the donor-acceptor distance in CT complexes. We report here the syntheses of the two diastereomeric [3.3]paracyclophane quinhydrones *(1)*/*(2)* and a comparison of their CT absorptions.



(1) *(2)*

6,9,16,19-Tetramethoxy-2,13-dithia[4.4]paracyclophane was obtained by cyclization of 1,4-bis(bromoethyl)-2,5-dimethoxybenzene[3] with the disodium salt of 1,4-bis(mercaptomethyl)-2,5-dimethoxybenzene[2] [*tert*-butanol/ethanol (1:1), dilution principle, 65% yield, ratio of diastereomers *(3)* and *(4)* about 1:1[4]]. Oxidation of the *(3)*/*(4)* mixture (3-chloroperbenzoic acid, chloroform, 24 h, 20°C, 90%) yielded the corresponding disulfones *(5)*/*(6)* which, on gas phase pyrolysis[5] (600°C, 0.01 torr), afforded the tetramethoxy[3.3]paracyclophanes *(7)* and *(8)* (ratio 2:1, total yield 40%)[6] together with the compounds *(12)* and *(13)* mentioned below. The separation of the diastereomers *(7)* and *(8)* was achieved by fractional crystallization from *n*-hexane. *(7)*[7]: m.p. 104–105°C (from ethanol); ^{1}H-NMR ($CDCl_3$): δ = 1.8—3.2 (m, 12H, methylene), 3.71 (s, 12H, methoxy), 6.40 (s, 4H, aromatic); *(8)*[7]: m.p. 224—225°C (from *n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 1.6—3.3 (m, 12H, methylene), 3.66 (s, 12H, methoxy), 6.21 (s, 4H, aromatic). The assignment to the pseudo-*ortho*-structure *(7)* and the pseudogeminal structure *(8)*, respectively, is based on the ratio of yields, and on the differences in the melting points and δ-values for the aromatic protons (cf. [2]).

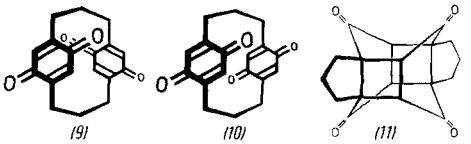


(3), X = S
(5), X = SO_2

(4), X = S
(6), X = SO_2

(7) *(8)*

By ether cleavage of *(7)* with methylmagnesium iodide (25 min, 170°C, under argon) and subsequent oxidation of the tetrahydroxy[3.3]paracyclophane with lead(IV) acetate (acetic acid, 10 min, 55°C) pseudo-*ortho*-[3.3](2,5)-*p*-benzoquinonophane *(9)*[7] was obtained [pale yellow crystals, m.p. 264—266°C (dec.), 72% yield; ^{1}H-NMR ($CDCl_3$): δ = 1.9—3.1 (m, 12H, methylene), 6.29 (s, 4H, ring). Analogously, ether cleavage of compound *(8)* and subsequent lead(IV) acetate oxidation yielded pseudogeminal [3.3](2,5)-*p*-benzoquinonophane *(10)*[7] [yellow crystals, dec. >300°C; 65% yield; ^{1}H-NMR ($CDCl_3$): δ = 1.5—3.3 (m, 12H, methylene), 6.46 (d, *J* = 1.5 Hz, 4H, ring)]. The assignment of the diastereomers *(9)* and *(10)*, based on that of *(7)* and *(8)*, is confirmed by the photochemistry of these compounds: on irradiation (solid state, 300 W Osram Ultra-Vitalux) *(10)* underwent almost complete conversion within minutes into an isomer which was obtained from dioxane as colorless crystals (dec. >250°C; 83% yield). According to ^{1}H-NMR [in $CDCl_3$: δ = 1.6—2.2 (m, 12H, methylene), 3.32 (s, 4H, methine), no olefinic or aromatic absorptions], IR, and UV spectra this compound has the cage structure *(11)* resulting from *(10)* by double intramolecular cycloaddition of the two pairs of coplanar quinone double bonds. In agreement with the results obtained for the [2.2](2,5)-*p*-benzoquinonophanes[8] the pseudo-*ortho*-compound *(9)* does not undergo intramolecular cycloadditions due to the unfavorable orientation of the double bonds.



(9) *(10)* *(11)*

Catalytic hydrogenation of *(9)* (Pd/C, dioxane, 20°C) yielded the quinhydrone *(1)*[7] as brown microcrystals, m.p. (dec.) 272—274°C (from benzene/acetone), yield 74%; MS: M^+ calc. for $C_{18}H_{18}O_4$ 298.1205, obs. 298.1212; ^{1}H-NMR ([D_6]-DMSO): δ = 1.6—3.0 (m, 12H, methylene), 6.10 (s, 2H, ring), 6.26 (s, 2H, ring), 8.52 (s, 2H, hydroxyl); IR (KBr): ν(C=O) 1638, ν(OH) 3400 cm^{-1}. Under the same conditions the pseudogeminal quinhydrone *(2)*[7] was obtained in 67% yield from *(10)*: glittering black crystals (from dioxane), dec. >300°C; MS: M^+ calc. for $C_{18}H_{18}O_4$ 298.1205, obs. 298.1212; ^{1}H-NMR ([D_6]-DMSO): δ = 1.4—3.0 (m, 12H, methylene), 5.96 (s, 2H, ring), 6.17 (s, 2H, ring), 8.54 (s, 2H, hydroxyl); ν(C=O) 1620, ν(OH) 3230 cm^{-1}.

The electronic spectra of *(1)* and *(2)* (Fig. 1) resemble those of the respective quinhydrones of the [2.2]paracyclophane series. The differences in the absorptions due to the different donor-acceptor orientations are, however, much more pronounced for the diastereomer pair *(1)*/*(2)*: Whereas a strong CT absorption is observed for *(2)* in the 350—630 nm region [λ_{max} = 462 nm (ε = 3210)], *(1)* shows only a weak absorption shoulder around 500 nm with ε = 105; however, in contrast to *(2)*, a strong CT absorption at λ_{max} = 346 nm (ε = 1904) is found for *(1)*.

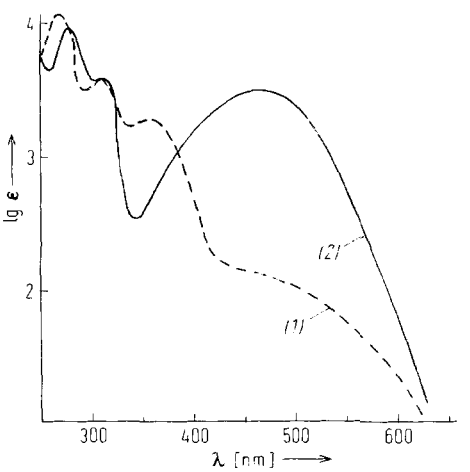
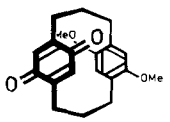
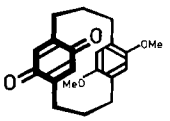


Fig. 1. Electronic spectra of the [3.3]paracyclophane quinhydrones *(1)* and *(2)* (in dioxane).



(12)



(13)

The dimethyl ethers (12) and (13), corresponding to (1) and (2), were formed unexpectedly (5% yield each) on gas phase pyrolysis of (5)/(6) and were separated by chromatography (silica, benzene): (12)[7] forms dark red needles (from methylcyclohexane), m.p. 202—203 °C; MS: M^+ calc. for $C_{20}H_{22}O_4$ 326.1518, obs. 326.1522; ^{1}H-NMR ($CDCl_3$): δ = 1.8—3.3 (m, 12H, methylene), 3.73 (s, 6H, methoxy), 6.16 (s, 2H, ring), 6.29 (s, 2H, ring). (13)[7] crystallizes from methylcyclohexane as brick-red needles, m.p. 218—219 °C; MS: M^+ calc. for $C_{20}H_{22}O_4$ 326.1518, obs. 326.1522; ^{1}H-NMR ($CDCl_3$): δ = 1.65—3.3 (m, 12H, methylene), 3.67 (s, 6H, methoxy), 6.00 (s, 2H, ring), 6.35 (s, 2H, ring). The electronic spectra of (12) and (13) agree very well with those of the respective quinhydrones (1) and (2): in the 350—650 nm region (13) shows a strong CT absorption [λ_{max} = 475 nm (ε = 3000), in chloroform] having about 30-fold greater intensity than (12) for which, on the other hand, an additional CT absorption at shorter wave-length is observed [λ_{max} = 367 nm (ε = 1740), shoulder 500 nm (ε = 100), in chloroform]. For (13) it was shown by the concentration independence (10^{-3}—10^{-5} M) that intermolecular donor-acceptor interactions do not contribute detectably to the CT absorption.

Comparison of the electronic spectra of the pairs of diastereomers (1)/(2) and (12)/(13) reveals an even stronger orientation dependence of the CT absorption for the quinhydrones of the [3.3]paracyclophane series than was found in the [2.2]paracyclophane group. For the reasons mentioned in the introduction, we think that the results now obtained provide a general description of the orientation dependence of CT interactions in donor-acceptor complexes of the quinhydrone type.

Received: September 26, 1977 [Z 843a IE]
German version: Angew. Chem. 89, 839 (1977)

CAS Registry numbers:
(1), 64474-72-2; (2), 64425-70-3; (3), 64519-32-0; (4), 64425-69-0; (5), 64519-31-9; (6), 64425-68-9; (7), 64425-67-8; (8), 64519-30-8; (9), 64474-71-1; (10), 64425-66-7; (11), 64425-65-6; (12), 64474-70-0; (13), 64425-64-5; 1,4-bis(2-bromoethyl)-2,5-dimethoxybenzene, 64425-63-4; 1,4-bis(mercaptomethyl)-2,5-dimethoxybenzene, disodium salt, 59416-85-2; tetrahydroxy-[3.3]paracyclophane, 64440-84-2

[1] Orientation effects on charge-transfer interactions, Part 13.—Part 12: *C. P. Herz, H. A. Staab*, Angew. Chem. *89*, 407 (1977); Angew. Chem. Int. Ed. Engl. *16*, 394 (1977).

[2] *W. Rebafka, H. A. Staab*, Angew. Chem. *85*, 831 (1973); *86*, 234 (1974); Angew. Chem. Int. Ed. Engl. *12*, 776 (1973); *13*, 203 (1974); Chem. Ber. *110*, 3333 (1977); *H. A. Staab, C. P. Herz, H.-E. Henke, ibid. 110*, 3351 (1977); *H. A. Staab, H. Haffner, ibid. 110*, 3358 (1977); *H. A. Staab, V. Taglieber, ibid. 110*, 3366 (1977); *D. Schweitzer, K. H. Hausser, V. Taglieber, H. A. Staab*, Chem. Phys. *14*, 183 (1976); cf. the MO calculations of *H. Vogler, G. Ege, H. A. Staab*, Tetrahedron *31*, 2441 (1975); Mol. Phys. *33*, 923 (1977).

[3] Diethyl 2,5-dimethoxybenzene-1,4-diacetate was treated with $LiAlH_4$ in tetrahydrofuran to give 1,4-bis(2-hydroxyethyl)-2,5-dimethoxybenzene (m.p. 130 °C, 87%) which with phosphorus tribromide/benzene yielded 1,4-bis(2-bromoethyl)-2,5-dimethoxybenzene (m.p. 122—123 °C, 80%) (*V. Taglieber*, Ph. D. Thesis, Univ. Heidelberg 1976).

[4] Chromatography (silica/chloroform) of the (3)/(4) mixture gave the two diastereomers in a pure state (m.p. 185 °C and 216 °C); the assignment to (3) and (4) has not yet been possible.

[5] *M. Haenel, H. A. Staab*, Tetrahedron Lett. *1970*, 3585; Chem. Ber. *106*, 2190, 2203 (1973); *M. Haenel, A. Flatow, V. Taglieber, H. A. Staab*, Tetrahedron Lett. *1977*, 1733.

[6] Starting from 7,10,18,21-tetramethoxy-2,15-dithia[5.5]paracyclophane the two diastereomeric 6,9,16,19-tetramethoxy[4.4]paracyclophanes (m.p. 179—180 °C and 217—218 °C) were obtained analogously; they are precursors of the corresponding [4.4]paracyclophane quinhydrones (*D. Johnston, B. Starker, C. P. Herz, H. A. Staab*, unpublished).

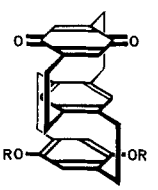
[7] Elemental analyses and spectroscopic data are in agreement with the structures suggested.

[8] *H. Irngartinger, R.-D. Acker, W. Rebafka, H. A. Staab*, Angew. Chem. *86*, 705 (1974); Angew. Chem. Int. Ed. Engl. *13*, 674 (1974).

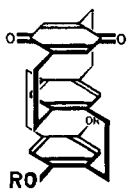
Indirectly Transmitted Charge-Transfer Interactions: Multilayered [2.2]Paracyclophane Quinhydrones[1]

By *Heinz A. Staab, Udo Zapf*, and *Anneliese Gurke*[*]

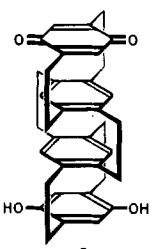
Intramolecular fixation of donor-acceptor systems in the rigid skeleton of cyclophanes led to information regarding orientation and distance dependences of charge-transfer (CT) interactions which is inaccessible by the investigation of regular intermolecular CT complexes[1,2]. Using the same concept an attempt was made to answer the question whether an indirect transmission of CT interactions occurs if donor and acceptor are not in direct spatial contact but are separated by intercalated aromatic π-electron systems. For this purpose donor-acceptor cyclophanes were to be synthesized where the donor and acceptor units are in the external positions of a multilayered [2.2]paracyclophane. Interesting representatives of this group of compounds would be quinhydrones of triple- or quadruple-layered [2.2]paracyclophanes like (1) or (5). As in the case of quinhydrones of simple [2.2]- and [3.3]paracyclophanes[1,2a], for these multilayered quinhydrones pairs of stereoisomers with different donor-acceptor orientation are to be expected ((1)/(2), for example). The electronic spectra of these compounds were expected to provide evidence about the problem of indirect transmission of CT interactions and its orientation dependence.



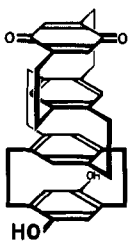
(11), R = H
(3), R = Me



(2), R = H
(4), R = Me



(5)

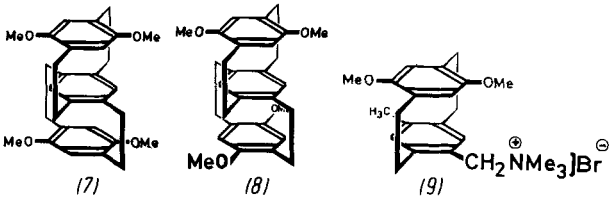


(6)

As in the previous syntheses of cyclophane quinhydrones[1,2a,3], the corresponding tetramethoxy compounds (7) and (8) were key intermediates for the preparation of (1) and (2). By analogy with the syntheses of other multilayered cyclophanes[4], crossed 1,6-Hofmann elimination of (2,5-dimethoxy-4-methylbenzyl)trimethylammonium bromide[2b] and pseudo-*ortho*-4,7-dimethoxy-12-methyl-15-trimethylammoniomethyl[2.2]paracyclophane bromide (9) seemed to be a suitable approach for the syntheses of (7) and (8). The reaction of pseudo-*ortho*-4,7-dimethoxy-12,15-dimethyl[2.2]-

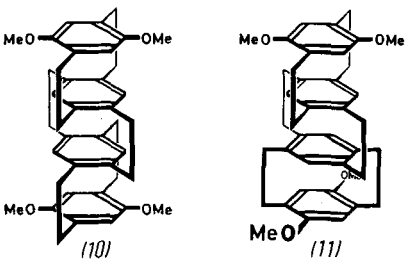
[*] Prof. Dr. H. A. Staab, Dipl.-Chem. U. Zapf, A. Gurke
Max-Planck-Institut für medizinische Forschung
Abteilung Organische Chemie
Jahnstrasse 29, D-6900 Heidelberg (Germany)

paracyclophane[5] with *N*-bromosuccinimide (90% of the equivalent amount, CCl_4) resulted in pseudo-*ortho*-4-bromomethyl-7-methyl-12,15-dimethoxy[2.2]paracyclophane which yielded *(9)*[6] (dec. >230°C, about 50% overall yield) with trimethylamine in ether. Equimolar amounts of *(9)* and (2,5-dimethoxy-4-methylbenzyl)trimethylammonium bromide were converted into the hydroxides (silver oxide, water) which were heated 12 h in boiling xylene (water separator, addition of phenothiazine). The reaction product separated from insoluble polymers yielded, by chromatography (silica, benzene), a mixture of the two diastereomeric tetramethoxy[2.2]paracyclophanes[2a,b] and the quadruple-layered tetramethoxy[2.2]paracyclophanes *(10)* and *(11)* (total yields 14,5%) and subsequently in 15.5% yield *(7)*/*(8)* which were separated by fractional crystallization from acetone or by chromatography (silica, benzene, *n*-hexane, 3:2): *(7)*[6] forms colorless needles, m.p. 204—205°C (from methanol), *(8)*[6] colorless needles, m.p. 226—228°C (from acetone). The assignment to *(7)* and *(8)*, respectively, is possible on the basis of ^{1}H-NMR: Whereas for the pseudo-*ortho*/pseudo-*ortho* linked *(7)* all four methoxy groups and all four protons of the two external rings are equivalent, this is not true for *(8)* since here the pseudo-*ortho*/pseudogeminal linkage leads for the methoxy groups and the protons of the two external rings to different orientations with regard to the methylene bridges between the neighboring [2.2]paracyclophane unit. Indeed, for *(8)* a doubling of the ^{1}H-NMR signals for the methoxy groups and the protons for the external rings is observed: *(7)*: $\delta = 2.15$—3.6 (m, 16H, methylene), 3.32 (s, 12H, methoxy), 5.51 (s, 4H, external ring), 6.13 (s, 2H, internal ring); *(8)*: $\delta = 2.1$—3.65 (m, 16H, methylene), 3.30 (s, 6H, methoxy), 3.33 (s, 6H, methoxy), 5.45 (s, 2H, external ring), 5.50 (s, 2H, external ring), 5.61 (s, 2H, internal ring); in C_6D_6[7] (80 MHz).



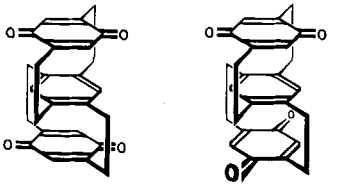
(7) *(8)* *(9)*

The quadruple-layered tetramethoxy[2.2]paracyclophanes *(10)*/*(11)* were also obtained when *(9)* alone was subjected to 1,6-Hofmann elimination (14% yield). The separation of the diastereomers which would be necessary for the syntheses of the quinhydrones *(5)* and *(6)* has not yet proved possible by chromatography because of the extremely similar properties of *(10)* and *(11)*; a partial separation has been achieved by fractional crystallization from acetone/carbon tetrachloride (3:1).



(10) *(11)*

Ether cleavage of *(7)* with methylmagnesium iodide (1 h, 160—190°C, under nitrogen) and subsequent oxidation with silver oxide in acetone led, after chromatography on silica from chloroform, in 60% yield to the benzoquinonophane *(12)*[6]: orange needles, dec. >250°C; MS: M^+ calc. for $C_{26}H_{22}O_4$ 398.1518; obs. 398.1517; ^{1}H-NMR ($CDCl_3$): $\delta = 2.0$—3.3 (m, 16H, methylene), 5.70 (s, 4H, quinonoid), 6.26 (s, 2H, internal ring). Analogously, compound *(8)* gave the diastereomeric benzoquinonophane *(13)*[6]: orange needles, dec. >260°C; yield 40%; MS: M^+ calc. for $C_{26}H_{22}O_4$ 398.1518, obs. 398.1517; ^{1}H-NMR ($CDCl_3$): $\delta = 2.05$—3.15 (m, 16H, methylene), 5.69 (s, 2H, quinone), 5.74 (s, 2H, quinone), 6.18 (s, 2H, internal ring). In contrast to the preparation of the simple [2.2]- and [3.3]paracyclophane quinhydrones[1,2], catalytic hydrogenation of *(12)* and *(13)* gave mixtures of the tetrahydroxy compound and unreacted benzo-



(12) *(13)*

quinonophane—probably due to the smaller stabilization of the quinhydrone stage—together with quinhydrone which could not yet be isolated from these mixtures.

The dimethyl ethers *(3)* and *(4)* of the quinhydrones *(1)* and *(2)*, however, were obtained—obviously due to incomplete demethylation—as by-products (*ca.* 2% yields) of the syntheses of *(12)* and *(13)*, respectively, and were separated by chromatography (silica, chloroform): *(3)* forms red needles, m.p. 224—226°C (from methanol); MS: M^+ calc. for $C_{28}H_{28}O_4$ 428.1987, obs. 428.1960; ^{1}H-NMR ($CDCl_3$): $\delta = 2.0$—3.5 (m, 16H, methylene), 3.61 (s, 6H, methoxy), 5.60 (s, 2H, external ring), 5.66 (s, 2H, external ring), 6.16 (s, 2H, internal ring); *(4)* forms dark red crystals (from ethanol, dec. >260°C); MS: M^+ calc. for $C_{28}H_{28}O_4$ 428.1987, obs. 428.1981; ^{1}H-NMR ($CDCl_3$): $\delta = 1.8$—3.5 (m, 16H, methylene), 3.58 (s, 6H, methoxy), 5.56 (s, 2H, external ring), 5.65 (s, 2H, external ring), 5.85 (s, 2H, internal ring).

In the 350—550 nm region *(3)* and *(4)* show a broad CT absorption [*(3)*: $\lambda_{max} = 437$ nm ($\varepsilon = 2270$); *(4)*: $\lambda_{max} = 415$ ($\varepsilon = 2010$), chloroform]. Since this band is concentration-independent it must be due to an intramolecular CT transition which in "vertical conjugation" is transmitted through the π-system intercalated between donor and acceptor[8]. As is shown by comparison of *(3)* and *(4)*, however, the orientation dependence of CT absorptions, observed for simple donor-acceptor [2.2]paracyclophanes, is almost completely lost in this type of CT interactions.

Received: September 26, 1977 [Z 843b IE]
German version: Angew. Chem. 89, 841 (1977)

CAS Registry numbers:
(1), 64474-67-5; *(2)*, 64474-66-4; *(3)*, 64474-65-3; *(4)*, 64425-54-3; *(5)*, 64474-69-7; *(6)*, 64425-62-3; *(7)*, 64425-61-2; *(8)*, 64519-29-5; *(9)*, 64425-60-1; *(10)*, 64519-28-4; *(11)*, 64425-59-8; *(12)*, 64474-68-6; *(13)*, 64425-58-7; (2,5-dimethoxy-4-methylbenzyl)trimethyl ammoniumbromide, 64425-57-6; pseudo-*o*-4,7-dimethoxy-12,15-dimethyl[2.2]paracyclophane, 64425-56-5; pseudo-*o*-4-bromomethyl-7-methyl-12,15-dimethoxy[2.2]paracyclophane, 64425-55-4

[1] Orientation dependence of charge-transfer interactions, Part 14.—Part 13: *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 839 (1977); Angew. Chem. Int. Ed. Engl. *16*, 799 (1977).

[2] a) *W. Rebafka, H. A. Staab*, Angew. Chem. *85*, 831 (1973); *86*, 234 (1974); Angew. Chem. Int. Ed. Engl. *12*, 776 (1973); *13*, 203 (1974); Chem. Ber. *110*, 3333 (1977); b) *H. A. Staab, C. P. Herz, H.-E. Henke*, Chem. Ber. *110*, 3351 (1977); c) *H. A. Staab, H. Haffner*, Tetrahedron Lett. *1974*, 4397; Chem. Ber. *110*, 3358 (1977); *H. A. Staab, V. Taglieber, ibid. 110*, 3366 (1977); *D. Schweitzer, K. H. Hausser, V. Taglieber, H. A. Staab*, Chem. Phys. *14*, 183 (1976); d) cf. MO calculations of *H. Vogler, G. Ege, H. A. Staab*, Tetrahedron *31*, 2441 (1977); Mol. Phys. *33*, 923 (1977).

[3] *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 406, 407 (1977); Angew. Chem. Int. Ed. Engl. *16*, 392, 394 (1977).
[4] *D. T. Longone, H. S. Chow*, J. Am. Chem. Soc. *86*, 3898 (1964); *92*, 994 (1970); *T. Otsubo, S. Mizogami, I. Otsubo, Z. Tozuka, A. Sakagami, Y. Sakata, S. Misumi*, Bull. Chem. Soc. Japan *46*, 3519 (1973).
[5] *C. P. Herz*, unpublished.
[6] Analyses, molecular weights, and spectral data are in agreement with the structures claimed.
[7] This doubling of signals is not observed in $CDCl_3$ and CCl_4 (80 MHz).
[8] Cf. *H. Tatemitsu, T. Otsubo, Y. Sakata, S. Misumi*, Tetrahedron Lett. *1975*, 3059.

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Thioethers (sulfides) have attracted increasing interest as reagents for organic syntheses in recent years, for they are stable towards acids and bases, can form sulfur-stabilized carbanions, and can be transformed into compounds having different substitution patterns by reductive or oxidative cleavage of the C—S bond. A comprehensive survey of methods of synthesis of thioethers, the physical and chemical properties of these compounds, and their reactions has been written by *W. Tagaki*. [Sulfides in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 231—302; 210 references]

[Rd 966 IE]

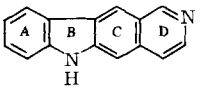
Control at the level of substrate supply in the synthesis of phenylpropanoids in plants is proposed by *U. Margna*. This offers an alternative to regulation at the level of enzyme activity. The activity of the key enzyme, phenylalanine ammonia lyase, often bears no relationship to the accumulation of phenylpropanoids; the actual enzyme activity usually exceeds by far that which is necessary for the measured rate of synthesis. Addition of exogenous phenylalanine also causes the synthesis of phenylpropanoids to increase. Protein metabolism and the synthesis of flavonoids and cinnamic acid derivatives in plants are however in a well balanced ratio. [Control at the Level of Substrate Supply—an Alternative in the Regulation of Phenylpropanoid Accumulation in Plant Cells. Phytochemistry *16*, 419—426 (1977); 120 references]

[Rd 982 IE]

The coordination of lipid degradation with the Krebs cycle is discussed by *P. W. Hochachka, J. R. Neely*, and *W. R. Driedzic*. The essential links between these two metabolic pathways are their mutual requirements for coenzyme A, NAD^+ and the oxidation capacity of $FADH_2$. The cell can thus maintain a precise coordination between fatty acid activation in the cytosol, the β-oxidation of fatty acids in the mitochondria, and the complete oxidation of acetyl coenzyme A to CO_2 *via* the Krebs cycle for a wide range of energy requirements and oxygen supply. [Integration of Lipid Utilization with Krebs Cycle Activity in Muscle. Federation Proc. *36*, 2009—2014 (1977); 57 references]

[Rd 983 IE]

The synthesis of 6*H*-pyrido[4,3-*b*]carbazole *(1)* and its derivatives is treated in a review by *M. Sainsbury*. *(1)* is the basic molecular framework of the alkaloids (*e.g.* ellipticin, olivacin, guatambin) which are found in the plant family *Apocyanaceae*. These substances are of biogenetic interest and their derivatives seem to be promising drugs for the treatment of cancer. The already known routes for the synthesis of the skeleton *(1)*

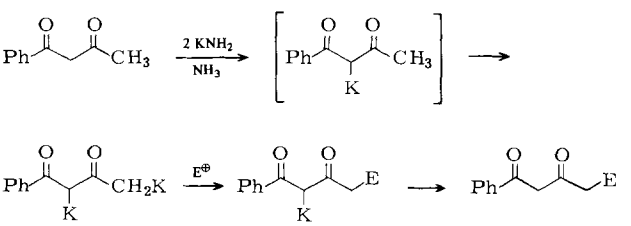


(1)

can be divided into three groups: 6-isoquinolone derivatives (rings C and D) are reacted with arylhydrazines according to the Fischer indole synthesis to give arylhydrazones which are subsequently cyclized. The framework *(1)* is synthesized from carbazoles (rings A, B and C) by *Vilsmeier* formylation, condensation with 2,2-diethoxyethylamine, hydrogenation, cyclization, and dehydrogenation. Other syntheses start with indoles, *e.g.* gramin derivatives, (rings A and B) which are condensed with substituted pyridines. Derivatives of *(1)* are formed by cyclization (ring C). [The Synthesis of 6*H*-Pyrido[4,3-*b*]carbazoles. Synthesis *1977*, 437—448; 33 references]

[Rd 984 IE]

Di- and polyalkali metal derivatives of organic compounds with functional groups are treated in a review by *E. M. Kaiser, J. D. Petty*, and *P. L. A. Knutson*. Di- and polyalkali metal derivatives, which give valuable compounds with electrophilic reagents, are formed from numerous organic compounds by the action of two or more equivalents of strong alkali metal bases (alkali metal amides, organolithium compounds). The



multiple metalation proceeds according to the following scheme: metalation of the most strongly acidic proton to give a weakly nucleophilic intermediate, subsequent metalation of a second proton producing a more strongly nucleophilic compound which usually reacts regiospecifically in the condensation with the electrophile at this anionic center. [Di- und Polyalkali Metal Derivatives of Heterofunctionally Substituted Organic Molecules. Synthesis *1977*, 509—550; 306 references]

[Rd 985 IE]

Mechanisms of polymerizations in the solid state are discussed by *G. Wegner* for the example of the four-center polymerization of diolefins, which lead to polymers with cyclobutane rings in the main chain, and the polymerization of diacetylenes. Both processes afford highly crystalline products, and in some cases it is possible to obtain macroscopic crystals practically devoid of defects. The reaction course as well as the crystal and molecular structure of the product depend upon the packing of the monomer molecules in the starting crystal. [Solid-State Polymerization Mechanisms. Pure Appl. Chem. *49*, 443—454 (1977); 36 references]

[Rd 971 IE]

Literature available about di- and polysulfides is extremely extensive. A survey of this field by *L. Field* lists 282 publications to have appeared up to 1973. About one third of them are review articles. Papers on disulfides and their oxidation products predominate, but surprisingly few of them are concerned with disulfides of biological importance. S—S bridges are of importance for the spatial structure, and hence for the physiological activity, of numerous proteins. The report deals with the physical properties and reactions of disulfides and methods for the synthesis of these compounds. [Disulfides and Polysulfides in *S. Oae:* Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 303—382; 282 references]

[Rd 967 IE]

The photolysis of saturated alcohols, ethers, and amines is considered in a survey by *C. von Sonntag* and *H.-P. Schuchmann*. These compounds are transparent in the near ultraviolet, only beginning to show significant absorption (except the amines) in the region of 200 nm. Although this spectral region is readily accessible experimentally, only little is known about the photolytic behavior of saturated alcohols, ethers, and amines, and the present report was written with the intention of stimulating research in this area. [Photolysis of Saturated Alcohols, Ethers, and Amines. Adv. Photochem. *10*, 59—145 (1977); 195 references]

[Rd 977 IE]

Protein inhibitors of α-amylase in wheat are reviewed by *V. Buonocore, T. Petrucci,* and *V. Silano*. Their localization, molecular properties, and biological significance are discussed. Further topics are their specificities of inhibition, the structural requirements necessary for an interaction between the enzyme and the inhibitor, and the significance of the presence of the inhibitors in foodstuffs. The article finally deals with the genetic aspects of inhibitor synthesis and the possibility of improving the nutritional value and insect resistance of wheat by the cultivation of new varieties. [Wheat Protein Inhibitors of α-Amylase. Phytochemistry *16*, 811—820 (1977); 87 references]

[Rd 980 IE]

The influence of drugs and hormones on lipolysis in heart is the subject of a report by *J. J. Lech, G. J. Jesmock,* and *D. N. Calvert*. In contrast to the lipase from adipose tissue, which has been shown to be directly influenced by cyclic AMP, hormonal control of the heart enzyme has so far only been indirectly inferred. The activation of lipolysis in heart muscle by hormones, drugs or physical exertion is thus possibly due to a mechanism which generally comes into action when endogenous substrates have to be used because of an increased energy requirement. [Effect of Drugs and Hormones on Lipolysis in Heart. Federation Proc. *36*, 2000—2008 (1977); 76 references]

[Rd 981 IE]

BOOK REVIEWS

Analysis with Ion-Selective Electrodes. By *P. L. Bailey*. Heyden, London—New York—Rheine 1976. 1st edit., xii, 228 pp., various figures and tables, bound, DM 43.50.

This is an interesting addition to the literature that has already appeared in this field, since it differs somewhat in its organization and in the selection of material from other comprehensive accounts of ion-selective electrodes. While it gives very exhaustive and clear information on all practical aspects, the theory must be said to be cut short to some extent. For example, a systematic presentation of potential-formation mechanisms would be welcome, and the beginner has to refer to other books in this field to understand the electrode processes.

The arrangement of the material is clear. In addition to sections on the general properties of ion-selective electrodes and on methods of measurement, each electrode type is treated in an independent chapter, the following classification having been selected: glass electrodes with the exception of pH electrodes, solid-state electrodes based on inorganic salts, electrodes based on organic ion exchangers and neutral complexing agents, and gas-sensitive electrodes. There is also a section on special types such as enzyme electrodes and tenside electrodes, and a detailed treatment of reference electrodes. Finally, general constructional principles are treated briefly and directions are given on the construction of ion-selective electrodes.

Since the book was conceived primarily as a practical introduction to the technique of potentiometric analysis, great value is placed on a critical account of electrode properties. This applies to the downright optimistic data published by many electrode manufacturers, to the various perturbing influence, and to the basic limits of sensible application of ion-selective electrodes. The term "selectivity" is treated as is customary in English-language literature: selectivity *coefficients* referred to specified conditions are used, and the value of selectivity *constants* for characterizing electrodes is fundamentally questioned. However, this concept is not undisputed.

In the measurement techniques, all methods including the continuous processes are described in real detail and the advantages and disadvantages of each are very realistically compared. This provides the beginner with a useful guide. In this connection a discussion is also given of the conditions under which ion-selective sensors, more sensitive than glass electrodes, can be used for the severe conditions of plant supervision.

Original papers up to 1975 have been taken into account and are abundantly cited, so that the book constitutes the most up to date literature review available at the present

time. It is this in particular that makes it valuable for an analyst already familiar with the field. For the beginner it is a useful practical introduction.

C. Harzdorf [NB 379 IE]

Handbook of Marine Science. Compounds from Marine Organisms. Vol. I. By *J. T. Baker* and *V. Murphy*. CRC Press, Inc., Cleveland 1976. 1st edit., 226 pp., bound, $ 29.95.

This book closes a large gap in the literature of this field. The authors review very comprehensively the investigations up to 1973 (445 references, 504 compounds isolated from marine organisms) and give tables showing molecular formulas, structural formulas, trivial names, and the biological activities of these compounds, arranged in order of increasing number of carbon atoms. This is followed by a section in which some of these compounds are discussed; here the compounds are arranged according to their structural characteristics. In these respects this book is valuable and the work that has gone into it must be applauded.

Unfortunately, it is impossible to avoid errors in a book of this kind. The reason for this is largely the long production time of three years; for example, the structural formula of saxitoxin has meanwhile been revised. There is also another shortcoming that should be avoided in the next edition: alongside the chemical classification it should be possible to find the substances according to the organism in which they occur (this is in fact most important for marine chemists and marine biologists). For example, on page 53 the constituents of the sponge *Phakellia flabellata* are mentioned and the relevant paper is cited in the bibliography. If, however, one wishes to work in reverse, *i.e.* to find what substances have been isolated from a given species, this appears to be impossible. One looks in vain in the index under "Phakellia"; under "Sponges" too there is nothing to be found, and yet pages have been devoted to sponge substances. The same is true for the keyword "Starfish" and the species names "Asterias" and "Acanthaster". Names are, however, given for species from which fewer substances have been isolated. Again, surugatoxin cannot be found under "S", but under "M", where it is included as a "mydriatic parasympatholytic agent"; the same situation occurs with tetrodotoxin, which is found under "H" ("hypotensive") and not under "T". This unreliable index considerably reduces the usefulness of the book which is a pity since so much trouble and labor has gone into it.

Nevertheless, the marine chemist will welcome the appearance of this Handbook; in spite of the above failings, its purchase will be worthwhile to all working in the field of marine chemistry.

Gerhard Habermehl [NB 384 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Treatise on Solid State Chemistry, Vol. 4: Reactivity of Solids. Edited by *N. B. Hannay*. Plenum Press, New York 1977. xvii, 721 pp., bound, $ 54.00.—ISBN 0-306-35050-5

Stereochemistry of Heterocyclic Compounds, Part 2: Oxygen, Sulfur, Mixed N, O, and S, Phosphorus Heterocycles. By *W. L. F. Armarego*. From the series "General Heterocyclic Chemistry Series". Edited by *E. C. Taylor* and *A. Weissberger*. John Wiley & Sons, New York 1977. xvii, 494 pp., bound, $ 54.00.—ISBN 0-471-03322-7

Organic Syntheses Via Metal Carbonyls, Vol. II. Edited by *I. Wender* and *P. Pino*. John Wiley & Sons, New York 1977. xiii, 742 pp., bound, $ 57.00.—ISBN 0-471-93367-8

Advances in Chemical Physics, Vol. XXXVI. Edited by *I. Prigogine* and *S. A. Rice*. John Wiley & Sons, New York 1977. ix, 541 pp., bound, $ 46.00.—ISBN 0-471-02274-8

Presse-Taschenbuch für Naturwissenschaft und Medizin 1977/78. Published by Boehringer Mannheim GmbH. Kroll-Verlag, Seefeld/Obb. 304 pp., flexible PVC, DM 25.—.

Viscosity & Diffusivity. A Predictive Treatment. By *J. H. Hildebrand*. John Wiley & Sons, New York 1977. xiv, 109 pp., bound, $ 12.00.—ISBN 0-471-03072-4

Metal-Ligand Interactions in Organic Chemistry and Biochemistry, Parts 1 and 2. Edited by *B. Pullman* and *N. Goldblum*. Vol. 9 of the series "The Jerusalem Symposia on Quantum Chemistry and Biochemistry". D. Reidel Publishing Company, Dordrecht/Boston 1977. Part 1: x, 396 pp., bound, $ 39.50—ISBN 90-277-0771-5; Part 2: viii, 400 pp., bound, $ 39.50.—ISBN 90-277-0754-5

Liquid Fuels From Coal. Edited by *R. T. Ellington*. Academic Press, New York 1977. xvii, 273 pp., bound, $ 14.50.—ISBN 0-12-237250-6

Koordinations-chemische Katalyse organischer Reaktionen. By *J. Pracejus*. Volume 64 of the series "Technische Fortschrittsberichte". Edited by *H. Fürst*. Verlag Theodor Steinkopff, Dresden 1977. 287 pp., bound, ca. DM 43.—.

Modern Practice of Gas Chromatography. By *R. L. Grob*. John Wiley & Sons, New York 1977. xvi, 654 pp., bound, $ 28.00.—ISBN 0-471-01564-4

Foreign Compound Metabolism in Mammals, Vol. 4. Senior Reporter: *D. E. Hathway*. The Chemical Society, London 1977. xiii, 411 pp., bound, £ 27.50.—ISBN 0-85186-038-9.—A volume in the series "Specialist Periodical Reports".

Chemistry and Physics of One-Dimensional Metals. Edited by *H. J. Keller*. From the series "NATO Advanced Study Institutes Series, Series B: Physics". Plenum Press, New York 1977. viii, 426 pp., bound, $ 54.00.—ISBN 0-306-35725-9

Diagnostik hämorrhagischer Diathesen. Edited by *A. Englhard* and *H. Lommel* in collaboration with *L. Róka* and *W. G. A. Ohler*. Volume 4 of the series "Methodische Fortschritte im medizinischen Laboratorium". Verlag Chemie, Weinheim 1977. 203 pp., bound, DM 58.—.—ISBN 3-527-25659-8

Semiempirical Methods of Electronic Structure Calculation, Part A: Techniques. Edited by *G. A. Segal*. Vol. 7 of the series "Modern Theoretical Chemistry". Edited by *W. H. Miller, H. F. Schaefer III, B. J. Berne*, and *G. A. Segal*. Plenum Press, New York 1977. xvii, 274 pp., bound, $ 39.50.—ISBN 0-306-33507-7

Synthetic Methods of Organic Chemistry, 31/1977 Yearbook. Edited by *W. Theilheimer*. S. Karger, Basel 1977. xvi, 621 pp., bound, DM 498.—.—ISBN 3-8055-2432-3

Chemistry. A Study of Matter. By *W. T. Lippincott, A. B. Garrett,* and *H. Verhoek*. John Wiley & Sons, New York 1977. 3rd Edit., xvi, 761 pp., bound, $ 20.00.—ISBN 0-471-29246-X

Liquid Chromatography of Polymers and Related Materials. Edited by *J. Cazes*. Vol. 8 of the series "Chromatographic Science Series". Marcel Dekker, New York 1977. viii, 180 pp., bound, SFr. 65.—.—ISBN 0-8247-6592-3

Ion Containing Polymers. Physical Properties and Structure. By *A. Eisenberg* and *M. King*. Vol. 2 of the series "Polymer Physics". Edited by *R. S. Stein*. Academic Press, New York 1977. xvi, 287 pp., bound, $ 27.50.—ISBN 0-12-235050-2

Tabulation of Infrared Spectral Data. By *D. Dolphin* and *A. Wick*. John Wiley & Sons, New York 1977. xvi, 549 pp., bound, $ 24.00.—ISBN 0-471-21780-8

Mechanism and Theory in Organic Chemistry. By *Th. H. Lowry* and *K. Schueller Richardson*. Harper & Row, New York 1977. xi, 748 pp., bound, £ 14.20.—ISBN 0-06-044082-1

Chemical Reactions as a Means of Separation. Sulfur Removal. Edited by *B. L. Crynes*. Vol. 11 of the series "Chemical Processing and Engineering". Edited by *L. F. Albright, R. N. Maddox,* and *J. J. McKetta*. Marcel Dekker, New York 1977. ix, 345 pp., bound, SFr. 98.—.—ISBN 0-8247-6374-2

Macromolecules 1: Structure and Properties. By *H.-G. Elias*. John Wiley & Sons, London 1977. lxxx, 532 pp., bound, $ 42.50.—ISBN 0-471-99487-1

Advances in Heterocyclic Chemistry, Vol. 21. Edited by *A. R. Katritzky* and *A. J. Boulton*. Academic Press, New York 1977. ix, 486 pp., bound, $ 49.00.—ISBN 0-12-020621-8

Organic Chemistry of Sulfur. Edited by *S. Oae*. Plenum Press, New York 1977. ix, 713 pp., bound, $ 48.00.—ISBN 0-306-30740-5

Chemical and Biochemical Applications of Lasers, Vol. II. Edited by *C. B. Moore*. Academic Press, New York 1977. ix, 288 pp., bound, $ 15.00.—ISBN 0-12-505402-5

IUPAC Physical Chemistry Division: Plasma Chemistry—2: Plasma Chemistry and Transport Phenomena in Thermal Plasmas. Pergamon Press, Oxford 1977, bound.—ISBN 0-08-020999-8

Immunologie, Immunpathologie und Immunität. By *S. Sell*. Verlag Chemie GmbH, Weinheim 1977. xviii, 353 pp., paper, DM 44.—.—ISBN 3-527-25576-1

Global Chemical Cycles and Their Alterations by Man. Report of the Dahlem Conference of Nov. 15—19, 1976 in Berlin. Edited by *W. Stumm*. Vol. 2 of the "Physical and Chemical Sciences Research Reports". Abakon Verlagsgesellschaft, Berlin 1977. 347 pp., paper, *ca.* DM 60.—.—ISBN 3-8200-1207-9

Proceedings of the Second International Symposium on Nitrite in Meat Products, Zeist/Netherlands, Sept. 7—10, 1976. Edited by *B. J. Tinbergen* and *B. Krol*. Centre for Agricultural Publishing and Documentation, Wageningen 1977. 326 pp., paper, Dfl. 65.00.—ISBN 90-220-0607-7

Analytical Chemistry, Vol. 4. Edited by *R. S. Porter* and *J. F. Johnson*. Plenum Press, New York 1977. ix, 251 pp., bound, $ 33.00.—ISBN 0-306-35244-2

Introduction to Liquid State Chemistry. By *Y. Marcus*. John Wiley & Sons, London 1977. xviii, 357 pp., bound, £ 12.50.—ISBN 0-471-99448-0

Anisotropy Effects in Superconductors. Edited by *H. W. Weber*. Plenum Press, New York 1977. 316 pp., bound, $ 39.00.—ISBN 0-306-31006-6

IUPAC Organic Chemistry Division: Carotenoids—4. Main Lectures Presented at the 4th International Symposium on Carotenoids, Berne, Aug. 29—29, 1975. Edited by *B. C. L. Weedon*. Pergamon Press, Oxford 1977. pp. 97—243, bound, DM 75.—.—ISBN 0-08-020974-2

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone (06201) 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*) Pappelallee 3, P.O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition in English
Volume 16 · Number 12
December 1977
Pages 807 – 884

The Selectivity of Chemical Reactions Disguised by Diffusion. Part I: Chemical Selectivity Disguised by Mixing[**]

By Paul Rys[*]

A mixing-reaction model (MIRE) is used to develop criteria, readily accessible by experiment, which permit the chemist to decide whether and when mixing effects influence the product distribution in competitive consecutive or parallel reactions. The validity of these criteria is demonstrated by comparison of prediction and experiment in the examples used.

1. Prologue

"Wissen allein ist nicht Zweck des Menschen auf der Erde; das Wissen muss sich im Leben auch betätigen." (H. Helmholtz)

Biological processes are probably the most interesting selective reactions: we meet them every day. Study of their fascinating specificity has led to numerous model representations by means of which we can now understand and explain some of the selectivity phenomena in the living and the nonliving environment. As successful as these *analyses* of selective biochemical partial processes may prove to be, they still cannot satisfy a *synthetically* oriented scientist, who will feel himself challenged by the difficult but exciting demand that he should apply his knowledge of selectivity principles to develop highly selective syntheses and industrial processes[1]. Setting this goal opens up to industrial chemistry a wide and promising field of research, inasmuch as more selective industrial chemical syntheses promise a better utilization of chemical raw materials and minimization of the byproducts burdening the environment.

It seems that the selectivity principle of enzymatic processes is based on an optimal combination of three partial processes, namely *diffusion*, *intermolecular adsorption* (complex formation), and *chemical change* (the making and breaking of bonds). In order to predict and understand the specificity of such complex reaction systems, it is not, however, sufficient to analyze these partial processes individually. It is rather their behavior on interaction that causes the observed selectivity effects and which therefore we must investigate.

In the present article and in Part II, which will follow later, we shall discuss one of these mutual relationships, namely the coupling of the diffusion processes with chemical changes. With the aid of the "engineering approach"—a model suitable for our purpose—simple criteria have been derived that allow the experimental chemist to decide, without much mathematics, *whether* and *when* diffusion processes will influence the product distribution in a chemical process. To provide a simpler overview, only reactions in solution are treated here, but, except where specifically stated otherwise, the selectivity criteria derived apply also to gas-phase reactions. Finally, no distinction is made here between "homogeneous" and "heterogeneous" reactions, as the fundamental principles discussed do not depend on the resolution of any measuring

[*] Prof. Dr. P. Rys
Technisch-Chemisches Laboratorium, ETH-Zentrum
CH-8092 Zürich (Switzerland)

[**] Part II (Selectivity Determining Properties of Encounter Complexes) will shortly appear in this journal.

instrument used. The discussion is limited to isothermal reaction systems.

2. Basic Concepts of Reactivity and Selectivity

"*A clear statement of the problem requires clear definitions*".

The concept of chemical selectivity is intimately linked to the concept of chemical reactivity, and it can therefore be defined only in connection with the latter. The rate constant of the chemical reaction may serve as an experimental measure of the reactivity. This reaction consists either of a single chemical step or of a sequence of several events. In the former case we shall speak of an *elementary* reaction, while in the latter we are dealing with a *complex* reaction.

What is the information that can be deduced from the rate constant of an elementary reaction? In principle, an answer could be provided by a rigorous description of the chemical dynamics by means of quantum mechanics: Solution of the *time-dependent* Schrödinger equation would first of all yield not only information about the energy states of all the molecules present in the system but also predictions about the rate of physical processes in which energy is transferred between degrees of freedom and between molecules. The chemical transformation of molecules in the various energy states could be treated correspondingly. Statistical averaging of the rates of all these elementary steps over all possible energy states would lead to the mean measurable reaction rates. The mathematical complexity unfortunately prevents this procedure from being usable.

To be able, nevertheless, to calculate approximate relative reactivities of elementary reactions we nowadays use simpler methods. These start from the simplifying assumption that the pre-equilibrium energy-transfer processes are much faster than the actual chemical reaction. This assumption makes it possible, at least in principle, to use the solution of the *time-independent* Schrödinger equation to correlate the "static" properties of the molecules with the energetic and structural differences between the reacting molecules in the ground and the transition state and thus with the rate constants of elementary reactions. Static properties of the reactant or intermediate molecules, projected to the rate-limiting transition state, are described as reactivity indices, examples being free valence, localization energies, charge densities, *Brown*'s Z values, and *Dewar* reactivities. Finally, there are more modern models by means of which it is possible to predict even the influence that the reactants may mutually exert on their reactivity indices[2].

Before going any further, however, it is essential to take note of the following points:

1. The assumption that the calculated reactivity indices can be correlated with the measured rate constants is valid only for reactions whose rate is independent of the rate of diffusion of the reactants.
2. The rate constant determined by kinetic measurements is a macroscopic quantity. As such, it is a measure of the free activation enthalpy of the *over-all* chemical process. This process can be either an elementary or a complex reaction. A measured rate constant can never be referred with certainty to an elementary reaction or to the reactivity index calculated from it. It is true that a complex reaction can be traced by kinetic determination of consecutive, quasistationary intermediate products[3], but this is possible only in the most favorable cases. If no intermediate can be detected, then there is still no proof that an elementary reaction is in fact occurring. Here arises the critical question as to how conclusive kinetic measurements can be. How long must the lifetime of a species be for the species to be considered as a potential consecutive intermediate in a chemical reaction? Is it reasonable, for example, to postulate also rotamers or even certain solvation states and solvent structures as quasistationary intermediates? If so, then what is actually a chemical elementary step in solution?

All these questions will be treated in greater detail in Part II.

Kinetic chemical selectivity can be defined as the ratio of the rate constants of two competing elementary or complex chemical reactions. Correspondingly, thermodynamic selectivity would be defined as the ratio of the equilibrium constants of the competing reactions. For known kinetic orders of the competing reactions the chemical selectivity can be determined experimentally from the product distribution. This, however, gives the *intrinsic* (actual) chemical selectivity only if the rate constants compared refer solely to the events of bond making and breaking. If, on the other hand, diffusion or adsorption effects influence the measured reaction rates and the product distribution, then we speak of the selectivities as *disguised by diffusion* or *disguised by adsorption*[4].

3. Partial Processes in a Chemical Reaction

In a chemical process the reactants may pass through partial processes that precede the chemical change before the actual chemical event (bond formation and bond opening) can occur. For a clear discussion of the possible diffusion effects it will

1. Macroscopic mixing process (convection)

AAAA	BBBB	AABBAABB
AAAA	BBBB	AABBAABB
AAAA	BBBB	BBAABBAA
AAAA +	BBBB ⟶	BBAABBAA
AAAA	BBBB	AABBAABB
AAAA	BBBB	AABBAABB

2. Microscopic mixing process (diffusion)

AABBAABB	BABABABA
AABBAABB	ABABABAB
BBAABBAA	BABABABA
BBAABBAA ⟶	ABABABAB
AABBAABB	BABABABA
AABBAABB	ABABABAB

3. Encounter process (diffusion)

AB ⟺ (A, B)

Encounter complex

4. Chemical event

(A, B) ⟶ P

Scheme 1. Partial processes of a bimolecular unidirectional reaction in solution.

be useful to distinguish the partial processes outlined in Scheme 1.

At the beginning the two reactants A and B are mixed. During or after this mixing a diffusion process on the "molecular level" occurs, which leads to the encounter complex. This complex can either decompose or can undergo the chemical event that leads to the product P.

Such division into partial processes reminds us that discussions of reaction mechanisms are generally confined strictly to the event occurring within the solvent cage of the encounter complex. Therefore, the kinetics and product distribution provide access to reaction mechanisms only if the preceding diffusion step is much faster than the chemical event. If this condition is not fulfilled—and that is commoner than is generally assumed—then the *measured* kinetic data and selectivities are disguised by diffusion effects[*]. It is most important to distinguish two situations, each of which can lead to such diffusion effects, namely:

1. The observed kinetics of a reaction can be influenced by the *rate of mixing of the reacting solutions* (mixing-disguised kinetics).
2. The kinetics can be disguised by the *rate of formation of the encounter complex* (encounter-disguised kinetics).

It should be noted in this connection that in mixing-disguised reactions the encounter process (Scheme 1) may be considerably faster than the chemical event. Moreover, we cannot assume, as is often wrongly done, that every encounter-disguised reaction is also disguised by mixing. In the present Part I we shall discuss the influence of the mixing processes on the product distribution of consecutive and parallel reactions. Later, in Part II, we shall deal with the selectivity-determining influence of the encounter process.

Substrate selectivity:

$$A + B \rightleftarrows (A,B) \rightarrow A{-}B$$
$$C + B \rightleftarrows (C,B) \rightarrow C{-}B$$

The product distribution (A—B)/(C—B) can be influenced by diffusion effects

Positional selectivity:

$$A{-}X + C \rightleftarrows (A{-}X,C) \begin{cases} \nearrow A{-}X{-}C \\ \searrow C{-}A{-}X \end{cases}$$

The product distribution (A—X—C)/(C—A—X) is not influenced by diffusion effects

Scheme 2. Possible influence of preceding diffusion processes on the measured substrate and positional selectivity.

[*] The rate of an over-all process is *described* by its kinetics and is *determined* from the rates or the equilibrium positions of individual partial processes. Rate-*describing* partial processes are considered to be all those whose rate equations (differential equations) must be taken into account in the formulation of the over-all kinetics. It should be noted that, if rapidly established, equilibria are taken into the rate equation of the process because of the position of the equilibrium and not because of its kinetics. These equilibria are rate-*determining* and not rate-*describing*. If the kinetics of the total process are described by the kinetics of *one single* partial process, then that partial process is rate-*controlling*. If, however, two or more partial steps are rate-describing, the kinetic behavior of the over-all process is made up of a coupling of these rate-describing steps. The kinetics of one of these partial steps are then *disguised* by the others.

It is important to take account of the fact that, whatever their origin, diffusion effects can influence the measured substrate selectivity but not the positional selectivity (Scheme 2).

Let us consider *substrate*-selectivity first. We speak of this kind of selectivity when a reagent B can react with either compound A or compound C. We recognize that in this case each of the two reactions forms *its own* encounter complex and thus that the product ratio can be influenced by diffusion effects. In contrast to substrate selectivity we have *positional* selectivity, which, for example, determines the *ortho/meta/para*-isomer ratios in substitution reactions of arenes, these being largely independent of preceding diffusion effects. The isomers, which are represented in Scheme 2 as A—X—C and C—A—X, are all formed from the *same* encounter complex. Their ratio thus depends on the likelihood of success in the collisions *within* this encounter complex, and thus not directly on preceding diffusion processes.

To explain the positional selectivities of diffusion-controlled reactions, we must briefly discuss the difference between gas-phase chemical reactions and those in the liquid phase. Whereas the encounter complex in gas-phase reactions lasts essentially for only one collision between the reactants, it can be estimated[5,6] that in general the corresponding encounter complex in the usual solvents at room temperature survives some 10 to 1000 collisions (cage effect). The consequence is that in liquid-phase encounter-controlled reactions isomers are formed in various amounts, which are determined by the chemical reactivities of the various positions; within 10 to 1000 collisions a "selection" of reaction positions according to the chemical reactivities is quite possible. Indeed, it is only in the extreme case, when *every* collision within the encounter complex leads to the chemical event (*collision*-controlled reaction), that a statistical distribution of isomers according to the number of reaction positions can be observed. This is what occurs in the collision-controlled events in the gas phase.

4. Mixing-Disguised Chemical Reactions in Solution

"*Measured kinetics is not what it seems*". (*J. Wei*[7])

A comprehensive mathematical description of the mixing process between two liquids is extremely complicated. It would not be useful to discuss here the numerous model representations, especially as many of them define indices that, although they do in fact characterize the mixing process, are not so far accessible experimentally. To develop, for mixing-disguised reactions, selectivity criteria that will be readily applicable by, and useful to, experimental chemists we shall here make use of a simple *MI*xing-*RE*action model (MIRE)[8,9]. This permits us to describe clearly the coupling between the partial processes displayed in Scheme 1 and to determine the influences that result from this coupling upon the product distribution. The discussion will first be confined to wholly miscisble reaction solutions. Immiscible reaction solutions could be treated similarly, but including consideration of the corresponding solubility parameters of the reactants. Reviews should be consulted for an exhaustive treatment of mixing processes[10,11].

4.1. The Concept of a Simple Mixing-Reaction Model

When two solutions are mixed together they first of all form small liquid elements. The size of the resulting *eddies*, *i.e.* the "segregation length" of the reaction mixture, depends on the turbulence, which is produced *e.g.* by mechanical stirring. If one assumes that, to a first approximation, these eddies are spherical droplets, then their average[*] radius $\mathscr{R}$ can be estimated from turbulence theory[10, 11].

Values of $\mathscr{R} = 10^{-2}$ to 10^{-3} cm are found for the usual solvents such as water, ethanol, or hexane, and this corresponds to an agglomeration of 10^{12} to 10^{15} molecules. In general, the mean size of these liquids elements increases with increasing viscosity of the reaction medium. The stirring imposes on the eddies a convective transport, namely eddy diffusion or dispersion, which leads to a "macroscopic homogeneity" of the reaction mixture (first partial process in Scheme 1). In this state further mixing takes place, but now mainly by diffusion on the molecular level[**] (second partial process in Scheme 1[***]).

The relaxation time of this diffusion process is obtained from the lifetime τ_D of the eddy, which in turn can be estimated from the $\mathscr{R}$ values and the mean diffusion coefficients D of the dissolved molecules (10^{-5} to 10^{-6} cm^2/s) by the relation $\tau_D \approx 0.05\,\mathscr{R}^2/D$. τ_D is in the region of 0.01 to 1 s. Hence it must be concluded that every chemical event that can occur in a time shorter than 0.01—1.0 s may be hindered by mixing processes.

4.2. Competitive Consecutive Reaction Disguised by Mixing

In what follows we shall derive mixing criteria for a competitive consecutive reaction (Scheme 3) that

1. is *first*-order with respect to the reactants A, B, and R and
2. is not encounter-disguised. The latter is the case when the chemical event (Scheme 1) takes place more slowly than the dissociation of the encounter complex formed in a low, quasistationary concentration.

$$A + B \underset{k_{d1}}{\overset{k_{a1}}{\rightleftharpoons}} (A,B) \xrightarrow{k_{r1}} R \qquad \text{Primary reaction}$$

$$R + B \underset{k_{d2}}{\overset{k_{a2}}{\rightleftharpoons}} (R,B) \xrightarrow{k_{r2}} S \qquad \text{Secondary reaction}$$

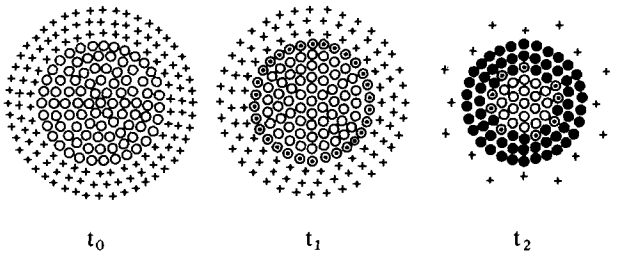
$k_1 = k_{a1} k_{r1}/k_{d1}$: second-order rate constant of the primary reaction
$k_2 = k_{a2} k_{r2}/k_{d2}$: second-order rate constant of the secondary reaction

Scheme 3. Competitive consecutive second-order reaction.

Furthermore, a reaction system with very efficient mechanical stirring is assumed, in which the eddy diffusion, *i.e.* the mutual displacement of the eddies, is much faster than molecular diffusion into or out of the eddies. In Scheme 1 this would mean that the macroscopic mixing process occurs faster than the microscopic mixing. If this condition is fulfilled, we can make the simplifying assumption that the concentration on the eddy surface at any one time corresponds to that in the surrounding solution.

4.2.1. A Qualitative Description[8]

For a clear qualitative understanding of the effect of mixing on the product distribution in a competitive consecutive reaction, it is assumed in the schematic representation of the mixing process (Scheme 4) that the reactant B, being the mobile reactant, diffuses into the liquid eddy in which the molecules A, R, and S are dissolved as immobilized reactants or products[*]. For the sake of simplicity these eddies are represented as spherical liquid elements of constant radius. A simplification of this kind does not detract from the validity of the qualitative conclusions.



Scheme 4. Schematic representation of a mixing-disguised competitive consecutive second order reaction (cf. Scheme 3). Reaction times: $t_0 < t_1 < t_2$. Mobile component: reactant B (+). Immobile components: substrate A (○); primary product R (⊙); secondary product S (●).

In a competitive consecutive reaction *one* molecule A can "bind" *two* molecules of the reactant B in two reactions steps. After a first time interval A and B will have reacted at the periphery of an eddy to produce the primary product R. In a further time interval a molecule B can react with a further molecule A to form R, but only if it succeeds in diffusing through the peripheral zone of R molecules already formed without being trapped there by the substance R in a reaction affording the secondary product S. This succeeds less often, the longer the relaxation time of the diffusion process is in comparison to the relaxation time [**] of the secondary reaction. In the extreme case a mixing-controlled reaction will convert all the R into S before the molecule B finds a further molecule A. Thus, at the end of the reaction practically only the secondary product S is present and no primary product R can be detected. In this case the selectivity k_1/k_2 loses its influence on the product distribution.

4.2.2. The Quantitative Description[8, 9]

The mathematical description of a mixing-reaction system can be arrived at from a mass balance for the components

[*] Practical limits to subdivision of the eddies is set by the energy uptake of the mixing system: $\mathscr{R}$ is inversely proportional to only the 4th root of the stirring energy taken up [11].

[**] Further mixing could conceivably occur by repeated coalescence and re-formation of the eddies. However, on the basis of present knowledge of the dependence of coalescence frequency on turbulence [12], and on the basis of an estimated maximal possible rate of redispersion, it can be assumed that this process plays only a minor role in the mixing of reaction solutions.

[***] This microscopic mixing is characterized by the degree of segregation. It can have values between 1 for unmixed and 0 for completely mixed reaction solutions.

[*] In reality all the reactants are mobile. This has been taken into account in the quantitative description (Section 4.2.2), as far as it proved necessary.

[**] The relaxation time is the time that elapses until a significant quantity in the process has achieved the $(1 - 1/e)$-th part ($= 63.2\,\%$) of the change from the initial value ($t = 0$) to its final value ($t = \infty$).

i in a differential volume element that is fixed in space. This procedure leads to the continuity equation (1), which describes the change in the concentration of the component i with respect to time at a fixed point in space. This change results from the motion of species i and its chemical reaction:

$$\frac{\partial[\mathrm{i}]}{\partial t} = -(\nabla \cdot \vec{N}_\mathrm{i}) + \mathbf{r}_\mathrm{i} \tag{1}$$

([i] = concentration of the component i; ∇ = "del" or "nabla" operator; $\vec{N}_\mathrm{i}$ = the flux vector of the component i; t = time; $\mathbf{r}_\mathrm{i}$ = rate of formation of the component i).

If the flux $\vec{N}_\mathrm{i}$ results only from concentration gradients of the components i, *i.e.* the influence of temperature and pressure gradients as well as of field forces can be neglected, we arrive at equation (2):

$$\frac{\partial[\mathrm{i}]}{\partial t} = -(\nabla \cdot [\mathrm{i}]\vec{v}) + (\nabla [\sum_\mathrm{i}] D_\mathrm{i} \nabla x_\mathrm{i}) + \mathbf{r}_\mathrm{i} \tag{2}$$

([$\sum_\mathrm{i}$] = sum of the concentrations of all components in the system (including the solvent); D_i = diffusion coefficient of the component i; $\vec{v}$ = mean velocity[*], x_i = mole fraction of the component i).

If now, for the diffusion in the eddy, it is valid to assume that [$\sum_\mathrm{i}$] and the diffusion coefficient are constant, and that in dilute solutions the molar mean velocity is zero, then it follows from equation (2) that:

$$\frac{\partial[\mathrm{i}]}{\partial t} = D_\mathrm{i} \nabla^2 [\mathrm{i}] + \mathbf{r}_\mathrm{i} \tag{3}$$

(∇^2 = the Laplacian operator).

For spherical eddies of constant radius equation (3) can be rewritten in polar coordinates:

$$\frac{\partial[\mathrm{i}]}{\partial t} = D_\mathrm{i}\left(\frac{\partial^2[\mathrm{i}]}{\partial r^2} + \frac{2}{r}\frac{\partial[\mathrm{i}]}{\partial r}\right) + \mathbf{r}_\mathrm{i} \tag{4}$$

In the competitive consecutive reaction according to Scheme 3 the following relations can be derived for the rates of formation $\mathbf{r}_\mathrm{i}$[**]:

$$\mathbf{r}_\mathrm{A} = -k_1[\mathrm{A}][\mathrm{B}] \tag{5}$$
$$\mathbf{r}_\mathrm{B} = -k_1[\mathrm{A}][\mathrm{B}] - k_2[\mathrm{R}][\mathrm{B}] \tag{6}$$
$$\mathbf{r}_\mathrm{R} = k_1[\mathrm{A}][\mathrm{B}] - k_2[\mathrm{R}][\mathrm{B}] \tag{7}$$
$$\mathbf{r}_\mathrm{S} \doteq k_2[\mathrm{R}][\mathrm{B}] \tag{8}$$

For the calculation of the reaction behavior and the product distribution of this mixing-reaction system the initial conditions and the boundary conditions must be laid down. The initial conditions are taken when the eddies are built ($t = 0$) assuming that no diffusion and reaction in the eddy have taken place until this moment. If the reaction is carried out batchwise, and hence discontinuously, *i.e.* if one of the reactant solutions is first prepared and the other is mixed into it, the initial conditions depend on the rate at which the two solutions are united. If the addition is *slow*, each eddy encounters new initial conditions set up by the reaction behavior of its predecessors. This is a situation that the experimental chemist meets daily in the laboratory. For the model calculations considered here the simplifying assumption was made that the reactant solutions are united *instantaneously*. The same initial conditions then apply to all the eddies formed (see below). The conditions in a continuously operated stirred vessel are again quite different. In comparison with the conditions under discontinuous operation, we note that the entering reactant stream of B molecules now meets fewer A but more of already formed R and S molecules. Furthermore, the initial conditions depend on the macroscopic mixing state in the stirred vessel, and hence on the site of addition of the reactant stream.

The boundary conditions are obtained from the symmetry of the eddy that is assumed to be spherical: at first there is no concentration gradient at the center of the eddy, and thus also no material flux [eq. (9)].

$$\left(\frac{\partial[\mathrm{i}]}{\partial r}\right)_{r=0} = 0 \tag{9}$$

A further boundary condition is obtained by applying the mass balance of all the mobile components to the eddy and to the solution around it [eq. (10)].

$$V_\mathrm{s}\left(\frac{\partial[\mathrm{i}]}{\partial t}\right)_{r \geq \mathscr{R}} = -S_\mathrm{e} D_\mathrm{i}\left(\frac{\partial[\mathrm{i}]}{\partial r}\right)_{r=\mathscr{R}} \tag{10}$$

(V_s = volume of outer solution; S_e = eddy surface; $\mathscr{R}$ = eddy radius)

The left-hand side of equation (10) gives the time variation of the concentration of i in the outer solution around the eddy. The right-hand side describes the flow of the component i through the eddy surface. Rearranging, we obtain the boundary condition (11).

$$\left(\frac{\partial[\mathrm{i}]}{\partial t}\right)_{r \geq \mathscr{R}} = -3\frac{V_\mathrm{e} D_\mathrm{i}}{V_\mathrm{s} \mathscr{R}}\left(\frac{\partial[\mathrm{i}]}{\partial r}\right)_{r=\mathscr{R}} \tag{11}$$

(V_e = eddy volume)

The system given by equations (4) to (8) and also the initial and boundary conditions can be normalized by using the following dimensionless quantities:

$$\mathbf{X} = \frac{r}{\mathscr{R}};\ \mathbf{T} = \frac{Dt}{\mathscr{R}^2};\ \mathbf{A}_\mathrm{A} = \frac{[\mathrm{A}]}{[\mathrm{A}]_0};\ \mathbf{B}_\mathrm{B} = \frac{[\mathrm{B}]}{[\mathrm{B}]_0};\ \boldsymbol{\Omega}_\mathrm{A} = \frac{[\mathrm{R}]}{[\mathrm{A}]_0}$$
$$\mathbf{E} = \frac{[\mathrm{A}]_0}{[\mathrm{B}]_0};\ \boldsymbol{\varphi}^2_{\mathrm{B},1} = \frac{\mathscr{R}^2 k_1 [\mathrm{B}]_0}{D};\ \boldsymbol{\varphi}^2_{\mathrm{B},2} = \frac{\mathscr{R}^2 k_2 [\mathrm{B}]_0}{D};\ \boldsymbol{\alpha} = \frac{V_\mathrm{A}}{V_\mathrm{B}} \tag{12}$$

(V_A and V_B = reaction volumes of the substrate A and the reactant B; the subscript 0 denotes the initial concentrations before mixing)

For this normalization it is permissible to use the simplifying assumption that all the components A, B, R, and S have the same diffusion coefficient ($D_\mathrm{i} = D$). This leads to the system of equations (13) to (15). Since the concentration distribution of the secondary product S has no direct influence on the selectivity behavior of the reaction system, the corresponding continuity equation for S is superfluous when it comes to

[*] This term denotes the velocity caused by the bulk motion within the eddy.

[**] If all the quantities in equations (4) to (8) are expressed in cgs units, the k_1 and k_2 must be divided by 10^3 to obtain the usual dimensions of $1\ \mathrm{mole}^{-1}\ \mathrm{s}^{-1}$.

calculating the product distribution. The total amount of S is obtained from the mass balance for the whole system.

$$\frac{\partial \mathbf{A}_A}{\partial \mathbf{T}} = \frac{\partial^2 \mathbf{A}_A}{\partial \mathbf{X}^2} + \frac{2}{\mathbf{X}} \frac{\partial \mathbf{A}_A}{\partial \mathbf{X}} - \varphi^2_{B,1} \mathbf{A}_A \mathbf{B}_B \tag{13}$$

$$\frac{\partial \mathbf{B}_B}{\partial \mathbf{T}} = \frac{\partial^2 \mathbf{B}_B}{\partial \mathbf{X}^2} + \frac{2}{\mathbf{X}} \frac{\partial \mathbf{B}_B}{\partial \mathbf{X}} - \mathbf{E}\mathbf{B}_B(\varphi^2_{B,1} \mathbf{A}_A + \varphi^2_{B,2} \Omega_A) \tag{14}$$

$$\frac{\partial \Omega_A}{\partial \mathbf{T}} = \frac{\partial^2 \Omega_A}{\partial \mathbf{X}^2} + \frac{2}{\mathbf{X}} \frac{\partial \Omega_A}{\partial \mathbf{X}} + \mathbf{B}_B(\varphi^2_{B,1} \mathbf{A}_A - \varphi^2_{B,2} \Omega_A) \tag{15}$$

If we assume that the eddy consists of the solution of reactant B, then for batchwise operation with instantaneous unification of the reactant solutions and instantaneous dispersion we obtain the following initial and boundary conditions:

Initial conditions: $\mathbf{T}=0$

$\mathbf{X}<1$: $\mathbf{A}_A=0$; $\mathbf{B}_B=1$; $\Omega_A=0$
$\mathbf{X}=1$: $\mathbf{A}_A=1$; $\mathbf{B}_B=1$; $\Omega_A=0$

Boundary conditions: $\mathbf{T}>0$

$$\mathbf{X}=0\text{: } \frac{\partial \mathbf{A}_A}{\partial \mathbf{X}}=0;\ \frac{\partial \mathbf{B}_B}{\partial \mathbf{X}}=0;\ \frac{\partial \Omega_A}{\partial \mathbf{X}}=0$$

$$\mathbf{X}=1\text{: } \frac{\partial \mathbf{A}_A}{\partial \mathbf{T}} = -\frac{3}{\alpha}\frac{\partial \mathbf{A}_A}{\partial \mathbf{X}};\ \frac{\partial \Omega_A}{\partial \mathbf{T}} = -\frac{3}{\alpha}\frac{\partial \Omega_A}{\partial \mathbf{X}};\ \frac{\partial \mathbf{B}_B}{\partial \mathbf{T}} = -\frac{3}{\alpha}\frac{\partial \mathbf{B}_B}{\partial \mathbf{X}}$$

It follows from equations (13) to (15) and from the boundary conditions that the product distribution of a completely reacted (100% conversion) competitive consecutive reaction with given initial and boundary conditions is determined unambiguously by the four quantities $\mathbf{E}$, α, $\varphi^2_{B,1}$ and $\varphi^2_{B,2}$. The φ^2 values are proportional to the ratio of the relaxation times of the microscopic mixing processes and the chemical reaction. They show how strongly a step in the chemical reaction is hindered by preceding mixing processes. This hindrance by diffusion is represented quantitatively in Figure 1[*]. The smaller $\varphi^2_{B,2}$ is, the closer will the relative yields X_S of the secondary product S approach the values for the reaction-controlled case. X_S is defined as the fraction of B molecules that has reacted to give S after 100% conversion:

$$X_S = \frac{2(S)_\infty}{2(S)_\infty + (R)_\infty} \tag{16}$$

($(R)_\infty$ and $(S)_\infty$ = total amounts of R and S formed after infinite time)

As the $\varphi^2_{B,2}$ values increase, X_S becomes increasingly strongly disguised by diffusion effects and approaches the value of 1. The more marked this disguise by mixing, the smaller becomes the influence of the intrinsic selectivity $\varphi^2_{B,1}/\varphi^2_{B,2}$ (or k_1/k_2) on the product distribution.

[*] For the model calculations in Figures 1 to 9, B was taken as an immobile reactant, *i.e.* the diffusion term in equations (14) and (24) was neglected. Analysis of the cost-evaluation for MIRE calculations showed that this simplifying procedure has negligibly little influence on the calculated predictions but that it reduces decisively the time of the calculation.

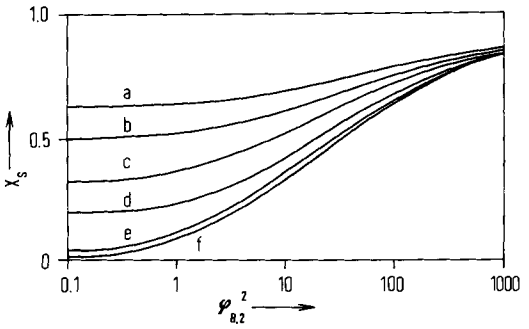


Fig. 1. MIRE model for a competitive consecutive second-order reaction: Calculated relative yields X_S as a function of the mixing modulus $\varphi^2_{B,2}$ for several (a—f) intrinsic selectivities $\varphi^2_{B,1}/\varphi^2_{B,2}$ (a = 1; b = 2; c = 5; d = 10; e = 10^2; f = 10^4). Assumptions: spherical eddy; $\mathbf{E}=1$; $\alpha=1$.

As Figure 2 shows, the influence of the ratio of the reaction volumes α on X_S is not particularly strong. The dependence of the product distribution in mixing-disguised reaction systems on $\mathbf{E}$ can be seen in Figure 3.

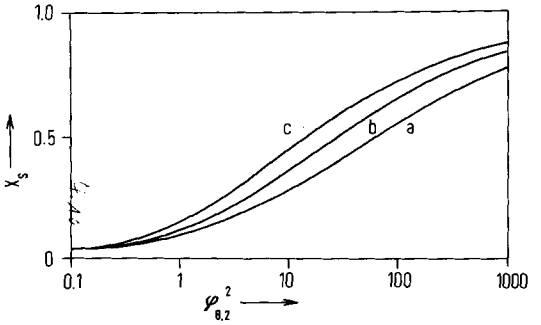


Fig. 2. MIRE model for a competitive consecutive second-order reaction: Calculated relative yields X_S as a function of the mixing modulus $\varphi^2_{B,2}$ for several ratios (a—c) of the reaction volumes α (a = 0.1; b = 1.0; c = 10). Assumptions: spherical eddy; $\alpha\mathbf{E}=1$; $\varphi^2_{B,1}/\varphi^2_{B,2}=100$.

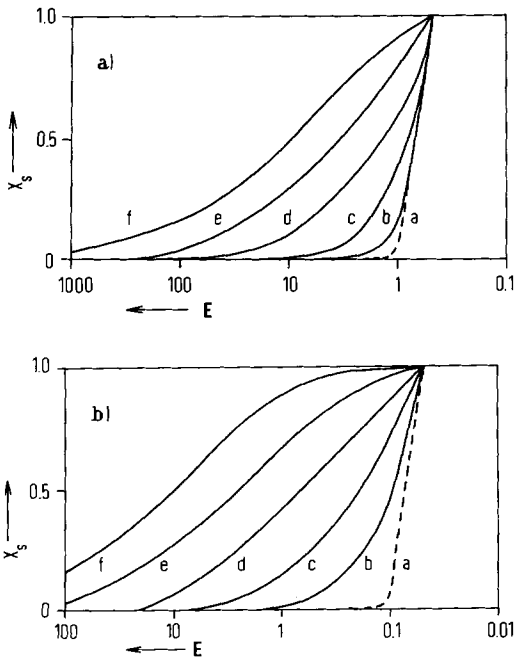


Fig. 3. MIRE model for a competitive consecutive second-order reaction: Calculated relative yields X_S as a function of $\mathbf{E}$ for several (a—f) values of $\mathbf{E}\varphi^2_{B,2}$ ($a \ll 1$; reaction-controlled; b = 1; c = 10; d = 10^2; e = 10^3; f = 10^4). Assumptions: spherical eddy; $\varphi^2_{B,1}/\varphi^2_{B,2}=100$; $\alpha=1$ (Fig. 3a), $\alpha=10$ (Fig. 3b).

The curves in Figure 3, calculated for $\varphi^2_{B,1}/\varphi^2_{B,2}=100$, also characterize the behavior of the reaction at $\varphi^2_{B,1}/\varphi^2_{B,2}>100$ to a good approximation. An indication in that direction was given already by the curves in Figure 1: the selectivity curves e and f for $\varphi^2_{B,1}/\varphi^2_{B,2}=10^2$ and 10^4 lie close together.

Summarizing, the following simple mixing criteria are obtained for the experimenter when, for example, the molar ratio has the value of $\alpha\mathbf{E}=1$:

$\varphi^2_{B,2}<0.1$: mixing effect negligible
$\varphi^2_{B,2}\approx 1$: mixing effect possibly present
$\varphi^2_{B,2}>10$: mixing effect certainly present

4.2.3. Experimental Results

Although chemists in the laboratory and in production plants have to deal daily with diffusion effects that can be traced back to mixing processes, there are relatively few experimental investigations[13-18] that can be used for comparison with MIRE calculations. Moreover, it is precisely for mixing-disguised rapid reactions that the intrinsic (undisguised) kinetics essential for this comparison are so often unknown. Many of the previous models are not amenable, or only difficultly so, to experimental testing[19].

Mixing-disguised product distributions have long been suspected in aromatic nitrations. In many studies the remarkable observation has been reported that on equimolar nitration of durene (1,2,4,5-tetramethylbenzene) mainly dinitrodurene and unchanged durene were found, but hardly any mononitrodurene[20-22,14]. Similar observations have been made with other substrates[23,28]. These experimental results are in apparent contradiction to the general knowledge of the mechanism of electrophilic aromatic substitution, according to which the second nitration should be slower than the first by a factor of $>10^6$ because of the deactivating effect of the first nitro group. *Willstätter* and *Kubli*[24], and also *Olah*[25], sought to explain the apparently faster second nitration by reaction mechanistic considerations. Many other authors, however, pointed to mixing effects as the possible cause[14,21,22,26-29]. The product-determining influence of such mixing effects was questioned particularly by *Olah*[30].

The MIRE model presented above permits mixing effects and their influence on the product distribution to be investigated in systematic experiments. The necessary information is provided by the mixing modulus $\varphi^2_{B,2}$ derived as above: if the intrinsic selectivities exceed about 100 (in aromatic nitration they usually exceed 10^6), then the product distribution and thus the relative yield X_S are almost wholly determined by the $\varphi^2_{B,2}$ values; this is true for constant $\mathbf{E}$ and α, for given initial conditions (Fig. 1). X_S is expected to be most sensitive for $\varphi^2_{B,2}$ values between 1 and 10^3. Experimentally, these values can be easily varied by means of the quantities $\mathscr{R}$, $[B]_0$, k_2, and D:

1. The mixing modulus $\varphi^2_{B,2}$ is most influenced by the eddy radius $\mathscr{R}$ which is applied as its square. If the other reaction conditions are unchanged, $\mathscr{R}$ can be varied by the stirring speed or by the method of mixing (mixing chamber). This dependence of the product distribution on the stirring system has been demonstrated experimentally, for example in the nitration of durene[22]. Since it is not yet possible to determine $\mathscr{R}$ exactly by independent measurements, the values of $\varphi^2_{B,2}$ cannot be calculated[*]. Thus, a *quantitative* comparison of the experimentally determined and the calculated X_S values is not feasible.
2. Such a comparison is, however, possible under constant stirring conditions. The selectivity curves can be determined for given values of α by corresponding variations of $[A]_0$, $[B]_0$, and thus of $\mathbf{E}$ and $\varphi^2_{B,2}$ and can then be compared with the calculated predictions[14,15,17]. Figure 4 shows a comparison of such curves for five arenes, *i.e.* for five k_2 values. From the relative positions of these curves the relative k_2 values have been determined as follows: prehnitene/durene/mesitylene/*m*-xylene[**]/*p*-xylene = 300/100/20/3/1. If it becomes possible to determine even one of these values under reaction-controlled conditions, then the rate constants k_2 of the other arenes can be obtained from the relative values[15].

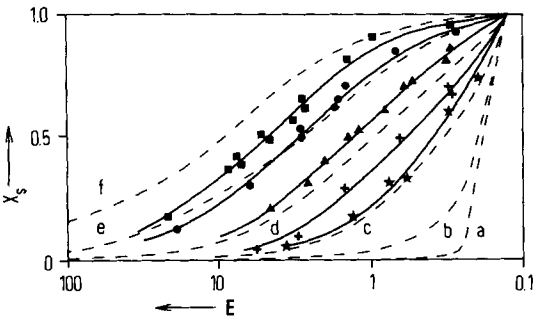


Fig. 4. Mixing-disguised nitration of aromatic compounds (A) by $NO_2^+PF_6^-$ (B) in nitromethane (20°C) [15]. $\alpha=4$. Experimental results: ⋆ *p*-xylene; + *m*-xylene; ▲ mesitylene = 1,3,5-trimethylbenzene; ● durene = 1,2,4,5-tetramethylbenzene; ■ prehnitene = 1,2,3,4-tetramethylbenzene. Calculated curves (broken curves) for several (a—f) values of $\mathbf{E}\varphi^2_{B,2}$ ($a\ll 1$, reaction-controlled; $b=1$; $c=10$; $d=10^2$; $e=10^3$; $f=10^4$). $\varphi^2_{B,1}/\varphi^2_{B,2}=100$. The curves calculated for $\varphi^2_{B,1}/\varphi^2_{B,2}=100$ also represent to a good approximation the predictions for $\varphi^2_{B,1}/\varphi^2_{B,2}>100$ (cf. Fig. 1).

This comparison of the experimental data with the MIRE calculations is, strictly speaking, possible only because the intrinsic kinetics of the chemical reaction are known: the second nitration by nitronium salts is of first order in both R and B[15].

Azo coupling is another reaction that is often disguised by mixing. For the interpretation of its product distribution one must take into account not only the mixing processes discussed above but also the following effects[17]: First, the primary coupling in the competitive consecutive reaction (Scheme 3) generally consists of two (or more) parallel reactions, and they in turn may be mixing-disguised. For example, in the coupling of 1-naphthol derivatives (A) the reaction may occur in position 2 or 4. The bisazo product (S) is then formed from two monoazo products (R) that themselves differ in reactivity. Secondly, it must be remembered that azo-coupling liberates protons which, even with macroscopic buffering, lead to *local* pH gradients in the reaction zone. In mixing-disguised reactions in which these pH gradients cannot be sufficiently rapidly evened out this leads to a shift in the preceding

[*] The $\mathscr{R}$ values can in fact be calculated by turbulence theory [10, 11, 16], but the results cannot be tested experimentally and must be regarded only as approximate.

[**] Interpretation of the results for *m*-xylene is made difficult by the fact that more than one mononitro compound is formed in the first nitration step.

acid-base equilibria of the reactants in the reaction zone and thus influences the reaction rates. Thirdly, the primary or secondary reaction may generally be base-catalyzed. In this case the rate of each reaction step is influenced by the *local* concentration gradient of bases in the eddy.

For a test of the usefulness of the MIRE model for characterizing the reaction behavior of mixing-disguised azo couplings it proved possible to find conditions[17] that avoided the complications mentioned above. As Figure 5 shows, the agreement between the experimental results and the calculated predictions is remarkable. The calculated values were fitted to the experimental data by using the characteristic time $\mathscr{R}^2/D = 1$ s. Thence it can be concluded that, for the reaction conditions used, the eddies have a mean radius $\mathscr{R} = ca.\ 3\times10^{-3}$ cm and a lifetime τ_D of about 5×10^{-2} s.

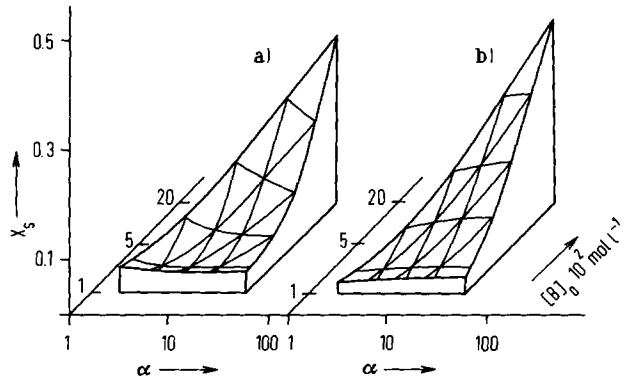


Fig. 5. Mixing-disguised azo coupling of 5-hydroxy-2-naphthalenesulfonic acid with diazotized aniline at pH 10.8 (22°C; $I = 0.2$) [17]. a) Experimental results: $\alpha E = 2$; $k_1/k_2 = 1850$. b) Calculated behavior $\alpha E = 2$; $\varphi^2_{B,1}/\varphi^2_{B,2} > 1000$ (I is the ionic strength).

On the assumption that the preceding acid-base equilibria of the coupling components and of the diazonium ion in the reaction zone are set up very rapidly in comparison with the mixing process, a mixing criterion [eq. (17)] can be set up for azo coupling under conditions close to practice[17].

$$\varphi^2_{B,2} = \frac{\mathscr{R}^2[B]_{tot,0}k_2}{D}\left(\frac{K_R}{K_R+[H_3O^{\oplus}]_l}\right)\left(\frac{[H_3O^{\oplus}]_l^2}{K_1K_2+[H_3O^{\oplus}]_l^2}\right) \qquad (17)$$

($[B]_{tot,0}$ = total concentration of the diazo component at time $t = 0$; K_R = acidity constant of the monazo dye; K_1 = equilibrium constant of the diazonium-diazohydroxide equilibrium; K_2 = acidity constant of the diazohydroxide; $[H_3O^{\oplus}]_l$ = local $H_3O^{\oplus}$ concentration)

The *local* $H_3O^{\oplus}$ concentration is a complex function of the rates of the primary and secondary coupling and of the local (microscopic) buffer capacity of the reaction system. It is, however, smaller than the macroscopically measurable $H_3O^{\oplus}$ concentration and could be calculated by means of equation (4). The rate constant k_2 may also be a function of the local concentration of general bases, in cases where the proton abstraction from the σ-complex is the rate-limiting step in the second coupling[31].

3. The $\varphi^2_{B,2}$ values and thus X_S can be influenced by change in the viscosity of the reaction medium. The change in D and $\mathscr{R}$ due to viscosity can be calculated with the aid of equations given by *Kolmogoroff*[11] and by *Wilke* and *Chang*[32]. The expected effect of viscosity on X_S has been confirmed experimentally for the case of a mixing-disguised azo coupling[16].

4.3. Competitive Parallel Reaction Disguised by Mixing

For competitive parallel reactions (Scheme 5) assumptions should apply that are analogous to those made for competitive consecutive reactions (Scheme 3), namely that the reactions

1. are each of *first*-order with respect to the reactants A, B, and C, and
2. are not encounter-disguised.

Furthermore, for this reaction system too, the condition should be fulfilled that the microscopic mixing process is the rate-limiting part of the mixing process.

$$A + B \underset{k_{d3}}{\overset{k_{a3}}{\rightleftharpoons}} (A,B) \xrightarrow{k_{r3}} P$$

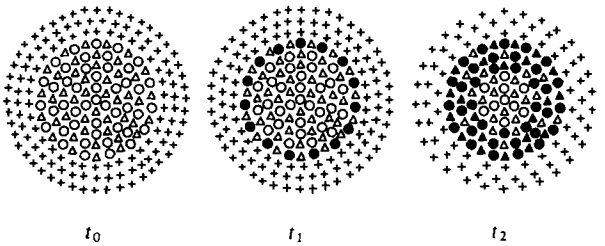
$$C + B \underset{k_{d4}}{\overset{k_{a4}}{\rightleftharpoons}} (C,B) \xrightarrow{k_{r4}} Q$$

$k_3 = k_{a3}k_{r3}/k_{d3}$ and $k_4 = k_{a4}k_{r4}/k_{d4}$: second-order rate constants

Scheme 5. Competitive parallel second-order reaction.

4.3.1. A Qualitative Description[8]

The qualitative effect of the microscopic mixing process on the product distribution in competitive parallel reactions can be illustrated (Scheme 6) in a manner analogous to that used for the competitive consecutive reaction (Scheme 4).



Scheme 6. Schematic representation of a mixing-disguised, competitive parallel second order reaction (cf. Scheme 5). Reaction times: $t_0 < t_1 < t_2$. Mobile component: reactant B (+). Immobile components: substrate A (○); substrate C (△); product P (●); product Q (▲).

Here the substrates A and C compete for the same reactant B. If the reaction with A is faster than that with C, then in the first time interval more of the product P will be formed in the boundary zone of the eddy. At a later point in time a B molecule must, in order to react with another A molecule, penetrate a zone that has become enriched in the compound C which is less reactive than A. For this reason the reactivity of C appears at this time to be greater than predicted from the selectivity k_3/k_4. In the extreme case of a mixing-*controlled* reaction the measured product distribution becomes 1:1. In this case the selectivity k_3/k_4 loses its influence.

4.3.2. The Quantitative Description[8,9]

The mathematical description of competitive parallel reactions is carried out similarly to that for the competitive con-

secutive reactions. The following relationships for r_i are introduced into equation (4):

$$r_A = -k_3[A][B] \quad (18)$$
$$r_B = -k_3[A][B] - k_4[C][B] \quad (19)$$
$$r_C = -k_4[C][B] \quad (20)$$
$$r_P = k_3[A][B] \quad (21)$$
$$r_Q = k_4[C][B] \quad (22)$$

The same general remarks apply for the initial conditions here as for the consecutive reaction. The boundary conditions are set by equations (9) to (11). If the same assumption ($D_i = D$) applies for normalization, and if we use the dimensionless quantities defined above but supplement them with the quantities:

$$\Gamma_C = \frac{[C]}{[C]_0}; \quad M = \frac{[C]_0}{[A]_0}$$

$$\varphi^2_{B,3} = \frac{\mathscr{R}^2 k_3 [B]_0}{D}; \quad \varphi^2_{B,4} = \frac{\mathscr{R}^2 k_4 [B]_0}{D},$$

then we arrive at the system (23) to (25) for the components A, B, and C. Since the concentration distribution of the products P and Q has no direct influence on the selectivity behavior of the reaction system, the corresponding continuity equations for P and Q are superfluous for calculating the product distribution. The total yields of the products are obtained from the mass balance over the whole system.

$$\frac{\partial A_A}{\partial T} = \frac{\partial^2 A_A}{\partial X^2} + \frac{2}{X}\frac{\partial A_A}{\partial X} - \varphi^2_{B,3} A_A B_B \quad (23)$$

$$\frac{\partial B_B}{\partial T} = \frac{\partial^2 B_B}{\partial X^2} + \frac{2}{X}\frac{\partial B_B}{\partial X} - E B_B(\varphi^2_{B,3} A_A + \varphi^2_{B,4} \Gamma_C M) \quad (24)$$

$$\frac{\partial \Gamma_C}{\partial T} = \frac{\partial^2 \Gamma_C}{\partial X^2} + \frac{2}{X}\frac{\partial \Gamma_C}{\partial X} - \varphi^2_{B,4} \Gamma_C B_B \quad (25)$$

If here too we assume that the eddies are composed of the solution of the reaction component B, then for batchwise operation with instantaneous union of the reaction solutions we obtain the following initial and boundary conditions:

Initial conditions: $T = 0$

$X < 1$: $A_A = 0$; $\Gamma_C = 0$; $B_B = 1$
$X = 1$: $A_A = 1$; $\Gamma_C = 1$; $B_B = 1$

Boundary conditions: $T > 0$

$$X = 0: \quad \frac{\partial A_A}{\partial X} = 0; \quad \frac{\partial \Gamma_C}{\partial X} = 0; \quad \frac{\partial B_B}{\partial X} = 0$$

$$X = 1: \quad \frac{\partial A_A}{\partial T} = -\frac{3}{\alpha}\frac{\partial A_A}{\partial X}; \quad \frac{\partial \Gamma_C}{\partial T} = -\frac{3}{\alpha}\frac{\partial \Gamma_C}{\partial X}; \quad \frac{\partial B_B}{\partial T} = -\frac{3}{\alpha}\frac{\partial B_B}{\partial X}$$

The product distribution from a completely reacted competitive parallel reaction system is determined, for given initial and boundary conditions, by the five quantities **E**, **M**, α, $\varphi^2_{B,3}$, and $\varphi^2_{B,4}$. The φ^2 criteria here again show how strongly the chemical event is hindered by mixing processes. The hindrance due to diffusion is presented quantitatively in Figures 6 to 9[*]. The relative yield X_Q of the product Q is defined as the proportion of the B molecules that, after 100 % conversion, have reacted to form Q. In general, one can apply the same remarks as in the discussion of the reaction behavior for the competitive consecutive reactions; the Figures speak for themselves.

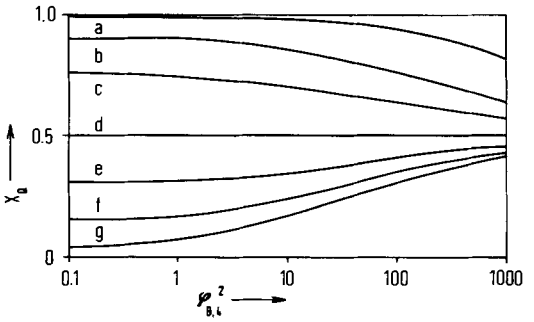


Fig. 6. MIRE model for a competitive parallel second-order reaction: Calculated relative yields X_Q as a function of the mixing modulus $\varphi^2_{B,4}$ for several (a—g) intrinsic selectivities $\varphi^2_{B,3}/\varphi^2_{B,4}$ (a = 0.01; b = 0.1; c = 0.3; d = 1.0; e = 3; f = 10; g = 100). Assumptions: spherical eddy; **E** = 1; **M** = 1; α = 1.

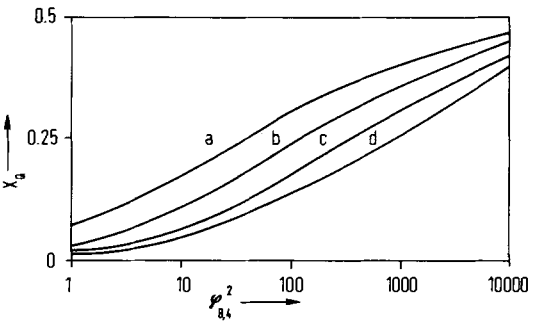


Fig. 7. MIRE model for a competitive parallel second-order reaction: Calculated relative yields X_Q as a function of the mixing modulus $\varphi^2_{B,4}$ for several (a—d) values of **E** (a = 1; b = 2; c = 5; d = 10). Assumptions: spherical eddy; $\varphi^2_{B,3}/\varphi^2_{B,4} = 100$; **M** = 1; α = 1.

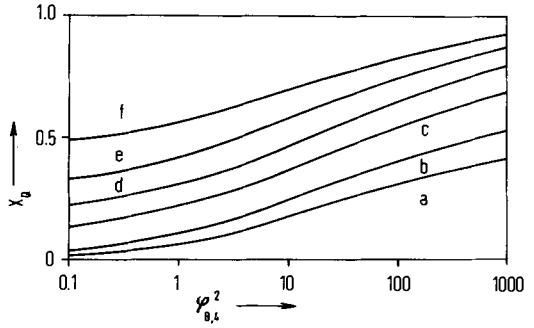


Fig. 8. MIRE model for a competitive parallel second-order reaction: Calculated relative yields X_Q as a function of the mixing modulus $\varphi^2_{B,4}$ for several (a—f) values of **M** (a = 1; b = 2; c = 5; d = 10; e = 20; f = 50). Assumptions: spherical eddy: $\varphi^2_{B,3}/\varphi^2_{B,4} = 100$; **E** = 1; α = 1.

[*] Cf. footnote on p. 812

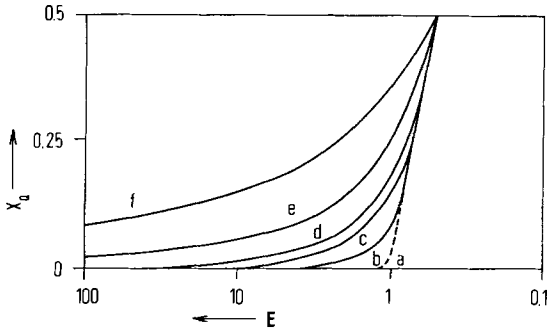


Fig. 9. MIRE model for a competitive parallel second-order reaction: Calculated relative yields X_Q as a function of **E** for several (a—f) values of $\mathbf{E}\varphi^2_{B,4}$ ($a \ll 1$, reaction-controlled; $b = 0.1$; $c = 1$; $d = 10$; $e = 10^2$; $f = 10^3$). Assumptions: spherical eddy; $\varphi^2_{B,3}/\varphi^2_{B,4} = 100$; $\mathbf{M} = 1$; $\alpha = 1$.

4.3.3. Experimental Results

The results of MIRE calculations (Figs. 6 to 9) lead to the question of how much, if any, importance attaches to the countless relative reactivities that have been determined by means of competitive parallel reactions. This method is used just for those cases in which the reaction to be studied is too fast for direct kinetic measurements[33]. It was *Tolgyesi*[29] who first drew attention to the limitations of this competitive method.

Unfortunately, none of the available experimental results are suitable for direct comparison with the MIRE calculations[*].

Finally, we shall consider the numerous aspects of mixing-disguised product distributions also in the case of bromination of resorcinol: If resorcinol in methanol is treated with an equimolar amount of molecular bromine, the monobromo isomers are formed, as well as the dibromo isomers and 2,4,6-tribromoresorcinol[35, 36]. As expected the degree of substitution decreases when the rate of stirring is increased, *i.e.* with more effective mixing. If one investigates the isomer ratio of the dibromo products one finds that the relative proportion of the 2,4-isomer increases with increasing intensity of stirring; this is shown in Figure 10.

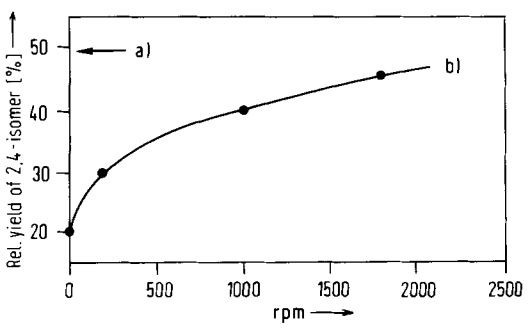


Fig. 10. Bromination of resorcinol (A) with molecular bromine (B) in methanol (22 °C) [35]. Dependence of the relative yield of 2,4-dibromo isomer on the stirring speed $[A]_0 = [B]_0 = 5 \times 10^{-2}$ mol l^{-1}; $\alpha = 1$. a) Stopped-flow mixing chamber; b) propeller stirring.

This result may at first seem surprising, for we have established that positional selectivity does not depend on diffusion effects (Scheme 2). In this result, therefore, it cannot be a matter of positional selectivity that determines the isomer distribution. In fact, it could be shown[35] that the 2,4-dibromo isomer is formed *via* the resorcinolate or monobromoresorcinolate, whereas the 4,6-dibromo isomer is formed from resorcinol derivatives. Thus, the isomer ratio is, exceptionally, a function of substrate selectivity and can be influenced by diffusion effects. The substrate ratio resorcinol/resorcinolate, and hence also the isomer ratio of the dibromo products, depends on the pH of the reaction solution. Since protons are liberated during the bromination, the pH in the reaction zone decreases. The consequence is that on the eddy surface the 4,6-dibromo isomer is formed in preference as the reaction continues. With intensive stirring the pH gradient is more rapidly destroyed, shifting the isomer ratio in favor of 2,4-dibromoresorcinol. This pH effect is superposed by the rate-reducing action of the bromide ion formed, which with bromine forms the tribromide ion. This product inhibition finally leads to a decrease in the disguising effect of mixing.

[*] Investigations are in progress [34].

5. Concluding Remarks on Mixing-Disguised Selectivity

In the above considerations the pride of place was given to chemical processes whose rates and product distributions were influenced by microscopic mixing processes. In Part II we shall start with microscopically mixed reaction systems in which encounter processes between the reactants may disguise the selectivity.

Because of its simplicity, the model presented here is suitable also for the experimental chemist; it can be adapted to any other form of kinetics. The model is, however, capable of refinement, if that should prove necessary. For example, the simplifying assumption of a "constant" eddy radius could be given up, and instead the size of the liquid element as a function of time could be built into the model. Such refinements do not at present promise any essentially new aspects. At the present state of knowledge it is interesting to speculate what influence local product concentration gradients due to mixing might have on the reaction behavior in autocatalytic systems. The insight gained into the behavior of mixing-disguised reaction systems is not just of interest to the synthetic chemist; it also shows the possibility of measuring the mixing state indirectly at any desired place in a reaction vessel.

This excursion into a hitherto neglected area of chemical kinetics was made possible by the collaboration of an expert and enthusiastic group of associates. The experimental basis of the studies reported was provided in particular by Drs. F. Pfister, P. Eugster, E. Crivelli, F. Nabholz and M. Aellen. Model presentation of the results was first made possible by Dr. R. J. Ott's creative and skilled assistance. The author is deeply indebted to all these colleagues and to Professor J. R. Bourne for many valuable ideas and discussions. Some of our own investigations were financially supported by the Swiss National Science Foundation (Project No. 2.62072) and by Ciba-Geigy AG, Basel.

Received: January 25, 1977 [A 191 IE]
German version: Angew. Chem. *89*, 847 (1977)
Translated by Express Translation Service, London

[1] A review of the few previous *biomimetic* reactions is given by *R. Breslow*, Chem. Soc. Rev. *1*, 553 (1972).
[2] *G. Klopman:* Chemical Reactivity and Reaction Paths. Wiley, New York 1974.
[3] *P. Rys, P. Skrabal, H. Zollinger*, Angew. Chem. *84*, 921 (1972); Angew. Chem. Int. Ed. Engl. *11*, 874 (1972); *R. Huisgen, ibid. 82*, 783 (1970) and *9*, 751 (1970).
[4] *P. Rys*, Acc. Chem. Res. *9*, 345 (1976).
[5] *J. Frenkel:* Kinetic Theory of Liquids. Oxford University Press, Oxford 1946; *A. M. North:* The Collision Theory of Chemical Reactions in Liquids. Methuen, London 1964; *W. Jost, K. Hauffe:* Diffusion. Steinkopff Verlag, Darmstadt 1972, p. 91; *R. E. Weston, Jr., H. A. Schwarz* in: Fundamental Topics in Physical Chemistry. Prentice-Hall, Englewood Cliffs, New York 1972.
[6] *I. D. Clark, R. P. Wayne* in: Comprehensive Chemical Kinetics. Vol. II. Elsevier, Amsterdam 1969, Chap. 4.
[7] *J. Wei* in: Applied Kinetics. Publication of the Am. Chem. Soc., Washington, D.C., 1967.
[8] *R. J. Ott, P. Rys*, Helv. Chim. Acta *58*, 2074 (1975).
[9] *F. Nabholz, R. J. Ott, P. Rys*, Helv. Chim. Acta *60*, 2926 (1977); 2nd European Conference on Mixing, Cambridge (England) 1977.
[10] *H. Tennekes, J. L. Lumley*, A First Course in Turbulence. MIT Press, Cambridge, Mass. 1972; *J. O. Hinze:* Turbulence. McGraw-Hill, New York 1959; *V. W. Uhl, J. B. Gray:* Mixing: Theory and Practice. Academic Press, New York 1967; *J. T. Davies:* Turbulence Phenomena. Academic Press, London 1972; *S. Nagata:* Mixing: Principles and Applications. Wiley, New York 1975; *R. S. Brodkey:* Turbulence in Mixing Operations. Academic Press, New York 1975; see also the comprehensive discussions by *K. B. Bischoff* in: Applied Kinetics. Publication of the Am. Chem. Soc., Washington, D. C., 1967 and by *J. J. Evangelista, S. Katz, R. Shinnar*, AIChE J. *15*, 843 (1969).
[11] *A. N. Kolmogoroff*, C. R. Acad. Sci. USSR *30*, 301 (1941); *L. D. Landau, E. M. Lifshitz:* Fluid Mechanics. Pergamon Press, Oxford 1959.
[12] *C. R. Treleaven, A. H. Tobgy*, Eng. Sci. *28*, 413 (1973).
[13] *E. L. Paul, R. E. Treybal*, AIChE J. *17*, 718 (1971); *A. Zoulalian, J. Villermaux*, Adv. Chem. Ser. *133*, 348 (1974); *C. Aubry, J. Villermaux*, Chem. Eng. Sci. *30*, 457 (1975).
[14] *F. Pfister, P. Rys, H. Zollinger*, Helv. Chim. Acta *58*, 2093 (1975).
[15] *F. Nabholz, P. Rys*, Helv. Chim. Acta *60*, 2937 (1977).
[16] *J. R. Bourne, U. Mörgeli, P. Rys*, 2nd European Conference on Mixing, Cambridge (England) 1977.
[17] *J. R. Bourne, E. Crivelli, P. Rys*, Helv. Chim. Acta *60*, 2944 (1977).
[18] *T. T. Szabo, E. B. Nauman*, AIChE J. *15*, 575 (1969); *O. Bilous, E. L. Piret, ibid. 1*, 480 (1955); *J. C. Mecklenburgh*, Can. J. Chem. Eng. *48*, 279 (1970).
[19] See also the comprehensive review by *O. Miyawaki, H. Tsujikawa, Y. Uraguchi*, J. Chem. Eng. Jpn. *8*, 63 (1975); *D. P. Rao, L. L. Edwards*, Chem. Eng. Sci. *28*, 1179 (1973); *A. Zoulalian, J. Villermaux*, Chem. React. Eng. *11*, 348 (1974); *P. V. Danckwerts*, Chem. Eng. Sci. *8*, 93 (1958); *T. N. Zwietering, ibid. 11*, 1 (1959).
[20] *R. Fittig, P. Jannasch*, Z. für Chemie *1870*, 162; *J. W. Nef*, Justus Liebigs Ann. Chem. *237*, 1 (1886); *J. C. Cain*, Ber. Dtsch. Chem. Ges. *28*, 967 (1895); *L. Rügheimer, M. Handel, ibid. 29*, 2171 (1896); *F. Francis*, J. Chem. Soc. *89*, 1 (1906); Ber. Dtsch. Chem. Ges. *39*, 3798 (1906).
[21] *G. Illuminati, M. P. Illuminati*, J. Am. Chem. Soc. *75*, 2159 (1953); *R. C. Fuson:* Reactions of Organic Compounds. Wiley, New York 1962, p. 33.
[22] *S. B. Hanna, E. Hunziker, T. Saito, H. Zollinger*, Helv. Chim. Acta *52*, 1537 (1969).
[23] Review in: *J. G. Hoggett, R. B. Moodie, J. R. Penton, K. Schofield:* Nitration and Aromatic Reactivity. Cambridge University Press, Cambridge 1971.
[24] *R. Willstätter, H. Kubli*, Ber. Dtsch. Chem. Ges. *42*, 4151 (1909).
[25] *G. A. Olah*, Acc. Chem. Res. *4*, 240 (1971).
[26] *A. W. Francis*, J. Am. Chem. Soc. *48*, 655 (1926).
[27] *P. F. Christy, J. H. Ridd, N. D. Stears*, J. Chem. Soc. *B 1970*, 797; *J. H. Ridd* in: Studies on Chemical Structure and Reactivity. Methuen, London 1960.
[28] *J. H. Ridd*, Acc. Chem. Res. *4*, 248 (1971).
[29] *W. S. Tolgyesi*, Can. J. Chem. *43*, 343 (1965).
[30] *G. A. Olah, S. J. Kuhn, S. H. Flood*, J. Am. Chem. Soc. *83*, 4571 (1961); *G. A. Olah, N. A. Overschuk*, Can. J. Chem. *43*, 3279 (1965).
[31] Mechanism of azo coupling: *H. Zollinger:* Chemie der Azofarbstoffe. Birkhäuser, Basel 1958.
[32] *C. R. Wilke, P. Chang*, AIChE J. *1*, 264 (1955).
[33] *G. A. Olah, S. J. Kuhn, A. Mlinko*, J. Chem. Soc. *1956*, 4257; *G. A. Olah, S. J. Kuhn, S. H. Flood*, J. Am. Chem. Soc. *83*, 4571, 4583 (1961); *G. A. Olah, S. J. Kuhn, S. H. Flood, J. C. Evans, ibid. 84*, 3687 (1962); *G. A. Olah, S. J. Kuhn, ibid. 84*, 3684 (1962).
[34] *M. Aellen*, Dissertation ETH, No. 5998, Zürich 1977.
[35] *P. Eugster*, Dissertation ETH, No. 5013, Zürich 1973.
[36] *J. R. Bourne, P. Rys, K. Suter*, Chem. Eng. Sci. *32*, 711 (1977).

Titanium Tetrachloride in Organic Synthesis

New synthetic methods (21)

By Teruaki Mukaiyama[*]

Titanium tetrachloride can accelerate numerous organic reactions. Valuable syntheses of, *e.g.*, allyl sulfides, amides, enamines, and ketones are based upon transformations of functional groups with $TiCl_4$. Particular mention should also be made of carbon-carbon linkage with $TiCl_4$ which permits the synthesis of hydroxy ketones and carbonyl compounds of the Michael adduct type. $TiCl_4$ reduced *in situ* is suitable for the reduction of chloroarenes or the linkage of two aldehyde molecules to give an alkene.

1. Introduction

During the decade that has elapsed since the widespread introduction of strong bases such as alkyllithium and potassium hydride into organic chemistry, much effort has been devoted to the generation of carbanions from various types of compounds; this has led to a revolution in the field of organic synthesis. On account of their many interesting reactions, the carbanions of sulfur compounds and the dianion of ethyl acetoacetate have frequently been employed in synthetic work.

Apart from the development of reactions carried out under basic conditions, it would also appear important to explore new reactions executed in acidic media. For example, if active electrophiles were to be generated by the use of acid new synthetic reactions could then be developed as very welcome alternatives to existing procedures, especially in arranging efficient synthetic schemes for preparations of complex molecules.

[*] Prof. Dr. T. Mukaiyama
Department of Chemistry, Faculty of Science
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113 (Japan)

From this standpoint, the promotion of organic reactions by Lewis acids was re-examined in our laboratory, and titanium tetrachloride was found to be useful in developing synthetic reactions. The chemistry of low-valent titanium compounds has already made remarkable advances in the field of polymer chemistry; typically, in olefinic polymerization according to *Ziegler* and *Natta*, these compounds have been recognized as indispensable. Although titanium compounds are considered as unique reagents, there has been no systematic research. Titanium tetraalkoxides have been utilized as catalysts of transesterification[1], and $TiCl_4$ has been effectively employed in various dehydration reactions[2].

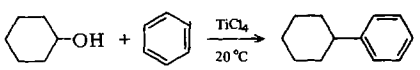
In this review, recent advances in synthetic reactions using titanium tetrachloride will be described, with particular emphasis on our recent work in the following three fields: 1) transformation of various organic functional groups by the use of titanium tetrachloride; 2) carbon-carbon bond formation using titanium tetrachloride; and 3) synthetic reactions utilizing low-valent titanium compounds generated *in situ* from titanium tetrachloride.

2. Transformations of Organic Functional Groups with Titanium Tetrachloride

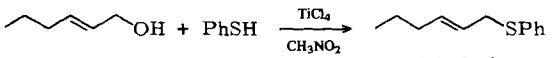
Titanium tetrachloride is known as one of the typical Lewis acids, and it has a strong affinity for organic oxygenated compounds. Furthermore, $TiCl_4$ has a powerful dehydrating action; these typical characteristics of $TiCl_4$ are manifested in the following functional group transformations.

The condensation reactions of alcohols with aromatic compounds or thiols proceed rapidly in the presence of $TiCl_4$. For example, cyclohexylbenzene *(1)* is obtained in 91% yield when cyclohexanol is treated with $TiCl_4$ in benzene[3].

Similarly, an important synthetic intermediate, allyl phenyl sulfide *(2)*, is prepared in fairly good yield by the reaction of 2-hexen-1-ol and thiophenol in the presence of $TiCl_4$ in nitromethane[3].

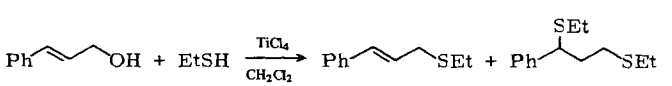


(1), 91%



(2), 63%

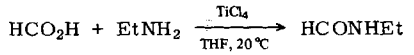
When dichloromethane is employed as a solvent in the preparation of allyl sulfides, addition of thiol to carbon-carbon double bond takes place to give bis-sulfides, *e.g.* 1,3-bis(ethylthio)-1-phenylpropane *(3)*, as a minor product[3].



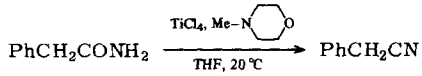
56% *(3)*, 23%

Hence $TiCl_4$ promotes the addition of thiol to the alkene; details of the addition reaction of thiols to other alkenes will be discussed later.

Further, $TiCl_4$ is used as a dehydration reagent in the formation of carboxamides *(4)* from carboxylic acids and amines[2a], and in the transformation of primary amides into nitriles[2b].

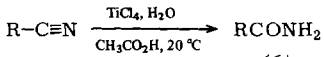


(4), 82%



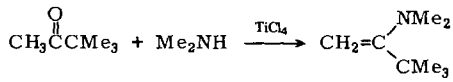
(5), 83%

In contrast to the above transformation of phenylacetamide into the nitrile *(5)*, various nitriles are converted to the corresponding carboxamides *(6)* by $TiCl_4$-promoted hydrolysis in acetic acid, and none of the corresponding carboxylic acids can be detected[4]. The yield of hydrolysis of benzonitrile (R = Ph) or pivalonitrile (R = *t*-Bu) can be increased to 64% or 87%, respectively, by conducting the reaction in highly concentrated solution. Butyramide (R = *n*-Pr) and isobutyramide (R = *i*-Pr) are formed in 88 and 65% yield, respectively.

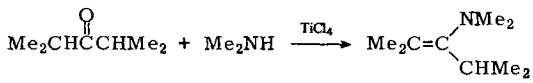


(6)

Ketones are rapidly transformed into the corresponding enamines, *e.g. (7)* and *(8)*, by reaction with stoichiometric amounts of $TiCl_4$ and secondary amines, and highly hindered as well as ordinary enamines are prepared by this way[2c]. Examination of the effect of several other metal halides on enamine formation shows the following halides to be active: $AlCl_3$, $SnCl_4$, $FeCl_3$, and $AsCl_3$, but none of them appears better than $TiCl_4$.



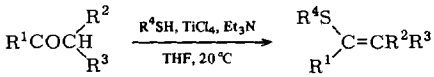
(7), 94%



(8), 72%

A similar concept is utilized in a convenient synthesis of various vinyl sulfides of type *(9)* directly from carbonyl compounds[5]. Relatively little work has been reported on the direct preparation of vinyl sulfides from carbonyl compound except for the elimination of thiols from thioacetals by acid catalyst and dehydration of hindered hemithioacetal.

The yield of vinyl sulfides on use of $TiCl_4$ markedly depends on reaction condition, *i.e.*, order of addition of reagents



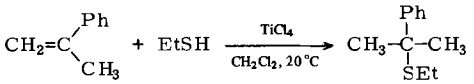
(9)

Table 1. Synthesis of vinyl sulfides of type *(9)*.

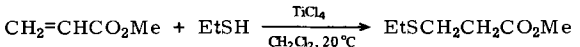
R^1	R^2	R^3	R^4	Yield [%]
Ph	Ph	H	Et	91
Ph	H	Me	Ph	72
$PhCH_2$	H	Me	Et	87
H	—$(CH_2)_4$—		Et	79

(ketone, thiol, $TiCl_4$, and triethylamine). The most favorable result is obtained when a THF solution of thiol and triethylamine is added dropwise to a solution of $TiCl_4$ and ketone with vigorous stirring.

As mentioned in the preparation of the sulfides *(2)* and *(3)* from alcohol and thiol, $TiCl_4$ activates not only oxygen functions but also carbon-carbon double bonds. Accordingly, thiols add to various alkenes in excellent yields in the presence of $TiCl_4$[6], *e.g.* to the alkenes *(10)* and *(11)*.

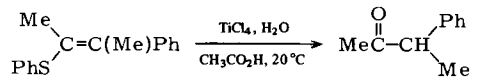


(10) quant.

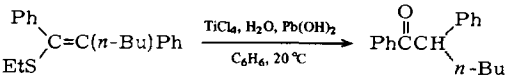


(11) 94%

Addition of thiols to alkenes suggests that vinyl sulfide is sufficiently activated by $TiCl_4$ to react with water, forming ketones. Hydrolysis of vinyl sulfides generally needs rather drastic conditions; an exception is the mercury(II)-promoted hydrolysis[7] reported by *Corey et al.* Titanium tetrachloride has a remarkable effect on the hydrolysis of vinyl sulfides; the corresponding ketones *(12)* and *(13)* are obtained in high yields without any by-products under mild conditions[8]. Even 2-aryl vinyl sulfides, for which Hg^{II}-promoted hydrolysis requires an elevated temperature, are hydrolyzed almost quantitatively at room temperature. In the case of ethyl vinyl sulfide, the yield of ketone is increased by the addition of $PbO/Pb(OH)_2$ to remove resulting ethanethiol simultaneously; with phenyl vinyl sulfide such a measure has no significant effect.

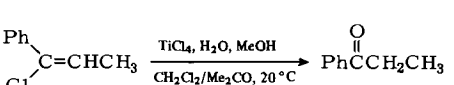


(12), 97%

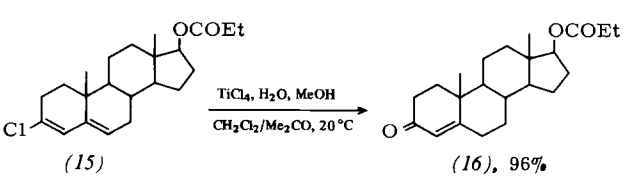


(13), 91%

Vinyl chloride derivatives are regarded as useful carbonyl equivalents in organic synthesis, but the hydrolysis of vinyl chlorides remains a problem because the reaction must be carried out under drastic conditions, *i.e.*, in excess concentrated sulfuric acid or in a mixture of sulfuric acid and acetic acid[9]. Like vinyl sulfides, vinyl chlorides undergo ready hydrolysis on combined use of $TiCl_4$ and CH_3OH-H_2O in dichloromethane/acetone; the corresponding ketones are produced in excellent yields[10]. For example, the chlorosteroid *(15)* is smoothly converted at room temperature into testosterone propionate in 96% yield without hydrolysis of the ester function.



(14), 85%



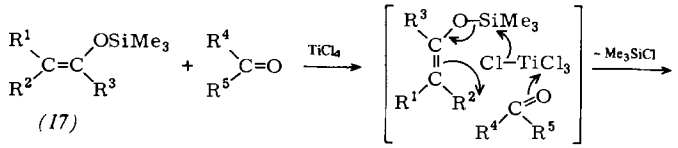
(15) *(16)*, 96%

3. Carbon-Carbon Bond Formation with Titanium Tetrachloride

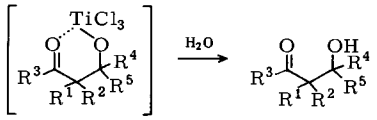
3.1. Synthesis of β-Hydroxy Ketones and Related Reactions

Aldol condensation has long been recognized as one of the most versatile synthetic tools in organic chemistry. The reaction is usually carried out under basic condition, and dimers, polymers, or self-condensation products or α,β-unsaturated carbonyl compounds are invariably formed as by-products. These undesirable side reactions frequently limit the utility of this otherwise efficient reaction. In order to alleviate these difficulties, useful synthetic procedures have been developed, especially under basic conditions, by *Wittig et al.*[11] using lithio derivatives of imines and by *Corey et al.*[12] using lithio derivatives of hydrazones. In addition, *Stork et al.*[13] and *House et al.*[14] reported the selective formation of lithium enolates which in the presence of metal salts lead to cross aldols under almost neutral condition. Vinyloxyborane has been successfully used in our laboratory for the preparation of cross aldols under neutral condition[15].

Powerful activation of carbonyl groups by $TiCl_4$ led to the assumption that silyl enol ethers of type *(17)* could readily attack carbonyl compounds to form trimethylsilyl chloride and the titanium salt of the aldol-type product. In this case, undesirable dissociation of the adduct would be inhibited by the formation of a stable titanium chelate *(18)* whose hydrolysis would yield the desired β-hydroxy ketone *(19)*.



(17)



(19)

Table 2. Synthesis of β-hydroxy ketones of type *(19)*.

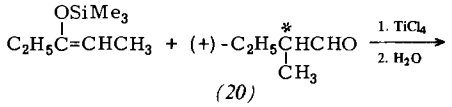
	R^1	R^2	R^3	R^4	R^5	T [°C]	Yield [%]
a	H	Ph	Me	$PhCH_2CH_2$	H	−78	95
b	H	—$(CH_2)_3$—		$PhCH_2CH_2$	H	−78	95
c	H	H	Ph	Me	Me	20	73
d	H	—$(CH_2)_4$—		*i*-Pr	H	−78	92

In fact, the aldol-type product *(19)* is selectively obtained in excellent yield, without accompanying self-condensation products, when the silyl enol ether *(17)* is treated with stoichiometric amounts of ketone or aldehyde and $TiCl_4$ in dichloro-

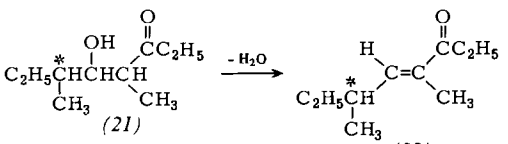
methane[16]. With aldehydes, the reaction proceeds even at −78 °C, whereas in the case of ketone, a reaction temperature of 0 °C or room temperature is required (Table 2).

The synthesis of β-hydroxy ketones is also promoted by various other metal salts, including $SnCl_4$ and $BF_3 \cdot OEt_2$; however, $TiCl_4$ is greatly superior to both these reagents with regard to product yield.

(+)-Manicone *(22)*, one of the alarm pheromones, is readily synthesized from (+)-1-methylbutanal *(20)* *via* the β-hydroxy ketone *(21)*[17].

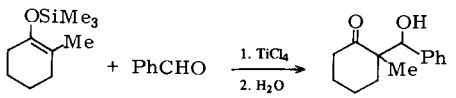


(20)

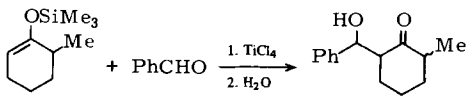


(21) *(22)*

The regiospecificity of the above syntheses is proved by the reactions of two structurally isomeric silyl enol ethers, namely 1-methyl-2-trimethylsiloxy-1-cyclohexene *(23)* and 6-methyl-1-trimethylsiloxy-1-cyclohexene *(24)*[16b]. The reaction of *(23)* with benzaldehyde affords two stereoisomers of 2-(α-hydroxybenzyl)-2-methyl-1-cyclohexanone, whereas *(24)* reacts with benzaldehyde to give four stereoisomers of 2-(α-hydroxybenzyl)-6-methyl-1-cyclohexanone. Accordingly, the addition reaction appears to take place regiospecifically at the double bond of the silyl enol ether.

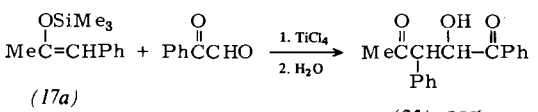


(23) 58%

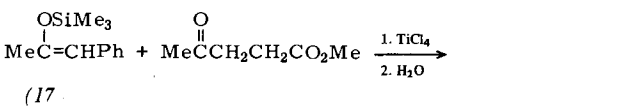


(24) 81%

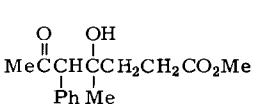
Furthermore, a high functional group selectivity is observed when two different kinds of carbonyl group, such as aldehyde, ketone and ester, are present in the same molecule. If phenylglyoxal is treated with the silyl enol ether *(17a)* at −78 °C, the α-hydroxy γ-diketone *(25)* is obtained exclusively, and no addition products to the ketone function are detected. The reaction of methyl levulinate with *(17a)* also affords the 4-hydroxy 6-oxo ester *(26)* as sole product at room temperature[16b].



(17a) *(25)*, 83%

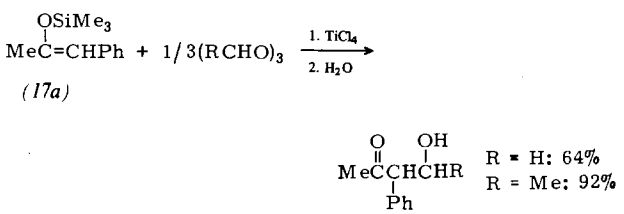


(17)



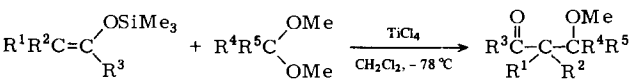
(26), 53%

In general, condensation reactions of ketones with formaldehyde give not only compounds with one CH_2OH group but also unsymmetrical bis- and poly(hydroxymethyl) products, and hence it is difficult to prepare a desired mono(hydroxymethyl) compound exclusively. However, *(17a)* reacts with 1,3,5-trioxane or paraaldehyde in the presence of $TiCl_4$ to give exclusively 1:1 adducts in good yields[16b].



(17a)

Trimethylsilyl enol ethers also react with acetals or methyl orthoformate in the presence of $TiCl_4$ to give β-alkoxy ketones or β-oxo acetals, respectively, at low temperature (Table 3)[18]. In the case of methyl orthoformate, only the β-oxo acetal is obtained; β-alkoxy δ-diketone which is formed on subsequent reaction with silyl enol ether is not isolated.

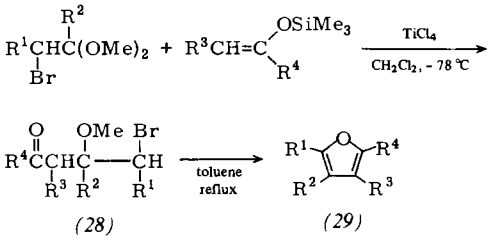


(17) *(27)*

Table 3. Synthesis of β-methoxy ketones and acetals of type *(27)*.

R^1	R^2	R^3	R^4	R^5	Yield [%]
H	H	Ph	$NCCH_2CH_2$	H	60
Ph	H	Me	$-(CH_2)_5-$		91
H	$-(CH_2)_4-$		H	OMe	71

Various substituted furans *(29)* are readily prepared by application of the $TiCl_4$-promoted reaction of α-halo acetals with silyl enol ethers[19]. For instance, β-alkoxy γ-bromo



(28) *(29)*

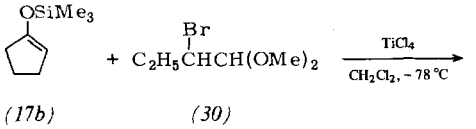
Table 4. Synthesis of furan derivatives *(29)*.

R^1	R^2	R^3	R^4	Yield [%]
H	H	Ph	Me	69
n-Bu	H	H	*t*-Bu	71
Et	H	Ph	Me	82
$-(CH_2)_4-$		H	Ph	77

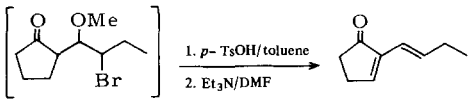
ketones *(28)*, prepared from α-bromo acetals and silyl enol ether, are readily converted into the corresponding furans *(29)* by refluxing in toluene (Table 4).

Many of the reported syntheses of furan derivatives involve several reaction steps and the yields are not always satisfactory. With the present method a general route is now available for preparation of substituted furans.

Cyclopentenone derivatives *(31)* are obtained in good yields instead of the furan compound when 2-(1-alkoxy-2-bromoalkyl)cyclopentanones, derived from the silyl enol ether *(17b)* and acetals *(30)*, are heated in the presence of *p*-toluenesulfonic acid[20].

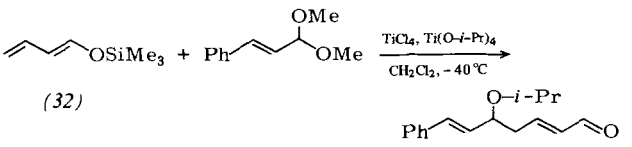


(17b) *(30)*

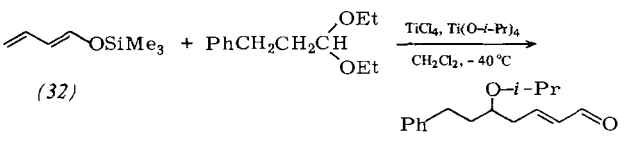


(31), 70%

δ-Alkoxy α,β-unsaturated aldehydes such as *(33)* and *(34)*, which are valuable synthetic intermediates because of their polyfunctionality, are prepared in good yields from dienyloxysilanes such *(32)* and acetals[21]. Reaction of acetals and *(32)*, prepared from crotonaldehyde or dimethylacrolein and chlorotrimethylsilane, in the presence of $TiCl_4$ alone gives only polymers. However, the desired aldehydes *(33)* and *(34)* are obtained in good yields by treating acetals and the silane *(32)* at −40 °C in the joint presence of $TiCl_4$ and $Ti[O—CH(CH_3)_2]_4$. Under these conditions undesirable side reactions are suppressed.



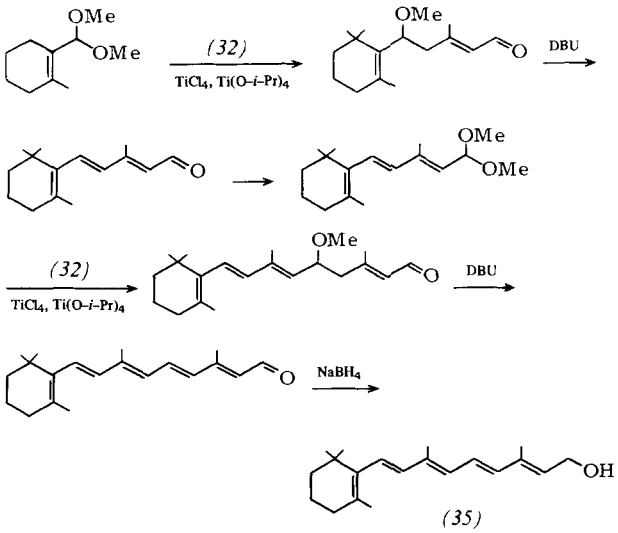
(32) *(33)*, 80%



(32) *(34)*, 79%

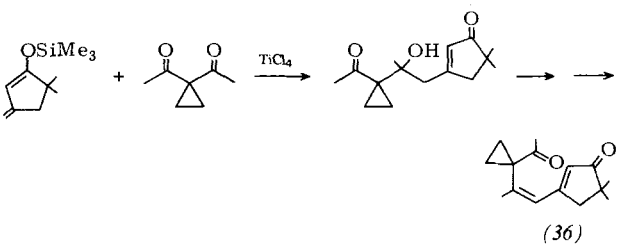
A similar reaction for the preparation of polyenic acetals is reported by *Krasnaya et al.* using 1-ethoxyisoprene and $ZnCl_2$, but the reaction is not so clear-cut and gives the desired product in lower yield than the present method[22].

δ-Alkoxy α,β-unsaturated aldehydes of type *(33)* and *(34)* are easily converted into polyenic aldehydes by elimination of alcohol. This can be accomplished by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) or 1,5-diazabicyclo-[4.3.0]non-5-ene in the presence of molecular sieves 3 Å or 4 Å[23]. The syntheses of some natural products such as



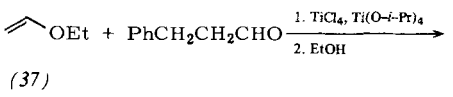
(35)

vitamin A *(35)*[24a], variotin[24b], and hypacrone *(36)*[25] are readily accomplished with dienyloxysilanes.

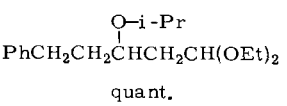


(36)

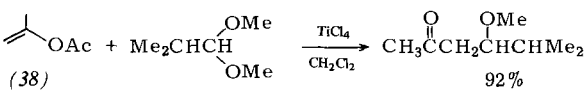
Similarly, enol ethers[26] and enol esters[27] can also be employed as nucleophiles in the aldol reaction. Ethyl vinyl ether *(37)* or isopropenyl acetate *(38)* reacts with an acetal or aldehyde in the presence of $TiCl_4$ or a mixture of $TiCl_4$ and $Ti[O—CH(CH_3)_2]_4$ and the addition product is obtained in good yield.



(37)

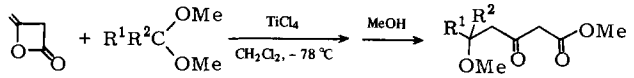


quant.



(38) 92%

Diketene *(39)* is also employed as a nucleophile in place of silyl enol ethers or isopropenyl acetate in the $TiCl_4$-promoted reaction. *Kucherov et al.* reported that the reaction of diketene with acetaldehyde diethyl acetal in the presence of Lewis acid, *i.e.* $BF_3 \cdot OEt_2$, affords ethyl α-(1-ethoxyethyl)-acetoacetate[28]. Contrary to the above result, δ-alkoxy β-oxo esters of type *(40)* (Table 5) are obtained exclusively by the treatment of diketene with acetals at −78 °C or −20 °C in dichloromethane, while no α-(1-alkoxyalkyl)acetoacetate is isolated[29].

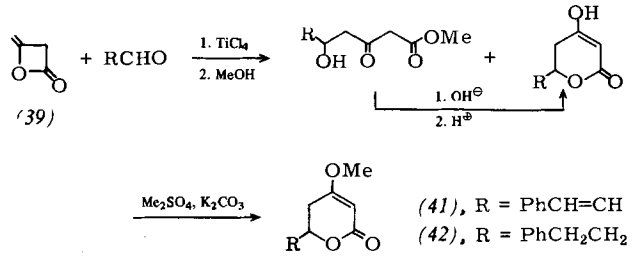


(39) (40)

Table 5. Synthesis of δ-methoxy-β-oxo carboxylic acids of type *(40)*.

R^1	R^2	Yield [%]
i-Pr	H	77
$PhCH_2CH_2$	Me	87
$CH_3COCH_2CH_2$	Me	76
H	OMe	68

Likewise, δ-hydroxy β-oxo ester and dihydropyrone are prepared by the $TiCl_4$-promoted reaction of diketene with various aldehydes at −78 °C, and the reaction has been applied to the synthesis of kawain *(41)* and dihydrokawain *(42)*[30].

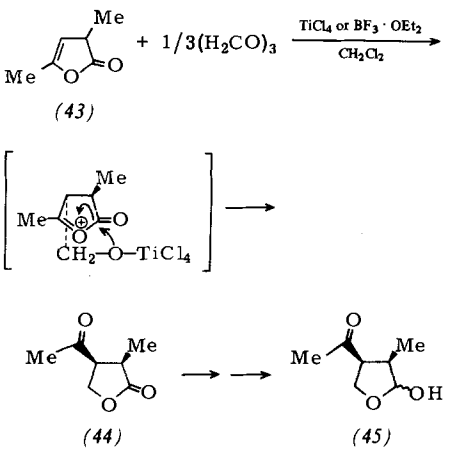


(39)

(41), R = PhCH=CH
(42), R = $PhCH_2CH_2$

The dianion of acetoacetic ester is known as an invaluable reagent for the introduction of the —CH_2—CO—CH_2—CO— unit into carbonyl compounds. Whereas this reaction requires basic conditions, on use of diketene and $TiCl_4$ the same unit is introduced in good yield under acidic conditions.

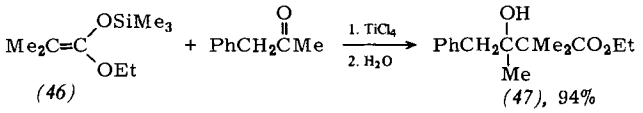
2-Methyl-β-angelicalactone *(43)*, an enol acetate, reacts with trioxane in the presence of $TiCl_4$ or $BF_3 \cdot OEt_2$ to afford β-acetyl-α-methyl-γ-butyrolactone (*cis*:*trans* = 85:15) in 73% yield[31]. Preferential formation of the *cis*-isomer may be due to the steric effect of the methyl groups of angelicalactone. This *cis*-lactone *(44)* has successfully led to antibiotics such as botryodiplodin *(45)*[32].



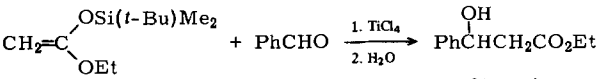
(43) (44) (45)

The synthesis of β-hydroxy esters such as *(47)*, *(49)*, and *(51)* is accomplished by the $TiCl_4$-promoted reaction of ketene alkyl trialkylsilyl acetals *(46)*, *(48)*, and *(50)* with carbonyl compounds[33].

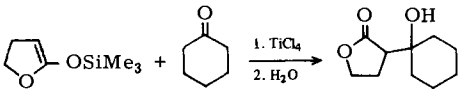
The Reformatsky reaction usually employed for preparing such esters is generally carried out under drastic conditions and is often accompanied by formation of an α,β-unsaturated ester. Recently, several investigators reported that β-hydroxy esters are obtained by employing the α-metalated carboxylic esters. Furthermore, it was recently shown in our laboratory that β-hydroxy esters are obtained in high yields under neutral conditions by treating a vinyloxyborane with carbonyl compounds[15]. The present $TiCl_4$-promoted reaction carried out under acidic conditions affords various β-hydroxy esters, including β-(1-hydroxyalkyl)-γ-butyrolactones such as *(51)* in excellent yields without formation of α,β-unsaturated esters.



(46) (47), 94%

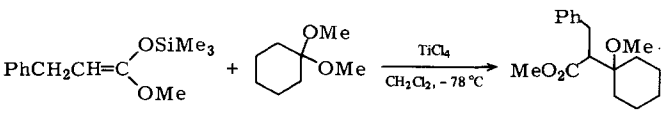


(48) (49), 84%

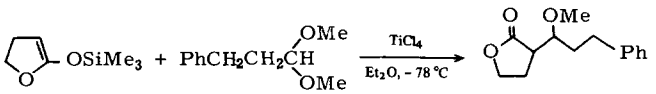


(50) (51), 88%

Similarly, β-alkoxy esters like *(52)* and lactones like *(53)* are prepared in good yields by the reaction of ketene alkyl trialkylsilyl acetals with various acetals of aldehydes and ketones in the presence of $TiCl_4$ under mild conditions[34].

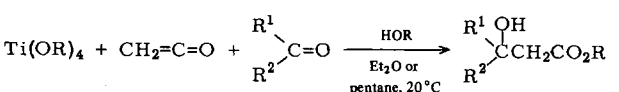


(52), 92%



(50) (53), 75%

The preparation of β-hydroxy esters by the reaction of titanium tetraalkoxide, ketene, and ketone has been reported[35] by *Vuitel et al.* However, in the case of aldehyde,



(54)

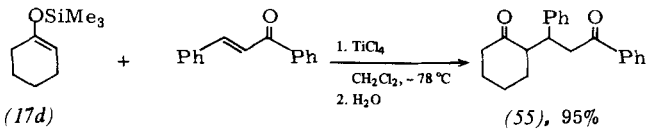
a considerable amount of hydroxy diester is formed along with a normal product *(54)*.

3.2. Michael Addition

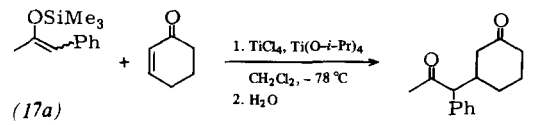
The $TiCl_4$-promoted reaction of α,β-unsaturated ketones with silyl enol ethers of type *(17)* results in the formation of 1,5-dicarbonyl compounds (Michael adducts) such as *(55)*

and *(56)* in fairly good yields instead of the aldol-type product[36].

In general, the Michael reaction of α,β-unsaturated carbonyl compounds and ketones is carried out under basic condition. The resulting 1,5-dicarbonyl compounds frequently undergo further transformation, and self-condensation of starting material is also observed. In contrast, the $TiCl_4$-promoted Michael reaction proceeds under very mild conditions (−78 °C); the side reactions are therefore largely suppressed and the 1,5-dicarbonyl compounds are formed in good yields. In some cases, when highly $TiCl_4$-sensitive compounds such as isopropenyl trimethylsilyl ether, 2-cyclohexen-1-one, or isopropenyl methyl ketone are employed, the reaction must be carried out in the joint presence of $TiCl_4$ and $Ti[O—CH(CH_3)_2]_4$.

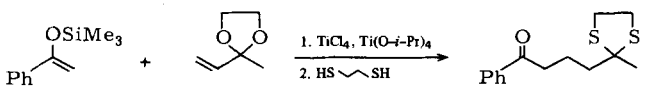


(17d) *(55)*, 95%



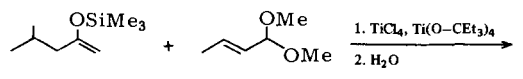
(17a) *(56)*, 70%

The combined use of $TiCl_4$ and $Ti[O—CH(CH_3)_2]_4$ is also applicable to the Michael reaction of α,β-unsaturated acetals such as *(57)* with silyl enol ethers; subsequent treatment of the reaction mixture with ethanedithiol gives the corresponding δ-oxothioacetals[36b].

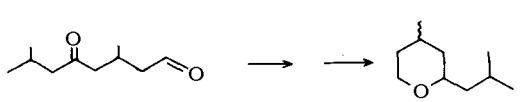


(17c) *(57)*

However, when crotonaldehyde dimethyl acetal *(58)* is treated with silyl enol ether in the presence of $TiCl_4$/$Ti[OCH(CH_3)_2]_4$, the desired Michael product is not formed but a β-alkoxy ketone. In such cases, the acetal is treated with $TiCl_4$ and $Ti[O—CEt_3]_4$ prior to addition of silyl enol ether in order to replace at least one of the methoxy groups by the bulky Et_3CO group and thus introduce steric hindrance around the acetal group. Subsequent treatment of the mixture with silyl enol ether gives the Michael product almost exclusively, and dihydro rose oxide *(59)* is readily synthesized by this reaction[36b].

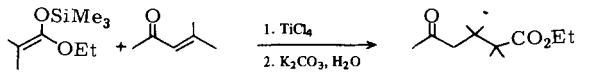


(58)



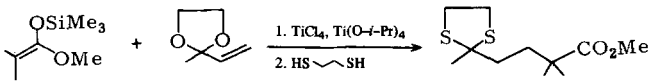
(59)

Ketene alkyl trimethylsilyl acetals also react with α,β-unsaturated ketones or their acetals in the presence of $TiCl_4$, in some cases together with $Ti[O—CH(CH_3)_2]_4$, to give the Michael products, δ-oxo esters *(60)*, in good yields[37].



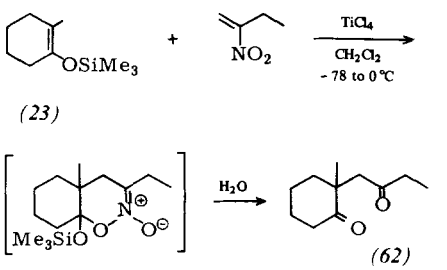
(60), 72%

Ethylene thioacetals *(61)* arise on treatment of ketene alkyl trialkylsilyl acetals with acetals of α,β-unsaturated ketones in the presence of $TiCl_4$ and $Ti[O—CH(CH_3)_2]_4$ and subsequent reaction with ethanedithiol[37].



(57) *(61)*, 90%

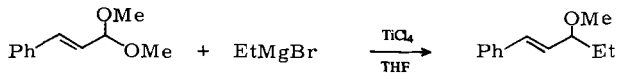
Similarly, *Yoshikoshi et al.* reported that the Michael reaction of nitroolefins and silyl enol ethers also proceeds in the presence of $TiCl_4$ or $SnCl_4$, and affords the Michael product, which is easily hydrolyzed to the 1,4-diketone *(62)* without having to be isolated. The high regiospecificity observed in the selective formation of 1,4-diketones demonstrates that no double bond migration of silyl enol ethers takes place during the reaction[38].



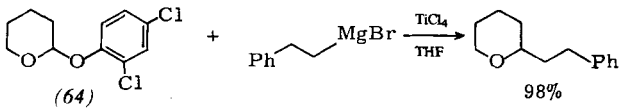
(23) *(62)*

3.3. Other Carbon-Carbon Linkages

Alkylation of acetals with Grignard reagent is accomplished by the use of $TiCl_4$. While acetals derived from α,β-unsaturated aldehydes such as *(63)* react smoothly with Grignard reagent, those derived from aliphatic aldehydes and ketones do not react at all. However, good yields of alkylation products can be obtained in the latter case if mixed acetals, in particular alkyl 2,4-dichlorophenyl acetals, are employed in place of the above mentioned acetals[39].



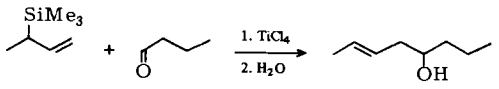
(63) 83%



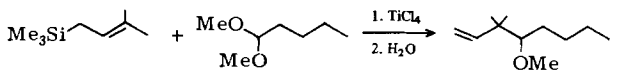
(64) 98%

Another alkylation reaction is reported by *Sakurai et al.*, *i.e.* the treatment of carbonyl compounds or acetals with allylsilanes in the presence of $TiCl_4$ to give β,γ-unsaturated

alcohols or ethers such as *(65)* and *(66)*. The synthetic utility of the reaction lies in the regiospecific transformation of the allylic group into a carbonyl or an acetal function, attack occurring exclusively at the γ-position of the allylsilanes[40].

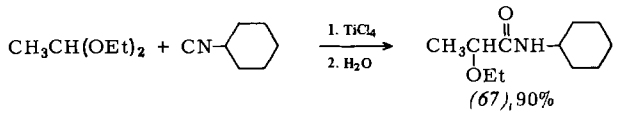


(65), 89%



(66), 80%

Acetal-$TiCl_4$ complexes immediately react with isocyanides at −70°C, and α-alkoxy carboxamides like *(67)* are formed in better yields than in the Passerini reaction[41].



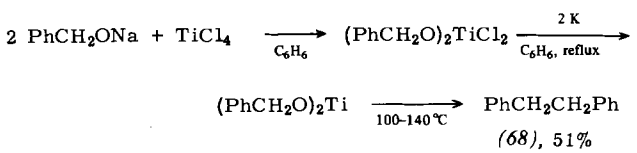
(67), 90%

Sato et al. reported that $TiCl_4$ exhibits a remarkable effect on the photochemical reaction of α,β-unsaturated ketones with methanol. Two types of reaction are observed under these conditions: a) cyclization to form dihydrofuran, and b) replacement of the carbonyl function by a dimethoxymethyl group[42]. In both cases an additional carbon atom is introduced.

4. Syntheses with Titanium Tetrachloride Reduced *in situ*

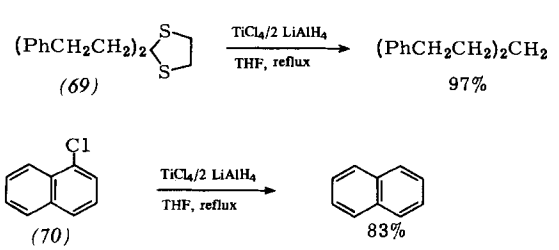
In the present Section an attempt is made to survey synthetic reactions utilizing low-valent titanium compounds accessible from $TiCl_4$ and reducing reagents. The reactions of $TiCl_3$ are not included (for review, see [43]).

The pioneering work by *van Tamelen* on reductive coupling of allylic or benzylic alcohols to form hydrocarbons such as *(68)*[44] demonstrated the fascinating potential of low-valent titanium compounds in organic synthesis.



(68), 51%

Sulfides and haloarenes, *e.g. (69)* and *(70)*, are easily reduced to the corresponding hydrocarbons in good yields

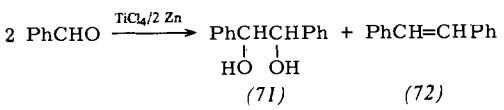


(69) 97%

(70) 83%

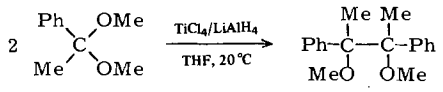
by the low-valent titanium compounds obtained from $TiCl_4$ and two equivalents of $LiAlH_4$[45].

When aldehydes or ketones are treated with low-valent titanium compounds produced from $TiCl_4$ and Zn, reductive coupling readily proceeds and, depending on the reaction conditions, the diol *(71)* or the alkene *(72)* is obtained in excellent yield[46]. In THF at room temperature 98 % of *(71)* and 1 % of *(72)*, are formed, and in boiling dioxane 98 % of *(72)* and no *(71)*.

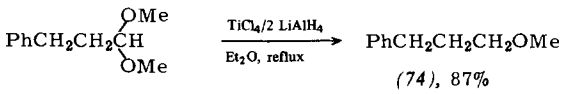


(71) *(72)*

On combined use of $TiCl_4$ and $LiAlH_4$ instead of Zn, reductive coupling of acetals derived from aromatic aldehydes or ketones also affords the diol ether *(73)*. However, when acetals of aliphatic aldehydes or ketones are treated with $TiCl_4$ and two equivalents of $LiAlH_4$, one of the alkoxy groups is reduced to afford the ether, *e.g. (74)*[47].

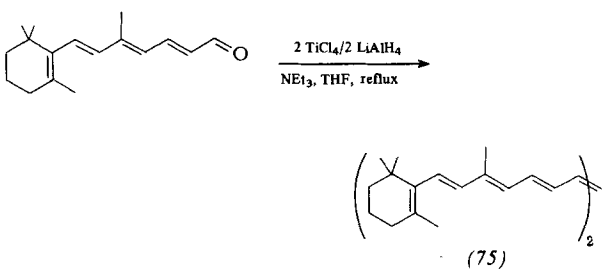


(73), 97%



(74), 87%

The reduction by the $TiCl_4/LiAlH_4$ reagent is applicable to the preparation of symmetrical polyalkenes. In the presence of a tertiary amine as proton sponge, polyenic ketones or aldehydes are readily converted into the polyenes by treatment with equimolar amounts of $TiCl_4/LiAlH_4$. β-Carotene *(75)* has been synthesized in this way from retinal in good yield[48].

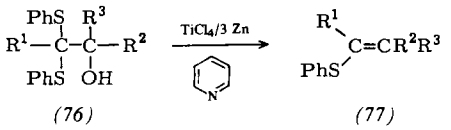


(75)

Similar reductive couplings of carbonyl compounds have also been reported independently by *Tyrlik et al.*[49] and by *McMurry et al.*[50] (see ref. [43]); they used combinations of $TiCl_3$ and reducing reagents.

The use of low-valent titanium compound has also been applied to the reduction of β-hydroxy sulfides to alkenes such as vinyl sulfides, styrene derivatives, and *exo*-methylene compounds. β-Hydroxy thioacetals of type *(76)*, which are easily prepared from carbonyl compounds and α-lithio thioacetals, are reduced by $TiCl_4/Zn$ in the presence of tertiary amines to give the corresponding vinyl sulfides *(77)* in good yields (Table 6)[51]. As mentioned before, the resulting vinyl sulfides are easily hydrolyzed to ketones with $TiCl_4$. Hence a combination of these two reactions provides a con-

venient route for joining two carbonyl compounds to form a new one.

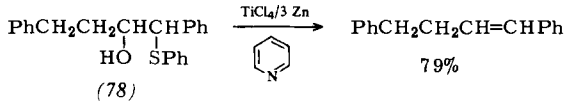


(76) (77)

Table 6. Synthesis of vinyl sulfides of type *(77)*.

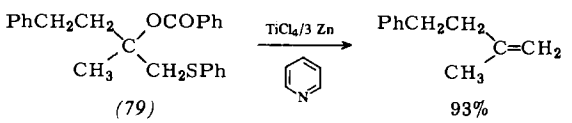
R^1	R^2	R^3	Yield [%]
H	n-C_5H_{11}	H	84
H	Ph	Me	91
H	—$(CH_2)_5$—		90
n-Bu	n-C_5H_{11}	H	82

Styrene derivatives can be synthesized by reduction of β-hydroxy sulfides *(78)*, prepared from aldehydes or ketones and the α-lithio benzyl phenyl sulfides, with $TiCl_4$ and Zn[52].



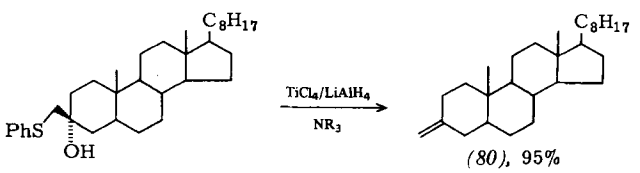
(78)

A general synthetic method for the synthesis of terminal alkenes from ketones proceeds *via* β-hydroxy sulfides which are readily available from ketones and phenylthiomethyllithium. Reductive elimination of β-hydroxy sulfides leads to the terminal alkenes in fairly good yields according to *Coates et al.* by acylation of β-hydroxy sulfides and subsequent reduction with Li/NH_3[53]. The same reductive elimination takes place even at room temperature when β-arylthioalkyl benzoates *(79)* are treated with $TiCl_4$/Zn in pyridine[54].



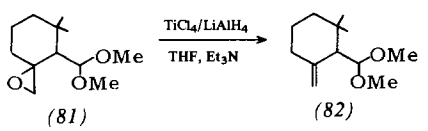
(79) 93%

When $TiCl_4/LiAlH_4$ is employed as reducing reagent, the reaction of β-hydroxy sulfides in the presence of a tertiary amine directly affords the corresponding terminal alkenes in high yields, and the benzoylation step becomes unnecessary[55]. The steroid derivative *(80)* is synthesized in benzene/dioxane.



(80), 95%

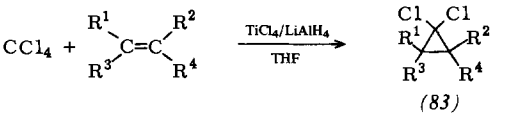
Another preparative entry to terminal alkenes starts from epoxides. For example, the epoxy acetal *(81)* is reduced to the *exo*-methylene acetal *(82)* with $TiCl_4/LiAlH_4$ in the presence of triethylamine[56].



(81) (82)

The same reduction with $TiCl_3$ was also recently reported by *McMurry*[57].

All the alkene syntheses mentioned above proceed as β-eliminations. In addition, reductive α-eliminations of polyhalogenated compounds can also be accomplished with low-valent



(83)

Table 7. Synthesis of 1,1-dichlorocyclopropane derivatives *(83)*.

R^1	R^2	R^3	R^4	Yield [%]
—$(CH_2)_4$—		H	H	79
—$(CH_2)_6$—		H	H	82
Me	Me	Me	Me	65
—$O(CH_2)_3$—		H	H	79

titanium compounds, and have been applied for the preparation of *gem*-dichlorocyclopropanes *(83)* in good yields by treatment of carbon tetrachloride and alkene with a low-valent titanium compound prepared from equimolar amounts of $TiCl_4$ and $LiAlH_4$ (Table 7)[58]. This method is useful in view of its facile execution and the ready availability of the starting materials.

5. Conclusion

Titanium tetrachloride is a valuable reagent promoting various synthetic reactions, both in cases requiring a stoichiometric amount of $TiCl_4$ and on use of a catalytic amount of $TiCl_4$ together with other metal salts.

In order to synthesize complex molecules, exploration of new reactions proceeding smoothly under almost neutral conditions without any assistance of acids or bases is urgently required. When exploring such reactions, it is often profitable to make use of characteristic properties of various elements such as phosphorus and sulfur which are prone to undergo "oxidation-reduction condensation"[59]. Furthermore, a combination of first row elements could also become an important tool for developing new synthetic reactions.

Received: December 28, 1976 [A 190 IE]
German version: Angew. Chem. *89*, 858 (1977)

[1] Chem. Eng. News *33*, 4226 (1955).
[2] a) *J. P. Wilson, H. Weingarten*, Can. J. Chem. *48*, 983 (1971); b) *W. Lehnert, W. Künger*, Tetrahedron Lett. *1971*, 1501; c) *W. A. White, H. Weingarten*, J. Org. Chem. *32*, 213 (1967).
[3] *T. Mukaiyama, T. Izawa*, unpublished results.
[4] *T. Mukaiyama, K. Kamio, S. Kobayashi, H. Takei*, Chem. Lett. *1973*, 357.
[5] *T. Mukaiyama, K. Saigo*, Chem. Lett. *1973*, 479.
[6] *T. Mukaiyama, T. Izawa, K. Saigo, H. Takei*, Chem. Lett. *1973*, 355.
[7] *E. J. Corey, J. I. Shulman*, J. Org. Chem. *35*, 777 (1970).
[8] *T. Mukaiyama, K. Kamio, S. Kobayashi, H. Takei*, Bull. Chem. Soc. Jpn. *45*, 3723 (1972).
[9] *L. Velluz, G. Nominé, J. Mathieu*, Angew. Chem. *72*, 725 (1960); *R. Bucourt, J. Tessier, G. Nominé*, Bull. Soc. Chem. Fr. *1963*, 1923; *S. Julia, ibid. 1954*, 780.
[10] *T. Mukaiyama, T. Imamoto, S. Kobayashi*, Chem. Lett. *1973*, 261, 715.
[11] *G. Wittig, H. Reiff*, Angew. Chem. *80*, 8 (1968); Angew. Chem. Int. Ed. Engl. 7, 7 (1968); *G. Wittig, A. Hesse*, Org. Synth. *50*, 66 (1970).
[12] *E. J. Corey, D. Enders*, Tetrahedron Lett. *1976*, 3, 11; *E. J. Corey, D. Enders, M. G. Bock, ibid. 1976*, 7.
[13] *G. Stork, M. Isobe*, J. Am. Chem. Soc. *97*, 4745 (1975).

[14] *H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead*, J. Am. Chem. Soc. *95*, 3310 (1973).
[15] *T. Mukaiyama, K. Inomata, M. Muraki*, J. Am. Chem. Soc. *95*, 967 (1973); Bull. Chem. Soc. Jpn. *46*, 1807 (1973).
[16] a) *T. Mukaiyama, K. Narasaka, K. Banno*, Chem. Lett. *1973*, 1011; b) J. Am. Chem. Soc. *96*, 7503 (1974).
[17] *K. Banno, T. Mukaiyama*, Chem. Lett. *1976*, 279.
[18] *T. Mukaiyama, M. Hayashi*, Chem. Lett. *1974*, 15.
[19] *T. Mukaiyama, H. Ishihara, K. Inomata*, Chem. Lett. *1975*, 527.
[20] *H. Ishihara, K. Inomata, T. Mukaiyama*, Chem. Lett. *1975*, 531.
[21] *T. Mukaiyama, A. Ishida*, Chem. Lett. *1975*, 319.
[22] *I. N. Nazarov, Zh. A. Krasnaya*, Dokl. Akad. Nauk SSSR *118*, 716 (1958); *121*, 1034 (1958); *Zh. A. Krasnaya, V. F. Kucherov*, Zh. Obshch. Khim. *32*, 64 (1962); Chem. Abstr. *52*, 11737 (1958); *53*, 1183 (1959); *57*, 16671 (1962).
[23] *A. Ishida, T. Mukaiyama*, Chem. Lett. *1975*, 1167.
[24] a) *T. Mukaiyama, A. Ishida*, Chem. Lett. *1975*, 1201; b) *ibid.*, in press.
[25] *Y. Hayashi, M. Nishizawa, T. Sakan*, Chem. Lett. *1975*, 387.
[26] *E. Kitazawa, T. Imamura, K. Saigo, T. Mukaiyama*, Chem. Lett. *1975*, 569.
[27] *T. Mukaiyama, T. Izawa, K. Saigo*, Chem. Lett. *1974*, 323.
[28] *S. S. Yufit, V. F. Kucherov*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 1658; Chem. Abstr. *55*, 9273 (1961).
[29] *T. Izawa, T. Mukaiyama*, Chem. Lett. *1974*, 1189.
[30] *T. Izawa, T. Mukaiyama*, Chem. Lett. *1975*, 161.
[31] *T. Mukaiyama, J. Hanna, T. Inoue, T. Sato*, Chem. Lett. *1974*, 381.
[32] *T. Mukaiyama, M. Wada, J. Hanna*, Chem. Lett. *1974*, 1181.
[33] *K. Saigo, M. Osaki, T. Mukaiyama*, Chem. Lett. *1975*, 989.
[34] *K. Saigo, M. Osaki, T. Mukaiyama*, Chem. Lett. *1976*, 769.
[35] *L. Vuitel, A. J. Guillarmod*, Synthesis *1972*, 608; Helv. Chim. Acta *57*, 1703 (1974).
[36] a) *K. Narasaka, K. Soai, T. Mukaiyama*, Chem. Lett. *1974*, 1223; b) *K. Narasaka, K. Soai, Y. Aikawa, T. Mukaiyama*, Bull. Chem. Soc. Jpn. *49*, 779 (1976).
[37] *K. Saigo, M. Osaki, T. Mukaiyama*, Chem. Lett. *1976*, 163.
[38] *M. Miyashita, T. Yanami, A. Yoshikoshi*, J. Am. Chem. Soc. *98*, 4679 (1976).
[39] *H. Ishikawa, T. Mukaiyama*, Chem. Lett. *1975*, 305.
[40] *A. Hosomi, H. Sakurai*, Tetrahedron Lett. *1976*, 1295; *A. Hosomi, M. Endo, H. Sakurai*, Chem. Lett. *1976*, 941.
[41] *T. Mukaiyama, K. Watanabe, M. Shiono*, Chem. Lett. *1974*, 1457.
[42] *T. Sato, G. Izumi, T. Imamura*, Tetrahedron Lett. *1975*, 2191.
[43] *J. E. McMurry*, Acc. Chem. Res. *7*, 281 (1974).
[44] *E. E. van Tamelen, M. A. Schwartz*, J. Am. Chem. Soc. *87*, 3277 (1965).
[45] *T. Mukaiyama, M. Hayashi, K. Narasaka*, Chem. Lett. *1973*, 291.
[46] *T. Mukaiyama, T. Sato, J. Hanna*, Chem. Lett. *1973*, 1041.
[47] *T. Mukaiyama, H. Ishikawa*, unpublished results.
[48] *A. Ishida, T. Mukaiyama*, Chem. Lett. *1976*, 1127.
[49] *S. Tyrlik, M. I. Wolchowicz*, Bull. Soc. Chim. Fr. *1973*, 2147.
[50] *J. E. McMurry, M. P. Fleming*, J. Am. Chem. Soc. *96*, 4708 (1974).
[51] *T. Mukaiyama, M. Shiono, T. Sato*, Chem. Lett. *1974*, 37.
[52] *S. Song, M. Shiono, T. Mukaiyama*, Chem. Lett. *1974*, 1161.
[53] *R. L. Sowerby, R. M. Coates*, J. Am. Chem. Soc. *94*, 4758 (1972).
[54] *T. Mukaiyama, T. Watanabe, M. Shiono*, Chem. Lett. *1974*, 1523.
[55] *Y. Watanabe, M. Shiono, T. Mukaiyama*, Chem. Lett. *1975*, 871.
[56] *T. Mukaiyama, K. Saigo, O. Takazawa*, Chem. Lett. *1976*, 1033.
[57] *J. E. McMurry, M. P. Fleming*, J. Org. Chem. *40*, 2555 (1975).
[58] *T. Mukaiyama, M. Shiono, K. Watanabe, M. Onaka*, Chem. Lett. *1975*, 711.
[59] *T. Mukaiyama*, Angew. Chem. *88*, 111 (1976); Angew. Chem. Int. Ed. Engl. *15*, 94 (1976).

Spontaneous Alternating Copolymerization *via* Zwitterion Intermediates

By Takeo Saegusa [*]

This article describes a new concept of copolymerization which occurs spontaneously without any added catalyst. A nucleophilic monomer (M_N) combines with an electrophilic one (M_E) to generate a zwitterion $^{+}M_N—M_E^{-}$, which is responsible for the initiation and propagation of copolymerization. Twenty-three novel copolymerizations have been explored on the basis of the new concept. M_N monomers which have been investigated are five- and six-membered cyclic imino ethers, dihydro-2(3*H*)-furanimine, an azetidine, a cyclic phosphinic acid ester and a Schiff base; the M_E monomers include β-propiolactone, a cyclic dicarboxylic acid anhydride, a sultone, acrylic acid, acrylamide, a β-hydroxyalkyl acrylate and ethylenesulfonamide. In most combinations, alternating 1:1 copolymers were produced. In addition to the above-mentioned combinations, the alternating 1:1 copolymerization of cyclic phosphite with α-keto acid was discovered.

1. General Scheme

Induction of a polymerization reaction usually requires a catalyst, an initiator or high energy radiation. This article describes a new concept of copolymerization without the addition of an initiator. Interaction of two monomers affords a zwitterion, which is the responsible species for the copolymerization.

In organic chemistry, the reaction between a nucleophile and an electrophile is a typical example of a reaction which takes place without added catalyst. The nucleophile-electrophile reactions are classified into three categories according to the charge of the reactants:

1. both reactants are charged [*e.g.* eq. (a)],
2. one reactant is charged and the other is neutral [*e.g.* eq. (b) and (c)],
3. both reactants are neutral [*e.g.* eq. (d)].

$$Me_4\overset{\oplus}{N}OH^{\ominus} + Et_3\overset{\oplus}{O}BF_4^{\ominus} \longrightarrow EtOH + Et_2O + Me_4\overset{\oplus}{N}BF_4^{\ominus} \quad (a)$$

$$Me_3N + Me_3\overset{\oplus}{S}Cl^{\ominus} \longrightarrow Me_4\overset{\oplus}{N}Cl^{\ominus} + Me_2S \quad (b)$$

$$\overset{\oplus}{Na}CN^{\ominus} + EtI \longrightarrow EtCN + Na^{\oplus}I^{\ominus} \quad (c)$$

$$Me_3N + MeI \longrightarrow Me_4\overset{\oplus}{N}I^{\ominus} \quad (d)$$

[*] Prof. Dr. T. Saegusa
Department of Synthetic Chemistry
Kyoto University, Kyoto 606 (Japan)

The concept of spontaneous alternating copolymerization described here is based upon the reaction pattern of the third category[1]. Thus, a monomer having nucleophilic reactivity (M_N) is admixed with an electrophilic monomer (M_E) to produce a zwitterion *(1)*, which is called a "genetic zwitterion".

$$M_N + M_E \longrightarrow {}^{\oplus}M_N\text{–}M_E^{\ominus} \quad (e)$$
(1)

The genetic zwitterion is responsible for initiation as well as for propagation of the chain. Two molecules of *(1)* react with each other to produce the first propagating species *(2)* [eq. (f)], which continues to grow by successive reactions with *(1)* [eq. (g)]. Hereafter, the propagating species, *(2)* and *(3)*, are called "macrozwitterions".

$$(1) + (1) \longrightarrow {}^{\oplus}M_NM_E\text{–}M_NM_E^{\ominus} \quad (f)$$
(2)

$$(2) + n(1) \longrightarrow {}^{\oplus}M_N\text{–}(M_EM_N)_{n+1}\text{–}M_E^{\ominus} \quad (g)$$
(3)

The reaction between two macrozwitterions *(3)* leads to a sharp increase in the degree of polymerization of the propagating species [eq. (h)].

$${}^{\oplus}M_N\text{–}(M_EM_N)_m\text{–}M_E^{\ominus} + {}^{\oplus}M_N\text{–}(M_EM_N)_n\text{–}M_E^{\ominus} \longrightarrow {}^{\oplus}M_N\text{–}(M_EM_N)_{m+n+1}\text{–}M_E^{\ominus} \quad (h)$$

The contribution of the reaction of eq. (h) to the total reaction becomes substantial at the stage of high conversions, where the concentration of *(3)* is quite high.

Intramolecular reactions between the cationic and anionic sites in a single macrozwitterion can produce so-called "macrocycles" [eq. (i)]. However, the contribution of this reaction is usually small.

$${}^{\oplus}M_N\text{–}(M_EM_N)_n\text{–}M_E^{\ominus} \longrightarrow \boxed{\text{–}(M_NM_E)_{n+1}\text{–}} \quad (i)$$

A series of consecutive reactions—shown in equations (g), (h) and (i)—leads to formation of a copolymer with the alternating structure $\cdots M_NM_EM_NM_E\cdots$. Besides the above mentioned elementary reactions, the reaction between a free monomer and one of the ionic sites (cationic or anionic) of the zwitterion (genetic or macro) can also occur in some cases [eqs. (j) and (k)].

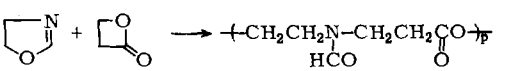
$${}^{\oplus}M_N\text{–}(M_EM_N)_n\text{–}M_E^{\ominus} \xrightarrow{M_N} {}^{\oplus}M_NM_N\text{–}(M_EM_N)_n\text{–}M_E^{\ominus} \quad (j)$$

$${}^{\oplus}M_N\text{–}(M_EM_N)_n\text{–}M_E^{\ominus} \xrightarrow{M_E} {}^{\oplus}M_N\text{–}(M_EM_N)_n\text{–}M_EM_E^{\ominus} \quad (k)$$

The above homopropagations disturb the alternating arrangements of M_N and M_E units in the product. Alternating propagation [eqs. (e) and (f)] and homopropagation [eqs. (j) and (k)] compete with each other. Whether homopropagation is excluded or not depends upon the reactivity characteristics of the monomers. Alternating copolymer is produced when a dipole-dipole reaction between M_N and M_E monomers producing *(1)* occurs in preference to ion-dipole reactions between ionic centers of zwitterions and monomers.

2. Alternating Copolymerization between 2-Oxazoline and β-Propiolactone[2]

Alternating copolymerization of 2-oxazoline *(4)* with β-propiolactone *(5)* is described first in order to illustrate the general character of this new type of copolymerization.

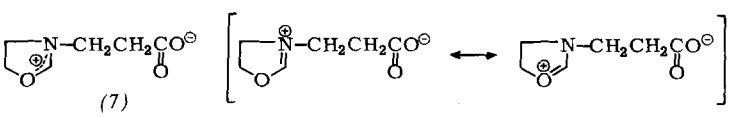


(4) *(5)* *(6)*

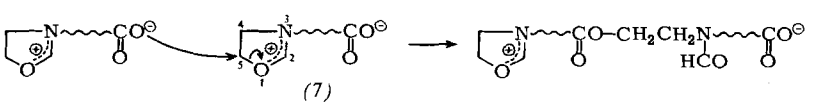
When a solution of an equimolar mixture of *(4)* and *(5)* in an aprotic polar solvent such as DMF was kept at room temperature, the solution gradually became viscous, and after one day the alternating copolymer *(6)* was formed in almost quantitative yield[2].

In this copolymerization, *(4)* behaves as M_N and *(5)* as M_E. A zwitterion *(7)* is the key intermediate for the polymerization. The onium ring derived from *(4)* is opened by nucleophilic attack of the carboxylate anion at C-5 [eq. (l)].

Figure 1 shows the variation of two parameters during the course of copolymerization; the solid line shows the relation between the molecular weight of the copolymer and the percent conversion, while the broken line shows the change of the quotient of the amount of copolymer divided by its



(7)



(7) (l)

molecular weight. This quotient is proportional to the number of copolymer molecules. The number of macrozwitterions, *i.e.* copolymer molecules, increases at the beginning (points 1—3), then reaches a maximum (point 4), and finally decreases as the conversion becomes higher (points 5—7). The shapes

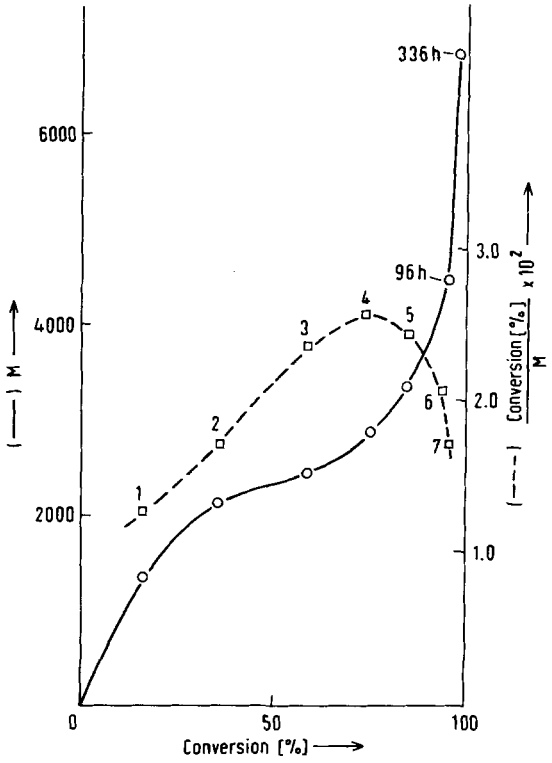


Fig. 1. Copolymerization of 2-oxazoline *(4)* with β-propiolactone *(5)* in DMF at 40°C [2]. 1 to 7, see text.

of the curves reflect the ratio of formation and consumption of the macrozwitterions [eqs. (f) and (h), respectively]. Before point 4, the reaction according to eq. (f) is faster than that according to eq. (h) because the concentration of both monomers is high and formation of the genetic zwitterion *(7)* is favored. This relationship is reversed after point 4, since the concentration of macrozwitterions becomes higher,

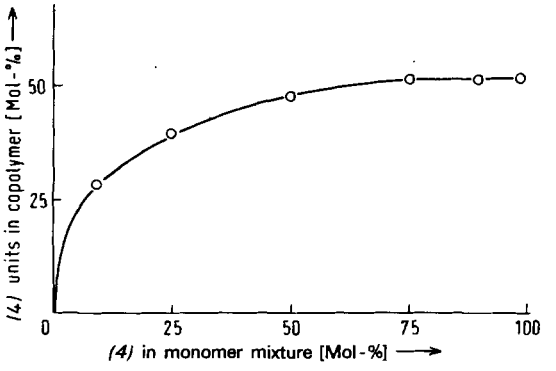


Fig. 2. Copolymerization of 2-oxazoline *(4)* with β-propiolactone *(5)* in acetonitrile at 25°C [1a].

the monomer concentration decreases, and the macrozwitterions preferably react with each other. At the transition stage (points 3—5), where the polyaddition reaction according to eq. (g) predominates, the change in number of macrozwitterions is small.

Figure 2 shows the change in copolymer composition with varying monomer feed ratios. When the mole fraction of 2-oxazoline *(4)* in the monomer mixture is less than 50% (and correspondingly the fraction of β-propiolactone *(5)* is greater than 50%), the carboxylate end-group of the zwitterion reacts not only with cyclic onium sites of the zwitterions but also with free β-propiolactone *(5)* to produce copolymers consisting of more than 50% of β-propiolactone units. The reaction of carboxylate anions with *(5)* corresponds to the propagation of the anionic polymerization of *(5)*, which is quite possible under the conditions of alternating copolymerization, *i.e.* at room temperature in a polar aprotic solvent. In mixtures with more than 50% *(4)*, however, the cationic homopropagation of 2-oxazoline *(4)* is very slow under these conditions[3, 4]; consequently the propagation of a genetic zwitterion leads exclusively to an alternating copolymer.

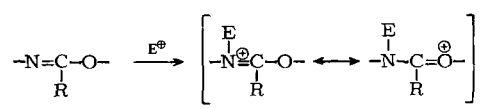
Copolymerizations of 2-oxazoline *(4)* with α-methyl-β-propiolactone and with α,α-dimethyl-β-propiolactone proceeded in a similar way[5]. The overall rates of copolymerization follow the sequence *(5)* > α-methyl- > α,α-dimethyl-β-propiolactone. This sequence is consistent with the order of reactivity of the β-lactones towards nucleophiles[6].

3. Scope of Copolymerization

So far six monomers of type M_N and seven monomers of type M_E have been examined as reactants for this novel copolymerization. Thus, the number of possible combinations of copolymerization is six times seven, *i.e.*, forty-two. Of these, 23 have been examined. Table 1 summarizes the results. In all 23 combinations, copolymerization took place as expected, without any added catalyst.

As mentioned above, the character of copolymerization, *i.e.* alternating or non-alternating, depends upon the reactivity characteristics of the monomers. In Table 1, a letter A in parentheses indicates that alternating copolymerization is possible under a wide variety of reaction conditions, a letter B means that an alternating copolymerization is possible under suitable reaction conditions, and a letter C indicates those cases in which alternating copolymerization has not yet been realized.

Of the monomers of type M_N, 2-oxazolines *(8)*, 5,6-dihydro-4*H*-1,3-oxazines *(10)*, 4,5-dihydro-2(3*H*)furanimine *(12)* and 2-phenyl-1,3,2-dioxaphospholane *(16)* are quite reactive. The responsible functional group in *(8)*, *(10)* and *(12)* is the imino ether group (imidate group) *(32)*, which reacts with electrophiles to give a cation *(33)* stabilized by ammonium-oxonium resonance. Thus, cyclic imidates are highly polarizable and reactive nucleophiles.



(32) *(33)*

Table 1. M_N and M_E monomers, cationic and anionic groups and combinations. Empty fields: not examined. (A): alternating copolymerization under almost all conditions, (B) alternating copolymerization under certain conditions, (C) no alternating copolymerization.

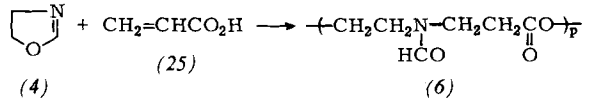
M_N \ M_E	(5)	(21)	(23)	$CH_2=CHCO_2H$ (25)	$CH_2=CHCONH_2$ (26)	$CH_2=CHCOCH_2CH_2OH$ (28)	$CH_2=CHSO_2NH_2$ (30)
$-M_E^{\ominus}$	$-CH_2CH_2CO^{\ominus}$ (20)	$-CCH_2CH_2CO^{\ominus}$ (22)	$-(CH_2)_3SO_3^{\ominus}$ (24)	$-CH_2CH_2CO^{\ominus}$ (20)	$-CH_2CH_2C^{\ominus}(=O)NH$ (27)	$-CH_2CH_2COCH_2CH_2O^{\ominus}$ (29)	$-CH_2CH_2S^{\ominus}(=O)_2NH$ (31)
$^{\oplus}M_N-$							
(8)	(9)	[2, 5] R=H [≡(4)] (B) R=Me (C)	[7] R=H (A)	[8] R=H (C) R=Me (B)	[9] R=H (A) R=Me (A)	[10] R=H (A) R=Me (A)	[11] R=Me (A)	[12] R=Me (B)
(10)	(11)	[13] R=H (B) R=Me (C) R=Ph [≡(34)] (C)			[13] R=H (A) R=Me (A) R=Ph (A)	[10] R=H	[11] R=H (A)	
(12)	(13)	[14] R=CH_2Ph (B)			[14] R=CH_2Ph (A)			
(14)	(15)	[15]			[15]			
(16)	(17)	[16] (A)		[17] (A)	[16] (A)	[16] (A)		[17] (A)
ArCH=NAr' (18)	$ArCH=\overset{\oplus}{N}-$ Ar (19)	[18] Ar=Ar'=Ph (C)	[18] Ar=Ar'=Ph (A)		[18] Ar=Ar'=Ph (B)			

Trivalent phosphorus compounds such as *(16)* are also known to be strong nucleophiles of high polarizability. In other words, M_N monomers of type *(8)*, *(10)*, *(12)* and *(16)* are soft nucleophiles and they prefer soft electrophiles to hard electrophiles of the onium-zwitterion type. It is seen in Table 1 that the combinations of copolymerizations between soft M_N monomers [*(8)*, *(10)*, *(12)* and *(16)*] and soft M_E monomers [*(25)*, *(26)*, *(28)* and *(30)*] have a strong tendency to form alternating copolymers. Dipole-dipole reactions are favored in these combinations.

Studies carried out on M_N and M_E monomers have led to new findings which are of importance not only for polymer chemistry but also for preparative organic chemistry. The following sections deal with these new developments.

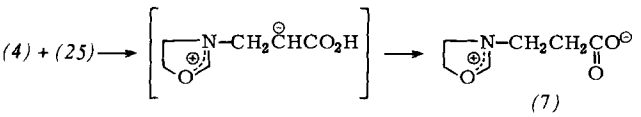
4. Copolymerization of Acrylic Monomers with Nitrogen-Containing Nucleophilic Monomers

An equimolar mixture of 2-oxazoline *(4)* and acrylic acid *(25)* in acetonitrile was heated at 60°C in the presence of a small amount of *p*-methoxyphenol as radical inhibitor. The reaction mixture became viscous, and the alternating copolymer *(6)* was formed[9].



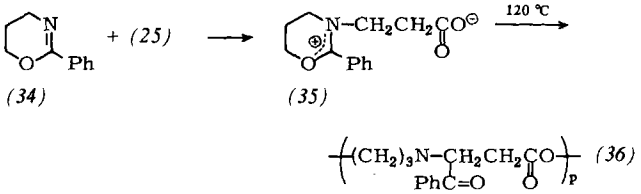
(4) + $CH_2=CHCO_2H$ *(25)* → $-(CH_2CH_2N(HCO)-CH_2CH_2CO)_p-$ *(6)*

The structure of the product *(6)* is the same as that of the 2-oxazoline/β-propiolactone copolymer, *i.e.* acrylic acid is converted into the same repeat unit as that formed in the ring-opening of β-propiolactone *(5)*. A reaction scheme leading to a zwitterion *(7)* has been suggested, which involves nucleophilic attack of *(4)* on the acrylic acid *(25)* followed by proton migration.



(4) + *(25)* → [N–CH_2–$\overset{\ominus}{C}$HCO_2H] → N–$CH_2CH_2CO^{\ominus}$ *(7)*

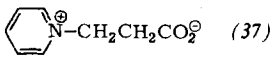
Indeed, from an equimolar mixture of 2-phenyl-5,6-dihydro-4*H*-1,3-oxazine *(34)* and acrylic acid *(25)* in acetonitrile at 5°C, a zwitterion *(35)* was in fact isolated as a crystalline solid[19]. *(35)* is very hygroscopic, but can be converted into a less-hygroscopic form which contains one mol of water of crystallization and melts at 145–146°C. When heated in bulk at 120°C *(35)* polymerizes to *(36)*, which corresponds to the alternating copolymer of *(34)* with *(25)*. These findings support the reaction scheme involving intermediary zwitter-



(34) + *(25)* → *(35)* (120 °C) → $-(CH_2)_3N(PhC{=}O)-CH_2CH_2CO-_p$ *(36)*

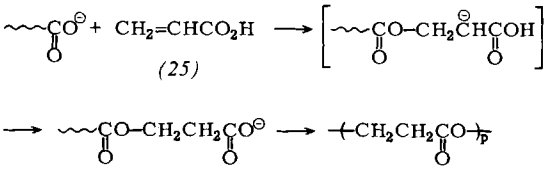
ions.—The copolymerization of acrylic acid with cyclic phosphorus compounds is described in Section 5.

The above observed reaction pattern of acrylic acid, *i.e.* addition of a nucleophile to the electron-deficient double bond and subsequent proton migration, was hitherto not so familiar. A series of our studies, however, have shown it to be quite a general reaction pattern. For example, reaction of pyridine and acrylic acid affords the zwitterion *(37)* which is usually prepared from pyridine and β-propiolactone *(5)*[20].



(37)

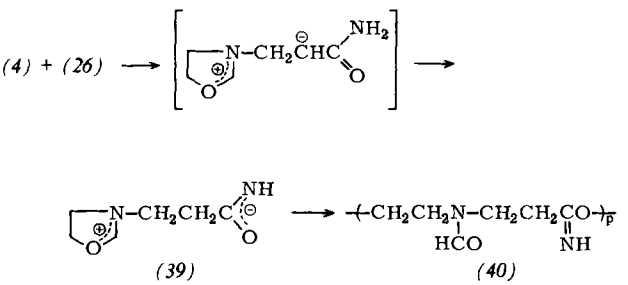
More interesting is the polymerization of acrylic acid, in which proton migration leads to formation of poly-β-propiolactone *(38)*. This reaction is initiated by phosphane, pyridine and other basic catalysts, including even alkali metal hydroxides[21]. The propagation involves repeated addition of a carboxylate anion to the double bond of the monomer followed by migration of a proton.



(25) *(38)*

Interestingly, the reaction pattern of the acrylic acid polymerization described above is also observed in the formation of poly-β-alanine from acrylamide *(26)*[22].

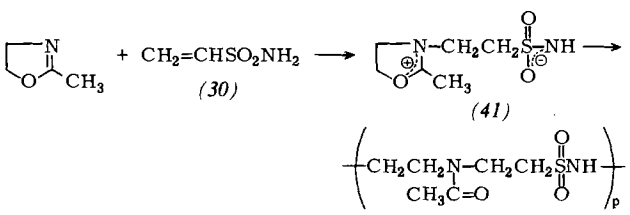
Copolymerizations of acrylamide *(26)* with cyclic imino ethers proceed similarly[10], *i.e.* addition of the cyclic imino ether monomer to the olefinic bond of *(26)* followed by proton migration. Thus, for example, the zwitterion *(39)* is the key intermediate in the copolymerization of *(26)* with *(4)*[10].



(4) + *(26)* *(39)* *(40)*

The anionic moiety of *(39)* is ambifunctional, *i.e.* depending upon the nature of electrophile, it may react either at the oxygen or at the nitrogen atom. Analysis of the copolymers has established that reaction takes place at the oxygen atom in this case.—The copolymerization of acrylamide with cyclic phosphorus compounds is described in Section 5.1.

In this connection, the scheme for copolymerization of ethylenesulfonamide *(30)* with 2-methyl-2-oxazoline is also outlined[12]. In this case, an ambifunctional anionic group of the zwitterion reacts at the nitrogen atom.



(30) *(41)*

The reactions of the anionic groups, both in *(39)* and in *(41)* (and the corresponding macrozwitterions), are regiospecific, although the reaction sites are completely different. An understanding of this regiospecificity requires further studies to be carried out.

Copolymerizations of β-hydroxyalkyl acrylates with cyclic imino ethers proceed similarly. Here too, the genetic zwitterion is formed first by nucleophilic addition of cyclic imino ether to the CC double bond of the acrylate; this is followed by transfer of the proton from the hydroxyl group to the transient carbanion site[11].

5. Copolymerization of Cyclic Phosphorus Compounds with Electrophilic Monomers

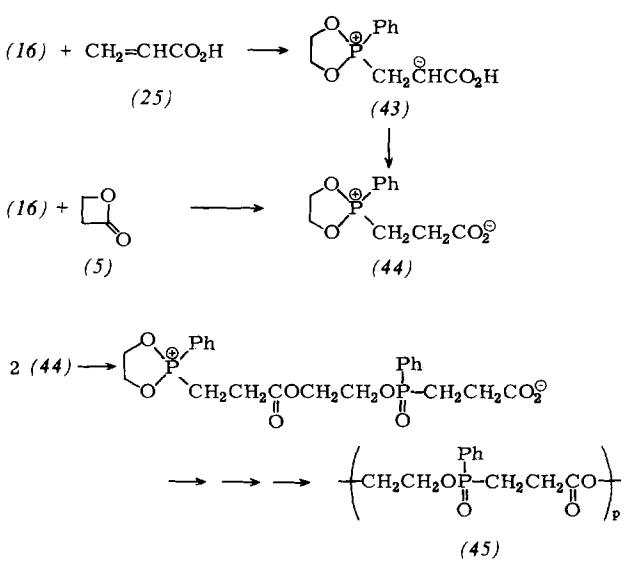
The reaction of two cyclic phosphorus compounds, 2-phenyl-1,3,2-dioxaphospholane *(16)* and 2-phenoxy-1,3,2-dioxaphospholane *(42)*, with several M_E monomers led to novel copolymerizations. Interesting patterns of polymerization as well as of synthetic organic reactions of phosphorus compounds were discovered.



(16) *(42)*

5.1. Copolymerization of the Dioxaphospholane *(16)* and Related Synthetic Reactions

2-Phenyl-1,3,2-dioxaphospholane *(16)* has been successfully copolymerized with the electrophilic monomers *(5)*[16], *(23)*[17], *(25)*[16], *(26)*[16], *(30)*[17], acrylic esters[23], vinyl

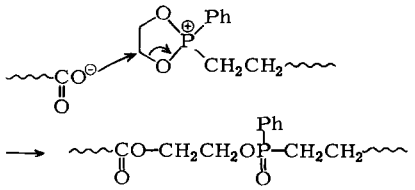


(16) + *(25)* *(43)* *(16)* + *(5)* *(44)* 2 *(44)* *(45)*

ketones[23], and *o*- and *p*-formylbenzoic acids[24] to give the respective 1:1 alternating copolymers.

The copolymerization of *(16)* with β-propiolactone *(5)* and with acrylic acid *(25)* afforded the same alternating copolymer *(45)*[16]. The zwitterion *(44)* is the key intermediate in both cases.

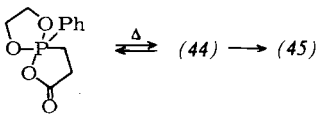
In the reaction with *(5)*, *(44)* is formed directly by ring-opening. In the case of acrylic acid *(25)*, the carbanionic zwitterion *(43)* is first formed and is then rapidly converted into *(44)* by migration of a proton. An analogous reaction scheme for the acrylic acid component has already been mentioned in Section 4. The reaction between phosphonium ring and carboxylate anion, which is responsible for the propagation of genetic and macrozwitterions, proceeds according to the Arbuzov reaction [eq. (m)].



(m)

It should be noted that the trivalent phosphorus in *(16)* is converted into the pentavalent state during copolymerization.

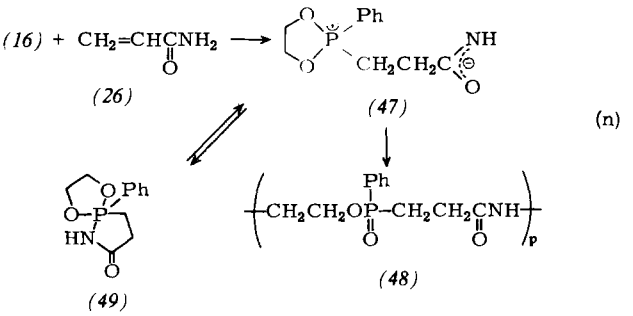
The above copolymerizations take place only at 100°C or higher temperatures[16]. At room temperature, reaction of an equimolar mixture of *(16)* and *(25)* in ether afforded a crystalline material (m.p. 80°C) having structure *(26)* in an almost quantitative yield[25].



(46)

It is reasonably assumed that *(46)* is formed by covalent bonding between the phosphonium and the carboxylate groups in *(44)*; the reaction is probably reversible. Heating of *(46)* to 150°C in DMF or in substance leads to the copolymer *(45)*[16]. At higher temperatures, the P—OC(O) bond in *(46)* undergoes heterolytic cleavage to give the zwitterion *(44)*, which promotes the polymerization. Thus, this reaction is a novel type of ring-opening polymerization which is initiated thermally and proceeds *via* zwitterion intermediates.

A similar copolymerization of *(16)* is observed also with acrylamide *(26)* [eq. (n)][16].

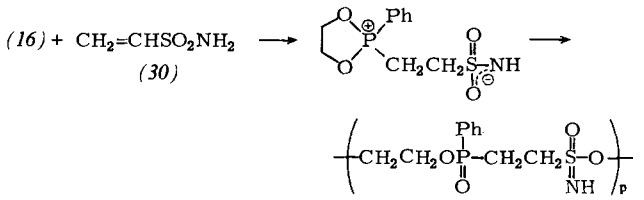


(n)

As in the above case, the pentavalent compound *(49)* (m.p. 158°C) could be isolated at lower temperatures, *e.g.* 50°C, and polymerized at 120°C[16]. This is the second example of a "thermally-induced ring-opening polymerization *via* zwitterion intermediates".

The ambifunctional anionic group of the zwitterion *(47)* in the above copolymerization (namely, of *(16)* with *(26)*) reacts exclusively at nitrogen. In contrast, in the copolymerization of *(4)* with *(26)* (Section 4) the reaction occurs at oxygen.

Copolymerization of *(16)* with ethylenesulfonamide *(30)* produces an alternating copolymer *(50)*; here the sulfonamide anion reacts at the oxygen atom[17].



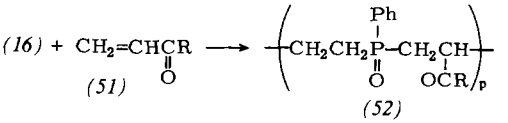
(50)

Table 2 summarizes the reaction sites of two ambifunctional anions for reaction with the oxonium ring from cyclic imino ethers and the phosphonium ring. Regiospecificity was quite high in all cases. Elucidation of these phenomena may represent an interesting problem for future studies.

Table 2. Reactive sites in the reaction of ambifunctional anions with cations.

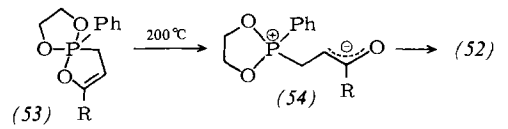
Anion \ Cation		
	oxygen	nitrogen
	nitrogen	oxygen

Alternating copolymerization of *(16)* with methyl acrylate *(51a)* and with the vinyl ketones *(51b)* and *(51c)* occurred at 130°C to give alternating copolymers *(52)* having lower molecular weights (700—1600)[23].



(a), R = OMe; *(b)*, R = Me; *(c)*, R = Ph

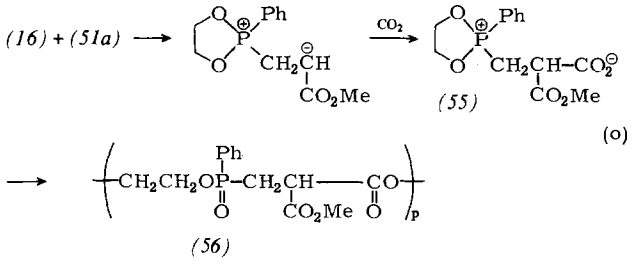
At room temperature or 50°C, pentavalent phosphorus compounds *(53a)* and *(53b)* were isolated from equimolar mixtures of the combinations *(16)*/*(51a)* and *(16)*/*(51b)*, respectively[23]. On heating to 200°C, *(53a)* and *(53b)* give the polymers *(52a)* and *(52b)*, respectively. Thus, these are additional examples of a "thermally-induced ring-opening polymerization". Zwitterions *(54)* having an enolate anion partial structure are assumed to be the intermediates in the 1:1 alternating copolymerizations of *(16)* with *(51a)* to *(51c)* and in the homopolymerization of *(53a)* and *(53b)*.



(53) R

(a), R = OMe; (b), R = Me

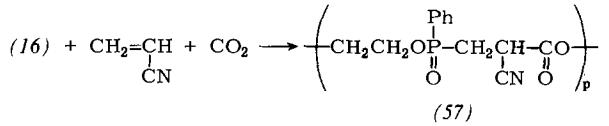
When the copolymerization of (16) with (52a) is carried out under CO_2 (atmospheric pressure) a 1:1:1 alternating terpolymer (56) is formed[26]. The following scheme [eq. (o)] explains this novel alternating terpolymerization, in which a zwitterion (55) is the key intermediate.



(o)

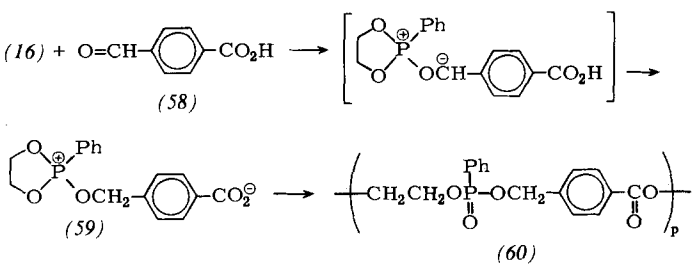
(56)

Two outstanding findings must be pointed out here, namely the incorporation of carbon dioxide into terpolymer without the aid of any added catalyst, and the production of a 1:1:1 alternating terpolymer. An isolated sample of (53a) dissolved in acetonitrile was readily copolymerized with CO_2 at room temperature to give the product (56). Moreover, combination of (16) and acrylonitrile under CO_2 atmosphere also gave an alternating terpolymer (57).



(57)

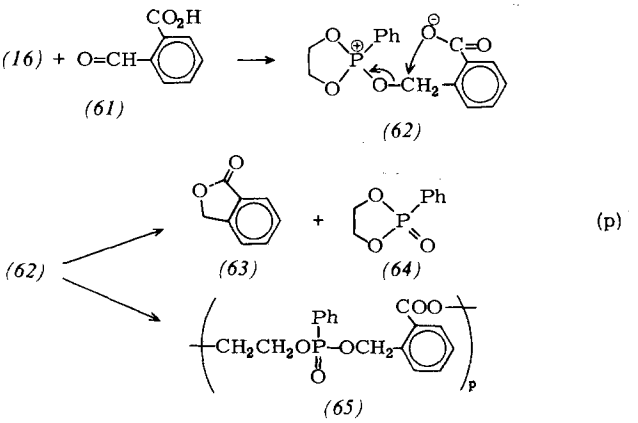
Another interesting copolymerization is that of (16) with *p*-formylbenzoic acid (58), in which an alternating copolymer (60) was produced[24]. The genetic zwitterion (59) is the responsible key intermediate; it is formed by bonding of the phosphorus atom of (16) to the formyl oxygen of (58) and subsequent hydrogen transfer.



(58) (59) (60)

In the reaction of (16) with *o*-formylbenzoic acid (61), however, a lactone (63) was the major product. The linear alternating copolymer (65) was merely a minor product.

Formation of the lactone (63) is ascribed to the intramolecular cyclization of the zwitterion (62) [as indicated by an arrow in (62)]. The cyclic phosphonate (64) could indeed be isolated in an amount corresponding to that expected according to



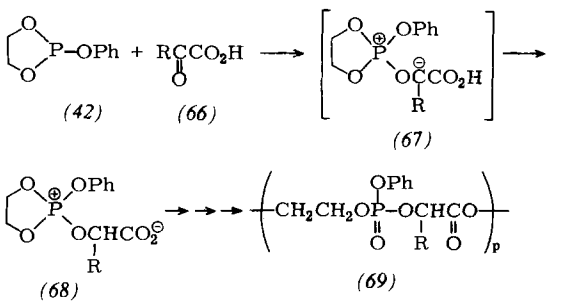
(61) (62) (63) (64) (65)

(p)

eq. (p). Copolymerizations of (16) with (58) and with (61) are closely related to the copolymerization of (42) with α-keto acids described in Section 5.2.

5.2. Copolymerization of the Dioxaphospholane (42) with α-Keto Acids and Related Synthetic Reactions

2-Phenoxy-1,3,2-dioxaphospholane (42), which is not listed in Table 1, displays an interesting polymerization behavior: it is readily copolymerized with α-keto acids (66) at temperatures higher than 120°C without addition of catalyst[27].

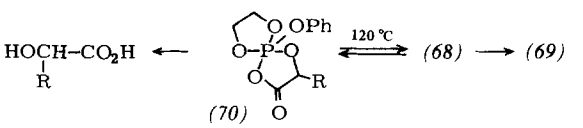


(42) (66) (67) (68) (69)

(a), R = Me; (b), R = Ph

It must be mentioned that the trivalent phosphorus in monomer (42) is oxidized to the pentavalent state in the copolymer repeat unit; correspondingly the α-keto acid (66) is incorporated in the copolymer (69) in the reduced form as α-hydroxylic acid. In addition, this is the first instance of an α-keto acid being polymerized through bond-opening of the carbonyl double-bond.

At lower temperatures, *e.g.* −20°C in diethyl ether, the pentaoxyphosphoranes (70a) and (70b) (m.p. 87 and 60—62°C, respectively) could be isolated[28]. On heating (70a) in substance to 120°C the polymer (69a) was formed. This is also an example of a "thermally-induced ring-opening polymerization *via* zwitterions". A reversible interconversion of (70) and (68) is assumed to take place.

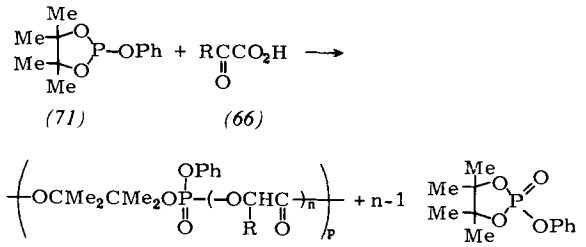


(70)

(a), R = Me; (b), R = Ph

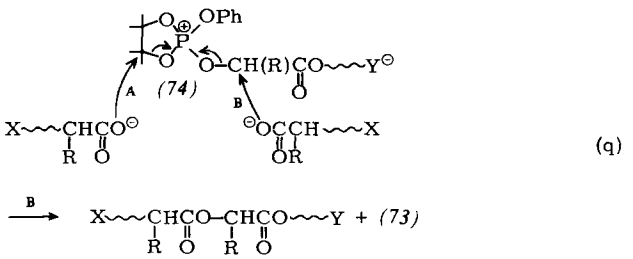
The synthesis of pentaoxyphosphoranes *(70)* is very important not only from the point of view of polymer chemistry but also in the sector of phosphorus chemistry. *(70)* readily undergoes hydrolysis to give the corresponding α-hydroxylic acid. Thus, this reaction constitutes a new synthetic method for the reduction of α-keto acids to α-hydroxylic acids under very mild conditions. For preparative purposes, the isolation of *(70)* is unnecessary[29]. Furthermore, *(70)* can be regarded as a mixed anhydride linkage and as such comes into the category of so-called "high-energy" compounds, which play an important role in biological reactions. Reactions of *(70)* with nucleophilic and electrophilic reagents have led to several novel syntheses[30]. In addition, *(70)* is readily homopolymerized at room temperature in presence of an anionic catalyst[31].

When a fully substituted cyclic phosphite such as *(71)* is subjected to reaction with α-keto acids, a copolymer *(72)* consisting mainly of the α-hydroxylic acid ester unit is obtained[32].



(71) *(66)* *(72)* *(73)*

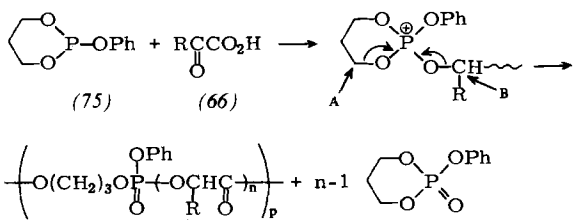
This result can be explained as shown in eq. (q). The carboxylate anion attacks mainly the carbon atom located outside of the phosphonium ring of the zwitterion *(74)* (reaction course B), for attack at the ring carbon atoms (course A) is greatly hindered by the methyl groups.



(q)

Polymerization *via* course B represents the first example of a novel type of polymerization which may appropriately be termed as a "reductive polymerization of a α-keto acid".

In the copolymerization of six-membered cyclic phosphites *(75)* with α-keto acids *(66)*, the propagation corresponding to course B [see eq. (q)] occurs concurrently. The copolymer



(75) *(66)* *(76)* (n > 1)

(76) thus obtained contains an excess amount of α-hydroxylic acid ester units[33].

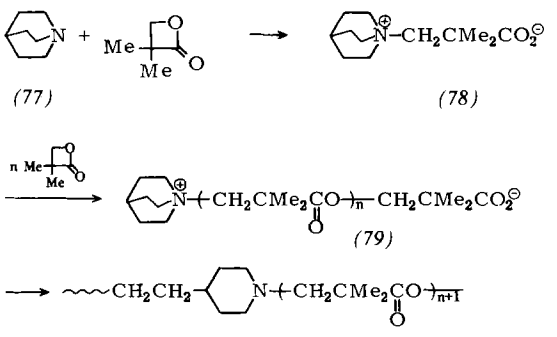
Since the six-membered phosphonium ring does not very readily undergo ring-opening, propagation according to course B can not be suppressed.

6. Related Copolymerizations

In this connection mention must first be made of spontaneous copolymerization between two kinds of vinyl monomers. Examples of spontaneous copolymerizations between electron-accepting and electron-donating monomers include the combinations of vinylidene cyanide/vinyl ether[34], 2,4,6-trinitrostyrene/4-vinylpyridine[35] and acrylonitrile/vinyl ether[36]. These copolymerizations are assumed to involve a free radical mechanism which proceeds *via* the charge-transfer complex species formed by interaction between two kinds of monomers. Furthermore, *Hayashi et al.*[37] recently reported the spontaneous copolymerization of nitroethylene and vinyl ether, involving three elementary reaction processes:

1. cycloaddition between two monomers,
2. anionic polymerization of nitroethylene induced by the cycloadduct, and
3. ring-opening polymerization of the cycloadduct.

Before completing our studies on spontaneous copolymerizations *via* zwitterion intermediates, several copolymerizations have been reported which are closely related to the concept presented in this article. *Wilson* and *Beaman*[38] have reported on the polymerization of pivalolactone initiated by cyclic amines such as quinuclidine *(77)*, *N*-substituted aziridines, and *N*-methylazetidine. These authors observed that more than one molecule of the cyclic amine employed as initiator was incorporated in each polymer molecule. This finding was explained in terms of participation of the cyclic amine in the copolymerization. For example, zwitterions *(78)* and *(79)* were postulated in the case of *(77)*.

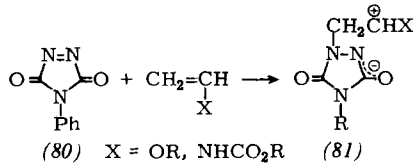


(77) *(78)* *(79)*

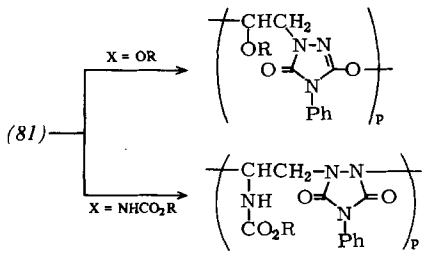
Butler et al.[39-41] have described the alternating copolymerizations of 4-phenyl-1,2,4-triazoline-3,5-dione *(80)* with vinyl ethers and with vinyl carbamate. Zwitterions of type *(81)* are assumed to be the key intermediates.

The anionic part of the zwitterion *(81)* is ambifunctional. Which of the two reaction sites reacts, depends upon the nature of the electrophilic monomer (see also Table 2).

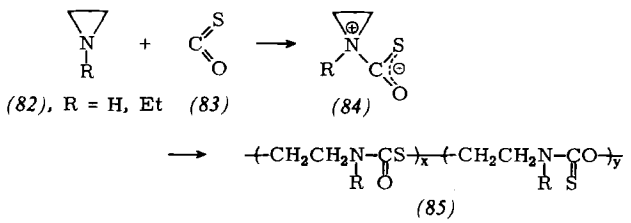
The spontaneous alternating copolymerization between aziridines *(82)* and carbonyl sulfide *(83)* is also interesting[42].



(80) X = OR, $NHCO_2R$ (81)



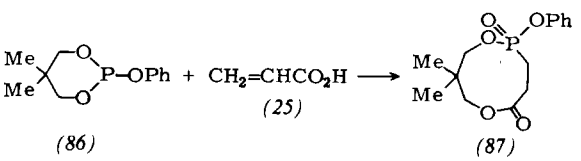
A zwitterion of structure (84) may be assumed as the key intermediate species. The anionic site of (84) is ambifunctional; the COS repeat unit having two different isomeric structures is formed.



(82), R = H, Et (83) (84)

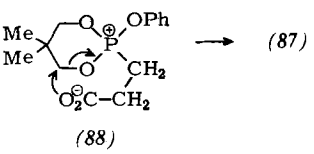
(85)

The reaction of 5,5-dimethyl-2-phenoxy-1,3,2-dioxaphosphorinane (86) with acrylic acid to give the nine-membered cyclic phosphonate (87) should also be mentioned[43] here, since this reaction proves to be related to the copolymerization of cyclic phosphorus compounds (16), (42) and (75) with electrophilic monomers.



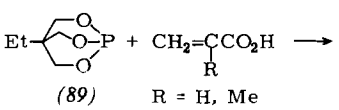
(86) (25) (87)

The formation of (87) can be explained in terms of an intramolecular reaction of a zwitterion of structure (88).

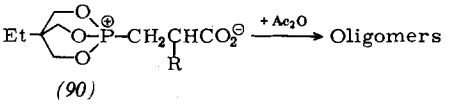


(88)

The spontaneous copolymerization of cyclic compounds containing trivalent phosphorus is described in two patents. One of the patents[44] deals with the preparation of co-oligomers by reaction of bicyclic phosphites (89) with acrylic or methacrylic acid in the presence of acetic anhydride. *Inter alia*, the zwitterion (90) was postulated as the key intermediate. The products were proposed as potential flame retardants.

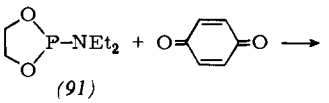


(89) R = H, Me

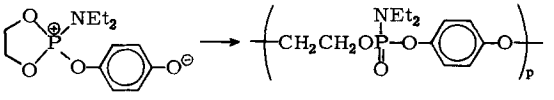


(90)

The other patent[45] describes the alternating copolymerization of the cyclic phosphorus compound (91) with *p*-benzoquinone. This copolymerization may well be explained by the intermediacy of the zwitterion (92).



(91)



(92)

7. Conclusion

In this article a new concept of spontaneous copolymerization has been described, on the basis of which various new copolymerizations have been discovered. This new concept has also proven very useful in the exploration of organic synthetic reactions. The discovery of new M_N and M_E monomers is essential for further development in this sector of polymer chemistry; and it is to be hoped that some unique applications might be discovered on the basis of this new concept of copolymerization.

Received: November 30, 1976 [A 189 IE]
German version: Angew. Chem. 89, 867 (1977)

[1] For reviews see: a) *T. Saegusa*, Chem. Technol. 5, 295 (1975); b) *T. Saegusa, S. Kobayashi, Y. Kimura, H. Ikeda*, J. Macromol. Sci., Chem. *A-9*, 641 (1975); c) *T. Saegusa, S. Kobayashi, Y. Kimura*, Pure Appl. Chem. *48*, 307 (1976).
[2] *T. Saegusa, H. Ikeda, H. Fujii*, Macromolecules *5*, 354 (1972).
[3] *T. Saegusa, H. Ikeda, H. Fujii*, Polym. J. *3*, 35 (1972).
[4] *T. Saegusa, H. Ikeda, H. Fujii*, Macromolecules *6*, 315 (1973).
[5] *T. Saegusa, S. Kobayashi, Y. Kimura*, Macromolecules 7, 1 (1974).
[6] *Y. Yamashita, Y. Ishikawa, T. Tsuda*, Kogyo Kagaku Zasshi *66*, 104 (1963).
[7] *T. Saegusa, Y. Kimura, S. Kobayashi*, Lecture presented at the 23rd Meeting of the Soc. Polymer Sci., Japan, April 1973.
[8] *T. Saegusa, H. Ikeda, S. Hirayanagi, Y. Kimura, S. Kobayashi*, Macromolecules *8*, 259 (1975).
[9] *T. Saegusa, S. Kobayashi, Y. Kimura*, Macromolecules 7, 139 (1974).
[10] *T. Saegusa, S. Kobayashi, Y. Kimura*, Macromolecules 8, 374 (1975).
[11] *T. Saegusa, Y. Kimura, S. Kobayashi*, Lecture presented at the 25th Meeting of the Soc. Polymer Sci., Japan, 1975; Macromolecules *10*, 239 (1977).
[12] *T. Saegusa, S. Kobayashi, J. Furukawa*, Makromolecules *9*, 728 (1976).
[13] *T. Saegusa, Y. Kimura, S. Kobayashi*, Lecture presented at the 23rd Meeting of the Soc. Polymer Sci., Japan, 1973; Macromolecules *10*, 236 (1977).
[14] *T. Saegusa, Y. Kimura, K. Sano, S. Kobayashi*, Macromolecules 7, 546 (1974).
[15] *T. Saegusa, Y. Kimura, S. Sawada, S. Kobayashi*, Macromolecules 7, 956 (1974).
[16] *T. Saegusa, Y. Kimura, N. Ishikawa, S. Kobayashi*, Macromolecules *9*, 724 (1976).

[17] T. Saegusa, S. Kobayashi, J. Furukawa, Macromolekules 10, 73 (1977).
[18] T. Saegusa, S. Kobayashi, J. Furukawa, Macromolecules 8, 703 (1975).
[19] T. Saegusa, S. Kobayashi, Y. Kimura, Macromolecules, 10, 236 (1977).
[20] T. Saegusa, Y. Kimura, S. Kobayashi, unpublished results.
[21] T. Saegusa, S. Kobayashi, Y. Kimura, Macromolecules 7, 256 (1974).
[22] D. S. Breslow, G. E. Hule, A. S. Mallach, J. Am. Chem. Soc. 79, 3760 (1957).
[23] T. Saegusa, S. Kobayashi, Y. Kimura, Macromolecules 10, 64 (1977).
[24] T. Saegusa, T. Yokoyama, Y. Kimura, S. Kobayashi, Lecture presented at the 26th Meeting of the Soc. Polymer Sci., Japan, May 1976.
[25] T. Saegusa, S. Kobayashi, Y. Kimura, J. Chem. Soc. Chem. Commun. 1976, 443.
[26] T. Saegusa, S. Kobayashi, Y. Kimura, Macromolecules 10, 68 (1977).
[27] T. Saegusa, T. Yokoyama, Y. Kimura, S. Kobayashi, Lecture presented at the 26th Meeting of the Soc. Polymer Sci., Japan, May 1976 in Tokyo; Macromolecules, in press.
[28] T. Saegusa, S. Kobayashi, Y. Kimura, T. Yokoyama, J. Am. Chem. Soc. 98, 7843 (1976).
[29] T. Saegusa, S. Kobayashi, Y. Kimura, T. Yokoyama, unpublished.
[30] T. Saegusa, T. Hashimoto, S. Kobayashi, unpublished.
[31] T. Saegusa, T. Yokoyama, unpublished.
[32] T. Saegusa, T. Yokoyama, K. Kawabe, unpublished.
[33] T. Saegusa, T. Yokoyama, Y. Kimura, S. Kobayashi, Lecture presented at the 25th Polymer Symposium of the Soc. Polymer Sci., Japan, October 1976 in Nagoya.
[34] F. F. Miller, H. Gilbert, Can. Pat. 569262 (1959), B. F. Goodrich Co.; H. Gilbert, F. F. Miller, S. J. Averill, E. J. Carlson, V. L. Folt, H. H. Heller, F. D. Stewart, R. F. Schmidt, H. L. Trumbull, J. Am. Chem. Soc. 78, 1669 (1956).
[35] N. C. Yang, Y. Gaoni, J. Am. Chem. Soc. 86, 5023 (1964).
[36] S. Tazuke, S. Okamura, J. Polym. Sci. A-1, 7, 715 (1969).
[37] N. Kushibiki, M. Irie, K. Hayashi, J. Polym. Sci. A-1, 13, 77 (1975).
[38] D. R. Wilson, R. G. Beaman, J. Polym. Sci. A-1, 8, 216 (1970).
[39] G. B. Butler, L. J. Guilbault, S. R. Turner, J. Polym. Sci. B, 9, 115 (1971).
[40] L. J. Guilbault, S. R. Turner, G. B. Butler, J. Polym. Sci. B, 10, 1 (1972).
[41] K. B. Wagener, G. B. Butler, J. Org. Chem. 38, 3070 (1973).
[42] H. Yokota, M. Kondo, J. Polym. Sci. A-1, 9, 13 (1971).
[43] J. S. Clovis, F. R. Sullivan, Tetrahedron Lett. 1971, 2263.
[44] J. S. Clovis, F. R. Sullivan, US-Pat. 3755270 (1973), Rohm and Haas; Chem. Abstr. 80, 27846 (1974).
[45] H. Kobayashi, H. Ohama, Y. Kodaira, Jap. Pat. 71-02352 (1971), Asahi Chem. Ind.; Chem. Abstr. 74, 14269 (1971).

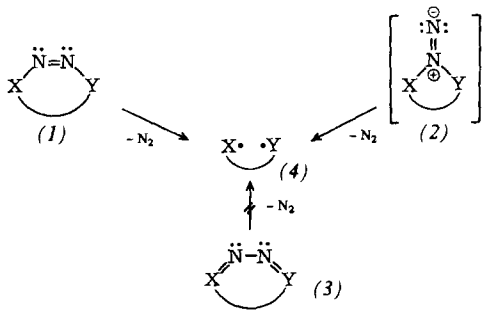
Thermal and Photochemical Cycloelimination of Nitrogen

By Herbert Meier and Klaus-Peter Zeller[*]

Cyclic azo compounds including heteroaromatics with a N=N bond of strong double-bond character can eliminate molecular nitrogen on addition of sufficient thermal energy or on electronic excitation. Some substrates decompose spontaneously, others are moderately or even extremely resistant to N_2-elimination. From a preparative point of view this type of reaction opens a variety of interesting possibilities, *e.g.* the synthesis of small carbocycles or heterocycles, strained bi- and polycycles, as well as cage compounds. From a theoretical mechanistic viewpoint, current importance attaches to the primary fragments such as carbenes, diradicals, trimethylene, trimethylenemethane, dipoles, ylides, antiaromatic 4π-systems, unstable cycloalkynes, and arynes.

1. Introduction

Cycloelimination is the reverse reaction of cycloaddition[1-3]. Cycloeliminations of nitrogen constitute a particularly interesting and extensive section of this field[4-8]. The structural basis for the elimination of molecular nitrogen is provided by the cyclic azo compound *(1)* and its isomer *(2)*.



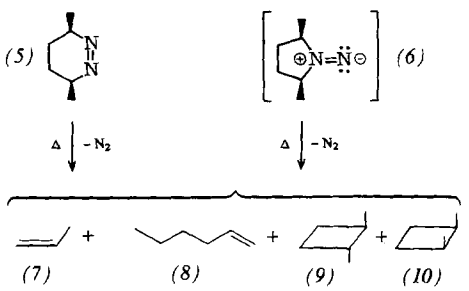


Table 1. Thermal decomposition of the equivalent systems *(5)* [type *(1)*] and *(6)* [type *(2)*] at 306°C in the gas phase. *(6)* was produced *in situ* from the *N*-methanesulfonamide. Compound *(7)* is formed by $[\pi 2_s + \pi 2_s + \pi 2_s]$-cycloreversion, compound *(8)* by [1.5]-H-shift, compounds *(9)* and *(10)* by stereoselective ring closure [10].

Yield [%]	*(7)*	*(8)*	*(9)*	*(10)*
From *(5)*	74.7	0.5	8.5	16.3
From *(6)*	74.0	0.7	9.1	16.2

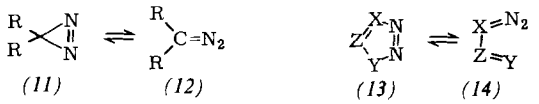
[*] Prof. Dr. H. Meier, Doz. Dr. K.-P. Zeller
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-7400 Tübingen 1 (Germany)

Compounds *(2)* occur only as short-lived intermediates; their decomposition is, for example, a subject of the theory of chelotropic reactions[9]. The equivalent systems *(5)* and *(6)*, corresponding to *(1)* and *(2)*, undergo a very similar decomposition[10] (Table 1).

Cyclic azo compounds exist in large numbers, ranging from three-membered rings to macro-rings, and among them we include systems *(1)*, where X and/or Y = N, O, S, Se, CR_2, *etc.*, that contain N=N bonds with strong double-bond character.

In open-chain compounds and in large rings the *trans*-configuration of the azo group is thermodynamically more stable than the *cis*-configuration, whose higher energy content is due mainly to repulsion of the free electron pairs. In analogy to cyclooctene, 1,2-diaza-1-cyclooctene is the smallest azo-ring system existing in a stable *trans*-form[11, 12]. The ring strain in smaller rings prevents their existence as free *trans*-isomers under normal conditions.

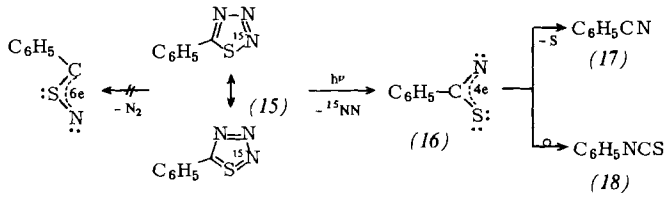
As a further structural characteristic, the ring-chain valence isomerism of some 1,2-diaza-heterocycles should be noted, especially for three-membered *(11)*[13, 14] and five-membered rings *(13)*.



(11) *(12)* *(13)* *(14)*

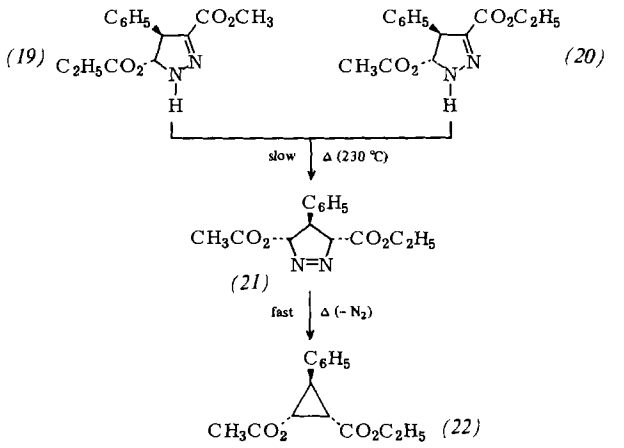
For the system *(13)* ⇄ *(14)* with X, Z = CR, N and Y = CR_2, NR, O, or S, 16 isomers are to be expected; some of these are unknown, in other cases only the cyclic or only the open-chain structure is so far known, *e.g.* in the 1,2,3-thiadiazoles and the α-diazocarbonyl compounds respectively[15]. To a further category belong systems in which *(13)* and *(14)* exist in thermal equilibrium, as in suitably substituted 1,2,3-triazoles[16–18]. In principle, it should be noted that nitrogen can be eliminated from a diazo, diazonium, or an azide structure.

Unlike cyclic azo compounds, but like all systems with an N—N bond of weak double-bond character, the cyclic azines are incapable of eliminating nitrogen. Isotopic labeling shows *(15)* to eliminate $^{15}N{\equiv}N$ selectively, in accord with the higher order of the N^2—N^3 bond[19].



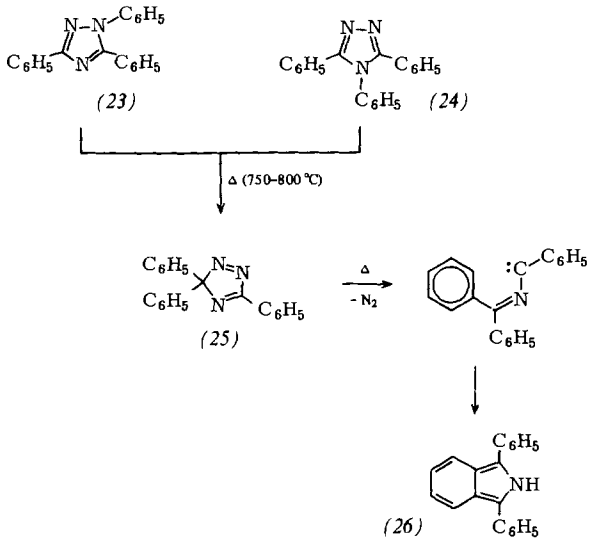
(15) *(16)* *(17)* *(18)*

However, compounds not at first containing an azo function can eliminate nitrogen if a suitable substrate can be formed in a preceding isomerization; a current example is the thermolysis of 2-pyrazolines *(19)* and *(20)* initiated by proton migration[20].



(19) *(20)* *(21)* *(22)*

Under drastic thermal or photolytic conditions larger groups may migrate or ring structures may isomerize, for which 1,2,4-triazoles *(23)* and *(24)* may be cited as examples[21].

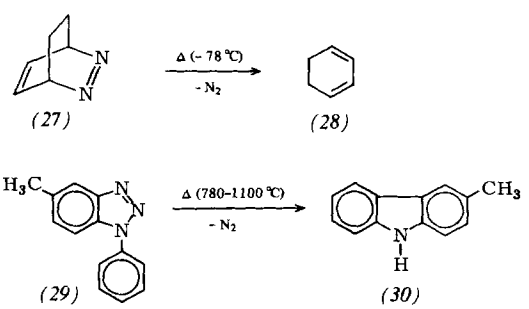


(23) *(24)* *(25)* *(26)*

2. Performance of the Reaction

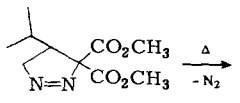
2.1. Thermolysis

Thermal cycloelimination of nitrogen can be effected from a substrate in solution, in a purely liquid phase, or in the gaseous state. The observed decomposition temperatures vary between −78 °C for spontaneous decomposition of 2,3-diazabicyclo[2.2.2]octa-2,5-diene *(27)*[22–24] and up to 1100 °C for the gas-phase pyrolysis of benzotriazole *(29)*[25].

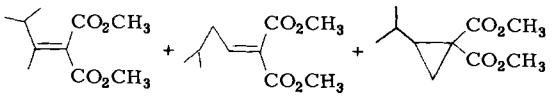


(27) *(28)* *(29)* *(30)*

Most of the experiments are carried out at atmospheric pressure, but thermolyses have also been effected in high vacuum and at pressures up to 5000 atm[26]. The activation barrier to N_2-elimination and thus the decomposition temperature can sometimes be considerably depressed; in this connection heterogeneous or homogeneous catalysts must be distinguished from agents incorporated in the product. Substances investigated for this purpose include metals (Cu, Pt, Pd), metal salts (Cu^+, Cu^{2+}, Ag^+), metal complexes (Fe, Rh), organometallics (C_4H_9Li), aluminum oxide, bases, and Lewis acids. Table 2 gives the change in the thermodynamic activation parameters and the influence of the catalyst on the nature of the products obtained in the pyrolysis of 1-pyrazoline *(31)*[27].



(31)

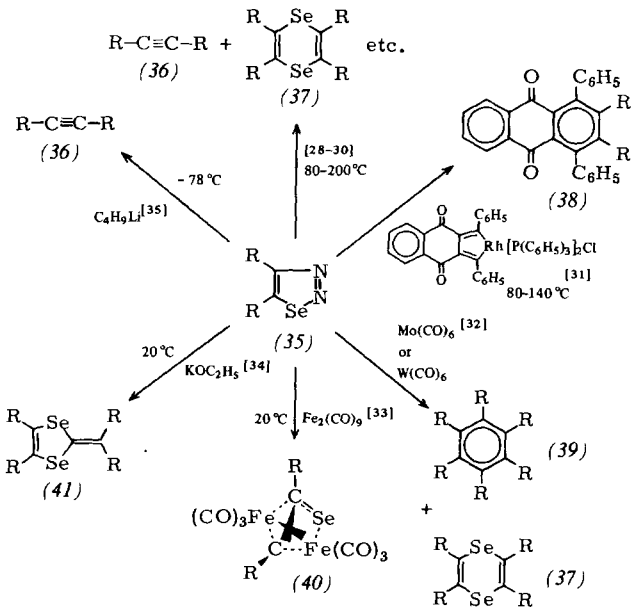


(32) *(33)* *(34)*

Table 2. Thermal decomposition of 1-pyrazoline *(31)*. Yields in *n*-butanol at 105 °C with and without $CuCl_2 \cdot 2H_2O$ as catalyst (cat.); activation parameters at 35 °C with and without catalyst.

Yield [%]		*(32)*	*(33)*	*(34)*
Without cat.		24.6	44.3	31.1
With cat.		15.5	5.3	79.2
Activation parameter	E_a [kcal/mol]	ΔH [kcal/mol]	ΔS [cal K^{-1} mol]	ΔG [kcal/mol]
Without cat.	24.0 ± 0.5	23.3	−10.3 ± 1.4	27.1
With cat.	13.2 ± 0.7	12.6	−29.3 ± 2.3	21.9

The synthetically valuable ability to induce decompositions yielding a variety of products can be demonstrated on the



example of 1,2,3-selenadiazoles *(35)*, occurring between −78 °C and +200 °C with or without catalysts.

2.2. Photolysis

On considering the local symmetry of *cis*- and *trans*-azo groups[36, 37], it can be recognized that the longest-wave transition in the *trans*-configuration is parity-forbidden (see Fig. 1). Even for the *cis*-isomer its intensity is relatively low ($\lambda_{max} \approx 360$ nm, $\varepsilon_{max} \approx 100$—760), since the transition moment resulting from the weak overlap of n_- and π^* is small. Nevertheless, this intensity suffices to effect efficient photolysis.

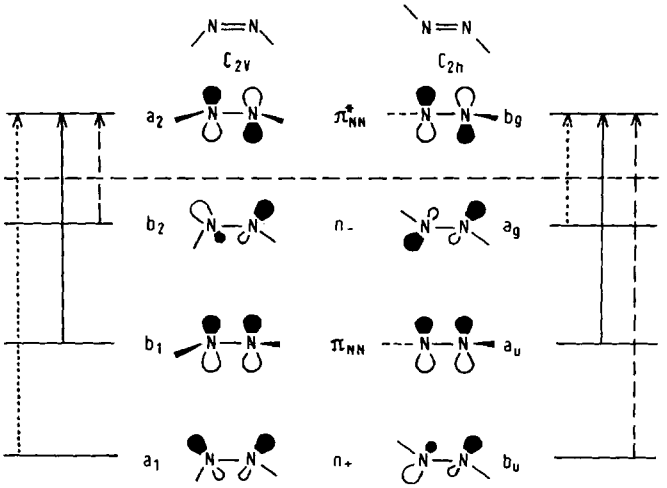


Fig. 1. Electron transitions in *cis*- and *trans*-azo compounds.

The situation exactly the opposite for the $n_+ \rightarrow \pi^*$ transition, which is hard to assign in the UV spectra.

Intense absorptions with $f \geq 0.3$ correspond to $\pi\pi^*$-excitations. Conjugation shifts them bathochromically from the vacuum-UV region. 1,2-Diazaheteroarenes show characteristic $\pi \rightarrow \pi^*$ transitions for this system. The influence on the π^*-excitation is smaller.

Direct or triplet-sensitized photolyses of cyclic azo compounds are known for all three states of aggregation. Singlet energy transfer has also been observed[37]. The quantum yields Φ for the evolution of nitrogen in the gas phase are often around 1, but in solution they are generally considerably lower; examples are shown in Table 3.

Table 3. Quantum yields Φ of the elimination of N_2 in the photolysis of compounds *(42)* to *(48)*.

Substrate	 *(42)*	 *(43)*	 *(44)*	 *(45)*	 *(46)*	 *(47)*	 *(48)*
Φ	1.0	0.022	0.88	0.12	0.002	0.45	0.012
Ref.	[38]	[39]	[40]	[40]	[41]	[40]	[40]

The reactivity, in particular the tendency to eliminate N_2, may differ markedly between $n\pi^*$ and $\pi\pi^*$ excitation states[41a].

2.3. Influence of the Reaction Conditions

The choice of the reaction conditions (medium, substrate concentration, temperature, wavelength region) can have a

Note: Due to a pagination error by the printer, p. 837 is followed by p. 840. This omission is without effect on the text of the present article.

decisive influence on product formation, as may be illustrated by some examples. 1-Benzoylbenzotriazole *(49)* forms photochemically a fragment *(50)* and this can stabilize itself by ring closure, reaction with the solvent, or polymerization. Table 4 shows the product pattern obtained under various conditions[42].

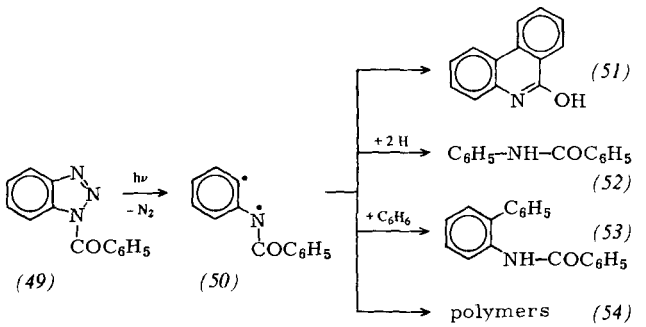
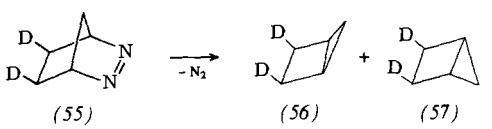


Table 4. Relative yields in the photolysis of 1-benzoylbenzotriazole *(49)* with variation of concentration, solvent, and wavelength (filter).

Initial concn. [mol/l]	Solvent	Filter	Rel. yield [%] (51)	(52)	(53)	(54)
$0.9 \cdot 10^{-3}$	$C_6H_6/CHCl_3$ 1:1	Quartz	—	7	81	12
$1.0 \cdot 10^{-1}$	$C_6H_6/CHCl_3$ 1:1	Quartz	18	5	11	66
$1 \cdot 10^{-2}$	C_6H_6	Corex	8	—	65	27
$1 \cdot 10^{-2}$	$CHCl_3$	Corex	15	18	—	67
$1 \cdot 10^{-2}$	$C_6H_6/CHCl_3$ 1:1	Pyrex	9	10	57	24
$1 \cdot 10^{-2}$	$C_6H_6/CHCl_3$ 1:1	Quartz	5	6	39	50

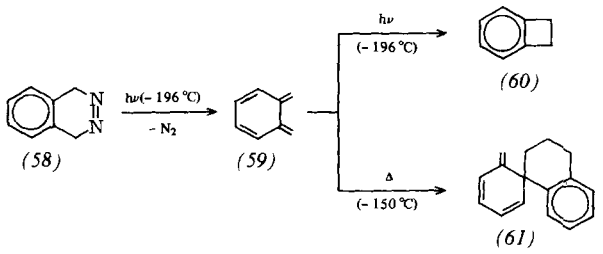
There are often extremely striking differences between thermolysis, direct photolysis, and sensitized photoreaction, arising as a result of the different conditions, possible modes of deactivation, or excitation processes of the primary fragments. This may be illustrated by the following examples.

In *(55)*[43], the degree of double retention or inversion, and thus the stereoselectivity, changes according to the methods, as shown by the figures for *(56)* and *(57)*:

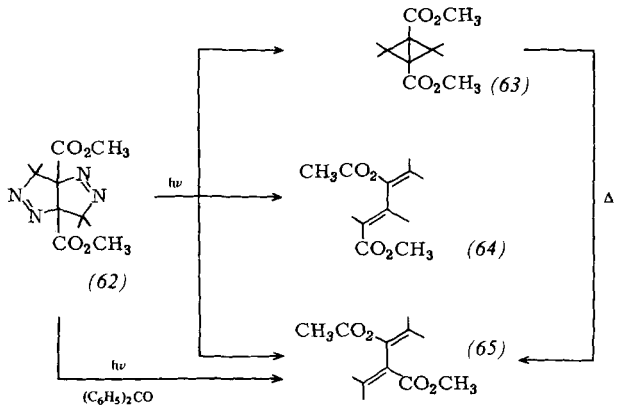


	(56):(57)		(56):(57)
180°C, 100—200 torr	1:3	hν, in benzene	1:1.5
Gas phase, 1—2 torr	1:1	hν, solid −70°C	1:1.05
Gas phase, 350—760 torr	1:1.5		

For the photolysis of *(58)*[44] the secondary thermal or photochemical activation is of decisive importance.



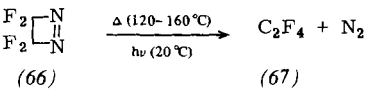
Whereas on direct photolysis *(62)* affords a mixture *(63)*:*(64)*:*(65)* = 48:24:28, only *(65)* is produced on triplet sensitization[45].



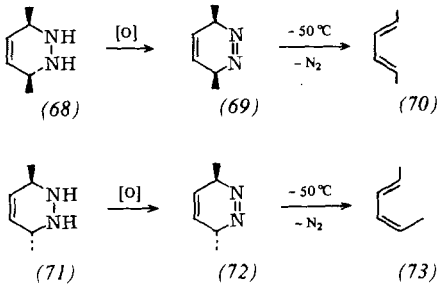
3. Primary Fragments and Subsequent Reactions

3.1. Stable Primary Fragments

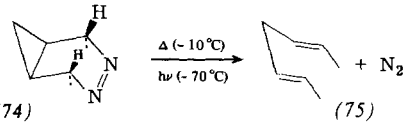
The primary fragments arising on the elimination of nitrogen are only rarely stable, isolable compounds. Examples are provided by 3,4-dihydro-1,2-diazetes such as *(66)*[46-48]



and 3,6-dihydropyridazines such as *(69)* and *(70)*. The latter compounds decompose in the sense of a symmetry-allowed,



concerted $[\pi 4_s + \pi 2_s]$-cycloreversion[49]. The place of the C=C double bond in *(69)* may be taken by a cyclopropane ring, which is equivalent to it in many respects[49, 50].



Bicyclic and polycyclic compounds also readily eliminate nitrogen if they contain this structural unit. Compounds in which the cyclopropane ring is not *anti* but *syn* to the azo bridge behave like ordinary 3,4,5,6-tetrahydropyridazines: they eliminate N_2 only photochemically or at elevated temperatures[51].

1,2,4-Triazines and 1,2,4,5-tetrazines react with alkenes, ketene acetals, or 2*H*-azirines to form [4+2]-cycloadducts that contain respectively, a 3,6-dihydro-1,2,4-triazine or 3,6-

dihydro-1,2,4,5-tetrazine structural component and also eliminate nitrogen *in situ*[52,53].

3.2. Unstable Primary Fragments

Cycloelimination of nitrogen generally leads first to unstable intermediates. Thus, diazirines *(11)* afford carbenes R_2C: *(4a)*, directly or by way of the valence-isomeric diazoalkanes *(12)*. Diradicals or dipolar species *(4)* are formed from larger ring systems *(1)* (Table 5).

The primary fragments stabilize themselves by subsequent intra- or intermolecular reactions; the most important of these are treated in Sections 3.3 to 3.8.

Table 5. Summary of primary fragments *(4)* from azo compounds *(1)* containing five or six ring members.

(1) → *(4b)*

Typ	X	Z	Y	
(4b1)	CR_2	CR_2	CR_2	Trimethylene
(4b2)	CR_2	$C{=}CR_2$	CR_2	Trimethylenemethane
(4b3)	CR_2	CR_2	$C{=}CR_2$	
(4b4)	CR_2	C=O	CR_2	
(4b5)	C=O	CR_2	C=O	
(4b6)	CR_2	O	CR_2	Carbonyl ylides
(4b7)	CR_2	S	CR_2	Thiocarbonyl ylides
(4b8)	C=O	O	CR_2	
(4b9)	NR	CR_2	CR_2	
(4b10)	NR	C=O	CR_2	
(4b11)	NR	CR_2	NR	
(4b12)	NR	$C{=}CR_2$	NR	
(4b13)	NR	C=NR	NR	
(4b14)	NR	C=O	NR	
(4b15)	NR	C=S	NR	
(4b16)	S	C=NR	NR	

(1) → *(4c)*

Type	X	Z	Y	
(4c1)	CR_2	CR	CR	Vinylcarbenes
(4c2)	NR	CR	CR	
(4c3)	S	CR	CR	
(4c4)	Se	CR	CR	
(4c5)	NR	CR	N	
(4c6)	NR	N	CR	Nitrilimines
(4c7)	S	CR	N	
(4c8)	NR	N	N	Azides

(1) → *(4d)*

Type	X	Z	Z'	Y
(4d1)	CR_2	CR_2	CR_2	CR_2
(4d2)	NR	CR_2	CR_2	NR
(4d3)	C=O	O	CR_2	CR_2

(1) → *(4e)*

Type	X	Z	Z'	Y
(4e1)	NR	CR_2	CR	CR
(4e2)	NR	C=O	CR	CR
(4e3)	NR	C=NR	CR	CR
(4e4)	NR	SO_2	CR	CR
(4e5)	S	C=O	CR	CR
(4e6)	C=O	O	CR	CR

(1) → *(4f)*

Type	X	Z	Z'	Y
(4f1)	CR	CR	CR	CR
(4f2)	N	CR	CR	CR

3.3. Ring Closures

Species of type *(4b)* to *(4f)* and larger fragments of this type can undergo ring closure immediately.

Three-membered ring compounds *(76)* are obtained from *(4b)* in this way, specifically cyclopropanes from *(4b1)* to *(4b3)*, oxiranes from *(4b6)*, thiiranes from *(4b7)*, aziridines from *(4b9)* and *(4b12)*, and diaziridines from *(4b11)*, *(4b13)*, and *(4b14)*.

(4b) → *(76)*

However, most of the investigations were carried out on 4,5-dihydro-3*H*-pyrazoles (1-pyrazolines), the first thermolysis having been recorded as early as 1888[54]. The product pattern depends markedly on the reaction conditions. In general, the proportion of three-membered ring compounds in the products is larger on photolysis than on thermolysis. Cycloelimination of nitrogen has proved particularly useful for the preparation of strained bicyclic and polycyclic compounds (for the synthesis

(77) → *(78)* → *(79)*

of bicyclo[*n*.1.0]alkanes *(78)*, $n=1$ to 6, see *e.g.*[43,55–59]). It was by this method that, *inter alia*, the first synthesis of unsubstituted prismane *(82)* was successfully accomplished[60].

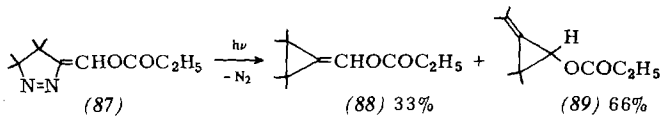
(80) → *(81)* → *(82)*

Bispyrazolines such as *(83)* yield biscyclopropanes, *e.g. (86)*, in a series of steps[61].

(83) → *(84)* + *(85)* → *(86)*

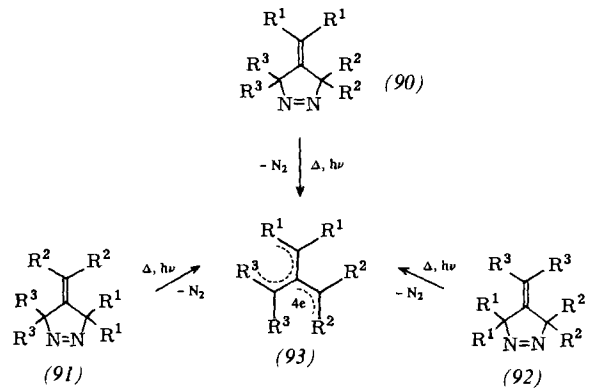
(84) : *(85)* = 85 : 11

Elimination of nitrogen from 1-pyrazolines containing an *exo*-methylene group in position 3 or 4 leads to methylenecyclopropanes; as shown by the example of *(87)*, this may also involve rearrangement of the original σ-bonded skeleton[62].



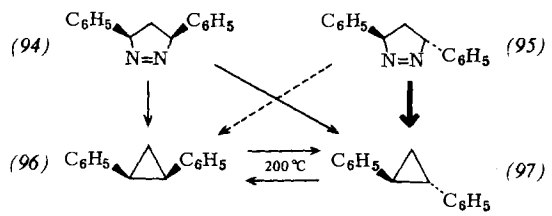
(87) (88) 33% (89) 66%

The primary fragment from the normal 1-pyrazolines yields trimethylene, which is a π-type 1,3-diradical, but a substituted trimethylenemethane is obtained from 4-methylenepyrazolines, as shown in formulas *(90)* to *(92)*; both intermediate stages can exist and react in sterically distinguishable singlet and triplet states.



(90) (91) (93) (92)

The stereochemistry of product formation is particularly important. Depending on the substrate, method, and medium, all possible types of process can be observed, from stereospecific through stereoselective to purely random; for example, the *trans*-isomer *(95)* of 3,5-diphenyl-1-pyrazoline shows high stereoselectivity both photochemically and thermally[63], while the *cis*-isomer *(94)* does not (Table 6).



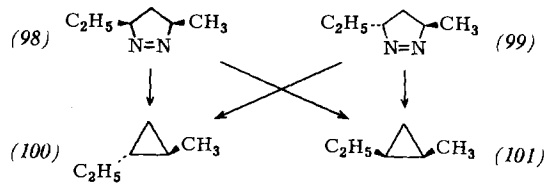
(94) (95) (96) (97)

Table 6. Steric course of the cycloelimination of nitrogen from 1-pyrazolines *(94)* and *(95)*.

Substrate	Method	Rel. Yield [%] (96)	(97)
(94)	Δ (45 °C)	44	56
(94)	*hν*	51.5	48.5
(95)	Δ (45 °C)	8	92
(95)	*hν*	14.5	85.5

By way of contrast, the stereoselectivity of methyl 3,5-dimethyl-1-pyrazoline-3-carboxylate is independent of the configuration but specific for the method, namely photolysis[64].

Two recent papers[65,66] report the stereochemical course of the reaction based on the absolute configuration of the 1-pyrazolines used. Thermolysis of the stereoisomeric 3-ethyl-5-methyl-1-pyrazolines *(98)* and *(99)*, for example, gave the results collected in Table 7[66].

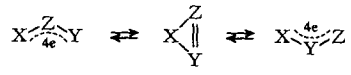


(98) (99) (100) (101)

Table 7. Thermolysis of 1-pyrazolines *(98)* and *(99)* at 292 °C in the gas phase.

Products \ Substrate	(98)	(99)
(100)		
Yield [%]	65.7	27.1
Dominant stereochemistry	Rotation at C-5	Double inversion
Retention of configuration [%]	14.2 ± 0.4	22.5 ± 0.5
(101)		
Yield [%]	32.1	70.6
Dominant stereochemistry	Double inversion	Rotation at C-3
Retention of configuration [%]	36.5 ± 2.9	0.85 ± 0.02

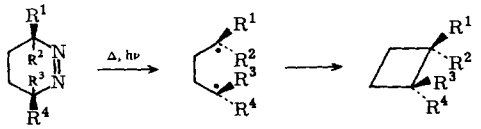
Cyclization of the species *(4c)*, X = CR_2, Y = Z = CR, makes possible the very valuable photochemical synthesis of cyclopropenes *(102)* from 3*H*-pyrazoles by way of vinyldiazo compounds and vinylcarbenes *(4c1)*.



(4c) *(102)* *(4c')*

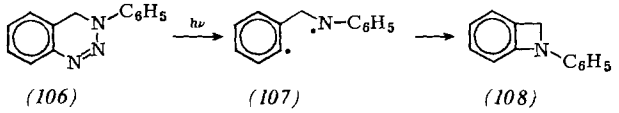
From the heteroanalogous fragments *(4c2)* to *(4c8)* having X = NR, S, or Se there arise cyclic conjugated 4π systems with potential antiaromatic character. Like the oxirenes *(102)*, X = O, Y = Z = CR[15], these three-membered rings *(102)* can be detected only by the establishment of the equilibrium *(4c)* ⇄ *(4c')* or by isomerizations such as the conversion of 1*H*-azirines into 2*H*-azirines[67–70].

1,4-Diradicals *(4d1)* cyclize to give four-membered rings. On thermal or direct photochemical fragmentation of 3,4,5,6-tetrahydropyridazines of type *(103)* with aliphatic substituents, cyclobutanes *(105)* are formed with retention of configuration[71,72]; however, on triplet-sensitized decomposition or in the case of aryl-substituted substrates the stereoselectivity decreases as a result of the longer lifetime of the diradicals.



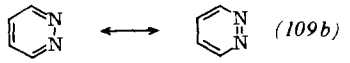
(103) *(104)* *(105)*

Among the cyclizations of the compounds *(4e1)* to *(4e5)* special mention should be made of the synthesis of the first stable benzazetine *(108)*[73].

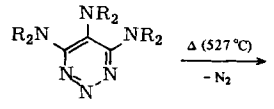


(106) *(107)* *(108)*

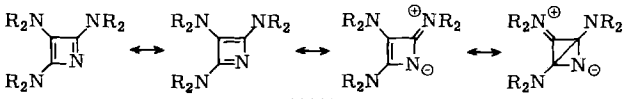
X-Ray structure analysis and theoretical calculations show that the bond between the two nitrogens of pyridazines *(109)* has mainly single-bond character[74]. The small contribution from the limiting structure *(109b)* is in line with the drastic conditions needed for elimination of the nitrogen as N_2.

(109a)  *(109b)*

Cyclization of the fragments *(4f)* leads to the cyclobutadiene system. This could be realized experimentally by high-temperature pyrolysis of the benzo[*c*]cinnolines to biphenylenes[75] and by vacuum flash-thermolysis of 4,5,6-tris(dimethylamino)-1,2,3-triazine *(110)* to the resonance-stabilized tris(dimethylamino)azacyclobutadiene, compound *(111)*, which is stable at $-80\,^{\circ}C$[76,77].



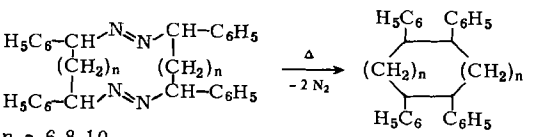
(110)



(111)

R = CH_3

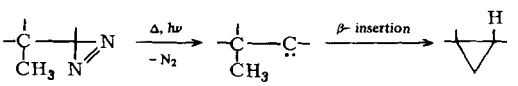
Diradicals produced from seven-, eight- and higher-membered rings also undergo ring closure reactions[78–81]; macrorings of structure *(112)* decompose thermally in steps to *(113)*[11,82].



n = 6,8,10 *(112)* *(113)*

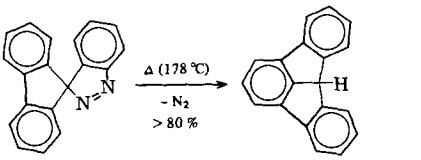
3.4. Ring Closures Involving Substituents

In certain substrates the direct cyclization of the primary fragment *(4)* may be replaced in whole or in part by involvement with a substituent leading to a larger ring. The reactive center X attacks the β- or γ-position of Y, removing a hydrogen atom which undergoes a [1.3]- or [1.4]-shift to become attached to Y. This type of reaction includes the formation of cyclopropanes *(116)* from diazirines *(114)*[83,84], of the

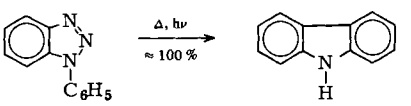


(114) *(115)* *(116)*

fluorenes, *e.g.* fluoradene *(118)*[85], from 3*H*-indazoles *(117)*, and especially the formation of carbazole *(120)* or related systems from 1,2,3-triazoles *(119)*[86,87].



(117) *(118)*

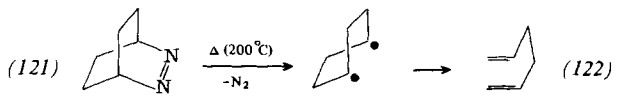


(119) *(120)*

In 1-benzoyl-1,2,3-triazoles both the phenyl group[42,88] and the carbonyl oxygen[89] may take part in the cyclization. Attacks at the β- and γ-position have been observed in the fragmentation of 1,2,3-triazines[76,90].

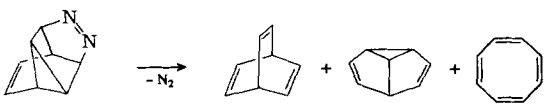
3.5. Rearrangements (Valence Isomerizations)

In contrast to the synchronous cycloeliminations of nitrogen from 3,6-dihydropyridazines (Section 3.1), 3,4,5,6-tetrahydropyridazines such as *(121)*[91] undergo a two-stage decomposition which is terminated by ring-closure (Section 3.3) or ring-opening reactions. The ring opening should often be regarded not as direct stabilization of the primary fragment but as due to thermal or photochemical valence isomerization of the initially formed cyclization product. The compound *(123)*



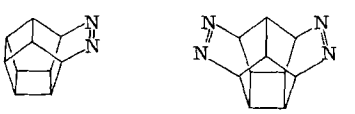
(121) *(122)*

may be instanced here as undergoing a complicated valence isomerization[92]: on thermolysis only *(124)* is formed, on direct photolysis a mixture *(124)*, *(125)*, and *(126)* in the proportions of 24:73:3, and on sensitized photolysis only *(125)*.



(123) *(124)* *(125)* *(126)*

The cage structures *(127)* and *(128)* provide access to the $(CH)_{10}$ hypersurface[93].



(127) *(128)*

The most commonly observed rearrangement of the primary fragments is a [1.2]-shift of hydrogen atoms or of alkyl or aryl groups. The carbenes formed from diazirines are thus converted into alkenes[83]. Special mention must be made in this connection of the tetrazoles, which by double elimination of the nitrogen afford carbenes that are prone to rearrangement[94–96].

The primary products *(4b1)* and *(4b9)* formed from 4,5-dihydro-3*H*-pyrazoles and 4,5-dihydro-1,2,3-triazoles are con-

verted by 1,2-shifts into, respectively, alkenes and azomethines of type *(129)*.

(4b1), (4b9) $X=\overset{R_2}{\overset{|}{C}}-CR_2 \longrightarrow X=CR-CR_3$

X = CR_2, NR *(129)*

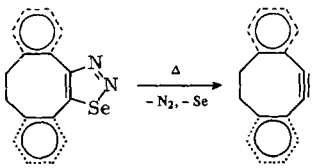
Systems *(130)* containing cumulated double bonds are formed analogously from *(4c)*, specifically ketenimines from *(4c2)*[68,87], thioketenes from *(4c3)*[97-100], selenoketenes

(4c) $X=\overset{R}{\overset{|}{C}}-Y \longrightarrow X=C=YR$ *(130)*

from *(4c4)*[101], carbodiimides from *(4c5)*[102-104], and isothiocyanates from *(4c7)*[103,105-107].

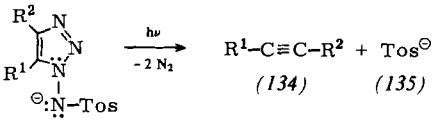
3.6. Fragmentations

Further cleavage of the primary fragments is particularly favorable if energy-deficient species such as S, Se, CO, CO_2, N_2, or SO_2 are thereby eliminated. 1,2,3-Thiadiazoles and 1,2,3,4-thiatriazoles can be converted into alkynes or nitriles respectively by way of *(4c3)* and *(4c7)* with loss of sulfur. The preparation of alkynes[108-110] and particularly of the highly reactive and often unstable cycloalkynes[28-30,35,111-114a] by thermolysis of 1,2,3-selenadiazoles such as *(132)* from *(131)*[113,114] is of special synthetic value.



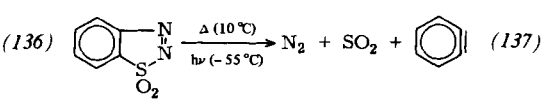
(131) *(132)*

Double N_2 elimination with the formation of alkynes *(134)* occurs on starting from 1-(tosylamino)-1,2,3-triazole anions *(133)*[115-117].

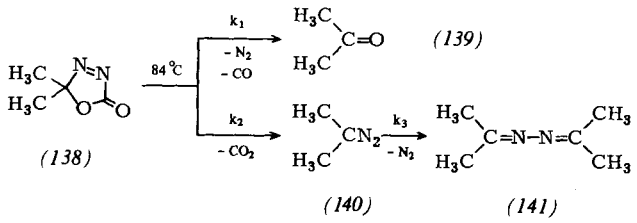


(133) *(134)* *(135)*

1,2,3-Benzothiadiazole 1,1-dioxide *(136)* is a suitable precursor of dehydrobenzene *(137)*, since it loses both nitrogen and sulfur dioxide[118,119].

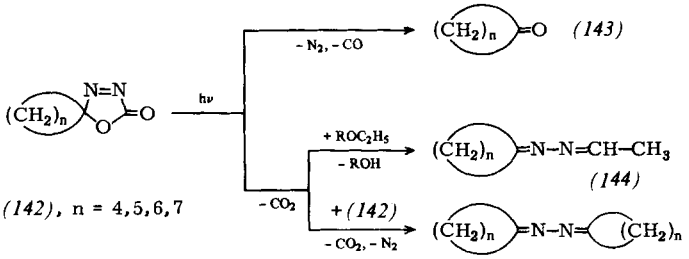


Of special interest is the fragmentation of 5*H*-1,3,4-oxadiazol-2-ones *(138)*. Nitrogen, carbon monoxide, and carbon dioxide are expected as gaseous products. On thermolysis, formation of ketones *(139)*, diazo compounds and azines *(141)* was observed, the decomposition always obeying first-order kinetics[120,122a].

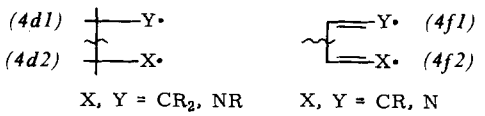


CCl_4: $k_1 = 10^4\ s^{-1}$, $k_2 = 0.25 \times 10^4\ s^{-1}$; *(139)*:*(140)* = 8:1.
CH_3OH: $k_1 = 0.9 \times 10^4\ s^{-1}$, $k_2 = 4 \times 10^4\ s^{-1}$; *(139)*:*(140)* = 1:2.

Photochemically in benzene, N_2 and CO were eliminated almost completely (quantum yield 0.6)[121,122]. In ethers a considerably more complex reaction sets in, with, additionally, the elimination of CO_2; the ether acts both as solvent and as reactant[121,122,122b,122c].



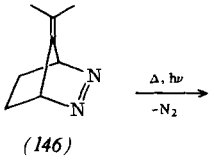
The primary fragments *(4d)* to *(4f)* formed from six-membered rings can undergo cleavage into alkenes, azomethines, alkynes, or nitriles as possible modes of stabilization.



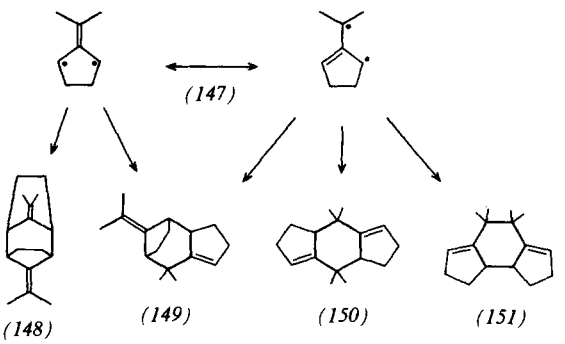
X, Y = CR_2, NR X, Y = CR, N

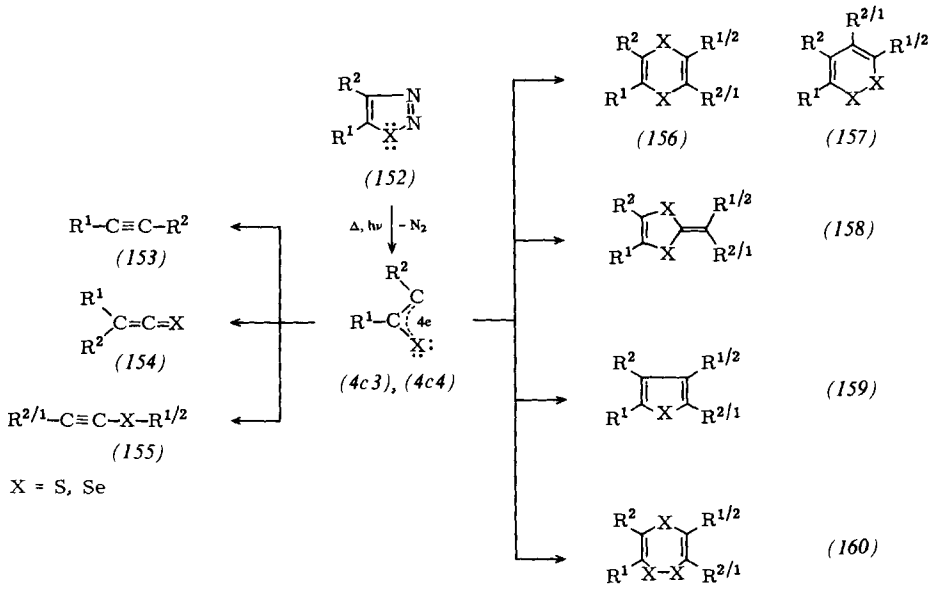
3.7. Cyclodimerizations

Diradicals or dipolar primary fragments can readily stabilize themselves by dimerization into rings of twice the size. Numerous examples of this type of reaction are known in the formation of alkenes from carbenes up to the synthesis of eight-membered rings[73]. Here we have selected the cyclodimerization of trimethylenemethane *(147)*[123].



(146)





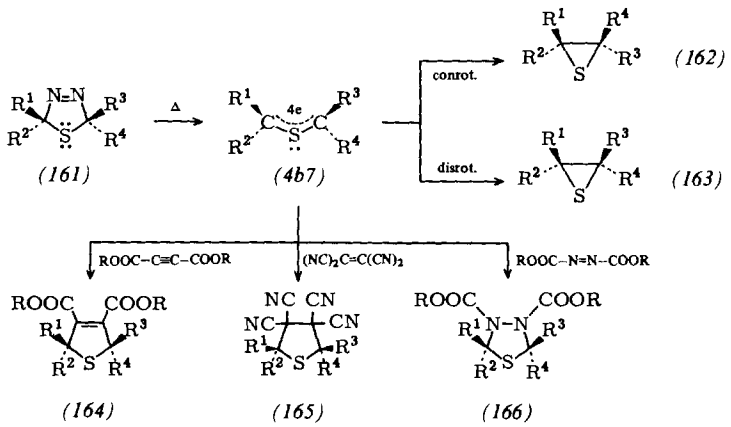
Cyclodimerizations may be accompanied by eliminations, additions, and rearrangements. Elegant examples of this are provided by the 1,2,3-thiadiazoles and 1,2,3-selenadiazoles *(152)*, which in very simple manner yield five-, six- and seven-membered heterocycles with one, two, or three heteroatoms[29,30,97–100,111,112,124–128].

Nitrile imines *(4c6)*, the primary fragments from tetrazoles, dimerize to dihydrotetrazines which are readily converted into 1,2,4,5-tetrazines with loss of hydrogen[129,130].

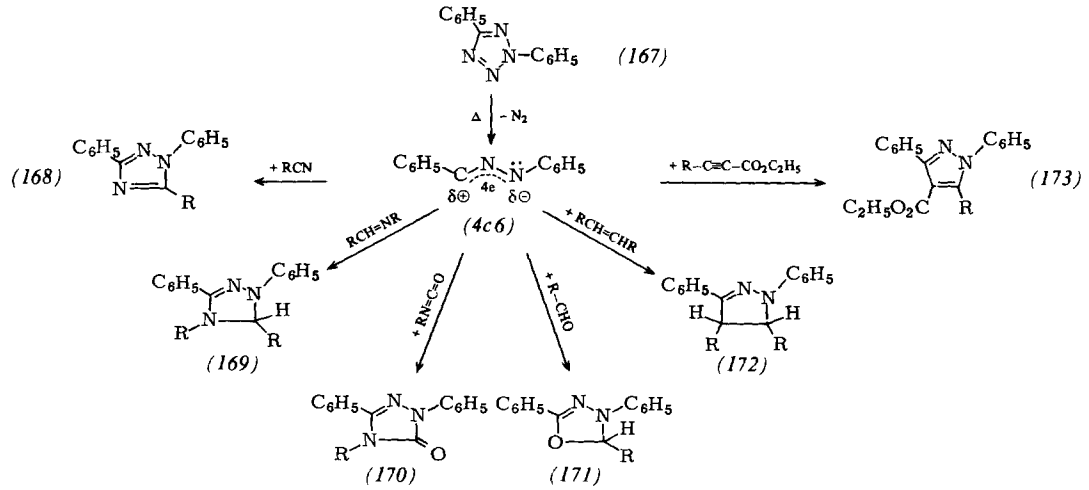
3.8. Trapping Reactions and Reactions with the Solvent

The intermolecular reactions relevant for "saturation" of the primary fragments are abstraction of hydrogen and insertion into solvent molecules. Particularly interesting are the directed capture reactions leading to cycloadducts. Photochemical or thermal denitrogenation of 3*H*-diazirines in the presence of alkenes leads to stereospecific cycloaddition of the intermediate singlet carbene to give cyclopropane derivatives[131,132].

1,3-Diradical species of type *(4b)* can occasionally be trapped by alkenes[123], isocyanates[133,134], enamines[135], *etc.* Special interest attaches to the stereochemical course of this cycloaddition. The thiocarbonyl ylides of type *(4b7)* formed from 2,5-dihydro-1,3,4-thiadiazoles *(161)* by $[_{\pi}4_s+_{\pi}2_s]$-cycloreversion have been selected as specific examples[136–138a]. They can be trapped as the heterocycles *(164)*—*(166)*.



A number of trapping reactions are known for the more unsaturated species of type *(4c)*. Thus, vinylcarbenes *(4c1)* with furan or benzene give 1,1-cycloadducts and with buta-



diene or *N*-phenylmaleimide they give 1,3-cycloadducts[85,139–141]. *(4c3)* can be trapped by carbon disulfide[124,125]. Trapping reactions for the nitrile imines *(4c6)* that are accessible from tetrazoles *(167)* are particularly numerous[129,142,143].

4. Reaction Mechanisms

4.1. Elimination Processes

Table 8 gives a review of the kinetic parameters of thermal N_2-evolution from some of the compounds in the classes considered in this article. The various possibilities for the cycloelimination of nitrogen on addition of thermal energy in the form of translational or vibration energy have been collected in Figure 2. As a first step the substrate can cleave

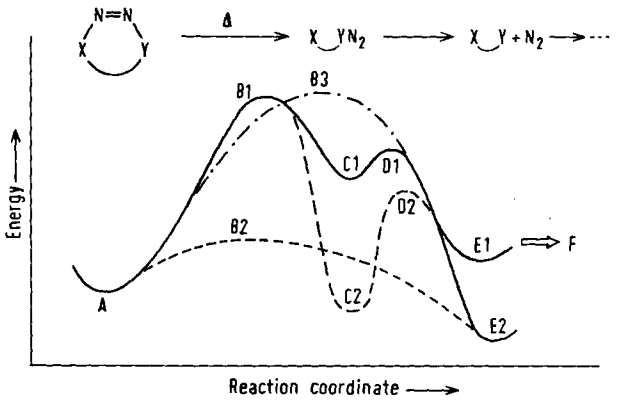


Fig. 2. Course of the thermal cycloelimination of nitrogen. (Substrate A; products E_2; F; intermediates C_1, C_2, E_1; transition states B_1 to B_3, D_1, D_2.)

a single bond of the azo function either homolytically or heterolytically, giving rise to a generally energy-rich diradical or dipolar species (route $A \rightarrow B_1 \rightarrow C_1$). With diazirines or maximally unsaturated five-membered ring systems, however, the open-chain valence isomer may be obtained (cf. Section 1), whose formation may indeed be exothermic (route $A \rightarrow B_1 \rightarrow C_2$). Nitrogen is eliminated when a second activation barrier is overcome, and the primary fragment namely a carbene, a diradical or a dipole is formed (route $C_1 \rightarrow D_1 \rightarrow E_1$, or $C_2 \rightarrow D_2 \rightarrow E_1$). Besides such short-lived species which stabilize themselves in subsequent reactions ($E_1 \rightarrow F$) (cf. Section 3), stable molecules may also occur as primary fragments. This is especially common in symmetry-allowed synchronous reactions (route $A \rightarrow B_2 \rightarrow E_2$). Finally, the synchronous though symmetry-forbidden process is described by route $A \rightarrow B_3 \rightarrow E_1$ or E_2.

The photochemical elimination of nitrogen can be effected by direct irradiation, usually in the longest-wave absorption band (cf. Section 2) and, in contrast to the situation with open-chain azo compounds, often also by triplet-sensitization. It is rarely possible to reach the T_1 level by intersystem crossing (ISC) without a sensitizer. As shown in Figure 3,

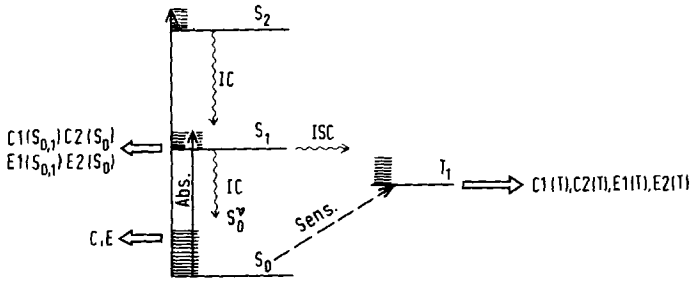


Fig. 3. Course of the photochemical cycloelimination of nitrogen.

N_2-elimination occurs on attainment of the dissociation limit at S_1 or T_1, by crossing of a repulsion term (predissociation), or by internal conversion (IC) to a highly vibrationally excited electronic ground state S_0^v. If the nonadiabatic photoreaction at C_1 or C_2 (Fig. 2) does not lead back to the energy hypersurface of the ground state, then a second (thermal or electronic) activation is necessary. From spectroscopic findings and differences in reactive behavior it can be concluded that the intermediate species C_1 and E_1 can appear in various electronic or spin states, depending on the method used. (For examples of elimination processes see Sections 2 and 3.)

4.2. Synchronous Elimination of Nitrogen

Symmetrical substrates that have equivalent single bonds to the azo group have the possibility of eliminating nitrogen synchronously. This is particularly relevant in retention of orbital symmetry. Pyridazine (Fig. 4) and its 3,6-dihydro derivative (Fig. 5) may be used as examples.

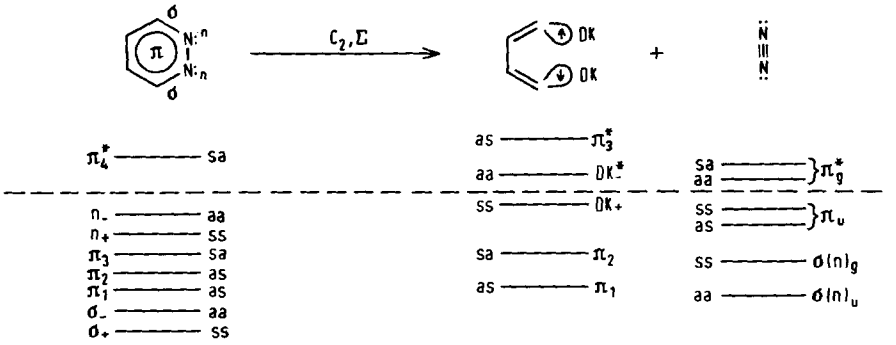
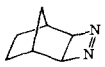
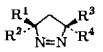
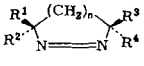
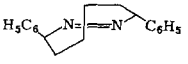


Fig. 4. Orbital correlation for the fragmentation of pyridazine.

Table 8. Activation parameters for the thermal cycloelimination of nitrogen.

Substrate	R^1	R^2	R^3	R^4	n	T [°C]	$K \cdot 10^4$ [s^{-1}]	log A	E_a [kcal/mol]	$\Delta H^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [cal K^{-1} mol^{-1}]	Ref.
	F	F						13.4	32.5		0.5	[144]
	Cl	C_6H_5				100–145		14.0	30.45 ± 0.09		3.2	[84, 145]
	Br	C_6H_5						13.75	27.36		2.1	[146]
						120	$5.46 \cdot 10^{-2}$	16.4 ± 0.1	38.95 ± 0.25		13.5	[46]
						118.5				33.1 ± 0.5	5.4 ± 1	[47]
						25			32.4		− 2.6	[127]
						25	1.27	14.15	24.6 ± 0.1		4.2 ± 0.4	[106]
						20	3.89			27.2 ± 0.9	16.6 ± 1.8	[119]
	H	H	H	H		237	50.5	15.93 ± 0.13	42.4 ± 0.3		11.2 ± 0.6	[147]
	H	H	CH_3	H		230	65.6	15.70 ± 0.15	41.0 ± 0.3		10.1 ± 0.7	[147]
	H	H	CH_3	CH_3		211	54.2	15.85 ± 0.3	40.0 ± 0.2		10.8 ± 0.2	[147]
	CH_3	H	CH_3	H		224	56.3	15.54 ± 0.11	40.3 ± 0.3		9.4 ± 0.5	[147]
	H	CH_3	CH_3	H		220	64.4	15.67 ± 0.11	40.2 ± 0.3		10.0 ± 0.5	[147]
	CH_3	H	CH_3	CH_3		215	92.8	15.42 ± 0.21	39.0 ± 0.4		8.4 ± 0.9	[147]
	CH_3	CH_3	CH_3	CH_3		219	52	14.49 ± 0.12	37.7 ± 0.4		4.6 ± 0.8	[147]
	C_6H_5	H	C_6H_5	H						25.0 ± 1.0	0 ± 3	[63]
	H	C_6H_5	C_6H_5	H		90	23.6 ± 0.5	14.1	27.0 ± 0.4		3.4 ± 1.3	[148–150]
						188	61.7 ± 0.6	13.24	32.6 ± 0.3		− 1.1 ± 0.5	[151, 152]
						25	$9.3 \cdot 10^{-3}$			26.0	3.3	[136]
	C_6H_5	H	C_6H_5	H	2	79.5	$5.6 \cdot 10^{-4}$			26.7 ± 1.2	2.4 ± 4	[153]
	H	C_6H_5	C_6H_5	H	2	62.5	$5.4 \cdot 10^{-4}$			24.6 ± 1.1	− 0.4 ± 3	[153]
	C_6H_5	H	C_6H_5	H	3	80	$4.3 \cdot 10^{-4}$		29.7			[154]
	C_6H_5	H	C_6H_5	H	4	80	$2.3 \cdot 10^{-4}$		26.0			[154]
						80	$3.5 \cdot 10^{-8}$		36.7			[154]
						−3.5			37.3 ± 0.3		8.7	[155]
						−3.5	0.77		18.9 ± 1.5			[155]
						240	212.0		44.6 ± 0.2		10.5	[156]
						150	0.36		39.2 ± 0.3		11	[156]
						25	0.85		22.1 ± 0.4		4.1 ± 1.1	[156a]
						199	3.32		41.4 ± 0.3		10.3	[156]

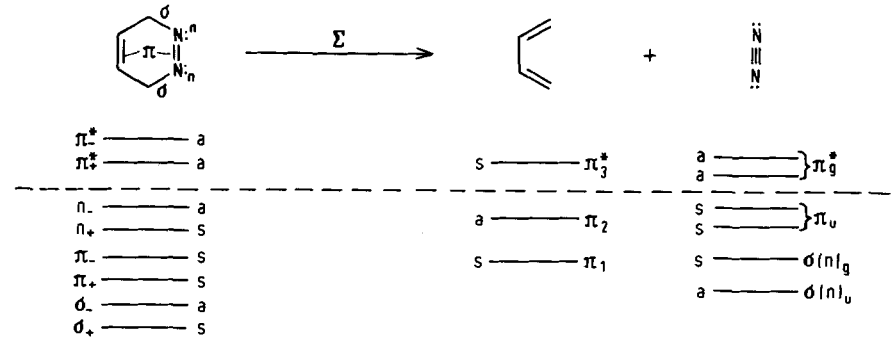


Fig. 5. Orbital correlation for the fragmentation of 3,6-dihydropyridazine.

Whereas the transition in the ground state

$$(\sigma_+)^2(\sigma_-)^2(\pi_+)^2(\pi_-)^2(n_+)^2(n_-)^2 \rightarrow (\pi_1)^2(\pi_2)^2/(\sigma_u)^2(\sigma_g)^2(\pi_u)^4$$

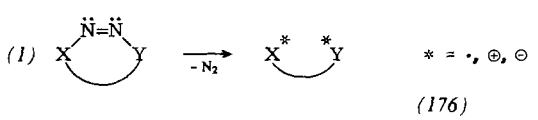
for 3,6-dihydropyridazine is symmetry-allowed, such a correlation is not possible for pyridazine. As can be deduced from Figures 4 and 5, energy-deficient photoprocesses are symmetry-forbidden for both systems.

4.3. Intermediates

Ejection of an N_2 molecule from diazirines affords derivatives of bivalent carbon[157]. The many theoretical[158] and spectroscopic contributions to the electronic structure of carbenes provide a fascinating chapter in the chemistry of reactive intermediates. It has now been established that the parent substance has a triplet ground state *(174)* with an equilibrium angle H—C—H of about 136°. The triplet methylene and its mono- and di-deuterated derivatives can be produced by photolysis of diazirine[159] or deuterated diazirines[159, 160] in solid xenon and then observed by ESR spectroscopy (zero field parameters: $D/hc = 0.6881\ cm^{-1}$, $E/hc = 0.00346\ cm^{-1}$). In spite of the triplet ground state, the lowest singlet *(175)* with an energy minimum at an H—C—H angle of *ca.* 105°[158, 161] is the reactive species in thermolyses and direct photolyses[162].



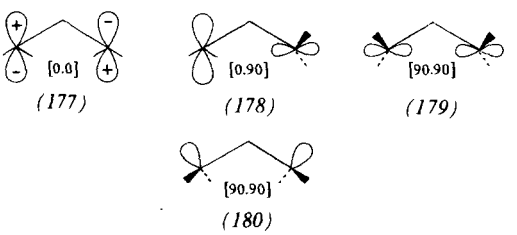
On ejection of molecular nitrogen from five- or higher-membered rings one obtains, at least formally, intermediates *(176)* with terminal reaction centers (X, Y), that can be considered either as diradicals or as dipoles and whose nature is determined by whether conjugative interactions are possible between X and Y.



(176)

Whereas the structure of these intermediates of type *X—Z—Y* in some [5→3+2]-processes has been provided by spectroscopic and quantum-mechanical investigations, final conclusions about the homologous species, *e.g.* 1,4-diradicals, have so far been drawn mainly indirectly, mostly from the stereochemistry of the cyclization products.

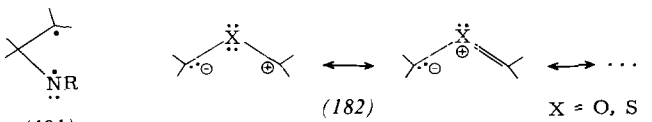
Cycloelimination of nitrogen from 1-pyrazolines has led to an extremely wide variety in the stereochemistry of the reaction products, depending on the way the reaction is carried out, the degree of substitution, and the nature of the substituents (see Section 3.3). This phenomenon may have its origin in the occurrence of stereochemically different trimethylenes in singlet or triplet states. Of the many spatial structures of trimethylene *Hoffmann*[163] has calculated the [0,0]-*(177)*, [0,90]-*(178)*, and [90,90]-geometry *(179)* of the π-diradical as extreme cases.



(177) *(178)* *(179)* *(180)*

According to this work, the antisymmetric [0,0]-trimethylene, which can form cyclopropane by the conrotatory route, is the most stable form at angles above 120°; at angles below 120° the [90,90]-form, which easily passes directly into cyclopropane, is certainly more stable. It is interesting that *Jean* and *Salem*[164] find [90,90]-trimethylene *(180)* with pyramidal terminal methylene groups to be still more energy-deficient than the singlet *(179)* by about 6.2 kcal/mol. *(180)* owes its relative stability mainly to 1,3-zwitterion admixtures. EHMO calculations[163] favor the existence of a mobile excited singlet trimethylene whose presence is deduced from the product pattern after direct photolysis[165]. Ketone-sensitized photolysis probably gives triplet trimethylene, which is identical with the adduct of $^3CH_2$ to alkenes[165]. On substitution by electronegative groups the chances of the appearance of 1,3-zwitterions in place of the 1,3-diradicals are increased. The very small solvent effect, however, speaks against this[166]. Nevertheless, it must finally be mentioned that, especially in some bicyclic compounds, the experimental findings can be explained in terms of a two-stage mechanism[167, 168]. Yet, for most of the 1-pyrazolines the mechanism of synchronous elimination of nitrogen with the formation of the trimethylene intermediate appears to be proved by the course followed by the activation energy on stepwise alkylation[147] or arylation[63] and particularly conclusively by kinetic deuterium

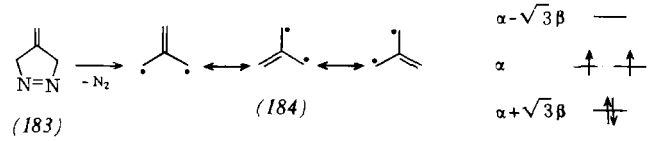
isotope effects[169]. N_2-elimination from 4,5-dihydro-1*H*-1,2,3-triazoles produces a molecule *(181)* that is comparable with trimethylene, if we allow for replacement of a methylene group by NR[170].



(181) *(182)* X = O, S

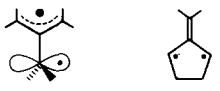
In contrast to the trimethylenes, the primary fragments *(182)* from 2,5-dihydro-1,3,4-oxadiazoles and -thiadiazoles contain terminal reaction centers conjugated with each other *via* the heteroatom. Carbonyl ylides and thiocarbonyl ylides[136–138] that are isoelectronic with allyl anions and accordingly cyclize in conrotatory manner are thus derived.

The liberation of nitrogen from 4-methylene-1-pyrazoline *(183)* leads to trimethylenemethane *(184)*, which is one of the molecules of greatest theoretical interest[171]. Its central carbon shows the maximal bond order (N = 1.732) and minimal free valence (F = 0) that can be associated with an sp^2-carbon. Trimethylenemethane serves as a model for the calculation of HMO bond orders and negative spin densities in the triplet state.



(183) *(184)*

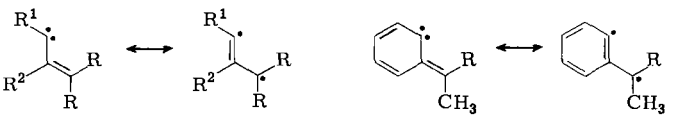
Even simple MO considerations give for *(184)* a triplet ground state[171]. This is supported by more recent calculations[172], according to which the lowest singlet state is alleged to lie 18—21 kcal/mol above the triplet ground state. In contrast to planar triplet trimethylenemethane, a geometry corresponding to *(184a)* was assumed for this state; the planar singlet trimethylene is separated from it only by a few kcal/mol[172,172a].



(184a) *(185)*

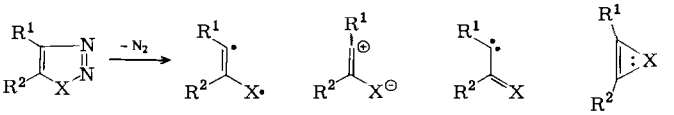
According to the conclusions from correlation diagrams[173], the thermal decomposition of pyrazolines in a concerted reaction should not lead directly to the triplet ground state. This can, however, be attained by $n\pi^*$ excitation followed by ISC and elimination of nitrogen. The ESR detection of triplet trimethylenemethane *(184)* on photolysis *(183)* in Fluorolube[174] is in excellent agreement with this. The signal intensity changes with temperature (20—80 K), the Curie law being strictly obeyed, whereby it is proved that the triplet molecule does in fact represent the ground state[175]. The calculated triplet-singlet separation for unsubstituted trimethylenemethane is so large that the triplet character of the ground state remains intact even after severe disturbance by substituents[176,177]. Thermally produced trimethylenemethane can reach the ground state only by ISC, but this process must compete with both conrotatory and disrotatory permitted ring closure to methylenecyclopropane; if the excess of vibrational energy is easily given up, it is possible that in this manner the methylene groups never become equivalent in the course of the reaction. For the trimethylenemethane derivative *(185)* *Berson et al.*[178] were able to prove the existence of at least two reactive states, only one of which is a triplet state. A nonplanar geometry analogous to *(184a)* was proposed for the reactive singlet molecule because of the stereo- and regiospecificity of the alkene adducts. Experimental results indicate an upper limit of 3.5 kcal/mol for the singlet-triplet energy gap in the trimethylenemethane derivative *(185)*[188].

3*H*-Pyrazoles undergo photochemical ring opening to yield vinyldiazoalkanes which form vinylcarbenes in a second photochemical step. Although the reaction products presumably arise in the singlet state[179], these carbenes have a triplet ground state characterized by an ESR spectrum[85,139,180–182,189]. The zero field parameters of *(186)* (*e.g.* $R^1 = R^2 = C_6H_5$, $R = CH_3$: $D/hc = 0.358\ cm^{-1}$. $E/hc = 0.0206\ cm^{-1}$) are in accord with a considerable contribution from the vinylcarbene limiting structure *(186a)*[180]. In systems of the type *(187)* strong delocalization of one electron over the π-system must be assumed; the other electron is localized in a σ-orbital on the benzene ring ($R = CO_2CH_3$: $D/hc = 0.111\ cm^{-1}$, $E/hc = 0.0069\ cm^{-1}$)[181,139].



(186a) *(186b)* *(187a)* *(187b)*

The primary fragments produced on N_2-elimination from heteroarenes *(152)* are formulated as 1,3-diradicals *(188)*, 1,3-dipoles *(189)*, and heteroanalogous α-oxocarbenes *(190)*[42,68,87,125,126].



(152) *(188)* *(189)* *(190)* *(191)*

X = S
X = NR

Radical intermediates but no triplet 1,3-diradicals could be detected[183] on photolysis (−170 °C) of 1,2,3-thiadiazoles *(152)*, X = S, in the crystalline state or in solidified hexafluorobenzene. All three structures could be utilized to explain the formation of the reaction products isolated.

Meanwhile, there has been proof of the appearance of the potentially antiaromatic thiirenes *(191)* X = S, and 1*H*-azirines *(191)*, X = NH, as further intermediate stages. The participation of such "symmetrical" species follows from the product composition, from the low-temperature matrix photolysis of deuterated[184] and ^{13}C-labeled[185] 1,2,3-thiadiazoles, from the formation of 2-phthalimido-2*H*-azirine in the photolysis of 1-phthalimido-1,2,3-triazole[68,10], and from the distribution of ^{13}C in the thermolysis products of ^{13}C-labeled 1,2,3-triazoles[69]. The antiaromatic character of the three-mem-

bered rings *(191)* has been supported by *ab-initio*[186] and MINDO[187] calculations.

Considerations similar in principle to those outlined above probably apply to the nature of the primary fragments derived by the elimination of nitrogen from other heteroaromatic five-membered rings; many of these primary fragments have not been investigated either theoretically or experimentally.

Received: December 2, 1976 [A 188 IE]
German version: Angew. Chem. *89*, 876 (1977)
Translated by Express Translation Service, London

[1] *R. Huisgen*, Angew. Chem. *80*, 329 (1968); Angew. Chem. Int. Ed. Engl. *7*, 321 (1968).
[2] Cf. *R. W. Hoffmann*, Angew. Chem. *83*, 595 (1971); Angew. Chem. Int. Ed. Engl. *10*, 529 (1971).
[3] Cf. *G. W. Griffin*, Angew. Chem. *83*, 604 (1971); Angew. Chem. Int. Ed. Engl. *10*, 537 (1971).
[4] *B. P. Stork, A. J. Duke:* Extrusion Reactions. Pergamon Press, Oxford 1967.
[5] *V. Zanker* in Houben-Weyl: Methoden der organischen Chemie. Thieme, Stuttgart 1975, Vol. IV/5a, p. 546ff.
[6] *W. Rundel* in Houben-Weyl: Methoden der organischen Chemie. Thieme, Stuttgart 1975, Vol. IV/5b, p. 1131ff.
[7] *K. Mackenzie* in *S. Patai:* The Chemistry of the Hydrazo, Azo and Azoxy Groups. Wiley, London 1975, Vol. 1, p. 329ff.
[8] *R. J. Drewer* in *S. Patai:* The Chemistry of the Hydrazo, Azo and Azoxy Groups. Wiley, London 1975, Vol. 2, p. 935ff.
[9] *R. B. Woodward, R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781 (1969); references cited therein.
[10] *P. B. Dervan, T. Uyehara*, J. Am. Chem. Soc. *98*, 2003 (1976).
[11] *C. G. Overberger, M. S. Chi, D. G. Pucci, J. A. Barry*, Tetrahedron Lett. *1972*, 4565.
[12] *G. Vitt, E. Hädicke, G. Quinkert*, Chem. Ber. *109*, 518 (1976).
[13] *E. Voigt, H. Meier*, Angew. Chem. *87*, 109 (1975); Angew. Chem. Int. Ed. Engl. *14*, 103 (1975).
[14] *E. Voigt, H. Meier*, Chem. Ber. *108*, 3326 (1975).
[15] *H. Meier, K.-P. Zeller*, Angew. Chem. *87*, 52 (1975); Angew. Chem. Int. Ed. Engl. *14*, 32 (1975).
[16] *M. E. Hermes, F. D. Marsh*, J. Am. Chem. Soc. *89*, 4760 (1967).
[17] *G. Himbert, D. Frank, M. Regitz*, Chem. Ber. *109*, 370 (1976).
[18] Cf. *L. A. Burke, J. Elguero, G. Leroy, M. Sana*, J. Am. Chem. Soc. *98*, 1685 (1976).
[19] *A. Holm, N. Harrit, N. H. Toubro*, J. Am. Chem. Soc. *97*, 6197 (1975).
[20] *W. M. Jones*, J. Am. Chem. Soc. *82*, 3136 (1960); references cited therein.
[21] *T. L. Gilchrist, C. W. Rees, C. Thomas*, J. Chem. Soc. Perkin I *1975*, 12.
[22] *R. Askani*, Chem. Ber. *98*, 2551 (1965).
[23] *N. Rieber, J. Alberts, J. A. Lipsky, D. M. Lemal*, J. Am. Chem. Soc. *91*, 5668 (1969).
[24] *J. P. Snyder, L. Lee, V. T. Bandurco, C. Y. Yu, R. J. Boyd*, J. Am. Chem. Soc. *94*, 3260 (1972).
[25] *C. Wentrup*, Helv. Chim. Acta *55*, 1613 (1972).
[26] *R. C. Neumann, E. W. Ertley*, J. Am. Chem. Soc. *97*, 3130 (1975).
[27] *K. Tortschanoff, H. Kisch, O. E. Polansky*, Justus Liebigs Ann. Chem. *1975*, 449.
[28] *H. Meier, I. Menzel*, Chem. Commun. *1971*, 1059.
[29] *H. Meier, E. Voigt*, Tetrahedron *28*, 187 (1972).
[30] *H. Meier, M. Layer, W. Combrink, S. Schniepp*, Chem. Ber. *109*, 1650 (1976).
[31] *G. Odenigbo*, Dissertation, Universität Tübingen 1976.
[32] *H. Meier, H. Kolshorn*, unpublished.
[33] *P. G. Mente, C. W. Rees*, J. Chem. Soc. Chem. Commun. *1972*, 418; *T. L. Gilchrist, P. G. Menge, C. W. Rees*, J. Chem. Soc. Perkin I *1972*, 2165.
[34] *J. Lalezari, A. Shafiee, M. Yalpani*, J. Org. Chem. *38*, 338 (1973); *M. H. Ghandehari, D. Davalian, M. Yalpani, M. H. Partovi, ibid. 39*, 3906 (1974).
[35] *H. Meier*, Synthesis *1972*, 235.
[36] *H. Rau*, Angew. Chem. *85*, 248 (1973); Angew. Chem. Int. Ed. Engl. *12*, 224 (1973).
[37] *P. S. Engel, C. Steel*, Acc. Chem. Res. *6*, 275 (1973); references cited therein.
[38] *C. Steel*, J. Phys. Chem. *67*, 1779 (1963).
[39] *W. D. K. Clark, C. Steel*, J. Am. Chem. Soc. *93*, 6347 (1971).
[40] *P. S. Engel, L. Shen*, Can. J. Chem. *52*, 4040 (1974).
[41] *N. A. Porter*, Ph. D. Thesis, Harvard University 1969.
[41a] *R. M. Pagni, M. N. Burnett, J. R. Dodd*, J. Am. Chem. Soc. *99*, 1872 (1977).
[42] *H. Meier, I. Menzel*, Justus Liebigs Ann. Chem. *739*, 56 (1970).
[43] *W. R. Roth, M. Martin*, Justus Liebigs Ann. Chem. *702*, 1 (1967).
[44] *C. R. Flynn, J. Michl*, J. Am. Chem. Soc. *95*, 5800 (1973).
[45] *M. Franck-Neumann, D. Martina, C. Dietrich-Buchecker*, Tetrahedron Lett. *1975*, 1763; *M. Franck-Neumann, D. Martina, ibid. 1975*, 1767.
[46] *J. J. Cosa, H. E. Gsponer, E. H. Staricco, C. A. Vallana*, J. Chem. Soc. Faraday Trans. I *1973*, 1817.
[47] *N. Rieber, J. Alberts, J. A. Lipsky, D. M. Lemal*, J. Am. Chem. Soc. *91*, 5668 (1969).
[48] *H. J. Emeleus, G. L. Hurst*, J. Chem. Soc. *1962*, 3276.
[49] *J. A. Berson, S. S. Olin*, J. Am. Chem. Soc. *91*, 777 (1969).
[50] *J. A. Berson, S. S. Olin*, J. Am. Chem. Soc. *92*, 1086 (1970).
[51] *L. A. Paquette, M. J. Epstein*, J. Am. Chem. Soc. *95*, 6717 (1973).
[52] Summary: *K. McKenzie* in *S. Patai:* The Chemistry of the Hydrazo, Azo and Azoxy Groups. Wiley, London 1975, Vol. 1, p. 419ff.
[53] Summary: *J. Sauer*, Angew. Chem. *78*, 233 (1966); Angew. Chem. Int. Ed. Engl. *5*, 211 (1966).
[54] *E. Buchner*, Ber. Dtsch. Chem. Ges. *21*, 2640 (1888).
[55] *R. Criegee, A. Rimmelin*, Chem. Ber. *90*, 414 (1957).
[56] *W. Rundel, P. Kästner*, Justus Liebigs Ann. Chem. *737*, 87 (1970).
[57] *G. Tourand, J. Streith*, Tetrahedron Lett. *1972*, 3575.
[58] *M. Schneider, G. Mössinger*, Tetrahedron Lett. *1974*, 3081.
[59] *W. Welter, M. Regitz*, Tetrahedron Lett. *1976*, 1473.
[60] *T. J. Katz, N. Acton*, J. Am. Chem. Soc. *95*, 2738 (1973).
[61] *E. L. Allred, J. C. Hinshaw*, J. Am. Chem. Soc. *90*, 6885 (1968).
[62] *A. C. Day, M. C. Whiting*, J. Chem. Soc. *1966*, 464.
[63] *M. Schneider, H. Strohäcker*, Tetrahedron *32*, 619 (1976).
[64] *T. V. van Auken, K. L. Rinehart*, J. Am. Chem. Soc. *84*, 3742 (1962).
[65] *R. L. Dreibelbis, H. N. Khatri, H. M. Walborsky*, J. Org. Chem. *40*, 2074 (1975).
[66] *T. C. Clarke, L. A. Wendling, R. G. Bergman*, J. Am. Chem. Soc. *97*, 5638 (1975); *99*, 2740 (1977).
[67] *A. Krantz, J. Laureni*, J. Am. Chem. Soc. *96*, 6768 (1974).
[68] *T. L. Gilchrist, G. E. Gymer, C. W. Rees*, J. Chem. Soc. Perkin I *1975*, 1; J. Chem. Soc. Chem. Commun. *1973*, 835.
[69] *T. L. Gilchrist, C. W. Rees, C. Thomas*, J. Chem. Soc. Perkin I *1975*, 8.
[70] *T. L. Gilchrist, G. E. Gymer, C. W. Rees*, J. Chem. Soc. Perkin I *1973*, 555.
[71] *P. D. Bartlett, N. A. Porter*, J. Am. Chem. Soc. *90*, 5317 (1968).
[72] *P. B. Devan, T. Uyehara*, J. Am. Chem. Soc. *98*, 1262, 2004 (1976).
[73] *R. W. Hoffmann, W. Sieber*, Angew. Chem. *77*, 810 (1965); Angew. Chem. Int. Ed. Engl. *4*, 786 (1965).
[74] *R. N. Castle* in *A. Weisberger, E. C. Taylor:* The Chemistry of Heterocyclic Compounds. Wiley, New York 1973, Vol. 28, p. 2.
[75] *J. A. H. MacBride*, J. Chem. Soc. Chem. Commun. *1972*, 1219.
[76] *G. Seybold, U. Jersak, R. Gompper*, Angew. Chem. *85*, 918 (1973); Angew. Chem. Int. Ed. Engl. *12*, 847 (1973).
[77] Cf. also *C. W. Rees, R. C. Storr, P. J. Whittle*, J. Chem. Soc. Chem. Commun. *1976*, 411; references cited therein.
[78] *C. G. Overberger, J. Tashlick, M. Bernstein, R. G. Hiskey*, J. Am. Chem. Soc. *80*, 6556 (1958).
[79] *C. G. Overberger, C. Yaroslavsky*, Tetrahedron Lett. *1965*, 4315.
[80] *C. G. Overberger, J. W. Stoddard*, J. Am. Chem. Soc. *92*, 4922 (1970).
[81] *S. F. Gait, M. E. Peek, C. W. Rees, R. C. Storr*, J. Chem. Soc. Perkin I *1974*, 1248.
[82] *S. G. Mylonakis, S. Seltzer*, J. Am. Chem. Soc. *90*, 5487 (1968).
[83] Cf. *e.g. A. Mansoor, I. D. R. Stevens*, Tetrahedron Lett. *1966*, 1733.
[84] *M. T. H. Liu, D. H. T. Chien*, Can. J. Chem. *52*, 246 (1974); cf. *W. E. Jones, J. S. Wassou, M. T. H. Liu*, J. Photochem. *5*, 311 (1976).
[85] *G. Baum, R. Bernard, H. Shechter*, J. Am. Chem. Soc. *89*, 5307 (1967).
[86] *C. Graebe, F. Ullmann*, Justus Liebigs Ann. Chem. *291*, 16 (1896).
[87] *E. M. Burgess, R. Carithers, L. McCullagh*, J. Am. Chem. Soc. *90*, 1923 (1968).
[88] For the photochemistry of 1-hydroxybenzotriazole cf. *E. Lüddecke*, Dissertation, Universität Tübingen 1976; *M. P. Serré*, J. Heterocycl. Chem. *11*, 245 (1974).
[89] *R. Huisgen, M. Seidel*, Chem. Ber. *94*, 2509 (1961).
[90] *H. Neunhoeffer, H.-D. Vötter, H. Gais-Mutterer*, Tetrahedron Lett. *1973*, 219; references cited therein.
[91] *S. G. Cohen, R. Zand*, J. Am. Chem. Soc. *84*, 586 (1962).
[92] *H. E. Zimmerman, R. J. Boettcher, N. E. Buehler, G. E. Keck*, J. Am. Chem. Soc. *97*, 5635 (1975).
[93] *E. L. Allred, B. R. Beck*, Tetrahedron Lett. *1974*, 437; *Kei-Wei Shen*, J. Am. Chem. Soc. *93*, 3064 (1971).
[94] *R. Gleiter, W. Retting, C. Wentrup*, Helv. Chim. Acta *57*, 2111 (1974).
[95] *C. Wentrup*, Tetrahedron *30*, 1301 (1974).
[96] *C. Thétaz, C. Wentrup*, J. Am. Chem. Soc. *98*, 1258 (1976).
[97] *H. Meier, H. Bühl*, J. Heterocycl. Chem. *12*, 605 (1975).
[98] *K.-P. Zeller, H. Meier, E. Müller*, Justus Liebigs Ann. Chem. *766*, 32 (1972).
[99] *G. Seybold, C. Heibel*, Angew. Chem. *87*, 171 (1975); Angew. Chem. Int. Ed. Engl. *14*, 248 (1975).

[100] *H. Bühl, B. Seitz, H. Meier*, Tetrahedron *33*, 449 (1977).
[101] *H. Meier, I. Menzel*, Tetrahedron Lett. *1972*, 445.
[102] *P. A. Smith, E. Leon*, J. Am. Chem. Soc. *80*, 4647 (1958).
[103] *W. Kirmse*, Angew. Chem. *71*, 381 (1959).
[104] *L. Birkofer, A. Ritter, P. Richter*, Chem. Ber. *96*, 2750 (1963).
[105] *W. Kirmse*, Chem. Ber. *93*, 2353 (1960).
[106] *K. A. Jensen, S. Burmeister, T. A. Bak*, Acta Chem. Scand. *21*, 2792 (1967).
[107] *A. Holm, N. Harrit, N. H. Toubro*, J. Am. Chem. Soc. *97*, 6197 (1975).
[108] *I. Lalezari, A. Shafiee*, Tetrahedron Lett. *1969*, 5105.
[109] *I. Lalezari, A. Shafiee, M. Yalpani*, J. Org. Chem. *36*, 2836 (1971); J. Heterocycl. Chem. *9*, 1411 (1972); J. Pharm. Sci. *62*, 61 (1973).
[110] *H. Goldolab, I. Lalezari*, J. Heterocycl. Chem. *12*, 801 (1975).
[111] *H. Meier, M. Layer, A. Zetzsche*, Chem.-Ztg. *98*, 460 (1974).
[112] *H. Meier, S. Schniepp, W. Combrink*, Chem.-Ztg. *99*, 461 (1975).
[113] *H. Meier, H. Gugel*, Synthesis *1976*, 338.
[114] *H. Meier, H. Gugel, H. Kolshorn*, Z. Naturforsch. *B31*, 1270 (1976).
[114a] *H. Meier, H. Petersen*, Synthesis, in press.
[115] *G. W. Krakower, H. A. van Dine*, J. Org. Chem. *31*, 3467 (1966).
[116] *F. G. Willey*, Angew. Chem. *76*, 144 (1964); Angew. Chem. Int. Ed. Engl. *3*, 138 (1964).
[117] *H. Meier, I. Meinzel*, Synthesis *1971*, 215.
[118] *G. Wittig, R. W. Hoffmann*, Chem. Ber. *95*, 2718 (1962).
[119] *R. W. Hoffmann, W. Sieber, G. Guhn*, Chem. Ber. *98*, 3470 (1965).
[120] *S. L. Lee, A. M. Cameron, J. Warkentin*, Can. J. Chem. *50*, 2326 (1972); Chem. Commun. *1970*, 1074.
[121] *H. Meier, D. Daniil*, Chem.-Ztg. *100*, 89 (1976).
[122] *D. Daniil, H. Meier*, J. Heterocycl. Chem. *13*, 649 (1976).
[122a] *D. Daniil, U. Merkle, H. Meier*, Synthesis, in press.
[122b] *D. Daniil, G. Gauglitz, H. Meier*, Photochem. Photobiol. *26*, 225 (1977).
[122c] *D. Daniil, H. Meier*, Tetrahedron Lett. *1977*, 3155.
[123] *J. A. Berson, R. J. Bushby, J. M. McBride, M. Tremelling*, J. Am. Chem. Soc. *93*, 1544 (1971); *J. A. Berson, D. M. McDaniel, L. R. Corwin, J. H. Davis, ibid. 94*, 5508 (1972); *J. A. Berson, D. M. McDaniel, L. R. Corwin, ibid. 94*, 5509 (1972); *M. S. Platz, D. R. Kelsey, J. A. Berson, N. J. Turro, M. Mirbach, ibid. 99*, 2009 (1977).
[124] *H. K. Spencer, M. P. Cava*, J. Org. Chem. *41*, 730 (1976).
[125] *K.-P. Zeller, H. Meier, E. Müller*, Tetrahedron Lett. *1971*, 537.
[126] *W. Kirmse, L. Horner*, Justus Liebigs Ann. Chem. *614*, 4 (1958).
[127] *Soon-Yung Hong, J. E. Baldwin*, Tetrahedron *24*, 3878 (1968).
[128] *S. Hünig, E. Fleckenstein*, Justus Liebigs Ann. Chem. *738*, 192 (1970).
[129] *R. Huisgen, J. Sauer, M. Seidel*, Chem. Ber. *94*, 2503 (1961).
[130] *P. Scheiner, J. F. Dinda*, Tetrahedron *26*, 2619 (1970).
[131] *R. A. Moss, J. R. Przybyla*, Tetrahedron *25*, 647 (1969).
[132] *M. T. H. Liu, D. H. T. Chien*, J. Chem. Soc. Perkin II *1974*, 937.
[133] *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. Int. Ed. Engl. *2*, 565 (1963).
[134] *R. Neidlein, K. Salzmann*, Synthesis *1975*, 52.
[135] *E. Van Loock, J. M. Vandensavel, G. L'abbé, G. Smets*, J. Org. Chem. *38*, 2916 (1973).
[136] *J. Buter, S. Wassenaar, R. M. Kellogg*, J. Org. Chem. *37*, 4045 (1972).
[137] *P. Raynolds, S. Zonnebelt, S. Bakker, R. M. Kellogg*, J. Am. Chem. Soc. *96*, 3146 (1974).
[138] *J. Buter, P. W. Raynolds, R. M. Kellogg*, Tetrahedron Lett. *1974*, 2901.
[138a] Cf. *T. Sasaki, S. Eguchi, Y. Hirako*, Heterocycles (Sendai, Japan) *4*, 1901 (1976).
[139] *G. L. Closs, L. Riemenschneider Kaplan*, J. Am. Chem. Soc. *91*, 2168 (1969).
[140] *M. Franck-Neumann, C. Buchecker*, Tetrahedron Lett. *1973*, 2875.
[141] *M. Franck-Neumann, C. Buchecker*, Angew. Chem. *82*, 549 (1970); Angew. Chem. Int. Ed. Engl. *9*, 526 (1970).
[142] *J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann*, Chem. Ber. *100*, 60 (1967); *R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, V. Weberndörfer, ibid. 100*, 1580 (1967); *R. Huisgen, R. Grashey, H. Knupfer, R. Kunz, M. Seidel, ibid. 97*, 1085 (1964); *R. Huisgen, R. Grashey, M. Seidel, G. Wallbillich, H. Knupfer, R. Schmidt*, Justus Liebigs Ann. Chem. *653*, 105 (1962); *R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland, G. Wallbillich*, J. Org. Chem. *24*, 892 (1959).
[143] *T. Sasaki, K. Kanematsu*, J. Chem. Soc. *C 1971*, 2147.
[144] *E. W. Neuvar, R. A. Mitsch*, J. Phys. Chem. *71*, 1229 (1967).
[145] *H. M. Frey, M. T. H. Liu*, J. Chem. Soc. *A 1970*, 1916.
[146] *M. T. H. Liu, K. Toriyama*, J. Phys. Chem. *76*, 797 (1972).
[147] *R. J. Crawford, A. Mishra*, J. Am. Chem. Soc. *88*, 3963 (1966).
[148] *B. K. Bandlish, A. W. Garner, M. L. Hodges, J. W. Timberlake*, J. Am. Chem. Soc. *97*, 5856 (1975).
[149] *J. C. Martin, J. W. Timberlake*, J. Am. Chem. Soc. *92*, 978 (1970).
[150] *J. W. Timberlake, B. K. Bandlish*, Tetrahedron Lett. *1971*, 1393.
[151] *R. J. Crawford, D. M. Cameron, H. Tokumaga*, Can. J. Chem. *52*, 4025 (1974).
[152] *P. S. Engel, L. Shen*, Can. J. Chem. *52*, 4040 (1974).
[153] *J. Buter, S. Wassenaar, R. M. Kellogg*, J. Org. Chem. *37*, 4045 (1972).
[154] *K. R. Kopecley, J. Soler*, Can. J. Chem. *52*, 2111 (1974).
[155] *C. G. Overberger, J. W. Stoddard, C. Yaroslavsky, H. Katz, J.-P. Anselme*, J. Am. Chem. Soc. *91*, 3226 (1969); *E. L. Allred, J. C. Himshaw, A. L. Johnson, ibid. 91*, 3382 (1969).
[156] *E. L. Allred, J. C. Himshaw*, Chem. Commun. *1969*, 1021; Tetrahedron Lett. *1972*, 387.
[156a] *J. P. Snyder, D. N. Harpp*, J. Am. Chem. Soc. *98*, 7821 (1976); see, however [156].
[157] *H. M. Frey*, Adv. Photochem. *4*, 225 (1966).
[158] Summary: *J. F. Harrison* in *W. Kirmse:* Carbene Chemistry. 2nd Edit. Academic Press, New York 1971, p. 159.
[159] *R. A. Bernheim, H. W. Bernard, P. S. Wang, L. S. Wood, P. S. Skell*, J. Chem. Phys. *53*, 1280 (1970).
[160] *E. Wasserman, V. J. Kuck, R. S. Hutton, W. A. Yager*, J. Am. Chem. Soc. *92*, 7491 (1970).
[161] *M. J. S. Dewar, R. C. Haddon, W.-K. Li, W. Thiel, P. K. Weiner*, J. Am. Chem. Soc. 97, 4540 (1975).
[162] *H. D. Roth*, J. Am. Chem. Soc. *93*, 4935 (1971).
[163] *R. Hoffmann*, J. Am. Chem. Soc. *90*, 1475 (1968); cf. *A. K. Q. Siu, W. M. St. John, E. F. Hayes, ibid. 92*, 7249 (1970).
[164] *Y. Jean, L. Salem, J. Chem. Soc. Chem. Commun. 1971*, 382.
[165] *R. Moore, A. Mishra, R. Crawford*, Can. J. Chem. *46*, 3305 (1968).
[166] *D. E. McGreer*, Can. J. Chem. *43*, 1398, 1407 (1965).
[167] *M. P. Schneider, R. J. Crawford*, Can. J. Chem. *48*, 628 (1970).
[168] *P. B. Condit, R. G. Bergman*, Chem. Commun. *1971*, 4.
[169] *B. H. Al-Sader, R. J. Crawford*, Can. J. Chem. *46*, 3302 (1968).
[170] *P. Scheiner*, J. Am. Chem. Soc. *90*, 988 (1968); *88*, 4759 (1966).
[171] Review: *F. Weiss*, Qu. Rev. Chem. Soc. *24*, 278 (1970); *P. Dowd*, Acc. Chem. Res. *5*, 242 (1972).
[172] *W. T. Bordon*, J. Am. Chem. Soc. *97*, 2906 (1975); *J. H. Danis, W. A. Goddard, ibid. 98*, 303 (1976); references cited therein.
[172a] For the potential surface of singlet trimethylenemethane cf. *E. R. Davidson, W. T. Borden*, J. Am. Chem. Soc. *99*, 2053 (1977).
[173] *W. T. Borden*, Tetrahedron Lett. *1967*, 259.
[174] *P. Dowd*, J. Am. Chem. Soc. *88*, 2587 (1966).
[175] *R. J. Baseman, D. W. Pratt, M. Chow, P. Dowd*, J. Am. Chem. Soc. *98*, 5726 (1976).
[176] *M. S. Platz, J. M. McBride, R. D. Little, J. J. Harrison, A. Shaw, S. E. Potter, J. A. Berson*, J. Am. Chem. Soc. *98*, 5725 (1976).
[177] *B. K. Carpenter, R. D. Little, J. A. Berson*, J. Am. Chem. Soc. *98*, 5723 (1976).
[178] *J. A. Berson, L. R. Corwin, J. H. Davis*, J. Am. Chem. Soc. *96*, 6177 (1974).
[179] *L. Schrader*, Tetrahedron *29*, 1833 (1973).
[180] *G. E. Palmer, J. R. Bolton, D. R. Arnold*, J. Am. Chem. Soc. *96*, 3708 (1974).
[181] *G. L. Closs, L. Riemenschneider Kaplan, V. I. Bendall*, J. Am. Chem. Soc. *89*, 3376 (1967).
[182] *A. B. Ernin, D. R. Arnold, L. A. Karnischky, E. Strom*, J. Am. Chem. Soc. *92*, 6218 (1970); *D. R. Arnold, A. B. Ernin, P. H. Kasai, ibid. 91*, 784 (1969).
[183] *P. Krauss, K.-P. Zeller, H. Meier, E. Müller*, Tetrahedron *27*, 595 (1971).
[184] *A. Krantz, J. Laureni*, J. Am. Chem. Soc. *96*, 6768 (1974).
[185] *J. Laureni, A. Krantz, R. A. Hajdu*, J. Am. Chem. Soc. *98*, 7872 (1976); *A. Krantz, J. Laureni, ibid. 99*, 4842 (1977).
[186] *W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, J. A. Pople*, Fortschr. Chem. Forsch. *40*, 1 (1973).
[187] *M. J. S. Dewar, C. A. Ramsden*, J. Chem. Soc. Chem. Commun. *1973*, 688.
[188] *M. S. Platz, J. A. Berson*, J. Am. Chem. Soc. *99*, 5178 (1977).
[189] *D. R. Arnold, R. W. Humphreys, W. J. Leigh, G. E. Palmer*, J. Am. Chem. Soc. *98*, 6225 (1976).

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

Quantitative Trace Analysis of Metals by Field Desorption Mass Spectrometry[**]

By *Wolf Dieter Lehmann* and *Hans-Rolf Schulten*[*]

The great sensitivity of field desorption mass spectrometry (FD-MS)[1] for the detection of metal cations became clear in the first studies on organic and inorganic salts[2a]: the signals for sodium and potassium were several orders of magnitude more intense than those of the organic ions[2b]. By means of FD-MS, cesium has been quantitatively determined in the picogram range in a number of solvents, body fluids, and environmental samples[3]. The detection limit for cesium by the FD technique lies in the lower femtogram region (10^{-15} g). Quantitative determination of metal cations—as in the case of organic ions[4]—requires integrating recording owing to the fluctuations of the FD ion currents.

In order to put the quantitative trace analysis of metals on a firm methodological footing, we have coupled a magnetic mass spectrometer with a multi-channel analyzer. Using this approach we have made the first FD-MS determinations of the distribution of the lithium isotopes ^{6}Li and ^{7}Li (natural abundance 7.5 % and 92.5 % respectively[5]) in some commercial lithium salts and an environmental sample.

The measurements were performed with a double focusing mass spectrometer (Varian MAT 731) with a mono FD ion source of our own construction and indirect heating of the FD emitter by a tunable argon laser (Spectra Physics, Model 166). The ion currents were recorded electrically and accumulated by a multi-channel analyzer (C-1024, Varian). The magnetic scan of the spectrometer controlled the multi-channel analyzer externally during the accumulation. Integrating electrical recording of low-intensity FI and FD ion currents with a multi-channel analyzer has already been described[6].

The determination of the isotopic distribution of the metals presented in this communication is a facile analytical procedure because the ion currents are powerful, because the emitter quality plays only a subordinate role, because the coupling of the mass spectrometer and the multi-channel analyzer can be quickly modified to accommodate a variety of analytical problems, and because the averaging of several hundred scans requires only 10 to 30 min. An experimental accuracy of several tenths of a percent was achieved by accumulation of several hundred scans (Table 1).

Table 1. Determination of the isotopic ratio of ^{6}Li and ^{7}Li by FD-MS with a multi-channel analyzer.—Compounds *(1)*—*(5)* were purchased from Merck AG, Darmstadt (Art. No. 5686, Suprapur; 5675, Erg. B. 6; 5668, Suprapur; 5688, molten; 5663, Suprapur), ^{6}Li-enriched compound *(6)* from Rohstoff-Einfuhr GmbH, Düsseldorf. The sample of Rhine water *(7)* was taken at the bank of the river, Kilometer 625 (August 25, 1977).—Over 300 scans were averaged in each case. The mean experimental error was 0.3 %.

Sample		^{6}Li [%]	^{7}Li [%]
(1)	LiF	10.6	89.4
(2)	LiCl	10.2	89.8
(3)	LiBr	5.8	94.2
(4)	LiI	2.9	97.1
(5)	$LiNO_3$	9.3	90.7
(6)	^{6}LiF	91.7	8.3
(7)	Rhine water	7.4	92.6

The data show that the distribution of the lithium isotopes in the salts examined deviates considerably from the mean natural distribution. The large variations observed are probably due to isotopic fractionation processes occurring during the production and purification of the products since the natural variation in the distribution of the lithium isotopes is much smaller[7]. The molecular weights of *(1)*—*(5)* calculated with the experimentally determined lithium distribution differ by 0.12 to 0.02 % from the values calculated with the natural isotopic abundances. However, much greater differences could occur if $[Li]^+$ is attached to a neutral molecule M (cationization[2a, 8]). Thus, for instance, the isotopic ratios found on analysis of $[M+Li]^+$ groups deviated from the mean natural lithium distribution, corresponding instead—within the limits of experimental accuracy—to the distribution in the salts used for cationization[9]. Deviations of the same magnitude are to be expected if the metal is incorporated into a product by chemical synthesis and a direct isotope analysis is performed on the new compound.

The LiF sample *(6)* shows a high degree of enrichment of ^{6}Li and is therefore suitable as internal standard for a quantitative determination of lithium. In a sample of Rhine water *(7)*, approximately the mean natural distribution was found. Knowledge of these two distributions permits quantitative determination of the lithium content of Rhine water by the method of isotopic dilution (Fig. 1).

Evaluation of the experimental data from Figure 1 gives a value of 8.3 µg Li/l for the water sample. The total error of this determination does not exceed 5 %.

[*] Dr. W. D. Lehmann, Dr. H.-R. Schulten [+]
Institut für Physikalische Chemie der Universität
Wegelerstrasse 12, D-5300 Bonn (Germany)

[+] To whom correspondence should be addressed.

[**] Quantitative Field Desorption Mass Spectrometry, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen. We are indebted to Dr. *D. Haaks*, Gesamthochschule Wuppertal, for his help in the laser experiments, to Dr. *H. M. Schiebel*, Technische Universität Braunschweig, for his help in measurements with the multi-channel analyzer, and to Prof. Dr. *H. J. Meyer*, Universität Bonn, for a sample of ^{6}Li-enriched lithium fluoride.—Part 6: *W. D. Lehmann, H.-R. Schulten, H. M. Schiebel*, Z. Anal. Chem., in press.

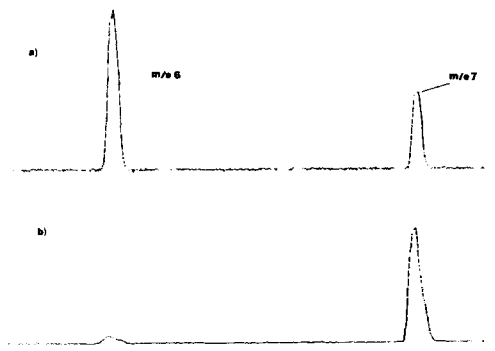


Fig. 1. Lithium isotopic distribution in Rhine water [2 µl; 100 scans were accumulated in each case]: a) with addition of 36.0 pg of Li *(6)*: ^{6}Li 67.5 %, ^{7}Li 32.5 %; b) original sample: ^{6}Li 7.4 %, ^{7}Li 92.6 %.

The results clearly demonstrate that field desorption mass spectrometry in conjunction with a multi-channel analyzer represents a powerful method for the trace analysis of metals. By use of the isotope dilution technique quantitative determinations of high sensitivity and accuracy can be accomplished without prior treatment of the original biological or environmental sample.

Received: September 7, 1977 [Z 832 IE]
German version: Angew. Chem. *89*, 890 (1977)

CAS Registry numbers:
Li, 7439-93-2; H_2O, 7732-18-5

[1] *H. D. Beckey, H.-R. Schulten*, Angew. Chem. *87*, 425 (1975); Angew. Chem. Int. Ed. Engl. *14*, 403 (1975).
[2] a) *H.-R. Schulten, H. D. Beckey*, Org. Mass Spectrom. *6*, 885 (1972); b) *H.-R. Schulten, F. W. Röllgen, ibid. 10*, 649 (1975).
[3] *W. D. Lehmann, H.-R. Schulten*, Anal. Chem. *49*, 1744 (1977).
[4] *H.-R. Schulten*, Cancer Treat. Rep. *60*, 501 (1976). *I. Jardine, M. N. Kan, C. Fenselau, R. Brundrett, M. Colvin, G. Wood, P.-Y. Lau, R. Charlton* in *E. R. Klein, P. D. Klein*: Proceedings of the Second International Conference on Stable Isotopes, Oct. 1975, Oak Brook, Ill., National Technical Information Service, U.S. Department of Commerce, Springfield, Va., ERDA CONF-751027, 1976, p. 138; *H.-R. Schulten, W. D. Lehmann, M. Jarman* in *A. P. De Leenheer, R. R. Roncucci*: Quantitative Mass Spectrometry in Life Sciences. Elsevier, Amsterdam 1977, p. 187; *W. D. Lehmann, H. D. Beckey, H.-R. Schulten, ibid.* p. 177; *S. Pfeifer, H. D. Beckey, H.-R. Schulten*, Z. Anal. Chem. *284*, 193 (1977); *W. D. Lehmann, H.-R. Schulten*, Angew. Chem. *89*, 180 (1977); Angew. Chem. Int. Ed. Engl. *16*, 184 (1977); Biomed. Mass Spectrom., in press.
[5] *P. de Bièvre*, Commission of the European Communities, Central Bureau for Nuclear Measurements, Geel (1974).
[6] a) *J. H. Reynolds, H. d'A. Heck, M. Anbar*, Biomed. Mass Spectrom. *2*, 299 (1975); b) *H. J. Heinen* in *D. Price, J. F. J. Todd*: Dynamic Mass Spectrometry, Vol. 5. Heyden and Sons, London 1977.
[7] *H. J. Svec, A. R. Anderson, Jr.*, Geochim. Cosmochim. Acta *29*, 633 (1965), and references cited therein.
[8] *F. W. Röllgen, H.-R. Schulten*, Org. Mass Spectrom. *10*, 660 (1975).
[9] *U. Giessmann, H. J. Heinen*, unpublished.

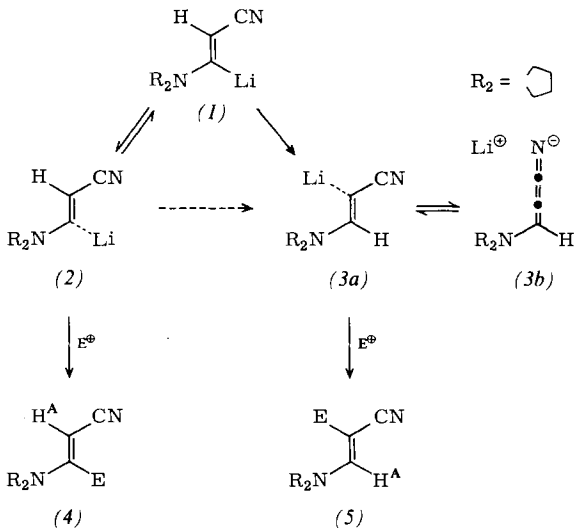
Functional Vinyl Carbanions—Deprotonation of β-(1-Pyrrolidinyl)acrylonitrile[1]

By *Richard R. Schmidt* and *Jörg Talbiersky*[*]

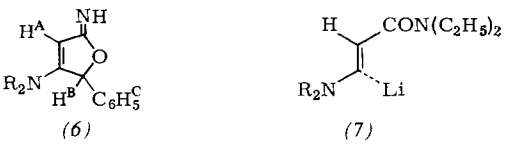
Highly selective reactions of polyfunctional systems are of great importance in synthetic chemistry. *trans*-β-(1-Pyrrolidinyl)acrylonitrile *(1)*, a derivative of the polyfunctional species formylacetonitrile, can react with strong bases or nucleophiles by Michael addition, addition to the carbonitrile group, and deprotonation at the α and β position[2]. We have now found that deprotonations with lithium diisopropylamide in tetrahydrofuran are very selective and temperature dependent; no significant competition from addition reactions is observed.

Thus, below −105 °C, kinetically controlled deprotonation occurs exclusively at the β position. The functional vinyllithium derivative *(2)* is of great preparative utility as a β-acylvinyl anion equivalent[2, 3]. Retention of stereochemistry is observed on reaction with electrophiles to give the cyano-enamines *(4a)*—*(4d)*; *(4d)* equilibrates with the cyclic isomer *(6)*. The lithiated acrylonitrile *(2)* is unstable at room temperature, unlike the corresponding acrylamide *(7)*. At temperature above −100 °C *(2)* already rearranges very slowly, and at higher temperatures fast and almost quantitatively, into the thermodynamically more stable vinyllithium derivative *(3)*[4]. At −15 °C *(3)* can be obtained directly from *(1)*, albeit in somewhat lower yield; at this temperature there is still no serious competition from addition reactions. Transition of the vinyllithium derivative into the mesomeric imine anion *(3b)* probably plays an important role in the conversion of *(2)* into *(3)*[4], for the analogous reaction was not observed under comparable conditions in the case of *(7)* owing to pronounced interaction between the lithium atom and the carboxamide group[2].

Compound *(3)* is an equivalent of the monoanion of formylacetonitrile; it reacts with electrophiles with retention to give the cyano-enamines *(5a)*—*(5d)*. In this way it proves possible to monosubstitute the very reactive compound α-formylacetonitrile at the α position conveniently, specifically, and in high yield[5].



(a): E = D; *(b)*: E = CH_3^B; *(c)*: E = CH_3^C–CH_2^B; *(d)*: E = $C_6H_5^C$–CH^B(OH)



Experimental

Compound *(1)* (0.74 g, 6 mmol) is dissolved under N_2 in dry THF (10 ml) and added dropwise within 3 min to a vigorously stirred and cooled mixture (temperature *T*, Table 1)

[*] Prof. Dr. R. R. Schmidt
Fachbereich Chemie der Universität
Postfach 7733, D-7750 Konstanz (Germany)
Dipl.-Chem. J. Talbiersky
Institut für Organische Chemie der Universität
Pfaffenwaldring 55, D-7000 Stuttgart 80 (Germany)

Table 1. Products of types *(4)* and *(5)* [a].

Compound	Electrophile	Reaction conditions T [°C]	t_1 [min]	t_2 [h]	M.p. [°C] or B.p. [°C/torr] [b]	Yield [c] [%]	^{1}H-NMR data [d] H^A	H^B	H^C
(4a)	D—OCH_3	−113	40	0.25	55	95	3.63 (s)	—	—
(4b)	CH_3—I	−113	40	3	59	74	3.55 (s)	2.17 (s)	—
(4c)	C_2H_5—I	−113	40	10	$90/10^{-3}$	35	3.55 (s)	2.55 (q)	1.22 (t)
(4d) + *(6)*	C_6H_5—CHO	−113	40	3	130—135 [e]	42	3.78 (s)	6.17 (s)	7.67—7.12 (m)
							4.87 (s)	5.80 (s)	7.38 (s)
(5a)	D—OCH_3	− 76	60	0.25	55	82	7.17 (s)	—	—
(5b) [g]	CH_3—I	− 76 [f]	60 [f]	1 [f]	$70/10^{-3}$	73 [f]	6.72 (s)	1.95 (s)	—
(5c)	C_2H_5—I	− 76	60	3	$70/10^{-3}$	83	6.71 (s)	2.30 (q)	1.12 (t)
(5d)	C_6H_5—CHO	− 76	60	1	109	92	6.82 (s)	5.65 (d)	7.62—7.13 (m)

[a] All compounds gave correct elemental analyses.
[b] Oven temp. in bulb tube distillation.
[c] Isolated yields.
[d] δ values, $CDCl_3$, TMS int.
[e] Decomposition.
[f] At $T = -15$ °C, $t_1 = 1$ min, $t_2 = 15$ min, 66 % of *(5b)* are obtained.
[g] Alternative preparation: *F. Texier, J. Bourgois*, J. Heterocycl. Chem. *12*, 503 (1975); the physical data (b.p., ^{1}H-NMR) are in agreement.

of dry THF (40 ml), diisopropylamine (1 ml, 7 mmol), and *tert*-butyllithium (4 ml, 7 mmol) in *n*-pentane (*ca.* 1.75 M solution). After reaction time t_1 (Table 1), electrophile (7 mmol) is added, and after time t_2 (Table 1) the mixture is worked up with water/chloroform at room temperature.

Received: August 29, 1977 [Z 830 IE]
German version: Angew. Chem. *89*, 891 (1977)

CAS Registry numbers:
(1), 23220-68-0; *(2)*, 64147-04-2; *(3a)*, 64147-05-3; *(4a)*, 64147-06-4; *(4b)*, 64147-07-5; *(4c)*, 64147-08-6; *(4d)*, 64147-09-7; *(5a)*, 64175-34-4; *(5b)*, 57988-67-7; *(5c)*, 64147-10-0; *(5d)*, 64147-11-1; *(6)*, 64147-12-2; CH_3OD, 1455-13-6; CH_3I, 74-88-4; C_2H_5I, 75-03-6; C_6H_5CHO, 100-52-7

[1] Vinyl Anions, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 3: *R. R. Schmidt, B. Schmid*, Tetrahedron Lett. *1977*, 3583.
[2] *R. R. Schmidt, J. Talbiersky*, Angew. Chem. *88*, 193 (1976); Angew. Chem. Int. Ed. Engl. *15*, 171 (1976); and references cited therein.
[3] *T. Cohen, D. A. Bennett, A. J. Mura*, J. Org. Chem. *41*, 2506 (1976).
[4] Non-functional acrylic acid derivatives have been α-metalated by halogen-metal exchange: *H. L. Elbe, G. Köbrich*, Tetrahedron Lett. *1974*, 2557; and references cited therein.
[5] Concerning the monoalkylation of β-dicarbonyl compounds: *J. H. Clark, J. H. Miller*, J. Chem. Soc. Chem. Commun. *1977*, 64.

A New Method for the Introduction of Trifluoromethyl Groups[**]

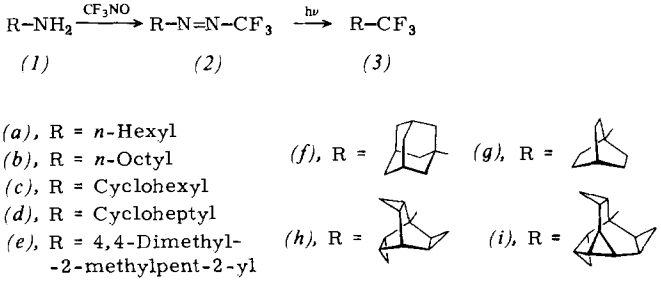
By *Peter Gölitz* and *Armin de Meijere*[*]

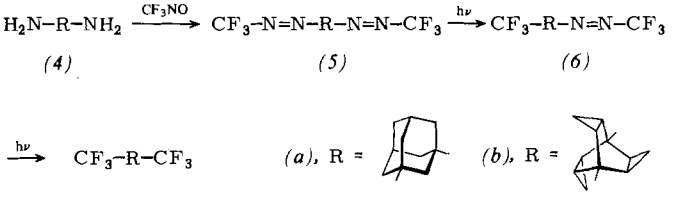
The strongly negative inductive effect of the CF_3 substituent endows it with the ability of stabilizing otherwise unstable molecules, making them isolable as trifluoromethyl derivatives[1]. Moreover, many trifluoromethyl derivatives display an enhanced pharmacological activity relative to the unsubstituted analogs[2].

Several methods are known for the trifluoromethylation of arenes[3]; however, they are unsuitable for the preparation of corresponding aliphatic compounds[4] or are successful only in special cases[2, 5].

We have now found a method for the mild introduction of the CF_3 group into primary, secondary, and tertiary positions by photolysis of trifluoromethylazo compounds, which are readily accessible from the corresponding amines by reaction with trifluoronitrosomethane[6].

The pale yellow azo compounds *(2)* are far more stable thermally and towards acids than the corresponding methylalkyldiazenes[7]. However, they readily undergo photochemical cleavage with liberation of nitrogen. In highly viscous solvents such as *tert*-butyl alcohol or hexadecane, the resulting radicals afford the trifluoromethyl derivatives *(3)* in good yields by "cage recombination" (Table 1).





An undesired side reaction occurs in some cases, in which stable olefins can be formed by hydrogen abstraction from the position α to the radical center (Table 1, examples *(1c)*, *(1d)*, *(1e)*). The extremely mild reaction conditions also permit the trifluoromethylation of highly sensitive polycyclic systems (Table 1, examples *(1h)*, *(1i)*). The same procedure can be used to prepare bis-trifluoromethyl derivatives *(7)* from diamines *(4)* (Table 1); in these cases, however, the intermediate trifluoromethylazo(trifluoromethyl) derivatives *(6)* are also isolated besides the desired product.

[*] Prof. Dr. A. de Meijere, Dipl.-Chem. P. Gölitz
Organisch-chemisches Institut der Universität
Tammannstrasse 2, D-3400 Göttingen (Germany)

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

Table 1. Trifluoromethyl compounds from mono- and diamines (cf. *Experimental*).

Starting compound	Products, isolated yields [%] (conversion [%])		Irradiation time [h]	Method
(1) [a]	*(2)* [b]	*(3)* [b]		
(a)	80	42 (54)	24	A
(b)	75	69 (95)	48	B
(c)	70	43 (50) [c]	96	A
(d)	68	34 (75) [d]	70	A
(e)	75	7 (100) [e]	72	B
(f)	74	40 (85) [f]	96	B
(g)	61	30 (75)	96	B
(h)	80	65 (85)	96	B
(i)	50	40 (100)	48	B
(4) [a]	*(5)* [b]	*(6)* [b] *(7)* [b]		
(a)	65	35 (60) 30 (60)	96	B
(b)	82	40 (65) 32 (65)	96	B

[a] Commercially available amines *(1a)*—*(1f)* were used without further purification; *(1g)*: *C. A. Grob, M. Ohta, E. Renk, A. Weiss*, Helv. Chim. Acta *41*, 1191 (1958); *(1h)*, *(1i)*, and *(4b)*: *O. Schallner*, Dissertation, Göttingen 1974; *(4a)*: *H. Stetter, C. Wolff*, Chem. Ber. *93*, 1366 (1960). [b] The structures of the new compounds were confirmed by IR, ^{1}H- and ^{13}C-NMR spectra, and by elemental analyses. [c] By-product: cyclohexene (18 %). [d] By-product: cycloheptene (17 %). [e] Major product: 4,4-dimethyl-2-methylpent-1-ene (47 %). [f] Preparation of *(3f)* from adamantanecarboxylic acid and SF_4 has already been reported [5]; however, other authors [8] failed to obtain *(3f)* under almost identical conditions.

CAS Registry numbers:
(1a), 111-26-2; *(1b)*, 111-86-4; *(1c)*, 108-91-8; *(1d)*, 5452-35-7; *(1e)*, 107-45-9; *(1f)*, 768-94-5; *(1g)*, 1193-42-6; *(1h)*, 64252-94-4; *(1i)*, 64252-95-5; *(2a)*, 64252-96-6; *(2b)*, 64252-97-7; *(2c)*, 705-93-1; *(2d)*, 64252-98-8; *(2e)*, 64252-99-9; *(2f)*, 64253-00-5; *(2g)*, 64253-01-6; *(2h)*, 64253-02-7; *(2i)*, 64253-03-8; *(3a)*, 693-09-4; *(3b)*, 55757-34-1; *(3c)*, 401-75-2; *(3d)*, 64253-04-9; *(3e)*, 64253-05-0; *(3f)*, 40556-44-3; *(3g)*, 64253-06-1; *(3h)*, 64253-07-2; *(3i)*, 64253-08-3; *(4a)*, 10303-95-4; *(4b)*, 64252-90-0; *(5a)*, 64252-85-3; *(5b)*, 64252-87-5; *(6a)*, 64252-88-6; *(6b)*, 64252-92-2; *(7a)*, 40556-46-5; *(7b)*, 64252-93-3; trifluoronitrosomethane, 334-99-6; cyclohexene, 110-83-8; cycloheptene, 628-92-2; 4,4-dimethyl-2-methylpent-1-ene, 107-39-1

[1] *I. L. Knunyants, V. R. Polishchuk*, Russ. Chem. Rev. *44*, 339 (1975).
[2] *W. A. Gregory, J. G. Whitney*, US-Pat. 3414615 (1968).
[3] *Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, E. Chikami*, Chem. Pharm. Bull. *18*, 2334 (1971); *J. H. Simons, C. J. Lewis*, J. Am. Chem. Soc. *60*, 492 (1938); *W. R. Hasek, W. C. Smith, V. A. Engelhardt, ibid. 82*, 543 (1960).
[4] *E. B. Davidson*, J. Org. Chem. *27*, 2267 (1962).
[5] *A. M. Aleksandrov, G. I. Danilenko, L. M. Yagupol-skii*, Zh. Org. Khim. *9*, 951 (1975).
[6] *A. S. Filatov, M. A. Englin*, Zh. Obshch. Khim. *38*, 24 (1968); *K. Chakravorty, J. M. Pearson, M. Szwarc*, J. Phys. Chem. *73*, 746 (1969).—CF_3NO is commercially available.
[7] For instance, the trifluoromethylazo group is stable towards SbF_5 in SO_2ClF: *P. Gölitz, A. de Meijere*, unpublished results.
[8] *A. P. Chardin, A. D. Popov, P. A. Protopopov*, Zh. Vses. Khim. Obshch. *21*, 593 (1976).

Experimental

I. Trifluoromethylazo compounds: Trifluoronitrosomethane is passed into a stirred solution of the amine (10 mmol) in methanol (50 ml) maintained at −70 °C in a 250-ml three-necked round-bottom flask fitted with a gas inlet tube, gas exit, and low-temperature thermometer until a persistent blue color appears (11 mmol). The solution is allowed to warm to room temperature within 1 h, water (100 ml) is then added and the mixture extracted with pentane (3 × 30 ml). The combined extracts are dried over magnesium sulfate and concentrated on a rotary evaporator (with compounds containing more than 10 C atoms) or by means of a 30-cm packed column. The residue is purified by gas chromatography (1-m column, 10 % SE 30 on Chromosorb W-AW DMCS/60—80 mesh, gas flowrate 100 ml/min).

II. Trifluoromethyl compounds, method A: A solution of the trifluoromethylazo compound *(2)* (5 mmol) in hexadecane (40 ml) is irradiated in a cylindrical photolysis vessel with a 450-W medium pressure mercury vapor lamp (Hanovia 679 A-36) through a Pyrex immersion well at room temperature for 24—96 h (cf. Table 1). The volatile components of the reaction mixture are distilled off at 0.1 torr and 80 °C oil-bath temperature (250-ml flask) and condensed into a receiver cooled with liquid N_2. The condensate, consisting of the product *(3)* and starting material *(2)*, is separated into its components by gas chromatography (5-m column, 10 % SE 30 on Chromosorb W-AW DMCS/60—80 mesh, gas flowrate 100 ml/min).—*Method B:* A solution of *(2)* or *(5)* (5 mmol) in *tert*-butyl alcohol is irradiated at 25 °C as described for method II A. After addition of water (100 ml) the mixture is worked up with pentane, as described for method I. The residue consisting of the product *(3)* (or *(6)* and *(7)*) and starting material *(2)* (or *(5)*) with solvent, which is obtained on evaporation of the pentane, is separated into its components by preparative gas chromatography (conditions as for A).

Received: August 31, 1977 [Z 828 IE]
German version: Angew. Chem. *89*, 892 (1977)

Oxidation and Reduction of Methylthio-Substituted π-Systems and the Electron Distribution in Their Radical Ions[1,2]

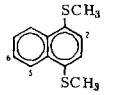
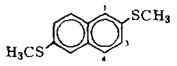
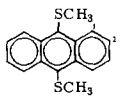
By *Hans Bock* and *Georg Brähler*[*]

So far, only few molecules M have so far been both reduced to the radical anion $M^{\bullet\ominus}$ and oxidized to the radical cation $M^{\bullet\oplus}$[3-5], although a comparison of the experimental spin densities $\rho^{\ominus}$ and $\rho^{\oplus}$, with one another and with calculated charge distributions for M, $M^{\bullet\ominus}$, and $M^{\bullet\oplus}$, is of topical interest[3]. In particular, two classes of compounds have proved to be suitable for such studies, *i.e.* large π-systems capable of adequate delocalization of ⊕ and ⊖ charges, and molecules containing both donor and acceptor regions[5], in which electron holes ⊕ are localized predominantly in the donor moiety and excess charges ⊖ largely in the acceptor moiety. In the following, methylthio-substituted π-systems are presented as examples of a further class of compounds able to form both radical cations and radical anions: characterized by suitable substituents which hardly affect the radical anion $M^{\bullet\ominus}$ while effecting considerable stabilization of the radical cation $M^{\bullet\oplus}$.

H_3CS-substituted derivatives of benzene, naphthalene, or anthracene[6] are conveniently prepared[2] by reduction of the corresponding sulfonyl chlorides with red phosphorus/iodine in glacial acetic acid and subsequent methylation. On disubstitution the first ionization energy lies below 8 eV[2,7] and, therefore[5a], oxidation with $AlCl_3$ in nitromethane affords radical cations which are generally stable at room temperature. Reduction to the radical anions is accomplished electrochemically at a Pt cathode in H_3CCN/DMF cooled to 200 K with $Bu_4N^{\oplus}\,ClO_4^{\ominus}$ as supporting electrolyte. The experimental data are compiled in Table 1, and two typical ESR spectra are reproduced in Figure 1.

[*] Prof. Dr. H. Bock, Dipl.-Chem. G. Brähler
Chemische Institute der Universität, Anorganische Chemie II
Theodor-Stern-Kai 7, D-6000 Frankfurt am Main 70 (Germany)

Table 1. First ionization energies IE_1 of 1,4- and 2,6-di(methylthio)naphthalene and of 9,10-di(methylthio)anthracene, as well as ESR coupling constants $a_{H,\mu}$ and g values for their radical cations and radical anions.

Compound	IE_1^v [eV]	μ	$a^{\oplus}_{H,\mu}$ [a] [mT]	$a^{\ominus}_{H,\mu}$ [a] [mT]	$g^{\oplus}$	$g^{\ominus}$
	7.58	2	0.215	0.211	2.0075	2.0025
		5	0.090	0.319		
		6	0.040	0.150		
		CH_3	0.365	0.021		
	7.59	1	0.371	0.46 [b]	2.0068	2.0027
		3	<0.04	0.071		
		4	0.059	0.46 [b]		
		CH_3	0.220	<0.02		
	7.44	1	0.131	0.097	2.0058	2.0045
		2	0.075	0.030		
		CH_3	0.220	<0.01		

[a] The coupling constants and their assignments are supported by deuterations, ESR spectral simulation, and INDO open-shell calculations [1].
[b] Degeneracy precludes more precise determination.

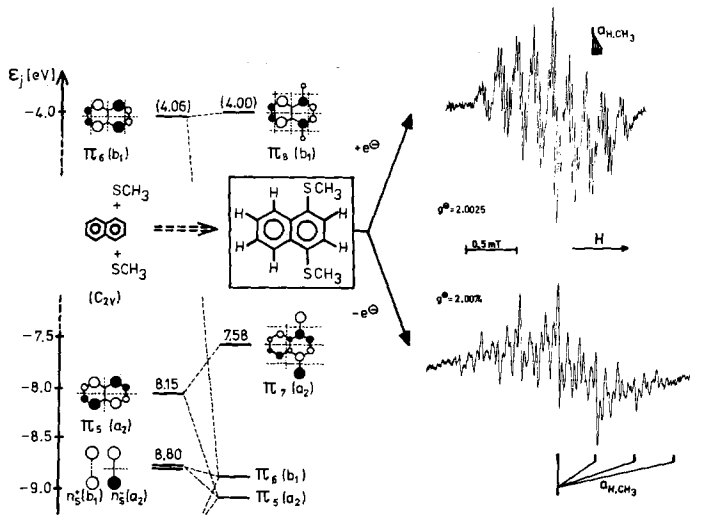


Fig. 1. Effects of H_3CS on cyclic π-systems can be satisfactorily predicted by HMO calculations with parameters determined by photoelectron spectroscopy [8]: 1,4-substitution of naphthalene raises the highest occupied orbital $\pi_7(a_2)$ by admixture of $n_s^-(a_2)$ components while the lowest unoccupied orbital $\pi_8(b_1)$ is hardly perturbed. Accordingly, the 1st ionization energy falls from 8.15 to 7.58 eV. In contrast to that of unsubstituted naphthalene, the radical cation is stable at room temperature, and yet a stable radical anion can also be generated. Furthermore, methyl proton coupling constants $a^{\oplus}_{H,CH_3} > a^{\ominus}_{H,CH_3}$ or values $g^{\oplus} > g^{\ominus}$ [4] confirm that the sulfur atoms accommodate a significant portion of the spin population only in the radical cation—as already suggested by the orbital diagrams.

The experimental data for the isomolecular radical ions of methylthioarenes (Table 1) illustrate the MO prediction that energetically adjacent orbitals of like symmetry undergo pronounced mixing on perturbation of π-systems, while distant ones hardly interact[9] (Fig. 1): The 1st ionization energies decrease and the large *S*-methyl coupling constants and g values[4] clearly demonstrate the stabilizing influence of RS substituents in radical cations. Comparison with the radical ions of the parent compound naphthalene[4]

	$a^{\oplus}_H$[mT]	$a^{\ominus}_H$[mT]
H----------	0.554	0.495
H----------	0.206	0.183

shows that the alternancy $a^{\oplus}_{H,\mu} \approx a^{\ominus}_{H,\mu}$[4,9] is removed mainly due to deviations of the RS-substituted radical cations (Table 1): in the 1,4-derivative one observes, *e.g.* unequal constants $a^{\oplus}_{H,2} \neq a^{\oplus}_{H,6}$ or much too low a coupling constant $a^{\oplus}_{H,5}$, whereas comparable constants $a^{\ominus}_{H,2} \approx a^{\ominus}_{H,6}$ and a relatively large coupling constant $a^{\ominus}_{H,5}$ are still found for the radical anion.

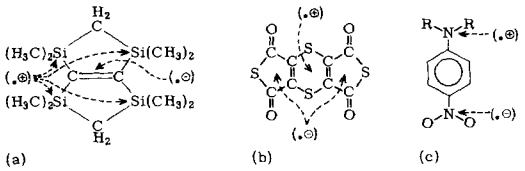
The principle of stabilizing the radical cations of anion-forming systems by donor substituents at suitable sites is applicable to numerous compounds, including the 9,10-anthracene derivative in spite of the twisted *S*-methyl groups (Table 1)[2].

Received: July 19, 1977 [Z 825 IE]
German version: Angew. Chem. *89*, 893 (1977)

CAS Registry numbers:

Table 1 (compound, $g^{\oplus}$, $g^{\ominus}$ as A, B, C ... from top to bottom): A, 10075-73-7; B, 64161-69-9; C, 34468-37-6; D, 10075-77-1; E, 64114-10-9; F, 64161-70-2; G, 10075-83-9; H, 64161-71-3; I, 64114-07-4

[1] Radical Ions, Part 14.—Part 13: *H. Bock, G. Brähler, A. Tabatabai, A. Semkow, R. Gleiter*, Angew. Chem. *89*, 745 (1977); Angew. Chem. Int. Ed. Engl. *16*, 724 (1977).
[2] Dissertation *G. Brähler*, Universität Frankfurt 1977.
[3] Chem. Soc. Spec. Period. Rep., Electron Spin Reson. *1*, 98 (1973); *2*, 97 (1974); *3*, 84 (1976); and references cited therein.
[4] Cf. *K. Scheffler, H. B. Stegmann:* Elektronenspinresonanz. Springer, Heidelberg 1970; *F. Gerson:* Hochauflösende ESR-Spektroskopie. Verlag Chemie, Weinheim 1967; and references cited therein.
[5] Prototypes are:



a) *H. Bock, G. Brähler, G. Fritz, E. Matern*, Angew. Chem. *88*, 765 (1976); Angew. Chem. Int. Ed. Engl. *15*, 669 (1976); b) *F. Gerson, Ch. Wydler, F. Kluge*, J. Magn. Reson. *26*, 271 (1977); c) *D. H. Geske, J. L. Ragle, M. A. Bambenek, A. L. Balch*, J. Am. Chem. Soc. *86*, 987 (1964); *B. M. Latte, R. W. Taft, ibid. 89*, 5172 (1967).
[6] *A. Zweig, H. Maurer, B. G. Roberts*, J. Org. Chem. *32*, 1322 (1967); and references cited therein.
[7] *H. Bock, G. Wagner, J. Kroner*, Tetrahedron Lett. *1971*, 3713; Chem. Ber. *105*, 3850 (1972).
[8] With $\alpha_C = 6.15$ eV, $\beta_{CC} = 3.1$ eV, $\alpha_S = 8.9$ eV, and $\beta_{CS} = 1.6$ eV a regression line $-\varepsilon_j^{HMO} = 0.294 + 0.980\, IE_n^v$ with the low standard error SE = 0.13 eV is obtained for 52 ionization energies of RS-substituted aromatic compounds.
[9] Cf., *e.g. E. Heilbronner, H. Bock:* The HMO Model and its Application, Vol. 1. Verlag Chemie, Weinheim and Wiley, Chichester, 1976, pp. 196ff.

Ba_3As_{14}, The First Compound with the Cluster Anion As_7^{3-}[*]

By *Walter Schmettow* and *Hans Georg von Schnering*[*]

In the reaction of metallic barium with arsenic in the ratio Ba : As = 1 : 4 to 1 : 5 at temperatures between 1000 and 1100 K the polyarsenide Ba_3As_{14} is produced in the form of black prismatic crystals with a dull metallic luster. The compound is isotypic with Sr_3P_{14} and Ba_3P_{14}[1]. On treatment with hot dilute sulfuric acid Ba_3As_{14} decomposes with deposition of a reddish brown amorphous substance (polyarsane?).

Ba_3As_{14} crystallizes monoclinically in the space group $P2_1/n$ with $a = 1003.3(2)$, $b = 1363.9(2)$, $c = 685.4(1)$ pm, $\beta = 90.15(1)°$, $Z = 2$ formula units per unit cell[2]. The structural determination (Syntex $P\bar{1}$ diffractometer, $Mo_{K\alpha}$ radiation; 2072 reflections *hkl*; $R = 0.036$, anisotropic) gave the following values for the atomic positions [*x*; *y*; *z*]: Ba(1) in 2(a) [0;0;0]; in 4(e) the atom Ba(2) is located at [0.3722; 0.1557; 0.1939], As(1) at [0.1859; 0.5039; 0.8908], As(2) at [0.1385; 0.3574; 0.0987], As(3) at [0.8246; 0.5597; 0.4356], As(4) at [0.9743; 0.1868; 0.3272], As(5) at [0.8732; 0.0786; 0.5561], As(6) at [0.1308; 0.2216; 0.8733], As(7) at [0.7799; 0.2186; 0.1234].

The cluster anion As_7^{3-} has a heptaarsanortricyclic structure and is directly comparable in all respects with the polyanions P_7^{3-}[3] and Sb_7^{3-}[4] (Fig. 1). The As—As bond lengths depend, as in the other groups, on the function in the nortricyclic skeleton; on average they are: $A = 249.8$, $B = 239.9$, and $C = 243.2$ pm. The sequence $A > C > B$ is typical for all previously investigated heterosubstituted cluster anions having a nortricyclic structure[5]. Particularly noteworthy are the very short atomic distances of type B in comparison with the sum of the covalent radii. The most important bond angles are: $\alpha = 60$, $\beta = 105.2$, $\gamma = 99.0$ and $\delta = 101.2°$. The Ba atoms are bound to (8+2) or (7+3) As atoms. The bond lengths vary between 332.1 and 385.1 pm.

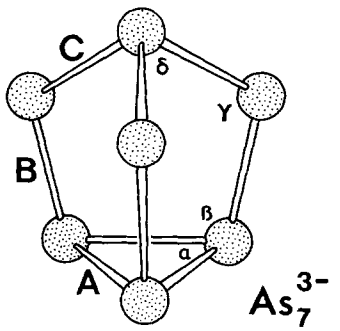


Fig. 1. Polyanion As_7^{3-} in Ba_3As_{14}; bond lengths and angles indicated (cf. text).

The description as a formal anion As_7^{3-} is justified not only in the sense of the Zintl-Klemm formalism[6], but is also supported in particular by the variation in the bond lengths and bond angles in comparison to neutral heteronortricyclic compounds[5]. Moreover, in the anion the distance between the formally negatively charged divalent bridging atoms is relatively large and the height of the cluster relatively small.

Received: September 12, 1977 [Z 835 IE]
German version: Angew. Chem. 89, 895 (1977)

CAS Registry numbers:
Ba_3As_{14}, 64413-38-3

[1] *H. G. v. Schnering, W. Dahlmann*, Naturwissenschaften *58*, 623 (1971); *59*, 420 (1972).
[2] $P2_1/n$, not $P2_1/c$ as given in ref. [1].
[3] *H. G. v. Schnering*, "Catenation of Phosphorus Atoms", in *A. Rheingold:* Homoatomic Rings, Chains and Macromolecules of Main Group Elements. Elsevier, Amsterdam 1977.
[4] *J. D. Corbett, D. G. Adolphson, D. J. Merryman, P. A. Edwards, F. J. Armatis*, J. Am. Chem. Soc. *97*, 6267 (1975).
[5] *W. Hönle, H. G. v. Schnering*, Z. Anorg. Allg. Chem., in press.
[6] Cf. *H. Schäfer, B. Eisenmann, W. Müller*, Angew. Chem. *85*, 742 (1973); Angew. Chem. Int. Ed. Engl. *12*, 694 (1973).

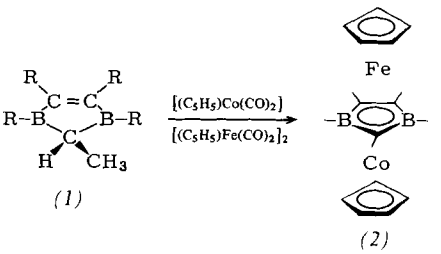
[*] Prof. Dr. H. G. v. Schnering, Dr. W. Schmettow
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1/Büsnauer Strasse 171, D-7000 Stuttgart 80 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Dr. *K. Peters* carried out the intensity measurements, and Ing. *J. Curda* assisted with the experiments.

(η-Cyclopentadienyl)cobalt-μ-(η-diborolenyl)-(η-cyclopentadienyl)iron—A Triple Decker Sandwich Complex Containing Two Different Metals[1]

By *Walter Siebert* and *Manfred Bochmann*[*]

The difunctional Lewis acid 1,3-diborolene *(1)* ($R = C_2H_5$) reacts with nickelocene and with octacarbonyldicobalt to give the mononuclear complexes $(\eta\text{-}C_5H_5)Ni(\eta\text{-}C_3B_2R_4CH_3)$[2] and $(CO)_3Co(\eta\text{-}C_3B_2R_4CH_3)$[3], respectively, in which the ligand acts as a three-electron acceptor. If *(1)* is allowed to react simultaneously with carbonylcyclopentadienylmetal complexes of iron and cobalt as suppliers of one- and two-electron donor groups, then the green diamagnetic species *(2)* is formed.



(1) *(2)*

This dinuclear complex, which is stable to heat and air and highly soluble in apolar solvents, is assigned a place in the series of isoelectronic triple decker sandwich complexes[4] $(\eta\text{-}C_5H_5)M(\mu\text{-}B_nC_{5-n}R_5)M'(\eta\text{-}C_5H_5)$ between μ-borolebis(cyclopentadienyliron)[5] ($n = 1$) and μ-(1,2,4-triborolan-3,5-diyl)bis(cyclopentadienylcobalt)[6] ($n = 3$). In *(2)* three 6π-ligand systems are held together by two different d^6-metal ions. This is the first example of a "mixed metal" triple decker sandwich complex with 30 valence electrons[7]. If *(2)* is regarded as a metallacarbaborane then 16 skeletal electrons are required for bonding in the 7-atom C_3B_2CoFe cluster [(2*n*+2)-rule for *closo* compounds[8]], which are supplied by C (3 × 3), B (2 × 2), C_5H_5Co (2), and C_5H_5Fe (1).

The analytical and spectroscopic data of *(2)* confirm our structural proposal of a triple decker sandwich. In the ^1H-NMR spectrum [δ = 4.00 (S, 5), 3.33 (S, 5), 2.63 (Q, 4), 1.97 (S, 3), 1.78 ("S", 10), 1.52 (T, 6); in CS_2 rel. TMS int.] two Cp signals occur (Cp = C_5H_5), of which we assign the downfield signal to the CpCo group. In contrast to the *C*-ethyl protons,

[*] Prof. Dr. W. Siebert, Dipl.-Chem. M. Bochmann
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

the *B*-ethyl protons show only one broad signal (apparent singlet). The ^{11}B-NMR signal [$\delta = 19.6$; in CS_2 rel. to $BF_3 \cdot OEt_2$] lies in the expected range and is shifted upfield by 49 ppm relative to *(1)*. Apart from the molecular ion Cp_2CoFeL^+ ($L = \{(1) - H\}$; $I_{rel} = 100\,\%$ rel. to $^{11}B_2{}^{59}Co^{56}Fe$), the mass spectrum contains only Cp_nM ions Cp_2Co^+ (6), Cp_2Fe^+ (3), $CpCo^+$ (2), and $CpFe^+$ (4).

(η-Cyclopentadienyl)cobalt-μ-(1,3,4,5-tetraethyl-2-methyl-1,3-diborolenyl)-(η-cyclopentadienyl)iron (2)

A mixture of *(1)*[9] (0.58 g, 3.05 mmol), $CpCo(CO)_2$ (0.56 g, 3.11 mmol), and $[CpFe(CO)_2]_2$ (0.71 g, 2.01 mmol) in $(EtOCH_2CH_2)_2O$ (1 ml) is heated to 180—200 °C under N_2 for 6 h. The solvent is removed, and the residue is taken up in hexane and filtered (G3 frit). After chromatography of the solution over dry silica gel (Woelm 100—200) hexane is drawn off and Cp_2Fe removed by vacuum sublimation. The deep green product crystallizes from Et_2O/CH_3CN (1:4) at −25 °C as long, highly intergrown leaflets. Compound *(2)* sublimes above 120 °C and slowly liquifies above 270 °C in a sealed tube. Yield 0.125 g (9.5 %).

Received: September 2, 1977 [Z 836 IE]
German version: Angew. Chem. 89, 895 (1977)

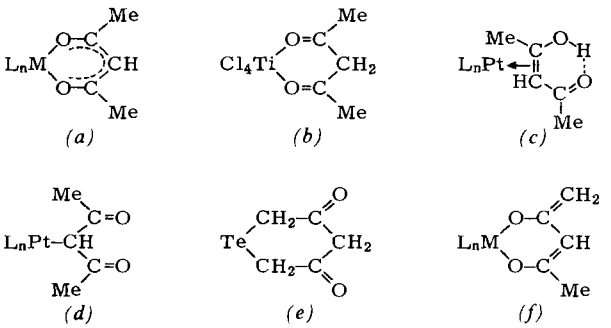
CAS Registry numbers:
(1), 18067-54-4; *(2)*, 64475-53-2; $CpCo(CO)_2$, 12078-23-8; $[CpFe(CO)_2]_2$, 12169-77-6

[1] Triple Decker Compounds, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 3: *W. Siebert, W. Rothermel*, Angew. Chem. *89*, 346 (1977); Angew. Chem. Int. Ed. Engl. *16*, 333 (1977).
[2] *W. Siebert, M. Bochmann*, Angew. Chem. *89*, 483 (1977); Angew. Chem. Int. Ed. Engl. *16*, 468 (1977).
[3] *M. Bochmann*, Diplomarbeit, Universität Marburg 1977.
[4] *W. Siebert*, Nachr. Chem. Tech. Lab. *25*, 597 (1977).
[5] *G. E. Herberich et al.*, lecture presented at the IIIrd International Meeting on Boron Chemistry, Ettal, July 1976.
[6] *D. C. Beer, V. R. Miller, L. G. Sneddon, R. N. Grimes, M. Mathew, G. J. Palenik*, J. Am. Chem. Soc. *95*, 3046 (1973).
[7] *J. W. Lauher, M. Elian, R. H. Summerville, R. Hoffmann*, J. Am. Chem. Soc. *98*, 3219 (1976).
[8] *K. Wade*, Chem. Br. *11*, 177 (1975); and references cited therein.
[9] *P. Binger*, Angew. Chem. *80*, 288 (1968); Angew. Chem. Int. Ed. Engl. *7*, 286 (1968).

A New Coordination Form of Acetylacetone[**]

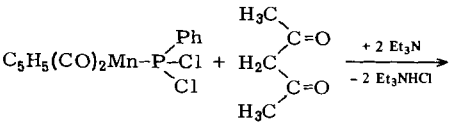
By *Joachim von Seyerl, Dietmar Neugebauer*, and *Gottfried Huttner*[*]

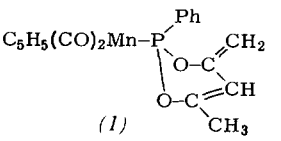
Acetylacetone (2,4-pentanedione) is one of the most thoroughly studied potentially bidentate ligands. Although it is coordinated in most cases as the enolate *(a)*, bonding as β-diketone *(b)*, as π-ligand *(c)*, or as σ-organyl groups *(d, e)* has also been observed on various occasions[1].



The alternative *(f)*, in which acetylacetone occurs as dienediolate, has not yet been described. We now wish to report the first example of this novel coordination.

Dicarbonyl(η-cyclopentadienyl)(phenyldichlorophosphane)manganese reacts with acetylacetone in the presence of triethylamine to give compound *(1)*:





(1)

Apart from the molecular ion $M^{\oplus}$ ($m/e = 382$) the mass spectrum of *(1)* contains the following characteristic fragments: $M^{\oplus} - 2CO$ (326), $C_5H_5Mn{-}PPh(O)^{\oplus}$ (244), and $C_5H_5Mn^{\oplus}$ (120).—The ^{1}H-NMR spectrum exhibits the signals expected for the *cis*-dienediolate group (δ values, TMS int., [D_8]toluene): H^a 3.75, H^b 4.32, H^c 4.58, H^d 1.25 (cf. Fig. 1). The structure of *(1)* was established by X-ray analysis[2]. The dienediolate group is strictly planar. The CC distances of this "ligand" do not show the alternation of bond length expected for the diene structure, since the *exo*-methylene group and the methyl group are subject to about the same degree of disorder in the crystal.

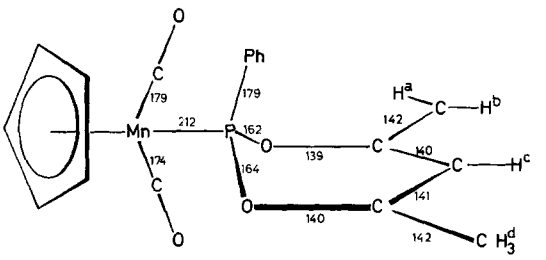


Fig. 1. Structure of complex *(1)* with interatomic distances [pm] and designation of the H atoms in the 1,3-diene-2,4-diolate group. The CC distances are averaged over single and double bonds since the methyl and methylene groups are disordered in the crystal.

The unusual double enolization of acetylacetone is probably induced by the possibility of forming two highly stable covalent P—O bonds.

Procedure

All operations are performed under N_2 with thoroughly dried reagents.—Triethylamine (2 ml) is added to a solution of $C_5H_5(CO)_2Mn(PPhCl_2)$ (1 g, 2.82 mmol) in freshly distilled acetylacetone (6 ml) and the mixture stirred at 10 °C for 16 h. Triethylammonium chloride is filtered off, and the filtrate chromatographed on silica gel (Merck, 0.06—0.2 mm; column 30 × 2.5 cm) at −15 °C. The first fractions (*n*-pentane/toluene 2:1) contain $C_5H_5(CO)_3Mn$ and a little of the starting material. The main fraction (toluene) gives analytically pure *(1)* (500 mg, 45 %) on removal of the solvent and recrystallization from toluene/pentane.

Received: September 22, 1977 [Z 838 IE]
German version: Angew. Chem. 89, 896 (1977)

[*] Prof. Dr. G. Huttner, Dipl.-Chem. J. v. Seyerl, D. Neugebauer
Lehrstuhl für Synthetische Anorganische Chemie der Universität
Postfach 7733, D-7750 Konstanz (Germany)

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

CAS Registry numbers:
(1), 64314-94-9; $C_5H_5(CO)_2Mn(PPhCl_2)$, 12276-83-4; acetylacetone, 123-54-6

[1] *J. P. Collman*, Angew. Chem. *77*, 154 (1965); Angew. Chem. Int. Ed. Engl. *4*, 132 (1965); *B. Bock, K. Flatau, H. Junge, M. Kuhr, H. Musso, ibid. 83*, 239 (1971) and *10*, 225 (1971), respectively; *D. W. Thompson*, Struct. Bonding *9*, 27 (1971).

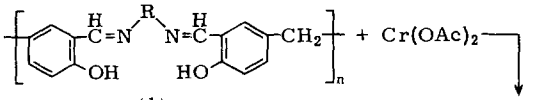
[2] Measurement: Syntex-$P2_1$; solution: Syntex-XTL. $a = 746.8$, $b = 1506.5$, $c = 1500.9$ ppm, space group $P2_1/c$, $Z = 4$; 1249 reflections ($I \geq 3\sigma$); $R_1 = 0.061$.

Addition Compounds with Polymeric Chromium(II)-Schiff Base Complexes

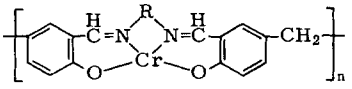
By *Wolfgang Sawodny* and *Manfred Riederer*[*]

The complex chemistry of chromium in oxidation state +2 is somewhat underdeveloped because most organic ligands are unable to resist the powerful reducing action of the Cr^{2+} ion. Only recently have such air-sensitive complexes been reported[1,2]. Complexes with Schiff base ligands have not previously been described.

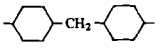
We have now obtained stable Schiff base complexes *(2)* by reaction of the polymer *(1)* with Cr^{2+}.



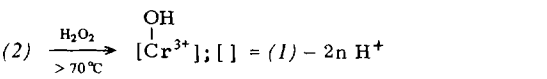
(1)



(2a), R = $-(CH_2)_3N(CH_2)_3-$ (CH$_3$ on N)

(2b), R = 

The yellowish green compound *(2a)* and the green compound *(2b)* are formed in more than 90% yield and are insoluble in all the common solvents. They are surprisingly stable. No change can be seen after several weeks' exposure to air. Oxidation to the Cr^{3+} complex with equivalent amounts of hydrogen peroxide occurs only on heating:



(2) $\xrightarrow[>70\,^\circ C]{H_2O_2}$ [OH, Cr^{3+}]; [ ] = *(1)* − 2n H^+

The IR spectra of the complexes *(2)* contain the bands characteristic for coordinated Schiff bases (*(2a)*: 1615, 1525, 1320 cm^{-1}. *(2b)*: 1615, 1525, 1322 cm^{-1}). Magnetic measurements at room temperature indicate a low-spin configuration of the d^4 system (μ_{eff} for *(2a)* 2.97, for *(2b)* 2.93 μ_B) as also found for complexes of chromium(II) within *o*-phenylenebis(dimethylarsane)[2b].

Addition properties

The ability of monomeric Schiff base complexes to crystallize with one or several molecules of solvent has been known for some time[3]. However, it has hardly been the subject of directed studies. The first steps in this direction by *H. Krebs et al.*[4] for Cu^{2+} and Ni^{2+} have not yet been published.

We have now investigated the addition behavior of polymeric Schiff base complexes of a series of metal ions and found that the chelate complex *(2b)* can accept the largest number of guest molecules per coordination center. In order to produce the adducts the solid polymeric complex was exposed to a nitrogen atmosphere saturated with potential guest molecules at normal pressure (Table 1).

Table 1. Addition capacity of polymeric chromium(II) Schiff base complexes *(2b)*.

Guest molecule (G)	Molar ratio of G/Cr^{2+} in the adduct with *(2b)*
CH_3OH	4.81
Pyridine	4.00
Benzene	3.12
H_2O	2.87
CCl_4	1.77
Cyclohexane	1.54
Cumene	1.20
n-Pentane	1.16

In most cases equilibrium is reached within 2 h (thermal balance). The number of guest molecules that can be added apparently depends upon both the polarity and the size and shape of the guest. The addition compounds are stable only under equilibrium conditions. Slow liberation of the added component occurs on exposure to air. The guest compound can be removed quantitatively by heating; the process is reversible. For example, complete liberation of benzene added to *(2b)* in a benzene-saturated nitrogen atmosphere requires a temperature of 160 °C; slightly below this temperature significant addition can again be observed. The polymeric Schiff base complexes are characterized by a greater ability to undergo addition of a large number of neutral molecules, as compared with monomeric compounds. Addition even occurs above the boiling points of the guest molecules, with approximate retention of reversibility.

Procedure

All operations are performed under N_2 and with oxygen-free solvents. Polymeric Schiff base *(1)* (2 mmol) is dissolved in hot freshly distilled dimethylformamide (DMF) and sodium acetate (4 mmol) is suspended by stirring in the solution. Freshly prepared chromium(II) acetate (2 mmol) is dissolved in a minimum volume of DMF and added dropwise at 100 °C. Reaction is allowed to continue for 24 h at this temperature, the amorphous precipitate appearing on cooling is filtered off, washed with DMF and H_2O, then extracted for 24 h with methanol (Soxhlet) and dried in a high vacuum at 105 °C.

In order to prepare the addition compounds a dried current of N_2 is saturated with the guest molecules in an efficient washbottle and passed over the Schiff base complex for 2 d.

Received: September 14, 1977 [Z 839a IE]
German version: Angew. Chem. *89*, 897 (1977)

CAS Registry numbers:
(1a), 64425-30-5; *(1b)*, 64425-31-6; *(2a)*, 64475-70-3; *(2b)*, 64440-58-0

[*] Prof. Dr. W. Sawodny, Dipl.-Chem. M. Riederer
Abteilung für Anorganische Chemie der Universität
Oberer Eselsberg, D-7900 Ulm (Germany)

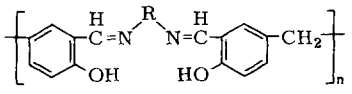
[1] *L. F. Larkworthy, J. M. Tabatabai*, Inorg. Chim. Acta *21*, 265 (1977); J. Chem. Soc. Dalton *1976*, 814; *L. F. Larkworthy, K. C. Patel, J. K. Trigg*, J. Chem. Soc. *A 1971*, 2766.

[2] a) *F. Mani, G. Scapacci*, Inorg. Chim. Acta *16*, 163 (1976); *A. Dei, F. Mani*, Inorg. Chem. *15*, 2574 (1976); b) *F. Mani, P. Stoppioni, L. Sacconi*, J. Chem. Soc. Dalton *1975*, 461; c) *F. Mani, L. Sacconi*, Inorg. Chim. Acta *4*, 365 (1970).
[3] *P. Pfeiffer, E. Buchholz, O. Bauer*, J. Prakt. Chem. *129*, 163 (1931); *A. L. Crumbliss, F. Basolo*, Inorg. Chem. *10*, 1676 (1971); *S. G. Clarkson, B. C. Lane, F. Basolo, ibid. 11*, 662 (1972); *C. Floriani, G. Fachinetti, F. Calderazzo*, J. Chem. Soc. Dalton *1973*, 765.
[4] Cf. *K. Pachali*, Dissertation, Universität Stuttgart 1970.

Palladium(II) and Platinum(II) Complexes with Polymeric Schiff Base Ligands

By *Manfred Riederer, Erna Urban*, and *Wolfgang Sawodny*[*]

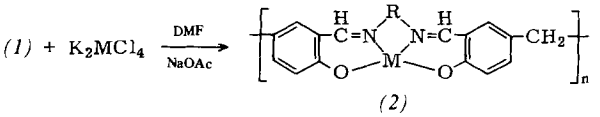
Although complexes of monomeric Schiff bases have been the subject of numerous studies, these ligands have hardly featured in the chemistry of the platinum metals[1]; in particular, only very few bridged coordination units have been described[2]. On the other hand, polymeric Schiff base complexes with ligands of type *(1)*



(1)

are known only for few metals[3, 4].

By means of the reaction



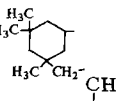
(2)

M = Pd^{2+}, Pt^{2+}

(a): R = $-(CH_2)_x-$; x = 2–8, 10, 12

(b): R = $-CH_2-CH(CH_3)-$

(c): R =



(d): R = $[-(CH_2)_3-\overset{\overset{CH_3}{|}}{N}-(CH_2)_3-]^+ I^-$ (CH_3)

we have now obtained the first palladium(II) and platinum(II) complexes of structure *(2)*. The polymeric ligands *(1a—d)* were prepared by polycondensation of 5,5'-methylenebis(salicylaldehyde) with the corresponding amines [*(1d)* was quaternized with CH_3I in a second reaction step]. The yields of the Pd^{2+} complexes were *ca.* 40% for MNRN rings with $m \leq 8$ members, and over 80% for $m \geq 9$; the yields of the Pt^{2+} complexes are lower in all cases (*ca.* 30%). The yellow, green, or brown compounds are insoluble in all the usual solvents.

The IR spectra exhibit characteristic bands at 1630—1618, 1535—1515, and 1319—1304 cm^{-1}, in agreement with findings for analogous monomeric palladium Schiff base complexes[2]. In the Pd^{2+} compounds *(2)* the bands of the free ligands at 1585 and 1278 cm^{-1} can no longer be observed, indicating together with the results of elemental analyses that all chelating centers of the polymeric ligand are occupied. In contrast, complete occupation of the coordination sites cannot be achieved for the Pt^{2+} compounds *(2)* with small rings ($m \leq 8$).

[*] Prof. Dr. W. Sawodny, Dipl.-Chem. M. Riederer, E. Urban
Abteilung für Anorganische Chemie der Universität
Oberer Eselsberg, D-7900 Ulm (Germany)

Since the ν(MCl) band of K_2PdCl_4 (335 cm^{-1}) or K_2PtCl_4 (325 cm^{-1}) is absent from the spectrum of the products *(2)*, as are the OH bands of *(1)*, fourfold coordination of the dianionic chelate ligand to the metal ion can be regarded as confirmed.

We have examined the thermal stability of the Pd^{2+} compound *(2a)* as a function of the size of the $MN(CH_2)_xN$ ring by simultaneous TG/DTA measurements (10°C/min, N_2 as inert gas). We find the expected stability maximum for the five- and six-membered rings; the stability of the larger rings is essentially independent of ring size (Fig. 1).

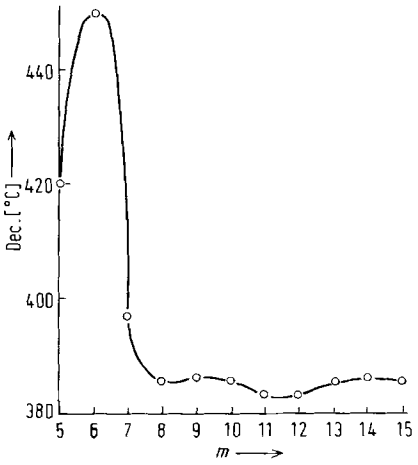


Fig. 1. Plot of thermal stability of the Pd^{2+} complexes *(2a)* *vs.* number of ring members *(m)* in the $PdN(CH_2)_xN$ system.

Like all polymeric Schiff base complexes of divalent metals, the Pd^{2+} and Pt^{2+} compounds are able to intercalate organic molecules[4].

Procedure

Preparation of (1): 5,5'-Methylenebis(salicylaldehyde) (10 mmol) is dissolved with stirring in freshly distilled dimethylformamide (DMF) (50 ml). After addition of amine (10 mmol) the resulting H_2O is removed with the aid of a water separator with toluene as entraining agent. Condensation is complete after 2—5 h. Compound *(1)* is precipitated from the cooled solution with ethanol, filtered off, and dried. *(1d):* the corresponding polymeric Schiff base is dissolved in DMF and heated under reflux for 18 h with an equivalent amount of CH_3I. After cooling and precipitation with glacial acetic acid the product is washed with ether and dried.

Preparation of (2): Sodium acetate (4 mmol) is suspended in a solution of compound *(1)* (2 mmol) in freshly distilled DMF. K_2MCl_4, M = Pd, Pt (2 mmol), dissolved in a minimum volume of dimethyl sulfoxide (DMSO), is added dropwise at 100°C. After cooling, the amorphous precipitate is filtered off, washed with DMF and DMSO, and dried in a high vacuum at 100°C.

Received: September 14, 1977 [Z 839b IE]
German version: Angew. Chem. *89*, 899 (1977)

CAS Registry numbers:
(1a) (x = 2), 64475-61-2; *(1a)* (x = 3), 64475-60-1; *(1a)* (x = 4), 64475-59-8; *(1a)* (x = 5), 64475-58-7; *(1a)* (x = 6), 64475-57-6; *(1a)* (x = 7), 64475-56-5; *(1a)* (x = 8), 64475-55-4; *(1a)* (x = 10), 64440-85-3; *(1a)* (x = 12), 64440-86-4; *(1b)*, 64490-34-2; *(1c)*, 64475-54-3; *(1d)*, 64457-60-9; *(2a)* (x = 2, M = Pd), 64475-74-7; *(2a)* (x = 3, M = Pd), 64475-73-6; *(2a)* (x = 4, M = Pd), 64475-72-5; *(2a)* (x = 5, M = Pd), 64475-71-4; *(2a)* (x = 6, M = Pd), 64475-75-8; *(2a)* (x = 7, M = Pd), 64475-76-9; *(2a)* (x = 8, M = Pd), 64475-77-0; *(2a)* (x = 10, M = Pd), 64457-04-1; *(2a)* (x = 12, M = Pd), 64457-05-2; *(2a)* (x = 2, M = Pt), 64475-78-1; *(2a)* (x = 3, M = Pt), 64475-79-2; *(2a)* (x = 4, M = Pt), 64475-80-5; *(2a)* (x = 5, M = Pt), 64475-81-6; *(2a)* (x = 6, M = Pt), 64475-82-7; *(2a)* (x = 7, M = Pt), 64475-83-8; *(2a)* (x = 8, M = Pt), 64475-84-9; *(2a)* (x = 10, M = Pt),

64457-06-3; *(2a)* ($x=12$, M=Pt), 64457-07-4; *(2b)* (M=Pd), 64535-84-8; *(2b)* (M=Pt), 64535-85-9; *(2c)* (M=Pd), 64475-66-7; *(2c)* (M=Pt), 64475-67-8; *(2d)* (M=Pd), 64475-68-9; *(2d)* (M=Pt), 64475-69-0; 5,5'-methylenebis-(salicylaldehyde), 3046-82-0; NH_2—$(CH_2)_2$—NH_2, 107-15-3; NH_2—$(CH_2)_3$—NH_2, 109-76-2; NH_2—$(CH_2)_4$—NH_2, 110-60-1; NH_2—$(CH_2)_5$—NH_2, 462-94-2; NH_2—$(CH_2)_6$—NH_2, 124-09-4; NH_2—$(CH_2)_7$—NH_2, 646-19-5; NH_2—$(CH_2)_8$—NH_2, 373-44-4; NH_2—$(CH_2)_{10}$—NH_2, 646-25-3; NH_2—$(CH_2)_{12}$—NH_2, 2783-17-7; NH_2—CH_2—$CH(CH_3)$—NH_2, 78-90-0; NH_2—$CH_2C(CH_3)CH_2CH(NH_2)CH_2C(CH_3)_2CH_2$, 2855-13-2; NH_2—$(CH_2)_3$—$N(Me)$—$(CH_2)_3$—NH_2, 105-83-9

[1] *R. H. Holm, G. W. Everett, A. Chakravorty*, Prog. Inorg. Chem. *7*, 83 (1966).

[2] *K. Dey, R. L. De*, J. Inorg. Nucl. Chem. *37*, 1530 (1975).

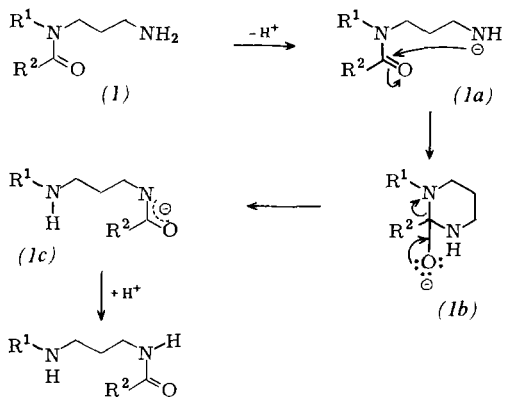
[3] *C. S. Marvel, N. Tarköy*, J. Am. Chem. Soc. *79*, 6000 (1957); *H. A. Goodwin, J. C. Bailar jr., ibid. 83*, 2467 (1961); *A. P. Terentev, V. V. Rode, E. G. Rukhadze*, Vysokomol. Soedin. *2*, 1557 (1960).

[4] *W. Sawodny, M. Riederer*, Angew. Chem. *89*, 897 (1977); Angew. Chem. Int. Ed. Engl. *16*, 859 (1977).

The "Zip" Reaction: A New Method for Ring Expansion; Synthesis of 17- and 21-Membered Polyaminolactams[1]

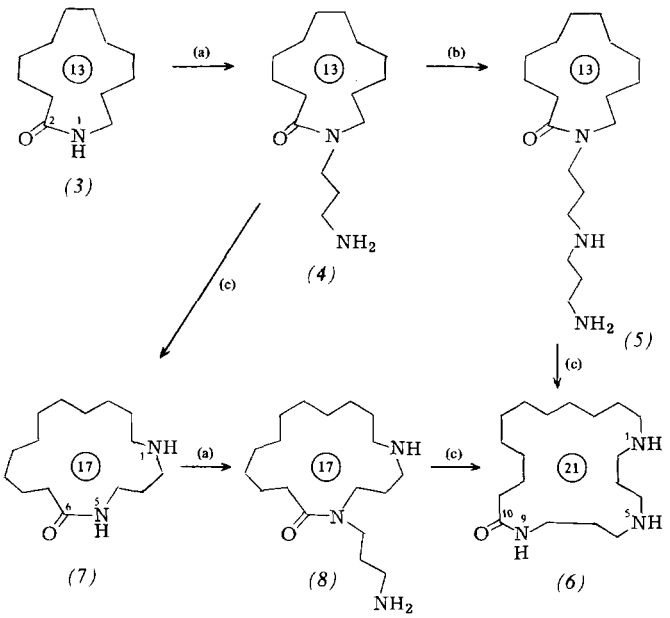
By *Urs Kramer, Armin Guggisberg, Manfred Hesse*, and *Hans Schmid* (deceased)[*]

Type *(1)* derivatives of trimethylenediamine, in which one of the amino groups is primary and the other is part of a *N,N*-disubstituted carboxamide, isomerize in the presence of a base[2]. The trimethylene derivative *(2)* is then formed which contains a secondary amino group and a monosubstituted amide.



If R^1 and R^2 of *(1)* are members of a lactam ring, then the reaction results in an expansion of the ring by four members. This type of reaction was first discovered in the structural elucidation of the *Oncinotis* alkaloids[3] (for a related reaction with substituted secondary amides cf. [4]).

If the sodium salt of 1-azacyclotridecan-2-one *(3)* is reacted with acrylonitrile and the resulting nitrile subsequently hydrogenated catalytically (C_2H_5OH/H_2SO_4, H_2/Pt, 4.2 atm), then 1-(3-aminopropyl)-1-azacyclotridecan-2-one *(4)* is formed in 82% yield. With *(4)* the same reaction sequence affords the 13-membered diaminolactam *(5)* in 78% yield. *(5)* reacts with potassium (3-amino)propylamide[5] in trimethylenediamine (30 min, 20°C) to give 1,5,9-triazacycloheneicosan-10-one *(6)* in 90% yield. This 21-membered diaminolactam was also synthesized by a stepwise ring expansion to verify its structure: the base catalyzed transamidation [potassium (3-amino)propylamide, 30 min, 20°C] of *(4)* yields 1,5-diazacycloheptadecan-6-one *(7)*. This 17-membered compound can, after tosylation of the basic amine nitrogen, again be alkylated with acrylonitrile and subsequently detosylated (electrolysis: 0°C, 24 V, 0.1 to 0.7 A, cathode: distilled Hg, anode: electrographite)[6]. After catalytic hydrogenation to *(8)*, *(6)* is produced under the previously described conditions for transamidation. The identity of the two preparations synthesized by different routes was confirmed by their IR and mass spectra, their behavior on thin layer chromatography and their reaction with the fluram fluorescence reagent[7]. The initial compounds were also characterized by IR and mass spectra, all compounds with at least one primary or secondary amino group were additionally characterized by means of their *N*-acetyl derivatives.



(a) Na salt of the amide + CH_2=CH–CN; H_2/Pt

(b) CH_2=CH–CN; H_2/Pt

(c) $K[NH(CH_2)_3NH_2]$; H_3O^+

The structurally isomeric bases *(5)* and *(6)* were distinguished by means of their IR spectra [*(5)*: 1625 cm^{-1}; *(6)*: 1650 + 1515 cm^{-1}; both in $CHCl_3$], by thin layer chromatography [Al_2O_3-GF 254 (Merck), $CHCl_3/CH_3OH$ (2:1): R_f value for *(5)*: 0.0, for *(6)*: 0.11], by the fluram test[7] [*(5)*: strong, light green fluorescence for primary amines; *(6)*: no fluorescence at 360 nm] as well as on the basis of their ^{1}H-NMR spectra.

It is remarkable that this novel ring expansion reaction proceeds using one, two or more trimethyleneamino expansion units and that in all cases very good yields are obtained[8]. One of the driving forces for this reaction is the formation of the resonance-stabilized amide anion of type *(1c)*. We describe this reaction as the "zip" reaction in analogy with the behavior of a zip fastener.

Received: September 22, 1977 [Z 846 IE]
German version: Angew. Chem. *89*, 899 (1977)

CAS Registry numbers:
(3) Na salt, 13390-78-8; *(4)*, 64414-61-5; *(5)*, 64414-60-4; *(6)*, 64414-59-1; *(7)*, 64414-58-0; *(8)*, 64414-57-9; acrylonitrile, 107-13-1; potassium (3-amino)-propylamide, 56038-00-7

[*] Prof. Dr. M. Hesse, Dipl.-Chem. U. Kramer, A. Guggisberg, Prof. Dr. H. Schmid (deceased)
Organisch-chemisches Institut der Universität
Rämistrasse 76, CH-8001 Zürich (Switzerland)

[1] Part 2 of Transamidation Reactions (part of the dissertation of *U. Kramer*). This work was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung.—Part 1: [2].

[2] *A. Guggisberg, U. Kramer, E. Stephanou, B. Dabrowski, R. Charubala, Ch. Heidelberger, M. Hesse, H. Schmid*, Helv. Chim. Acta, in press.
[3] *A. Guggisberg, M. M. Badawi, M. Hesse, H. Schmid*, Helv. Chim. Acta *57*, 414 (1974).
[4] *J. A. Davies, C. H. Hassall, I. H. Rogers*, J. Chem. Soc. *C 1969*, 1358.
[5] *C. A. Brown*, J. Chem. Soc. Chem. Commun. *1975*, 222.
[6] *L. Horner, H. Neumann*, Chem. Ber. *98*, 1715, 3462 (1965); *A. Guggisberg, P. van den Broek, M. Hesse, H. Schmid, E. Schneider, K. Bernauer*, Helv. Chim. Acta *59*, 3013 (1976).
[7] *S. Udenfried, S. Stein, P. Böhlen, W. Dairman, W. Leimgruber, M. Weigele*, Science *178*, 871 (1972).
[8] *U. Kramer, A. Guggisberg, M. Hesse, H. Schmid*, Helv. Chim. Acta, in press.

A Stable Acyclic Alkoxyhalosulfurane: Chlorotris(2,2,2-trifluoro-1-trifluoromethylethoxy)sulfurane[**]

By *Gerd-Volker Röschenthaler*[*]

As recently discovered[1], chloroalkoxysulfuranes are stable at room temperature, provided that the tetracoordinated sulfur(IV) atom is incorporated in a five-membered ring. An acyclic compound of type $ClS(OR)_3$ has now been prepared for the first time by the action of elemental chlorine on the sulfoxylic diester *(1)* of 2,2,2-trifluoro-1-trifluoromethylethanol in 85% yield according to the overall equation[2]

$$3\,S[OCH(CF_3)_2]_2 + 2\,Cl_2 \rightarrow 2\,ClS[OCH(CF_3)_2]_3 + SCl_2$$
$$\quad (1) \qquad\qquad\qquad (2)$$

The new sulfurane *(2)* is a colorless crystalline solid which is extremely sensitive to moisture and is rapidly hydrolyzed by an equivalent amount of water to HCl, $(CF_3)_2CHOH$, and the sulfurous diester $O{=}S[OCH(CF_3)_2]_2$[3]. The compound is stable for several days at 78 °C.

$$2\,(2) \xrightarrow{\Delta} \begin{cases} \longrightarrow (1) + SCl_2 + 2(CF_3)_2CHOH + 2(CF_3)_2CO \\ /\!/\!\longrightarrow 2\,O{=}S[OCH(CF_3)_2]_2 + 2\,ClCH(CF_3)_2 \end{cases}$$

Degradation resembling an Arbuzov reaction could not be observed.

In the same way as sulfur tetrafluoride can oxidize phosphorus(III) compounds to fluorophosphoranes[4], the sulfurane *(2)* is also able to transfer $(CF_3)_2CHO$ onto the phosphite $P[OCH(CF_3)_2]_3$[5] after the manner of a redox reaction to form a pentaalkoxyphosphorane[5].

$$2\,(2) + 2\,P[OCH(CF_3)_2]_3 \rightarrow (1) + SCl_2 + 2\,P[OCH(CF_3)_2]_5$$

The composition and structure of the new compounds *(1)* and *(2)* were confirmed by elemental analysis and mass and NMR spectra (^1H, ^{19}F). While the mass spectrum [70 eV, *m/e* (rel. int.)] of *(1)* exhibits the molecular ion at 366 (4%) [69 (100%), CF_3^+], the sulfurane *(2)* shows the fragment $[M-Cl]^+$ at 533 (100%) as the ion of highest mass[1,6] whose great intensity indicates that a sulfonium ion is favored in the degradation process.—The signals in the ^1H-NMR spectra (10% solution in $CFCl_3$, TMS int. standard) are expectedly split by HF coupling into septets [*(1)*: $\delta_H = -4.82$, $^3J_{HF} = 5.4$ Hz; *(2)*: $\delta_H = -4.71$, $^3J_{HF} = 5.2$ Hz] and in the ^{19}F-NMR spectra into doublets with the same coupling constants [*(1)*: $\delta_F = 75.0$; *(2)*: $\delta_F = 72.1$]. Nonequivalence of the $(CF_3)_2CHO$ groups[7] of *(2)*, which would apply in the case of a trigonal-bipyramidal structure, could not yet be detected as detailed studies are precluded by crystallization of the sulfurane from the solvents used at temperatures below 0 °C.

Procedure

Sulfur dichloride (5.15 g, 0.05 mol) is added dropwise with exclusion of moisture to lithium 2,2,2-trifluoro-1-trifluoromethylethoxide[8] (17.40 g, 0.1 mol) and stirred at room temperature for 2 h. Compound *(1)* is evaporated from the LiCl produced in a high vacuum and subsequently distilled (b.p. 51—52 °C/50 torr); yield 16.5 g (90%).

Chlorine (1.56 g, 0.22 mol) is condensed under high vacuum onto compound *(1)* (10.98 g, 0.30 mol) and maintained at 0 °C for 24 h. After removal of volatile reaction products, identified as excess Cl_2 (0.15 g) and SCl_2 (0.87 g), analytically pure *(2)* (9.60 g, 85%) is obtained.

Received: September 23, 1977 [Z 849 IE]
German version: Angew. Chem. *89*, 900 (1977)

CAS Registry numbers:
(1), 64490-36-4; *(2)*, 64490-35-3; lithium 2,2,2-trifluoro-1-trifluoromethylethoxide, 29649-10-3

[1] *J. C. Martin, T. M. Balthazor*, J. Am. Chem. Soc. *99*, 152 (1977).
[2] The presumed intermediate 1:1 adduct $Cl_2S[OCH(CF_3)_2]_2$ probably decomposes to *(2)*, Cl_2, and $ClSOCH(CF_3)_2$, which is shown experimentally to undergo metathesis to SCl_2 and *(1)*.
[3] *R. A. de Marco, T. A. Kovacina, W. B. Fox*, J. Fluorine Chem. *6*, 93 (1975).
[4] *R. Schmutzler* in *V. Gutmann*: Halogen Chemistry, Vol. 2. Academic Press, New York 1967, p. 31.
[5] *D. R. Dakternieks, G.-V. Röschenthaler, R. Schmutzler*, J. Fluorine Chem., in press.
[6] *M. Allan, A. F. Janzen, C. J. Willis*, Can. J. Chem. *46*, 3671 (1968); *K. C. Hodges, D. Schomburg, J. V. Weiss, R. Schmutzler*, J. Am. Chem. Soc. *99*, 6096 (1977).
[7] *J. A. Gibson, G.-V. Röschenthaler, V. Wray*, J. Chem. Soc. Dalton Trans. *1977*, 1492.
[8] *R. E. A. Dear, W. B. Fox, R. J. Fredericks, E. E. Gilbert, D. K. Huggins*, Inorg. Chem. *9*, 2590 (1970).

[*] Dr. G.-V. Röschenthaler
Lehrstuhl B für Anorganische Chemie der Technischen Universität
Pockelsstrasse 4, D-3300 Braunschweig (Germany)

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

Carbonyl Olefination with (Triphenylstannyl)methyllithium[**]

By *Thomas Kauffmann, Reinhard Kriegesmann*, and *Annegret Woltermann*[*]

Carbonyl olefination with trimethylsilylmethyllithium and its derivatives[1] (Peterson reaction) has gained increasing importance as an alternative to the Wittig reaction and its variants[2]. Analogous reactions are possible with triphenylstannylmethyllithium *(1)*[3]:

The reagent *(1)* was obtained almost quantitatively (see Experimental procedure) from the known triphenylstannylmethyl iodide *(3)*[4]. Reaction with one mol.-equiv. of aldehyde or ketone (benzophenone does not react) led to the previously unknown 2-triphenylstannylethanol derivatives *(2b)* (Table 1), which at 110—175 °C formed the given olefins in good yield. It is still unclear into which compounds the Ph_3Sn group is converted during the elimination processes.

[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. R. Kriegesmann, A. Woltermann
Organisch-chemisches Institut der Universität
Orléans-Ring 23, D-4400 Münster (Germany)

[**] New Reagents, Part 8.—This work was supported by the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen and the Fonds der Chemischen Industrie. Part 7: *Th. Kauffmann, U. Koch, F. Steinseifer, A. Vahrenhorst*, Tetrahedron Lett. *1977*, 3341.

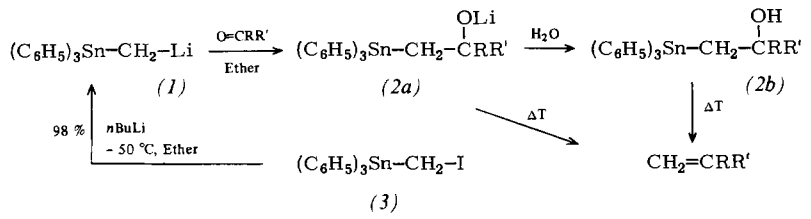


Table 1. 2-Triphenylstannylethanols of type *(2b)* and their thermolyses.

Carbonyl compound	Alcohol *(2b)* [a] R	R'	M.p. [°C]	Yield [%]	Thermolysis *t* [min]	*T* [°C]	Olefin	Yield [b] [%]
Benzaldehyde	H	C_6H_5	136	65	15	140 [c]	Styrene	84 (55)
					300	110 [d]		95 (62)
Butanal	H	C_3H_7	64—65	31	60	170 [c]	1-Pentene	100 (31)
					120	132 [e]		100 (31)
Heptanal	H	C_6H_{13}	75	26	180	132 [e]	1-Octene	71 (18)
Acetophenone	CH_3	C_6H_5	104	41	45	75 [c]	α-Methyl-	71 (29)
					90	110 [d]	styrene	70 (29)
Cyclohexanone	—(CH_2)$_5$—		100	37	45	170 [c]	Methylene-	95 (35)
					120	132 [e]	cyclohexane	96 (35)

[a] The structure is confirmed by elemental analysis, ^{1}H-NMR and mass spectra; the melting points are corrected.
[b] Referred to isolated pure *(2b)*; values in brackets based on carbonyl compound.
[c] Dry heating.
[d] In toluene.
[e] In chlorobenzene.

Table 2. Carbonyl olefination without isolation of *(2b)*.

Carbonyl compound	*t* [min]	Thermolysis *T* [°C]	Solvent	Olefin	Yield [a] [%]
Benzaldehyde	120	110	Toluene	Styrene	87 (48)
Butanal	90	132	Chlorobenzene	1-Pentene	75
Cyclohexanone	180	132	Chlorobenzene	Methylene-cyclohexane	86 (26)

[a] Referred to carbonyl compound; data in brackets: without hydrolysis of *(2a)*.

In order to avoid losses in preparative carbonyl olefinations with *(1)* (cf. Table 1 and Table 2) isolation of the sensitive alcohols *(2b)* should be circumvented, but not the hydrolysis of the lithium alkoxides *(2a)* which leads to considerable increases in yields (Table 2). Such olefinations and in all likelihood possible olefinations with analogous organotin compounds could in many cases offer advantages over corresponding reactions with silicon compounds, since the bond energy of the C—Sn bond is notably lower than that of the C—Si bond (52 and 70 kcal/mol, respectively[5]).

Experimental procedure

(Triphenylstannyl)methyllithium (1): A solution of *n*-butyllithium (5 mmol) in *n*-hexane (*ca.* 2 M solution) is added dropwise within 1 min to a solution of (triphenylstannyl)methyl iodide (2.45 g, 5 mmol) in anhydrous ether (50 ml) under N_2 at −50 °C, and the mixture stirred for 5 min (hydrolysis with D_2O and ^{1}H-NMR spectroscopic investigation of the product shows that *(1)* is formed in 98 % yield).

Styrene from benzaldehyde: A solution of benzaldehyde (5 mmol, 0.51 ml) in ether (10 ml) is added dropwise with stirring to the above mentioned ether solution of *(1)* under N_2 at −50 °C. After warming to room temperature the mixture is treated with 5 ml water and 20 ml toluene. The ether is then removed by distillation and the remaining mixture boiled under reflux for 2 h. Gas chromatographic analysis of the reaction mixture yields 453 mg (87 %) styrene.

Received: September 1, 1977 [Z 834 IE]
German version: Angew. Chem. *89*, 900 (1977)

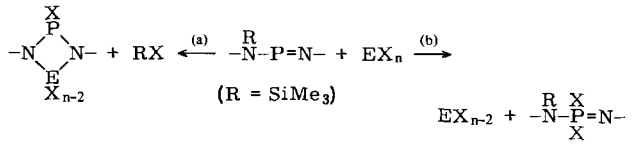
CAS Registry numbers:
(1), 64331-89-1; *(2b)* (R = H, R' = C_6H_5), 64331-87-9; *(2b)* (R = H, R' = C_6H_{13}), 64331-88-0; *(2b)* (R = H, R' = C_3H_7), 64331-86-8; *(2b)* (R = CH_3, R' = C_6H_5), 64331-85-7; *(2b)* (R, R' = —(CH_2)$_5$—), 64331-84-6; *(3)*, 33550-56-0; styrene, 100-42-5; 1-octene, 111-66-0; 1-pentene, 109-67-1; α-methylstyrene, 300-57-2; methylenecyclohexane, 108-87-2; benzaldehyde, 100-52-7; heptanal, 111-71-7; butanal, 123-72-8; acetophenene, 98-86-2; cyclohexanone, 108-94-1

[1] *D. J. Peterson*, J. Org. Chem. *33*, 780 (1968).
[2] Cf. *B.-T. Gröbel, D. Seebach*, Chem. Ber. *110*, 852 (1977).
[3] According to preliminary experiments triphenylplumbylmethyllithium also reacts analogously: *R. Kriegesmann*, Dissertation, Universität Münster, planned for 1979.
[4] *D. Seyferth, S. B. Andrews*, J. Organomet. Chem. *30*, 151 (1971); *R. D. Taylor, J. L. Wardell, ibid. 77*, 311 (1974).
[5] For values of mean dissociation energies of compounds $(CH_3)_4M$ cf. *G. E. Coates, M. L. H. Green, P. Powell, K. Wade:* Principles of Organometallic Chemistry. Methuen, London 1968, p. 4.

Four-Membered Phosphorus-Nitrogen-Metal Heterocycles with Zwitterionic Structure[**]

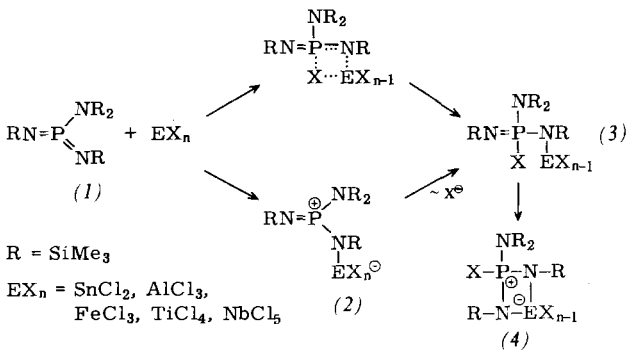
By *Edgar Niecke, Rainer Kröher,* and *Siegfried Pohl*[*]

The synthesis of four-membered heterocycles from aminesilylated aminoiminophosphanes and metal halides (a) is limited to a small number of elements due to the α-elimination of many of the Lewis acids (b)[1].



In the reactions of λ^5-phosphorus-nitrogen ylides with EX_n we observed cyclizing halosilane elimination[2] [in analogy with (a)] as well as adduct formation, in place of (b), to yield the cyclic zwitterions *(4)* which have a $\overset{\oplus}{P}N_2\overset{\ominus}{E}$ skeleton.

As is exemplified by the reaction of bis(trimethylsilyl)-aminobis(trimethylsilylimino)phosphorane *(1)* with main group and transition metal halides, this reaction allows access to novel phosphorus-nitrogen-metal heterocycles *(4c—e)*[9] and also the stabilization of rarely occurring coordination numbers of the metal atoms (Table 1: *(4a, d)*).



We suspect that the heterocycles are formed by intramolecular ring closure from the intermediates *(3)* which are themselves produced by a four-centered reaction. The first step of the reaction possibly involves a stage with a highly reactive phosphenium species having a triply coordinated phosphorus[3], the electrophilic phosphorus being then stabilized by chloride migration.

The composition and constitution of compounds *(4)* as four-membered PN_2E rings with zwitterion structure have been established by elemental analysis, molecular weight determinations, mass spectra[4], (^1H,^{31}P)-NMR and characteristic IR data (Table 1) and by X-ray structure analysis in the case of *(4d)*.

Whereas the coordination of the metals in *(4a,b,e)* (CN = 3, 4, 6) results, as expected[5], in magnetic equivalence of the trimethylsilyl groups bound directly to the ring, in *(4d)* these substituents are anisochronous. These findings, which were confirmed by the $^{13}C\{^1H\}$-NMR spectra of *(4d)*[6], are in accord with a trigonal-bipyramidal coordination of the titanium atom with one N atom being in the axial and the other in the equatorial position. ^1H- and $^{13}C\{^1H\}$-NMR measurements at high temperatures show that the two pertinent $SiMe_3$ groups equilibrate at 37(2) °C independently of the concentration of the solution[7]. This speaks in favor of an intramolecular process occurring at the titanium atom

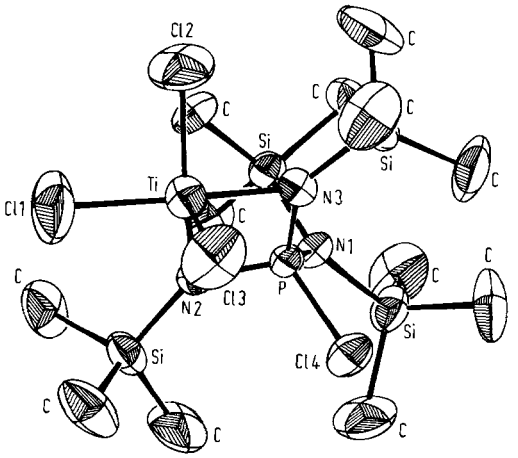


Fig. 1. Molecular structure of *(4d)* (without the H atoms; vibration ellipsoids are shown with a probability of 50 %).

Most important bond lengths [pm] and angles [°]:

Ti—Cl1 225.1(3), Ti—Cl2 223.5(3), Ti—Cl3 219.7(3), Ti—N2 201.0(5), Ti—N3 204.8(5), P—N2 161.3(5), P—N3 159.7(5), P—N1 162.2(5), P—Cl4 203.6(3); Cl1—Ti—Cl2 92.1(1), Cl1—Ti—Cl3 102.0(1), Cl1—Ti—N2 90.1(2), Cl1—Ti—N3 155.8(2), Cl2—Ti—Cl3 108.7(1), Cl2—Ti—N2 140.7(2), Cl2—Ti—N3 90.3(2), Cl3—Ti—N2 109.2(2), Cl3—Ti—N3 100.1(2), N2—Ti—N3 73.1(2), Ti—N2—P 94.8(2), Ti—N3—P 93.8(2), N2—P—N3 97.8(3).

Table 1. Properties and spectroscopic data of the zwitterions *(4)*.

	$E^{(CN)}$	$\delta(^{31}P)$ [a]	$\delta(^1H)$ [a] $NSiMe_3$	$(^4J_{HP})$ $N(SiMe_3)_2$	ν(NPN) [b] [cm^{-1}]	ν(PCl) [b] [cm^{-1}]	M.p. [°C]	Color
(4a)	$Sn^{(3)}$	17.7 [c]	0.24 (0.45 Hz)	0.51	1155, 1108	530	117	white
(4b)	$Al^{(4)}$	26.3	0.27 (0.65 Hz)	0.54	1147, 1089	556	132	white
(4c)	$Fe^{(4)}$	[d]	[d]	[d]	1135, 1080	535	>110 (dec.)	red-brown
(4d)	$Ti^{(5)}$	18.0	0.53 ([e]) 0.57 ([e])	0.49	1100, 1058	543	> 90 (dec.)	orange
(4e)	$Nb^{(6)}$	28.1	0.62 (0.65 Hz)	0.56	1071, 1002	558	>130 (dec.)	yellow

[a] 30 percent solution in CH_2Cl_2 with TMS as internal (^1H-NMR) or H_3PO_4 as external standard (^{31}P-NMR) at room temperature. [b] Nujol mull. [c] $J_{P^{117,119}Sn} = 191.6, 197.1$ Hz. [d] Substance is paramagnetic. [e] Not resolved.

[*] Priv.-Doz. Dr. E. Niecke, Dipl.-Chem. R. Kröher
Anorganisch-Chemisches Institut der Universität
Tammannstrasse 4, D-3400 Göttingen (Germany)
Dr. S. Pohl
Fakultät für Chemie der Universität
Universitätsstrasse, D-4800 Bielefeld 1 (Germany)

[**] Part 14 of Studies on Phosphazenes with Coordination Numbers of 2 and 3.—Part 13: *E. Niecke, H. G. Schäfer,* Angew. Chem. *89*, 817 (1977); Angew. Chem. Int. Ed. Engl. *16*, 783 (1977).

(Berry pseudorotation or turnstile rotation) as has been suggested in the interpretation of exchange phenomena with pentacoordinated phosphorus[8].

The titanium compound *(4d)* crystallizes monoclinically, space group $P2_1/n$; $a = 943.9(1)$, $b = 1718.3(3)$, $c = 1724.2(3)$ pm; $\beta = 92.12(1)°$; $V = 2795 \cdot 10^6$ pm^3; $Z = 4$. Refinement with the structure factors from 3866 observed reflections $[I > 1.968\,\sigma(I)]$ gave an unweighted R value of 7.0 %

($R_w = 6.5\,\%$). Figure 1 represents the molecular structure of *(4d)* and shows the vibration ellipsoids of the atoms (the positions of the H atoms could not be localized).

The four-membered ring formed from the Ti, N2, P and N3 atoms is planar within the limit of error. The coordination of the titanium atom can be described as a distorted trigonal bipyramid. The two ring nitrogen atoms occupy different positions (axial and equatorial) which confirms the findings of NMR spectroscopy. The chlorine atoms bound to the titanium also have larger coefficients for the anisotropic temperature factors than the chlorine atom bound to the phosphorus; these findings are probably due to a dynamic defect as has been found in solution.

Experimental Procedure

A solution of 7.3 g (0.02 mol) *(1)* in 10 ml toluene is added dropwise with stirring under an atmosphere of N_2 to a suspension of 0.02 mol of the metal halide in 20 ml toluene at room temperature. The reaction mixture is then stirred for 5 h.

(4a, b): The solvent is evaporated off at 40 °C/0.1 torr and the residue is sublimed twice at 75 °C/0.1 torr *(4a)* or 85 °C/0.1 torr *(4b)*. Yields 7.8 g (70 %) *(4a)* and 4.5 g (45 %) *(4b)*.

(4c): The reaction solution is allowed to stand until crystallization occurs (*ca.* 80 h). A single recrystallization affords 7.6 g (72 %) *(4c)*.

(4d, e): The reaction solution is cooled to −20 °C when *(4d)* and *(4e)* crystallize out. Recrystallization gives 6.8 g (55 %) *(4d)* and 4.6 g (37 %) *(4e)*.

Received: September 9, 1977 [Z 841 IE]
German version: Angew. Chem. *89*, 902 (1977)

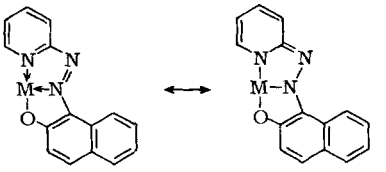
CAS Registry numbers:
(1), 52111-28-1; *(4a)*, 64413-72-5; *(4b)*, 64413-71-4; *(4c)*, 64413-70-3; *(4d)*, 64413-69-0; *(4e)*, 64413-68-9; $SnCl_2$, 7772-99-8; $AlCl_3$, 7446-70-0; $FeCl_3$, 7705-08-0; $TiCl_4$, 7550-45-0; $NbCl_5$, 10026-12-7; ^{13}C, 14762-74-4

[1] Review: *E. Niecke, O. J. Scherer*, Nachr. Chem. Tech. *23*, 395 (1975).
[2] With the formation of heterocycles of the type
$RN=\overline{P(X)-N(R)-E(X_{n-2})-NR}$ ($R=SiMe_3$; $EX_n=BCl_3$, $SiCl_4$): *E. Niecke, R. Kröher*, unpublished.
[3] The formation of the heterocycle
$R_2N-\overset{\oplus}{P}(Me)-\underline{N(R)-SiMe_2-N}-\overset{\ominus}{A}lCl_3$ as a side product which is isomeric with *(4b)* speaks in favor of this; this reaction can be explained by the migration of methanide from *(2)*.
[4] MS (70 eV) in *m/e*: M (based on the most abundant isotopic species) 555 (2 %) *(4a)*, 499 (2 %) *(4b)*, 526 (1 %) *(4c)*; {M − EX_n, −Me} 350 (100 %) *(4a,b,c)*.
[5] An almost planar arrangement of the ring nitrogen is assumed.
[6] $\delta(^{13}C)=5.67$, 6.34, $^3J_{CP}=2.0$, 2.8 Hz ($NSiC_3$); 3.28, $^3J_{CP}=3.6$ Hz ($-N(SiC_3)_2$); 30 percent solution in $CDCl_3$ (TMS int.) at room temperature.
[7] 2 to 30 percent solution in $ClCH_2CH_2Cl$ (^1H) or $CDCl_3$ (^{13}C).
[8] a) *R. S. Berry*, J. Chem. Phys. *32*, 933 (1960); b) *P. Gillespie, P. Hoffmann, K. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, I. Ugi*, Angew. Chem. *83*, 691 (1971); Angew. Chem. Int. Ed. Engl. *10*, 687 (1971).
[9] Heterocycles with the skeleton $PN_2E^{(CN)}$, $E=Al^{(4)}$, $Sn^{(6)}$ are known: a) *H. Schmidbaur, K. Schwirten, H. H. Pickel*, Chem. Ber. *102*, 564 (1969); b) *O. J. Scherer, G. Schnabl*, Inorg. Chim. Acta *19*, L 38 (1976).

Intramolecular Oxidative Addition of Azopyridine to Phosphorus(III)[1]

By *Alfred Schmidpeter* and *Josef Helmut Weinmaier*[*]

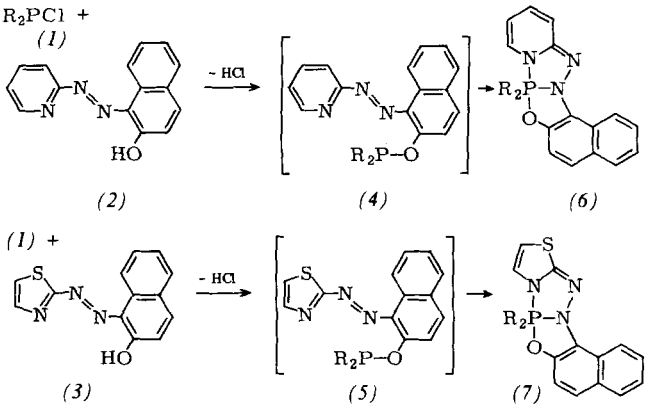
1-(2-Pyridylazo)- and 1-(thiazol-2-ylazo)-2-naphthol, *(2)* and *(3)*, called PAN and TAN, are used as indicators for complexometric titration and as reagents for solvent extraction and spectrophotometric determination of numerous metal ions. They act as monovalent tridentate chelate ligands. Their bonding to the metal ion might be largely determined by a synergic $d\rightarrow\pi^*$ electron transfer from the metal to the azopyridine system[2]. Expressed in terms of valence bonds, a redox relationship *(B)* is superposed upon the donor/acceptor relationship *(A)* between ligand and metal ion.



(A) *(B)*

M = Metal equivalent

Like metal ions, trivalent phosphorus can also simultaneously accept and donate electrons. Indeed, in principle, *(2)* and *(3)* react with chlorophosphanes *(1)* in the same way as with metal ions, *i.e.* as tridentate ligands. Owing to the higher reducing power of P^{III}, however, the oxidative addition in the sense of formula *(B)* is realized, and the bicyclophosphoranes *(6)* and *(7)* are formed.

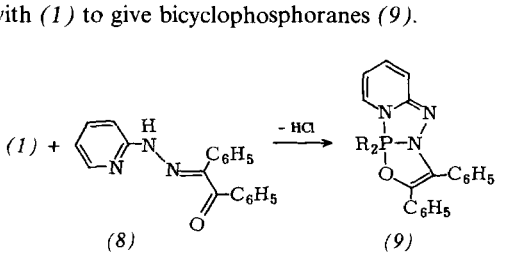


(2) *(4)* *(6)*

(3) *(5)* *(7)*

The reactions most likely proceed *via* the substitution intermediates *(4)* and *(5)*. The second step is then [4+1] cycloaddition at P^{III}[3], which is normally restricted to certain heterodienes, but in this intramolecular version is also observed with the azopyridine system[4, 5].

N'-(2-Pyridyl)benzil monohydrazone *(8)* contains a seven-membered chain having the same functionality as in *(2)* but with a 1,5-shifted proton. Like *(2)* it forms metal chelates[6] and reacts with *(1)* to give bicyclophosphoranes *(9)*.



(8) *(9)*

The upfield shift of the ^{31}P-NMR signals (Table 1) confirms that the phosphorus in *(6)*, *(7)*, and *(9)* achieves pentacoordination. The bicyclic should be planar, *i.e.* meridionally incorporated in the trigonal-bipyrimidal configuration. This is supported by the fact that the substituents on the phosphorus when $R^1=R^2$ are equivalent in the ^1H-NMR spectrum and that their signals are split with $^{2,3}J_{PH}$ coupling constants

[*] Prof. Dr. A. Schmidpeter, Dipl.-Chem. J. H. Weinmaier
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-8000 München 2 (Germany)

(J_{PCH} = 13 to 15 Hz, $J_{P(N,O)CH}$ = 14 to 15 Hz) that are typical for the equatorial position. Exceptions are *(9i)* with non-equivalent methylene members in the dioxaphospholane ring and presumably also *(9j)*. Here the axial-equatorial position of the third ring forces the bicyclic into the facial position (cf. Ref.[7]). The two thiazole protons in *(7)* give ABX signals with $\delta^1H(4) = 6.0$ to 6.7; $J_{PNCH} = 1.0$ to 1.5 Hz and $\delta^1H(5) = 5.6$ to 5.0; $J_{PNCCH} = 1.4$ to 4.2 Hz.

Table 1. Color, melting point [°C] and $\delta(^{31}P)$ of the compounds *(6)*, *(7)*, and *(9)*. When no melting point is quoted the compound is an oil.

	R^1	R^2	*(6)*		*(7)*		*(9)*	
(a)	CH_3	CH_3	dark red	−35.2	dark red	−34.9	dark red 107—108	−39.2
(b)	CH_3	C_6H_5					orange	−37.8
(c)	C_6H_5	C_6H_5	orange 160—162	−44.0	red 184—186	−45.8	red 164—166	−48.0
(d)	CH_3	$(CH_3)_2N$					red	−37.1
(e)	$(CH_3)_2N$	$(CH_3)_2N$	orange 155—158	−35.9	light yellow 141—143	−37.6	red	−40.0
(f)	CH_3O	CH_3O	dark yellow 130 (dec.)	−48.6	red 152—153	−49.0	red	−52.5
(g)	C_6H_5O	C_6H_5O	red	−59.1	dark red	−54.8		
(h)	$CH_3NC_2H_4NCH_3$						orange 115—117	−34.2
(i)	OC_2H_4O						yellow 110 (dec.)	−28.4
(j)	OC_6H_4O						dark yellow	−29.4

Experimental

A suspension of *(2)*, *(3)*, or *(8)* (20 mmol) and triethylamine (20 mmol) in anhydrous benzene (30 ml) is treated under N_2 with chlorophosphane *(1)* (20 mmol). After one hour's stirring at room temperature, the triethylammonium chloride is separated off by filtration, washed with benzene, and the combined filtrates concentrated by evaporation. The crude product is then chromatographed on Al_2O_3 and/or recrystallized from acetonitrile. In some cases the products could not be crystallized.

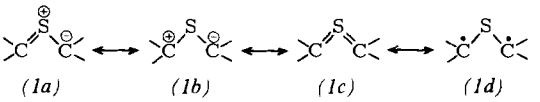
Received: October 6, 1977 [Z 852 IE]
German version: Angew. Chem. *89*, 903 (1977)

[1] Part 25 of Four- and Five-Membered Phosphorus Heterocycles. This work was supported by the Fonds der Chemischen Industrie.—Part 24: *P. Friedrich, G. Huttner, J. Luber, A. Schmidpeter*, Chem. Ber. *111*, (1978), in press.
[2] *D. A. Balderin, A. B. P. Lever, R. V. Parish*, Inorg. Chem. *8*, 107 (1969).
[3] *A. Schmidpeter, J. H. Weinmaier*, Angew. Chem. *87*, 517 (1975); Angew. Chem. Int. Ed. Engl. *14*, 489 (1975).
[4] The same applies for the second step in the addition of *(2)* and *(3)* to a 1,2,4,3λ^3-triazaphosphole: *A. Schmidpeter, M. Junius, J. H. Weinmaier, J. Barrans, Y. Charbonnel*, Z. Naturforsch. *32b*, 841 (1977).
[5] The 4+1 addition of azopyridine to a carbene has been described by *J. Markert, E. Fahr*, Tetrahedron Lett. *1967*, 4337.
[6] *B. Chiswell, F. Lions, M. L. Tomlinson*, Inorg. Chem. *3*, 492 (1964).
[7] *A. Schmidpeter, D. Schomburg, W. S. Sheldrick, J. H. Weinmaier*, Angew. Chem. *88*, 851 (1976); Angew. Chem. Int. Ed. Engl. *15*, 781 (1976).

Stable Thiocarbonyl Ylides

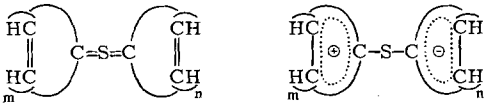
By *Kazuhiro Nakasuji, Keitaro Nishino, Ichiro Murata, Hisanobu Ogoshi*, and *Zen'ichi Yoshida*[*]

Thiocarbonyl ylides *(1)* constitute a new class of compounds, conventionally represented by many resonance structures such as the 1,3-dipolar *(1b)*[1], the quadrivalent sulfur *(1c)*[2], and the biradical structure *(1d)*. Since the first report on clear-cut evidence for the intermediacy of the thiocarbonyl ylide by *Kellogg et al.*[3], much attention has been focused on the preparation of stable thiocarbonyl ylides[4].



(1a) *(1b)* *(1c)* *(1d)*

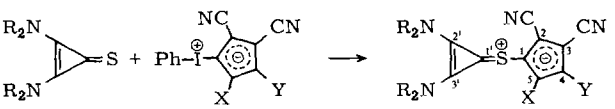
The thiocarbonyl ylide of general formula *(2)*, containing two odd unsaturated rings might be stabilized by participation of the aromatic dipolar structure *(2a)* in the ground state in which each of the two oppositely charged rings satisfies the Hückel rule. The simplest compound of this type is *(2)*, $m = 1$, $n = 2$. We now report the synthesis of the first example of this type of thiocarbonyl ylide.



(2) *(2a)*

Since the 1,2-bis(diisopropylamino)cyclopropenyl[5a] and the tricyanocyclopentadienyl[6] systems have been shown to give stable cations and anions, respectively, our attention turned to the reaction of bis(diisopropylamino)cyclopropenethione *(3)*[5a] with 1-phenyliodonium 2,3,5-tricyanocyclopentadienide *(4a)*[7] or 1-phenyliodonium 2,3,4-tricyanocyclopentadienide *(4b)*[7].

Reactions of equimolecular amounts of *(3)* and *(4a)* or *(4b)* in refluxing chloroform afford the expected thiocarbonyl ylides *(5a)* and *(5b)*, respectively[4d]. In both cases, no starting materials were left after 1.5 h and the products obtained essentially pure by chromatography (short column, Al_2O_3, CH_2Cl_2). *(5a)*, colorless needles from CH_2Cl_2/hexane, m.p. 248—250 °C, 86 % yield; *(5b)*, colorless prisms from CH_2Cl_2/hexane, m.p. 269—271 °C, 71 % yield. Both thiocarbonyl ylides appear to be quite stable under atmospheric condition. Their



(3) *(4a)*, X = CN, Y = H *(5a)*, X = CN, Y = H
R = *i*-C_3H_7 *(4b)*, X = H, Y = CN *(5b)*, X = H, Y = CN

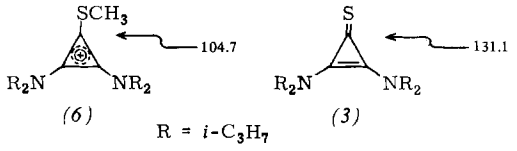
[*] Dr. K. Nakasuji, K. Nishino, Prof. Dr. I. Murata [+]
Department of Chemistry, Faculty of Science, Osaka University
Toyonaka, Osaka 560 (Japan)
Dr. H. Ogoshi, Prof. Dr. Z. Yoshida
Department of Synthetic Chemistry, Kyoto University
Yoshida, Kyoto 606 (Japan)
[+] To whom correspondence should be addressed.

Table 1. Selected physical properties of *(5a)* and *(5b)*.

	(5a)	*(5b)*
^{13}C-NMR (in $CDCl_3$, TMS internal)		
C-1	109.2	109.9
C—CN	97.4, 98.9, 102.0	97.7, 101.7, 102.5
C-4	108.9	
C-5		105.1
C-1′	124.5	124.8
C-2′, C-3′	131.1	130.9
IR (KBr) [cm^{-1}]		
C≡N	2210	2210
Cyclopropene [5]	1898, 1550	1900, 1550
UV (CH_3CN) λ_{max} [nm] (log ε)		
	240 (4.61), 278 (4.23)	223 (4.49), 243 (4.45) s, 285 (4.29), 295 (4.26)
^{1}H-NMR (100 MHz, $CDCl_3$, TMS internal)		
4-H	6.78 (1H, s)	
5-H		6.56 (1H, s)

structures were unambiguously established by their elemental analyses and spectra (Table 1).

The upfield shift of the C-1 signal in the ^{13}C-NMR spectrum of *(5a)* and *(5b)* is comparable with that of the cyclopentadienide ion (δ = 102.1)[8]; this indicates an enhanced electron density at this carbon atom and is consonant with the similar chemical shifts of 4-H in the ^{1}H-NMR spectrum of *(5a)* and 3-H of potassium 1,2,4-tricyanocyclopentadienide (δ = 6.67). On the other hand, the chemical shift noted for



C-1′ lies between those of the reference compounds *(6)*[9] and *(3)*[9]. These findings suggest a partial double bond character of the (C-1′)—S bond. Hence structure *(1a)* should play an important role in stabilizing the thiocarbonyl ylides *(5a)* and *(5b)*.

Received: September 9, 1977 [Z 837 IE]
German version: Angew. Chem. *89*, 904 (1977)

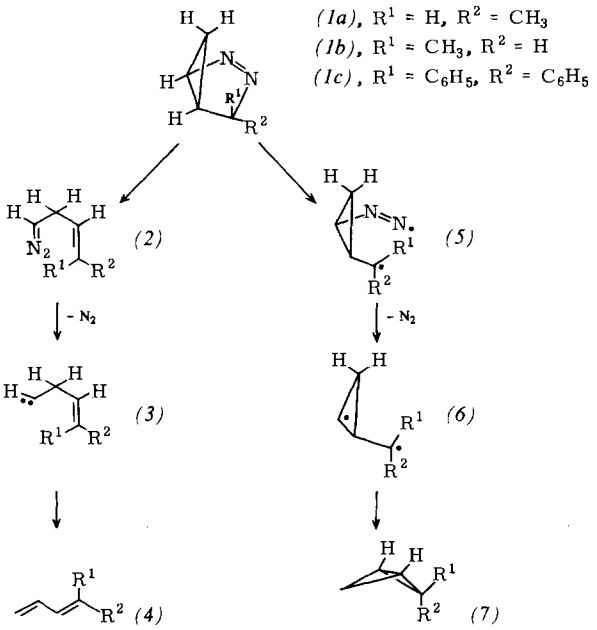
CAS Registry numbers:
(1a), 53283-20-8; *(3)*, 41597-07-3; *(4a)*, 51062-49-8; *(4b)*, 51062-49-8; *(5a)*, 64315-04-4; *(5b)*, 64315-05-5

[1] Cf. *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. Int. Ed. Engl. *2*, 565 (1963).
[2] Cf. *M. P. Cava, M. V. Lakshmikantham*, Acc. Chem. Res. *8*, 139 (1975).
[3] *R. M. Kellogg, S. Wassenaar*, Tetrahedron Lett. *1970*, 1987; *R. M. Kellogg, S. Wassenaar, J. Buter, ibid. 1970*, 4689.
[4] a) *W. J. Middleton*, J. Org. Chem. *31*, 3731 (1966); b) *S. Tamagaki, S. Oae*, Tetrahedron Lett. *1972*, 1159; c) *G. F. Koser, S.-M. Yu*, J. Org. Chem. *41*, 125 (1976); d) thiocarbonyl ylides with substituted cyclopentadienyl system: *P. Gronski, K. Hartke*, Tetrahedron Lett. *1976*, 4139; e) *A. J. Arduenge, E. M. Burgess*, J. Am. Chem. Soc. *98*, 5020, 5021 (1976).
[5] a) *Z. Yoshida, H. Konishi, Y. Tawara, H. Ogoshi*, J. Am. Chem. Soc. *95*, 3043 (1973); b) *A. Krebs*, Angew. Chem. *77*, 10 (1965); Angew. Chem. Int. Ed. Engl. *4*, 10 (1965); *Y. Kitahara, M. Funamizu*, Bull. Chem. Soc. Jpn. *37*, 1897 (1964).
[6] *O. W. Webster*, J. Am. Chem. Soc. *88*, 3046 (1966).
[7] *K. Friedrich, W. Amann*, Tetrahedron Lett. *1973*, 3689.
[8] *H. Spiesecke, W. G. Schneider*, Tetrahedron Lett. *1961*, 468.
[9] *H. Konishi*, Ph. D. Dissertation, Kyoto University 1976.

Formation of Diazo Compounds on Decomposition of 2,3-Diazabicyclo[3.1.0]hex-2-enes: [3+2]-Cycloreversions[**]

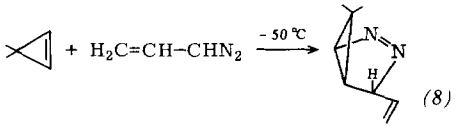
By *Manfred Schneider* and *Bernd Csacsko*[*]

The reaction products obtained on thermal or photochemical decomposition of *(1)* differ fundamentally from those of other bicyclic 1-pyrazolines[1]. Thus *(1a)* gives *trans*-1,3-pentadiene *(4a)*, and *(1b)* affords *cis*-1,3-pentadiene *(4b)*[2]. This was interpreted in terms of the intermediacy of carbenes. The first reaction step was formulated as a 1,3-dipolar retroaddition leading to a diazo compound *(2)*. The reaction products then arise from *(2) via* the carbene *(3)*. On the other hand, formation of bicyclo[1.1.0]butane *(7)* on decomposition of *(1c)* was regarded as evidence for the simultaneous occurrence of diazenyl and cyclopropyl diradicals *(5)* and *(6)*, respectively[3].



The isolation and identification of *(2)* as the principal or sole decomposition product of *(1)* would constitute unequivocal proof of the carbene mechanism and rule out the formation of diradicals *(6)*. This has not previously been accomplished[4]. We now report the first successful experiments in a typical series of compounds.

1,3-Dipolar cycloaddition of 3-diazo-1-propene to 3,3-dimethylcyclopropene[5] at −50 °C furnishes 6,6-dimethyl-4-*exo*-vinyl-2,3-diazabicyclo[3.1.0]hex-2-ene *(8)* in 70% yield, b.p. 58 °C/4 torr. Only the *exo* isomer is formed[6].

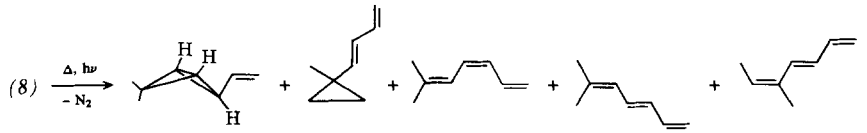


Compound *(8)* decomposes thermally (*n*-octane, 40—70 °C; $\Delta H^{\neq} = 24.8 \pm 1$ kcal/mol; $\Delta S^{\neq} = -1 \pm 2$ cal/mol K) and photochemically (*n*-pentane, 0 °C; Hanau TQ 150, Pyrex filter) with

[*] Dr. M. Schneider, B. Csacsko
Institut für Chemie der Universität Hohenheim
Garbenstrasse 30, D-7000 Stuttgart 70 (Germany)

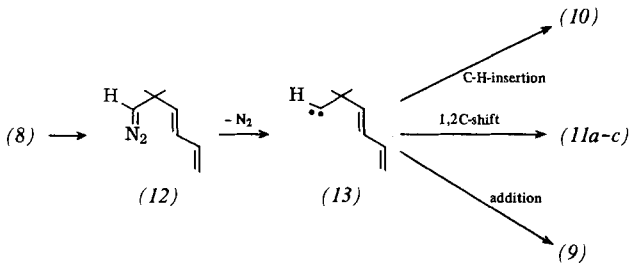
[**] This work was supported by the Deutsche Forschungsgemeinschaft. We are grateful to Prof. Dr. *M. Regitz* for valuable discussions, and to Dr. *P. Binger* for supplying the substituted cyclopropenes.

formation of 2,2-dimethyl-4-*exo*-vinylbicyclo[1.1.0]butane *(9)*, 1-(*trans*-1,3-butadienyl)-1-methylcyclopropane *(10)*, the *Z*- and *E*-6-methyl-1,3,5-heptatrienes *(11a)* and *(11b)*, and of *(11c)*, tentatively identified as *E*-5-methyl-1,3,5-heptatriene[7]. All the compounds are stable under the reaction conditions. The trienes *(11a—c)* can be separated by preparative gas chromatography, but polymerize rapidly at room temperature and must therefore be kept at −78 °C under N_2. Above 150 °C compound *(9)* quantitatively rearranges [$t_{1/2}$ (170 °C) = 60 min] to *(11b)* in a [$_\sigma2_s + _\sigma2_a$] process. The

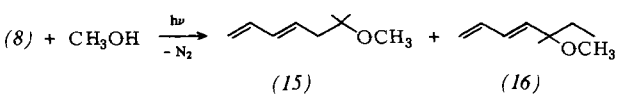


	(9)	(10)	(11a)	(11b)	(11c)
photochemical [%]	24.0	21.8	12.1	35.3	6.8
thermal [%]	16.8	18.8	–	56.2	8.2

formation of all products can be explained as intramolecular secondary reactions of a carbene *(13)* formed from *(8)* *via* the diazo compound *(12)*.



This conclusion is also supported by the finding that only traces of *(9)*, *(10)*, *(11a—c)* are formed on photolysis of *(8)* in methanol *(14)*. Instead, the methyl ethers *(15)* and *(16)* are formed in 80 and 20 % yield, respectively[8].

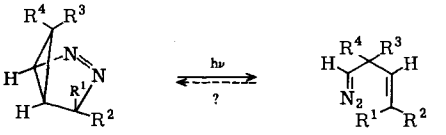


Brief heating of *(8)* in *n*-octane to +80 °C gives a deep yellow solution whose IR spectrum displays the intense diazo group band at $\nu = 2060\,cm^{-1}$. The UV spectrum exhibits a broad band at $\lambda_{max} = 460$ nm ($\varepsilon \approx 8$) and a further maximum at $\lambda_{max} = 219$ nm ($\varepsilon \approx 17000$), and is practically identical with the spectrum of diazoethane in the visible region. Solutions obtained in this way (up to 0.5 M) likewise afford *(15)* and *(16)* with methanol and react with 2-naphthol and with 3,5-dinitrobenzoic acid with evolution of N_2 to form the corresponding derivatives.

UV irradiation of a solution of *(8)* in [D_8]tetrahydrofuran at −50 °C in the NMR spectrometer[9] leads to rapid disappearance of the signals of *(8)* and formation of *(12)*. On use of monochromatic light ($\lambda = 331 \pm 12$ nm) for excitation of the $n \rightarrow \pi^*$ band of *(8)* at $\lambda_{max} = 331$ ($\varepsilon = 370$) or on use of suitable filter solutions[9], it is possible to suppress the further reaction of *(12)* and to record its ^{1}H-NMR spectrum [in [D_8]THF: $\delta = 1.20$ (s, 6H), 3.72 (s, 1H), 4.70—5.40 (m, 2H), 5.70—6.50 (m, 3H)]. Apart from *(12)*, only traces of *(9)*, *(10)*, and *(11a—c)* are found. Hence the diazo compound *(12)* is the sole reaction product of photochemical (and most likely also thermal) decomposition of *(8)*. At room temperature it can be detected in solution for only *ca.* 2 h, and decomposes with formation of *(9)*, *(10)*, and *(11a—c)*.

In the same way we have studied the low-temperature photolysis of *(1a—i)* and were able to record the ^{1}H-NMR spectra of the diazo compounds *(17a—i)* formed practically exclusively in all cases.

It is clear from these results that the decomposition reactions of 2,3-diazabicyclo[3.1.0]hex-2-enes proceed *via* diazo compounds and carbenes and that 1,3-diradicals play only a minor role (if any) in product formation.



(1a-i) *(17a-i)*

(a), $R^1 = H$, $R^2 = CH_3$, $R^3 = R^4 = H$
(b), $R^1 = CH_3$, $R^2 = H$, $R^3 = R^4 = H$
(c), $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = R^4 = H$
(d), $R^1 = Vinyl$, $R^2 = H$, $R^3 = R^4 = H$
(e), $R^1 = H$, $R^2 = Vinyl$, $R^3 = R^4 = H$
(f), $R^1 = H$, $R^2 = CH_3$, $R^3 = R^4 = CH_3$
(g), $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = R^4 = CH_3$
(h), $R^1 = H$, $R^2 = Vinyl$, $R^3 = CH_3$, $R^4 = C_6H_5$
(i), $R^1 = H$, $R^2 = Vinyl$, $R^3 = C_6H_5$, $R^4 = CH_3$

The thermal decomposition reactions can be regarded as the [3+2] cycloreversion of a thermally allowed [$_\pi4_s + _\pi2_s$] addition. In no case were we able (within the limits of accuracy of the NMR method) to observe this reaction with formation of the starting compound *(1)* since the decomposition of the diazo compounds was faster.

Received: September 5, 1977 [Z 844 IE]
German version: Angew. Chem. *89*, 905 (1977)

CAS Registry numbers:
(1a), 35553-11-8; *(1b)*, 35553-12-9; *(1c)*, 40323-01-1; *(1d)*, 64625-60-1; *(1e)*, 64586-10-3; *(1f)*, 64586-09-0; *(1g)*, 64586-08-9; *(1h)*, 64625-59-8; *(1i)*, 64586-07-8; *(8)*, 64586-06-7; *(9)*, 64586-05-6; *(10)*, 64586-04-5; *(11a)*, 64586-03-4; *(11b)*, 18304-14-8; *(11c)*, 64586-02-3; *(12)*, 64586-01-2; *(15)*, 64586-00-1; *(16)*, 64585-99-5; *(17a)*, 64585-98-4; *(17b)*, 64585-97-3; *(17c)*, 64585-96-2; *(17d)*, 64585-95-1; *(17e)*, 64585-94-0; *(17f)*, 64585-93-9; *(17g)*, 64585-92-8; *(17h)*, 64585-91-7; 3-diazo-1-propene, 2032-04-4; 3,3-dimethylcyclopropene, 3907-06-0

[1] *M. Schneider, A. Erben, I. Merz*, Chem. Ber. *108*, 1271 (1975).
[2] *D. F. Eaton, R. G. Bergman, G. S. Hammond*, J. Am. Chem. Soc. *94*, 1351 (1972).
[3] *P. G. Gassman, W. J. Greenlee*, J. Am. Chem. Soc. *95*, 980 (1973).
[4] This was possible only in systems in which the diazo compound is stabilized by electron-poor substituents such as CO_2Me [*M. Franck-Neumann, C. Buchecker*, Tetrahedron Lett. *1969*, 2659] or $PO(OMe)_2$ [*W. Welter, M. Regitz, ibid. 1976*, 1473].
[5] *P. Binger*, Synthesis *1974*, 190.
[6] The ^{13}C-NMR spectrum of *(8)* shows only eight lines. The coupling constant in the ^{1}H-NMR spectrum $J_{2,3} = 2.0$ Hz supports the *exo* structure; a value of *ca.* 7 Hz would be expected for the *endo* compound: *D. H. Aue, G. S. Helwig*, Tetrahedron Lett. *1974*, 721.

[7] All the compounds were characterized unequivocally by spectroscopy; the stereochemical assignment of *(11a—c)* is based on reference data for isomeric 1,3,5-hexatrienes: *E. Havinga*, personal communication; *T. S. Sorensen*, Can. J. Chem. *42*, 2781 (1964).

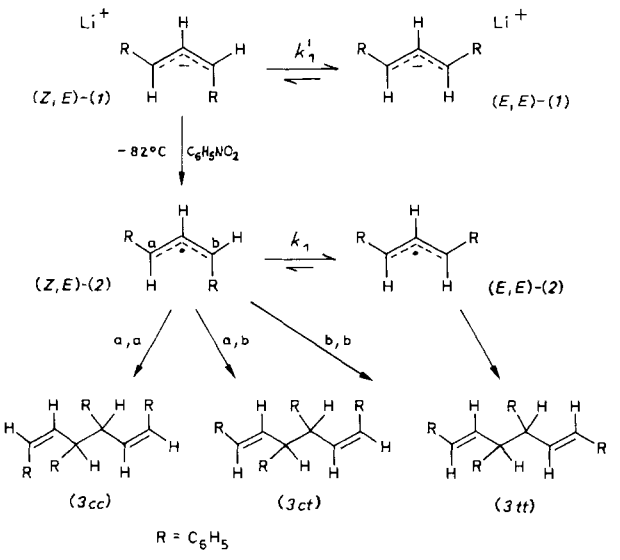
[8] Compare the reaction of diazoneopentane with methanol: *W. Kirmse, K. Horn*, Tetrahedron Lett. *1967*, 1827.

[9] Lamp: Philips SP 1000 W; irradiation *via* a quartz light conductor leading directly into the NMR instrument (Bruker HX90R with a modified sample head). A mixture of $NiSO_4 \cdot 7H_2O$ (250 g), $CoSO_4 \cdot 6H_2O$ (50 g), and H_2SO_4 (1 g) in H_2O (1 l) was used as filter solution to absorb most of the visible and infrared radiation.

Formation of the (*Z*,*E*)-1,3-Diphenylallyl Radical from the (*Z*,*E*)-1,3-Diphenylallyl Anion by Electron Transfer—Comparison of the Rotational Barriers of the Radical and the Anion[**]

By *Gernot Boche* and *Dieter R. Schneider*[*]

The rotational barriers of allyl radicals[1] and their relationship with allyl resonance[2, 3] are questions of topical interest. In addition, we were also interested in the rotational barriers of allyl systems having the same topology but differing in the number of π-electrons, and hence in their charge.



The preparation of the (*Z*,*E*)-1,3-diphenylallyl radical (*Z*,*E*)-*(2)* from the (*Z*,*E*)-1,3-diphenylallyl anion (*Z*,*E*)-*(1)* was accomplished by electron transfer[4]: addition of (*Z*,*E*)-*(1)* in tetrahydrofuran (THF) to nitrobenzene in THF[5] led, even at −82 °C, to immediate[6] oxidation. Work-up afforded the products of radical dimerization *(3cc)*, *(3ct)*, and *(3tt)*[7] in 97% yield. They were separated and isolated as mixtures of diastereomers by preparative thin-layer chromatography (silica gel; light petroleum : ether = 95 : 5).

Structural proof was provided by spectroscopy[8].

(3cc): NMR ($CDCl_3$): decoupling of the benzyl protons gave two AB systems of approximately equal intensity for the olefinic protons; $J_{cis} = 12.0$ and 12.2 Hz. IR (CS_2): no absorption between 920 and 1020 cm^{-1}. UV (dioxane): $\lambda_{max} = 246$ nm, $\varepsilon = 18490$. *(3tt)*[9]: NMR: decoupling of the benzyl protons gave two AB systems of approximately equal intensity for the olefin protons, with $J_{trans} = 15.8$ and 16.0 Hz. IR: bands at 950 and 959 cm^{-1}. UV: $\lambda_{max} = 253$ nm, $\varepsilon = 21380$. *(3ct)*: NMR: simultaneous decoupling of all benzyl signals was unsuccessful. IR: band at 952 cm^{-1}. UV: $\lambda_{max} = 253$ nm ($\varepsilon = 26490$).

The relative yields are of particular significance. While diffusion-controlled dimerization[10] of the allyl radical (*Z*,*E*)-*(2)* should give the ratio *(3cc)* : *(3ct)* : *(3tt)* = 25 : 50 : 25, we found the values listed in Table 1.

Table 1. Yields [%] of the dimers *(3cc)*, *(3ct)*, and *(3tt)*.

T [°C]	*(3cc)*	*(3ct)*	*(3tt)*
−82	10±5	20±10	70±10
−67	6±4	14±10	80±10
+25	0	10±5	90±5

Since the allyl radical (*E*,*E*)-*(2)* isomeric to (*Z*,*E*)-*(2)* leads exclusively to the dimer *(3tt)* and the anion (*Z*,*E*)-*(1)* is configurationally stable under the reaction conditions, the radical isomerization (*Z*,*E*)-*(2)* → (*E*,*E*)-*(2)* must compete with the diffusion-controlled dimerization of (*Z*,*E*)-*(2)* even at −82 °C. The deviation of the yields from the statistical values cannot be explained in terms of selectivity during the dimerization of the allyl radical (*Z*,*E*)-*(2)* because the diastereomers are formed in the ratio 1 : 1 in the case of *(3cc)* and *(3tt)* (see NMR data).

In accord with the above qualitative demonstration of a very low rotational barrier of the radical (*Z*,*E*)-*(2)*, approximate solution of the formal kinetics of competition between isomerization and dimerization with the aid of the dimerization rate constant $k_2 = 4.5 \times 10^8$ l/mol·s, determined from a viscosity measurement of the reaction medium at −67 °C[11], gives the value $k_{1(-67\,°C)} < 5 \times 10^8\ s^{-1}$. This value corresponds to $\Delta G^{\neq}_{-67\,°C} > 3.7$ kcal/mol. Comparison with the rotational barriers of other allyl radicals[1] shows that the upper limit for (*Z*,*E*)-*(2)* should lie at $\Delta G^{\neq}_{-67\,°C} \approx 9$ kcal/mol.

Thus, in contrast to the allyl anion (*Z*,*E*)-*(1)* of like topology [$k'_{1(-38\,°C)}$ (THF/HMPA) $= 1.9 \times 10^{-4}\ s^{-1}$, corresponding to $\Delta G^{\neq}_{-38\,°C} = 17.9$ kcal/mol], the allyl radical (*Z*,*E*)-*(2)* exhibits pronounced configurational lability[12]. This conclusion is in agreement with *Brauman*'s recently published result[3] that the resonance energy of the allyl radical is at least 4.9 kcal/mol lower than that of the allyl anion, and demonstrates afresh that uncharged π-systems are configurationally less stable than charged ones[13,14].

Received: September 19, 1977 [Z 851 IE]
German version: Angew. Chem. *89*, 907 (1977)

[*] Priv.-Doz. Dr. G. Boche, Dipl.-Chem. D. R. Schneider
Institut für Organische Chemie der Universität
Karlstrasse 23, D-8000 München 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *D. R. S.* acknowledges a study grant from the Studienstiftung des Deutschen Volkes.

[1] *P. J. Krusic, P. Meakin, B. E. Smart*, J. Am. Chem. Soc. *96*, 7382 (1974); *R. Sustmann, H. Trill, F. Vahrenholt, D. Brandes*, Chem. Ber. *110*, 255 (1977).

[2] *W. v. E. Doering, G. H. Beasley*, Tetrahedron *29*, 2231 (1973); *A. B. Trenwith*, Int. J. Chem. Kinet. *5*, 67 (1973); *W. R. Roth, G. Ruf, P. W. Ford*, Chem. Ber. *107*, 48 (1974); *G. Levin, W. A. Goddard III*, J. Am. Chem. Soc. *97*, 1649 (1975).

[3] *A. H. Zimmermann, J. Brauman*, J. Am. Chem. Soc. *99*, 3565 (1977).

[4] *G. Boche, D. R. Schneider*, Tetrahedron Lett. *1976*, 3657.

[5] Use of nitroaromatic compounds in electron transfer reactions: *G. A. Russell, E. D. Janzen, E. T. Strom*, J. Am. Chem. Soc. *86*, 1887 (1964).

[6] The wine-red color of the solution of (*Z*,*E*)-*(1)* vanishes immediately on dropwise addition to the nitrobenzene solution. Work-up by protonation with CH_3OH after 1 min. The same result was obtained on use of I_2 as oxidizing agent. Hg^I and Hg^{II} chloride led solely to the dimer *(3tt)*[7].

[7] *c* = *cis* and *t* = *trans* refer to the configuration of the phenyl groups R attached to the double bond. *(3cc)*, *(3ct)*, and *(3tt)* gave correct C,H analyses.

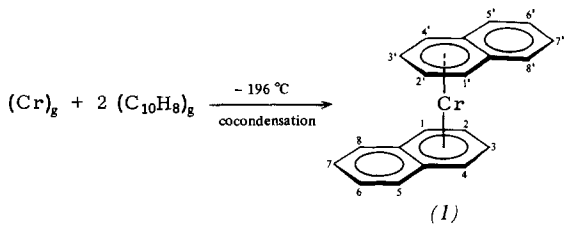
[8] We are indebted to Prof. *H. Kessler*, Universität Frankfurt, for recording the 270-MHz spectra.
[9] *S. Sustmann, Ch. Rüchhardt, A. Bieberbach, G. Boche*, Tetrahedron Lett. *1972*, 4729.
[10] *K. U. Ingold* in *J. K. Kochi*: Free Radicals. Wiley, New York 1973, Vol. I, pp. 37ff.
[11] *P. Debye*, Trans. Electrochem. Soc. *82*, 265 (1942).
[12] These results suggest that the faster isomerization of allyl anions in the presence of catalytic amounts of oxygen (personal communication, Prof. *H. Ahlbrecht*, Universität Giessen, and Prof. *M. Schlosser*, Université de Lausanne; *G. Boche, A. Bieberbach*, unpublished results) is attributable to a reversible electron transfer with intermediate formation of configurationally more labile allyl radicals.
[13] *G. Boche, A. Bieberbach, H. Weber*, Angew. Chem. *87*, 550 (1975); Angew. Chem. Int. Ed. Engl. *14*, 562 (1975); Tetrahedron Lett. *1976*, 1021.
[14] *Note added in proof* (October 26, 1977): *Ab initio* 4-31-G calculations also indicate that the rotational barrier of the allyl radical (21.2 kcal/mol) is smaller than that of the allyl anion (27.6 kcal/mol); *G. Boche, H. U. Wagner*, unpublished results.

Bis(η^6-naphthalene)chromium(0)[**]

By *Christoph Elschenbroich* and *Reinhart Möckel*[*]

It is surprising that more than two decades after the original preparation of bis(η-benzene)chromium(0)[1] the corresponding naphthalene complex, the parent compound of bis(η-arene)metal complexes of fused six-membered ring aromatics, has still not been isolated. The sole representative of this class so far reported is the dicationic complex bis(η^6-naphthalene)ruthenium(II)[2]; its attempted reduction to the neutral complex was unsuccessful.

Among the few synthetic methods available for bis(η-arene)-metal complexes, the classical reductive Friedel-Crafts reaction[1] and its variants[3] lead to π-complexes of partially hydrogenated arenes when applied to fused six-membered ring systems, at least when the metal belongs to the first transition series[4]. The reaction of metal halide with arene radical anion merely appears suitable for obtaining ESR proof of the existence of the desired compounds[5]. We have now synthesized bis(η^6-naphthalene)chromium(0) *(1)* by cocondensation of metal atom and ligand[6].



(1)

After recrystallization from light petroleum, *(1)* is obtained as brown crystals of analytically confirmed composition $C_{20}H_{16}Cr$ which decompose with sublimation of naphthalene on exposure to air. The complex is readily soluble in tetrahydrofuran (THF) and toluene, but poorly soluble in dimethoxyethane and aliphatic hydrocarbons, and can be sublimed without extensive decomposition at 80 °C/10^{-4} torr.

The presence of a homogeneous bis(naphthalene) sandwich complex is confirmed *inter alia* by the mass spectrum (FD-MS: m/e=308, 100 %, M^+; 309, 12.3 % $[M+1]^+$). In particular, the absence of a mass line at m/e=312 and characterization of the ligand by gas chromatography after cleavage of *(1)* demonstrate that formation of the hydrogenation product bis(η^6-tetralin)chromium(0) can be suppressed on synthesis by the cocondensation technique.

In the ^{1}H-NMR spectrum of *(1)* (D_8-THF) the protons of the complexed ring appear as an A_2B_2 system [δ=4.50 m ($H_{2,3,2',3'}$), 5.40 m ($H_{1,4,1',4'}$)] whereas the protons on the free ring—as also in structurally closely related bis(η^5-indenyl)-iron[7]—give rise to a singlet [δ=6.98 s ($H_{5,6,7,8,5',6',7',8'}$)]. Air oxidation of *(1)* in solution leads to the radical cation $(1)^+$ with ESR data (THF, −80 °C): $\langle g\rangle$=1.986, $a(^1H_{1,4,1',4'})$ =3.65 G, $a(^{53}Cr)$=18.2 G.

The thermal stability of *(1)* (dec. 160 °C) is significantly lower than that of $Cr(C_6H_6)_2$ (m.p. 283—284 °C), possibly due to the greater gain in resonance energy on transition of naphthalene from the π-coordinated to the free state, as compared with benzene.

Drastic differences in reactivity are found for the complex cations: In contrast to $Cr(C_6H_6)_2^+$, which is stable for several days in aqueous solution (pH neutral, room temperature), the radical cation $(1)^+$ decomposes with a half-life of 25 min under these conditions (ESR measurements). In solvent THF decomposition is so fast that cooling to −80 °C is necessary for recording ESR spectra. To a lesser extent this lability is also manifested by the neutral complex. Thus *(1)* reacts instantaneously at room temperature in THF with 2,2'-bipyridine to give $Cr(bpy)_3$, recognizable by its intense reddish brown color, the color change red→blue→red→yellow upon controlled air oxidation and identified *via* ESR characterization of the cation $[Cr(bpy)_3]^+$ [8]. The mild conditions necessary for substitution of the π-bonded naphthalene are astonishing, for ligand exchange in bis(η-benzene)chromium(0) occurs only at high temperatures and pressures (substitution of C_6H_6 by CO, PF_3, bpy,tpy[9]) or with $AlCl_3$ catalysis (substitution by other arenes[10]).

Procedure

In a 1-liter flask (−196 °C, $<10^{-3}$ torr) Cr (0.664 g, 12.8 mmol) is evaporated within 2 h from a heatable Mo wire (diam. 1 mm) spiral (12 V, 40 A). Naphthalene vapor (*ca.* 40 g, 312 mmol) is simultaneously introduced *via* a heatable inlet. A condensate is formed which appears reddish brown as a thin layer. After warming to room temperature the condensate is dissolved in THF. Filtration and removal of solvent leave a residue which is placed in a high vacuum at +50 °C for 4 h to remove excess naphthalene. Recrystallization from light petroleum (−80 °C) gives dark brown crystals of *(1)* which are pyrophoric when finely divided (yield 0.68 g, 17.8 % based on evaporated Cr).

Received: October 3, 1977 [Z 853 IE]
German version: Angew. Chem. *89*, 908 (1977)

CAS Registry number:
(1), 33085-81-3

[*] Prof. Dr. Ch. Elschenbroich, R. Möckel
Fachbereich Chemie der Universität
Lahnberge, D-3550 Marburg 1 (Germany)

[**] Metal π-Complexes of Benzene Derivatives, Part 8. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 7: *Ch. Elschenbroich, J. Heck*, Angew. Chem. *85*, 497 (1977); Angew. Chem. Int. Ed. Engl. *16*, 479 (1977).

[1] *E. O. Fischer, W. Hafner*, Z. Naturforsch. *B10*, 665 (1955).
[2] *E. O. Fischer, Ch. Elschenbroich, C. G. Kreiter*, J. Organomet. Chem. 7, 481 (1967).
[3] *F. Hein, H. Kleinwächter*, Monatsber. Dtsch. Akad. Wiss. Berlin *60*, 607 (1960).
[4] *H. G. Essler*, Dissertation, Technische Universität München 1960. Control experiments with the systems $C_{10}H_8/AlCl_3/Al/CrCl_3/C_6H_5Cl$ (as solvent) and $Li^+C_{10}H_8^-/CrCl_3(THF)_3/THF$ after work-up also gave bis(η^6-tetralin)chromium(0) as the main product when performed in our laboratory.
[5] *G. Henrici-Olivé, S. Olivé*, J. Organomet. Chem. *9*, 325 (1967); J. Am. Chem. Soc. *92*, 4831 (1970).
[6] Cf. "Metal Atoms in Chemical Synthesis" Angew. Chem. *87*, No. 7 and 9 (1975); Angew. Chem. Int. Ed. Engl. *14*, No. 4 and 5 (1975); *P. L. Timms*, Adv. Organomet. Chem. *15*, 53 (1977).

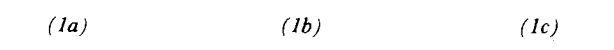
[7] *R. B. King, M. B. Bisnette*, Inorg. Chem. *3*, 796 (1964).
[8] *S. Herzog, R. Taube*, Z. Chem. *2*, 208 (1962); cf. also *E. König*, Z. Naturforsch. *A 19*, 1139 (1964).
[9] *E. O. Fischer, K. Öfele*, Chem. Ber. *90*, 2532 (1957); *Th. Kruck, ibid. 97*, 2018 (1964); *J. H. Behrens, K. Meyer, A. Müller*, Z. Naturforsch. *B 20*, 74 (1965).
[10] *F. Hein, K. Kartte*, Z. Anorg. Allg. Chem. *307*, 22 (1960); *E. O. Fischer, J. Seeholzer, ibid. 312*, 244 (1961).

Octalene[**]

By *Emanuel Vogel, Hans-Volker Runzheimer, Frank Hogrefe, Bernd Baasner*, and *Johann Lex*[*]

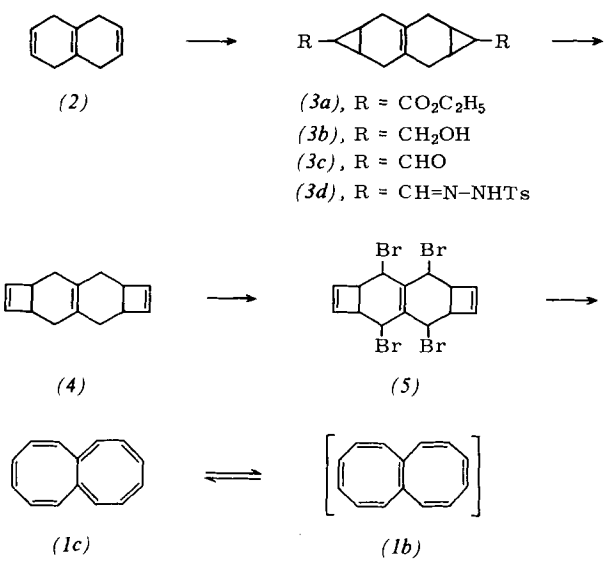
Dedicated to Professor Otto Bayer on the occasion of his 75th birthday

Annulenoannulenes[1], bicyclic ring systems consisting of two *ortho*-condensed annulenes, are presently one of the main topics of interest in the field of "non-benzenoid aromatics". Of the various representatives of these annulene derivatives the [4*n*]annuleno[4*n*]annulenes made up of two [4*n*]annulenes are of special interest, since unlike their structural units they possess $(4n+2)$ π-electrons and thus possibly constitute a new class of aromatic compounds.



(1a) *(1b)* *(1c)*

The prototype of the [4*n*]annuleno[4*n*]annulenes is the 14π-system octalene *(1)* ([8]annuleno[8]annulene), the eight-membered ring homolog of naphthalene. All previous attempts to synthesize compound *(1)* have so far failed[2,3]. Hence the question whether *(1)* has an aromatic [*(1a)*] or an olefinic structure [*(1b)* and/or *(1c)*] has hitherto been dealt with merely on a theoretical basis[4]. According to recent calculations[4b-4f] the resonance stabilization of a planar octalene is not sufficient (deficit of *ca.* 50 kcal/mol)[4b] to overcome the strain on planarization of the two eight-membered rings. Consequently, a nonplanar olefinic structure is proposed for *(1)*. This prediction leaves the double-bond isomerism in *(1)*, which has hardly been dealt with in previous work[5], as the actual octalene structural problem.



(2) *(3a)*, R = $CO_2C_2H_5$; *(3b)*, R = CH_2OH; *(3c)*, R = CHO; *(3d)*, R = CH=N–NHTs

(4) *(5)*

(1c) *(1b)*

In this communication we wish to report the synthesis of octalene and some of its properties.

The concept of preparing *(1)* from the tetracycle *(4)* was the deciding factor for selection of the recently described 2:1 adduct *(3a)*[6] of ethyl diazoacetate to isotetralin *(2)* as starting compound. The dialdehyde *(3c)* required for the cyclopropane→cyclobutene ring expansion was most advantageously obtained by reduction of *(3a)* with lithium aluminum hydride in ether and oxidation of the resulting diol *(3b)* [m.p. 164—165 °C (from ethyl acetate); yield 95 %] with chromium trioxide/pyridine. Chromatographic work-up on silica gel (CH_2Cl_2) and subsequent recrystallization from ethyl acetate afforded colorless *(3c)* [m.p. 172—173 °C; yield 53 %; ^{1}H-NMR ($CDCl_3$): δ = 1.62—1.94 (m, 6 cyclopropyl-H), 1.94—2.54 (m, 8 allyl-H), 9.20 (d, 2 aldehyde-H); IR (KBr): 1680 cm^{-1} (C=O)].

Reaction of *(3c)* with *p*-toluenesulfonyl hydrazide in boiling ethanol smoothly afforded the ditosylhydrazone *(3d)* [m.p. 230—232 °C (dec.); yield 83 %]. On heating *(3d)* with sodium methoxide in 3-ethyl-3-pentanol at 140 °C (1 h), a mixture of the hydrocarbons *(4)*, *(2)*, and tricyclo[6.4.0.$0^{3,6}$]dodeca-1(8),4,10-triene was obtained, from which *(4)* crystallized out on addition of a little ethanol and cooling to −20 °C (15 hours' standing) [colorless needles (from ethanol), m.p. 74—75 °C; yield 15 %; ^{1}H-NMR (CCl_4): δ = 1.65—2.45 (m, 8 sec. allyl-H), 2.97 (m, 4 tert. allyl-H), 5.85 (s, 4 olefinic H); IR (KBr): 1620 cm^{-1} (cyclobutene C=C stretching vibration)].

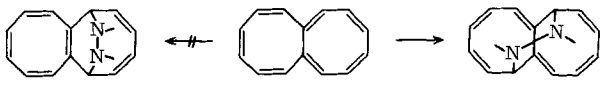
(4) reacts relatively rapidly (15 min) with a 4.4-fold molar amount of *N*-bromosuccinimide in boiling carbon tetrachloride in the presence of azoisobutyronitrile to give a mixture of bromides, from which an oily fraction consisting essentially of tetrabromides [*(5)*] can be isolated by chromatography on silica gel (CH_2Cl_2). Since attempts to carry out a separation of isomers led to high losses, the crude tetrabromide fraction was directly dehalogenated with sodium iodide in acetone (reflux, 24 h) (this and the following operations were carried out with stringent exclusion of air). The dehalogenated product was taken up in pentane (yellow solution) and chromatographed on silica gel (pentane). On removal of solvent there remained a dark yellow liquid mixture of hydrocarbons, the main component (*ca.* 70 %) of which was isolated by preparative gas chromatography (SE 30 column, 170 °C) and subsequent short-path distillation. The pure hydrocarbon thus obtained, an extremely air-sensitive lemon-yellow liquid of b.p. 50—52 °C/1 torr and m.p. −5 to −4 °C [yield 8—10 % referred to *(4)*] was, as will be shown below, the desired octalene.

The ^{1}H-NMR spectrum (CCl_4) of the hydrocarbon shows only olefinic absorption, at δ = 5.65 (m, 10H) and δ = 6.30 [d with J = 12 Hz (A part of an AB system), 2H]. A similar absorption pattern (multiplet with a superposed 2-proton doublet) is observed in the spectrum of 7,8-dimethylenecyclooctа-1,3,5-triene[7]. This finding would suggest that octalene has the structure *(1c)*. In agreement with this the ^{13}C-NMR spectrum of the compound [($CDCl_3$/TMS): δ = 142.62, 136.34, 131.46, 131.43, 129.01, 127.59, 126.90] exhibits seven signals—a four-line spectrum would be expected for the double bond isomer *(1b)*—, of which one is due to quaternary C atoms. Since *(1c)* is chiral, implying the presence of 14 different carbon atoms, the room-temperature ^{13}C-NMR spectrum

[*] Prof. Dr. E. Vogel, Dipl.-Chem. H.-V. Runzheimer, Dipl.-Chem. F. Hogrefe, Dr. B. Baasner
Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)
Dr. J. Lex
Institut für Anorganische Chemie der Universität
Greinstrasse 6, D-5000 Köln 41 (Germany)

[**] Based on a Plenary lecture delivered at the III. International Symposium on Novel Aromatic Compounds (ISNA), San Francisco, August 1977.

must represent an averaged spectrum arising by rapid conformational processes. Support for this explanation follows from the observed change in shape of the ^{13}C-NMR spectrum on lowering the temperature[8]. The remaining spectra of the hydrocarbon [UV (cyclohexane): $\lambda_{max} = 315$ nm ($\varepsilon = 3300$); IR (neat): 1600, 1621, 1660 cm^{-1} (C=C valence vibration); mass spectrum: $m/e = 180$ (M^+, 35 %), 179 (100 %), 178 (88 %), 165 (65 %), 153 (23 %), 152 (45 %)] though less informative are nevertheless consistent with the olefinic octalene structure *(1c)*.



(6) *(1c)* *(7)*

Independent proof of the presence of octalene has in the meantime been provided by an X-ray structural analysis carried out by *J. Lex*[9] on the 1:1 adduct [m.p. 165—166 °C (dec.); yield 30 %] obtained on reaction of the hydrocarbon with 4-phenyl-1,2,4-triazolinedione (PTAD) in acetone at room temperature. According to the analysis, the adduct does not have the structure *(6)* which could have been expected from the behavior of 7,8-dimethylenecycloocta-1,3,5-triene towards dienophiles (1,4-addition with participation of the exocyclic double bonds)[7b], but the structure *(7)*. An attractive possible explanation for the formation of *(7)* is provided by the assumption of a thermally allowed synchronous [8+2] cycloaddition[10] of PTAD to *(1c)*. Since PTAD is ascribed an electrophilic nature[11], there remains, however, the mechanistic alternative that *(7)* is formed from octalene *via* a zwitterionic homotropylium intermediate.

A representation of the three-dimensional structure of the adduct *(7)* is given in Figure 1. Remarkably, *(7)* is distinguished by a twofold symmetry axis. Also worthy of mention is the 90.3° torsion angle C6—C7—C7′—C6′, for this explains why *(7)* is colorless despite the presence of six conjugated double bonds.

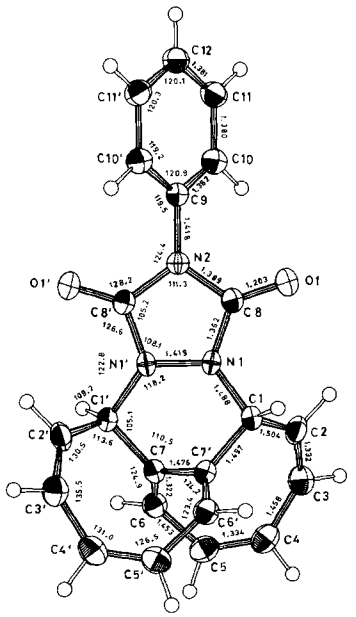


Fig. 1. Molecular structure of the 1:1-adduct *(7)* of octalene and 4-phenyl-1,2,4-triazolinedione.

The search for the double-bond isomer *(1b)* of octalene has so far met without success[12]. Obviously *(1b)* is so strongly disfavored energetically compared to *(1c)* that it does not play a significant role in the presumed equilibrium between the two double bond isomers.

Received: August 1, 1977 [Z 856a IE]
revised: October 10, 1977
German version: Angew. Chem. *89*, 909 (1977)

CAS Registry number:
Octalene, 257-55-6

[1] a) *T. M. Cresp, F. Sondheimer*, J. Am. Chem. Soc. *97*, 4412 (1975); b) *T. Kashitani, S. Akiyama, M. Iyoda, M. Nakagawa, ibid. 97*, 4424 (1975); c) *S. Akiyama, M. Iyoda, M. Nakagawa, ibid. 98*, 6410 (1976); d) *T. M. Cresp, F. Sondheimer, ibid. 99*, 194 (1977).

[2] a) *A. Streitwieser, Jr., S. Andreades* (unpublished experiments) cited in *A. Streitwieser, Jr.*: Molecular Orbital Theory for Organic Chemists. Wiley, New York 1961; b) *R. Breslow, W. Horspool, H. Sugiyama, W. Vitale*, J. Am. Chem. Soc. *88*, 3677 (1966); c) *S. Ozawa*, Diss. Abstr. B *27* (7—9), 2656 (1967); d) *J. A. Elix, M. V. Sargent, F. Sondheimer*, J. Am. Chem. Soc. *92*, 973 (1970).

[3] For the generation of [4]annuleno[4]annulene (butalene) see: *R. Breslow, J. Napierski, T. C. Clarke*, J. Am. Chem. Soc. *97*, 6275 (1975); some derivatives of [4]annuleno[8]annulene having olefinic properties are described by *G. Schröder, H. Röttele*, Angew. Chem. *80*, 665 (1968); Angew. Chem. Int. Ed. Engl. *7*, 635 (1968).

[4] a) *D. P. Craig*, J. Chem. Soc. *1951*, 3175 (in this first theoretical study of octalene an aromatic structure was postulated for the hydrocarbon; see, however, the following works); b) *N. L. Allinger, C. Gilardeau*, Tetrahedron *1967*, 1569; c) *D. H. Lo, M. A. Whitehead*, J. Am. Chem. Soc. *91*, 238 (1969); d) *M. J. S. Dewar, C. de Llano, ibid. 91*, 789 (1969); e) *B. A. Hess, Jr., L. J. Schaad, ibid. 93*, 305 (1971); f) *M. Randić, ibid. 99*, 444 (1977).

[5] In the detailed theoretical analysis of the molecular structure and the electronic spectrum of octalene by *N. L. Allinger* [4b] the possible existence of *(1c)* was not taken into consideration.

[6] *E. Vogel, F. Hogrefe*, Angew. Chem. *86*, 779 (1974); Angew. Chem. Int. Ed. Engl. *13*, 735 (1974).

[7] a) *F. A. L. Anet, B. Gregorovich*, Tetrahedron Lett. *1966*, 5961; b) *J. A. Elix, M. V. Sargent, F. Sondheimer*, Chem. Commun. *1966*, 508; J. Am. Chem. Soc. *92*, 962 (1970).

[8] *J. F. M. Oth, K. Müllen, H.-V. Runzheimer, P. Mues, E. Vogel*, Angew. Chem. *89*, 910 (1977); Angew. Chem. Int. Ed. Engl. *16*, 872 (1977).

[9] The adduct *(7)* crystallizes monoclinically (4 molecules per unit cell) in the space group C2/c; lattice constants: $a = 15.161(3)$, $b = 13.247(3)$, $c = 9.835(3)$ Å; $\beta = 124.65(2)°$; $d_{calc} = 1.453$, $d_{exp} = 1.44$ g/cm^3. 1447 independent reflections were measured on an automatic single crystal diffractometer (CAD-4, Enraf Nonius) with Mo-K_α radiation ($3° \leq \theta \leq 30°$, $I \geq 2\sigma_I$). Use of direct methods permitted determination of the positional parameters of the heavy atoms. The hydrogen atoms were located by difference Fourier synthesis. Refinement of the atomic parameters by the method of least squares (C,N,O anisotropic, H isotropic) converged to an *R*-value of 0.041.

[10] Cf. also the [8+2] cycloaddition of acetylenedicarboxylic ester to heptafulvene: *W. v. E. Doering, D. W. Wiley*, Tetrahedron *11*, 183 (1960).

[11] a) *R. Huisgen, W. E. Konz, U. Schnegg*, Angew. Chem. *84*, 765 (1972); Angew. Chem. Int. Ed. Engl. *11*, 715 (1972); b) *H. Isaksen, J. P. Snyder*, Tetrahedron Lett. *1977*, 889.

[12] On the existence of double-bond isomers in substituted cyclooctatetraenes see *L. A. Paquette*, Tetrahedron *1975*, 2855.

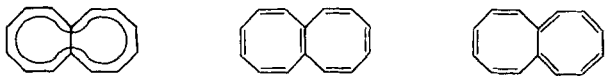
Configuration, Conformation, and Dynamics of Octalene

By *Jean F. M. Oth, Klaus Müllen, Hans-Volker Runzheimer, Peter Mues*, and *Emanuel Vogel*[*]

We were recently able to demonstrate by ^{13}C-NMR spectroscopy that the 12π-system heptalene contains alternating

[*] Prof. Dr. J. F. M. Oth, Priv.-Doz. Dr. K. Müllen
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule
Universitätstrasse 16, CH-8092 Zürich (Switzerland)
Dipl.-Chem. H.-V. Runzheimer, P. Mues, Prof. Dr. E. Vogel
Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)

single and double bonds and undergoes a rapid isodynamic π-bond shift[1]. The method has also proved useful for gaining an insight into the π-bonding and conformational features in the case of the 14π-system octalene[2]. We report here on the double bond configuration, conformation, and dynamics of the octalene molecule[3].



(1a) *(1b)* *(1c)*

The room-temperature ^{13}C-NMR spectrum of octalene (Fig. 1b) shows seven signals, one of which is ascribed to quaternary C-atoms. This finding ruled out both the configuration with central double bond *(1b)*[4] (conformations with C_{2h} or C_{2v} symmetry[3]) as well as the aromatic structure *(1a)* with planar eight-membered rings[5], for in each of these cases only a four-line spectrum is to be expected.

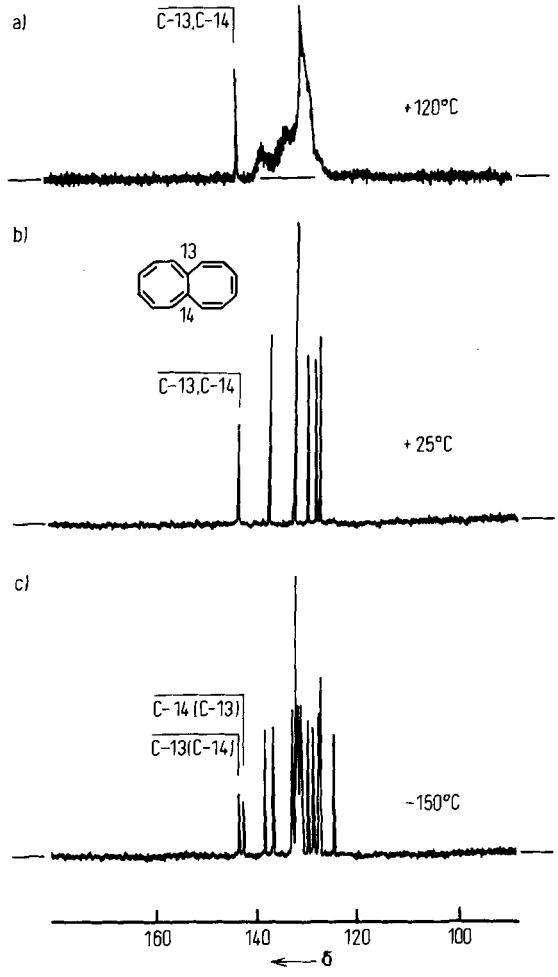


Fig. 1. ^{13}C-NMR spectra (25 MHz, ^{1}H-decoupled) of octalene at a) +120°C, b) +25°C (here coincidental overlapping of two signals occurs), c) −150°C.

At first sight the observed ^{13}C-NMR spectrum (and likewise the more recently analyzed 360-MHz ^{1}H-NMR spectrum[6]) is consistent only with a structure of type *(1c)*, in which no rapid π-bond shift takes place. This interpretation raises some problems, if the conformation of the molecule is considered. The most plausible conformation of *(1c)* is constructed from tub shaped cyclooctatetraene and cyclooctatriene fragments which have a common single bond. Such a three-dimensional structure with C_1 symmetry (Fig. 2) is chiral and should not show seven but 14 chemical shifts.

In this connection it is informative that the ^{13}C-NMR spectra are temperature-dependent: a broadening of all signals takes place below −100°C. Further lowering of the temperature leads to splitting. As expected, at −150°C a 14-line spectrum is obtained (Fig. 1c). This temperature dependence may be regarded as due to conformational processes, namely independent ring inversions of the cyclooctatetraene and cyclooctatriene fragments. The inversion of each of these rings is an isodynamic process, which effects the pairwise averaging of the 14 magnetic environments.

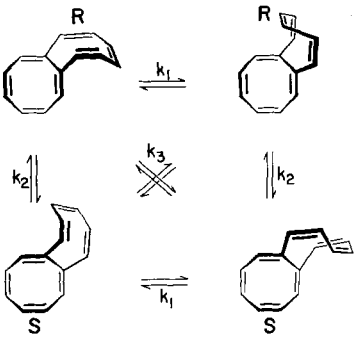


Fig. 2. Conformational mobility of octalene.

The presence of three consecutive single bonds in the cyclooctatriene ring would suggest that its inversion (k_1) proceeds much more rapidly than that of the cyclooctatetraene ring (k_2). As can be deduced from Figure 2 the same exchange is expected irrespective of which of the two rings inverts. An analysis of the NMR line shape thus will afford only the sum k_1+k_2 of the rate constants of the two inversion processes. A value of *ca.* 300 s^{-1} is obtained for k_1+k_2 from the ^{13}C-NMR spectrum at −115°C. Assuming $k_1 \gg k_2$ this affords a value of $\Delta G^{\neq}(k_1) \approx 8$ kcal/mol for the free enthalpy of activation for the inversion of the cyclooctatriene ring.

The conformational mobility of octalene includes a remarkable stereodynamic situation: while one enantiomeric form is converted into the other form (R⇌S) by inversion of the cyclooctatetraene ring, the stereochemistry remains unchanged after inversion of the cyclooctatriene ring. The synchronous inversion of both rings (k_3) would also lead to an enantiomer interconversion but would leave the magnetic environments of the nuclei (in achiral solvents) unaltered.

The dynamic process k_3 implicates a transition state with planarized perimeter. The occurrence of a peripheral π-bond shift in the octalene is coupled with the same geometrical prerequisite[7a,7b]. The possibility that such an isodynamic process could take place prompted us to investigate the high-temperature ^{13}C-NMR spectra. Above 80°C a broadening of the signals occurs in the spectra, from which the signal of the quaternary carbon is revealingly excluded (Fig. 1a). Apparently this change of shape is determined by an isodynamic peripheral π-bond shift *(v)*. The 4-line spectrum to be expected in the region of rapid exchange has so far defied observation since the compound polymerizes at higher temperatures. From the line shape of the ^{13}C-NMR spectrum at 120°C the rate constant of the π-bond shift is determined as $v \approx 200$ s^{-1}; it corresponds to a free enthalpy of activation of $\Delta G^{\neq}(v) \approx 20$ kcal/mol.

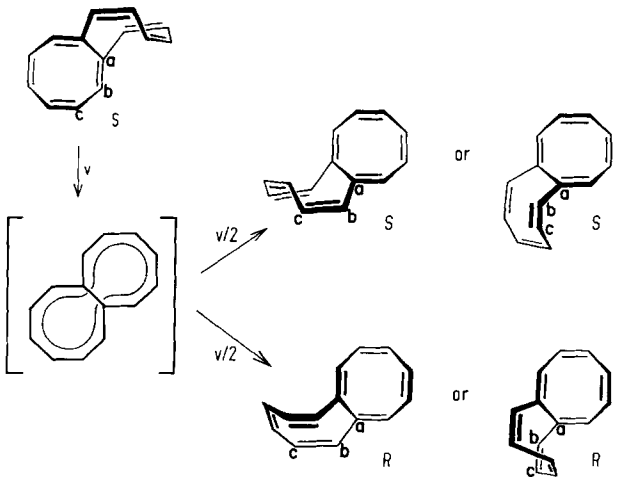


Fig. 3. π-Bond shift in octalene.

If one considers the planar structure *(1a)* with delocalized π bonds as the transition state of the π-bond shift, then $\Delta G^{+}(v) \approx \Delta H^{+}(v)$ corresponds to the difference of the enthalpy of formation of *(1a)* (planar) and *(1c)* (C_1 symmetry). This quantity is made up of the energy *demand*, ΔH_E, for planarization of both rings and the energy *gain*, ΔH_{STAB}, resulting from bond delocalization in the planar 14π-system. Since the experimentally inaccessible energy term ΔH_E can be estimated to be *ca.* 35 kcal/mol[8], a value of

$$\Delta H_{STAB} = \Delta H_E - \Delta H^{+}(v) \approx 15 \text{ kcal/mol}$$

is obtained for the stabilization energy.

That ΔH_{STAB} in the case of octalene with the planar structure *(1a)* is smaller than in the case of [14]annulene[9] must be attributed to the destabilizing effect of the central bond[10].

Eight isometric structures (4*R*, 4*S*) contribute to the dynamics of the octalene molecule. Each structure is interconvertible with any one of the other seven *via* one of the processes k_1, k_2, k_3 or v (Figures 2 and 3). The rate of enantiomer transformation is $k_2 + k_3 + v/2$. That the previously hypothetically assumed synchronous inversion of both rings (k_3) does in fact take place follows from the observed peripheral double bond migration v: the common transition state *(1a)* of the two processes reverts in the case of k_3 without effective π-bond shift into the ground state. The energy profiles of the dynamic processes by which an octalene structure is transformed into the seven other isometric structures are shown schematically in Figure 4.

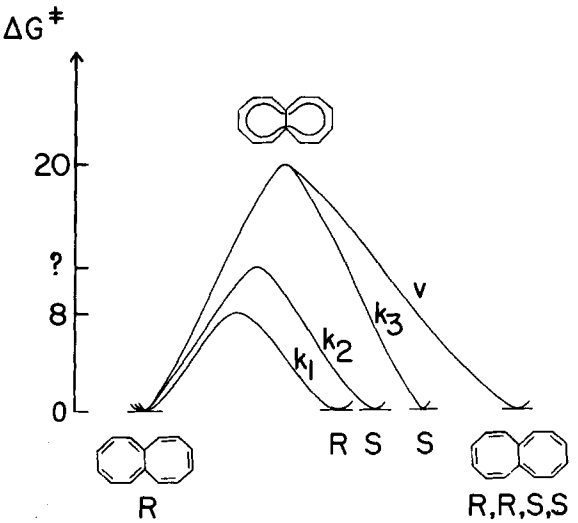


Fig. 4. Energy profiles for the transformations of octalene.

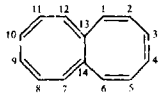
In the discussion of the energy hypersurface of octalene a structure of the type *(1b)* must also be taken into account. If the formation enthalpies of the octalene structures *(1c)* (C_1 symmetry) and *(1b)* (C_{2h} symmetry) are estimated on the basis of thermochemical group increments[11] the isomer *(1c)* would appear to be 5—6 kcal/mol more stable than *(1b)*[12]. The equilibrium between *(1c)* and *(1b)* which could adjust itself by a π-bond shift [again *via (1a)*], should therefore lie far over on the side of *(1c)*. At the same time it follows that a directed synthesis of *(1b)* is possible only at low temperature.

Received: August 25, 1977 [Z 856b IE]
revised: October 13, 1977
German version: Angew. Chem. *89*, 910 (1977)

CAS Registry number:
Octalene, 257-55-6

[1] *E. Vogel, H. Königshofen, J. Wassen, K. Müllen, J. F. M. Oth*, Angew. Chem. *86*, 777 (1974); Angew. Chem. Int. Ed. Engl. *13*, 732 (1974).
[2] *E. Vogel, H.-V. Runzheimer, F. Hogrefe, B. Baasner, J. Lex*, Angew. Chem. *89*, 909 (1977); Angew. Chem. Int. Ed. Engl. *16*, 871 (1977).
[3] The illustrated formulas describe the possible configurations without consideration of conformations. The latter are described more closely in a further text by their symmetry or by the spatial representation (see Figures).
[4] *N. L. Allinger, C. Gilardeau*, Tetrahedron *1967*, 1569.
[5] *D. P. Craig*, J. Chem. Soc. *1951*, 3175.
[6] The recording of the ^{1}H-NMR spectra at higher field strength (360 MHz) is made necessary by the small differences in the chemical shifts. The analysis of the room temperature spectrum, which is essentially simplified by decoupling experiments, affords six chemical shifts as well as some vicinal H,H coupling constants:

$\delta(H\text{-}1) = \delta(H\text{-}6) = 6.300$ ppm
$\delta(H\text{-}2) = \delta(H\text{-}5) = 5.706$ ppm
$\delta(H\text{-}3) = \delta(H\text{-}4) = 5.706$ ppm
$\delta(H\text{-}7) = \delta(H\text{-}12) = 5.693$ ppm
$\delta(H\text{-}8) = \delta(H\text{-}11) = 5.639$ ppm
$\delta(H\text{-}9) = \delta(H\text{-}10) = 5.780$ ppm



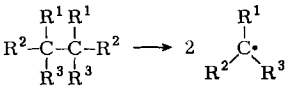
$J_{7,8} = J_{11,12} = 4.4$ Hz
$J_{8,9} = J_{10,11} = 13.3$ Hz
$J_{1,2} = J_{5,6} = 11.9$ Hz
$J_{9,10} = 7.0$ Hz.

[7] a) *J. F. M. Oth*, Pure Appl. Chem. *25*, 573 (1971); b) *K. Müllen*, Habilitationsschrift, ETH Zürich 1977.
[8] ΔH_E corresponds to the difference in the formation enthalpies of a hypothetical planar structure with localized double bonds and the real structure. The value of ΔH_E results from the activation enthalpy of the ring inversion in cyclooctatetraene (14 kcal/mol [7a]), from that for the inversion of the cyclooctatriene fragment (8 kcal/mol) and from that contribution which is due to the increased angular strain at the central bond and to the increasing non-bonding interaction of the hydrogen atoms.
[9] *J. F. M. Oth*, unpublished results.
[10] *D. H. Lo, M. A. Whitehead*, J. Am. Chem. Soc. *91*, 238 (1969).
[11] *G. J. Janz*: Thermodynamic Properties of Organic Compounds. Academic Press, New York, London 1967; *K. B. Wiberg*: Determination of Organic Structures by Physical Methods. Academic Press, New York, London 1971, Vol. 3, p. 207; *S. W. Benson*: Thermochemical Kinetics. Wiley, New York 1968.
[12] This value includes the gain in conjugation energy for a planar butadiene fragment in *(1c)* of 3.5 kcal/mol. It is further assumed that the ring strain is the same in *(1b)* (C_{2h} conformation) and *(1c)*.

Observation of a Linear Relationship Between Thermal Stability and Strain Energy of Alkanes[**]

By *Christoph Rüchardt, Hans-Dieter Beckhaus, Goetz Hellmann, Siegried Weiner*, and *Robert Winiker*[*]

C—C single bonds in hydrocarbons are cleaved homolytically between room temperature[1] and about 700 °C (ethane)[2], depending on the structure of the groups bound to the C atoms concerned.



This exceptionally high increase in thermolysis rate, corresponding to a factor of *ca.* 10^{30}, has, as yet, been explained only in an unsatisfactory qualitative manner[1]. Attempts at quantitative interpretation are almost completely lacking[3].

We have now found a linear relationship ($r = 0.98$) between free activation energies $\Delta G^{\neq}$ (300 °C)[4] of the thermolyses of a large number of aliphatic hydrocarbons[5] (see Tab. 1) and their strain energies E_s estimated by force-field calculations (see Tab. 1) according to *Engler-Schleyer*[6] (see Fig. 1).

$$\Delta G^{\neq} = -0.60(\pm 0.03)\,E_s + 65.6(\pm 1.0)\ \text{kcal/mol} \qquad \text{(I)}$$

This shows that the ground state strain energy of the alkanes is the crucial factor determining their thermal stability.

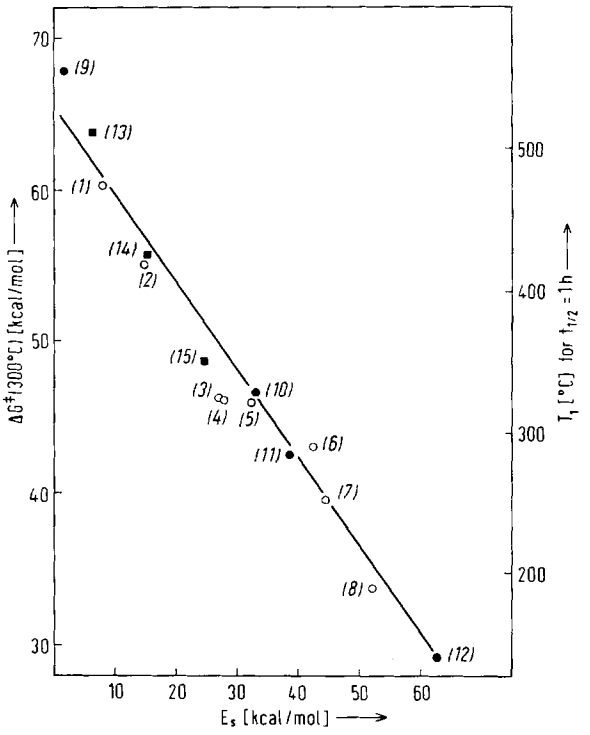


Fig. 1. Relationship between decomposition temperatures T_1 [°C] for $t_{1/2} = 1$ h [4], $\Delta G^{\neq}$ of thermolysis at 300 °C and strain energy E_s [6] of hydrocarbons mentioned in Table 1. ● = C_t—C_t series; ○ = C_q—C_q series; ■ = non-symmetrical bond cleavage.

Product analyses for compounds *(1)*—*(12)* show that bond cleavage occurs mainly at the central C—C bond; compounds *(13)*—*(15)* most likely lose a *tert*-butyl radical in the rate determining step of the thermolysis.

It is remarkable that this relationship is evidently independent of whether homolysis occurs between two quaternary C atoms [C_q—C_q series, *(1)*—*(8)* and *(15)*], between two tertiary C atoms [C_t—C_t series, *(9)*—*(12)*] or between a quaternary C atom and a tertiary [*(14)*] or a secondary

Table 1. Decomposition temperatures T_1 (for $t_{1/2} = 1$ h) [4], free activation enthalpies $\Delta G^{\neq}$ of thermolysis at 300 °C and strain energies E_s [a] of saturated aliphatic hydrocarbons $R^1R^2R^3C$—$CR^1R^2R^3$.

	R^1	R^2	R^3	T_1 [°C] ($t_{1/2} = 1$ h)	$\Delta G^{\neq}$ (300 °C) [kcal/mol]	E_s [a] [kcal/mol]
(1)	Me	Me	Me	490	60.5	7.8
(2)	Me	Me	Et	420	55.3	14.9
(3)	Me	Me	*i*-Pr	329	46.4	26.3
(4)	Me	Me	CH_2CMe_3	321	46.3	27.8
(5)	Me	Me	C_6H_{11}	315	45.8	32.1
(6)	Et	Et	Et	285	43.1	42.4
(7)	Me	Et	C_6H_{11}	250	39.6	44.3
(8)	Me	Me	*t*-Bu	195	33.7	51.8
(9)	Me	Me	H	565 [b]	68 [b]	2.0
(10)	*d,l*-C_6H_{11}	*t*-Bu	H	329	46.7	32.6
(11)	*meso*-C_6H_{11}	*t*-Bu	H	285	42.6	38.5
(12)	*t*-Bu	*t*-Bu	H	141	29.6	62.7
(13)	2,2,4,4-Tetramethylpentane [c]			502	63.9	6.4
(14)	2,2,3,4,4-Pentamethylpentane [c]			415	55.8	15.1
(15)	2,2,3,3,4,4-Hexamethylpentane [c]			350	48.8	24.9

[a] Enthalpy of formation ΔH_f calculated using force fields according to [6a], minus hypothetical enthalpy of formation of strain-free molecule [6b].
[b] *W. Tsang*, J. Chem. Phys. *43*, 352 (1965).
[c] In order to calculate T_1 ($t_{1/2} = 1$ h) the experimental rate data k_{exp} were subject to statistical correction, *viz* $k_1 = k_{exp}/2$, as two equivalent bonds per molecule can suffer homolysis.

[*] Prof. Dr. Chr. Rüchardt, Dr. H.-D. Beckhaus, Dr. G. Hellmann, Dipl.-Chem. S. Weiner, Dipl.-Chem. R. Winiker
Chemisches Laboratorium der Universität
Albertstr. 21, D-7800 Freiburg (Germany)

[**] Thermolabile Hydrocarbons, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Otto Röhm Gedächtnisstiftung.—Part 4: *H.-D. Beckhaus, G. Hellmann, C. Rüchardt*, Chem. Ber., in press.

C atom [(13)]. On the other hand, the deviation of the thermal stability of ethane from this correlation does indicate that the type of bond can be significant. The remarkable difference in stability of diastereomers (10) and (11)[5c] also results in quite different bond lengths[8].

According to the above relationship, the C—C bond energy of a hypothetical strain-free alkane is calculated as $D \approx 76$ kcal/mol[9], which is of the expected order of magnitude[10].

The slope of the straight line in Figure 1 shows that only 60% of the change in strain energy E_s is reflected in activation enthalpy differences $\Delta\Delta G^{+}$ and $\Delta\Delta H^{+}$. It can be concluded that about 40% of strain energy prevails at the transition state of the thermolysis reaction, obviously largely independent of structure. Therefore, for radical recombination, *i.e.* the reverse reaction of thermolysis, an activation energy corresponding to 40% of the ground state strain energy E_s is required.

Received: October 3, 1977 [Z 850 IE]
German version: Angew. Chem. 89, 913 (1977)

[1] *K. Ziegler*, Angew. Chem. *61*, 168 (1949).
[2] *A. Burcat, G. B. Skinner, R. W. Crossley, K. Scheller*, Int. J. Chem. Kinet. *5*, 345 (1973); and references cited therein.
[3] Cf. *H.-D. Beckhaus, C. Rüchardt*, Chem. Ber. *110*, 878 (1977).
[4] The temperature at which the halflife period of unimolecular decomposition is 1 h (see Fig. 1) is the more exact value, as it can be estimated without extrapolation. A linear correlation ($r = 0.998$) was found for T_1 [°C] ($t_{1/2} = 1$ h) against ΔG^{+} (300 °C).
[5] Results from [3] and a) Diplomarbeit *R. Winiker*, Universität Freiburg 1976; b) Diplomarbeit *S. Weiner*, Universität Freiburg 1977; c) Dissertation *G. Hellmann*, Universität Freiburg 1977.
[6] a) *E. M. Engler, J. D. Andose, P. v. R. Schleyer*, J. Am. Chem. Soc. *95*, 8005 (1973); b) *P. v. R. Schleyer, J. E. Williams, K. R. Blanchard, ibid. 92*, 2377 (1970).—The relationship in Figure 1 is all the more remarkable as the force field was parametrized for low-strained alkanes; thermochemical measurements afforded good agreement between calculated and experimentally estimated strain energies [5c, 7] for a number of compounds mentioned in Table 1.
[7] Diplomarbeit *G. Kratt*, Universität Freiburg 1976.
[8] *H.-J. Lindner, B. Kitschke*, unpublished results. Different P—P bond lengths in diastereomers of diphosphane complexes were reported recently: *G. Huttner, P. Friedrich, H. Willenberg, H.-D. Müller*, Angew. Chem. *89*, 268 (1977); Angew. Chem. Int. Ed. Engl. *16*, 260 (1977).
[9] Calculated according to $D = E_a = \Delta G^{+} - T\Delta S^{+} + 2RT$ with $\Delta S^{+} = 15$ cal/mol·K. By assuming an isentropical series the error is insignificant [5c].
[10] $D = 78.2$ kcal/mol was estimated for the central bond of 2,3-dimethylbutane: *K. W. Egger, A. T. Cocks*, Helv. Chim. Acta *56*, 1516, 1537 (1973).

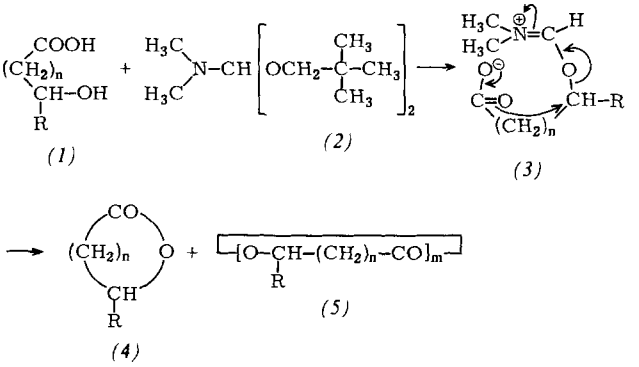
A New Lactone Synthesis

By *Helmut Vorbrüggen* and *Konrad Krolikiewicz*[*]

Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday

In the recently published cyclizations of ω-hydroxycarboxylic acids to medium or large lactone rings, activation of the carboxylic[1] or of the hydroxy groups[2] gives rise to polar intermediates in which the ends of the chains are attracted by opposite charges and thus react with each other[3].

Since the esterification of carboxylic acids with amide acetals[4,5] gives rise also to such a polar intermediate by activation of the alcoholic hydroxyl group, we have added slowly and simultaneously toluene solutions of ω-hydroxy acids[1] and *N,N*-dimethylformamide dineopentylacetal (2)[4] to boiling toluene. During this reaction the lactones (4) were formed *via* the polar intermediates (3) in yields of *ca.* 40—50% together with varying amounts of the oligomers (5) ($m = 2, 3, 4$)[6]. ω-Hydroxyoctanoic acid (1a) did not yield any monomeric lactone (4a) but only the oligomers (5a) ($m = 2, 3, 4$; cf. Table 1).



(1) (2) (3)

(4) (5)

$ClCH_2-(CH_2)_6-COO-CH_2CH_2Cl$

(6)

Table 1. Lactones (4) and (5) from ω-hydroxycarboxylic acids (1).

(1)	n	R	Reaction conditions	(4)	Yield [%] (5)		
					m=2	m=3	m=4
(a)	6	H	16 h/110 °C	—	14.3	10.8	9.2
(b)	10	n-C_6H_{13}	19 h/110 °C [a]	48.3	11.8	4.6	1.9
(c)	14	H	15 h/110 °C	40.0	16.6	3.9	1.4

[a] A concentrated solution of (1b) and (3) in methylene chloride gave on standing for 1 week at 24 °C some unreacted (1b) and a small amount of (4b) as well as a large amount of (5b) ($m = 2$).

As to be expected from intermediates of type (3), this lactonization occurs *via* a Walden inversion of a chiral center at the hydroxyl-carrying carbon atom. Optically active 12-hydroxystearic acid (1b) [$n = 10$, R = n-C_6H_{13}] thus afforded the lactone (4b) [CD (dioxane) $\lambda = 218$ nm, $\Delta\varepsilon = +0.589$] in 48% yield. Saponification of (4b) with methanolic KOH and a second lactonization with (2) gave the lactone (4b) [CD (dioxane) $\lambda = 218$ nm, $\Delta\varepsilon = -0.681$] with opposite configuration at C-12.

On using boiling 1,2-dichloroethane instead of toluene as solvent, the reaction of (1a) with (2) afforded the 2-chloroethyl ester (6) [$m/e = 161, 135, 122, 97$] as major product. The compound (6) is probably formed *via* attack of the carboxylate anion on 1,2-dichloroethane with formation of the β-chloroethyl ester and subsequent attack of the newly formed Cl^- on C-8 which is activated by reaction with (2)[7].

Procedure:

2.4 g (8 mmol) 12-hydroxystearic acid and 2.08 g (9 mmol) *N,N*-dimethylformamide dineopentylacetal were each dissolved in 100 ml anhydrous toluene and, using two special addition funnels (Normag No. 8056), added with stirring during 19 h to 100 ml boiling toluene. After two further hours' stirring at 130 °C the mixture was evaporated and the residue (3.0 g) chromatographed on 150 g Al_2O_3 (neutral, Woelm A III). After discarding the first 400 ml eluate, the next 1.5 l hexane afforded 1.092 g (48.3%) (4b) as colorless oil.

Received: October 17, 1977 [Z 863 IE]
German version: Angew. Chem. 89, 914 (1977)

[*] Prof. Dr. H. Vorbrüggen, K. Krolikiewicz
Research Laboratories of Schering AG, Berlin/Bergkamen
Postfach 650311, D-1000 Berlin 65 (Germany)

[1] *E. J. Corey, K. C. Nicolaou*, J. Am. Chem. Soc. *96*, 5614 (1974); *E. J. Corey, D. J. Brunelle, P. J. Stork*, Tetrahedron Lett. *1976*, 3405; *H. Gerlach, A. Thalmann*, Helv. Chim. Acta *57*, 2661 (1974); *S. Masamune, S. Kamata, W. Schilling*, J. Am. Chem. Soc. 97, 3515 (1975); *T. Mukaijama, M. Usui, K. Saigo*, Chem. Lett. *1976*, 49.
[2] *T. Kurihara, Y. Nakajima, O. Mitsunobu*, Tetrahedron Lett. *1976*, 2455.
[3] Compare review on macrolide synthesis: *K. C. Nicolaou*, Tetrahedron *33*, 683 (1977).
[4] *H. Brechbühler, H. Büchi, H. Hatz, J. Schreiber, A. Eschenmoser*, Angew. Chem. *75*, 296 (1963); Angew. Chem. Int. Ed. Engl. *2*, 212 (1963); Helv. Chim. Acta *48*, 1746 (1965).
[5] *H. Vorbrüggen*, Angew. Chem. *75*, 296 (1963); Angew. Chem. Int. Ed. Engl. *2*, 211 (1963); Justus Liebigs Ann. Chem. *1974*, 821.
[6] The oligomers were identified by mass spectrometry. For the field desorption mass spectra of *(5b)* [$m=3$ (M+H), $m/e=847$; $m=4$ (M+H), $m/e=1129$] we are indebted to *H. Schwarz*, Technische Universität Berlin.
[7] The possible conversion of primary and secondary alcohols with *(2)* and halide ions into the corresponding primary and secondary halides is being investigated.

Preparation and Reactions of a Cyclic Phosphaallene Ylide

By *Hans Jürgen Bestmann, Kurt Roth*, and *Rolf W. Saalfrank*[*]

In the crystalline state diethoxyvinylidenetriphenylphenylphosphorane *(1)* has a bent structure ($\sphericalangle PC_\alpha C_\beta = 125.6°$); however, the ^{1}H-NMR spectrum of a toluene solution shows only one sharp triplet and quartet for the two C_2H_5 groups. Hence we conclude that a fast inversion of the triphenylphosphonio group takes place in solution[1]. The structure of *(1)* suggests that cyclic phosphaallene ylides should also be capable of existence in the case of small rings[2]. We now report the synthesis and reactions of the first representative of this class of compounds.

If a solution of *(1)* in toluene is refluxed for 3 d then the crystalline product 1,3-diethoxy-1,1-diphenyl-1λ^5-phosphaindole *(5)* can subsequently be isolated (m.p., ^{1}H- and ^{31}P-NMR data, and yields of all new compounds are listed in Table 1). We consider the following mechanism to account for the formation of *(5)* from *(1)*: the phosphaallene ylide *(1)* first rearranges to *(3)*; it has not yet been established whether the phosphonium alkoxide *(2)* occurs as intermediate[3]. Compound *(3)* can be described in terms of the two principal limiting structures *(3A)* and *(3B)* which differ in their geometry and electron distribution. Reaction proceeds from *(3B)* in which intramolecular electrophilic attack by the C_β atom on one of the phenyl groups furnishes the intermediate σ complex *(4)*, which stabilizes by proton migration to form *(5)*.

The action of acetyl chloride on *(5)* leads to ethyl acetate and the phosphonium chloride *(6)*. The latter can be converted by sodium bis(trimethylsilyl)amide[4] at −25 °C into the five-membered cyclic phosphaallene ylide *(7)*, which is isolable in crystalline form. The compound can be stored for a limited period with cooling. The strong negative shift of the phosphorus signal in the ^{31}P-NMR spectrum [$\delta = -38.5$] relative to that of *(1)* [$\delta = -2.8$] is particularly striking.

The following reactions of *(7)* provide proof of its structure: Ethanol is added to form *(5)*[3]. Hydrolysis in an aqueous medium leads to the phosphane oxide *(8)*, also formed from *(5)* under the same conditions. Compound *(7)* reacts with methyl iodide to form the phosphonium iodide *(11)*.

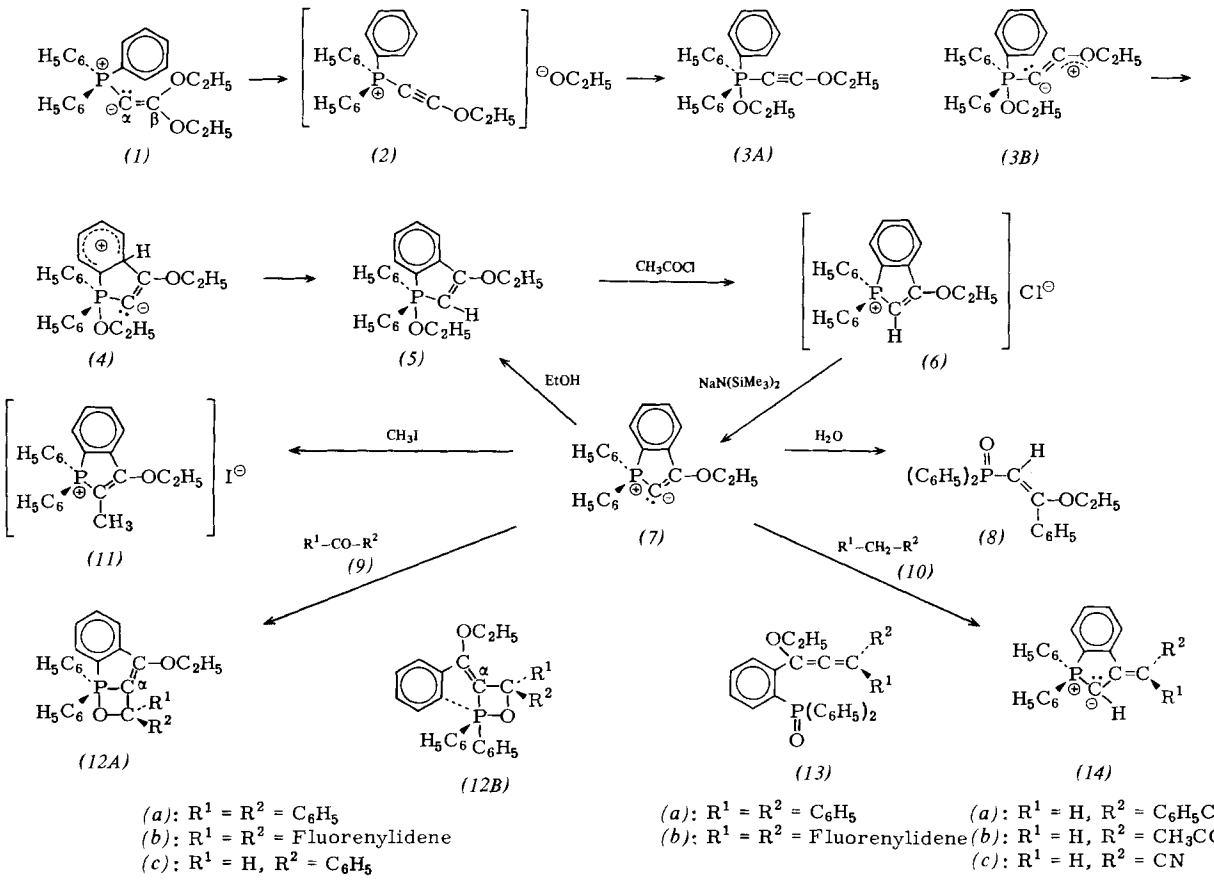
Particular interest attaches to the reaction of *(7)* with carbonyl compounds in connection with mechanistic considerations concerning the course of the Wittig reaction. The phosphaallene ylide *(7)* reacts with aldehydes or ketones which do not possess an acidic CH_2 group to form the crystalline primary products of the Wittig reaction *(12A)*. The given arrangement of ligands on the pentacoordinated phosphorus (^{31}P-NMR: $\delta = +52.0$ to $+57.6$) is based on the known rules concerning the entry and departure of nucleophilic groups in interconversion of tetra- and pentacoordinated phosphorus compounds[5] and on the X-ray structure analysis of the adduct formed from hexaphenylcarbodiphosphorane with hexafluoroacetone[6]. Rupture of the P—C bond in the 1,2-oxaphosphetanes *(12A)* should only be possible if a ligand rearrangement of *(12A)* directed towards *(12B)* becomes effective[5]. How-

Table 1. Melting points, NMR data, and yields.

Compound	M.p. [°C]	^{31}P-NMR [a]	^{1}H-NMR (τ-values) OCH_2	OCH_2CH_3	P—C—*H* (J_{PH} in Hz)	Yield [%]
(5)	189 (dec.)	+73.6 [b]	6.65 [b] 5.98	8.97 8.80	4.92 (19)	81
(6)	182 (dec.)	−26.6 [c]	5.27 [c]	8.43	2.80 (22)	91
(7)	>60 (dec.)	−38.5 [b]	4.84 [b]	8.50		93
(8)	151	−20.0 [c]	5.96 [c]	8.60	4.68 (10)	81
(11)	175 (dec.)	−31.0 [c]	5.06 [c]	8.44	7.57 (15) [d]	62
(12a)	135 (dec.)	+57.6 [c]	6.05 [c]	8.98		74
(12b)	178 (dec.)	+56.9 [c]	6.68 [c]	9.23		70
(12c)	139 (dec.)	+52.0 [c]	6.10 [c, e]	8.89	4.40 (13.5) [f]	83
(13a)	179	−30.7 [c]	6.65 [c]	9.16		96
(13b)	154	−31.2 [c]	6.48 [c]	9.24		76
(14a)	197 (dec.)	−26.1 [c]			3.25 (37)	48
(14b)	185 (dec.)	−26.1 [c]			3.67 (36)	46
(14c)	196 (dec.)	−21.5 [c]			5.84 (29)	45

[a] 100 MHz PFT technique, δ values rel. to ext. H_3PO_4. [b] In C_6D_6. [c] In $CDCl_3$. [d] P—C—CH_3 in place of P—C—H. [e] The CH_2 group appears as a multiplet owing to its diastereotopism. [f] P—O—CH and P—C—CH in place of P—C—H.

[*] Prof. Dr. H. J. Bestmann, Dipl.-Chem. K. Roth, Priv.-Doz. Dr. R. W. Saalfrank
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-8520 Erlangen (Germany)



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

(a): $R^1 = R^2 = C_6H_5$
(b): $R^1 = R^2$ = Fluorenylidene

(a): R^1 = H, $R^2 = C_6H_5CO$
(b): R^1 = H, $R^2 = CH_3CO$
(c): R^1 = H, R^2 = CN

ever, such a pseudorotation is extremely difficult for steric reasons. Compounds *(12A)* are therefore remarkably stable. When heated dry to above its melting point *(12a)* undergoes 96% conversion into the allene *(13a)* (IR: $\nu_{C=C=C}$ 1933, $\nu_{P=O}$ 1198 cm^{-1}). After several hours' heating of *(12b)* in boiling toluene 76% of the allene *(13b)* (IR: $\nu_{C=C=C}$ 1930, $\nu_{P=O}$ 1197 cm^{-1}) and 8% of fluorenone are isolated, the latter being formed by retro-cycloaddition.

Compounds having acidic CH_2 groups [*(10)*, R^1 and R^2 are groups exerting a $-I$ effect] react with *(7) via* Michael addition and subsequent elimination of ethanol[7] to give the phosphaindoline ylides *(14)*, which are describable by several resonance structures.

Received: September 12, 1977 [Z 842 IE]
German version: Angew. Chem. *89*, 915 (1977)

CAS Registry numbers:
(1), 21882-77-9; *(1)* (ylide form), 53472-13-2; *(3A)*, 64627-16-3; *(5)*, 64627-15-2; *(6)*, 64627-14-1; *(7)*, 64627-13-0; *(7)* (ylide form), 64627-00-5; *(8)*, 64627-12-9; *(9a)*, 119-61-9; *(9b)*, 486-25-9; *(9c)*, 100-52-7; *(10a)*, 28652-72-4; *(10b)*, 67-64-1; *(10c)*, 75-05-8; *(11)*, 64627-11-8; *(12a)*, 64627-10-7; *(12b)*, 64627-09-4; *(12c)*, 64627-08-3; *(13a)*, 64627-07-2; *(13b)*, 64627-06-1; *(14a)*, 64627-05-0; *(14a)* (ylide form), 64627-01-6; *(14b)*, 64627-04-9; *(14b)* (ylide form), 64627-02-7; *(14c)*, 64627-03-8; *(14c)* (ylide form), 64626-99-9

[1] Review: *H. J. Bestmann*, Angew. Chem. *89*, 361 (1977); Angew. Chem. Int. Ed. Engl. *16*, 349 (1977).
[2] A cyclic phosphaallene ylide has been postulated as intermediate: *H. A. E. Aly, J. H. Barlow, D. R. Russel, D. J. H. Smith, M. Swindles, S. Tripett*, J. Chem. Soc. Chem. Comm. *1976*, 449.
[3] Cf. *H. Schmidbaur, H. Stühler, W. Buchner*, Chem. Ber. *106*, 1238 (1973).
[4] *H. J. Bestmann, W. Stransky, O. Vostrowsky*, Chem. Ber. *109*, 1694 (1976).
[5] Cf. *D. Marquarding, F. Ramirez, I. Ugi, P. Gillespie*, Angew. Chem. *85*, 99 (1973); Angew. Chem. Int. Ed. Engl. *12*, 91 (1973).
[6] *G. Chioccola, J. J. Daly*, J. Chem. Soc. *A 1968*, 568. Concerning the adducts of akylidenetriphenylphosphoranes and ketenes, cf. *G. Wittig, A. Haag*, Chem. Ber. *96*, 1535 (1963).
[7] *H. J. Bestmann, R. W. Saalfrank*, Chem. Ber. *109*, 403 (1976); *H. J. Bestmann, M. Ettlinger, R. W. Saalfrank*, Justus Liebigs Ann. Chem. *1977*, 276.

Simple Stereoselective Synthesis of Eburnamonine[**]

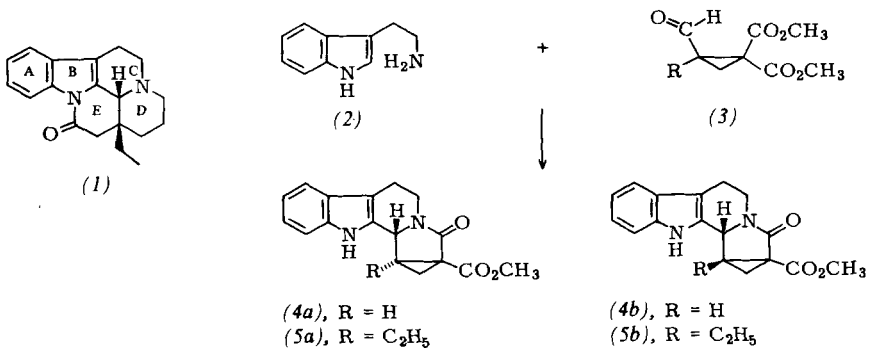
By *Friederike Klatte, Ulrich Rosentreter*, and *Ekkehard Winterfeldt*[*]

The regioselective ring-opening of cyclopropane derivatives with defined configurations can be used for the stereoselective synthesis of sp^3-hybridized centers[1]. In the intensively studied field of vincamines[2] we first chose to study the synthetic potential of eburnamonine *(1)* in which the *cis*-D,C linkage represents the critical stereochemical problem in this series.

We found a high degree of selectivity in the condensation of cyclopropanaldehyde *(3)*[3] with tryptamine *(2)*. When R = H, *(4a)* (*trans* isomer) is isolated exclusively as the kinetic product, and also when $R = C_2H_5$ the main product (85%) is *(5a)*—with only 15% of *(5b)* being formed. During the cyclization the indole residue thus attacks, in all cases, from the side which is turned away from the cyclopropane system. When R = H the configuration can easily be assigned with

[*] Prof. Dr. E. Winterfeldt, F. Klatte, Dipl.-Chem. U. Rosentreter
Organisch-chemisches Institut der Technischen Universität
Schneiderberg 1 B, D-3000 Hannover 1 (Germany)

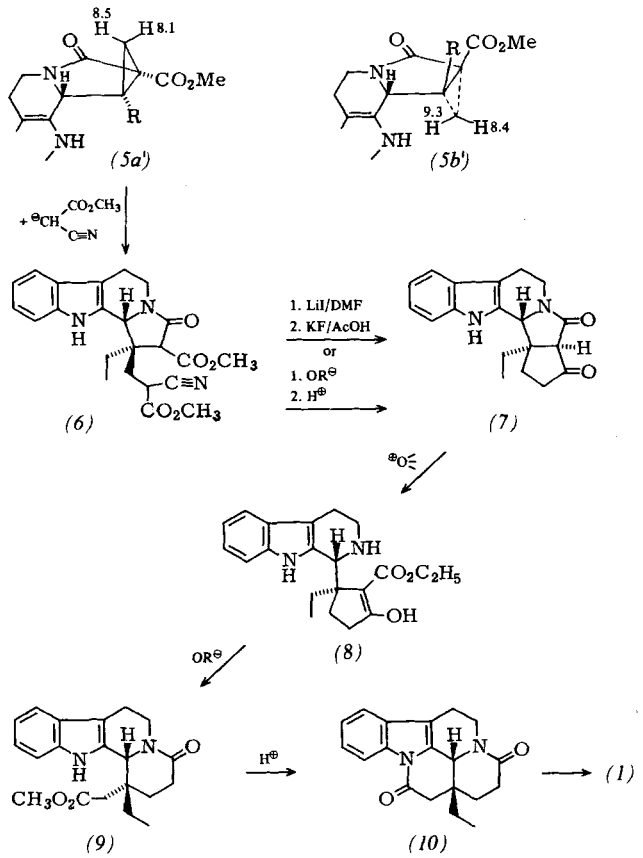
[**] Reactions of Indole Derivatives, Part 36. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (*U. R.* thanks the Fonds der Chemischen Industrie for a Promotionsstipendium).—Part 35: *J. Müller, E. Winterfeldt*, Chem. Ber., in the press.



(1) (2) (3)

(4a), R = H (4b), R = H
(5a), R = C_2H_5 (5b), R = C_2H_5

the aid of the coupling constants of the crucial hydrogen atoms (*trans* coupling $J = 0$ Hz, *cis* coupling $J = 5.5$ Hz[4]); this is confirmed by the unusually large chemical shift of one of the cyclopropane protons of *(4b)* (obtained by the action of base on *(4a)*[5]) which is shielded by the indole aromatic ring in the *cis* position. Ring-opening reactions with *(5a)* proceed with excellent regioselectivity; with the Li salt of methyl cyanoacetate *(6)* is formed as the only reaction product. *(6)* can be converted to the lactam ketone *(7)* by two different routes (see formula scheme), with triethyloxonium hexafluorophosphate and subsequent hydrolysis *(7)* yields the β-ketoester *(8)*.



(5a') (5b') (6) (7) (8) (9) (10) (1)

Treatment of *(8)* with methoxide and subsequent reesterification affords the lactam ester *(9)* with a high degree of selectivity; *(9)* forms the dilactam *(10)* in trifluoroacetic acid at room temperature. Selective reduction according to the procedure of *Borch*[6] finally gives a good yield of eburnamonine *(1)* which shows identity with an authentic sample in all its properties[7].

Received: September 13, 1977 [Z 840 IE]
German version: Angew. Chem. *89*, 916 (1977)

CAS Registry numbers:
(1), 2580-88-3; *(2)*, 61-54-1; *(3a)*, 55502-70-0; *(3b)*, 64585-90-6; *(4a)*, 64625-58-7; *(4b)*, 64585-89-3; *(5a)*, 64625-57-6; *(5b)*, 64585-88-2; *(6)*, 64585-87-1; *(7)*, 64585-86-0; *(8)*, 64585-85-9; *(9)*, 64585-84-8; *(10)*, 64585-83-7; Li salt of methyl cyanoacetate, 64585-82-6

[1] Cf. *S. Danishefsky, R. K. Singh*, J. Am. Chem. Soc. *97*, 3239 (1975); *S. Danishefsky, G. Rovnyak*, J. Org. Chem. *40*, 114 (1975); *R. K. Singh, S. Danishefsky, ibid. 41*, 1668 (1976); *S. Danishefsky, R. Doehner*, Tetrahedron Lett. *1977*, 3031; *K. Kondo, E. Hiro, D. Tunemoto, ibid. 1976*, 4489; *K. Kondo, T. Umemoto, Y. Takahatake, D. Tunemoto, ibid. 1977*, 113; *D. Tunemoto, N. Araki, K. Kondo, ibid. 1977*, 109; *J. F. Ruppert, J. D. White*, J. Chem. Soc. Chem. Commun. *1976*, 976.

[2] Cf. *P. Pfäffli, W. Oppolzer, R. Wenger, H. Hauth*, Helv. Chim. Acta *58*, 1131 (1975); *J. L. Herrmann, G. R. Kieczykowski, S. E. Normandin, R. H. Schlessinger*, Tetrahedron Lett. *1976*, 801; *A. Buzas, C. Herisson, G. Lavielle*, C. R. Acad. Sci. *C 283*, 763 (1976); *D. Cartier, J. Levy, J. LeMen*, Bull. Soc. Chim. Fr. *1976*, 1961; *K. H. Gibson, J. E. Saxton*, Tetrahedron *33*, 833 (1977); and references cited therein.

[3] We used a modified procedure of *D. T. Warner* (J. Org. Chem. *24*, 1536 (1959)) for the synthesis of *(3a)* (R = H) and *(3b)* (R = C_2H_5).

[4] *K. L. Williamson*, J. Am. Chem. Soc. *85*, 516 (1963).

[5] Details of the distribution of the stereoisomers and thermodynamic control will be given in a later publication.

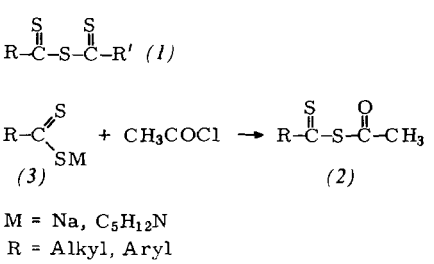
[6] *R. F. Borch*, Tetrahedron Lett. *1968*, 61.

[7] We thank Dr. *H. Hauth* (Sandoz AG, Basel) for the comparison sample of eburnamonine. All compounds mentioned gave correct elemental analyses and were characterized spectroscopically.

Isolation of Acyl Thioacyl Sulfides

By *Shinzi Kato, Katsumi Sugino, Masatoshi Yamada, Tomonori Katada*, and *Masateru Mizuta*[*]

Whereas the preparation and characterization of the bis(thioacyl) sulfides *(1)* have already been reported[1], all previous attempts to isolate the acyl thioacyl sulfides *(2)*, which *Houben* and *Schultz*[2] had tried to synthesize as long ago as 1910, have so far failed.



(1) (3) (2)

M = Na, $C_5H_{12}N$
R = Alkyl, Aryl

[*] Prof. Dr. S. Kato [+], K. Sugino, M. Yamada, T. Katada, Prof. Dr. M. Mizuta
Department of Chemistry, Faculty of Engineering, Gifu University
Kagamihara, Gifu 504 (Japan)
[+] Author to whom correspondence should be addressed.

Table 1. Physical properties of the acyl thioacyl sulfides of type RC(S)—S—C(O)R'.

	R	R'	Yield [%]	m.p. [°C]	IR [b] [cm^{-1}] νC=O	νC=S	UV, Vis [c] λ_{max} [nm]	^{1}H-NMR (CCl_4) δ
(2a)	p-$CH_3C_6H_4$	CH_3	95	>0	1738 1710	1240	325, 340 sh 586	2.38 (s, 3H, CH_3), 2.48 (s, 3H, p-CH_3) 7.2—8.0 (q, 4H, C_6H_4)
(2b)	p-$CH_3OC_6H_4$	CH_3	94	>0	1740 1710	1245	346, 340 sh 586	2.43 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O) 6.75—8.00 (q, 4H, C_6H_4)
(2c)	C_6H_5	CH_3	93	oil	1740 1710	1230	310, 340 sh 577	2.42 (s, 3H, CH_3), 7.1—8.0 (m, 5H, C_6H_5)
(2d)	p-ClC_6H_4	CH_3	90	>0	1740 1710	1240	315, 340 sh 581	2.46 (s, 3H, CH_3), 7.3—8.0 (q, 4H, C_6H_4)
(2e) [a]	*i*-Pr	CH_3	79	oil	1723 1712	1198	302, 519	1.24 (d, 6H, CH_3), 2.38 (s, 3H, CH_3CO) 3.95 (m, 1H, CH)

[a] Very unpleasant smell. [b] Neat. [c] In cyclohexane.

We now wish to report the isolation and characterization of the acyl(thioacyl) sulfides *(2a)* to *(2e)* (see Table 1). They were obtained by reaction of sodium or piperidinium dithiocarboxylates *(3)* with acetyl chloride at 0°C. The structures were determined by UV, IR, ^{1}H-NMR spectroscopy and by elemental analysis. The UV absorption at 310 to 350 nm is due to the π→π* transition, and that at 570—585 nm to the n→π* transition of the thiocarbonyl group. The latter is shifted bathochromically much more strongly than in the bis(thioacyl) sulfides[1]. The acyl thioacyl sulfides are more sensitive to moisture than the bis(thioacyl) sulfides.

Synthesis of *(2a)*: To a stirred suspension of sodium 4-methyldithiobenzoate (380 mg, 2 mmol) in anhydrous *n*-hexane (20 ml) is added acetyl chloride (157 mg, 2 mmol) below 0°C and the reaction mixture stirred for 5 min under an argon atmosphere. The color of the solution changes from colorless to deep sky blue. The insoluble components are removed by filtration. Evaporation of the solvent under reduced pressure affords *(2a)* in almost quantitative yield.

Received: October 6, 1977 [Z 855 IE]
German version: Angew. Chem. *89*, 917 (1977)

CAS Registry numbers:
(2a), 64586-19-2; *(2b)*, 64586-18-1; *(2c)*, 64586-17-0; *(2d)*, 64586-16-9; *(2e)*, 64586-15-8; *(3a)*, 53724-36-0; acetyl chloride, 75-36-5

[1] *S. Kato, T. Katada, M. Mizuta*, Angew. Chem. *88*, 844 (1976); Angew. Chem. Int. Ed. Engl. *15*, 766 (1976); *S. Kato, T. Tukagi, T. Katada, M. Mizuta*, Angew. Chem. *89*, 820 (1977); Angew. Chem. Int. Ed. Engl. *16*, 786 (1977).
[2] *J. Houben, K. M. L. Schultz*, Ber. Dtsch. Chem. Ges. *43*, 2381 (1910).

The First Reaction of the N_2 Ligand with Bases; Reduction of Coordinated Dinitrogen by Nucleophilic Attack[1]

By *Dieter Sellmann* and *Woldemar Weiss*[*]

The following simplified reaction scheme [eq. (a)] is generally postulated for the reduction of N_2 ligands in transition metal complexes[2]:

$$[\overset{\ominus}{M}\text{–}\overset{\oplus}{N}\equiv N] \longleftrightarrow [\overset{\oplus}{M}\text{–}\overset{\cdot\cdot}{N}\text{=}\overset{\ominus}{N}:] \xrightarrow{2\,H^+} [\overset{\oplus}{M}\text{–}\underset{H}{\overset{\oplus}{N}}\text{=}NH]^{2+} \qquad (a)$$

[*] Professor Dr. D. Sellmann, Dr. W. Weiss
Laboratorium für Anorganische und Analytische Chemie der Gesamthochschule
Warburger Str. 100, D-4790 Paderborn (Germany)

A change in oxidation state of the metal M is accompanied by a transfer of electrons from the metal to the N_2 ligand, which then reacts with electrophilic reagents—*e.g.* H^+—or carbocations. The reactions of the complexes $[M(N_2)_2(diphos)_2]$ (M = Mo, W) with acids and alkyl or acyl halides and the reduction of N_2 in Ziegler-Natta systems are interpreted in this way[3,4].

We have now found that coordinated dinitrogen can be reduced in a fundamentally different and new way according to eq. (b):

$$[\overset{\ominus}{M}\text{–}\overset{\oplus}{N}\equiv N] \xrightarrow{X^-} [\overset{\ominus}{M}\text{–}\underset{X}{\overset{\oplus}{N}}\text{=}\overset{\ominus}{N}:]^- \xrightarrow{H^+} [\overset{\ominus}{M}\text{–}\underset{X}{\overset{\oplus}{N}}\text{=}NH] \qquad (b)$$

The oxidation state of the metal remains unchanged; the reduction of the N_2 ligand proceeds by external nucleophilic attack of $X^{\ominus}$—*e.g.* a carbanion—and subsequent protonation of the resulting diazenido complex. In the reactions investigated by us, both reaction steps can be observed separately. The reaction

$$C_5H_5(CO)_2Mn\text{–}N\equiv N + LiC_6H_5 \xrightarrow[-30\,°C]{THF} \underset{(1)}{Li[C_5H_5(CO)_2Mn\text{–}\underset{C_6H_5}{N}\text{=}N]}$$

affords the red-brown adduct *(1)*. The reaction can be monitored easily by IR spectroscopy; the ν_{N_2} absorption of $C_5H_5Mn(CO)_2N_2$ at 2165 cm^{-1} disappears and two new bands due to the ν_{CO} modes of *(1)* at 1868 and 1760 cm^{-1} can be observed. Concomitant partial decomposition and side reactions lead to acylate complexes, such as *e.g.* $Li[C_5H_5(CO)_2Mn\text{—}C(O)C_6H_5]$[5]. Addition of a stoichiometric amount of H_2SO_4 to the reaction mixture affords the deep red neutral phenyldiazene complex *(2)*, together with several side products, *e.g.* the hydroxyphenylcarbene complex $C_5H_5(CO)_2Mn\text{—}C(OH)C_6H_5$ [ν_{CO}(THF/Et_2O): 1954, 1887 cm^{-1}].

$$[C_5H_5(CO)_2Mn\text{–}\underset{C_6H_5}{N}\text{=}N]^- + H^+ \xrightarrow[0\,°C]{Et_2O/H_2O} \underset{(2)}{C_5H_5(CO)_2Mn\text{–}\underset{C_6H_5}{N}\text{=}NH}$$

(2) can be isolated chromatographically at −60°C [ν_{CO}(CH_2Cl_2, −62°C): 1955, 1885 cm^{-1}; ^{1}H-NMR (90 MHz, CD_2Cl_2, −62°C, rel. TMS): 14.50 (s, δNH), 7.55 (m, δC_6H_5), 4.65 (s, δC_5H_5); attempts to obtain a mass spectrum have so far failed[7]]. Addition of the tetrahydrofuran adduct $C_5H_5Mn(CO)_2THF$ to the reaction mixture leads to conversion of the deep red mononuclear complex *(2)* into the deep blue binuclear phenyldiazene complex *(3)*:

$$(2) + C_5H_5(CO)_2Mn(THF) \xrightarrow[-30\,^\circ C]{Et_2O} C_5H_5(CO)_2Mn-\underset{\underset{C_6H_5}{|}}{N}=\underset{|}{N}-Mn(CO)_2C_5H_5 + THF$$
$$(3)$$

(3) can be separated from decomposition products and any carbene complex still present by chromatography at −30 °C. Contrary to *(2)*, we were able to detect *(3)* also in the mass spectrum. [Spectroscopical data of *(3)*: $\nu_{CO}(CH_2Cl_2$, −62 °C): 1936, 1848 cm^{-1}; ^{1}H-NMR (90 MHz, $(CD_3)_2CO$, −62 °C, rel. TMS): 15.38 (s, δNH), 7.57 (m, δC_6H_5), 5.07 (s, δC_5H_5), 4.65 (s, δC_5H_5); MS (70 eV, T_Q 20 °C): M^+ at *m/e* 458]. Recrystallization from CH_2Cl_2 at −35 °C/−78 °C affords *(2)* and *(3)* as red-black and blue-black crystals, respectively. They are extremely sensitive towards oxidation, heat, acids and bases, and have to be handled at temperatures below −30 °C. Thermal decomposition of *(2)* in THF solution yields the starting N_2 complex:

$$C_5H_5(CO)_2Mn-\underset{\underset{C_6H_5}{|}}{N}=NH \xrightarrow[20\,^\circ C]{THF} C_5H_5(CO)_2Mn-N\equiv N + C_6H_6$$

The composition and structure of *(2)* and *(3)* have been confirmed by additional independent syntheses:

$$\underset{(4)}{C_5H_5(CO)_2Mn-\underset{\underset{C_6H_5}{|}}{N}H-NH_2} + H_2O_2 \xrightarrow[-78\,^\circ C]{THF/Cu^{2+}} 2\,H_2O + (2) + (3) + \text{decomposition products}$$

Oxidation of the phenylhydrazine complex *(4)*[6] yields a mixture of *(2)* and *(3)*. Separation and reaction of *(2)* with $C_5H_5(CO)_2MnTHF$ gives *(3)* again.

Our findings prove that ligating dinitrogen can be reduced by base addition under preservation of the N_2 coordination site. Addition reactions of $H^\ominus$-ions are under investigation to elucidate the relevance of the reaction for the mechanism of biological N_2 fixation.

Procedure

A solution of $C_5H_5Mn(CO)_2N_2$ (1450 mg, 7.1 mmol) in tetrahydrofuran (50 ml) is treated at −30 °C with a solution of LiC_6H_5 (7.1 mmol) in diethyl ether (16 ml). After 2 h the solvent is removed from the mixture by evaporation. The residue is dissolved in 40 ml of ether at −30 °C and neutralized by adding 18 ml 0.41 N H_2SO_4; the deep red ether phase is decanted off and dried over Na_2SO_4 at −30 °C. The solution is divided into two parts; the first part is evaporated, dissolved in toluene and chromatographed on SiO_2 at −60 °C. A yellow zone of $C_5H_5Mn(CO)_3$ is followed by a deep red zone, yielding after collection and evaporation 60 mg (5.9 %) $C_5H_5Mn(CO)_2N_2HC_6H_5$. The second part of the ether solution is allowed to react with 1240 mg (5 mmol) $C_5H_5Mn(CO)_2THF$ for 30 min at −30 °C. After evaporation and warming up to +20 °C for 3 min, the crude product is chromatographed on SiO_2 with toluene at −30 °C. After elution of $C_5H_5Mn(CO)_3$ and $C_5H_5Mn(CO)_2C(OH)C_6H_5$ a blue-black zone is eluted with toluene/THF = 1 : 1, which yields 70 mg (4.3 %) $[C_5H_5Mn(CO)_2]_2N_2HC_6H_5$. All reactions—including the synthesis of LiC_6H_5—are carried out under argon.

Received: October 17, 1977 [Z 857 IE]
German version: Angew. Chem. 89, 918 (1977)

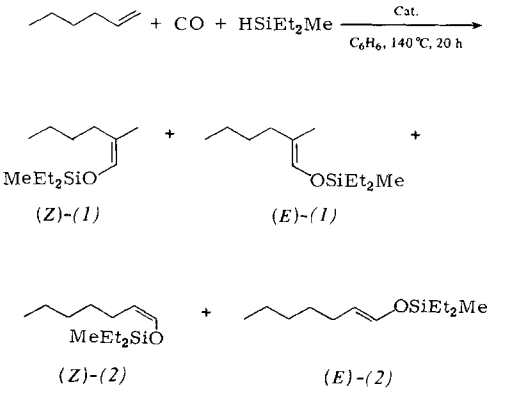
[1] Reactions of Complexed Ligands, Part 23. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 22. *D. Sellmann, E. Kleinschmidt*, Z. Naturforsch. *B 32*, 1010 (1977).
[2] Cf. *J. R. Postgate*: The Chemistry and Biochemistry of Nitrogen Fixation, Plenum Press, London 1971.
[3] Cf. *J. Chatt, A. J. Pearman, R. L. Richards*, J. Organomet. Chem. *101*, C 45 (1975); *J. Chatt, ibid. 100*, 17 (1975).
[4] Cf. *F. W. van der Weij, J. H. Teuben*, J. Organomet. Chem. *120*, 223 (1976).
[5] *E. O. Fischer, A. Maasböl*, Chem. Ber. *100*, 2445 (1967).
[6] Synthesis and proof of structure: *(4)* is obtained by reaction of $C_5H_5Mn(CO)_2THF$ with $C_6H_5N_2H_3$; the coordination of the C_6H_5NH group on the Mn center follows from the chemical shifts of NH and NH_2 protons on coordination.
[7] *Note added in proof* (11. 11. 1977): In the meantime a mass spectrum of *(2)* could be obtained: 15 eV, $T_S = -10$ °C, M^+ at *m/e* 282.

Catalyst-Dependent Product Distribution in the Reaction of 1-Hexene with a Hydrosilane and Carbon Monoxide[1]

By *Yoshio Seki, Shinji Murai, Akihiko Hidaka*, and *Noboru Sonoda*[*]

The $Co_2(CO)_8$-catalyzed reaction of cycloalkenes with hydrosilanes and carbon monoxide[2] gives only one product, a siloxymethylenecycloalkane, and the regioselectivity of this novel reaction type has yet to be elucidated. We now report the catalyst-dependent product distribution in the reaction of a linear *n*-alkene. Reaction of 1-hexene with diethyl(methyl)-silane and carbon monoxide affords four isomeric derivatives of siloxymethylene (regio- and stereoisomers); the effective catalysts found are listed in Table 1.

All of the effective catalysts are also known to be hydroformylation catalysts[3]. The total yields and the ratio of straight chain isomers (Table 1) are also similar to those observed in hydroformylation. A very good yield was obtained using $RhCl(PPh_3)_3/Et_3N$. The addition of triethylamine has already been reported to eliminate the induction period for hydroformylation of 1-pentene catalyzed by $RhCl(CO)(PPh_3)_2$[4]. A regioselectivity of 92 % was achieved by the addition of n-Bu_3P, as against 83 % for PPh_3, in the reaction using $Co_2(CO)_8$ (cf. Table 1; the corresponding proportions of straight chain



[*] Y. Seki, Prof. Dr. S. Murai [+], A. Hidaka, Prof. Dr. N. Sonoda
Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565 (Japan)
[+] To whom correspondence should be addressed.

Table 1. Reaction of 1-hexene with Et_2MeSiH and CO [a].

Catalyst [mmol]	Yield [b] (%)	Product distribution [%] (Z)-(1)	(E)-(1)	(Z)-(2)	(E)-(2)	Σ (2) [c] [%]
$Ru_3(CO)_{12}$ (0.4)	40	4	7	44	45	89
$RhCl(PPh_3)_3$ (0.4)	41	9	9	58	24	82
$RhCl(PPh_3)_3$ (0.4) + Et_3N (1.0)	88	8	13	56	23	79
$Co_2(CO)_8$ (0.4)	57	16	16	43	25	68
$Co_2(CO)_8$ (0.4) + nBu_3P (1.0)	18	2	6	70	22	92
$Co_2(CO)_8$ (0.4) + Ph_3P (1.0)	77	7	10	59	24	83

[a] Reaction conditions: 1-hexene (30 mmol), Et_2MeSiH (10 mmol), CO (50 kg/cm²), and catalyst in benzene (20 ml), 140 °C, 20 h.
[b] Determined by GLC.
[c] Proportion of straight-chain enol ethers (Z)-(2) plus (E)-(2) as determined by GLC in overall product.

isomers in the overall product of analogous hydroformylations of 1-hexene are 89.6 % and 62.4 %, respectively[5]).

These results clearly suggest that the new catalyzed reactions of olefins with hydrosilanes and carbon monoxide have basic features closely resembling those of hydroformylation.

Experimental:

A solution of 1-hexene (3.7 ml, 30 mmol), diethyl(methyl)silane (1.02 g, 10 mmol), triethylamine (0.1 g, 1 mmol), and $RhCl(PPh_3)_3$ (0.37 g, 0.4 mmol) in benzene (20 ml) is placed in a 100-ml stainless steel autoclave. The autoclave is flushed with N_2 (50 kg/cm²) and CO (50 kg/cm²), then charged with CO (50 kg/cm²) and heated at 140 °C with stirring. After 20 h, the autoclave is cooled and depressured. Analysis of the reaction mixture by GLC (Silicon OV-1, 5 %, on Uniport KS, 6 m, 115 °C) with an internal standard (*n*-tetradecane, RRT (relative retention time) = 1) showed it to contain enol silyl ethers [(Z)-(1), RRT = 0.36; (E)-(1), 0.39; (Z)-(2), 0.45; (E)-(2), 0.60] and disiloxane [$(Et_2MeSi)_2O$, RRT = 0.19] in 88 % (total) and 11 % yields, respectively. The relative yields of the enol silyl ethers are shown in Table 1. Analytical samples were obtained by fractional distillation (b.p. 105—115 °C/12 torr) followed by repeated preparative GLC[6].

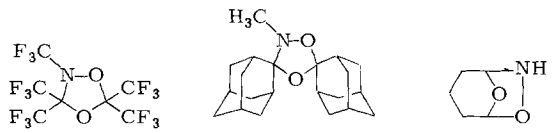
Received: September 2, 1977 [Z 847 IE]
German version: Angew. Chem. 89, 919 (1977)

[1] Transition Metal Reactions of Silanes, Part 4.—Part 3: *Y. Seki, S. Murai, I. Yamamoto, N. Sonoda*, Angew. Chem. *89*, 818 (1977); Angew. Chem. Int. Ed. Engl. *16*, 789 (1977).
[2] *Y. Seki, A. Hidaka, S. Murai, N. Sonoda*, Angew. Chem. *89*, 196 (1977); Angew. Chem. Int. Ed. Engl. *16*, 174 (1977); *Y. Seki, A. Hidaka, S. Makino, S. Murai, N. Sonoda*, J. Organomet. Chem., in press.
[3] *J. Falbe*, Carbon Monoxide in Organic Synthesis. Springer-Verlag, Berlin 1970; *F. E. Paulk*, Catal. Rev. *6*, 49 (1972); *L. Marko* in *R. Ugo*: Aspects of Homogeneous Catalysis, Vol. 2. D. Reidel, Dordrecht 1974, p. 1.
[4] *D. Evans, J. A. Osborn, G. Wilkinson*, J. Chem. Soc. *A 1968*, 3133.
[5] *E. R. Tucci*, Ind. Eng. Chem. Prod. Res. Dev. *9*, 516 (1970).
[6] The IR (neat) and NMR (CCl_4) data are: (Z)-(1), IR 1670 cm^{-1} (C=C); NMR 1.48 (d, CH_3C=C), 2.00 (m, CH_2C=C), 5.90 (s, HC=C). (E)-(1), 1670 cm^{-1} (C=C); 1.50 (d, CH_3C=C), 1.83 (m, CH_2C=C), 5.92 (s, HC=C). (Z)-(2), 1660 cm^{-1} (C=C); 1.96 (m, CH_2C=C), 4.30 (dt, J = 6 and 8 Hz, CH=COSi), 6.02 (d, J = 6 Hz, C=CHOSi). (E)-(2), 1660 cm^{-1} (C=C); 1.80 (m, CH_2C=C), 4.80 (dt, J = 12 and 6 Hz, HC=COSi), 6.08 (d, J = 12 Hz, C=CHOSi).

Comment on the Publication Entitled "Synthesis of a Stable 1,3,4-Dioxazolidine"[1]

By *Gerwalt Zinner* and *Helmut Blass*[*]

Contrary to the authors' assumption, compound *(1)* described by *Varwig* and *Mews*[1] is not the first (stable) derivative



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

of this ring type, correctly designated 1,4,2-dioxazolidine, since the set of locants 1,4,2 is lower than 1,3,4. The adamantanone derivate *(2)*[2] and the bicyclic derivative *(3)*[3] were reported five years ago.

Received: November 8, 1977 [Z 865 IE]
German version: Angew. Chem. *89*, 920 (1977)

[*] Prof. Dr. G. Zinner, H. Blass
Institut für Pharmazeutische Chemie der Technischen Universität
Beethovenstrasse 55, D-3300 Braunschweig (Germany)

[1] *J. Varwig, R. Mews*, Angew. Chem. *89*, 675 (1977); Angew. Chem. Int. Ed. Engl. *16*, 646 (1977).
[2] *G. Zinner, B. Geister*, Chem.-Ztg. *96*, 693 (1972); the data given are supplemented by the mass spectrum (70 eV, 170 °C): m/e = 329 M^+ (10), 179 (100), 162 (100), 150 (90); we are grateful to Dr. *H.-M. Schiebel*, Gesellschaft für Biotechnologische Forschung, Braunschweig-Stöckheim, for recoding the spectrum.
[3] *G. Eikelmann, W. Heimberger, G. Nonnenmacher, W. M. Weigert*, Justus Liebigs Ann. Chem. *759*, 183 (1972).

BOOK REVIEWS

Handbuch der Arzneimittel-Analytik (Handbook of Drug Analysis). By *S. Ebel*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., x, 417 pp., 3 figs., 354 tables, plastic binding , DM 118.—.

This new handbook differs from the earlier works on drug analysis in that first place has not been given to the analytical procedure with subsequent treatment of the substances appearing in the various fractions. Instead, extensive lists of analytically important data are provided for some 600 drugs. The division of the material into pharmacologically important groups is both novel and useful. In the first place the user can obtain an impression of the substance in question from the medical information that is almost always known for a drug, but he can also see, without a time-wasting search,

what method of identification or quantitative determination will be most useful in a given case. The number of important cross references could be increased; in the case of hypnotics, for example, there is no reference to benzodiazepines.

The clearly tabulated information about the drugs provides an unusual wealth of individual data. These range from the formula, name, salts, molecular weight, identification reactions, UV spectra, and solubilities to chromatographic behavior and possible methods of quantitative determination. In these tables the methods of chromatography (qualitative and quantitative TLC, GC, HPLC) are treated in special detail, in line with their importance.

Welcome too are the numerous indications of possible sources of error, *e.g.* the warning that identical R_f values of a sample and a reference substance do not constitute proof of identity.

The book leaves no room for criticism as regards its scope or its topicality. Its value in the future depends on how rapidly it can be updated in later editions to reflect the steadily changing range of products on the market. Already some of the materials included (*e.g.* Aminorex and Iproniazid) are no longer manufactured.

Supported by 2000 references to the literature, the work is a "Handbook" in the true sense. In spite of the high price it can be recommended without any reservations as a reference work in analytical laboratories and for supplementing the practical exercises in the study of pharmaceutical analysis.

Norbert Kreutzkamp [NB 392 IE]

Thermochemical Kinetics. Methods for the Estimation of Thermochemical Data and Rate Parameters. By *S. W. Benson*, John Wiley & Sons, Inc., New York 1976. 2nd edit., xi, 320 pp., 15 figs., bound, $ 28.50.

This is a considerably expanded second edition of the very condensed collection, first published in 1968, of formulas and approximation methods for estimating essential thermodynamic data and kinetic parameters for reactions taking place in the gaseous state.

In the intervening years the monograph has earned a place as a standard work. Its particular value lies mainly in the numerous and logically arranged examples of calculations and in the large number of numerical examples reproduced in the text and in a special Appendix.

In the new version the material of the second chapter (Methods for the Estimation of Thermochemical Data) is expanded into six new sections which deal with the compensation effect and with radicals. As reworked, the third chapter is devoted solely to unimolecular reactions, and a new section on the Arrhenius parameters for bimolecular and termolecular reactions has been added.

Chapter 5 (Analysis of Complex Reaction Systems) has been extended by a further section (Steady-State Hypothesis); in an Appendix there is a new table of ionic and atomic polarizabilities. With these additions the book constitutes a very useful source of information to all chemists who have to consider the thermal and kinetic parameters of gas reactions in their work.

The author has taken the trouble to work the large number of new experimental results in the field into his second edition. As an experienced practical chemist he has decided, for the time being, to retain the calorie as the unit of energy and to limit the recalculations into SI units to a brief indication. This will make it much easier for the user to evaluate the data in the literature.

The book is well produced. Its importance is such that, in spite of its price, it deserves the wider availability that would follow from a German translation.

Theodor Ackermann [NB 387 IE]

Römpps Chemie-Lexikon (Römpp's Chemical Dictionary). Vol. 6: T—Z. By *O.-A. Neumüller*. Franckh'sche Verlagshandlung W. Keller & Co., Stuttgart 1977. 7th edit., 660 pp., +16 pp. Appendix, 135 figs., bound, DM 160.—.

The present volume 6 of this lexicon, which begins with Θ and ends with zyto, completes the 7th edition. The author took a full five years to work through the 30000 key words, and it paid off. Right up to the last volume one can sense the editor's effort to bring the keywords into line with the most recent state of the art (it is by no means uncommon to find references from 1976). Many keywords appear for the first time; some such are transition state, overvoltage, twistane, trifluoromethanesulfonic acid, and triforine. Depending on its specific importance, text that has grown too large has been pruned to a sensible length, other parts have been adjusted to the state of the science. The transition elements are now given 3.5 columns, whereas previously 9 lines were considered sufficient. The contribution on ultrasound has been considerably expanded, as also has been the one on vinyl chloride that recently came into the news. Where useful, structural formulas have been added (*e.g.* for Xylenol Blue). Remarkable also are the changes among industrial products: many new names appear and many have vanished. The tabular review of the sources of vitamins is very clear.

The last volume contains additionally an Index Appendix. This consists of a formula index by the *Hill* method and an index of English and French expressions with their German equivalents, the French part being distinctly slimmer than the English with its *ca.* 8000 terms.

There is much evidence of the meticulous care taken by the author, the collaborators, and the publisher in this production. One would only like to know that these praiseworthy efforts have proved worthwhile, and the publisher and the author can only learn this if as many colleagues as possible use Römpp, collect suggestions for the next edition, and do not forget to send them to the publisher. In such a rapidly changing field as chemistry this must be considered well in advance.

Christian Weiske [NB 390 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Rare Gas Solids, Vol. II. Edited by *M. L. Klein* and *J. A. Venables*. Academic Press, London 1977. xi, 610—1252 pp., bound, £ 26.00.—ISBN 0-12-413502-1

Contemporary Quantum Chemistry. An Introduction. By *J. Goodisman*. Plenum Press, New York 1977. x, 375 pp., bound, $ 39.00.—ISBN 0-306-30947-5

DIN Deutsches Institut für Normung e. V.: English Translations of German Standards 1977. List Including the Announcement of December 1976 in "DIN-Mitteilungen". Beuth Verlag GmbH, Berlin 1977. 200 pp., paper.

Rechenmethoden und ihre Anwendung in Physik und Chemie. By *H. Horvath*. Vol. 78 of "BI Hochschultaschenbücher". Bibliographisches Institut, Mannheim 1977. 142 pp., paper, DM 9.90.—ISBN 3-411-00078-3

Steroidhormone. Biosynthese, Stoffwechsel, Wirkung. By *L. Träger*. Springer-Verlag, Berlin 1977. vii, 349 pp., bound, DM 58.—.—ISBN 3-540-08012-0

VDI-Berichte Nr. 290: Verfahrenstechnik 1976. Lectures at Annual Conference in Düsseldorf. VDI-Verlag, Düsseldorf 1977. 561 pp., paper, DM 198.—.—ISBN 3-18-090290-6

Chemistry of Natural Protein Fibers. Edited by *R. S. Asquith*. John Wiley & Sons, London 1977. xx, 417 pp., bound, £ 20.00.—ISBN 0-471-99518-5

Developments in Food Carbohydrate-1. Edited by *G. G. Birch* and *R. S. Shallenberger*. Applied Science Publishers Ltd., London 1977. x, 189 pp., bound, $ 25.00.—ISBN 0-85334-733-6

Electron Spectroscopy: Theory, Techniques and Applications, Vol. 1. Edited by *C. R. Brundle* and *A. D. Banker*. Academic Press, London 1977. xv, 459 pp., bound £ 24.00.—ISBN 0-12-137801-2

Der feste Zustand. Eine Einführung in die Festkörperchemie anhand sieben ausgewählter Beispiele. Für Studenten der Chemie und der Physik. By *W. J. Moore*. From the series "uni-text". Vieweg, Braunschweig 1977. viii, 164 pp., paper, DM 22.80.—ISBN 3-528-03026-7

The Chemistry of Pyrroles. By *R. A. Jones* and *G. P. Bean*. Vol. 34 of the series "Organic Chemistry". Edited by *A. T. Blomquist* and *H. H. Wasserman*. Academic Press, London 1977. ix, 525 pp., bound, £ 21.00.—ISBN 0-12-389840-4

Oxides and Oxide Films, Vol. 5. Edited by *A. K. Vijh*. From the series "The Anodic Behavior of Metals and Semiconductors". Edited by *A. K. Vijh*. Marcel Dekker, New York 1977. xi, 184 pp., bound, SFr. 84.—.—ISBN 0-8247-6580-X

Physik für Naturwissenschaftler II. Elektrizität und Magnetismus, Optik. By *H. Neuert*. Vol. 728 of "BI Hochschultaschenbücher". Bibliographisches Institut, Mannheim 1977. pp. 179—373, paper, DM 12.80.—ISBN 3-411-00728-1

Organometallic Chemistry Reviews; Annual Surveys: Silicon-Tin-Lead. Edited by *D. Seyferth* and *R. B. King*. Journal of Organometallic Chemistry Library 4. Elsevier Scientific Publishing Company, Amsterdam 1977. 547 pp., bound, Dfl. 134.00.—ISBN 0-444-41591-2

The Prostaglandins, Vol. 3. Edited by *P. W. Ramwell*. Plenum Press, New York 1977. xii, 359 pp., bound, $ 47.40.—ISBN 0-306-37793-4

Hard and Soft Acids and Bases. By *Tse-Lok Ho*. Academic Press, New York 1977. xii, 209 pp., bound, $ 19.50.—ISBN 0-12-3500-50-8

Corrigendum

The following corrections should be made to the article "Heinrich Wieland Centennial: His Lifework and His Legacy Today" by *B. Witkop*, Angew. Chem. Int. Ed. Engl. *16*, 559 (1977):

1) *Leipelt*'s middle name was not *Carl* but *Konrad*.
2) *Leipelt* was not hanged but beheaded. Hanging as carried out under the Nazi Regime was a particularly slow and painful method of execution, reserved for only the "worst offenders".
3) *Leipelt* had hardly any contact with *Kurt Huber*. Nor is he known to have had contact with Frau *Huber*, apart from attempting to collect money for her. No further information is to be found in *Clara Huber*'s publication cited in ref.[90].
4) The trial was not a mock trial but a normal, essentially open trial.
5) The President of the Court was not *Freisler* but "Volksgerichtsrat" *Diescher*, who conducted the proceedings in a more or less civilized way.
6) *Wieland* did not exchange a handclaps with *Leipelt*. That was impossible in the courtroom. He was only able, while the court was being held *in camera*, to shake hands with the accused not involved in that part of the case. This he did insofar as they were members of his Institute.

We are grateful to Professor *Valentin Freise* for pointing out these errors.

Warning on copyright

Before photocopying, xerocopying or reproducing an article from this journal please check whether you may be violating the legal provisions of copyright and thus rendering yourself liable to prosecution.
Copyright law allows the photocopying of individual articles only, and then only as single copies for private or personal use. The production of copies for any other purpose is not permitted without payment of copyright fees.

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie, GmbH, D-6940 Weinheim, 1977. – Printed in West Germany by Zechnersche Buchdruckerei, Speyer/Rnein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Only single copies of contributions, or parts thereof, may be reproduced for personal use. Copies reproduced and used other than for private purposes in an industrial or commercial undertaking are subject to copyright and, in such cases, a copyright fee must be paid to the VG Wissenschaft GmbH, Grosser Hirschgraben 17/21, Frankfurt/Main 1, from whom conditions of payment can be obtained on request.

Editorial office: Boschstrasse 12, D-6940 Weinheim, Germany, Telephone (06201) 14036. Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie, GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, D-6940 Weinheim, Germany

Correspondence concerning advertisements should be addressed to Verlag Chemie, GmbH. (Advertising Manager *R. J. Roth*). Pappelallee 3. P. O. Box 1260/1280, D-6940 Weinheim, Germany. Telephone Weinheim (06201) 14031, Telex 465516 vchwh d.

AUTHOR INDEX

G.E. = Reference to Volume *89* (1977) of the German Edition of Angewandte Chemie. References are given for Review Articles and Short Communications only.

"G.E. —" indicates an Abstract or a Book Review.

ABELES, R. H. 60
Achenbach, H. 191 [G.E. 198]
Acheson, R. M. 558
Adam, W. 713 [G.E. 762]
Adamiak, D. A. 330 [G.E. 336]
Adelhelm, M. 461 [G.E. 476]
Aeissen, H. 545 [G.E. 569]
Ahlers, H. 119, 710 [G.E. 107, 760]
Albery, W. J. 285 [G.E. 295]
Alcock, C. B. 491
Ali, S. M. 419
Allcock, H. R. 147 [G.E. 153]
Almgreen, T. 491
Alper, H. 41 [G.E. 43]
Amann, A. 471, 473 [G.E. 488, 489]
Anger, V. 661
Angerbauer, R. 783 [G.E. 822]
Appel, R. 180, 263, 402 [G.E. 203, 268, 415]
Arnold, R. 46 [G.E. 56]
Aroney, M. J. 663 [G.E. 725]
Atzmüller, M. 325 [G.E. 338]
Aumann, R. 50 [G.E. 47]

BAASNER, B. 871 [G.E. 909]
Bachhuber, H. 780 [G.E. 828]
Bailey, P. L. 804
Baker, J. T. 805
Ballschmiter, K. 645 [G.E. 680]
Baltes, H. 413 [G.E. 425]
Banerjee, A. K. 200
Barker, J. M. 732
Bartel, K. 707 [G.E. 752]
Bartetzko, R. 400 [G.E. 414]
Bartholomé, E. 62, 202
Bartoli, G. 557
Bastian, V. 718 [G.E. 763]
Bates, G. S. 585 [G.E. 602]
Bauer, G. 477 [G.E. 493]
Bayer, E. 117 [G.E. 120]
Becker, G. 463 [G.E. 477]
Becker, W. 481 [G.E. 486]
Beckhaus, H.-D. 875 [G.E. 913]
Behrens, U. 722 [G.E. 750]
Bell, E. A. 60
Belluš, D. 406 [G.E. 420]
Benson, S. W. 883
Bernal, I. 172, 334 [G.E. 186, 342]
Berning, W. 777 [G.E. 825]
Bestmann, H. J. 45, 268, 349, 877 [G.E. 55, 275, 361, 915]
Bieber, W. 175 [G.E. 199]
Biekert, E. 62, 202
Binger, P. 249 [G.E. 254]
Binkley, S. 122
Bischof, P. 110 [G.E. 122]
Bladauski, D. 474 [G.E. 490]
Blass, H. 882 [G.E. 920]
Block, R. 294 [G.E. 317]
Blomberg, C. 271
Boche, G. 869 [G.E. 907]
Bochmann, M. 468, 857 [G.E. 483, 895]
Bock, H. 104, 105, 613, 724, 855 [G.E. 105, 106, 631, 745, 893]
Bockrath, B. 122
Böddeker, K. W. 607 [G.E. 624]
Boehm, H.-P. 265 [G.E. 259]
Boersma, J. 60
Boiteux, A. 419
Bojanovski, D. 695 [G.E. 717]
Bollinger, D. M. 656 [G.E. 667]
Boos, K. S. 695 [G.E. 717]
Bopp, H. 653 [G.E. 659]
Both, G. W. 200
Bovermann, G. 642 [G.E. 681]
Brachtel, G. 43 [G.E. 45]
Bradshaw, T. K. 556
Brähler, G. 724, 855 [G.E. 745, 893]
Braun, H. 471, 473 [G.E. 488, 489]
Breuer, A. 169 [G.E. 175]
Bruce, M. I. 60, 73, 355 [G.E. —, 75, —]
Brüntrup, G. 255 [G.E. 265]
Brylikowska-Piotrowicz, J. 107 [G.E. 109]
Bualek, S. 790 [G.E. 830]
Buchner, W. 795 [G.E. 836]
Buhleier, E. 548 [G.E. 564]
Bührens, K.-G. 173, 398 [G.E. 195, 412]
Buonocore, V. 804
Buračas, P. 707 [G.E. 752]
Burger, K. 54, 55 [G.E. 60, 61]
Busch, G. E. 60
Bustin, M. 122

CADDY, P. 648 [G.E. 671]
Calas, R. 488 [G.E. 502]
Calderazzo, F. 299 [G.E. 305]
Calvert, D. N. 804
Campaigne, E. 122
Carroll, W. E. 793 [G.E. 838]
Catsimpoolas, N. 420
Cheng, C. C. 122
Cheng, P.-T. 654 [G.E. 658]
Cherbas, L. F. 200
Chevrier, B. 788 [G.E. 819]
Chwala, A. 661
Clark, G. M. 60
Clemens, M. J. 200
Cohen, N. 201
Cohen, R. L. 421
Coppens, P. 32 [G.E. 33]
Corcoran, J. W. 585 [G.E. 602]
Cornish-Bowden, A. 61
Craine, L. 315 [G.E. 323]
Csacsko, B. 867 [G.E. 905]

DARENSBOURG, D. J. 60
Darensbourg, M. Y. 60
Daves, Jr., G. D. 122
Davis, R. E. 169 [G.E. 175]
Dawson, R. 491
Dederer, B. 179 [G.E. 190]
Dehmlow, E. V. 493 [G.E. 521]
Dehnicke, K. 545 [G.E. 569]
de Meijere, A. 854 [G.E. 892]
Derouane, E. G. 100 [G.E. 103]
des Abbayes, H. 41 [G.E. 43]
Des Roches, D. 41 [G.E. 43]
Deutscher, J. 704 [G.E. 746]
Diebold, T. 788 [G.E. 819]
Diercks, H. 313 [G.E. 327]
Dietrich, H. 474 [G.E. 490]
Dittmar, G. 554 [G.E. 566]
Dorfman, L. M. 122
Driedzic, W. R. 803
Dumesic, J. A. 335
Dumont, W. 540, 541 [G.E. 559, 561]
Du Mont, W.-W. 792 [G.E. 832]
Dunoguès, J. 488 [G.E. 502]
Dyong, I. 553 [G.E. 565]

EBEL, S. 157, 882 [G.E. 129, —]
Eberl, K. 654 [G.E. 657]
Ebert, H.-D. 269 [G.E. 276]
Ebsworth, E. A. V. 482 [G.E. 495]
Egert, E. 336
Eggelte, H. J. 713 [G.E. 762]
Ehrhardt, M. 491
Eidenschink, R. 100 [G.E. 103]
Elgavi, A. 181, 182 [G.E. 188, 189]
Elschenbroich, C. 479, 870 [G.E. 497, 908]
Engel, N. 394 [G.E. 408]
Enkelmann, V. 416 [G.E. 432]
Erben, A. 192 [G.E. 187]
Erdmann, D. 100 [G.E. 103]
Erdtmann, G. 558
Ermer, O. 411, 658, 798 [G.E. 431, 665, 833]
Ernst, L. 481 [G.E. 486]
Ernst, V. 200
Eschenmoser, A. 459 [G.E. 475]
Evers, J. 659 [G.E. 673]

FADEL, S. 704 [G.E. 746]
Falk, H. 470 [G.E. 487]
Färcaşiu, D. 315 [G.E. 323]
Faria dos Santos Filho, P. 647 [G.E. 672]
Faulstich, H. 267 [G.E. 274]
Fehlhammer, W. P. 641, 707 [G.E. 660, 752]
Feigel, M. 256 [G.E. 266]
Félix, G. 488 [G.E. 502]
Fels, G. 651, 652 [G.E. 676, 677]
Ferrier, H. M. 482 [G.E. 495]
Feyen, P. 115 [G.E. 119]
Field, L. 804
Fischer, E. O. 401, 465 [G.E. 416, 481]
Fischer, G. 780 [G.E. 828]
Fischer, H. 53 [G.E. 52]
Fischler, I. 200
Fisher, L. R. 490
Flek, J. 123
Fluck, E. 420
Follmann, R. 462 [G.E. 478]
Fonselius, S. H. 491
Förster, H. 429 [G.E. 443]
Franck, B. 651, 652 [G.E. 676, 677]
Franck-Neumann, M. 323 [G.E. 331]
Fraser-Reid, B. 553 [G.E. 565]
Freidlina, R. Kh. 271
Frickel, F. 475 [G.E. 491]
Friedrich, E. 413 [G.E. 426]
Friedrich, P. 102, 260, 314, 401, 465, 485, 543 [G.E. 110, 268, 325, 416, 481, 499, 553]
Frinquelli, F. 732
Fritz, H. 198 [G.E. 174]
Fritz, J. S. 335
Fukumoto, K. 60
Furuichi, Y. 200

GAIS, H.-J. 196, 244 [G.E. 201, 251]
Gamon, N. 404 [G.E. 418]
Gattermayer, R. 547 [G.E. 556]
Gerson, F. 657 [G.E. 666]
Gieren, A. 179 [G.E. 190].
Giese, B. 125, 178, 466 [G.E. 162, 178, 482]
Gilb, W. 191 [G.E. 177]
Gindner, F. 719 [G.E. 753]
Ginsburg, D. 420
Glaser, E. 549 [G.E. 558]
Glatz, B. 728 [G.E. 742]
Gleiter, R. 110, 113, 400, 724 [G.E. 122, 116, 414, 745]
Glemser, O. 789 [G.E. 829]
Goddard, R. 334 [G.E. 342]
Göhring, W. 642 [G.E. 681]
Gölitz, P. 854 [G.E. 892]
Gölz, H. 728 [G.E. 742]
Gombler, W. 723 [G.E. 740]
Gosney, I. 487 [G.E. 502]
Gossauer, A. 418, 481 [G.E. 429, 486]
Gotor, V. 539 [G.E. 563]
Grasshoff, K. 491
Gray, G. R. 200
Green, M. 648, 793 [G.E. 671, 838]
Greif, N. 712 [G.E. 765]
Griesler, J. 46 [G.E. 56]
Griffin, G. W. 171 [G.E. 181]
Grimme, W. 717 [G.E. 754]
Grobe, J. 248 [G.E. 257]
Grubmayr, K. 470 [G.E. 487]
Grüning, B. 481 [G.E. 486]
Grunwald, P. 714 [G.E. 761]
Grütze, J. 325 [G.E. 338]
Guggisberg, A. 861 [G.E. 899]
Gunsser, W. 714 [G.E. 761]
Günther, H. J. 246 [G.E. 253]
Gurke, A. 801 [G.E. 841]
Gutekunst, G. 463 [G.E. 477]

HAAS, G. 728 [G.E. 742]
Häfelinger, G. 47 [G.E. 48]
Hägele, G. 477 [G.E. 493]
Hagemann, H. 743 [G.E. 789]
Haider, R. 110 [G.E. 122]
Häkli, H. 405 [G.E. 419]
Halstenberg, M. 263 [G.E. 268]
Hammer, R. 485 [G.E. 499]
Hamsen, A. 119 [G.E. 107]
Hanack, M. 121
Harris, R. L. N. 779 [G.E. 816]
Hartenstein, J. 730 [G.E. 739]
Hartog, F. A. 271
Hase, H.-L. 187, 257, 258 [G.E. 194, 263, 264]
Hauel, N. 475 [G.E. 491]
Hecht, H.-J. 474 [G.E. 490]
Heck, J. 479 [G.E. 497]
Heck, R. F. 335
Hegedus, L. S. 335
Heggemeier, H. 791 [G.E. 831]
Heicklen, J. 733
Heimbach, P. 252, 253 [G.E. 260, 261]
Heitzmann, M. 469 [G.E. 485]
Heizmann, P. 645 [G.E. 680]
Hekman, M. 406 [G.E. 420]
Hellmann, G. 875 [G.E. 913]
Hellmann, H. 62, 202
Helmchen, G. 116, 728 [G.E. 119, 742]
Henco, K. 538 [G.E. 567]
Hengesbach, J. 42 [G.E. 43]
Hengge, E. 403 [G.E. 417]
Henner, B. J. L. 482 [G.E. 495]
Henschler, D. 271
Heppke, G. 318 [G.E. 328]
Herberhold, M. 193, 194 [G.E. 191, 192]
Herberich, G. E. 42 [G.E. 43]
Hermentin, P. 48 [G.E. 58]
Herrmann, W. A. 172, 334, 555 [G.E. 186, 342, 557]
Herz, C. P. 392, 394, 799 [G.E. 406, 407, 839]
Hess, B. 61, 419
Hess, H. 407 [G.E. 423]
Hesse, M. 861 [G.E. 899]
Heumann, K. G. 114, 719 [G.E. 118, 753]
Heusel, G. 642 [G.E. 681]
Hevesi, L. 100 [G.E. 103]
Hidaka, A. 174, 881 [G.E. 196, 919]
Hillard III, R. L. 399 [G.E. 413]
Hinze, R.-P. 418 [G.E. 429]
Hirabayashi, T. 105 [G.E. 106]
Hoberg, H. 183, 539 [G.E. 179, 563]
Hochachka, P. W. 803
Hoekstra, M. S. 321 [G.E. 334]
Höfle, B. 262, 727 [G.E. 272, 742]
Hofmann, P. 400, 536 [G.E. 414, 551]
Hofmann, W. 794, 795 [G.E. 835, 836]
Hoffmann, M. 751 [G.E. 773]
Hoffmann, R. 114 [G.E. 118]
Hoffmann, R. W. 475 [G.E. 491]
Hogrefe, F. 871 [G.E. 909]
Holl, P. 722 [G.E. 748]
Hollfelder, H. 401 [G.E. 416]
Holzbach, G. 117 [G.E. 120]
Hopf, H. 191 [G.E. 177]
Hoppe, D. 462, 544 [G.E. 478, 553]
Hoppe, R. 43, 484 [G.E. 45, 498]
Hori, A. 787 [G.E. 820]
Horner, M. 410 [G.E. 424]
Howard, J. A. K. 793 [G.E. 838]
Howden, M. E. 60
Hugelin, B. 253 [G.E. 261]
Huisgen, R. 572 [G.E. 589]
Huizenga, J. R. 60
Hund, F. 87 [G.E. 89]
Hundt, R. 547 [G.E. 556]
Hünig, S. 410, 777 [G.E. 424, 825]
Huppatz, J. L. 779 [G.E. 816]
Hutchinson, D. W. 556
Huttner, G. 102, 260, 314, 401, 465, 485, 858 [G.E. 110, 268, 325, 416, 481, 499, 896]

IKEDA, M. 270
Irngartinger, H. 187 [G.E. 194]
Ishikawa, K. 171 [G.E. 181]

JACKSTIESS, W. 478 [G.E. 494]
Jacob, E. 461 [G.E. 476]
Jaeger, E. 317 [G.E. 330]
Jäger, V. 246 [G.E. 253]
Jansen, L. 294 [G.E. 317]
Jansen, M. 314, 534 [G.E. 326, 567]
Jay, K. 466 [G.E. 482]
Jesmock, G. J. 804
Jesson, J. P. 513 [G.E. 507]
Jödden, K. 464 [G.E. 480]
Josefsson, B. 491
Joussen, R. 709 [G.E. 759]
Jung, G. 642 [G.E. 681]
Jutzi, P. 41, 330, 639 [G.E. 44, 339, 675]

KAISER, E. M. 803
Kakeya, N. 552 [G.E. 558]
Kalinowski, H.-O. 264 [G.E. 270]
Kametani, T. 60
Kanaoka, Y. 137 [G.E. 142]
Kanellakopulos, B. 261 [G.E. 271]
Karsch, H. H. 56 [G.E. 57]
Kaschig, J. 550 [G.E. 570]
Katada, T. 786, 879 [G.E. 820, 917]
Kato, S. 786, 787, 879 [G.E. 820, 820, 917]
Kauffmann, Th. 53, 119, 709, 710, 862 [G.E. 52, 107, 759, 760, 900]
Kaupp, G. 552, 657 [G.E. 555, 666]
Keat, R. 797 [G.E. 829]
Keller, E. 188, 542, 731 [G.E. 197, 568, 738]
Kemmitt, R. D. W. 60
Kemnitz, K. 266 [G.E. 273]
Kessler, H. 256 [G.E. 266]
Khac, Tri Ngo 324 [G.E. 332]
Kinas, R. 330 [G.E. 336]
Kirby, G. W. 490
Kisfaludy, L. 317 [G.E. 330]
Kisielowski, L. 268 [G.E. 275]
Kistenmacher, T. J. 557
Klages, C.-P. 725, 726 [G.E. 743, 744]
Klatte, F. 878 [G.E. 916]
Klauke, E. 735 [G.E. 797]
Klein, H.-F. 485 [G.E. 499]
Kloeters, W. 45 [G.E. 55]
Klöppel, H. 719 [G.E. 753]
Klöter, G. 707 [G.E. 754]
Knauer, K.-H. 113 [G.E. 116]
Knoll, F. 402 [G.E. 415]
Knowles, J. R. 285 [G.E. 295]
Knutson, P. L. A. 803
Koerner von Gustorf, E. A. 200
Köhler, F. H. 722 [G.E. 748]
Kölle, U. 42 [G.E. 43]
Kölmel, M. 545 [G.E. 569]
Koroleff, F. 491
Korte, E.-H. 790, 791 [G.E. 830, 831]
Kosbahn, W. 780 [G.E. 826]
Kothe, G. 52 [G.E. 51]
Kovar, D. 403 [G.E. 417]
Krabbe, H. J. 790, 791 [G.E. 830, 831]
Kraemer, A. D. 49 [G.E. 48]
Kramer, U. 861 [G.E. 899]
Krauch, H. 61
Krause, J. 100 [G.E. 103]
Krause-Göing, R. 183 [G.E. 179]
Kräutler, B. 459 [G.E. 475]
Krebs, B. 313 [G.E. 327]
Kreiss, W. 113 [G.E. 117]
Kreissl, F. R. 102, 314, 401, 543, 654 [G.E. 110, 325, 416, 553, 657]
Kreiter, C. G. 193 [G.E. 191]
Kremling, K. 491
Kricheldorf, H. R. 550 [G.E. 570]
Krief, A. 100, 540, 541 [G.E. 103, 559, 561]
Kriegesmann, R. 862 [G.E. 900]
Kröher, R. 864 [G.E. 902]
Krolikiewicz, K. 876 [G.E. 914]
Kroth, H.-J. 792 [G.E. 832]
Krüger, C. 183, 334, 539 [G.E. 179, 342, 563]
Kübel, B. 394 [G.E. 408]
Kuhla, D. E. 661
Kühle, E. 735 [G.E. 797]
Kühn, A. 412 [G.E. 427]
Kühne, K. 61
Kunz, W. 61
Kuster, T. 115 [G.E. 120]

L'ABBÉ, G. 403, 475 [G.E. 420, 492]
Lam-Chi, Q. 553 [G.E. 565]
Lang, E. 331 [G.E. 340]
Lange, B. 262, 727 [G.E. 272, 742]
Langenbach, H.-J. 188 [G.E. 197]
Lech, J. J. 804
Le Clef, B. 182 [G.E. 189]
Ledwith, A. 732
Lee, T. V. 419
Leenders, L. H. G. 200
Lehmann, W. D. 184, 852 [G.E. 180, 890]
Lentz, D. 729 [G.E. 741]
Leonhard, K. 649 [G.E. 656]
Lesiecki, H. 269 [G.E. 276]
Levin, D. H. 200
Lex, J. 871 [G.E. 909]
Ley, H. 62, 202
Liebl, R. 637 [G.E. 670]
Lillie, T. J. 487 [G.E. 502]
Lindahl, T. 61
Lindner, E. 269 [G.E. 276]
Lindner, H. J. 336
Lindner, T. L. 314 [G.E. 325]
Liu, L.-K. 169 [G.E. 175]
Lloyd, D. 487 [G.E. 502]
Lohmann, J.-J. 323 [G.E. 331]
Lombardino, J. G. 661
London, I. M. 200
Löw, M. 317 [G.E. 330]
Lu, A. Y. H. 201
Luber, J. 546 [G.E. 554]
Lubosch, W. 264 [G.E. 270]
Lüdemann, H.-D. 331 [G.E. 340]
Luger, P. 52 [G.E. 51]
Lüke, H.-W. 535 [G.E. 550]
Lüstorff, J. 695 [G.E. 717]
Lutz, Walter 707 [G.E. 754]
Lutz, Werner 413 [G.E. 426]

MAAS, G. 711 [G.E. 763]
Maass, G. 538 [G.E. 567]
Mahr, C. 420
Maier, G. 49 [G.E. 51]
Malik, K. U. 123
Malisch, W. 408 [G.E. 421]
Mandl, J. R. 640 [G.E. 679]
Mannschreck, A. 405 [G.E. 419]
Margna, U. 803
Marino, G. 732
Märkl, G. 637 [G.E. 670]
Markus, M. 61
Marr, G. 335
Marshall, G. R. 201
Martens, J. 318 [G.E. 328]
Martin, H.-D. 103, 406 [G.E. 111, 420]
Martin, R. 248 [G.E. 257]
Marzilli, L. G. 557
Masaki, M. 552 [G.E. 558]
Masamune, S. 585 [G.E. 602]
Mattes, R. 260 [G.E. 269]
Mäusle, H.-J. 112 [G.E. 114]
Maycock, A. L. 60
Mayer, R. 660
Mayr, A. 641 [G.E. 660]
McGiff, J. C. 123
Mehrotra, A. K. 490
Meier, H. 555, 835 [G.E. 562, 876]
Meister, J. 178 [G.E. 178]
Melchior, M. T. 315 [G.E. 323]
Mendenhall, G. D. 225 [G.E. 220]
Mengel, R. 317 [G.E. 328]
Menke, K. 191 [G.E. 177]
Mennemann, K. 260 [G.E. 269]
Merz, A. 57, 467 [G.E. 54, 484]
Mews, R. 56, 646, 789 [G.E. 53, 675, 829]
Milchereit, A. 539 [G.E. 563]
Minamikawa, J. 270
Mitchell, J. C. 121
Mizuta, M. 786, 787, 879 [G.E. 820, 820, 917]
Mohmand, S. 104, 105 [G.E. 105, 106]
Möckel, R. 870 [G.E. 908]
Möller, U. 248 [G.E. 257]
Moore, R. E. 419
Morbach, W. 180 [G.E. 203]
Morley, R. 60
Mosbach, K. 60
Mues, P. 872 [G.E. 910]
Muetterties, E. L. 557
Mukaiyama, T. 817 [G.E. 858]
Müllen, K. 170, 872 [G.E. 176, 910]
Müller, A. 183, 468, 705 [G.E. 189, 479, 748]
Müller, H.-D. 260 [G.E. 268]

Müller, R. 332 [G.E. 341]
Müller, W. M. 548 [G.E. 564]
Müller-Buschbaum, Hk. 674 [G.E. 704]
Mulzer, J. 255 [G.E. 265]
Munekata, E. 267 [G.E. 274]
Murai, S. 174, 789, 881 [G.E. 196, 818, 919]
Murata, I. 784, 866 [G.E. 821, 904]
Murphy, V. 804
Murray, J. D. 419
Musso, H. 415 [G.E. 430]
Muthukrishnan, S. 200
Muxfeldt, H. 728 [G.E. 742]

NABBEFELD, E. F. 253 [G.E. 261]
Nagy, J. B. 100 [G.E. 103]
Naiman, A. 708 [G.E. 758]
Nakasuji, K. 784, 866 [G.E. 821, 904]
Needleman, P. 122
Neely, J. R. 803
Nefedov, O. M. 646 [G.E. 674]
Neidlein, R. 49 [G.E. 48]
Neufeldt, S. 733
Neugebauer, D. 858 [G.E. 896]
Neumüller, O.-A. 883
Nickel, U. 266 [G.E. 273]
Niecke, E. 486, 783, 864 [G.E. 501, 817, 902]
Nishino, K. 866 [G.E. 904]
Nolte, H. 420
Norred, W. P. 201
Nöth, H. 478 [G.E. 494]
Nöthe, D. 261 [G.E. 271]
Nyburg, S. C. 654 [G.E. 658]

OAE, S. 732, 803
Oakenfull, D. G. 490
O'Brien, E. 648 [G.E. 671]
Oehlinger, G. 659 [G.E. 673]
Ogoshi, H. 866 [G.E. 904]
Öhler, E. 327 [G.E. 344]
Ohno, A. 732
Ohya-Nishiguchi, H. 657 [G.E. 666]
Oppolzer, W. 10 [G.E. 10]
Orchin, M. 656 [G.E. 667]
Oschmann, W. 42 [G.E. 43]
Oth, J. F. M. 872 [G.E. 910]
Ottoway, J. H. 61

PADWA, A. 121
Page, M. I. 449 [G.E. 456]
Pakzad, B. 319 [G.E. 329]
Panster, P. 408 [G.E. 421]
Parfitt, G. D. 122
Paulsen, H. 52 [G.E. 51]
Pearson, J. M. 660
Perlstein, J. H. 519 [G.E. 534]
Perutz, R. N. 200
Peters, K. 177 [G.E. 202]
Petrucci, T. 804
Petty, J. D. 803
Pfaltz, A. 459 [G.E. 475]
Pfeffer, M. 793 [G.E. 838]
Pilati, T. 170 [G.E. 176]
Pisciotti, F. 488 [G.E. 502]
Plesser, T. 419
Podstawczyńska, I. 702 [G.E. 737]
Pohl, L. 100 [G.E. 103]
Pohl, S. 789, 864 [G.E. 829, 902]
Pohmakotr, M. 320 [G.E. 333]
Poisel, H. 777 [G.E. 824]
Pommer, H. 423 [G.E. 437]
Porter, M. 660
Praefcke, K. 318, 319 [G.E. 328, 329]
Prantz, E. 328 [G.E. 345]
Pratt, A. C. 557
Präve, P. 205 [G.E. 211]
Preetz, W. 108, 173, 398 [G.E. 108, 195, 412]
Preiner, G. 328 [G.E. 343]
Primeau, J. L. 553 [G.E. 565]
Prinzbach, H. 103, 198 [G.E. 111, 174]
Pritzkow, H. 729 [G.E. 741]
Protschuk, G. 321 [G.E. 334]
Puff, H. 547 [G.E. 556]

QUAST, H. 109, 177, 643 [G.E. 112, 202, 668]

RANGANATHAN, D. 490
Ranganathan, S. 490
Rankin, D. W. H. 482 [G.E. 495]
Ranu, R. S. 200
Rasetti, V. 459 [G.E. 475]
Rasmussen, J. K. 335
Rauchschwalbe, R. 331 [G.E. 340]
Raude, E. 544 [G.E. 553]
Reed, F. J. S. 482 [G.E. 495]
Rees, D. A. 214 [G.E. 228]
Reetz, M. T. 44, 712 [G.E. 46, 765]
Regitz, M. 711 [G.E. 763]
Reich, S. 441 [G.E. 467]
Reichardt, Ch. 404 [G.E. 418]
Reinehr, D. 253 [G.E. 261]
Reinhardt, R. 715, 716 [G.E. 756, 757]
Renger, B. 264 [G.E. 270]
Rentzepis, P. M. 60
Rewicki, D. 474 [G.E. 490]
Richardson, M. 419
Richter, M. 471 [G.E. 488]
Ried, W. 653 [G.E. 659]
Riederer, M. 859, 860 [G.E. 897, 898]
Ring, H. 50 [G.E. 47]
Ringel, G. 486 [G.E. 501]
Rist, G. 406 [G.E. 420]
Ritter, M. 641 [G.E. 660]
Robbiani, R. 120 [G.E. 115]
Roberts, S. M. 419
Robertson, H. E. 482 [G.E. 495]
Rockett, B. W. 335
Rodewald, G. 46 [G.E. 56]
Rodriguez, E. 121
Roloff, A. 252, 253 [G.E. 260, 261]
Rösch, L. 247, 480 [G.E. 257, 497]
Röschenthaler, G.-V. 862 [G.E. 900]
Rosentreter, U. 878 [G.E. 916]
Ross, K.-H. 177 [G.E. 202]
Roth, H. D. 419
Roth, K. 877 [G.E. 915]
Roth, L. 202
Rothe, M. 113 [G.E. 117]
Rothermel, W. 333 [G.E. 346]
Röttinger, E. 332 [G.E. 341]
Roundhill 335
Rowold, A. 651 [G.E. 676]
Ruch, E. 65 [G.E. 67]
Rüchardt, Ch. 875 [G.E. 913]
Ruhs, A. 465 [G.E. 481]
Runge, F. 272
Runzheimer, H.-V. 871, 872 [G.E. 909, 910]
Ruppert, I. 311, 718 [G.E. 336, 763]
Rys, P. 123, 807 [G.E. —, 847]

SAALFRANK, R. W. 185, 877 [G.E. 184, 915]
Saenger, W. 330 [G.E. 336]
Saegusa, T. 826 [G.E. 867]
Sainsbury, M. 803
Sandhoff, K. 273 [G.E. 283]
Sandmeier, D. 268 [G.E. 275]
Sandorfy, C. 337
Sandow, T. 716 [G.E. 757]
Sarkar, S. 183, 468, 705 [G.E. 189, 479, 748]
Sato, P. H. 200
Satzinger, G. 730 [G.E. 739]
Sauer, W. 51 [G.E. 49]
Sauter, H. 406 [G.E. 420]
Sawodny, W. 859, 860 [G.E. 897, 898]
Schaden, G. 50 [G.E. 50]
Schäfer, H. 780 [G.E. 826]
Schäfer, H.-G. 783 [G.E. 817]
Schäfer, H. J. 413 [G.E. 425]
Scharf, H.-D. 400 [G.E. 414]
Schaumann, E. 722 [G.E. 750]
Scheer, S. 714 [G.E. 761]
Schenkluhn, H. 252 [G.E. 260]
Scherer, O. J. 486 [G.E. 500]
Scheuer, P. J. 335
Schickaneder, H. 54, 55 [G.E. 60, 61]
Schiess, P. 469 [G.E. 485]
Schinzer, D. 44 [G.E. 46]
Schlimme, E. 695 [G.E. 717]
Schmettow, W. 857 [G.E. 895]
Schmid, G. 268 [G.E. 275]
Schmid, G. 249, 785 [G.E. 258, 823]
Schmid, H. 861 [G.E. 899]
Schmidbaur, H. 417, 639, 640, 722 [G.E. 428, 678, 679, 748]
Schmidpeter, A. 546, 549, 704, 865 [G.E. 554, 558, 747, 903]
Schmidt, A. 202
Schmidt, R. R. 48, 783, 853 [G.E. 58, 822, 891]
Schmidt, U. 327, 328, 777 [G.E. 344, 345, 824]
Schmidt, W. 203
Schmidtchen, F. P. 720 [G.E. 751]
Schnabl, G. 486 [G.E. 500]
Schneider, D. R. 869 [G.E. 907]
Schneider, E. 717 [G.E. 754]
Schneider, M. 192, 867 [G.E. 187, 905]
Schneller, S. W. 122
Schöllhorn, R. 199 [G.E. 193]
Schöllkopf, U. 339 [G.E. 351]
Schrader, B. 197, 790, 791 [G.E. 200, 830, 831]
Schrauzer, G. N. 233 [G.E. 239]
Schuchardt, U. 249, 647 [G.E. 254, 672]
Schuchmann, H.-P. 804
Schulte, G. 553 [G.E. 565]
Schulte, K.-W. 187, 257 [G.E. 194, 263]
Schulten, H.-R. 184, 852 [G.E. 180, 890]
Schulz, G. 251, 252 [G.E. 255, 256]
Schulz, G. E. 23 [G.E. 24]
Schulz, H. 119 [G.E. 107]
Schulze, J. 249 [G.E. 258]
Schurig, V. 110 [G.E. 113]
Schuster, F. 715 [G.E. 756]
Schuster, P. 337
Schwarz, G. 550 [G.E. 570]
Schwarz, W. 407 [G.E. 423]
Schweig, A. 187, 257, 258 [G.E. 194, 263, 264]
Schwerdtfeger, H.-J. 108 [G.E. 108]
Sedelmeier, G. 103 [G.E. 111]
Šedivec, V. 123
Seebach, D. 264, 320, 321 [G.E. 270, 333, 334]
Seel, F. 123
Seibl, J. 120 [G.E. 115]
Seibles, J. C. 656 [G.E. 667]
Seki, Y. 174, 789, 881 [G.E. 196, 818, 919]
Sekutowski, J. C. 183, 539 [G.E. 179, 563]
Sellmann, D. 464, 880 [G.E. 480, 918]
Semkow, A. 724 [G.E. 745]
Seppelt, K. 322, 729, 707 [G.E. 325, 741, 754]
Seppelt, W. 198 [G.E. 174]
Seufert, A. 41, 330 [G.E. 44, 339]
Seuring, A. 157 [G.E. 129]
Seuring, B. 264 [G.E. 270]
Sevrin, M. 541 [G.E. 561]
Seybold, G. 365 [G.E. 377]
Shatkin, A. J. 200
Sheldrick, W. S. 481 [G.E. 486]
Shostakovsky, V. M. 646 [G.E. 674]
Siebert, W. 333, 468, 857 [G.E. 346, 483, 895]
Sieger, H. 396 [G.E. 410]
Silano, V. 804
Simon, H. 318, 319 [G.E. 328, 329]
Simonetta, M. 170 [G.E. 176]
Sinfelt, J. H. 271
Skorna, G. 259 [G.E. 267]
Smart, L. E. 648 [G.E. 671]
Smith, K. A. 419
Smith, T. A. 490
Söderhäll, S. 61
Solouki, B. 105 [G.E. 106]
Sommer, S. 58 [G.E. 59]
Sommerfeld, C.-D. 169 [G.E. 175]
Somorjai, G. A. 92 [G.E. 94]
Sonoda, N. 174, 789, 881 [G.E. 196, 818, 919]
Spiegel, E. 109, 177 [G.E. 112, 202]
Spiekermann, M. 197 [G.E. 200]
Spitzner, D. 46 [G.E. 55]
Sprecher, C. A. 189 [G.E. 185]
Staab, H. A. 392, 394, 799, 801 [G.E. 406, 407, 839, 841]
Staiger, G. 116 [G.E. 119]
Stark, M. 552 [G.E. 555]
Stawitz, J. 643 [G.E. 668]
Stec, W. J. 330 [G.E. 336]
Steglich, W. 46, 251, 252, 394 [G.E. 56, 255, 256, 408]
Steiner, W. 639 [G.E. 675]
Steinle, J. 265 [G.E. 259]
Steinmann, L. 47 [G.E. 48]
Stelander, B. 191 [G.E. 182]
Stephan, W. 44 [G.E. 46]
Steudel, R. 112, 715, 716 [G.E. 114, 756, 757]

Stober, R. 415 [G.E. 430]
Stone, F. G. A. 793 [G.E. 838]
Storch, W. 478 [G.E. 494]
Stork, L. 413 [G.E. 425]
Strähle, J. 545 [G.E. 569]
Stückler, P. 654 [G.E. 657]
Sugino, K. 879 [G.E. 917]
Sujdak, R. J. 122
Sundermeyer, W. 707 [G.E. 754]
Süss-Fink, M. 193, 194 [G.E. 191, 192]

TABATABAI, A. 724 [G.E. 745]
Taeger, E. 272
Tagaki, W. 803
Takagi, T. 786, 787 [G.E. 820, 820]
Talbiersky, J. 853 [G.E. 891]
Tamura, Y. 270
Taticchi, A. 732
Tautz, H. 546 [G.E. 554]
Terent'ev, A. B. 271
Terragno, N. A. 123
Tesky, F.-M. 789 [G.E. 829]
Thankachan, C. 654 [G.E. 658]
Thompson, D. G. 797 [G.E. 829]
Tidwell, T. T. 654 [G.E. 658]
Tilhard, H.-J. 119, 710 [G.E. 107, 760]
Todesco, P. E. 557
Todo, E. 784 [G.E. 821]
Toppet, S. 475 [G.E. 492]
Topsøe, H. 335
Towers, G. H. N. 121
Treichel, P. M. 335
Trickes, G. 555 [G.E. 562]
Troxler, E. 253 [G.E. 261]
Tümmler, B. 538 [G.E. 567]
Turro, N. J. 660

UFER, G. 651, 652 [G.E. 676, 677]
Ugi, I. 259 [G.E. 267]
Unglert, C. 645 [G.E. 680]
Urban, E. 860 [G.E. 898]

VAHRENHORST, A. 119 [G.E. 107]
Vahrenkamp, H. 188, 332, 542, 731 [G.E. 197, 341, 568, 738]
Varwig, J. 646 [G.E. 675]
Vasilvizky, A. E. 646 [G.E. 674]
Verhelst, G. 403 [G.E. 420]
Vermeulen, G. 403 [G.E. 420]
Viehe, H. G. 181, 182, 191 [G.E. 188, 189, 182]
Vieweger, C. 265 [G.E. 259]
Vogel, E. 169, 170, 871, 872 [G.E. 175, 176, 909, 910]
Vögtle, F. 175, 325, 396, 429, 548 [G.E. 199, 338, 410, 443, 564]
Vollhardt, K. P. C. 271, 399, 708 [G.E. —, 413, 758]
von Schnering, H. G. 177, 857 [G.E. 202, 895]
von Seyerl, J. 858 [G.E. 896]
von Sonntag, C. 804
Vorbrüggen, H. 876 [G.E. 914]
Vordermaier, G. 269 [G.E. 276]
Voss, J. 725, 726 [G.E. 743, 744]

WADE, A. E. 201
Wagemann, W. 170 [G.E. 176]
Wailes, P. C. 335
Walter, W. 535 [G.E. 550]
Wambach, K.-R. 484 [G.E. 498]
Wegner, G. 416, 804 [G.E. 432, —]
Wehner, W. 325, 548 [G.E. 338, 564]
Weidenhammer, K. 261, 555 [G.E. 271, 557]
Weigert, W. M. 62, 202
Weigl, J. W. 374 [G.E. 386]
Weiner, S. 875 [G.E. 913]
Weinmaier, J. H. 549, 865 [G.E. 558, 903]
Weiss, A. 659 [G.E. 673]
Weiss, R. 788 [G.E. 819]
Weiss, W. 880 [G.E. 918]
Welsh, E. J. 214 [G.E. 228]
Welz, E. 785 [G.E. 823]
Werner, H. 1, 324, 412, 649, 794, 795 [G.E. 1, 332, 427, 656, 835, 836]
Westman, A. E. R. 490
Whitelock, J. D. 482 [G.E. 495]
Wiberg, N. 328, 780 [G.E. 343, 828]
Wiechert, R. 506 [G.E. 513]
Wiedner, H. 317 [G.E. 328]
Wieland, Th. 267 [G.E. 274]
Wienand, H. 261 [G.E. 271]
Wihler, H.-D. 402 [G.E. 415]
Willenberg, H. 260 [G.E. 268]
Williams, R. J. P. 766 [G.E. 805]
Winnik, M. A. 557
Winiker, R. 875 [G.E. 913]
Winslow, F. H. 660
Winter, G. 478 [G.E. 494]
Winterfeldt, E. 878 [G.E. 916]
Witkop, B. 559, 884 [G.E. 575, 922]
Witzke, J. 191 [G.E. 198]
Wohlleben, A. 417 [G.E. 428]
Woltermann, A. 53, 709, 710, 862 [G.E. 52, 759, 760, 900]
Woodward, P. 648 [G.E. 671]
Wünsch, E. 317 [G.E. 330]

YAMADA, M. 879 [G.E. 917]
Yamamoto, I. 789 [G.E. 818]
Yoshida, Z. 866 [G.E. 904]
Yu, Chih-Chou 475 [G.E. 492]

ZAGEFKA, H.-D. 199 [G.E. 193]
Zähner, H. 687 [G.E. 696]
Zannoni, V. G. 200
Zapf, U. 801 [G.E. 841]
Zeiss, W. 407 [G.E. 423]
Zeller, K.-P. 781, 835 [G.E. 827, 876]
Zettl, C. 54, 55 [G.E. 60, 61]
Ziegler, M. L. 261, 555, 704 [G.E. 271, 557, 746]
Zilch, H. 418 [G.E. 429]
Zimmer, R. 547 [G.E. 556]
Zimmer-Gasser, B. 639 [G.E. 678]
Zinner, G. 882 [G.E. 920]
Zuberbühler, A. D. 189 [G.E. 185]
Zundel, G. 337
Zwaschka, F. 704 [G.E. 747]
Zwierzak, A. 107, 702 [G.E. 109, 737]

SUBJECT INDEX

FP = Full paper (review article) LA = Literature abstract
SC = Short communication
G.E. = Reference to Volume *89* (1977) of the German Edition of Angewandte Chemie.
References are given for Review Articles and Short Communications only.

ABSOLUTE configuration, Relationship between the infrared rotatory dispersion of liquid-crystalline solutions of chiral molecules and their ~ (SC) 791 [G.E. 831]
Acetylacetone, New coordination form (SC) 858 [G.E. 896]
Acetylene, 3,4-Bis(trimethylsilyl)benzocyclobutene—synthesis by ~ cotrimerization and conversion into 1,2-dihydrocyclobuta[c]benzyne (SC) 399 [G.E. 413]
Transition metal-catalyzed cyclizations (LA) 271
Transition metal catalyzed reactions of organic halides with carbon monoxide, olefins, and ~-s (LA) 335
Activation volume, Determination of ~ $\Delta V^{\neq}$ of simple molecular rearrangements by high-resolution ^{1}H-NMR spectroscopy at high pressures (SC) 331 [G.E. 340]
Acyl chlorides, Unstable intermediates in the gaseous phase: Thermal decomposition of ~ RCOCl (SC) 105 [G.E. 106]
Reactions of ~, triethylamine, or ketenes with phosgeniminium salts (SC) 182 [G.E. 189]
N-Acyl isocyanides (SC) 262 [G.E. 272]
Acyl thioacyl sulfides, Isolation (SC) 879 [G.E. 917]
Addition, Intramolecular oxidative ~ of azopyridine to phosphorus(III) (SC) 865 [G.E. 903]
Addition compounds with polymeric chromium(II)-Schiff base complexes (SC) 859 [G.E. 897]
Adenine nucleotides, Investigations of translocation of mitochondrial ~ by means of nucleotide analogs (FP) 695 [G.E. 717]
Alcohols, Photolysis of saturated ~, ethers, and amines (LA) 804
Aldehydes, Homologization of ~ and ketones to thiiranes or S-vinyl thiocarbamates via 2-alkylimino-1,3-oxathiolanes (SC) 462 [G.E. 478]
Alkali metal complexes, Kinetics of formation by bicyclic cryptates (SC) 538 [G.E. 567]
Alkali metal derivatives, Di- and poly-~ of organic compounds (LA) 803
Alkaloids, Diastereoselective synthesis of the aporphine alkaloid (+)-cataline. Hydroxylation with vanadium(V) trifluoride oxide (SC) 730 [G.E. 739]
Simple stereoselective synthesis of eburnamonine (SC) 878 [G.E. 916]
Alkanes, Observation of a linear relationship between thermal stability and strain energy of ~ (SC) 875 [G.E. 913]
Alkylation of diethyl phosphoramidates—A simple route from primary to secondary amines (SC) 107 [G.E. 109]
Alkyne complexes, Synthesis of alkyne-bridged dinuclear complexes by reaction of trans-halotetracarbonyl(methylcarbyne)tungsten with methylenebis(diphenylarsane) (SC) 465 [G.E. 481]
Allylacetophenone, Doubly deprotonated ~. First example of a "direct" E^5 synthon (SC) 320 [G.E. 333]
Allyl alcohols, C—C linkage of carboxylic acids with ~ using 2-phenylglycine as vehicle (SC) 394 [G.E. 408]
Alternating copolymerization, Spontaneous ~ via zwitterion intermediates (FP) 826 [G.E. 867]
Aluminacyclopentadiene, Novel organonickel compounds from (pentaphenyl)-~ (SC) 183 [G.E. 179]
Aluminum, Bindung of urease to anodized sheet ~ (SC) 714 [G.E. 761]
Aluminum compounds, Synthesis and properties of tris(trimethylsilyl)aluminum (SC) 480 [G.E. 497]
Synthesis and structure determination of a 1,4-dialuminacyclohexadiene (SC) 539 [G.E. 563]
Amides, N-Acyl-N'-arylsulfonyldiazenes; detection and use in the synthesis of ~ (SC) 728 [G.E. 742]
Aminating reagents, O-Mesitylenesulfonylhydroxylamine and related ~ (LA) 270
Amines, Crown ether catalyzed reduction of aromatic nitro compounds to give ~ (SC) 41 [G.E. 43]
Alkylation of diethyl phosphoramidates—A simple route from primary to secondary ~ (SC) 107 [G.E. 109]
Photolysis of saturated alcohols, ethers, and ~ (LA) 804
Amino acid esters, Facile synthesis of α,β-dehydro ~ (SC) 327 [G.E. 344]
Amino acids, Synthesis of N-protected ~ with the aid of stannyl azides (SC) 550 [G.E. 570]
"Uncommon" ~ in plants (LA) 60
p-Aminophenols, Synthesis of substituted ~ from p-phenylenediamines (SC) 266 [G.E. 273]
Aminophosphanes, Synthesis of a secondary aminophosphane (SC) 486 [G.E. 501]
Amino sugars and N-glycosides by oxyamination of unsaturated carbohydrate derivatives (SC) 553 [G.E. 565]
Ammonium salts, Vinylenedionium salts containing different onium groups (SC) 471 [G.E. 488]
Reactions of (2-dialkylsulfoniovinyl)trialkyl-~ (SC) 473 [G.E. 489]
Inclusion of anions in macrotricyclic quaternary ~ (SC) 720 [G.E. 751]
α-Amylase, Protein inhibitors of ~ in wheat (LA) 804
Analytical chemistry, Grundlagen der analytischen Chemie (Book Review) 123
Analytical methods, Fully automatic potentiometric titrations (FP) 157 [G.E. 129]
The electro-optical Kerr effect in conformational analysis (FP) 663 [G.E. 725]
Angiotensin, Structure-activity relations of antagonists of the renin-~ system (LA) 201
Annelation reactions, Use of malononitrile for ~ (LA) 122
[15]Annulenone, syn-4,13;6,11-Dimethano-~, a 14π-analog of tropone—Synthesis and X-ray structure analysis (SC) 170 [G.E. 176]
Anthracene radical cations, Radical cation of [2.2](9,10)anthracenophane as a model for dimeric ~ (SC) 657 [G.E. 666]
[2.2](9,10)Anthracenophane, Radical cation of ~ as a model for dimeric anthracene radical cations (SC) 657 [G.E. 666]
Anthraquinones, Synthesis of hypericin and related mesonaphthodianthrones by alkaline dimerization of hydroxy-~ (SC) 46 [G.E. 56]
Antibiotics, Macrolides. Recent progress in chemistry and biochemistry (FP) 585 [G.E. 602]
Some aspects of ~ research (FP) 687 [G.E. 696]
Arabinoadenosine 3'-phosphate, Facile synthesis (SC) 317 [G.E. 328]
Aromaticity, "Organic metals"—intermolecular migration of ~ (FP) 519 [G.E. 534]
Arsabenzene, 1-Aryl-4-methoxyarsacyclohexadiene→2-aryl-~ rearrangement—An organoelement analog of the cyclohexadienol→benzene rearrangement (SC) 637 [G.E. 670]
Arsanes, Phenyl-[2,2-dimethyl-1-(trimethylsiloxy)propylidene]arsane, an arsane with an isolated As=C bond (SC) 463 [G.E. 477]
Synthesis of alkyne-bridged dinuclear complexes by reaction of trans-halotetracarbonyl(methylcarbyne)tungsten with methylenebis(diphenylarsane) (SC) 465 [G.E. 481]
2C-chain elongation of lithioalkanes with diphenylvinylarsane and phenyl vinyl selenide (SC) 710 [G.E. 760]
Arsenic compounds, Lithiomethyl(diphenyl)-arsane oxide, a new reagent (SC) 53 [G.E 52]
Catalytic activity by opening of metal-metal bonds (SC) 188 [G.E. 197]
An organometallic five-membered ring with hetero-metal-metal bonding (SC) 332 [G.E. 341]
Versatile principle for the synthesis of functionalized hydrocarbons via organo-~ (SC) 709 [G.E. 759]
Ba_3A_{14}, the first compound to contain the cluster anion As_7^{3-} (SC) 857 [G.E. 895]
Arsonium ylides, Reaction with carbonyl compounds—Effect of substituents at arsenic (SC) 487 [G.E. 502]
Ascorbic acid, Reaction with dicyanocobyrinic heptamethyl ester (SC) 481 [G.E. 486]
Asymmetric induction in the total synthesis of 19-norsteroids (LA) 201
Atmosphere, Analysis of soil ~ by gas chromatography (LA) 419
Atmospheric chemistry (Book Review) 733
2H-Azirines, Nickel(II)-catalyzed synthesis of pyrroles from ~ and activated ketones (SC) 647 [G.E. 672]
Photochemistry (LA) 121
Azo compounds, [2+2]- and [4+2]-cycloadditions of arylazoalkenes (SC) 58 [G.E. 59]
Azodicarboxylates, 2,3-Dioxabicyclo[2.2.2]octane by selective reduction of double bonds with ~ (SC) 713 [G.E. 762]
Azuleno[4,5,6-cd]phenalene; a novel nonalternant isomer of benzo[a]pyrene (SC) 784 [G.E. 821]

BARBIER reaction—A one-step alternative for syntheses via organomagnesium compounds (LA) 271
Barium compounds, Ba_3A_{14}, the first compound to contain the cluster anion As_7^{3-} (SC) 857 [G.E. 895]
Barium disilicide, Crystal structure at high pressures (SC) 659 [G.E. 673]
Benzimidazole, Model of internal monooxygenase catalyzed reactions: copper-catalyzed autoxidation of bis(1-methylbenzimidazol-2-yl)methane (SC) 189 [G.E. 185]
Benzocyclobutene, 3,4-Bis(trimethylsilyl)-~—Synthesis by acetylene cotrimerization and conversion into 1,2-dihydrocyclobuta[c]benzyne (SC) 399 [G.E. 413]
Benzocyclobutenone, Formation by gas-phase pyrolysis (SC) 469 [G.E. 485]
Benzoin, 2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexaoxa-2,11-cyclooctadecadiene: A new crown ether from ~ (SC) 467 [G.E. 484]
Benzo[a]pyrene, Synthesis of perdeuterio-~ (SC) 656 [G.E. 667]
Azuleno[4,5,6-cd]phenalene; a novel nonalternant isomer of ~ (SC) 784 [G.E. 821]
5H-[1]Benzoselenino[2,3-b]pyridine—A novel heterocyclic ring system (SC) 319 [G.E. 329]
2,1,3-Benzothiadiazine, A novel heteroaromatic system: 2,1,3-Benzothiadiazinylium derivatives (SC) 780 [G.E. 826]

Bicyclo[3.2.0]heptanones, Uses (LA) 419
Bicyclo[5.1.0]octa-2,4-dienes, Carbo-Claisen rearrangement of 8-endo-phenyl-~ (SC) 711 [G.E. 763]
Bicyclophosphoranes, Intramolecular oxidative addition of azopyridine to phosphorus(III) (SC) 865 [G.E. 903]
Bilatriene-abc, A geometrically isomeric ~ (SC) 470 [G.E. 487]
Bile pigments, A geometrically isomeric bilatriene-abc (SC) 470 [G.E. 487]
Binding energy, entropy, and enzymic catalysis (FP) 449 [G.E. 456]
Biological technology, Utilization of microbes—Modern developments in ~ (FP) 205 [I.E. 211]
Biorhythms, Pineal gland ~ (LA) 122
Birth control, Role in the survival of the human race (FP) 506 [G.E. 513]
2,6-Bisazoniabicyclo[5.1.0]octa-2,5-diene, Degenerate Cope rearrangement of ~ dication (SC) 643 [G.E. 668]
Bis(thioacyl) sulfide, New aliphatic thiacylating reagents; preparation of tert-butyl esters of aliphatic dithiocarboxylic acids via ~ (SC) 786 [G.E. 820]
2,4-Diisopropyl-1,3-dithietane-2,4-diyl bis(dithioisobutyrate), a dimeric form of ~ (SC) 787 [G.E. 820]
Bis(trimethylsilyl)magnesium—The first organosilylmagnesium compound isolated (SC) 247 [G.E. 257]
Boc-azide, Serious detonation during the preparation of tert-butyloxycarbonyl azide (~) (SC) 115 [G.E. 119]
Bonding, Experimental electron densities and chemical ~ (FP) 32 [G.E. 33]
The surface chemical bond (FP) 92 [G.E. 94]
Early history of the quantum mechanical treatment of the chemical bond (FP) 87 [G.E. 89]
The Pauli principle and chemical ~ in molecules and solids (FP) 294 [G.E. 317]
Novel 3z-2e bond system (SC) 248 [G.E. 257]
Bond lengths, Diastereomers with differing ~: Structure analysis of the diastereomeric forms of μ-(1,2-dichloro-1,2-diphenyldiphosphane)bis(pentacarbonylchromium) (SC) 260 [G.E. 268]
Boranes, Synthesis and dynamic behavior of pentamethylcyclopentadienyl-~ (SC) 41 [G.E. 44]
New nido-carbaborane type by η^1—η^5 rearrangement of pentamethylcyclopentadienyl-~ (SC) 330 [G.E. 339]
Borates, Isolation of isomeric iodohydro-~ of type $[B_{10}H_{10-n}I_n]^{2-}$ (SC) 398 [G.E. 412]
Borole, Two routes to complex derivatives (SC) 42 [G.E. 43]
Boron compounds, Isolation of halohydroborates of type $[B_{10}H_{10-n}X_n]$ (SC) 173 [G.E. 195]
Δ^4-1,3,2-Diazaborolines as complex ligands (SC) 249 [G.E. 258]
Crystal structure of B_2S_3: Four-membered B_2S_2 rings and six-membered B_3S_3 rings (SC) 313 [G.E. 327]
μ-Thiadiborolene-bis(η-thiadiborolenecobalt)—A "homogeneous" triple-decker sandwich with three heterocyclic ligands (SC) 333 [G.E. 346]
Boron-nitrogen heterocycles, New pathways to four-membered ~ (SC) 478 [G.E. 494]
Bromine compounds, Difluorooxobromine(V) ion, $BrOF_2^+$ (SC) 461 [G.E. 476]
Butadiene, Control of the direction of addition in the nickel-catalyzed 2:1-cooligomerization of ~ with monoolefins by perturbation of the monoolefin (SC) 252 [G.E. 260]
Control of the nickel-catalyzed cooligomerization of butadiene with Schiff bases by cocatalysts (SC) 253 [G.E. 261]
tert-Butylation, Side reactions in peptide synthesis: ~ of tryptophan (SC) 317 [G.E. 330]
tert-Butyloxycarbonyl azide, Serious detonation during the preparation of ~ (Boc-azide) (SC) 115 [G.E. 119]
CALCIUM isotope effect, Dependence of ~ upon electrolyte concentration in ion-exchange chromatography (SC) 719 [G.E. 753]
Carbaboranes, New nido-carbaborane type by η^1—η^5 rearrangement of pentamethylcyclopentadienylboranes (SC) 330 [G.E. 339]
Carbanions, Nucleophilic substitution of vinylic hydrogen atoms by ~ (SC) 44 [G.E. 46]
Fast reactions of ~ and carbocations in solution (LA) 122
Carbene reactions, CIDNP studies on ~ (LA) 419
Carbenes, Thermal and photochemical cycloelimination of nitrogen (FP) 835 [G.E. 876]
Carbene addition to dicarbonyl(η-cyclopentadienyl)cobalt (SC) 555 [G.E. 557]
α-Oxocarbene-oxirene isomerization: Photolysis of [1-^{13}C]-2-diazo-1-phenyl-1-propanone and [2-^{13}C]-1-diazo-1-phenyl-2-propanone (SC) 781 [G.E. 827]
Carbocations, Fast reactions of carbanions and ~ in solution (LA) 122
Carbo-Claisen rearrangement of 8-endo-phenylbicyclo[5.1.0]octa-2,4-dienes (SC) 711 [G.E. 763]
Carbodiimides, New reagents for synthesis of heterocycles from ~ and phosgeniminium salts (SC) 181 [G.E. 188]
Silatautomeric organyl-~/cyanamides (SC) 311 [G.E. 336]
~ as source of isocyanide and carbonyl ligands (SC) 641 [G.E. 660]
"Carbodiphosphoranes" by a new rearrangement of phosphorus ylides (SC) 417 [G.E. 428]
Carbohydrates, α-Glycosidic linkage of D-ribofuranose (SC) 48 [G.E. 58]
Tetraaxial conformation of 1,2,3,4-tetra-O-benzoyl-β-D-xylopyranose (SC) 52 [G.E. 51]
Amino sugars and N-glycosides by oxyamination of unsaturated carbohydrate derivatives (SC) 553 [G.E. 565]
Simple de-novo synthesis of reactive pseudoglycals (hex-2-enopyranosides)—Stereospecific α-glycoside coupling (SC) 783 [G.E. 822]
Structure of ketoses and their biologically important phosphate esters in solution (LA) 201
Carbon disulfide, Intramolecular mobility in ~ complexes of manganese (SC) 193 [G.E. 191]
Acceptor function of η^2-bonded ~ ligands (SC) 194 [G.E. 192]
Carbon monoxide, Synthetic and mechanistic aspects of inorganic insertion reactions. Insertion of ~ (FP) 299 [G.E. 305]
Elimination of ~ from cyclic carbonyl compounds by flow pyrolysis (SC) 50 [G.E. 50]
Reaction of olefins with silane and ~ catalyzed by $Co_2(CO)_8$ (SC) 174 [G.E. 196]
$Co_2(CO)_8$ catalyzed reactions of cyclic ethers with hydrosilanes and ~ (SC) 789 [G.E. 818]
Catalyst dependent product distribution in the reaction of 1-hexene with a hydrosilane and ~ (SC) 881 [G.E. 919]
Transition metal catalyzed reactions of organic halides with ~, olefins, and acetylenes (LA) 335
Carbonylation, δ-Lactones by ~ of vinyloxiranes (SC) 50 [G.E. 47]
Carbonyl compounds, Elimination of CO from cyclic ~ by flow pyrolysis (SC) 50 [G.E. 50]
Carbonyl groups and thiocarbonyl groups (LA) 732
Carbonyl olefination with (triphenylstannyl)-methyllithium (SC) 862 [G.E. 900]
Carbonyl ylides, Electrocyclic ring opening reactions of ethylene oxides (FP) 572 [G.E. 589]
Carboxylic acids, C—C linkage of ~ with allyl alcohols using 2-phenylglycine as vehicle (SC) 394 [G.E. 408]
Carbyne complexes, Triphenylsilyl-~ of tungsten (SC) 401 [G.E. 416]
Carcinogens, Synthesis of perdeuteriobenzo[a]pyrene (SC) 656 [G.E. 667]
Azuleno[4.5,6-cd]phenalene; a novel nonalternant isomer of benzo[a]pyrene (SC) 784 [G.E. 821]
(+)-Cataline, Diastereoselective synthesis of the aporphine alkaloid ~. Hydroxylation with vanadium(V) trifluoride oxide (SC) 730 [G.E. 739]
Catalysis, Advances in phase-transfer ~ (FP) 493 [G.E. 521]
Titanium tetrachloride in organic synthesis (FP) 817 [G.E. 858]
Catalyst dependent product distribution in the reaction of 1-hexene with a hydrosilane and carbon monoxide (SC) 881 [G.E. 919]
Recent developments in heterogeneous ~, especially ~ by metals (LA) 271
Applications of Mössbauer spectroscopy to the study of heterogeneous ~ (LA) 335
Cationization, Quantitative field desorption mass spectrometry; stable isotope dilution and ~ (SC) 184 [G.E. 180]
Ceramics, Phosphates in ~ (LA) 490
Chain elongation, Titanium tetrachloride in organic synthesis (FP) 817 [G.E. 858]
Lithiomethyl(diphenyl)arsane oxide, a new reagent (SC) 53 [G.E. 52]
C—C linkage of carboxylic acids with allyl alcohols using 2-phenylglycine as vehicle (SC) 394 [G.E. 408]
2C-~ of lithioalkanes with diphenylvinylarsane and phenyl vinyl selenide (SC) 710 [G.E. 760]
Charge transfer interactions, Indirectly transmitted ~: Multilayered [2.2]paracyclophane quinhydrones (SC) 801 [G.E. 841]
Chemical dictionary, Römpps Chemie-Lexikon (Book Review) 883
Chemiluminescence, Analytical applications (FP) 225 [G.E. 220]
Chemisorption, The surface chemical bond (FP) 92 [G.E. 94]
Chirality, Chiral derivatives of achiral molecules. Standard classes and the problem of a right-left classification (FP) 65 [G.E. 67]
Chlorine isotopes, Determination of reaction enthalpy in the ion-exchange of ~ (SC) 114 [G.E. 118]
Chlorobenzenes, Formation of chlorophenols by microbial transformation of ~ (SC) 645 [G.E. 680]
N-Chlorocarbonyl isocyanate, Synthesis and reactions (FP) 743 [G.E. 789]
Chlorofluorocarbon/ozone theory—A scientific status report (FP) 513 [G.E. 507]
Chlorofluorocarbons, The chlorofluorocarbon/ozone theory—A scientific status report (FP) 513 [G.E. 507]
(Chloromethylene)triphenylphosphorane (SC) 180 [G.E. 203]
Chlorophenols, Formation by microbial transformation of chlorobenzenes (SC) 645 [G.E. 680]
Chlorotris(2,2,2-trifluoro-1-trifluoromethylethoxy)sulfurane, A stable acyclic alkoxyhalosulfurane: ~ (SC) 862 [G.E. 900]
Chromatin, Elucidation of structure and specificity (LA) 122
Chromatography, Column ~ on triacetylcellulose. Preparative separation of enantiomeric diaziridines (SC) 405 [G.E. 419]
Chromium complexes, cis-Bis(dinitrogen)tetrakis(trimethylphosphane)chromium (SC) 56 [G.E. 57]
Acceptor function of η^2-bonded CS_2 ligands (SC) 194 [G.E. 192]
Δ^4-1,3,2-Diazaborolines as complex ligands (SC) 249 [G.E. 258]
Synthesis of dinuclear complexes containing PCl_2 and PF_2 bridges (SC) 408 [G.E. 421]
$[C_5H_5(CO)_2Mn—N_2H_2—Cr(CO)_5]$, a complex with a diazene bridge and two different coordination centers (SC) 464 [G.E. 480]
μ-(η-Biphenyl)bis[(η-benzene)chromium(0)]—The arenechromium analog of biferrocene (SC) 479 [G.E. 497]
Pentacarbonyl(dimesitylgermanediyl)chromium(0) (SC) 639 [G.E. 675]
Addition compounds with polymeric chro-

mium(II)-Schiff base complexes (SC) 859 [G.E. 897]
Bis(η⁶-naphthalene)chromium(0) (SC) 870 [G.E. 908]
Chronology of chemistry, Chronologie Chemie 1800—1970 (Book Review) 733
Claisen rearrangement, Carbo-~ of 8-endophenylbicyclo[5.1.0]octa-2,4-dienes (SC) 711 [G.E. 763]
Cluster anion, Ba_3A_{14}, the first compound to contain the ~ As_7^{3-} (SC) 857 [G.E. 895]
Cobalt complexes, Partial nitrosylation of dicarbonyl(η-cyclopentadienyl)cobalt (SC) 172 [G.E. 186]
"Supersandwich"-type trinuclear complexes with a spiro center (SC) 324 [G.E. 332]
μ-Thiadiborolene-bis(η-thiadiborolenecobalt)—A "homogeneous" triple-decker sandwich with three heterocyclic ligands (SC) 333 [G.E. 346]
Carbene addition to dicarbonyl(η-cyclopentadienyl)cobalt (SC) 555 [G.E. 557]
Synthesis and reactivity of hetero dinuclear complexes containing a Mn—Co bond (SC) 649 [G.E. 656]
$Co_5(CO)_{11}(PR_2)_3$, a novel type of pentanuclear cluster (SC) 731 [G.E. 738]
$Co_2(CO)_8$ catalyzed reactions of cyclic ethers with hydrosilanes and carbon monoxide (SC) 789 [G.E. 818]
An unusually facile electrophilic substitution at the cyclopentadienyl ring in a half-sandwich complex (SC) 794 [G.E. 835]
Detection of rigid rotamers in disubstituted cyclopentadienylcobalt complexes (SC) 795 [G.E. 836]
(η-Cyclopentadienyl)cobalt-μ-(η-diborolenyl)(η-cyclopentadienyl)iron—A triple decker sandwich complex containing two different metals (SC) 857 [G.E. 895]
Cobalt compounds, Reaction of olefins with silane and carbon monoxide catalyzed by $Co_2(CO)_8$ (SC) 174 [G.E. 196]
Catalytic activity by opening of metal-metal bonds (SC) 188 [G.E. 197]
An organometallic five-membered ring with hetero-metal-metal bonding (SC) 332 [G.E. 341]
Cobalt-catalyzed one-step synthesis of annelated pyridines (SC) 708 [G.E. 758]
Cobyrinic heptamethyl ester, Reaction of dicyano-~ with ascorbic acid (SC) 481 [G.E. 486]
Coenzyme B_{12}, New developments in the field of vitamin B_{12}: Enzymatic reactions dependent upon corrins and ~ (FP) 233 [G.E. 239]
Collision activation mass spectrometry with novel analysis technique (SC) 120 [G.E. 115]
Complexation chromatography, Resolution of a chiral olefin by ~ on an optically active rhodium(I) complex (SC) 110 [G.E. 113]
Complexes, New varieties of sandwich ~ (FP) 1 [G.E. 1]
Complex ligands, New coordination form of acetylacetone (SC) 858 [G.E. 896]
Configuration, Assignment of ~ of olefins, diols, and epoxides. Quantitative analysis of their stereoisomeric mixtures (SC) 100 [G.E. 103]
Conformation, Tetraaxial ~ of 1,2,3,4-tetra-O-benzoyl-β-D-xylopyranose (SC) 52 [G.E. 51]
Configuration, ~, and dynamics of octalene (SC) 972 [G.E. 910]
Determination of ~ of hydrocarbon chains in solution by photochemical probes (LA) 557
Conformational analysis, The electro-optical Kerr effect in ~ (FP) 663 [G.E. 725]
Conformers, Chair and boat: stable ~ of an eight-membered ring system (SC) 185 [G.E. 185]
Conjugation, Through-bond interaction between two mutually perpendicular systems—A new possibility of ~ (SC) 110 [G.E. 122]
Contraception, Role of birth control in the survival of the human race (FP) 506 [G.E. 513]
Coordination, New ~ form of acetylacetone (SC) 858 [G.E. 896]
Cope rearrangement, Degenerate ~ of the 2,6-bisazoniabicyclo[5.1.0]octa-2,5-diene dication (SC) 643 [G.E. 668]
Carbo-Claisen rearrangement of 8-endophenylbicyclo[5.1.0]octa-2,4-dienes (SC) 711 [G.E. 763]
Copolymerization, Spontaneous alternating ~ via zwitterion intermediates (FP) 826 [G.E. 867]
Copper compounds, Model of internal monooxygenase catalyzed reactions: copper-catalyzed autoxidation of bis(1-methylbenzimidazol-2-yl)methane (SC) 189 [G.E. 185]
Corrinoids, (A→D)-Cyclization of a nickel(II) Δ^{18}-dehydro-1-methylidene-1,19-secocorrinate (SC) 459 [G.E. 475]
Reaction of dicyanocobyrinic heptamethyl ester with ascorbic acid (SC) 481 [G.E. 486]
Corrins, New developments in the field of vitamin B_{12}: Enzymatic reactions dependent upon ~ and coenzyme B_{12} (FP) 233 [G.E. 239]
(A→D)-Cyclization of a nickel(II) Δ^{18}-dehydro-1-methylidene-1,19-secocorrinate (SC) 459 [G.E. 475]
Crown ethers, Crown ether catalyzed reduction of aromatic nitro compounds to give amines (SC) 41 [G.E. 43]
"Noncyclic ~": The terminal group concept (SC) 396 [G.E. 410]
2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexaoxa-2,11-cyclooctadecadiene: A new crown ether from benzoin (SC) 467 [G.E. 484]
Cryptates, Kinetics of alkali metal complex formation by bicyclic ~ (SC) 538 [G.E. 567]
Noncyclic ~ (SC) 548 [G.E. 564]
Cubanes, Synthesis and absolute configuration of enantiomerically pure D_3-trishomo-~ (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane) and trishomocubanones (SC) 116 [G.E. 119]
Hydrogenation (SC) 415 [G.E. 430]
Cubane structure, $[\eta^5\text{-}C_5H_5Mo(CO)_3HgMo]_4$, a metal cluster with ~ (SC) 704 [G.E. 746]
Cyanamides, Silatautomeric organylcarbodiimides/~ (SC) 311 [G.E. 336]
Cyclization, 4-Hydroxy-2-cyclopenten-1-ones from ketones and 3-nitropropionyl chloride. A facile method for the construction of five-membered rings (SC) 321 [G.E. 334]
Cycloadditions, Intramolecular [4+2] and [3+2] ~ in organic synthesis (FP) 10 [G.E. 10]
[2+2]- and [4+2]-~ of arylazoalkenes (SC) 58 [G.E. 59]
Geometrical dependence of [2π+2σ]photocycloaddition (SC) 103 [G.E. 111]
Cycloaddition of phenyl isocyanate to a diaziridinimine (SC) 109 [G.E. 112]
Extension of the scope of anionic ~ by activating organoelement groups (SC) 119 [G.E. 107]
Palladium(0)-catalyzed [2σ+2π]~ of methylenecyclopropane to alkenes (SC) 249 [G.E. 254]
Photochemical [2+2]-~ between parallel CC and NN double bonds (SC) 777 [G.E. 825]
Cyclobutadiene, Diradical-type behavior of tri-tert-butyl-~ (SC) 51 [G.E. 49]
Observed and calculated electron-density distribution in the bonds of a rectangular ~ (SC) 187 [G.E. 194]
Reversible transition between a [4]radialene and a ~ by electron transfer (SC) 410 [G.E. 424]
Cyclodepsipeptides, Synthesis by cyclooligomerization (SC) 113 [G.E. 117]
Cycloelimination, Thermal and photochemical ~ of nitrogen (FP) 835 [G.E. 876]
Cycloheptadienes, Models for the biosynthesis of naturally occurring divinylcyclopropanes and ~ (SC) 192 [G.E. 187]
Cyclohexanes, Substituted phenyl-~—A new class of liquid-crystalline compounds (SC) 100 [G.E. 103]
Cyclohexasilane, Preparation (SC) 403 [G.E. 417]
cis,trans-1,5-Cyclooctadienes (SC) 406 [G.E. 420]
Cyclooctasulfur, Detection of S_6 and S_7 in molten ~ (SC) 112 [G.E. 114]
Cyclopentadiene, An unusually facile electrophilic substitution at the cyclopentadienyl ring in a half-sandwich complex (SC) 794 [G.E. 835]
Cyclopentadienone, A trimeric ~ derivative by photolysis of 3,5-diphenyl-4H-thiopyran-4-one 1,1-dioxide with daylight (SC) 653 [G.E. 659]
Cyclopentadienylborane, Synthesis and dynamic behavior of pentamethyl-~ (SC) 41 [G.E. 44]
(η-Cyclopentadienyl)cobalt-μ-(η-diborolenyl)(η-cyclopentadienyl)iron—A triple decker sandwich complex containing two different metals (SC) 857 [G.E. 895]
2-Cyclopenten-1-ones, 4-Hydroxy-~ from ketones and 3-nitropropionyl chloride. A facile method for the construction of five-membered rings (SC) 321 [G.E. 334]
Cyclophanes, [2.2.2.2](1,2,3,5)cyclophane (SC) 191 [G.E. 177]
Cyclopropenes as vinylcarbenoids: intermolecular carbene-addition reactions of sulfinyl- and sulfonylcyclopropenes at room temperature (SC) 323 [G.E. 331]
Cyclopropenone, Novel transformation of diphenyl-~: Double bond cleavage in the reaction with platinum complexes (SC) 793 [G.E. 838]
Cycloreversion, Formation of diazo compounds on degradation of 2,3-diazabicyclo[3.1.0]hex-2-enes: [3+2]-cycloreversion (SC) 867 [G.E. 905]
Cyclotetra(λ^3-phosphazanes), $(RPNCH_3)_4$, — Synthesis and crystal structure analysis (SC) 407 [G.E. 423]

DECARBOXYLATIVE dehydration of β-hydroxycarboxylic acids by redox condensation: a novel olefin synthesis (SC) 255 [G.E. 265]
α,β-Dehydro amino acid esters, Facile synthesis (SC) 327 [G.E. 344]
Dehydro amino acids, Activation of double bonds in ~: A model for pyridoxal-containing enzymes in elimination-addition reactions (SC) 328 [G.E. 345]
Deprotonation, Doubly deprotonated allylacetophenone. First example of a "direct" E^5 synthon (SC) 320 [G.E. 333]
Functional vinyl carbanions—~ of β-(1-pyrrolidinyl)acrylonitrile (SC) 853 [G.E. 891]
Depsipeptides, Synthesis of cyclo-~ by cyclooligomerization (SC) 113 [G.E. 117]
Desalination, Principles of osmotic ~ (FP) 607 [G.E. 624]
Detergents, Micelles of ionic ~ in aqueous solutions (LA) 490
Detonation, Serious ~ during the preparation of tert-butyloxycarbonyl azide (Boc-azide) (SC) 115 [G.E. 119]
Deuteriobenzo[a]pyrene, Synthesis of per-~ (SC) 656 [G.E. 667]
1,4-Dialuminacyclohexadiene, Synthesis and structure determination (SC) 539 [G.E. 563]
Diastereoisomers with differing bond lengths: structure analysis of the diastereomeric forms of μ-(1,2-dichloro-1,2-diphenyldiphosphane)bis(pentacarbonylchromium) (SC) 260 [G.E. 268]
2,3-Diazabicyclo[3.1.0]hex-2-enes, Formation of diazo compounds on degradation of ~: [3+2]-cycloreversion (SC) 867 [G.E. 905]
Δ^4-1,3,2-Diazaborolines as complex ligands (SC) 249 [G.E. 258]
Diazadiphosphetidine, A ~ with ring-stabilized "pentaamidophosphorus" (SC) 263 [G.E. 268]
cis-2-Telluro-1,3,2λ^5,4λ^3-~—A fluxional redox system (SC) 486 [G.E. 500]
Synthesis of bridged 1,3,2λ^3,4λ^3—~ (SC) 797 [G.E. 829]
Diazene, N-Acyl-N'-arylsulfonyl-~-s; detection and use in synthesis of amides (SC) 728 [G.E. 742]

cis- and trans-~ (Diimine) (SC) 780 [G.E. 828]
Diazene complexes, $[C_5H_5(CO)_2Mn—N_2H_2—Cr(CO)_5]$, a complex with a diazene bridge and two different coordination centers (SC) 464 [G.E. 480]
Diazene derivatives, First reaction of the N_2 ligand with bases; reduction of coordinated dinitrogen by nucleophilic attack (SC) 880 [G.E. 918]
Diaziridines, Column chromatography on triacetylcellulose. Preparative separation of enantiomeric ~ (SC) 405 [G.E. 419]
Synthesis and chemistry of alkylidene-~ (SC) 475 [G.E. 492]
Diaziridinimine, Cycloaddition of phenyl isocyanate to a ~ (SC) 109 [G.E. 112]
Spiro compounds having a nonplanar 1,4-dihydropyridine ring from ~-s and dimethyl acetylenedicarboxylate (SC) 177 [G.E. 202]
Diazoacetate, Reaction of alkenylfurans with ethyl ~ (SC) 646 [G.E. 674]
Diazo compounds, α-Oxocarbene-oxirene isomerization: Photolysis of [1-^{13}C]-2-diazo-1-phenyl-1-propanone and [2-^{13}C]-1-diazo-1-phenyl-2-propanone (SC) 781 [G.E. 827]
Formation on degradation of 2,3-diazabicyclo[3.1.0]hex-2-enes: [3 + 2]-cycloreversion (SC) 867 [G.E. 905]
Diazomethane, Iso-~ complexes (SC) 707 [G.E. 752]
"o,p'-Dibenzene" (3—6-η-tricyclo[6.2.2.0^{2,7}]-dodeca-3,5,9,11-tetraene)tricarbonyliron, a stable transition metal complex of ~ (SC) 717 [G.E. 754]
1,3-Diborolenes, η-Cyclopentadienyl(η-diborolenyl)nickel—A diamagnetic nickelocene analog (SC) 468 [G.E. 483]
α-Dicarbonyl systems, Interaction between the nonbonding orbitals of ~ and π or Walsh orbitals (SC) 400 [G.E. 414]
Dichloronitronium ion, Dichloronitronium hexachloroantimonate, $ONCl_2SbCl_6$ (SC) 545 [G.E. 569]
Dichlorophosphoranes, Hydrogenolysis of trisubstituted ~—A new method for deoxygenation of oxophosphoranes (SC) 552 [G.E. 558]
Dicyanocobyrinic heptamethyl ester, Reaction with ascorbic acid (SC) 481 [G.E. 486]
Dicyanophosphide (SC) 704 [G.E. 747]
Dienes, Selective monofunctionalization of non-conjugated ~ by nitrogen dioxide/iodine monoaddition (SC) 246 [G.E. 253]
Imidazolidin-2-ones by anodic oxidation of conjugated ~ in the presence of dimethylurea (SC) 413 [G.E. 425]
Difluorooxobromine(V) ion, $BrOF_2^+$ (SC) 461 [G.E. 476]
1,2-Dihydrocyclobuta[c]benzyne, 3,4-Bis(trimethylsilyl)benzocyclobutene—Synthesis by acetylene cotrimerization and conversion into ~ (SC) 399 [G.E. 413]
2,3-Dihydro-1,4-dioxocin, 6,7-Diphenyl-~ (SC) 552 [G.E. 555]
1,4-Dihydropyridine, Spiro compounds having a nonplanar ~ ring from diaziridinimines and dimethyl acetylenedicarboxylate (SC) 177 [G.E. 202]
Diimine, cis- and trans-Diazene (~) (SC) 780 [G.E. 828]
Diimine complexes, $[C_5H_5(CO)_2Mn—N_2H_2—Cr(CO)_5]$, a complex with a diazene bridge and two different coordination centers (SC) 464 [G.E. 480]
syn-4,13;6,11-Dimethano[15]annulenone, a 14π-analog of tropone—Synthesis and X-ray structure analysis (SC) 170 [G.E. 176]
Dimethyl sulfoxide, Site of protonation of ~—Raman spectroscopic data (SC) 197 [G.E. 200]
Dinitrogen complexes, The first reaction of the N_2 ligand with bases; reduction of coordinated dinitrogen by nucleophilic attack (SC) 880 [G.E. 918]
Diols, Assignment of configuration of olefins, ~, and epoxides. Quantitative analysis of their stereoisomeric mixtures (SC) 100 [G.E. 103]
2,3-Dioxabicyclo[2.2.2]octane by selective reduction of double bonds with azodicarboxylate (SC) 713 [G.E. 762]
2,3:6,7-Dioxa-bis-σ-homotropones. Synthesis and cis ⇄ trans-isomerization (SC) 198 [G.E. 174]
Dioxacyclooctadiene, Chair and boat: stable conformers of an eight-membered ring system (SC) 185 [G.E. 185]
1,3,4-Dioxazolidine, Synthesis of a stable ~ (SC) 646, 882 [G.E. 675, 920]
1,3-Diphenylallyl anion, Formation of the (Z,E)-1,3-diphenylallyl radical from the (Z,E)-~ by electron transfer—Comparison of the rotational barriers of the radical and the anion (SC) 869 [G.E. 907]
1,3-Diphenylallyl radical, Formation of the (Z,E)-~ from the (Z,E)-1,3-diphenylallyl anion by electron transfer—Comparison of the rotational barriers of the radical and the anion (SC) 869 [G.E. 907]
6,7-Diphenyl-2,3-dihydro-1,4-dioxocin (SC) 552 [G.E. 555]
Diphosgene, Isocyanide synthesis with ~ (SC) 259 [G.E. 267]
1λ^5,3λ^5-Diphosphacyclobutadiene, Synthesis of a stabilized ~ (SC) 402 [G.E. 415]
Dipole metathesis (SC) 54 [G.E. 60]
Dipoles, General procedure for generating conjugated 1,x ~ (SC) 55 [G.E. 61]
Diradicals, Thermal and photochemical cycloelimination of nitrogen (FP) 835 [G.E. 876]
Disulfane oxides, Bis(trifluoromethyl)disulfane oxide $CF_3S(O)SCF_3$ (SC) 723 [G.E. 740]
1,3-Dithietane, 2,4-Diisopropyl-~-2,4-diyl bis-(dithioisobutyrate), a dimeric form of bis-(thioacyl) sulfide (SC) 787 [G.E. 820]
Dithiocarboxylic acids, New aliphatic thiacylating reagents; preparation of tert-butyl esters of aliphatic ~ via bis(thioacyl) sulfide (SC) 786 [G.E. 820]
Dithiohemiacetals, Cyclic ~—Synthesis and properties (SC) 196 [G.E. 201]
Divinylcyclopropanes, Models for the biosynthesis of naturally occurring ~ and cycloheptadienes (SC) 192 [G.E. 187]
DNA ligases of eukaryotes (LA) 61
Double bond cleavage, Novel transformation of diphenylcyclopropenone: ~ in the reaction with platinum complexes (SC) 793 [G.E. 838]
Double bonds, Activation of ~ in dehydro amino acids: a model for pyridoxal-containing enzymes in elimination-addition reactions (SC) 328 [G.E. 345]
Dodecahedrane, Symmetry and vibrational frequencies (SC) 411 [G.E. 431]
Drinking water, Soluble organic compounds present in ~ (LA) 335
Drug analysis, Handbuch der Arzneimittel-Analytik (Book Review) 882
Drug metabolism, Effect of vitamins (LA) 200
Drug-metabolizing enzyme systems of liver microsomes (LA) 201
Effect of dietary lipids on drug metabolizing enzymes (LA) 201
Drugs, Flexible drug molecules and dynamic receptors (FP) 766 [G.E. 805]
Influence of ~ and hormones on lipolysis in heart (LA) 804
EBURNAMONINE, Simple stereoselective synthesis (SC) 878 [G.E. 916]
Electrochemistry, Electrochemical reduction of 2,2,2-trichloroethanols (SC) 57 [G.E. 54]
Imidazolidin-2-ones by anodic oxidation of conjugated dienes in the presence of dimethylurea (SC) 413 [G.E. 425]
Angewandte Elektrochemie (Book Review) 202
Electrodes, Analysis with ion-selective ~ (Book Review) 804
Electron densities, Experimental ~ and chemical bonding (FP) 32 [G.E. 33]
Observed and calculated electron-density distribution in the bonds of a rectangular cyclobutadiene (SC) 187 [G.E. 194]
Comparison of calculated and experimental electron difference densities of tetracyanoethylene (SC) 257 [G.E. 263]
An economic basis for electron difference density calculations (SC) 258 [G.E. 264]
Electron distribution, Oxidation and reduction of methylthio-substituted π-systems and the ~ in their radical ions (SC) 855 [G.E. 893]
Electron transfer, Reversible transition between a [4]radialene and a cyclobutadiene by ~ (SC) 410 [G.E. 424]
Formation of the (Z,E)-1,3-diphenylallyl radical from the (Z,E)-1,3-diphenylallyl anion by ~—Comparison of the rotational barriers of the radical and the anion (SC) 869 [G.E. 907]
Electrophilic substitution, An unusually facile ~ at the cyclopentadienyl ring in a half-sandwich complex (SC) 794 [G.E. 835]
Electrophotography (FP) 374 [G.E. 386]
Emodin, Synthesis of protohypericin from ~ (SC) 46 [G.E. 55]
Enamines, N,N-Bis(trimethylsilyl)-~—Stereoselective synthesis from N,N-bis(trimethylsilyl)thioformamide (SC) 535 [G.E. 550]
Energy transfer, Electronic ~ (LA) 660
Enol ethers, Synthesis of α,β-unsaturated cyclic ketones by sensitized photooxidation of silyl ~ (SC) 413 [G.E. 426]
Chemistry of O-silyl ~ (LA) 335
Entanglement of thread molecules and its influence on the properties of polymers (FP) 751 [G.E. 773]
Entropy, binding energy, and enzymic catalysis (FP) 449 [G.E. 456]
Enzyme catalysis, Efficiency and evolution (FP) 285 [G.E. 295]
Entropy, binding energy, and enzymic catalysis (FP) 449 [G.E. 456]
Enzymes, Organic fluorescence reagents in the study of ~ and proteins (FP) 137 [G.E. 142]
Suicide inactivators for ~ (LA) 60
Immobilized ~ (LA) 60
Drug-metabolizing enzyme systems of liver microsomes (LA) 201
Effect of dietary lipids on drug metabolizing ~ (LA) 201
Epoxides, Assignment of configuration of olefins, diols, and ~. Quantitative analysis of their stereoisomeric mixtures (SC) 100 [G.E. 103]
ESR spectroscopy, Oxidation and reduction of methylthio-substituted π-systems and the electron distribution in their radical ions (SC) 855 [G.E. 893]
Ethers, "Noncyclic crown ~": The terminal group concept (SC) 396 [G.E. 410]
$Co_2(CO)_8$ catalyzed reactions of cyclic ~ with hydrosilanes and carbon monoxide (SC) 789 [G.E. 818]
Photolysis of saturated alcohols, ~, and amines (LA) 804
Ethylbenzene, Ortho-para protonation of toluene and ~ in super acids (SC) 315 [G.E. 323]
Ethylene oxides, Electrocyclic ring opening reactions (FP) 572 [G.E. 589]
Ethynylphosphonium salts, Simple synthesis of (arylethynyl)triphenylphosphonium salts (SC) 45 [G.E. 55]
FIELD desorption mass spectrometry, Quantitative ~; stable isotope dilution and cationization (SC) 184 [G.E. 180]
Quantitative trace analysis of metals by ~ (SC) 852 [G.E. 890]
Five-membered rings, 4-Hydroxy-2-cyclopenten-1-ones from ketones and 3-nitropropionyl chloride. A facile method for the construction of ~ (SC) 321 [G.E. 334]
Flash thermolysis of organic compounds (FP) 365 [G.E. 377]
Flexirubin, Total synthesis of ~ dimethyl ether (SC) 191 [G.E. 198]
Flow pyrolysis, Elimination of CO from cyclic carbonyl compounds by ~ (SC) 50 [G.E. 50]
Fluorescence reagents, Organic ~ in the study of enzymes and proteins (FP) 137 [G.E. 142]

Fluorination, Oligo(difluorophosphoranes) by direct ~ of tertiary phosphanes (SC) 718 [G.E. 763]
Fluorine compounds, Fluorinated isocyanates and their derivatives as intermediates for biologically active compounds (FP) 735 [G.E. 797]
Trifluoromethylamine, CF_3NH_2 (SC) 707 [G.E. 754]
The Te—O—Fe system: $Te(OTeF_5)_6$ (SC) 729 [G.E. 741]
Fluorocarbons, The chlorofluorocarbon/ozone theory—A scientific status report (FP) 513 [G.E. 507]
Force field calculations, Structures of two highly strained tetracyclododecanes (SC) 798 [G.E. 833]
Fulvalenes and fulvenes of a heterocyclic system with 12π electrons—Pseudophenafulvenes and pentapseudophenafulvalenes (SC) 49 [G.E. 48]
Fulvenes and fulvalenes of a heterocyclic system with 12π electrons—Pseudophenafulvenes and pentapseudophenafulvalenes (SC) 49 [G.E. 48]
Furans, Reaction of alkenyl-~ with ethyl diazoacetate (SC) 646 [G.E. 674]

GERMYLENE complexes, Pentacarbonyl(dimesitylgermanediyl)chromium(0) (SC) 639 [G.E. 675]
Glass, Werkstoff Glas (Book Review) 61
Glycosides, α-Glycosidic linkage of D-ribofuranose (SC) 48 [G.E. 58]
Amino sugars and N-~ by oxyamination of unsaturated carbohydrate derivatives (SC) 553 [G.E. 565]
Simple de-novo synthesis of reactive pseudoglycals (hex-2-enopyranosides)—Stereospecific α-glycoside coupling (SC) 783 [G.E. 822]

HALOGEN donors, Temperature dependence of the selectivity of the ~ $XCCl_3$ (SC) 466 [G.E. 482]
Halogen elimination, Electrochemical reduction of 2,2,2-trichloroethanols (SC) 57 [G.E. 54]
Hazardous materials, Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe (Book Review) 271
Heat of hydrogenation of compounds containing isolated and conjugated C=N double bonds (SC) 47 [G.E. 48]
Helical hydrocarbons, New type of ~—Novel C—C coupling by sulfone pyrolysis (SC) 325 [G.E. 358]
Heme biosynthesis, Total synthesis of [^{14}C]- and [^{3}H]-labeled tripyrrole precursors for ~ (SC) 651 [G.E. 676]
Hemiacetals, Cyclic dithio-~—Synthesis and properties (SC) 196 [G.E. 201]
Hemin, Role in the regulation of protein synthesis in erythroid cells (LA) 200
Hemopolymers, Synthetic ~ for reversible binding of molecular oxygen (SC) 117 [G.E. 120]
cyclo-Heptasulfur, Crystal and molecular structure (SC) 715 [G.E. 756]
cyclo-Heptasulfur oxide, Bond interaction in sulfur rings: crystal and molecular structure (SC) 716 [G.E. 757]
Hereditary disorders, Biochemistry of sphingolipid storage diseases (FP) 273 [G.E. 283]
Heteroanions, Thio-~—Unusual metal-ligand interaction and reactions (SC) 705 [G.E. 748]
Heterocycles, Thermal and photochemical cycloelimination of nitrogen (FP) 835 [G.E. 876]
New reagents for synthesis of ~ from carbodiimides and phosgeniminium salts (SC) 181 [G.E. 188]
Four-membered phosphorus-nitrogen-metal heterocycles with zwitterionic structure (SC) 864 [G.E. 902]
Heterocyclic compounds, An introduction to the chemistry of ~ (Book Review) 558
1,4,7,10,13,16-Hexaoxa-2,11-cyclooctadecadiene,2,3,11,12-Tetraphenyl-~: A newcrown ether from benzoin (SC) 467 [G.E. 484]
1-Hexene, Catalyst dependent product distribution in the reaction of ~ with a hydrosilane and carbon monoxide (SC) 881 [G.E. 919]
Holography, Photodielectric polymers for holographic use (FP) 441 [G.E. 467]
Homotropones, 2,3:6,7-Dioxa-bis-σ-~. Synthesis and cis⇄trans isomerization (SC) 198 [G.E. 174]
Hormones, Influence of drugs and ~ on lipolysis in heart (LA) 804
Hydrazine, X-Ray structure analysis of N-phenyl-N′-sulfinyl-~ (SC) 179 [G.E. 190]
Hydride elimination, Stereoselective ~ from organo lithium and -magnesium compounds (SC) 44 [G.E. 46]
1,2-Hydride shift, Anomalous nucleophilic substitution in (chloromethyl)silane: ~ (SC) 639 [G.E. 678]
Hydrocarbons, Versatile principle for the synthesis of functionalized ~ via organoarsenic compounds (SC) 709 [G.E. 759]
Determination of the conformation of hydrocarbon chains in solution by photochemical probes (LA) 557
Hydrogen bond, The ~ (Book Review) 337
Hydrogenolysis of trisubstituted dichlorophosphoranes—A new method for deoxygenation of oxophosphoranes (SC) 552 [G.E. 558]
Hydrosilanes, $Co_2(CO)_8$ catalyzed reactions of cyclic ethers with ~ and carbon monoxide (SC) 789 [G.E. 818]
Hydroxylation, Diastereoselective synthesis of the aporphine alkaloid (+)-cataline. ~ with vanadium(V) trifluoride oxide (SC) 730 [G.E. 739]
Hypericin, Synthesis of ~ and related mesonaphthodianthrones by alkaline dimerization of hydroxyanthraquinones (SC) 46 [G.E. 56]

IMIDAZOLIDIN-2-ones by anodic oxidation of conjugated dienes in the presence of dimethylurea (SC) 413 [G.E. 425]
N-Imidoyl isocyanides (SC) 727 [G.E. 742]
Imines, Photochemistry (LA) 557
Imino ethers, Reactions of phosgeniminium salts with nitriles, ~, and imidoyl chlorides—Synthesis of 4,6-dichloro-2-(dialkylamino)-pyrimidines (SC) 189 [G.E. 182]
Inclusion compounds, Inclusion of anions in macrotricyclic quaternary ammonium salts (SC) 720 [G.E. 751]
7bH-Indeno[1,2,3-jk]fluorenide, Lithium ~, an organolithium compound having a "sandwich" structure (SC) 474 [G.E. 490]
η^5-Indenylrhodium(I) complexes, Reactivity; cyclocotrimerization of alkynes with alkenes (SC) 648 [G.E. 671]
Infrared rotatory dispersion, ~ of liquid-crystalline solutions of chiral molecules (SC) 790 [G.E. 830]
Relationship between the ~ of liquid-crystalline solutions of chiral molecules and their absolute configuration (SC) 791 [G.E. 831]
Inhibitors, Suicide inactivators for enzymes (LA) 60
Protein ~ of α-amylase in wheat (LA) 804
Inorganic chemistry, Anorganisches Grundpraktikum (Book Review) 420
Insertion reactions, Synthetic and mechanistic aspects of inorganic ~. Insertion of carbon monoxide (FP) 299 [G.E. 305]
Interaction orbital, Interaction between the nonbonding orbitals of α-dicarbonyl systems and π or Walsh orbitals (SC) 400 [G.E. 414]
Intercalation compounds, Demonstration of the ionic structure of $TaS_2 \cdot NH_3$ (SC) 199 [G.E. 193]
Internal monooxygenase, A model of ~ catalyzed reactions: copper-catalyzed autoxidation of bis(1-methylbenzimidazol-2-yl)methane (SC) 189 [G.E. 185]
Intramolecular cycloadditions, Intramolecular [4+2] and [3+2] cycloadditions in organic synthesis (FP) 10 [G.E. 10]
Iodine, Selective monofunctionalization of nonconjugated dienes by nitrogen dioxide/~ monoaddition (SC) 246 [G.E. 253]
Iodobenzenes, Regiospecific synthesis of mono- and polyiodo derivatives of benzene (SC) 488 [G.E. 502]
Iodohydroborates, Isolation of isomeric ~ of type $[B_{10}H_{10-n}I_n]^{2-}$ (SC) 398 [G.E. 412]
Ion exchange, Determination of reaction enthalpy in the ~ of chlorine isotopes (SC) 114 [G.E. 118]
Ion-exchange chromatography, Dependence of the calcium isotope effect upon the electrolyte concentration in ~ (SC) 719 [G.E. 753]
Ionization barrier of trityl chloride in sulfur dioxide (SC) 256 [G.E. 266]
Ion-selective electrodes, Analysis with ~ (Book Review) 804
Iron complexes, Two routes to complex derivatives of borole (SC) 42 [G.E. 43]
Phosphorus-bridged trinuclear complexes having contiguous metal-metal bonds (SC) 542 [G.E. 568]
(3—6-η-Tricyclo[6.2.2.0^{2,7}]dodeca-3,5,9,11-tetraene)tricarbonyliron, a stable transition metal complex of "o,p′-dibenzene" (SC) 717 [G.E. 754]
Base-stabilized silylene-~ (SC) 785 [G.E. 823]
Iron compounds, The first oxoferrate(III) having a ring structure: $Na_{14}[Fe_6O_{16}]$ (SC) 43 [G.E. 45]
Catalytic activity by opening of metal-metal bonds (SC) 188 [G.E. 197]
An organometallic five-membered ring with hetero-metal-metal bonding (SC) 332 [G.E. 341]
Isocyanates, Fluorinated ~ and their derivatives as intermediates for biologically active compounds (FP) 735 [G.E. 797]
Synthesis and reactions of N-chlorocarbonyl isocyanate (FP) 743 [G.E. 789]
Cycloaddition of phenyl isocyanate to a diaziridinimine (SC) 109 [G.E. 112]
Catalyzed rearrangement of nitrile oxides to ~ (SC) 555 [G.E. 562]
Isocyanides, Recent applications of α-metalated ~ in organic synthesis (FP) 339 [G.E. 351]
Synthesis with diphosgene (SC) 259 [G.E. 267]
N-Acyl ~ (SC) 262 [G.E. 272]
Carbodiimides as source of isocyanide and carbonyl ligands (SC) 641 [G.E. 660]
N-Imidoyl ~ (SC) 727 [G.E. 742]
Isodiazomethane complexes (SC) 707 [G.E. 752]
Isoelectric focusing (Book Review) 420
Isothiocyanato complexes, Isolation and vibrational spectra of bond-isomeric hexakis(thiocyanato) complexes of ruthenium(III) and osmium(III) (SC) 108 [G.E. 108]
Isotope effect, Dependence of calcium ~ upon electrolyte concentration in ion-exchange chromatography (SC) 719 [G.E. 753]

KERR effect, The electro-optical ~ in conformational analysis (FP) 663 [G.E. 725]
Ketene derivatives, Dimers of ketenylidene- and N-phenylketeniminylidenetriphenylphosphorane (SC) 268 [G.E. 275]
Ketenes, [2+2]- and [4+2]-cycloadditions of arylazoalkenes (SC) 58 [G.E. 59]
Reactions of acyl chlorides, triethylamine, or ~ with phosgeniminium salts (SC) 182 [G.E. 189]
Ketene synthons, Reactions (LA) 490
Ketenyl complex, p-Tolylketenyl as novel dihapto 3-electron ligand (SC) 102 [G.E. 110]
Ketones, N-(Trimethylsilyl)amino acid trimethylsilyl esters as reagents for directed self-condensation of methyl ~ under mild conditions (SC) 251 [G.E. 255]
Condensation of α-acylaminoalkyl methyl ~ to give N-acylpyrroles (SC) 252 [G.E. 256]
4-Hydroxy-2-cyclopenten-1-ones from ~ and 3-nitropropionyl chloride. A facile method for the construction of five-membered rings (SC) 321 [G.E. 334]
Doubly deprotonated allylacetophenone.

First example of a "direct" E^5 synthon (SC) 320 [G.E. 333]
Synthesis of α,β-unsaturated cyclic ~ by sensitized photooxidation of silyl enol ethers (SC) 413 [G.E. 426]
Homologization of aldehydes and ~ to thiiranes or S-vinyl thiocarbamates via 2-alkylimino-1,3-oxathiolanes (SC) 462 [G.E. 478]
Nickel(II)-catalyzed synthesis of pyrroles from 2H-azirines and activated ~ (SC) 647 [G.E. 672]
Ketoses, Structure of ~ and their biologically important phosphate esters in solution (LA) 201
Kinetic data, Review of methods for analysis of ~ in biochemistry (LA) 61
Kinetics, Thermochemical ~. Methods for the estimation of thermochemical data and rate parameters (Book Review) 883
Krebs cycle, Coordination of lipid degradation with the ~ (LA) 803

LACTAMS, Reaction of monothiodicarboximides with phosphorus ylides: A new synthesis of ω-alkylidene-~ (SC) 418 [G.E. 429]
A new cis-stereospecific β-lactam ring closure (SC) 544 [G.E. 553]
The zip reaction: A new method for ring expansion; synthesis of 17- and 21-membered polyamino-~ (SC) 861 [G.E. 899]
Lactones, δ-~ by carbonylation of vinyloxiranes (SC) 50 [G.E. 47]
A new lactone synthesis (SC) 876 [G.E. 914]
Layer compounds, $[Zn_2Cr(OH)_6]X \cdot 2H_2O$, new ~ capable of anion exchange and intracrystalline swelling (SC) 265 [G.E. 259]
Lipid degradation, Coordination with the Krebs cycle (LA) 803
Lipids, Effect of dietary ~ on drug metabolizing enzymes (LA) 201
Lipolysis, Influence of drugs and hormones on ~ in heart (LA) 804
Liquid crystals, Substituted phenylcyclohexanes—A new class of ~ (SC) 100 [G.E. 103]
Selenol esters—A novel class of ~ (SC) 318 [G.E. 328]
Infrared rotatory dispersion of liquid-crystalline solutions of chiral molecules (SC) 790 [G.E. 830]
Relationship between the infrared rotatory dispersion of liquid-crystalline solutions of chiral molecules and their absolute configuration (SC) 791 [G.E. 831]
Lithium compounds, Stereoselective hydride elimination from organomagnesium compounds and organo-~ (SC) 44 [G.E. 46]
Lithiomethyl(diphenyl)arsane oxide, a new reagent (SC) 53 [G.E. 52]
Extension of the scope of anionic cycloadditions by activating organoelement groups (SC) 119 [G.E. 107]
Lithium 7bH-indeno[1,2,3-jk]fluorenide, an organo-~ having a "sandwich" structure (SC) 474 [G.E. 490]
2C-chain elongation of lithioalkanes with diphenylvinylarsane and phenyl vinyl selenide (SC) 710 [G.E. 760]
Quantitative trace analysis of metals by field desorption mass spectrometry (SC) 852 [G.E. 890]

MACROLIDES, Recent progress in chemistry and biochemistry (FP) 585 [G.E. 602]
Magnesium compounds, Stereoselective hydride elimination from organo-lithium compounds and organo-~ (SC) 44 [G.E. 46]
Bis(trimethylsilyl)magnesium—The first organosilylmagnesium compound isolated (SC) 247 [G.E. 257]
Malononitrile, Use for annelation reactions (LA) 122
Manganese complexes, Preparation of halogen-bridged cationic dinuclear complexes of manganese and rhenium (SC) 56 [G.E. 53]
Intramolecular mobility in CS_2 complexes of manganese (SC) 193 [G.E. 191]
Acceptor function of η^2-bonded CS_2 ligands (SC) 194 [G.E. 192]
$[C_5H_5(CO)_2Mn—N_2H_2—Cr(CO)_5]$, a complex with a diazene bridge and two different coordination centers (SC) 464 [G.E. 480]
Unsaturated organometallic intermediates: Electronic structure and structural dynamics of $(\eta^5\text{-}C_5H_5)Mn(CO)_2$ (SC) 536 [G.E. 551]
Synthesis and reactivity of hetero dinuclear complexes containing a Mn—Co bond (SC) 649 [G.E. 656]
First reaction of the N_2 ligand with bases; reduction of coordinated dinitrogen by nucleophilic attack (SC) 880 [G.E. 918]
Marine organisms, Toxins (LA) 335
Marine science, Handbook of ~ (Book Review) 805
Mass spectrometry, Collision activation ~ with novel analysis technique (SC) 120 [G.E. 115]
Quantitative field desorption ~; stable isotope dilution and cationization (SC) 184 [G.E. 180]
Quantitative trace analysis of metals by field desorption ~ (SC) 852 [G.E. 890]
Effective method for designing synthetic approaches to natural products (LA) 60
Membrane bound processes, Investigations of mitochondrial adenine nucleotide translocation by means of nucleotide analogs (FP) 695 [G.E. 717]
Mercury compounds, $[\eta^5\text{-}C_5H_5Mo(CO)_3\text{-}HgMo]_4$, a metal cluster with cubane structure (SC) 704 [G.E. 746]
Metabolic regulation, Control at the level of substrate supply (LA) 803
Metalation, Cyclo-~ reactions (FP) 73 [G.E. 75]
Metal clusters, Study of ~ (LA) 557
Metathesis, Dipole ~ (SC) 54 [G.E. 60]
5-Methoxysemibullvalene (SC) 475 [G.E. 491]
Methylene complexes, Novel synthesis of μ-~ (SC) 334 [G.E. 342]
Methylenecyclopropane, Palladium(0)-catalyzed $[2\sigma+2\pi]$ cycloadditions to alkenes (SC) 249 [G.E. 254]
Micelles of ionic detergents in aqueous solutions (LA) 490
Michaelis-Arbuzov reaction, Phosphoranes as intermediates (SC) 477 [G.E. 493]
Microbial transformation, Formation of chlorophenols by ~ of chlorobenzenes (SC) 645 [G.E. 680]
Microbiology, Mikrobiologie (Book Review) 420
Microorganisms, Utilization of microbes—Modern developments in biological technology (FP) 205 [G.E. 211]
Microsomes, Drug-metabolizing enzyme systems of liver ~ (LA) 201
Mitochondria, Investigations of mitochondrial adenine nucleotide translocation by means of nucleotide analogs (FP) 695 [G.E. 717]
Mixing-reaction model, The selectivity of chemical reactions disguised by diffusion. Part I: Chemical selectivity disguised by mixing (FP) 807 [G.E. 847]
Molecular states and molecular orbitals (FP) 613 [G.E. 631]
Molybdates, Halogenonitrosyl-~—Simple, monomeric Mo^{II} complexes (SC) 183 [G.E. 189]
Molybdenum complexes, A monothiooxalato-O,S-oxo complex of molybdenum containing two S_2^{2-} ligands (SC) 260 [G.E. 269]
Asymmetrical bridge complexes of type $\eta^3\text{-}C_7H_7(CO)_2Mo(OR)_3Mo\text{-}\eta^7\text{-}C_7H_7$ with two Mo centers of different oxidation number (SC) 261 [G.E. 271]
Halogenonitrosylmolybdates—Isolation of the first classical Mo^I complex (SC) 468 [G.E. 479]
$[\eta^5\text{-}C_5H_5Mo(CO)_3HgMo]_4$, a metal cluster with cubane structure (SC) 704 [G.E. 746]
Dichloro(porphyrinato)molybdenum(IV)—Synthesis and structure (SC) 788 [G.E. 819]
Monofunctionalization, Selective ~ of non-conjugated dienes by nitrogen dioxide/iodine monoaddition (SC) 246 [G.E. 253]
Monothiooxalate, A monothiooxalato-O,S-oxo complex of molybdenum containing two S_2^{2-} ligands (SC) 260 [G.E. 269]
Mössbauer spectroscopy, Applications to the study of heterogeneous catalysis (LA) 335
Applications of ~ (Book Review) 420

anti-1,2:3,4-NAPHTHALENE dioxide, A complementary route to ~; direct oxidation of arenes with m-chloroperbenzoic and (SC) 171 [G.E. 181]
Naphthalene pentoxide, Synthesis and structure analysis (SC) 169 [G.E. 175]
Naphthaleno[2]paracyclophanes, Intramolecular quinhydrone of the [2](1,4)naphthaleno[2]paracyclophane series (SC) 394 [G.E. 407]
Naphthalenophanes, Synthesis and stereochemistry of strained ~ (SC) 175 [G.E. 199]
Stereoisomeric quinhydrones of the [2.2](1,4)naphthalenophane series (SC) 392 [G.E. 406]
Naphthodianthrones, Synthesis of hypericin and related meso-~ by alkaline dimerization of hydroxyanthraquinones (SC) 46 [G.E. 56]
Natural products, Effective method for designing synthetic approaches to ~ (LA) 60
Nervous system, Biochemistry of sphingolipid storage diseases (FP) 273 [G.E. 283]
Neutron activation tables (Book Review) 558
Neutron diffraction, Experimental electron densities and chemical bonding (FP) 32 [G.E. 33]
Nickel catalysts, Control of the direction of addition in the nickel-catalyzed 2:1-cooligomerization of butadiene with monoolefins by perturbation of the monoolefin (SC) 252 [G.E. 260]
Control of the nickel-catalyzed cooligomerization of butadiene with Schiff bases by cocatalysts (SC) 253 [G.E. 261]
Nickel complexes, Two routes to complex derivatives of borole (SC) 42 [G.E. 43]
"Supersandwich"-type trinuclear complexes with a spiro center (SC) 324 [G.E. 332]
(A→D)-Cyclization of a nickel(II) Δ^{18}-dehydro-1-methylidene-1,19-secocorrinate (SC) 459 [G.E. 475]
Nickel compounds, Novel organo-~ from (pentaphenyl)aluminacyclopentadiene (SC) 183 [G.E. 179]
Nickel(II)-catalyzed synthesis of pyrroles from 2H-azirines and activated ketones (SC) 647 [G.E. 672]
Nickelocene, η-Cyclopentadienyl(η-diborolenyl)nickel—A diamagnetic ~ analog (SC) 468 [G.E. 483]
Nitrile oxides, Catalyzed rearrangement to isocyanates (SC) 555 [G.E. 562]
Nitriles, Reactions of phosgeniminium salts with ~, imino ethers, and imidoyl chlorides—Synthesis of 4,6-dichloro-2-(dialkylamino)pyrimidines (SC) 189 [G.E. 182]
Nitro compounds, Crown ether catalyzed reduction of aromatic ~ to give amines (SC) 41 [G.E. 43]
Nitrogen complexes, cis-Bis(dinitrogen)tetrakis(trimethylphosphane)chromium (SC) 56 [G.E. 57]
Hexameric $KN_2Co[P(CH_3)_3]_3$—A novel potassium-dinitrogen cluster (SC) 485 [G.E. 499]
Nitrogen compounds, New pathways to four-membered boron-nitrogen heterocycles (SC) 478 [G.E. 494]
Detection of an orthonitrate by vibrational spectroscopy: $Na_3[NO_4]$ (SC) 534 [G.E. 567]
Dichloronitronium hexachloroantimonate, $ONCl_2SbCl_6$ (SC) 545 [G.E. 569]
Photochemical [2+2]-cycloaddition between parallel CC and NN double bonds (SC) 777 [G.E. 825]
Nitrogen cycloelimination, Thermal and photochemical cycloelimination of nitrogen (FP) 835 [G.E. 876]
Nitrogen dioxide, Selective monofunctionalization of non-conjugated dienes by ~/iodine monoaddition (SC) 246 [G.E. 253]

C-Nitroso compounds, Electrophilic ~ (LA) 490
Nitrosylation, Partial ~ of dicarbonyl(η-cyclopentadienyl)cobalt (SC) 172 [G.E. 186]
Nitrosylmolybdates, Halogeno-~—Isolation of the first classical Mo^I complex (SC) 468 [G.E. 479]
NMR-spectroscopy, Determination of the activation volume $\Delta V^{\neq}$ of simple molecular rearrangements by high-resolution ^1H-~ at high pressures (SC) 331 [G.E. 340]
Nuclear reactions with heavy ions (LA) 60
Nucleic acids, The dependence of translation on the 5'-terminal methylation of m-RNA (LA) 200
Stereoselectivity in the binding of transition-metal chelates to nucleic acid constituents (LA) 557
Nucleophilic substitution, ~ of vinylic hydrogen atoms by carbanions (SC) 44 [G.E. 46] ~ (LA) 557
Nucleosides, Chemistry and biochemistry of C-~ (LA) 122

OCTALENE (SC) 871 [G.E. 909]
Configuration, conformation, and dynamics of ~ (SC) 872 [G.E. 910]
Olefins, Assignment of configuration of ~, diols, and epoxides. Quantitative analysis of their stereoisomeric mixtures (SC) 100 [G.E. 103]
Resolution of a chiral olefin by complexation chromatography on an optically active rhodium(I) complex (SC) 110 [G.E. 113]
Reaction with silane and carbon monoxide catalyzed by $Co_2(CO)_8$ (SC) 174 [G.E. 196]
Polar effects in addition of alkyl radicals to ~ (SC) 178 [G.E. 178]
An olefin with unusually large C—C≡C angles (SC) 658 [G.E. 665]
Transition metal catalyzed reactions of organic halides with carbon monoxide, ~, and acetylenes (LA) 335
Olefin synthesis, Decarboxylative dehydration of β-hydroxycarboxylic acids by redox condensation: a novel ~ (SC) 255 [G.E. 265]
Orbitals, Molecular states and molecular ~ (FP) 613 [G.E. 631]
"Organic metals"—The intermolecular migration of aromaticity (FP) 519 [G.E. 534]
Organometallic chemistry, Reviews (LA) 60
Surveys of work published in 1975 (LA) 335
Orthonitrate, Detection of an ~ by vibrational spectroscopy: $Na_3[NO_4]$ (FP) 534 [G.E. 567]
Oscillation, Phenomena of ~ in biological systems (LA) 419
Osmium complexes, Isolation and vibrational spectra of bond-isomeric hexakis(thiocyanato) complexes of ruthenium(III) and osmium(III) (SC) 108 [G.E. 108]
Osmotic desalination, Principles (FP) 607 [G.E. 624]
Oxazolinones, C—C linkage of carboxylic acids with allyl alcohols using 2-phenylglycine as vehicle (SC) 394 [G.E. 408]
Oxirane ring opening, Facile synthesis of arabinoadenosine 3'-phosphate (SC) 317 [G.E. 328]
Oxirene, α-Oxocarbene-~ isomerization: Photolysis of [1-^{13}C]-2-diazo-1-phenyl-1-propanone and [2-^{13}C]-1-diazo-1-phenyl-2-propanone (SC) 781 [G.E. 827]
α-Oxocarbene-oxirene isomerization: Photolysis of [1-^{13}C]-2-diazo-1-phenyl-1-propanone and [2-^{13}C]-1-diazo-1-phenyl-2-propanone (SC) 781 [G.E. 827]
Oxoferrate(III), First ~ having a ring structure: $Na_{14}[Fe_6O_{16}]$ (SC) 43 [G.E. 45]
Oxometalates with planar coordination (FP) 674 [G.E. 704]
Oxophosphoranes, Hydrogenolysis of trisubstituted dichlorophosphoranes—A new method for deoxygenation of ~ (SC) 552 [G.E. 558]
Oxozincates, Coordination number 3 in ~: $Rb_8[OZnO_2ZnO_2ZnO_2ZnO]$ and $K_2[Zn_6O_7]$ (SC) 484 [G.E. 498]
Oxyamination, Amino sugars and N-glycosides by ~ of unsaturated carbohydrate derivatives (SC) 553 [G.E. 565]
Oxygen, Synthetic hemopolymers for reversible binding of molecular ~ (SC) 117 [G.E. 120]
Oxygenase, Model of internal mono-~ catalyzed reactions: Copper-catalyzed autoxidation of bis(1-methylbenzimidazol-2-yl)methane (SC) 189 [G.E. 185]
Ozone, The chlorofluorocarbon/~ theory—A scientific status report (FP) 513 [G.E. 507]

PALLADIUM(0)-catalyzed [2σ + 2π] cycloadditions of methylenecyclopropane to alkenes (SC) 249 [G.E. 254]
Palladium complexes, General method for the synthesis of sandwich-type complexes with a Pd—Pd or Pt—Pt bond (SC) 412 [G.E. 427]
Palladium(II) and platinum(II) complexes with polymeric Schiff base ligands (SC) 860 [G.E. 898]
Palladium compounds, Novel 3z-2e bond system (SC) 248 [G.E. 257]
Paracyclophane quinhydrones, Indirectly transmitted charge-transfer interactions: Multilayered [2.2]-~ (SC) 801 [G.E. 841]
Diastereomeric [3.3]-~ (SC) 799 [G.E. 839]
Pauli principle, The ~ and chemical bonding in molecules and solids (FP) 294 [G.E. 317]
Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane, Synthesis and absolute configuration of enantiomerically pure D_3-trishomocubanes (~) and trishomocubanones (SC) 116 [G.E. 119]
Peptide synthesis, Side reactions in ~: tert-butylation of tryptophan (SC) 317 [G.E. 330]
Repetitive ~ with insoluble polymer-bound reagents and solubilizing macromolecular peptide carriers (SC) 642 [G.E. 681]
Peroxides, 2,3-Dioxabicyclo[2.2.2]octane by selective reduction of double bonds with azodicarboxylate (SC) 713 [G.E. 762]
Phallisin, Resynthesis of phalloidin and ~ from the seco-compounds (SC) 267 [G.E. 274]
Phalloidin, Resynthesis of ~ and phallisin from the seco-compounds (SC) 267 [G.E. 274]
Phase-transfer catalysis, Phase-transfer catalyzed alkylation of diphenylphosphinic amide—A new versatile synthesis of primary and secondary amines (SC) 702 [G.E. 737]
Phenethylamines and tryptamines; related compounds of plant origin (LA) 490
Phenylcyclohexanes, Substituted ~—A new class of liquid-crystalline compounds (SC) 100 [G.E. 103]
p-Phenylenediamines, Synthesis of substituted p-aminophenols from ~ (SC) 266 [G.E. 273]
2-Phenylglycine, C—C linkage of carboxylic acids with allyl alcohols using ~ as vehicle (SC) 394 [G.E. 408]
Phosgeniminium salts, New reagents for synthesis of heterocycles from carbodiimides and ~ (SC) 181 [G.E. 188]
Reactions of acyl chlorides, triethylamine, or ketenes with ~ (SC) 182 [G.E. 189]
Reactions with nitriles, imino ethers, and imidoyl chlorides—synthesis of 4,6-dichloro-2-(dialkylamino)pyrimidines(SC)189 [G.E. 182]
Phosphaallene ylide, Preparation and reactions of a cyclic ~ (SC) 877 [G.E. 915]
Phosphanes, Synthesis of acyldiarylphosphane oxides—Key compounds in the oxidation of acyldiaryl-~ with molecular oxygen (SC) 269 [G.E. 276]
Oligo(difluorophosphoranes) by direct fluorination of tertiary ~ (SC) 718 [G.E. 763]
$Co_5(CO)_{11}(PR_2)_3$, a novel type of pentanuclear cluster (SC) 731 [G.E. 738]
5λ^5-Phosphaspiro[4.4]nonane, 5-Methyl-~—The simplest pentaalkylphosphorane yet obtained (SC) 722 [G.E. 748]
Phosphate esters, Structure of ketoses and their biologically important ~ in solution (LA) 201
Phosphates in ceramics (LA) 490
β-Phosphatrimethinecyanine dye, Preparation (SC) 404 [G.E. 418]
Phosphazenes, Poly(organo-~)—Unusual new high polymers (FP) 147 [G.E. 153]
$(RPNCH_3)_4$, cyclotetra(λ^3-~)—Synthesis and crystal structure analysis (SC) 407 [G.E. 423]
Phosphonium salts, Simple synthesis of (arylethynyl)triphenyl-~ (SC) 45 [G.E. 55]
Phosphoramidates, Alkylation of diethyl ~—A simple route from primary to secondary amines (SC) 107 [G.E. 109]
Phosphorane, (Chloromethylene)triphenyl-~ (SC) 180 [G.E. 203]
Dimers of ketenylidene- and N-phenylketeniminylidene-triphenyl-~ (SC) 268 [G.E. 275]
~-s as intermediates in the Michaelis-Arbuzov reaction (SC) 477 [G.E. 493]
5-Methyl-5λ^5-phosphaspiro[4.4]nonane — The simplest pentaalkyl-~ yet obtained (SC) 722 [G.E. 748]
Intramolecular oxidative addition of azopyridine to phosphorus(III) (SC) 865 [G.E. 903]
Phosphorus compounds, Phosphacumulene ylides and phosphaallene ylides (FP) 349 [G.E. 361]
Diastereomers with differing bond lengths: structure analysis of the diastereomeric forms of μ-(1,2dichloro-1,2-diphenyldiphosphane) bis (pentacarbonylchromium) (SC) 260 [G.E. 268]
Diazadiphosphetidine with ring-stabilized "pentaamidophosphorus" (SC) 263 [G.E. 268]
Phenyl(trimethylphosphonio)methanidyl, a novel 3-electron bridge ligand (SC) 314 [G.E. 325]
Absolute configuration of the cancerostatic S(−)-cyclophosphamide (SC) 330 [G.E. 336]
Synthesis of dinuclear complexes containing PCl_2 and PF_2 bridges (SC) 408 [G.E. 421]
cis-2-Telluro-1,3,2λ^5, 4λ^3-diazadiphosphetidine—A fluxional redox system (SC) 486 [G.E. 500]
1,2,4,3λ^3-Triazaphospholes synthesized by reductive (σ^4→σ^2)-elimination at phosphorus (SC) 546 [G.E. 554]
Double ring-closure additions to o-(methyleneamino)-phenyl phosphites (SC) 549 [G.E. 558]
Hydrogenolysis of trisubstituted dichlorophosphoranes—A new method for deoxygenation of oxophosphoranes (SC) 552 [G.E. 558]
Phosphorus-bridged trinuclear complexes having contiguous metal-metal bonds (SC) 542 [G.E. 568]
Diphosphinomethanide/phosphoniumbismethylide: a novel ligand combination for transition metals (SC) 640 [G.E. 679]
Bis[trimethylphosphorio(-onio)]methanide, a "semi-ylidic" ligand in transition metal complexes (SC) 654 [G.E. 657]
Dicyanophosphide (SC) 704 [G.E. 747]
Phase-transfer catalyzed alkylation of diphenylphosphinic amide—A new versatile synthesis of primary and secondary amines (SC) 702 [G.E. 737]
An imino-bridged triaza-λ^5-phosphetine (SC) 783 [G.E. 817]
Synthesis of bridged 1,3,2λ^3,4λ^3-diazadiphosphetidines (SC) 797 [G.E. 829]
Phosphorus-tin ylide, Dimeric bis(di-tert-butylphosphino)stannanediyl: A cyclic ~ (SC) 792 [G.E. 832]
Phosphorus ylides, "Carbodiphosphoranes" by a new rearrangement of ~ (SC) 417 [G.E. 428]
Reaction of monothiodicarboximides with ~: A new synthesis of ω-alkylidenelactams (SC) 418 [G.E. 429]
Molecular structure of $[\eta\text{-}C_5H_5(CO)_2Re{=}C(C_6H_5)P(CH_3)_3][BCl_4]$ (SC) 543 [G.E. 553]
Photochemistry, Photochemical [2 + 2]-cycloaddition between parallel CC and NN double bonds (SC) 777 [G.E. 825]

α-Oxocarbene-oxirene isomerization: Photolysis of [1-^{13}C]-2-diazo-1-phenyl-1-propanone and [2-^{13}C]-1-diazo-1-phenyl-2-propanone (SC) 781 [G.E. 827]
The ~ of 2H-azirines (LA) 121
Aspects of the ~ of organo-transition metal compounds (LA) 200
The ~ of imines (LA) 557
Photochromism of rhodamine derivatives (SC) 113 [G.E. 116]
Photocycloaddition, Geometrical dependence of [2π + 2σ]-~ (SC) 103 [G.E. 111]
Photodielectric polymers for holographic use (FP) 441 [G.E. 467]
Photoelectron spectrometry, Unstable intermediates in the gaseous phase: The thermal decomposition of alkyl sulfides RS_nR (SC) 104 [G.E. 105]
Unstable intermediates in the gaseous phase: The thermal decomposition of acyl chlorides RCOCl (SC) 105 [G.E. 106]
Photolysis, A trimeric cyclopentadienone derivative by ~ of 3,5-diphenyl-4H-thiopyran-4-one 1,1-dioxide with daylight (SC) 653 [G.E. 659]
~ of saturated alcohols, ethers, and amines (LA) 804
Photooxidation, Synthesis of α,β-unsaturated cyclic ketones by sensitized ~ of silyl enol ethers (SC) 413 [G.E. 426]
~ of polymers (LA) 660
Picosecond chemistry (LA) 60
Pineal gland biorhythms (LA) 122
Planar coordination, Oxometalates with ~ (FP) 674 [G.E. 704]
Plastics, Einführung in die Chemie und Technologie der Kunststoffe (Book Review) 272
Platinum complexes, A general method for the synthesis of sandwich-type complexes with a Pd—Pd or Pt—Pt bond (SC) 412 [G.E. 427]
Novel monobridged dinuclear platinum species (SC) 482 [G.E. 495]
Novel transformation of diphenylcyclopropenone: Double bond cleavage in the reaction with ~ (SC) 793 [G.E. 838]
Palladium(II) and platinum(II) complexes with polymeric Schiff base ligands (SC) 860 [G.E. 898]
Poisons, Die Giftliste (Book Review) 202
Polar effects in the addition of alkyl radicals to olefins (SC) 178 [G.E. 178]
Polyethers, Noncyclic cryptates (SC) 548 [G.E. 564]
Polymeric carriers, Repetitive peptide synthesis with insoluble polymer-bound reagents and solubilizing macromolecular peptide carriers (SC) 642 [G.E. 681]
Polymerization, Crystallographic analysis of a topochemical ~ (SC) 416 [G.E. 432]
~ (LA) 732
Mechanism of ~ in the solid state (LA) 804
Polymers, Poly(organophosphazenes)—Unusual new high ~ (FP) 147 [G.E. 153]
Photodielectric ~ for holographic use (FP) 441 [G.E. 467]
Entanglement of thread molecules and its influence on the properties of ~ (FP) 751 [G.E. 773]
Photooxidation of ~ (LA) 660
~ which become electrical conductors on irradiation (LA) 660
Polyphosphazenes, Poly(organophosphazenes)—Unusual new high polymers (FP) 147 [G.E. 153]
Polysaccharides, Secondary and tertiary structure of ~ in solutions and gels (FP) 214 [G.E. 228]
Porphyrins, Dichloro(porphyrinato)molybdenum(IV)—Synthesis and structure (SC) 788 [G.E. 819]
Potassium-dinitrogen cluster, Hexameric $KN_2Co[P(CH_3)_3]_3$—A novel ~ (SC) 485 [G.E. 499]
Potentiometric titrations, Fully automatic ~ (FP) 157 [G.E. 129]
Proline, Simple synthesis of racemic ~ (SC) 777 [G.E. 824]
Propellanes (Book Review) 420
Prostaglandins, Synthesis and function in the heart (LA) 122
Influence on the behavior of blood vessels (LA) 123
Proteinase inhibitors of plants and microorganisms (LA) 419
Proteins, Structural rules for globular ~ (FP) 23 [G.E. 24]
Organic fluorescence reagents in the study of enzymes and ~ (FP) 137 [G.E. 142]
Protein synthesis, Role of hemin in the regulation of ~ in erythroid cells (LA) 200
Protohypericin, Synthesis from emodin (SC) 46 [G.E. 55]
Protonation, Site of ~ of dimethyl sulfoxide—Raman spectroscopic data (SC) 197 [G.E. 200]
Ortho-para ~ of toluene and ethylbenzene in super acids (SC) 315 [G.E. 323]
Pseudoglycals, Simple de-novo synthesis of reactive ~ (hex-2-enopyranosides)—Stereospecific α-glycoside coupling (SC) 783 [G.E. 822]
Pyrazine imines, Heat of hydrogenation of compounds containing isolated and conjugated C=N double bonds (SC) 47 [G.E. 48]
Pyrenophorin, Synthesis and determination of the absolute configuration of ~ and vermiculin (SC) 264 [G.E. 270]
Pyridines, Cobalt-catalyzed one-step synthesis of annelated ~ (SC) 708 [G.E. 758]
6H-Pyrido[4,3-b]carbazole, Synthesis (LA) 803
Pyridoxal-containing enzymes, Activation of double bonds in dehydro amino acids: a model for ~ in elimination-addition reactions (SC) 328 [G.E. 345]
(Pyridylazo)naphthol, Intramolecular oxidative addition of azopyridine to phosphorus(III) (SC) 865 [G.E. 903]
Pyrimidine nucleosides, Syntheses and rearrangements of 5-substituted ~ and pyrimidine nucleotides (LA) 556
Pyrimidines, New synthesis of ~ and pyrimidinones (SC) 779 [G.E. 816]
Pyrimidinones, New synthesis of pyrimidines and ~ (SC) 779 [G.E. 816]
Pyro-compounds, Inorganic ~ (LA) 60
Pyrometallurgy, Principles of ~ (Book Review) 491
Pyrroles, Condensation of α-acylaminoalkyl methyl ketones to give N-acyl-~ (SC) 252 [G.E. 256]
Nickel(II)-catalyzed synthesis of pyrroles from 2H-azirines and activated ketones (SC) 647 [G.E. 672]
Total synthesis of [^{14}C]- and [^{3}H]-labeled tripyrrole precursors for heme biosynthesis (SC) 651 [G.E. 676]
Pyrrolidine, Simple synthesis of racemic proline (SC) 777 [G.E. 824]
β-(1-Pyrrolidinyl)acrylonitrile, Functional vinyl carbanions—Deprotonation of ~ (SC) 853 [G.E. 891]
Pyrrolodiazines (LA) 661

QUANTUM chemistry, Early history of the quantum mechanical treatment of the chemical bond (FP) 87 [G.E. 89]
Quinhydrones, Stereoisomeric ~ of the [2.2](1,4)naphthalenophane series (SC) 392 [G.E. 406]
An intramolecular quinhydrone of the [2](1,4)naphthaleno[2]paracyclophane series (SC) 394 [G.E. 407]
Diastereomeric [3.3]paracyclophane ~ (SC) 799 [G.E. 839]
Indirectly transmitted charge-transfer interactions: Multilayered [2.2]paracyclophane ~ (SC) 801 [G.E. 841]

[4]RADIALENE, Reversible transition between a ~ and a cyclobutadiene by electron transfer (SC) 410 [G.E. 424]
Radical anions, Thiathione ~: Are (—S)$_2$C=S groups electron traps? (SC) 724 [G.E. 745]
ESR spectroscopy studies on the radical anion of [^{33}S]-2,2,4,4-tetramethylpentane-3-thione (SC) 726 [G.E. 744]
Radical cations, Radical cation of [2.2](9,10)anthracenophane as a model for dimeric anthracene ~ (SC) 657 [G.E. 666]
Radical ions, Oxidation and reduction of methylthio-substituted π-systems and the electron distribution in their ~ (SC) 855 [G.E. 893]
Radicals, Polar effects in the addition of alkyl ~ to olefins (SC) 178 [G.E. 178]
Reaction enthalpy, Determination of ~ in the ion-exchange of chlorine isotopes (SC) 114 [G.E. 118]
Formation of the (Z,E)-1,3-diphenylallyl radical from the (Z,E)-1,3-diphenylallyl anion by electron transfer—Comparison of the rotational barriers of the radical and the anion (SC) 869 [G.E. 907]
Reactions, Reaktionen der organischen Chemie (Book Review) 61
Reactivity, Basis and limitations of the ~-selectivity principle (FP) 125 [G.E. 162]
Rearrangements, Determination of activation volume $\Delta V^{\neq}$ of simple molecular ~ by high-resolution ^{1}H-NMR spectroscopy at high pressures (SC) 331 [G.E. 340]
Thermal rearrangement of silylmethyl acetates (SC) 712 [G.E. 765]
Free-radical ~ in telomerization (LA) 271
Receptors, Flexible drug molecules and dynamic ~ (FP) 766 [G.E. 805]
Redox condensation, Decarboxylative dehydration of β-hydroxycarboxylic acids by ~: A novel olefin synthesis (SC) 255 [G.E. 265]
Redox systems, cis-2-Telluro-1,3,2λ^5,4λ^3-diazadiphosphetidine—A fluxional ~ (SC) 486 [G.E. 500]
Reduction, Electrochemical ~ of 2,2,2-trichloroethanols (SC) 57 [G.E. 54]
Renin, Structure-activity relations of antagonists of the ~-angiotensin system (LA) 201
Rhenium, Molecular structure of [η-$C_5H_5(CO)_2Re{=}C(C_6H_5)P(CH_3)_3][BCl_4]$ (SC) 543 [G.E. 553]
Rhenium complexes, Preparation of halogen-bridged cationic dinuclear complexes of manganese and rhenium (SC) 56 [G.E. 53]
Phenyl(trimethylphosphonio)methanidyl, a novel 3-electron bridge ligand (SC) 314 [G.E. 325]
Molecular structure of [η-$C_5H_5(CO)_2$-$Re{=}C(C_6H_5)P(CH_3)_3][BCl_4]$ (SC) 543 [G.E. 553]
Rhodamine, Photochromism of ~ derivatives (SC) 113 [G.E. 116]
Rhodium(I) complexes, Resolution of a chiral olefin by complexation chromatography on an optically active ~ (SC) 110 [G.E. 113]
Reactivity of η^5-indenyl-~; cyclocotrimerization of alkynes with alkenes (SC) 648 [G.E. 671]
D-Ribofuranose, α-Glycosidic linkage (SC) 48 [G.E. 58]
Ribonucleic acid, Dependence of translation on the 5'-terminal methylation of m-~ (LA) 200
Ring expansion, The zip reaction: A new method for ~; synthesis of 17- and 21-membered polyaminolactams (SC) 861 [G.E. 899]
Ring opening reactions, Electrocyclic ~ of ethylene oxides (FP) 572 [G.E. 589]
Rotamers, Detection of rigid ~ in disubstituted cyclopentadienylcobalt complexes (SC) 795 [G.E. 836]
Rotational barriers, Formation of the (Z,E)-1,3-diphenylallyl radical from the (Z,E)-1,3-diphenylallyl anion by electron transfer—Comparison of the ~ of the radical and the anion (SC) 869 [G.E. 907]
Rotatory dispersion, Infrared ~ of liquid-crystalline solutions of chiral molecules (SC) 790 [G.E. 830]
Relationship between the infrared ~ of liquid-crystalline solutions of chiral molecules and their absolute configuration (SC) 791 [G.E. 831]
Rubber, Vulcanization of natural and synthetic ~ (LA) 660

Ruthenium complexes, Isolation and vibrational spectra of bond-isomeric hexakis-(thiocyanato) complexes of ruthenium(III) and osmium(III) (SC) 108 [G.E. 108]

SANDWICH complexes, New varieties of ~ (FP) 1 [G.E. 1]
(η-Cyclopentadienyl)cobalt-(η-diborolen-yl)(η-cyclopentadienyl)iron—A triple decker sandwich complex containing two different metals (SC) 857 [G.E. 895]
Schiff base complexes, Addition compounds with polymeric chromium(II)-~ (SC) 859 [G.E. 897]
Palladium(II) and platinum(II) complexes with polymeric Schiff base ligands (SC) 860 [G.E. 898]
Schiff bases, Control of the nickel-catalyzed cooligomerization of butadiene with ~ by cocatalysts (SC) 253 [G.E. 261]
Seawater analysis, Methods of ~ (Book Review) 491
Seaweeds, Volatile compounds from ~ (LA) 419
Selectivity, Basis and limitations of the reactivity-~ principle (FP) 125 [G.E. 162]
The ~ of chemical reactions disguised by diffusion. Part I: Chemical ~ disguised by mixing (FP) 807 [G.E. 847]
Temperature dependence of ~ of the halogen donors $XCCl_3$ (SC) 466 [G.E. 482]
Disguised chemical selectivities (LA) 123
Selenides, α-Halogenoalkyl ~ and α-(phenylseleno)alkanide anions (SC) 541 [G.E. 561]
2C-chain elongation of lithioalkanes with diphenylvinylarsane and phenyl vinyl selenide (SC) 710 [G.E. 760]
Selenium compounds, 5H-[1]Benzoselenino[2,3-b]pyridine—A novel heterocyclic ring system (SC) 319 [G.E. 329]
Selenoacetals, Synthesis of di-~ and O-(trimethylsilyl)mono-~ (SC) 540 [G.E. 559]
Selenoalkanide anions, α-Halogenoalkyl selenides and α-(phenylseleno)alkanide anions (SC) 541 [G.E. 561]
Selenol esters, Synthesis of thiol esters and ~ from carboxylic acids and thiols or selenols, respectively (SC) 244 [G.E. 251]
~—A novel class of liquid-crystal compounds (SC) 318 [G.E. 328]
Semibullvalene, 5-Methoxy-~ (SC) 475 [G.E. 491]
Sesquiterpene lactones, Biological activity (LA) 121
Silanes, Reaction of olefins with silane and carbon monoxide catalyzed by $Co_2(CO)_8$ (SC) 174 [G.E. 196]
Preparation of cyclohexasilane, Si_6H_{12} (SC) 403 [G.E. 417]
Anomalous nucleophilic substitution in (chloromethyl)silane: 1,2-hydride shift (SC) 639 [G.E. 678]
Catalyst dependent product distribution in the reaction of 1-hexene with a hydrosilane and carbon monoxide (SC) 881 [G.E. 919]
Silicates, $K_6[Si_2Te_6]$—Synthesis and structure of the first tellurodisilicate (SC) 554 [G.E. 566]
Silicides, Crystal structure of barium disilicide at high pressures (SC) 659 [G.E. 673]
Silicon compounds, A novel 3z-2e bond system (SC) 248 [G.E. 257]
Silatautomeric organylcarbodiimides/cyanamides (SC) 311 [G.E. 336]
Synthesis and some reactions of 1,1-dimethyl-2,2-bis(trimethylsilyl)-1-silaethane (SC) 328 [G.E. 343]
Silylaluminum compounds, Synthesis and properties of tris(trimethylsilyl)aluminum (SC) 480 [G.E. 497]
Silyl compounds, N-(Trimethylsilyl)amino acid trimethylsilyl esters as reagents for directed self-condensation of methyl ketones under mild conditions (SC) 251 [G.E. 255]
Silyleneiron complexes, Base-stabilized ~ (SC) 785 [G.E. 823]
Silyl enol ethers, Synthesis of α,β-unsaturated cyclic ketones by sensitized photooxidation of ~ (SC) 413 [G.E. 426]
Chemistry (LA) 335
Silylmethyl acetates, Thermal rearrangement (SC) 712 [G.E. 765]
Soil atmosphere, Analysis by gas chromatography (LA) 419
Solvents, Handbook of analysis of organic ~ (Book Review) 123
Spatial requirements, Steric interactions in organic chemistry: ~ of substituents (FP) 429 [G.E. 443]
Sphingolipid storage diseases, Biochemistry (FP) 273 [G.E. 283]
Spiro compounds having a nonplanar 1,4-dihydropyridine ring from diaziridinimines and dimehyl acetylenedicarboxylate (SC) 177 [G.E. 202]
Stability, Observation of a linear relationship between thermal ~ and strain energy of alkanes (SC) 875 [G.E. 913]
Stannyl azides, Synthesis of N-protected amino acids with the aid of ~ (SC) 550 [G.E. 570]
Statistics, Lehrprogramm Statistik (Book Review) 202
Stereochemistry, Synthesis and ~ of strained naphthalenophanes (SC) 175 [G.E. 199]
Stereoscopic pictures, Strukturen der Materie und ihre Symmetrie in Stereobildern (Book Review) 336
Stereoselective synthesis, Simple ~ of eburnamonine (SC) 878 [G.E. 916]
Steric accelerations, Steric enhancement of chemical reactivity. The molecular structure of tris(tert-butyl)methyl p-nitrobenzoate (SC) 654 [G.E. 658]
Steric interactions in organic chemistry: Spatial requirements of substituents (FP) 429 [G.E. 443]
Steroids, Asymmetric induction in the total synthesis of 19-nor-~ (LA) 201
Strain energy, Observation of a linear relationship between thermal stability and ~ of alkanes (SC) 875 [G.E. 913]
Structural rules for globular proteins (FP) 23 [G.E. 24]
Sulfanes, Bis(trifluoromethyl)disulfane oxide $CF_3S(O)SCF_3$ (SC) 723 [G.E. 740]
Sulfides, Unstable intermediates in the gaseous phase: Thermal decomposition of alkyl ~ RS_nR (SC) 104 [G.E. 105]
Thioethers (~) (LA) 803
Literature concerning di- and poly-~ (LA) 804
Sulfinylhydrazine, X-Ray structure analysis of N-phenyl-N'-~ (SC) 179 [G.E. 190]
Sulfone pyrolysis, New type of helical hydrocarbon—Novel C—C coupling by ~ (SC) 325 [G.E. 358]
Sulfonium salts, Vinylenedionium salts containing different onium groups (SC) 471 [G.E. 488]
Reactions of (2-dialkylsulfoniovinyl)trialkylammonium salts (SC) 473 [G.E. 489]
Sulfonyldiazenes, N-Acyl-N'-aryl-~; detection and use in the synthesis of amides (SC) 728 [G.E. 742]
Sulfoxides, Site of protonation of dimethyl sulfoxide—Raman spectroscopic data (SC) 197 [G.E. 200]
Sulfur, Detection of S_6 and S_7 in molten cycloocta-~ (SC) 112 [G.E. 114]
Crystal and molecular structure of cycloheptа-~ (δ-S_7) (SC) 715 [G.E. 756]
Bond interaction in ~ rings: crystal and molecular structure of cyclo-hepta-~ oxide, S_7O (SC) 716 [G.E. 757]
Sulfuranes, A stable acyclic alkoxyhalosulfurane: Chlorotris(2,2,2-trifluoro-1-trifluoromethylethoxy)sulfurane (SC) 862 [G.E. 900]
Elemental ~ and its reactions (LA) 660
Sulfur compounds, Cyclopropenes as vinylcarbenoids: intermolecular carbene-addition reactions of sulfinyl- and sulfonylcyclopropenes at room temperature (SC) 323 [G.E. 331]
New aliphatic thiacylating reagents; preparation of tert-butyl esters of aliphatic dithiocarboxylic acids via bis(thioacyl) sulfide (SC) 786 [G.E. 820]
2,4-Diisopropyl-1,3-dithietane-2,4-diyl bis-(dithioisobutyrate), a dimeric form of bis-(thioacyl) sulfide (SC) 787 [G.E. 820]
Tris(tert-butylimino)sulfur(VI) and bis(tert-butylimino)(silylimino)sulfur(VI): The "Y-triene" structure (SC) 789 [G.E. 829]
Sulfur labels, Preparation of thiocarbonyl compounds containing isotopic ~ (SC) 725 [G.E. 743]
Super acids, Ortho-para protonation of toluene and ethylbenzene in ~ (SC) 315 [G.E. 323]
Surface, The ~ chemical bond (FP) 92 [G.E. 94]
The ~ of titanium dioxide (LA) 122
Symmetry, Strukturen der Materie und ihre Symmetrie in Stereobildern (Book Review) 336
Synthetic methods, Intramolecular [4+2] and [3+2] cycloadditions in organic synthesis (FP) 10 [G.E. 10]
Recent applications of α-metalated isocyanides in organic synthesis (FP) 339 [G.E. 351]
Phosphacumulene ylides and phosphaallene ylides (FP) 349 [G.E. 361]
Flash thermolysis of organic compounds (FP) 365 [G.E. 377]
Advances in phase-transfer catalysis (FP) 493 [G.E. 521]
Titanium tetrachloride in organic synthesis (FP) 817 [G.E. 858]

TANTALUM disulfide, Demonstration of the ionic structure of the intercalation compound $TaS_2 \cdot NH_3$ (SC) 199 [G.E. 193]
cis-2-Telluro-1,3,2λ⁵,4λ³-diazadiphosphetidine—A fluxional redox system (SC) 486 [G.E. 500]
Tellurodisilicate, $K_6[Si_2Te_6]$—Synthesis and structure of the first ~ (SC) 554 [G.E. 566]
Tellurophene (LA) 732
Tellurium oxide fluorides, The Te—O—Fe system: $Te(OTeF_5)_6$ (SC) 729 [G.E. 741]
Tetracyanoethylene, Comparison of calculated and experimental electron difference densities of ~ (SC) 257 [G.E. 263]
Tetracyclododecanes, Structures of two highly strained ~ (SC) 798 [G.E. 833]
Textile auxiliary agents, Handbuch der Textilhilfsmittel (Book Review) 661
Thermolysis, Flash ~ of organic compounds (FP) 365 [G.E. 377]
μ-Thiadiborolene-bis(η-thiadiboroleneco-balt)—A "homogeneous" triple-decker sandwich with three heterocyclic ligands (SC) 333 [G.E. 346]
6aλ⁴-Thiapentalenes, New synthetic methods for ~ (SC) 403 [G.E. 420]
Thiathione radical anions: Are (—S)₂C=S groups electron traps? (SC) 724 [G.E. 745]
Thienopyridines (LA) 732
Thiiranes, Homologization of aldehydes and ketones to ~ or S-vinyl thiocarbamates via 2-alkylimino-1,3-oxathiolanes (SC) 462 [G.E. 478]
Thioacyl sulfides, Isolation of acyl ~ (SC) 879 [G.E. 917]
Thiocarbonyl and carbonyl groups (LA) 732
Thiocarbonyl compounds, Preparation of ~ containing isotopic sulfur labels (SC) 725 [G.E. 743]
Thiocarbonyl ylides, Stable ~ (SC) 866 [G.E. 904]
Thiodicarboximides, Reaction of mono-~ with phosphorus ylides: A new synthesis of ω-alkylidenelactams (SC) 418 [G.E. 429]
Thioethers (sulfides) (LA) 803
Thioformamide, N,N-Bis(trimethylsilyl)enamines—Stereoselective synthesis from N,N-bis(trimethylsilyl)-~ (SC) 535 [G.E. 550]
Thioheteroanions—Unusual metal-ligand interaction and reactions (SC) 705 [G.E. 748]
Thioketenes, α-Thiolactones from ~ (SC) 722 [G.E. 750]

ESR spectroscopy studies on the radical anion of [^{33}S]-2,2,4,4-tetramethylpentane-3-thione (SC) 726 [G.E. 744]
α-Thiolactones from thioketenes (SC) 722 [G.E. 750]
Thiol esters, Synthesis of ~ and selenol esters from carboxylic acids and thiols or selenols, respectively (SC) 244 [G.E. 251]
Thiols (mercaptans) (LA) 732
Thiocyanato complexes, Isolation and vibrational spectra of bond-isomeric hexakis-(thiocyanato) complexes of ruthenium(III) and osmium(III) (SC) 108 [G.E. 108]
4H-Thiopyran-4-one 1,1-dioxide, Trimeric cyclopentadienone derivative by photolysis of 3,5-diphenyl-~ with daylight (SC) 653 [G.E. 659]
Thread molecules, Entanglement of ~ and its influence on the properties of polymers (FP) 751 [G.E. 773]
Through-bond interaction between two mutually perpendicular systems—A new possibility of conjugation (SC) 110 [G.E. 122]
Tin compounds, Structure of the first four-membered cyclic diorganyltin chalcogenides (SC) 547 [G.E. 556]
Dimeric bis(di-tert-butylphosphino)stannanediyl: A cyclic phosphorus-tin ylide (SC) 792 [G.E. 832]
Titanium dioxide, Surface (LA) 122
Titanium tetrachloride in organic synthesis (FP) 817 [G.E. 858]
Titrations, Fully automatic potentiometric ~ (FP) 157 [G.E. 129]
Toluene, Ortho-para protonation of ~ and ethylbenzene in super acids (SC) 315 [G.E. 323]
p-Tolylketenyl as novel dihapto 3-electron ligand (SC) 102 [G.E. 110]
Topochemical polymerization, Crystallographic analysis of a ~ (SC) 416 [G.E. 432]
Toxins from marine organisms (LA) 335
Trace analysis, Quantitative ~ of metals by field desorption mass spectrometry (SC) 852 [G.E. 890]
Transition-metal chelates, Stereoselectivity in the binding of ~ to nucleic acid constituents (LA) 557
Transition metal complexes, Cyclometalation reactions (FP) 73 [G.E. 75]
Transition metal compounds, Aspects of the photochemistry of organo-~ (LA) 200
Triacetylcellulose, Column chromatography on ~. Preparative separation of enantiomeric diaziridines (SC) 405 [G.E. 419]
Triaza-λ^5-phosphetine, An imino-bridged ~ (SC) 783 [G.E. 817]
1,2,4,3λ^3-Triazaphospholes synthesized by reductive ($\sigma^4 \rightarrow \sigma^2$)-elimination at phosphorus (SC) 546 [G.E. 554]
Trifluoromethylamine, CF_3NH_2 (SC) 707 [G.E. 754]
Trifluoromethylation, A new method for the introduction of trifluoromethyl groups (SC) 854 [G.E. 892]
(Triphenylstannyl)methyllithium, Carbonyl olefination with ~ (SC) 862 [G.E. 900]
Tripyrroles, Total synthesis of [^{14}C]- and [^{3}H]-labeled tripyrrole precursors for heme biosynthesis (SC) 651 [G.E. 676]
Tris(tert-butyl)methyl p-nitrobenzoate, Steric enhancement of chemical reactivity. Molecular structure of ~ (SC) 654 [G.E. 658]
Trishomocubanones, Synthesis and absolute configuration of enantiomerically pure D_3-trishomocubanes (pentacyclo[6.3.0.0^{2,6}.-0^{3,10}.0^{5,9}]undecane) and ~ (SC) 116 [G.E. 119]
Trityl chloride, Ionization barrier of ~ in sulfur dioxide (SC) 256 [G.E. 266]
Trivial names, Trivialnamenkartei (Book Review) 336
Tryptamines, Phenethylamines and ~; related compounds of plant origin (LA) 490
Tryptophan, Side reactions in peptide synthesis: tert-butylation of ~ (SC) 317 [G.E. 330]
Tungsten complexes, p-Tolylketenyl as novel dihapto 3-electron ligand (SC) 102 [G.E. 110]
Triphenylsilylcarbyne complexes of tungsten (SC) 401 [G.E. 416]
Synthesis of dinuclear complexes containing PCl_2 and PF_2 bridges (SC) 408 [G.E. 421]
Synthesis of alkyne-bridged dinuclear complexes by reaction of trans-halotetracarbonyl(methylcarbyne)-tungsten with methylenebis(diphenylarsane) (SC) 465 [G.E. 481]
Tungsten compounds, Phenyl(trimethylphosphonio)methanidyl, a novel 3-electron bridge ligand (SC) 314 [G.E. 325]
Thioheteroanions—Unusual metal-ligand interaction and reactions (SC) 705 [G.E. 748]

ULLMANNS Encyklopädie der technischen Chemie (Book Review) 62, 202
Urease, Binding of ~ to anodized sheet aluminum (SC) 714 [G.E. 761]

VANADIUM(V) compounds, Diastereoselective synthesis of the aporphine alkaloid (+)-cataline. Hydroxylation with vanadium(V) trifluoride oxide (SC) 730 [G.E. 739]
Vermiculin, Synthesis and determination of the absolute configuration of pyrenophorin and ~ (SC) 264 [G.E. 270]
Vinyl carbanions, Functional ~—Deprotonation of β-(1-pyrrolidinyl)acrylonitrile (SC) 853 [G.E. 891]
Vinylcarbenoids, Cyclopropenes as ~: Intermolecular carbene-addition reactions of sulfinyl- and sulfonylcyclopropenes at room temperature (SC) 323 [G.E. 331]
Vinyl cations, Stabilized ~ (LA) 121
Vinylenedionium salts containing different onium groups (SC) 471 [G.E. 488]
Vinyloxiranes, δ-Lactones by carbonylation of ~ (SC) 50 [G.E. 47]
Vinylic hydrogen atoms, Nucleophilic substitution of ~ by carbanions (SC) 44 [G.E. 46]
Vitamin B_{12}, New developments in the field of ~: Enzymatic reactions dependent upon corrins and coenzyme B_{12} (FP) 233 [G.E. 239]
Vitamins, Effect on drug metabolism (LA) 200
Vulcanization of natural and synthetic rubber (LA) 660

WIELAND, Heinrich Wieland centennial: His lifework and his legacy today (FP) 559, 884 [G.E. 575, 922]
Wittig reaction, ~ in industrial practice (FP) 423 [G.E. 437]
Carbonyl olefination with (triphenylstannyl)methyllithium (SC) 862 [G.E. 900]

X-RAY diffraction, Experimental electron densities and chemical bonding (FP) 23 [G.E. 33]
β-D-Xylopyranose, Tetraaxial conformation of 1,2,3,4-tetra-O-benzoyl-~ (SC) 52 [G.E. 51]

YLIDES, Phosphacumulene ~ and phosphaallene ~ (FP) 349 [G.E. 361]
"Carbodiphosphoranes" by a new rearrangement of phosphorus ~ (SC) 417 [G.E. 428]
Reaction of monothiodicarboximides with phosphorus ~: A new synthesis of ω-alkylidenelactams (SC) 418 [G.E. 429]
Stable thiocarbonyl ~ (SC) 866 [G.E. 904]
Preparation and reactions of a cyclic phosphaallene ylide (SC) 877 [G.E. 915]

ZINCATES, Coordination number 3 in oxo-~: $Rb_8[OZnO_2ZnO_2ZnO_2ZnO]$ and $K_2[Zn_6O_7]$ (SC) 484 [G.E. 498]
Zinc complexes, "Supersandwich"-type trinuclear complexes with a spiro center (SC) 324 [G.E. 332]
Zinc compounds, $[Zn_2Cr(OH)_6]X \cdot 2H_2O$, new layer compounds capable of anion exchange and intracrystalline swelling (SC) 265 [G.E. 259]
Zip reaction: A new method for ring expansion; synthesis of 17- and 21-membered polyaminolactams (SC) 861 [G.E. 899]
Zwitterions, Spontaneous alternating copolymerization via zwitterion intermediates (FP) 826 [G.E. 867]
Four-membered phosphorus-nitrogen-metal heterocycles with zwitterionic structure (SC) 864 [G.E. 902]